Supplementary information for

Catalytic Intermolecular Asymmetric [2π + 2σ] Cycloadditions of Bicyclo[1.1.0]butanes: Practical Synthesis of Enantioenriched Highly Substituted Bicyclo[2.1.1]hexanes

Ying-Jie Li,[†,§] Zhi-Long Wu,[†,§] Qiang-Shuai Gu,[‡,§] Tingting Fan,[‖,§] Ming-Hao Duan,[†] Lihong Wu,[†] Yu-Tao Wang,[†] Ji-Peng Wu,[†] Fang-Lei Fu,[†] Fan Sang,[‖] Ai-Ting Peng,[†] Yuyang Jiang,[†‖]* Xin-Yuan Liu,[‡*] and Jin-Shun Lin[†*]

[†]State Key Laboratory of Chemical Oncogenomics, Institute of Biopharmaceutics and Health Engineering, Tsinghua Shenzhen International Graduate School, Shenzhen, 518055, China

[‡]Shenzhen Grubbs Institute, Department of Chemistry, and Guangming Advanced Research Institute, Southern University of Science and Technology, Shenzhen 518055, China

[‖]Institute of Biomedical Health Technology and Engineering, Shenzhen Bay Laboratory, Shenzhen 518132, China

[§]These authors contributed equally: Ying-Jie Li, Zhi-Long Wu, Qiang-Shuai Gu, Tingting Fan.

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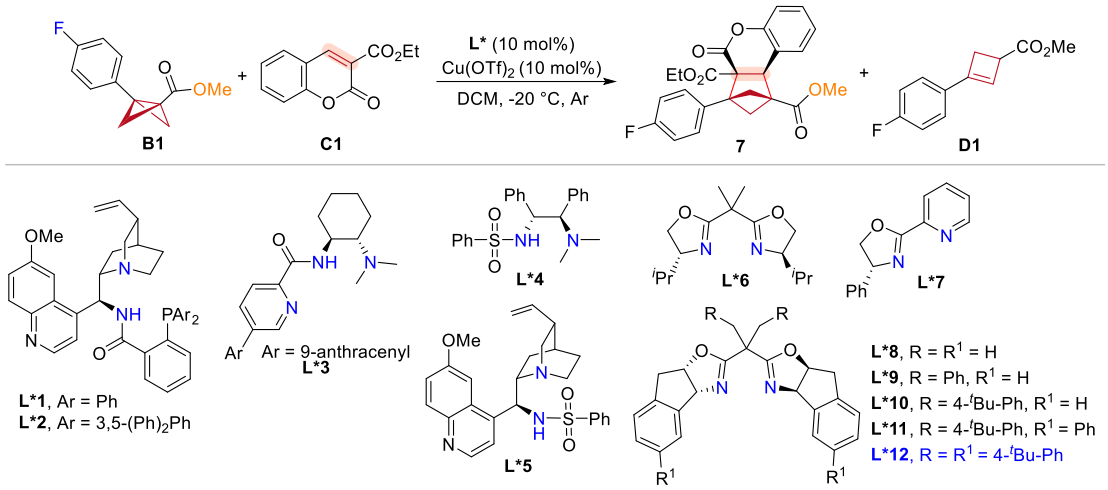
General information

All reactions involving air- or moisture-sensitive reagents and/or intermediates were carried out under argon atmosphere using Schlenk techniques. All dry solvents were either freshly distilled or purchased from a commercial supplier in extra-dry grade. Dry dichloromethane (DCM), chloroform ($CHCl_3$), and 1,2-Dichloroethane (DCE) were distilled from a suspension with calcium hydride (CaH_2). Tetrahydrofuran (THF, 99.9%, SuperDry, stabilizer free, with molecular sieves), *N,N'*-dimethylformamide (DMF, 99.8%, SuperDry) and methanol (MeOH, 99.9%, SuperDry, with molecular sieves) were purchased from *J&K Scientific*. Acetonitrile (CH_3CN, 99.9%, SuperDry, with molecular sieves) was purchased from *Meryer*. Reagents were purchased at the highest commercial quality from *Bidepharm*, *Leyan*, *Aladdin, and TCI* and used without further purification unless otherwise stated. $Cu(OTf)_2$ was purchased from *Aladdin*. Sonidegib was sourced from HwrkChem, while BMS-202 was acquired from Bidepharm. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 GF254 plates. Flash column chromatography was performed using Tsingtao silica gel (300-400 mesh). Visualization of TLC was achieved by the use of UV light (254 nm), iodine, or $KMnO_4$-stain. NMR spectra were recorded on Bruker AVANCE 400 spectrometer at 400 MHz for ^1H NMR, 101 MHz for ^{13}C NMR, and 376 MHz for ^{19}F NMR in $CDCl_3$ or d_6-DMSO with tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in ppm, and coupling constants are given in Hz. Data for ^1H NMR are recorded as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; p, pentet, m, multiplet; br, broad), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High-resolution mass spectral analysis (HRMS) data were obtained using Thermo Scientific™ Q Exactive™ Hybrid Quadrupole-Orbitrap™ Mass Spectrometer. Enantiomeric excess (e.e.) was determined using Agilent LC1260II high-performance liquid chromatography (HPLC) with a Hitachi detector (λ = 210, 230, 254, 273 nm). Column conditions are reported in the experimental section below.

1. Supplementary tables for experiments

Table S1 | Reaction condition optimization with BCB **B1** and ethyl coumarin-3-carbaoxylate **C1**: screening of different ligands



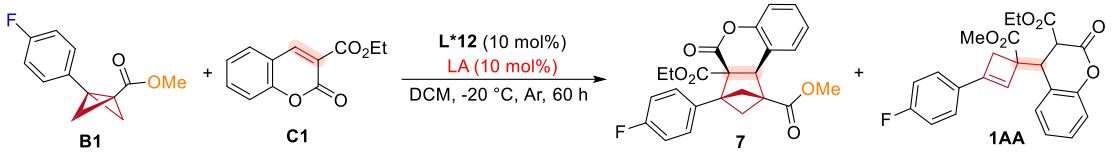
Entry	Ligand	Time (h)	Yield of **7** (%)[b]	E.e. (%)[c]	Yield of **D1**(%)[b]
1	**L*1**	40	N.R.	-	trace
2	**L*2**	40	N.R.	-	trace
3	**L*3**	40	trace	-	trace
4	**L*4**	40	50	0	trace
5	**L*5**	40	22	48	trace
6	**L*6**	60	19	23	55
7	**L*7**	60	46	10	35
8	**L*8**	60	82	12	trace
9	**L*9**	60	85	48	trace
10	**L*10**	60	85	60	trace
11	**L*11**	60	83	67	trace
12	**L*12**	60	85	84	trace

[a]Reaction conditions: **B1** (0.0525 mmol, 1.05 equiv.), **C1** (0.05 mmol, 1 equiv.), $Cu(OTf)_2$ (10 mol%), ligand (10 mol%), and dry DCM (0.5 mL) -20 °C under Ar;

[b]Yield was based on ^1H NMR analysis of the crude products using CH_2Br_2 as an internal standard;

[c]E.e. values were based on chiral HPLC analysis.

Table S2 | Reaction condition optimization with BCB **B1** and ethyl coumarin-3-carbaoxylate **C1**: screening of different Lewis acids.



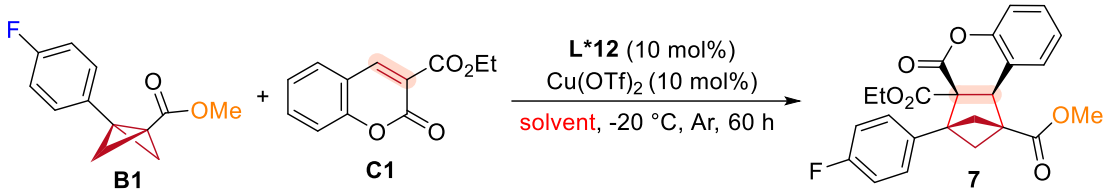
Entry	Lewis acid	Yield of **7** (%)[b]	E.e. of **7** (%)[c]	Yield of **1AA** (%)[b]	E.e. of **1AA** (%)[c]
1	$Sc(OTf)_3$	82	0	-	-
2	$Zn(OTf)_2$	90	80	6	88
3	$Ni(OTf)_2$	81	74	13	83
4	$Cu(ClO_4)_2·6H_2O$	90	78	-	-
5	$Cu(OTf)_2$	85	84	-	-

[a]Reaction conditions: **B1** (0.0525 mmol, 1.05 equiv.), **C1** (0.05 mmol, 1.0 equiv.), Lewis acid (10 mol%), **L*12** (10 mol%), and dry DCM (0.5 mL) -20 °C for 60 h under Ar;

[b]Yield was based on ^{1}H-NMR analysis of the crude products using CH_2Br_2 as an internal standard;

[c]E.e. values were based on chiral HPLC analysis.

Table S3 | Reaction condition optimization with BCB **B1** and ethyl coumarin-3-carbaoxylate **C1**: screening of different solvents.



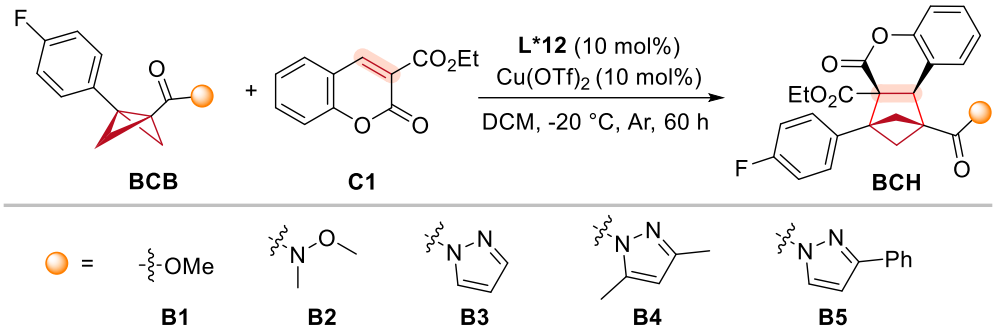
Entry	Solvent	Yield of **7** (%)[b]	E.e. of **7** (%)[c]
1	DCM	85	84
2	THF	85	44
3	PhCl	42	49
4	$CHCl_3$	60	59
5	$PhCF_3$	40	72

[a]Reaction conditions: **B1** (0.0525 mmol, 1.05 equiv.), **C1** (0.05 mmol, 1.0 equiv.), $Cu(OTf)_2$ (10 mol%), **L*12** (10 mol%), and dry solvent (0.5 mL) -20 °C for 60 h under Ar;

[b]Yield was based on ^1H NMR analysis of the crude products using CH_2Br_2 as an internal standard;

[c]E.e. values were based on chiral HPLC analysis.

Table S4 | Reaction condition optimization with **BCB** and ethyl coumarin-3-carbaoxylate **C1**: screening of different BCBs.



Entry	BCB	Yield of **BCH** (%)[b]	E.e. of **BCH** (%)[c]
1	**B1**	85	84
2	**B2**	50	98
3	**B3**	57	96
4	**B4**	**95**	**97**
5	**B5**	95	95

[a]Reaction conditions: **BCB** (0.0525 mmol, 1.05 equiv.), **C1** (0.05 mmol, 1.0 equiv.), $Cu(OTf)_2$ (10 mol%), **L*12** (10 mol%), and dry DCM (0.5 mL) -20 °C for 60 h under Ar;

[b]Yield was based on ^1H NMR analysis of the crude products using CH_2Br_2 as an internal standard;

[c]E.e. values were based on chiral HPLC analysis.

2. Supplementary figures for experiments

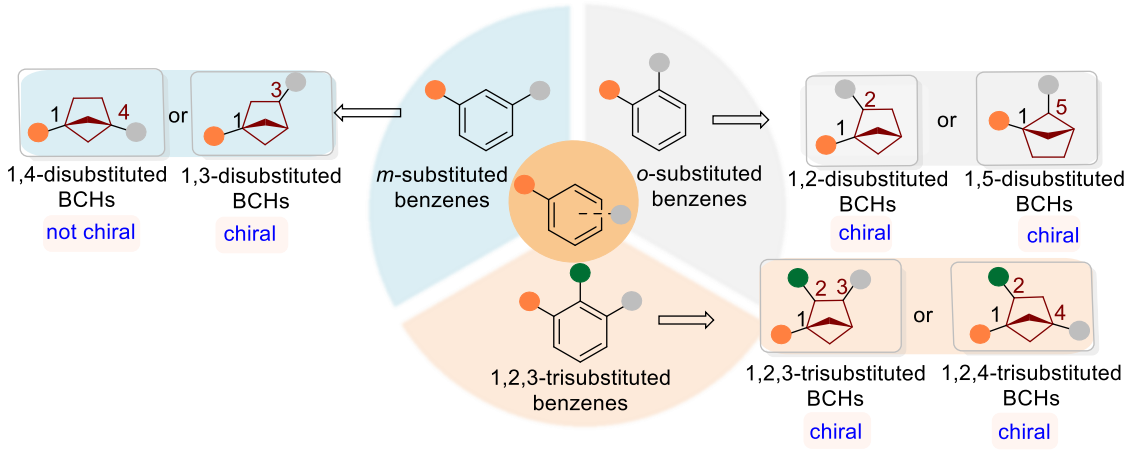


Figure S1 | Chiral saturated bicyclic hydrocarbon bioisosteres available for *ortho*-, *meta*-disubstituted and 1,2,3-trisubstituted benzenes.

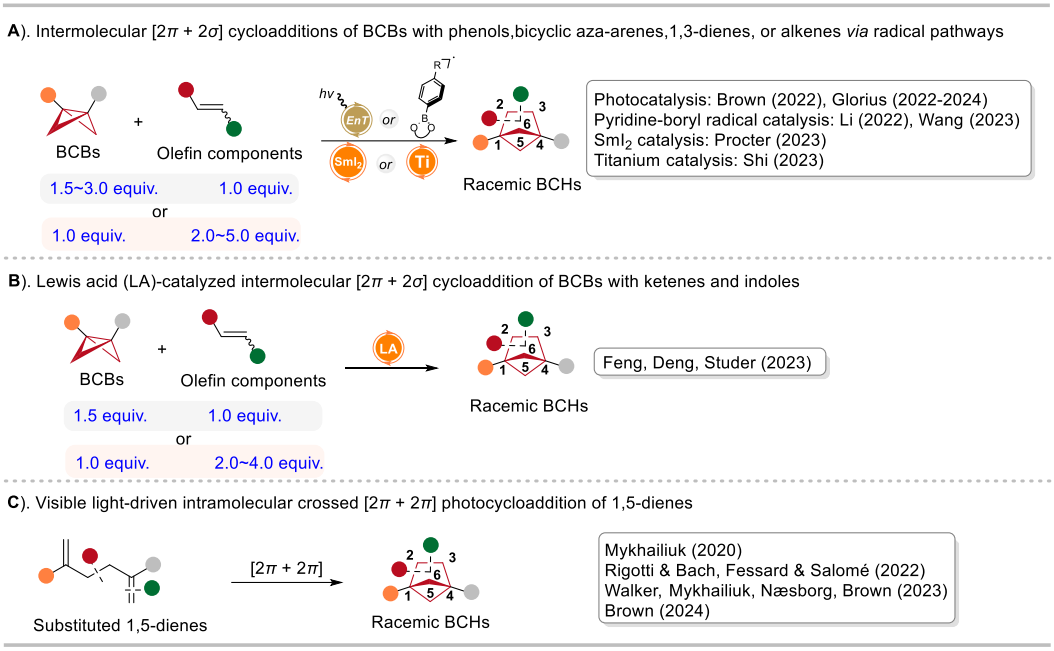
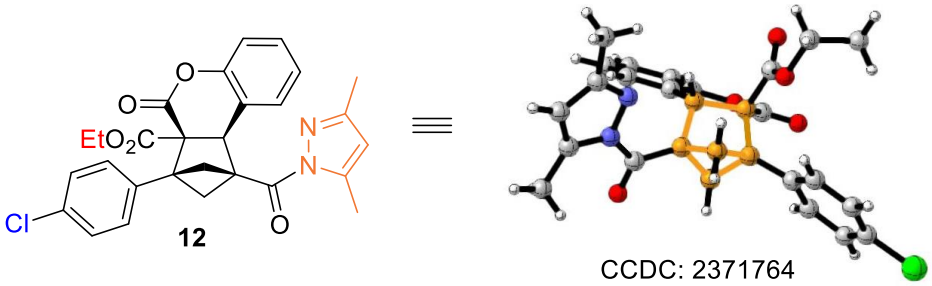


Figure S2. State-of-the-art strategies for the construction of the racemic BCHs



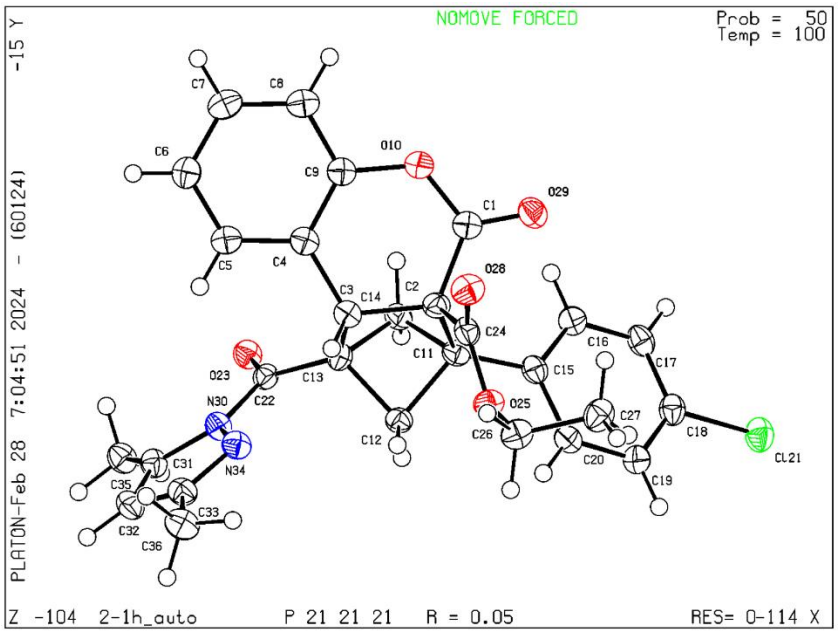
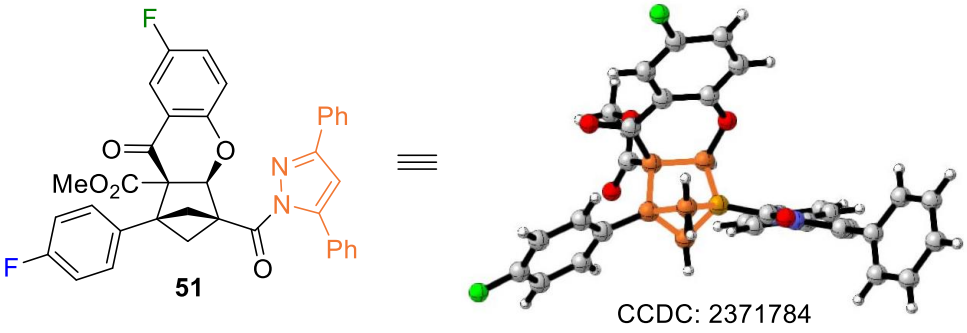


Figure S3 | The X-ray structure of 12.



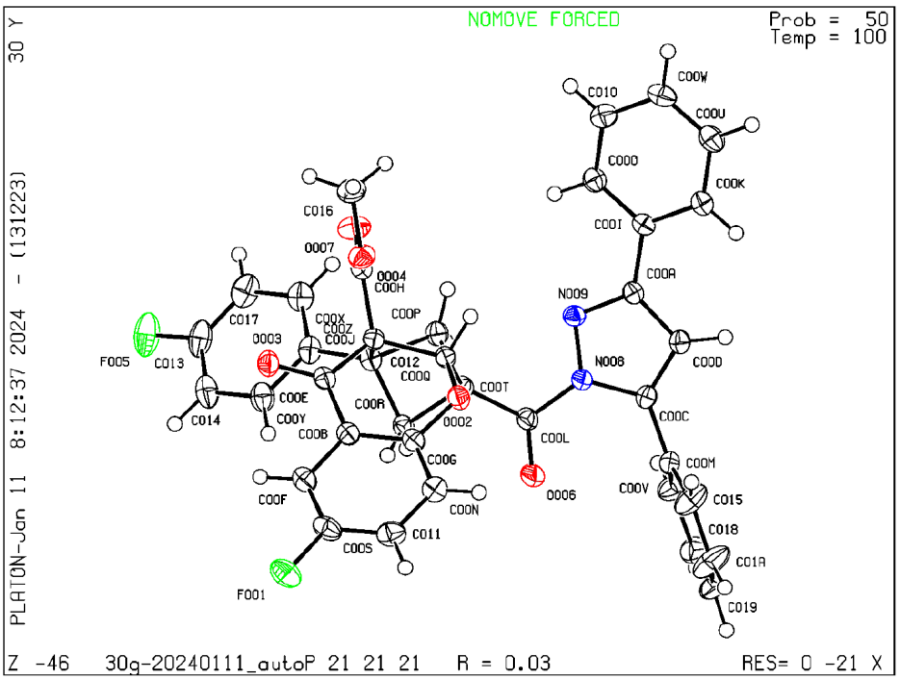


Figure S4 | The X-ray structure of 51.

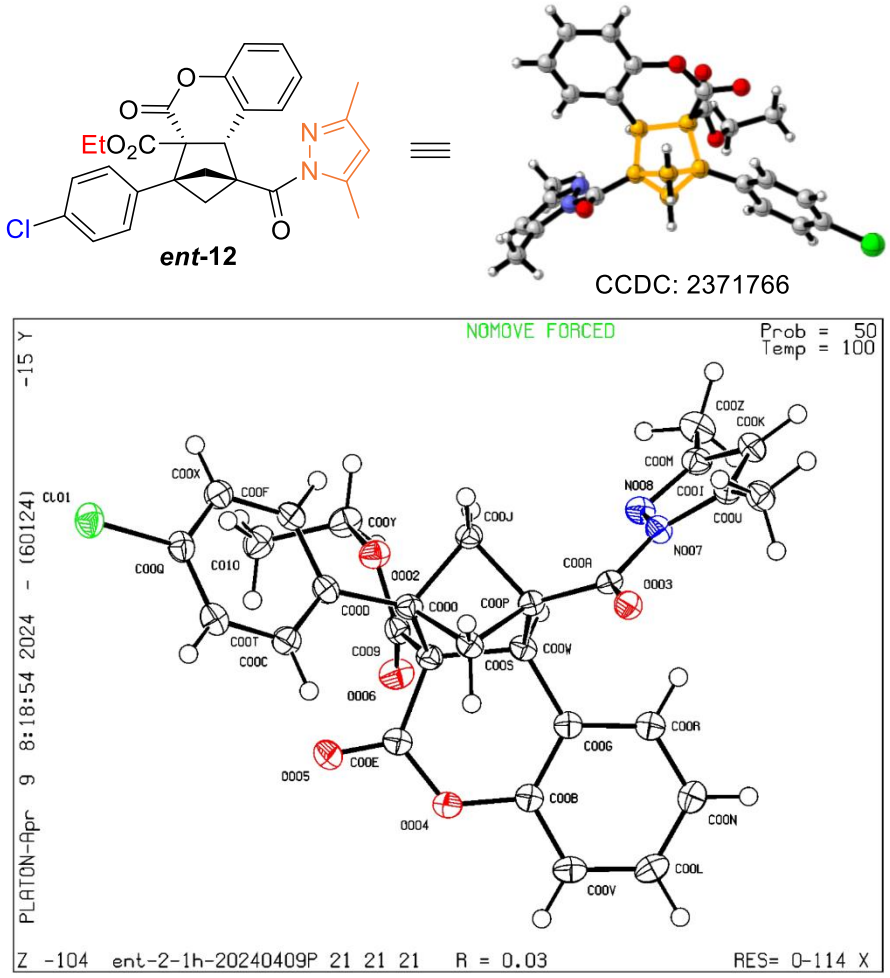


Figure S5 | The X-ray structure of *ent*-12.

3. General procedure for the synthesis of substrates

3.1 Synthesis of bicyclo[1.1.0]butanes (BCBs) substrates

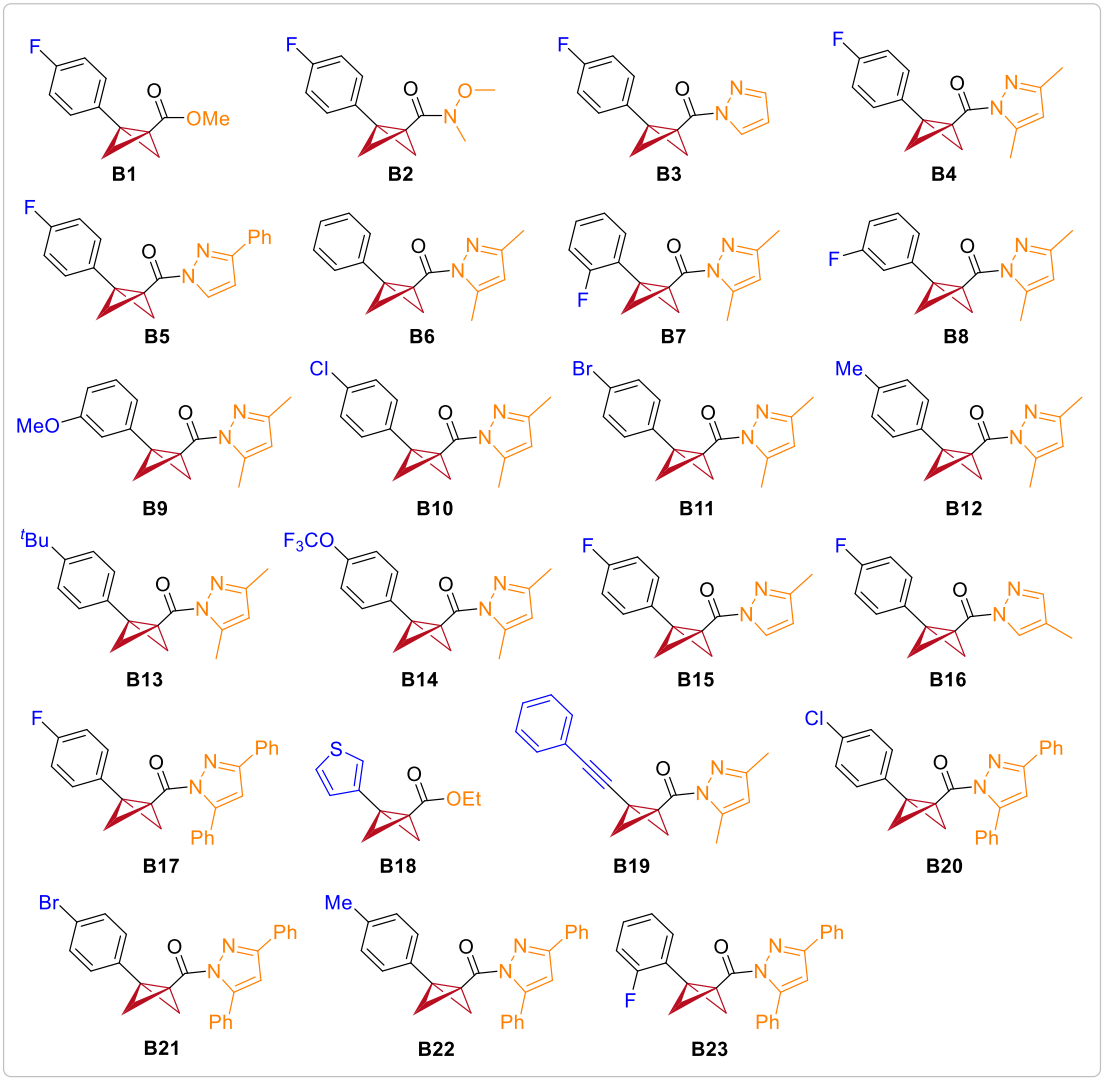
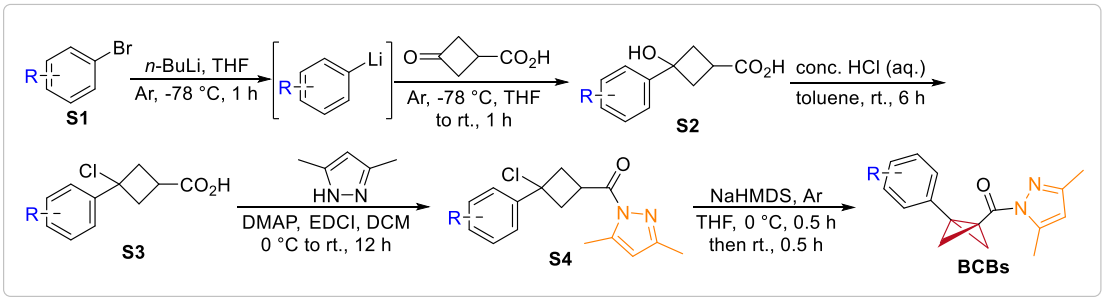


Figure S6 | Overview of **BCBs** substrates.

BCB substrates **B1**[1], **B4**[2], **B6**[2], **B8-B10**[2] and **B12**[2] are known compounds.

General Procedure 1.1



Step 1: Following the literature procedure,[2-3] to a solution of substituted bromobenzene

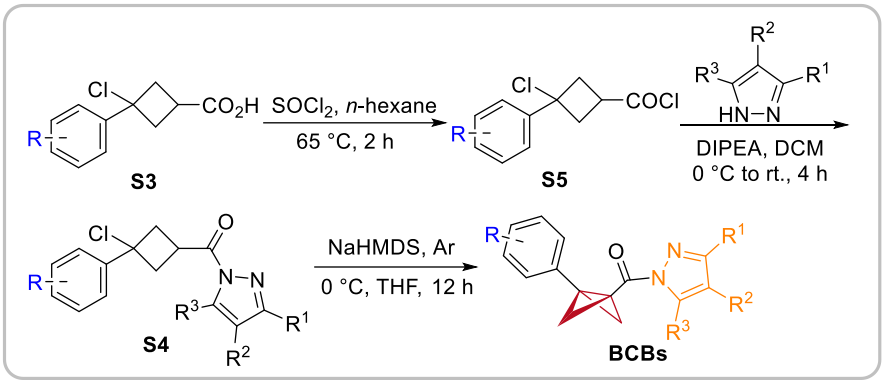
(**S1**, 42 mmol, 2.1 equiv.) in dry THF (40 mL) was added *n*-BuLi (2.4 M, 2.1 equiv.) dropwise at -78 °C under argon. The mixture was stirred for at least 1 h at -78 °C, and a solution of 3-oxocyclobutane-1-carboxylic acid (20 mmol, 1.0 equiv.) in dry THF (10 mL) was added dropwise at -78 ºC. Then, the solution was allowed to warm to room temperature, stirred for another 1 h, and quenched with a sat. solution of NH_4Cl (10 mL) and H_2O (10 mL). The organic layer was separated and washed with water (20 mL). The combined aqueous layers were acidified with HCl (1 M) to pH = 1 and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product **S2** was used for the next step without purification.

Step 2: Following the literature procedure,[2-3] to a solution of **S2** (17 mmol, 1.0 equiv.) in toluene (17 mL) was added conc. HCl (17 mL) dropwise at room temperature. The resulting mixture was stirred for 6 h at room temperature. The organic phase was separated and concentrated *in vacuo* to give compound **S3**. The crude product was used for the next step without purification.

Step 3: Following the literature procedure,[2-3] the above crude product **S3** (1.0 equiv.) was added to a round-bottomed flask, followed by 3,5-dimethyl-1*H*-pyrazole (1.1 equiv.), DMAP (1.0 equiv.), and DCM (0.3 M). The resulting solution was then cooled to 0 ℃. EDC hydrochloride (1.2 equiv.) was added, and the solution was stirred at room temperature overnight. The product mixture was transferred to a separatory funnel with DCM and then washed with 1N HCl solution (2 times) and brine (2 times). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a crude product, **S4**, which was used directly in the next step.

Step 4: Following the literature procedure,[2-3] NaHMDS (2M in THF, 1.2 equiv.) was added to a solution of **S4** (1.0 equiv.) in dry THF (0.5 M) under argon. The reaction mixture was stirred at 0 °C for 0.5 h and then allowed to warm to room temperature for an additional 0.5 h. The mixture was quenched with a saturated NH_4Cl solution, followed by water and then extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography on silica gel to afford **BCBs** (10%-45%, over 4 steps).

General Procedure 1.2

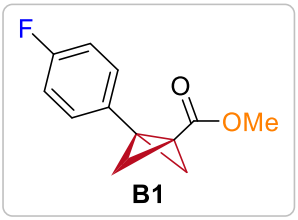


Following the literature procedure,[1] **S3** (15.5 mmol, 1.0 equiv.), hexane (20 mL), and DMF (1 drop) were added to a 100 mL round bottom flask. Thionyl chloride ($SOCl_2$, 38.75 mmol, 2.5 equiv.) was added dropwise over 10 min at room temperature. The mixture was stirred for 2 h at 65 °C. The solvent was concentrated *in vacuo* to afford a crude product, **S5**, which was used directly in the next step.

Following the literature procedure,[1] substituted pyrazole (18 mmol, 1.2 equiv.) and *N*,*N*-diisopropylethylamine (DIPEA, 15 mmol, 1 equiv.) were added to a vial and dissolved in CH_2Cl_2 (20 mL), then the solution was cooled to 0 °C. A solution of **S5** (15 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) was added dropwise. The mixture was then warmed to room temperature and stirred for 4 h. The reaction mixture was washed with water, and then the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product **S4**, which was used in the next step without further purification.

Following the literature procedure,[2-3] **S4** (15 mmol, 1.0 equiv.) was added to a 100 mL vial and dissolved in 30 mL THF under argon. NaHMDS (2M in THF, 18 mmol, 1.2 equiv.) was added, and the mixture was stirred at 0 °C overnight. The mixture was quenched with sat. NH_4Cl (10 mL) and water (10 mL), and then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography on silica gel to give **BCBs** (1.1-8.0 mmol, 11%-56%, over 4 steps).

BCB substrates **B4**, **B6-B12**, and **B14** were prepared according to **General Procedure 1.1**, and **B3**, **B5**, **B15-B17**, and **B20-B23** were prepared according to **General Procedure 1.2**.



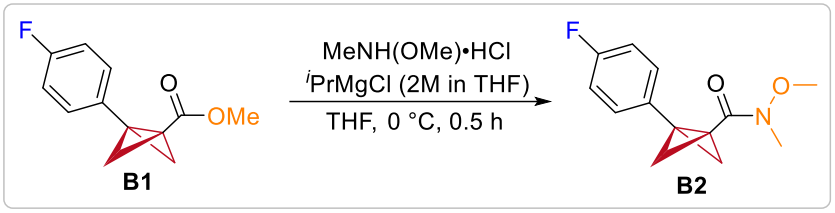
Methyl 3-(4-fluorophenyl)bicyclo[1.1.0]butane-1-carboxylate (B1)

The title compound was prepared according to the literature procedure[1].

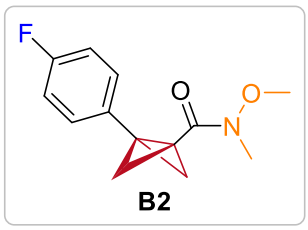
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 2H), 6.99 (t, *J* = 8.6 Hz, 2H), 3.49 (s, 3H), 2.88 (s, 2H), 1.60 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 162.1 (d, *J* = 246.1 Hz), 129.4 (d, *J* = 3.3 Hz), 127.5 (d, *J* = 8.4 Hz), 115.5 (d, *J* = 21.6 Hz), 51.8, 35.9, 32.3, 22.9.
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.1 (s, 1F).
The analytical data are consistent with those reported in the literature.[2]

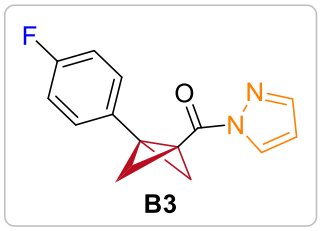
General synthesis of substrate B2



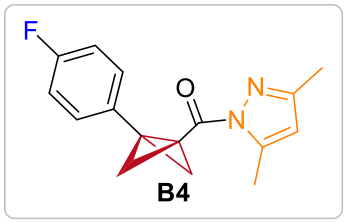
According to the literature procedure,[4] MeNH(OMe)·HCl (117 mg, 1.2 mmol, 1.2 equiv.) and ^{i}PrMgCl (1.2 mL, 2M in THF, 2.4 mmol, 2.40 equiv.) were sequentially added to the solution of **B1** (206 mg, 1.0 mmol, 1.0 equiv.) in dry THF (5 mL) at 0 °C. After stirring at 0 °C for 0.5 h, the reaction was quenched by saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography to afford the product **B2**.



3-(4-fluorophenyl)-*N*-methoxy-*N*-methylbicyclo[1.1.0]butane-1-carboxamide (B2)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 2H), 7.01 (t, *J* = 8.8 Hz, 2H), 3.68 (s, 3H), 3.13 (s, 3H), 2.96 (s, 2H), 1.62 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 161.9 (d, *J* = 245.4 Hz), 129.9 (d, *J* = 3.2 Hz), 127.8 (d, *J* = 8.1 Hz), 115.4 (d, *J* = 21.7 Hz), 61.3, 36.8, 33.5, 32.0, 22.1.
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.8 (s, 1F).
HRMS (ESI) m/z calcd. for $C_{13}H_{15}FNO_2$ $[M+H]^+$ 236.1082 , found 236.1085.



(3-(4-fluorophenyl)bicyclo[1.1.0]butan-1-yl)(1*H*-pyrazol-1-yl)methanone (B3)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 2.8, 0.7 Hz, 1H), 7.71 – 7.62 (m, 1H), 7.27 (dd, *J* = 8.8, 5.2 Hz, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 6.31 (dd, *J* = 2.9, 1.5 Hz, 1H), 3.52 (t, *J* = 1.3 Hz, 2H), 1.93 (t, *J* = 1.3 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 162.3 (d, *J* = 246.9 Hz), 143.8, 128.8, 128.5 (d, *J* = 3.2 Hz), 128.0 (d, *J* = 8.2 Hz), 115.6 (d, *J* = 21.8 Hz), 108.4, 39.2, 38.8, 25.3.
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.1 (s, 1F).
HRMS (ESI) m/z calcd. for $C_{14}H_{12}NaFN_2O$ $[M+Na]^+$ 265.0747, found 265.0749.



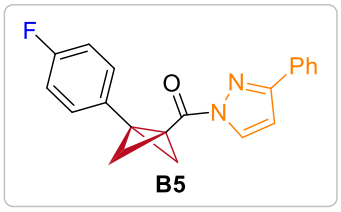
(3,5-dimethyl-1*H*-pyrazol-1-yl)(3-(4-fluorophenyl)bicyclo-[1.1.0]butan-1-yl)methanone (B4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 2H), 6.94 (t, *J* = 8.6 Hz, 2H), 5.83 (s, 1H), 3.36 (s, 2H), 2.21 (d, *J* = 3.4 Hz, 6H), 1.86 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 160.2 (d, *J* = 246.4 Hz), 149.5, 141.7, 127.1 (d, *J* = 3.0 Hz), 126.0 (d, *J* = 8.2 Hz), 113.4 (d, *J* = 21.8 Hz), 108.2, 36.9, 36.0, 24.2, 11.9, 11.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -116.6 (s, 1F).

The analytical data are consistent with those reported in the literature.[2]



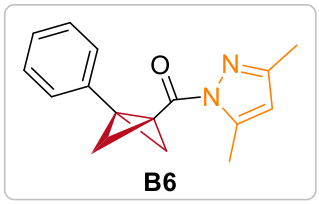
(3-(4-fluorophenyl)bicyclo[1.1.0]butan-1-yl)(3-phenyl-1*H*-pyrazol-1-yl)methanone (B5)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 2.8 Hz, 1H), 7.87 (d, *J* = 7.4 Hz, 2H), 7.50 – 7.38 (m, 3H), 7.30 (dd, *J* = 8.6, 5.3 Hz, 2H), 6.93 (t, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 2.8 Hz, 1H), 3.61 (s, 2H), 1.97 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 162.4 (d, *J* = 246.9 Hz), 155.2, 132.1, 130.1, 129.1, 128.8, 128.6 (d, *J* = 3.1 Hz), 128.0 (d, *J* = 8.3 Hz), 126.2, 115.7 (d, *J* = 21.9 Hz), 106.1, 39.4, 38.9, 25.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.2 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{20}H_{16}FN_2O$ $[M+H]^+$ 319.1241, found 319.1242.

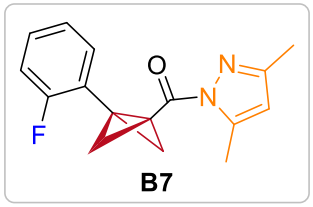


(3,5-dimethyl-1*H*-pyrazol-1-yl)(3-phenylbicyclo[1.1.0]butan-1-yl)methanone (B6)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 5H), 5.84 (s, 1H), 3.39 (s, 2H), 2.24 (s, 3H), 2.16 (s, 3H), 1.90 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 151.4, 143.6, 133.2, 128.4, 127.2, 126.3, 110.0, 38.9, 38.8, 26.5, 13.85, 13.81.

The analytical data are consistent with those reported in the literature.[2]



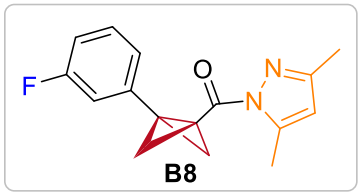
(3,5-dimethyl-1*H*-pyrazol-1-yl)(3-(2-fluorophenyl)-bicyclo-[1.1.0]butan-1-yl)methanone (B7)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (td, *J* = 7.8, 1.8 Hz, 1H), 7.23 – 7.15 (m, 1H), 7.06 (td, *J* = 7.6, 1.2 Hz, 1H), 6.97 (ddd, *J* = 11.2, 8.2, 1.1 Hz, 1H), 5.90 (s, 1H), 3.31 (d, *J* = 1.0 Hz, 2H), 2.33 (d, *J* = 0.7 Hz, 3H), 2.24 (s, 3H), 1.90 (d, *J* = 0.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.6 (d, *J* = 248.9 Hz), 151.6, 143.7, 130.0 (d, *J* = 3.3 Hz), 128.7 (d, *J* = 8.3 Hz), 124.1 (d, *J* = 3.6 Hz), 121.2 (d, *J* = 12.4 Hz), 115.7 (d, *J* = 21.8 Hz), 110.3, 40.5 (d, *J* = 3.6 Hz), 33.4 (d, *J* = 1.6 Hz), 23.9, 14.0, 13.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -115.5 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{16}H_{16}FN_2O$ $[M+H]^+$ 271.1241, found 271.1244.



B8

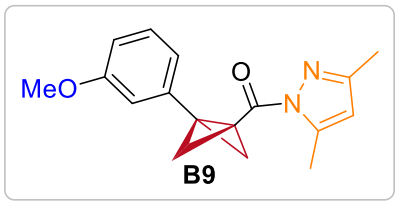
(3,5-dimethyl-1*H*-pyrazol-1-yl)(3-(3-fluorophenyl)-bicyclo-[1.1.0]butan-1-yl)methanone (B8)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.91 (td, *J* = 8.4, 2.3 Hz, 1H), 5.87 (s, 1H), 3.38 (s, 2H), 2.24 (d, *J* = 2.7 Hz, 6H), 1.89 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 162.8 (d, *J* = 245.8 Hz), 151.6, 143.7, 136.1 (d, *J* = 8.2 Hz), 129.9 (d, *J* = 8.5 Hz), 122.0 (d, *J* = 2.8 Hz), 114.1 (d, *J* = 21.3 Hz), 113.4 (d, *J* = 22.8 Hz), 110.2, 38.8, 37.4 (d, *J* = 1.6 Hz), 26.9, 13.9, 13.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.1 (s, 1F).

The analytical data are consistent with those reported in the literature.[2]



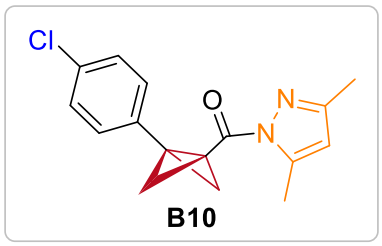
B9

(3,5-dimethyl-1*H*-pyrazol-1-yl)(3-(3-methoxyphenyl)-bicyclo[1.1.0]butan-1-yl)methanone (B9)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.0 Hz, 1H), 6.88 (dd, *J* = 7.7, 0.8 Hz, 1H), 6.84 – 6.81 (m, 1H), 6.76 (ddd, *J* = 8.2, 2.5, 0.7 Hz, 1H), 5.85 (s, 1H), 3.74 (s, 3H), 3.37 (s, 2H), 2.23 (s, 3H), 2.21 (d, *J* = 0.6 Hz, 3H), 1.88 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 159.6, 151.4, 143.7, 134.8, 129.4, 118.9, 113.0, 111.8, 110.0, 55.1, 38.9, 38.7, 26.5, 13.9, 13.8.

The analytical data are consistent with those reported in the literature.[2]



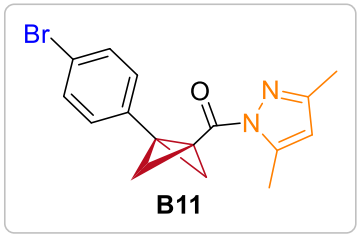
B10

(3-(4-chlorophenyl)bicyclo[1.1.0]butan-1-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (B10)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 4H), 5.86 (s, 1H), 3.37 (t, *J* = 1.1 Hz, 2H), 2.23 (s, 6H), 1.89 (t, *J* = 1.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 151.6, 143.8, 133.0, 132.0, 128.6, 127.6, 110.2, 38.8, 37.7, 26.7, 14.0, 13.8.

The spectral data are consistent with those reported in the literature.[2]



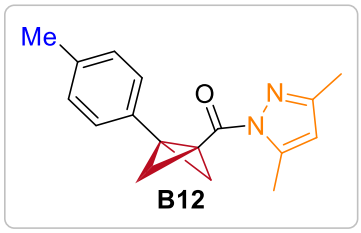
B11

(3-(4-bromophenyl)bicyclo[1.1.0]butan-1-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (B11)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.21 – 7.15 (m, 2H), 5.86 (s, 1H), 3.37 (t, *J* = 1.1 Hz, 2H), 2.24 (d, *J* = 0.7 Hz, 3H), 2.23 (s, 3H), 1.89 (t, *J* = 1.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 151.6, 143.8, 132.6, 131.5, 127.9, 121.1, 110.2, 38.8, 37.7, 26.7, 14.0, 13.8.

HRMS (ESI) m/z calcd. for $C_{16}H_{16}BrN_2O$ $[M+H]^+$ 331.0441, found 331.0440.



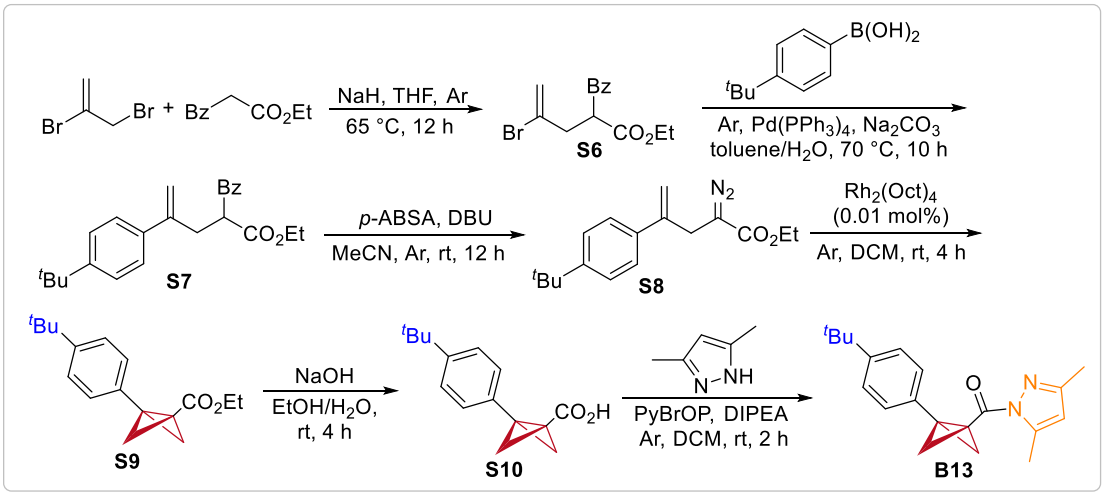
(3,5-dimethyl-1*H*-pyrazol-1-yl)(3-(p-tolyl)bicyclo[1.1.0]-butan-1-yl)methanone (B12)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.15 (m, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 5.84 (s, 1H), 3.36 (t, *J* = 1.1 Hz, 2H), 2.30 (s, 3H), 2.23 (s, 3H), 2.18 (d, *J* = 0.7 Hz, 3H), 1.88 (t, *J* = 1.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 151.3, 143.6, 137.0, 130.0, 129.1, 126.2, 109.9, 39.3, 38.8, 26.2, 21.2, 13.9, 13.8.

The spectral data are consistent with those reported in the literature.[2]

General synthesis of substrate B13



Following the literature procedure,[5] ethyl 3-oxo-3-phenylpropanoate (20 mmol, 1 equiv.) was added dropwise to a solution of NaH (20 mmol, 1 equiv.) in dry THF (30 mL) at 0 °C under argon. The mixture was stirred for 1 h at room temperature until all solids were dissolved. The reaction mixture was cooled to 0 °C, and 2,3-dibromopropene (22 mmol, 1.1 equiv.) was added dropwise. The reaction temperature was raised to 65 °C, and the reaction was stirred for 12 h. Upon completion, the reaction was quenched with sat. NH_4Cl (10 mL) and water (10 mL) was added. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography on silica gel to give **S6** (18.3 mmol, 91%) as a colorless liquid.

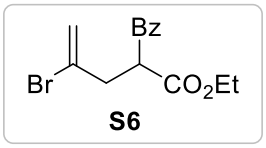
Following the literature procedure,[6] **S6** (3.11 g, 10.0 mmol, 1.0 equiv.), $Pd(PPh_3)_4$ (578 mg, 0.5 mmol, 5 mol%), Na_2CO_3 (4.24 g, 40 mmol, 4.0 equiv.), and 4-*tert*-butylphenylboronic acid (2.14 g, 12.0 mmol, 1.2 equiv.) were added to an oven-dried Schlenk tube equipped with a magnetic stir bar. The tube was evacuated and backfilled with argon three times. Subsequently, freshly degassed toluene (15 mL) and water (15 mL) were added via syringe. The reaction mixture was stirred at 70 °C for 10 h. Upon completion, the solvent was removed *in vacuo*, and the residue was diluted with water and then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography on silica gel to give **S7** (9.0 mmol, 90% yield).

Following the literature procedure,[7] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 9.0 mmol, 1 equiv.) was added dropwise to a solution of **S7** (9.0 mmol, 1.0 equiv.) and 4-acetoamidobenzenesulfonyl azide (*p*-ABSA, 9.0 mmol, 1.0 equiv.) in dry CH_3CN (50 mL) at 0 °C under argon. Upon the initial subsiding of the exotherm, additional *p*-ABSA (4.5 mmol, 0.5 equiv.) and DBU (4.5 mmol, 0.5 equiv.) were added. After an additional 12 h, the mixture was partitioned between water and EtOAc (3 × 50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography on silica gel to give **S8** (1.74 g, 6.1 mmol, 68% yield).

Following the literature procedure,[8] under argon, dry DCM (25 mL) and $Rh_2(Oct)_4$ (390 μL, c = 1.00 mg/ mL in DCM, 0.01 mol%) were added to a 100 mL oven-dried flask. **S8** (5.0 mmol, 1.0 equiv.) in dry DCM (10 mL) was then added dropwise to the former solution over 20 mins at room temperature. The reaction mixture was allowed to stir for an additional 4 h. Upon completion (monitored by TLC), the reaction mixture was concentrated and purified by column chromatography on silica gel to give **S9** (4.0 mmol, 80% yield).

Following the literature procedure,[9] **S9** (1.0 mmol, 1 equiv.) was dissolved in a mixture of ethanol (4.0 mL) and water (4.0 mL). NaOH (4.0 mmol, 4 equiv.) was added, and the mixture was stirred at room temperature for 4 h. Upon reaction completion, the mixture was diluted with ethyl acetate and water, and the phases were separated. The aqueous layer was acidified (pH ≈ 3) and extracted with EtOAc (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product **S10** (0.50 mmol, 50%).

Following the literature procedure,[10] to a solution of **S10** (1.07 mmol, 1.0 equiv.) and 3,5-dimethyl-1*H*-pyrazole (1.18 mmol, 1.1 equiv.) in anhydrous DCM (10 mL) at room temperature was added DIPEA (3.21 mmol, 3.0 equiv.), then bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP, 1.28 mmol, 1.2 equiv.). After 2 h, saturated aqueous $NaHCO_3$ was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The mixture was purified by column chromatography on silica gel (PE/EtOAc = 60/1) to give **B13** (0.56 mmol, 52%) as a yellow liquid.

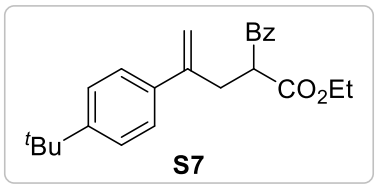


S6

Ethyl 2-benzoyl-4-bromopent-4-enoate (S6)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.01 (m, 2H), 7.64 – 7.57 (m, 1H), 7.53 – 7.47 (m, 2H), 5.74 – 5.68 (m, 1H), 5.45 (d, *J* = 1.8 Hz, 1H), 4.80 (t, *J* = 7.1 Hz, 1H), 4.15 (qd, *J* = 7.1, 0.7 Hz, 2H), 3.21 – 3.05 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 168.5, 136.0, 133.8, 129.8, 128.83, 128.78, 120.0, 61.7, 52.5, 40.5, 14.0.

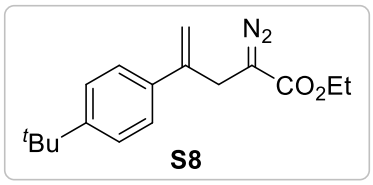


S7

Ethyl 2-benzoyl-4-(4-(*tert*-butyl)phenyl)pent-4-enoate (S7)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.35 – 7.32 (m, 2H), 7.30 – 7.25 (m, 2H), 5.26 (d, *J* = 1.2 Hz, 1H), 5.08 (d, *J* = 1.2 Hz, 1H), 4.47 (t, *J* = 7.2 Hz, 1H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.22 (ddd, *J* = 7.0, 4.5, 1.2 Hz, 2H), 1.32 (s, 9H), 1.14 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.0, 169.5, 150.8, 144.7, 137.1, 136.3, 133.4, 128.7, 128.6, 126.0, 125.3, 114.3, 61.4, 53.0, 34.6, 34.5, 31.3, 14.0.

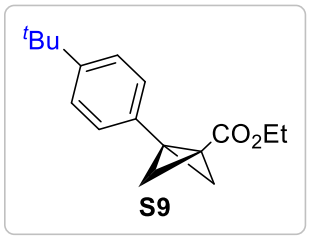


S8

Ethyl 4-(4-(*tert*-butyl)phenyl)-2-diazopent-4-enoate (S8)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 4H), 5.47 (d, *J* = 0.6 Hz, 1H), 5.13 (q, *J* = 1.2 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.50 (d, *J* = 1.2 Hz, 2H), 1.32 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 151.1, 142.5, 136.1, 125.6, 125.4, 114.1, 60.9, 34.6, 31.3, 29.0, 14.5 (Noted: the signal of $C{=}N_2$ was not observed).

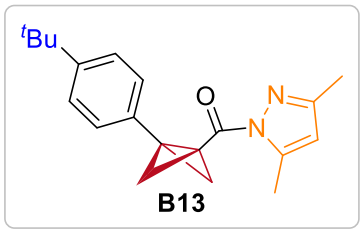


S9

Ethyl 3-(4-(*tert*-butyl)phenyl)bicyclo[1.1.0]butane-1-carboxylate (S9)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 2.92 (t, *J* = 1.2 Hz, 2H), 1.59 (t, *J* = 1.2 Hz, 2H), 1.28 (s, 9H), 0.91 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.90, 149.95, 130.38, 125.63, 125.34, 60.38, 35.85, 34.49, 32.94, 31.27, 22.72, 14.35.



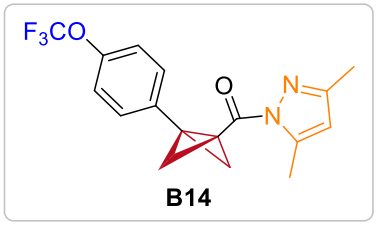
B13

(3-(4-(*tert*-butyl)phenyl)bicyclo[1.1.0]butan-1-yl)(3,5-dimethyl-1*H*-pyrazol-1-yl)methanone (B13)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.23 – 7.19 (m, 2H), 5.84 (s, 1H), 3.35 (s, 2H), 2.24 (s, 3H), 2.13 (s, 3H), 1.90 (s, 2H), 1.28 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 151.3, 150.3, 143.5, 130.0, 126.0, 125.3, 109.9, 39.3, 38.9, 34.5, 31.2, 26.2, 13.8, 13.6.

HRMS (ESI) m/z calcd. for $C_{20}H_{25}N_2O$ $[M+H]^+$ 309.1962, found 309.1961.



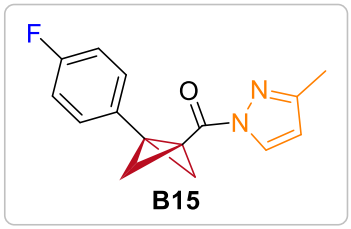
B14

(3,5-dimethyl-1*H*-pyrazol-1-yl)(3-(4-(trifluoromethoxy)-phenyl)bicyclo[1.1.0]butan-1-yl)methanone (B14)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.86 (s, 1H), 3.37 (s, 2H), 2.24 (s, 3H), 2.20 (s, 3H), 1.91 (s, 2H).

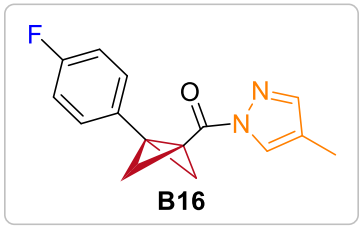
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 151.6, 148.4, 143.8, 132.3, 127.7, 120.9, 120.4

(q, J = 257.2 Hz), 110.2, 38.9, 37.3, 26.6, 13.81, 13.79.
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.9 (s, 3F).
HRMS (ESI) m/z calcd. for $C_{17}H_{16}F_3N_2O_2$ $[M+H]^+$ 337.1159, found 337.1161.



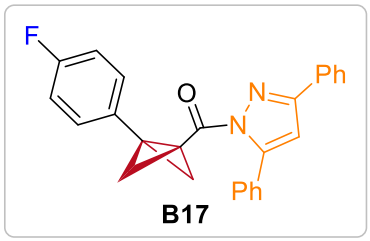
B15

(3-(4-fluorophenyl)bicyclo[1.1.0]butan-1-yl)(3-methyl-1*H*-pyrazol-1-yl)methanone (B15)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 2.7 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.00 – 6.90 (m, 2H), 6.13 (d, J = 2.7 Hz, 1H), 3.48 (s, 2H), 2.31 (s, 3H), 1.91 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 162.3 (d, J = 246.7 Hz), 153.7, 129.5, 128.7 (d, J = 3.1 Hz), 128.0 (d, J = 8.2 Hz), 115.6 (d, J = 21.9 Hz), 109.1, 38.8, 38.5, 25.1, 14.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.4. (s, 1F)
HRMS (ESI) m/z calcd. for $C_{15}H_{14}FN_2O$ $[M+H]^+$ 257.1085, found 257.1083.



B16

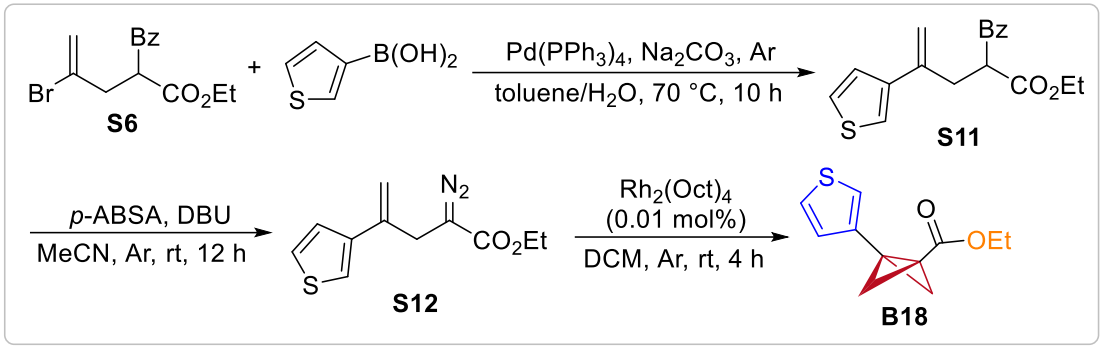
(3-(4-fluorophenyl)bicyclo[1.1.0]butan-1-yl)(4-methyl-1H-pyrazol-1-yl)methanone (B16)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.50 (s, 1H), 7.27 (dt, J = 5.2, 4.0 Hz, 2H), 6.95 (t, J = 8.7 Hz, 2H), 3.47 (t, J = 1.1 Hz, 2H), 2.04 (d, J = 0.6 Hz, 3H), 1.91 (t, J = 1.1 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 162.3 (d, J = 246.5 Hz), 145.4, 128.7 (d, J = 3.3 Hz), 127.9 (d, J = 8.1 Hz), 126.7, 119.2, 115.6 (d, J = 22.0 Hz), 38.7, 38.5, 25.0, 8.8.
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.4 (s, 1F).
HRMS (ESI) m/z calcd. for $C_{15}H_{14}FN_2O$ $[M+H]^+$ 257.1085, found 257.1084.



B17

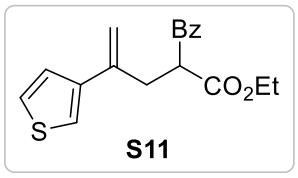
(3,5-diphenyl-1H-pyrazol-1-yl)(3-(4-fluorophenyl)-bicyclo[1.1.0]butan-1-yl)methanone (B17)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.1 Hz, 2H), 7.50 – 7.35 (m, 5H), 7.29 (d, J = 7.3 Hz, 1H), 7.19 (t, J = 7.6 Hz, 2H), 7.05 (t, J = 8.6 Hz, 2H), 6.74 (d, J = 7.4 Hz, 2H), 6.65 (s, 1H), 3.45 (s, 2H), 2.03 (s, 2H).
^{3}C NMR (101 MHz, $CDCl_3$) δ 168.3, 162.6 (d, J = 247.1 Hz), 153.3, 147.2, 132.0, 130.6, 129.0, 128.9 (d, J = 3.0 Hz), 128.8, 128.5, 128.2, 128.1 (d, J = 8.2 Hz), 127.9, 126.2, 115.7 (d, J = 22.0 Hz), 108.5, 39.7, 38.8, 26.9.
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.2 (s, 1F).
HRMS (ESI) m/z calcd. for $C_{26}H_{20}FN_2O$ $[M+H]^+$ 395.1554, found 395.1555.

General synthesis of substrate B18



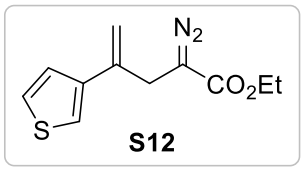
Ethyl 2-benzoyl-4-(thiophen-3-yl)pent-4-enoate (S11)

The title compound was prepared following the protocol for **S7**, using **S6** (9 mmol, 1.0 equiv.), $Pd(PPh_3)_4$ (0.45 mmol, 5 mol%), Na_2CO_3 (36 mmol, 4.0 equiv.), and thiophen-3-ylboronic acid (10.8 mmol, 1.2 equiv.) in a mixed solvent of toluene (15 mL) and water (15 mL). The crude product was purified through column chromatography on silica gel, yielding **S11** (8.7 mmol, 97%) as a yellow liquid.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H), 7.56 (ddd, *J* = 8.6, 2.4, 1.2 Hz, 1H), 7.49 – 7.39 (m, 2H), 7.30 – 7.24 (m, 1H), 7.21 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.17 (dd, *J* = 5.0, 1.3 Hz, 1H), 5.35 (s, 1H), 5.06 (d, *J* = 0.9 Hz, 1H), 4.58 (t, *J* = 7.2 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.18 (d, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8, 169.4, 141.6, 139.5, 136.3, 133.5, 128.7, 128.6, 125.9, 120.9, 113.6, 61.5, 53.0, 34.6, 14.0.

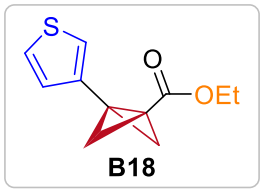


Ethyl 2-diazo-4-(thiophen-3-yl)pent-4-enoate (S12)

The title compound was prepared following the protocol for **S8**, using **S11** (8.7 mmol, 1.0 equiv.), *p*-ABSA (13.1 mmol, 1.5 equiv.), DBU (13.1 mmol, 1.5 equiv.), and dry CH_3CN (50 mL). The crude product was purified by column chromatography on silica gel, yielding **S12** (6.46 mmol, 74 %) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 3H), 5.50 (s, 1H), 5.10 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.45 (d, *J* = 0.5 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 140.4, 137.6, 125.9, 125.6, 121.4, 113.4, 61.0, 29.3, 14.5 (Noted: the signal of $C{=}N_2$ was not observed).



Ethyl 3-(thiophen-3-yl)bicyclo[1.1.0]butane-1-carboxylate (B18)

The title compound was prepared following the protocol for **B13**, using **S12** (6.46 mmol, 1.0 equiv.), $Rh_2(Oct)_4$ (0.5 mL, c = 1.00 mg/ mL in DCM, 0.01 mol%), and dry DCM (40 mL). The crude product was purified by column chromatography on silica gel, yielding **B18** (5.4 mmol, 83 %).

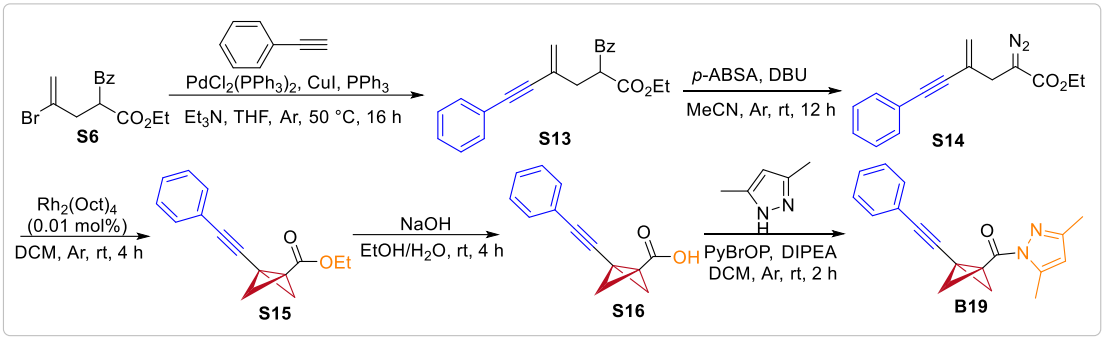
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.15 (dd, *J* = 3.0, 1.3 Hz,

1H), 6.97 (dd, *J* = 5.0, 1.3 Hz, 1H), 3.97 (q, *J* = 7.1 Hz, 2H), 2.87 (t, *J* = 1.0 Hz, 2H), 1.65 (s, 2H), 1.00 (t, *J* = 7.1 Hz, 3H).

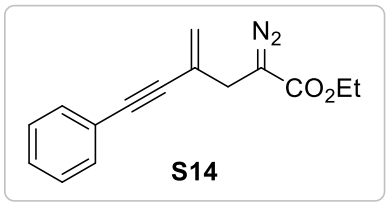
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 134.7, 126.1, 125.3, 121.2, 60.5, 37.3, 29.9, 21.4, 14.4.

HRMS (ESI) m/z calcd. for $C_{11}H_{13}O_2S$ $[M+H]^+$ 209.0631, found 209.0631.

General synthesis of substrate B19



Following the literature procedure,[11] an oven-dried flask containing a stirring bar was charged with **S6** (5.0 mmol, 1 equiv.), ethynylbenzene (5.0 mmol, 1 equiv.), $PdCl_2(PPh_3)_2$ (0.2 mmol, 4 mol%), CuI (0.3 mmol, 6 mol%), and PPh_3 (0.2 mmol, 4 mol%) under argon. To the mixture was added dry THF (5.0 mL) and Et_3N (7.0 mL), and the resulting mixture was stirred at 50 °C for 16 h. The reaction was then quenched with sat. NH_4Cl solution. The reaction mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography on silica gel to give **S13** (3.9 mmol, 78%) as a yellow liquid.

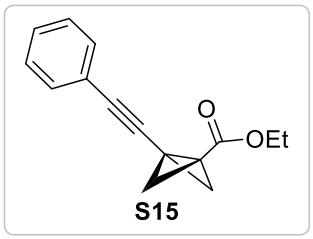


Ethyl 2-diazo-4-methylene-6-phenylhex-5-ynoate (S14)

The title compound was prepared following the protocol for **S8**, using **S13** (3.9 mmol, 1.0 equiv.), *p*-ABSA (5.9 mmol, 1.5 equiv.), DBU (5.9 mmol, 1.5 equiv.), and dry CH_3CN (30 mL). The crude product was purified through column chromatography on silica gel, yielding (3.15 mmol, 81 %) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (ddt, *J* = 3.9, 2.9, 1.5 Hz, 2H), 7.36 – 7.28 (m, 3H), 5.52 (q, *J* = 1.1 Hz, 1H), 5.43 (q, *J* = 1.5 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.24 (t, *J* = 1.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 131.6, 128.5, 128.3, 127.2, 122.8, 122.5, 90.3, 88.3, 61.0, 31.3, 14.5 (Noted: the signal of $C{=}N_2$ was not observed).



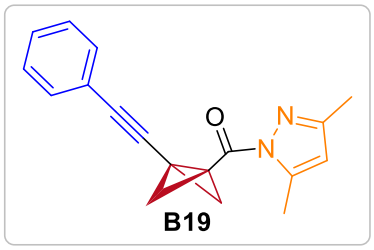
S15

Ethyl 3-(phenylethynyl)bicyclo[1.1.0]butane-1-carboxylate (S15)

The title compound was prepared following the protocol for **S9**, using **S14** (3.15 mmol, 1.0 equiv.), $Rh_2(Oct)_4$ (0.25 mL, c = 1.00 mg/ mL in DCM, 0.0001 equiv.), and dry DCM (40 mL). The crude product was purified by column chromatography on silica gel, yielding **S15** (2.3 mmol, 73 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.38 – 7.23 (m, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.70 (t, *J* = 0.9 Hz, 2H), 1.60 (d, *J* = 0.8 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 131.9, 128.25, 128.24, 122.8, 84.0, 81.7, 61.1, 40.9, 21.6, 18.1, 14.8.



B19

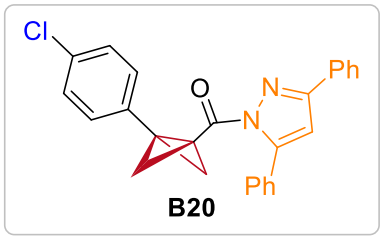
(3,5-dimethyl-1H-pyrazol-1-yl)(3-(phenylethynyl)bicyclo-[1.1.0]butan-1-yl)methanone (B19)

The title compound was prepared following the protocol for **B13**, using **S16** (1.08 mmol, 1 equiv.), PyBrOP (1.3 mmol, 1.2 equiv.), 3,5-dimethyl-1*H*-pyrazole (1.2 mmol, 1.1 equiv.), and dry DCM (10 mL). The crude product was purified by column chromatography on silica gel, yielding **B19** (0.78 mmol, 72 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 7.27 (dd, *J* = 5.2, 3.4 Hz, 3H), 5.97 (s, 1H), 3.11 (s, 2H), 2.53 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 151.9, 144.1, 131.9, 128.3, 128.2, 122.7, 110.6, 84.0, 83.3, 43.8, 24.0, 23.1, 14.2, 13.9.

HRMS (ESI) m/z calcd. for $C_{18}H_{17}N_2O$ $[M+H]^+$ 277.1336, found 277.1337.



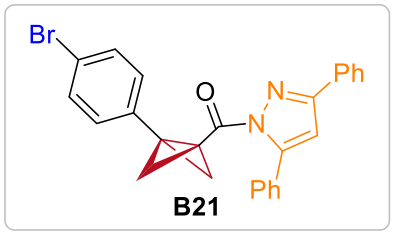
B20

(3-(4-chlorophenyl)bicyclo[1.1.0]butan-1-yl)(3,5-diphenyl-1H-pyrazol-1-yl)methanone (B20)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.86 (m, 2H), 7.47 (dd, *J* = 7.9, 5.6 Hz, 4H), 7.44 – 7.40 (m, 1H), 7.30 – 7.24 (m, 3H), 7.20 (t, *J* = 7.5 Hz, 2H), 6.70 – 6.66 (m, 2H), 6.65 (s, 1H), 3.45 (s, 2H), 2.04 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 153.3, 147.3, 132.4, 132.0, 131.8, 130.6, 129.0, 128.8, 128.5, 128.2, 127.94, 127.90, 126.2, 121.5, 108.5, 39.2, 38.7, 27.5.

HRMS (ESI) m/z calcd. for $C_{26}H_{20}ClN_2O$ $[M+H]^+$ 411.1259, found 411.1259.

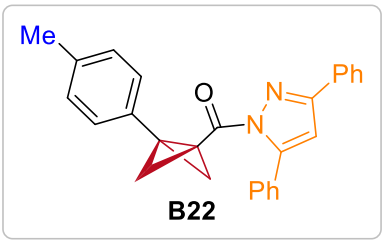


B21

(3-(4-bromophenyl)bicyclo[1.1.0]butan-1-yl)(3,5-diphenyl-1H-pyrazol-1-yl)methanone (B21)

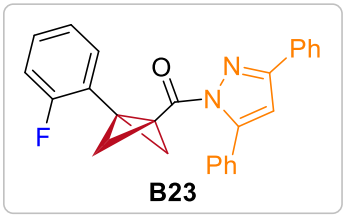
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.86 (m, 2H), 7.49 – 7.44 (m, 2H), 7.43 – 7.39 (m, 1H), 7.32 (s, 4H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 2H), 6.72 – 6.67 (m, 2H), 6.64 (d, *J* = 3.8 Hz, 1H), 3.44 (s, 2H), 2.03 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 153.3, 147.3, 133.5, 132.0, 131.8, 130.6, 129.1, 128.9, 128.8, 128.5, 128.2, 127.9, 127.7, 126.2, 108.5, 39.3, 38.8, 27.5.
HRMS (ESI) m/z calcd. for $C_{26}H_{20}BrN_2O$ $[M+H]^+$ 455.0754, found 455.0756.



B22

(3,5-diphenyl-1H-pyrazol-1-yl)(3-(p-tolyl)bicyclo-[1.1.0]butan-1-yl)methanone (B22)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.48 – 7.43 (m, 2H), 7.42 – 7.37 (m, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.26 – 7.21 (m, 1H), 7.16 (dd, *J* = 8.5, 0.7 Hz, 2H), 7.10 (t, *J* = 7.7 Hz, 2H), 6.63 (s, 1H), 6.62 – 6.58 (m, 2H), 3.46 (t, *J* = 1.4 Hz, 2H), 2.37 (s, 3H), 2.02 (t, *J* = 1.5 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 153.1, 147.1, 137.5, 132.1, 130.6, 129.7, 129.5, 128.9, 128.8, 128.3, 128.2, 127.7, 126.3, 126.2, 108.2, 41.0, 38.7, 27.1, 21.2.
HRMS (ESI) m/z calcd. for $C_{27}H_{23}N_2O$ $[M+H]^+$ 391.1805, found 391.1805.



B23

(3,5-diphenyl-1H-pyrazol-1-yl)(3-(2-fluorophenyl)bicyclo-[1.1.0]butan-1-yl)methanone (B23)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.45 (dd, *J* = 7.9, 6.5 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.30 – 7.27 (m, 1H), 7.26 – 7.20 (m, 3H), 7.12 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.06 – 7.00 (m, 3H), 6.68 (s, 1H), 3.47 – 3.41 (m, 2H), 1.98 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 161.8 (d, *J* = 249.4 Hz), 153.2, 147.2, 132.0, 130.9, 129.9 (d, *J* = 3.3 Hz), 129.01, 128.99 (d, *J* = 8.4 Hz), 128.8, 128.5, 128.4, 127.9, 126.2, 124.3 (d, *J* = 3.7 Hz), 121.1 (d, *J* = 12.1 Hz), 116.1 (d, *J* = 21.6 Hz), 108.6, 40.5, 40.4, 35.0 (d, *J* = 1.8 Hz), 25.3.
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.8 (s, 1F).
HRMS (ESI) m/z calcd. for $C_{26}H_{20}FN_2O$ $[M+H]^+$ 395.1554, found 395.1554.

3.2 Synthesis of coumarin substrates

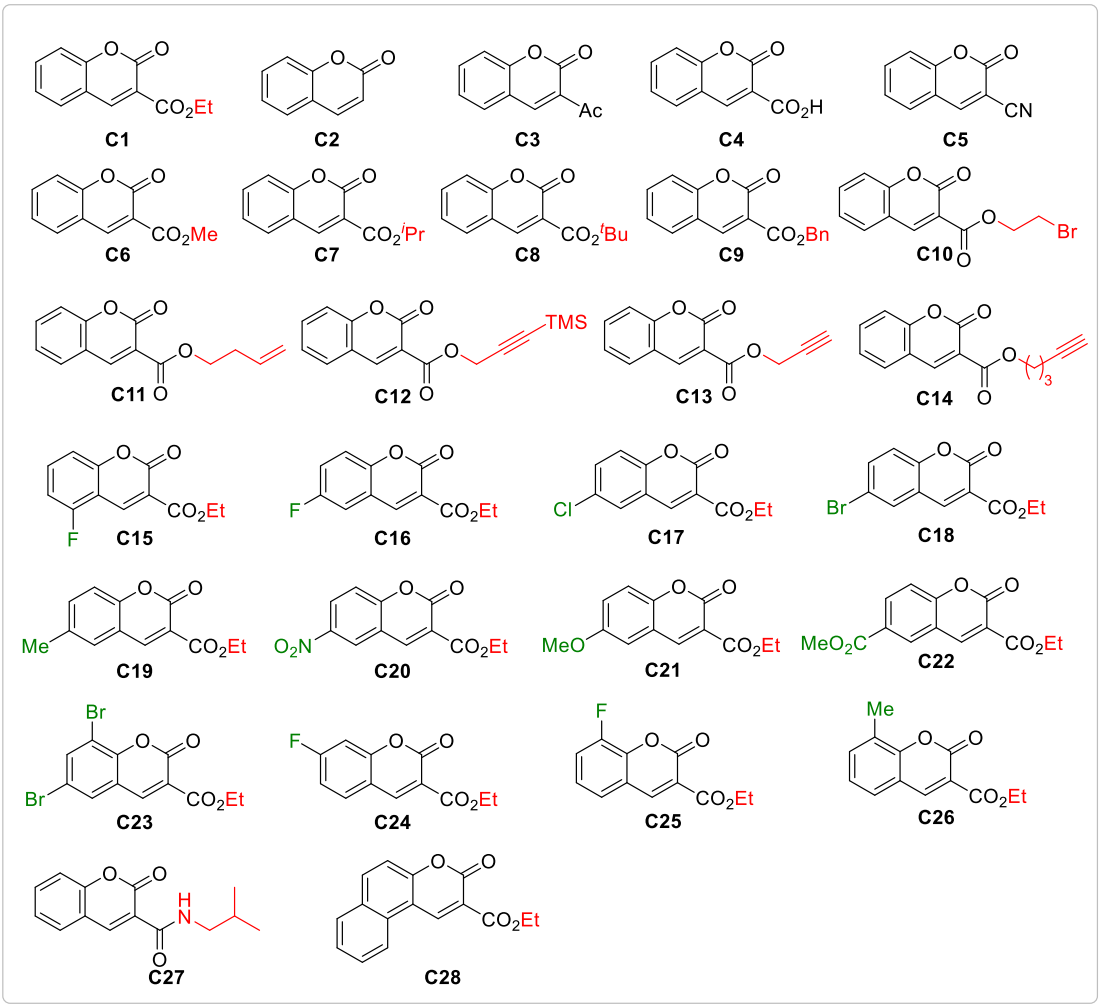
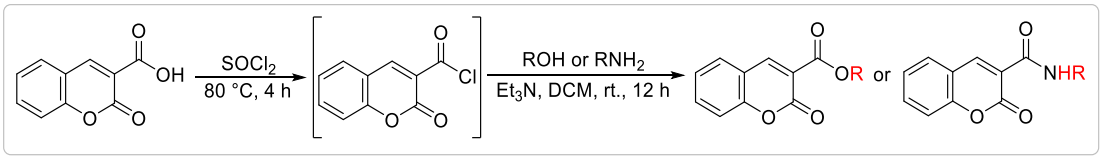


Figure S7 | Overview of coumarin substrates.

Coumarin substrates **C1-C10**, **C13**, **C15-C19**, **C21-C26**, and **C28** were known compounds. Substrates **C1** and **C3-C5** were commercially available and were used as received.

General Procedure 2.1

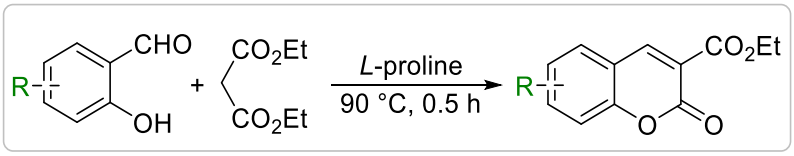


According to literature protocols[6,12] with slight modifications, a mixture of 2-oxo-2H-chromene-3-carboxylic acid (570 mg, 3 mmol, 1 equiv.) and $SOCl_2$ (1.3 mL, 18 mmol, 6 equiv.) was stirred at 80 °C for 4 h. Excess $SOCl_2$ was removed *in vacuo*, yielding 2-oxo-2*H*-chromene-3-carbonyl chloride, which was used directly in the subsequent step without further purification.

A solution of the intermediate (3 mmol) in dry DCM (6 mL) was added dropwise to a

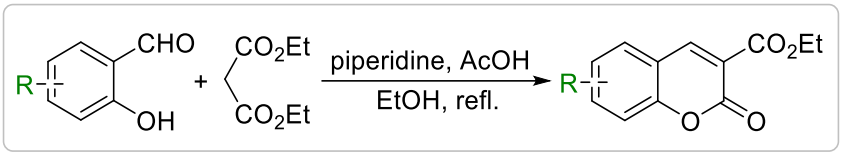
mixture of alcohol or amine (3.6 mmol，1.2 equiv.) and Et_3N (0.1 mL, 0.75 mmol, 0.25 equiv.) in dry DCM (6 mL) at 0 ℃. The reaction mixture was stirred at room temperature for 12 h until TLC confirmed complete conversion. After the removal of the solvent, the residue was purified by flash silica gel column chromatography to afford the product.

General Procedure 2.2

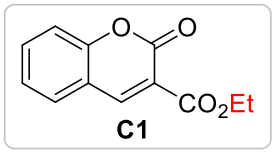


According to literature protocols,[13] a mixture of 2-hydroxybenzaldehyde (1.0 equiv.), diethyl malonate (1.0 equiv.), and *L*-proline (10 mol%) was heated at 90 ℃ for 0.5 h. Upon completion (monitored by TLC), the reaction mixture was cooled and recrystallized from ethanol to obtain yellow-colored crystalline coumarin derivatives.

General Procedure 2.3



According to the literature procedure,[14] diethyl malonate (1.8 mL, 12 mmol, 1.2 equiv.), piperidine (0.1 mL, 1 mmol, 0.1 equiv.), and glacial acetic acid (one drop) were added to the appropriate salicylaldehyde derivatives (10 mmol, 1.0 equiv.) in ethanol (12 mL). The mixture was refluxed for 4-30 h until the disappearance of the starting materials (monitored by TLC). After adding 50 mL of ice water, the crystalline solid formed was filtered, washed with cold 50% ethanol, and recrystallized from 50% ethanol to obtain the solid crystals. If the crystals were impure, column chromatography on silica gel (PE/EtOAc) was used for purification to obtain the desired product (40-85%).



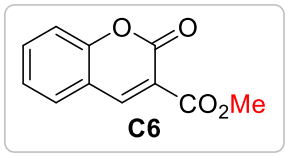
Ethyl 2-oxo-2H-chromene-3-carboxylate (C1)

The title compound was prepared from 2-hydroxybenzaldehyde (2.1 mL, 2.44 g, 20 mmol), diethyl malonate (3.0 mL, 3.20 g, 20 mmol), and *L*-proline (230 mg, 2 mmol) following **General Procedure 2.2**. Purification by recrystallization from ethanol afforded the product **C1** (3.4 g, 15.6 mmol, 78 % yield) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.70 – 7.59 (m, 2H), 7.40 – 7.30 (m, 2H), 4.43 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 156.7, 155.2, 148.6, 134.3, 129.5, 124.8, 118.3, 117.9, 116.8, 62.0, 14.2.

The spectral data are consistent with those reported in the literature[15].



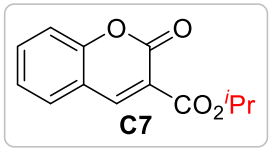
C6

Methyl 2-oxo-2*H*-chromene-3-carboxylate (C6)

The title compound was prepared from 2-oxo-2H-chromene-3-carboxylic acid (570 mg, 3 mmol) and MeOH (150 μL, 3.6 mmol) following **General Procedure 2.1**. Purification by flash column chromatography (PE/EtOAc = 2/1) afforded the product **C6** (554 mg, 2.71 mmol, 90% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.71 – 7.59 (m, 2H), 7.41 – 7.30 (m, 2H), 3.97 (s, 3H).

The spectral data are consistent with those reported in the literature.[16]



C7

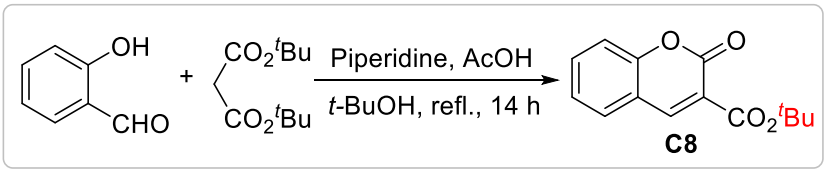
Isopropyl 2-oxo-2*H*-chromene-3-carboxylate (C7)

The title compound was prepared from 2-oxo-2H-chromene-3-carboxylic acid (570 mg, 3 mmol) and *i*-PrOH (280 μL, 3.6 mmol) following **General Procedure 2.1**. Purification by flash column chromatography (PE/EtOAc = 3/1) afforded the product **C7** (39 mg, 2.32 mmol, 77% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.70 – 7.58 (m, 2H), 7.40 – 7.29 (m, 2H), 5.27 (hept, J = 6.3 Hz, 1H), 1.40 (d, J = 6.3 Hz, 6H).

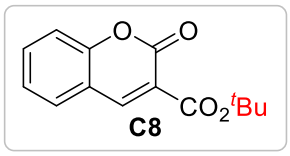
The spectral data are consistent with those reported in the literature.[16]

General synthesis of substrate C8



C8

According to the literature procedure,[17] 2-hydroxybenzaldehyde (366 mg, 3 mmol, 1.0 equiv.), di-*tert*-butyl malonate (649 mg, 3 mmol, 1.0 equiv.), piperidine (37 μL, 0.375 mmol, 12.5 mol%), and acetic acid (2 drops) were added to *t*-BuOH (1.5 mL). The reaction was refluxed for 14 h until the disappearance of 2-hydroxybenzaldehyde was confirmed by TLC. Upon cooling to room temperature and solvent removal, the residue was purified by flash silica gel column chromatography (PE/EtOAc = 10/1) to afford the product **C8** (230 mg, 31%) as a white solid.



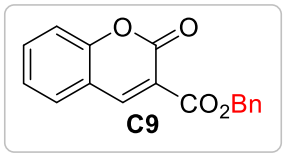
C8

***Tert*-butyl 2-oxo-2*H*-chromene-3-carboxylate (C8)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.66 – 7.57 (m, 2H), 7.37 – 7.29 (m, 2H), 1.61 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 156.8, 155.0, 147.4, 133.9, 129.3, 124.7, 119.7, 118.0, 116.7, 82.9, 28.1.

The spectral data are consistent with those reported in the literature.[17]



C9

Benzyl 2-oxo-2*H*-chromene-3-carboxylate (C9)

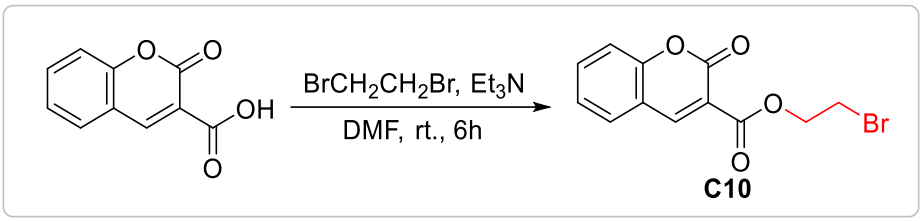
The title compound was prepared from 2-oxo-2H-chromene-3-carboxylic acid (570 mg, 3 mmol) and BnOH (380 μL, 3.6 mmol) following **General Procedure 2.1**. Purification by flash column chromatography (PE/EtOAc = 3/1) afforded the product **C9** (428 mg, 1.53 mmol, 51% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.68 – 7.62 (m, 1H), 7.60 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.48 (d, *J* = 6.7 Hz, 2H), 7.44 – 7.28 (m, 5H), 5.39 (s, 2H).

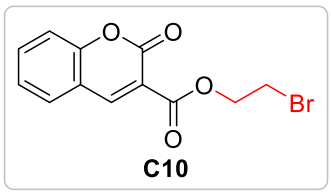
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 156.6, 155.3, 148.9, 135.4, 134.5, 129.6, 128.7, 128.5, 128.4, 124.9, 118.0, 117.9, 116.8, 67.5.

The spectral data are consistent with those reported in the literature.[16]

General synthesis of substrate C10



According to the literature procedure,[18] 2-oxo-2H-chromene-3-carboxylic acid (190 mg, 1 mmol, 1.0 equiv.) was mixed with 1,2-dibromoethane (345 μL, 4 mmol, 4.0 equiv.) and triethylamine (280 μL, 2 mmol, 2.0 equiv.) in DMF (5 mL) and stirred at ambient temperature for 6 h. Water (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed twice with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE/EtOAc = 10/1) to afford **C10** as a white solid (180 mg, 60%).



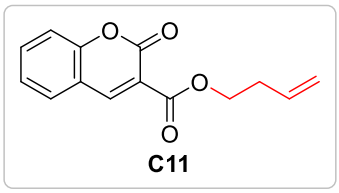
C10

2-bromoethyl 2-oxo-2*H*-chromene-3-carboxylate (C10)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.72 – 7.61 (m, 2H), 7.42 – 7.31 (m, 2H), 4.66 (t, *J* = 6.2 Hz, 2H), 3.66 (t, *J* = 6.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 156.5, 155.3, 149.3, 134.7, 129.7, 125.0, 117.8, 117.5, 116.9, 64.9, 28.3.

The spectral data are consistent with those reported in the literature.[18]



C11

But-3-en-1-yl 2-oxo-2*H*-chromene-3-carboxylate (C11)

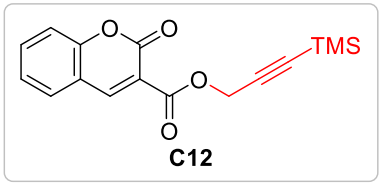
The title compound was prepared from 2-oxo-2H-chromene-3-carboxylic acid (570 mg, 3 mmol) and 3-Buten-1-ol (310 μL, 3.6 mmol) following **General Procedure 2.1**. Purification by flash column chromatography (PE/EtOAc = 5/1) afforded the product **C11** (710 mg, 2.91 mmol, 97% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.70 – 7.58 (m, 2H), 7.40 – 7.30 (m, 2H),

5.88 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.23 – 5.09 (m, 2H), 4.41 (t, *J* = 6.8 Hz, 2H), 2.60 – 2.48 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 156.6, 155.2, 148.6, 134.4, 133.7, 129.5, 124.8, 118.2, 117.9, 117.6, 116.8, 64.9, 33.0.

HRMS (ESI) m/z calcd. for $C_{14}H_{13}O_4$ $[M+H]^+$ 245.0809, found 245.0808.



3-(trimethylsilyl)prop-2-yn-1-yl 2-oxo-2*H*-chromene-3-carboxylate (C12)

The title compound was prepared according to **General Procedure 2.1**.

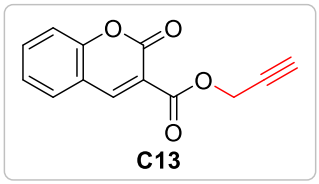
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 1.8 Hz, 1H), 7.72 – 7.62 (m, 2H), 7.41 – 7.33 (m, 2H), 4.96 (s, 2H), 0.20 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 157.0, 155.8, 149.9, 135.3, 130.3, 125.6, 118.3, 117.9, 117.4, 99.0, 93.5, 54.5, 0.3.

HRMS (ESI) m/z calcd. for $C_{16}H_{17}O_4Si$ $[M+H]^+$ 301.0891, found 301.0892.

General synthesis of substrate C13

Following a modified literature procedure,[19] TBAF (1.0 M in THF, 2 mL, 2.0 mmol, 2.0 equiv.) was added dropwise to a solution of **C12** (1 mmol, 1.0 equiv.) in anhydrous THF (5 mL). Then, the mixture was stirred for 12 h at room temperature. Upon completion (monitored by TLC), the reaction mixture was concentrated *in vacuo*, dissolved in EtOAc, and washed three times with water. The organic phase was washed with brine, dried, filtered, and concentrated. The residue was purified by silica gel chromatography (PE/EtOAc) to afford **C13**.

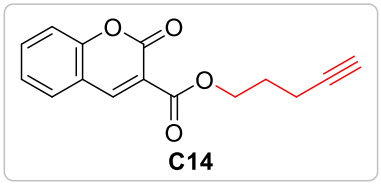


Prop-2-yn-1-yl 2-oxo-2*H*-chromene-3-carboxylate (C13)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.73 – 7.61 (m, 2H), 7.41 – 7.32 (m, 2H), 4.95 (d, *J* = 2.5 Hz, 2H), 2.56 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 156.4, 155.3, 149.5, 134.8, 129.7, 125.0, 117.7, 117.2, 116.9, 77.1, 75.6, 53.2.

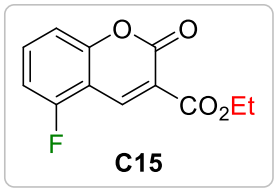
The spectral data are consistent with those reported in the literature.[16]



Pent-4-yn-1-yl 2-oxo-2*H*-chromene-3-carboxylate (C14)

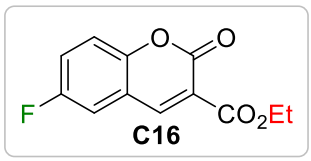
The title compound was prepared from 2-oxo-2*H*-chromene-3-carboxylic acid (380 mg, 2 mmol) and 4-pentyn-1-ol (223 μL, 2.4 mmol) following **General Procedure 2.1**. Purification by flash column chromatography (PE/EtOAc = 10/1)

afforded the product **C14** (251 mg, 0.98 mmol, 49% yield) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.70 – 7.59 (m, 2H), 7.40 – 7.31 (m, 2H), 4.47 (t, *J* = 6.2 Hz, 2H), 2.42 (td, *J* = 6.9, 2.4 Hz, 2H), 2.08 – 1.94 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 156.6, 155.3, 148.8, 134.4, 129.5, 124.9, 118.2, 117.9, 116.8, 83.0, 69.2, 64.4, 27.5, 15.3.
HRMS (ESI) m/z calcd. for $C_{15}H_{13}O_4$ $[M+H]^+$ 257.0809, found 257.0808.



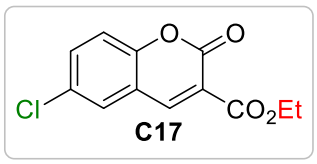
C15

Ethyl 5-fluoro-2-oxo-2*H*-chromene-3-carboxylate (C15)
The title compound was prepared according to **General Procedure 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.62 (td, *J* = 8.4, 6.2 Hz, 1H), 7.17 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.10 – 7.00 (m, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 159.3 (d, *J* = 258.9 Hz), 155.9, 155.4 (d, *J* = 4.3 Hz), 141.4 (d, *J* = 4.0 Hz), 134.8 (d, *J* = 9.9 Hz), 118.5 (d, *J* = 1.3 Hz), 112.6 (d, *J* = 4.0 Hz), 110.6 (d, *J* = 19.6 Hz), 108.4 (d, *J* = 18.8 Hz), 62.2, 14.2.
^{19}F NMR (376 MHz, $CDCl_3$) δ -116.5 (s, 1F).
The spectral data are consistent with those reported in the literature.[20]



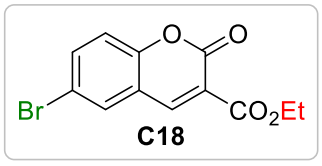
C16

Ethyl 6-fluoro-2-oxo-2*H*-chromene-3-carboxylate (C16)
The title compound was prepared according to **General Procedure 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.41 – 7.33 (m, 2H), 7.32 – 7.27 (m, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).
The spectral data are consistent with those reported in the literature.[21]



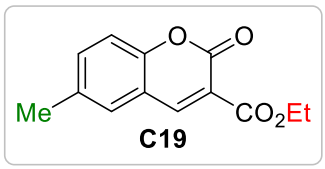
C17

Ethyl 6-chloro-2-oxo-2*H*-chromene-3-carboxylate (C17)
The title compound was prepared according to **General Procedure 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.62 – 7.57 (m, 2H), 7.35 – 7.30 (m, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).
The spectral data are consistent with those reported in the literature.[21]

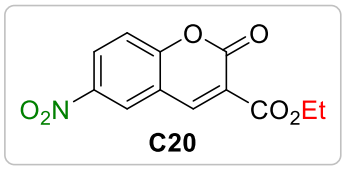


C18

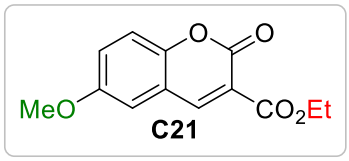
Ethyl 6-bromo-2-oxo-2*H*-chromene-3-carboxylate (C18)
The title compound was prepared according to **General Procedure 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.78 – 7.70 (m, 2H), 7.27 (s, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 156.0, 154.0, 147.0, 137.0, 131.5, 119.5, 119.4, 118.6, 117.4, 62.2, 14.2.
The spectral data are consistent with those reported in the literature.[22]



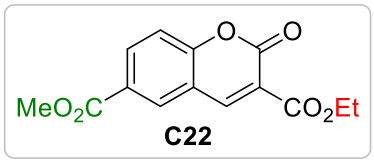
Ethyl 6-methyl-2-oxo-2*H*-chromene-3-carboxylate (C19)
The title compound was prepared according to **General Procedure 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 0.6 Hz, 1H), 7.45 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.27 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).
The spectral data are consistent with those reported in the literature.[21]



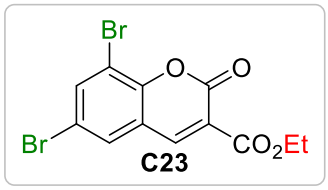
Ethyl 6-nitro-2-oxo-2*H*-chromene-3-carboxylate (C20)
The title compound was prepared according to **General Procedure 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.57 (d, *J* = 2.6 Hz, 1H), 8.50 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.51 (d, *J* = 9.1 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 158.3, 154.9, 146.9, 144.2, 128.6, 125.2, 120.6, 118.1, 117.8, 62.6, 14.2.
HRMS (ESI) m/z calcd. for $C_{12}H_{10}NO_6$ $[M+H]^+$ 264.0503, found 264.0503.



Ethyl 6-methoxy-2-oxo-2*H*-chromene-3-carboxylate (C21)
The title compound was prepared according to **GP 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.32 – 7.26 (m, 1H), 7.26 – 7.21 (m, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 4.42 (t, 2H), 3.87 (s, 3H), 1.45 – 1.38 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 156.9, 156.3, 149.7, 148.4, 122.6, 118.5, 118.1, 117.9, 110.6, 62.0, 55.9, 14.2.
The spectral data are consistent with those reported in the literature.[23]

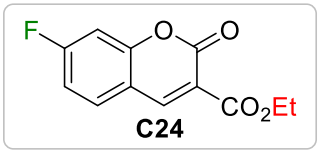


3-ethyl 6-methyl 2-oxo-2*H*-chromene-3,6-dicarboxylate (C22)
The title compound was prepared according to **General Procedure 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.35 (d, *J* = 2.1 Hz, 1H), 8.30 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 162.6, 157.7, 155.9, 148.1, 135.0, 131.5, 127.0, 119.2, 117.6, 117.1, 62.2, 52.6, 14.2.
HRMS (ESI) m/z calcd. for $C_{14}H_{13}O_6$ $[M+H]^+$ 277.0707, found 277.0707.



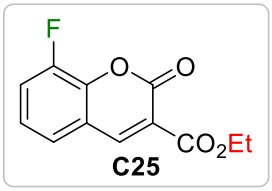
Ethyl 6,8-dibromo-2-oxo-2*H*-chromene-3-carboxylate (C23)
The title compound was prepared according to **GP 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.98 (d, *J* = 2.2 Hz, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H),

1.41 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 154.9, 151.0, 146.6, 139.5, 130.7, 120.2, 120.0, 117.2, 111.4, 62.4, 14.2.
The spectral data are consistent with those reported in the literature.[24]



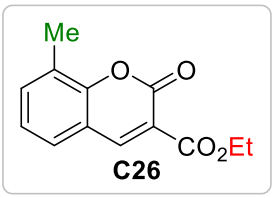
C24

Ethyl 7-fluoro-2-oxo-2*H*-chromene-3-carboxylate (C24)
The title compound was prepared according to **GP 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.66 (dd, *J* = 8.5, 6.0 Hz, 1H), 7.15 – 7.03 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1 (d, *J* = 258.0 Hz), 162.8, 156.6 (d, *J* = 13.5 Hz), 156.2, 148.1, 131.4 (d, *J* = 10.9 Hz), 116.9 (d, *J* = 3.2 Hz), 114.7 (d, *J* = 2.6 Hz), 113.3 (d, *J* = 23.2 Hz), 104.4 (d, *J* = 25.7 Hz), 62.0, 14.2.
^{19}F NMR (376 MHz, $CDCl_3$) δ -100.2 (s, 1F).
The spectral data are consistent with those reported in the literature.[25]



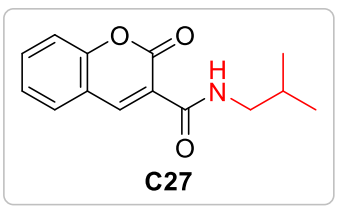
C25

Ethyl 8-fluoro-2-oxo-2*H*-chromene-3-carboxylate (C25)
The title compound was prepared according to **GP 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 1.3 Hz, 1H), 7.49 – 7.37 (m, 2H), 7.35 – 7.24 (m, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 155.2, 149.1 (d, *J* = 253.6 Hz), 147.9 (d, *J* = 2.7 Hz), 143.3 (d, *J* = 11.7 Hz), 124.7 (d, *J* = 6.5 Hz), 124.6 (d, *J* = 4.0 Hz), 120.5 (d, *J* = 17.2 Hz), 119.6 (d, *J* = 1.3 Hz), 119.3, 62.2, 14.2.
^{19}F NMR (376 MHz, $CDCl_3$) δ -132.3 (s, 1F).
The spectral data are consistent with those reported in the literature.[21]



C26

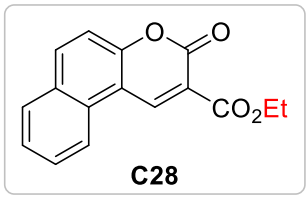
Ethyl 8-methyl-2-oxo-2*H*-chromene-3-carboxylate (C26)
The title compound was prepared according to **GP 2.3**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 156.9, 153.6, 148.9, 135.6, 127.2, 126.4, 124.4, 118.0, 117.7, 61.9, 15.4, 14.2.
The spectral data are consistent with those reported in the literature.[14]



C27

***N*-isobutyl-2-oxo-2*H*-chromene-3-carboxamide (C27)**
The title compound was prepared according to **GP 2.1**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.86 (br s, 1H), 7.70 – 7.60 (m, 2H), 7.40 – 7.32 (m, 2H), 3.28 (dd, *J* = 6.8, 5.9 Hz, 2H), 1.90 (hept, *J* = 6.7 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 161.4, 154.3, 148.2, 133.9, 129.7, 125.2, 118.6, 118.5, 116.6, 47.2, 28.4, 20.2.

The spectral data are consistent with those reported in the literature.[26]



C28

Ethyl 3-oxo-3*H*-benzo[*f*]chromene-2-carboxylate (C28)
The title compound was prepared from 2-hydroxy-1-naphthaldehyde, diethyl malonate, and *L*-proline following **GP 2.2**. Purification by flash column chromatography (PE/EtOAc) afforded the product **C28** as an off-white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 7.98 – 7.92 (m, 2H), 7.76 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 2H), 7.62 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 2H), 7.48 (dd, *J* = 9.0, 0.6 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 3H), 1.46 (t, *J* = 7.1 Hz, 4H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 156.9, 156.0, 144.5, 136.1, 130.2, 129.5, 129.3, 129.1, 126.6, 121.5, 116.7, 116.5, 112.3, 62.1, 14.3
The spectral data are consistent with those reported in the literature.[27]

3.3 Synthesis of other substrates

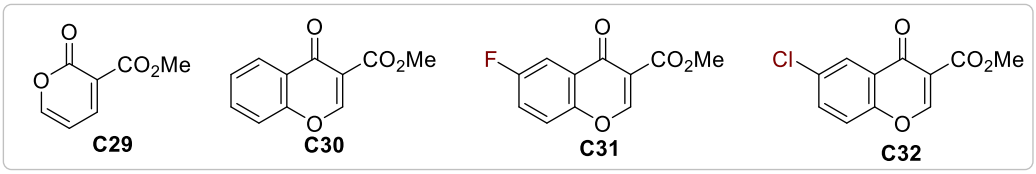
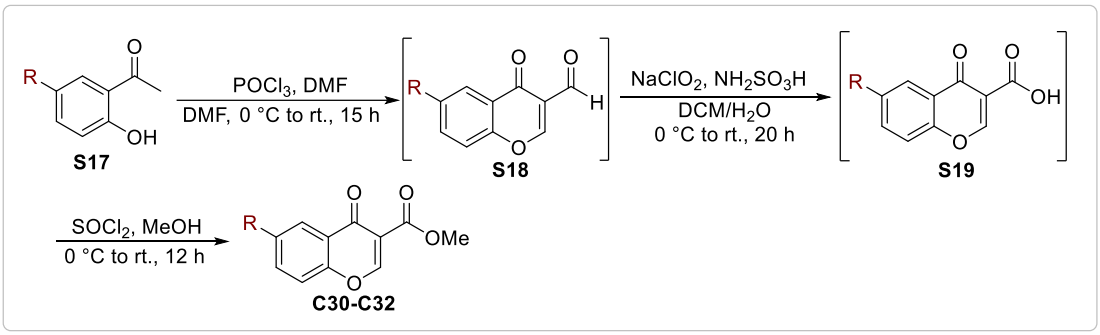


Figure S8 | Overview of other substrates.

Substrate 2-pyrone **C29** is commercially available. Chromone substrates **C30-C32**[28] are known compounds.

General Procedure of substrates C30-C32



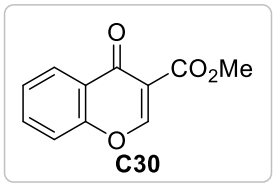
Compounds **C30-C32** were prepared following a modified procedure described in the literature[28-29], with **C30** serving as an example.

Step 1: A solution of *o*-hydroxyacetophenone (**S17**, 6.81 g, 50 mmol) in DMF (100 ml) was cooled to 0 °C in an ice bath. Phosphoryl chloride ($POCl_3$, 9.3 mL, 100 mmol, 2 equiv.) was then added dropwise for 10 min at 0 °C. The reaction mixture was allowed to warm to room temperature slowly in the cooling bath. After stirring for 15 h, the mixture was slowly poured into ice water (500 mL) with constant stirring until complete precipitation. The produced solid was filtered and washed with cold water and Et_2O, yielding chromone-3-carboxaldehyde (**S18**, 7.22 g, 41.4 mmol) as a yellow solid. The aldehyde intermediate was used directly in the next step without purification.

Step 2: Chromone-3-carboxaldehyde (**S18**, 2.09 g, 12 mmol) was dissolved in DCM (130 mL). Sulfamic acid (NH_2SO_3H, 5.83 g, 60 mmol, 5 equiv.) and water (115 mL) were added to the reaction mixture. The resulting mixture was then cooled to 0 °C in an ice bath. A solution of sodium chlorite ($NaClO_2$, 4.34 g, 48 mmol, 4 equiv.) in water (80 mL) was then added dropwise at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 20 h. The reaction mixture was extracted with DCM (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford chromone-3-carboxylic acid (**S19,** 1.73 g, 9.1 mmol) as a slightly yellow solid.

Step 3: Employing a slightly modified procedure from the literature,[29] chromone-3-carboxylic acid (**S19,** 570 mg, 3 mmol) was dissolved in MeOH (30 mL). Thionyl

chloride ($SOCl_2$, 5.7 mL, 75 mmol, 25 equiv.) was added dropwise to the stirred solution at 0 °C. The mixture was then allowed to warm to room temperature and was stirred for 12 h. The solution was concentrated *in vacuo* and purified by flash column chromatography (PE/EtOAc = 3/1 to 2/1) to afford methyl 4-oxo-4H-chromene-3-carboxylate (**C30**, 560 mg, 2.75 mmol, 92% yield) as an off-white solid.

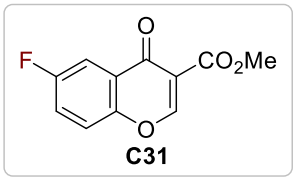


C30

Methyl 4-oxo-4H-chromene-3-carboxylate (C30)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.30 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.72 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 7.49 (dd, *J* = 15.9, 7.9 Hz, 2H), 3.94 (s, 3H).

The spectral data are consistent with those reported in the literature.[28]



C31

Methyl 6-fluoro-4-oxo-4H-chromene-3-carboxylate (C31)

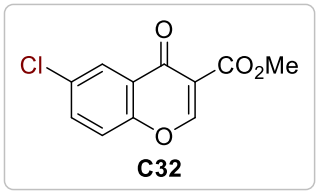
The title compound was prepared from 1-(5-fluoro-2-hydroxyphenyl)ethan-1-one (771 mg, 5 mmol) following the General Procedure described above. Purification by flash column chromatography (PE/EtOAc = 4/1 to 3/1) afforded the product **C31** (356 mg, 1.60 mmol, 32% yield over 3 steps) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.91 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.54 (dd, *J* = 8.9, 3.9 Hz, 1H), 7.45 (dd, *J* = 11.4, 4.7 Hz, 1H), 3.94 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (d, *J* = 1.7 Hz), 163.8, 162.2, 160.2 (d, *J* = 248.7 Hz), 151.8 (d, *J* = 1.6 Hz), 126.5 (d, *J* = 7.7 Hz), 122.5 (d, *J* = 25.6 Hz), 120.4 (d, *J* = 8.2 Hz), 115.4, 111.6 (d, *J* = 24.1 Hz), 52.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.2 (s, 1F).

The spectral data are consistent with those reported in the literature.[28]



C32

Methyl 6-chloro-4-oxo-4H-chromene-3-carboxylate (C32)

The title compound was prepared from 1-(5-chloro-2-hydroxyphenyl)ethan-1-one (853 mg, 5 mmol) following the General Procedure described above. Purification by flash column chromatography (PE/DCM = 3/1 to 0/1) afforded the product **C32** (506 mg, 2.12 mmol, 42% yield over 3 steps) as a pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.23 (s, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 3.94 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 163.6, 162.2, 153.9, 134.5, 132.4, 126.0 (d, *J* = 11.4 Hz), 119.9, 116.1, 52.6.

The spectral data are consistent with those reported in the literature[28].

4. Synthesis of the chiral ligands

Chiral ligands **L*1–L*5** were synthesized according to our previous reports.[30] Chiral ligands **L*6–L*7** were purchased from *Bidepharm*. Chiral ligands **L*8–L*10** were synthesized following a published procedure.[31] Chiral ligands **L*11–L*12** were prepared using a modified method.[32]

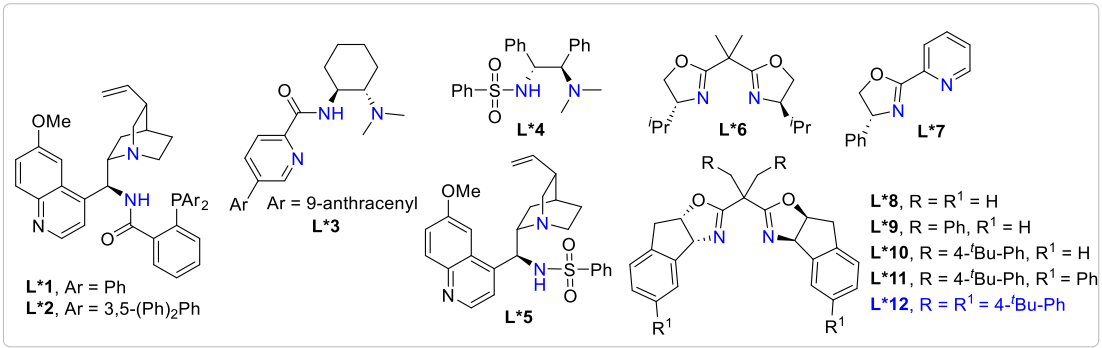
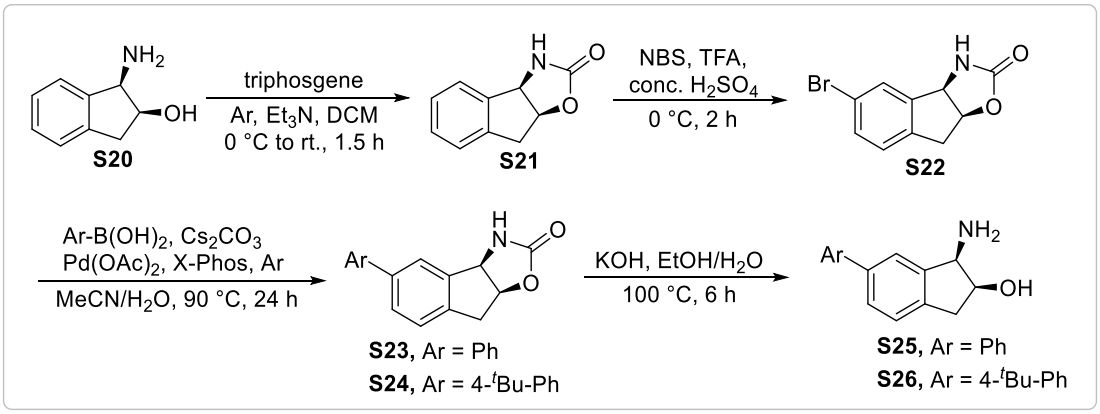


Figure S9 | Overview of the chiral ligands.

Synthesis of chiral Box ligands L*11 and L*12



Step 1: **S21** was synthesized by a published procedure.[33] **S20** (3.73 g, 25 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (100 mL) under argon. The temperature was lowered to 0 °C before the addition of triphosgene (2.67 g, 10 mmol, 0.4 equiv.) and NEt_3 (7.0 mL, 50 mmol, 2.0 equiv.). Stirring was continued at 0 °C for 1.5 h. The mixture was concentrated to 25 mL and washed with NH_4Cl (10 mL) and H_2O (2 × 10 mL). The combined aqueous layers were extracted with DCM (2 × 15 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated to give **S21** (23.75 mmol, 95%) as a white solid.

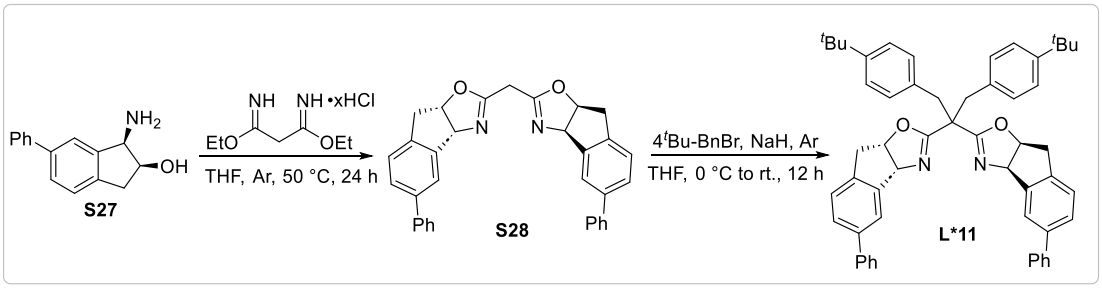
Step 2: **S22** was synthesized by a published procedure.[31b] **S21** (3.5 g, 20 mmol, 1.0 equiv.) was added in one portion to a mixture of CF_3CO_2H (20 mL) and conc. H_2SO_4 (5.6 mL) at 0 °C. *N*-Bromosuccinimide (3.91 g, 22 mmol, 1.1 equiv.) was added in portions and the resulting yellow suspension was stirred at 0 °C for 2 h. Water (70 mL) was slowly introduced, and the mixture was neutralized by carefully adding solid NaOH at 0 °C. The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic

phases were dried over Na_2SO_4 and concentrated to give **S22** (19.6 mmol, 98%) as a white solid.

Step 3: **S22** (15.5 mmol, 1.0 equiv.), $Pd(OAc)_2$ (0.155 mmol, 1 mol%), X-Phos (0.31 mmol, 2 mol%), Cs_2CO_3 (31 mmol, 2.0 equiv.), and phenylboronic acid (18.6 mmol, 1.2 equiv.) were added to an oven-dried Schlenk tube equipped with a magnetic stir bar. The tube was evacuated and backfilled with argon three times. Subsequently, freshly degassed MeCN (70 mL) and H_2O (23 mL) were added via a syringe. The reaction mixture was stirred at 85 °C for 24 h. Upon completion, the mixture was diluted with water and then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The mixture was purified by column chromatography (eluted with PE/EtOAc = 1/2) to give **S23** (15.3 mmol, 98%) as a white solid.
S24 was prepared following the same procedure.

Step 4: **S25** was synthesized by a published procedure.[32] **S23** (3.84 g, 15.3 mmol, 1.0 equiv.) and KOH (3.78 g, 67.3 mmol, 4.4 equiv.) were dissolved in a mixture of EtOH (38.3 mL) and H_2O (38.3 mL), and then heated at 100 °C for 6 h. The solution was cooled to room temperature and concentrated *in vacuo* to remove EtOH. The residue was extracted with EtOAc (3 × 30 mL), concentrated *in vacuo*, and purified by flash silica gel chromatography (eluted with EtOAc/MeOH = 1/2). Crude product **S25** (15.0 mmol, 98%) was obtained as a brown solid, which was used directly for the next step without further purification.
S26 was prepared following the same procedure.

Synthesis of **L*11**

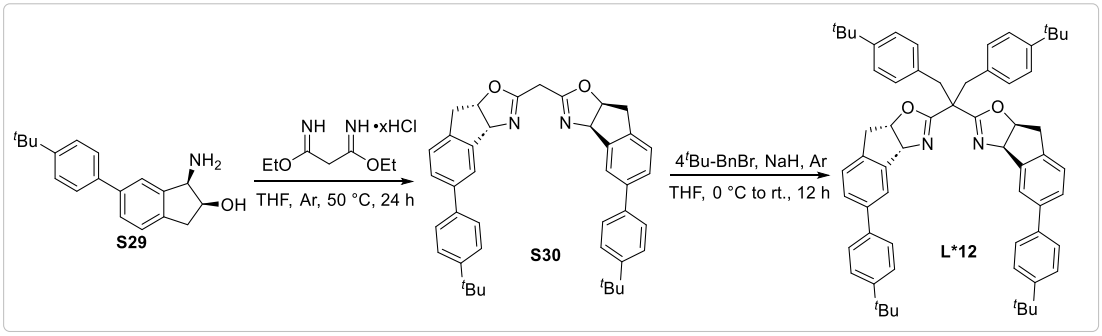


S27 was synthesized following a literature procedure with some modifications.[32] **S27** (3.45 g, 15.3 mmol, 1.0 equiv.) and diethyl malonimidate dihydrochloride (1.51 g, 6.5 mmol, 0.42 equiv.) and dry THF (70 mL) were added to an oven-dried Schlenk tube equipped with a magnetic stir bar. The reaction mixture was stirred at 50 °C for 20 h, then cooled to 0 °C. Aqueous sodium bicarbonate (0.5 M, 80 mL) was slowly added. The resulting precipitate was collected by filtration, washed with water (2 × 20 mL), and dried *in vacuo* to afford the crude product **S28** (3.15 mmol, 41.1%) as a brown solid, which was used directly for the next step without further purification.

To a solution of **S28** (482.6 mg, 1.0 mmol, 1.0 equiv.) in dry THF (30 mL) was added NaH (172.0 mg, 60% in mineral oil, 7.17 mmol, 7.17 equiv.) in portions at 0 °C under

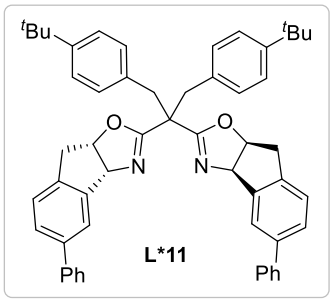
argon. The mixture was stirred at 0 °C for 30 minutes. A solution of *p-tert*-butyl benzyl bromide (1.11 g, 4.89 mmol, 4.89 equiv.) in dry THF (15 mL) was added dropwise, and the resulting mixture was stirred for 6 h at room temperature. Sat. NH_4Cl solution (10 mL) and water (30 mL) were added, and the mixture was repeatedly extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluted with PE: EtOAc = 5:1) to afford the pure chiral ligand **L*11** (0.83 mmol, 83%) as a white solid.

Synthesis of **L*12**



S30 was synthesized by a published procedure with some modifications.[32] **S29** (3.4 g, 12 mmol, 1.0 equiv.) and diethyl malonimidate dihydrochloride (1.32 g, 5.7 mmol, 0.48 equiv.) and dry THF (50 mL) were added to an oven-dried Schlenk tube equipped with a magnetic stir bar. The reaction mixture was stirred at 50 °C for 20 h, then cooled to 0 °C. Aqueous sodium bicarbonate (0.5 M, 60 mL) was slowly added. The mixture was concentrated *in vacuo* to remove THF. The resulting precipitate was collected by filtration, washed with water (2 × 30 mL), and dried *in vacuo* to afford the crude product **S30** (4.88 mmol, 85 %) as a reddish brown solid, which was directly used for the next step without further purification.

To a solution of **S30** (2.9 g, 4.88 mmol,1.0 equiv.) in dry THF (90 mL) was added NaH (1.37 g, 60% in mineral oil, 24.4 mmol, 5.0 equiv.) in portions at 0 °C under argon. The mixture was stirred at 0 °C for 30 minutes. A solution of *p-tert*-butyl benzyl bromide (2.78 g, 12.24 mmol, 2.5 equiv.) in dry THF (45 mL) was added dropwise, and the resulting mixture was stirred for 6 h at rt. Sat. NH_4Cl solution (30 mL) and water (90 mL) were added, and the mixture was repeatedly extracted with DCM (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was filtered, washed with EtOAc (2 × 20 mL), and dried *in vacuo* to afford the product **L*12** (2.7 mmol, 55 %) as a white solid. *(Note: If impurities were detected in the NMR, the product could be purified by recrystallization using petroleum ether (PE) and dichloromethane (DCM)).*

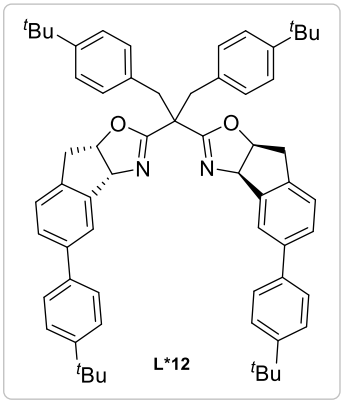


(3a*R*,3a'*R*,8a*S*,8a'*S*)-2,2'-(1,3-bis(4-(*tert*-butyl)phenyl)-propane-2,2-diyl)bis(5-phenyl-3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole) (L*11)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 2H), 7.64 (t, *J* = 8.8 Hz, 6H), 7.47 – 7.30 (m, 8H), 6.81 (d, *J* = 8.3 Hz, 4H), 6.67 (d, *J* = 8.2 Hz, 4H), 5.68 (d, *J* = 7.9 Hz, 2H), 5.38 (t, *J* = 7.2 Hz, 2H), 3.40 (dd, *J* = 18.3, 6.8 Hz, 2H), 3.27 – 3.10 (m, 4H), 3.00 (d, *J* = 14.3 Hz, 2H), 1.10 (s, 18H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 149.0, 142.3, 140.8, 140.7, 139.2, 133.0, 130.1, 128.9, 127.5, 127.4, 127.2, 125.6, 124.6, 124.4, 83.8, 76.6, 47.8, 39.2, 38.1, 34.2, 31.3.

HRMS (ESI) m/z calcd. for $C_{55}H_{55}N_2O_2$ $[M+H]^+$ 775.4258, found 775.4264.



(3a*R*,3a'*R*,8a*S*,8a'*S*)-2,2'-(1,3-bis(4-(*tert*-butyl)-phenyl)-propane-2,2-diyl)bis(5-(4-(*tert*-butyl)phenyl)-3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole) (L*12)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.66 – 7.58 (dd, *J* = 8.7, 7.0 Hz, 6H), 7.46 (d, *J* = 8.5 Hz, 4H), 7.36 (d, *J* = 7.9 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 4H), 6.65 (d, *J* = 8.3 Hz, 4H), 5.67 (d, *J* = 7.8 Hz, 2H), 5.36 (t, *J* = 6.8 Hz, 2H), 3.37 (dd, *J* = 18.2, 6.7 Hz, 2H), 3.20 (d, *J* = 14.3 Hz, 2H), 3.13 (s, 2H), 3.01 (d, *J* = 14.3 Hz, 2H), 1.36 (s, 18H), 1.10 (s, 18H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 150.3, 148.9, 142.2, 140.4, 138.8, 137.8, 132.9, 130.1, 127.2, 126.8, 125.8, 125.5, 124.5, 124.2, 83.8, 76.5, 47.6, 39.1, 38.0, 34.6, 34.2, 31.4, 31.3.

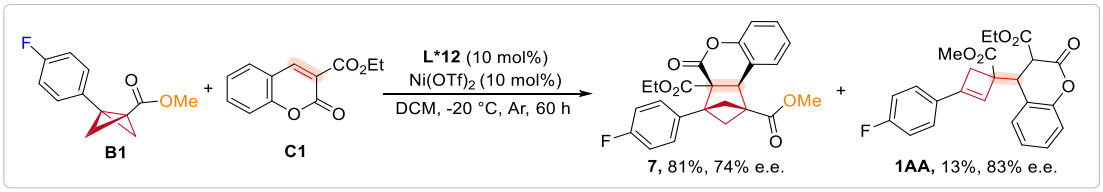
HRMS (ESI) m/z calcd. for $C_{63}H_{71}N_2O_2$ $[M+H]^+$ 887.5510, found 887.5519.

5. Optimization of the reaction conditions

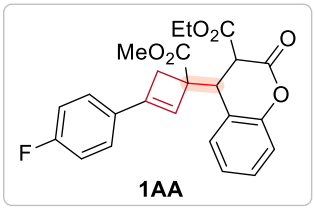
General procedure for the reaction conditions optimization:

Under an argon atmosphere, an oven-dried, resealable Schlenk tube equipped with a magnetic stir bar was charged with Lewis acid (0.005 mmol, 10 mol%) and chiral ligand (0.005 mmol, 10 mol%). Subsequently, the BCB substrate (0.0525 mmol, 1.05 equiv.), coumarin substrate (0.05 mmol, 1.0 equiv.), and anhydrous solvent (0.5 mL) were added. The reaction mixture was then stirred at -20 °C for 60 h. Upon completion (monitored by TLC), the reaction mixture was transferred to a flask, and the solvent was evaporated *in vacuo*. Approximately 0.5 mL of $CDCl_3$ was added and thoroughly mixed. CH_2Br_2 (8.69 mg, 0.05 mmol) was subsequently introduced using a micro-syringe, followed by thorough mixing. The yield was determined by ^1H NMR using the internal standard method. If required, the mixture was separated by PTLC (*n*-hexane/EtOAc), and the enantiomeric excess (e.e.) was determined by HPLC.

General synthesis of substrate 1AA:



Under an argon atmosphere, a magnetic stir bar-equipped, oven-dried resealable Schlenk tube was charged with $Ni(OTf)_2$ (1.78 mg, 0.005 mmol, 10 mol%) and **L*12** (4.44 mg, 0.005 mmol, 10 mol%). Subsequently, BCB substrate **B1** (10.8 mg, 0.0525 mmol, 1.05 equiv.), coumarin substrate **C1** (10.9 mg, 0.05 mmol, 1.0 equiv.), and anhydrous DCM (0.5 mL) were added. The reaction mixture was then stirred at -20 °C for 60 h. Upon completion (monitored by TLC), the solvent was evaporated *in vacuo*. The yield was determined by ^1H NMR using CH_2Br_2 as an internal standard. The mixture was separated by PTLC (*n*-hexane/EtOAc), and the enantiomeric excess (e.e.) was determined by HPLC.



Ethyl 4-(3-(4-fluorophenyl)-1-(methoxycarbonyl)-cyclobut-2-en-1-yl)-2-oxochromane-3-carboxylate (1AA)

HPLC analysis: CHIRALPAK® IA-3 (*n*-hexane/*i*-PrOH = 75/25, flow rate = 0.60 mL/min, λ = 254 nm), t_R (major) = 12.10 min, t_R (minor) = 13.64 min.

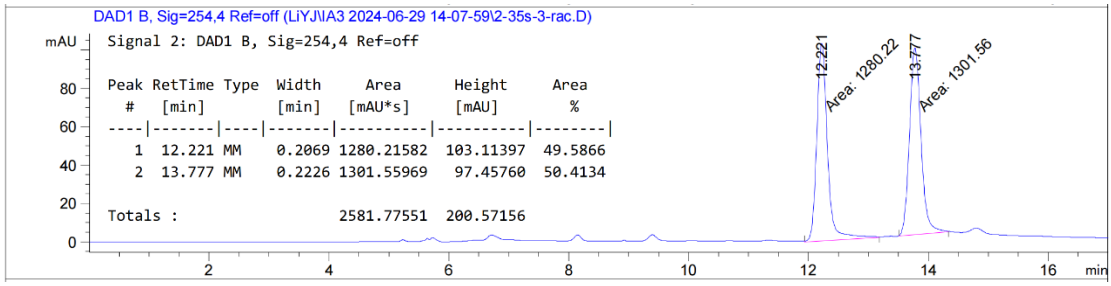
^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 4H), 7.16 – 7.10 (m, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.04 – 6.97 (m, 2H), 6.27 (s, 1H), 4.14 – 4.03 (m, 2H), 4.02 (d, *J* = 1.5 Hz, 1H), 3.93 (s, 1H), 3.69 (s, 3H), 3.14 (d, *J* = 13.4 Hz, 1H), 2.83 (d, *J* = 13.4 Hz, 1H), 1.07 (t, *J* = 7.2 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 167.1, 163.9, 163.1 (d, *J* = 249.3 Hz), 151.5, 146.6, 129.7, 129.6, 129.2 (d, *J* = 3.1 Hz), 126.9 (d, *J* = 8.3 Hz), 124.8 (d, *J* = 2.2 Hz), 124.5, 119.4, 117.2, 115.5 (d, *J* = 21.9 Hz), 62.5, 53.4, 52.3, 49.7, 45.1, 37.2, 13.8.

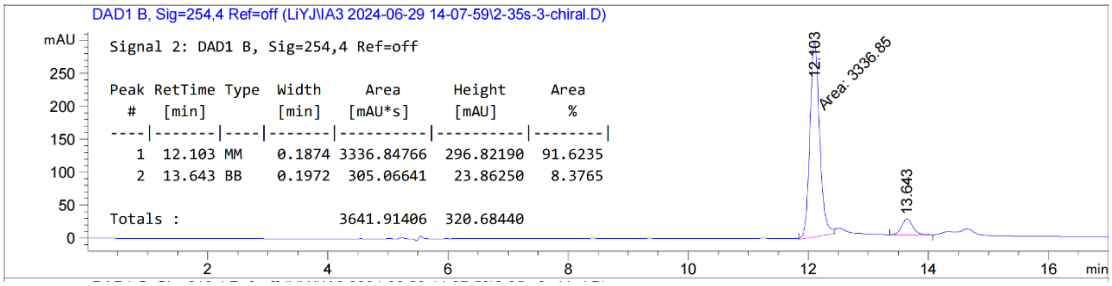
^{19}F NMR (376 MHz, $CDCl_3$) δ -111.5 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{25}H_{25}NaFO_7$ $[M+Na+CH_3OH]^+$ 479.1476, found 479.1483.

HPLC spectrum of ***rac*-1AA:**

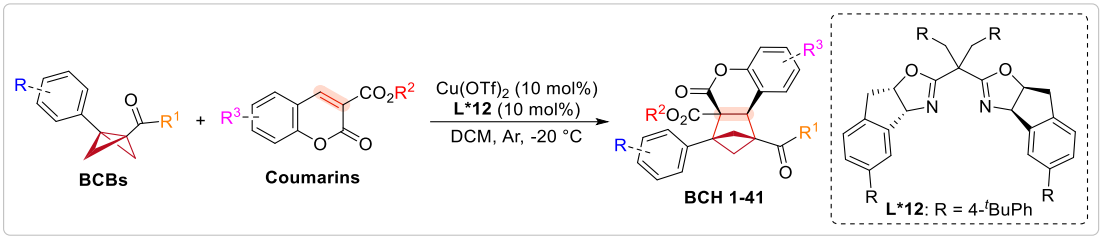


HPLC spectrum of **1AA:**



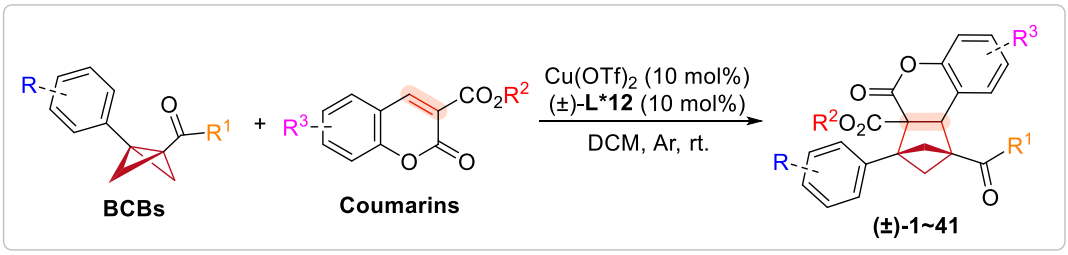
6. Substrate scope

6.1 General Procedure A: Cu/Box-catalyzed asymmetric cycloaddition of BCBs and substituted coumarins

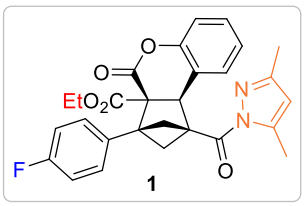


Under argon, an oven-dried, resealable Schlenk tube equipped with a magnetic stir bar was charged with $Cu(OTf)_2$ (7.23 mg, 0.02 mmol, 10 mol%), chiral Box ligand **L*12** (17.7 mg, 0.02 mmol, 10 mol%), and anhydrous DCM (2.0 mL). The solution was stirred for 1 h at ambient temperature, ensuring the complete dissolution of the triflate salt and forming a homogeneous light green solution of the ligand complex. This resulting solution was then cooled to -20 °C. BCB substrate (0.21 mmol, 1.05 equiv.) and coumarin substrate (0.10 mmol, 1.0 equiv.) were added under positive argon pressure. The sealed tube was stirred at -20 °C. Upon completion (monitored by TLC), the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (*n*-hexane/EtOAc) to afford the desired chiral BCHs.

The preparation of racemic BCH products (±)-**1~41**:



The racemate was prepared following the same procedure described above, and the reactions were conducted on a 0.05 mmol scale by using $Cu(OTf)_2$ (1.81 mg, 0.005 mmol, 10 mol%) and (±)-**L*12** (4.44 mg, 0.005 mmol, 10 mol%) as catalysts at room temperature in DCM (0.5 mL) for 24-48 h. Upon completion (monitored by TLC), the solvent was removed *in vacuo*, and the residue was purified by PTLC (eluent: *n*-hexane /EtOAc) to give the desired product.



Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (1)

The title compound was synthesized according to **General Procedure A** at -20 °C for 48 h. The product was purified by silica gel flash column chromatography (4-7% EtOAc in *n*-hexane) to afford the desired product **1** (85.1 mg, 87%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 10.99 min, t_R (major) = 12.83 min.

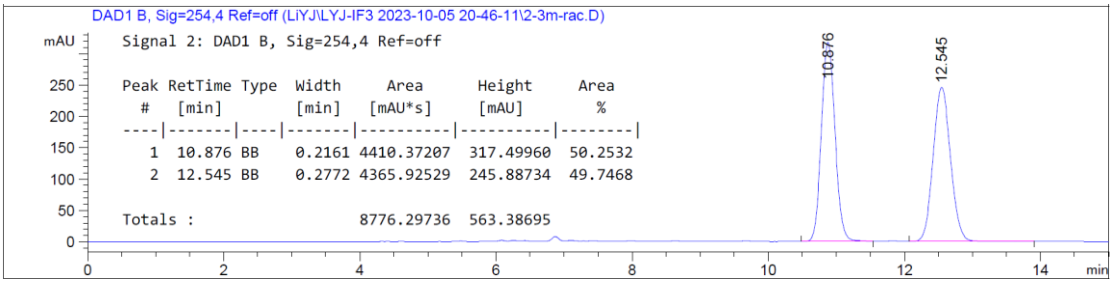
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 2H), 7.29 – 7.22 (m, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.04 – 6.92 (m, 3H), 6.48 (d, *J* = 7.3 Hz, 1H), 6.04 (s, 1H), 4.76 (s, 1H), 4.26 – 4.09 (m, 2H), 3.35 (dd, *J* = 9.4, 8.1 Hz, 1H), 2.51 (s, 3H), 2.40 (d, *J* = 7.8 Hz, 1H), 2.30 (t, *J* = 9.2 Hz, 1H), 2.25 (s, 3H), 2.12 (dd, *J* = 8.7, 1.8 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.3, 164.0, 162.2 (d, *J* = 245.8 Hz), 153.2, 150.6, 144.4, 134.0 (d, *J* = 3.2 Hz), 130.2 (d, *J* = 8.1 Hz), 129.5, 127.9, 124.9, 118.9, 117.5, 114.4 (d, *J* = 21.3 Hz), 111.3, 62.1, 60.8, 57.1, 56.7, 52.5, 48.3, 40.8, 14.3, 14.1, 13.9.

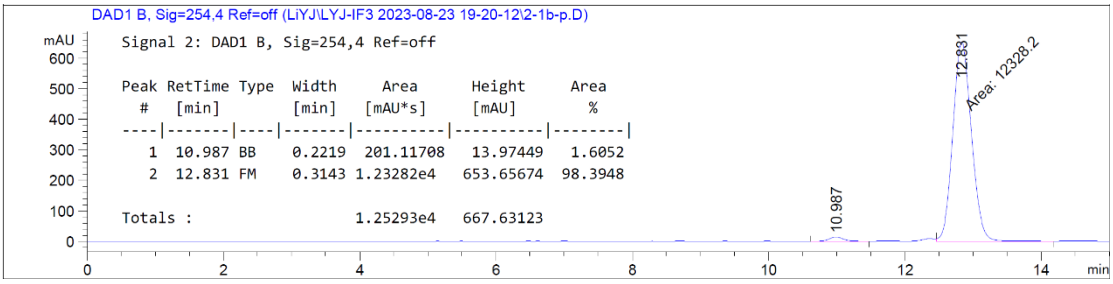
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.1 (s, 1F).

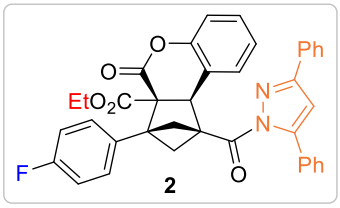
HRMS (ESI) m/z calcd. for $C_{28}H_{26}FN_2O_5$ $[M+H]^+$ 489.1821, found 489.1823.

HPLC spectrum of ***rac*-1:**



HPLC spectrum of **1:**





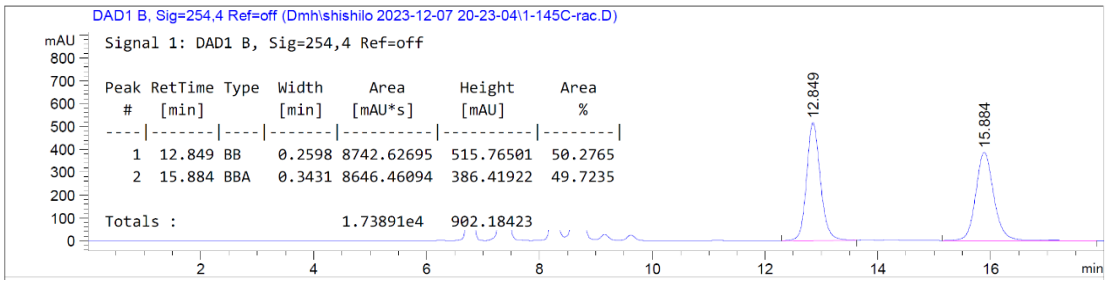
Ethyl (3a*S*,9b*S*)-1-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (2)

The title compound was synthesized according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (5-8% EtOAc in *n*-hexane) to afford the desired product **2** (119.7 mg, 98 %) as a white solid.

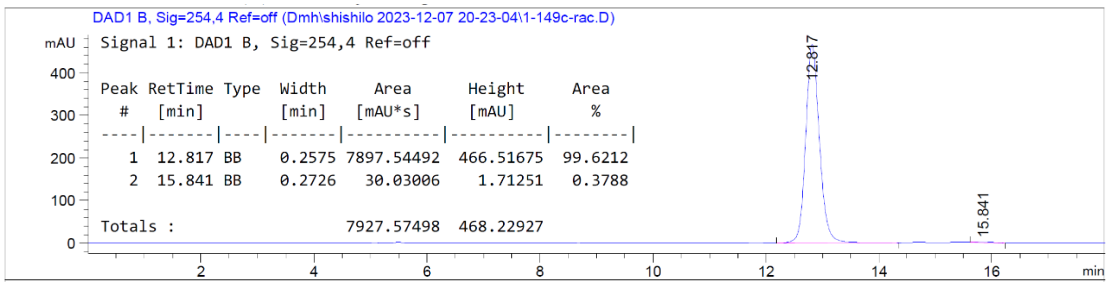
HPLC analysis: CHIRALPAK® IE-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.60 mL/min, λ = 254 nm), t_R (major) = 12.82 min, t_R (minor) = 15.84 min.

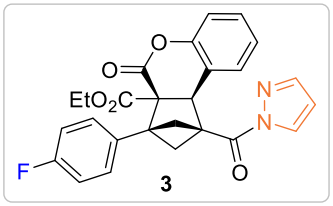
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.0 Hz, 2H), 7.52 – 7.33 (m, 10H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.06 – 6.95 (m, 3H), 6.84 (s, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 4.96 (s, 1H), 4.29 – 4.10 (m, 2H), 3.55 (t, *J* = 8.7 Hz, 1H), 2.52 (d, *J* = 7.8 Hz, 1H), 2.33 (t, *J* = 9.2 Hz, 1H), 2.15 (d, *J* = 8.7 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 169.4, 163.9, 162.3 (d, J = 246.0 Hz), 154.5, 150.7, 147.9, 133.9 (d, J = 3.1 Hz), 131.3, 130.3, 130.2 (d, J = 8.1 Hz), 129.9, 129.8, 129.3, 129.1 (s, 4C), 128.1 (s, 2C), 128.0, 126.2 (s, 2C), 125.0, 118.9, 117.7, 114.5 (d, J = 21.4 Hz), 109.9, 62.3, 60.9, 57.3, 57.0, 53.0, 48.8, 40.8, 14.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.7 (s, 1F).
HRMS (ESI) m/z calcd. for $C_{38}H_{30}FN_2O_5$ $[M+H]^+$ 613.2134, found 613.2133.
HPLC spectrum of ***rac*-2**



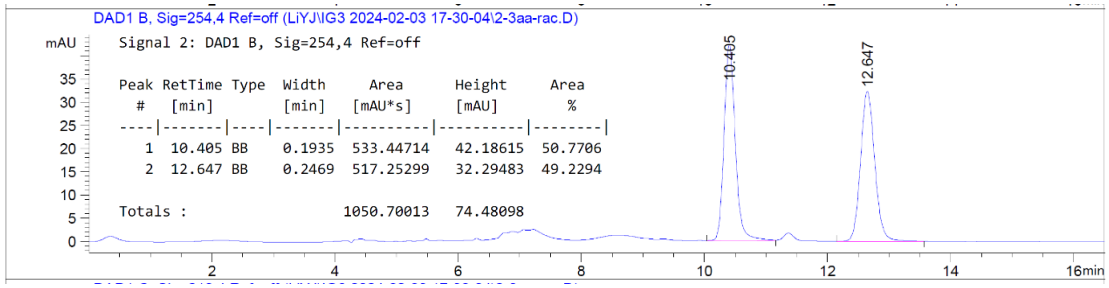
HPLC spectrum of **2:**



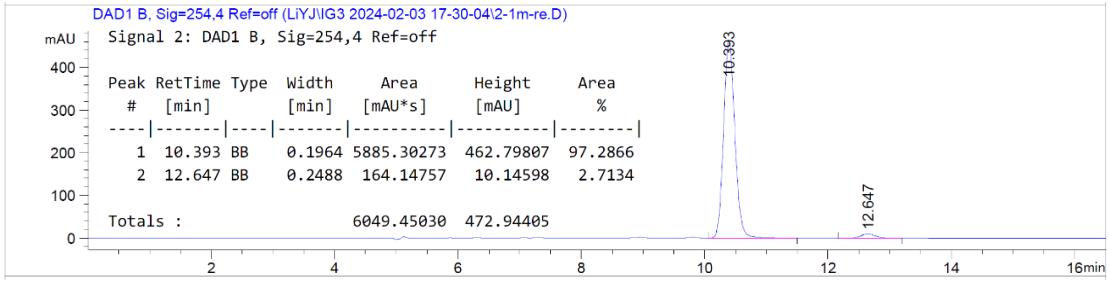


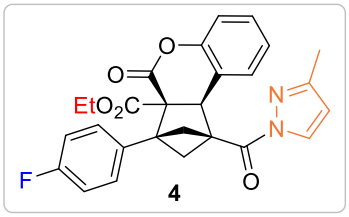
Ethyl (3a*S*,9b*S*)-3-(4-fluorophenyl)-4-oxo-1-(1*H*-pyrazole-1-carbonyl)-1,2,3,9b-tetrahydro-1,3-methanocyclopenta-[*c*]chromene-3a(4*H*)-carboxylate (3)

The title compound was synthesized according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (5-8% EtOAc in *n*-hexane) to afford the desired product **3** (62.2 mg, 68%) as a white solid.
HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 10.39 min, t_R (minor) = 12.65 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 2.8 Hz, 1H), 7.80 (d, J = 0.8 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.29 – 7.23 (m, 1H), 7.14 – 7.07 (m, 1H), 7.06 – 6.91 (m, 3H), 6.53 (dd, J = 2.8, 1.5 Hz, 1H), 6.43 (d, J = 7.2 Hz, 1H), 4.78 (d, J = 1.3 Hz, 1H), 4.27 – 4.10 (m, 2H), 3.39 (dd, J = 9.5, 8.0 Hz, 1H), 2.43 (d, J = 7.8 Hz, 1H), 2.35 (t, J = 9.2 Hz, 1H), 2.19 (dd, J = 8.8, 2.0 Hz, 1H), 1.15 (t, J = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1,168.9, 163.8, 162.2 (d, J = 246.1 Hz), 150.5, 145.1, 133.7 (d, J = 3.2 Hz), 130.1 (d, J = 8.2 Hz), 129.6, 128.7, 127.7, 125.0, 118.5, 117.6, 114.4 (d, J = 21.3 Hz), 110.0, 62.2, 60.6, 57.2, 55.9, 52.6, 48.1, 40.8, 13.9.
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.8 (s, 1F).
HRMS (ESI) m/z calcd. for $C_{26}H_{22}FN_2O_5$ $[M+H]^+$ 461.1507, found 461.1507.
HPLC spectrum of ***rac*-3:**



HPLC spectrum of **3:**





Ethyl (3a*S*,9b*S*)-3-(4-fluorophenyl)-1-(3-methyl-1*H*-pyrazole-1-carbonyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (4)

The title compound was synthesized according to **General Procedure A** at -20 °C for 63 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **4** (54.4 mg, 57%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 11.34 min, t_R (minor) = 12.77 min.

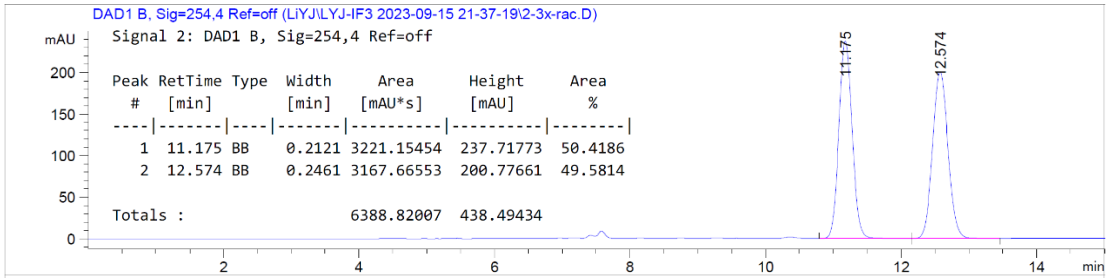
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 2.7 Hz, 1H), 7.35 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.27 (dd, *J* = 11.4, 4.1 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.05 – 6.92 (m, 3H), 6.49 (d, *J* = 7.5 Hz, 1H), 6.31 (d, *J* = 2.7 Hz, 1H), 4.76 (s, 1H), 4.26 – 4.12 (m, 2H), 3.37 (dd, *J* = 9.3, 8.2 Hz, 1H), 2.41 (d, *J* = 7.8 Hz, 1H), 2.38 – 2.28 (m, 4H), 2.17 (dd, *J* = 8.7, 1.7 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 168.5, 163.9, 162.2 (d, *J* = 245.9 Hz), 154.9, 150.6, 133.8 (d, *J* = 3.2 Hz), 130.1 (d, *J* = 8.1 Hz), 129.5, 129.4, 127.9, 125.0, 118.6, 117.5, 114.4 (d, *J* = 21.4 Hz), 110.7, 62.1, 60.7, 57.1, 55.9, 52.6, 48.0, 40.9, 14.2, 13.9.

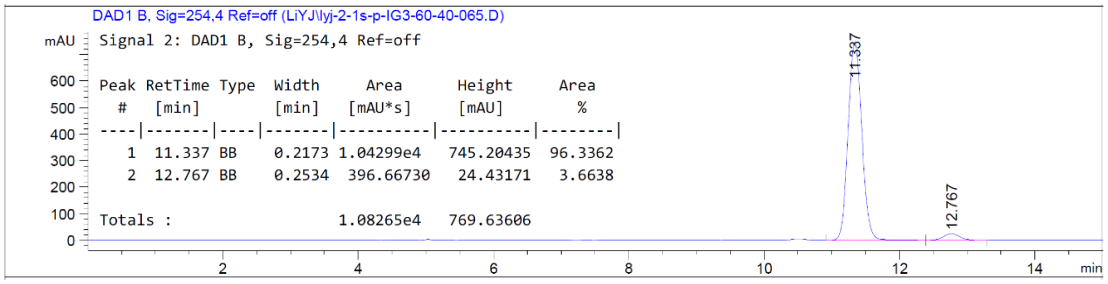
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9 (s, 1F).

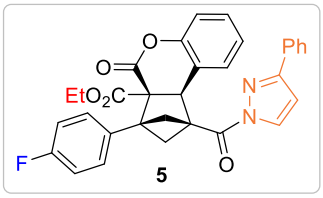
HRMS (ESI) m/z calcd. for $C_{27}H_{24}FN_2O_5$ $[M+H]^+$ 475.1664, found 475.1667.

HPLC spectrum of ***rac*-4:**



HPLC spectrum of **4:**





Ethyl (3a*S*,9b*S*)-3-(4-fluorophenyl)-4-oxo-1-(3-phenyl-1*H*-pyrazole-1-carbonyl)-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (5)

The title compound was synthesized according to **General Procedure A** at -20 °C for 63 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **5** (78.8 mg, 73%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 11.86 min, t_R (minor) = 16.43 min.

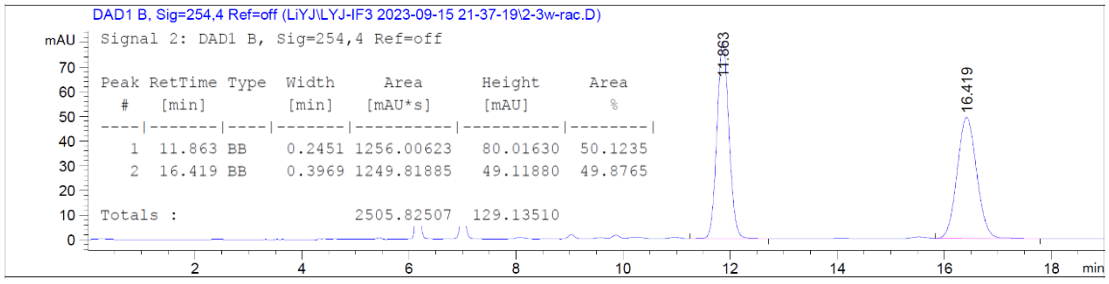
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 2.9 Hz, 1H), 7.85 (d, *J* = 7.0 Hz, 2H), 7.49 – 7.41 (m, 3H), 7.37 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.26 – 7.20 (m, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 8.7 Hz, 2H), 6.94 (t, *J* = 7.1 Hz, 1H), 6.87 (d, *J* = 2.9 Hz, 1H), 6.54 (d, *J* = 7.6 Hz, 1H), 4.88 (s, 1H), 4.29 – 4.13 (m, 2H), 3.56 – 3.46 (m, 1H), 2.49 (d, *J* = 7.8 Hz, 1H), 2.41 (t, *J* = 9.2 Hz, 1H), 2.22 (dd, *J* = 8.7, 1.9 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 168.8, 163.8, 162.2 (d, *J* = 246.2 Hz), 156.3, 150.6, 133.7 (d, *J* = 3.0 Hz), 131.4, 130.1 (d, *J* = 8.2 Hz), 130.0, 129.7 (s, 2C), 129.0 (s, 2C), 127.8, 126.3 (s, 2C), 125.1, 118.5, 117.6, 114.5 (d, *J* = 21.4 Hz), 107.7, 62.3, 60.7, 57.4, 55.9, 52.9, 48.2, 41.0, 14.0.

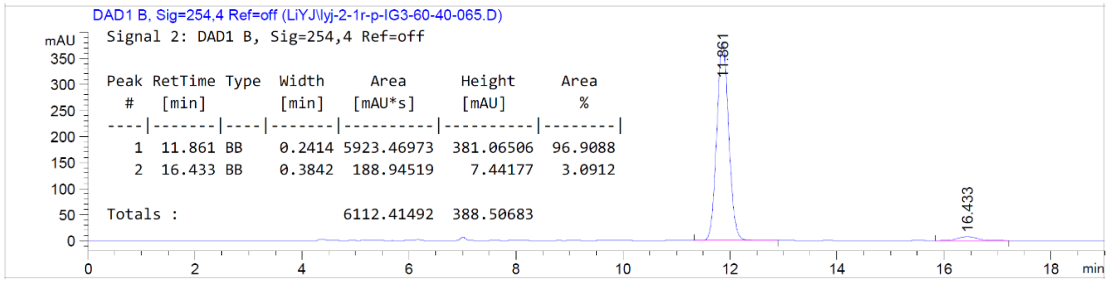
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.7 (s, 1F).

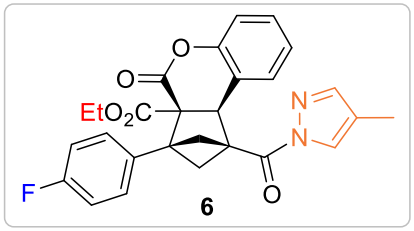
HRMS (ESI) m/z calcd. for $C_{32}H_{26}FN_2O_5$ $[M+H]^+$ 537.1821, found 537.1825.

HPLC spectrum of ***rac*-5:**



HPLC spectrum of **5:**





Ethyl (3a*S*,9b*S*)-3-(4-fluorophenyl)-1-(4-methyl-1*H*-pyrazole-1-carbonyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (6)

The title compound was synthesized according to **General Procedure A** at 0 °C for 60 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **6** (60.5 mg, 64%) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 70/30, flow rate = 0.55 mL/min, λ = 254 nm), t_R (major) = 10.12 min, t_R (minor) = 13.81 min.

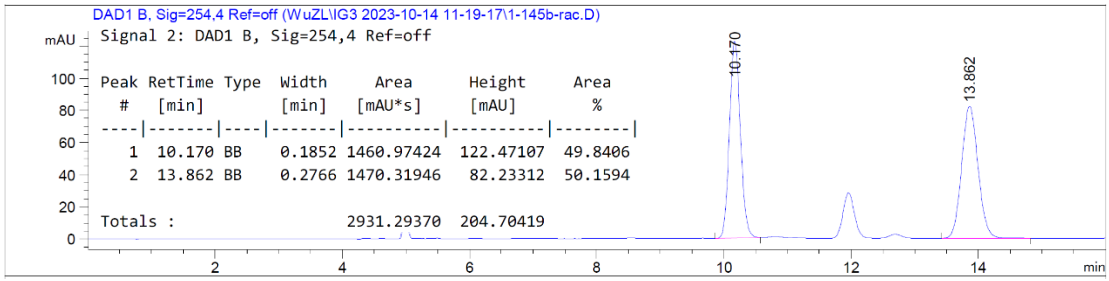
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.61 (s, 1H), 7.34 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.98 (dd, *J* = 17.5, 8.5 Hz, 3H), 6.47 (d, *J* = 7.5 Hz, 1H), 4.75 (s, 1H), 4.17 (M, 2H), 3.40 – 3.29 (m, 1H), 2.40 (d, *J* = 7.8 Hz, 1H), 2.32 (t, *J* = 9.2 Hz, 1H), 2.20 – 2.10 (m, 4H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 168.5, 163.8, 162.2 (d, *J* = 246.0 Hz), 150.5, 146.7, 133.8 (d, *J* = 3.1 Hz), 130.1 (d, *J* = 8.1 Hz), 129.6, 127.8, 126.4, 125.0, 120.9, 118.6, 117.5, 114.4 (d, *J* = 21.3 Hz), 62.1, 60.6, 57.1, 55.8, 52.6, 48.1, 40.7, 13.9, 9.0.

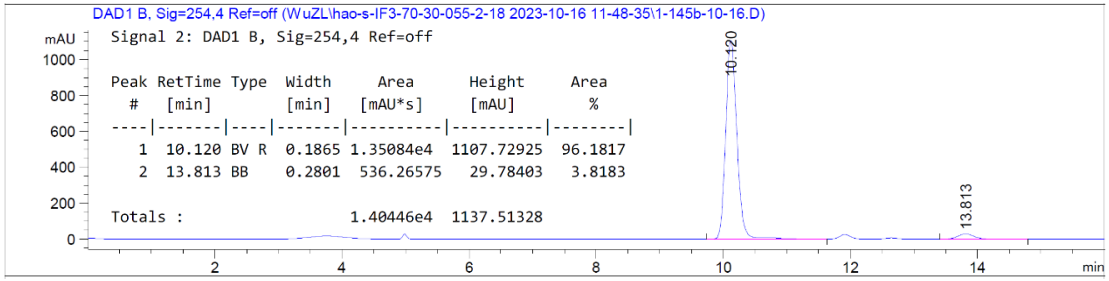
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9 (s, 1F).

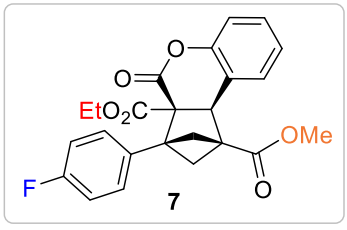
HRMS (ESI) m/z calcd. for $C_{27}H_{24}FN_2O_5$ $[M+H]^+$ 475.1664, found 475.1668.

HPLC spectrum of ***rac*-6:**



HPLC spectrum of **6:**



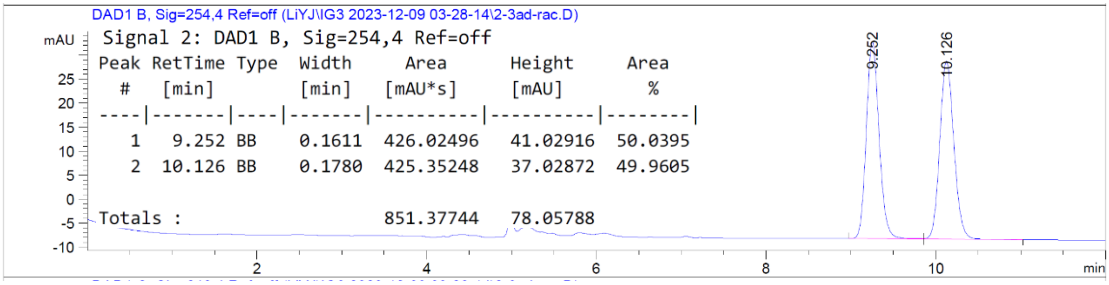


3a-ethyl 1-methyl (3a*S*,9b*S*)-3-(4-fluorophenyl)-4-oxo-2,3-dihydro-1,3-methanocyclopenta[*c*]chromene-1,3a(4*H*,9b*H*)-dicarboxylate (7)

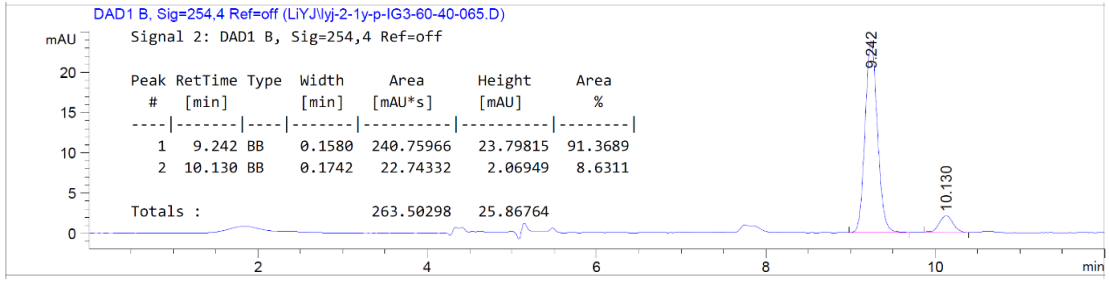
The title compound was synthesized according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (4-6% EtOAc in *n*-hexane) to afford the desired product **7** (51.9 mg, 61%) as a white solid.

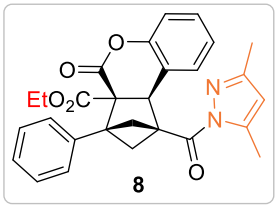
HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 9.24 min, t_R (minor) = 10.13 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 4H), 7.19 – 7.08 (m, 2H), 7.04 – 6.94 (m, 2H), 4.21 – 4.09 (m, 3H), 3.72 (s, 3H), 2.97 (dd, *J* = 8.8, 8.1 Hz, 1H), 2.25 (d, *J* = 7.6 Hz, 1H), 2.20 – 2.05 (m, 2H), 1.15 (t, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 169.0, 163.7, 162.2 (d, *J* = 246.3 Hz), 150.5, 133.5 (d, *J* = 3.3 Hz), 129.9 (d, *J* = 8.1 Hz), 129.7, 128.8, 124.9, 118.6, 117.5, 114.4 (d, *J* = 21.3 Hz), 62.2, 60.3, 57.5, 53.7, 51.9, 51.2, 46.4, 39.8, 13.9.
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.8 (s, 1F).
HRMS (ESI) m/z calcd. for $C_{24}H_{22}FO_6$ $[M+H]^+$ 425.1395, found 425.1396.
HPLC spectrum of ***rac*-7:**



HPLC spectrum of **7:**

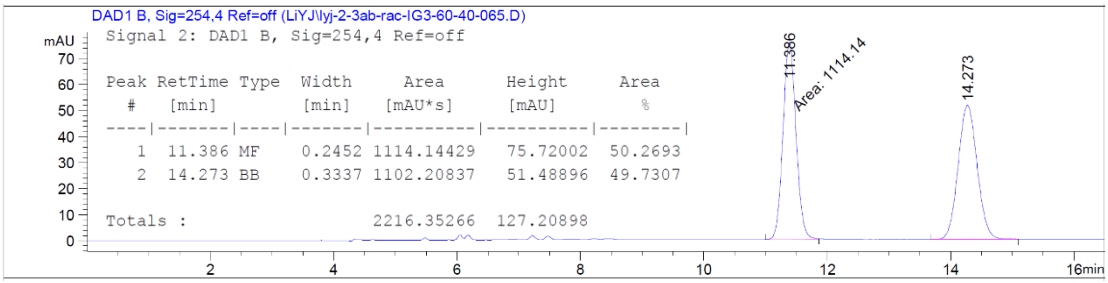




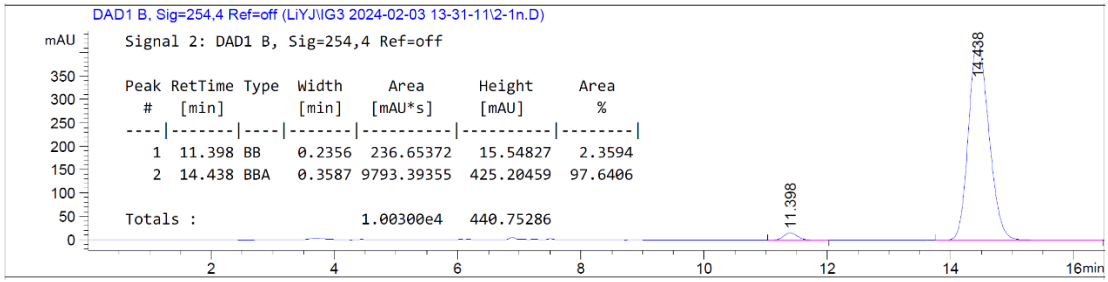
8

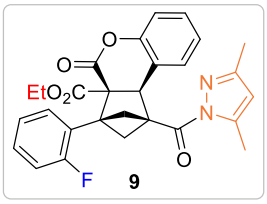
Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-4-oxo-3-phenyl-1,2,3,9b-tetrahydro-1,3-methanocyclopenta-[*c*]chromene-3a(4*H*)-carboxylate (8)

The title compound was synthesized according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **8** (88.3 mg, 94%) as a white solid.
HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 11.40 min, t_R (major) = 14.44 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 6.8 Hz, 2H), 7.35 – 7.21 (m, 4H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.96 (td, *J* = 7.6, 1.0 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 6.03 (s, 1H), 4.78 (s, 1H), 4.17 (qd, *J* = 7.1, 1.3 Hz, 2H), 3.38 (dd, *J* = 9.3, 8.2 Hz, 1H), 2.51 (s, 3H), 2.41 (d, *J* = 7.8 Hz, 1H), 2.32 (t, *J* = 9.2 Hz, 1H), 2.24 (s, 3H), 2.14 (dd, *J* = 8.7, 1.9 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.3, 163.9, 153.1, 150.7, 144.3, 138.2, 129.4, 128.4, 127.8, 127.5, 127.4, 124.8, 119.0, 117.5, 111.2, 62.0, 60.9, 57.3, 57.2, 52.6, 48.2, 40.8, 14.3, 14.1, 13.9.
HRMS (ESI) m/z calcd. for $C_{28}H_{27}N_2O_5$ $[M+H]^+$ 471.1915, found 471.1916.
HPLC spectrum of ***rac*-8:**



HPLC spectrum of **8:**





9

Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(2-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (9)

The title compound was synthesized according to **General Procedure A** at -20 °C for 72 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **9** (86.0 mg, 88%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 11.77 min, t_R (minor) = 12.56 min.

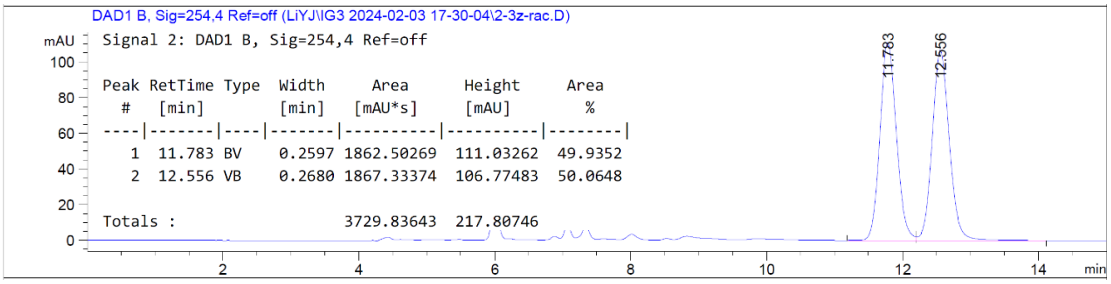
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (td, *J* = 7.7, 1.7 Hz, 1H), 7.31 – 7.22 (m, 2H), 7.17 – 7.07 (m, 2H), 7.06 – 6.93 (m, 2H), 6.50 (d, *J* = 7.1 Hz, 1H), 6.04 (d, *J* = 0.5 Hz, 1H), 4.81 (d, *J* = 1.7 Hz, 1H), 4.25 – 4.12 (m, 2H), 3.28 (dd, *J* = 9.4, 8.2 Hz, 1H), 2.52 (d, *J* = 0.6 Hz, 3H), 2.50 – 2.42 (m, 2H), 2.28 – 2.19 (m, 4H), 1.22 – 1.14 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.0, 164.0, 161.9 (d, *J* = 247.8 Hz), 153.1, 150.8, 144.3, 131.2 (d, *J* = 4.2 Hz), 129.4 (d, *J* = 8.8 Hz), 129.3, 127.7, 125.0 (d, *J* = 13.6 Hz), 124.7, 123.2 (d, *J* = 3.2 Hz), 119.0, 117.6, 115.2 (d, *J* = 22.3 Hz), 111.2, 62.0, 60.5, 57.7, 54.2, 51.8, 48.4, 41.8, 14.2, 14.0, 13.9.

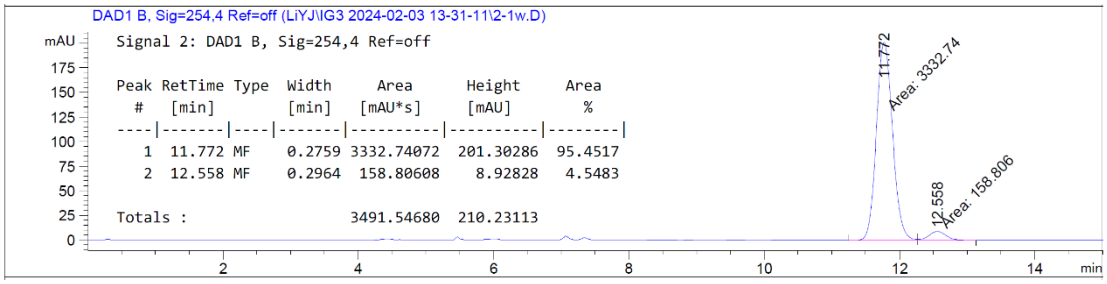
^{19}F NMR (376 MHz, $CDCl_3$) δ -112.0 (s, 1F).

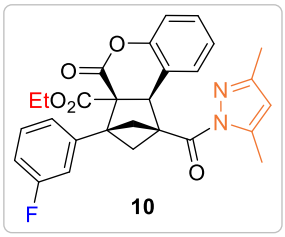
HRMS (ESI) m/z calcd. for $C_{28}H_{26}FN_2O_5$ $[M+H]^+$ 489.1821, found 489.1821.

HPLC spectrum of ***rac*-9:**



HPLC spectrum of **9:**





Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(3-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (10)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 60 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **10** (65.2 mg, 67%) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 70/30, flow rate = 0.55 mL/min, λ = 254 nm), t_R (major) = 10.70 min, t_R (minor) = 11.39 min.

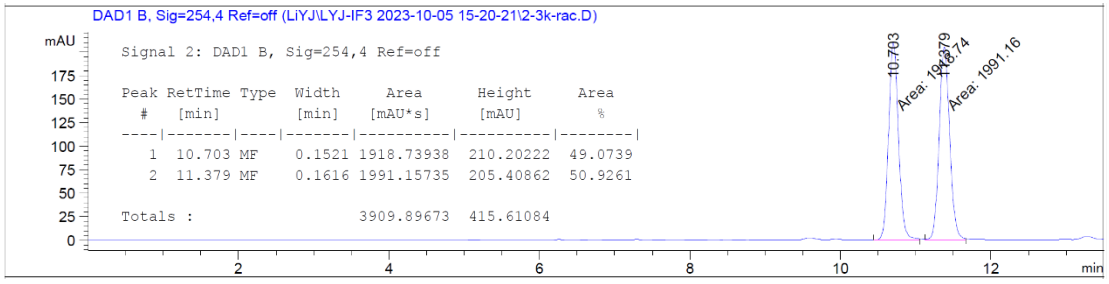
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 7.18 – 7.06 (m, 3H), 7.01 – 6.93 (m, 2H), 6.48 (d, *J* = 7.2 Hz, 1H), 6.04 (s, 1H), 4.76 (d, *J* = 1.2 Hz, 1H), 4.24 – 4.14 (m, 2H), 3.36 (dd, *J* = 9.5, 8.0 Hz, 1H), 2.51 (s, 3H), 2.40 (d, *J* = 7.8 Hz, 1H), 2.29 (t, *J* = 9.2 Hz, 1H), 2.25 (s, 3H), 2.14 (dd, *J* = 8.7, 1.9 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.2, 163.8, 162.1 (d, *J* = 244.8 Hz), 153.2, 150.6, 144.3, 140.7 (d, *J* = 7.6 Hz), 129.5, 128.8 (d, *J* = 8.1 Hz), 127.8, 124.9, 124.1 (d, *J* = 2.8 Hz), 118.8, 117.5, 115.6 (d, *J* = 22.0 Hz), 114.3 (d, *J* = 21.0 Hz), 111.2, 62.1, 60.9, 57.0, 56.8, 52.5, 48.2, 40.8, 14.2, 14.0, 13.9.

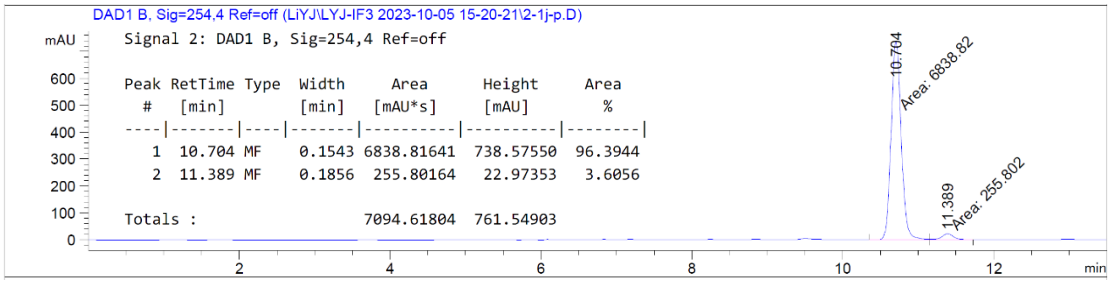
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.0 (s, 1F).

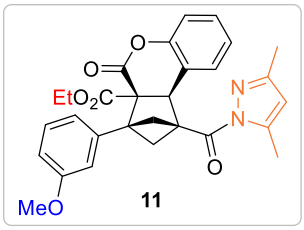
HRMS (ESI) m/z calcd. for $C_{28}H_{26}FN_2O_5$ $[M+H]^+$ 489.1821, found 489.1823.

HPLC spectrum of ***rac*-10:**



HPLC spectrum of **10:**





Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(3-methoxyphenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (11)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 60 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **11** (64.6 mg, 65%) as a white solid.

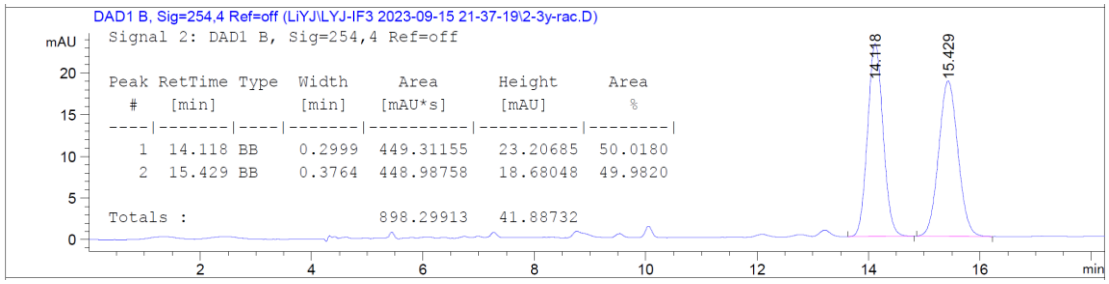
HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 14.17 min, t_R (major) = 15.44 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.03 – 6.90 (m, 3H), 6.83 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.47 (d, *J* = 7.2 Hz, 1H), 6.03 (s, 1H), 4.77 (d, *J* = 1.1 Hz, 1H), 4.19 (qd, *J* = 7.1, 2.8 Hz, 2H), 3.81 (s, 3H), 3.38 (dd, *J* = 9.4, 8.0 Hz, 1H), 2.51 (s, 3H), 2.41 (d, *J* = 7.8 Hz, 1H), 2.30 (t, *J* = 9.2 Hz, 1H), 2.25 (s, 3H), 2.15 (dd, *J* = 8.8, 1.9 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H).

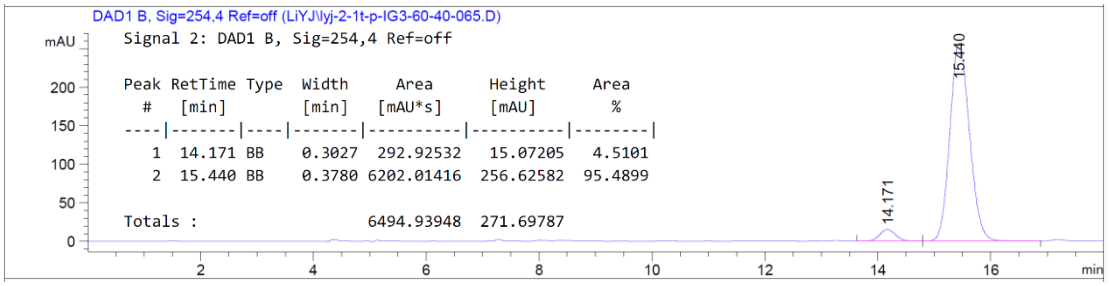
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.3, 163.9, 158.8, 153.1, 150.7, 144.3, 139.7, 129.4, 128.4, 127.8, 124.7, 120.8, 119.0, 117.5, 114.2, 113.0, 111.2, 62.0, 60.9, 57.4, 56.9, 55.2, 52.6, 48.2, 40.8, 14.2, 14.1, 13.9.

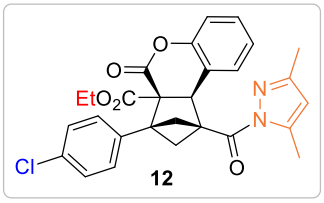
HRMS (ESI) m/z calcd. for $C_{29}H_{29}N_2O_6$ $[M+H]^+$ 501.2020, found 501.2021.

HPLC spectrum of ***rac*-11:**



HPLC spectrum of **11:**





Ethyl (3a*S*,9b*S*)-3-(4-chlorophenyl)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (12)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 62 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **12** (93.1 mg, 92%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65

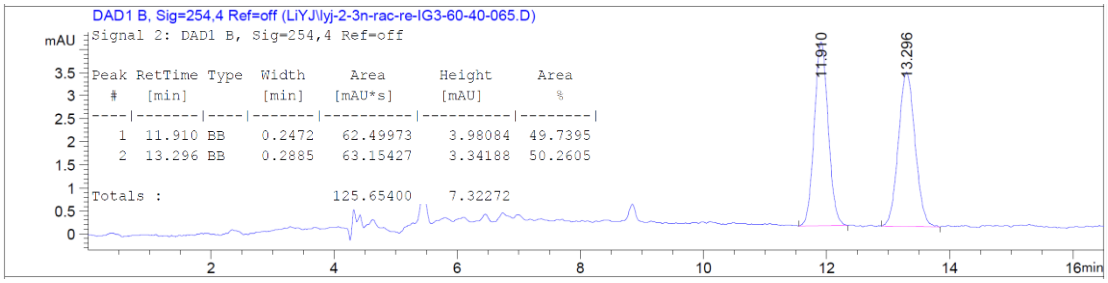
mL/min, λ = 254 nm), t_R (minor) = 11.71 min, t_R (major) = 12.98 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 5H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.97 (td, *J* = 7.6, 1.1 Hz, 1H), 6.48 (d, *J* = 7.1 Hz, 1H), 6.04 (s, 1H), 4.75 (d, *J* = 1.3 Hz, 1H), 4.25 – 4.12 (m, 2H), 3.34 (dd, *J* = 9.5, 8.0 Hz, 1H), 2.51 (d, *J* = 0.4 Hz, 3H), 2.40 (d, *J* = 7.9 Hz, 1H), 2.29 (t, *J* = 9.2 Hz, 1H), 2.25 (s, 3H), 2.11 (dd, *J* = 8.7, 2.0 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

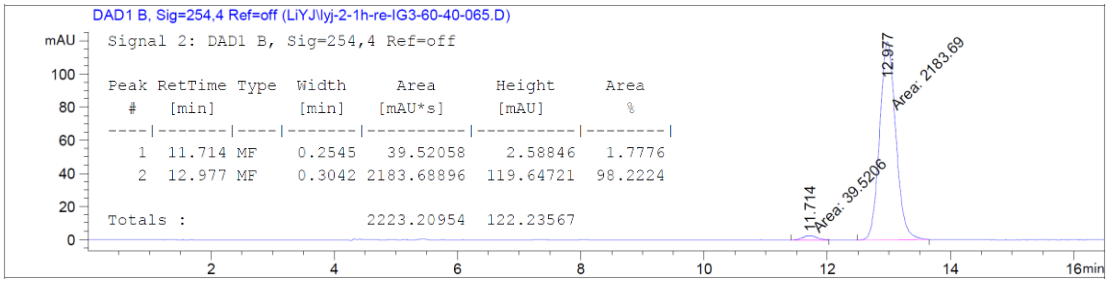
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 169.2, 163.9, 153.2, 150.6, 144.3, 136.7, 133.3, 129.8, 129.5, 127.8, 127.7, 124.9, 118.8, 117.5, 111.2, 62.1, 60.8, 57.1, 56.6, 52.4, 48.2, 40.8, 14.2, 14.0, 13.9.

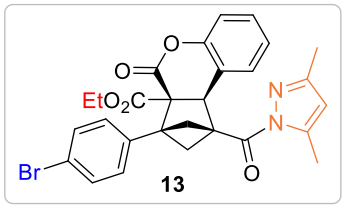
HRMS (ESI) m/z calcd. for $C_{28}H_{26}ClN_2O_5$ $[M+H]^+$ 505.1525, found 505.1525.

HPLC spectrum of ***rac*-12:**



HPLC spectrum of **12:**





13

Ethyl (3a*S*,9b*S*)-3-(4-bromophenyl)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (13)

The title compound was synthesized according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **13** (101.9 mg, 93%) as a white solid.

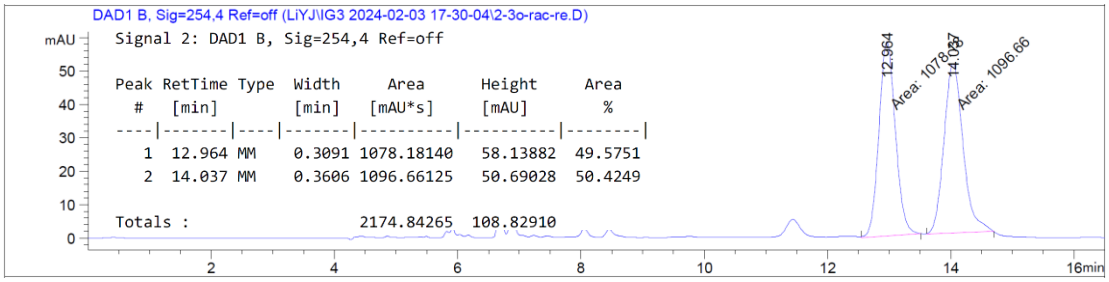
HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 13.00 min, t_R (major) = 14.08 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 7.29 – 7.23 (m, 3H), 7.13 – 7.06 (m, 1H), 6.97 (td, *J* = 7.6, 1.1 Hz, 1H), 6.48 (d, *J* = 7.1 Hz, 1H), 6.04 (s, 1H), 4.74 (d, *J* = 1.3 Hz, 1H), 4.26 – 4.11 (m, 2H), 3.34 (dd, *J* = 9.5, 8.0 Hz, 1H), 2.51 (d, *J* = 0.4 Hz, 3H), 2.39 (d, *J* = 7.9 Hz, 1H), 2.32 – 2.26 (m, 1H), 2.25 (s, 3H), 2.11 (dd, *J* = 8.7, 2.0 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

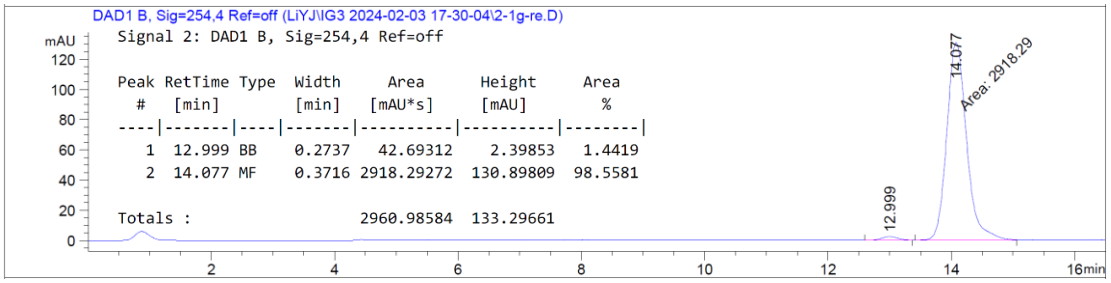
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.1, 163.9, 153.2, 150.6, 144.3, 137.2, 130.6, 130.2, 129.5, 127.8, 124.9, 121.6, 118.8, 117.5, 111.2, 62.1, 60.7, 57.1, 56.6, 52.4, 48.1, 40.7, 14.2, 14.0, 13.9.

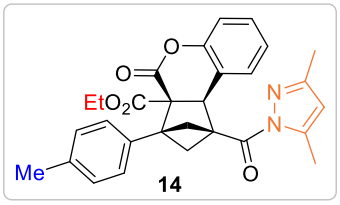
HRMS (ESI) m/z calcd. for $C_{28}H_{26}BrN_2O_5$ $[M+H]^+$ 549.1020, found 549.1020.

HPLC spectrum of ***rac*-13:**



HPLC spectrum of **13:**





Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-4-oxo-3-(*p*-tolyl)-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (14)

The title compound was synthesized according to **General Procedure A** at -20 °C for 72 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **14** (78.8 mg, 81%) as a white solid.

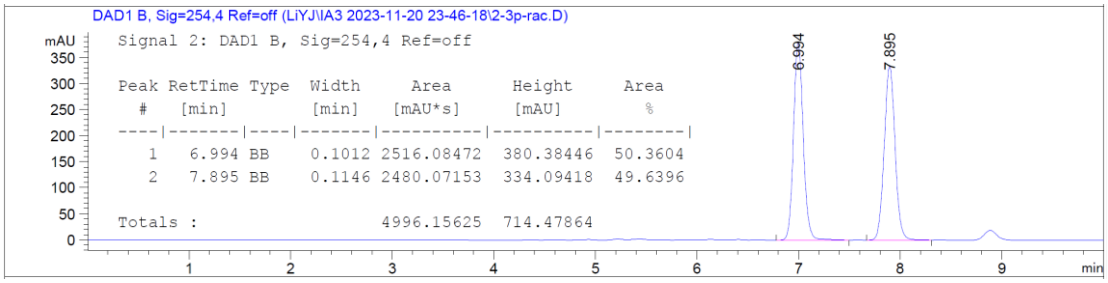
HPLC analysis: CHIRALPAK® IA-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 6.98 min, t_R (major) = 7.87 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 3H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.00 – 6.93 (m, 1H), 6.47 (d, *J* = 7.6 Hz, 1H), 6.03 (s, 1H), 4.76 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.44 – 3.29 (m, 1H), 2.51 (s, 3H), 2.40 (d, *J* = 7.8 Hz, 1H), 2.36 – 2.27 (m, 4H), 2.25 (s, 3H), 2.12 (dd, *J* = 8.8, 1.9 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

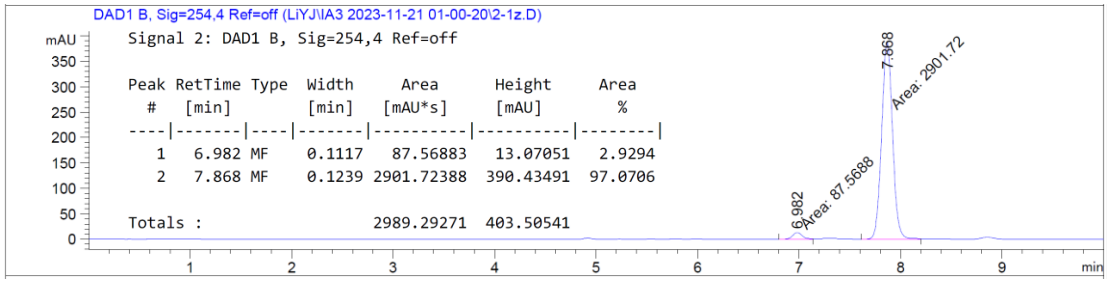
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 169.3, 164.0, 153.1, 150.7, 144.3, 137.0, 135.2, 129.4, 128.3, 128.2, 127.8, 124.7, 119.1, 117.5, 111.2, 61.9, 60.8, 57.2, 57.1, 52.6, 48.3, 40.8, 21.3, 14.3, 14.1, 13.9.

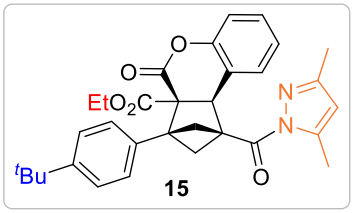
HRMS (ESI) m/z calcd. for $C_{29}H_{29}N_2O_5$ $[M+H]^+$ 485.2071, found 485.2072.

HPLC spectrum of ***rac*-14:**



HPLC spectrum of **14:**





Ethyl (3a*S*,9b*S*)-3-(4-(*tert*-butyl)phenyl)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (15)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 72 h. The product was purified by silica gel flash column chromatography (4-6% EtOAc in *n*-hexane) to afford the desired product **15** (45.4 mg, 43%) as a white solid.

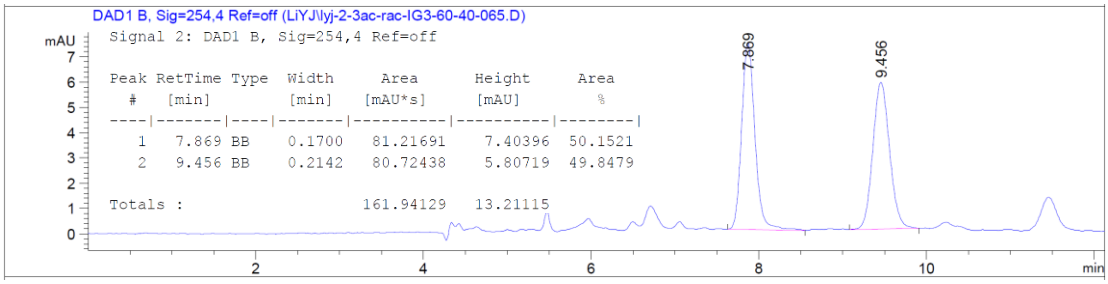
HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 7.89 min, t_R (minor) = 9.48 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 5H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.46 (d, *J* = 7.6 Hz, 1H), 6.03 (s, 1H), 4.76 (s, 1H), 4.25 – 4.12 (m, 2H), 3.39 – 3.29 (m, 1H), 2.51 (s, 3H), 2.42 (d, *J* = 7.8 Hz, 1H), 2.30 (t, *J* = 9.2 Hz, 1H), 2.26 (s, 3H), 2.13 (dd, *J* = 8.8, 1.8 Hz, 1H), 1.33 (s, 9H), 1.18 (t, *J* = 7.1 Hz, 3H).

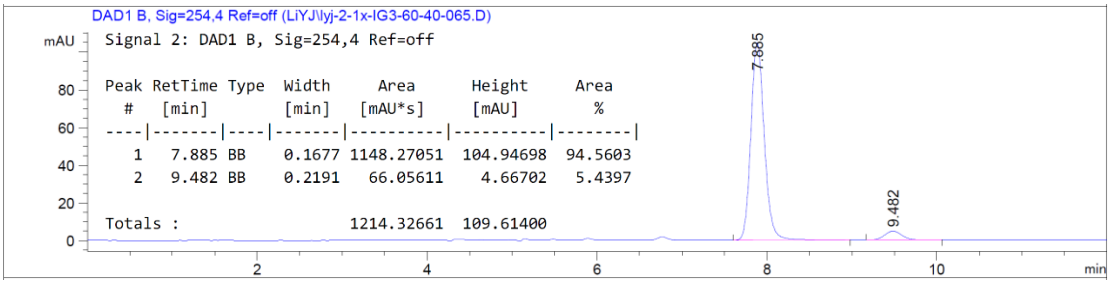
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 169.3, 164.0, 153.0, 150.7, 149.9, 144.3, 135.1, 129.3, 128.0, 127.7, 124.7, 124.4, 119.1, 117.5, 111.1, 61.9, 60.8, 57.2, 57.1, 52.5, 48.3, 40.8, 34.5, 31.4, 14.2, 14.1, 13.9.

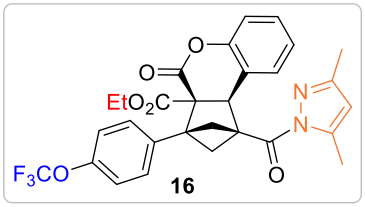
HRMS (ESI) m/z calcd. for $C_{32}H_{38}N_3O_5$ $[M+NH_4]^+$ 544.2806, found 544.2809.

HPLC spectrum of ***rac*-15:**



HPLC spectrum of **15:**





Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-4-oxo-3-(4- (trifluoromethoxy)phenyl)-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]-chromene-3a(4*H*)-carboxylate (16)

The title compound was synthesized on a 1.9 mmol scale according to **General Procedure A** at -20 °C for 48 h. The product was purified by silica gel flash column chromatography (4-6% EtOAc in *n*-hexane) to afford the desired product **16** (963.0 mg, 96%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 7.84 min, t_R (minor) = 8.51 min.

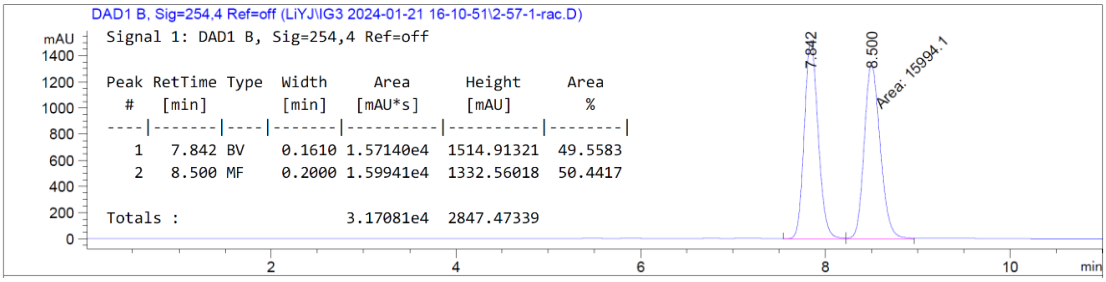
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H), 7.30 – 7.24 (m, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.10 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 6.48 (d, *J* = 7.0 Hz, 1H), 6.04 (d, *J* = 0.7 Hz, 1H), 4.75 (d, *J* = 1.4 Hz, 1H), 4.19 (qd, *J* = 7.1, 2.0 Hz, 2H), 3.34 (dd, *J* = 9.5, 8.0 Hz, 1H), 2.52 (d, *J* = 0.7 Hz, 3H), 2.41 (d, *J* = 7.8 Hz, 1H), 2.30 (t, *J* = 9.2 Hz, 1H), 2.26 (s, 3H), 2.13 (dd, *J* = 8.7, 2.0 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.1, 163.9, 153.2, 150.6, 148.4, 144.3, 136.8, 129.9, 129.5, 127.8, 124.9, 120.5 (d, *J* = 257.7 Hz), 119.8, 118.8, 117.5, 111.2, 62.1, 60.7, 57.1, 56.5, 52.4, 48.2, 40.8, 14.2, 14.1, 13.9.

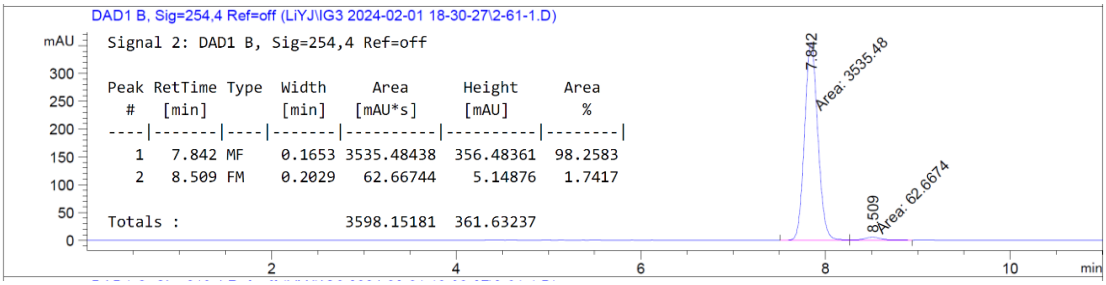
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.6 (s, 3F).

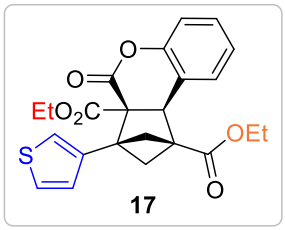
HRMS (ESI) m/z calcd. for $C_{29}H_{26}F_3N_2O_6$ $[M+H]^+$ 555.1738, found 555.1742.

HPLC spectrum of ***rac*-16:**



HPLC spectrum of **16:**





Diethyl (3a*S*,9b*S*)-4-oxo-3-(thiophen-3-yl)-2,3-dihydro-1,3-methanocyclopenta[*c*]chromene-1,3a(4*H*,9b*H*)-dicarboxylate (17)

The title compound was synthesized according to **General Procedure A** at -20 °C for 72 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **17** (59.7 mg, 70%) as a white solid.

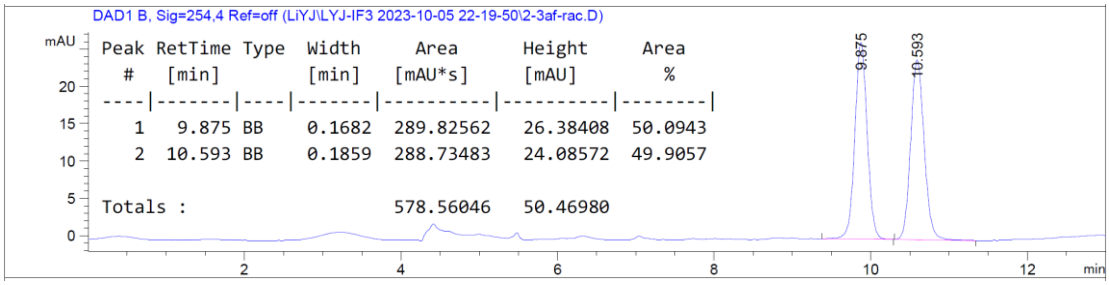
HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 10.21 min, t_R (minor) = 11.01 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 2H), 7.25 – 7.17 (m, 2H), 7.16 – 7.07 (m, 3H), 4.25 – 4.11 (m, 4H), 4.08 (d, *J* = 1.1 Hz, 1H), 2.90 (dd, *J* = 9.5, 7.8 Hz, 1H), 2.24 (d, *J* = 7.6 Hz, 1H), 2.18 (dd, *J* = 8.6, 1.9 Hz, 1H), 2.08 (t, *J* = 9.2 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H).

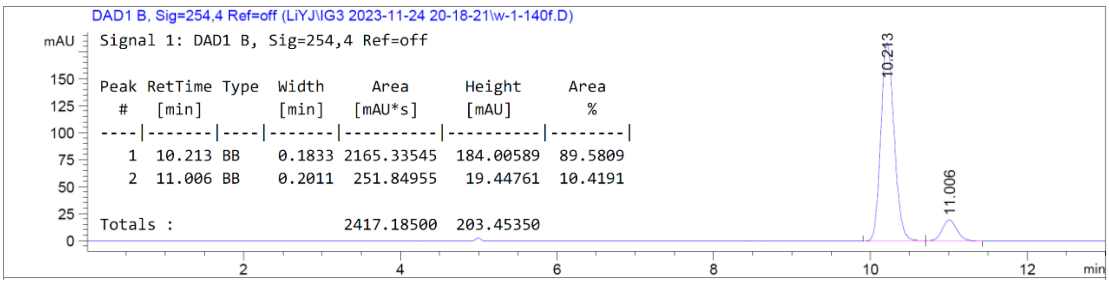
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.2, 163.8, 150.5, 138.7, 129.6, 129.0, 127.9, 124.8, 124.4, 123.6, 118.6, 117.4, 62.1, 61.0, 60.1, 54.7, 54.3, 51.0, 47.2, 40.0, 14.2, 13.9.

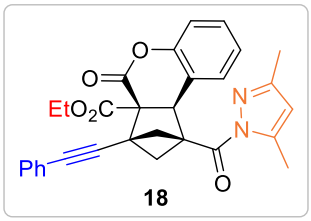
HRMS (ESI) m/z calcd. for $C_{23}H_{23}O_6S$ $[M+H]^+$ 427.1210, found 427.1213.

HPLC spectrum of ***rac*-17:**



HPLC spectrum of **17:**





18

Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-4-oxo-3-(phenylethynyl)-1,2,3,9b-tetrahydro-1,3-methano-cyclopenta[*c*]chromene-3a(4*H*)-carboxylate (18)

The title compound was synthesized according to **General Procedure A** at -20 °C for 72 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **18** (90.1 mg, 91%) as a white solid.

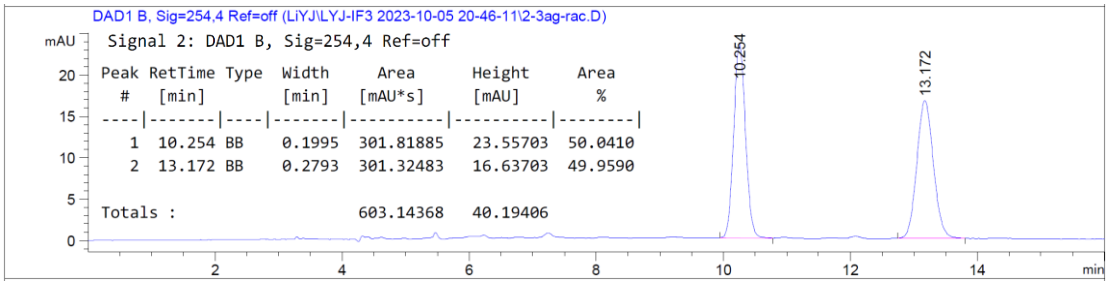
HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 10.65 min, t_R (minor) = 14.02 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.44 (m, 2H), 7.36 – 7.20 (m, 4H), 7.12 – 7.05 (m, 1H), 6.95 (td, *J* = 7.6, 1.1 Hz, 1H), 6.45 (d, *J* = 7.1 Hz, 1H), 6.02 (d, *J* = 0.5 Hz, 1H), 4.61 (d, *J* = 1.3 Hz, 1H), 4.37 – 4.23 (m, 2H), 2.97 (dd, *J* = 9.4, 8.1 Hz, 1H), 2.57 (d, *J* = 7.9 Hz, 1H), 2.51 (d, *J* = 0.4 Hz, 3H), 2.28 (dd, *J* = 8.8, 1.9 Hz, 1H), 2.21 (s, 3H), 2.12 (t, *J* = 9.2 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

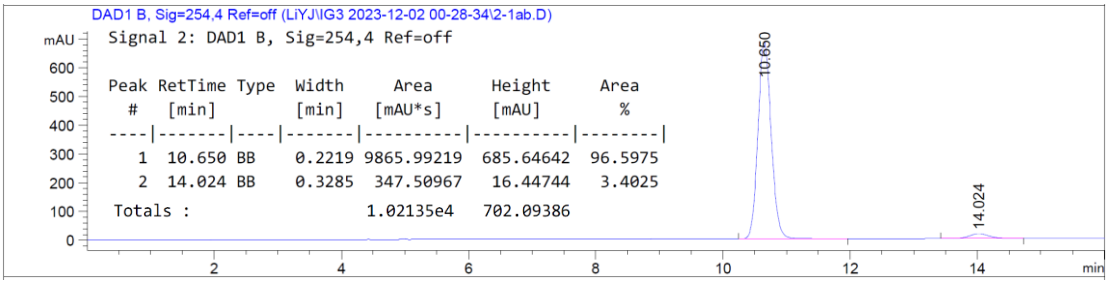
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 168.5, 163.4, 153.3, 150.5, 144.3, 132.0, 129.5, 128.1, 127.8, 124.8, 123.1, 118.4, 117.5, 111.3, 86.1, 84.8, 62.2, 60.1, 57.9, 50.6, 50.4, 45.4, 42.8, 14.2, 14.0.

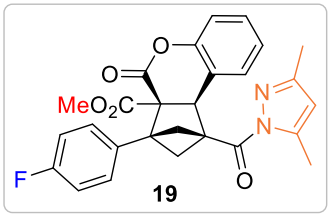
HRMS (ESI) m/z calcd. for $C_{30}H_{27}N_2O_5$ $[M+H]^+$ 495.1915, found 495.1915.

HPLC spectrum of ***rac*-18:**



HPLC spectrum of **18:**





19

Methyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (19)

The title compound was synthesized according to **General Procedure A** at -20 °C for 48 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **19** (80.8 mg, 85%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 75/25, flow rate = 0.60 mL/min, λ = 254 nm), t_R (minor) = 17.09 min, t_R (major) = 18.47 min.

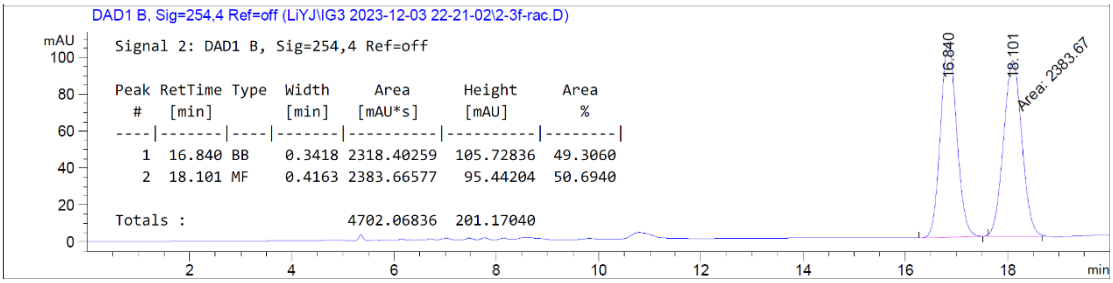
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 2H), 7.29 – 7.22 (m, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 7.04 – 6.93 (m, 3H), 6.48 (d, *J* = 7.5 Hz, 1H), 6.04 (s, 1H), 4.74 (s, 1H), 3.69 (s, 3H), 3.35 (dd, *J* = 9.4, 8.2 Hz, 1H), 2.51 (s, 3H), 2.40 (d, *J* = 7.9 Hz, 1H), 2.30 (t, 3H), 2.26 (s, 3H), 2.12 (dd, *J* = 8.8, 1.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 169.7, 164.0, 162.2 (d, *J* = 246.0 Hz), 153.3, 150.5, 144.3, 133.9 (d, *J* = 3.1 Hz), 130.1 (d, *J* = 8.1 Hz), 129.5, 127.9, 124.9, 118.8, 117.5, 114.4 (d, *J* = 21.3 Hz), 111.3, 60.6, 57.1, 56.6, 52.9, 52.4, 48.2, 40.7, 14.2, 14.1.

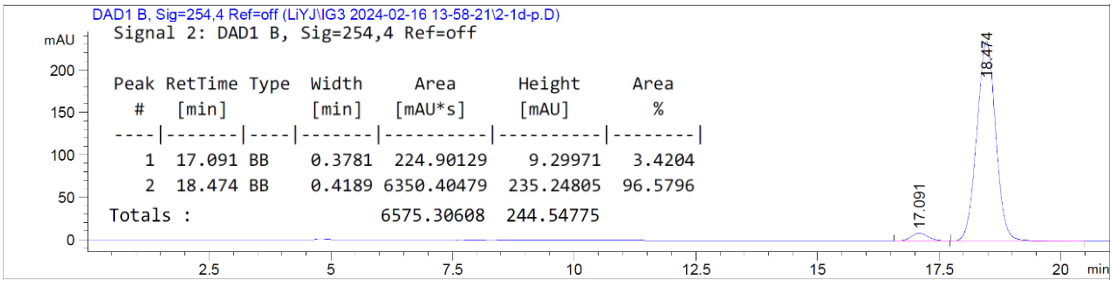
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9 (s, 1F).

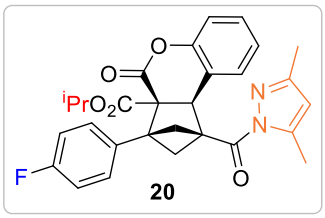
HRMS (ESI) m/z calcd. for $C_{27}H_{24}FN_2O_5$ $[M+H]^+$ 475.1664, found 475.1667.

HPLC spectrum of ***rac*-19:**



HPLC spectrum of **19:**





Isopropyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (20)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 48 h. The product was purified by silica gel flash column chromatography (4-6% EtOAc in *n*-hexane) to afford the desired product **20** (88.0 mg, 88%) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 90/10, flow rate = 0.50 mL/min, λ = 254 nm), t_R (minor) = 17.28 min, t_R (major) = 17.94 min.

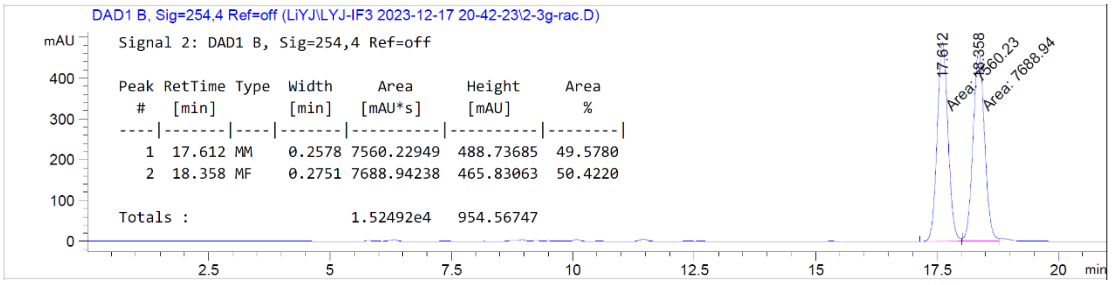
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H), 7.26 (t, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.04 – 6.93 (m, 3H), 6.48 (d, *J* = 7.4 Hz, 1H), 6.04 (s, 1H), 5.14 – 4.99 (m, 1H), 4.76 (s, 1H), 3.33 (t, *J* = 8.6 Hz, 1H), 2.51 (s, 3H), 2.40 (d, *J* = 7.7 Hz, 1H), 2.29 (t, 1H), 2.24 (s, 3H), 2.11 (d, *J* = 8.4 Hz, 1H), 1.17 (dd, *J* = 15.5, 6.1 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 168.8, 164.0, 162.1 (d, *J* = 245.6 Hz), 153.1, 150.6, 144.3, 134.1 (d, *J* = 3.0 Hz), 130.1 (d, *J* = 8.1 Hz), 129.4, 127.7, 124.8, 119.0, 117.4, 114.3 (d, *J* = 21.3 Hz), 111.2, 69.9, 61.0, 57.0, 56.5, 52.4, 48.2, 40.8, 21.4, 21.3, 14.2, 14.0.

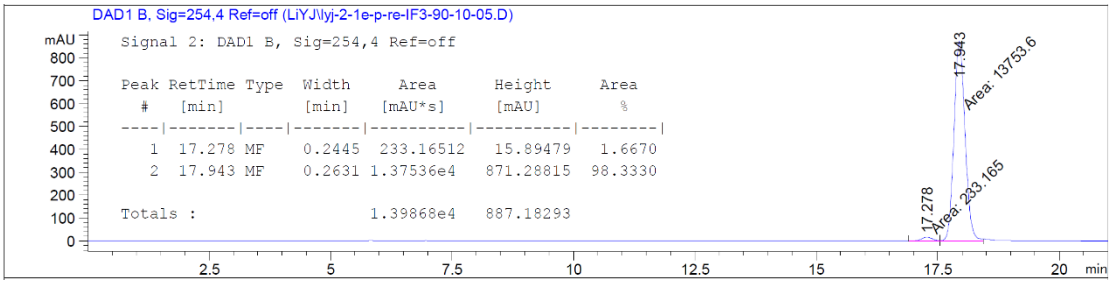
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.1 (s, 1F).

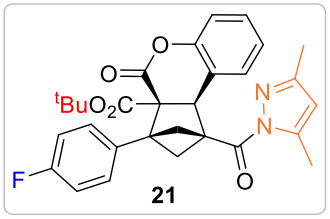
HRMS (ESI) m/z calcd. for $C_{29}H_{28}FN_2O_5$ $[M+H]^+$ 503.1977, found 503.1979.

HPLC spectrum of ***rac*-20:**



HPLC spectrum of **20:**





***Tert*-butyl (3a*R*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (21)**

The title compound was synthesized according to **General Procedure A** at -20 °C for 68 h. The product was purified by silica gel flash column chromatography (4-6% EtOAc in *n*-hexane) to afford the desired product **21** (43.4 mg, 42%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 75/25, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 12.97 min, t_R (minor) = 14.08 min.

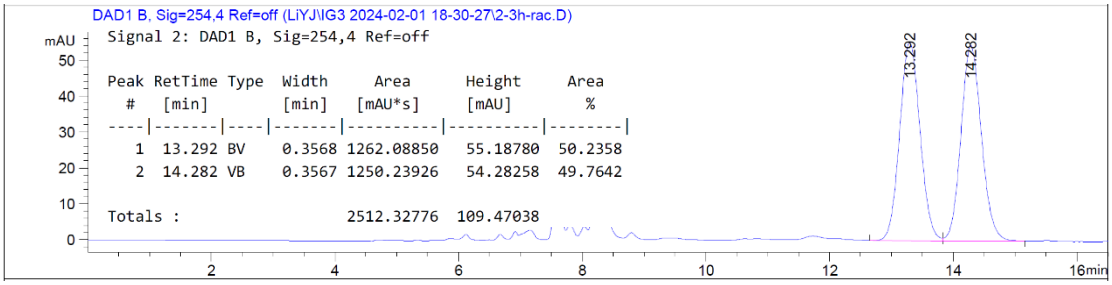
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.28 – 7.21 (m, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 7.03 – 6.93 (m, 3H), 6.47 (d, *J* = 7.5 Hz, 1H), 6.04 (s, 1H), 4.77 (s, 1H), 3.31 (dd, *J* = 9.2, 8.1 Hz, 1H), 2.52 (s, 3H), 2.38 (d, *J* = 7.7 Hz, 1H), 2.30 – 2.20 (m, 4H), 2.09 (dd, *J* = 8.6, 1.6 Hz, 1H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 168.2, 164.2, 162.1 (d, *J* = 245.8 Hz), 153.0, 150.6, 144.3, 134.2 (d, *J* = 3.2 Hz), 130.1 (d, *J* = 8.1 Hz), 129.3, 127.7, 124.7, 119.1, 117.3, 114.3 (d, *J* = 21.4 Hz), 111.1, 83.2, 61.4, 56.8, 56.4, 52.6, 48.2, 41.0, 27.8, 14.2, 14.0.

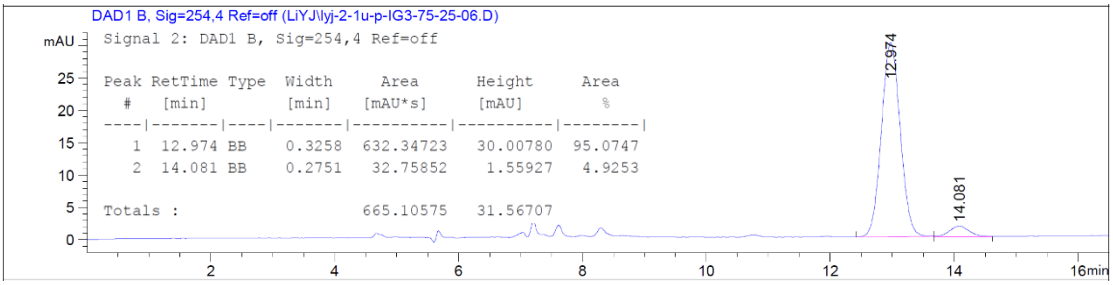
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.3 (s, 1F).

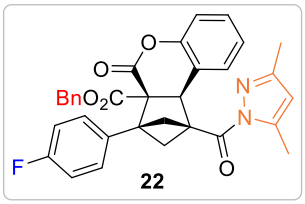
HRMS (ESI) m/z calcd. for $C_{30}H_{29}NaFN_2O_5$ $[M+Na]^+$ 539.1953, found 539.1959.

HPLC spectrum of ***rac*-21:**



HPLC spectrum of **21:**





Benzyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (22)

The title compound was synthesized according to **General Procedure A** at -20 °C for 48 h. The product was purified by silica gel flash column chromatography (4-7% EtOAc in *n*-hexane) to afford the desired product **22** (99.8 mg, 91%) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 70/30, flow rate = 0.55 mL/min, λ = 254 nm), t_R (minor) = 14.01 min, t_R (major) = 16.46 min.

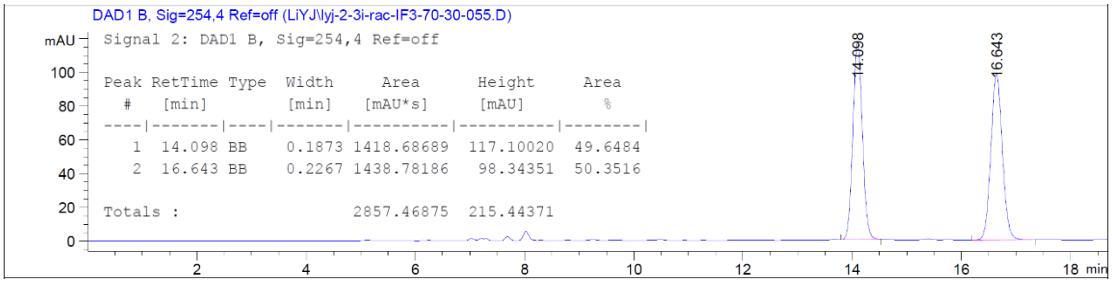
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.28 – 7.21 (m, 4H), 7.18 – 7.12 (m, 2H), 7.07 (d, *J* = 7.7 Hz, 1H), 6.99 – 6.92 (m, 3H), 6.43 (d, *J* = 7.6 Hz, 1H), 6.01 (s, 1H), 5.14 (dd, *J* = 58.6, 12.5 Hz, 2H), 4.73 (s, 1H), 3.30 (t, *J* = 8.7 Hz, 1H), 2.49 (s, 3H), 2.37 (d, *J* = 7.8 Hz, 1H), 2.30 (t, *J* = 9.2 Hz, 1H), 2.18 (s, 3H), 2.14 – 2.08 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.0, 163.9, 162.2 (d, *J* = 245.8 Hz), 153.2, 150.6, 144.3, 135.2, 133.9 (d, *J* = 2.9 Hz), 130.1 (d, *J* = 8.1 Hz), 129.5, 128.5, 128.3, 127.8, 127.6, 125.0, 118.8, 117.5, 114.4 (d, *J* = 21.3 Hz), 111.2, 67.3, 60.8, 57.1, 56.7, 52.4, 48.3, 40.8, 14.2, 14.1.

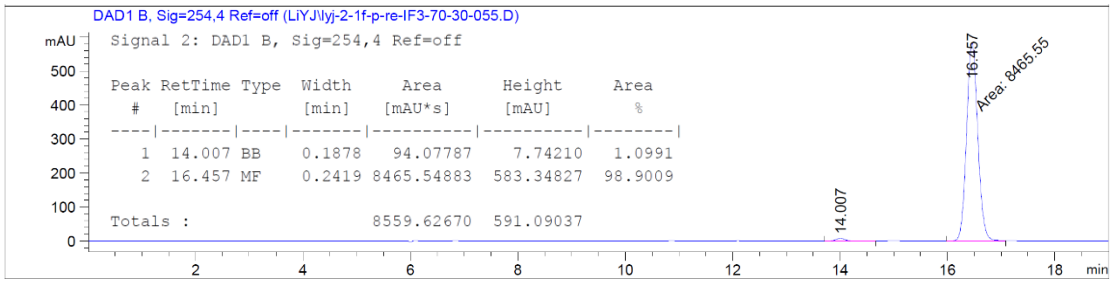
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.0 (s, 1F).

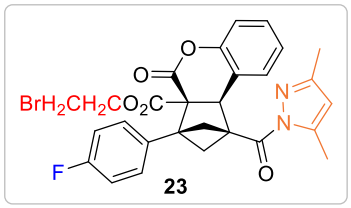
HRMS (ESI) m/z calcd. for $C_{33}H_{28}FN_2O_5$ $[M+H]^+$ 551.1977, found 551.1979.

HPLC spectrum of ***rac*-22:**



HPLC spectrum of **22:**





2-bromoethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (23)

The title compound was synthesized according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (4-7% EtOAc in *n*-hexane) to afford the desired product **23** (102.2 mg, 90%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 214 nm), t_R (minor) = 12.16 min, t_R (major) = 13.90 min.

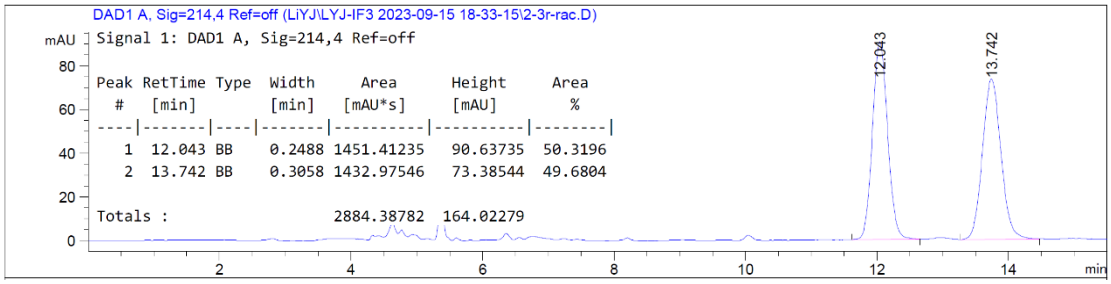
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 2H), 7.29 – 7.23 (m, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.04 – 6.94 (m, 3H), 6.48 (d, *J* = 7.2 Hz, 1H), 6.04 (s, 1H), 4.90 (d, *J* = 1.1 Hz, 1H), 4.55 (ddd, *J* = 12.5, 7.2, 5.5 Hz, 1H), 4.28 (dt, *J* = 11.7, 5.7 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.40 – 3.27 (m, 2H), 2.50 (s, 3H), 2.44 (d, *J* = 7.9 Hz, 1H), 2.31 (t, *J* = 9.2 Hz, 1H), 2.25 (s, 3H), 2.12 (dd, *J* = 8.8, 1.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 168.7, 163.8, 162.2 (d, *J* = 246.1 Hz), 153.3, 150.6, 144.3, 133.7 (d, *J* = 3.2 Hz), 130.2 (d, *J* = 8.1 Hz), 129.5, 127.8, 125.0, 118.8, 117.5, 114.4 (d, *J* = 21.4 Hz), 111.3, 64.4, 60.9, 57.2, 56.5, 52.5, 48.3, 40.6, 28.3, 14.2, 14.1.

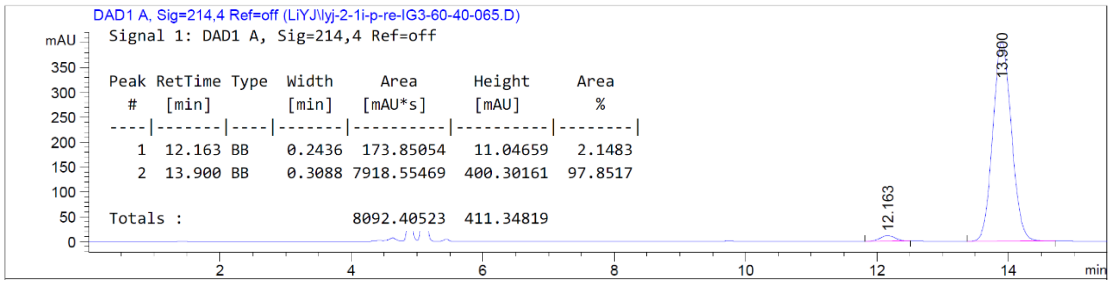
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.8 (s, 1F).

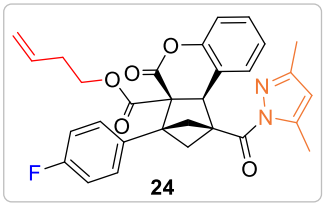
HRMS (ESI) m/z calcd. for $C_{28}H_{25}BrFN_2O_5$ $[M+H]^+$ 567.0926, found 567.0925.

HPLC spectrum of ***rac*-23:**



HPLC spectrum of **23:**





24

But-3-en-1-yl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (24)

The title compound was synthesized according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (4-7% EtOAc in *n*-hexane) to afford the desired product **24** (96.1 mg, 93%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 11.06 min, t_R (major) = 12.31 min.

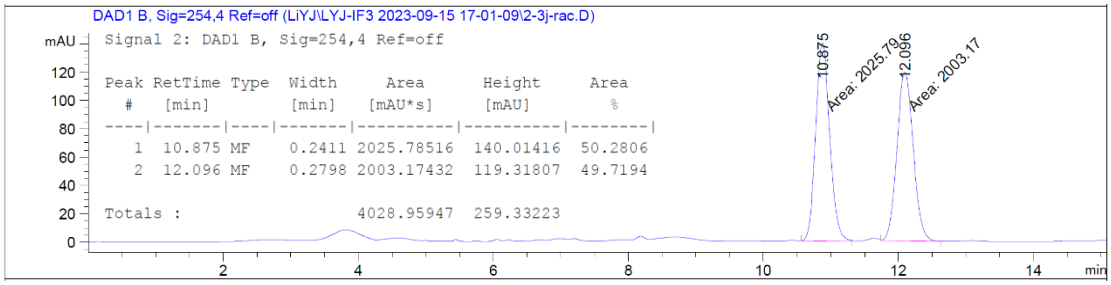
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H), 7.28 – 7.22 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.04 – 6.93 (m, 3H), 6.46 (d, *J* = 7.4 Hz, 1H), 6.04 (s, 1H), 5.60 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 4.99 – 4.85 (m, 2H), 4.75 (s, 1H), 4.28 (dt, *J* = 10.8, 6.6 Hz, 1H), 4.07 (dt, *J* = 10.8, 6.4 Hz, 1H), 3.33 (dd, *J* = 9.4, 8.1 Hz, 1H), 2.51 (s, 3H), 2.40 (d, *J* = 7.8 Hz, 1H), 2.35 – 2.21 (m, 6H), 2.11 (dd, *J* = 8.7, 1.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 169.1, 164.0, 162.1 (d, *J* = 245.8 Hz), 153.2, 150.6, 144.3, 134.0 (d, *J* = 3.2 Hz), 133.2, 130.1 (d, *J* = 8.1 Hz), 129.4, 127.8, 124.9, 118.8, 117.6, 117.4, 114.3 (d, *J* = 21.4 Hz), 111.2, 64.5, 60.7, 57.0, 56.4, 52.6, 48.3, 40.7, 32.9, 14.2, 14.0.

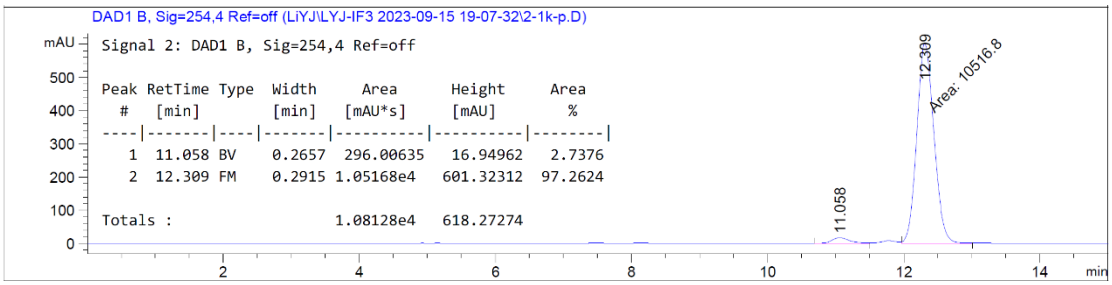
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.1 (s, 1F).

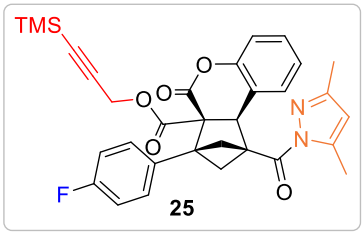
HRMS (ESI) m/z calcd. for $C_{30}H_{28}FN_2O_5$ $[M+H]^+$ 515.1977, found 515.1977.

HPLC spectrum of ***rac*-24:**



HPLC spectrum of **24:**





25

3-(trimethylsilyl)prop-2-yn-1-yl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]-chromene-3a(4*H*)-carboxylate (25)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 72 h. The product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 100/0 to 100/6) to afford the desired product **25** (105.9 mg, 93%) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 80/20, flow rate = 0.40 mL/min, λ = 254 nm), t_R (minor) = 14.63 min, t_R (major) = 15.67 min.

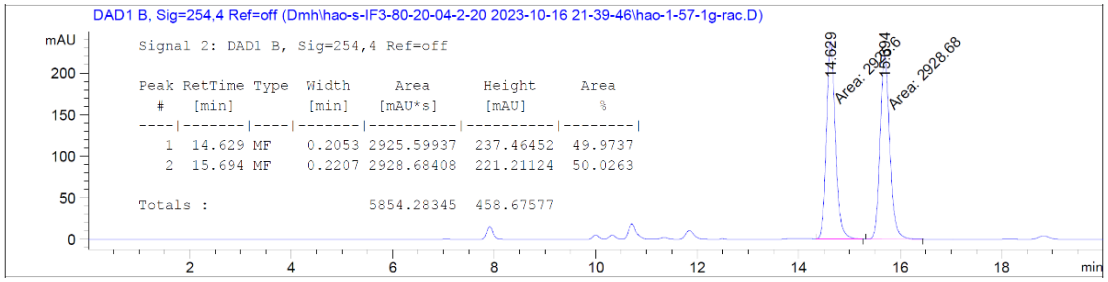
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 2H), 7.33 – 7.27 (m, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.09 – 6.96 (m, 3H), 6.52 (d, *J* = 7.2 Hz, 1H), 6.07 (s, 1H), 4.80 (s, 1H), 4.73 (dd, *J* = 82.0, 15.7 Hz, 2H), 3.37 (dd, *J* = 9.4, 8.1 Hz, 1H), 2.55 (s, 3H), 2.45 (d, *J* = 7.9 Hz, 1H), 2.35 (t, *J* = 9.3 Hz, 1H), 2.29 (s, 3H), 2.17 (dd, *J* = 8.8, 1.9 Hz, 1H), 0.15 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 168.4, 163.5, 162.2 (d, *J* = 246.0 Hz), 153.1, 150.6, 144.3, 133.7 (d, *J* = 3.2 Hz), 130.1 (d, *J* = 8.1 Hz), 129.5, 127.8, 124.9, 118.7, 117.5, 114.4 (d, *J* = 21.4 Hz), 111.2, 97.9, 93.0, 60.7, 57.1, 56.8, 54.0, 52.4, 48.2, 40.8, 14.2, 14.1, -0.4.

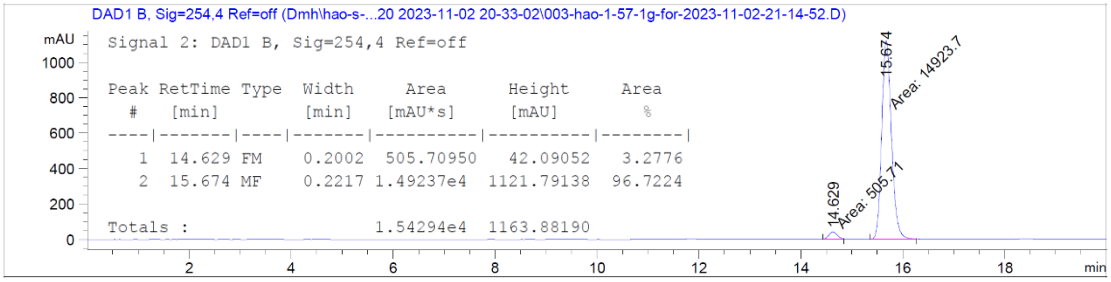
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9 (s, 1F).

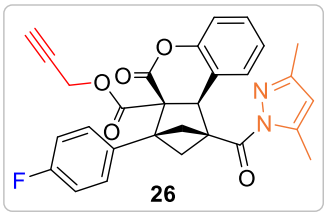
HRMS (ESI) m/z calcd. for $C_{32}H_{32}FN_2O_5Si$ $[M+H]^+$ 571.2059, found 571.2061.

HPLC spectrum of ***rac*-25:**



HPLC spectrum of **25:**





26

Prop-2-yn-1-yl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (26)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 72 h. The product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 100/0 to 100/6) to afford the desired product **26** (94.9 mg, 95%) as a white solid.

HPLC analysis: CHIRALPAK® IA-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 7.57 min, t_R (major) = 9.05 min.

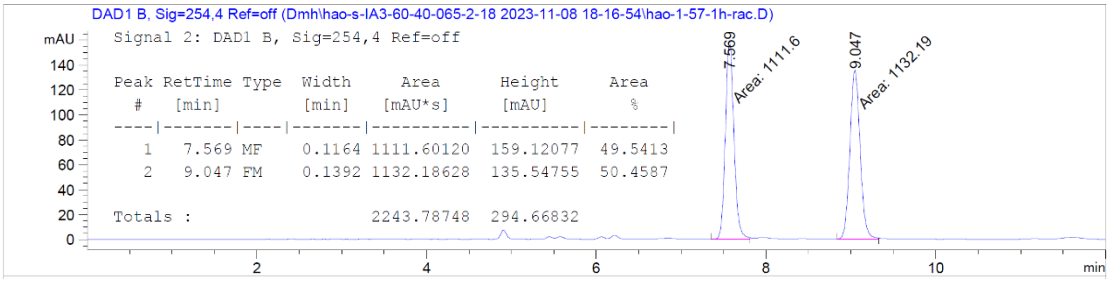
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.31 – 7.25 (m, 1H), 7.10 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.04 – 6.96 (m, 3H), 6.48 (d, *J* = 7.0 Hz, 1H), 6.04 (s, 1H), 4.79 (dd, *J* = 15.5, 2.4 Hz, 2H), 4.58 (dd, *J* = 15.5, 2.5 Hz, 1H), 3.31 (dd, *J* = 9.6, 8.1 Hz, 1H), 2.52 (s, 3H), 2.44 (dd, *J* = 7.0, 5.1 Hz, 2H), 2.31 (t, *J* = 9.3 Hz, 1H), 2.25 (s, 3H), 2.13 (dd, *J* = 8.8, 2.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 168.3, 163.5, 162.2 (d, *J* = 246.1 Hz), 153.2, 150.6, 144.3, 133.6 (d, *J* = 3.2 Hz), 130.1 (d, *J* = 8.1 Hz), 129.5, 127.8, 125.0, 118.7, 117.5, 114.4 (d, *J* = 21.4 Hz), 111.2, 76.6, 75.5, 60.7, 57.1, 56.8, 53.2, 52.2, 48.2, 40.7, 14.2, 14.0.

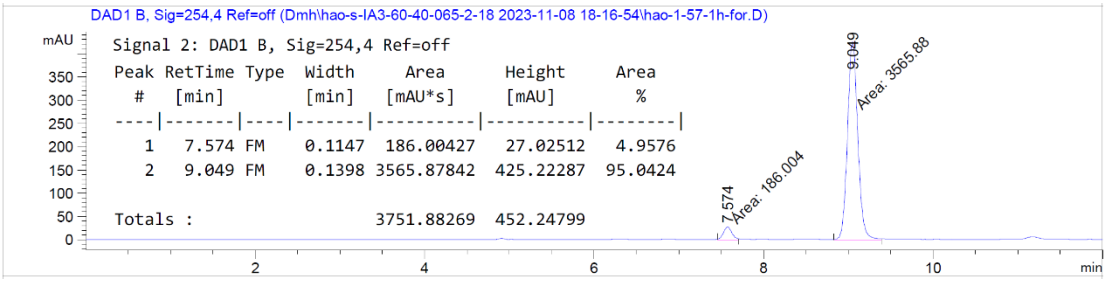
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.8 (s, 1F).

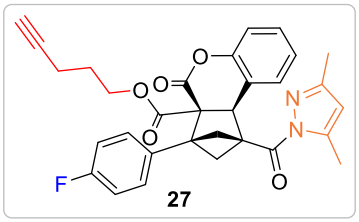
HRMS (ESI) m/z calcd. for $C_{29}H_{24}FN_2O_5$ $[M+H]^+$ 499.1664, found 499.1664.

HPLC spectrum of ***rac*-26:**



HPLC spectrum of **26:**





27

Pent-4-yn-1-yl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]-chromene-3a(4*H*)-carboxylate (27)

The title compound was synthesized according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (4-7% EtOAc in *n*-hexane) to afford the desired product **27** (94.5 mg, 90%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 13.11 min, t_R (minor) = 13.96 min.

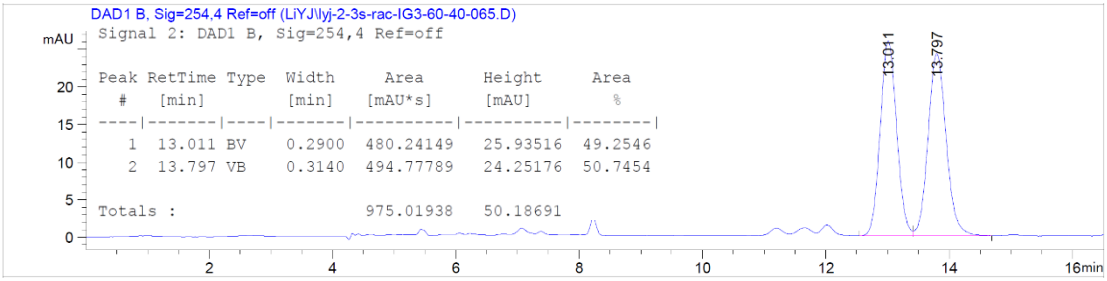
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.30 – 7.24 (m, 1H), 7.09 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.04 – 6.93 (m, 3H), 6.48 (d, *J* = 7.0 Hz, 1H), 6.04 (d, *J* = 0.6 Hz, 1H), 4.77 (d, *J* = 1.4 Hz, 1H), 4.30 – 4.19 (m, 2H), 3.33 (dd, *J* = 9.5, 8.0 Hz, 1H), 2.51 (s, 3H), 2.41 (d, *J* = 7.9 Hz, 1H), 2.30 (t, 1H), 2.26 (s, 3H), 2.13 (dd, *J* = 8.8, 2.0 Hz, 1H), 2.06 (ddd, *J* = 9.7, 4.8, 1.7 Hz, 2H), 1.88 (t, *J* = 2.6 Hz, 1H), 1.81 – 1.70 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 169.1, 163.9, 162.1 (d, *J* = 246.0 Hz), 153.2, 150.6, 144.3, 133.9 (d, *J* = 3.2 Hz), 130.0 (d, *J* = 8.1 Hz), 129.5, 127.8, 124.9, 118.8, 117.5, 114.4 (d, *J* = 21.3 Hz), 111.2, 82.6, 69.2, 64.3, 60.7, 57.0, 56.6, 52.5, 48.2, 40.7, 27.1, 14.9, 14.2, 14.1.

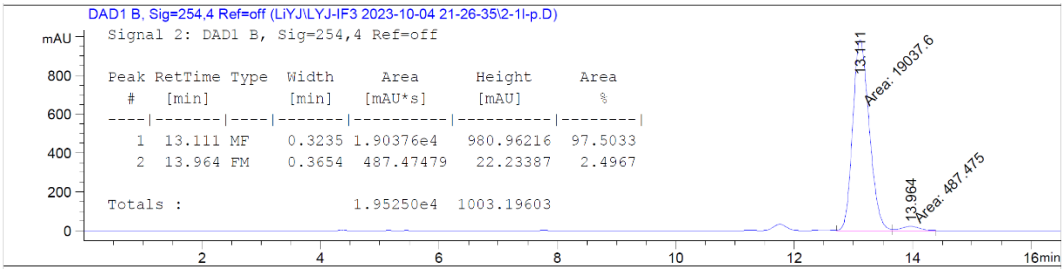
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.0 (s, 1F).

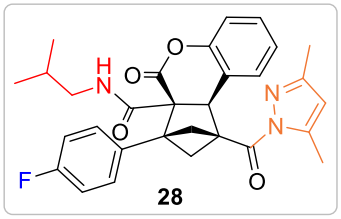
HRMS (ESI) m/z calcd. for $C_{31}H_{28}FN_2O_5$ $[M+H]^+$ 527.1977, found 527.1980.

HPLC spectrum of ***rac*-27:**



HPLC spectrum of **27:**





(3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-*N*-isobutyl-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[c]chromene-3a(4*H*)-carboxamide (28)

The title compound was synthesized according to **General Procedure A** at **25°C** for 72 h. The product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 100/0 to 100/6) to afford the desired product **28** (79.2 mg, 77 %) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 9.15 min, t_R (major) = 10.90 min.

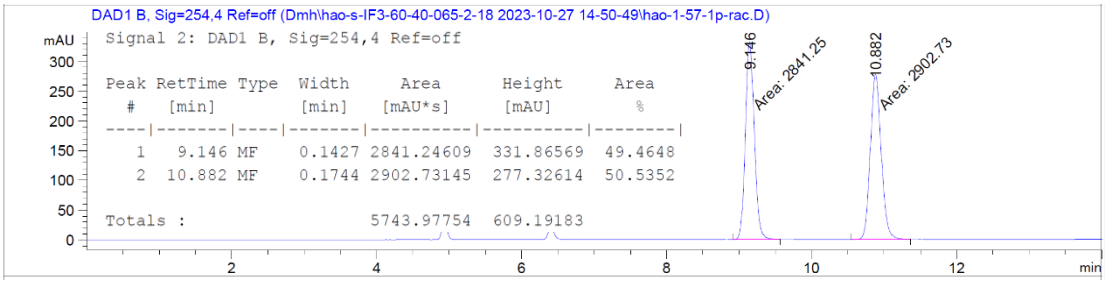
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 1H), 7.11 – 6.99 (m, 5H), 6.99 – 6.92 (m, 2H), 6.50 (d, *J* = 7.1 Hz, 1H), 6.03 (s, 1H), 5.64 (s, 1H), 3.37 (dd, *J* = 9.5, 7.7 Hz, 1H), 3.13 (dt, *J* = 13.3, 6.6 Hz, 1H), 2.85 (ddd, *J* = 13.1, 6.7, 4.9 Hz, 1H), 2.50 (s, 3H), 2.41 (t, *J* = 9.2 Hz, 1H), 2.31 (s, 3H), 2.21 (dd, *J* = 8.7, 1.8 Hz, 1H), 2.16 (d, *J* = 7.6 Hz, 1H), 1.68 – 1.53 (m, 1H), 0.74 (dd, *J* = 17.0, 6.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 168.5, 165.1, 162.4 (d, *J* = 246.9 Hz), 153.2, 149.8, 144.0, 133.6 (d, *J* = 3.2 Hz), 129.6 (d, *J* = 8.2 Hz), 129.0, 128.1, 125.1, 120.4, 116.7, 114.5 (d, *J* = 21.5 Hz), 111.2, 61.0, 59.8, 57.2, 48.0, 47.7, 45.8, 42.4, 27.9, 20.14, 20.09, 14.2, 14.1.

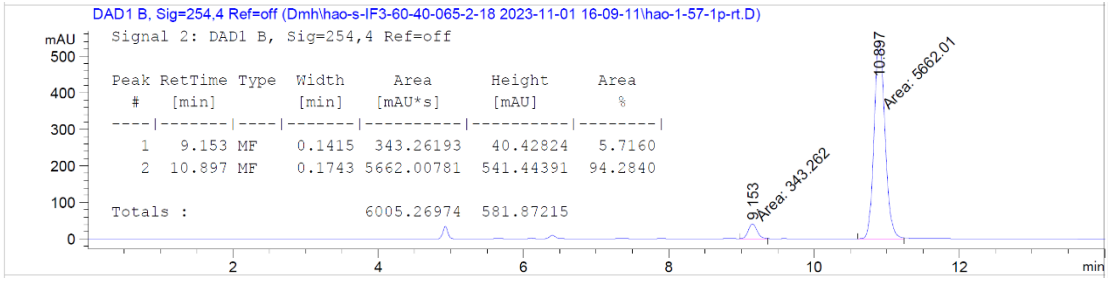
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.1 (s, 1F).

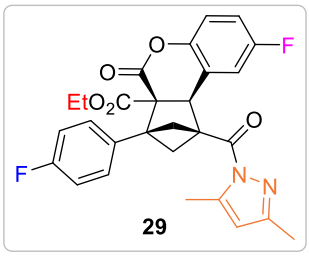
HRMS (ESI) m/z calcd. for $C_{30}H_{31}FN_3O_4$ $[M+H]^+$ 516.2293, found 516.2295.

HPLC spectrum of ***rac*-28:**



HPLC spectrum of **28:**





Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-8-fluoro-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (29)

The title compound was synthesized according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-

hexane) to afford the desired product **29** (91.8 mg, 91 %) as a white solid.

HPLC analysis: CHIRALPAK® IA-3 (*n*-hexane/*i*-PrOH = 90/10, flow rate = 0.60 mL/min, λ = 254 nm), t_R (minor) = 11.71 min, t_R (major) = 12.65 min.

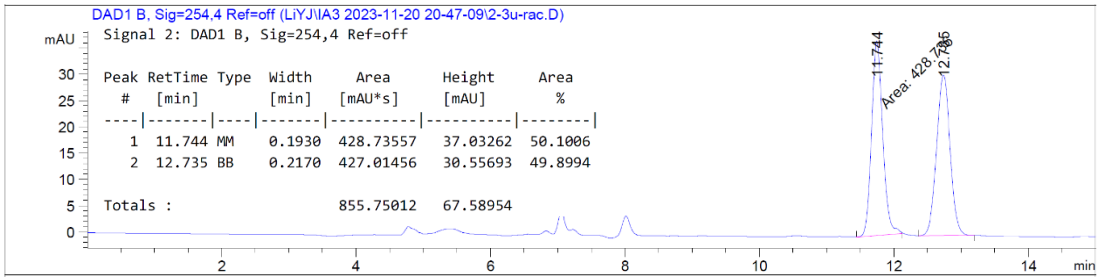
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 2H), 7.07 (dd, *J* = 9.0, 4.7 Hz, 1H), 7.04 – 6.92 (m, 3H), 6.16 (dd, *J* = 8.5, 2.9 Hz, 1H), 6.06 (s, 1H), 4.73 (s, 1H), 4.26 – 4.13 (m, 2H), 3.33 (dd, *J* = 9.4, 8.1 Hz, 1H), 2.52 (s, 3H), 2.41 (d, *J* = 7.9 Hz, 1H), 2.31 – 2.22 (m, 4H), 2.14 (dd, *J* = 8.8, 1.9 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.0, 163.7, 162.2 (d, *J* = 246.1 Hz), 159.0 (d, *J* = 244.4 Hz), 153.5, 146.7 (d, *J* = 2.5 Hz), 144.5, 133.7 (d, *J* = 3.1 Hz), 130.1 (d, *J* = 8.1 Hz), 120.4 (d, *J* = 7.8 Hz), 118.9 (d, *J* = 8.5 Hz), 116.5 (d, *J* = 23.7 Hz), 114.4 (d, *J* = 21.3 Hz), 114.1 (d, *J* = 24.1 Hz), 111.4, 62.1, 60.2, 57.0, 56.7, 52.4, 48.2, 40.7, 14.1, 14.0, 13.9.

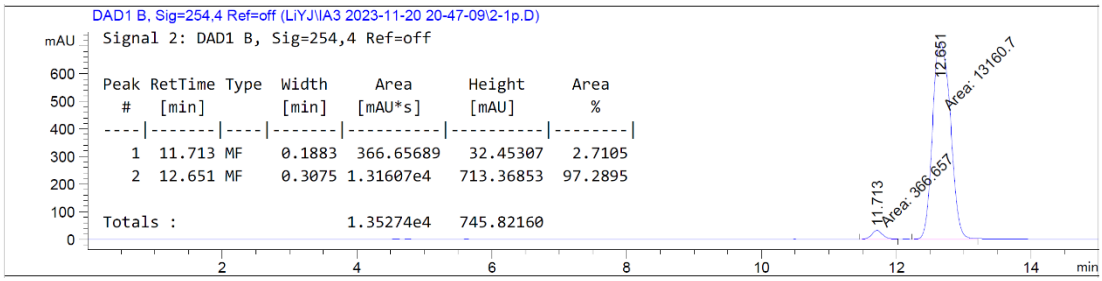
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9 (s, 1F), -117.3 (s, 1F).

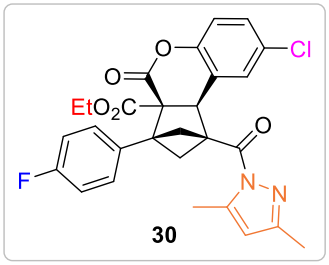
HRMS (ESI) m/z calcd. for $C_{28}H_{25}F_2N_2O_5$ $[M+H]^+$ 507.1726, found 507.1729.

HPLC spectrum of ***rac*-29:**



HPLC spectrum of **29:**





30

Ethyl (3a*S*,9b*S*)-8-chloro-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (30)

The title compound was synthesized according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **30** (96.4 mg, 92 %) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 7.59 min, t_R (minor) = 8.82 min.

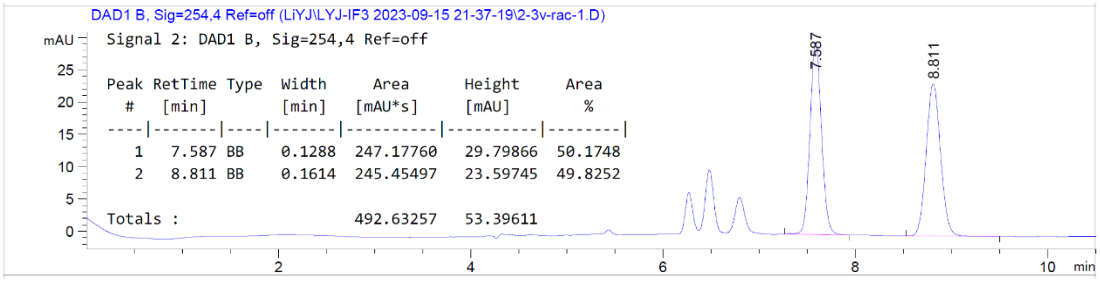
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 2H), 7.22 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.07 – 6.95 (m, 3H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.07 (s, 1H), 4.64 (s, 1H), 4.25 – 4.13 (m, 2H), 3.34 (dd, *J* = 9.3, 8.3 Hz, 1H), 2.54 (s, 3H), 2.43 (d, *J* = 7.9 Hz, 1H), 2.29 – 2.21 (m, 4H), 2.15 (dd, *J* = 8.8, 1.8 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.9, 163.4, 162.2 (d, *J* = 245.2 Hz), 153.5, 149.1, 144.5, 133.6 (d, *J* = 3.2 Hz), 130.1 (d, *J* = 8.1 Hz), 129.8, 129.5, 127.7, 120.6, 118.9, 114.4 (d, *J* = 21.4 Hz), 111.4, 62.2, 60.4, 57.0, 56.8, 52.2, 48.2, 40.7, 14.0 (s, 2C), 13.9.

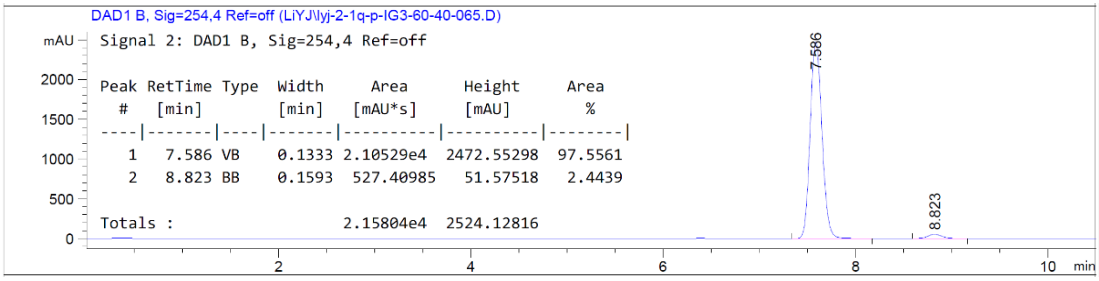
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.8 (s, 1F).

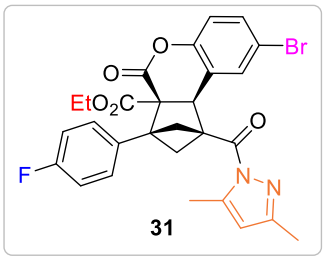
HRMS (ESI) m/z calcd. for $C_{28}H_{25}ClFN_2O_5$ $[M+H]^+$ 523.1431, found 523.1433.

HPLC spectrum of ***rac*-30:**



HPLC spectrum of **30:**





31

Ethyl (3a*S*,9b*S*)-8-bromo-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (31)

The title compound was synthesized according to **General Procedure A** at -20 °C for 48 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **31** (96.5 mg, 85 %) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 7.64 min, t_R (minor) = 9.19 min.

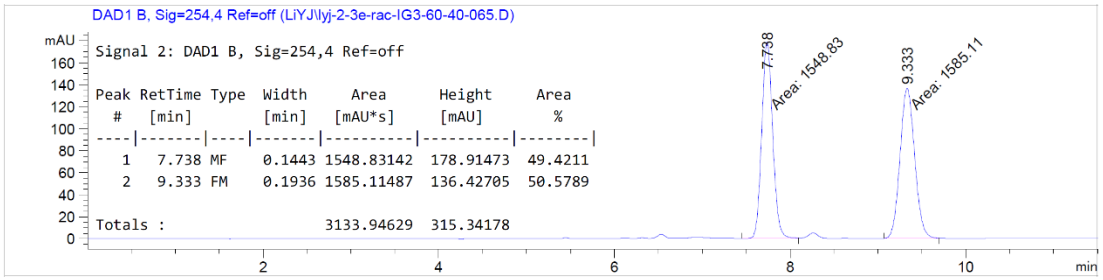
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 3H), 7.04 – 6.95 (m, 3H), 6.50 (d, *J* = 2.0 Hz, 1H), 6.07 (s, 1H), 4.61 (d, *J* = 1.0 Hz, 1H), 4.24 – 4.14 (m, 2H), 3.33 (dd, *J* = 9.3, 8.2 Hz, 1H), 2.55 (d, *J* = 0.6 Hz, 3H), 2.44 (d, *J* = 8.0 Hz, 1H), 2.28 – 2.21 (m, 4H), 2.15 (dd, *J* = 8.8, 1.8 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.8, 163.3, 162.2 (d, *J* = 246.1 Hz), 153.5, 149.7, 144.5, 133.6 (d, *J* = 3.2 Hz), 132.4, 130.8, 130.1 (d, *J* = 8.1 Hz), 121.0, 119.2, 117.3, 114.4 (d, *J* = 21.4 Hz), 111.4, 62.2, 60.4, 57.1, 56.8, 52.1, 48.1, 40.7, 14.09, 14.07, 13.9.

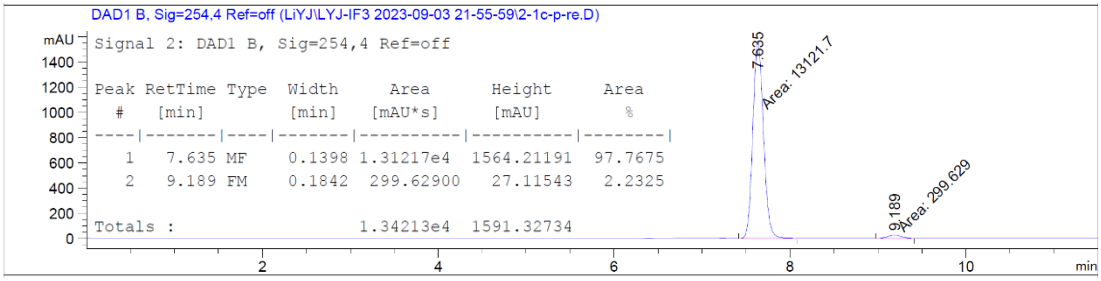
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.7 (s, 1F).

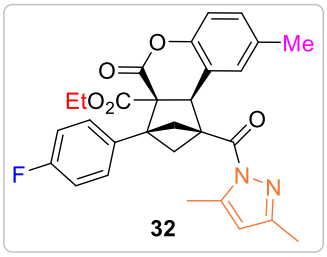
HRMS (ESI) m/z calcd. for $C_{28}H_{25}BrFN_2O_5$ $[M+H]^+$ 567.0926, found 567.0927.

HPLC spectrum of ***rac*-31:**



HPLC spectrum of **31:**





Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-8-methyl-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (32)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 60 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **32** (94.2 mg, 94%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 8.20 min, t_R (minor) = 10.86 min.

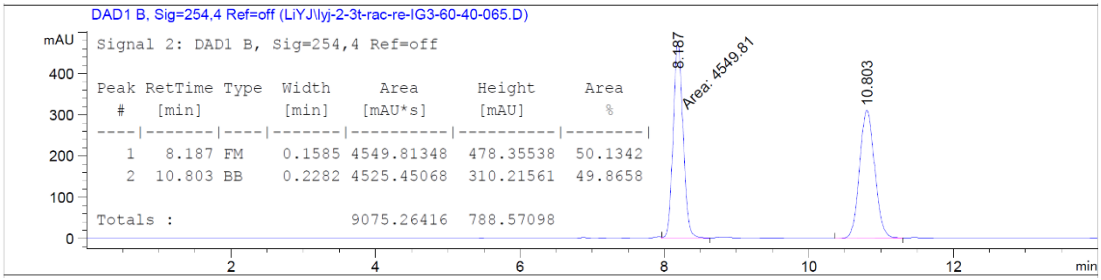
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 2H), 7.07 – 6.93 (m, 4H), 6.17 (s, 1H), 6.05 (s, 1H), 4.64 (s, 1H), 4.17 (qd, *J* = 7.1, 2.8 Hz, 1H), 3.35 (dd, *J* = 9.4, 8.1 Hz, 1H), 2.52 (s, 3H), 2.41 (d, *J* = 7.8 Hz, 1H), 2.31 – 2.22 (m, 4H), 2.13 (s, 3H), 2.10 (dd, *J* = 8.7, 1.8 Hz, 1H), 1.20 – 1.12 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.3, 164.1, 162.1 (d, *J* = 245.8 Hz), 153.2, 148.5, 144.2, 134.3, 134.1 (d, *J* = 3.2 Hz), 130.1 (d, *J* = 8.1 Hz), 130.0, 128.1, 118.4, 117.1, 114.3 (d, *J* = 21.3 Hz), 111.2, 62.0, 60.7, 57.0, 56.6, 52.4, 48.2, 40.7, 20.7, 14.1, 14.0, 13.9.

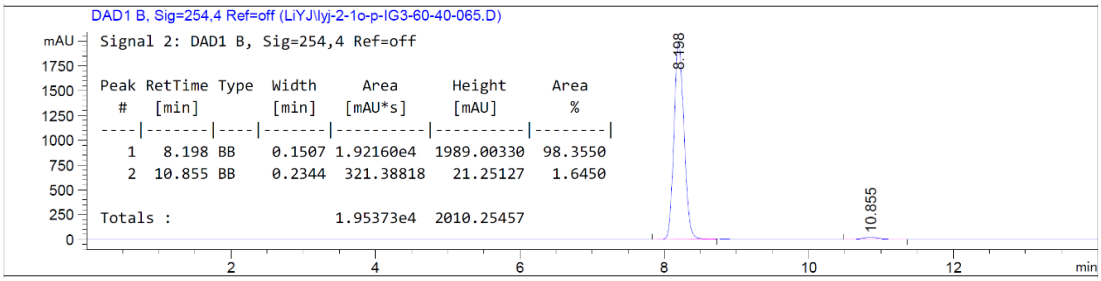
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.1 (s, 1F).

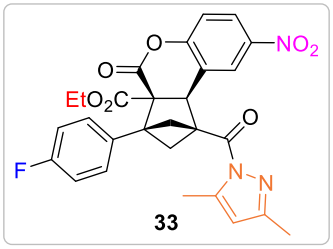
HRMS (ESI) m/z calcd. for $C_{29}H_{28}FN_2O_5$ $[M+H]^+$ 503.1977, found 503.1976.

HPLC spectrum of ***rac*-32:**



HPLC spectrum of **32:**





Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1H-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-8-nitro-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4H)-carboxylate (33)

The title compound was synthesized f according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (*n*-hexane: EtOAc = 100:0 to 100:6) to afford the desired product **33** (81.6 mg, 76%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 10.01 min, t_R (minor) = 12.56 min.

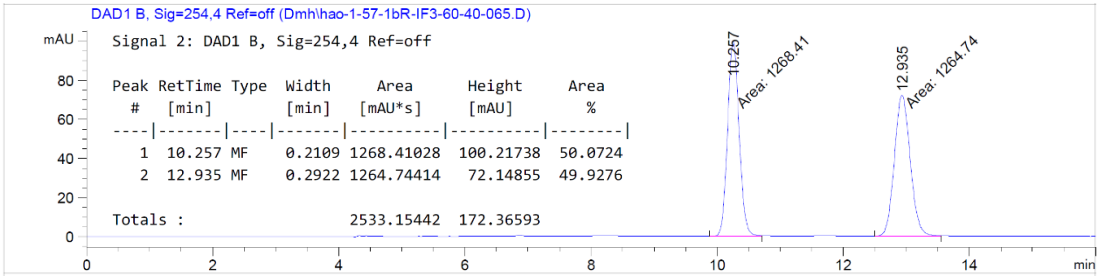
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.24 (d, *J* = 9.0 Hz, 1H), 7.01 (t, *J* = 8.7 Hz, 2H), 6.09 (s, 1H), 4.76 (s, 1H), 4.27 – 4.14 (m, 2H), 3.38 (td, *J* = 8.3, 1.1 Hz, 1H), 2.53 (s, 3H), 2.47 (d, *J* = 8.1 Hz, 1H), 2.27 – 2.18 (m, 5H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 168.4, 162.5, 162.3 (d, *J* = 246.5 Hz), 154.8, 153.9, 144.9, 144.3, 133.2 (d, *J* = 3.2 Hz), 130.1 (d, *J* = 8.2 Hz), 125.1, 124.1, 120.2, 118.5, 114.5 (d, *J* = 21.4 Hz), 111.7, 62.5, 60.2, 57.1, 57.0, 52.0, 48.0, 41.1, 14.08, 14.06, 13.9.

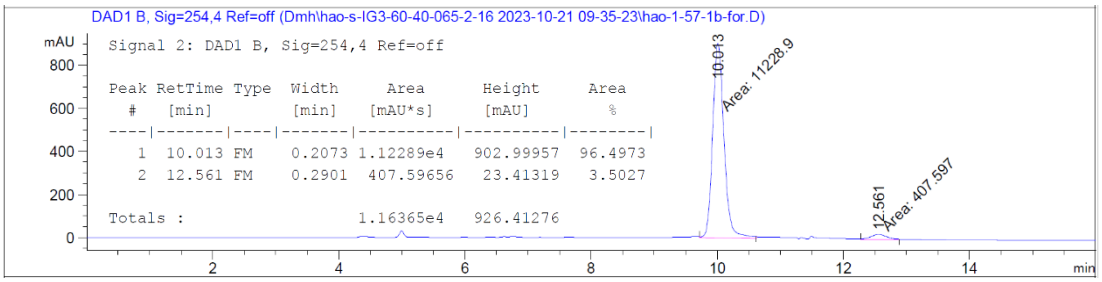
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.4 (s, 1F).

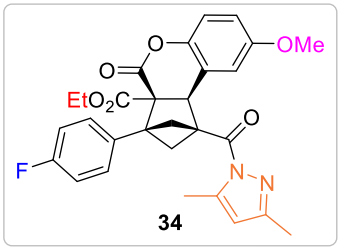
HRMS (ESI) m/z calcd. for $C_{28}H_{25}FN_3O_7$ $[M+H]^+$ 534.1671, found 534.1674.

HPLC spectrum of ***rac*-33:**



HPLC spectrum of **33:**





Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-8-methoxy-4-oxo-1,2,3,9b-tetrahydro-1,3-ethanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (34)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 60 h. The product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 100/0 to 100/6) to afford the desired product **34** (91.7 mg, 88%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 9.28 min, t_R (minor) = 11.17 min.

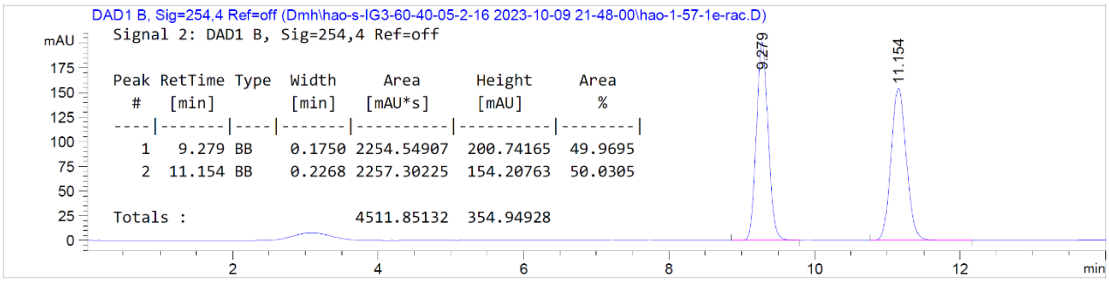
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 2H), 7.06 – 6.95 (m, 3H), 6.80 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.04 (d, *J* = 0.6 Hz, 1H), 5.95 (d, *J* = 2.9 Hz, 1H), 4.72 (d, *J* = 1.4 Hz, 1H), 4.24 – 4.13 (m, 2H), 3.55 (s, 3H), 3.33 (dd, *J* = 9.5, 7.9 Hz, 1H), 2.53 (s, 3H), 2.41 (d, *J* = 7.8 Hz, 1H), 2.31 – 2.22 (m, 4H), 2.13 (dd, *J* = 8.7, 2.0 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.3, 164.1, 162.1 (d, *J* = 245.8 Hz), 156.3, 153.2, 144.5, 144.3, 134.0 (d, *J* = 3.2 Hz), 130.1 (d, *J* = 8.1 Hz), 119.5, 118.3, 115.5, 114.3 (d, *J* = 21.3 Hz), 111.7, 111.2, 62.0, 60.4, 57.0, 56.6, 55.2, 52.7, 48.3, 40.7, 14.2, 14.0, 13.9.

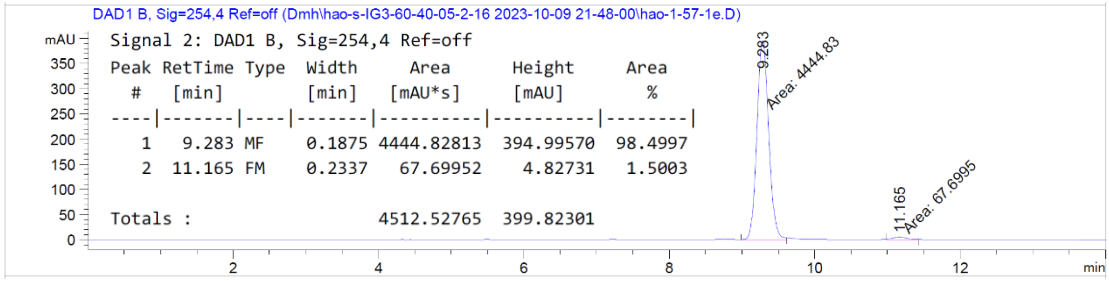
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.1 (s, 1F).

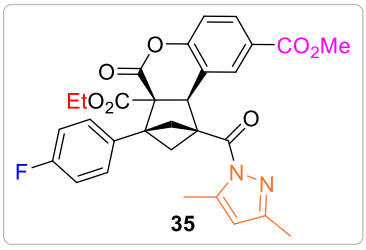
HRMS (ESI) m/z calcd. for $C_{29}H_{28}FN_2O_6$ $[M+H]^+$ 519.1926, found 519.1930.

HPLC spectrum of ***rac*-34:**



HPLC spectrum of **34:**





3a-ethyl 8-methyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]-chromene-3a,8(4*H*)-dicarboxylate (35)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 72 h. The product

was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 100/0 to 100/6) to afford the desired product **35** (89.1 mg, 82 %) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 8.58 min, t_R (minor) = 13.67 min.

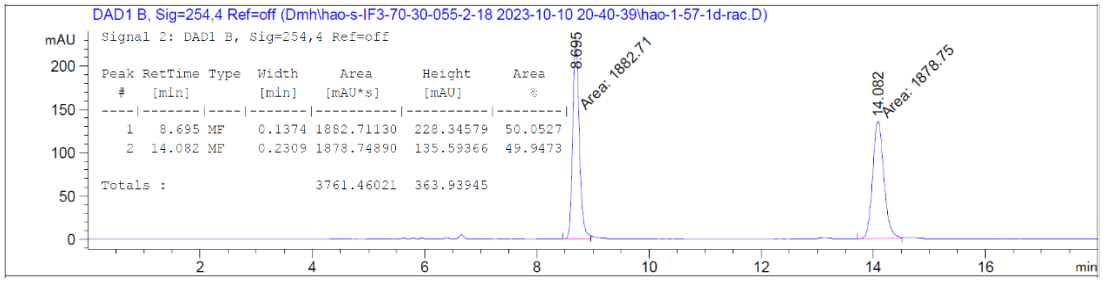
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.19 – 7.11 (m, 2H), 7.06 – 6.96 (m, 2H), 6.07 (s, 1H), 4.68 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.37 (dd, *J* = 9.3, 8.3 Hz, 1H), 2.52 (s, 3H), 2.46 (d, *J* = 8.0 Hz, 1H), 2.28 – 2.20 (m, 4H), 2.15 (dd, *J* = 8.9, 1.9 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 168.8, 165.6, 163.2, 162.2 (d, *J* = 246.2 Hz), 153.8, 153.5, 144.6, 133.6 (d, *J* = 3.3 Hz), 130.9, 130.1 (d, *J* = 8.1 Hz), 130.0, 126.7, 119.0, 117.5, 114.4 (d, *J* = 21.4 Hz), 111.2, 62.2, 60.5, 57.0, 56.9, 52.15, 52.08, 48.1, 40.9, 14.04, 13.99, 13.8.

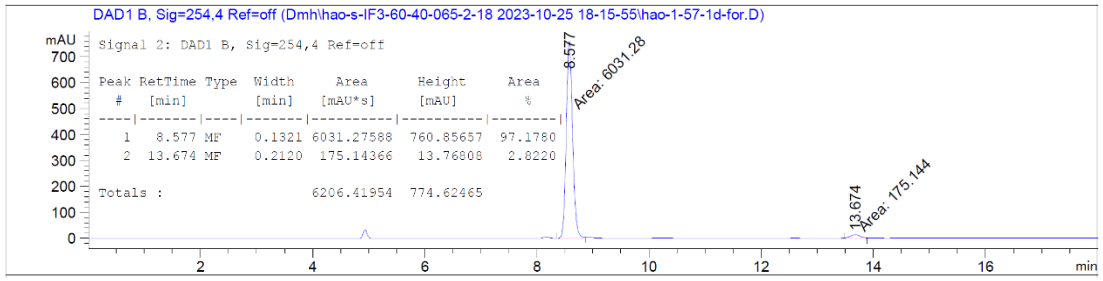
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.8 (s, 1F).

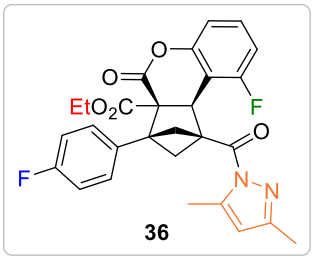
HRMS (ESI) m/z calcd. for $C_{30}H_{28}FN_2O_7$ $[M+H]^+$ 547.1875, found 547.1877.

HPLC spectrum of ***rac*-35:**



HPLC spectrum of **35:**





Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-9-fluoro-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[c]chromene-3a(4*H*)-carboxylate (36)

The title compound was synthesized according to **General Procedure A** at -20 °C for 72 h. The product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 100/0 to 100/6) to afford the desired product **36** (96.8 mg, 96%) as a white solid.

HPLC analysis: CHIRALPAK® IA-3 (*n*-hexane/*i*-PrOH = 80/20, flow rate = 0.50 mL/min, λ = 254 nm), t_R (minor) = 12.11 min, t_R (major) = 12.91 min.

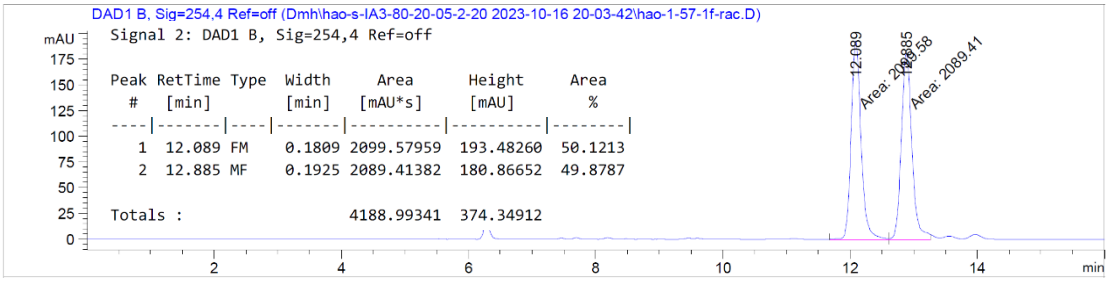
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.29 – 7.22 (m, 1H), 7.00 (t, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.71 (t, *J* = 8.8 Hz, 1H), 5.93 (s, 1H), 4.56 (s, 1H), 4.26 – 4.11 (m, 2H), 3.39 – 3.31 (m, 1H), 2.51 (s, 3H), 2.49 – 2.40 (m, 1H), 2.13 (d, *J* = 1.9 Hz, 1H), 2.11 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 168.8, 163.5, 162.2 (d, *J* = 246.1 Hz), 160.5 (d, *J* = 248.0 Hz), 152.2, 151.6 (d, *J* = 6.7 Hz), 144.1, 133.7 (d, *J* = 3.2 Hz), 130.14 (d, *J* = 8.11 Hz), 130.08 (d, *J* = 10.02 Hz), 114.4 (d, *J* = 21.4 Hz), 113.0 (d, *J* = 3.3 Hz), 111.2 (d, *J* = 21.7 Hz), 110.7, 108.0 (d, *J* = 21.4 Hz), 62.2, 60.4, 56.5, 55.6, 48.6, 47.6, 42.6, 14.2, 13.8 (s, 2C).

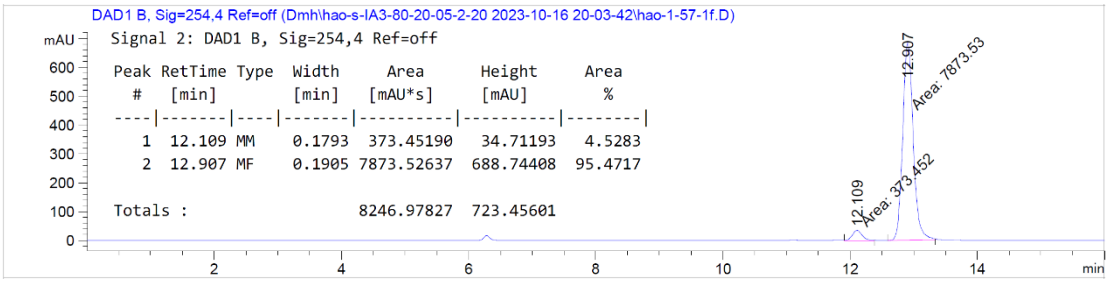
^{19}F NMR (376 MHz, $CDCl_3$) δ -113.8 (s, 1F), -114.9 (s, 1F).

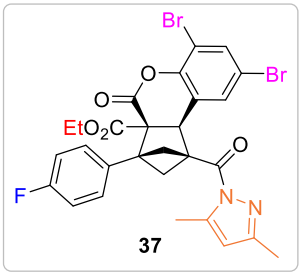
HRMS (ESI) m/z calcd. for $C_{28}H_{25}F_2N_2O_5$ $[M+H]^+$ 507.1726, found 507.1730.

HPLC spectrum of ***rac*-36:**



HPLC spectrum of **36:**





37

Ethyl (3a*S*,9b*S*)-6,8-dibromo-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (37)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 60 h. The product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 100/0 to 100/6) to afford the desired product **37** (99.8 mg, 77%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 9.02 min, t_R (minor) = 9.77 min.

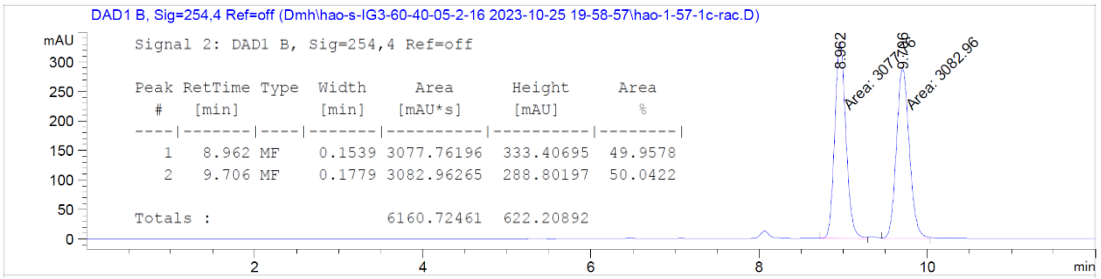
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 2.2 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.05 – 6.96 (m, 2H), 6.44 (d, *J* = 1.8 Hz, 1H), 6.07 (s, 1H), 4.61 (d, *J* = 1.3 Hz, 1H), 4.25 – 4.14 (m, 2H), 3.31 (dd, *J* = 9.4, 8.2 Hz, 1H), 2.54 (s, 3H), 2.45 (d, *J* = 8.0 Hz, 1H), 2.29 – 2.21 (m, 4H), 2.16 (dd, *J* = 9.0, 1.9 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 168.5, 162.3 (d, *J* = 246.3 Hz), 162.3, 153.6, 146.9, 144.5, 135.5, 133.2 (d, *J* = 3.3 Hz), 130.1 (d, *J* = 8.2 Hz), 129.8, 122.3, 117.1, 114.5 (d, *J* = 21.4 Hz), 112.0, 111.5, 62.3, 60.6, 57.3, 57.0, 52.5, 48.1, 40.9, 14.0, 13.9 (s, 2C).

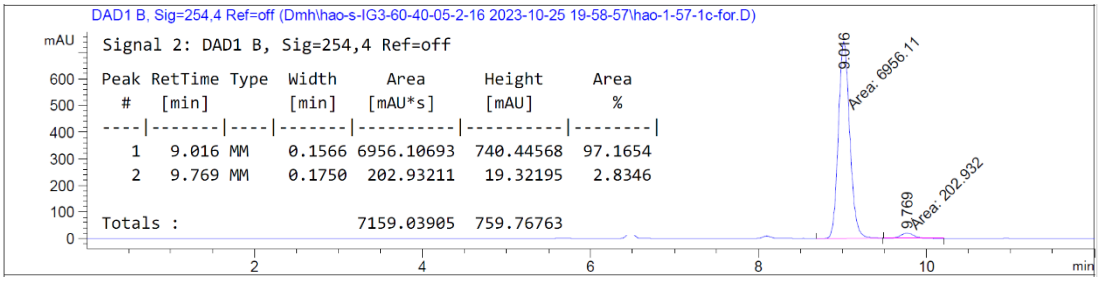
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.6 (s, 1F).

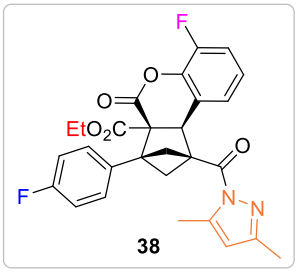
HRMS (ESI) m/z calcd. for $C_{28}H_{24}Br_2FN_2O_5$ $[M+H]^+$ 645.0031, found 645.0025.

HPLC spectrum of ***rac*-37:**



HPLC spectrum of **37:**





Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-6-fluoro-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (38)

The title compound was synthesized according to **General Procedure A** at -20 °C for 60 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **38** (84.0 mg, 83%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 10.98 min, t_R (major) = 14.05 min.

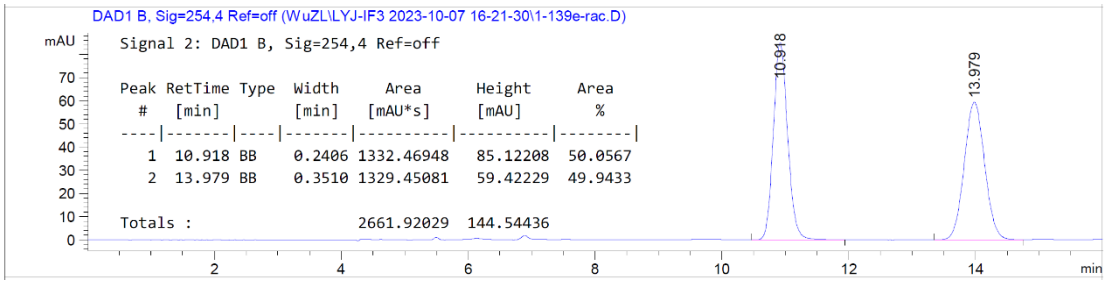
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.2, 5.6 Hz, 2H), 7.12 – 6.87 (m, 4H), 6.26 (d, *J* = 7.7 Hz, 1H), 6.04 (s, 1H), 4.79 (s, 1H), 4.26 – 4.14 (m, 2H), 3.34 (t, *J* = 8.7 Hz, 1H), 2.51 (s, 3H), 2.41 (d, *J* = 7.9 Hz, 1H), 2.35 – 2.23 (m, 4H), 2.15 (d, *J* = 8.3 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 168.9, 162.6, 162.2 (d, *J* = 246.1 Hz), 153.3, 150.0 (d, *J* = 251.5 Hz), 144.4, 139.1 (d, *J* = 11.4 Hz), 133.7 (d, *J* = 3.2 Hz), 130.1 (d, *J* = 8.1 Hz), 124.7 (d, *J* = 7.2 Hz), 122.7 (d, *J* = 3.5 Hz), 121.2, 116.3 (d, *J* = 17.7 Hz), 114.4 (d, *J* = 21.4 Hz), 111.3, 62.2, 60.6, 57.1, 56.7, 52.5, 48.1, 40.9, 14.2, 14.0, 13.9.

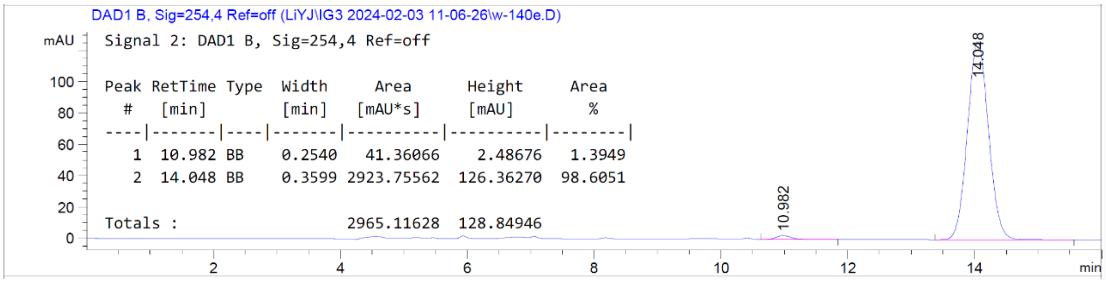
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9 (s, 1F), -131.9 (s, 1F).

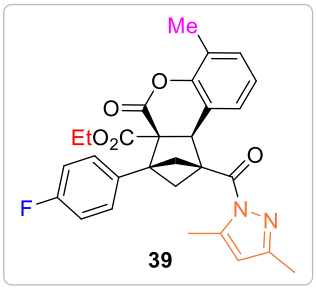
HRMS (ESI) m/z calcd. for $C_{28}H_{25}F_2N_2O_5$ $[M+H]^+$ 507.1726, found 507.1727.

HPLC spectrum of ***rac*-38:**



HPLC spectrum of **38:**





39

Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-6-methyl-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (39)

The title compound was synthesized according to **General Procedure A** at -20 °C for 40 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **39** (86.5 mg, 86%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 7.44 min, t_R (minor) = 8.23 min.

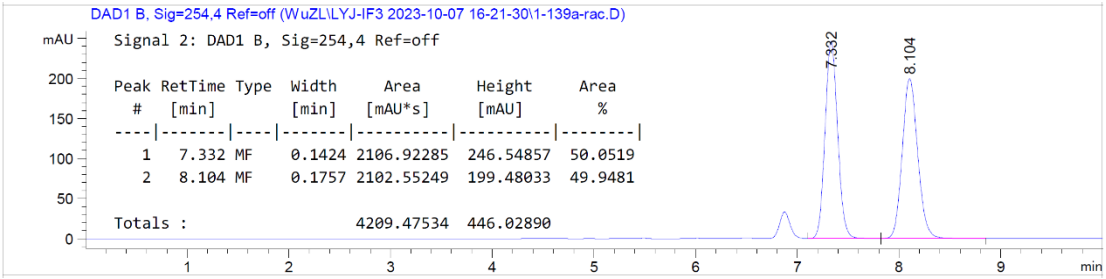
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H), 7.10 (d, *J* = 7.3 Hz, 1H), 6.99 (t, *J* = 8.7 Hz, 2H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.29 (d, *J* = 7.5 Hz, 1H), 6.03 (s, 1H), 4.73 (d, *J* = 0.9 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.34 (dd, *J* = 9.4, 8.0 Hz, 1H), 2.50 (s, 3H), 2.40 (d, *J* = 7.8 Hz, 1H), 2.35 (s, 3H), 2.30 (t, *J* = 9.2 Hz, 1H), 2.25 (s, 3H), 2.09 (dd, *J* = 8.7, 1.8 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.3, 164.1, 162.1 (d, *J* = 245.8 Hz), 153.1, 148.9, 144.3, 134.1 (d, *J* = 3.2 Hz), 131.0, 130.1 (d, *J* = 8.1 Hz), 126.7, 125.2, 124.2, 118.6, 114.3 (d, *J* = 21.3 Hz), 111.2, 62.0, 60.8, 57.2, 56.6, 52.6, 48.3, 40.7, 16.1, 14.2, 14.1, 13.9.

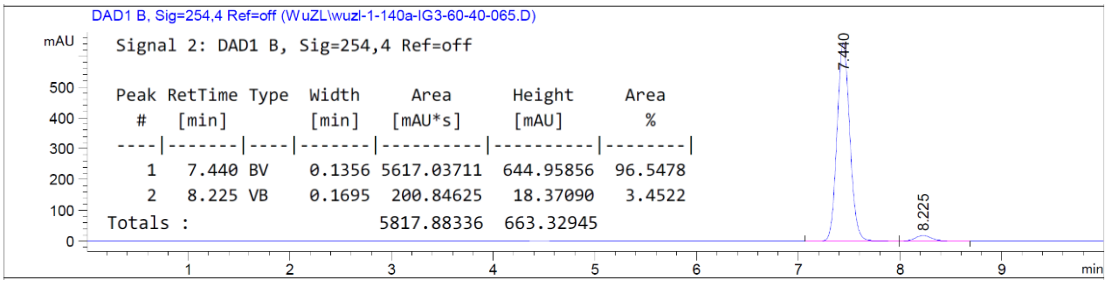
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.2 (s, 1F).

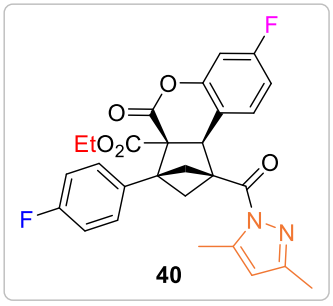
HRMS (ESI) m/z calcd. for $C_{29}H_{28}FN_2O_5$ $[M+H]^+$ 503.1977, found 503.1977.

HPLC spectrum of ***rac*-39:**



HPLC spectrum of **39:**





Ethyl (3a*S*,9b*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-7-fluoro-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (40)

The title compound was synthesized according to **General Procedure A** at -20 ℃ for 60 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **40** (81.6 mg, 81%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 9.08 min, t_R (major) = 12.69 min.

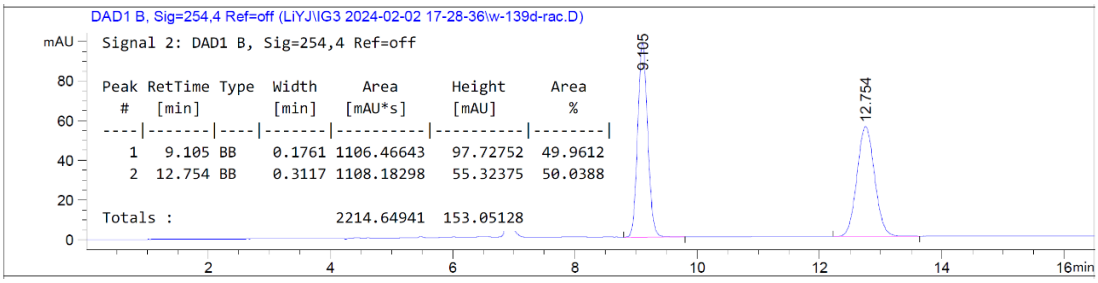
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.3, 5.5 Hz, 2H), 6.99 (t, *J* = 8.6 Hz, 2H), 6.83 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.70 (td, *J* = 8.3, 2.2 Hz, 1H), 6.47 (dd, *J* = 8.2, 6.2 Hz, 1H), 6.04 (s, 1H), 4.72 (s, 1H), 4.27 – 4.11 (m, 2H), 3.33 (t, *J* = 8.7 Hz, 1H), 2.51 (s, 3H), 2.40 (d, *J* = 7.9 Hz, 1H), 2.31 – 2.21 (m, 4H), 2.14 (d, *J* = 7.9 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.0, 163.4, 162.5 (d, *J* = 248.6 Hz), 162.2 (d, *J* = 246.0 Hz), 153.3, 151.3 (d, *J* = 11.9 Hz), 144.4, 133.7 (d, *J* = 3.2 Hz), 130.1 (d, *J* = 8.1 Hz), 129.1 (d, *J* = 9.4 Hz), 114.9 (d, *J* = 3.5 Hz), 114.4 (d, *J* = 21.4 Hz), 112.2 (d, *J* = 21.9 Hz), 111.3, 105.1 (d, *J* = 25.4 Hz), 62.1, 60.5, 56.9, 56.7, 52.0, 48.1, 40.8, 14.2, 14.0, 13.9.

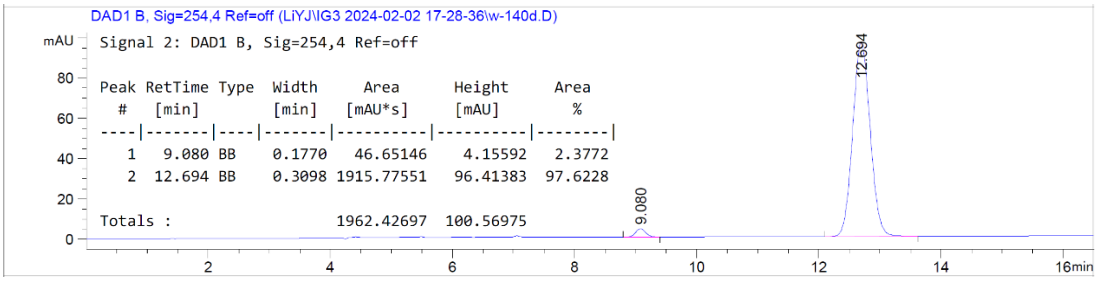
^{19}F NMR (376 MHz, $CDCl_3$) δ -110.7 (s, 1F), -114.9 (s, 1F).

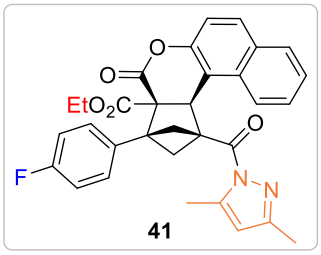
HRMS (ESI) m/z calcd. for $C_{28}H_{25}F_2N_2O_5$ $[M+H]^+$ 507.1726, found 507.1727.

HPLC spectrum of ***rac*-40:**



HPLC spectrum of **40:**





Ethyl (3a*S*,11c*S*)-1-(3,5-dimethyl-1*H*-pyrazole-1-carbonyl)-3-(4-fluorophenyl)-4-oxo-1,2,3,11c-tetrahydro-1,3-methanobenzo[*f*]cyclopenta[*c*]-chromene-3a(4*H*)-carboxylate (41)

The title compound was synthesized according to **General Procedure A** at -20 °C for 72 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **41** (52.1 mg, 48%) as a white solid.

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 8.60 min, t_R (minor) = 12.60 min.

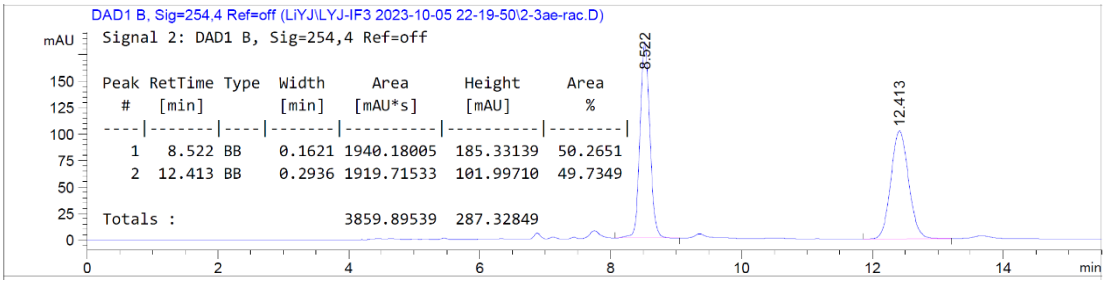
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 12.3, 8.5 Hz, 2H), 7.43 – 7.36 (m, 2H), 7.35 – 7.24 (m, 3H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 8.7 Hz, 2H), 5.74 (s, 1H), 4.89 (d, *J* = 1.0 Hz, 1H), 4.26 – 4.06 (m, 2H), 3.51 – 3.42 (m, 1H), 2.72 (t, *J* = 9.3 Hz, 1H), 2.46 (d, *J* = 8.2 Hz, 1H), 2.17 – 2.03 (m, 7H), 1.12 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 169.3, 164.4, 162.2 (d, *J* = 245.9 Hz), 152.7, 148.9, 144.4, 133.8 (d, *J* = 3.0 Hz), 131.6, 131.0, 130.5, 130.2 (d, *J* = 8.1 Hz), 128.6, 126.2, 124.9, 122.0, 117.6, 114.4 (d, *J* = 21.3 Hz), 112.4, 110.8, 62.1, 61.4, 56.6, 50.8, 47.5, 43.1, 14.1, 13.88, 13.86.

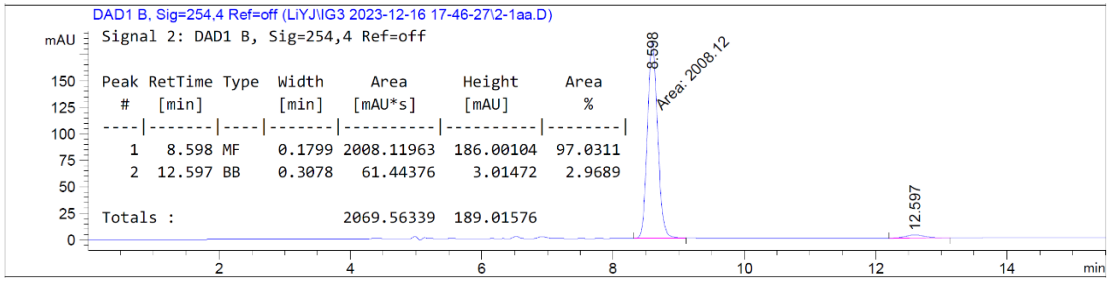
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.0 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{32}H_{28}FN_2O_5$ $[M+H]^+$ 539.1977, found 539.1981.

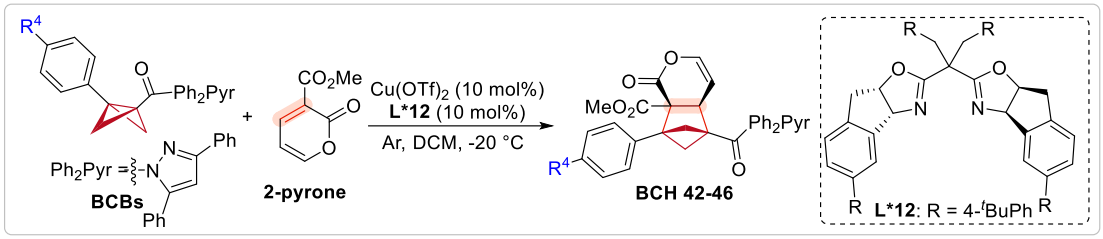
HPLC spectrum of ***rac*-41:**



HPLC spectrum of **41:**

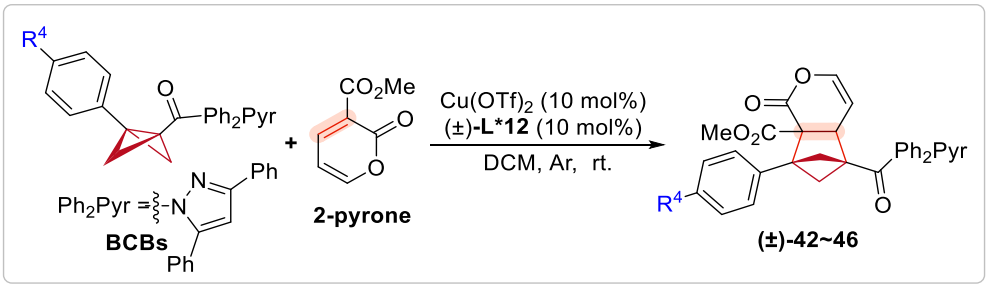


6.2 General Procedure B: Cu/Box-catalyzed asymmetric cycloaddition of BCB and 2-pyrone

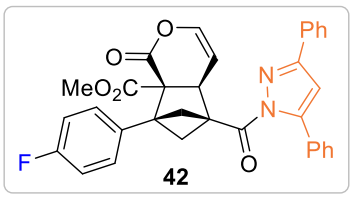


Under argon, an oven-dried, resealable Schlenk tube equipped with a magnetic stir bar was charged with $Cu(OTf)_2$ (7.23 mg, 0.02 mmol, 10 mol%), chiral Box ligand **L*12** (17.7 mg, 0.02 mmol, 10 mol%), and anhydrous DCM (2.0 mL). The solution was stirred for 1 h at ambient temperature, ensuring complete dissolution of the triflate salt and forming a homogeneous light green solution of the ligand complex, which was then cooled to -20 °C. BCB substrate (0.21 mmol, 1.05 equiv.) and 2-pyrone (0.20 mmol, 1.0 equiv.) were added under positive argon pressure. The sealed tube was stirred at -20 °C. Upon completion (monitored by TLC), the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (*n*-hexane/EtOAc) to afford the desired chiral cycloadduct. Due to the instability of the cycloadduct, which tends to decompose on silica gel, rapid column chromatography was necessary. Consequently, the NMR purity and HPLC purity of the cycloadduct were not very high due to partial decomposition during purification.

The preparation of racemic BCH products (±)-**42~46**:



The racemate was prepared following the same procedure described above, and the reactions were conducted on a 0.05 mmol scale by using $Cu(OTf)_2$ (1.81 mg, 0.005 mmol, 10 mol%) and (±)-**L*12** (4.44 mg, 0.005 mmol, 10 mol%) as catalysts at room temperature in DCM (0.5 mL) for 24-48 h. Upon completion(monitored by TLC), the solvent was removed *in vacuo*, and the residue was purified by PTLC (eluent: *n*-hexane /EtOAc)to give the desired product.



Methyl (4a*S*,7a*S*)-5-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-7-(4-fluorophenyl)-1-oxo-4a,5,6,7-tetrahydro-5,7-methanocyclopenta[*c*]pyran-7a(1*H*)-carboxylate (42)

The title compound was synthesized according to **General Procedure B** at -20 °C for 40 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **42**

(93.1 mg, 85%) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 9.82 min, t_R (minor) = 10.68 min.

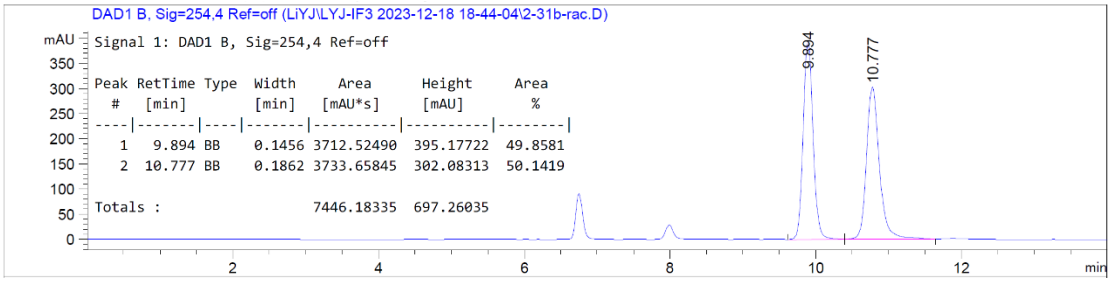
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 2H), 7.59 – 7.47 (m, 8H), 7.37 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.04 (t, *J* = 8.7 Hz, 2H), 6.84 (s, 1H), 6.69 (d, *J* = 6.4 Hz, 1H), 5.27 (dd, *J* = 6.3, 4.6 Hz, 1H), 4.23 (d, *J* = 4.2 Hz, 1H), 3.82 (s, 3H), 3.53 – 3.40 (m, 1H), 2.57 (d, *J* = 7.9 Hz, 1H), 2.42 (t, *J* = 9.0 Hz, 1H), 2.35 (dd, *J* = 8.5, 1.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 169.7, 163.6, 162.2 (d, *J* = 245.9 Hz), 154.3, 147.8, 141.4, 134.0 (d, *J* = 3.2 Hz), 131.3, 130.3, 129.9 (d, *J* = 8.2 Hz), 129.7, 129.2, 129.1 (s, 2C), 129.0 (s, 2C), 128.1 (s, 2C), 126.2 (s, 2C), 114.5 (d, *J* = 21.3 Hz), 109.7, 103.3, 60.3, 57.1, 55.4, 53.0, 50.3, 47.7, 41.7.

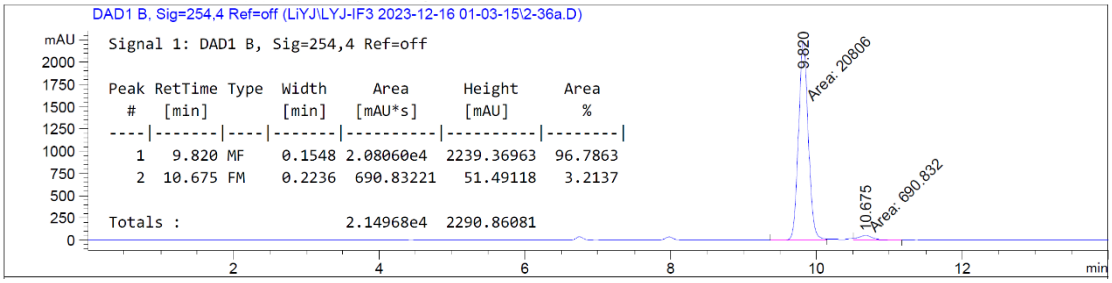
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.9 (s, 1F).

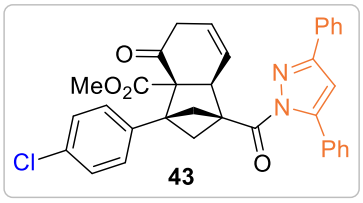
HRMS (ESI) m/z calcd. for $C_{33}H_{26}FN_2O_5$ $[M+H]^+$ 549.1821, found 549.1822.

HPLC spectrum of ***rac*-42:**



HPLC spectrum of **42:**





43

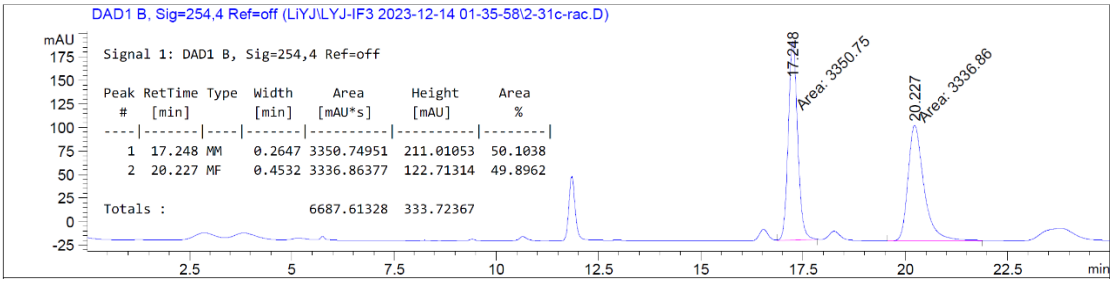
Methyl (4a*S*, 7a*S*)-7-(4-chlorophenyl)-5-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-1-oxo-4a,5,6,7-tetrahydro-5,7-methanocyclopenta[*c*]pyran-7a(1*H*)-carboxylate (43)

The title compound was synthesized according to **General Procedure B** at -20 °C for 40 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **43** (80.7 mg, 71%) as a white solid.

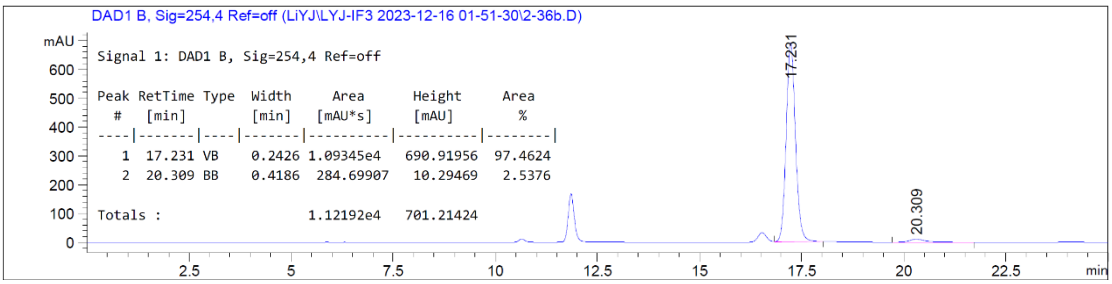
HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 80/20, flow rate = 0.55 mL/min, λ = 254 nm), t_R (major) = 17.23 min, t_R (minor) = 20.31 min.

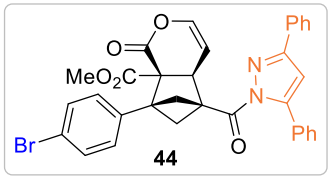
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.81 (m, 2H), 7.53 – 7.39 (m, 9H), 7.27 (s, 4H), 6.78 (s, 1H), 6.63 (dd, *J* = 6.4, 0.7 Hz, 1H), 5.21 (dd, *J* = 6.3, 4.6 Hz, 1H), 4.16 (d, *J* = 4.3 Hz, 1H), 3.76 (s, 3H), 3.42 – 3.34 (m, 1H), 2.51 (d, *J* = 7.9 Hz, 1H), 2.35 (t, *J* = 9.0 Hz, 1H), 2.28 (dd, *J* = 8.5, 1.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 169.6, 163.5, 154.3, 147.8, 141.3, 136.7, 133.4, 131.3, 130.3, 129.7, 129.6 (s, 2C), 129.2, 129.1 (s, 2C), 129.0 (s, 2C), 128.1 (s, 2C), 127.8 (s, 2C), 126.1 (s, 2C), 109.7, 103.3, 60.3, 57.0, 55.4, 53.1, 50.2, 47.7, 41.7.
HRMS (ESI) m/z calcd. for $C_{33}H_{26}ClN_2O_5$ $[M+H]^+$ 565.1525, found 565.1528.
HPLC spectrum of ***rac*-43:**



HPLC spectrum of **43:**

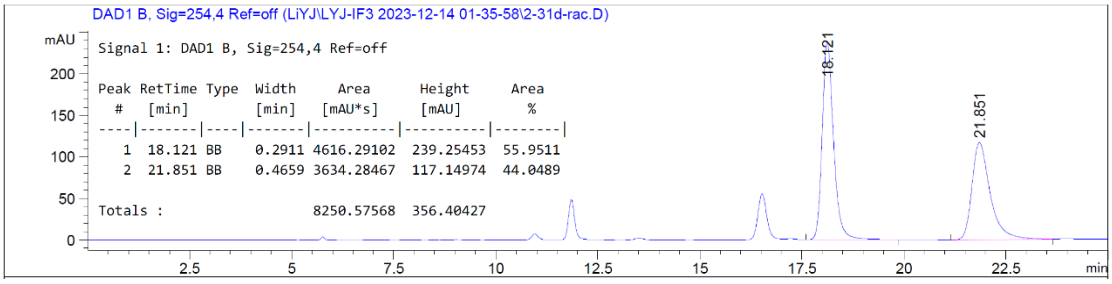




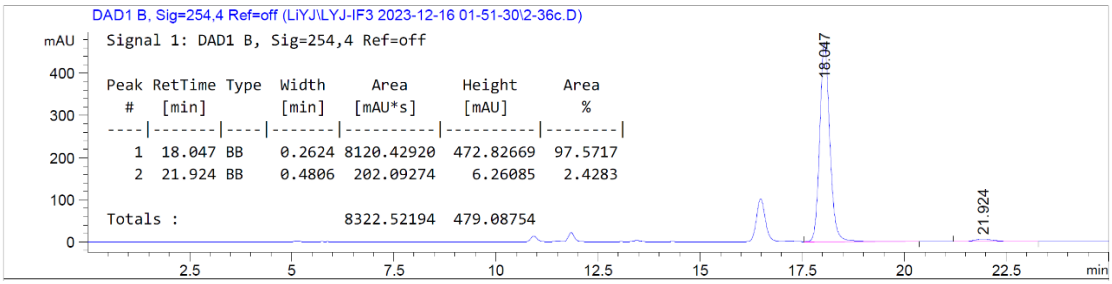
44

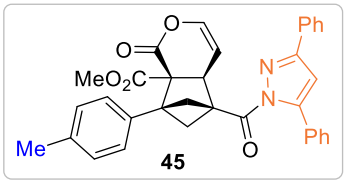
Methyl (4a*S*,7a*S*)-7-(4-bromophenyl)-5-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-1-oxo-4a,5,6,7-tetrahydro-5,7-methanocyclopenta[*c*]pyran-7a(1*H*)-carboxylate (44)

The title compound was synthesized according to **General Procedure B** at -20 °C for 40 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **44** (86.5 mg, 71%) as a white solid.
HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 80/20, flow rate = 0.55 mL/min, λ = 254 nm), t_R (major) = 18.05 min, t_R (minor) = 21.92 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.9 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.5 – 7.4 (m, 12H), 7.2 – 7.2 (m, 1H), 6.8 (s, 1H), 6.6 (dd, *J* = 6.4, 0.8 Hz, 1H), 5.2 (dd, *J* = 6.4, 4.6 Hz, 1H), 4.2 (d, *J* = 4.2 Hz, 1H), 3.8 (s, 4H), 3.4 (dd, *J* = 9.0, 8.3 Hz, 1H), 2.5 (d, *J* = 7.9 Hz, 1H), 2.4 – 2.2 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 169.6, 163.5, 154.3, 147.8, 141.3, 137.2, 131.3, 130.7 (s, 2C), 130.3, 130.0 (s, 2C), 129.7, 129.2, 129.1 (s, 2C), 129.0 (s, 2C), 128.1 (s, 2C), 126.2 (s, 2C), 121.7, 109.8, 103.3, 60.3, 57.1, 55.4, 53.1, 50.2, 47.7, 41.6.
HRMS (ESI) m/z calcd. for $C_{33}H_{26}BrN_2O_5$ $[M+H]^+$ 609.1020, found 609.1023.
HPLC spectrum of ***rac*-44:**



HPLC spectrum of **44:**





45

Methyl (4a*S*,7a*S*)-5-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-1-oxo-7-(p-tolyl)-4a,5,6,7-tetrahydro-5,7-methanocyclopenta[*c*]pyran-7a(1*H*)-carboxylate (45)

The title compound was synthesized according to **General Procedure B** at -20 ℃ for 40 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **45** (64.8 mg, 59%) as a white solid.

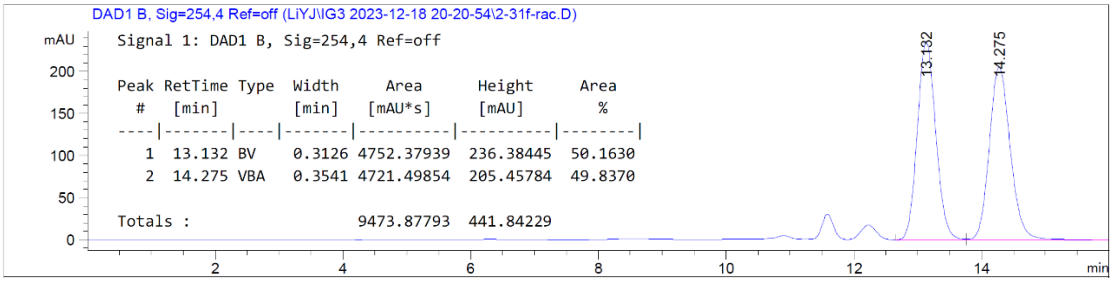
HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 12.84 min, t_R (minor) = 13.99 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 2H), 7.52 – 7.40 (m, 9H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.77 (s, 1H), 6.62 (d, *J* = 6.4 Hz, 1H), 5.19 (dd, *J* = 6.3, 4.6 Hz, 1H), 4.19 (d, *J* = 4.2 Hz, 1H), 3.75 (s, 3H), 3.46 – 3.35 (m, 1H), 2.50 (d, *J* = 7.9 Hz, 1H), 2.40 – 2.31 (m, 4H), 2.28 (dd, *J* = 8.5, 1.7 Hz, 1H).

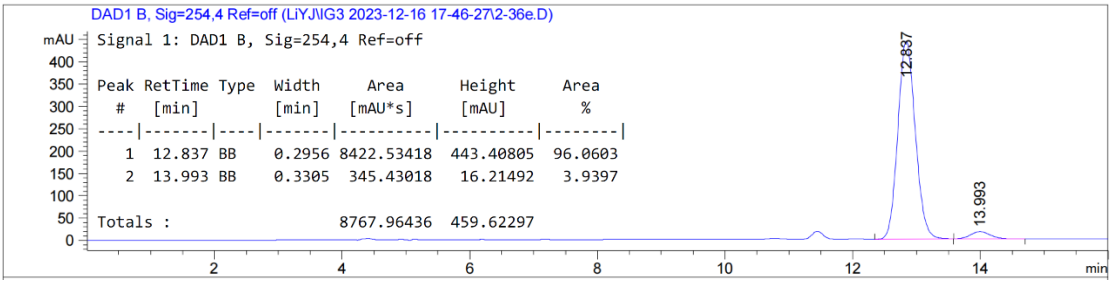
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.9, 163.6, 154.2, 147.8, 141.3, 137.1, 135.2, 131.4, 130.4, 129.6, 129.2, 129.1 (s, 2C), 129.0 (s, 2C), 128.4 (s, 2C), 128.1 (s, 2C), 128.0 (s, 2C), 126.2 (s, 2C), 109.7, 103.4, 60.4, 57.7, 55.5, 53.0, 50.4, 47.8, 41.7, 21.3.

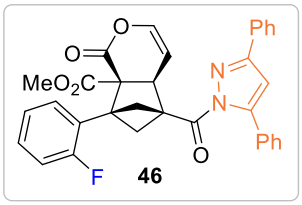
HRMS (ESI) m/z calcd. for $C_{34}H_{29}N_2O_5$ $[M+H]^+$ 545.2071, found 545.2078.

HPLC spectrum of ***rac*-45:**



HPLC spectrum of **45:**





Methyl (4a*S*,7a*S*)-5-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-7-(2-fluorophenyl)-1-oxo-4a,5,6,7-tetrahydro-5,7-methanocyclopenta[*c*]pyran-7a(1*H*)-carboxylate (46)

The title compound was synthesized according to **General Procedure B** at -20 °C for 40 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **46** (82.4 mg, 75%) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 80/20, flow rate = 0.55 mL/min, λ = 254 nm), t_R (major) = 17.74 min, t_R (minor) = 18.96 min.

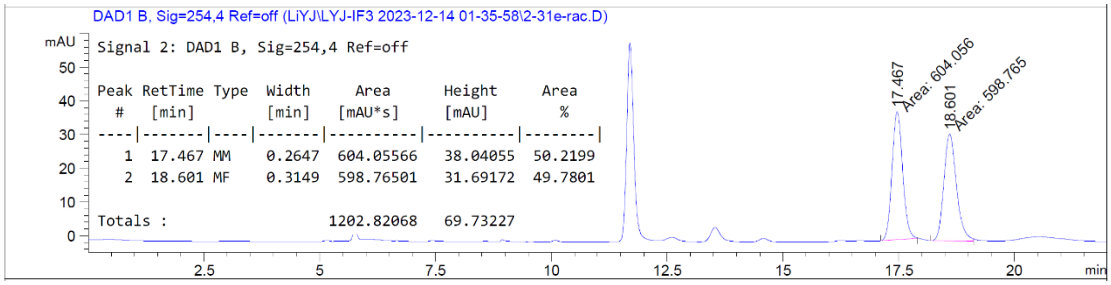
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 6.9 Hz, 2H), 7.54 – 7.38 (m, 10H), 7.31 – 7.25 (m, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 6.99 (dd, *J* = 10.4, 8.7 Hz, 1H), 6.78 (s, 1H), 6.64 (d, *J* = 6.4 Hz, 1H), 5.21 (dd, *J* = 6.3, 4.4 Hz, 1H), 4.25 (d, *J* = 3.7 Hz, 1H), 3.76 (s, 3H), 3.31 (t, *J* = 8.8 Hz, 1H), 2.56 (d, *J* = 7.8 Hz, 2H), 2.40 (dd, *J* = 8.9, 1.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 169.6, 163.6, 161.8 (d, *J* = 247.6 Hz), 154.2, 147.8, 141.4, 131.3, 131.0 (d, *J* = 4.2 Hz), 130.3, 129.6, 129.5 (d, *J* = 8.4 Hz), 129.2, 129.04 (s, 2C), 129.00 (s, 2C), 128.1 (s, 2C), 126.1 (s, 2C), 124.9 (d, *J* = 13.6 Hz), 123.3 (d, *J* = 3.3 Hz), 115.3 (d, *J* = 22.2 Hz), 109.7, 103.3, 60.1, 56.0, 54.6, 53.0, 49.5, 47.9, 42.80, 42.75.

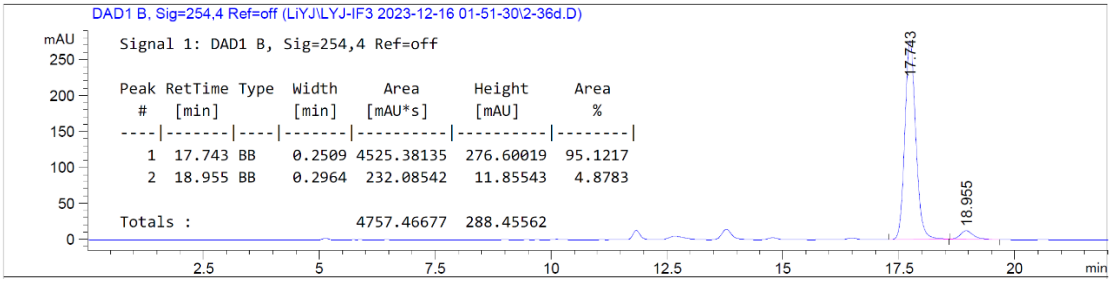
^{19}F NMR (376 MHz, $CDCl_3$) δ -112.4 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{33}H_{26}FN_2O_5$ $[M+H]^+$ 549.1821, found 549.1824.

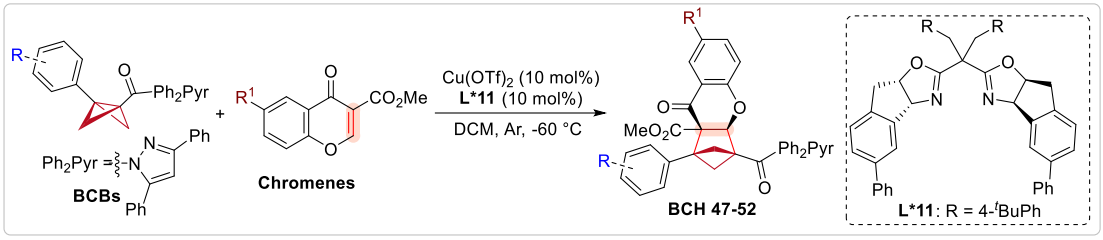
HPLC spectrum of ***rac*-46:**



HPLC spectrum of **46:**

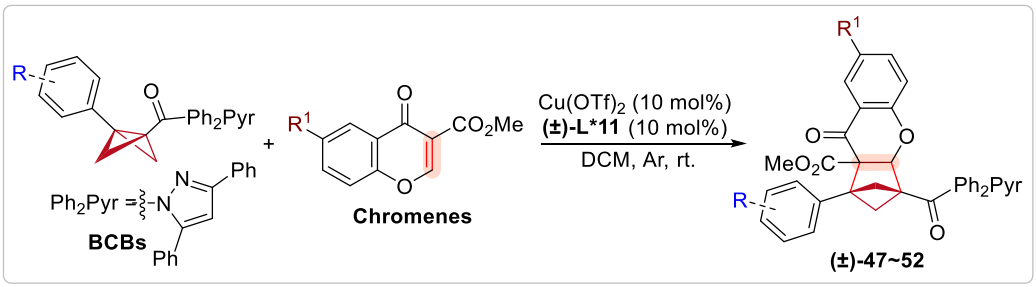


6.3 General Procedure C: Cu/Box-catalyzed asymmetric cycloaddition of BCB and substituted Chromenes

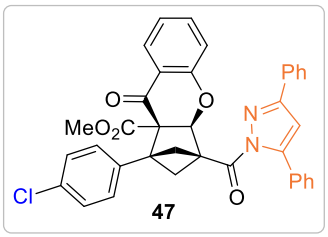


Under argon, an oven-dried, resealable Schlenk tube equipped with a magnetic stir bar was charged with $Cu(OTf)_2$ (7.23 mg, 0.02 mmol, 10 mol%), chiral Box ligand **L*11** (15.5 mg, 0.02 mmol, 10 mol%), and anhydrous DCM (2.0 mL). The solution was stirred for 1 h at ambient temperature, ensuring complete dissolution of the triflate salt and forming a homogeneous light green solution of the ligand complex, which was then cooled to -60 °C. BCB substrate (0.21 mmol, 1.05 equiv.) and substituted chromene (0.20 mmol, 1.0 equiv.) were added under positive argon pressure. The sealed tube was stirred at -60 °C. Upon completion (monitored by TLC), the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (*n*-hexane/EtOAc) to afford the desired chiral cycloadduct.

The preparation of racemic BCH products (±)-**47~52**:



The racemate was prepared following the same procedure described above, and the reactions were conducted on a 0.05 mmol scale by using $Cu(OTf)_2$ (1.81 mg, 0.005 mmol, 10 mol%) and (±)-**L*12** (4.44 mg, 0.005 mmol, 10 mol%) as catalysts at room temperature in DCM (0.5 mL) for 24-48 h. Upon completion (monitored by TLC), the solvent was removed *in vacuo*, and the residue was purified by PTLC (eluent: *n*-hexane /EtOAc)to give the desired product.

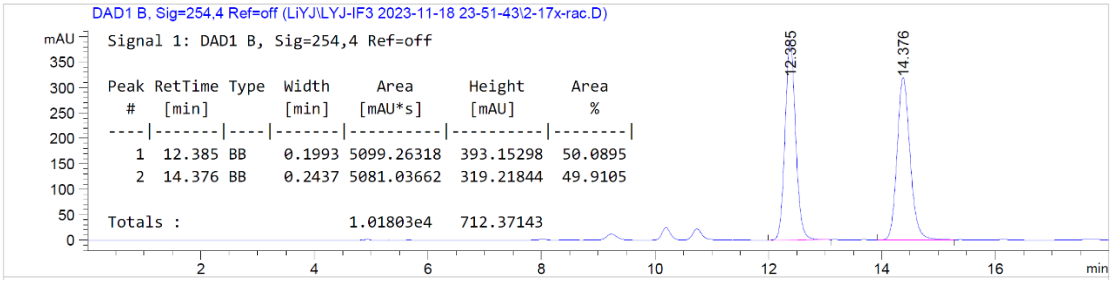


Methyl (3a*S*,9a*S*)-1-(4-chlorophenyl)-3-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-9-oxo-1,2,3,3a-tetrahydro-1,3-methanocyclopenta[*b*]chromene-9a(9*H*)-carboxylate (47)

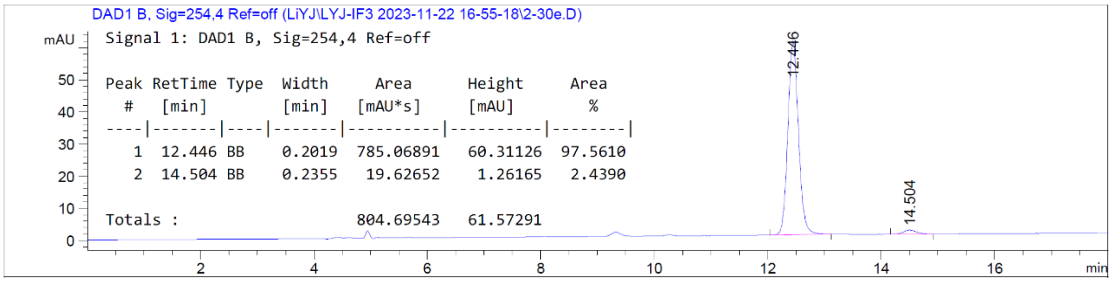
The title compound was synthesized according to **General Procedure C** at -20 °C for 40 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **47** (103.4 mg, 84%) as a white solid. The diastereomeric ratio (d.r.) was 15:1, as determined by the ^1H NMR of the crude product.

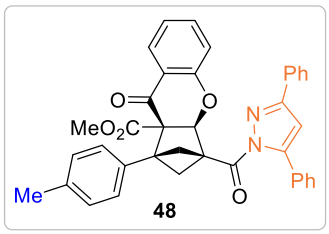
HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 12.45 min, t_R (minor) = 14.50 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.82 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.54 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.50 – 7.39 (m, 7H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.05 – 6.96 (m, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.81 (s, 1H), 6.20 (d, *J* = 2.0 Hz, 1H), 3.73 (s, 3H), 3.21 – 3.11 (m, 1H), 2.65 (t, *J* = 9.2 Hz, 1H), 2.42 (d, *J* = 8.2 Hz, 1H), 2.22 (dd, *J* = 8.6, 2.0 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 186.7, 170.2, 168.9, 160.5, 154.2, 147.8, 137.1, 136.7, 133.3, 131.4, 130.4, 129.7 (s, 2C), 129.5, 129.1, 129.04 (s, 2C), 128.97 (s, 2C), 128.1 (s, 2C), 127.7 (s, 2C), 127.0, 126.1 (s, 2C), 121.6, 119.4, 118.1, 109.6, 87.0, 63.5, 57.8, 56.3, 52.9, 45.6, 41.0.
HRMS (ESI) m/z calcd. for $C_{37}H_{28}ClN_2O_5$ $[M+H]^+$ 615.1681, found 615.1678.
HPLC spectrum of ***rac*-47:**



HPLC spectrum of **47:**





48

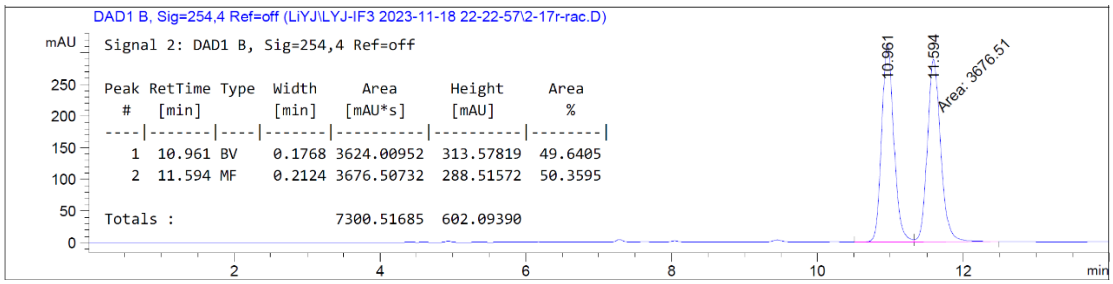
Methyl (3a*S*,9a*S*)-3-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-9-oxo-1-(p-tolyl)-1,2,3,3a-tetrahydro-1,3-methanocyclopenta[*b*]chromene-9a(9*H*)-carboxylate (48)

The title compound was synthesized according to **General Procedure C** at -20 ℃ for 48 h, using chiral Box ligand **L*12** (10 mol%). The product was purified by silica gel flash column chromatography (4-6% EtOAc in *n*-hexane) to afford the desired product **48** (110.2 mg, 93%) as a white solid.
HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 11.00 min, t_R (minor) = 11.67 min.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.86 (m, 1H), 7.83 (d, *J* = 6.9 Hz, 2H), 7.59 – 7.50 (m, 2H), 7.49 – 7.35 (m, 7H), 7.19 – 7.09 (m, 4H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.79 (s, 1H), 6.24 (d, *J* = 1.1 Hz, 1H), 3.71 (s, 3H), 3.18 (t, *J* = 8.9 Hz, 1H), 2.66 (t, *J* = 9.1 Hz, 1H), 2.42 (d, *J* = 8.1 Hz, 1H), 2.33 (s, 3H), 2.22 (dd, *J* = 8.4, 1.1 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 186.9, 170.4, 169.2, 160.5, 154.1, 147.8, 137.1, 136.9, 135.2, 131.5, 130.5, 129.5, 129.15, 129.12 (s, 2C), 129.0 (s, 2C), 128.3 (s, 2C), 128.1

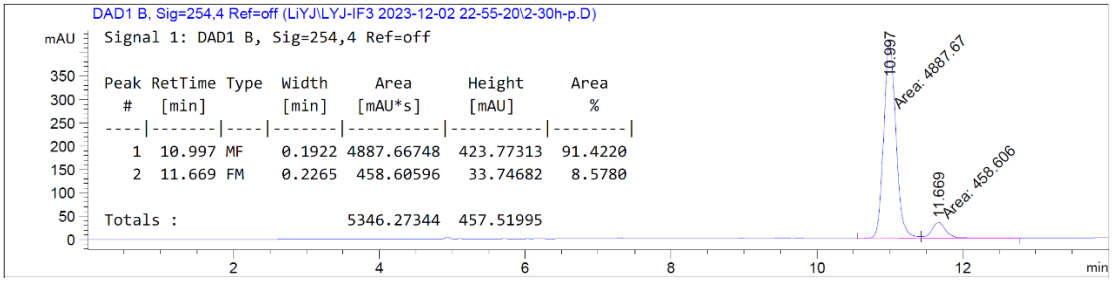
(s, 4C), 127.1, 126.2 (s, 2C), 121.6, 119.7, 118.1, 109.6, 87.3, 63.7, 58.0, 56.9, 52.9, 45.8, 41.1, 21.4.

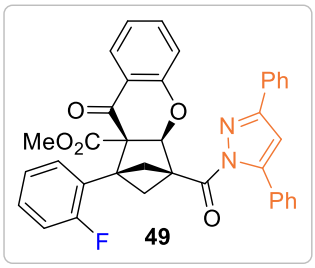
HRMS (ESI) m/z calcd. for $C_{38}H_{31}N_2O_5$ $[M+H]^+$ 595.2228, found 595.2230.

HPLC spectrum of ***rac*-48:**



HPLC spectrum of **48:**





49

Methyl (3a*S*,9a*S*)-3-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-1-(2-fluorophenyl)-9-oxo-1,2,3,3a-tetrahydro-1,3-methanocyclopenta[*b*]chromene-9a(9*H*)-carboxylate (49)

The title compound was synthesized according to **General Procedure C** at -20 °C for 40 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **49** (87.6 mg, 73%) as a white solid. The d.r. was 29:1, as determined by the ^{1}H NMR of the crude product.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 10.13 min, t_R (minor) = 10.95 min.

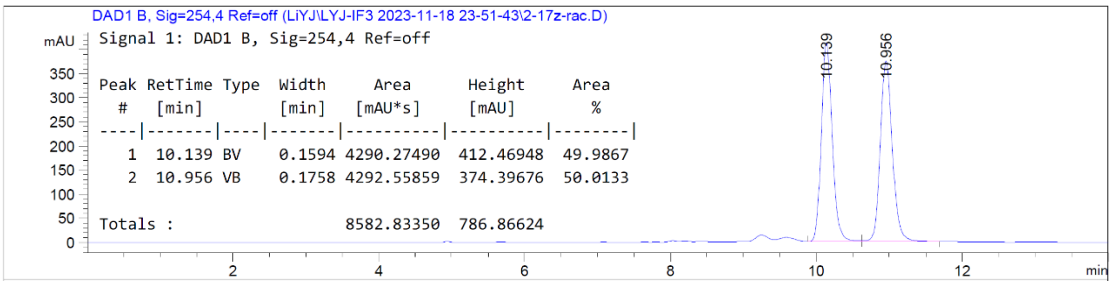
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.79 (m, 3H), 7.55 (dd, *J* = 7.2, 2.3 Hz, 2H), 7.51 – 7.39 (m, 8H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 6.99 (dd, *J* = 15.8, 7.9 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.81 (s, 1H), 6.32 (d, *J* = 1.9 Hz, 1H), 3.75 (s, 3H), 3.10 (t, *J* = 8.9 Hz, 1H), 2.81 (td, *J* = 9.3, 3.9 Hz, 1H), 2.46 (d, *J* = 8.2 Hz, 1H), 2.31 (dd, *J* = 9.0, 1.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.6, 169.9, 169.0, 161.5 (d, *J* = 247.5 Hz), 160.5, 154.1, 147.7, 136.8, 131.5, 131.2 (d, *J* = 4.2 Hz), 130.4, 129.5, 129.4, 129.03 (d, *J* = 9.2 Hz), 129.02, 128.9, 128.1, 127.2, 126.1, 125.0 (d, *J* = 13.8 Hz), 123.3 (d, *J* = 3.0 Hz), 121.5, 119.6, 117.9, 115.1 (d, *J* = 22.2 Hz), 109.5, 86.7, 63.9, 58.6, 53.9, 52.9, 46.0, 41.6.

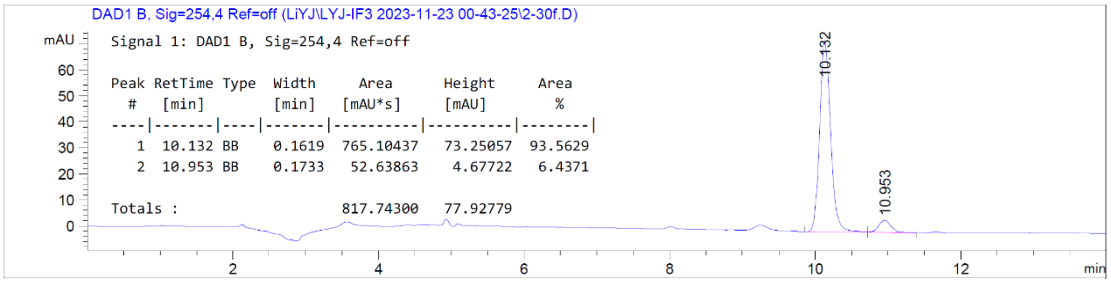
^{19}F NMR (376 MHz, $CDCl_3$) δ -112.0 (s, 1F).

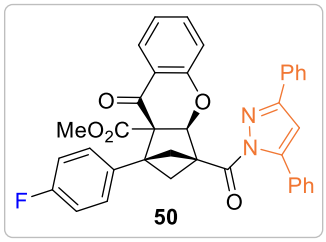
HRMS (ESI) m/z calcd. for $C_{37}H_{28}FN_2O_5$ $[M+H]^+$ 599.1977, found 599.1978.

HPLC spectrum of ***rac*-49:**



HPLC spectrum of **49:**





Methyl (3a*S*,9a*S*)-3-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-1-(4-fluorophenyl)-9-oxo-1,2,3,3a-tetrahydro-1,3-methanocyclopenta[*b*]chromene-9a(9*H*)-carboxylate (50)

The title compound was synthesized according to **General Procedure C** at -20 °C for 48 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **50** (114.1 mg, 95%) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 10.54 min, t_R (minor) = 12.09 min.

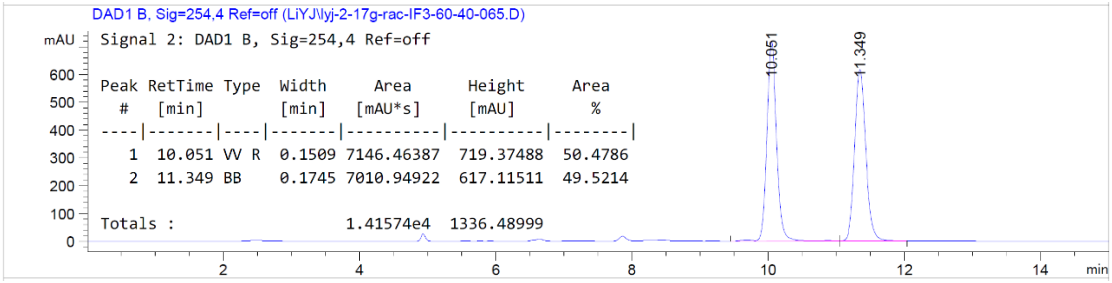
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.82 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.57 – 7.52 (m, 2H), 7.50 – 7.40 (m, 7H), 7.25 – 7.18 (m, 2H), 7.04 – 6.96 (m, 3H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.81 (s, 1H), 6.20 (d, *J* = 1.9 Hz, 1H), 3.73 (s, 3H), 3.20 – 3.12 (m, 1H), 2.65 (t, *J* = 9.2 Hz, 1H), 2.43 (d, *J* = 8.2 Hz, 1H), 2.22 (dd, *J* = 8.6, 2.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.8, 170.3, 169.0, 162.1 (d, *J* = 245.9 Hz), 160.5, 154.2, 147.7, 137.0, 133.9 (d, *J* = 3.3 Hz), 131.4, 130.4, 130.0 (d, *J* = 8.1 Hz), 129.5, 129.1, 129.03 (s, 2C), 128.96 (s, 2C), 128.1 (s, 2C), 127.0, 126.1 (s, 2C), 121.6, 119.4, 118.1, 114.4 (d, *J* = 21.4 Hz), 109.6, 87.1, 63.5, 57.8, 56.3, 52.9, 45.7, 41.0.

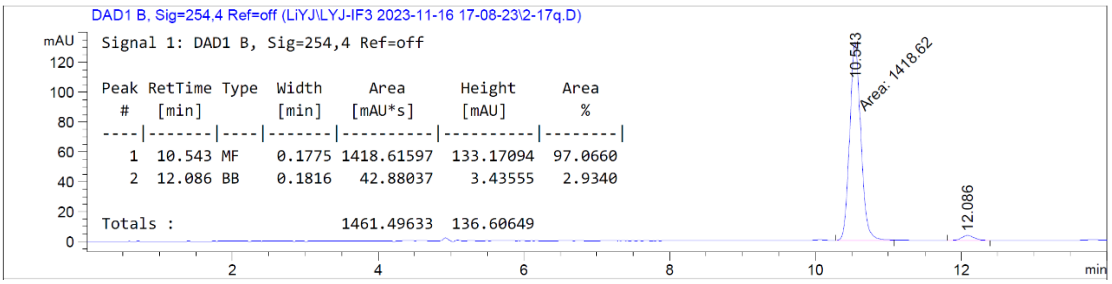
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.0 (s, 1F).

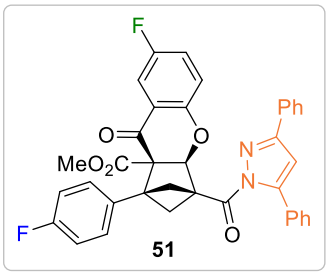
HRMS (ESI) m/z calcd. for $C_{37}H_{28}FN_2O_5$ $[M+H]^+$ 599.1977, found 599.1983.

HPLC spectrum of ***rac*-50:**



HPLC spectrum of **50:**





Methyl (3a*S*,9a*S*)-3-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-7-fluoro-1-(4-fluorophenyl)-9-oxo-1,2,3,3a-tetrahydro-1,3-methanocyclopenta[*b*]chromene-9a(9*H*)-carboxylate (51)

The title compound was synthesized according to **General Procedure C** at -20 °C for 48 h, with the addition of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate ($NaBAr^F_4$, 20 mol%). The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **51** (88.7 mg, 72%) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 9.74 min, t_R (minor) = 12.46 min.

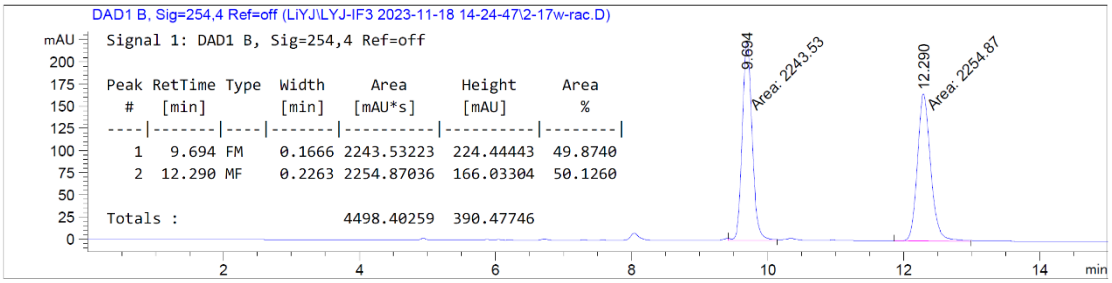
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 6.7 Hz, 2H), 7.59 – 7.37 (m, 9H), 7.27 – 7.09 (m, 3H), 7.00 (t, *J* = 8.4 Hz, 2H), 6.87 (dd, *J* = 8.9, 3.8 Hz, 1H), 6.81 (s, 1H), 6.19 (s, 1H), 3.73 (s, 3H), 3.17 (t, *J* = 8.8 Hz, 1H), 2.63 (t, *J* = 9.1 Hz, 1H), 2.41 (d, *J* = 8.1 Hz, 1H), 2.24 (d, *J* = 8.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.4, 170.0, 168.9, 162.2 (d, *J* = 246.3 Hz), 157.2 (d, *J* = 242.6 Hz), 156.7, 154.2, 147.8, 133.7 (d, *J* = 3.1 Hz), 131.4, 130.4, 130.0 (d, *J* = 8.0 Hz), 129.6, 129.2, 129.1 (s, 2C), 129.0 (s, 2C), 128.1 (s, 2C), 126.1 (s, 2C), 124.7 (d, *J* = 24.6 Hz), 119.9 (d, *J* = 7.3 Hz), 119.7 (d, *J* = 6.3 Hz), 114.5 (d, *J* = 21.4 Hz), 111.9 (d, *J* = 23.8 Hz), 109.7, 87.3, 63.2, 57.8, 56.4, 53.0, 45.6, 41.2.

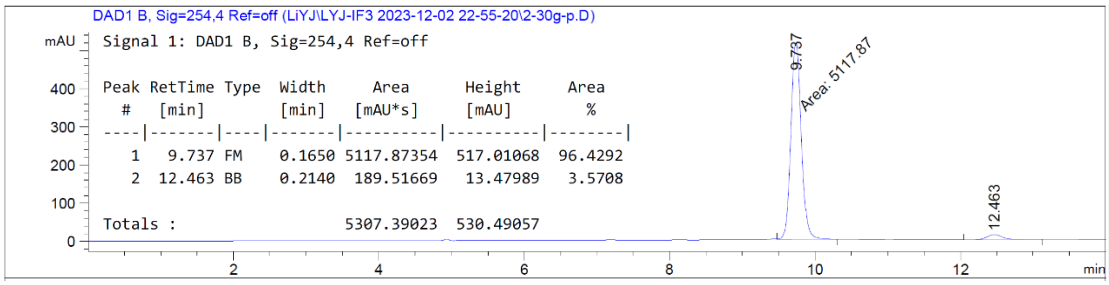
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.7 (s, 1F), -121.0 (s, 1F).

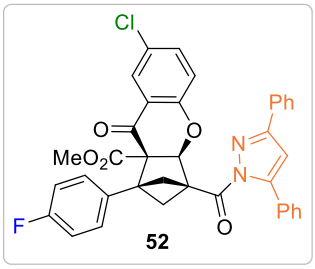
HRMS (ESI) m/z calcd. for $C_{37}H_{27}F_2N_2O_5$ $[M+H]^+$ 617.1883, found 617.1884.

HPLC spectrum of ***rac*-51**



HPLC spectrum of **51:**





Methyl (3a*S*,9a*S*)-7-chloro-3-(3,5-diphenyl-1*H*-pyrazole-1-carbonyl)-1-(4-fluorophenyl)-9-oxo-1,2,3,3a-tetrahydro-1,3-methanocyclopenta[*b*]chromene-9a(9*H*)-carboxylate (52)

The title compound was synthesized according to **General Procedure C** at -20 °C for 40 h. The product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford the desired product **52** (103.5 mg, 82%) as a white solid.

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 10.09 min, t_R (minor) = 11.58 min.

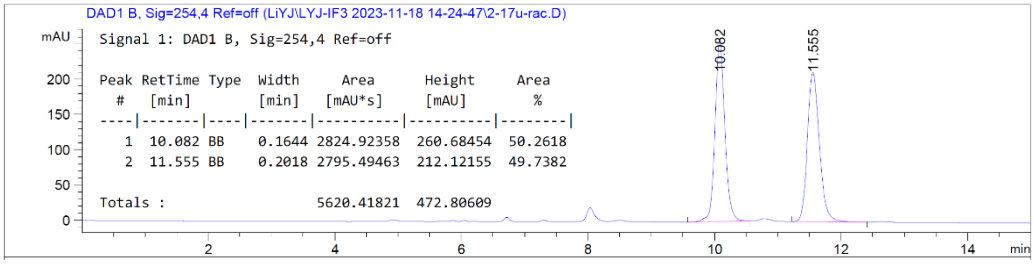
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 2.6 Hz, 1H), 7.81 – 7.76 (m, 2H), 7.56 – 7.49 (m, 2H), 7.50 – 7.41 (m, 6H), 7.35 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.21 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 1H), 6.81 (s, 1H), 6.18 (d, *J* = 1.7 Hz, 1H), 3.73 (s, 3H), 3.15 (t, *J* = 8.9 Hz, 1H), 2.63 (t, *J* = 9.2 Hz, 1H), 2.42 (d, *J* = 8.2 Hz, 1H), 2.25 (dd, *J* = 8.7, 1.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.0, 169.9, 168.8, 162.2 (d, *J* = 246.3 Hz), 158.9, 154.2, 147.8, 136.8, 133.6 (d, *J* = 3.3 Hz), 131.3, 130.3, 130.0 (d, *J* = 8.1 Hz), 129.6, 129.2, 129.05 (s, 2C), 128.98 (s, 2C), 128.1 (s, 2C), 127.0, 126.2 (s, 2C), 126.1, 120.0, 119.9, 114.5 (d, *J* = 21.4 Hz), 109.7, 87.4, 63.2, 57.8, 56.4, 53.0, 45.6, 41.2.

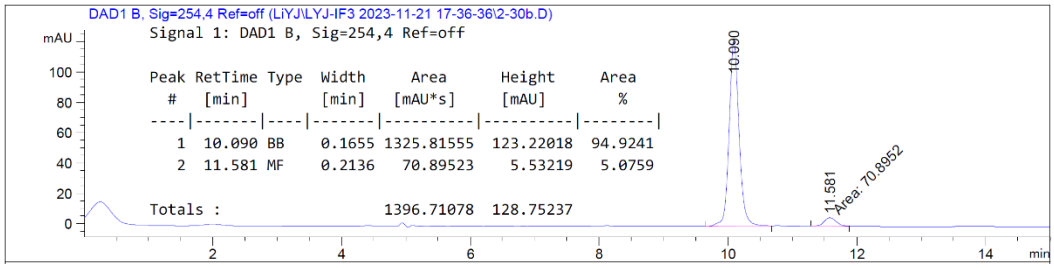
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.7 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{37}H_{27}ClFN_2O_5$ $[M+H]^+$ 633.1587, found 633.1587.

HPLC spectrum of ***rac*-52:**

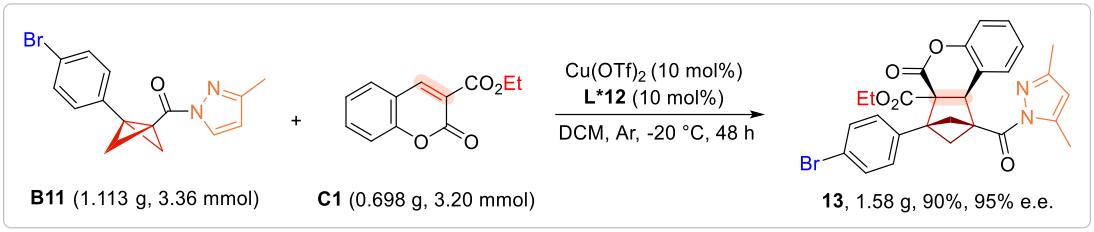


HPLC spectrum of **52:**



7. Gram-scale synthesis and synthetic applications

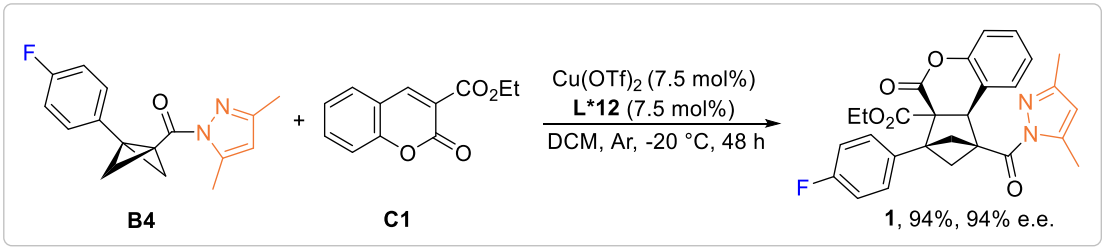
7.1 Gram-scale synthesis



Under argon, $Cu(OTf)_2$ (116 mg, 0.32 mmol, 10 mol%), **L*12** (284 mg, 0.32 mmol, 10 mol%), and anhydrous DCM (32 mL) were added to an oven-dried 100 mL Schlenk tube equipped with a magnetic stir bar. The mixture was stirred at room temperature for 1 h, then cooled to -20 °C. BCB substrate **B11** (1113 mg, 3.36 mmol, 1.05 equiv.) and coumarin substrate **C1** (698 mg, 3.20 mmol, 1.0 equiv.) were added under positive argon pressure. The tube was sealed and stirred at -20 °C for 48 h. Upon completion (monitored by TLC), the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (*n*-hexane/EtOAc) to afford the chiral BCH product **13** (1579 mg, 90%) as a white solid.

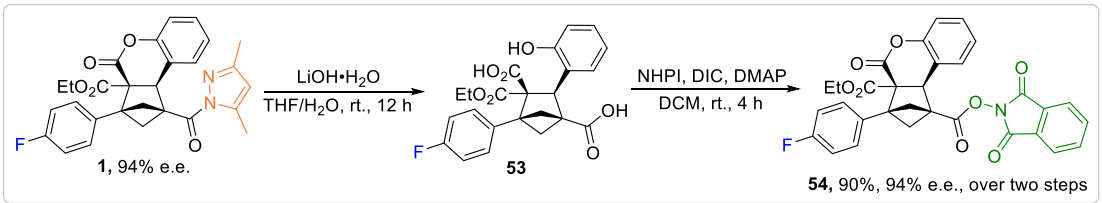
7.2 Synthetic applications

Synthesis of chiral BCH **1**:



Compound **1** was prepared following the protocol for compound **13** described in gram-scale synthesis, using BCB substrate **B4** (630 mg, 2.33 mmol, 1.05 equiv.) and coumarin substrate **C1** (484 mg, 2.22 mmol, 1.0 equiv.), $Cu(OTf)_2$ (58 mg, 0.165 mmol, 7.5 mol%), **L*12** (142 mg, 0.165 mmol, 7.5 mol%), and anhydrous DCM (22.0 mL). The sealed tube was stirred at -20 °C for 48 h. The crude product was purified through silica gel flash column chromatography (PE/EtOAc), yielding chiral cycloadduct **1** (1.02 g, 94%) as a white solid.

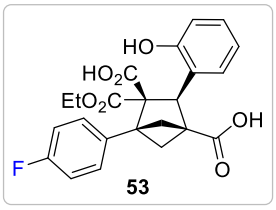
Synthesis of **54**:



Step 1: Compound **1** (1.02 g, 2.1 mmol, 1.0 equiv.) was dissolved in a mixture of THF

(10 mL) and H_2O (10 mL). Lithium hydroxide monohydrate (353 mg, 8.4 mmol, 4.0 equiv.) was added in one portion, and the mixture was stirred at room temperature for 12 h. The reaction mixture was then extracted with EtOAc (30 mL), and the organic phase was separated. The aqueous phase was acidified to pH = 1 with 1 N HCl and extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the carboxylic acid **53** as a white solid, which was used in the next step without further purification.

Step 2: **53** (~2.10 mmol, 1.0 equiv.), *N*-Hydroxyphthalimide (NHPI, 377 mg, 2.31 mmol, 1.1 equiv.), DMAP (28 mg, 0.23 mmol, 0.11 equiv.), and DCM (210 mL) were added to a 500 mL round-bottom flask. The mixture was stirred vigorously, and *N*,*N*'-diisopropylcarbodiimide (DIC, 0.79 mL, 5.04 mmol, 2.4 equiv.) was added dropwise *via* a syringe. The mixture was stirred vigorously at room temperature for 4 h. The reaction mixture was washed twice with water, and the combined aqueous phases were extracted twice with DCM. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography [eluent: PE/EtOAc] to yield **54** (1.05 g, 90%) as a white to pale yellow solid.



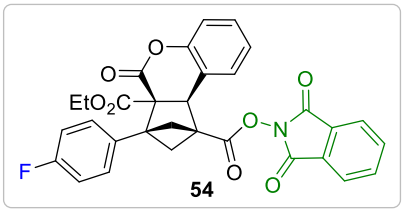
(2*S*,3*R*)-3-(ethoxycarbonyl)-4-(4-fluorophenyl)-2-(2-hydroxyphenyl)bicyclo[2.1.1]hexane-1,3-dicarboxylic acid (53)

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 2H, COO*H*), 9.31 (s, 1H, O*H*), 7.23 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.15 (d, *J* = 6.9 Hz, 1H), 7.07 (t, *J* = 8.9 Hz, 2H), 7.03 – 6.97 (m, 1H), 6.76 – 6.62 (m, 2H), 4.90 (s, 1H), 3.97 – 3.86 (m, 2H), 3.33 (s, 1H), 2.49 – 2.42 (m, 1H), 2.24 (dd, *J* = 7.3, 1.6 Hz, 1H), 1.96 – 1.87 (m, 1H), 0.84 (t, *J* = 7.1 Hz, 3H).

After D_2O exchange:

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.20 (d, *J* = 6.2 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.02 (dd, *J* = 17.1, 8.4 Hz, 3H), 6.74 – 6.62 (m, 2H), 4.87 (s, 1H), 3.90 (d, *J* = 6.8 Hz, 2H), 3.30 (t, *J* = 8.2 Hz, 1H), 2.22 (d, *J* = 7.1 Hz, 1H), 1.89 (d, *J* = 5.9 Hz, 1H), 0.81 (t, *J* = 7.0 Hz, 3H).

The experimental results confirmed the presence of three exchangeable hydrogen atoms, including two carboxylic acid hydrogens and one hydroxyl group, indicating the hydrolysis of the lactone moiety as well.



1-(1,3-dioxoisoindolin-2-yl) 3a-ethyl (3a*S*,9b*S*)-3-(4-fluorophenyl)-4-oxo-2,3-dihydro-1,3-methano-cyclo-penta[*c*]chromene-1,3a(4*H*,9b*H*)-dicarboxylate (54)

HPLC analysis: CHIRALPAK® IA-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 230 nm), t_R (major) = 12.96 min, t_R (minor) = 21.82 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.82 (dd, *J* = 5.5, 3.1 Hz,

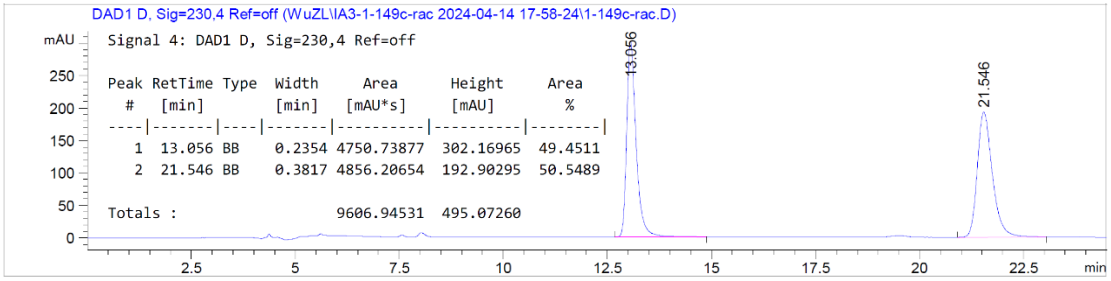
2H), 7.72 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.39 (td, *J* = 7.8, 1.7 Hz, 1H), 7.34 – 7.27 (m, 3H), 7.14 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.01 (t, *J* = 8.7 Hz, 2H), 4.34 (s, 1H), 4.27 – 4.09 (m, 2H), 3.23 – 3.14 (m, 1H), 2.62 (d, *J* = 7.8 Hz, 1H), 2.32 (d, *J* = 6.3 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 166.5, 163.3, 162.3 (d, *J* = 246.6 Hz), 161.6, 150.4, 134.9, 133.0 (d, *J* = 3.4 Hz), 130.1, 129.9 (d, *J* = 8.1 Hz), 129.9, 128.8, 125.6, 124.1, 117.4, 117.3, 114.5 (d, *J* = 21.5 Hz), 62.4, 60.2, 58.4, 51.5, 51.4, 46.7, 40.5, 13.9.

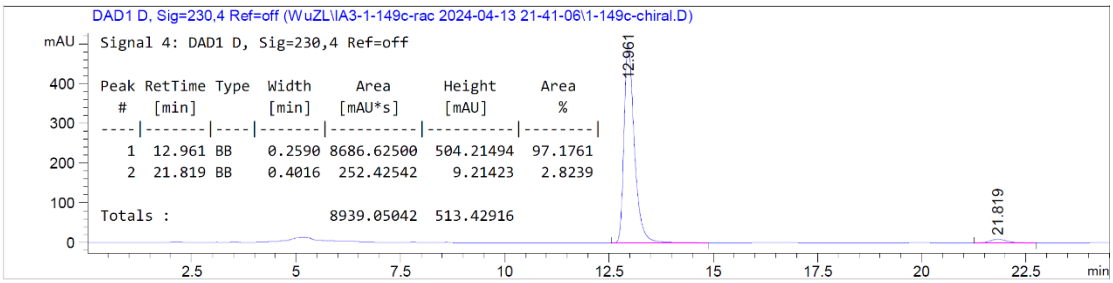
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.3 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{31}H_{23}FNO_8$ $[M+H]^+$ 556.1402, found 556.1413.

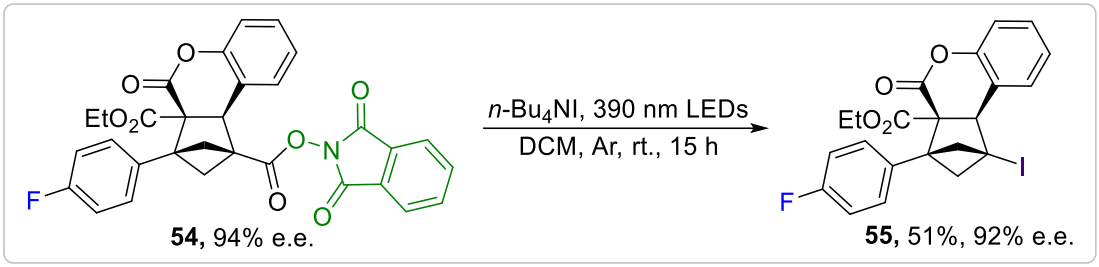
HPLC spectrum of ***rac*-54:**



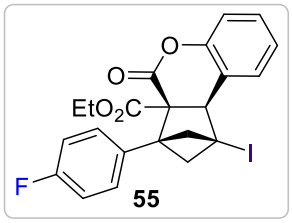
HPLC spectrum of **54:**



Synthesis of **55**:



Following a reported procedure with slight modifications[34], **54** (83 mg, 0.15 mmol, 1.0 equiv.) and tetrabutylammonium iodide (111 mg, 0.30 mmol, 2.0 equiv.), and anhydrous DCM (3 mL) were added to an oven-dried Schlenk tube equipped with a magnetic stir bar under argon. The reaction mixture was stirred under irradiation with a 12 W blue LED (390 nm) for 15 h. Upon complete consumption of **54**, the mixture was concentrated *in vacuo* and purified by flash column chromatography (PE/DCM = 10/1 to 4/1) to afford the product **55** (37.4 mg, 51%) as a white solid.



Ethyl (3a*S*,9b*R*)-3-(4-fluorophenyl)-1-iodo-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[c]chromene-3a(4H)-carboxylate (55)

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 8.33 min, t_R (minor) = 8.79 min.

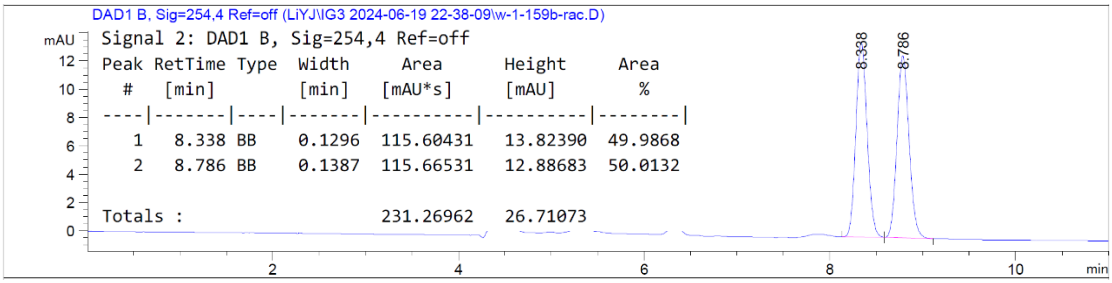
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.28 – 7.19 (m, 3H), 7.13 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.99 (t, *J* = 8.7 Hz, 2H), 4.20 – 4.06 (m, 2H), 3.88 (d, *J* = 2.3 Hz, 1H), 3.14 (dd, *J* = 9.9, 7.8 Hz, 1H), 2.59 (d, *J* = 7.8 Hz, 1H), 2.45 (dd, *J* = 9.8, 8.4 Hz, 1H), 2.30 (dd, *J* = 8.4, 2.2 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 163.4, 162.3 (d, *J* = 246.5 Hz), 150.7, 132.7 (d, *J* = 3.3 Hz), 131.6, 130.0 (d, *J* = 8.3 Hz), 129.9, 124.2, 117.8, 117.4, 114.5 (d, *J* = 21.4 Hz), 62.3, 62.0, 59.4, 55.5, 52.9, 49.2, 30.1, 13.8.

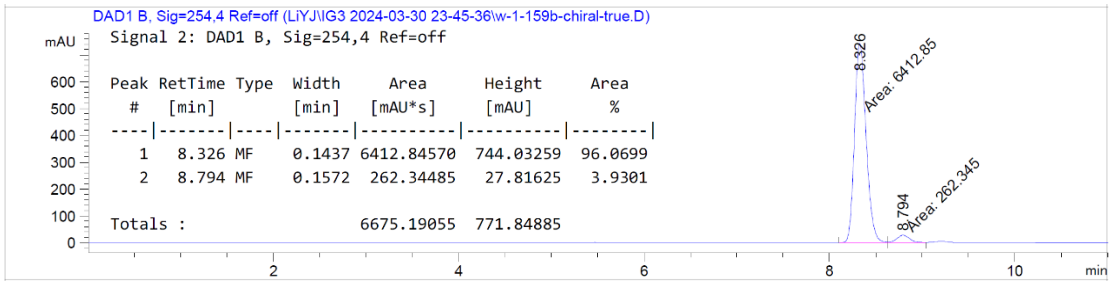
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.5 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{22}H_{19}FIO_4$ $[M+H]^+$ 493.0307, found 493.0315.

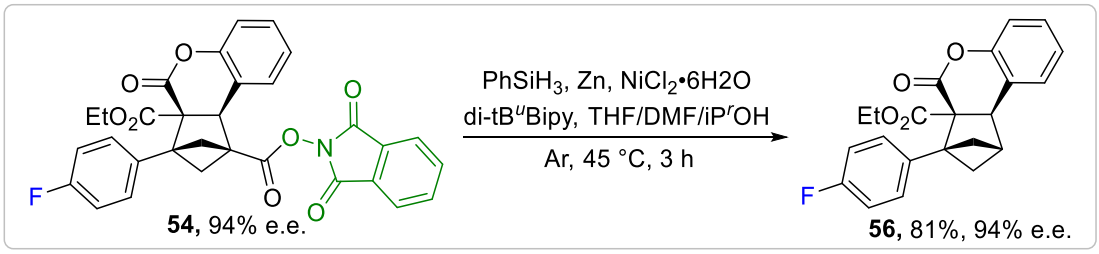
HPLC spectrum of ***rac*-55:**



HPLC spectrum of **55:**

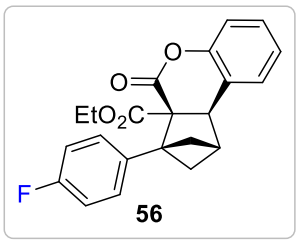


Synthesis of **56**:



Following a reported procedure with slight modifications[35], $NiCl_2 \cdot 6H_2O$ (48 mg, 0.20 mmol, 10 mol%), ligand 4,4'-di-*tert*-butyl-2,2'-bipyridine (di-^{t}BuBipy, 107 mg, 0.40 mmol, 20 mol%), and anhydrous DMF (2.0 mL) were added to an oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar under argon. The tube was sealed and stirred at room temperature for 10 minutes to form the catalyst solution in DMF. Under

argon, **54** (1.13 g, 2.03 mmol, 1.0 equiv.), Zn powder (66 mg, 1.0 mmol, 0.5 equiv.), anhydrous THF (10.0 mL), and isopropanol (1.0 mL) were added to an oven-dried 100 mL Schlenk tube equipped with a magnetic stir bar. The prepared catalyst solution in DMF and $PhSiH_3$ (380 μL, 3.0 mmol, 1.5 equiv.) were added in quick succession (*Note: phenylsilane should be added immediately after the addition of [Ni] stock solution.*). The Schlenk tube was placed in a preheated 45 °C oil bath and stirred for 3 h. Upon completion, the reaction mixture was cooled to room temperature and quenched with a saturated NH_4Cl solution and water (1:1 v/v). The mixture was extracted with EtOAc three times, and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (PE/EtOAc = 20/1 to 10/1) to afford the desired product **56** (600 mg, 81%) as a white solid.



56

Ethyl (3a*S*,9b*R*)-3-(4-fluorophenyl)-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (56)

HPLC analysis: CHIRALPAK® ID-3 (*n*-hexane/*i*-PrOH = 80/20, flow rate = 0.40 mL/min, λ = 254 nm), t_R (major) = 17.66 min, t_R (minor) = 18.43 min.

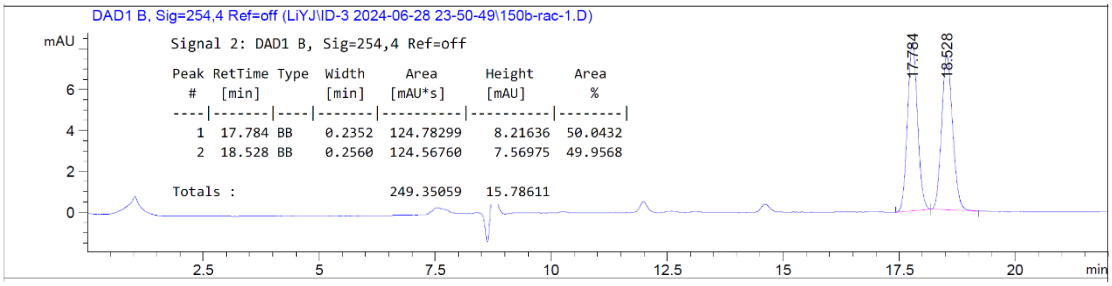
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 4H), 7.23 – 7.16 (m, 1H), 7.10 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.97 (t, *J* = 8.8 Hz, 2H), 4.21 – 4.06 (m, 2H), 3.83 (s, 1H), 2.70 (dd, *J* = 2.8, 1.2 Hz, 1H), 2.60 – 2.50 (m, 1H), 2.07 (dd, *J* = 7.8, 2.9 Hz, 1H), 1.87 – 1.78 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 164.3, 162.0 (d, *J* = 245.5 Hz), 150.4, 134.9 (d, *J* = 3.3 Hz), 129.8 (d, *J* = 8.1 Hz), 128.8, 128.7, 124.9, 121.4, 117.2, 114.2 (d, *J* = 21.2 Hz), 62.0, 61.9, 59.5, 50.2, 43.1, 42.1, 39.5, 13.9.

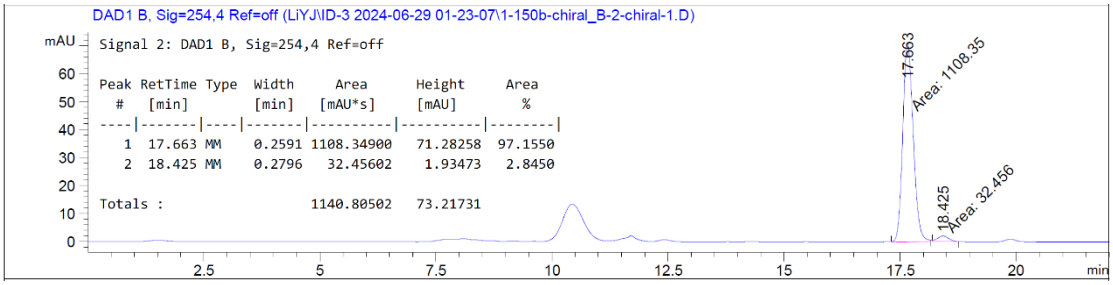
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.6 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{22}H_{20}FO_4$ $[M+H]^+$ 367.1340, found 367.1344.

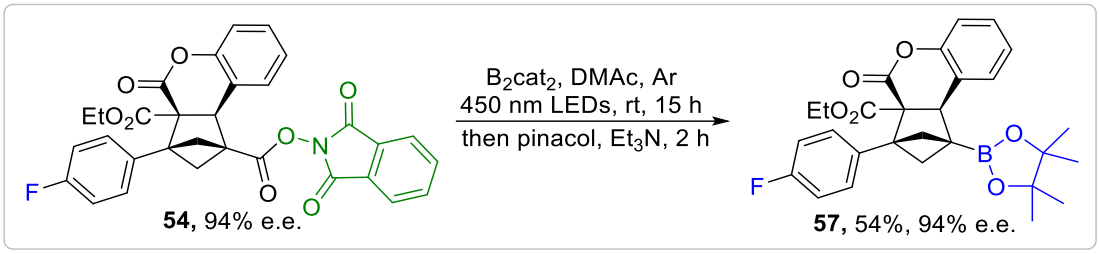
HPLC spectrum of ***rac*-56:**



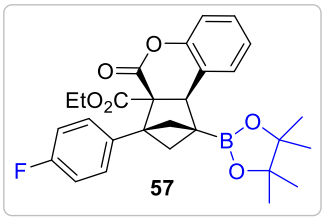
HPLC spectrum of **56:**



Synthesis of **57**:



Following a reported procedure[36], **54** (278 mg, 0.50 mmol, 1.0 equiv.) and bis(catecholato)diboron (B_2cat_2, 149 mg, 0.625 mmol, 1.25 equiv.) were added to an oven-dried Schlenk tube equipped with a magnetic stir bar. The tube was evacuated and backfilled with argon three times. Degassed DMAc (5 mL) was added under argon. The reaction mixture was stirred under blue LED (450 nm) irradiation for 15 h. Then, a solution of pinacol (245 μL, 2.0 mmol, 4 equiv.) in Et_3N (1.7 mL) was added to the reaction and stirred for another 2 h. The reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified using a short silica gel column to yield the desired boronic ester **57** (133.2 mg, 54%) as a white solid.



Ethyl (3a*S*,9b*R*)-3-(4-fluorophenyl)-4-oxo-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (57)

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 80/20, flow rate = 0.50 mL/min, λ = 254 nm), t_R (major) = 10.69 min, t_R (minor) = 11.42 min.

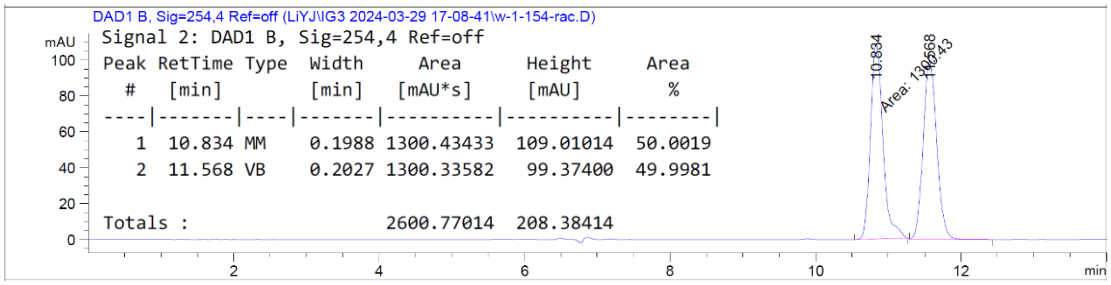
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.29 (dd, *J* = 6.0, 2.4 Hz, 3H), 7.15 – 7.05 (m, 2H), 6.99 – 6.92 (m, 2H), 4.16 – 4.07 (m, 2H), 4.00 (d, *J* = 1.8 Hz, 1H), 2.65 (dd, *J* = 9.4, 7.8 Hz, 1H), 2.08 (d, *J* = 7.7 Hz, 1H), 1.97 – 1.87 (m, 2H), 1.27 (s, 6H), 1.23 (s, 6H), 1.13 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 164.6, 161.9 (d, *J* = 245.2 Hz), 150.4, 135.1 (d, *J* = 3.1 Hz), 129.6 (d, *J* = 8.1 Hz), 129.5, 128.8, 124.3, 121.7, 117.2, 114.1 (d, *J* = 21.3 Hz), 83.9, 62.9, 61.7, 60.5, 52.3, 45.4, 40.1, 24.9, 24.7, 13.9.

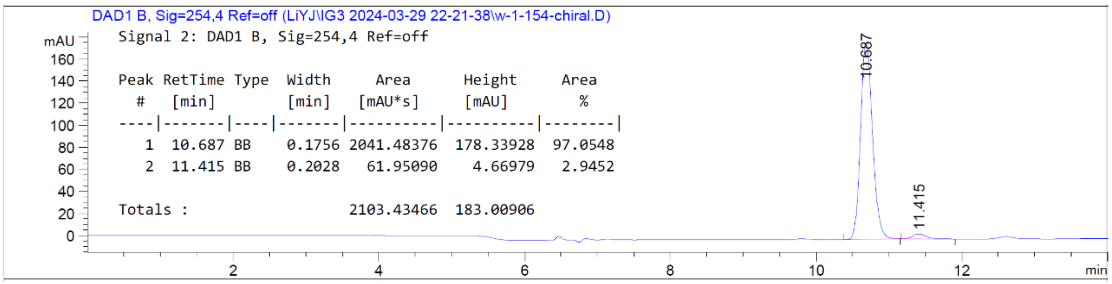
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.8 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{28}H_{31}BFO_6$ $[M+H]^+$ 493.2192, found 493.2200.

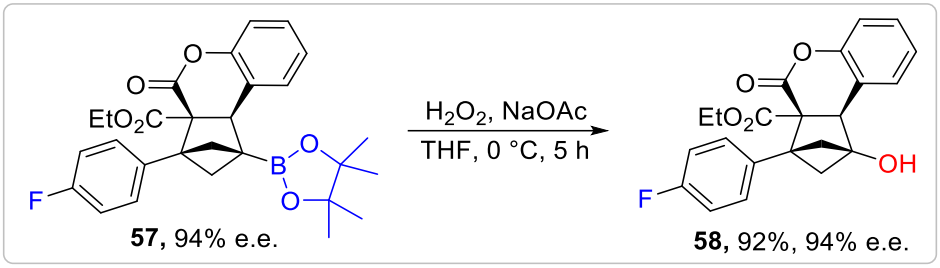
HPLC spectrum of ***rac*-57:**



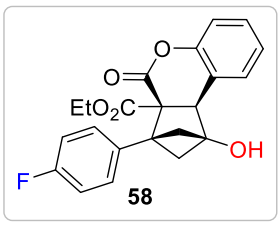
HPLC spectrum of **57:**



Synthesis of **58:**



Following a reported procedure with slight modifications[37], H_2O_2 (30 wt.% in water, 0.4 mL) was added dropwise to a solution of **57** (98.5 mg, 0.20 mmol, 1.0 equiv.) and sodium acetate (32.8 mg, 0.40 mmol, 2.0 equiv.) in THF (4.0 mL) at 0°C. The resulting mixture was stirred at 0 °C for 5 h. $Na_2S_2O_3$ was added, and the mixture was stirred at 0°C for 10 min. EtOAc (5 mL) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 5/1) to afford **58** (70.4 mg, 92%) as a pale-yellow solid.



Ethyl (3a*S*,9b*R*)-3-(4-fluorophenyl)-1-hydroxy-4-oxo-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (58)

HPLC analysis: CHIRALPAK® ID-3 (*n*-hexane/*i*-PrOH = 75/25, flow rate = 0.55 mL/min, λ = 254 nm), t_R (minor) = 10.01 min, t_R (major) = 11.81 min.

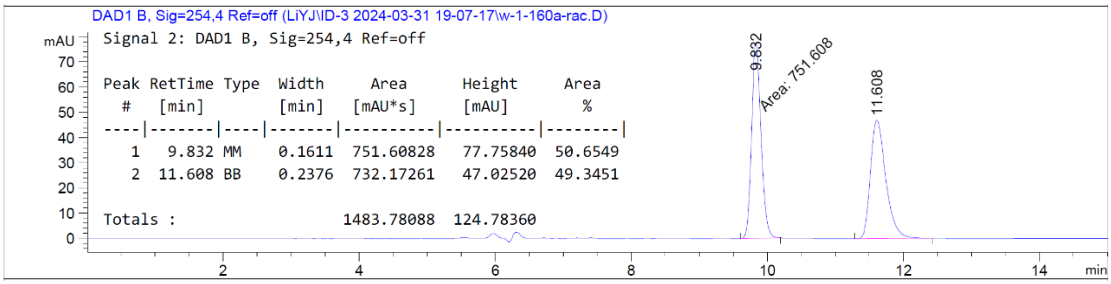
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 8.4 Hz, 2H), 4.24 – 4.00 (m, 2H), 3.63 (s, 1H), 3.33 (br s, 1H), 2.97 – 2.77 (m, 1H), 2.17 – 1.95 (m, 2H), 1.73 (d, *J* = 7.2 Hz, 1H), 1.14 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 163.9, 162.1 (d, *J* = 245.8 Hz), 150.4, 133.7 (d, *J* = 2.9 Hz), 130.4 (d, *J* = 8.1 Hz), 129.9, 129.3, 124.7, 118.1, 117.2, 114.3 (d, *J* = 21.3 Hz), 76.3, 62.1, 61.1, 50.5, 50.1, 47.4, 44.8, 13.8.

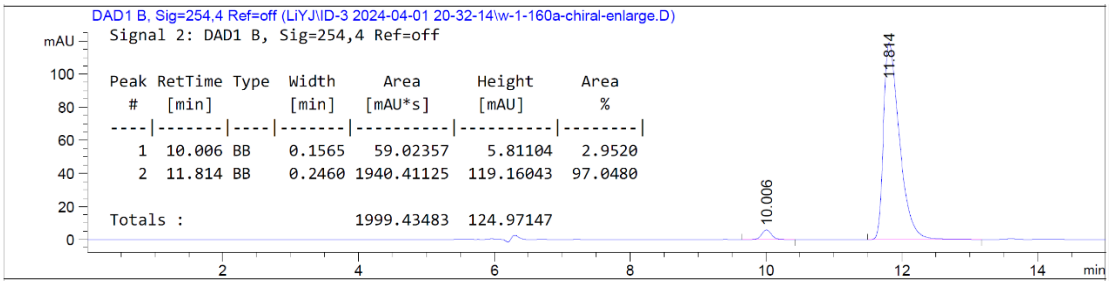
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.1 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{22}H_{19}NaFO_5$ $[M+Na]^+$ 405.1109, found 405.1114.

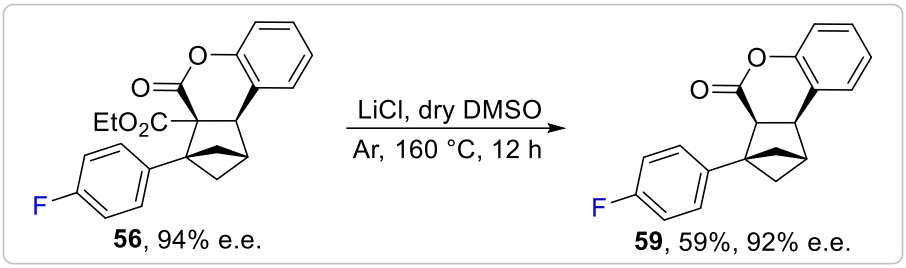
HPLC spectrum of ***rac*-58:**



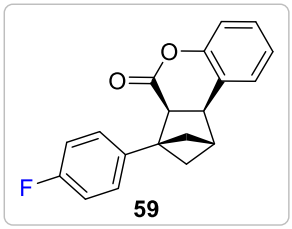
HPLC spectrum of **58:**



Synthesis of Compound 59:



Following a reported procedure with some modifications[38], anhydrous LiCl (209 mg, 4.92 mmol, 3.0 equiv.) was added to an oven-dried 25 mL Schlenk tube equipped with a magnetic stir bar under argon. The tube was evacuated and heated with a heat gun until the LiCl no longer adhered to the tube walls, followed by refilling with argon. This evacuation and refilling process was repeated three times. Under argon, **56** (600 mg, 1.64 mmol, 1.0 equiv.) and anhydrous DMSO (3.5 mL) were quickly added. The tube was then sealed and stirred at 160 °C for 12 h. The reaction mixture was cooled to room temperature and diluted with water (60 mL), then extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE/EtOAc = 40/1 to 10/1) to afford **59** (283 mg, 59%) as a pale yellow viscous solid.



(3a*S*,9b*S*)-3-(4-fluorophenyl)-2,3,3a,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromen-4(1*H*)-one (59)

HPLC analysis: CHIRALPAK® OD-3 (*n*-hexane/*i*-PrOH = 80/20, flow rate = 0.50 mL/min, λ = 254 nm), t_R (minor) = 13.04 min, t_R (major) = 17.51 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 2H), 7.18 – 7.10 (m, 3H), 7.01 (t, *J* = 8.7 Hz, 3H), 3.79 (d, *J* = 9.0 Hz, 1H), 3.34 (dd, *J* = 9.0, 1.7

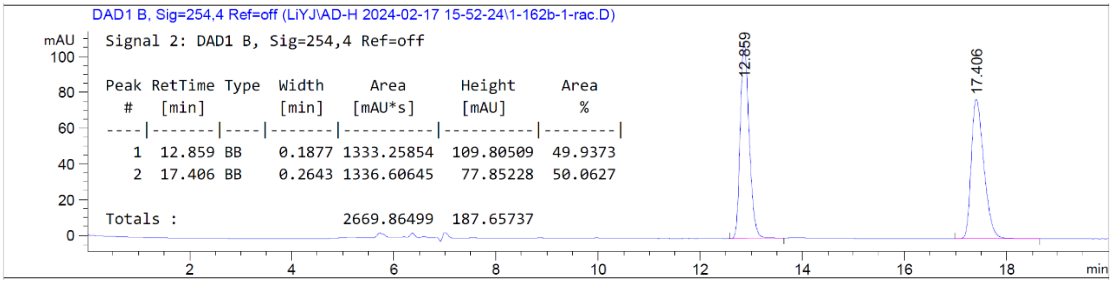
Hz, 1H), 2.74 (q, J = 2.8 Hz, 1H), 1.99 – 1.86 (m, 2H), 1.83 – 1.75 (m, 1H), 1.71 – 1.64 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 161.8 (d, J = 245.0 Hz), 151.2, 136.2 (d, J = 3.3 Hz), 128.5 (d, J = 12.1 Hz), 127.8 (d, J = 8.1 Hz), 124.7, 122.8, 117.0, 115.1 (d, J = 21.3 Hz), 59.9, 47.7, 45.1, 44.1, 42.8, 35.8.

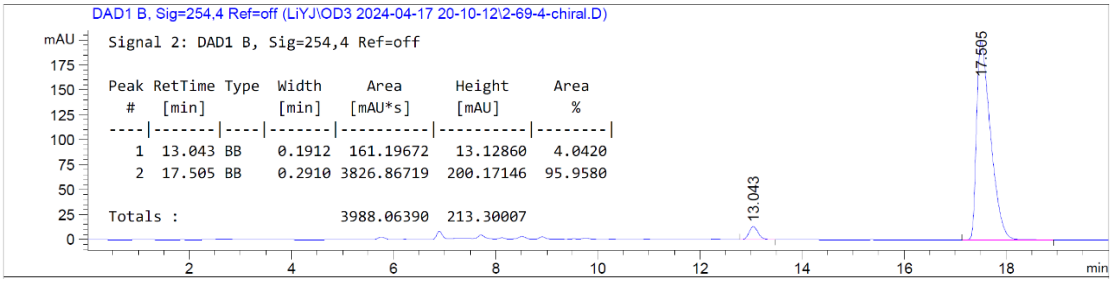
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.5 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{19}H_{16}FO_2$ $[M+H]^+$ 295.1129, found 295.1133.

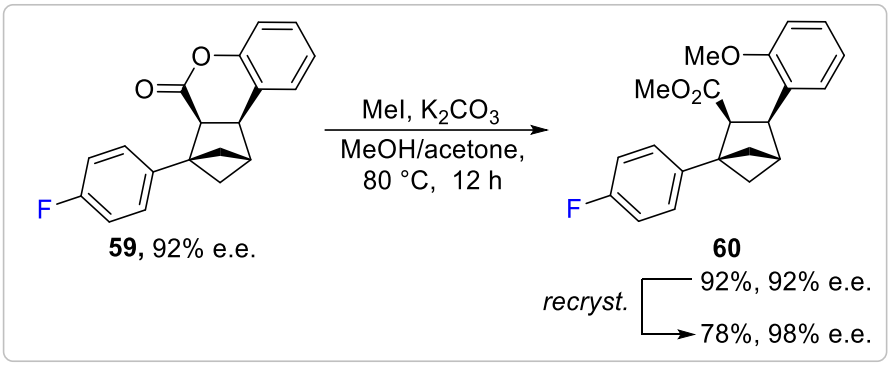
HPLC spectrum of ***rac*-59:**



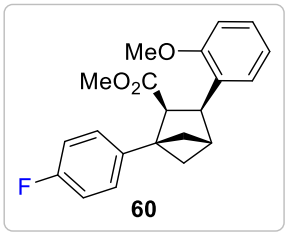
HPLC spectrum of **59:**



Synthesis of compound 60:



Following a reported procedure with some modifications[15], **59** (283 mg, 0.96 mmol, 1.0 equiv.) and K_2CO_3 (265 mg, 1.92 mmol, 2.0 equiv.) were added to an oven-dried Schlenk tube equipped with a magnetic stir bar under argon. Anhydrous methanol (1.5 mL), acetone (1.5 mL), and methyl iodide (818 mg, 5.76 mmol, 6.0 equiv.) were then added. The tube was sealed and stirred at 80 °C for 12 h. Upon completion (monitored by TLC), the mixture was cooled to room temperature, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 30/1) to afford **60** (300 mg, 0.88 mmol, 92%, 92% e.e.) as a white solid. The product was recrystallized from hot *n*-hexane to yield **60** (256 mg, 0.75 mmol, 78%, 98% e.e.) as a white solid.



60

Methyl (2*S*,3S)-1-(4-fluorophenyl)-3-(2-methoxyphenyl)-bicyclo[2.1.1]hexane-2-carboxylate (60)

HPLC analysis: CHIRALPAK® AD-H (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.60 mL/min, λ = 254 nm), t_R (major) = 6.21 min, t_R (minor) = 6.86 min.

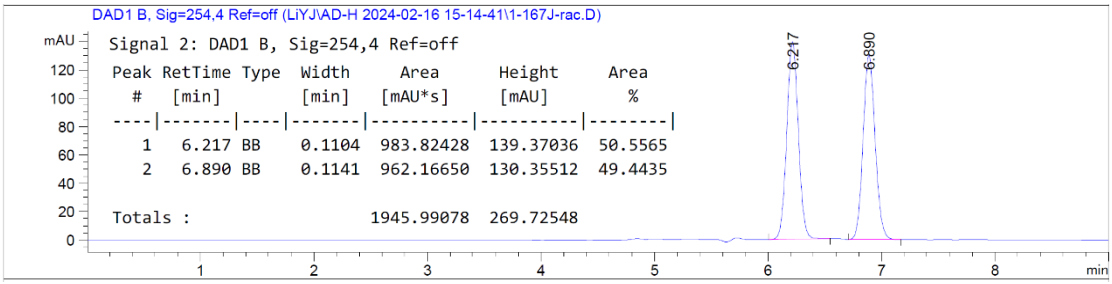
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.5 Hz, 2H), 7.11 (dd, *J* = 8.6, 5.4 Hz, 2H), 6.98 – 6.89 (m, 3H), 6.79 (d, *J* = 7.9 Hz, 1H), 3.86 (d, *J* = 8.7 Hz, 1H), 3.75 (s, 3H), 3.50 (dd, *J* = 8.9, 1.8 Hz, 1H), 3.16 (s, 3H), 2.84 (t, *J* = 2.9 Hz, 1H), 2.72 (dd, *J* = 9.8, 7.0 Hz, 1H), 1.95 – 1.87 (m, 2H), 1.79 (dd, *J* = 9.8, 6.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 161.6 (d, *J* = 243.9 Hz), 157.4, 137.7 (d, *J* = 3.3 Hz), 129.9, 127.4 (d, *J* = 8.1 Hz), 127.3, 126.5, 120.2, 114.9 (d, *J* = 21.3 Hz), 109.2, 57.1, 54.8, 54.3, 50.5, 45.5, 44.8, 37.4, 37.0.

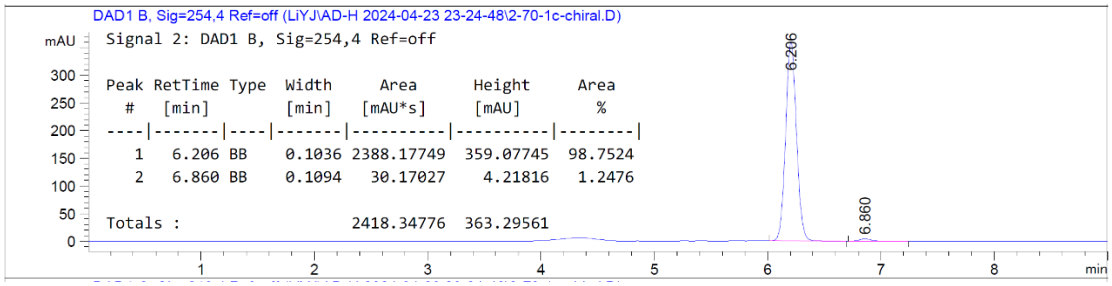
^{19}F NMR (376 MHz, $CDCl_3$) δ -116.6 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{21}H_{22}FO_3$ $[M+H]^+$ 341.1548, found 341.1552.

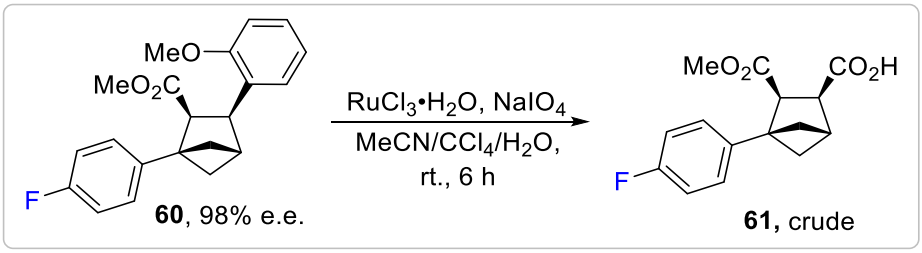
HPLC spectrum of ***rac*-60:**



HPLC spectrum of **60** (after recrystallization):



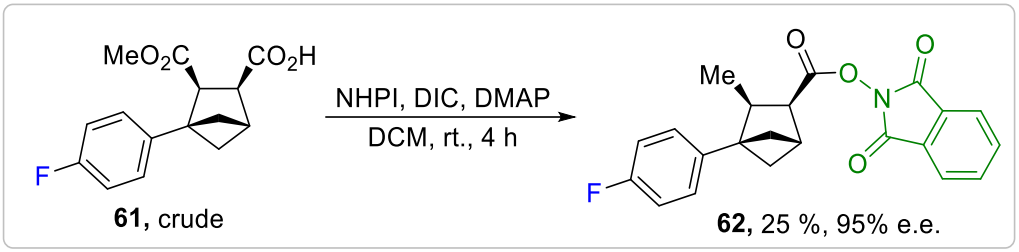
Synthesis of compound 61:



Following the reported procedures with some modifications[39], $NaIO_4$ (1.30 g, 6.0 mmol, 12.0 equiv.) was added to a solution of **60** (170.1 mg, 0.5 mmol, 1.0 equiv.) in MeCN (3.0 mL), CCl_4 (3.0 mL), and H_2O (3.0 mL). The mixture was stirred vigorously at room temperature, followed by the addition of $RuCl_3 \cdot H_2O$ (5.6 mg, 0.025 mmol, 0.05 equiv.) in H_2O (1.5 mL). The mixture was stirred vigorously at room temperature for 6

h, during which a large amount of white solid formed. Upon completion (monitored by TLC), 1 N HCl was added dropwise until the pH = 3, and the mixture was extracted three times with EtOAc. The combined organic layers were dried and concentrated to yield a yellow oily product **61,** which was used directly in the next step without further purification.

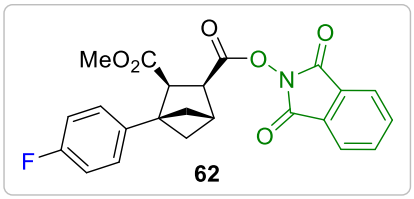
Synthesis of compound 62:



61, crude

62, 25 %, 95% e.e.

Compound **62** was prepared following the protocol for compound **54**, using **61** (~0.5 mmol), NHPI (90 mg, 0.55 mmol, 1.1 equiv.), DMAP (23 mg, 0.19 mmol, 0.11 equiv.), DIC (76 mg, 0.6 mmol, 1.2 equiv.), and DCM (20 mL). The reaction was conducted at room temperature for 4 h. The crude product was purified through silica gel flash column chromatography to afford **62** (52.9 mg, 25% over 2 steps from **60**) as a white solid.



62

3-(1,3-dioxoisoindolin-2-yl) 2-methyl (2*S*,3*S*)-1-(4-fluorophenyl)bicyclo[2.1.1]hexane-2,3-dicarboxylate (62)

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 19.89 min, t_R (minor) = 20.79 min.

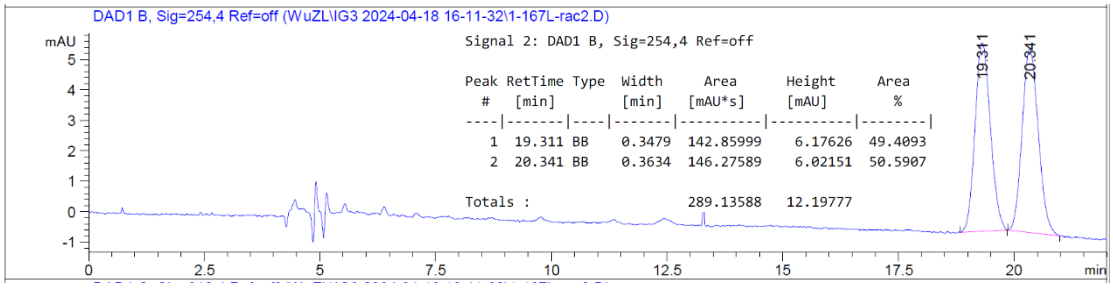
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.18 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 3.74 (d, *J* = 9.5 Hz, 1H), 3.61 (s, 3H), 3.47 (dd, *J* = 9.6, 2.0 Hz, 1H), 2.96 (d, *J* = 1.4 Hz, 1H), 2.67 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.01 (dd, *J* = 7.9, 2.2 Hz, 1H), 1.94 (dd, *J* = 7.3, 3.0 Hz, 1H), 1.71 (dd, *J* = 10.0, 7.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 168.8, 161.73 (d, *J* = 245.1 Hz), 161.70 (d, *J* = 2.7 Hz), 135.9 (d, *J* = 3.2 Hz), 134.8, 128.9, 127.8 (d, *J* = 8.0 Hz), 124.0, 115.1 (d, *J* = 21.2 Hz), 56.4, 52.00, 51.97, 46.5, 45.6, 38.9, 37.2.

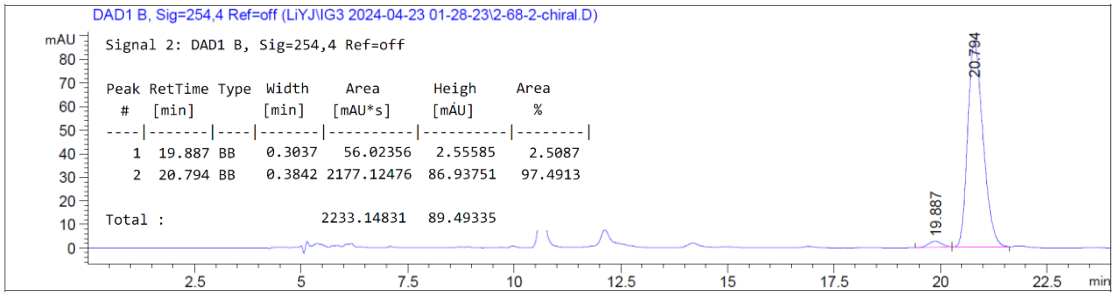
^{19}F NMR (376 MHz, $CDCl_3$) δ -115.8 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{23}H_{19}FNO_6$ $[M+H]^+$ 424.1191, found 424.1199.

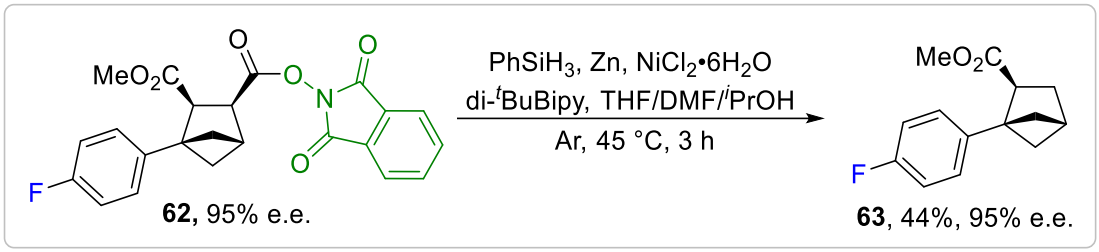
HPLC spectrum of ***rac*-62**:



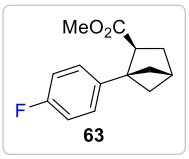
HPLC spectrum of **62**:



Synthesis of compound 63:



Compound **63** was prepared following the protocol for compound **56**, using **62** (52.9 mg, 0.125 mmol, 1.0 equiv.), $NiCl_2 \cdot 6H_2O$ (3.1 mg, 0.013 mmol, 10 mol%), and di-^{t}BuBipy (7.0 mg, 0.026 mmol, 20 mol%) in dry DMF (0.13 mL), $PhSiH_3$ (23 μL, 0.19 mmol, 1.5 equiv.), Zn powder (4.0 mg, 0.06 mmol, 0.5 equiv.), dry THF (0.63 mL), and *i*-PrOH (0.06 mL). The reaction was conducted at 45 °C for 3 h. The crude product was purified through silica gel flash column chromatography to afford **63** (13 mg, 44%) as a colorless oil.



Methyl (*S*)-1-(4-fluorophenyl)bicyclo[2.1.1]hexane-2-carboxylate (63)

HPLC analysis: CHIRALPAK® IC-3 (*n*-hexane/*i*-PrOH = 98/2, flow rate = 0.20 mL/min, λ = 260 nm), t_R (major) = 26.53 min, t_R (minor) = 27.82 min.

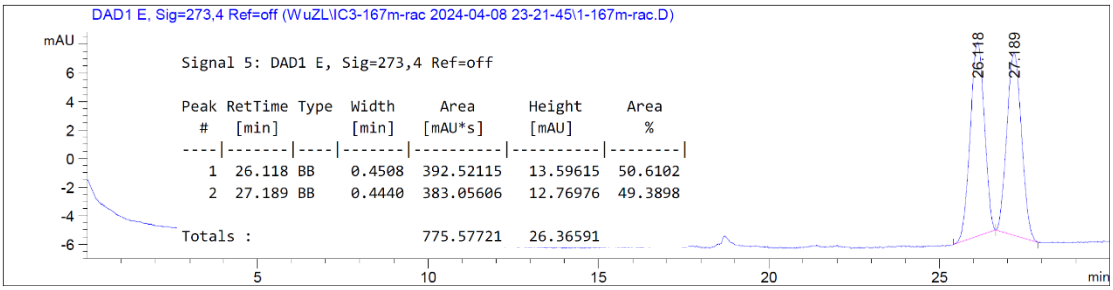
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.06 (m, 2H), 7.00 – 6.91 (m, 2H), 3.47 (s, 3H), 3.01 – 2.93 (m, 1H), 2.56 – 2.50 (m, 1H), 2.21 – 2.12 (m, 2H), 2.12 – 2.05 (m, 1H), 1.81 – 1.74 (m, 2H), 1.65 – 1.57 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 161.5 (d, J = 244.3 Hz), 137.8 (d, J = 3.3 Hz), 127.3 (d, J = 8.1 Hz), 114.8 (d, J = 21.3 Hz), 57.7, 51.2, 48.5, 46.3, 38.2, 35.1, 34.2.

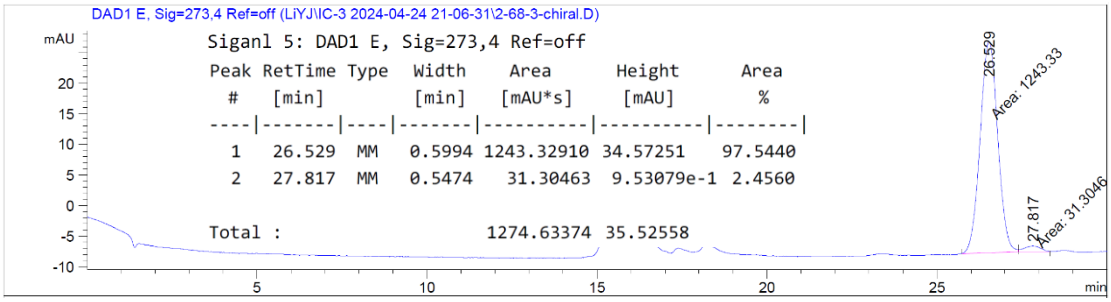
^{19}F NMR (376 MHz, $CDCl_3$) δ -116.7 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{14}H_{16}FO_2$ $[M+H]^+$ 235.1129, found 235.1132.

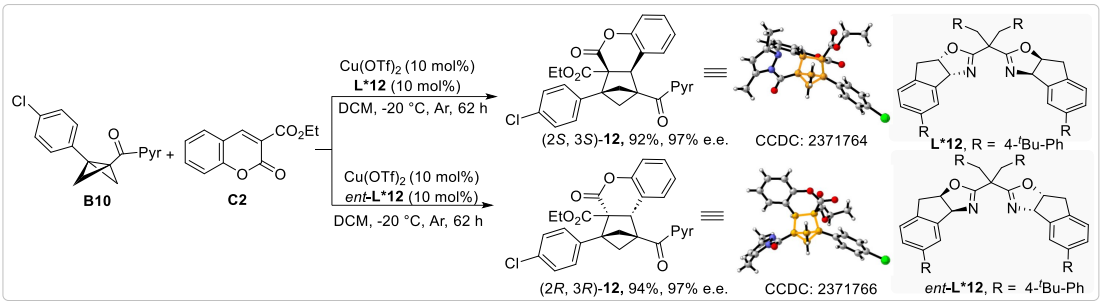
HPLC spectrum of ***rac*-63**:



HPLC spectrum of **63**:



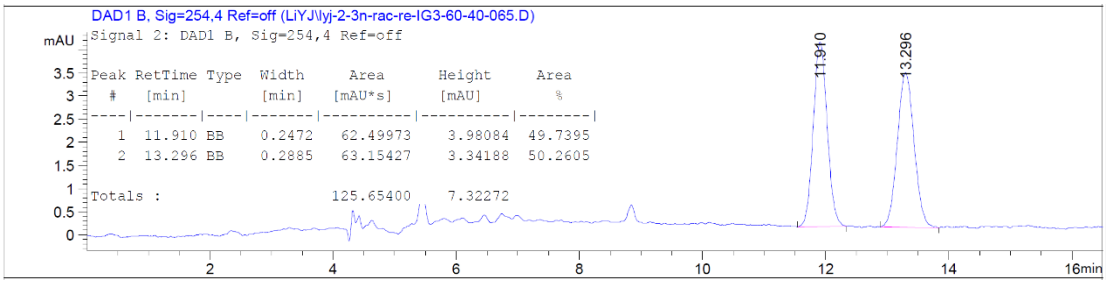
7.3 Stereodivergent synthesis of BCH 12



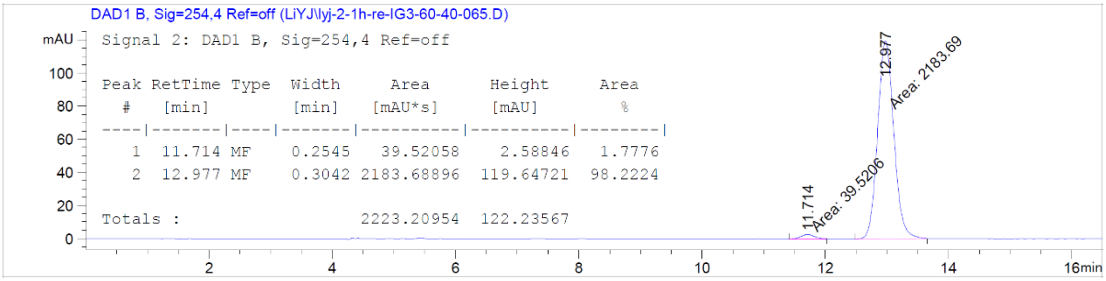
BCH (2*S*,3*S*)-12 was synthesized according to **General Procedure A**, utilizing BCB substrate **B10** (60.2 mg, 0.21 mmol, 1.05 equiv.) and coumarin substrate **C1** (43.6 mg, 0.10 mmol, 1.0 equiv.), $Cu(OTf)_2$ (7.23 mg, 0.02 mmol, 10 mol%), **L*12** (17.75 mg, 0.02 mmol, 10 mol%), and anhydrous DCM (2.0 mL). The sealed tube was stirred at -20 °C for 62 h. The crude product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford **BCH (2*S*,3*S*)-12** (93.1 mg, 92%) as a white solid.

BCH (2*R*,3*R*)-12 was synthesized according to **General Procedure A**, utilizing BCB substrate **B10** (30.1 mg, 0.105 mmol, 1.05 equiv.) and coumarin substrate **C1** (21.8 mg, 0.10 mmol, 1.0 equiv.), $Cu(OTf)_2$ (3.62 mg, 0.01 mmol, 10 mol%), *ent*-**L*12** (8.87 mg, 0.01 mmol, 10 mol%), and anhydrous DCM (1.0 mL). The sealed tube was stirred at -20 °C. The reaction was conducted at -20 °C for 62 h. The crude product was purified by silica gel flash column chromatography (5-7% EtOAc in *n*-hexane) to afford **BCH (2*R*,3*R*)-12** (47.5 mg, 94%) as a white solid.

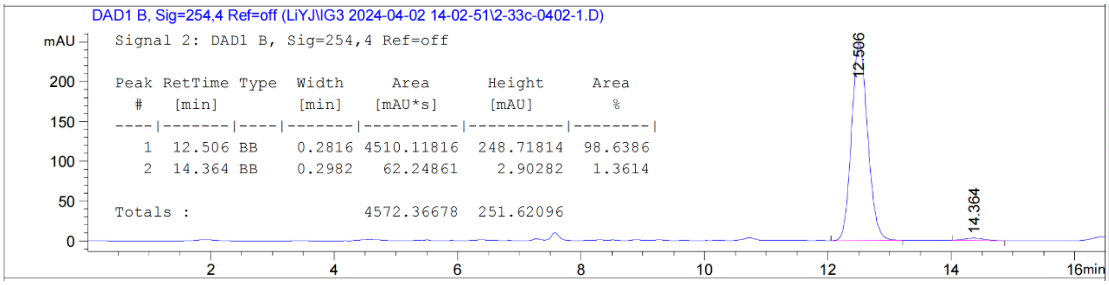
HPLC spectrum of ***rac*-12:**



HPLC spectrum of **(2*S*,3*S*)-12:**

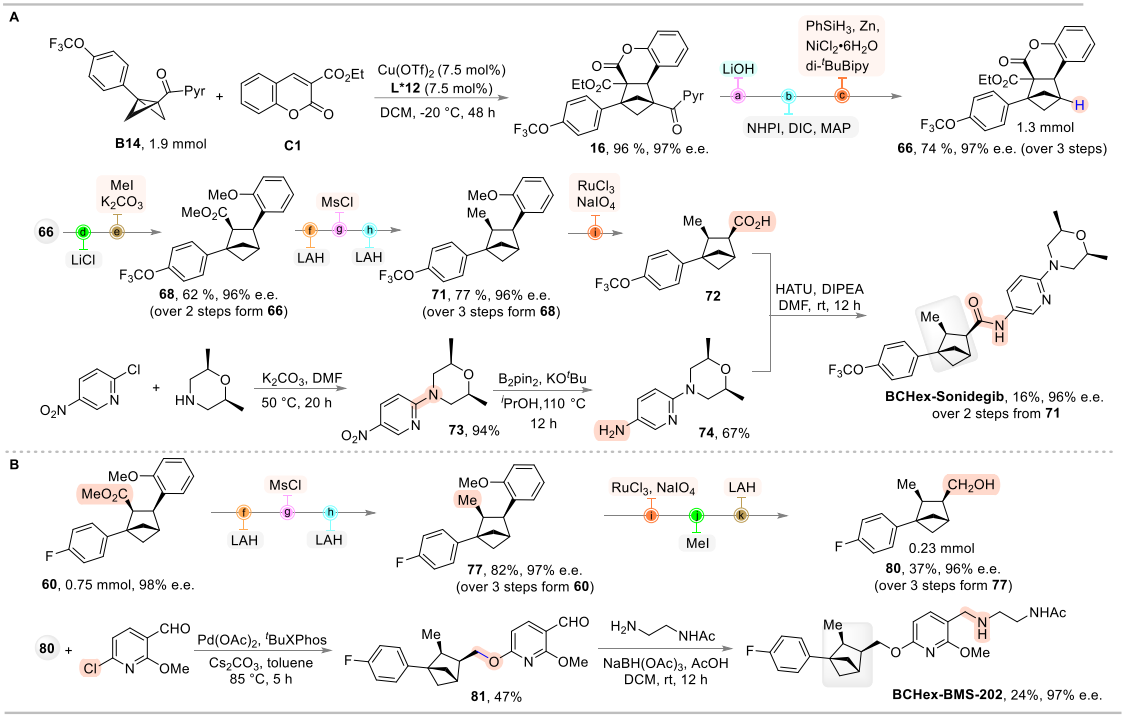


HPLC spectrum of **(2*R*,3*R*)-12:**


DAD1 B, Sig=254,4 Ref=off (LiYJ\IG3 2024-04-02 14-02-51\2-33c-0402-1.D)
Signal 2: DAD1 B, Sig=254,4 Ref=off
Peak RetTime Type Width Area Height Area
[min] [min] [mAU*s] [mAU] %
1 12.506 BB 0.2816 4510.11816 248.71814 98.6386
2 14.364 BB 0.2982 62.24861 2.90282 1.3614
Totals : 4572.36678 251.62096
12.506
14.364
mAU
200
150
100
50
0
2
4
6
8
10
12
14
16min

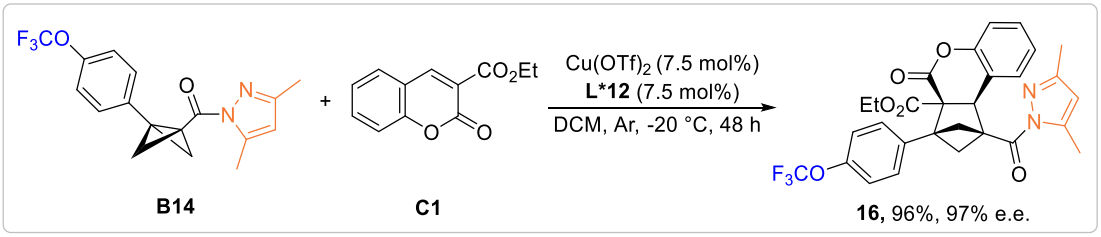
8. Bioisosteric replacements for bioactive compounds

8.1 Synthesis of Chiral BCHex-Sonidegib and BCHex-BMS-202



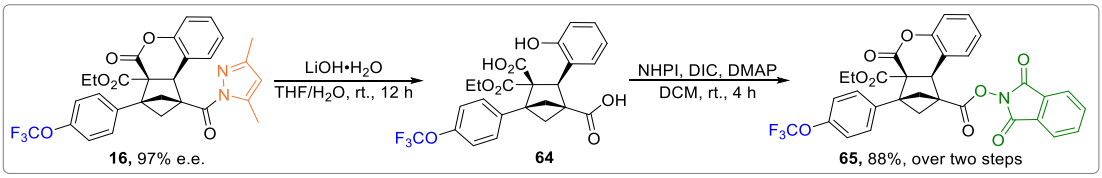
8.2 Synthesis of BCHex-Sonidegib as the bioisostere of Sonidegib

Synthesis of chiral BCH **16**:



Compound **16** was prepared following the protocol for **13**, using BCB substrate **B14** (636 mg, 1.9 mmol, 1.05 equiv.) and coumarin substrate **C1** (393 mg, 1.8 mmol, 1.0 equiv.), $Cu(OTf)_2$ (49 mg, 0.135 mmol, 7.5 mol%), **L*12** (120 mg, 0.135 mmol, 7.5 mol%), and anhydrous DCM (19.0 mL). The sealed tube was stirred at -20 °C for 48 h. The crude product was purified through silica gel flash column chromatography (PE/EtOAc), yielding **16** (963 mg, 96%) as a white solid.

Synthesis of compound **65:**

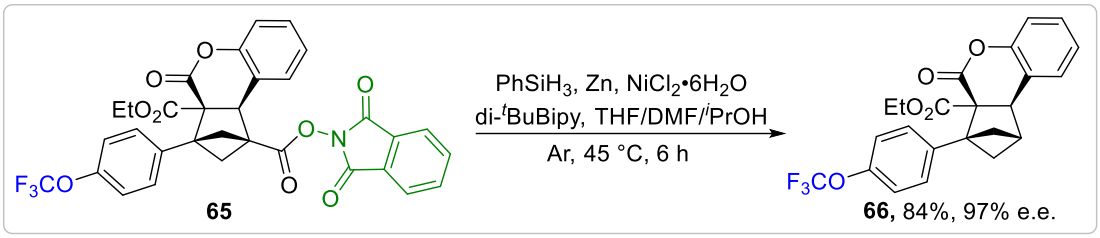


Compound **64** was prepared following the protocol for **53**, using **16** (963 mg, 1.74 mmol, 1.0 equiv.), $LiOH·H_2O$ (292 mg, 6.96 mmol, 4.0 equiv.), THF (9 mL), and H_2O (9 mL).

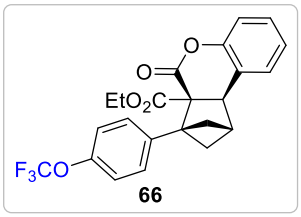
The reaction was conducted at room temperature for 12 h. Upon completion of the reaction workup, the carboxylic acid intermediate **64** was obtained as a white solid and was directly used in the next step.

Compound **65** was prepared following the protocol for **54**, using NHPI (312 mg, 1.91 mmol, 1.1 equiv.), DMAP (23 mg, 0.19 mmol, 0.11 equiv.), DIC (0.65 mL, 4.18 mmol, 2.4 equiv.), and DCM (170 mL). The reaction was conducted at room temperature for 4 h. The crude product was purified through silica gel flash column chromatography to afford **65** (950 mg, 88%) as a white to pale yellow solid.

Synthesis of compound 66



Compound **66** was prepared following the protocol for **56**, using **65** (950 mg, 1.53 mmol, 1.0 equiv.), $NiCl_2 \cdot 6H_2O$ (38 mg, 0.16 mmol, 10 mol%), and di-^{t}BuBipy (86 mg, 0.32 mmol, 20 mol%) in dry DMF (1.6 mL), $PhSiH_3$ (284 μL, 2.3 mmol, 1.5 equiv.), Zn powder (50 mg, 0.78 mmol, 0.5 equiv.), dry THF (8.0 mL), and *i*-PrOH (0.8 mL). The reaction was conducted at 45 °C for 6 h. The crude product was purified by silica gel flash column chromatography on silica gel (PE/EtOAc = 20/1 to 10/1), yielding **66** (553 mg, 84%) as a white solid.



Ethyl (3a*S*,9b*R*)-4-oxo-3-(4-(trifluoromethoxy)phenyl)-1,2,3,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromene-3a(4*H*)-carboxylate (66)

HPLC analysis: CHIRALPAK® IA-3 (*n*-hexane/*i*-PrOH = 85/15, flow rate = 0.45 mL/min, λ = 254 nm), t_R (major) = 11.07 min, t_R (minor) = 11.53 min.

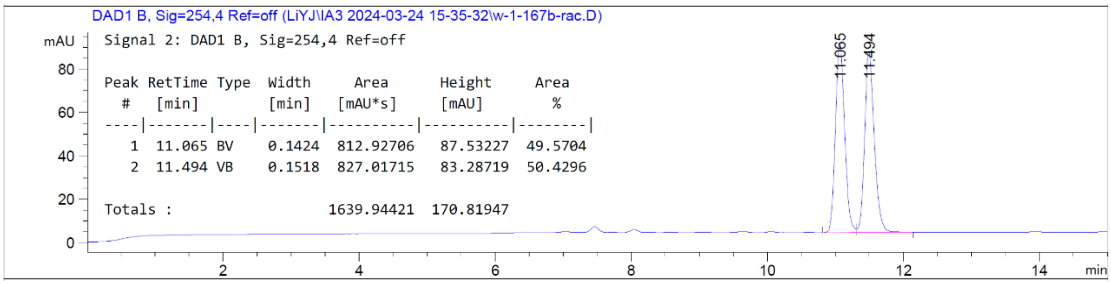
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 4H), 7.22 – 7.17 (m, 1H), 7.11 (t, *J* = 8.2 Hz, 3H), 4.22 – 4.06 (m, 2H), 3.84 (s, 1H), 2.72 (d, *J* = 1.6 Hz, 1H), 2.60 – 2.52 (m, 1H), 2.08 (dd, *J* = 7.7, 2.9 Hz, 1H), 1.85 – 1.79 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 164.2, 150.3, 148.2 (d, *J* = 1.8 Hz), 137.8, 129.7, 128.8, 128.7, 124.9, 121.3, 120.5 (d, *J* = 257.0 Hz), 119.7, 117.2, 61.9, 61.8, 59.5, 50.1, 43.2, 42.1, 39.5, 13.9.

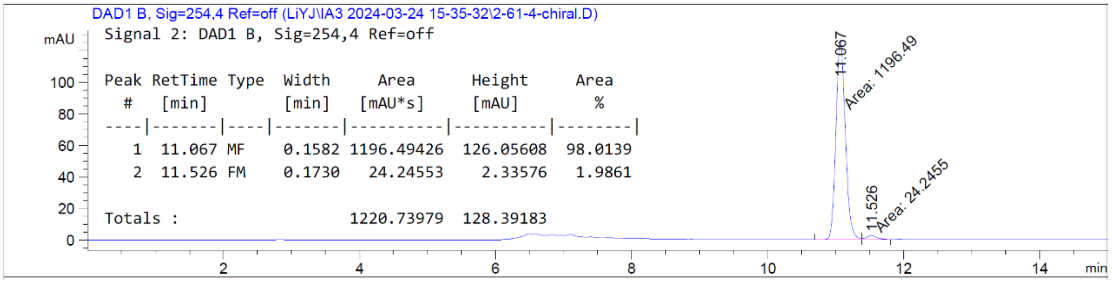
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.7 (s, 3F).

HRMS (ESI) m/z calcd. for $C_{23}H_{20}F_3O_5$ $[M+H]^+$ 433.1258, found 433.1253.

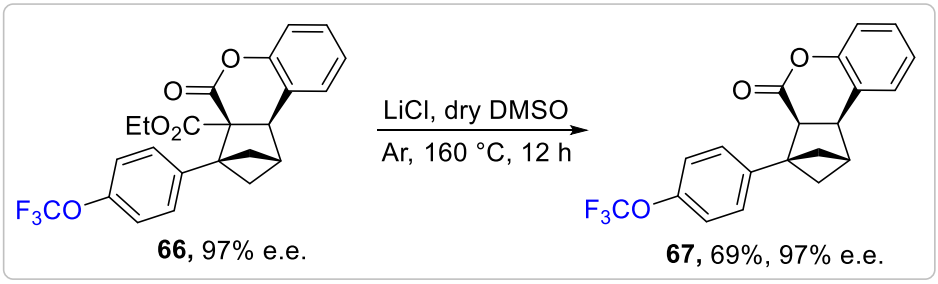
HPLC spectrum of ***rac*-66:**



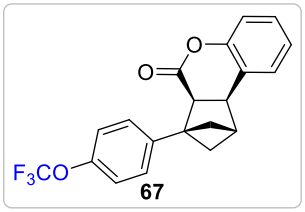
HPLC spectrum of **66:**



Synthesis of compound 67



Compound **67** was prepared following the protocol for **59**, using **66** (553 mg, 1.28 mmol, 1.0 equiv.), anhydrous LiCl (163 mg, 3.84 mmol, 3.0 equiv.), and dry DMSO (2.5 mL). The reaction was conducted at 160 °C for 12 h under argon. The crude product was purified by silica gel flash column chromatography (PE/EtOAc = 40/1 to 10/1), yielding **67** (320 mg, 69%) as a light yellow viscous solid.



(3a*S*,9b*R*)-3-(4-(trifluoromethoxy)phenyl)-2,3,3a,9b-tetrahydro-1,3-methanocyclopenta[*c*]chromen-4(1*H*)-one (67)

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (minor) = 7.96 min, t_R (major) = 9.65 min.

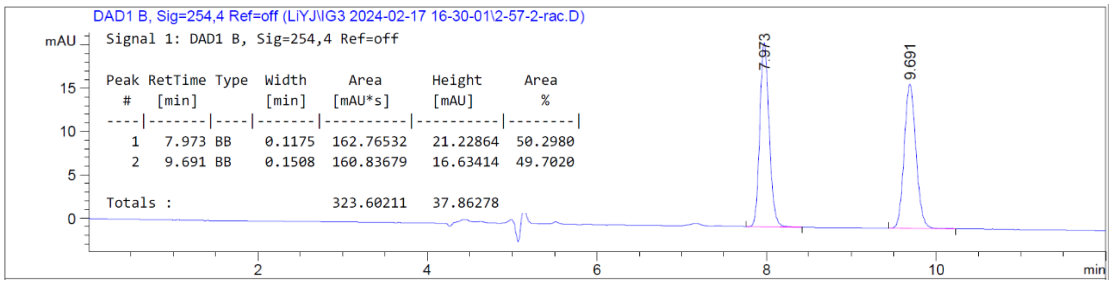
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.12 (m, 7H), 7.02 (d, *J* = 8.1 Hz, 1H), 3.83 (d, *J* = 9.0 Hz, 1H), 3.38 (dd, *J* = 9.0, 1.3 Hz, 1H), 2.77 (d, *J* = 1.8 Hz, 1H), 2.01 – 1.89 (m, 2H), 1.82 (d, *J* = 8.1 Hz, 1H), 1.73 – 1.65 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 151.1 (d, *J* = 3.5 Hz), 148.1, 139.0, 128.5, 127.6, 124.6, 122.6, 120.6, 120.5 (d, *J* = 256.8 Hz), 117.1, 59.8, 47.6, 45.2, 44.1, 42.8, 35.8.

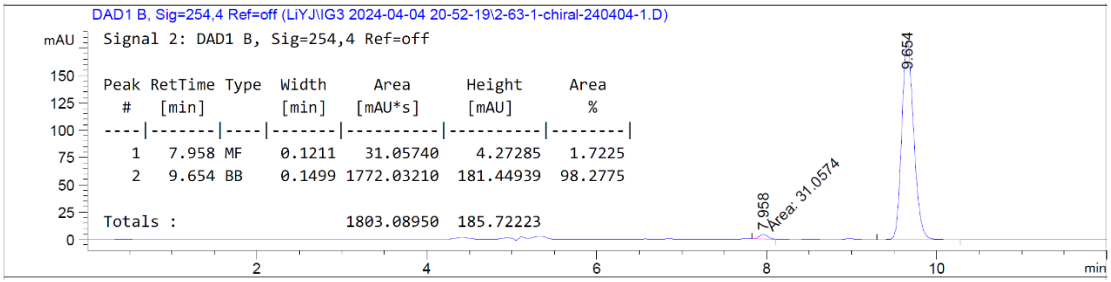
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.7 (s, 3F).

HRMS (ESI) m/z calcd. for $C_{20}H_{16}F_3O_3$ $[M+H]^+$ 361.1046, found 361.1049.

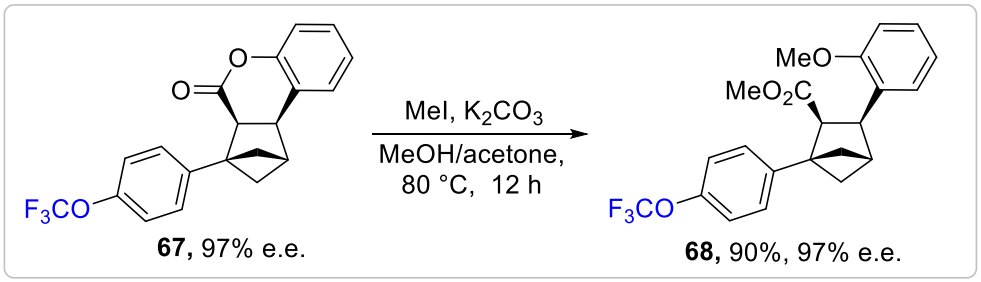
HPLC spectrum of ***rac*-67:**



HPLC spectrum of **67:**

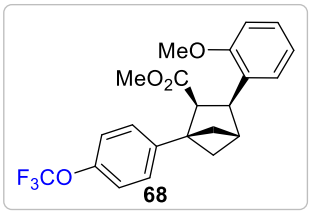


Synthesis of compound 68



67, 97% e.e. **68,** 90%, 97% e.e.

Compound **68** was prepared following the protocol for **60**, using **67** (320 mg, 0.89 mmol, 1.0 equiv.), iodomethane (758 mg, 5.34 mmol, 6.0 equiv.), potassium carbonate (185 mg, 1.34 mmol, 1.5 equiv.), dry methanol (1.1 mL), and acetone (1.1 mL). The reaction was conducted at 80 °C for 12 h under argon. The crude product was purified by silica gel flash column chromatography (PE/EtOAc = 30/1), yielding **68** (326 mg, 90%) as a white solid.



Methyl (2*S*,3*S*)-3-(2-methoxyphenyl)-1-(4-(trifluoromethoxy)phenyl)bicyclo[2.1.1]hexane-2-carboxylate (68)

HPLC analysis: CHIRALPAK® IA-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 5.46 min, t_R (minor) = 6.00 min.

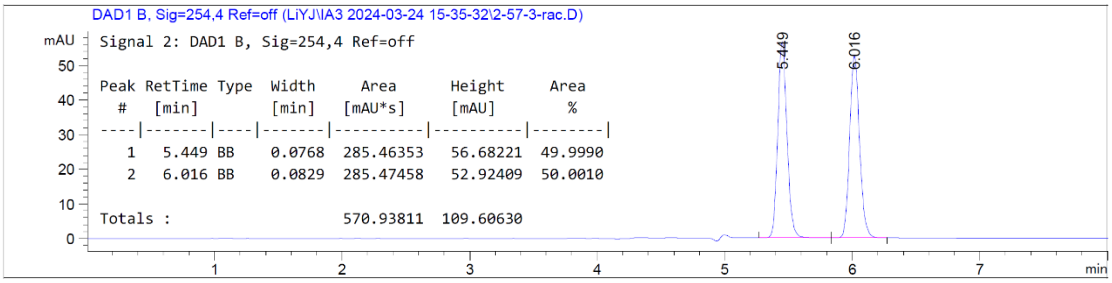
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 17.1, 8.6 Hz, 4H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 3.88 (d, *J* = 8.9 Hz, 1H), 3.76 (s, 3H), 3.52 (d, *J* = 8.9 Hz, 1H), 3.16 (s, 3H), 2.85 (s, 1H), 2.74 (dd, *J* = 9.7, 7.1 Hz, 1H), 1.97 – 1.89 (m, 2H), 1.80 (dd, *J* = 9.7, 6.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 157.4, 147.7 (d, *J* = 1.7 Hz), 140.7, 129.8, 127.3, 127.2, 126.5, 120.6, 120.5 (d, *J* = 256.8 Hz), 120.2, 109.2, 57.0, 54.8, 54.2, 50.5, 45.5, 44.8, 37.5, 37.1.

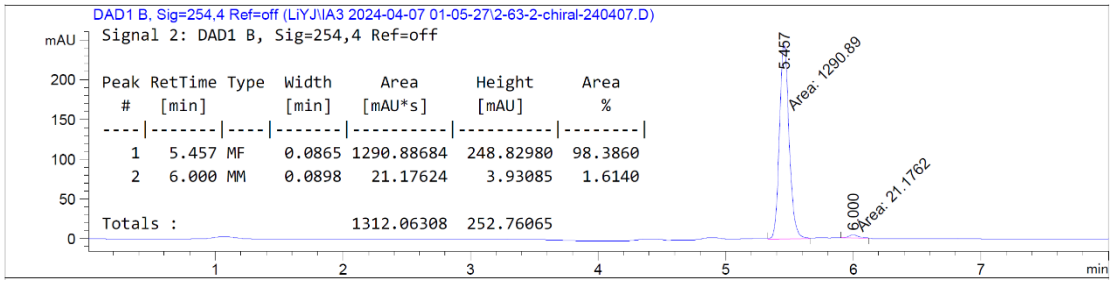
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.9 (s, 3F).

HRMS (ESI) m/z calcd. for $C_{22}H_{22}F_3O_4$ $[M+H]^+$ 407.1465, found 407.1463.

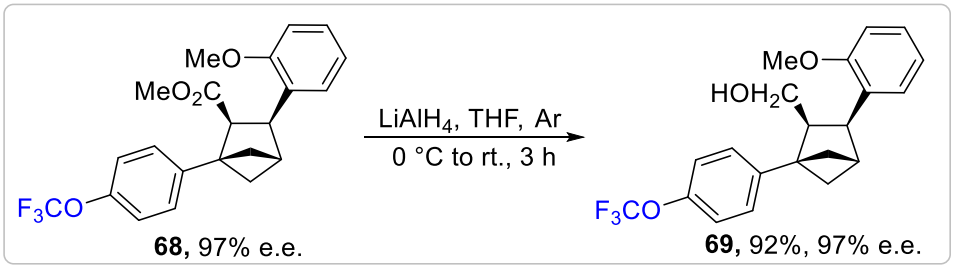
HPLC spectrum of ***rac*-68:**



HPLC spectrum of **68:**

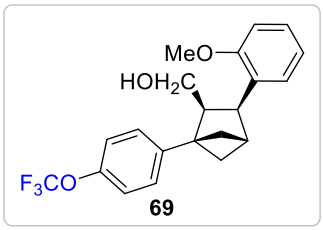


Synthesis of compound 69



68, 97% e.e. **69,** 92%, 97% e.e.

Following a reported procedure with some modifications[15], **68** (326 mg, 0.81 mmol, 1.0 equiv.) and anhydrous THF (1.6 mL) were added to an oven-dried 10 mL Schlenk tube equipped with a magnetic stir bar under argon. The solution was cooled to 0 °C, and $LiAlH_4$ (123 mg, 3.24 mmol, 4.0 equiv.) was slowly added (Note: vigorous hydrogen evolution occurs). The resulting suspension was gradually warmed up to room temperature and stirred for 3 h under argon. Upon completion (monitored by TLC), the reaction mixture was cooled to 0 °C and vigorously stirred, followed by incremental addition of moist Na_2SO_4. After complete consumption of $LiAlH_4$, stirring was continued for 5 minutes, the mixture was filtered, and the residue was washed with DCM. The solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (PE/EtOAc = 20/1 to 10/1) to afford **69** (282 mg, 92%) as a white to pale yellow solid.



69

((2*S*,3*S*)-3-(2-methoxyphenyl)-1-(4-(trifluoromethoxy)-phenyl)bicyclo[2.1.1]hexan-2-yl)methanol (69)

HPLC analysis: CHIRALPAK® ID-3 (*n*-hexane/*i*-PrOH = 80/20, flow rate = 0.50 mL/min, λ = 273 nm), t_R (major) = 8.83 min, t_R (minor) = 10.62 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.17 (m, 4H), 7.14 (d,

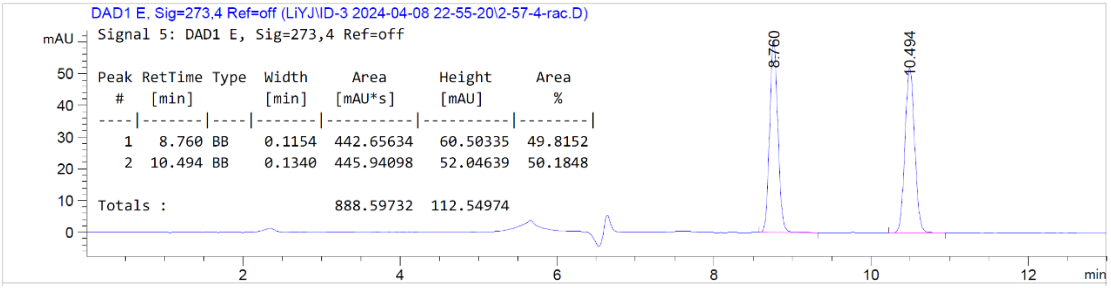
J = 8.2 Hz, 2H), 6.98 (td, J = 7.5, 1.1 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 3.89 (s, 3H), 3.81 (d, J = 8.8 Hz, 1H), 3.19 (dd, J = 11.6, 4.5 Hz, 1H), 3.11 (dd, J = 11.5, 6.4 Hz, 1H), 2.79 – 2.70 (m, 2H), 2.13 – 2.04 (m, 1H), 1.93 (dd, J = 4.6, 2.5 Hz, 1H), 1.86 – 1.80 (m, 2H), 1.55 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 147.6, 141.9, 129.9, 127.6, 127.5, 127.1, 121.1, 121.0, 120.5 (d, J = 256.8 Hz), 110.5, 62.4, 55.51, 55.48, 51.1, 46.5, 42.8, 38.7, 36.1.

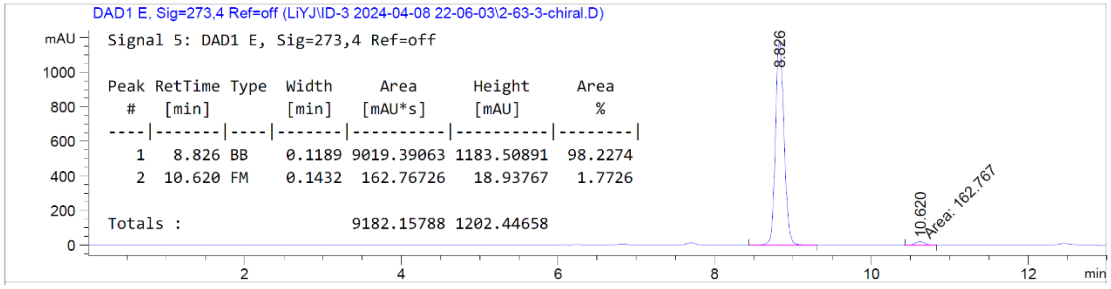
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.86 (s, 3F).

HRMS (ESI) m/z calcd. for $C_{21}H_{22}F_3O_3$ $[M+H]^+$ 379.1516, found 379.1519.

HPLC spectrum of ***rac*-69**:



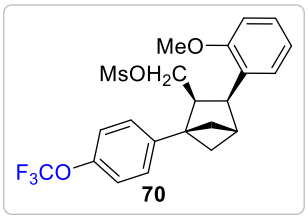
HPLC spectrum of **69**:



Synthesis of compound 70:

69, 96% e.e. **70**, 94%, 96% e.e.

Following a reported procedure with some modifications[38b], **69** (282 mg, 0.75 mmol, 1.0 equiv.), Et_3N (208 µL, 2.0 equiv.), and anhydrous DCM (2.0 mL) were added to an oven-dried Schlenk tube equipped with a magnetic stirrer under argon. The solution was cooled to 0 °C, and methanesulfonyl chloride (MsCl, 117 µL, 2.0 equiv.) was added dropwise. The reaction mixture was gradually warmed to room temperature and stirred for 1 h. Upon completion, as monitored by TLC, the solvent was removed *in vacuo*. The residue was purified by column chromatography (PE/EtOAc = 20/1-10/1) to afford the product **70** (322 mg, 94%) as a white solid.



(2*S*,3*S*)-(3-(2-methoxyphenyl)-1-(4-(trifluoromethoxy)-phenyl)bicyclo[2.1.1]hexan-2-yl)methyl methanesulfonate (70)

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 273 nm), t_R (major) = 6.79 min, t_R (minor) = 7.39 min.

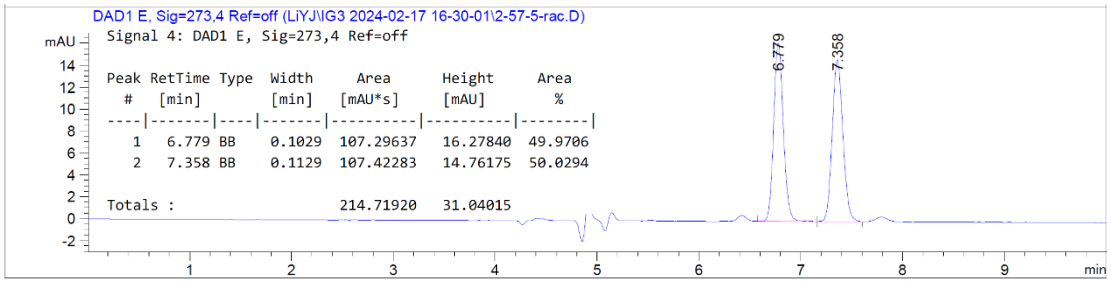
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 3H), 7.18 – 7.11 (m, 3H), 6.97 – 6.84 (m, 2H), 3.92 – 3.79 (m, 5H), 3.66 (dd, *J* = 10.0, 8.1 Hz, 1H), 2.97 (td, *J* = 8.0, 4.1 Hz, 1H), 2.77 (s, 1H), 2.20 (s, 3H), 2.15 – 2.09 (m, 1H), 2.00 (d, *J* = 5.5 Hz, 1H), 1.92 – 1.82 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 147.5, 141.7, 128.3, 127.9, 127.5, 126.6, 120.8, 120.51, 120.49 (d, *J* = 256.7 Hz), 110.1, 68.7, 55.5, 55.2, 46.2, 46.1, 42.6, 38.3, 36.1, 35.8.

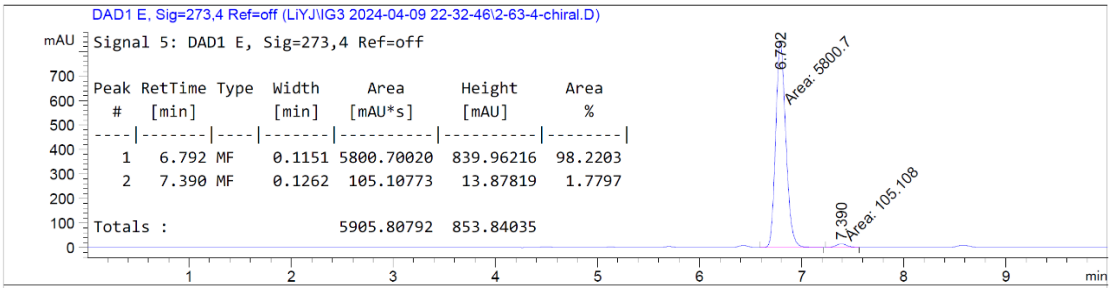
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.9 (s, 3F).

HRMS (ESI) m/z calcd. for $C_{22}H_{23}NaF_3O_5S$ $[M+Na]^+$ 479.1110, found 479.1121.

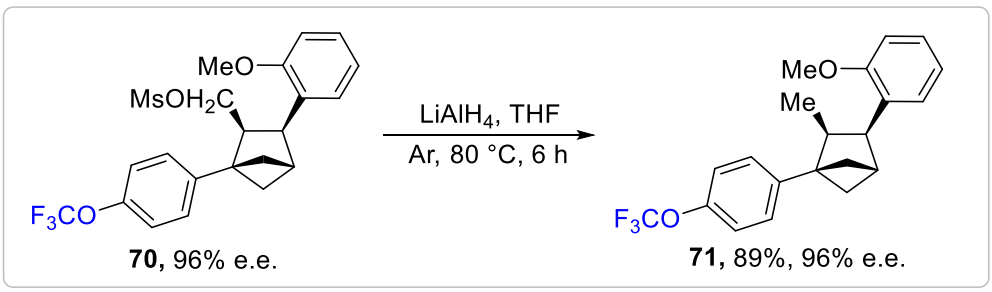
HPLC spectrum of ***rac*-70**:



HPLC spectrum of **70**:

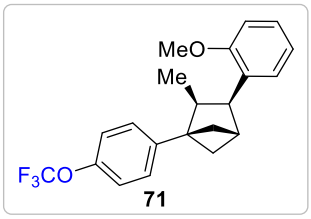


Synthesis of compound 71



Following a reported procedure with some modifications[40], **70** (322 mg, 0.71 mmol, 1.0 equiv.), and anhydrous THF (1.2 mL) were added to an oven-dried Schlenk tube equipped with a magnetic stirrer under argon. $LiAlH_4$ (108 mg, 2.84 mmol, 4.0 equiv.)

was added slowly. The mixture was stirred at 80 °C for 6 h. Upon completion, the reaction mixture was cooled to 0 °C and stirred vigorously while wet Na_2SO_4 was added in portions until the $LiAlH_4$ was fully consumed. The mixture was stirred for an additional 5 minutes, then filtered, and the residue was washed with DCM. The combined filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (PE/EtOAc = 50/1) to afford **71** (230 mg, 89%) as a white solid.



(2*S*,3*S*)-3-(2-methoxyphenyl)-2-methyl-1-(4-(trifluoro-methoxy)phenyl)bicyclo[2.1.1]hexane (71)

HPLC analysis: CHIRALPAK® IB N-3 (*n*-hexane/*i*-PrOH = 95/5, flow rate = 0.30 mL/min, λ = 273 nm), t_R (major) = 12.45 min, t_R (minor) = 13.40 min.

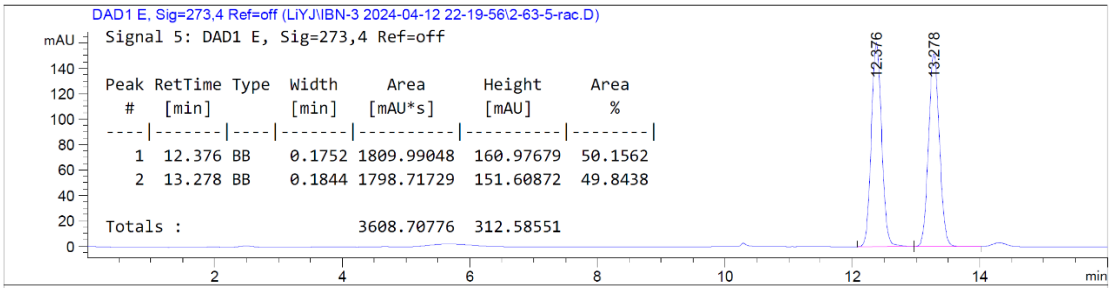
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (td, *J* = 7.7, 1.4 Hz, 1H), 7.17 – 7.09 (m, 5H), 6.93 (td, *J* = 7.4, 0.8 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 3.83 (s, 3H), 3.69 – 3.63 (m, 1H), 2.74 (t, *J* = 2.5 Hz, 1H), 2.71 – 2.55 (m, 1H), 2.03 (dd, *J* = 9.3, 7.0 Hz, 1H), 1.86 (dd, *J* = 6.3, 3.0 Hz, 1H), 1.84 – 1.79 (m, 2H), 1.55 (s, 1H), 0.36 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 147.3 (d, *J* = 1.8 Hz), 142.7, 131.0, 127.4, 126.8, 126.8, 120.54 (d, *J* = 256.4 Hz), 120.53, 120.1, 109.6, 56.6, 55.0, 45.9, 43.5, 42.2, 38.6, 35.1, 12.3.

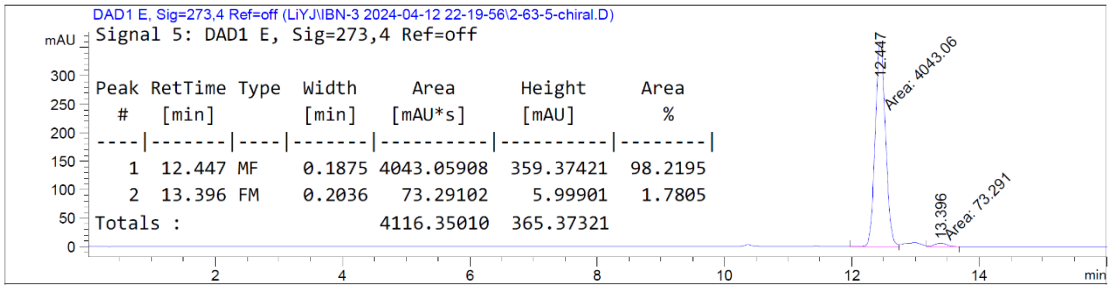
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.9 (s, 3F).

HRMS (ESI) m/z calcd. for $C_{21}H_{22}F_3O_2$ $[M+H]^+$ 363.1567, found 363.1572.

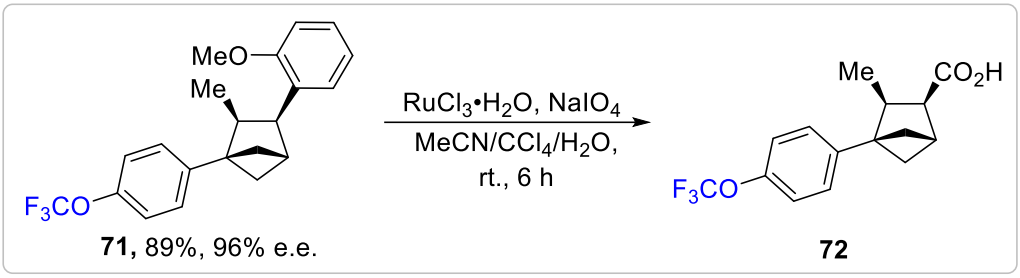
HPLC spectrum of ***rac*-71**:



HPLC spectrum of **71**:



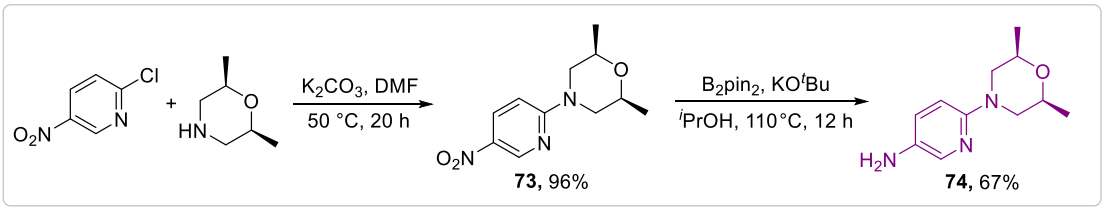
Synthesis of compound 72:



71, 89%, 96% e.e. **72**

Following the reported procedures with some modifications[39], $NaIO_4$ (804 mg, 3.7 mmol, 12.0 equiv.) was added to a solution of **71** (112 mg, 0.31 mmol, 1.0 equiv.) in MeCN (1.8 mL), CCl_4 (1.8 mL), and H_2O (1.8 mL). The mixture was stirred vigorously at room temperature, followed by the addition of $RuCl_3 \cdot H_2O$ (3.5 mg, 0.016 mmol, 0.05 equiv.) in H_2O (1.2 mL). The mixture was stirred vigorously at room temperature for 6 h, during which a large amount of white solid formed. Upon completion (monitored by TLC), 1 N NaOH solution was added dropwise until the pH = 12, and the mixture was washed with DCM. The aqueous phase was separated and acidified to pH = 2 by adding 1 N HCl, then extracted three times with EtOAc. The combined organic layers were dried and concentrated *in vacuo* to yield a yellow oily product **72**, which was used directly in the next step without further purification.

Synthesis of compound 74

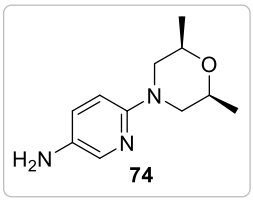


73, 96% **74,** 67%

Step 1: Following the literature procedure[41], 2-chloro-5-nitropyridine (317 mg, 2.0 mmol, 1.0 equiv.), *cis*-2,6-dimethylmorpholine (230 mg, 2.0 mmol, 1.0 equiv.), potassium carbonate (553 mg, 4.0 mmol, 4.0 equiv.), and anhydrous DMF (2.0 mL) were added to a dry 10 mL Schlenk tube equipped with a magnetic stir bar. The reaction mixture was heated at 50 °C for 20 h. Upon completion (monitored by TLC), the mixture was transferred to a separatory funnel. EtOAc and water were added, and the phases were separated. The aqueous phase was extracted with EtOAc twice. The combined organic layers were washed with water and then with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (PE/EtOAc = 4/1) to afford **73** (456 mg, 96%) as a yellow solid.

Step 2: Following the literature procedure[42], bis(pinacolato)diborane (472 mg, 1.86 mmol, 3.1 equiv.), potassium *t*-butoxide (80 mg, 0.72 mmol, 1.2 equiv.), and **73** (142 mg, 0.6 mmol, 1.0 equiv.) were added to a dry 25 mL Schlenk tube equipped with a magnetic stir bar under argon, followed by the addition of *i*-PrOH (2.4 mL). The reaction mixture was refluxed at 110 °C for 12 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with EtOAc, and then washed with saturated NaCl solution. The organic layers were dried over anhydrous

Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (DCM/MeOH = 100/1, with 1% Et_3N) to afford the brown oily product **74** (83 mg, 67%). **74** is prone to oxidation upon exposure to air and should be used immediately for subsequent reactions or stored under argon at 2-8 °C.



74

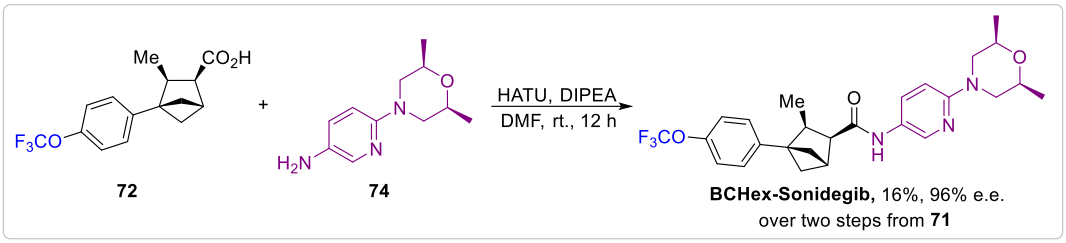
6-((2*R*,6*S*)-2,6-dimethylmorpholino)pyridin-3-amine (74)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 2.9, 0.7 Hz, 1H), 7.00 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.56 (dd, *J* = 8.8, 0.7 Hz, 1H), 3.85 – 3.71 (m, 4H), 2.42 (dd, *J* = 12.4, 10.3 Hz, 2H), 1.26 (d, *J* = 6.2 Hz, 6H).

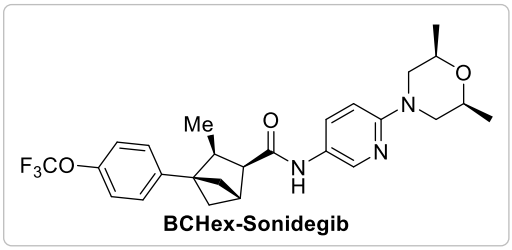
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 135.2, 134.7, 126.2, 108.4, 71.7, 52.4, 19.1.

The spectral data are consistent with those reported in the literature.[41]

Synthesis of BCHex-Sonidegib



Following the literature procedure[43], **72** (~ 0.2 mmol, 1.0 equiv.), **74** (50 mg, 0.24 mmol, 1.2 equiv.), HATU (92 mg, 0.24 mmol, 1.2 equiv.), and anhydrous DMF (2.0 mL) were added to a dry Schlenk tube under argon. DIPEA (70 μL, 0.4 mmol, 4.0 equiv.) was then added dropwise. The mixture was stirred at room temperature for 12 h and then quenched with water (5.0 mL). The mixture was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed sequentially with water and saturated NaCl solution. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative thin-layer chromatography (PTLC, PE/EtOAc = 2/1) to afford **BCHex-Sonidegib** (24.8 mg, 16%, over two steps from **71**).



(2*S*,3*S*)-*N*-(6-((2*R*,6*S*)-2,6-dimethylmorpholino)-pyridin-3-yl)-3-methyl-4-(4-(trifluoromethoxy)-phenyl)bicyclo[2.1.1]hexane-2-carboxamide (BCHex-Sonidegib)

HPLC analysis: CHIRALPAK® IF-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 7.27 min, t_R (minor) = 8.29 min.

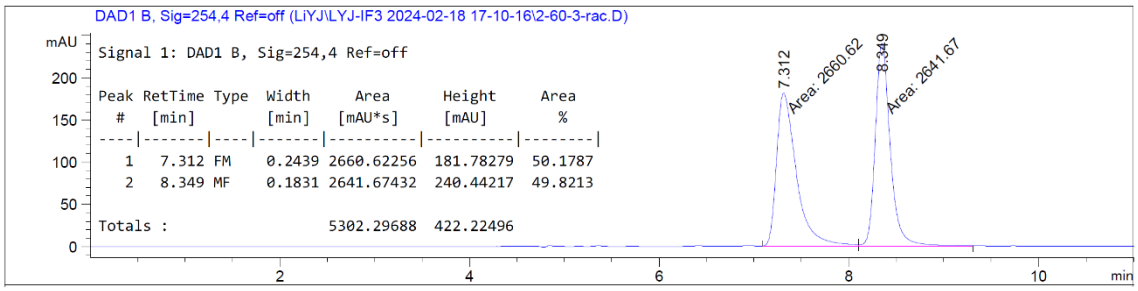
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 2.6 Hz, 1H), 7.93 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.20 (s, 1H), 7.17 – 7.10 (m, 4H), 6.63 (d, *J* = 9.1 Hz, 1H), 4.00 – 3.92 (m, 2H), 3.73 (ddd, *J* = 10.4, 6.3, 2.5 Hz, 2H), 3.06 (d, *J* = 9.2 Hz, 1H), 2.72 (s, 1H), 2.56 (d, *J* = 7.4 Hz, 1H), 2.50 (dd, *J* = 12.5, 10.7 Hz, 2H), 2.35 (dd, *J* = 9.7, 7.3 Hz, 1H), 1.83 (d, *J* = 2.9 Hz, 2H), 1.63 (dd, *J* = 9.7, 6.7 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 6H), 0.88 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 156.7, 147.6 (d, J = 1.5 Hz), 141.1, 140.1, 131.7, 127.5, 125.6, 120.8, 120.5 (d, J = 256.7 Hz), 107.0, 71.6, 56.1, 51.2, 50.5, 45.4, 42.3, 38.8, 35.4, 19.0, 12.6.

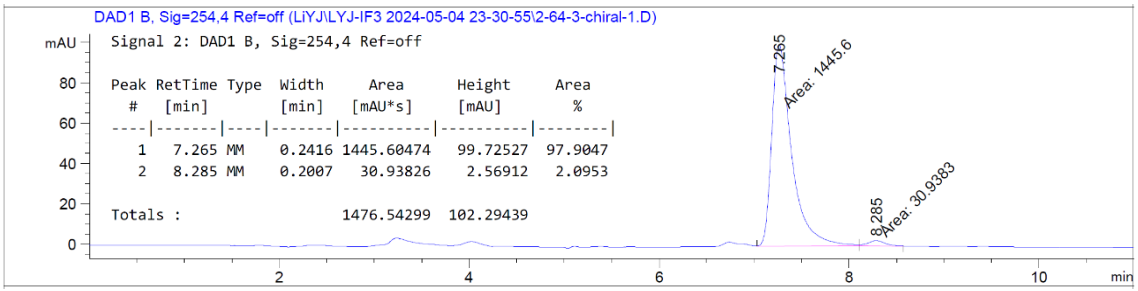
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.9 (s, 3F).

HRMS (ESI) m/z calcd. for $C_{26}H_{31}F_3N_3O_3$ $[M+H]^+$ 490.2312, found 490.2311.

HPLC spectrum of ***rac*-BCHex-Sonidegib**:

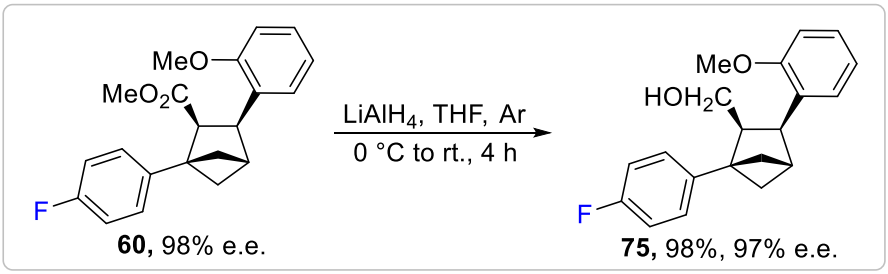


HPLC spectrum of **BCHex-Sonidegib**:



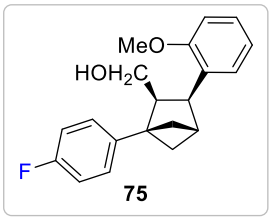
8.3 Synthesis of BCHex-BMS-202 as the bioisostere of BMS-202

Synthesis of compound 75



60, 98% e.e. **75,** 98%, 97% e.e.

Compound **75** was prepared following the protocol for **69**, using **60** (256 mg, 0.75 mmol, 1.0 equiv.), $LiAlH_4$ (114 mg, 3.00 mmol, 4.0 equiv.), and dry THF (1.5 mL). The reaction was conducted at room temperature for 4 h under argon. The crude product was purified through silica gel flash column chromatography (PE/EtOAc = 10/1) to afford **75** (232 mg, 99%) as a white solid.



((2*S*,3*S*)-1-(4-fluorophenyl)-3-(2-methoxyphenyl)bicyclo-[2.1.1]hexan-2-yl)methanol (75)

HPLC analysis: CHIRALPAK® ID-3 (*n*-hexane/*i*-PrOH = 80/20, flow rate = 0.50 mL/min, λ = 254 nm), t_R (major) = 12.50 min, t_R (minor) = 15.11 min.

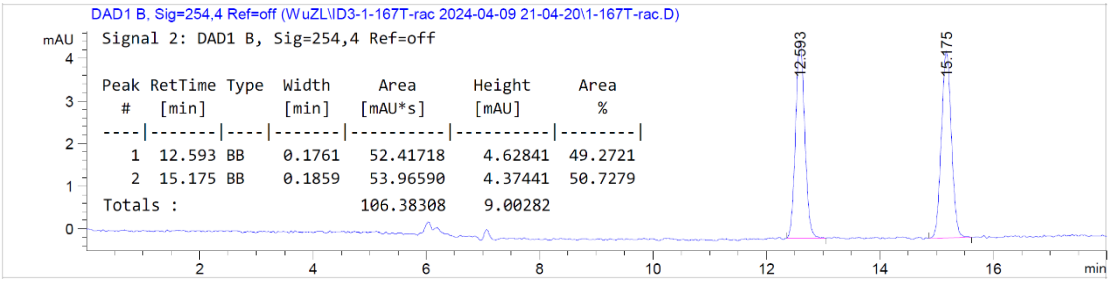
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.07 (m, 2H), 7.07 – 6.99 (m, 2H), 6.86 (t, *J* = 8.7 Hz, 3H), 6.78 (d, *J* = 7.0 Hz, 1H), 3.74 (s, 3H), 3.68 (d, *J* = 8.9 Hz, 1H), 3.12 – 2.95 (m, 2H), 2.60 (dd, *J* = 3.1, 2.0 Hz, 2H), 2.00 – 1.90 (m, 1H), 1.83 – 1.75 (m, 1H), 1.72 – 1.65 (m, 2H), 1.40 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (d, *J* = 244.3 Hz), 157.3, 138.9 (d, *J* = 2.8 Hz), 130.0, 127.6 (d, *J* = 7.7 Hz), 127.6, 127.1, 121.0, 115.3 (d, *J* = 21.1 Hz), 110.5, 62.5, 55.49, 55.46, 51.0, 46.5, 42.8, 38.7, 36.2.

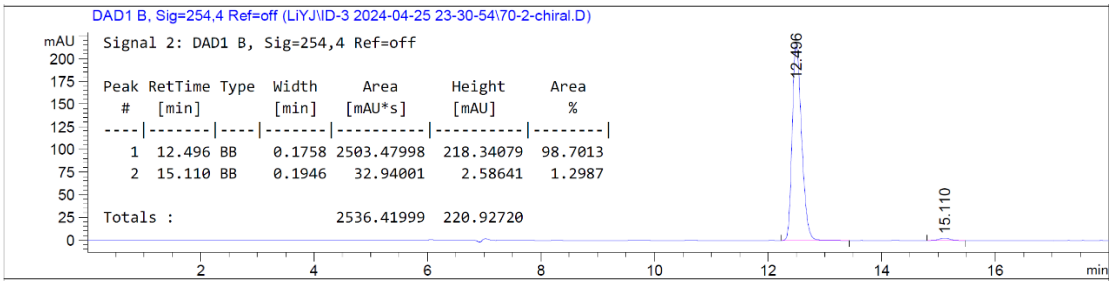
^{19}F NMR (376 MHz, $CDCl_3$) δ -116.4 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{20}H_{21}NaFO_2$ $[M+Na]^+$ 335.1418, found 335.1422.

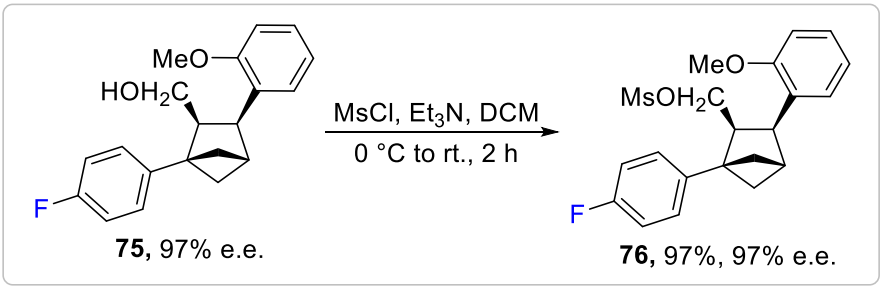
HPLC spectrum of ***rac*-75:**



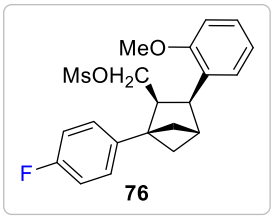
HPLC spectrum of **75:**



Synthesis of compound 76



Compound **76** was prepared following the procedure for **70**, using **75** (232 mg, 0.74 mmol, 1.0 equiv.), Et_3N (206 μL, 2.0 equiv.), MsCl (120 μL, 2.0 equiv.), and dry DCM (1.5 mL). The reaction was conducted at room temperature for 2 h under argon. The crude product was purified by silica gel flash column chromatography (PE/EtOAc = 15/1 to 10/1) to afford **76** (280 mg, 97%) as a white solid.



((2*S*,3*S*)-1-(4-fluorophenyl)-3-(2-methoxyphenyl)-bicyclo[2.1.1]hexan-2-yl)methyl methanesulfonate (76)

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 60/40, flow rate = 0.65 mL/min, λ = 254 nm), t_R (major) = 8.52 min, t_R (minor) = 9.48 min.

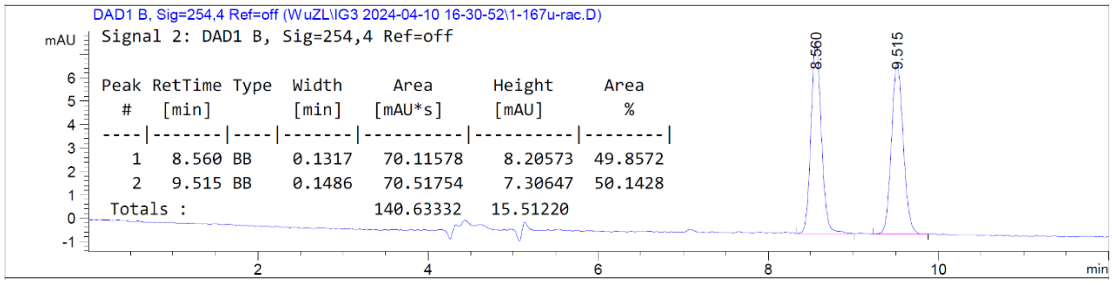
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (td, *J* = 7.9, 1.8 Hz, 1H), 7.17 – 7.10 (m, 3H), 7.01 – 6.84 (m, 4H), 3.87 – 3.83 (m, 4H), 3.83 – 3.78 (m, 1H), 3.67 (dd, *J* = 10.0, 7.1 Hz, 1H), 2.97 – 2.88 (m, 1H), 2.72 (s, 1H), 2.19 (s, 3H), 2.09 (t, *J* = 8.5 Hz, 1H), 1.98 – 1.93 (m, 1H), 1.86 – 1.78 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4 (d, *J* = 244.3 Hz), 157.9, 138.3 (d, *J* = 3.3 Hz), 128.6, 127.85, 127.75 (d, *J* = 7.7 Hz), 126.7, 120.5, 115.0 (d, *J* = 21.3 Hz), 110.1, 69.3, 55.5, 55.3, 46.4, 46.1, 42.7, 38.3, 36.1, 36.0.

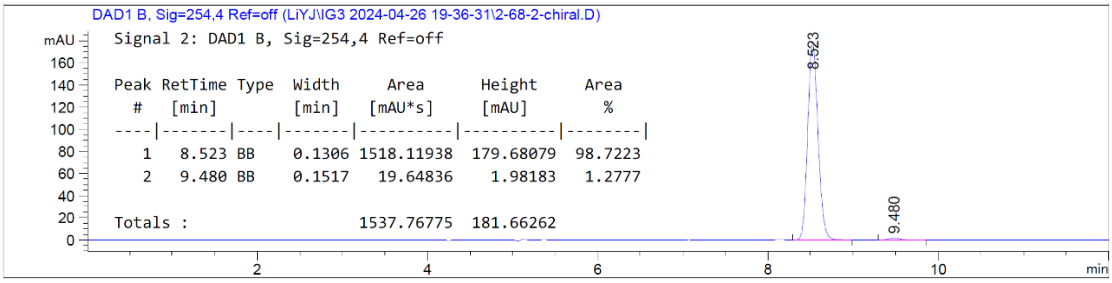
^{19}F NMR (376 MHz, $CDCl_3$) δ -116.4 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{21}H_{23}FNaO_4S$ $[M+Na]^+$ 413.1193, found 413.1202.

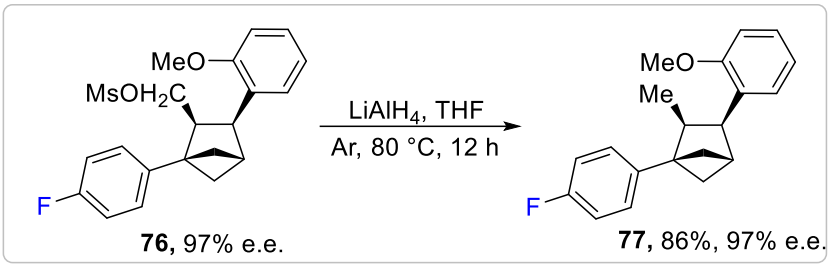
HPLC spectrum of ***rac*-76:**



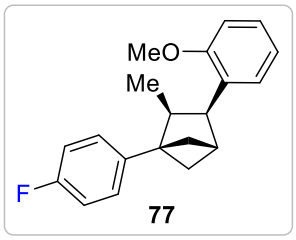
HPLC spectrum of **76:**



Synthesis of compound 77



Compound **77** was prepared following the protocol for compound **71**, using **76** (280 mg, 0.72 mmol, 1.0 equiv.), $LiAlH_4$ (109 mg, 2.88 mmol, 4.0 equiv.), and THF (1.2 mL). The reaction was conducted at 80 °C for 12 h under argon. The crude product was purified by silica gel flash column chromatography (PE/EtOAc = 50/1) to afford **77** (183 mg, 86%) as a white solid.



(2*S*,3*S*)-1-(4-fluorophenyl)-3-(2-methoxyphenyl)-2-methyl-bicyclo[2.1.1]hexane (77)

HPLC analysis: CHIRALPAK® IB N-3 (*n*-hexane/*i*-PrOH = 95/5, flow rate = 0.30 mL/min, λ = 254 nm), t_R (major) =13.14 min, t_R (minor) = 14.08 min.

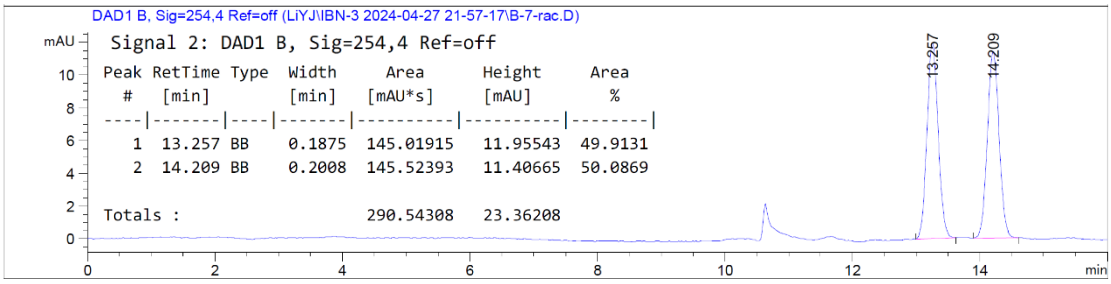
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 2H), 7.19 (t, *J* = 6.1 Hz, 2H), 7.12 – 7.03 (m, 3H), 6.98 (d, *J* = 7.9 Hz, 1H), 3.93 (s, 3H), 3.80 (d, *J* = 8.8 Hz, 1H), 2.86 (s, 1H), 2.76 (p, *J* = 7.1 Hz, 1H), 2.20 – 2.11 (m, 1H), 2.00 – 1.88 (m, 3H), 0.51 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3 (d, *J* = 243.6 Hz), 158.0, 139.7 (d, *J* = 2.9 Hz), 131.2, 127.7 (d, *J* = 7.7 Hz), 126.9, 120.2, 114.8 (d, *J* = 20.9 Hz), 109.7, 56.7, 55.1, 46.0, 43.6, 42.3, 38.7, 35.2, 12.5.

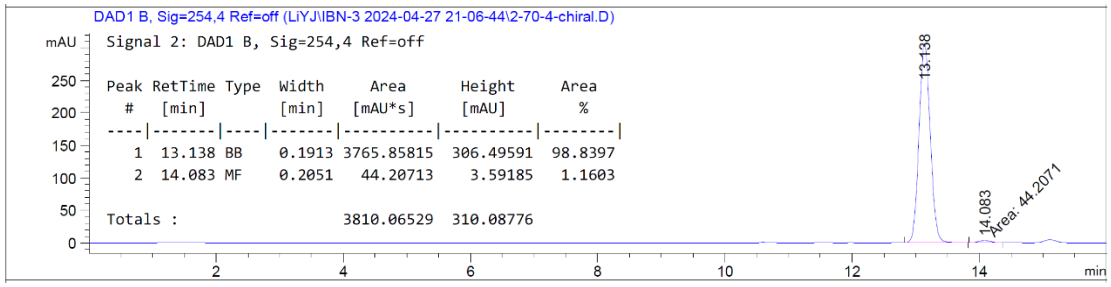
^{19}F NMR (376 MHz, $CDCl_3$) δ -117.3 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{20}H_{23}FO$ $[M+2H]^+$ 298.1722, found 298.1719.

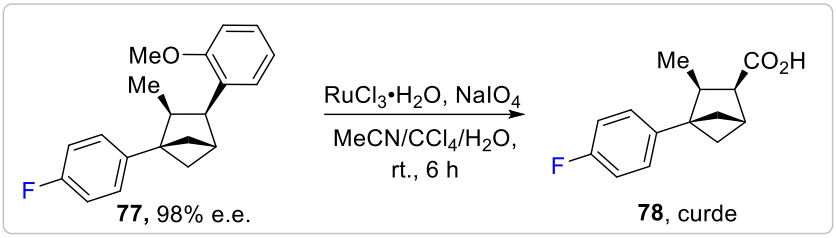
HPLC spectrum of ***rac*-77**



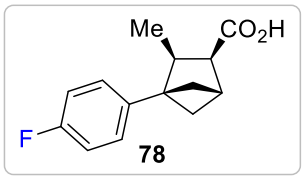
HPLC spectrum of **77:**



Synthesis of compound 78



Following the reported procedures with some modifications,[39] $NaIO_4$ (803 mg, 3.7 mmol, 12.0 equiv.) was added to a solution of **77** (90.4 mg, 0.31 mmol, 1.0 equiv.) in MeCN (1.8 mL), CCl_4 (1.8 mL), and H_2O (1.7 mL). The mixture was stirred vigorously at room temperature, followed by the addition of $RuCl_3 \cdot H_2O$ (3.5 mg, 0.016 mmol, 0.05 equiv.) in H_2O (1.0 mL). The mixture was stirred vigorously at room temperature for 6 h, during which a large amount of white solid formed. Upon completion (monitored by TLC), 1 N NaOH solution was added dropwise until the pH = 12, and the mixture was washed with DCM. The aqueous phase was separated and acidified to pH = 2 by adding 1 N HCl, then extracted three times with EtOAc. The combined organic layers were dried and concentrated to yield a yellow oily product **78**, which was used directly in the next step.



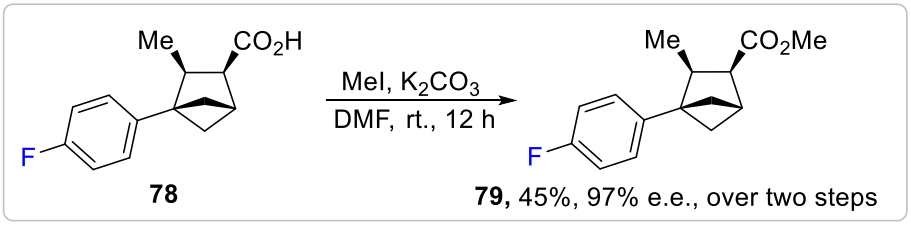
(2*S*,3*S*)-4-(4-fluorophenyl)-3-methylbicyclo[2.1.1]hexane-2-carboxylic acid (78)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 6.93 (m, 4H), 3.20 – 3.13 (m, 1H), 2.69 – 2.62 (m, 1H), 2.61 – 2.53 (m, 1H), 2.12 (dd, *J* = 9.8, 7.4 Hz, 1H), 1.83 – 1.74 (m, 2H), 1.64 – 1.58 (m, 1H), 0.87 (d, *J* = 7.1 Hz, 3H).

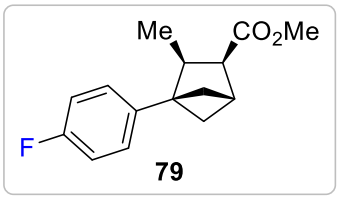
^{13}C NMR (101 MHz, $CDCl_3$) δ 179.2, 161.4 (d, *J* = 244.3 Hz), 137.9 (d, *J* = 3.3 Hz), 127.6 (d, *J* = 8.1 Hz), 114.9 (d, *J* = 21.3 Hz), 56.2, 48.6, 45.1, 41.8, 38.3, 35.4, 12.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -116.9 (s, 1F).

Synthesis of compound 79



Following a modified procedure from the literature[15], **78** (~0.28 mmol, 1.0 equiv.), K_2CO_3 (77 mg, 1.56 mmol, 2.0 equiv.), and DMF (1.0 mL) were added to a dry round-bottom flask. Methyl iodide (71 μL, 1.14 mmol, 2.0 equiv.) was then added dropwise. The mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified by column chromatography (PE/EA = 50/1) to yield **79** (34.4 mg, 45% over two steps) as a white solid.



Methyl (2*S*,3*S*)-4-(4-fluorophenyl)-3-methylbicyclo[2.1.1]-hexane-2-carboxylate (79)

HPLC analysis: CHIRALPAK® IG-3 (*n*-hexane/*i*-PrOH = 95/5, flow rate = 0.30 mL/min, λ = 273 nm), t_R (major) = 15.58 min, t_R (minor) = 16.38 min.

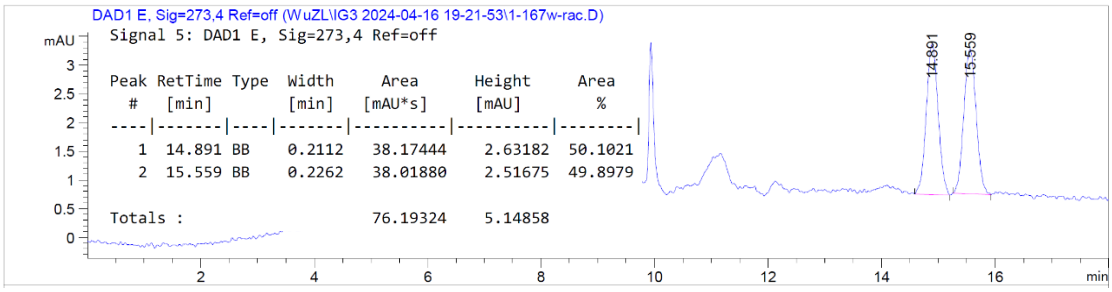
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 8.6, 5.6 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 3.69 (s, 3H), 3.12 (d, *J* = 9.4 Hz, 1H), 2.66 – 2.59 (m, 1H), 2.57 – 2.46 (m, 1H), 2.13 (dd, *J* = 9.8, 7.3 Hz, 1H), 1.76 (dt, *J* = 7.0, 3.4 Hz, 2H), 1.57 (dd, *J* = 9.8, 6.7 Hz, 1H), 0.77 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 161.4 (d, *J* = 243.9 Hz), 138.1 (d, *J* = 3.1 Hz), 127.6 (d, *J* = 7.8 Hz), 114.9 (d, *J* = 21.2 Hz), 56.1, 51.1, 48.8, 45.1, 41.8, 38.4, 35.5, 12.6.

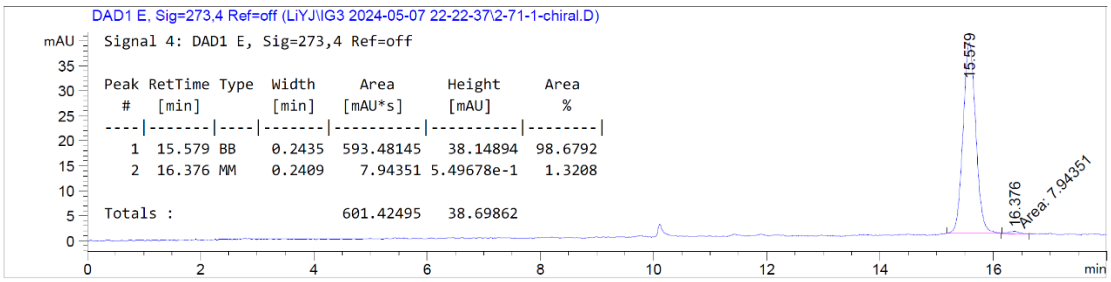
^{19}F NMR (376 MHz, $CDCl_3$) δ -117.0 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{15}H_{18}FO_2$ $[M+H]^+$ 249.1286, found 249.1290.

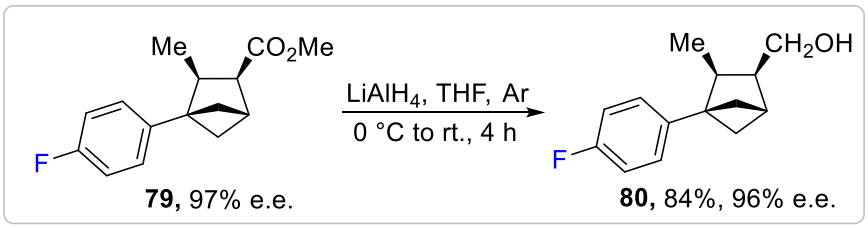
HPLC spectrum of ***rac*-79**:



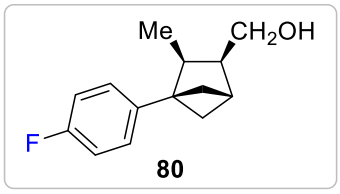
HPLC spectrum of **79**:



Synthesis of compound 80



The synthesis of **80** was carried out similarly to the procedure for compound **69**. Specifically, **79** (34.4 mg, 0.14 mmol, 1.0 equiv.) was treated with $LiAlH_4$ (0.28 mmol, 2.0 equiv.) in anhydrous THF (0.5 mL) at room temperature for 4 h. The reaction mixture was then purified by PTLC (PE/EtOAc = 5/1) to afford the desired product **80** (25.5 mg, 84%) as a colorless oil.



((2*S*,3*S*)-4-(4-fluorophenyl)-3-methylbicyclo[2.1.1]-hexan-2-yl)methanol (80)

HPLC analysis: CHIRALPAK® IA-3 (*n*-hexane/*i*-PrOH = 90/10, flow rate = 0.50 mL/min, λ = 273 nm), t_R (major) =11.67 min, t_R (minor) = 12.43 min.

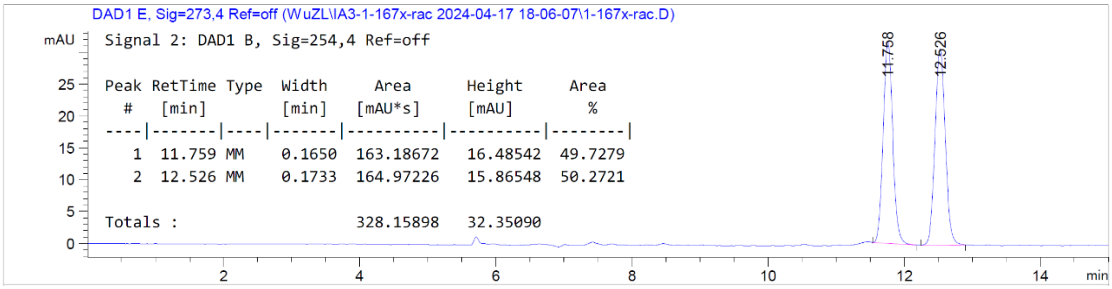
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 6.84 (m, 4H), 3.78 (dd, *J* = 10.1, 6.0 Hz, 1H), 3.61 (t, *J* = 9.6 Hz, 1H), 2.50 (s, 1H), 2.45 – 2.24 (m, 2H), 1.88 – 1.51 (m, 5H), 0.74 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2 (d, *J* = 243.6 Hz), 138.9 (d, *J* = 3.1 Hz), 127.5 (d, *J* = 7.8 Hz), 114.8 (d, *J* = 21.1 Hz), 63.0, 57.3, 45.7, 45.6, 40.3, 37.9, 33.4, 11.1.

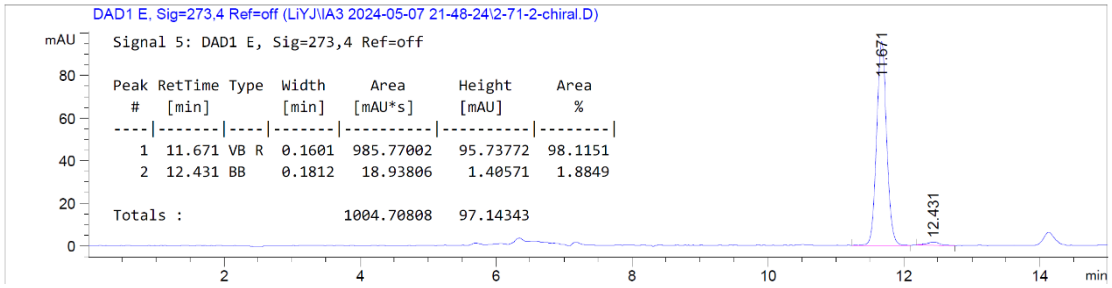
^{19}F NMR (376 MHz, $CDCl_3$) δ -117.4 (s, 1F).

HRMS (ESI) m/z calcd. for $C_{14}H_{16}F$ $[M+H-H_2O]^+$ 203.1230, found 203.1234.

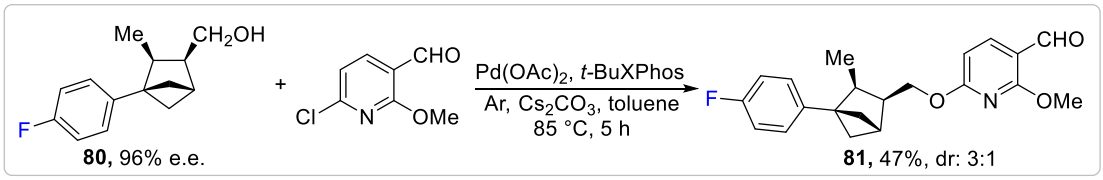
HPLC spectrum of ***rac*-80**:



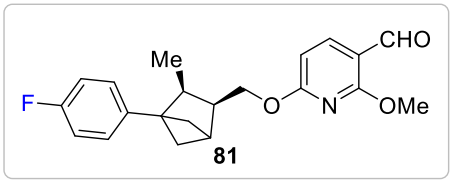
HPLC spectrum of **80**:



Synthesis of compound 81



Following the procedure in reference,[44] an oven-dried Schlenk tube was charged with **80** (25.5 mg, 0.12 mmol, 1.0 equiv.), 2-chloro-6-methoxy-3-pyridinecarbaldehyde (30.9 mg, 0.18 mmol, 1.5 equiv.), cesium carbonate (78.2 mg, 0.24 mmol, 2.0 equiv.), *t*-BuXPhos (10.2 mg, 0.024 mmol, 0.2 equiv.), palladium acetate (3.3 mg, 0.0144 mmol, 0.12 equiv.), and toluene (1.2 mL). The mixture was bubbled with argon for 5 minutes, the tube was then sealed, and the reaction mixture was stirred at 85 °C for 5 h. Upon completion (monitored by TLC), the mixture was cooled to room temperature, filtered through celite, and the filtrate was concentrated. The residue was purified by PTLC (PE/EtOAc = 10/1) to afford **81** (20 mg, 47%) as a pale-yellow oil.



6-(((2*S*,3*S*)-4-(4-fluorophenyl)-3-methyl-bicyclo[2.1.1]hexan-2-yl)methoxy)-2-methoxy-nicotinaldehyde (81)

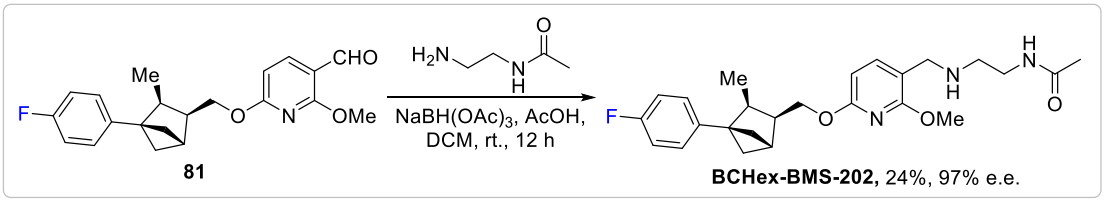
The major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.11 – 7.02 (m, 2H), 7.03 – 6.94 (m, 2H), 6.39 (d, *J* = 8.2 Hz, 1H), 4.54 – 4.29 (m, 2H), 4.05 (s, 3H), 2.77 – 2.61 (m, 1H), 2.56 – 2.49 (m, 1H), 2.45 – 2.30 (m, 1H), 1.87 – 1.77 (m, 2H), 1.70 – 1.58 (m, 2H), 0.81 (d, *J* = 7.2 Hz, 3H).

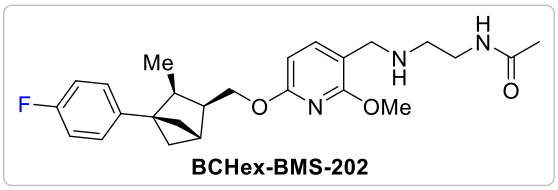
^{13}C NMR (101 MHz, $CDCl_3$) δ 187.6, 166.9, 165.1, 161.3 (d, *J* = 247.7 Hz), 140.2, 138.6 (d, *J* = 3.0 Hz), 127.5 (d, *J* = 7.8 Hz), 114.9 (d, *J* = 21.0 Hz), 112.0, 103.7, 67.2, 57.4, 53.8, 45.7, 42.3, 40.4, 38.4, 33.6, 29.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.2 (s, 1F).

Synthesis of BCHex-BMS-202



Following a modified procedure from the reference,[45] a dried round-bottom flask was charged with **81** (20 mg, 0.056 mmol, 1.0 equiv.), *N*-acetylethylenediamine (12 mg, 0.12 mmol, 2.0 equiv.), one drop of glacial acetic acid, and anhydrous DCM (2 mL). The mixture was stirred at room temperature for 0.5 h, and then sodium triacetoxyborohydride (38 mg, 0.18 mmol, 3.0 equiv.) was added. The mixture was stirred for 12 h and quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried and concentrated, and the residue was purified by PTLC (DCM/MeOH = 20/1, with 1% 7 M NH_3 in MeOH) to afford **BCHex-BMS-202** (6 mg, 24%).



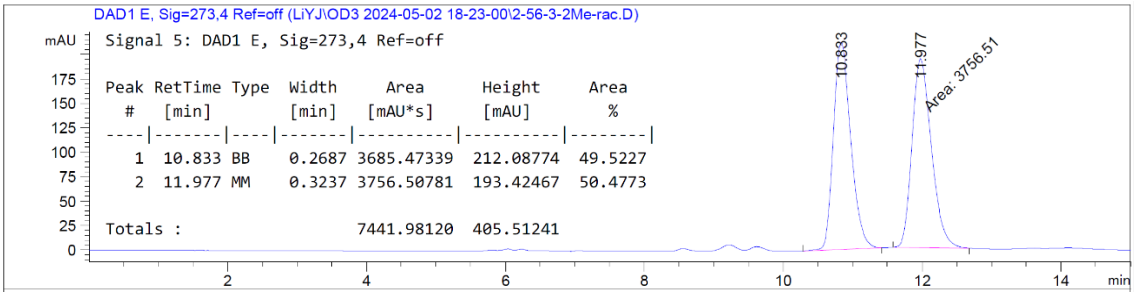
***N*-(2-(((6-(((2*S*,3*S*)-4-(4-fluorophenyl)-3-methylbicyclo[2.1.1]hexan-2-yl)methoxy)-2-methoxypyridin-3-yl)methyl)amino)-ethyl)acetamide (BCHex-BMS-202)**

HPLC analysis: CHIRALPAK® OD-3 (*n*-hexane/*i*-PrOH = 80/20, flow rate = 0.50 mL/min, λ = 273 nm), t_R (major) = 10.94min, t_R (minor) = 12.71 min.

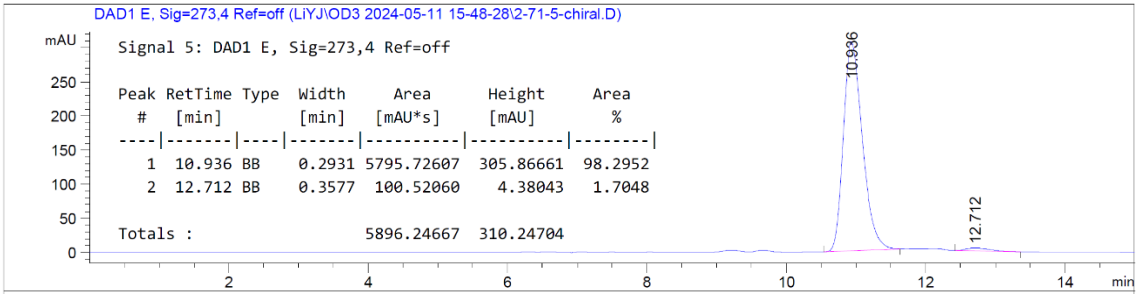
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.8 Hz, 1H), 7.11 – 7.02 (m, 2H), 7.02 – 6.93 (m, 2H), 6.33 – 6.22 (m, 2H), 4.38 (dd, *J* = 10.6, 6.6 Hz, 1H), 4.25 (dd, *J* = 10.6, 8.3 Hz, 1H), 3.95 (s, 3H), 3.67 (s, 2H), 3.35 (q, *J* = 5.6 Hz, 2H), 2.77 – 2.64 (m, 3H), 2.54 (t, *J* = 3.5 Hz, 1H), 2.42 – 2.34 (m, 1H), 1.98 (s, 3H), 1.85 – 1.75 (m, 2H), 1.68 – 1.60 (m, 2H), 0.81 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 163.5, 161.3 (d, *J* = 243.6 Hz), 160.9, 142.6, 138.8 (d, *J* = 3.3 Hz), 127.5 (d, *J* = 8.1 Hz), 114.8 (d, *J* = 21.3 Hz), 106.0, 101.7, 66.6, 57.3, 53.6, 46.9, 46.2, 45.7, 42.3, 40.4, 38.5, 36.9, 33.6, 23.0, 11.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.3 (s, 1F).
HRMS (ESI) m/z calcd. for $C_{25}H_{33}FN_3O_3$ $[M+H]^+$ 442.2501, found 442.2508.
HPLC spectrum of ***rac*-BCHex-BMS-202**:



HPLC spectrum of **BCHex-BMS-202**:



9. Biological studies of Chiral BCHex-Sonidegib and BCHex-BMS-202

9.1 Metabolic stability assay

Metabolic stability assay was conducted to evaluate the compounds' susceptibility to human liver microsomal degradation.[46] Compounds were prepared as 200 μM stock solution in methanol and subsequently diluted to 1 μM (1% methanol) in water for assays. The reaction mixture was composed of liver microsomes (equivalent to 0.1 mg/ml total protein) in 0.1 M phosphate buffer (pH 7.4). To initiate the reaction, the cofactor NADPH was added. Control, positive, and test compounds were introduced into the incubation mixture and pre-incubated for 5 minutes at 37°C. Following the start of the reaction, aliquots were collected at 0, 5, 10, 15, 30, and 45 minutes. The reaction was terminated by adding equal volume of ice-cold methanol containing an internal standard (135 ng/ml). Samples were vortexed and filtered through a 0.22 μm filter before analysis. All samples were separated by ultra-high-performance liquid chromatography (Vanquish UHPLC, Thermo Scientific™) and analyzed using QExactive Focus (Orbitrap, Thermo Scientific™, San Jose, USA). Data were acquired by Parallel Reaction Monitoring.

9.2 Solubility assay

Kinetic solubility assay was performed to determine the aqueous solubility of the compounds at different pH levels, following Enamine's aqueous solubility standard operating procedure.[39c] Compounds were initially prepared as 20 mM stock solutions in 100% DMSO. These were subsequently diluted in duplicate to a theoretical concentration of 400 μM using phosphate-buffered saline (PBS) at pH 7.4 and pH 2.0, with a final DMSO concentration of 2%. The diluted compounds in PBS were equilibrated at 37°C on a thermostatic shaker for 48 hours, then filtered through a 0.45 μm filter. The filtrates were further diluted 2-fold with acetonitrile containing 2% DMSO prior to measurement.

Calibration curves were generated concurrently. For pH 7.4, compound dilutions in acetonitrile/PBS (1:1) were prepared at theoretical concentrations of 0 μM (blank), 0.002 μM, 0.005 μM, 0.01 μM, 0.02 μM, 0.05 μM, 0.1 μM, 0.2 μM, 0.5 μM, 1 μM, and 2 μM. For pH 2.0, dilutions were prepared at 0 μM (blank), 5 μM,10 μM, 25 μM, 50 μM, 80 μM, 100 μM, 150 μM and 200 μM. All calibration samples contained 2% final DMSO.

All samples were analyzed using ultra-high-performance liquid chromatography (Vanquish UHPLC, Thermo Scientific™, USA) coupled with a QExactive Focus Orbitrap mass spectrometer (Thermo Scientific™, San Jose, USA). Data acquisition was carried out using Parallel Reaction Monitoring.

9.3 Log P assay

Log P assay was conducted to determine the lipophilicity of the compounds using a reverse-phase HPLC (RP-HPLC) method.[47] A standard mix comprising 4-acetylpyridine, aniline, phenol, benzene, toluene, chlorobenzene, and naphthalene was

employed to generate the calibration curve, encompassing a Log P range from 0.5 to 3.6. Uracil was utilized for determining column dead-time. Each compound was dissolved to approximately 2 mM in appropriate solvents. All HPLC analyses were conducted using an Alliance RP-HPLC system (Waters, Milford, MA, USA), consisting of an e2695 separation module and a 2998 PDA detector. The system was equipped with a XBridge C18 column (250 mm × 4.6 mm, 5.0 μm) (Waters, Milford, MA, USA) and partially controlled by Waters Empower 3 Chromatography software. The flow rate was set at 1 mL/min, with an injection volume of 10 μL. The mobile phase consisted of acetonitrile and water. Data acquisition was performed throughout the 12-minute run time, allowing for comprehensive analysis of the sample components. This setup enabled efficient separation and detection of the standard mix compounds, facilitating accurate calibration and subsequent sample analysis.

9.4 Cell Characterization

A549, NCI-H1975, PANC-1, MIA PaCa-1, and MIHA cell lines (**Table S5**) were characterized by Genetic Testing Biotechnology Corporation (Suzhou, China) using short tandem repeat (STR) markers.

Table S5 | The information of cell lines

Cell Line	Tissue or Disease	Culture Medium	Culture Condition
A549	Human lung cancer	RPMI-1640 + 10% FBS	37°C in 5% CO_2
NCI-H1975	Human lung cancer	RPMI-1640 + 10% FBS	37°C in 5% CO_2
PANC-1	Human pancreatic cancer	DMEM + 10% FBS	37°C in 5% CO_2
MIA PaCa-2	Human pancreatic cancer	DMEM + 10% FBS	37°C in 5% CO_2
MIHA	Human normal hepatocyte	RPMI-1640 + 10% FBS	37°C in 5% CO_2

9.5 Antitumor activity assay *in vitro*

Antitumor activities were evaluated using MTT assay *in vitro*. A549, NCI-H1975, PANC-1, MIA PaCa-1, and MIHA cells (0.8 - 1.2 × 10^4 cells/well) were seeded in 96-well plates with respective culture mediums (as detailed in **Table S5**) and incubated at 37°C, 5% CO_2 for 12 hours. Cells were then treated with various concentrations of test compounds, maintaining a final DMSO concentration of 0.5%, and further incubated for 48 hours under the same conditions. Afterwards, MTT solution was added to each well to achieve a final concentration of 0.5 mg/mL. The plates were then incubated at 37°C for 4 hours. After incubation, the media were carefully aspirated, and the resulting

formazan crystals were dissolved in 100 μL of DMSO per well. The absorbance was measured at 490 nm using a Tecan Infinite M1000 Pro microplate reader.

9.6 Colony formation assay

A549 cells (1×10^4/well) in the logarithmic growth phase were seeded in 6-well plates and incubated at 37°C, 5% CO_2 for 12 hours. Cells were then treated with various concentrations of test compounds for 5 days. After treatment, cells were fixed with 500 μL ice-cold methanol for 1 hour, and stained with crystal violet for 30 minutes at room temperature, air-dried, and photographed.

9.7 Apoptosis assay

A549 cells in logarithmic growth phase were seeded in 6-well plates and incubated at 37°C, 5% CO_2 for 12 hours. The cells were then treated with test compounds and incubated for an additional 48 hours under the same conditions. After treatment, cells were harvested using trypsin and stained with Annexin V-FITC and PI solution in binding buffer. The staining was performed in the dark at room temperature for 10 - 15 minutes. Finally, the samples were analyzed in flow cytometry of CytoFLEX (Beckman, America).

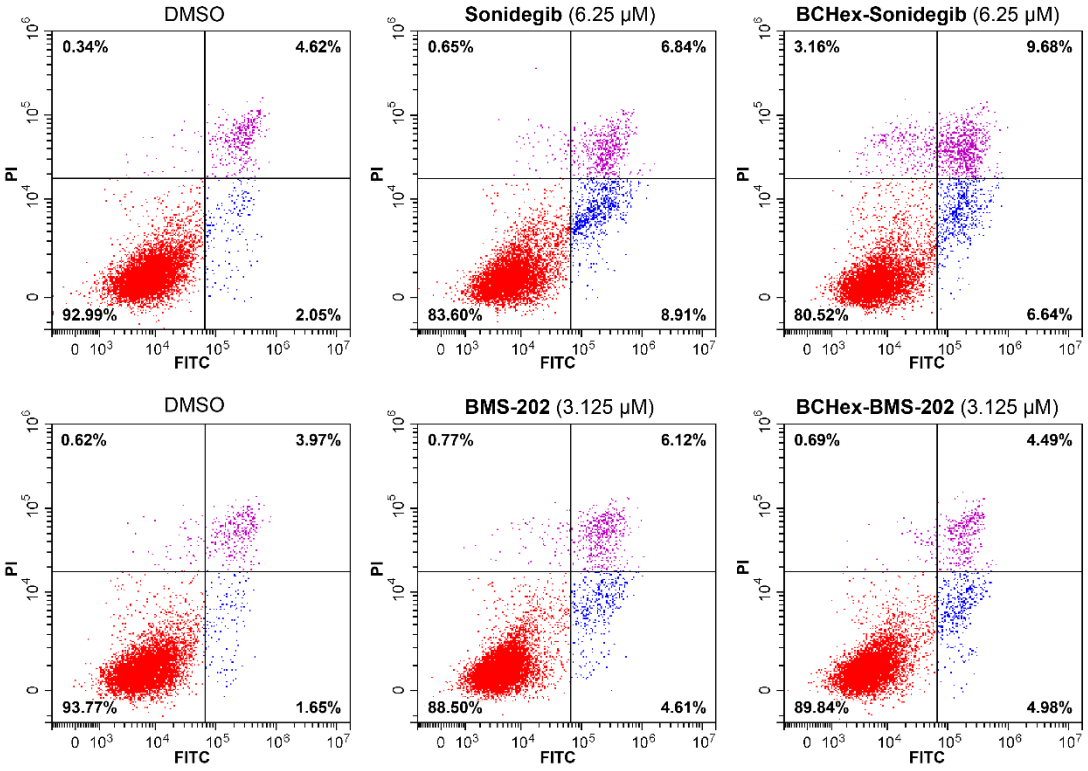
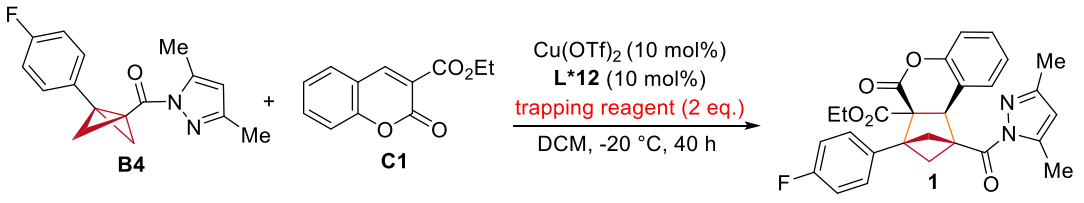


Figure S10 | Apoptosis assay of A549 cells treated with Sonidegib, BCHex-Sonidegib, BMS-202, and BCHex-BMS-202 for 48 hours, respectively.

10. Mechanistic studies

10.1 Radical trap experiments

According to the **General Procedure A**, under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with BCB substrate **B4** (14.2 mg, 0.0525 mmol, 1.05 equiv.) and coumarin substrate **C1** (10.9 mg, 0.05 mmol, 1.0 equiv.), $Cu(OTf)_2$ (1.81 mg, 0.005 mmol, 10 mol%), **L*12** (4.44 mg, 0.005 mmol, 10 mol%), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 15.6 mg, 0.10 mmol, 2.0 equiv.) or 2,6-di-*tert*-butyl-4-methylphenol (BHT, 22.0 mg, 0.10 mmol, 2.0 equiv.), and anhydrous DCM (0.5 mL). The sealed tube was stirred at -20 °C for 40 h. The yield was based on ^1H NMR analysis of the crude products using CH_2Br_2 as an internal standard.

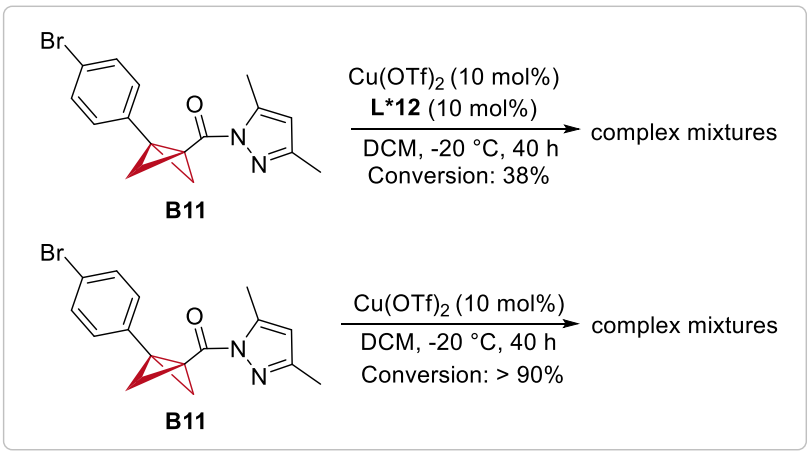


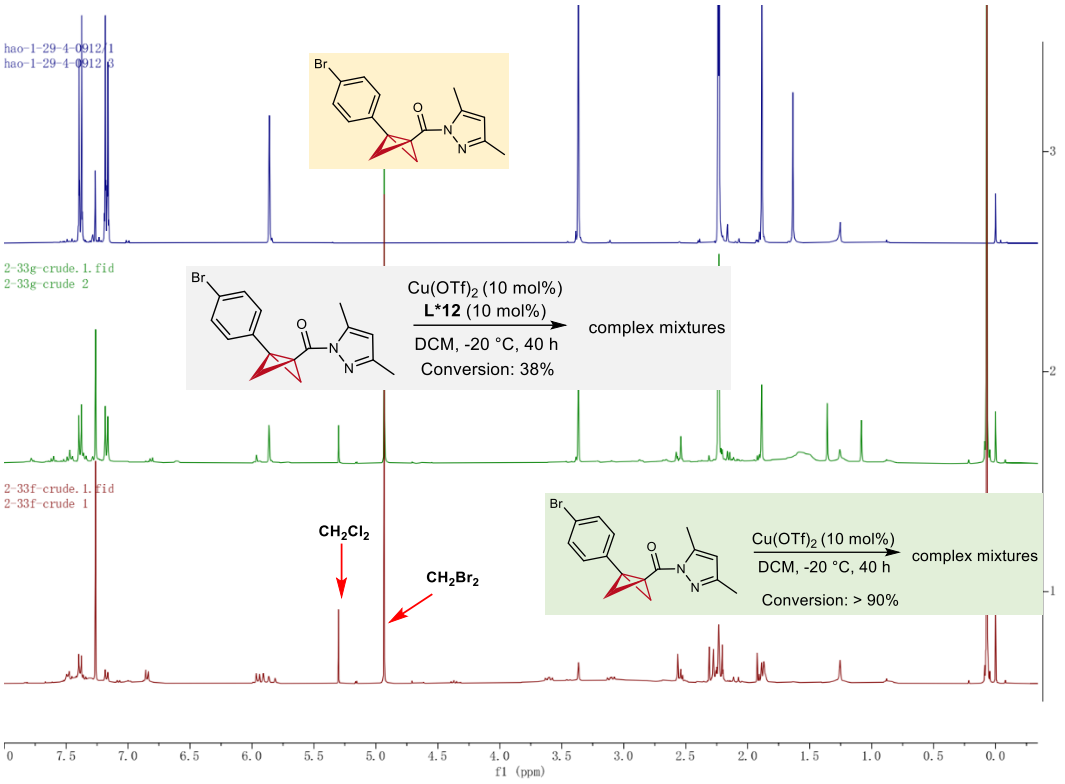
trapping reagent	yield (%)
none	95
TEMPO	95
BHT	86

10.2 Control experiments

a) The effect of ligand

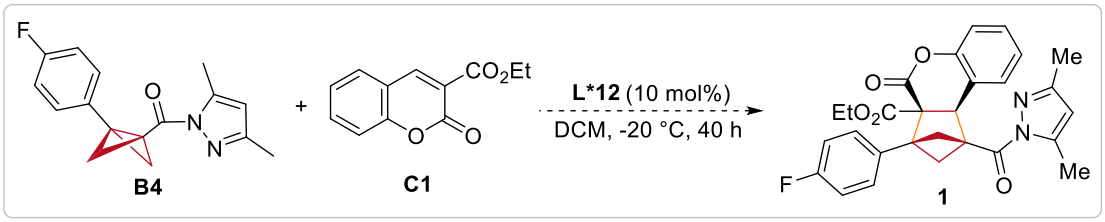
According to the **General Procedure A**, under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with BCB substrate **B11** (17.4 mg, 0.0525 mmol, 1.05 equiv.) and coumarin substrate **C1** (10.9 mg, 0.05 mmol, 1.0 equiv.), $Cu(OTf)_2$ (1.81 mg, 0.005 mmol, 10 mol%), **L*12** (4.44 mg, 0.005 mmol, 10 mol%) or no **L*12**, and anhydrous DCM (0.5 mL). The sealed tube was stirred at -20 °C for 40 h. The conversion and yield were based on ^1H NMR analysis of the crude products using CH_2Br_2 as an internal standard.

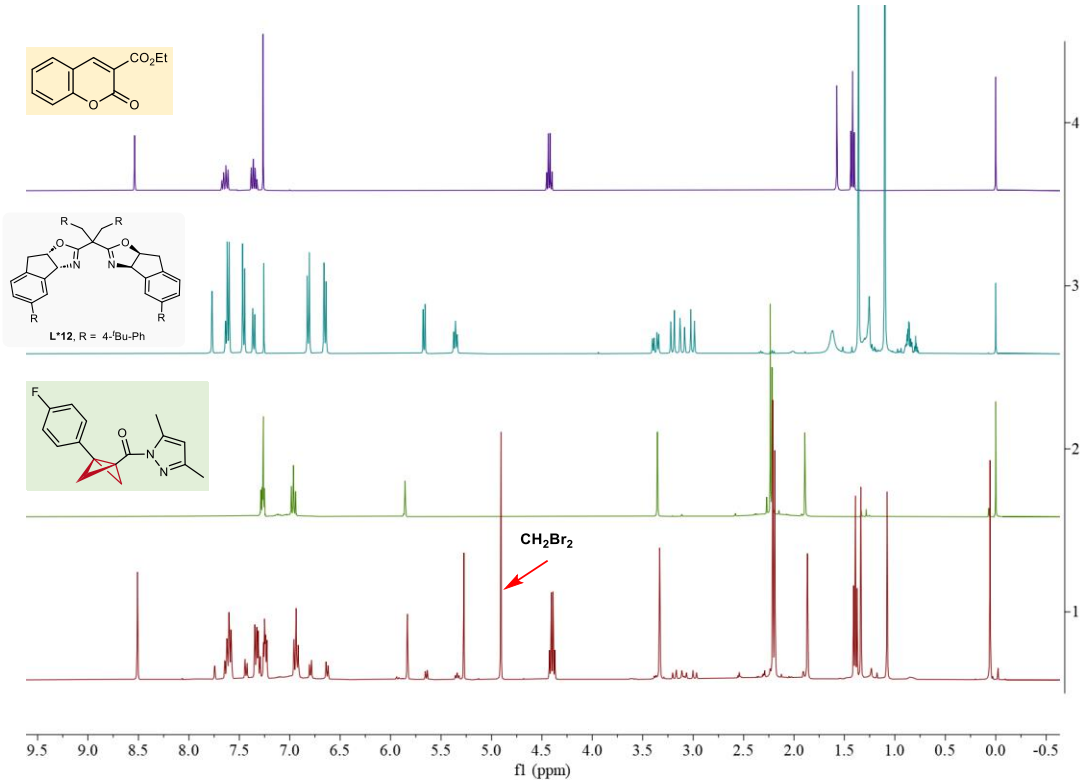




b)

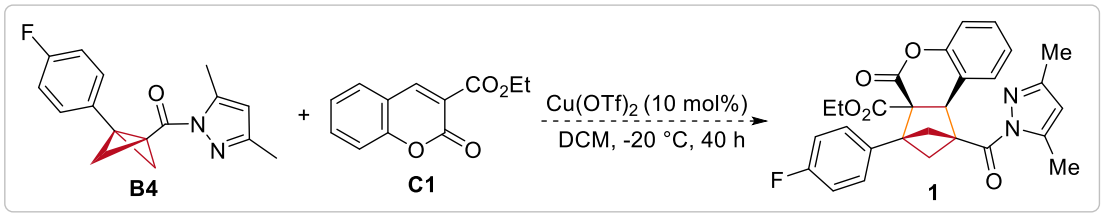
According to the **General Procedure A**, under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with BCB substrate **B4** (14.2 mg, 0.0525 mmol, 1.05 equiv.) and coumarin substrate **C1** (10.9 mg, 0.05 mmol, 1.0 equiv.), **L*12** (4.44 mg, 0.005 mmol, 10 mol%), and anhydrous DCM (0.5 mL). The sealed tube was stirred at -20 °C for 40 h. The conversion and yield were based on ^{1}H NMR analysis of the crude products using CH_2Br_2 as an internal standard.

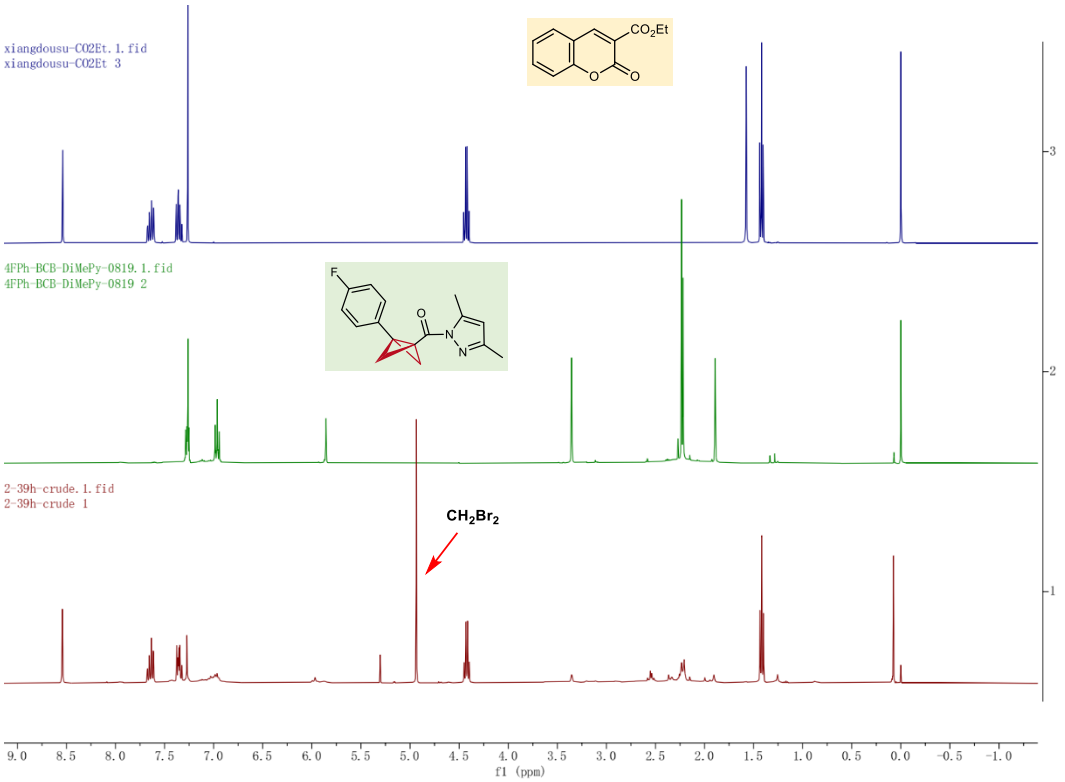




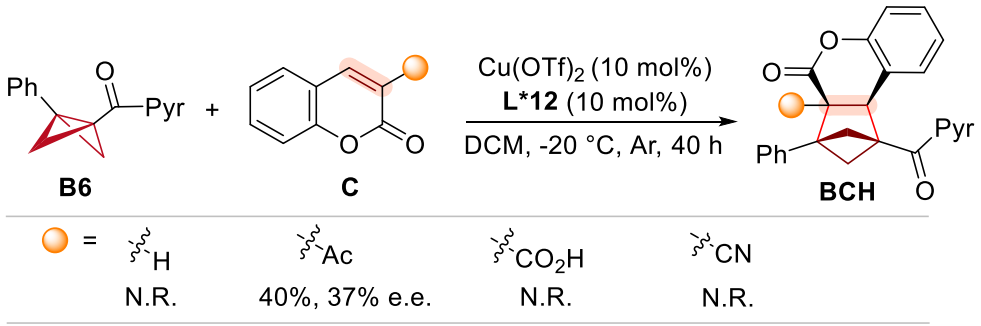
c)

According to the **General Procedure A**, under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with BCB substrate **B4** (14.2 mg, 0.0525 mmol, 1.05 equiv.) and coumarin substrate **C1** (10.9 mg, 0.05 mmol, 1.0 equiv.), $Cu(OTf)_2$ (1.81 mg, 0.005 mmol, 10 mol%), and anhydrous DCM (0.5 mL). The sealed tube was stirred at -20 °C for 40 h. The conversion and yield were based on ^1H NMR analysis of the crude products using CH_2Br_2 as an internal standard.





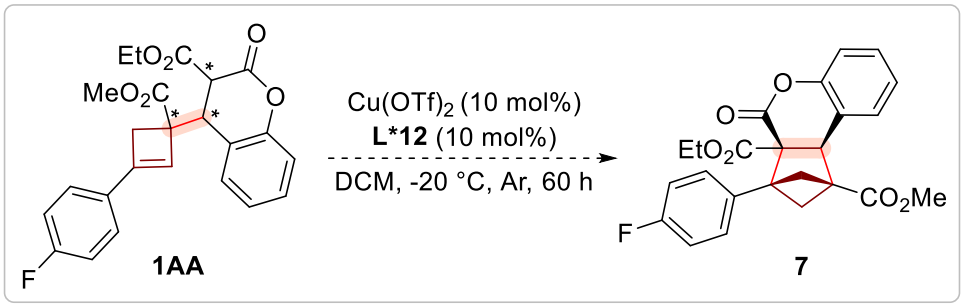
10.3



=	H	Ac	CO_2H	CN
	N.R.	40%, 37% e.e.	N.R.	N.R.

According to the **General Procedure A**, under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with BCB substrate **B6** (13.2 mg, 0.0525 mmol, 1.05 equiv.) and coumarin substrate **C** (0.05 mmol, 1.0 equiv.), $Cu(OTf)_2$ (1.81 mg, 0.005 mmol, 10 mol%), **L*12** (4.44 mg, 0.005 mmol, 10 mol%), and anhydrous DCM (0.5 mL). The sealed tube was stirred at -20 °C for 40 h. The yield was based on crude ^1H NMR analysis. If required, the mixture was separated by PTLC (*n*-hexane/EtOAc), and the enantiomeric excess (e.e.) was determined by HPLC.

10.4



Under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with **1AA** (0.01 mmol, 1.0 equiv.), $Cu(OTf)_2$ (0.36 mg, 0.001 mmol, 10 mol%), **L*12** (0.89 mg, 0.001 mmol, 10 mol%), and anhydrous DCM (0.2 mL). The sealed tube was stirred at -20 °C for 60 h. The yield was based on crude ^1H NMR analysis.

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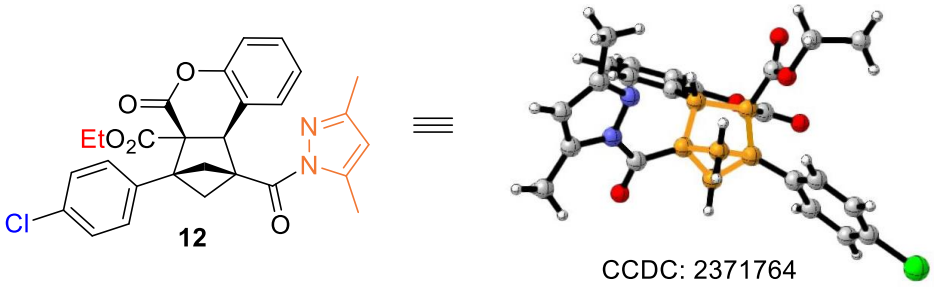
11. Computational details

Molecular properties (MW, clogP, tPSA) were calculated with ChemDraw 20.
The 2D structures of Sonidegib and BCHex-Sonidegib were converted into 3D conformations using the LigPrep module of the Schrödinger 2021-2 software. The 3D conformations of the above two molecules were superimposed using the Ligand Alignment tool. The distances between carbon atoms were measured and visualized using open-source PyMOL software (https://github.com/schrodinger/pymol-open-source).
The crystal structure of human Programmed cell death 1 ligand 1 (PD-L1) with the inhibitor BMS-202 (PDB ID: 5J89) was downloaded from the RCSB Protein Data Bank (https://www1.rcsb.org/). The protein structure was prepared using the Protein Preparation Wizard of the Schrödinger 2021-2 software, removing solvent molecules, including water, and retaining only chains A and B, along with the small molecule BMS-202. Ligand structure preparation was performed using the LigPrep module to generate 3D conformations and potential ionization states of BCHex-BMS-202 following the standard protocol. Induced Fit Docking[48] (IFD) module was used to simulate and predict the binding mode of BCHex-BMS-202 with the PD-L1 protein. Visualization analysis was performed using open-source PyMOL software (https://github.com/schrodinger/pymol-open-source).

12. X-ray crystallography

Experimental. Single crystals of BCH **12**, ***ent*-12**, and **51** were obtained by recrystallization from $CDCl_3$/*n*-hexane. A suitable crystal was selected and mounted on a suitable support on a **XtaLAB Synergy R, DW system, HyPix** diffractometer. The crystal was kept at a steady $T = 100.01(10)$ K during data collection. The structure was solved with the ShelXT[49] 2014/5 structure solution program using the dual solution method and by using **Olex2**[50] as the graphical interface. The model was refined with version 2018/3 of ShelXL[51] using Least Squares minimisation.

12.1 X-ray structure of BCH 12



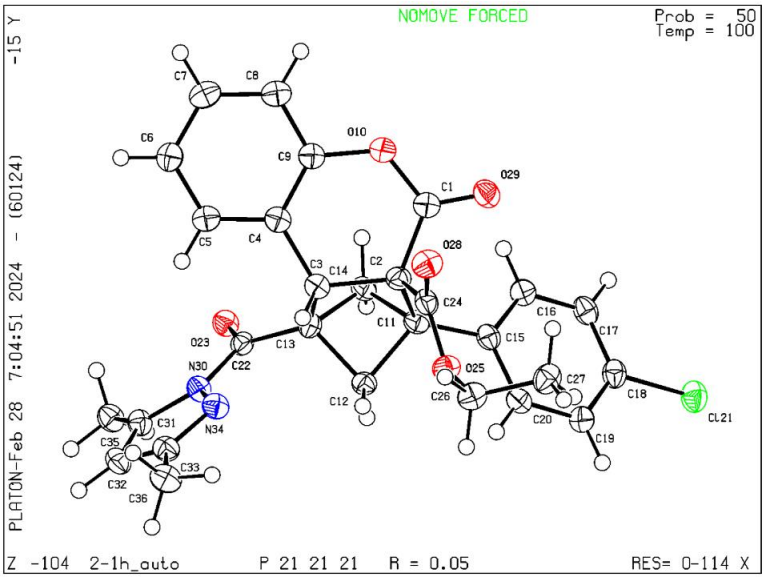


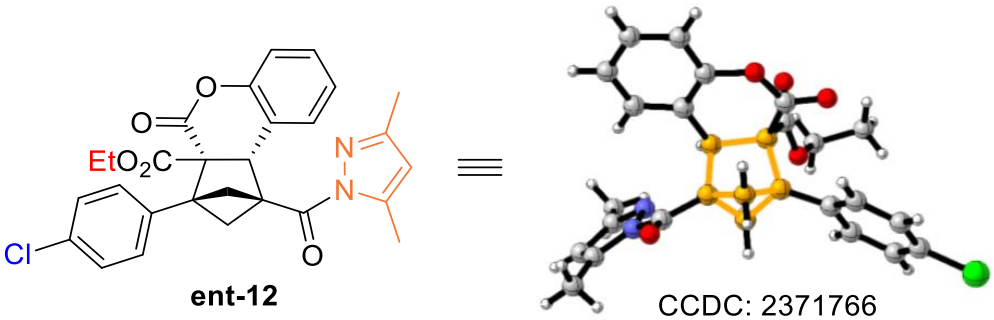
Figure S11 | The X-ray structure of **12**

Table S6 | Crystal data and structure refinement for **12**

Empirical formula	$C_{28}H_{25}ClN_2O_5$
Formula weight	504.95
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	10.8737(3)

b/Å	11.4063(3)
c/Å	19.2759(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2390.77(10)
Z	4
ρ_{calc}g/cm^3	1.403
μ/mm^{-1}	1.780
F(000)	1056.0
Crystal size/mm^3	0.1 × 0.1 × 0.1
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.008 to 153.306
Index ranges	-13 ≤ h ≤ 13, -13 ≤ k ≤ 14, -19 ≤ l ≤ 24
Reflections collected	11750
Independent reflections	4712 [R_{int} = 0.0365, R_{sigma} = 0.0343]
Data/restraints/parameters	4712/0/328
Goodness-of-fit on F^2	1.047
Final R indexes [I>=2σ (I)]	R_1 = 0.0457, wR_2 = 0.1193
Final R indexes [all data]	R_1 = 0.0523, wR_2 = 0.1267
Largest diff. peak/hole / e Å^{-3}	0.29/-0.38
Flack parameter	-0.035(10)

12.2 X-ray structure of *ent*-12



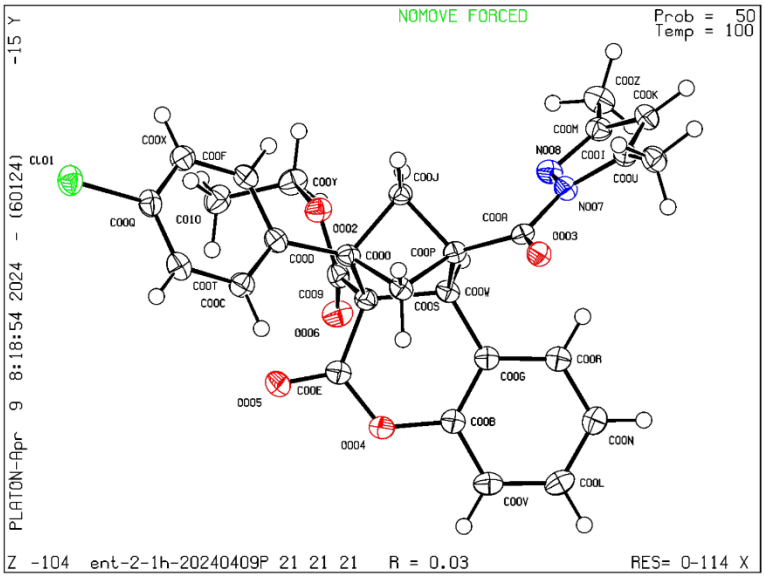


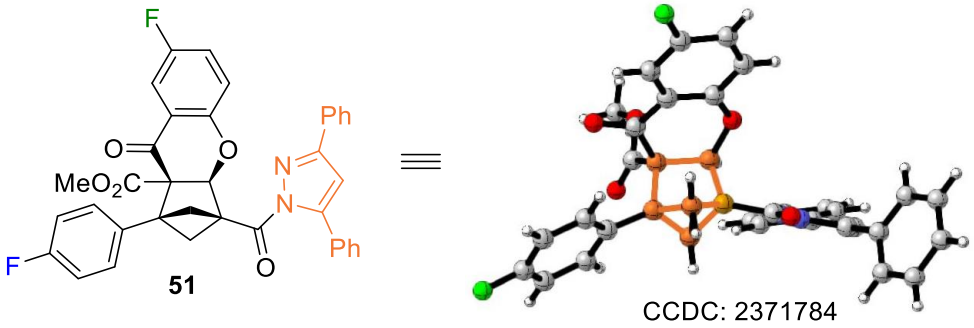
Figure S12 | The X-ray structure of ***ent*-12**

Table S7 | Crystal data and structure refinement for ***ent*-12**

Empirical formula	$C_{28}H_{25}ClN_2O_5$
Formula weight	504.95
Temperature/K	100.01(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	10.8716(2)
b/Å	11.4118(2)
c/Å	19.2857(3)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2392.67(7)
Z	4
ρ_{calc}g/cm^3	1.402
μ/mm^{-1}	1.779

F(000)	1056.0
Crystal size/mm^3	0.2 × 0.2 × 0.2
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	9.004 to 153.11
Index ranges	-13 ≤ h ≤ 12, -14 ≤ k ≤ 13, -23 ≤ l ≤ 24
Reflections collected	12071
Independent reflections	4733 [R_{int} = 0.0247, R_{sigma} = 0.0239]
Data/restraints/parameters	4733/0/328
Goodness-of-fit on F^2	1.035
Final R indexes [I>=2σ (I)]	R_1 = 0.0337, wR_2 = 0.0855
Final R indexes [all data]	R_1 = 0.0377, wR_2 = 0.0898
Largest diff. peak/hole / e Å^{-3}	0.24/-0.23
Flack parameter	-0.018(6)

12.3 X-ray structure of 51



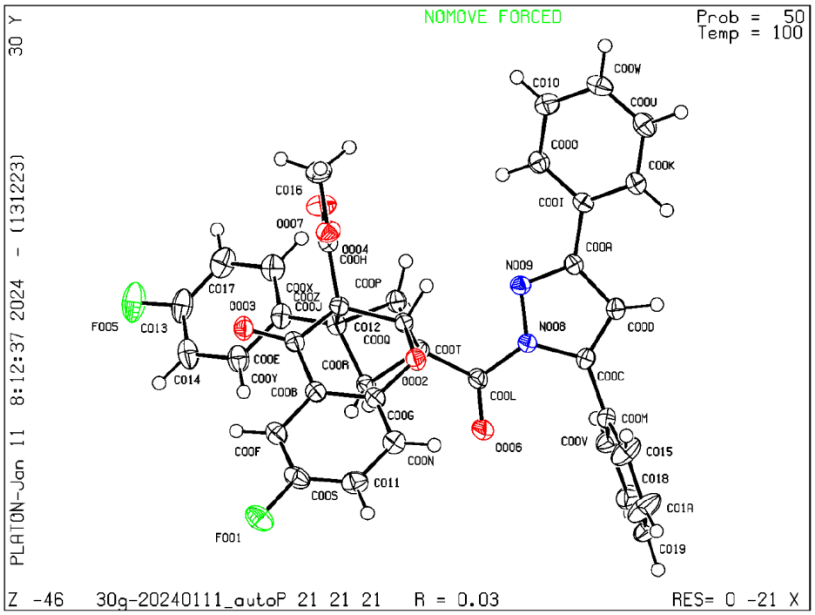


Figure S13 | The X-ray structure of **51.**

Table S8 | Crystal data and structure refinement for **51.**

Empirical formula	$C_{37}H_{26}F_2N_2O_5$
Formula weight	616.60
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	11.16990(10)
b/Å	13.51340(10)
c/Å	19.78870(10)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2986.97(4)
Z	4
ρ_{calc}g/cm^3	1.371

μ/mm^{-1}	0.831
F(000)	1280.0
Crystal size/mm^3	0.1 × 0.1 × 0.1
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.922 to 154.578
Index ranges	$-14 \leq h \leq 14$, $-16 \leq k \leq 16$, $-24 \leq l \leq 18$
Reflections collected	16467
Independent reflections	6047 [R_{int} = 0.0306, R_{sigma} = 0.0311]
Data/restraints/parameters	6047/0/416
Goodness-of-fit on F^2	0.906
Final R indexes [I>=2σ (I)]	R_1 = 0.0334, wR_2 = 0.1036
Final R indexes [all data]	R_1 = 0.0344, wR_2 = 0.1055
Largest diff. peak/hole / e $Å^{-3}$	0.22/-0.18
Flack parameter	0.05(6)

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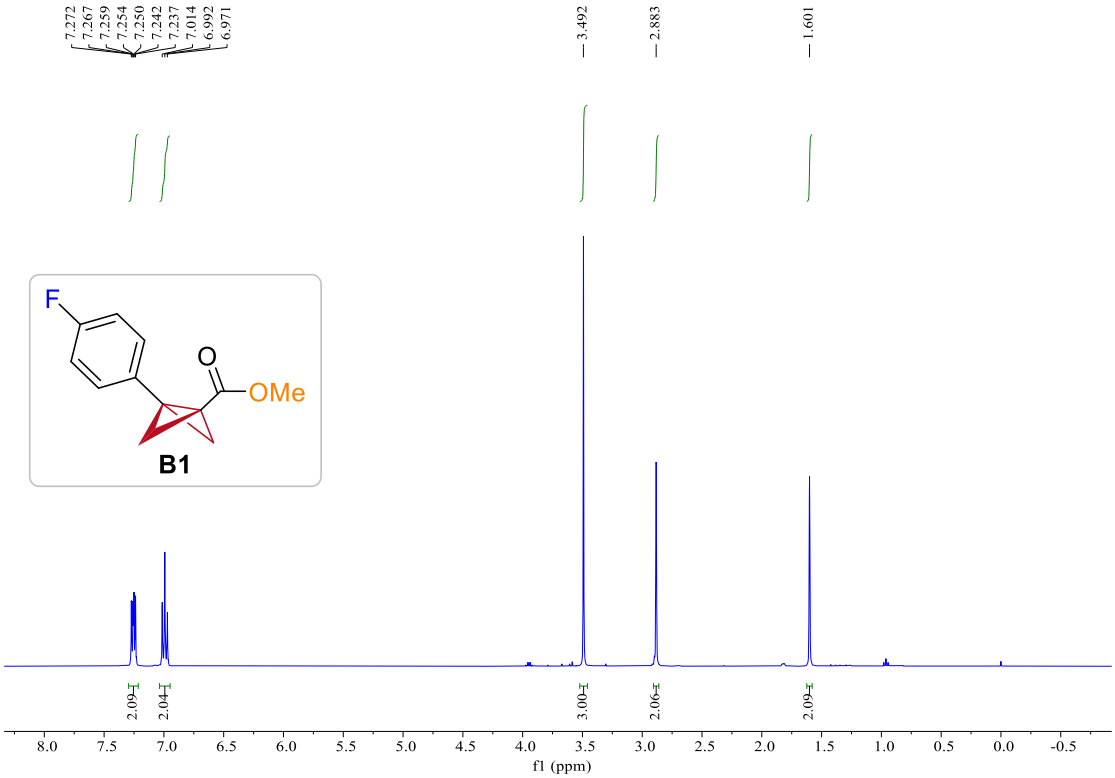
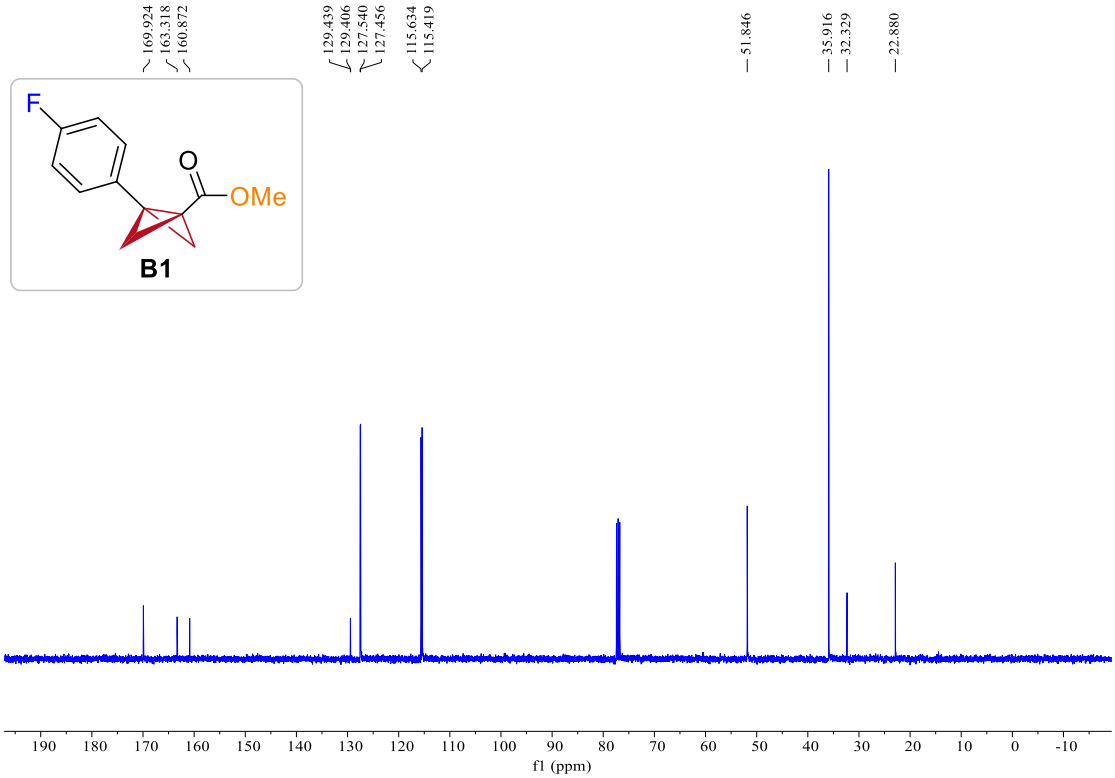
14. NMR spectra

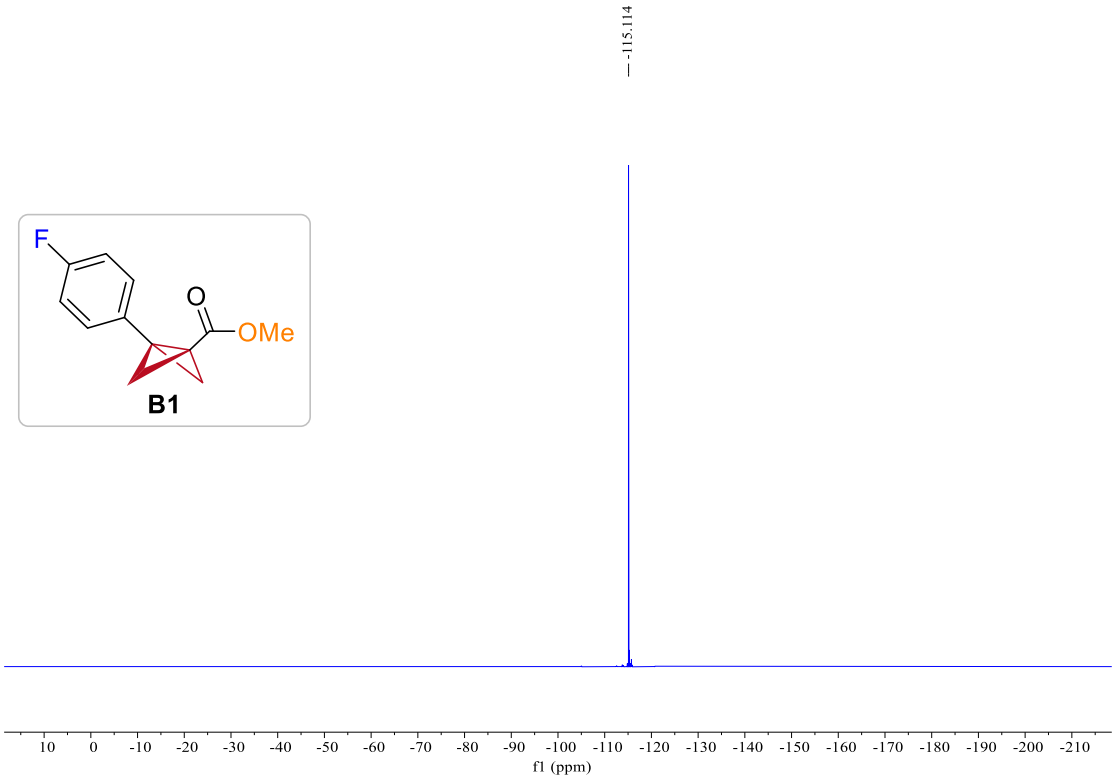
B1, ^{1}H NMR (400 MHz, $CDCl_3$)



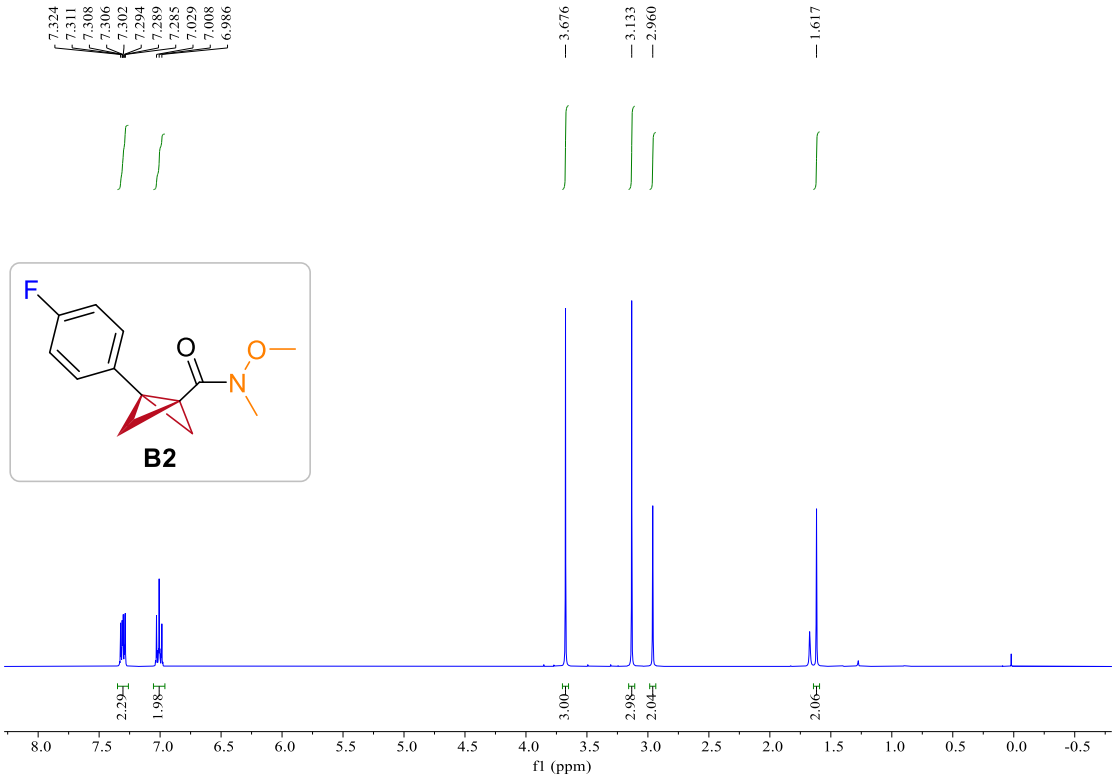
B1, ^{13}C NMR (101 MHz, $CDCl_3$)



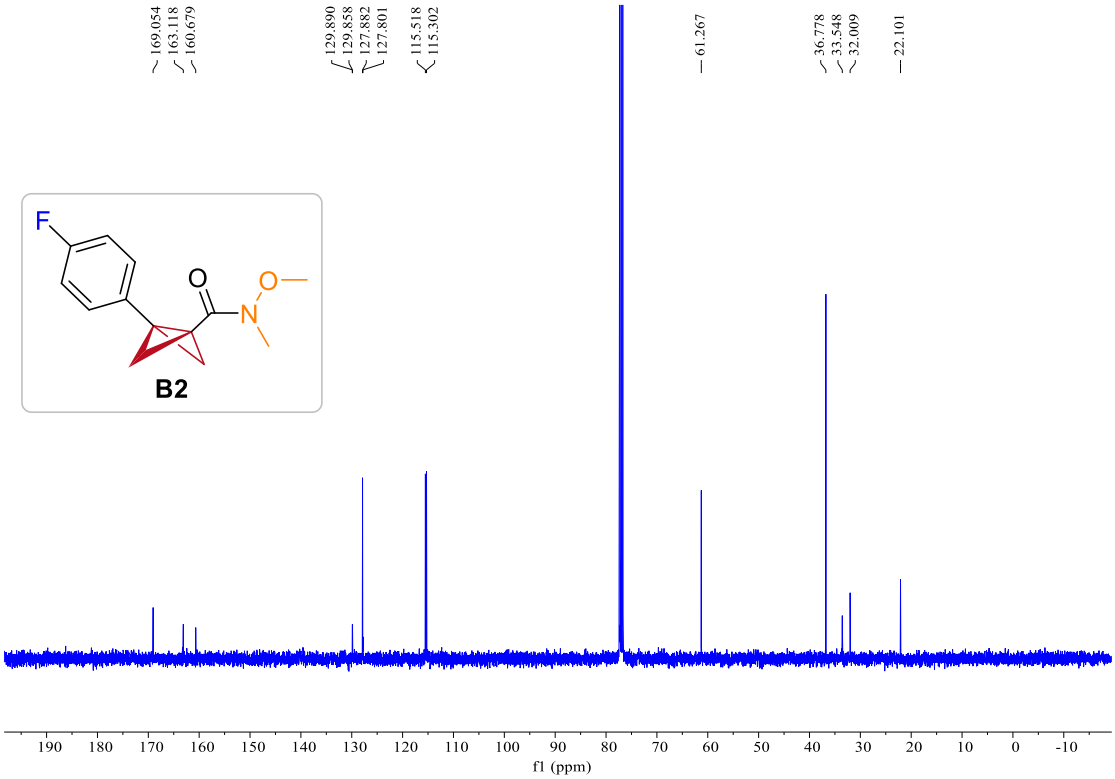
B1, ^{19}F NMR (376 MHz, $CDCl_3$)



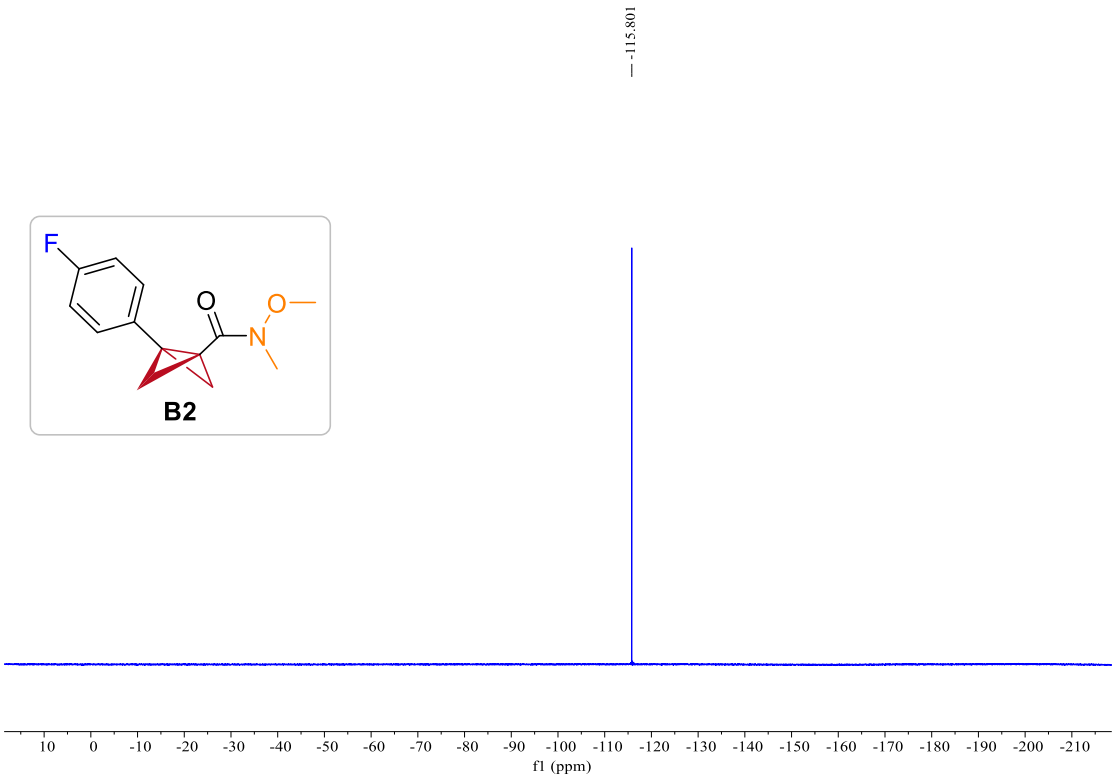
B2, ^{1}H NMR (400 MHz, $CDCl_3$)



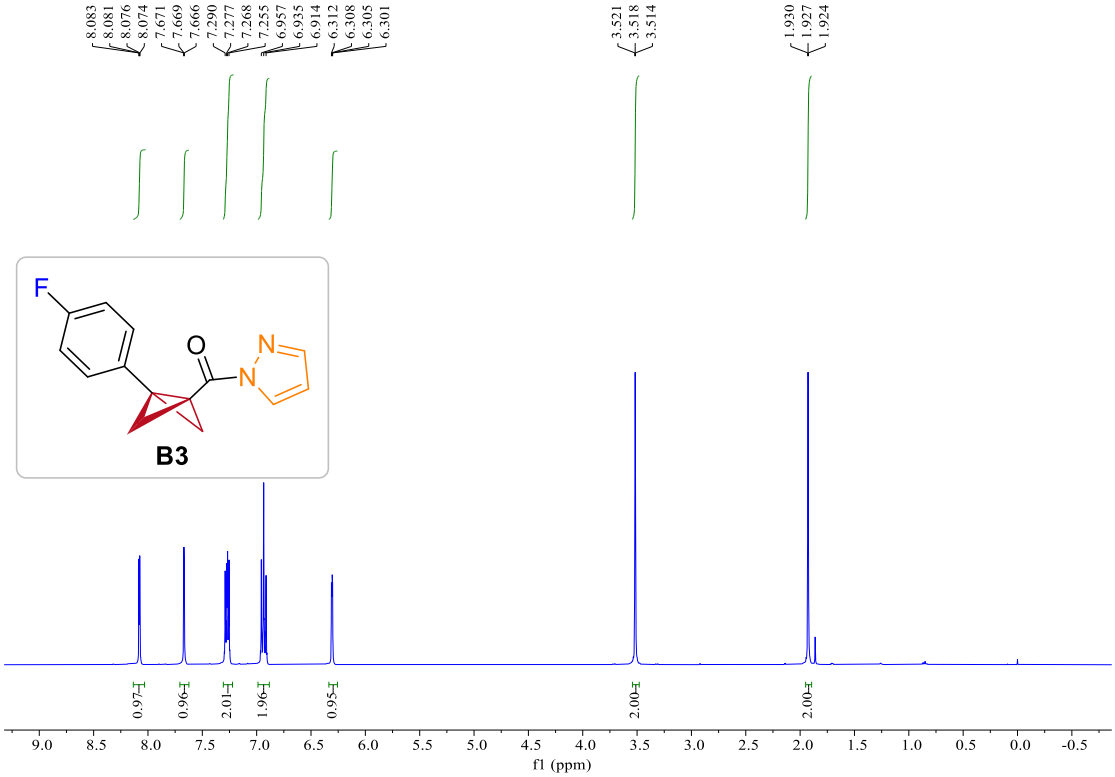
B2, ^{13}C NMR (101 MHz, $CDCl_3$)



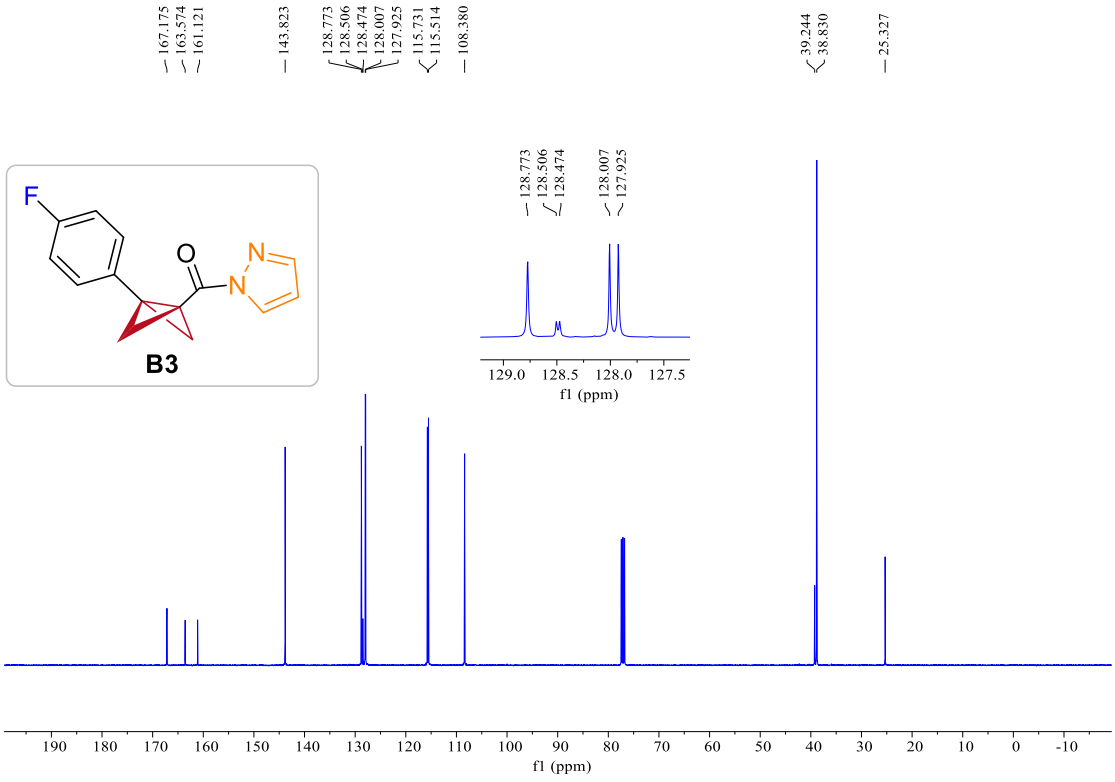
B2, ^{19}F NMR (376 MHz, $CDCl_3$)



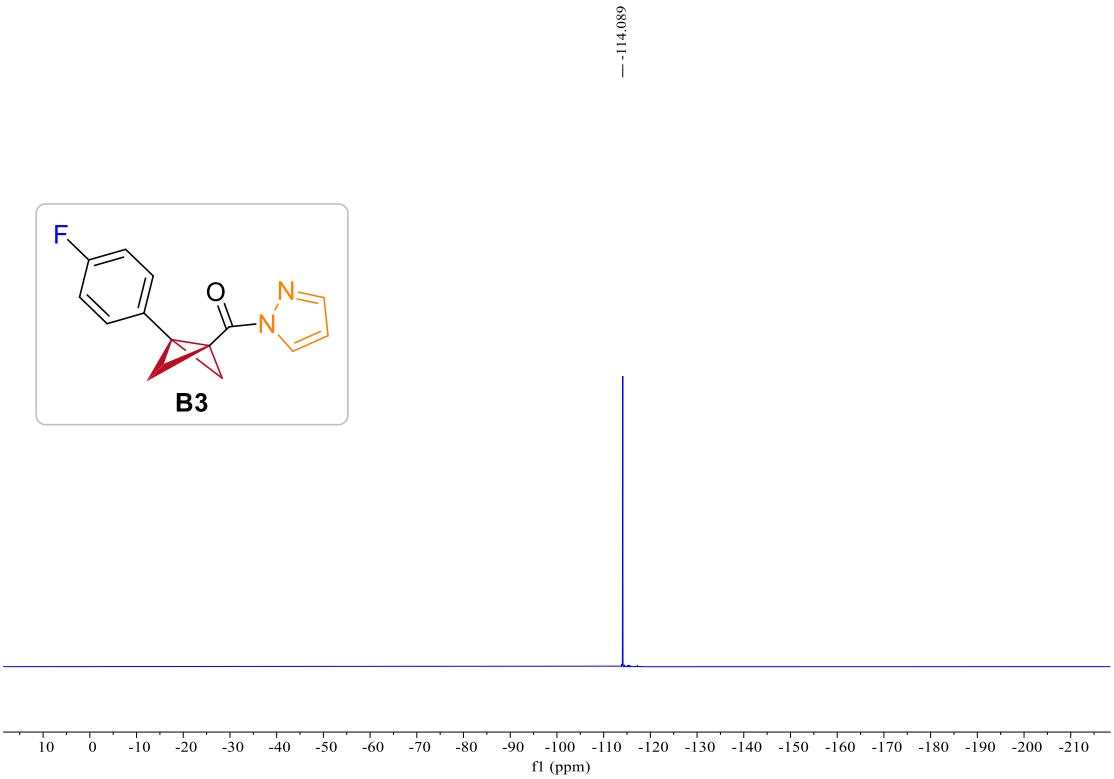
B3, ^{1}H NMR (400 MHz, $CDCl_3$)



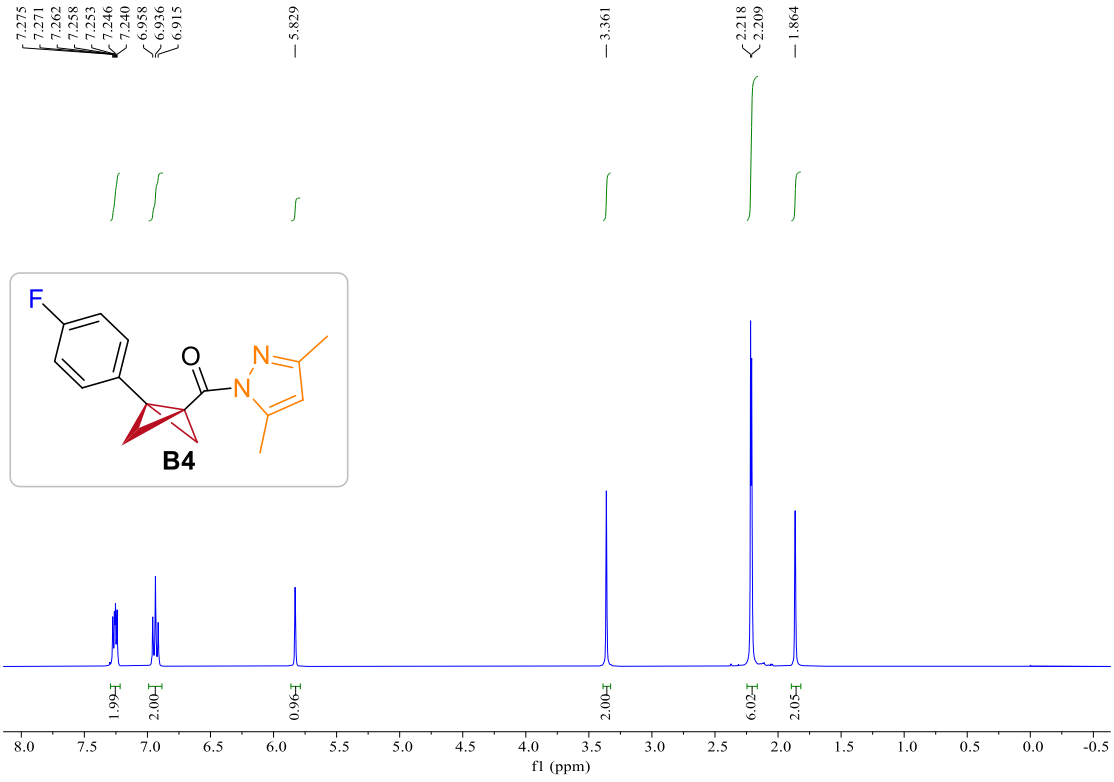
B3, ^{13}C NMR (101 MHz, $CDCl_3$)



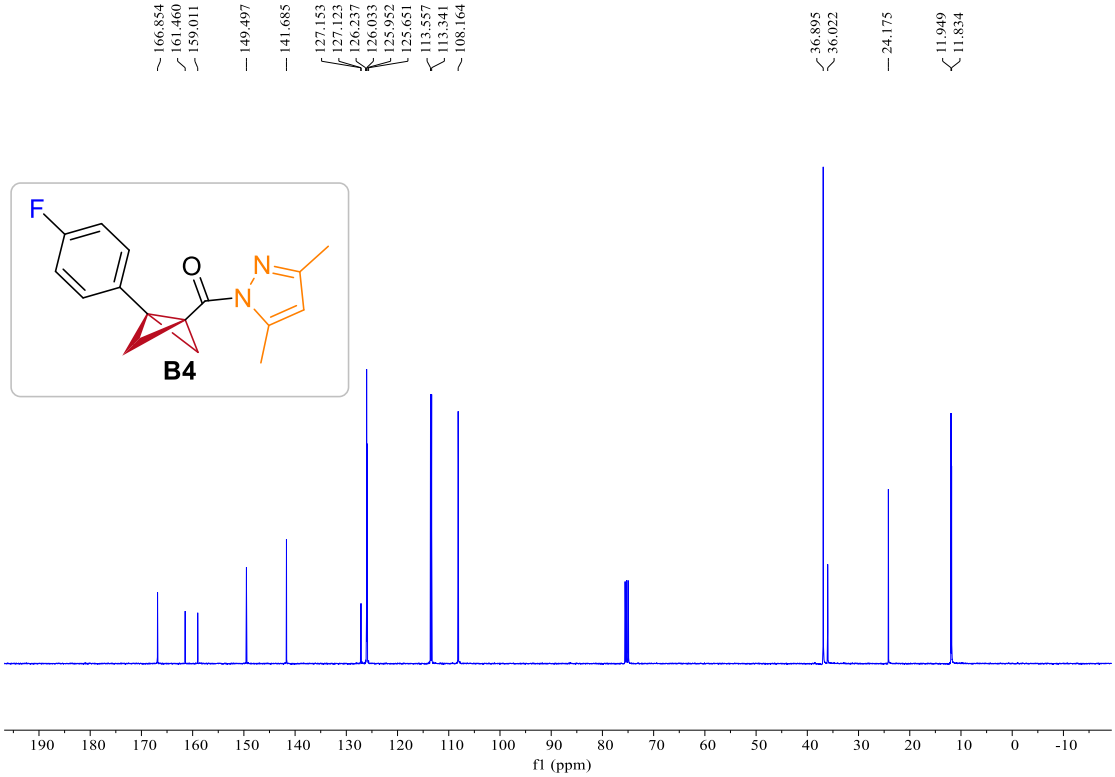
B3, ^{19}F NMR (376 MHz, $CDCl_3$)



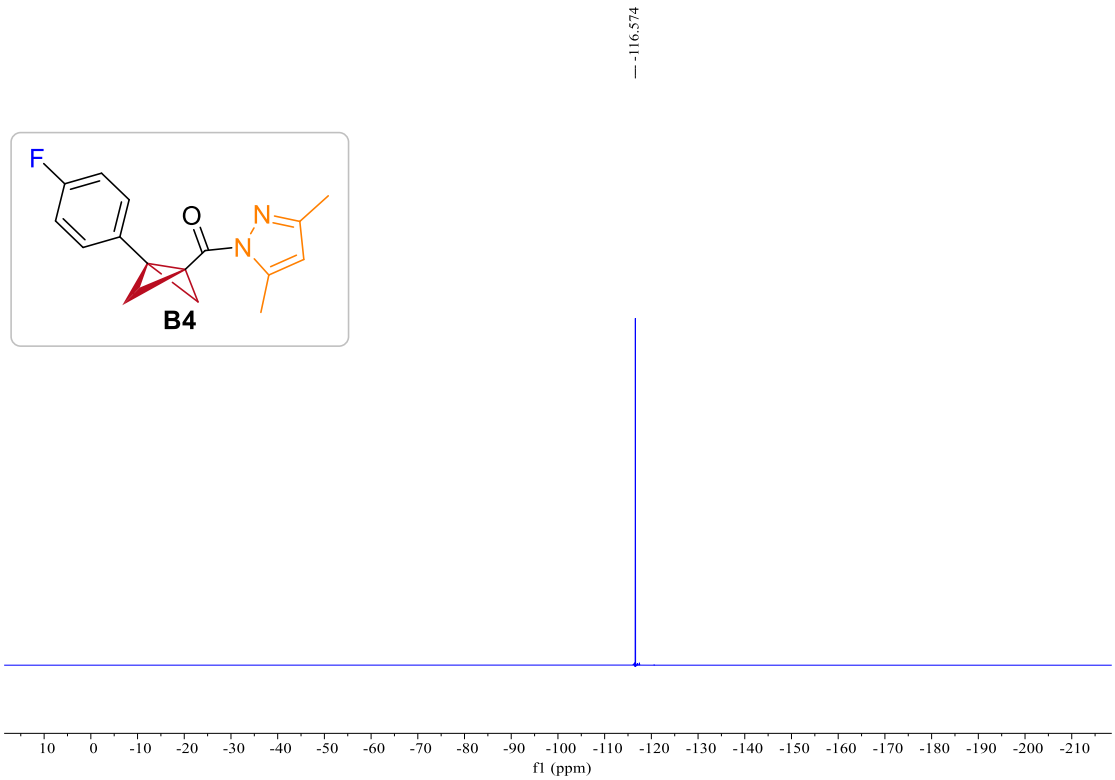
B4, ^{1}H NMR (400 MHz, $CDCl_3$)



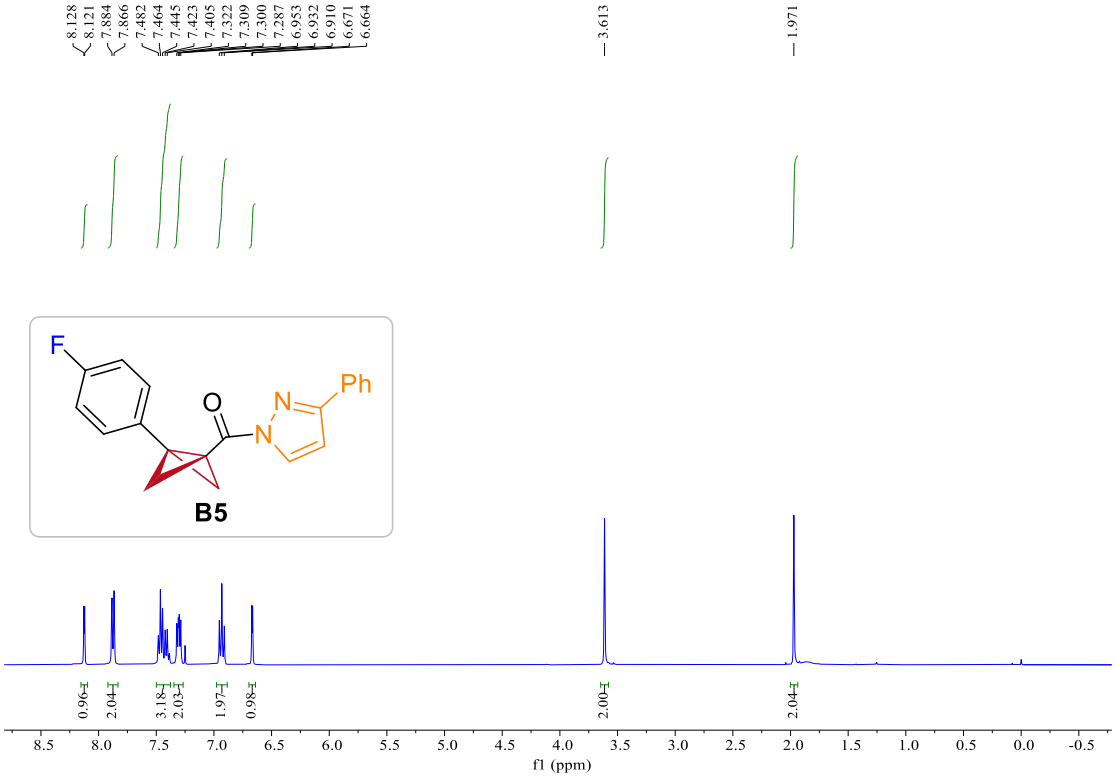
B4, ^{13}C NMR (101 MHz, $CDCl_3$)



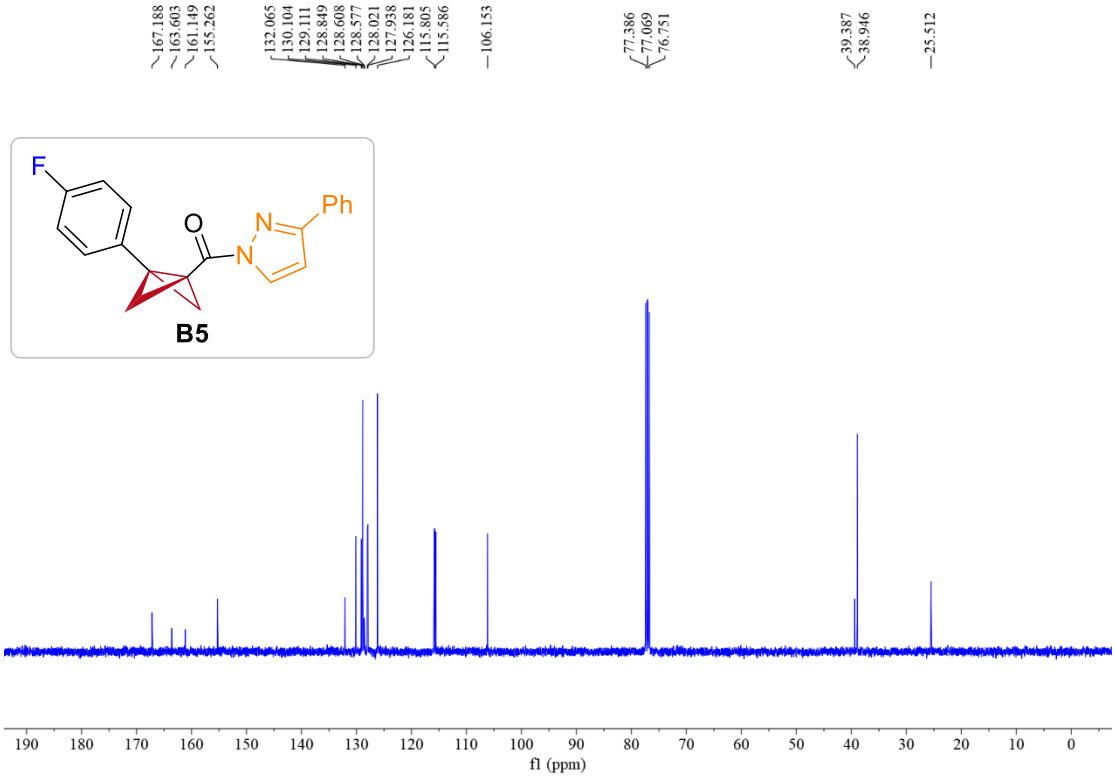
B4, ^{19}F NMR (376 MHz, $CDCl_3$)



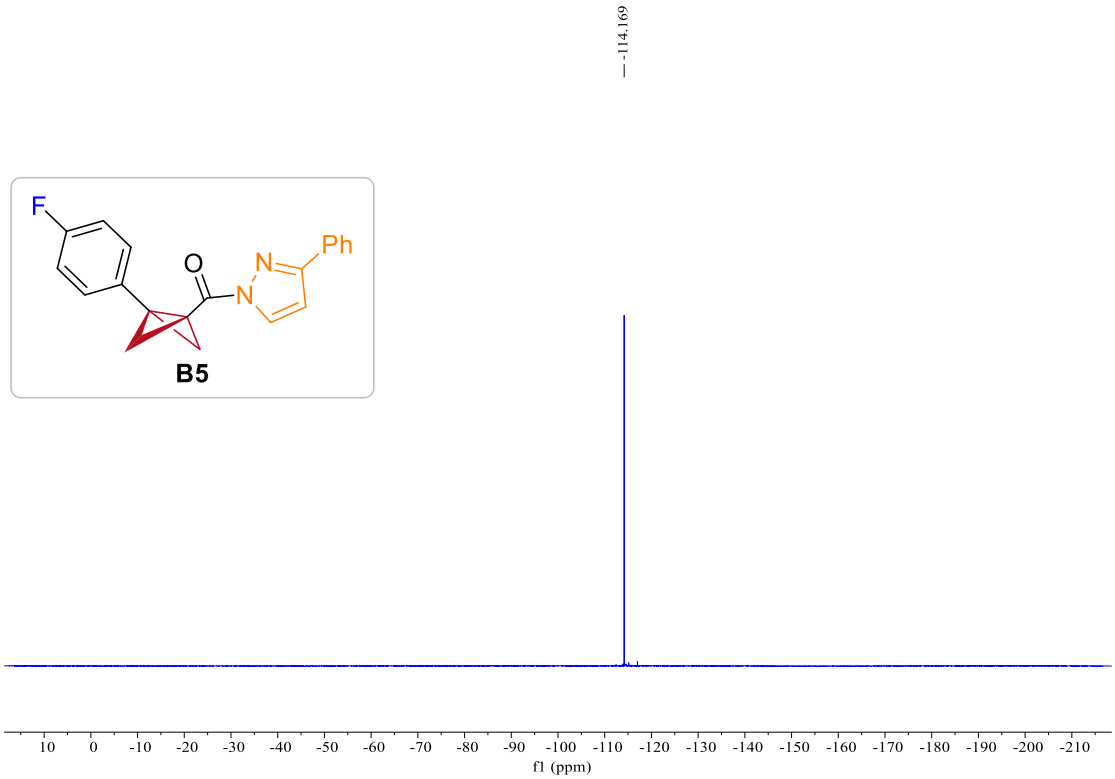
B5, ^{1}H NMR (400 MHz, $CDCl_3$)



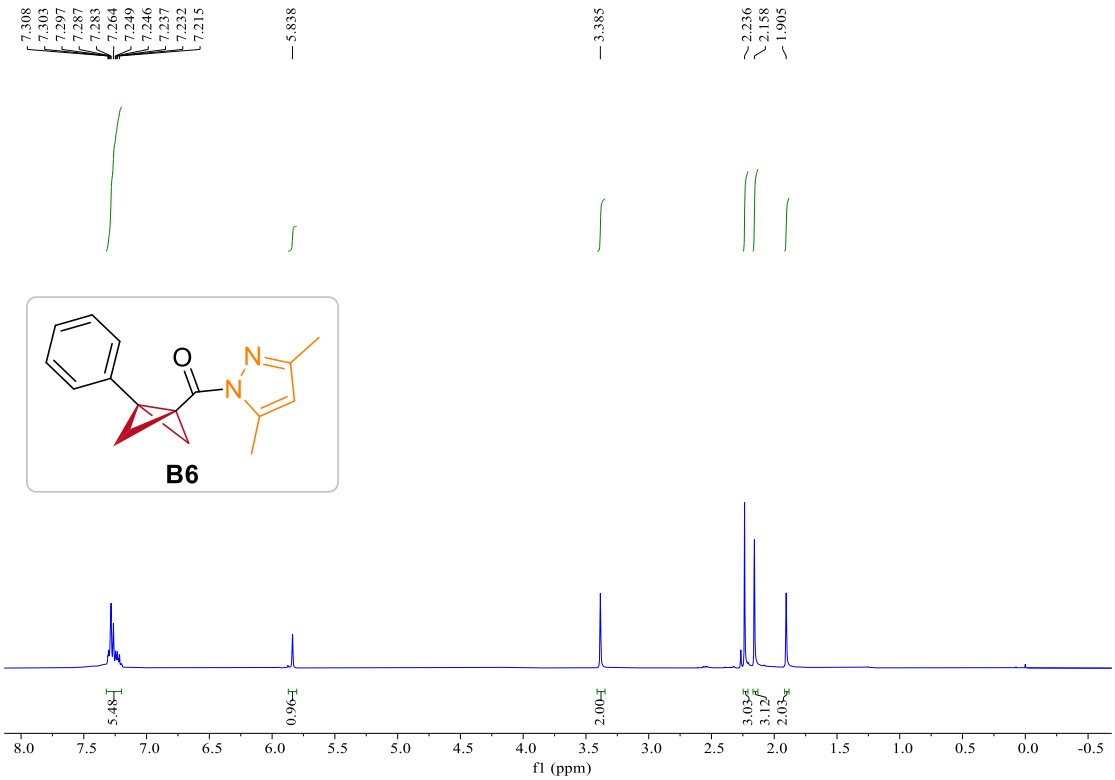
B5, ^{13}C NMR (101 MHz, $CDCl_3$)



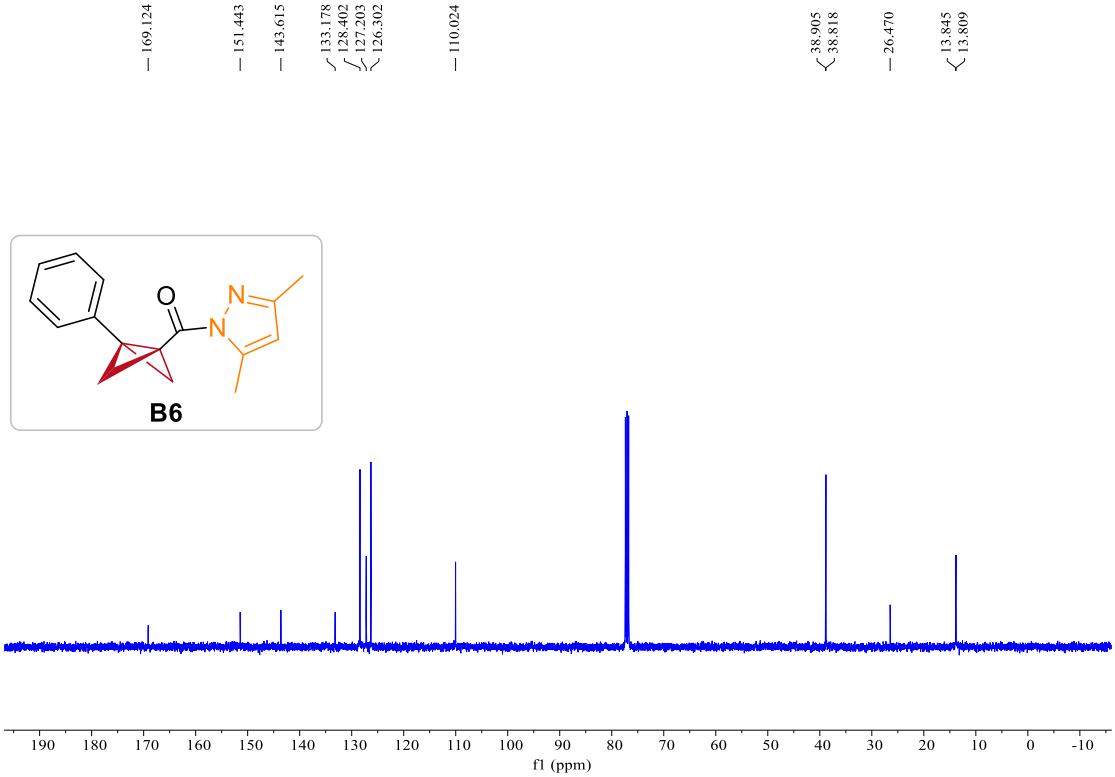
B5, ^{19}F NMR (376 MHz, $CDCl_3$)



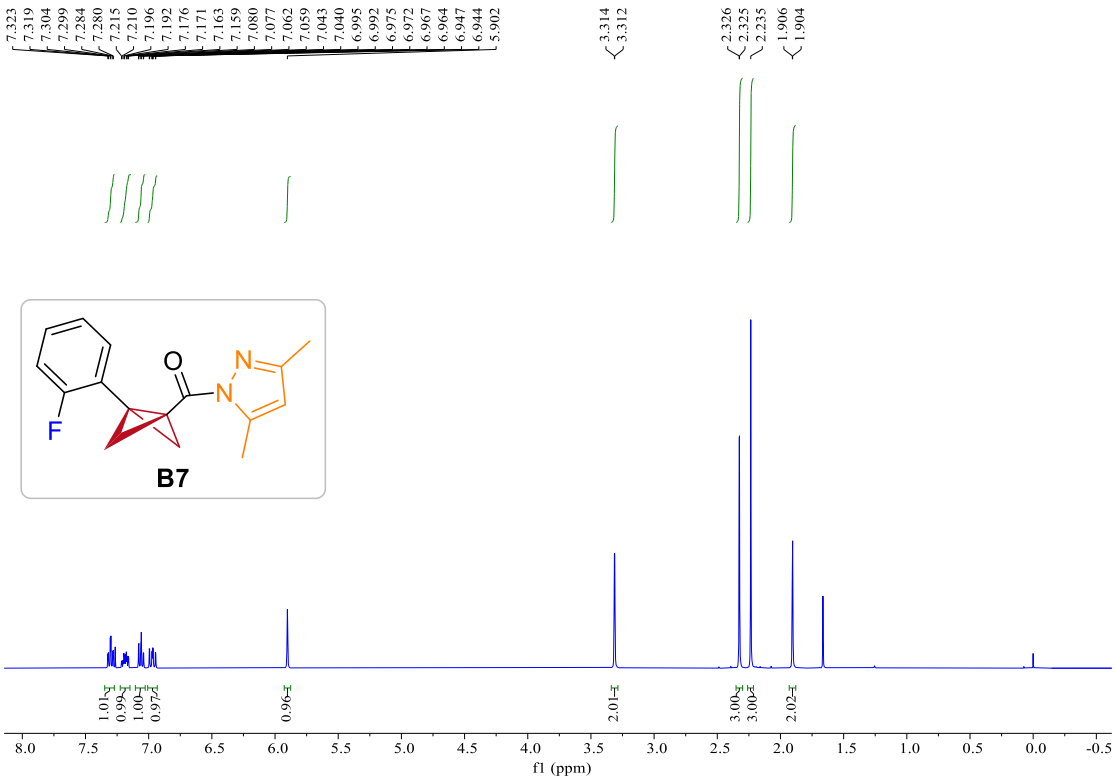
B6, ^{1}H NMR (400 MHz, $CDCl_3$)



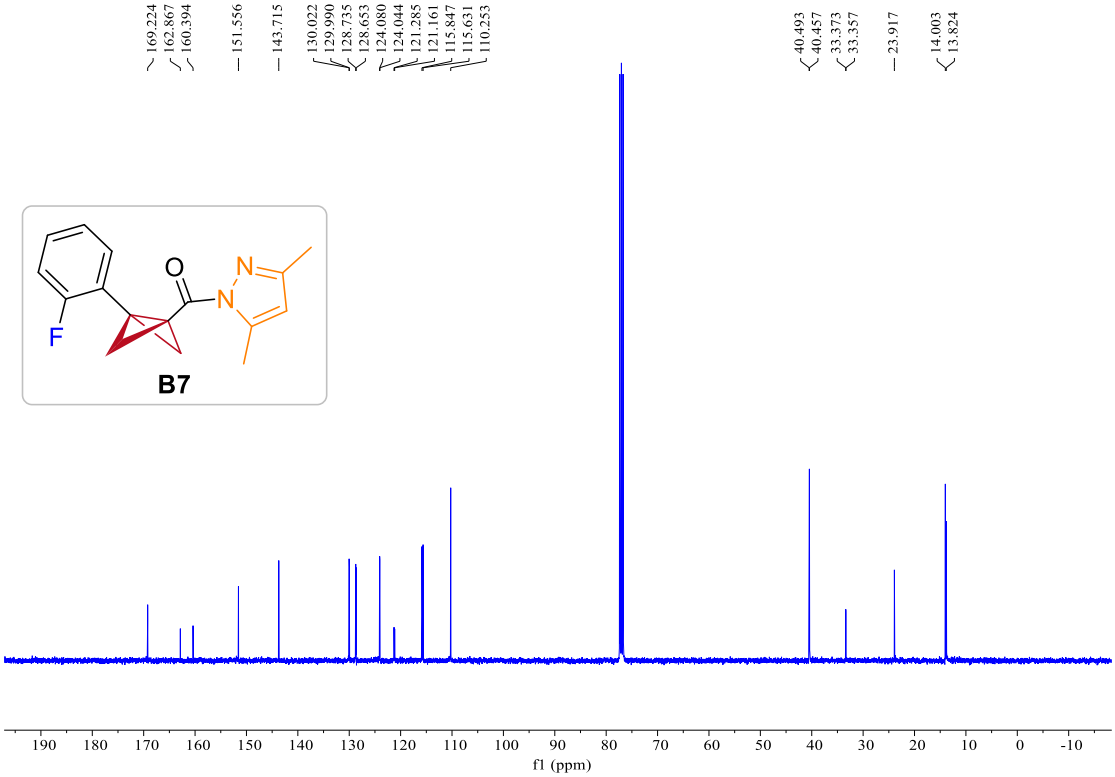
B6, ^{13}C NMR (101 MHz, $CDCl_3$)



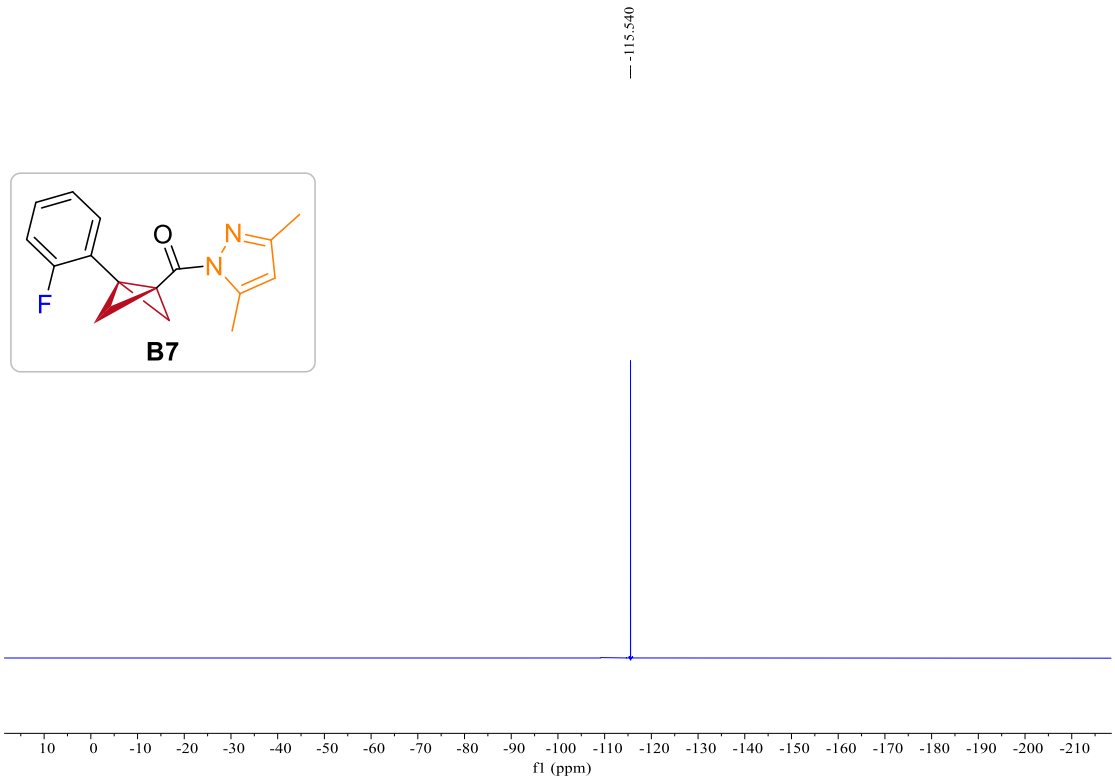
B7, ^{1}H NMR (400 MHz, $CDCl_3$)



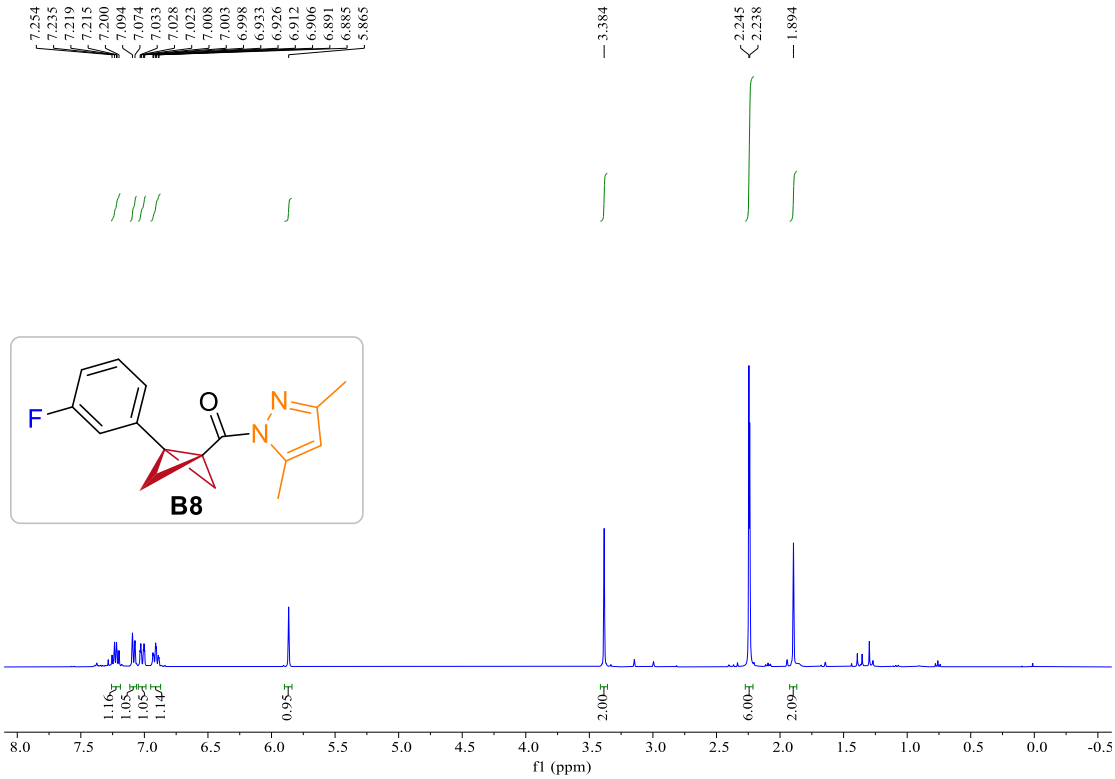
B7, ^{13}C NMR (101 MHz, $CDCl_3$)



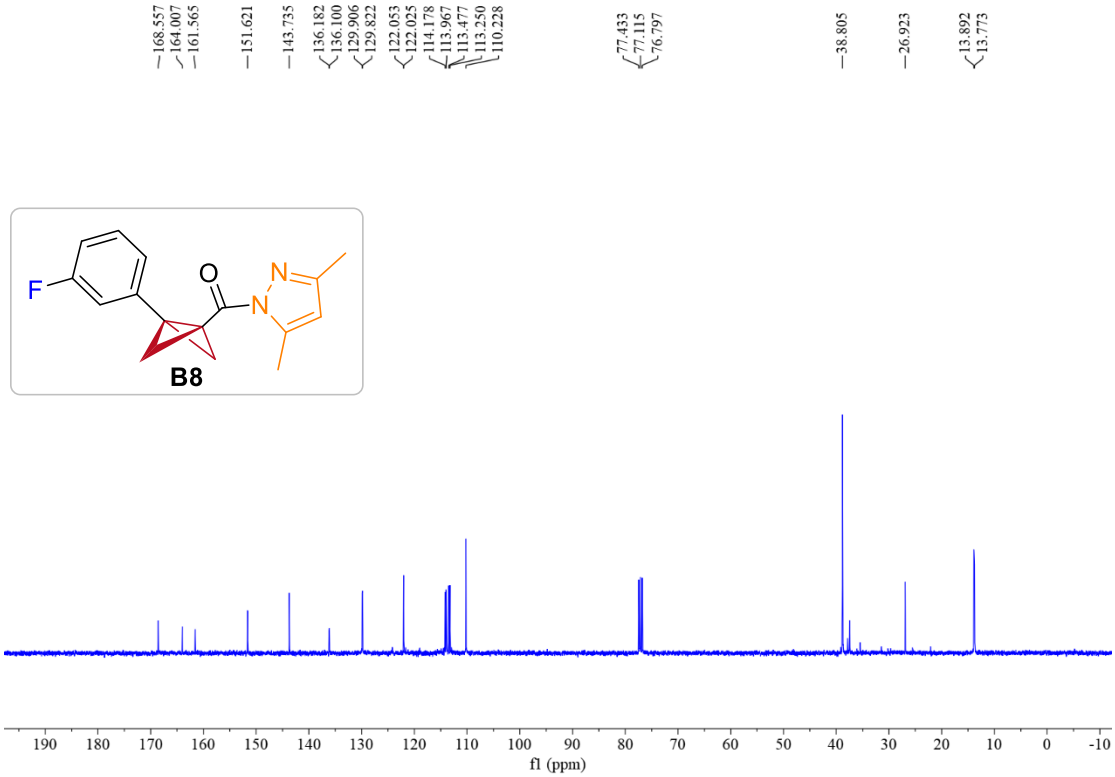
B7, ^{19}F NMR (376 MHz, $CDCl_3$)



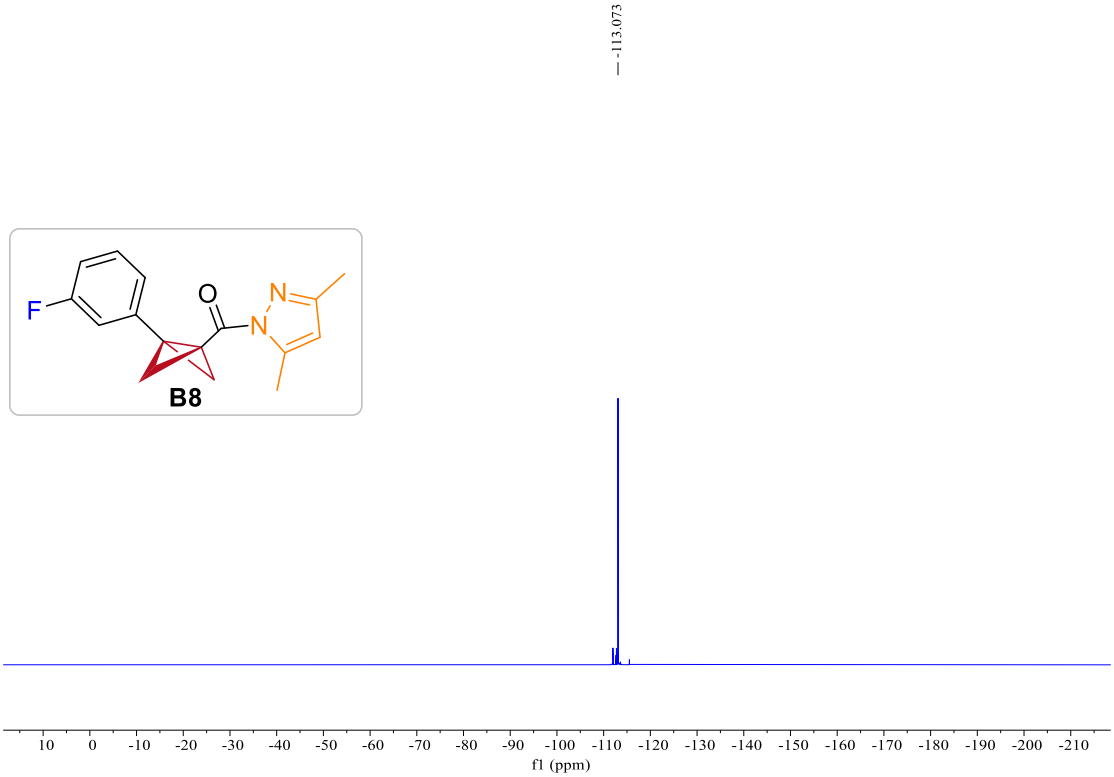
B8, ^{1}H NMR (400 MHz, $CDCl_3$)



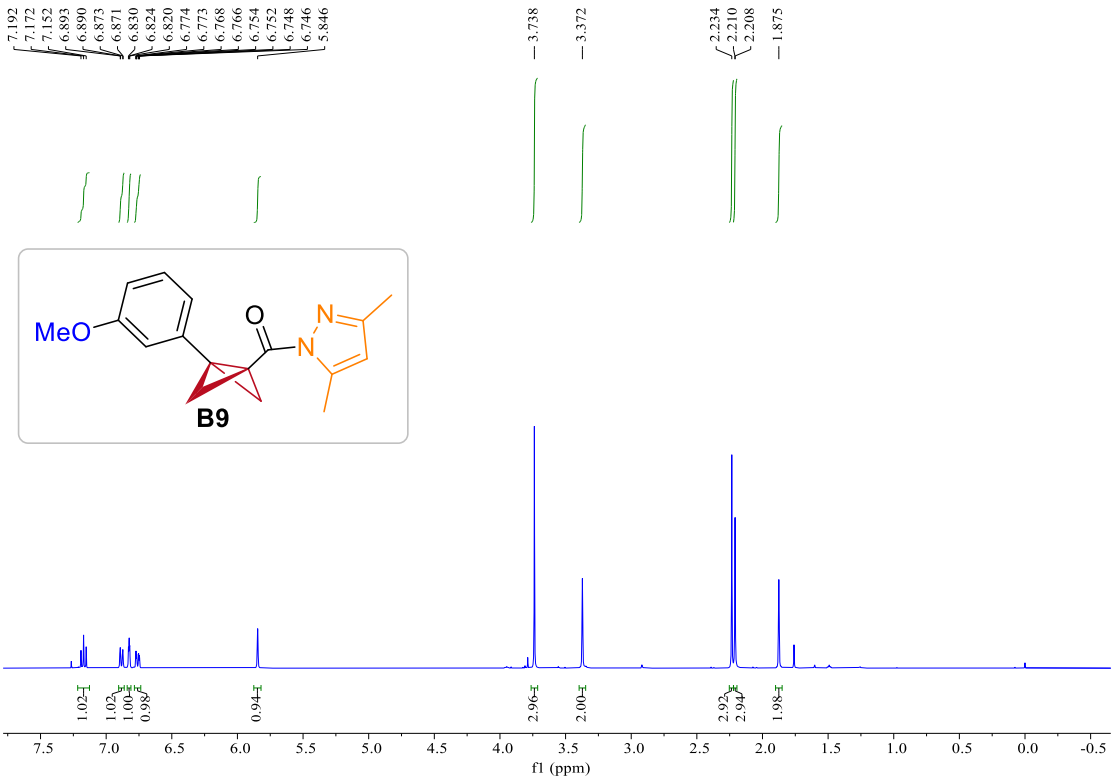
B8, ^{13}C NMR (101 MHz, $CDCl_3$)



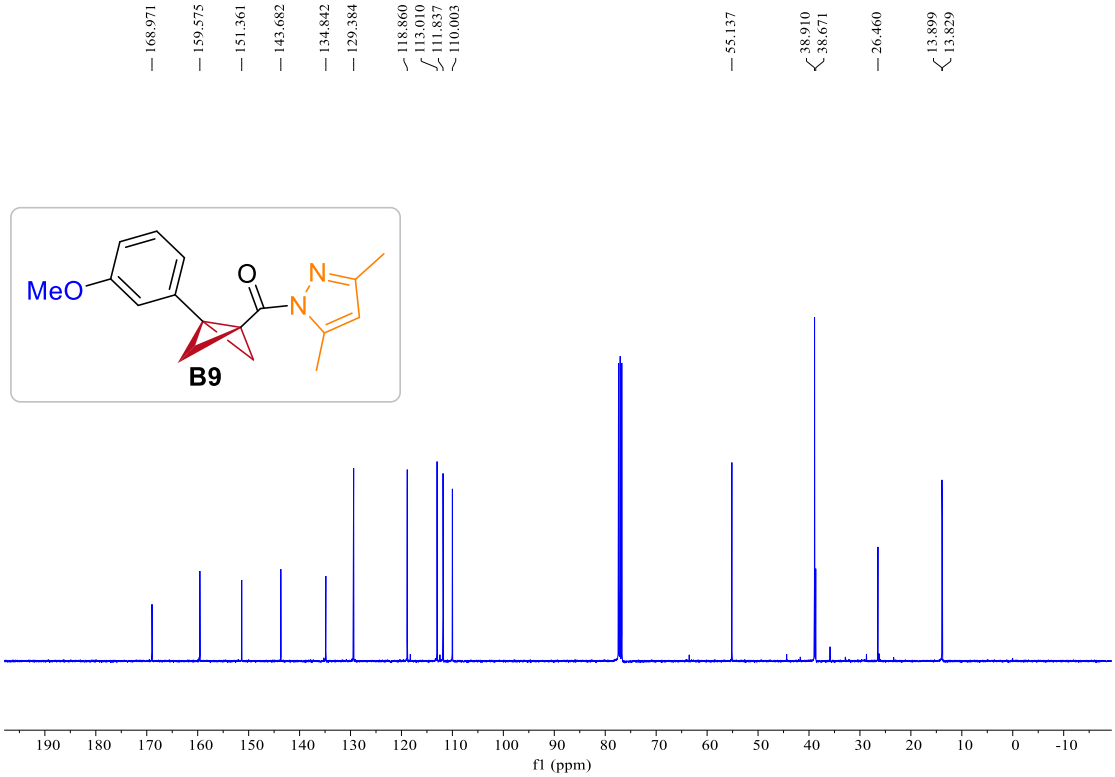
B8, ^{19}F NMR (376 MHz, $CDCl_3$)



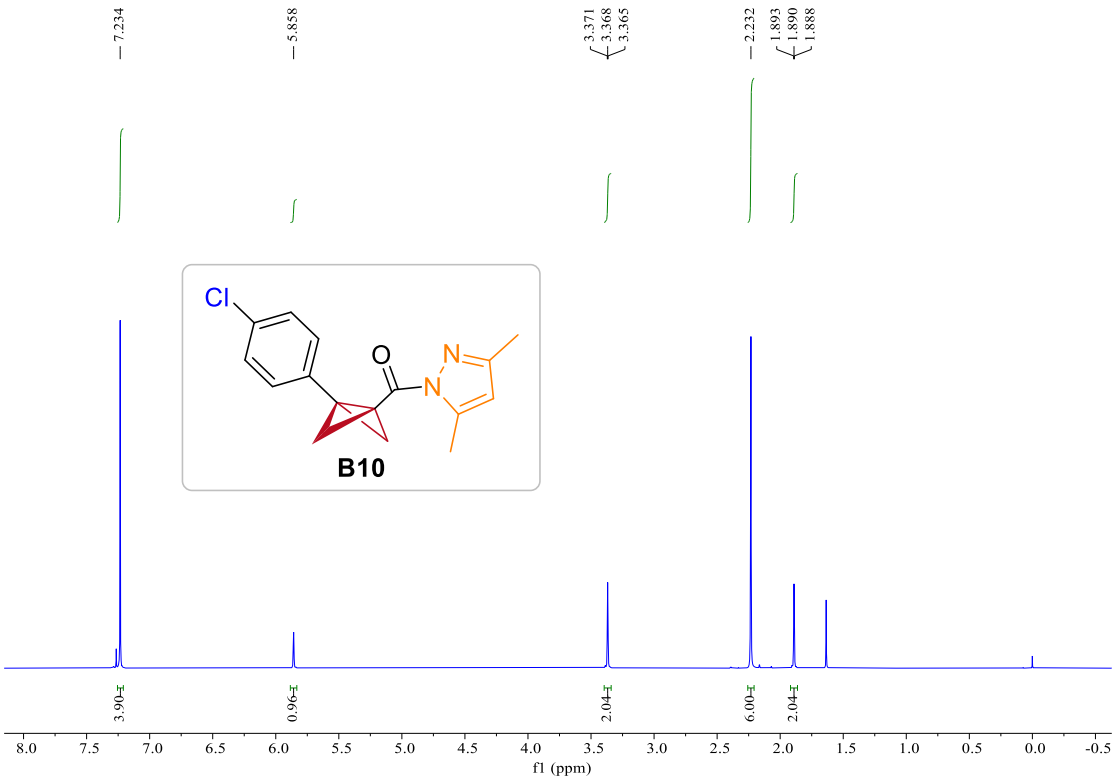
B9, ^{1}H NMR (400 MHz, $CDCl_3$)



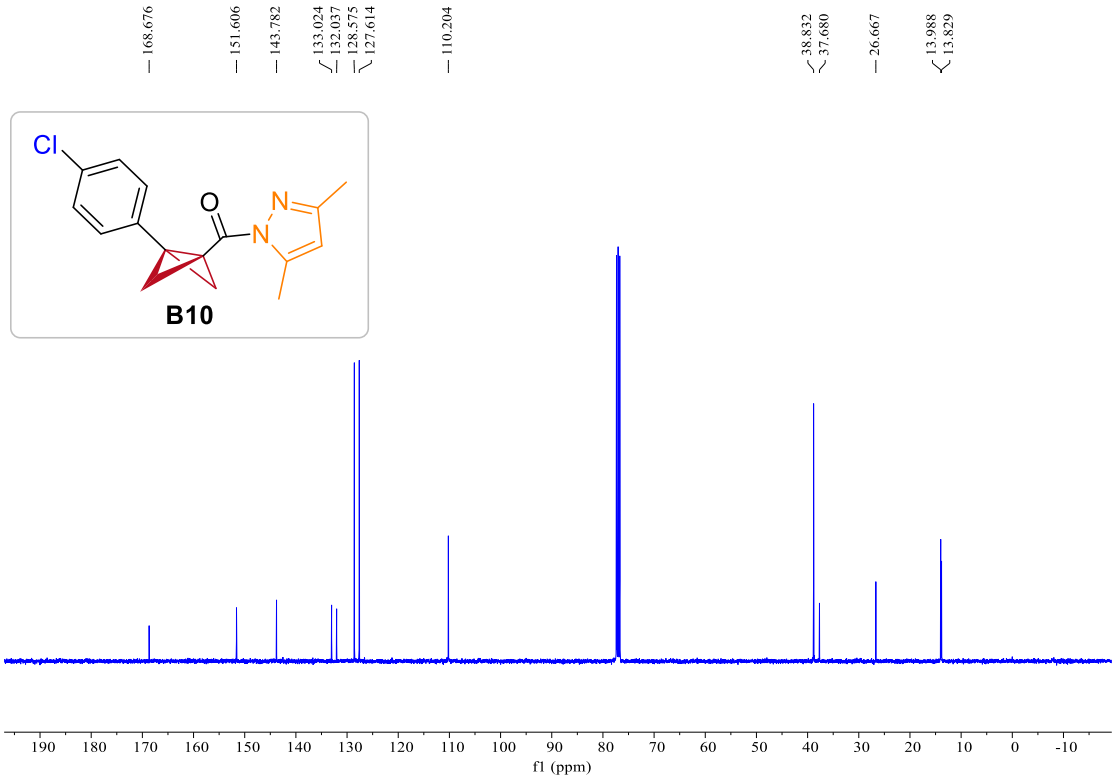
B9, ^{13}C NMR (101 MHz, $CDCl_3$)



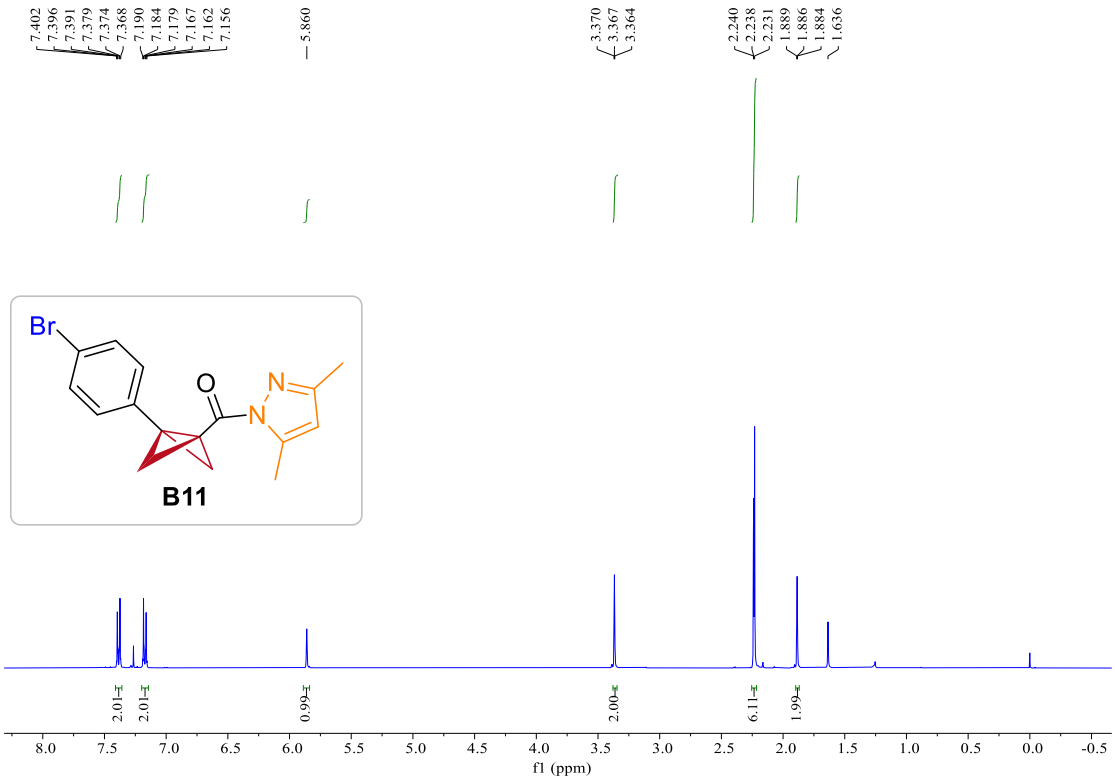
B10, ^{1}H NMR (400 MHz, $CDCl_3$)



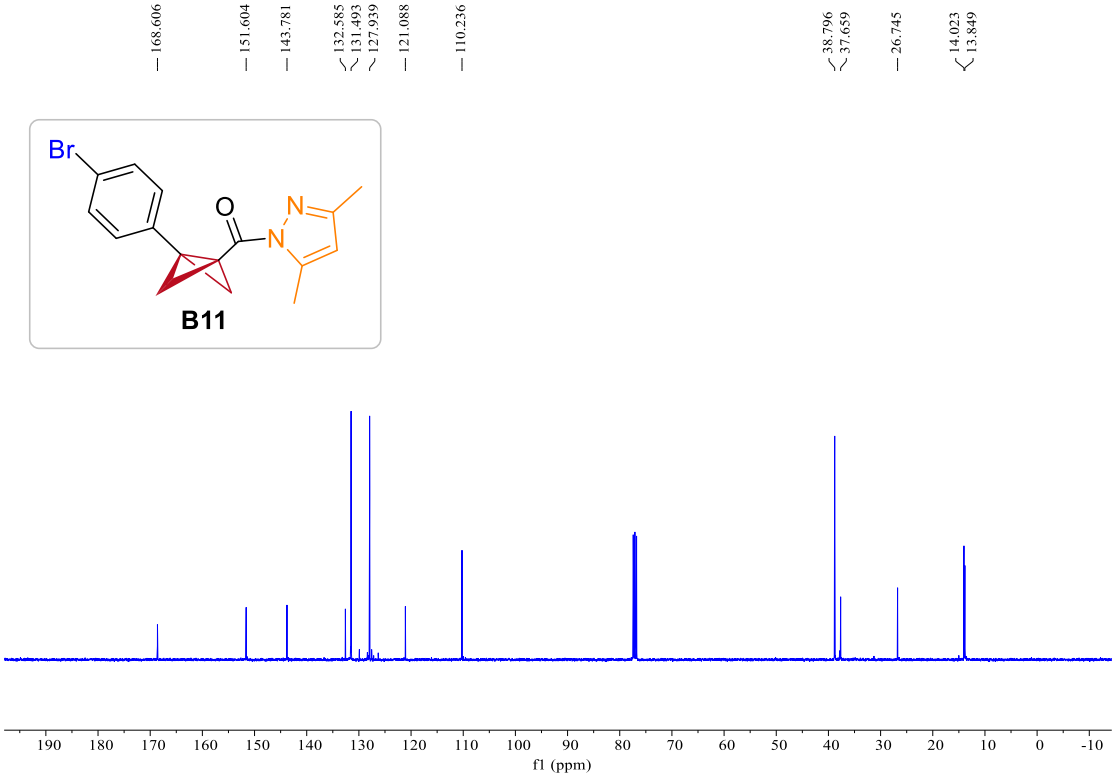
B10, ^{13}C NMR (101 MHz, $CDCl_3$)



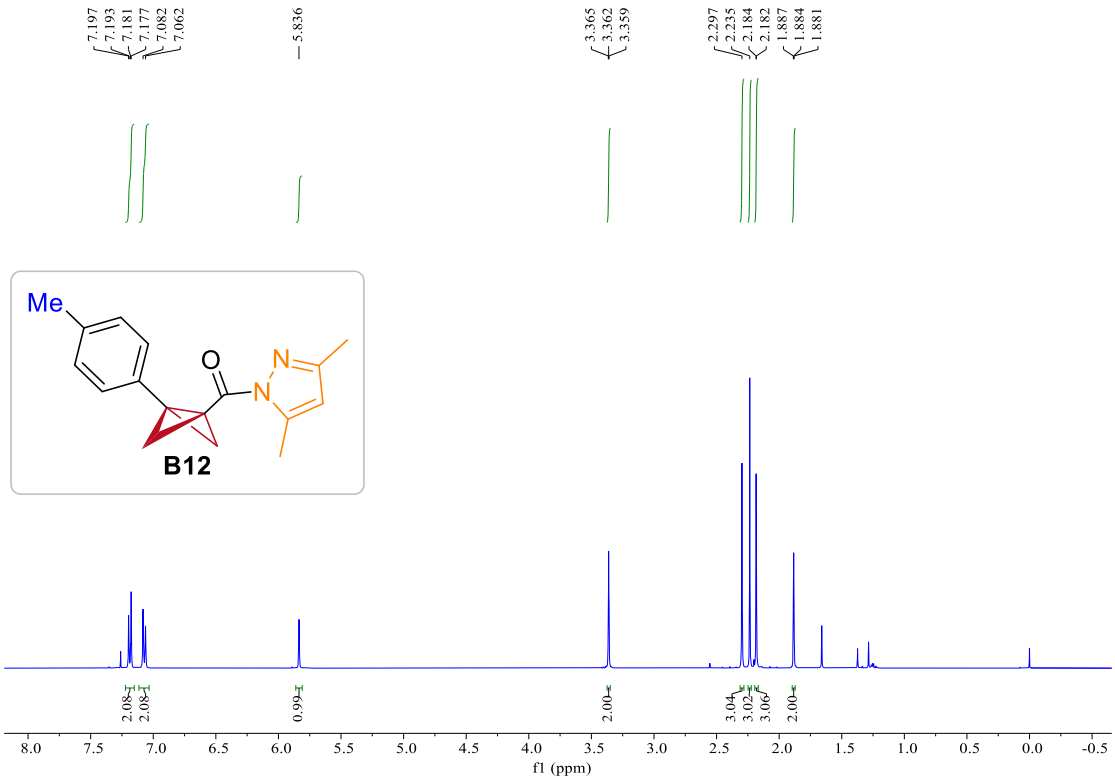
B11, ^{1}H NMR (400 MHz, $CDCl_3$)



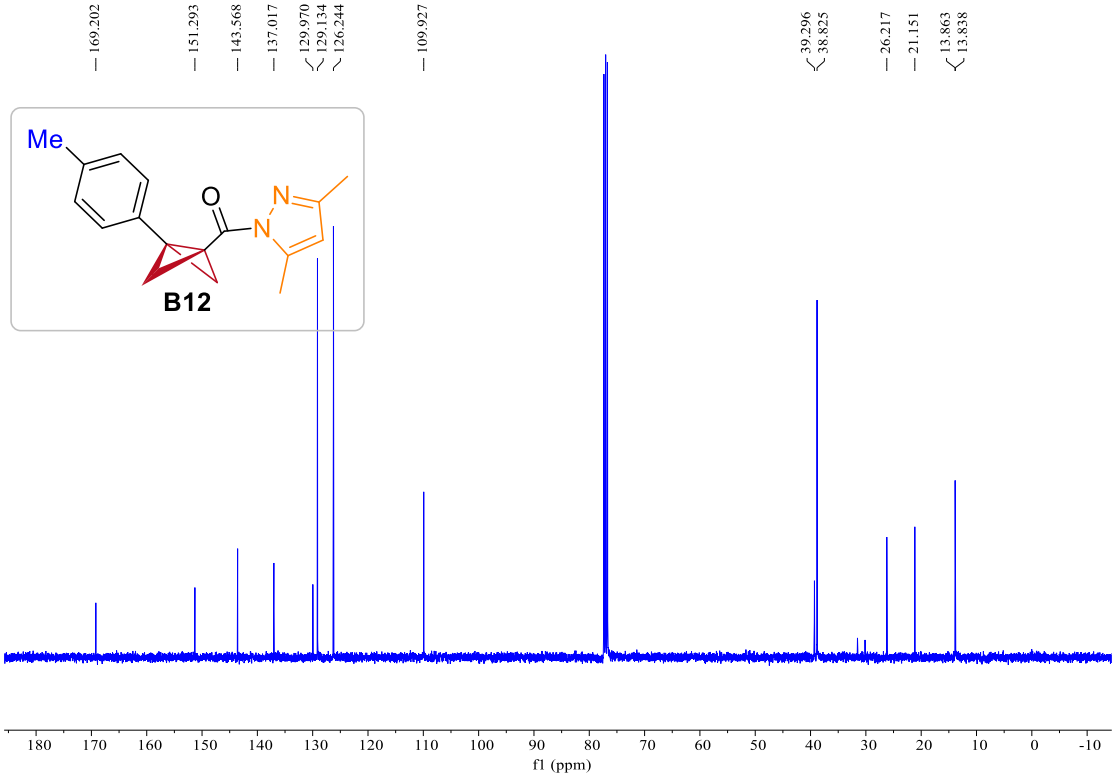
B11, ^{13}C NMR (101 MHz, $CDCl_3$)



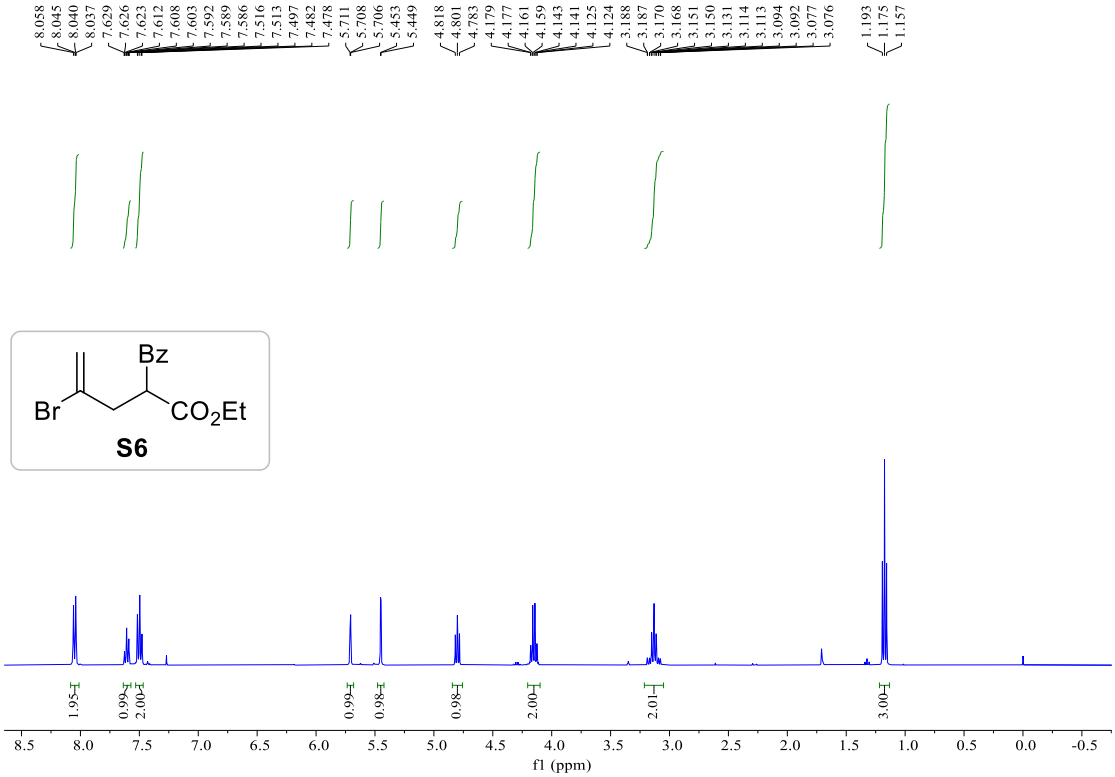
B12, ^{1}H NMR (400 MHz, $CDCl_3$)



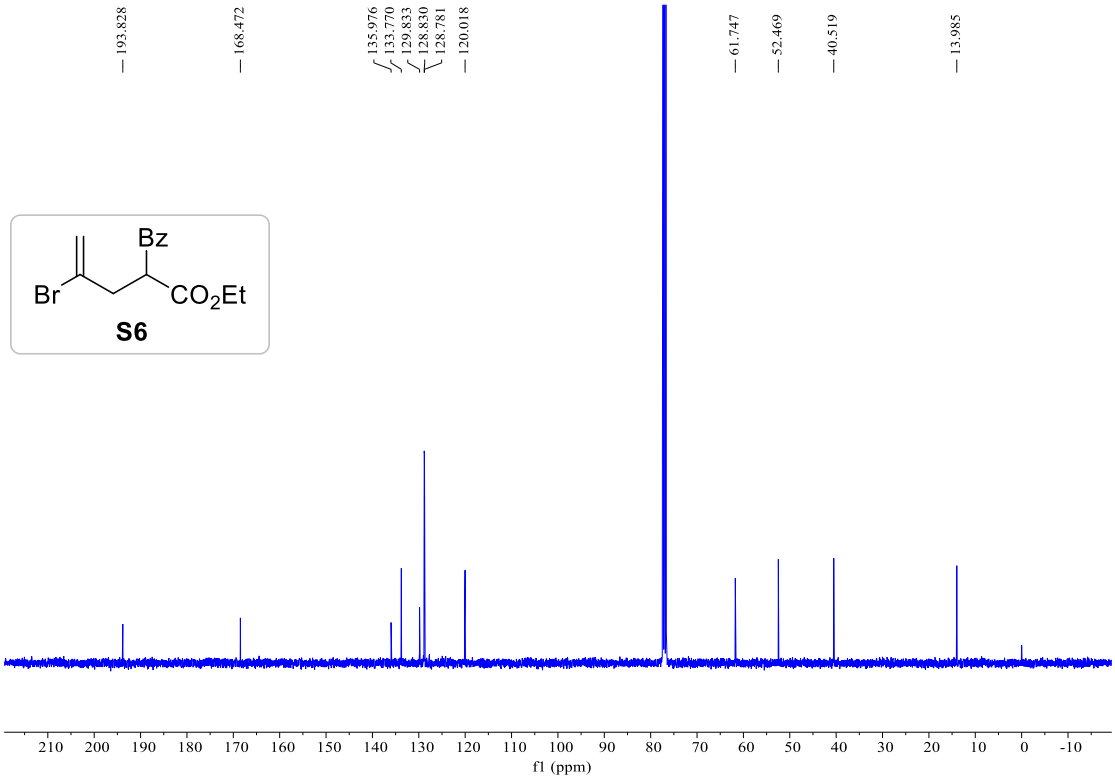
B12, ^{13}C NMR (101 MHz, $CDCl_3$)



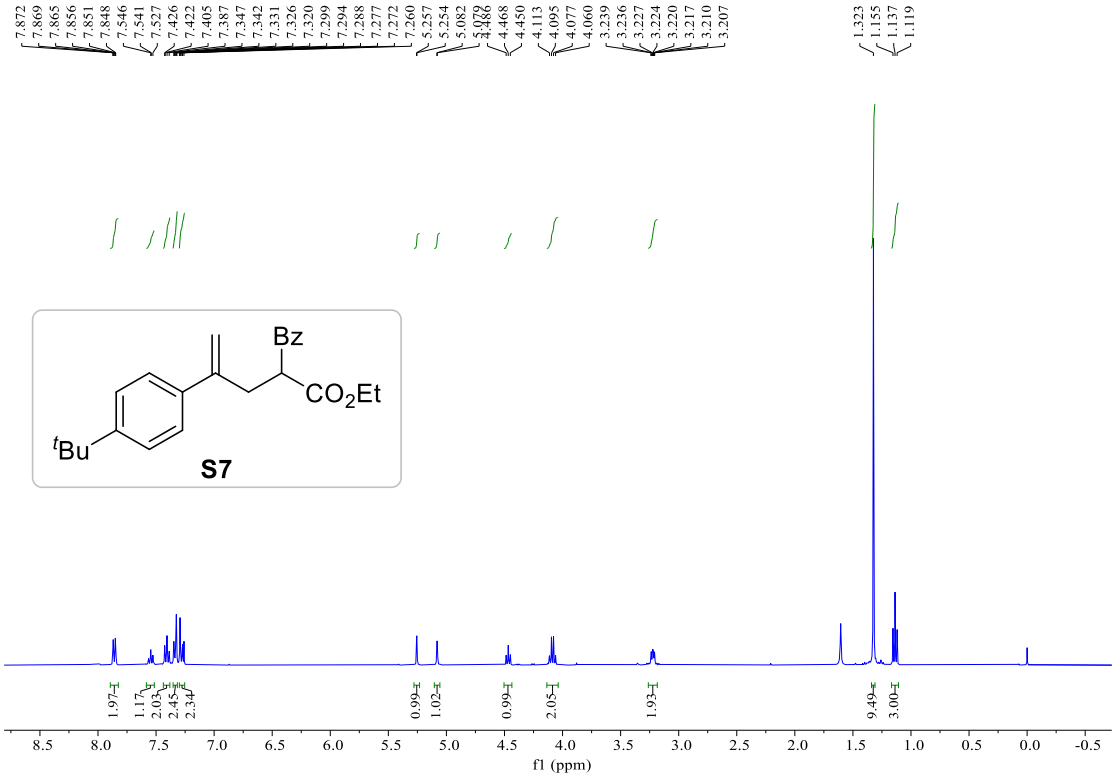
S6, ^{1}H NMR (400 MHz, $CDCl_3$)



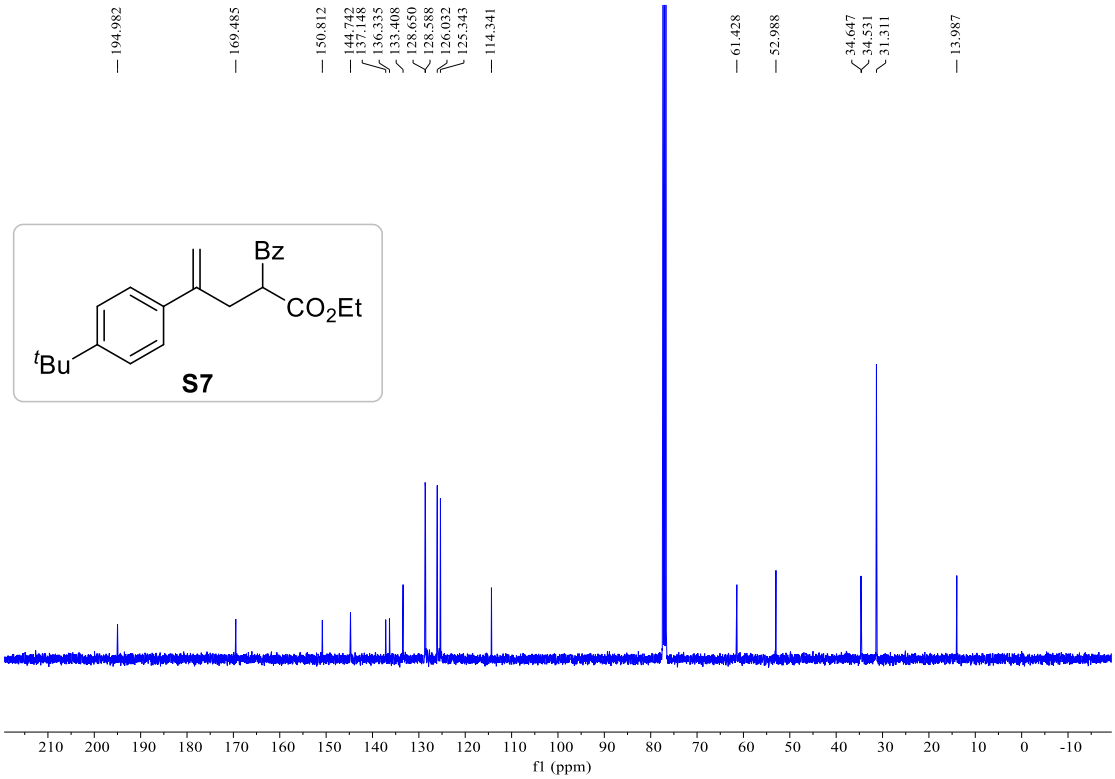
S6, ^{13}C NMR (101 MHz, $CDCl_3$)



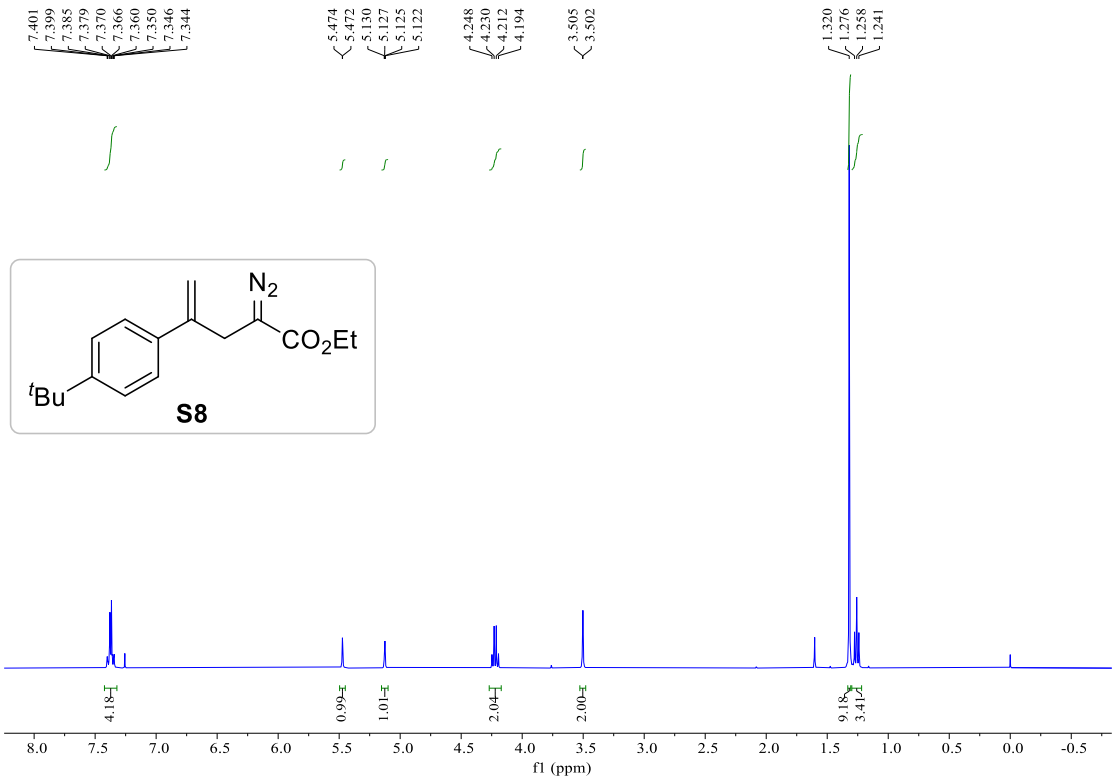
S7, ^{1}H NMR (400 MHz, $CDCl_3$)



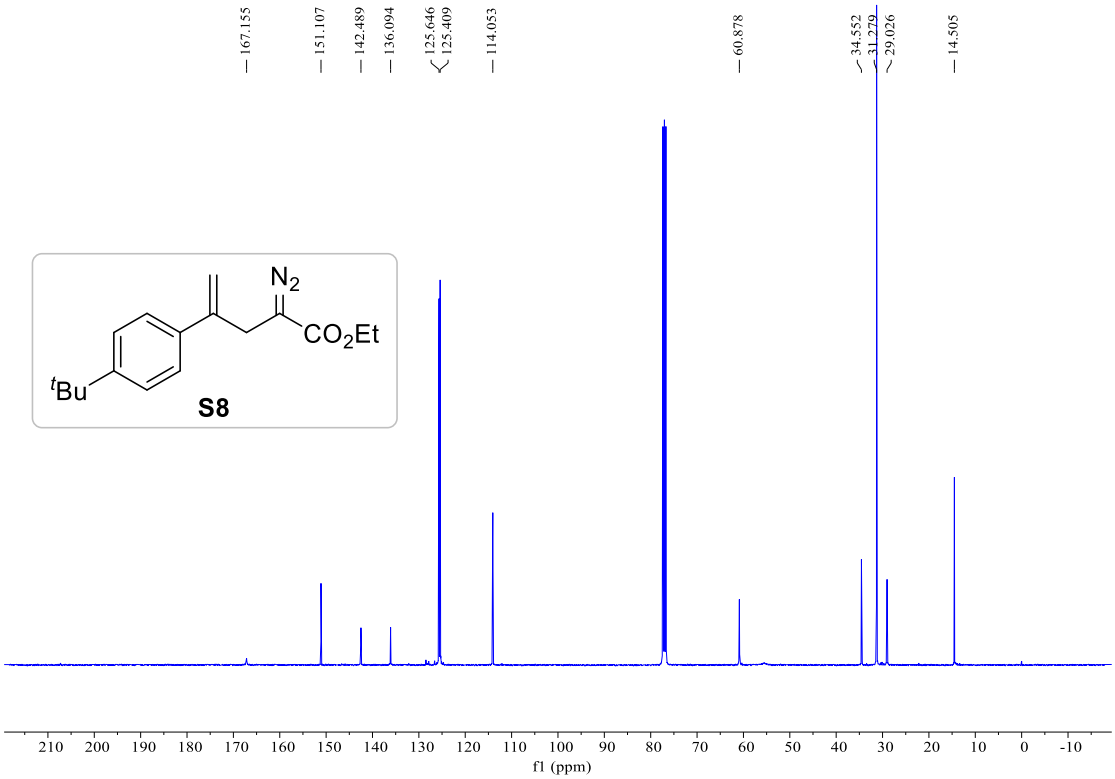
S7, ^{13}C NMR (101 MHz, $CDCl_3$)



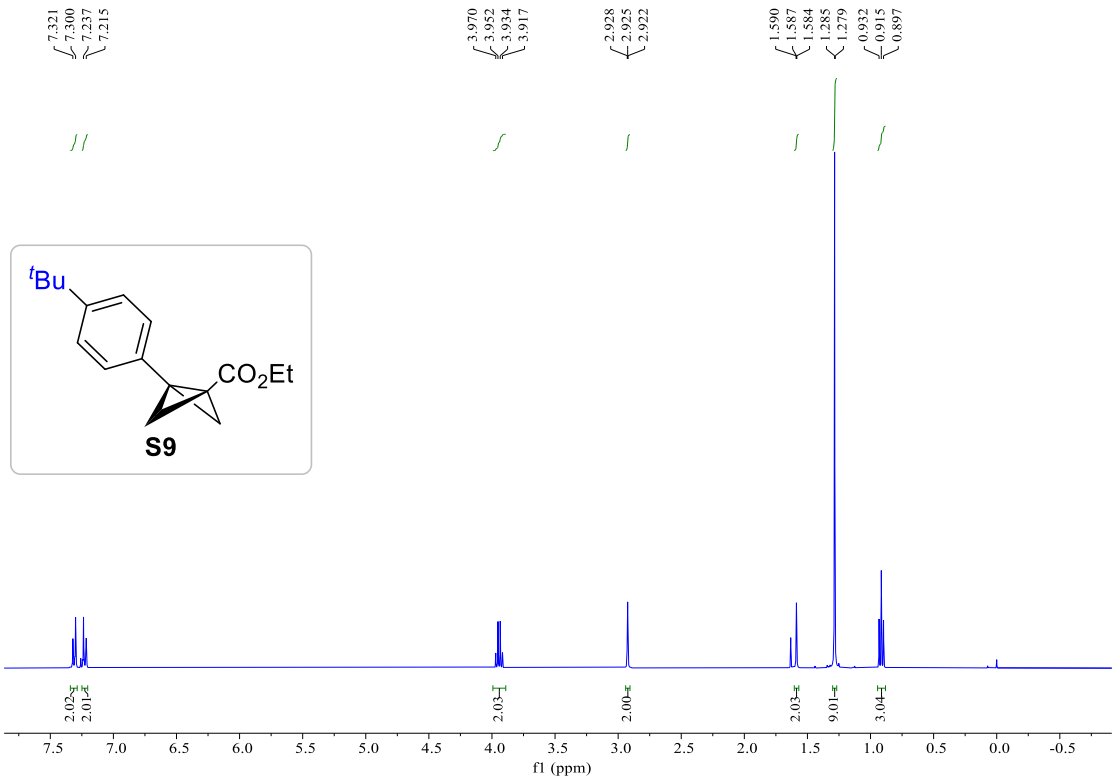
S8, ^{1}H NMR (400 MHz, $CDCl_3$)



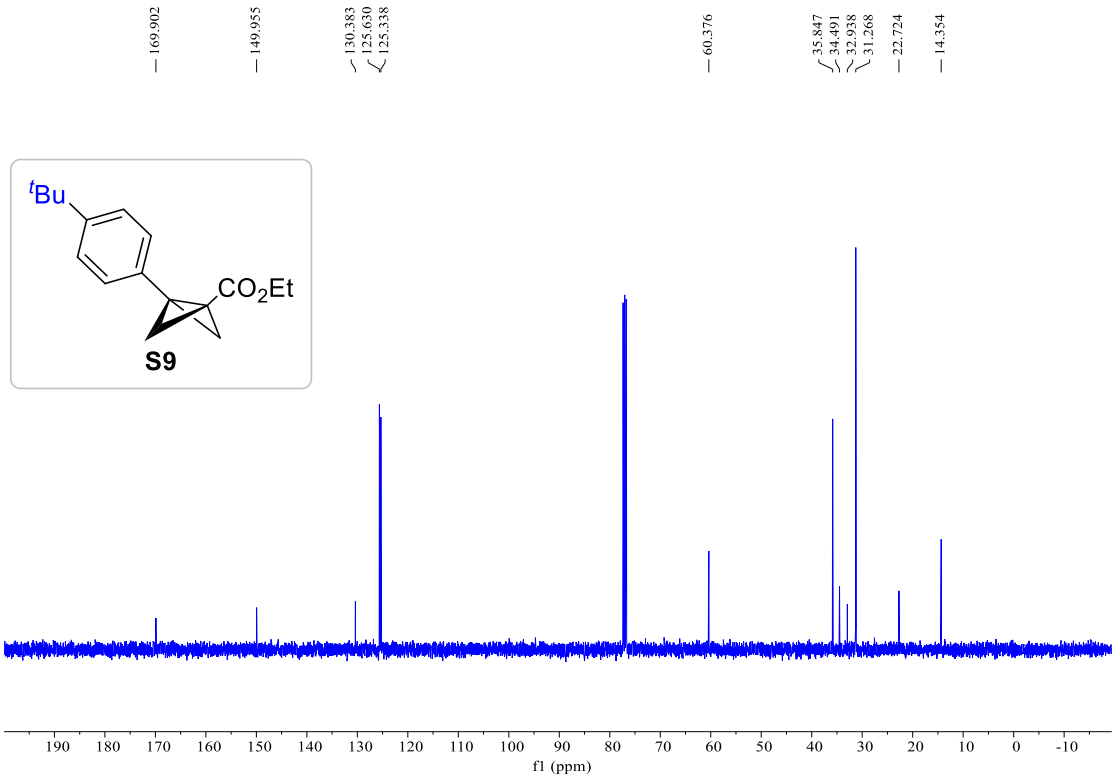
S8, ^{13}C NMR (101 MHz, $CDCl_3$)



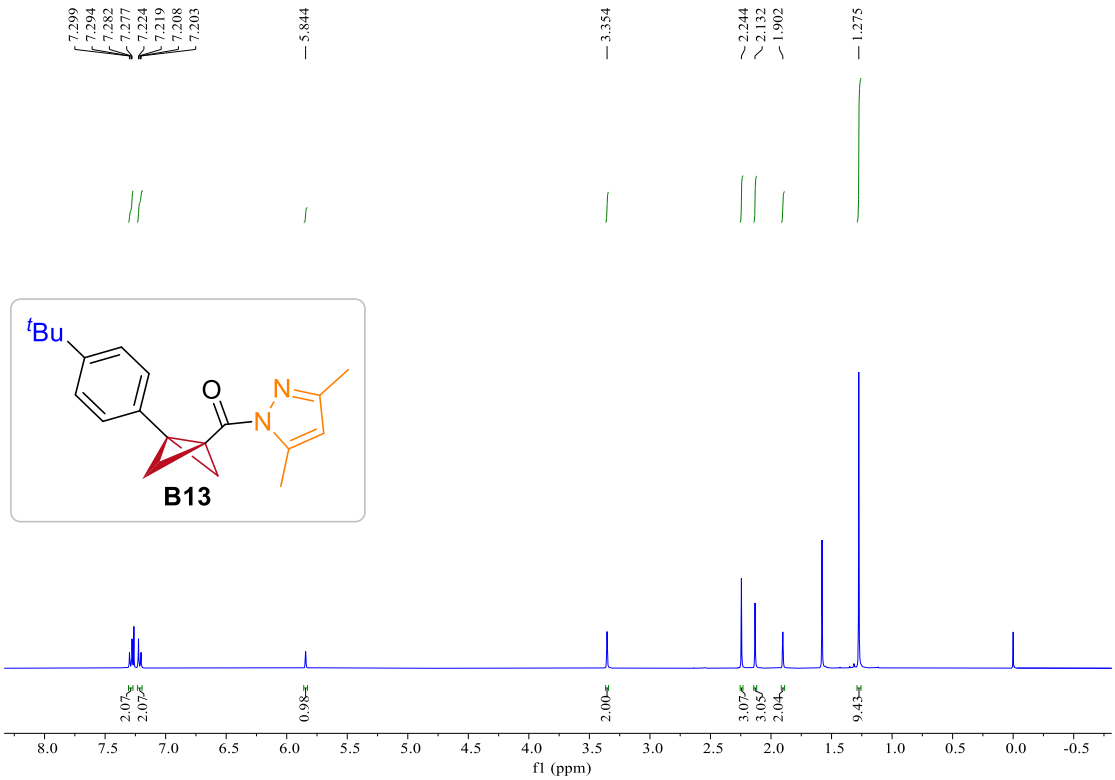
S9, ^{1}H NMR (400 MHz, $CDCl_3$)



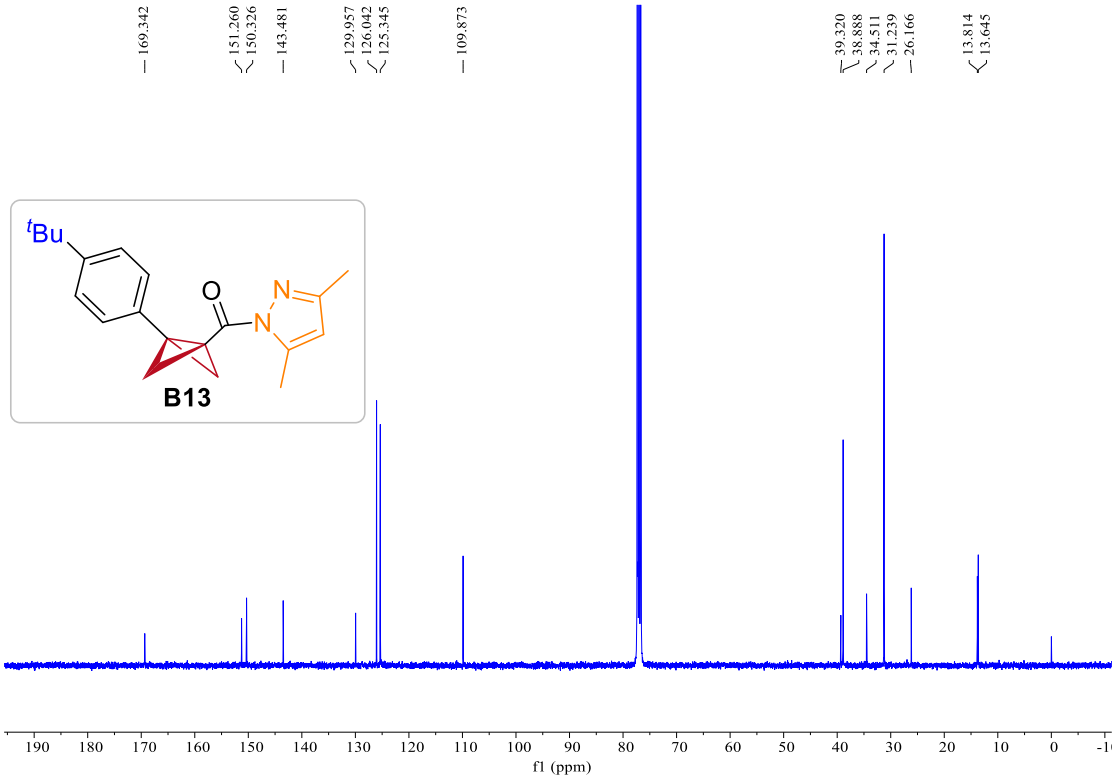
S9, ^{13}C NMR (101 MHz, $CDCl_3$)



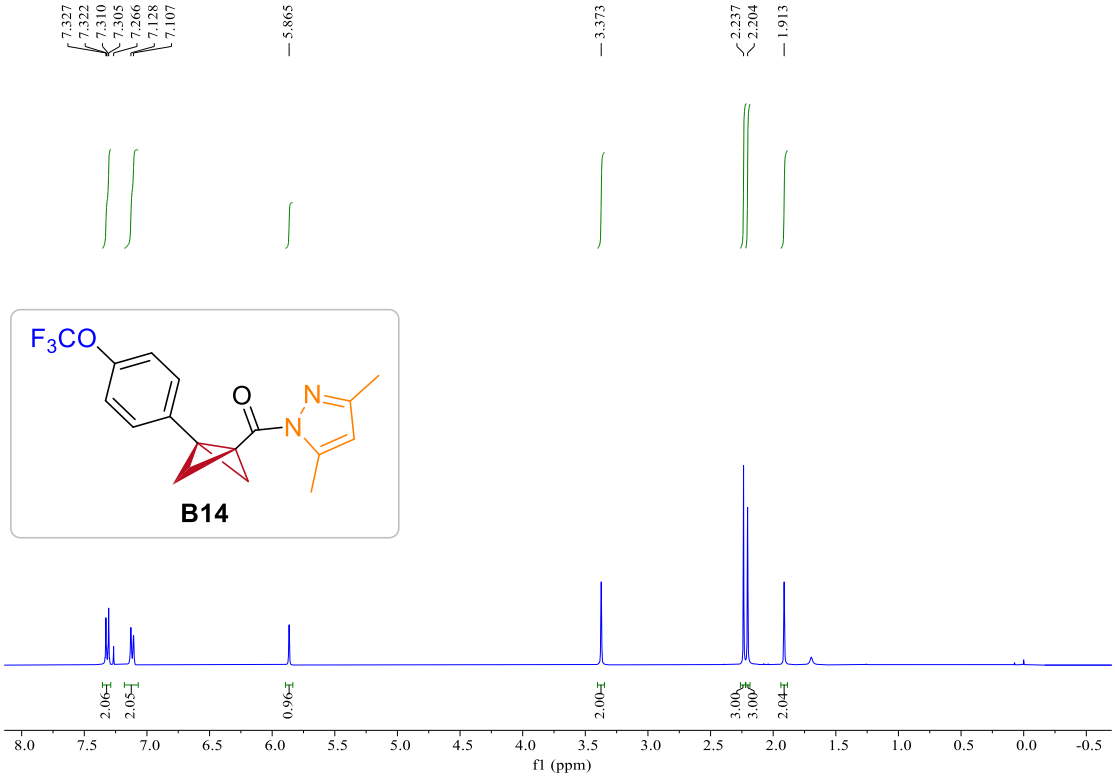
B13, ^{1}H NMR (400 MHz, $CDCl_3$)



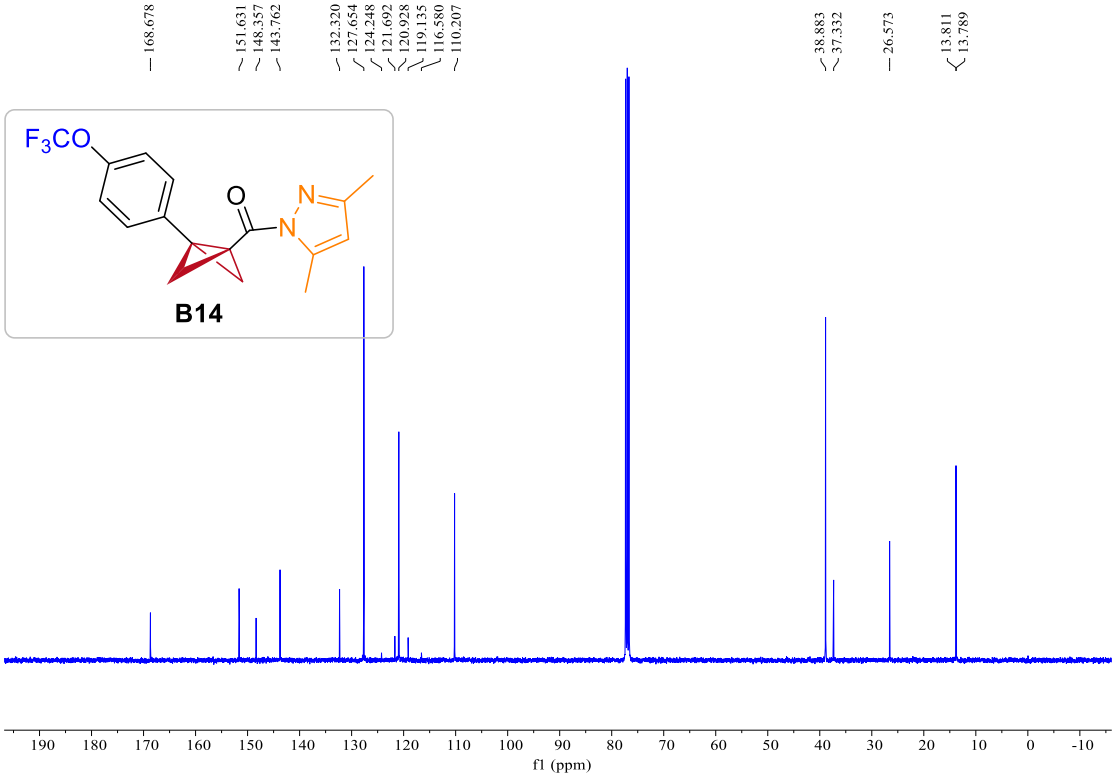
B13, ^{13}C NMR (101 MHz, $CDCl_3$)



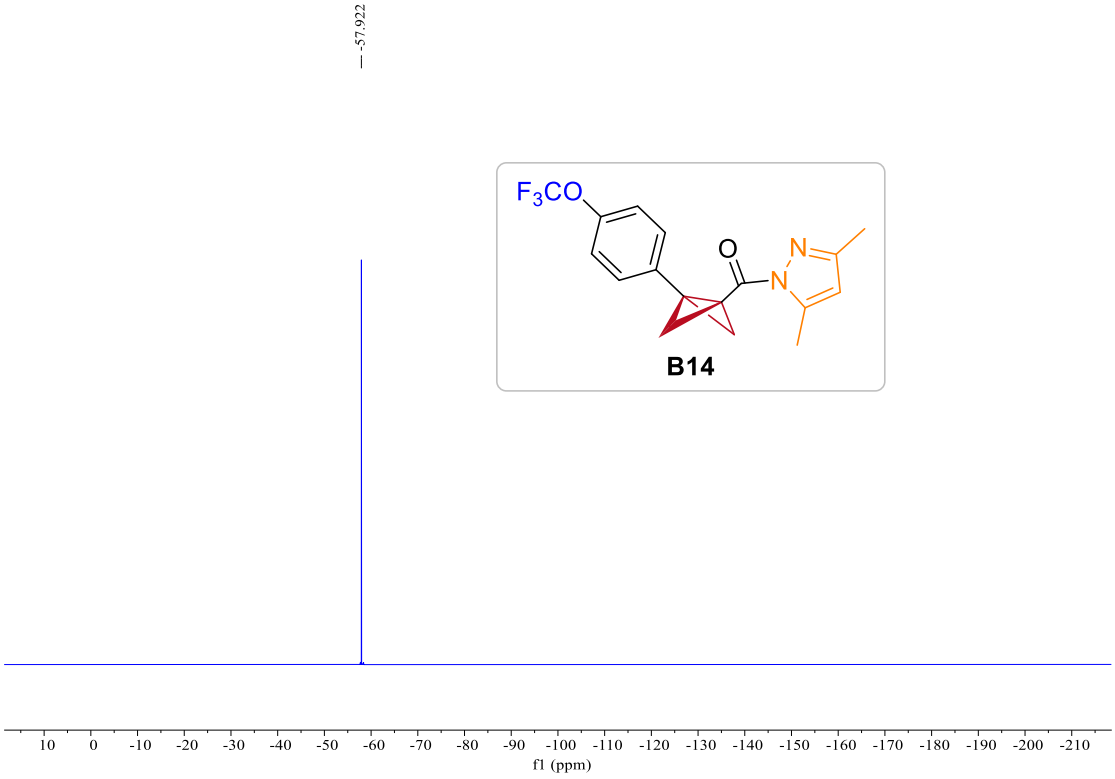
B14, ^{1}H NMR (400 MHz, $CDCl_3$)



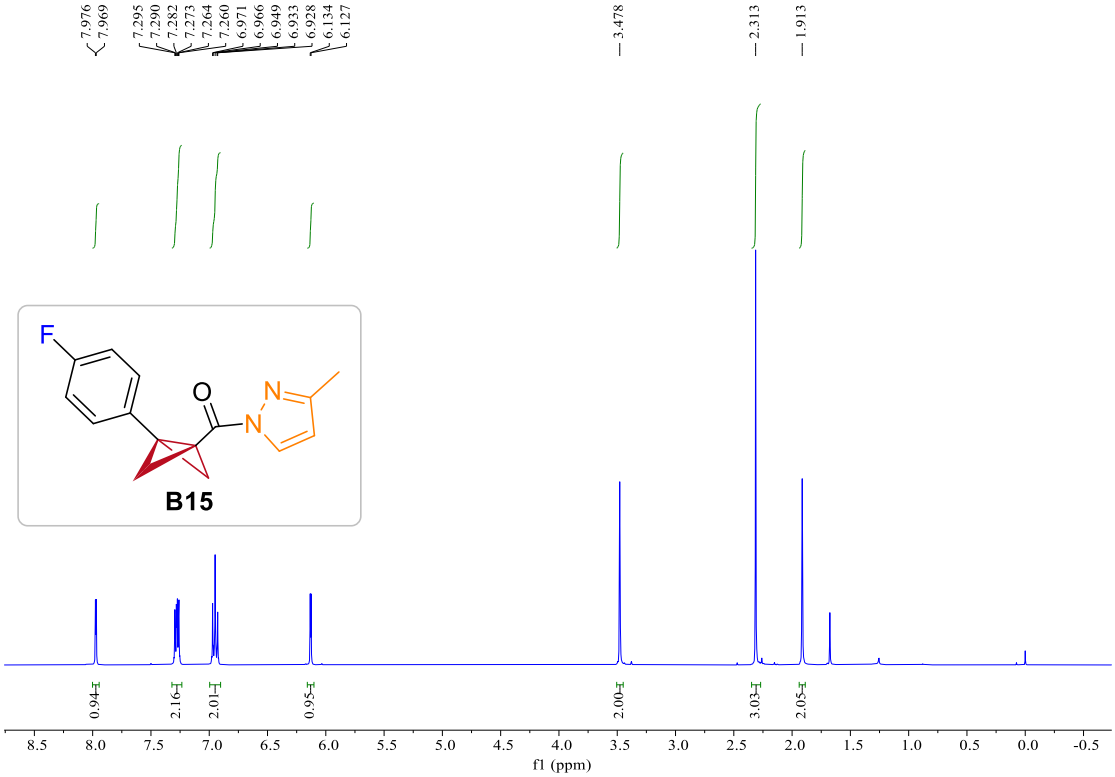
B14, ^{13}C NMR (101 MHz, $CDCl_3$)



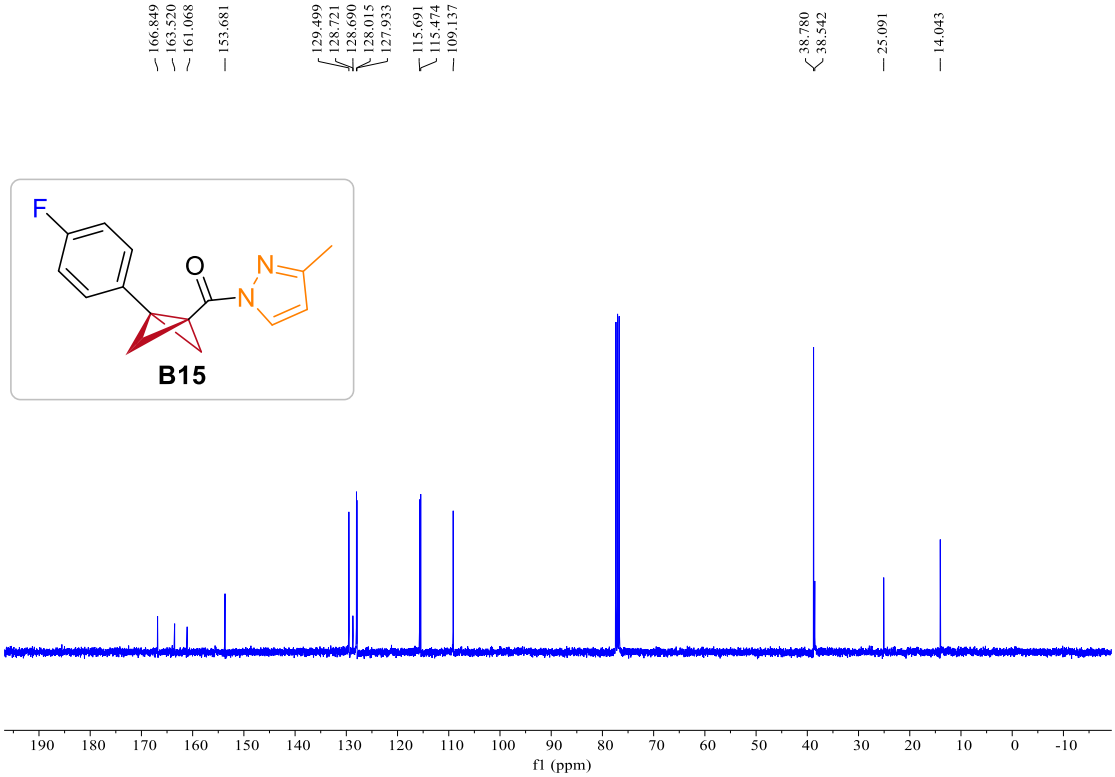
B14, ^{19}F NMR (376 MHz, $CDCl_3$)



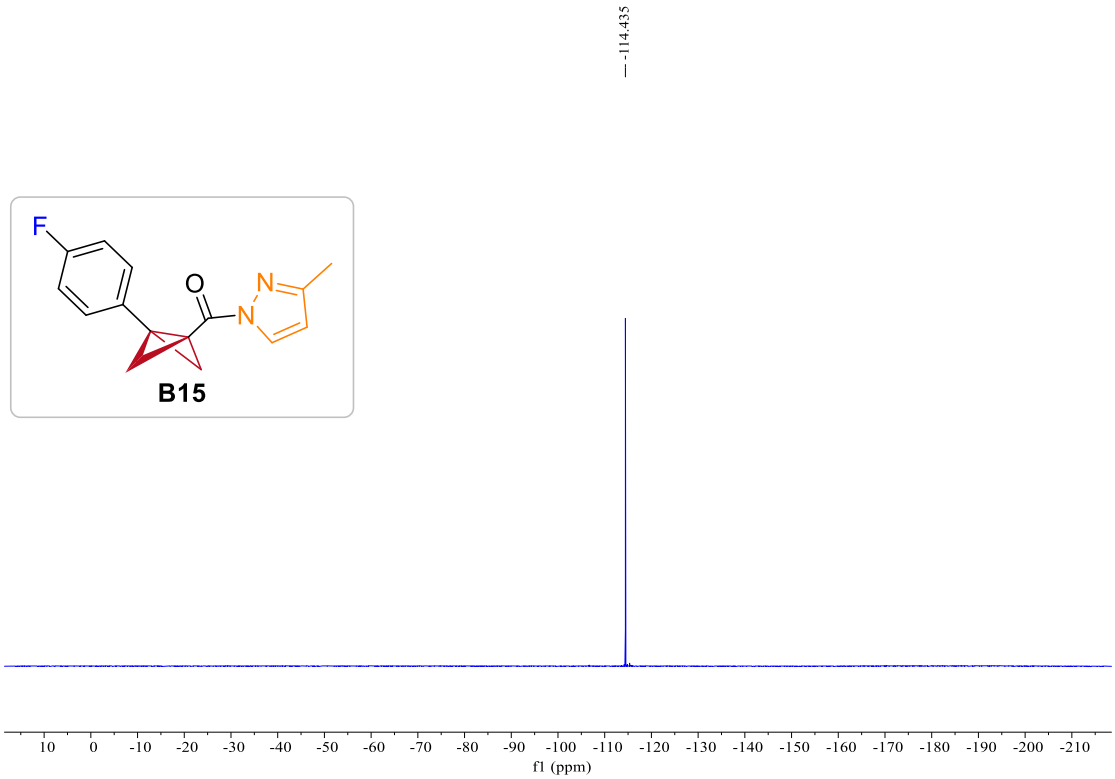
B15, ^{1}H NMR (400 MHz, $CDCl_3$)



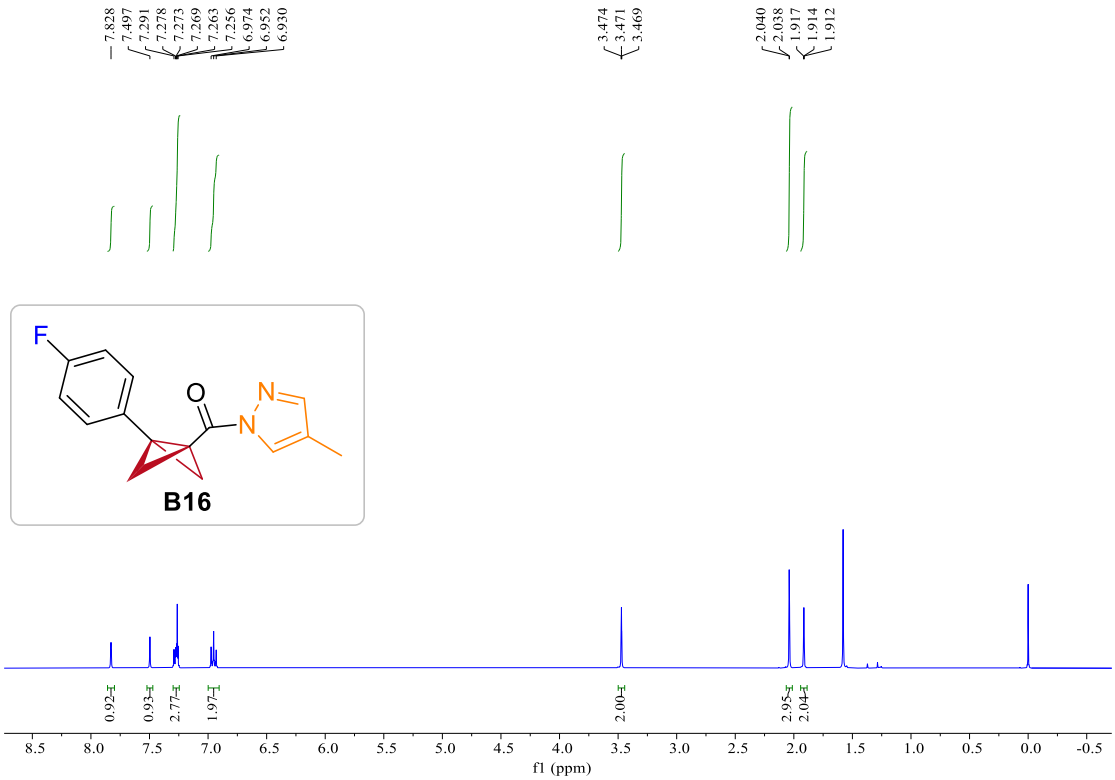
B15, ^{13}C NMR (101 MHz, $CDCl_3$)



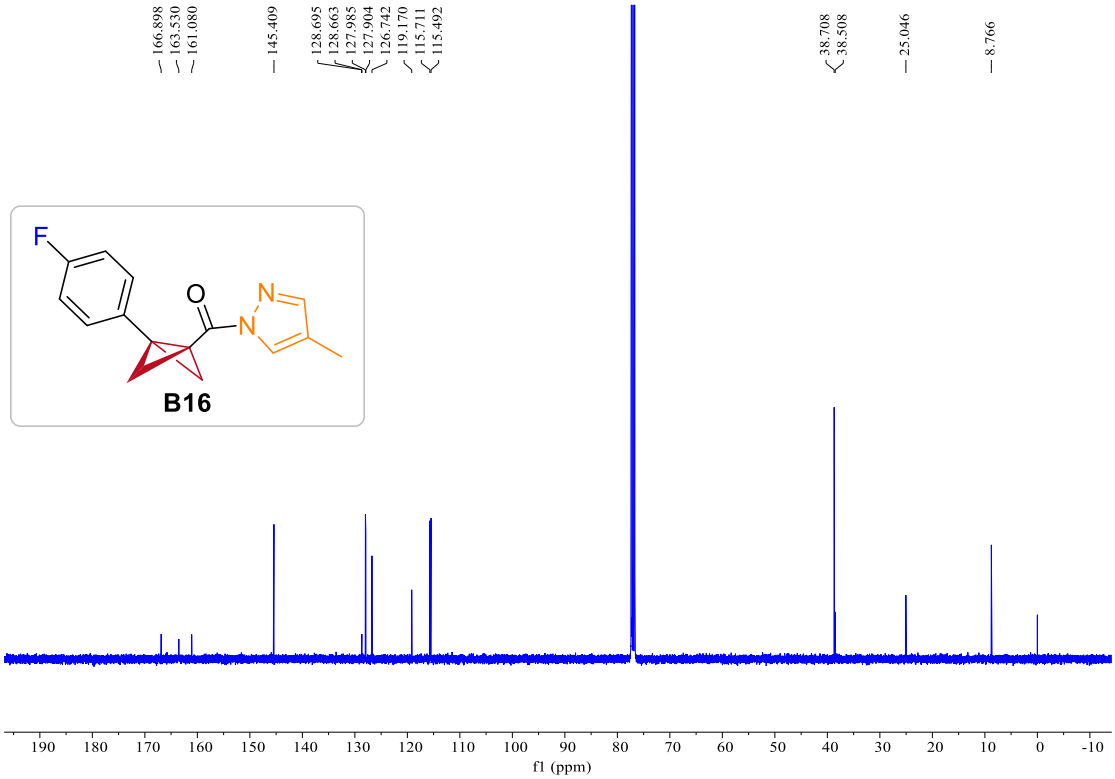
B15, ^{19}F NMR (376 MHz, $CDCl_3$)



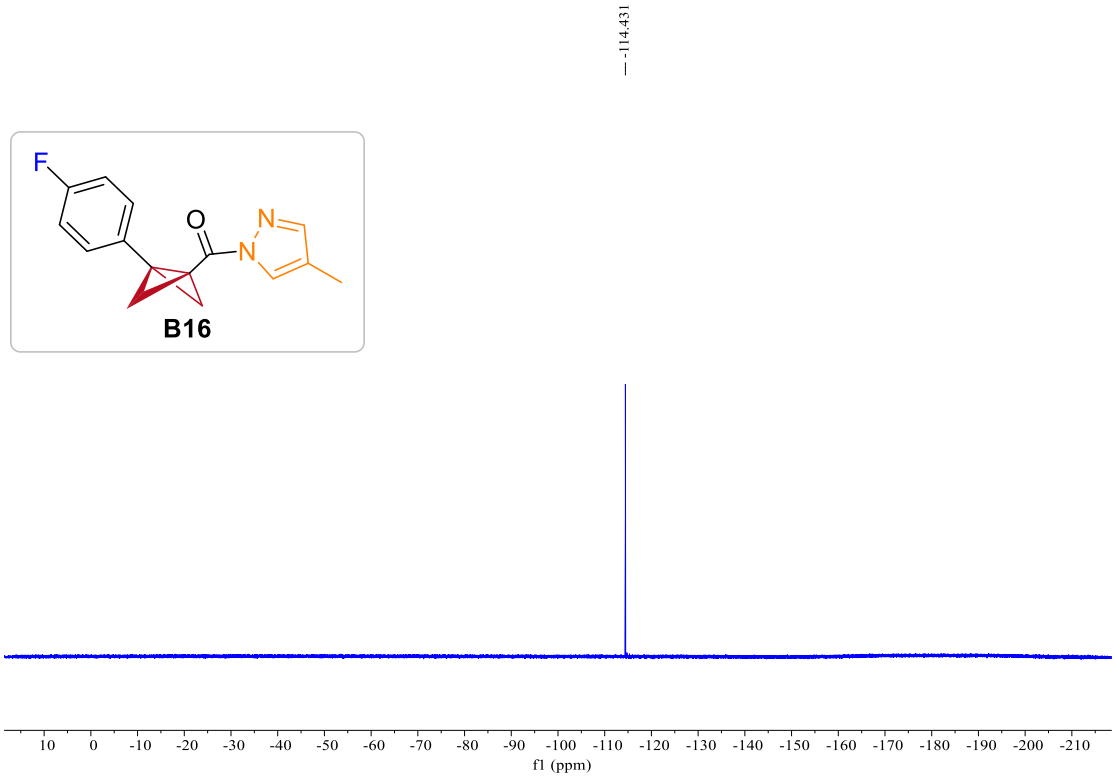
B16, ^{1}H NMR (400 MHz, $CDCl_3$)



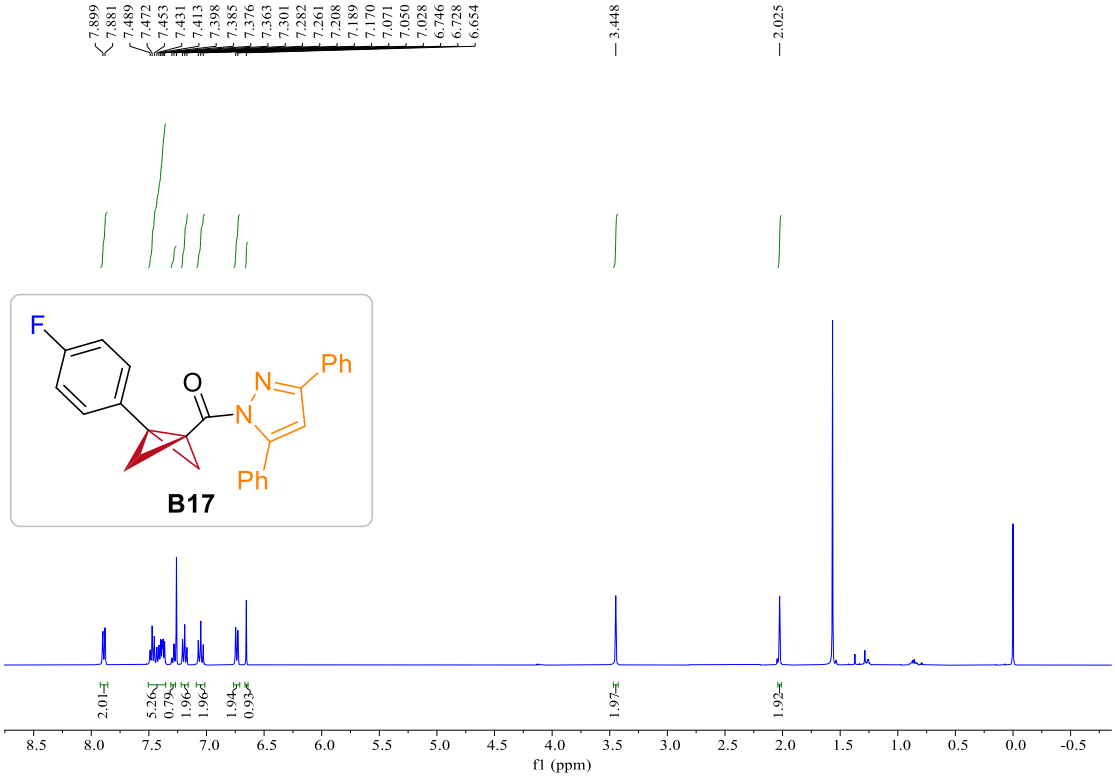
B16, ^{13}C NMR (101 MHz, $CDCl_3$)



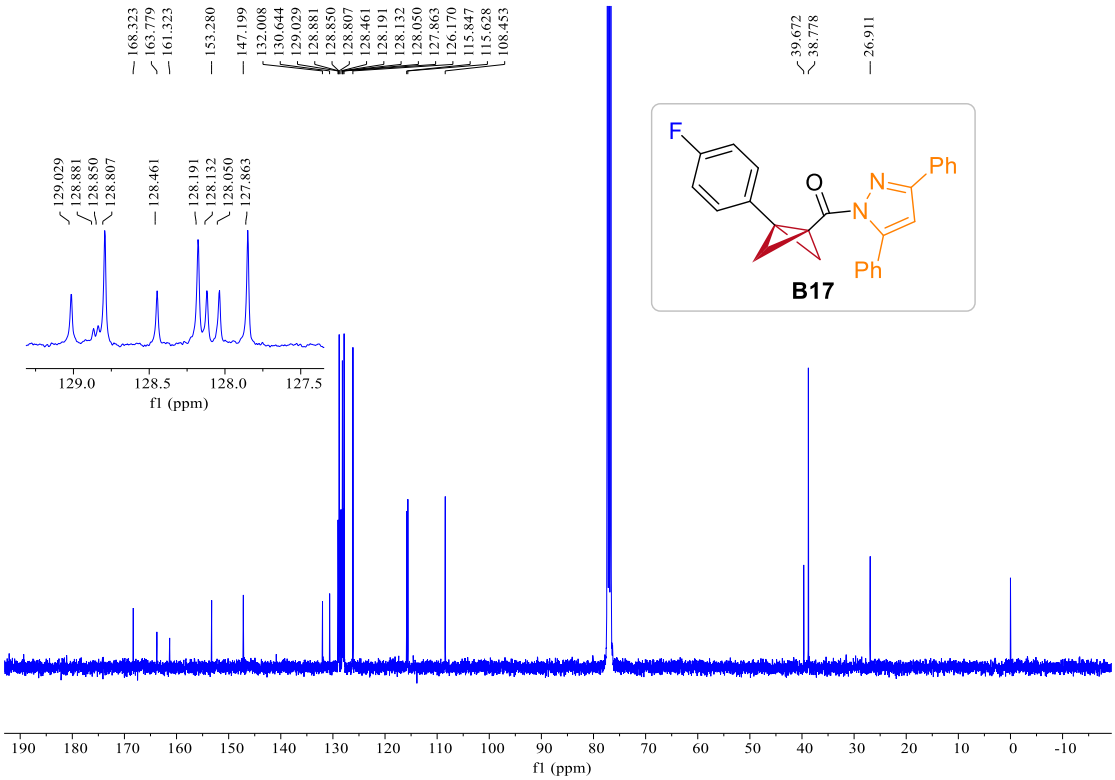
B16, ^{19}F NMR (376 MHz, $CDCl_3$)



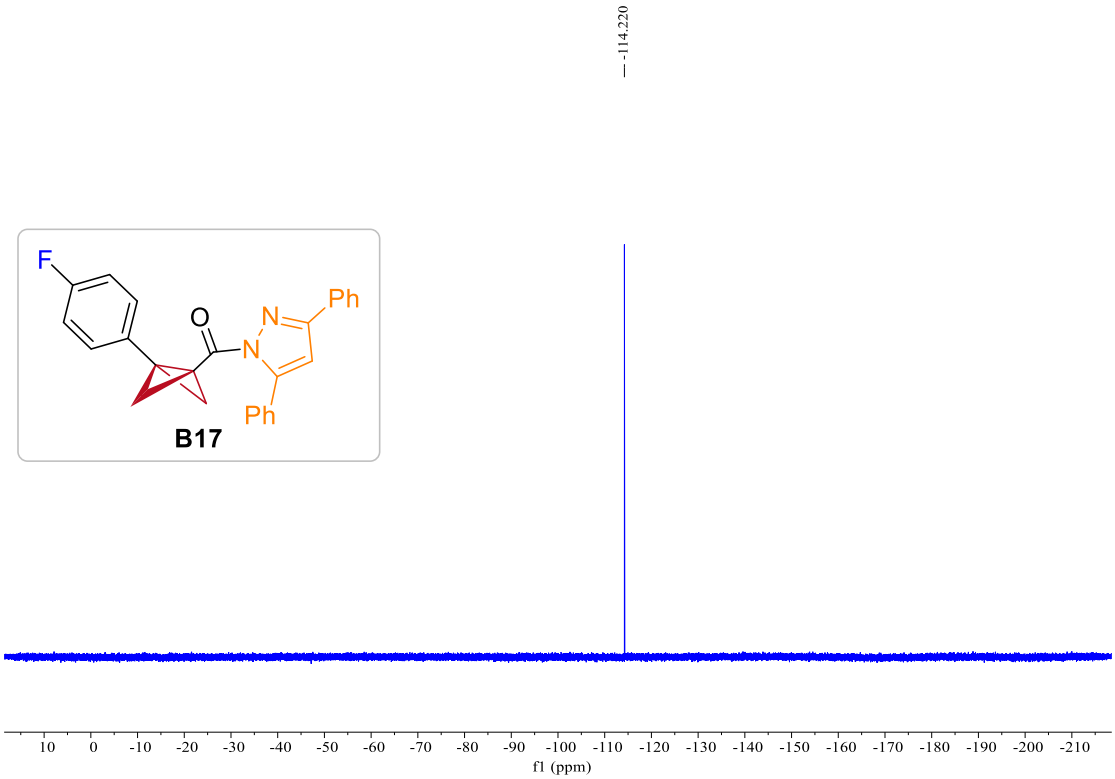
B17, ^{1}H NMR (400 MHz, $CDCl_3$)



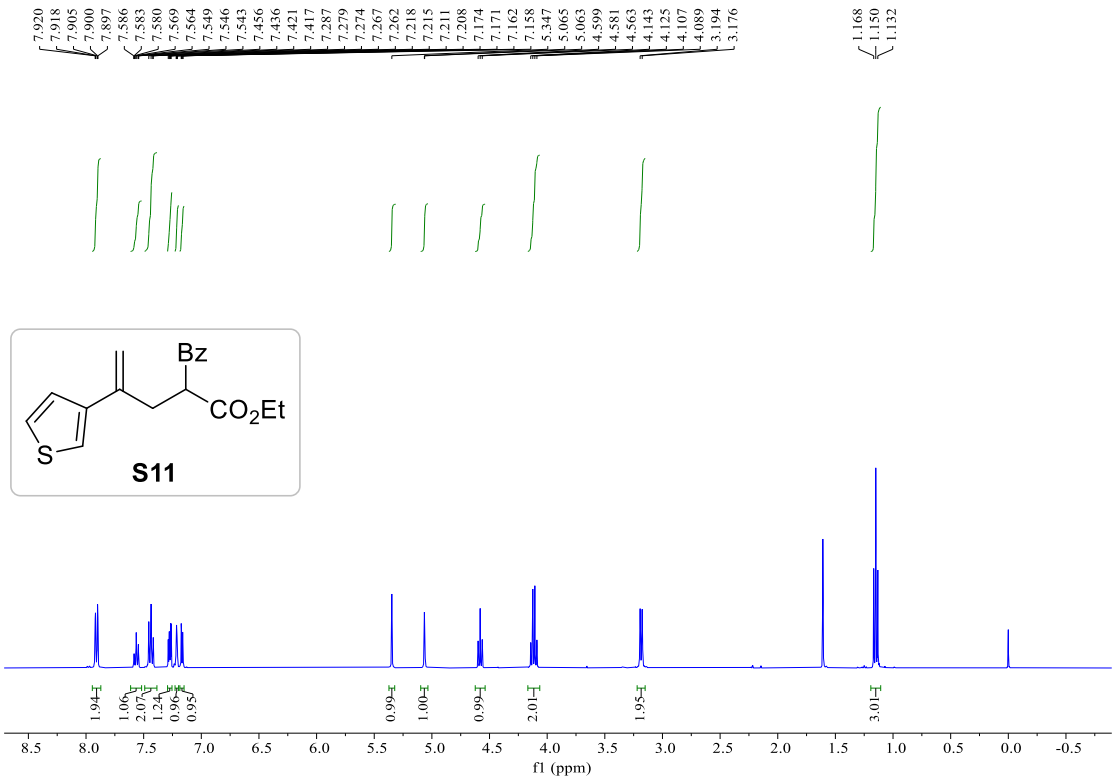
B17, ^{13}C NMR (101 MHz, $CDCl_3$)



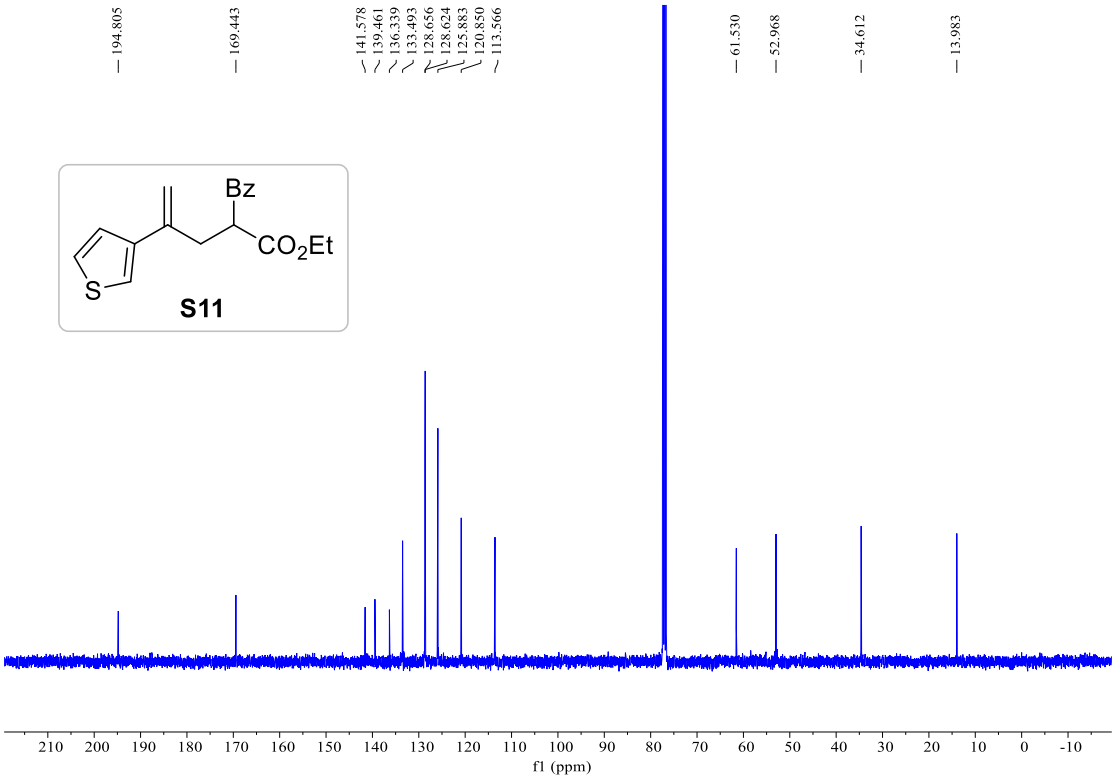
B17, ^{19}F NMR (376 MHz, $CDCl_3$)



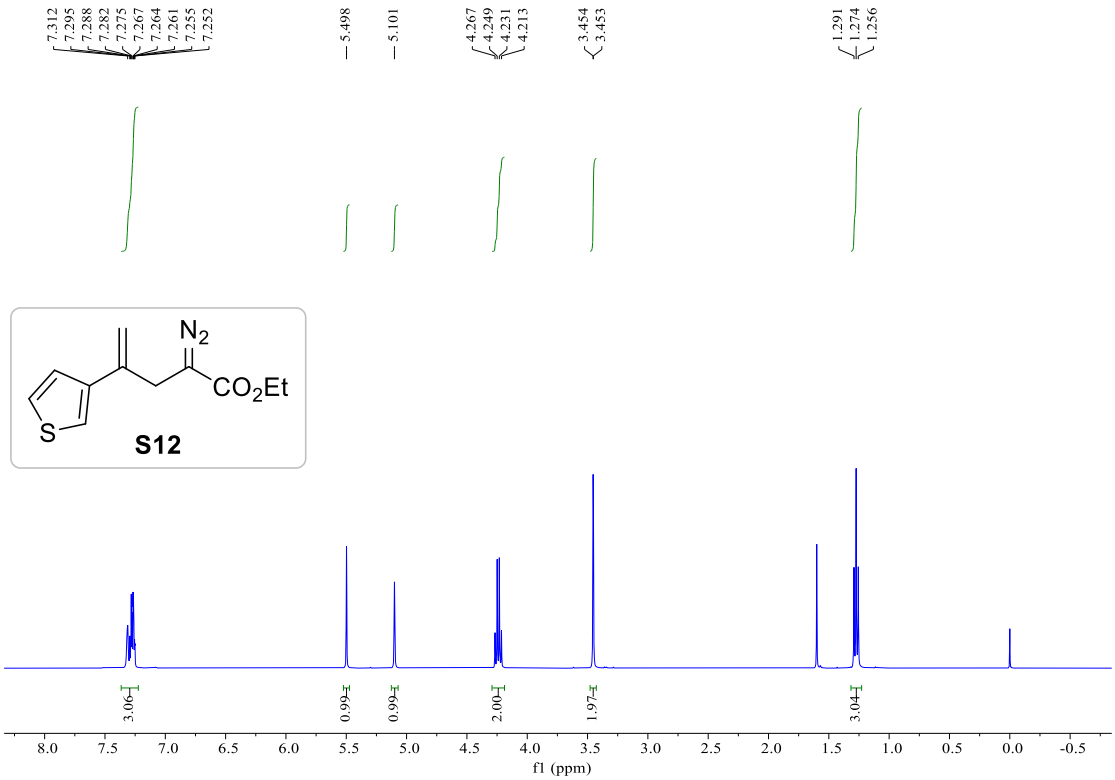
S11, ^{1}H NMR (400 MHz, $CDCl_3$)



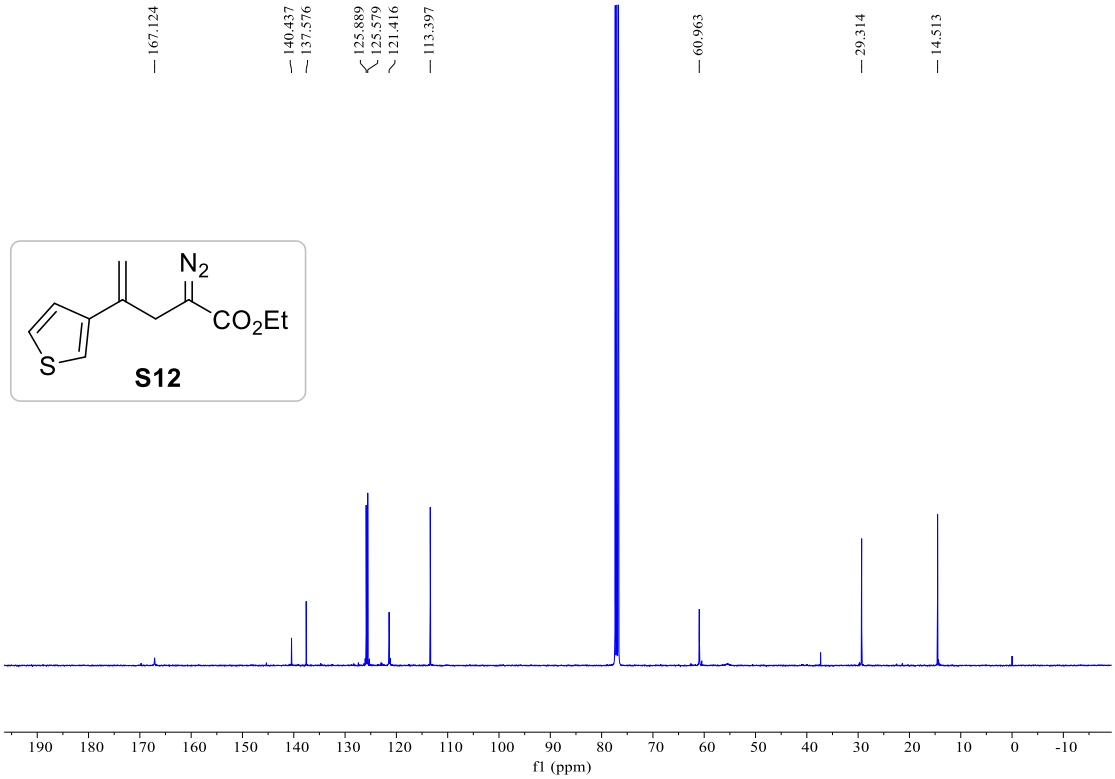
S11, ^{13}C NMR (101 MHz, $CDCl_3$)



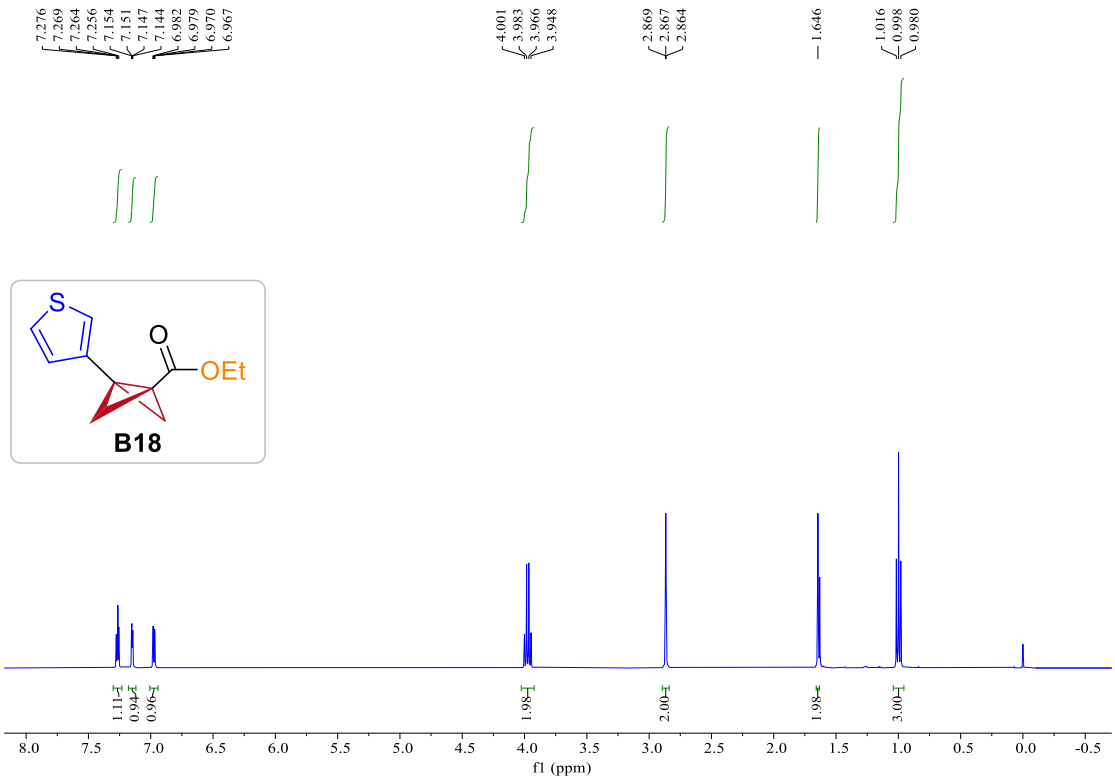
S12, ^{1}H NMR (400 MHz, $CDCl_3$)



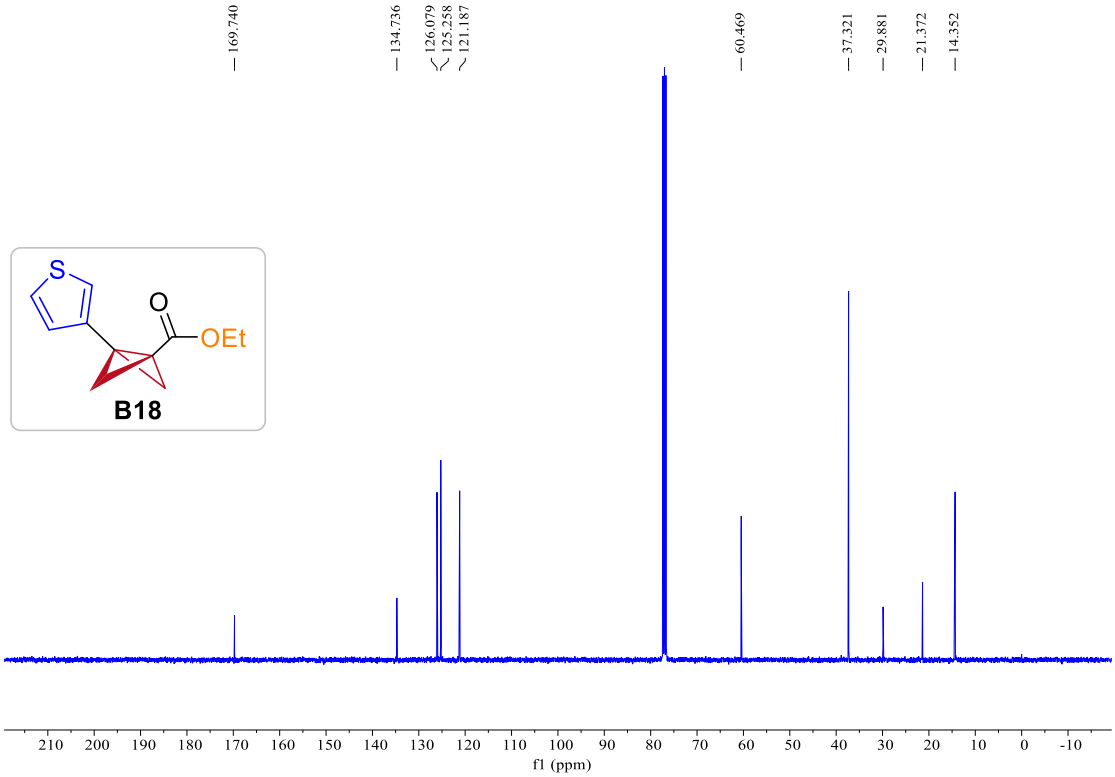
S12, ^{13}C NMR (101 MHz, $CDCl_3$)



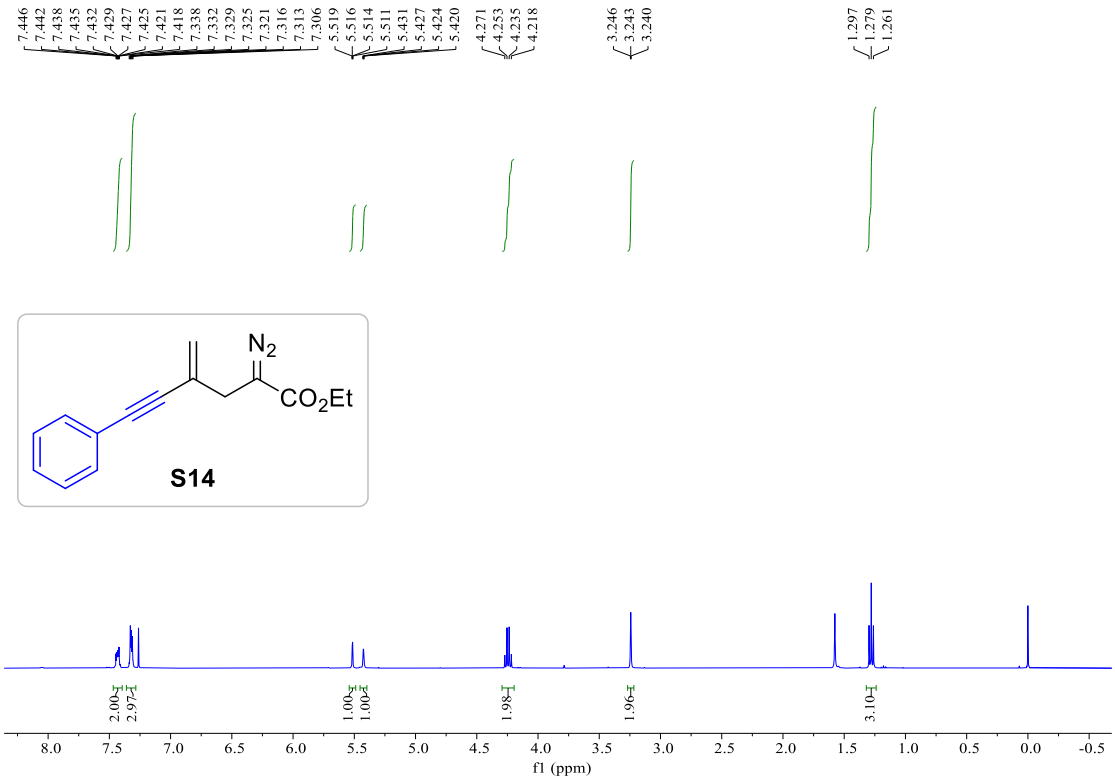
B18, ^{1}H NMR (400 MHz, $CDCl_3$)



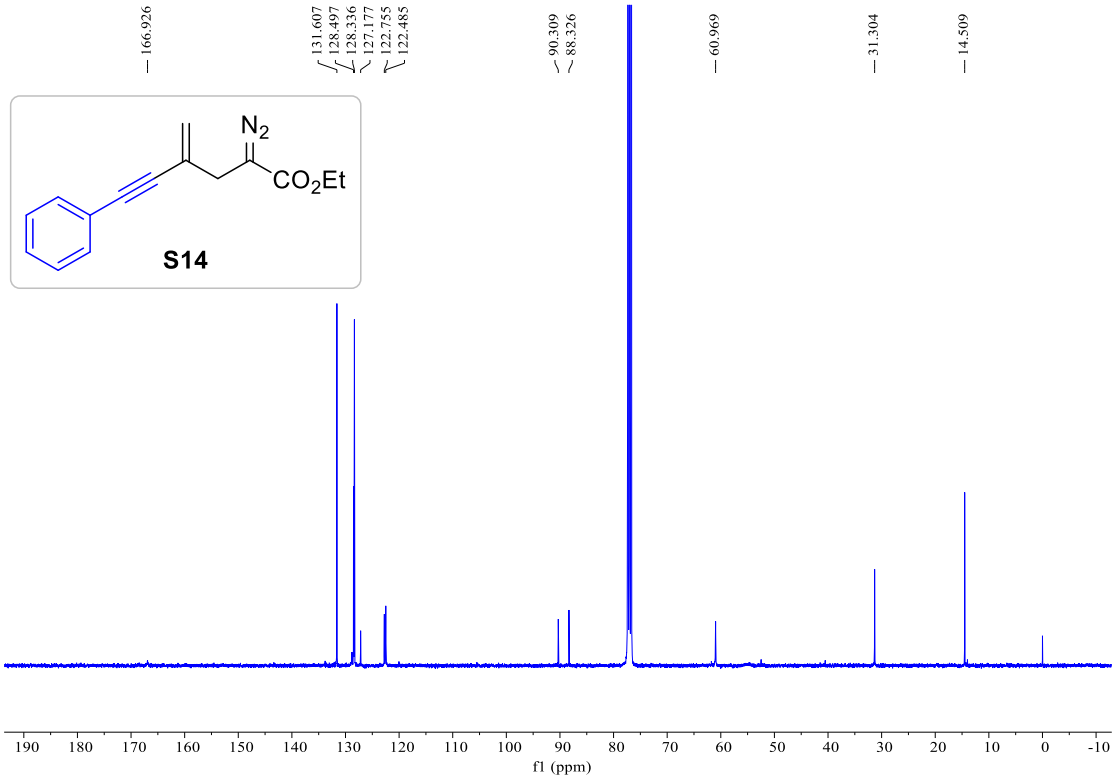
B18, ^{13}C NMR (101 MHz, $CDCl_3$)



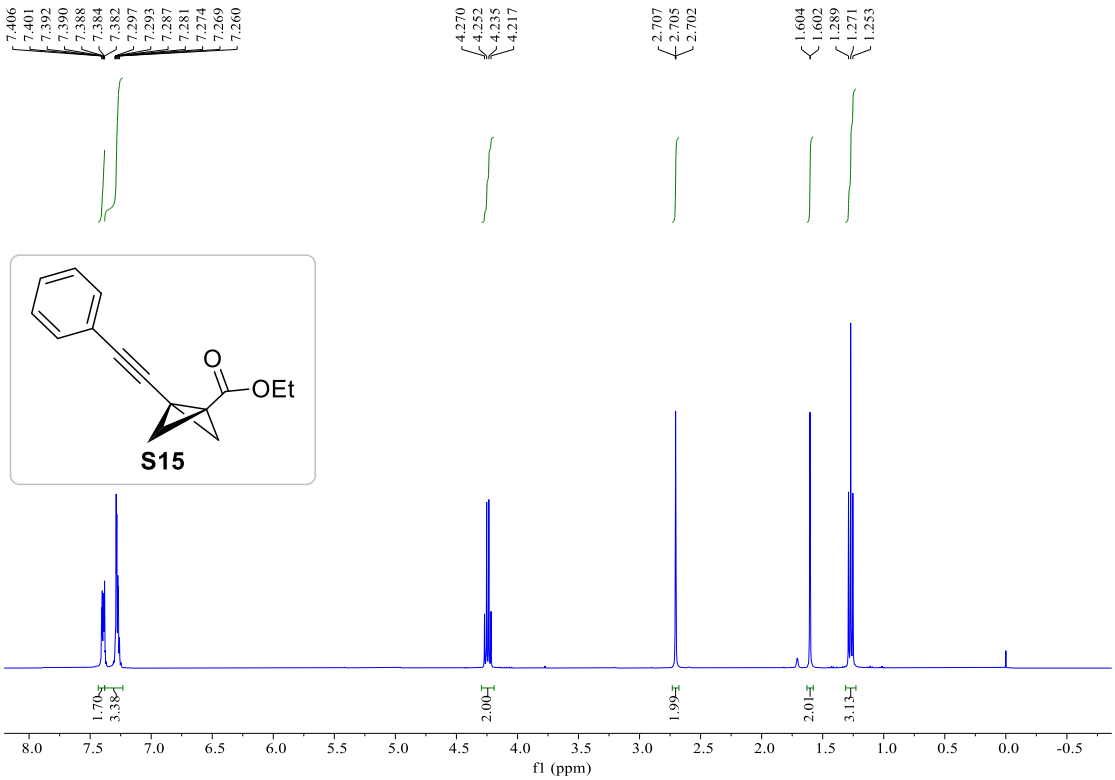
S14, ^{1}H NMR (400 MHz, $CDCl_3$)



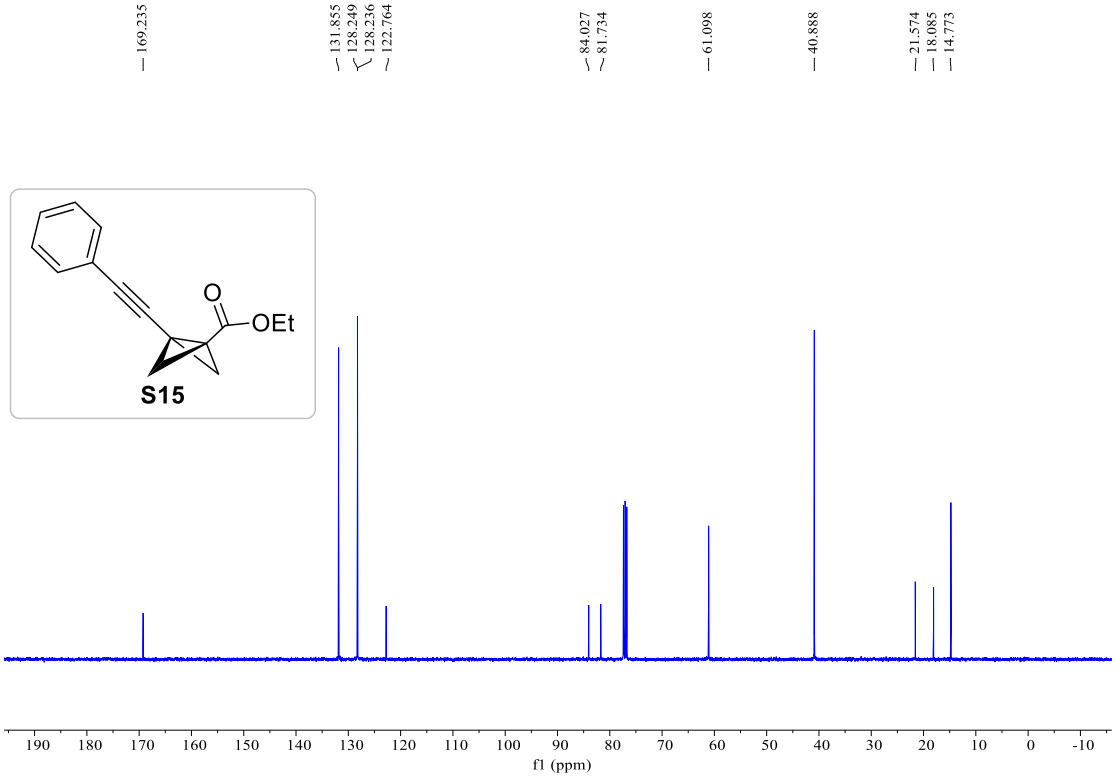
S14, ^{13}C NMR (101 MHz, $CDCl_3$)



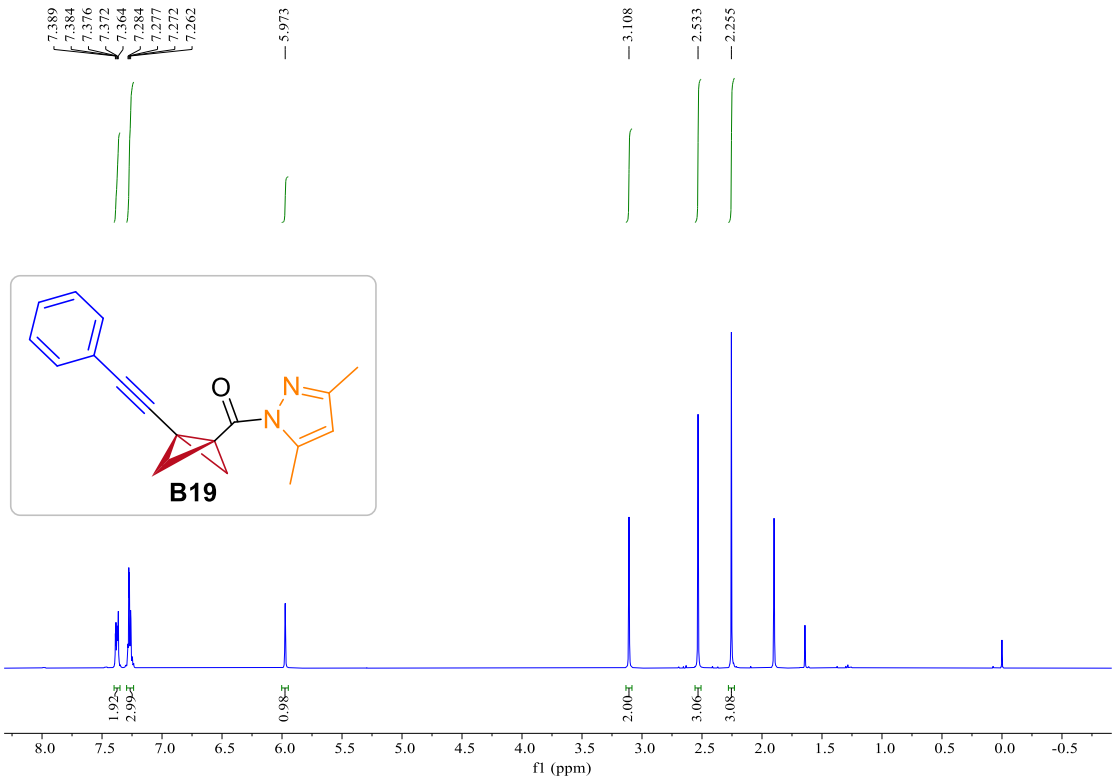
S15, ^{1}H NMR (400 MHz, $CDCl_3$)



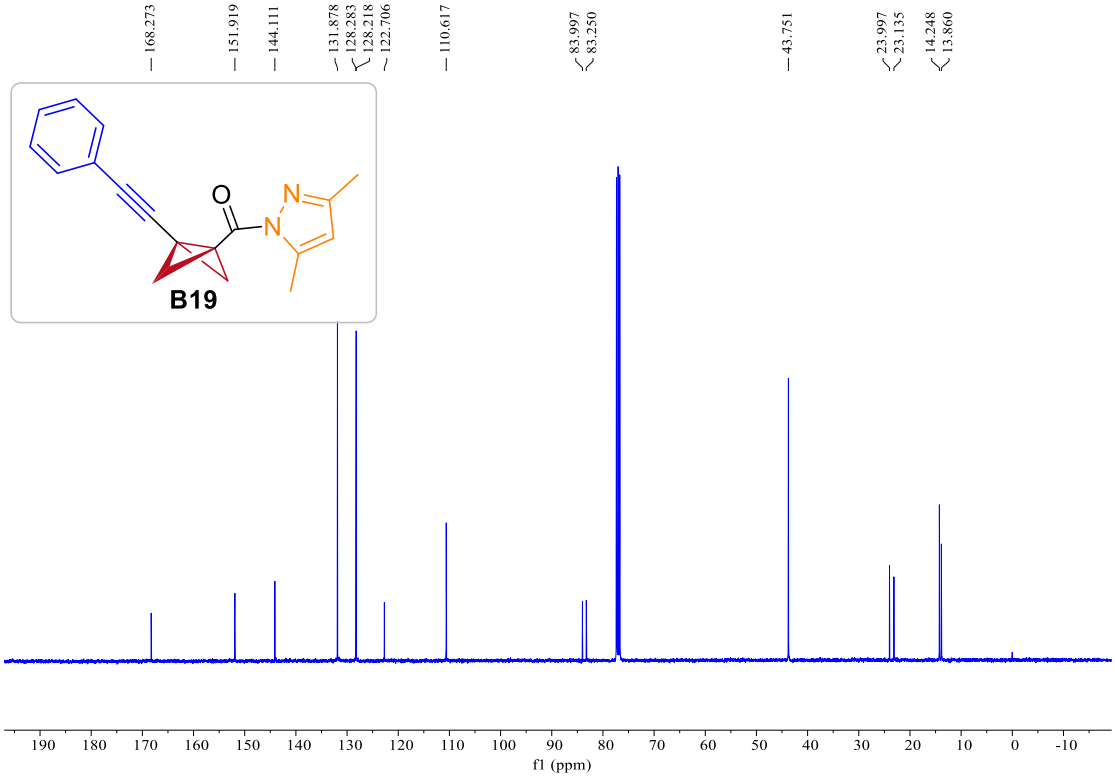
S15, ^{13}C NMR (101 MHz, $CDCl_3$)



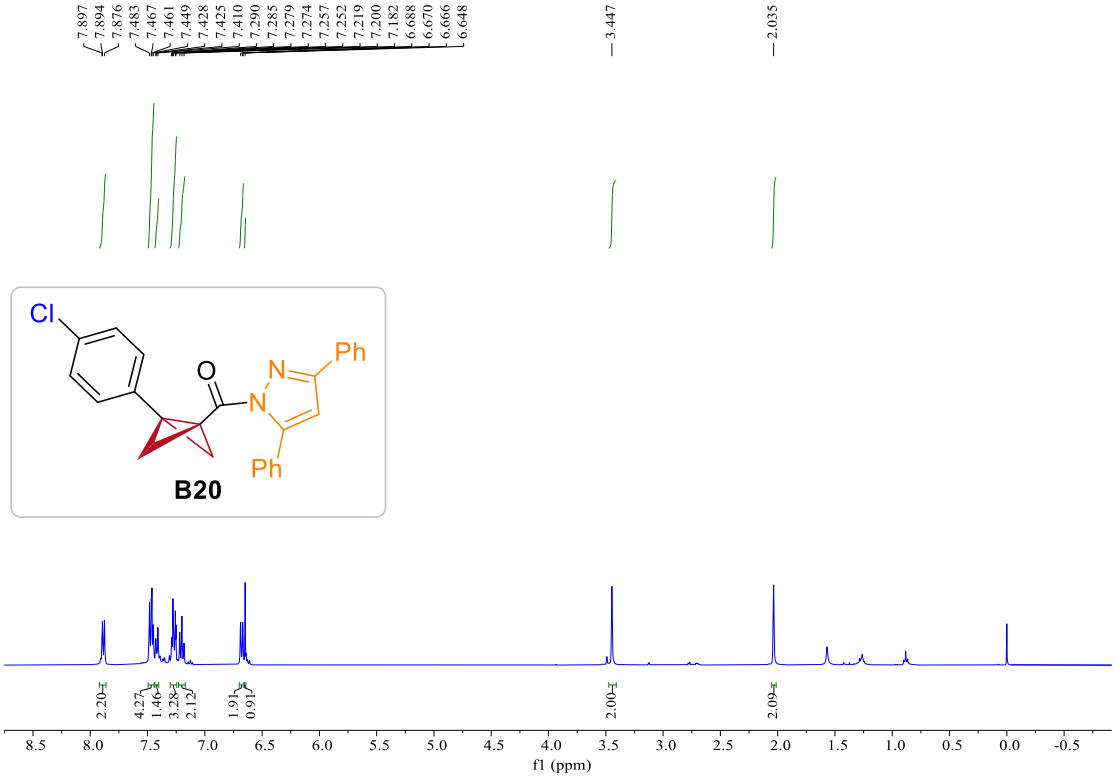
B19, ^{1}H NMR (400 MHz, $CDCl_3$)



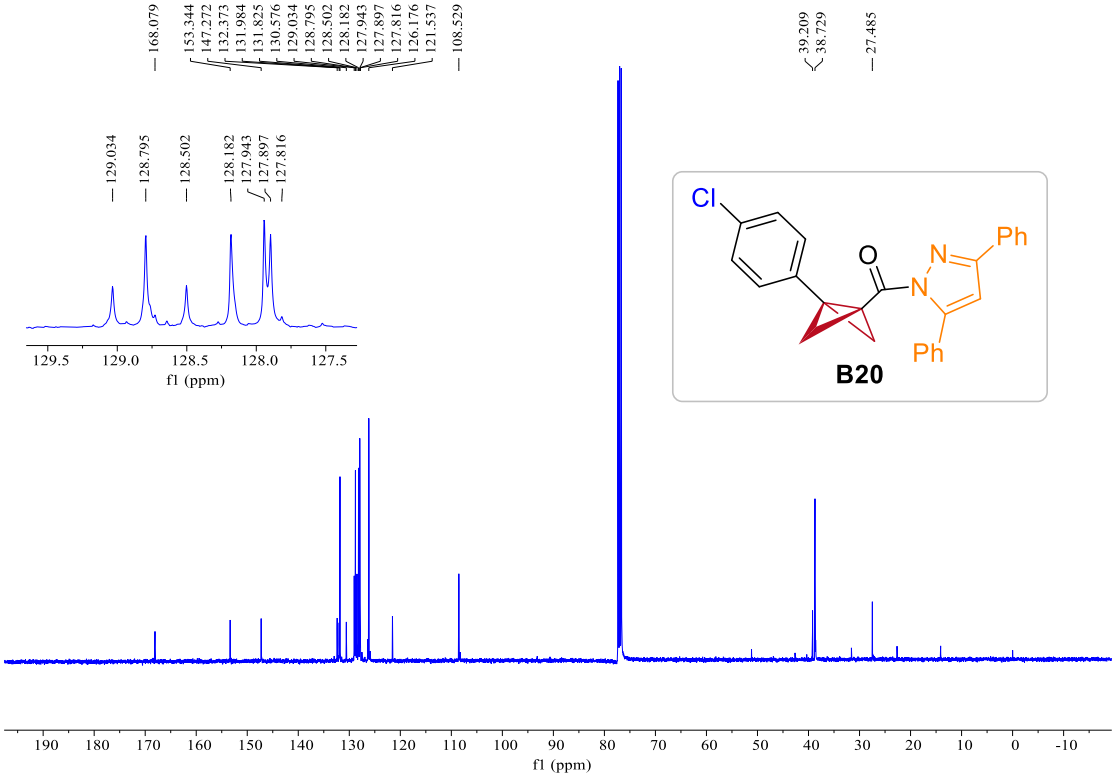
B19, ^{13}C NMR (101 MHz, $CDCl_3$)



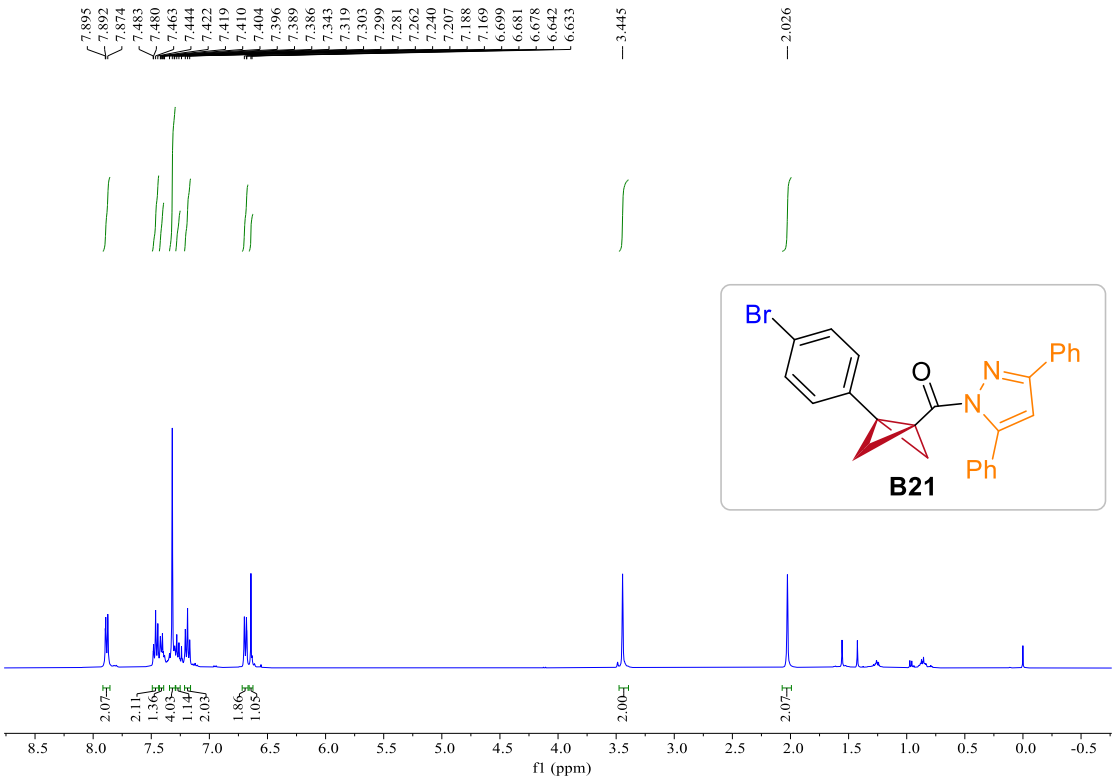
B20, ^{1}H NMR (400 MHz, $CDCl_3$)



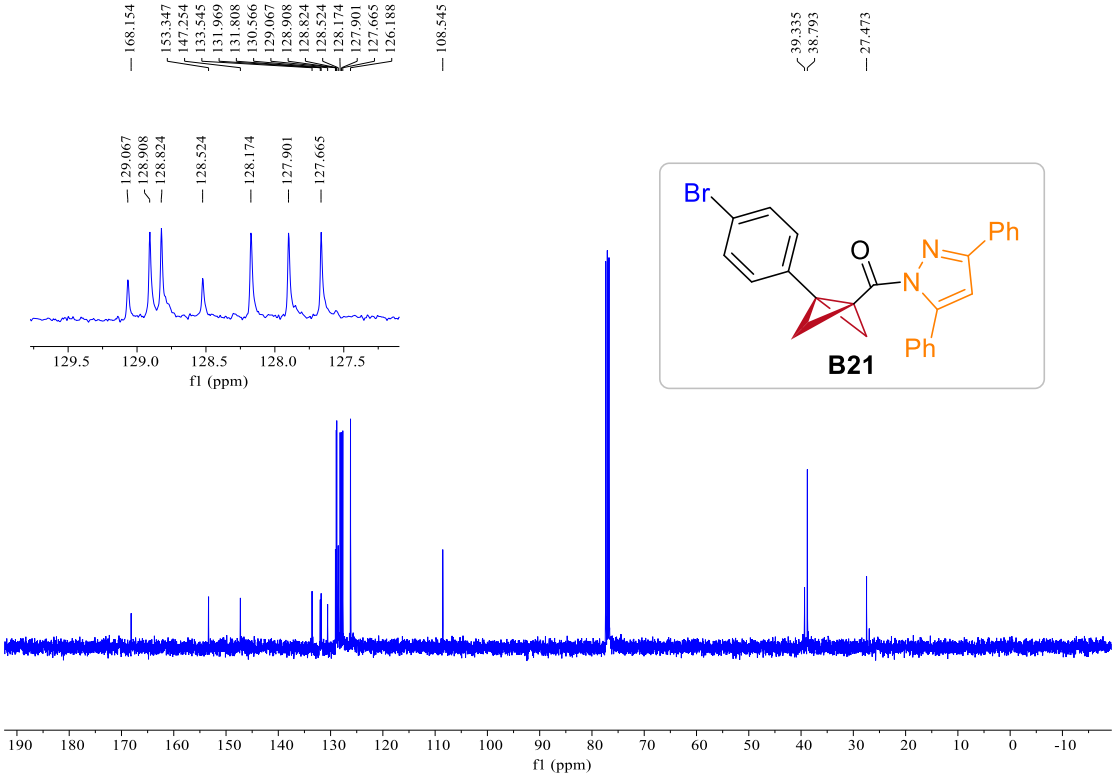
B20, ^{13}C NMR (101 MHz, $CDCl_3$)



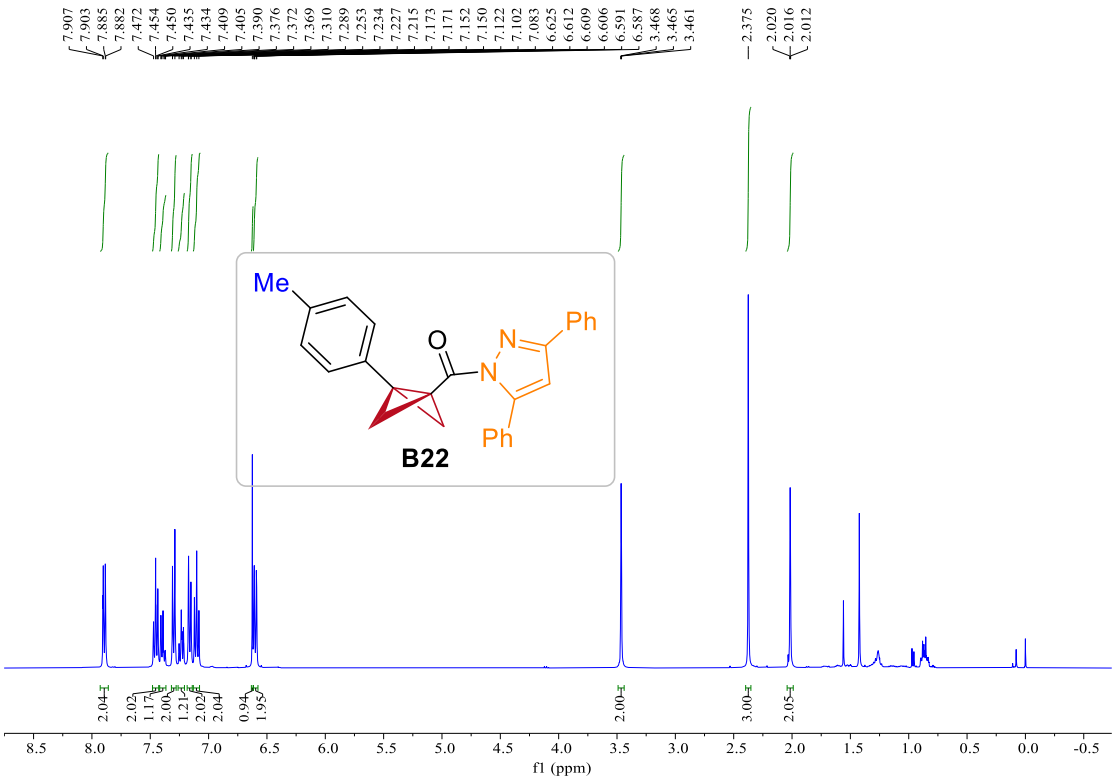
B21, ^{1}H NMR (400 MHz, $CDCl_3$)



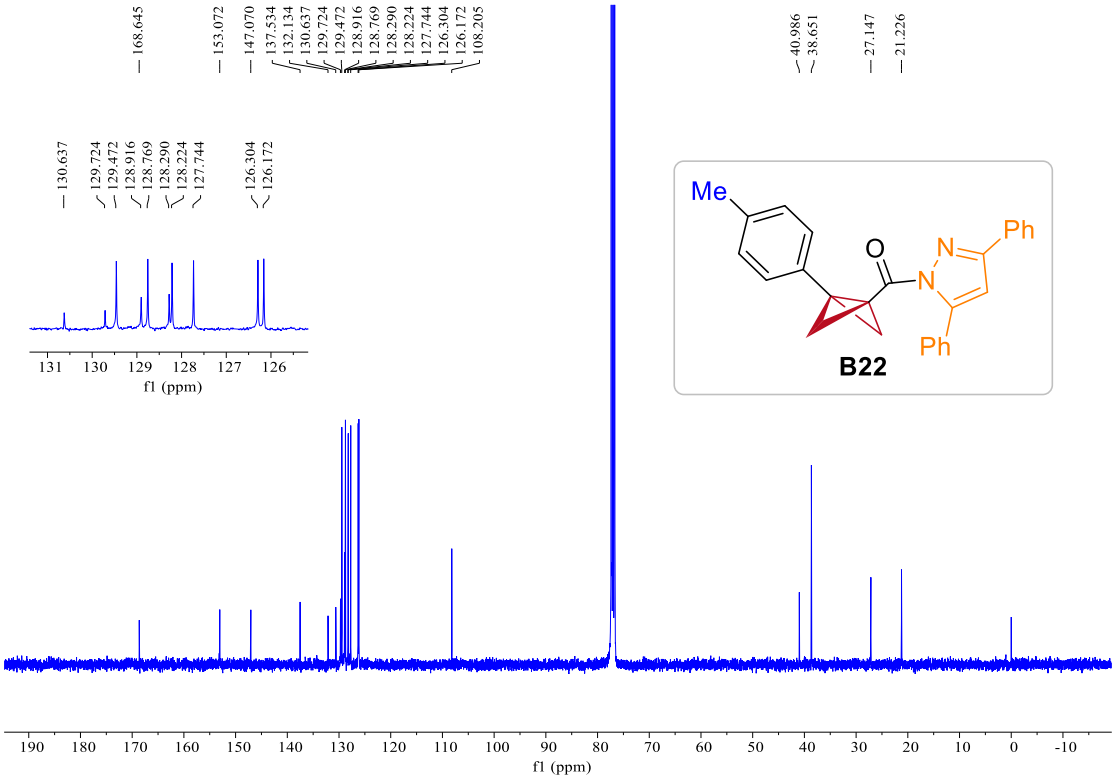
B21, ^{13}C NMR (101 MHz, $CDCl_3$)



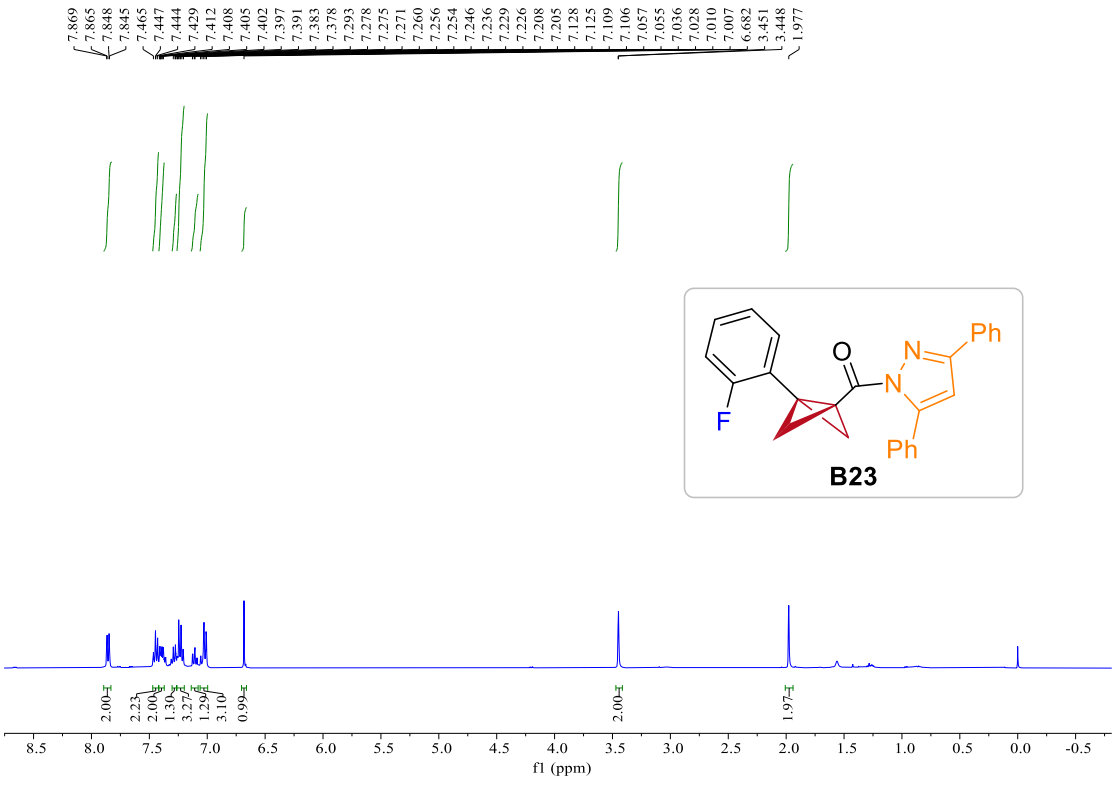
B22, ^{1}H NMR (400 MHz, $CDCl_3$)



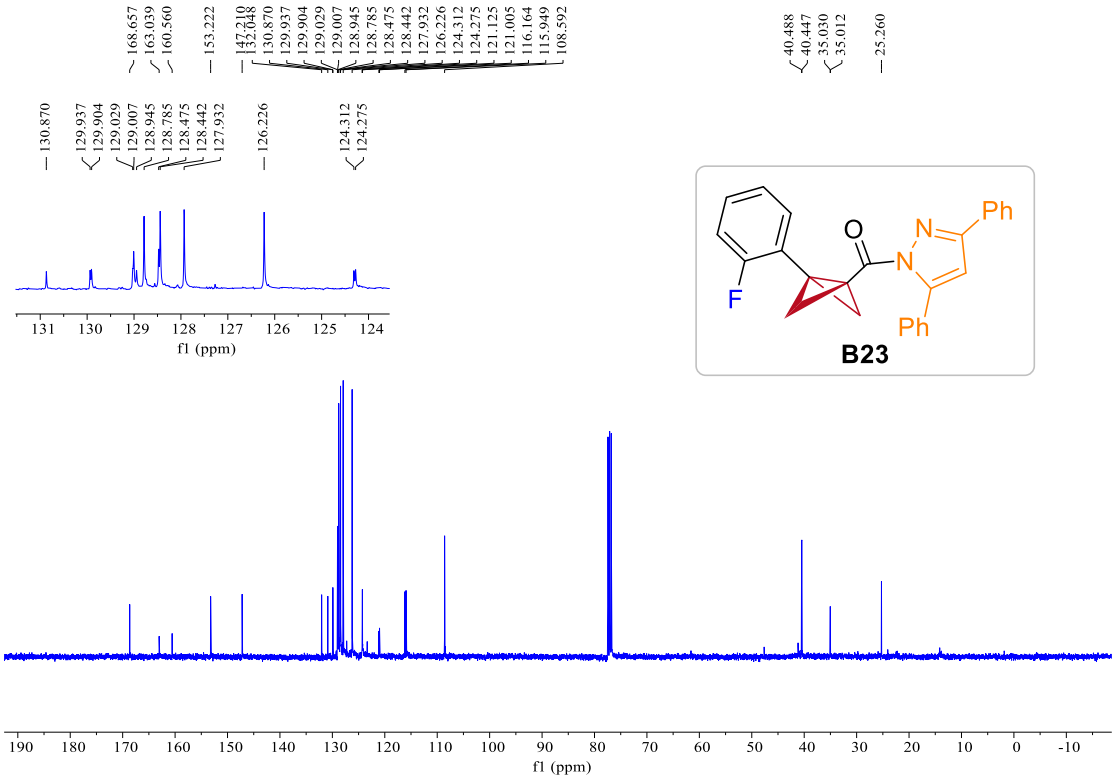
B22, ^{13}C NMR (101 MHz, $CDCl_3$)



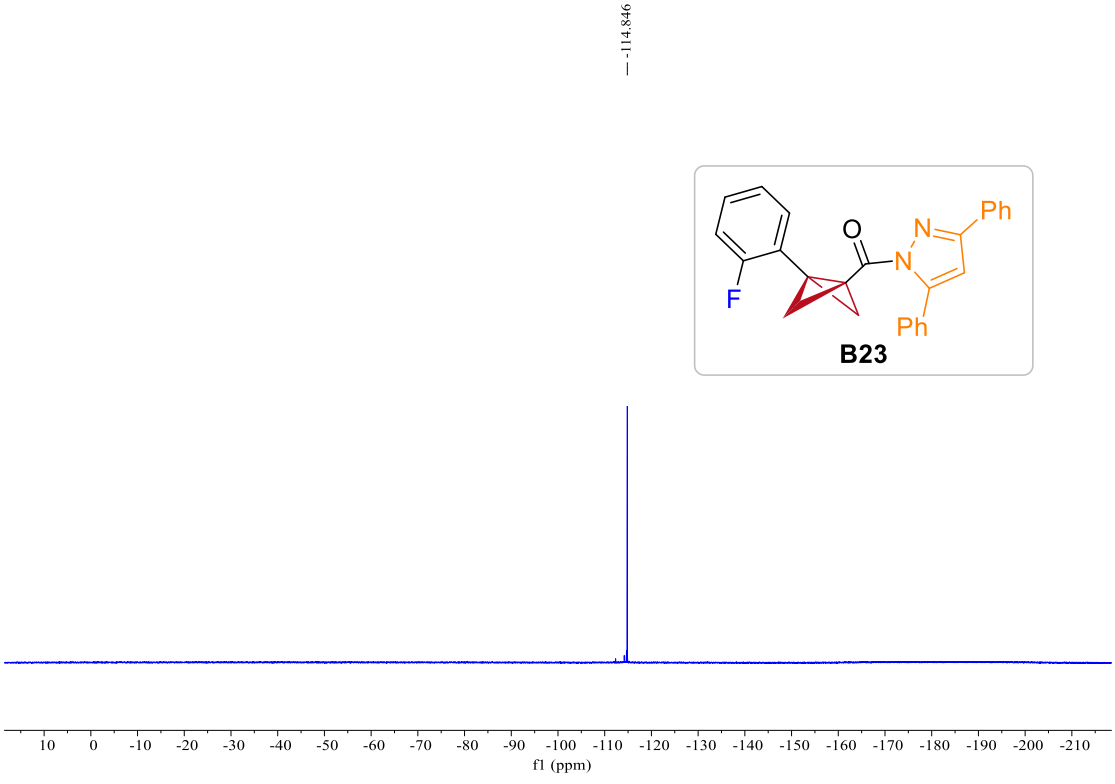
B23, ^{1}H NMR (400 MHz, $CDCl_3$)



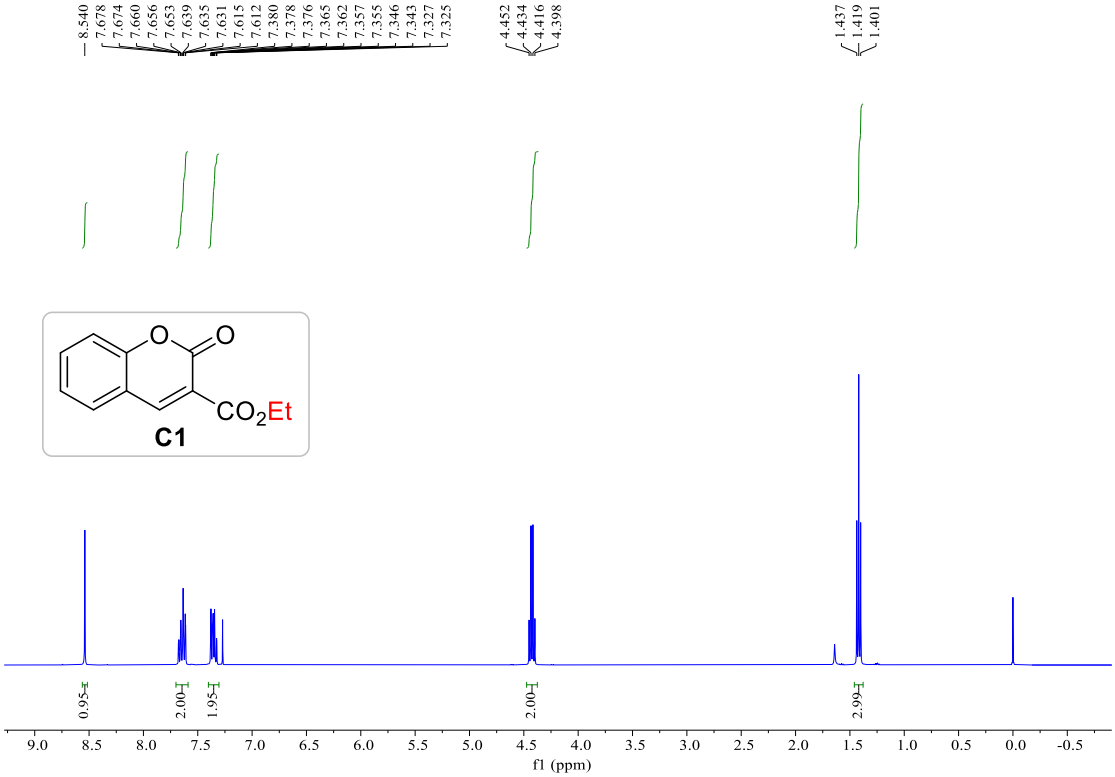
B23, ^{13}C NMR (101 MHz, $CDCl_3$)



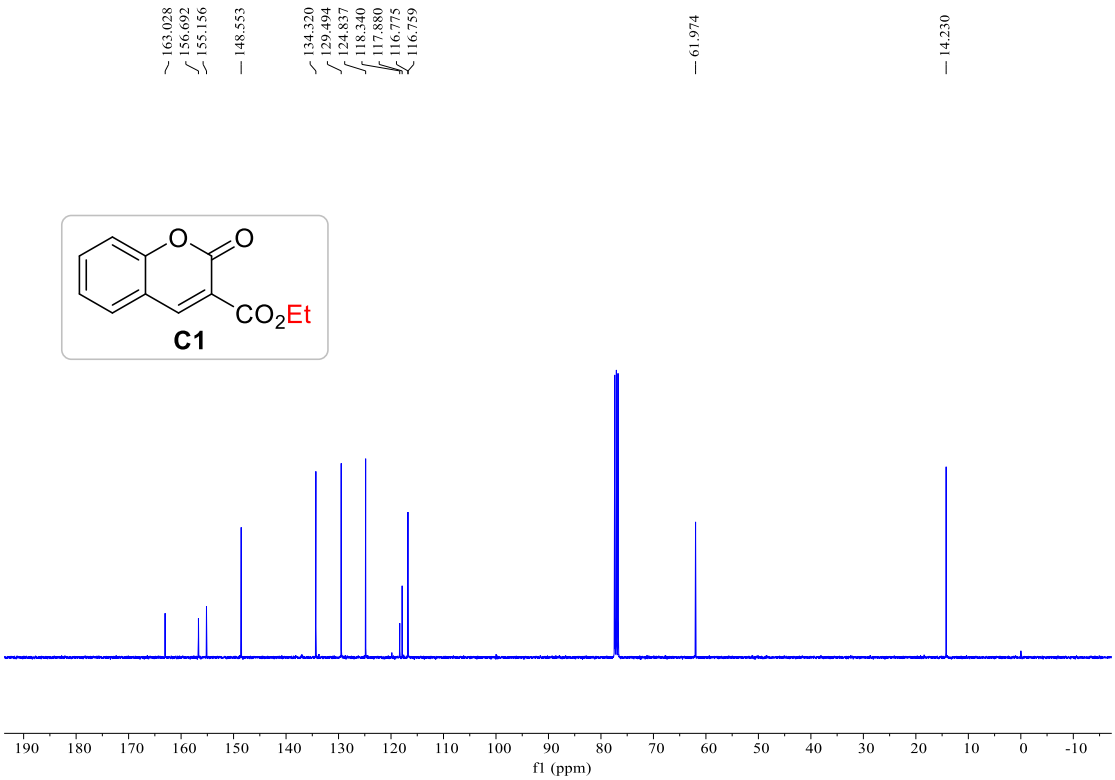
B23, ^{19}F NMR (376 MHz, $CDCl_3$)



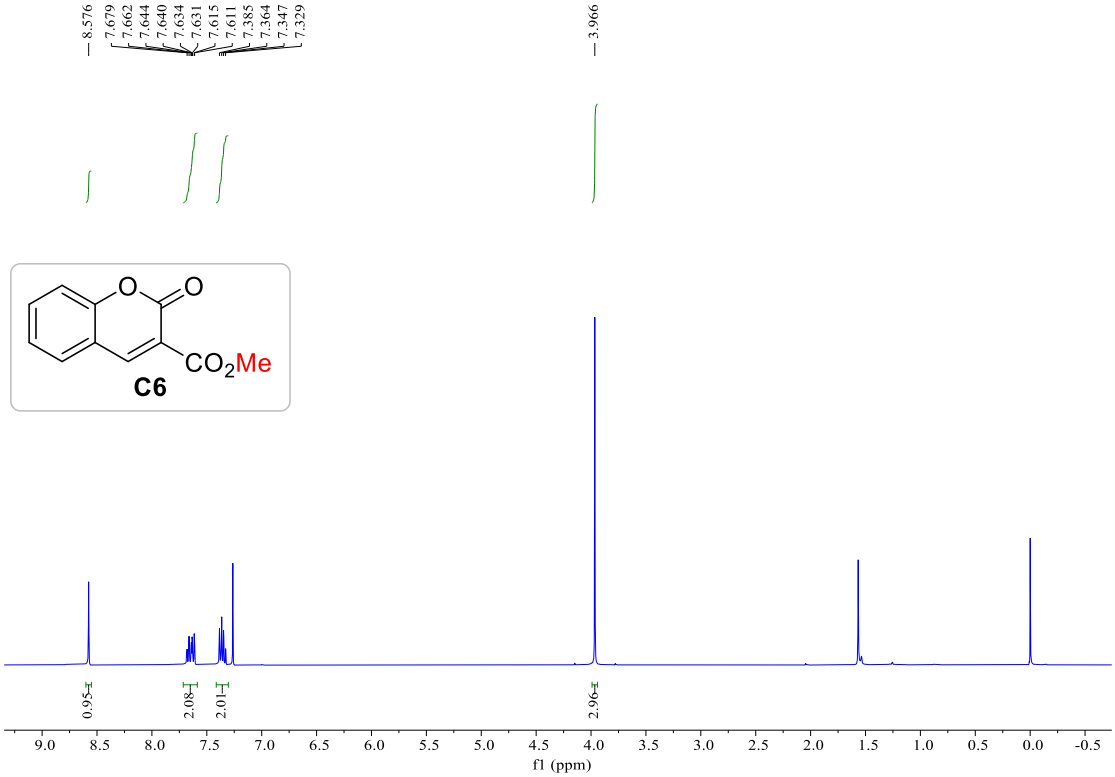
C1, ^{1}H NMR (400 MHz, $CDCl_3$)



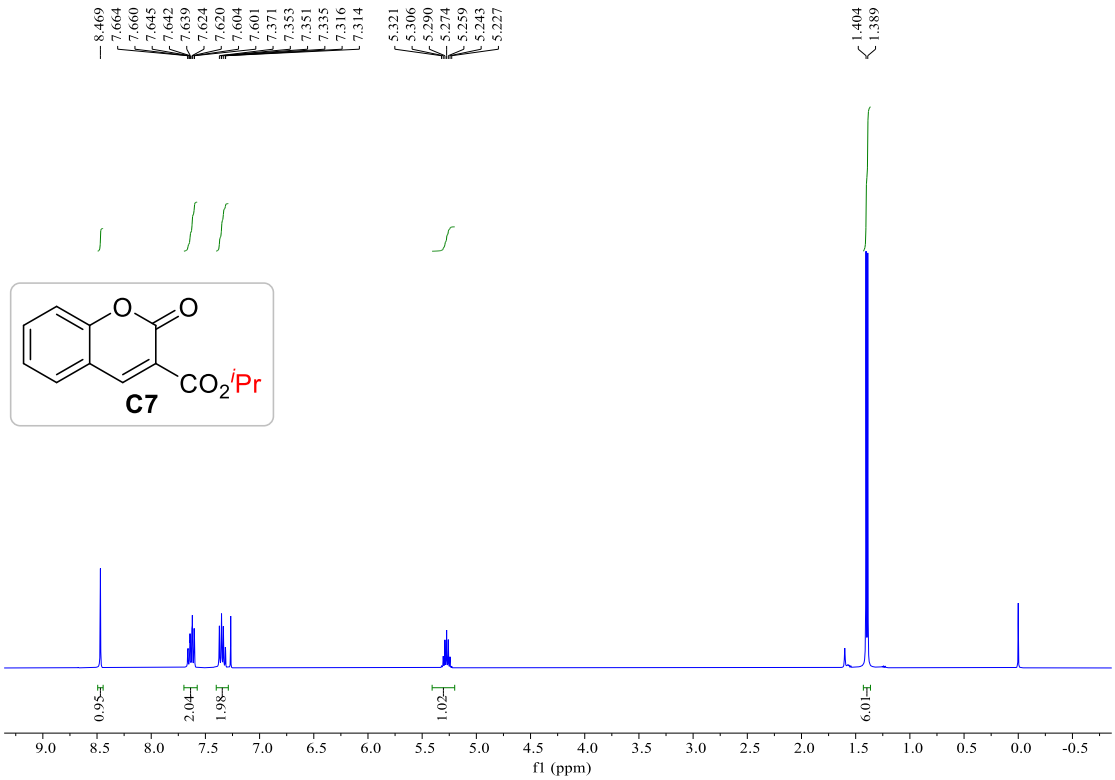
C1, ^{13}C NMR (101 MHz, $CDCl_3$)



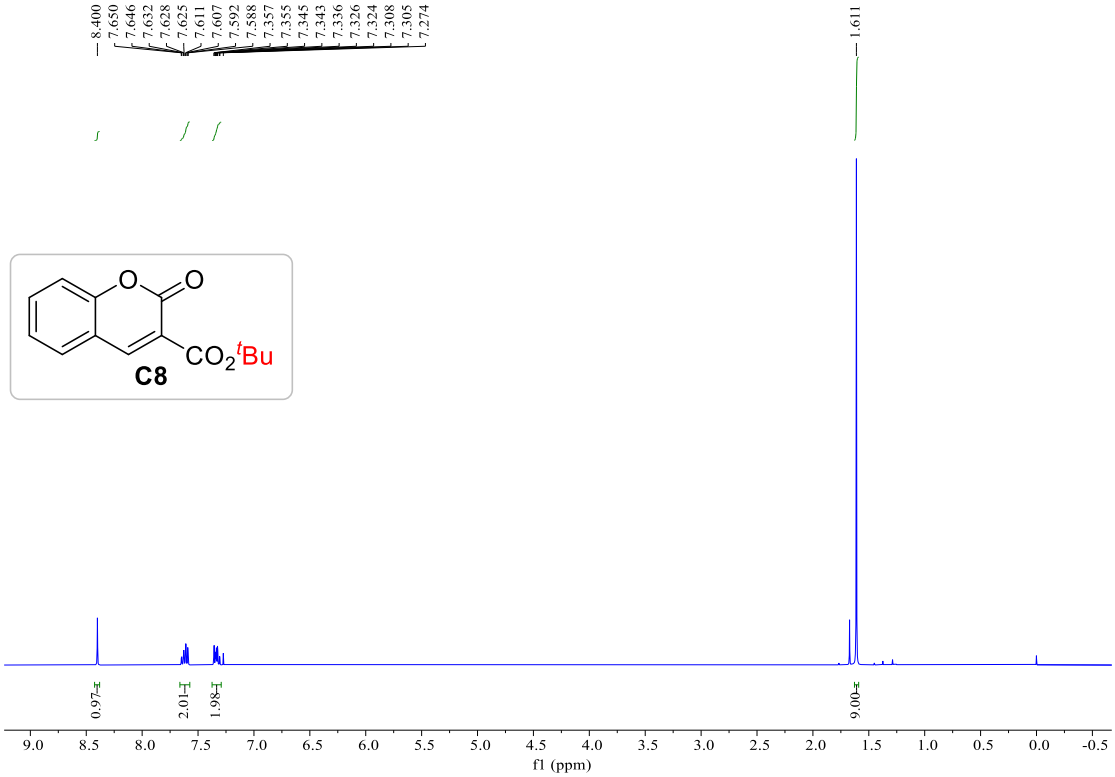
C6, ^{1}H NMR (400 MHz, $CDCl_3$)



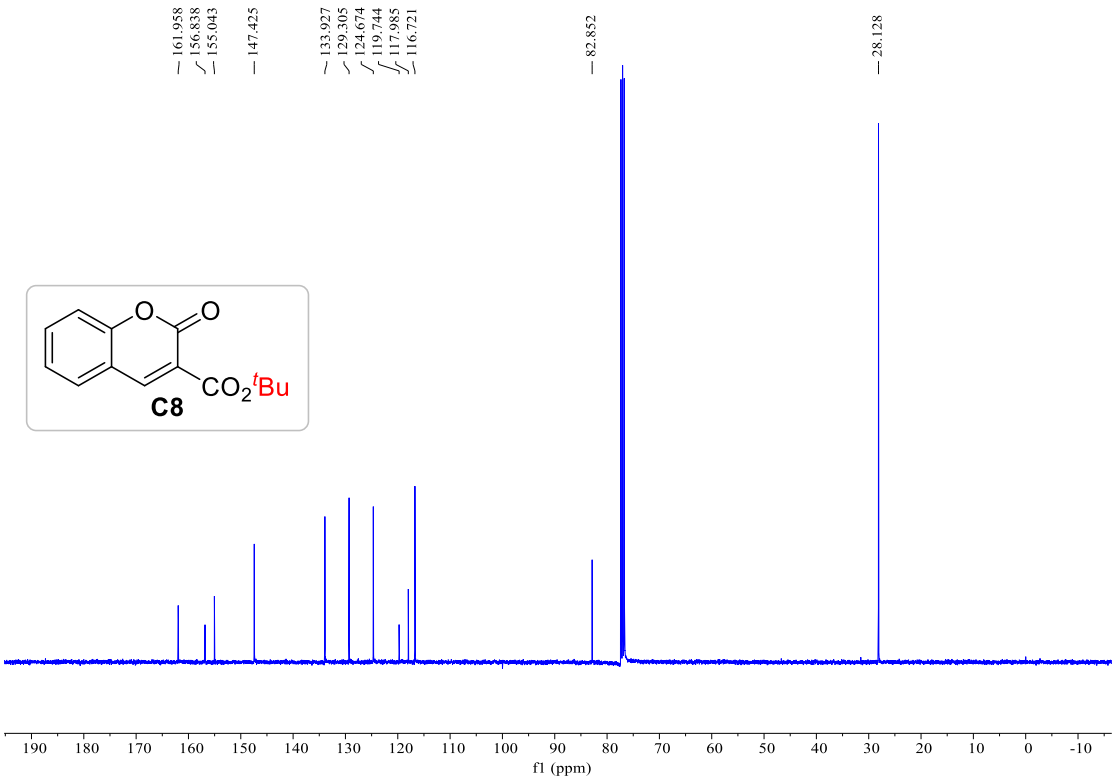
C7, ^{1}H NMR (400 MHz, $CDCl_3$)



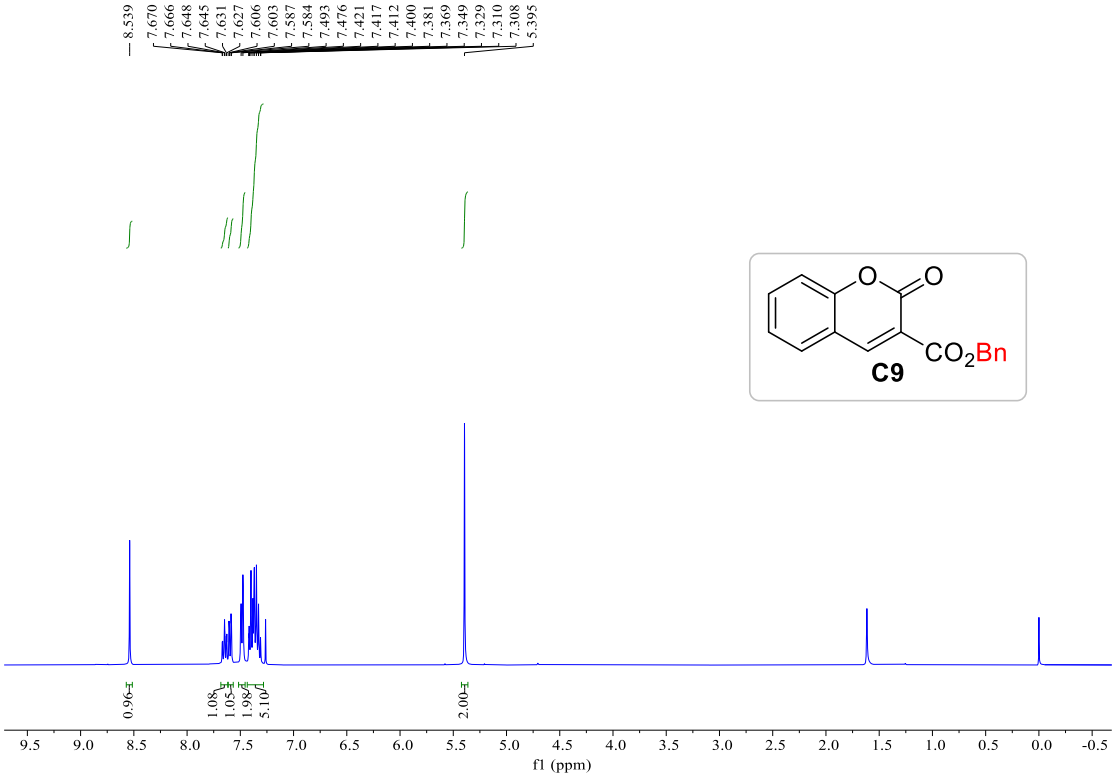
C8, ^{1}H NMR (400 MHz, $CDCl_3$)



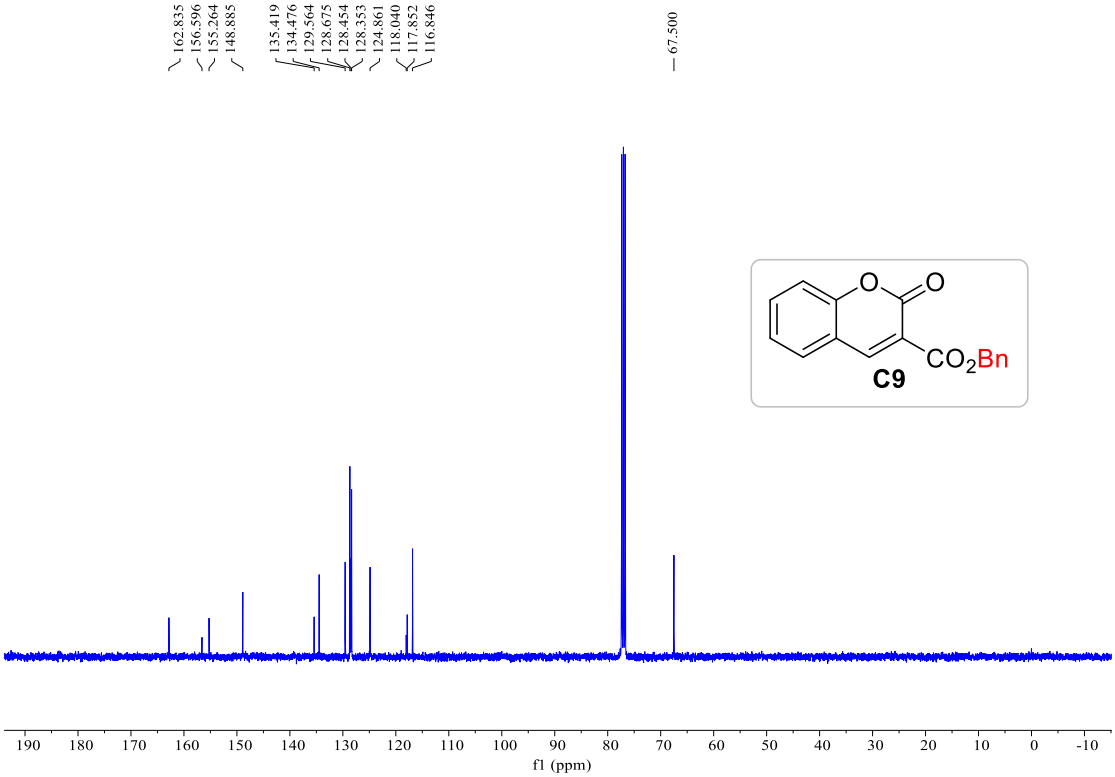
C8, ^{13}C NMR (101 MHz, $CDCl_3$)



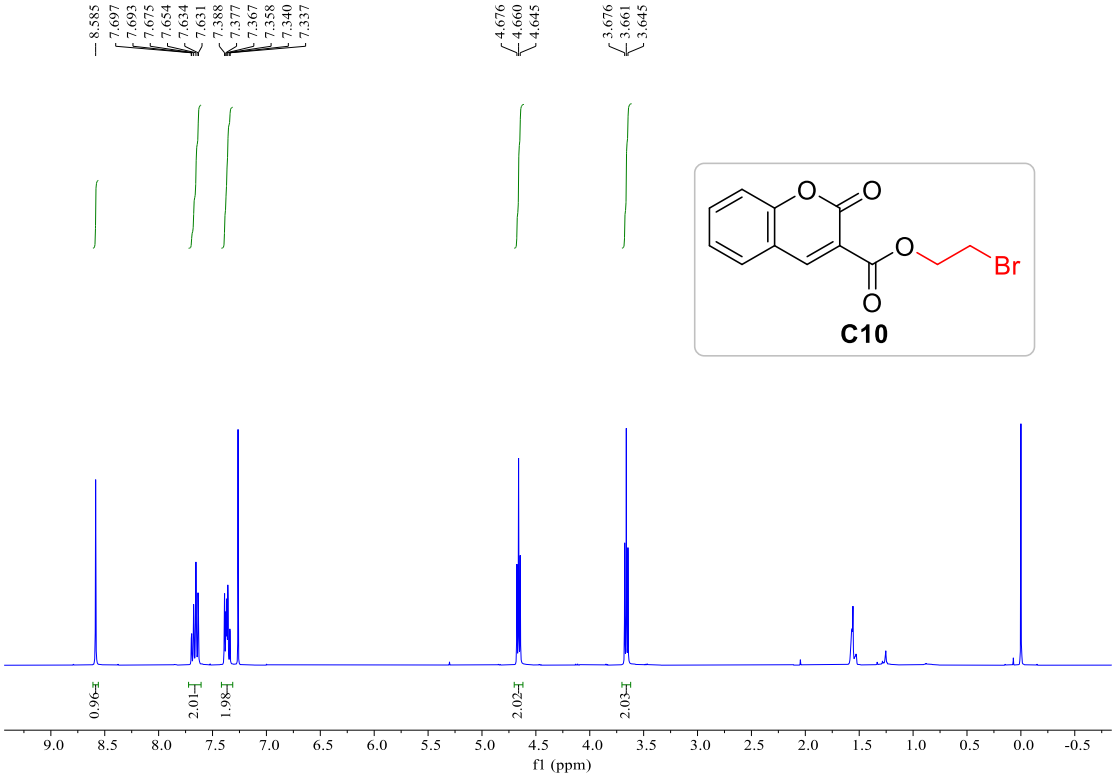
C9, ^{1}H NMR (400 MHz, $CDCl_3$)



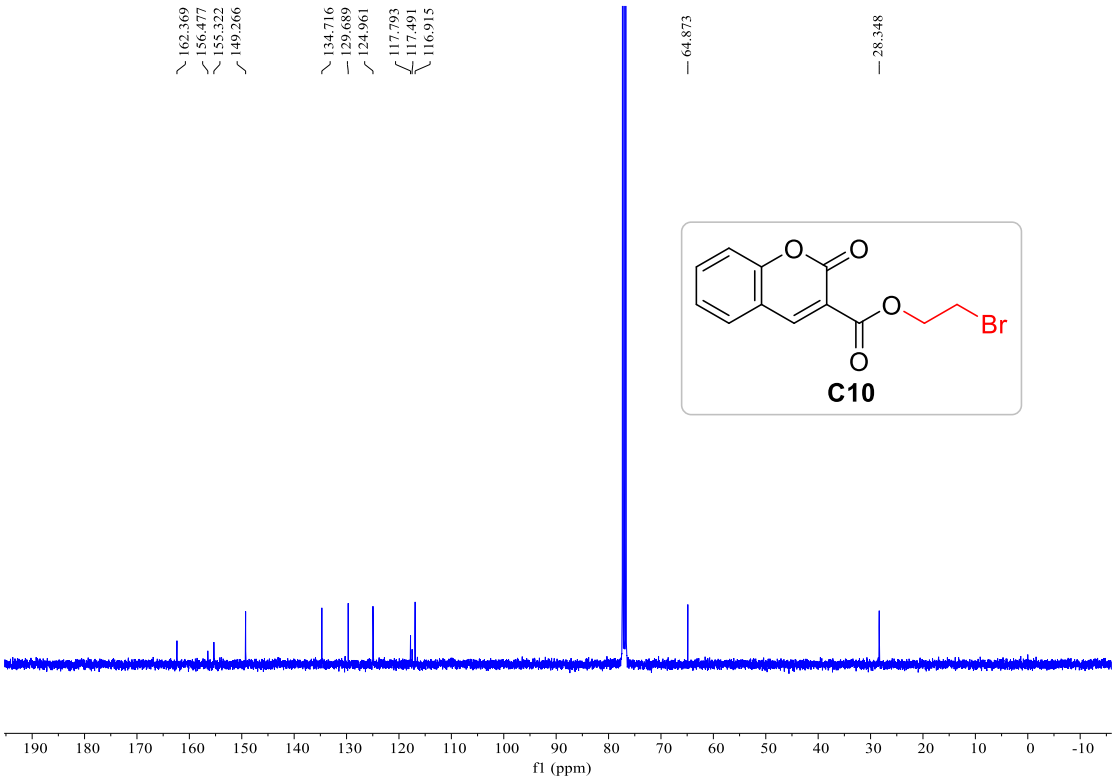
C9, ^{13}C NMR (101 MHz, $CDCl_3$)



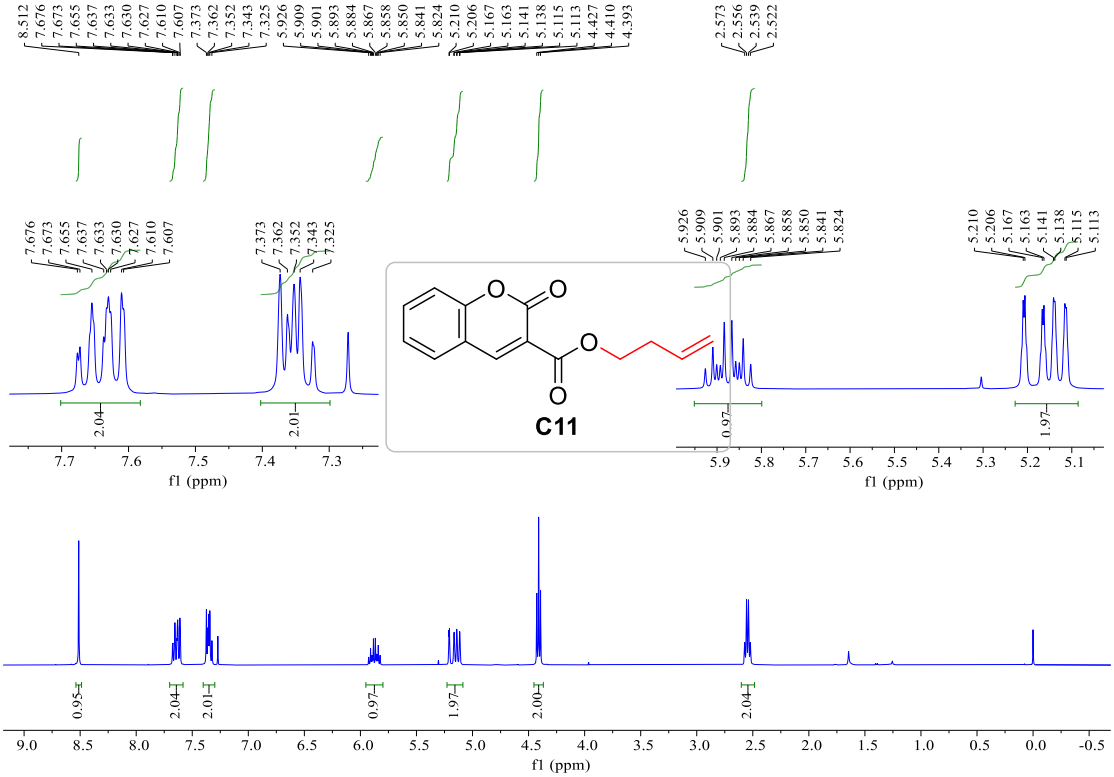
C10, ^{1}H NMR (400 MHz, $CDCl_3$)



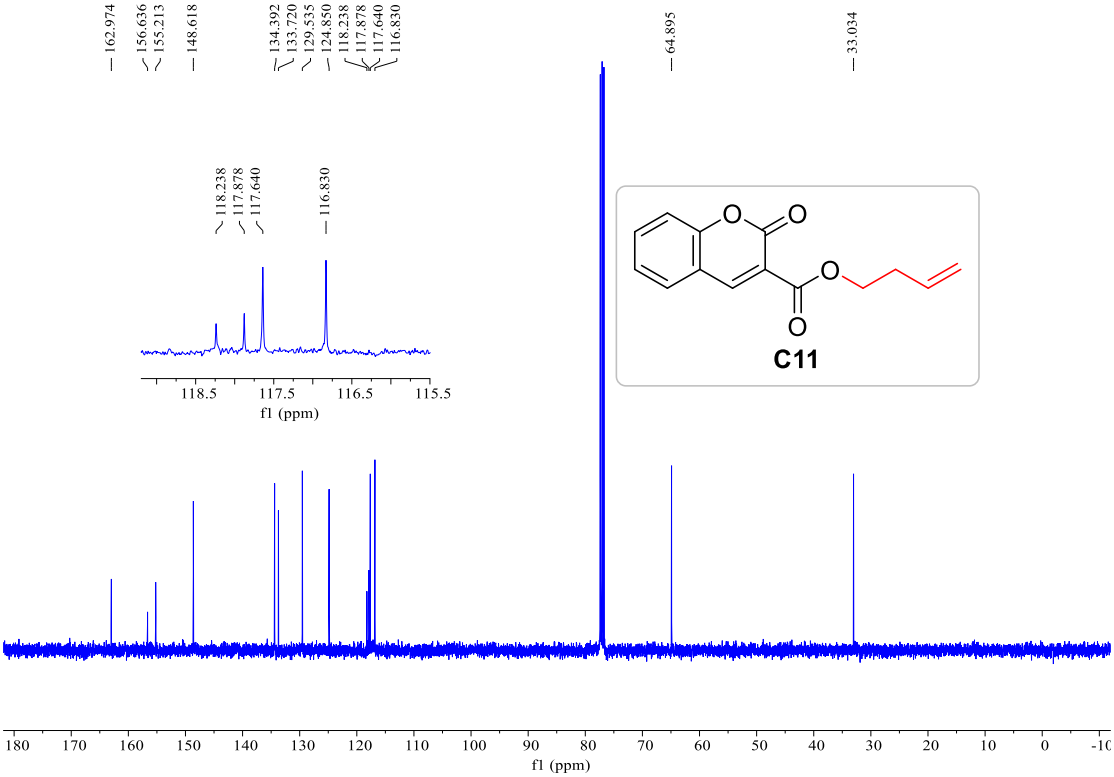
C10, ^{13}C NMR (101 MHz, $CDCl_3$)



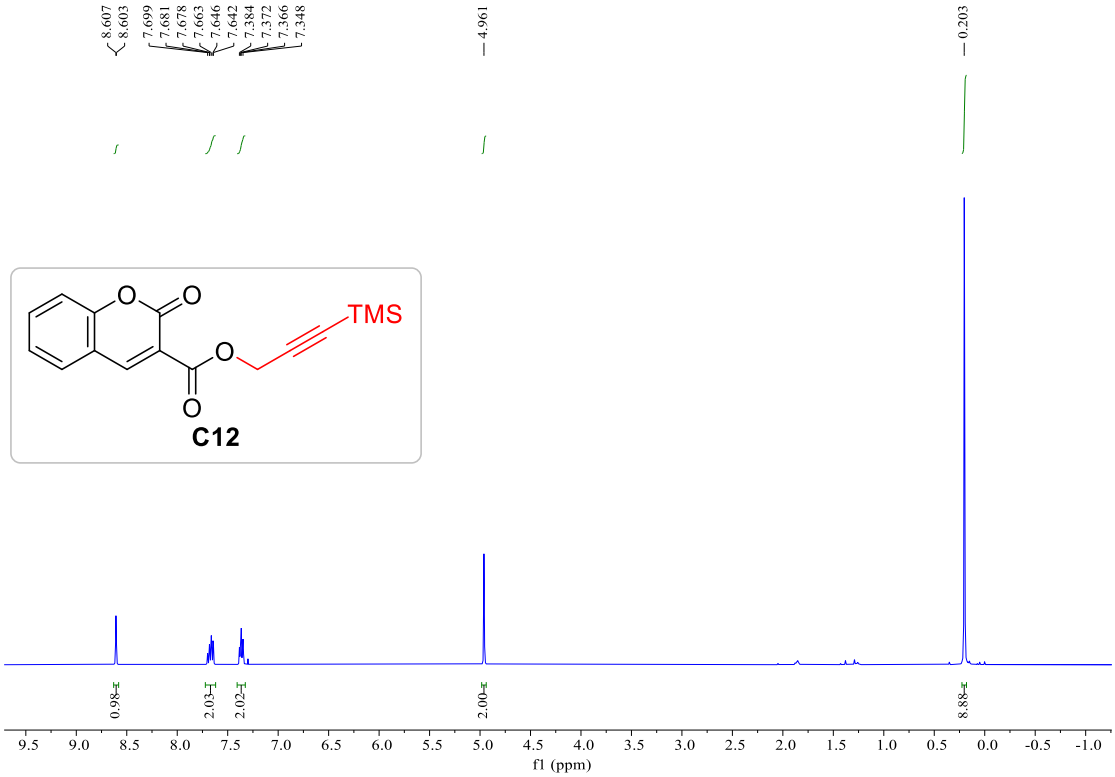
C11, ^{1}H NMR (400 MHz, $CDCl_3$)



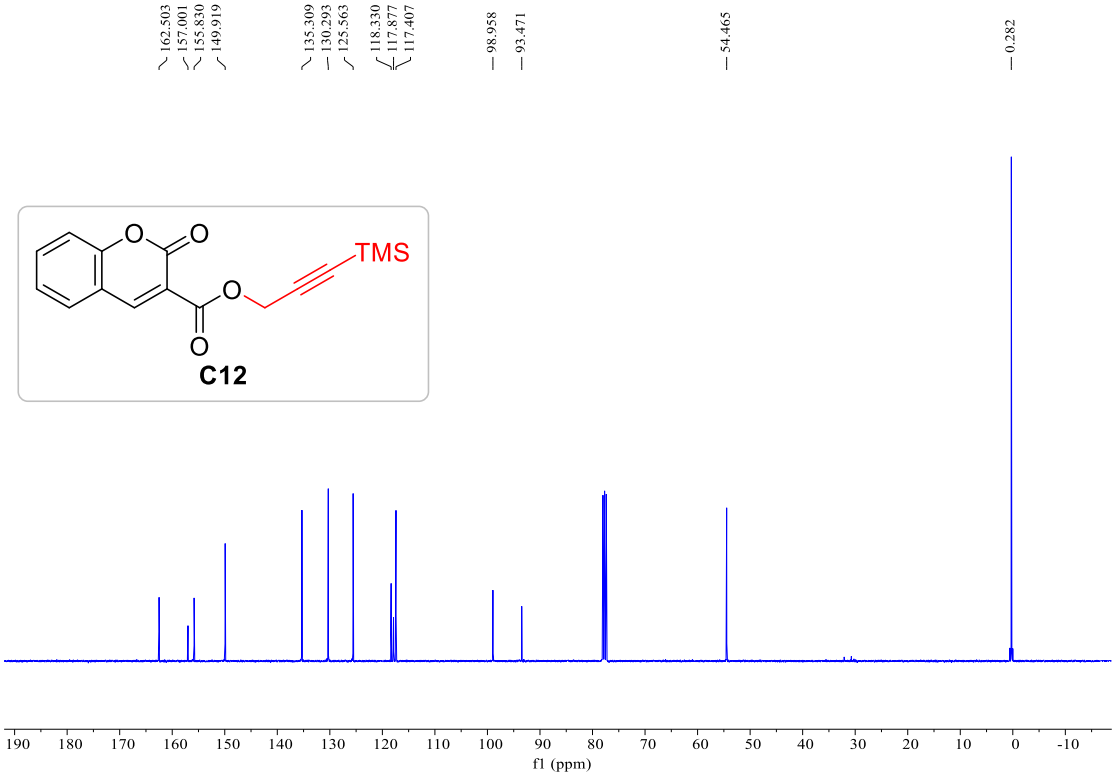
C11, ^{13}C NMR (101 MHz, $CDCl_3$)



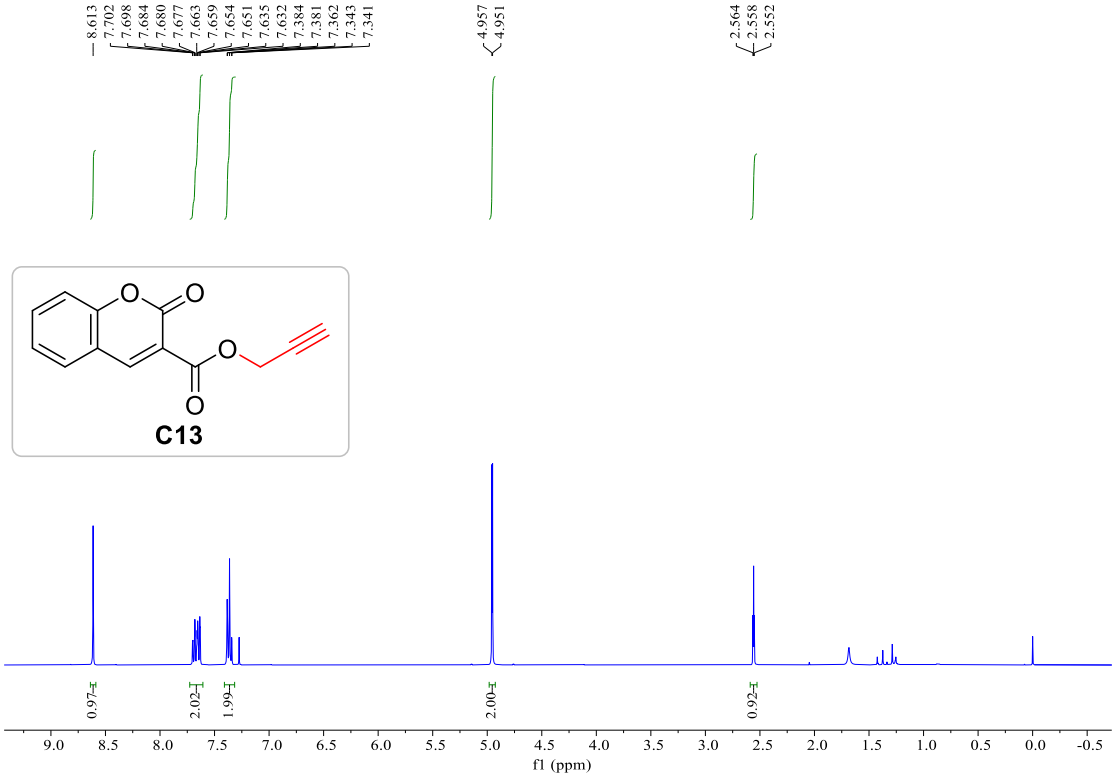
C12, ^{1}H NMR (400 MHz, $CDCl_3$)



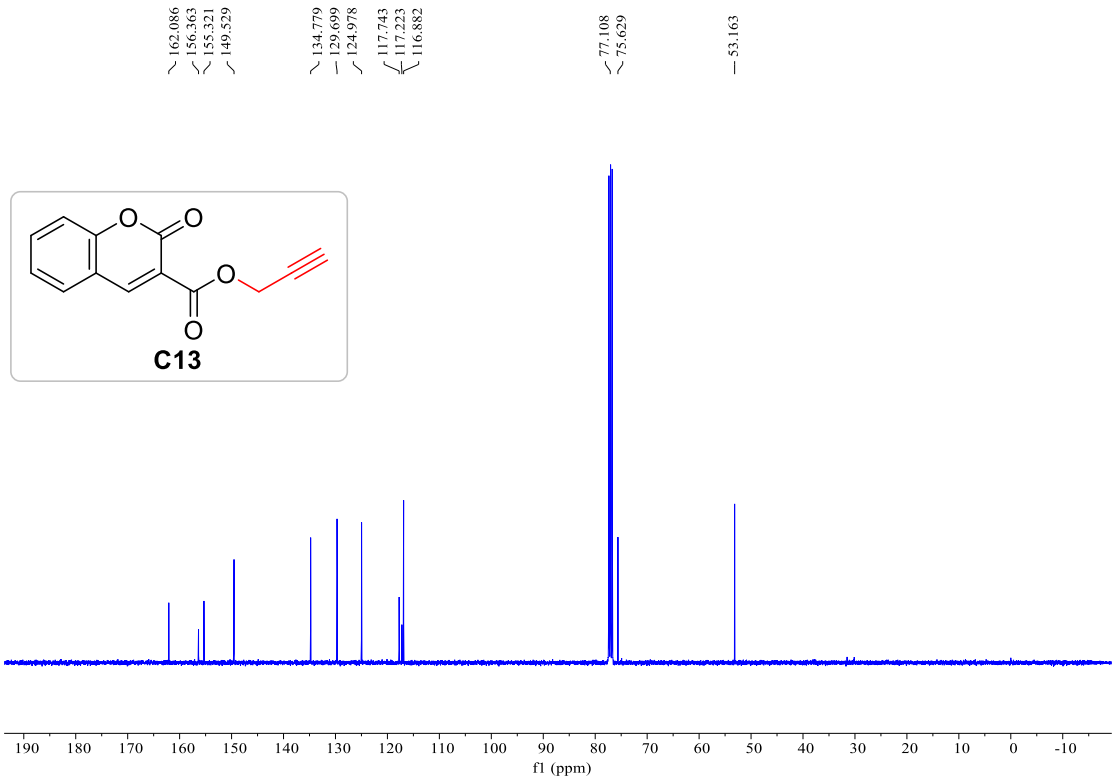
C12, ^{13}C NMR (101 MHz, $CDCl_3$)



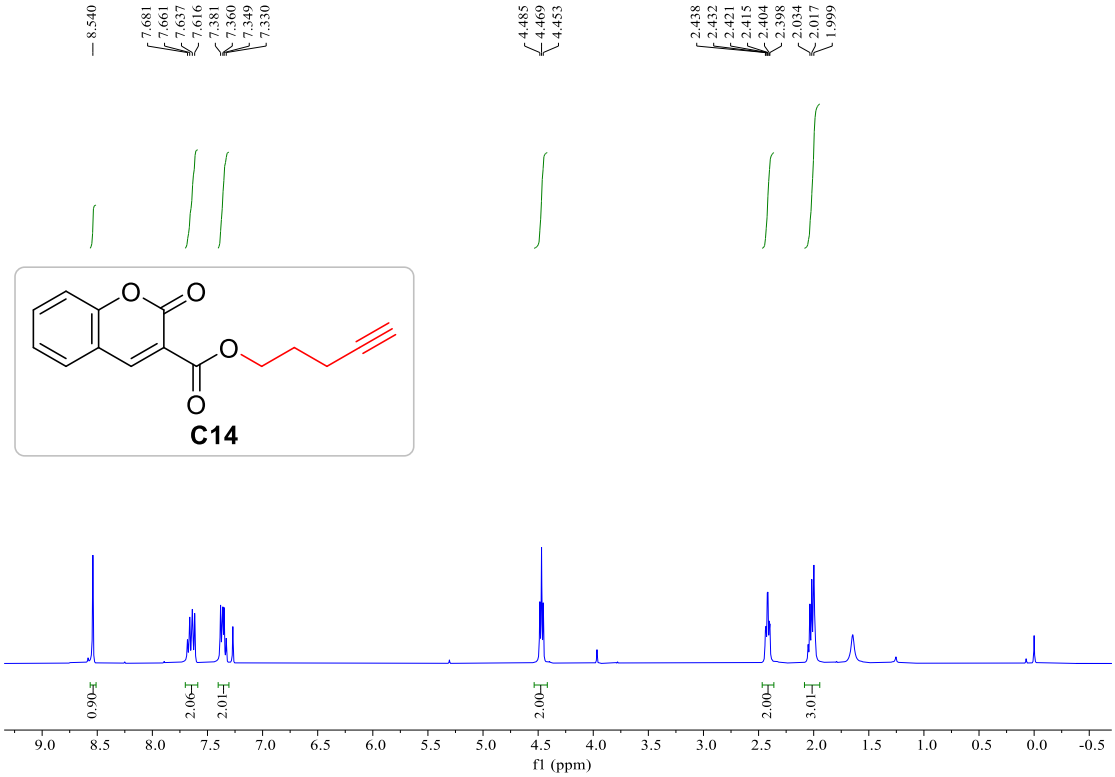
C13, ^{1}H NMR (400 MHz, $CDCl_3$)



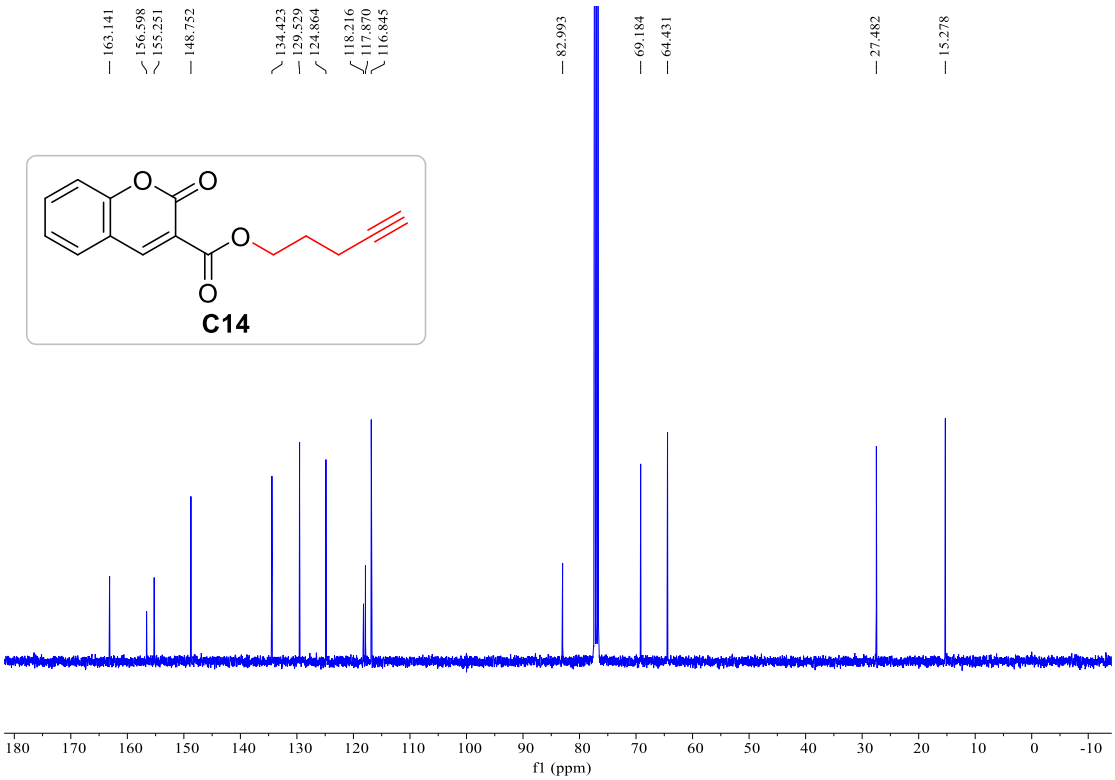
C13, ^{13}C NMR (101 MHz, $CDCl_3$)



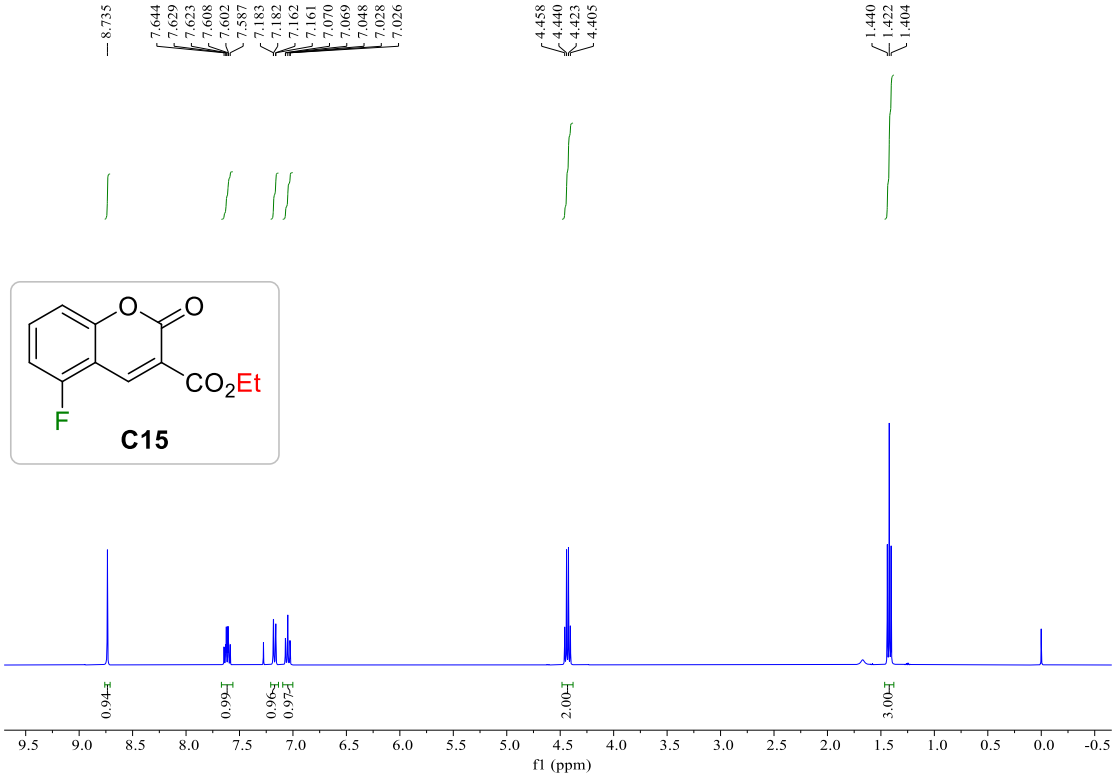
C14, ^{1}H NMR (400 MHz, $CDCl_3$)



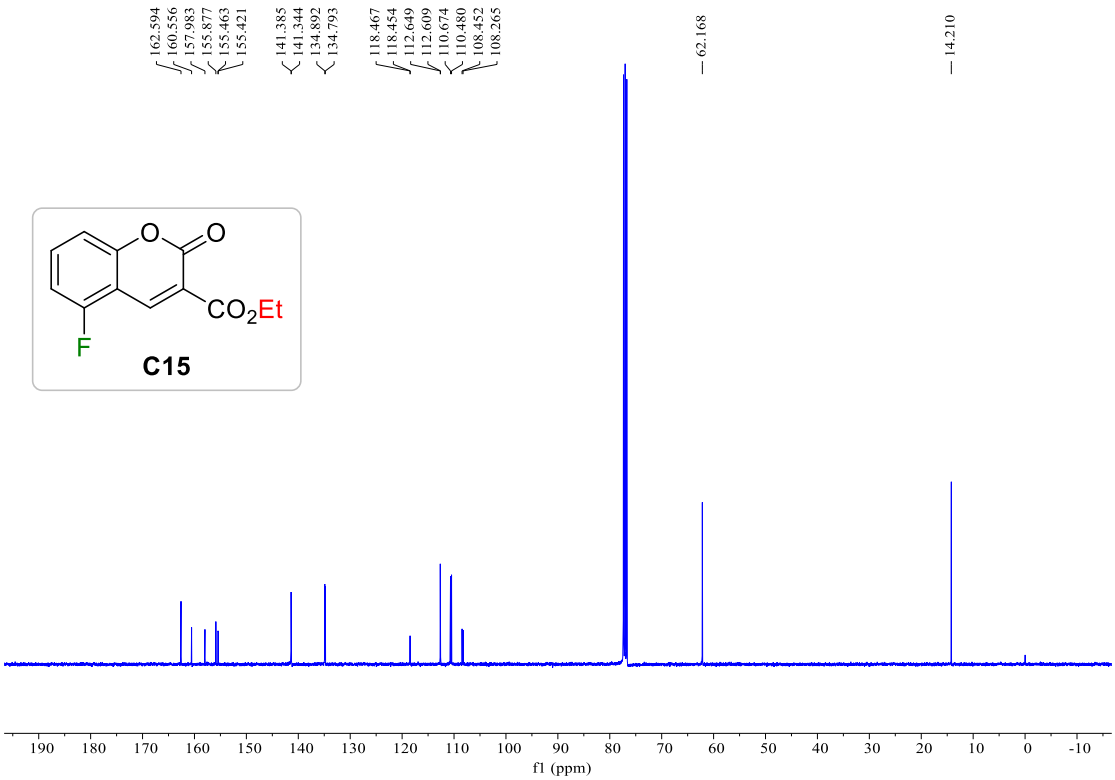
C14, ^{13}C NMR (101 MHz, $CDCl_3$)



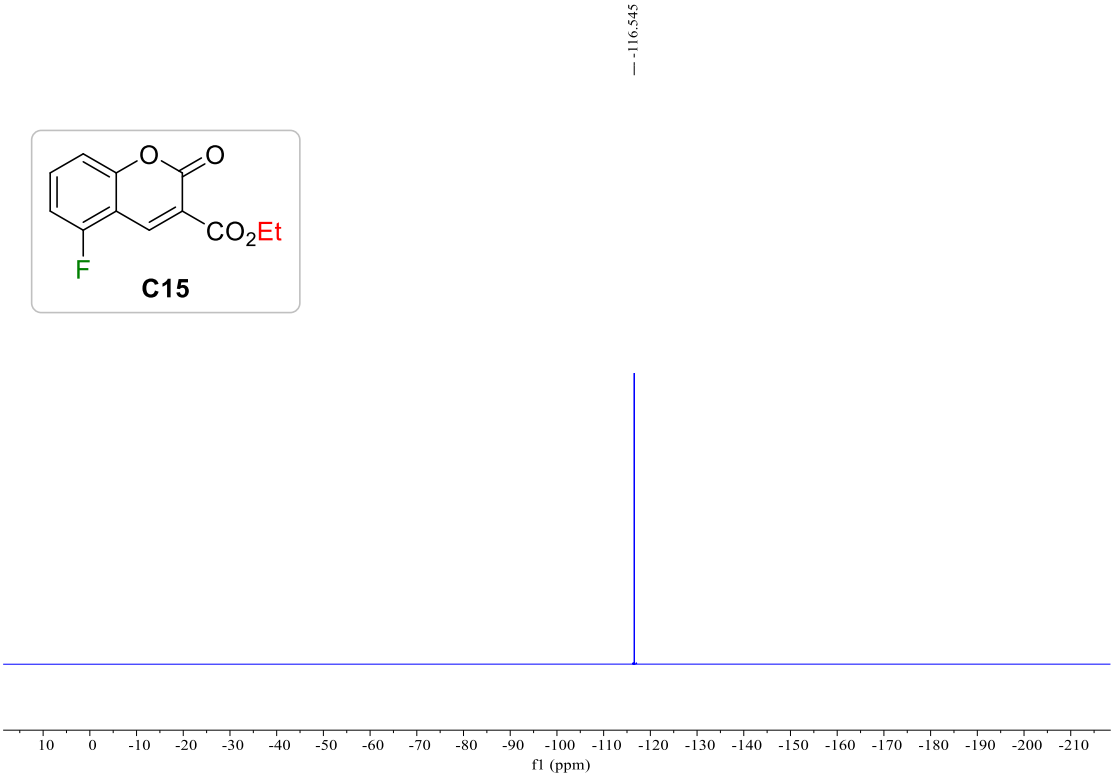
C15, ^{1}H NMR (400 MHz, $CDCl_3$)



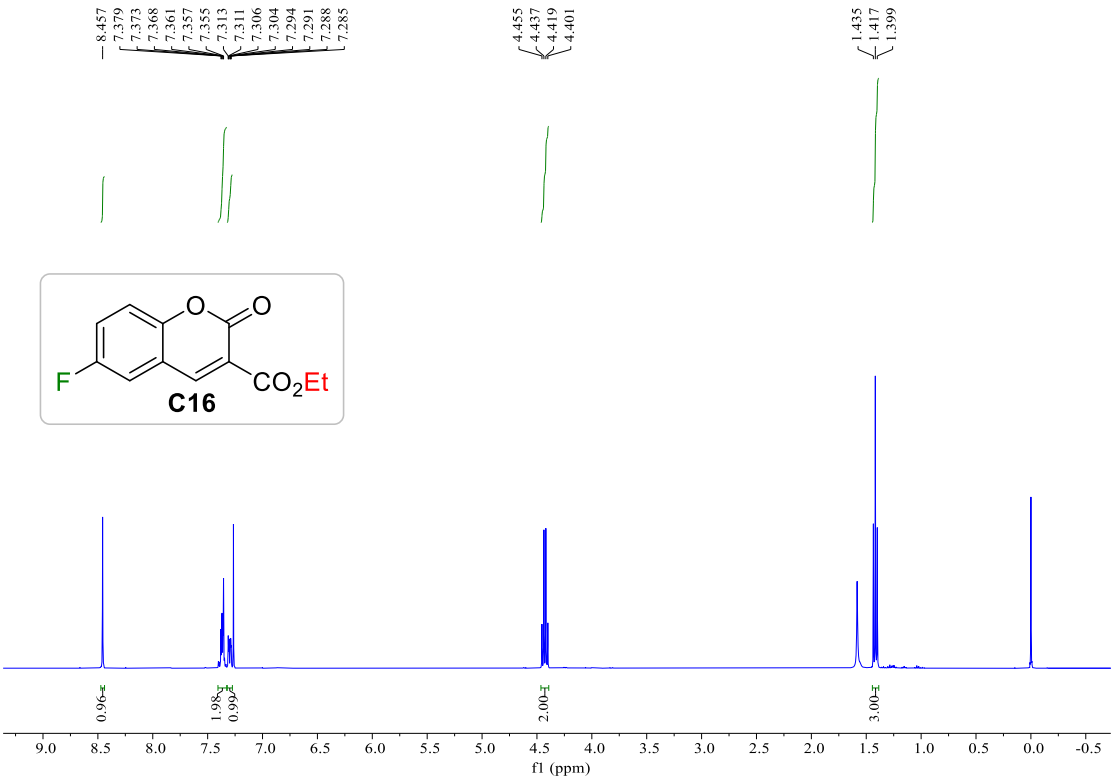
C15, ^{13}C NMR (101 MHz, $CDCl_3$)



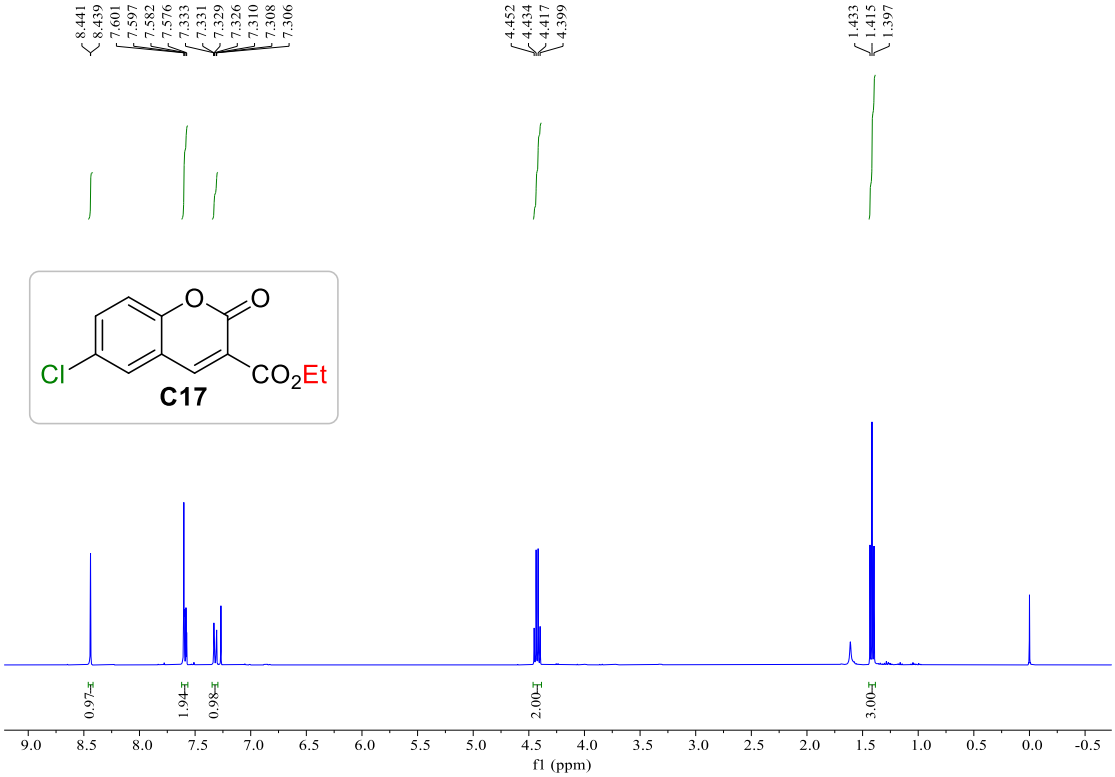
C15, ^{19}F NMR (376 MHz, $CDCl_3$)



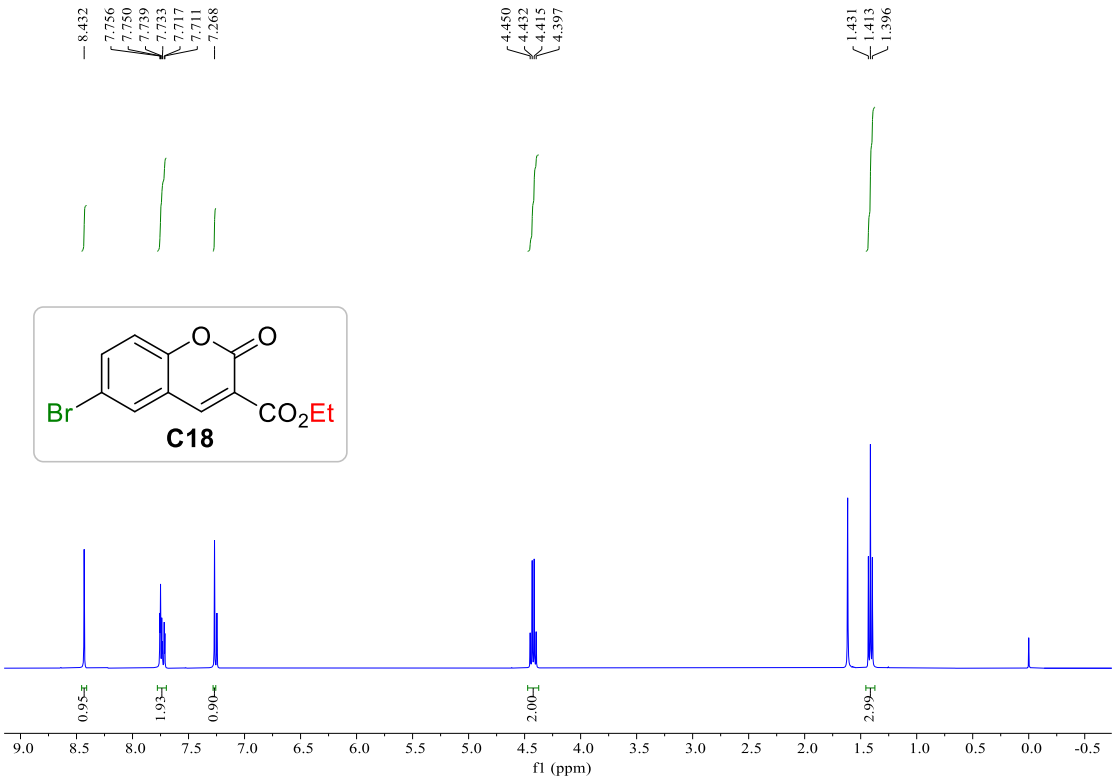
C16, ^{1}H NMR (400 MHz, $CDCl_3$)



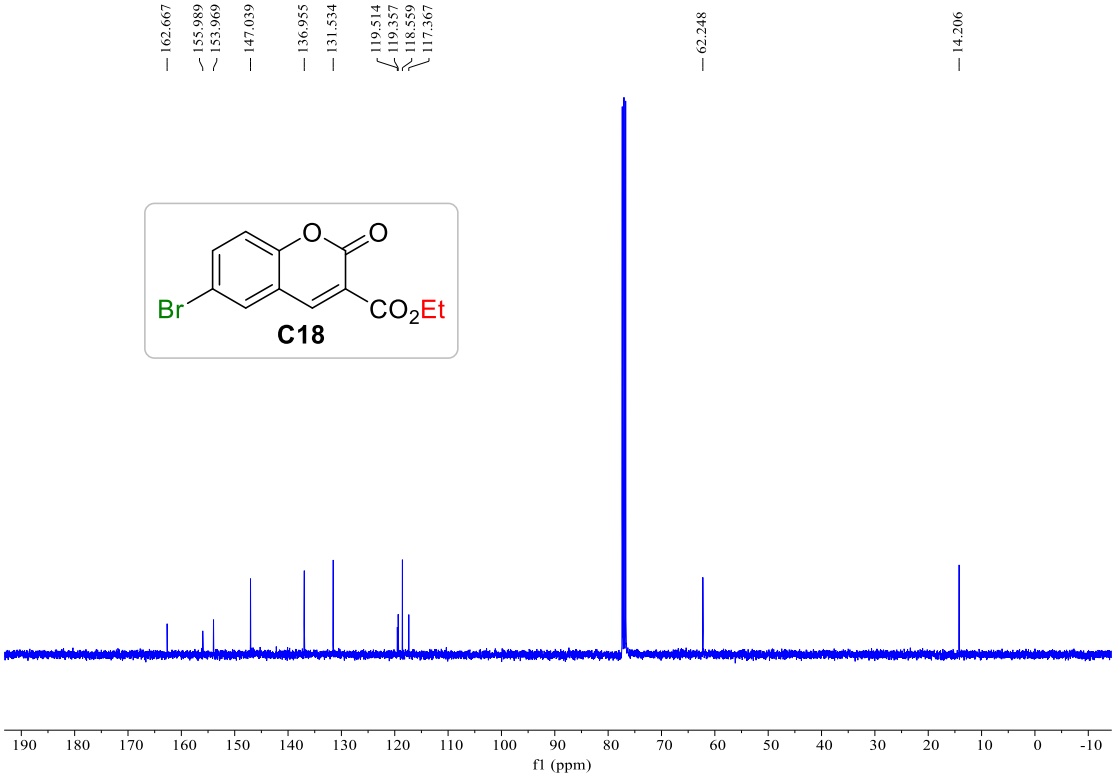
C17, ^{1}H NMR (400 MHz, $CDCl_3$)



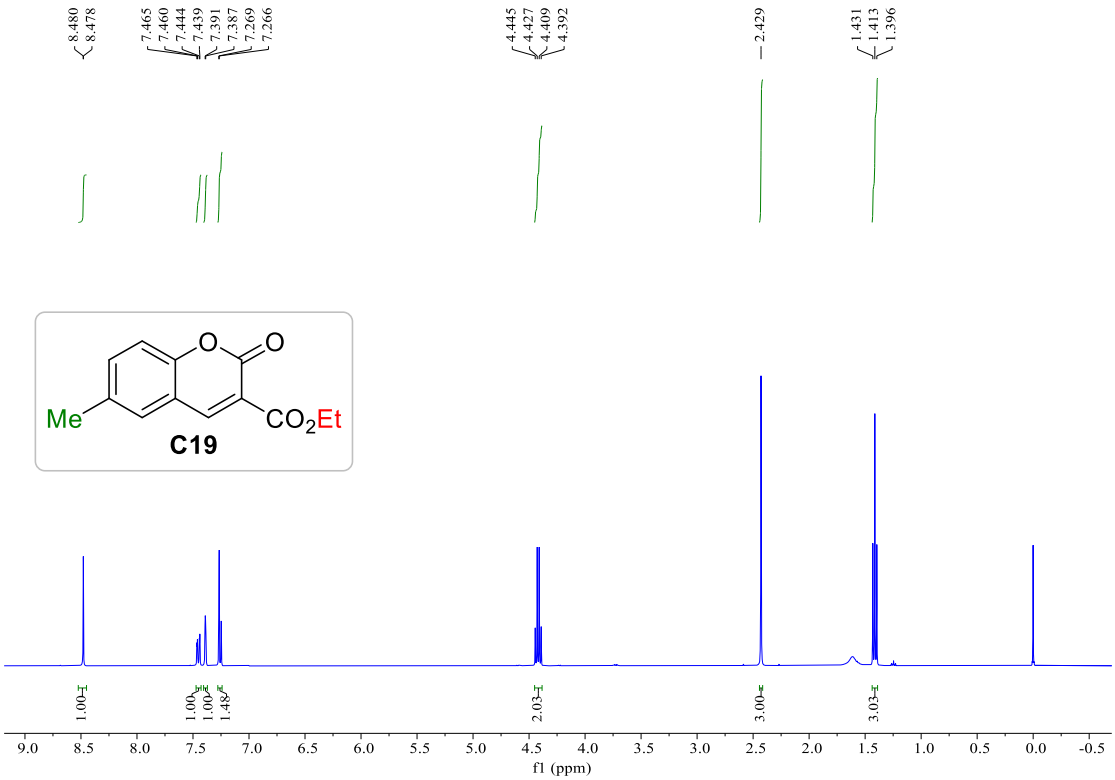
C18, ^{1}H NMR (400 MHz, $CDCl_3$)



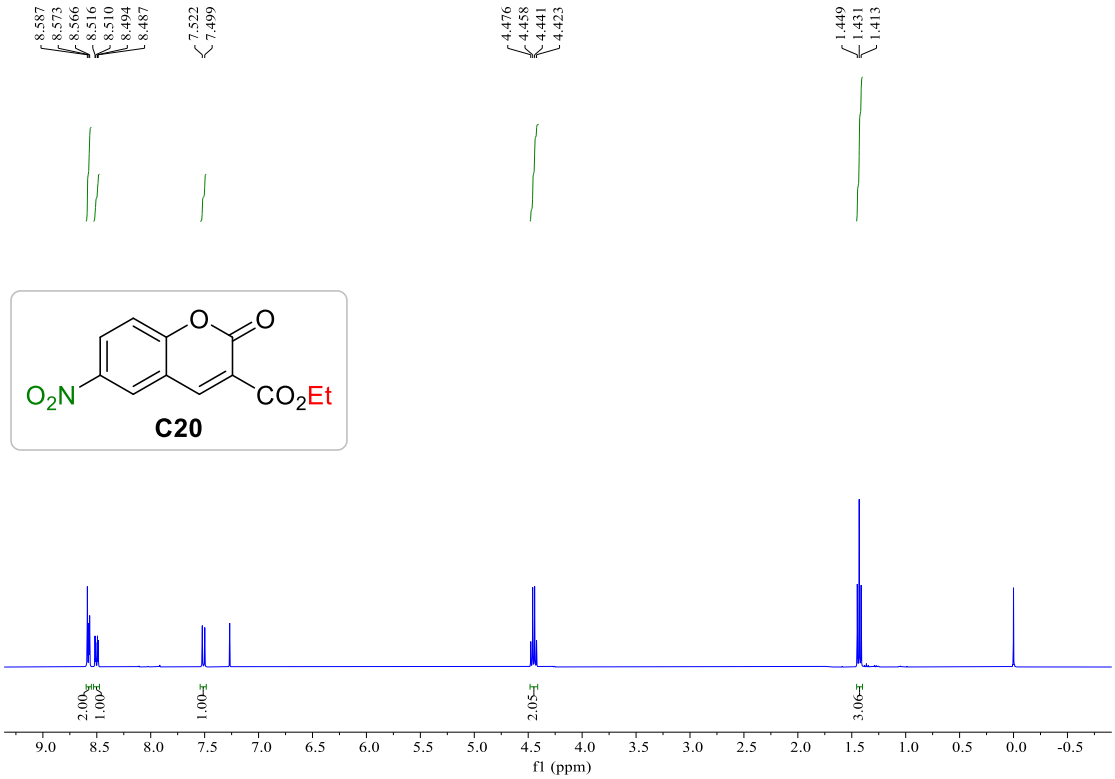
C18, ^{13}C NMR (101 MHz, $CDCl_3$)



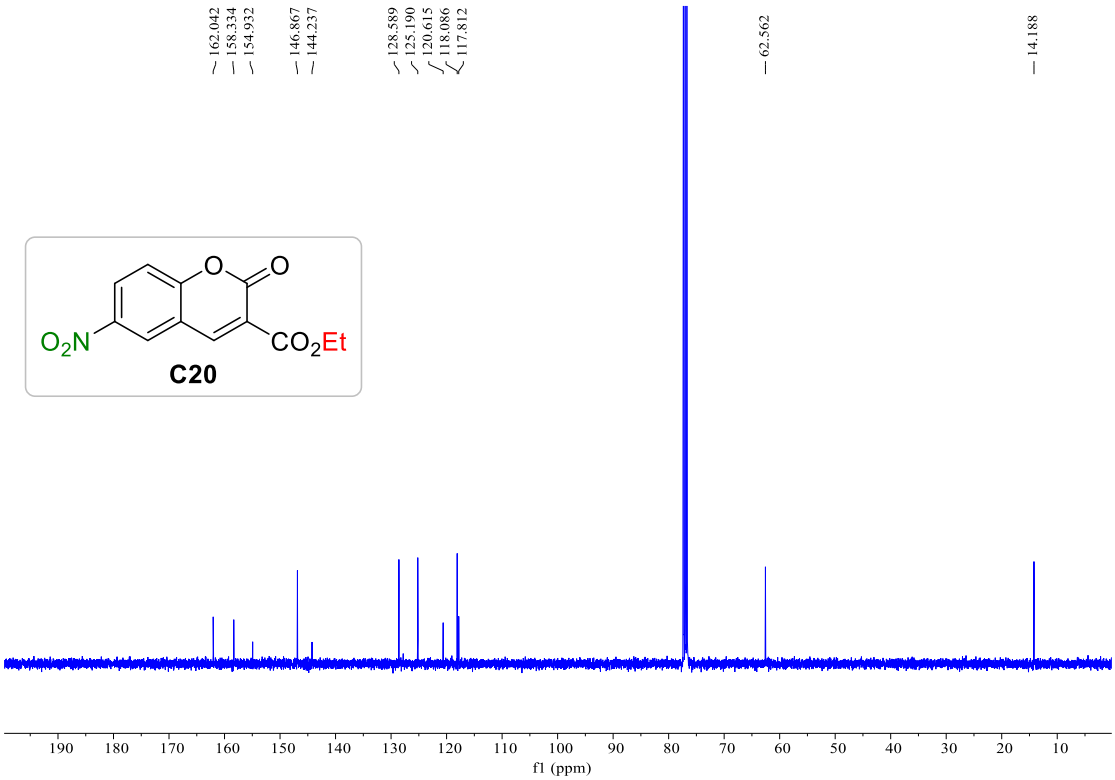
C19, ^{1}H NMR (400 MHz, $CDCl_3$)



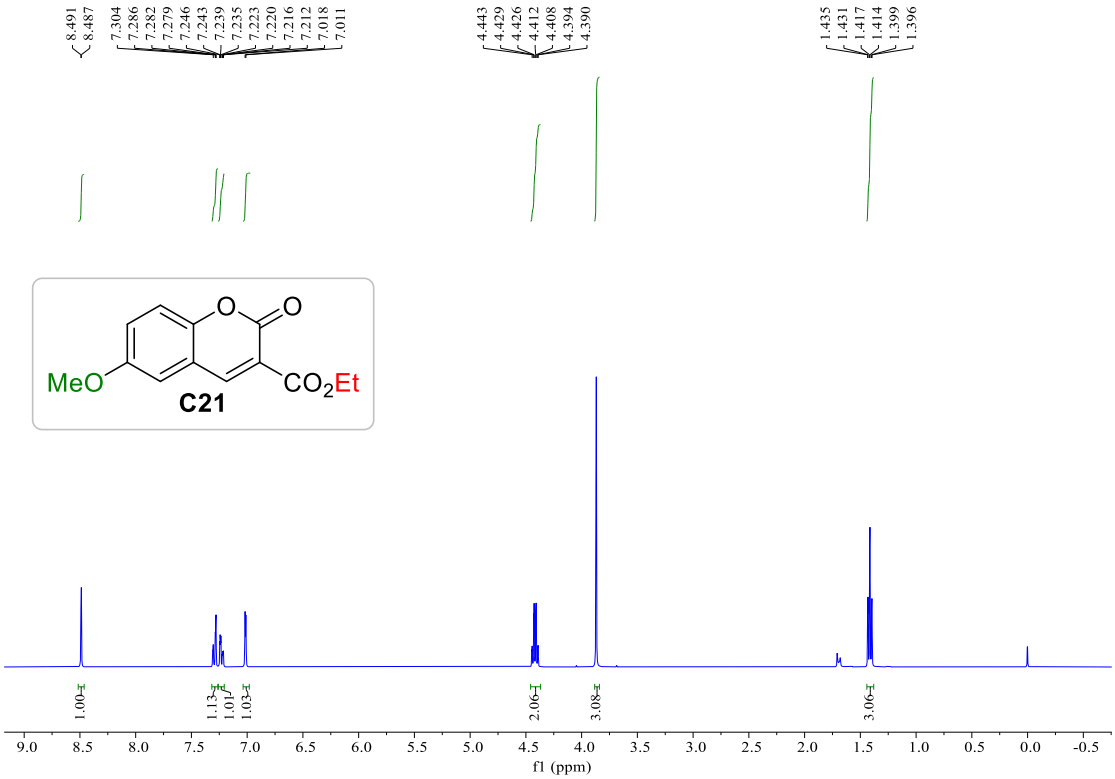
C20, ^{1}H NMR (400 MHz, $CDCl_3$)



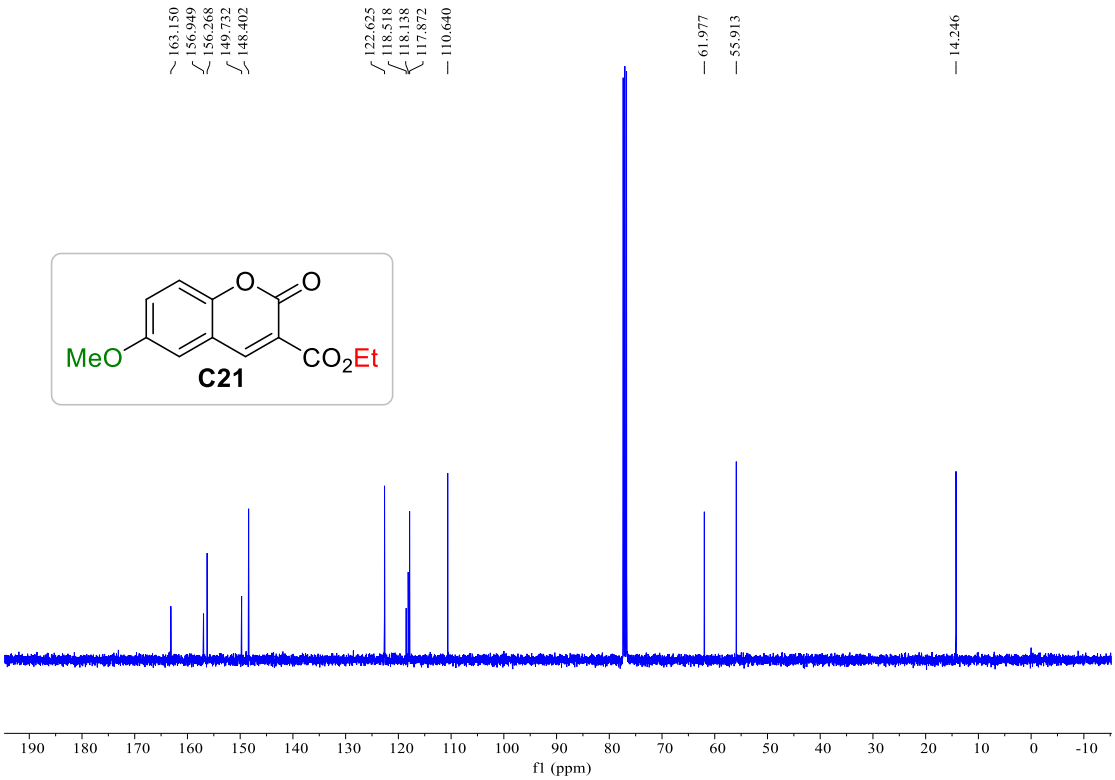
C20, ^{13}C NMR (101 MHz, $CDCl_3$)



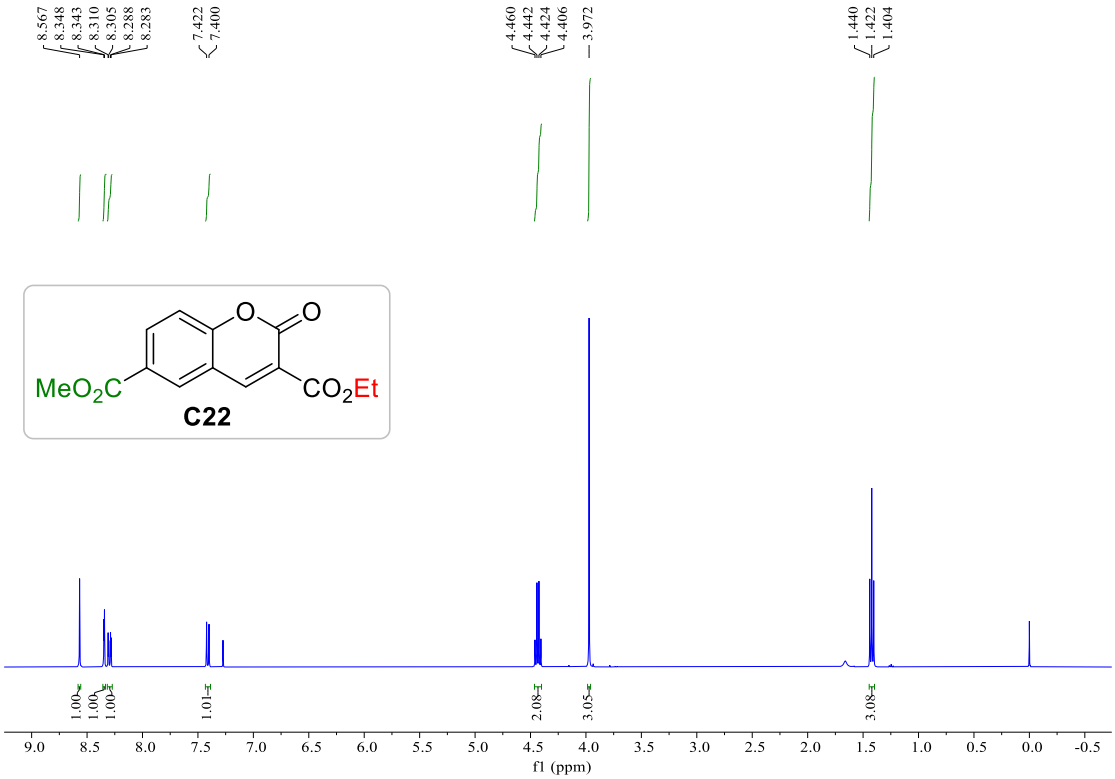
C21, ^{1}H NMR (400 MHz, $CDCl_3$)



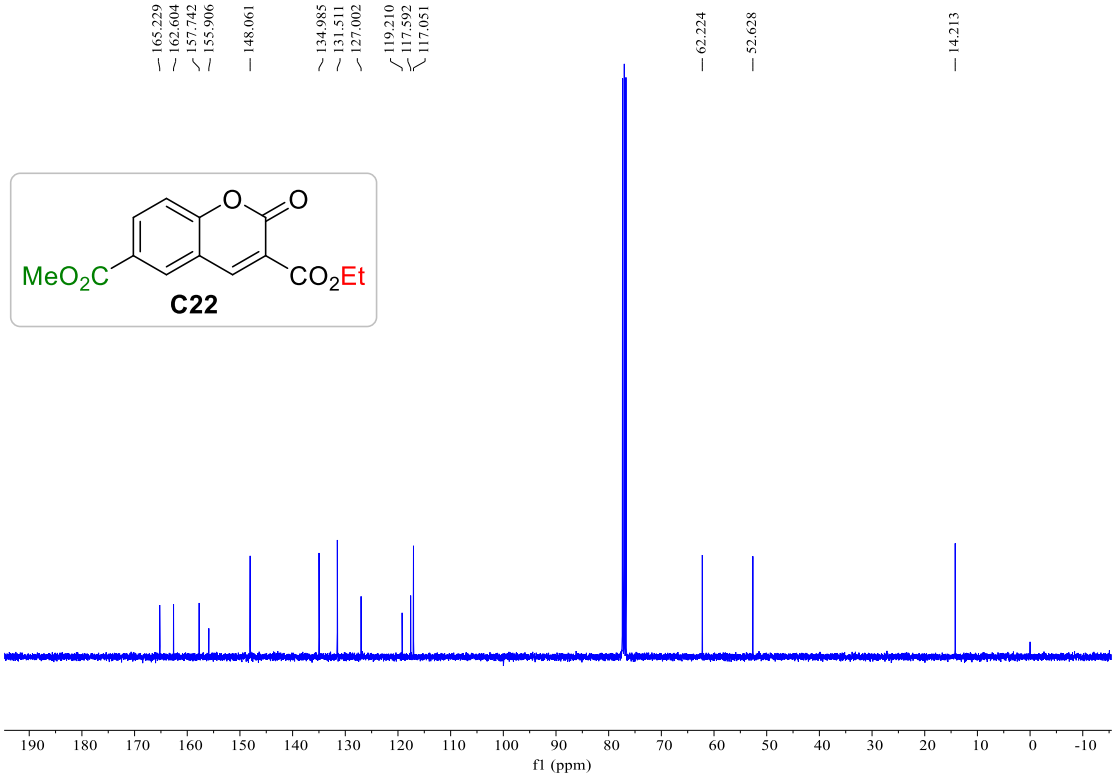
C21, ^{13}C NMR (101 MHz, $CDCl_3$)



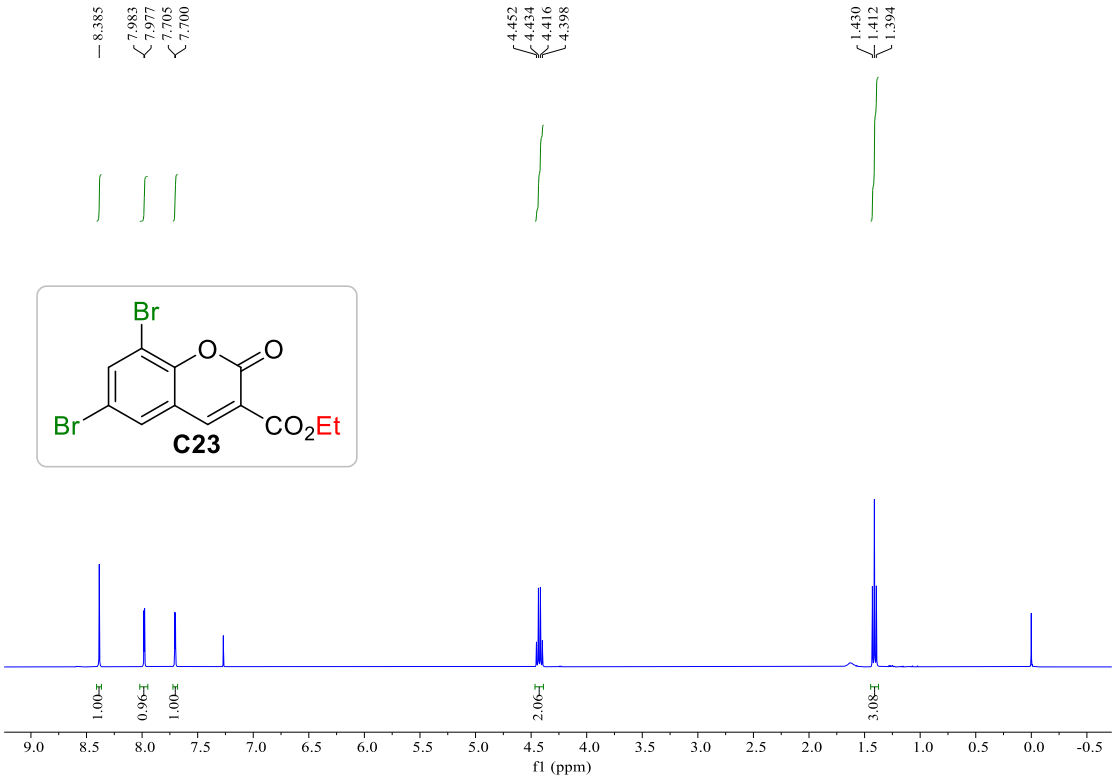
C22, ^{1}H NMR (400 MHz, $CDCl_3$)



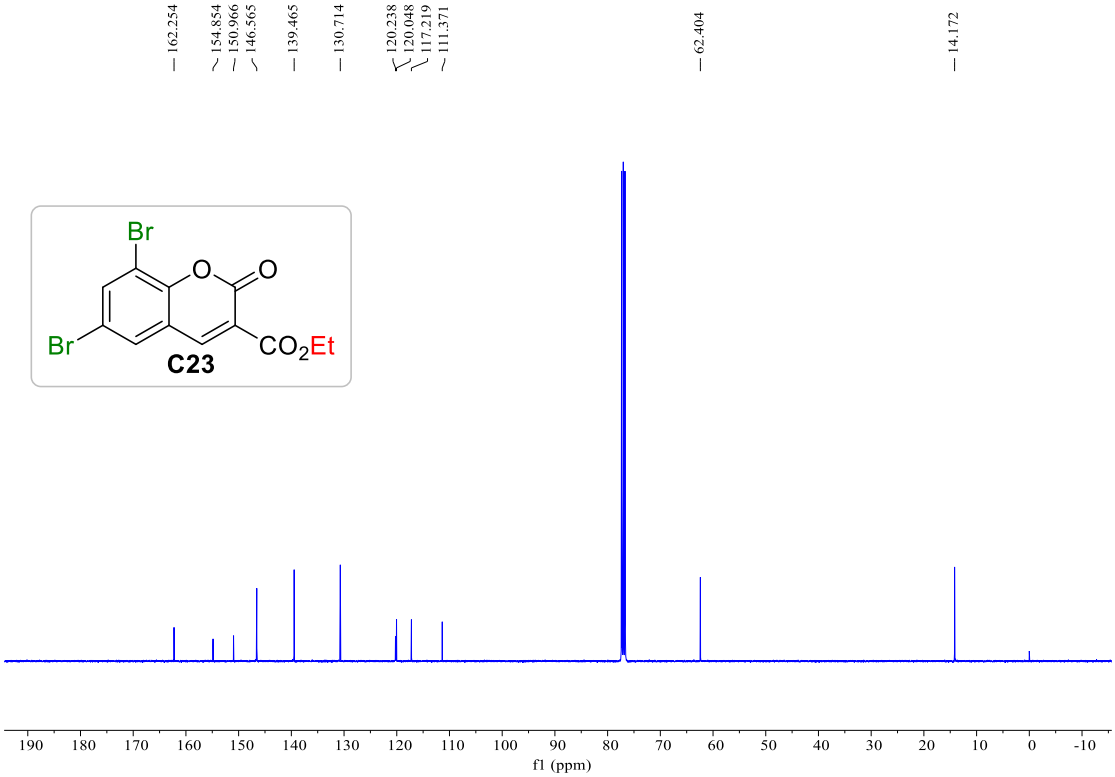
C22, ^{13}C NMR (101 MHz, $CDCl_3$)



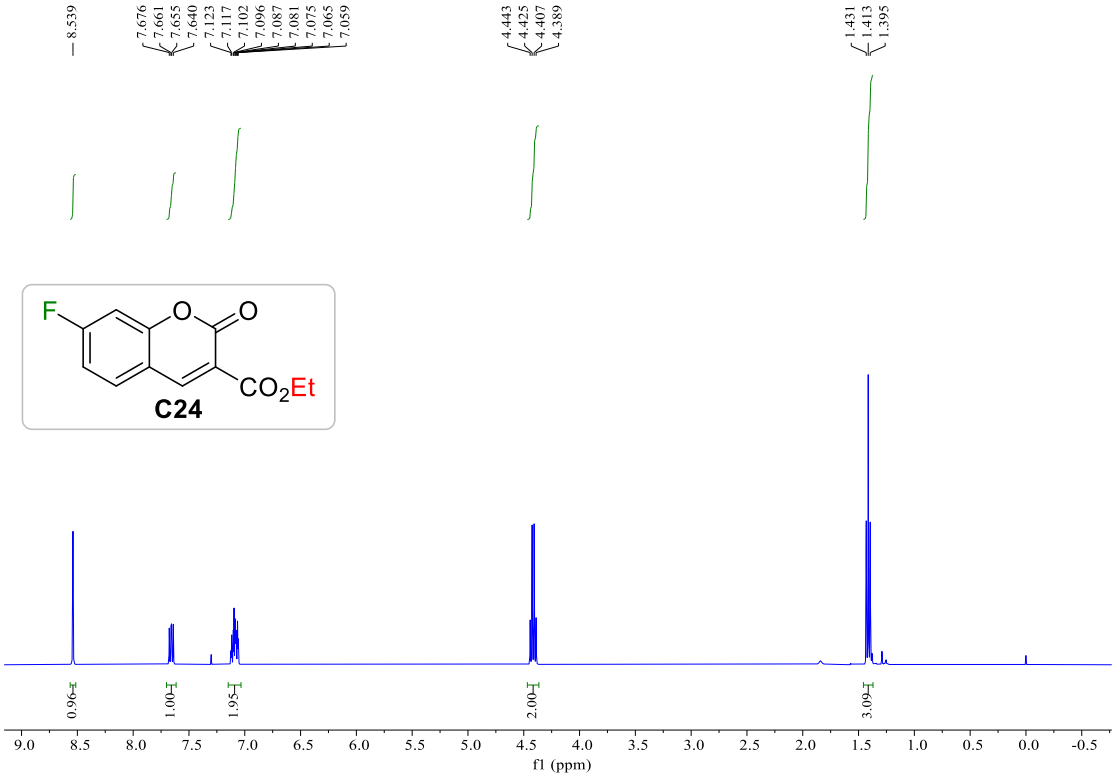
C23, ^{1}H NMR (400 MHz, $CDCl_3$)



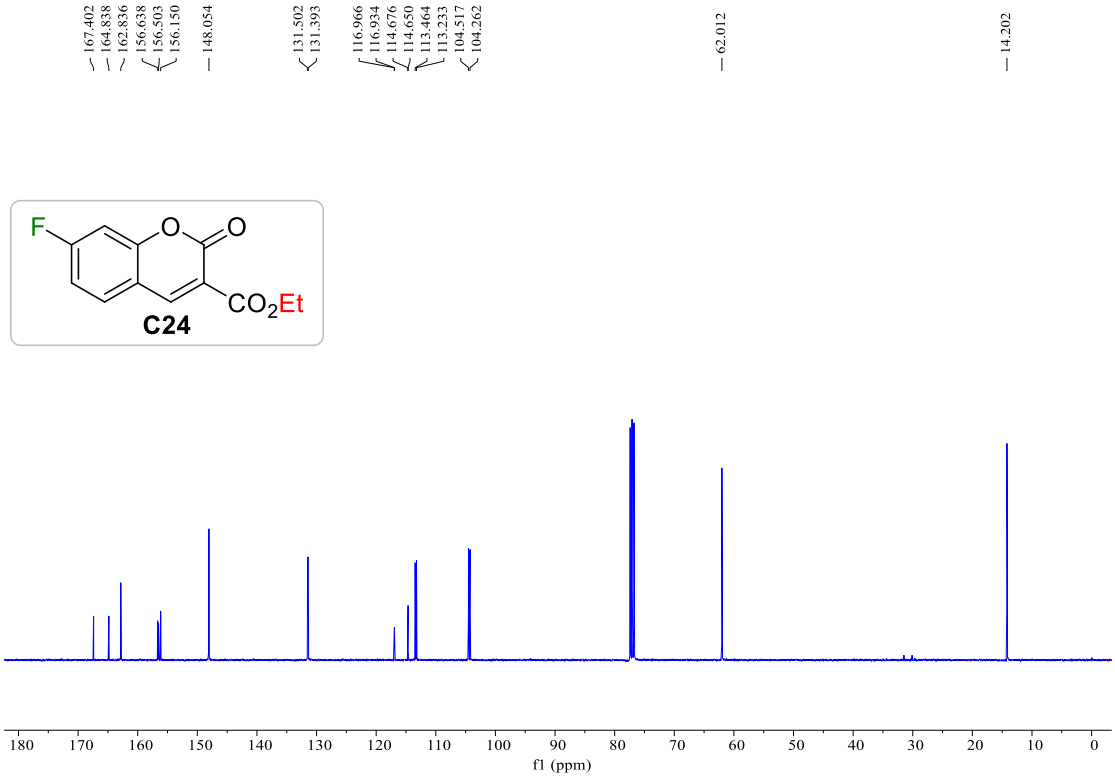
C23, ^{13}C NMR (101 MHz, $CDCl_3$)



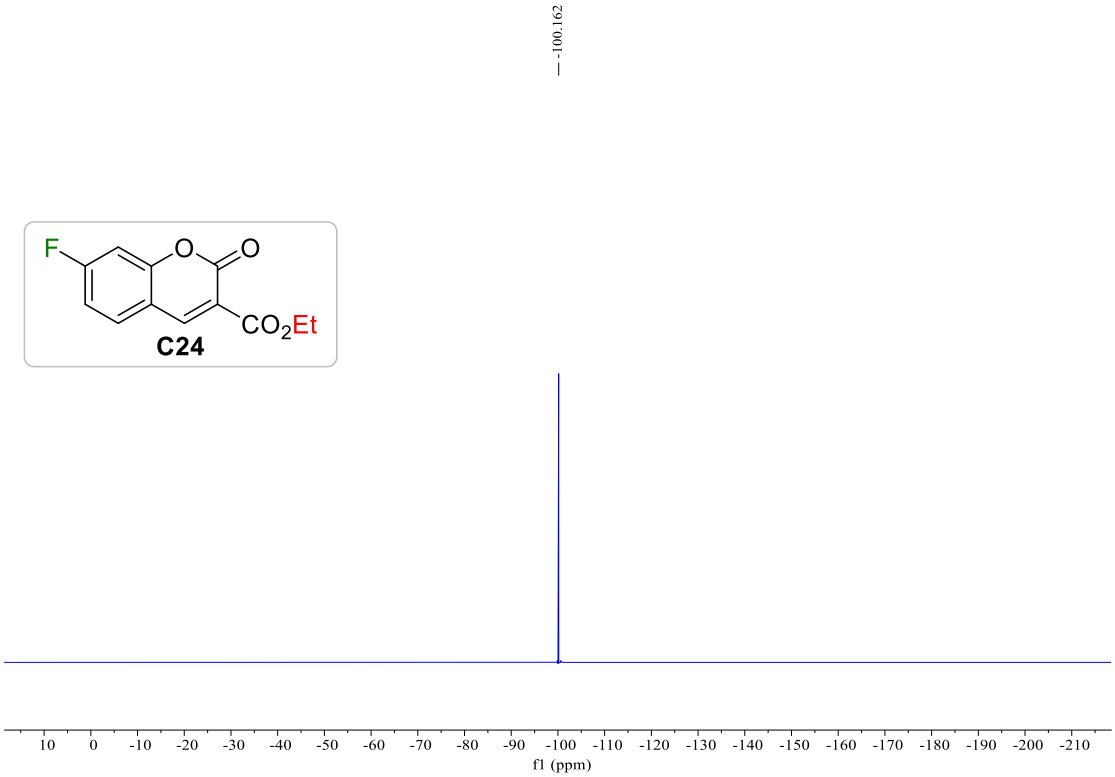
C24, ^{1}H NMR (400 MHz, $CDCl_3$)



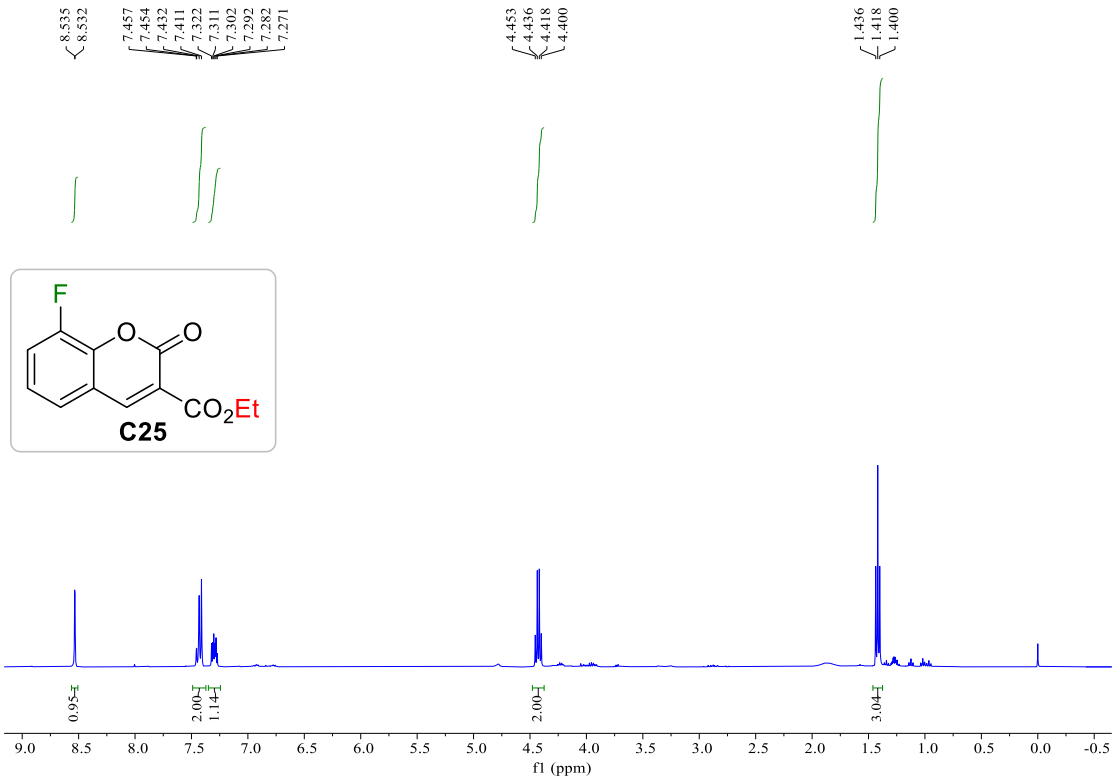
C24, ^{13}C NMR (101 MHz, $CDCl_3$)



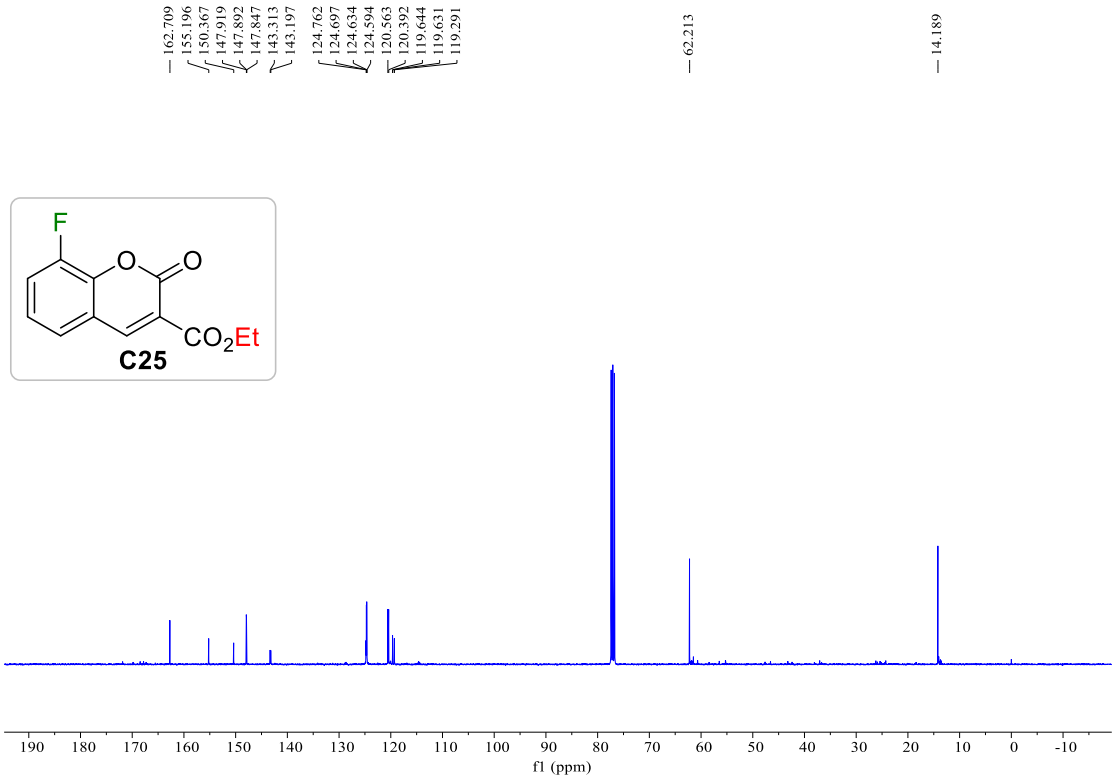
C24, ^{19}F NMR (376 MHz, $CDCl_3$)



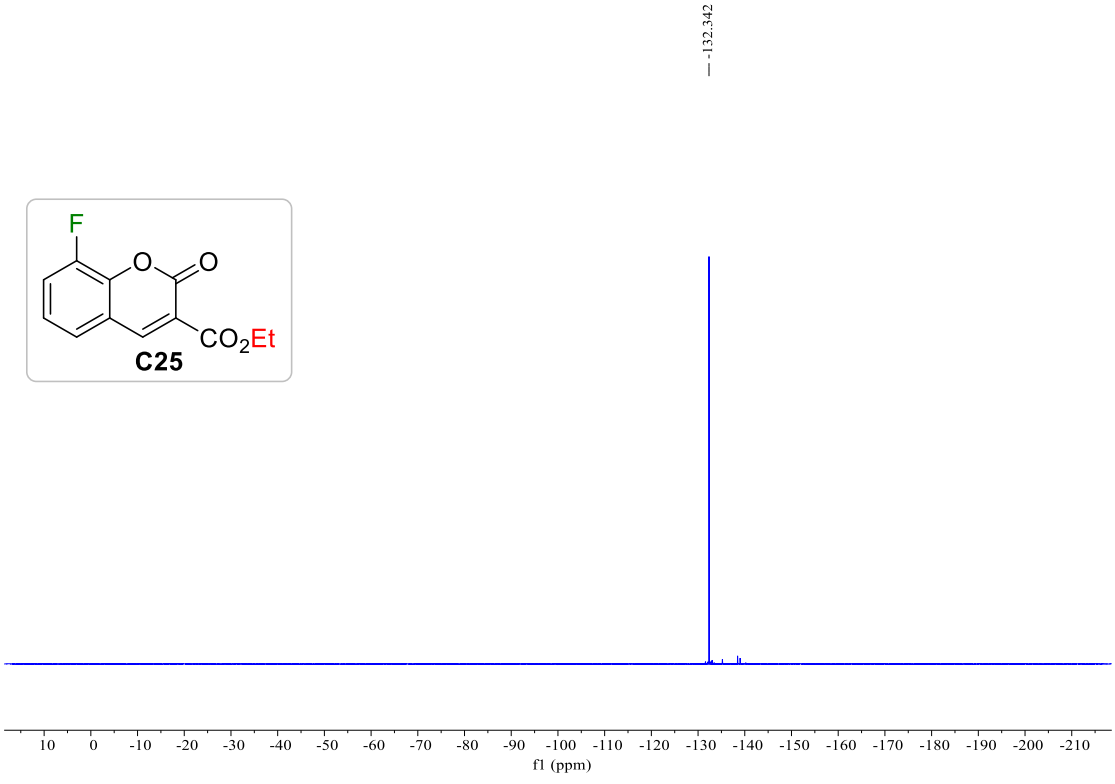
C25, ^{1}H NMR (400 MHz, $CDCl_3$)



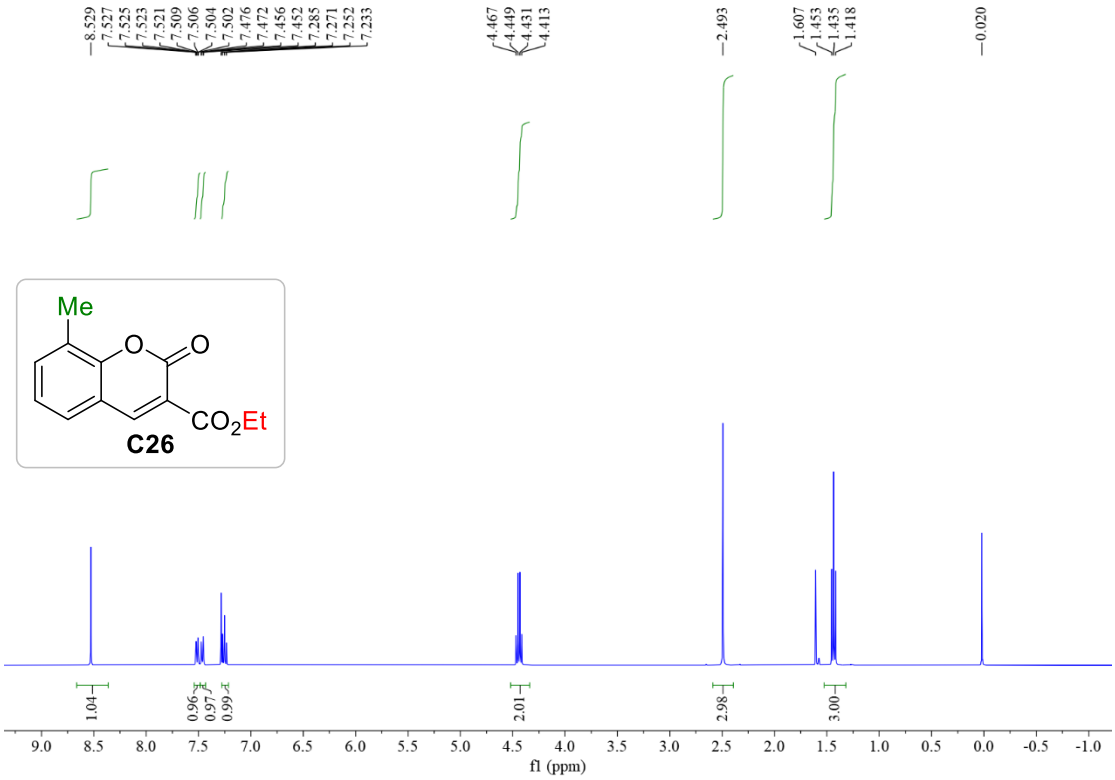
C25, ^{13}C NMR (101 MHz, $CDCl_3$)



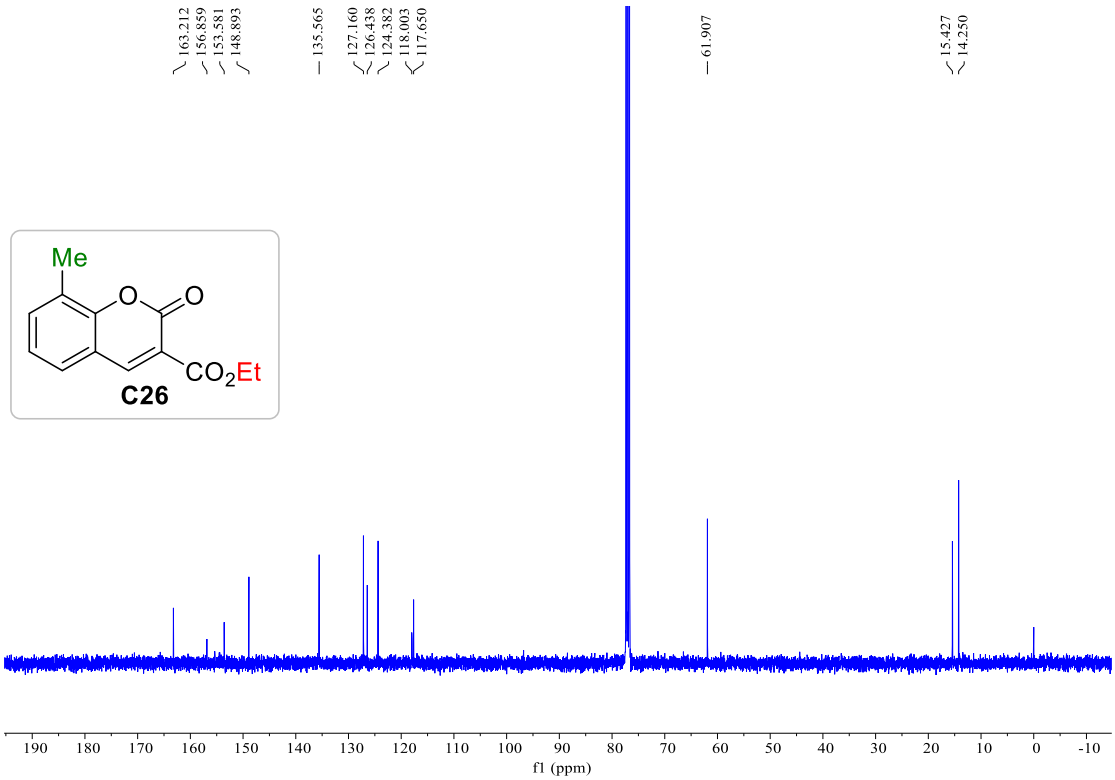
C25, ^{19}F NMR (376 MHz, $CDCl_3$)



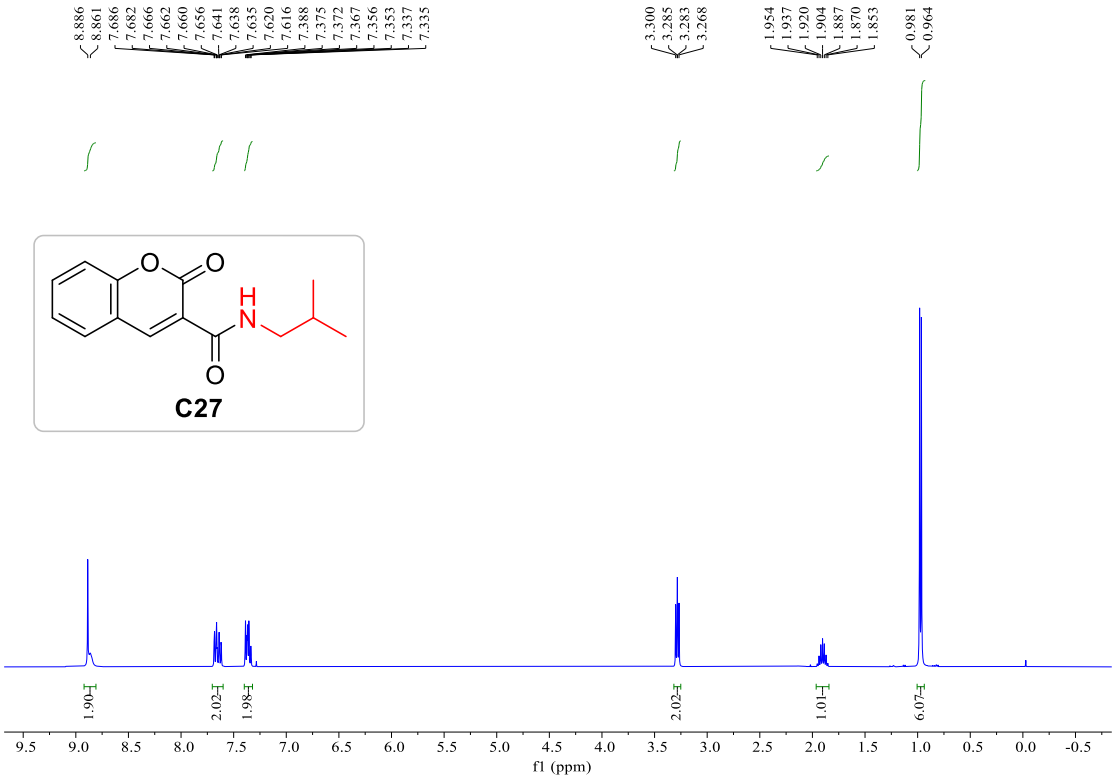
C26, ^{1}H NMR (400 MHz, $CDCl_3$)



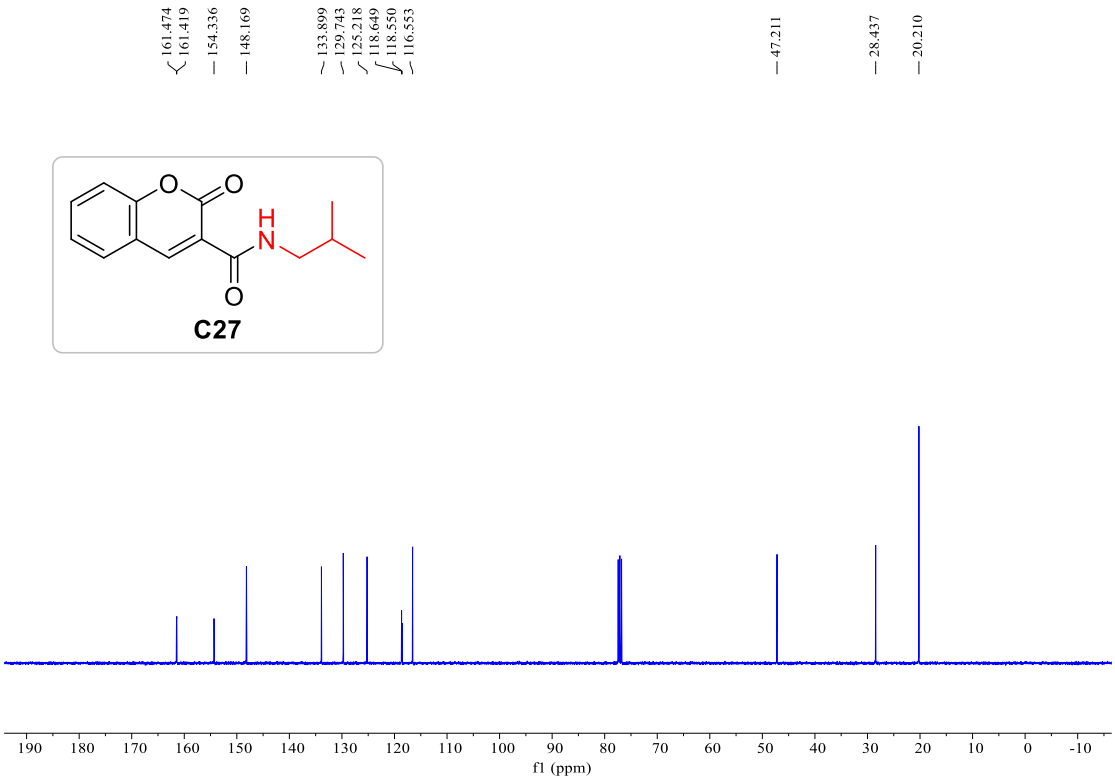
C26, ^{13}C NMR (101 MHz, $CDCl_3$)



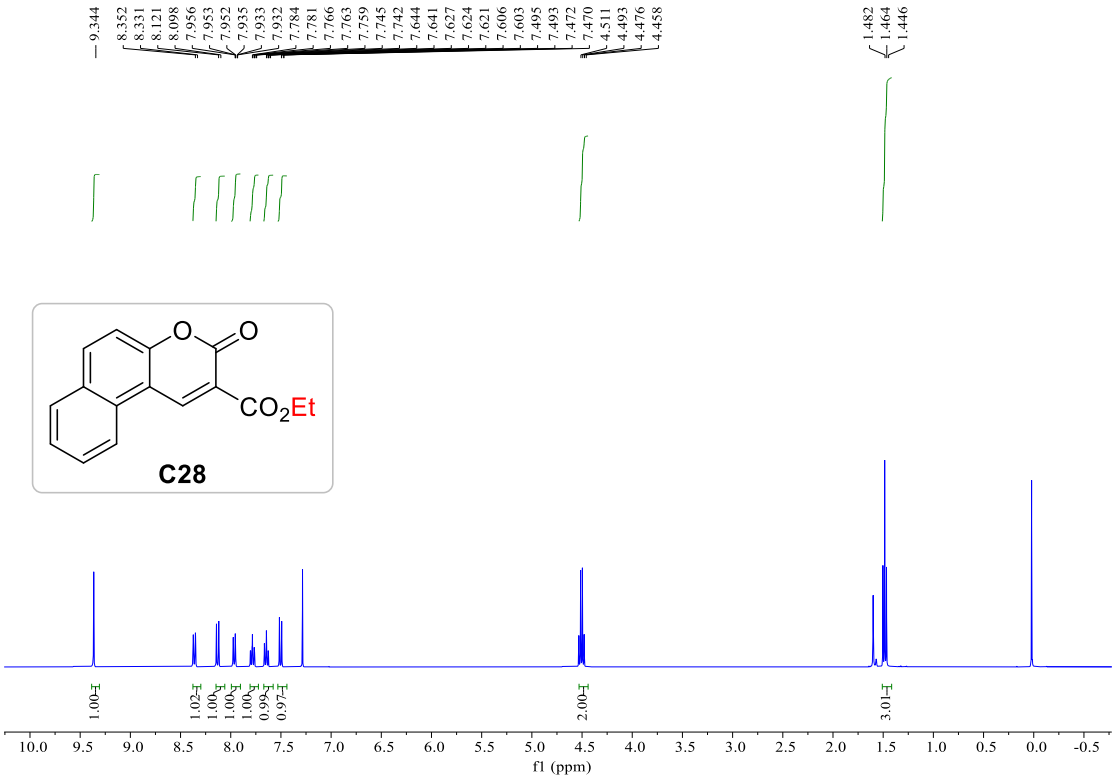
C27, ^{1}H NMR (400 MHz, $CDCl_3$)



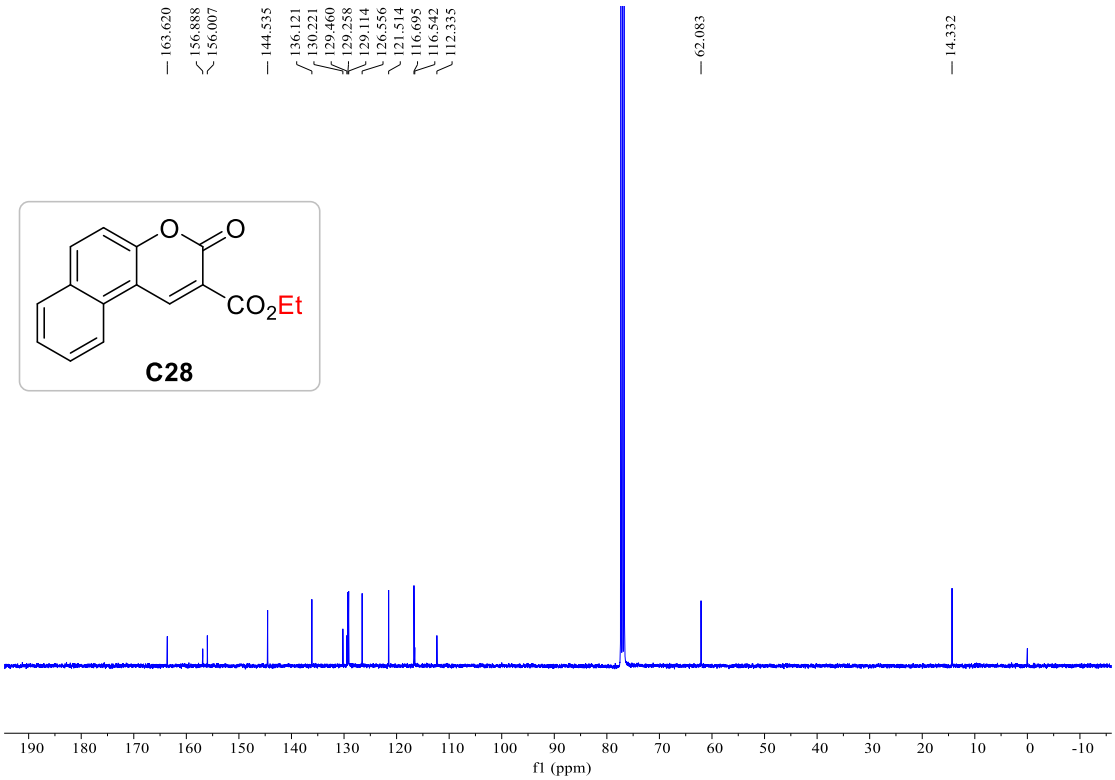
C27, ^{13}C NMR (101 MHz, $CDCl_3$)



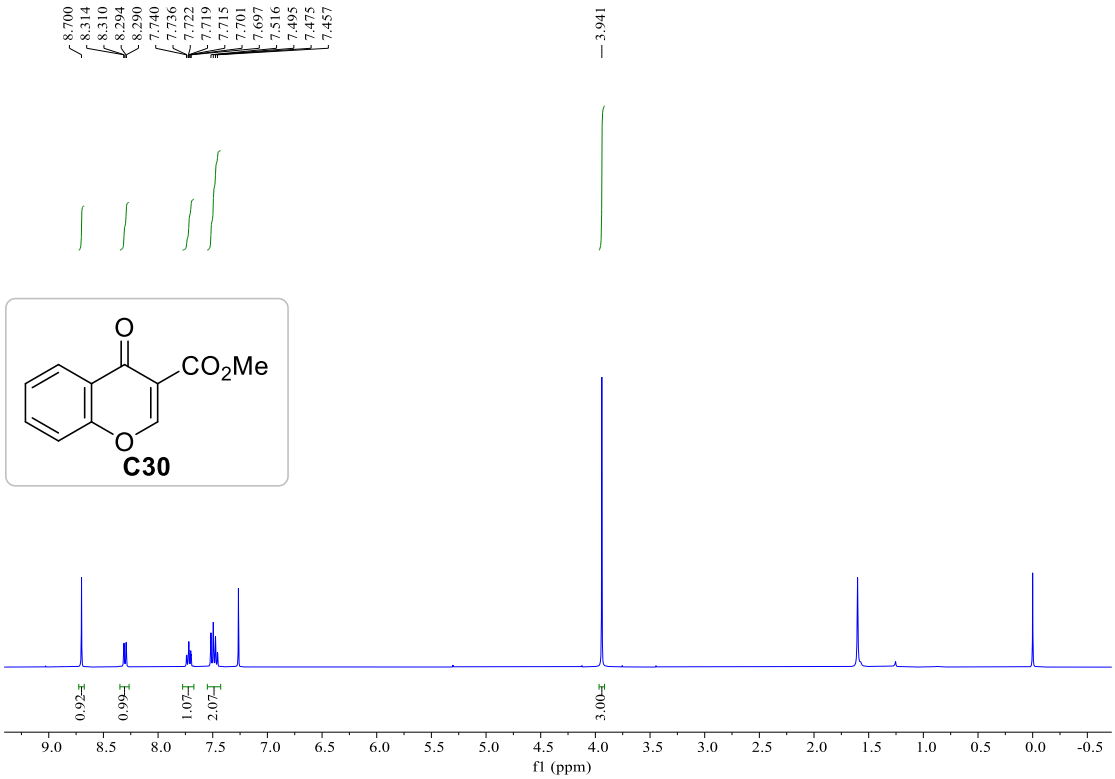
C28, ^{1}H NMR (400 MHz, $CDCl_3$)



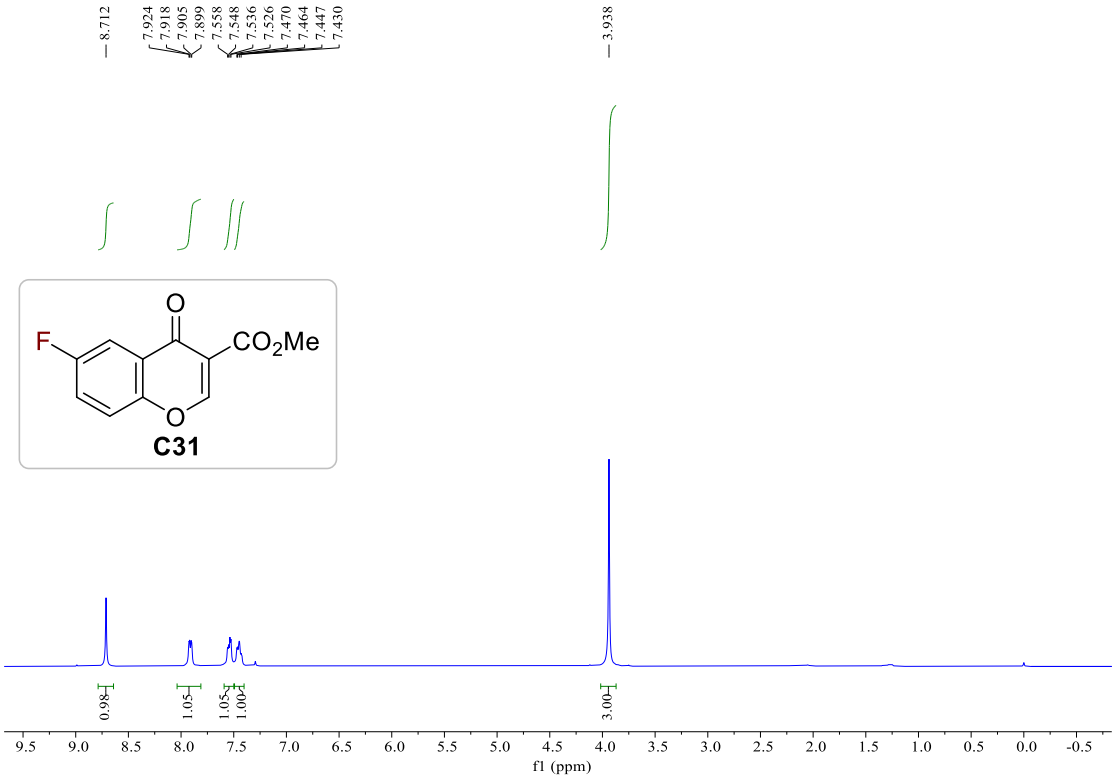
C28, ^{13}C NMR (101 MHz, $CDCl_3$)



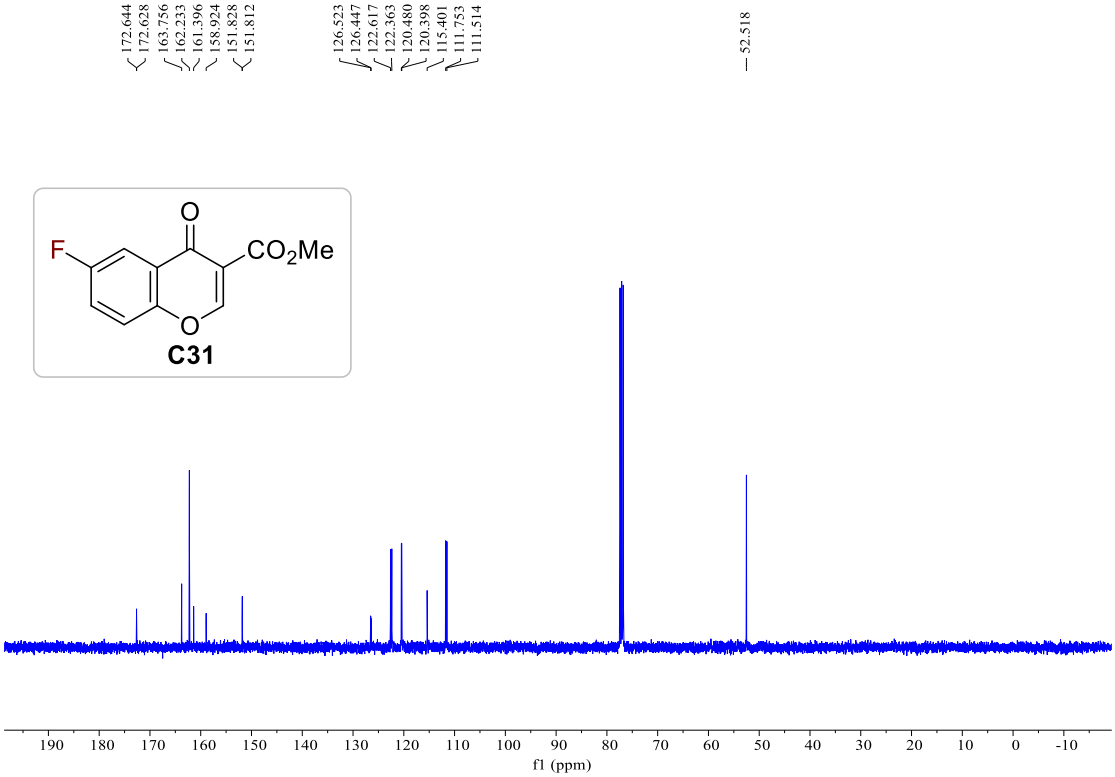
C30, ^{1}H NMR (400 MHz, $CDCl_3$)



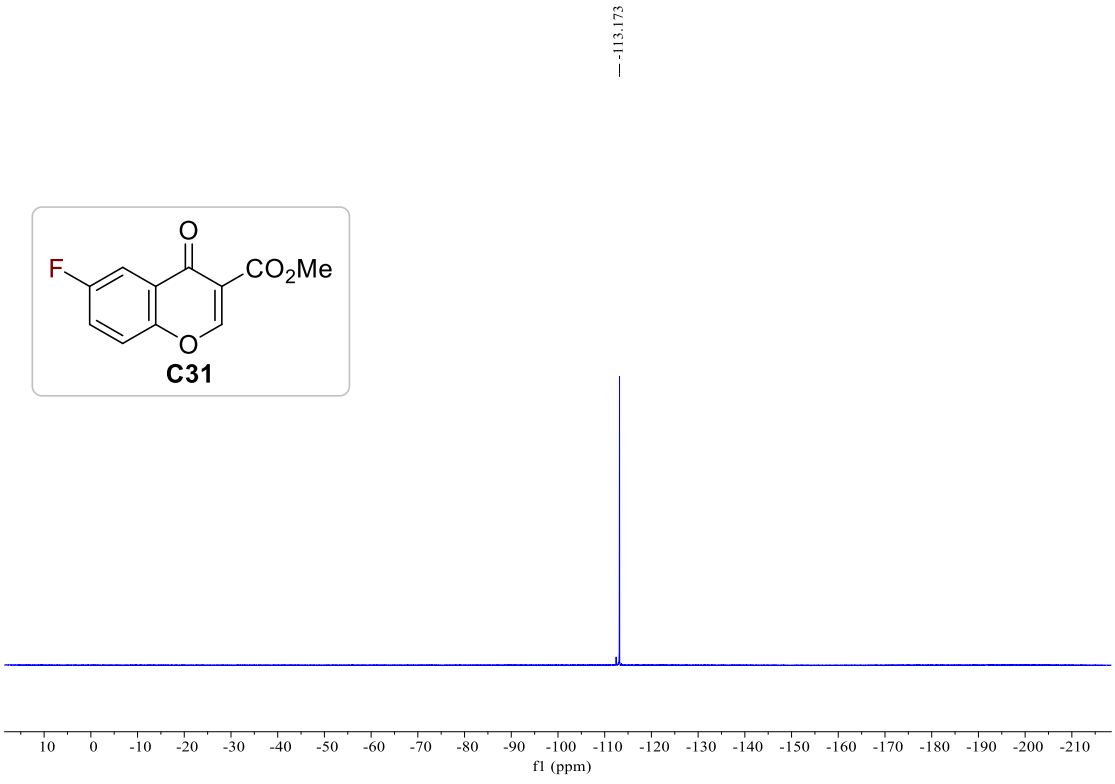
C31, ^{1}H NMR (400 MHz, $CDCl_3$)



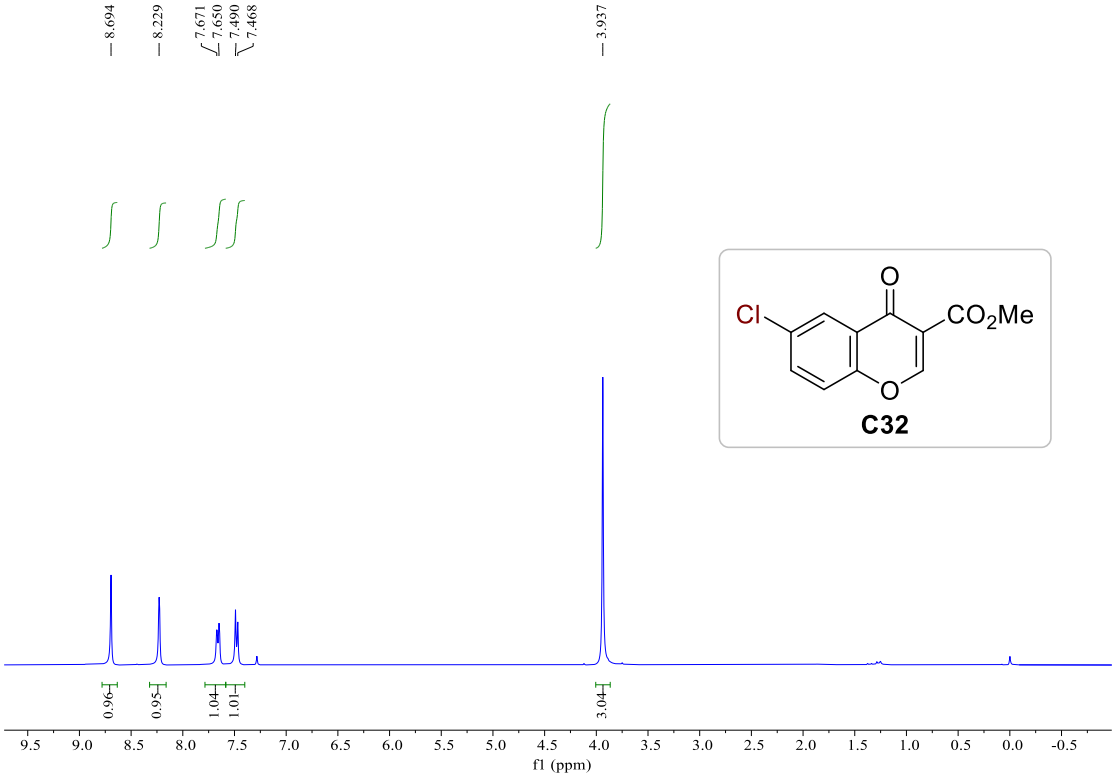
C31, ^{13}C NMR (101 MHz, $CDCl_3$)



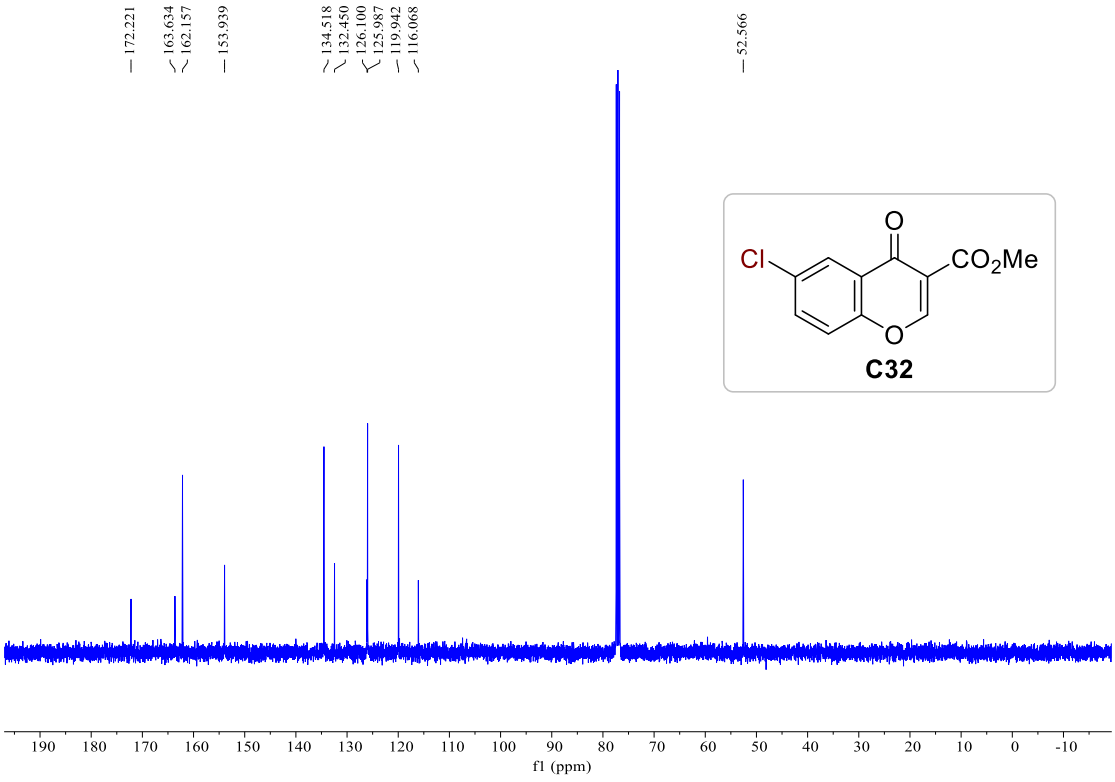
C31, ^{19}F NMR (376 MHz, $CDCl_3$)



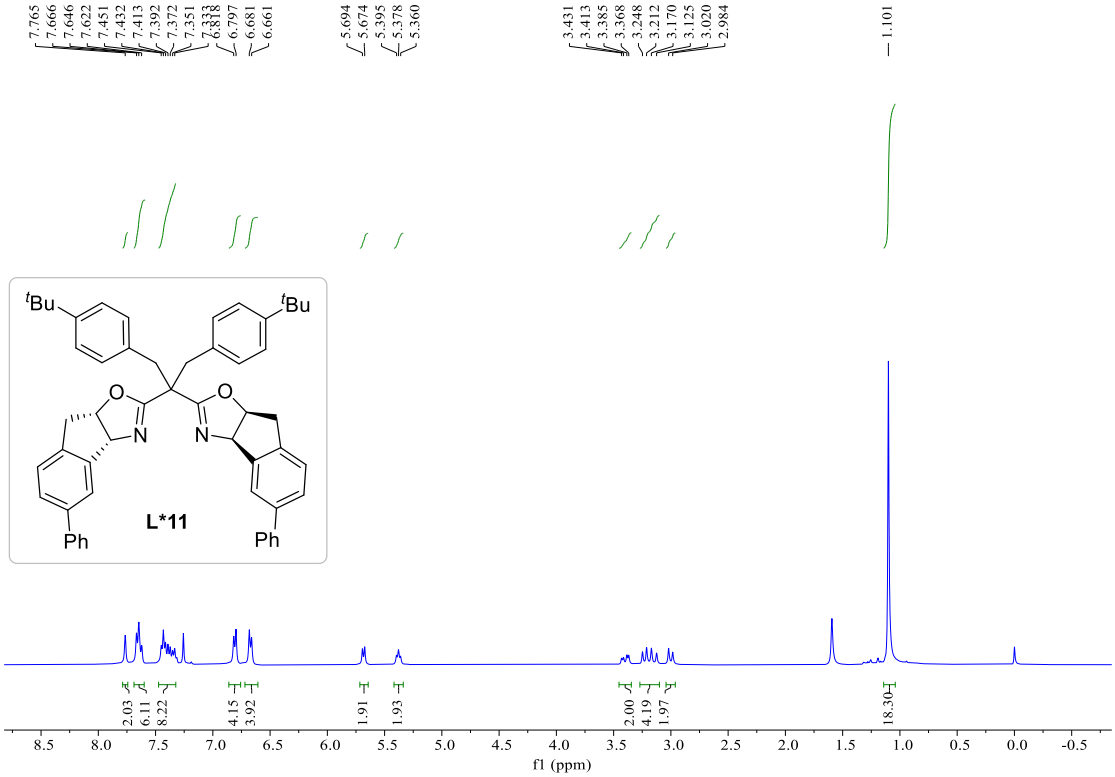
C32, ^{1}H NMR (400 MHz, $CDCl_3$)



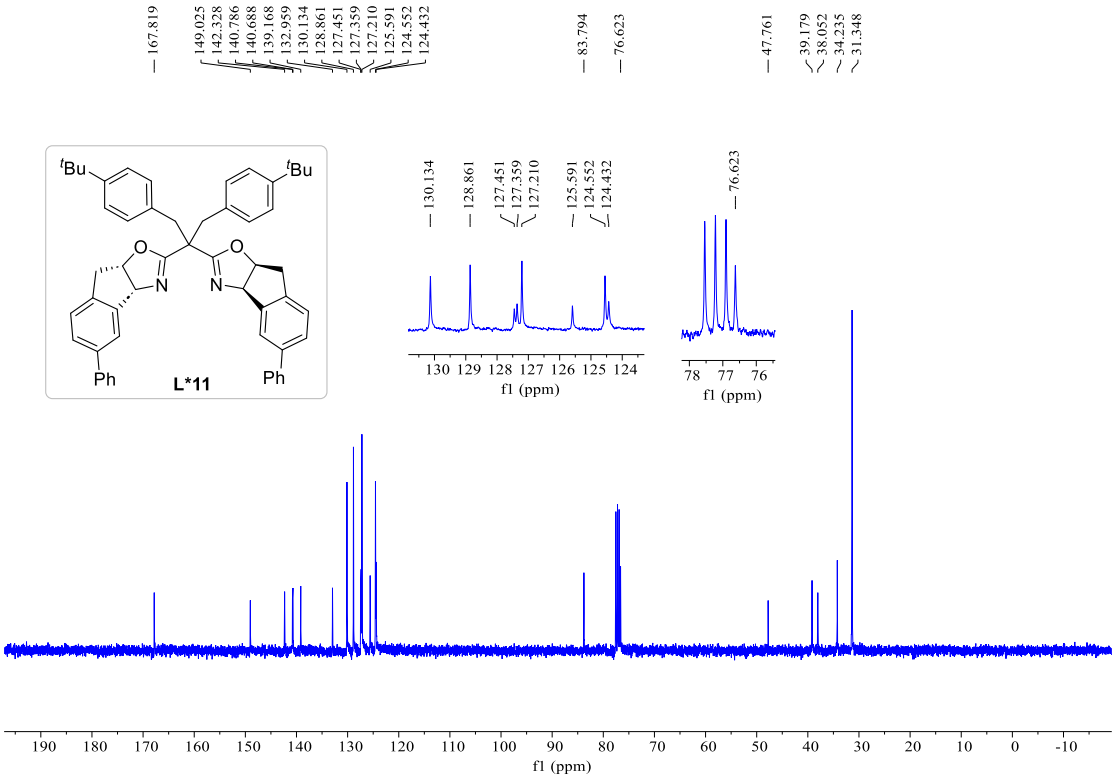
C32, ^{13}C NMR (101 MHz, $CDCl_3$)



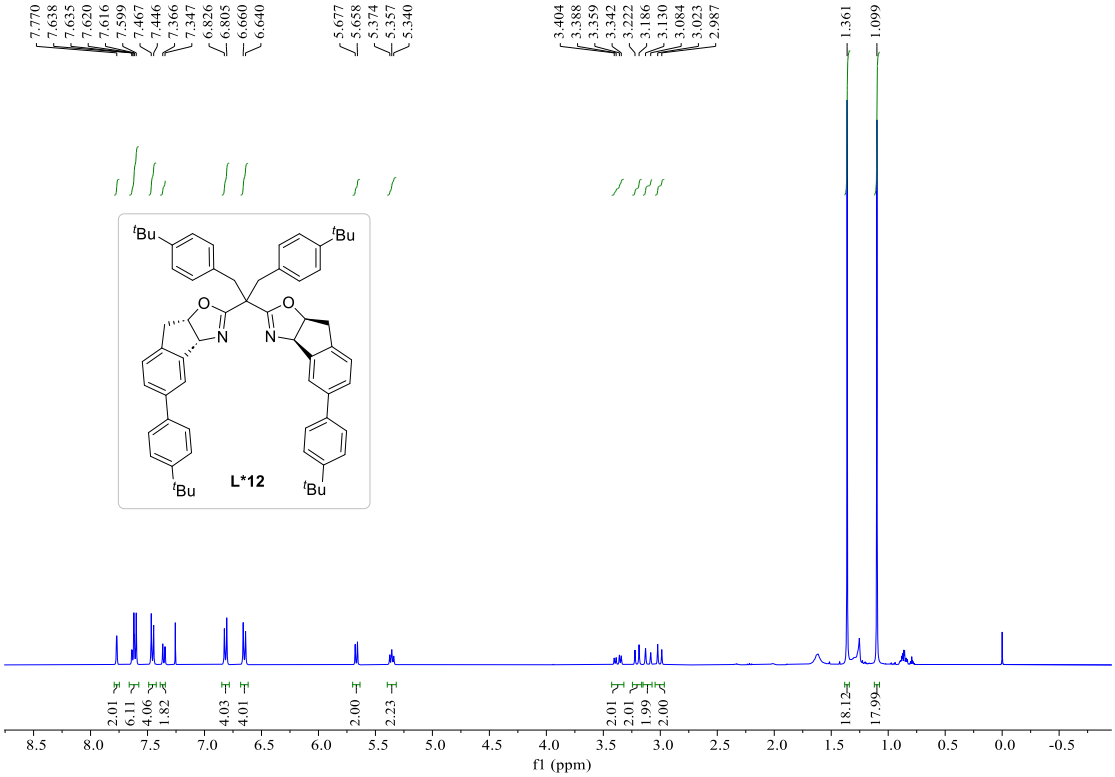
L*11, ^{1}H NMR (400 MHz, $CDCl_3$)



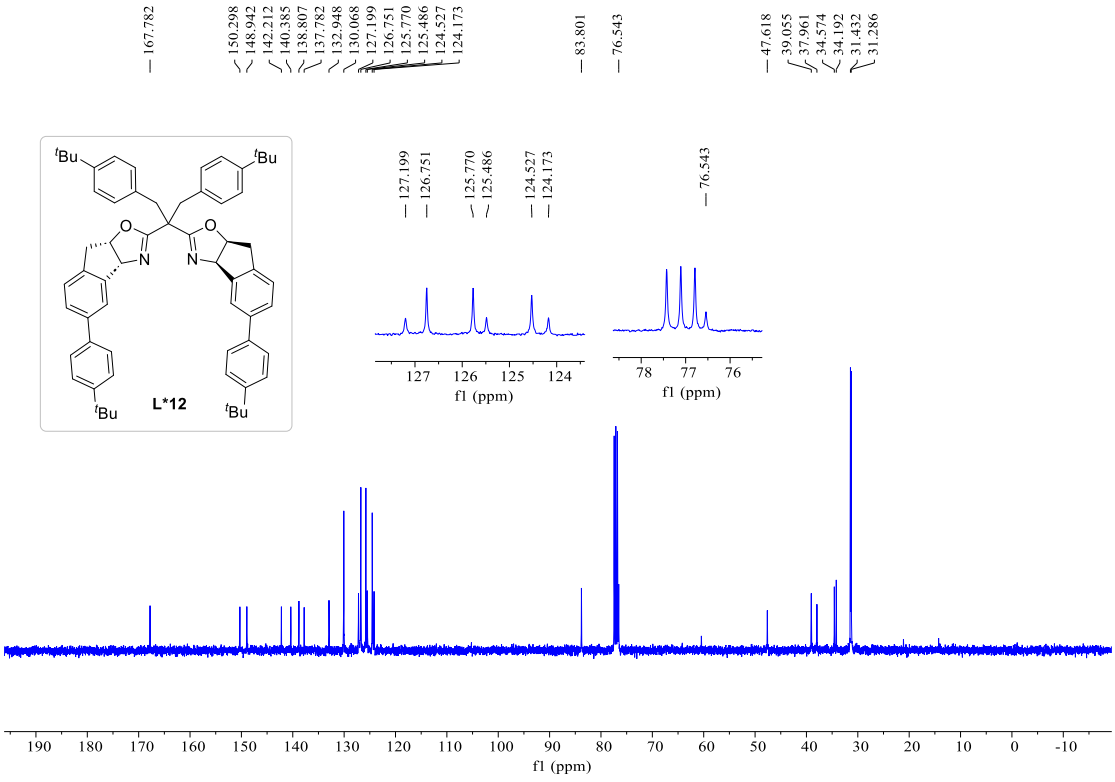
L*11, ^{13}C NMR (101 MHz, $CDCl_3$)



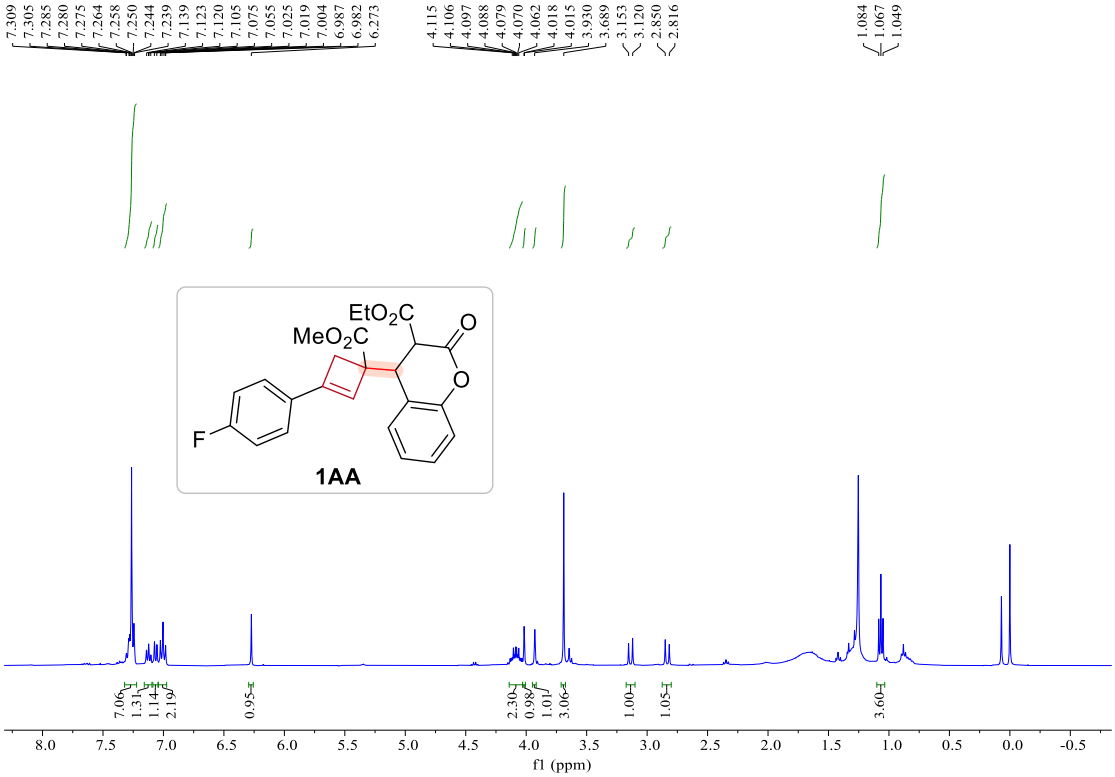
L*12, ^{1}H NMR (400 MHz, $CDCl_3$)



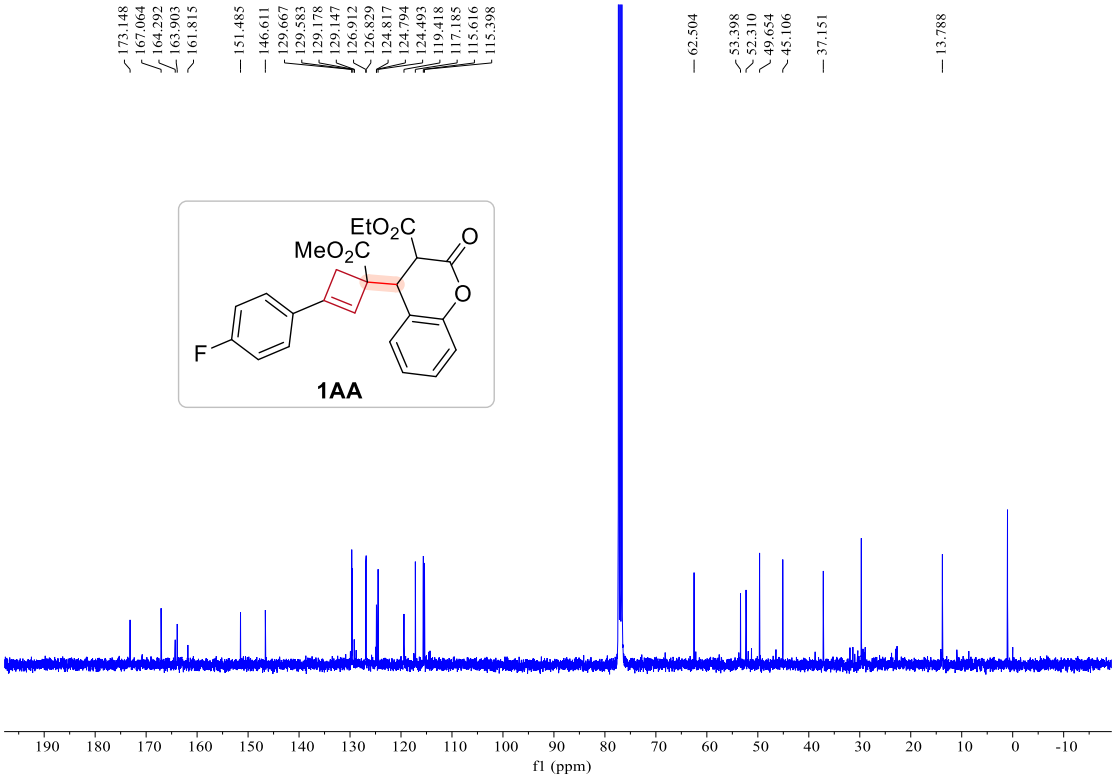
L*12, ^{13}C NMR (101 MHz, $CDCl_3$)



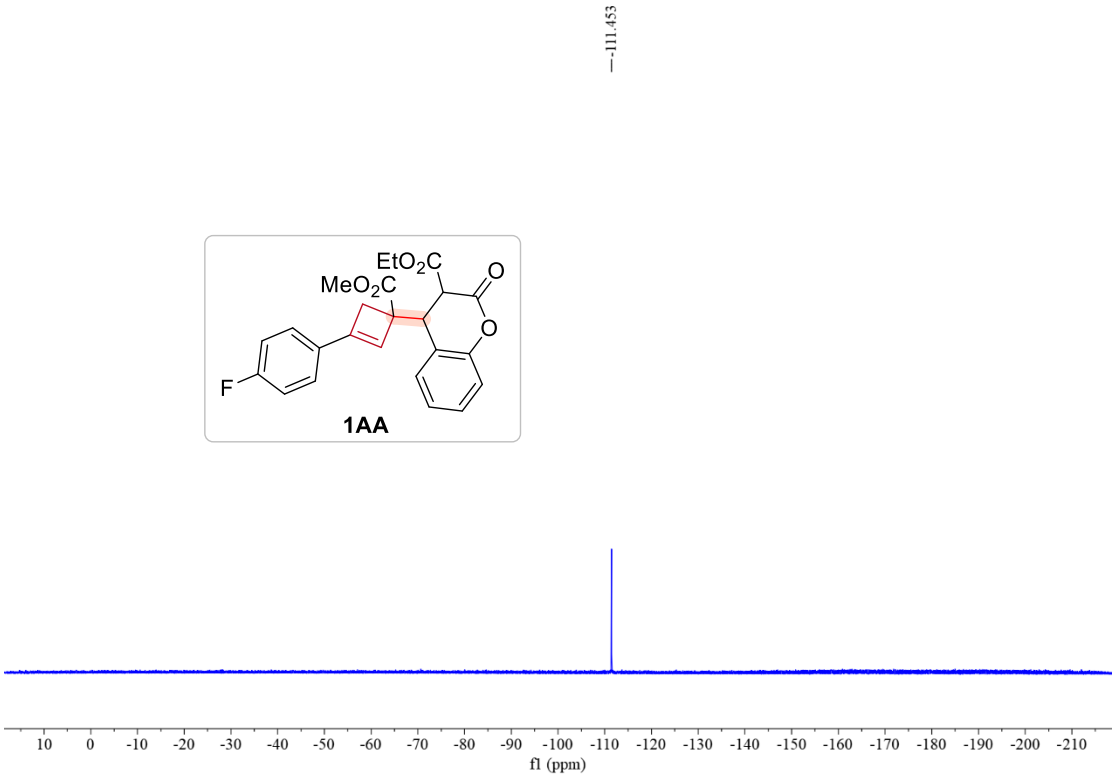
1AA, ^{1}H NMR (400 MHz, $CDCl_3$)



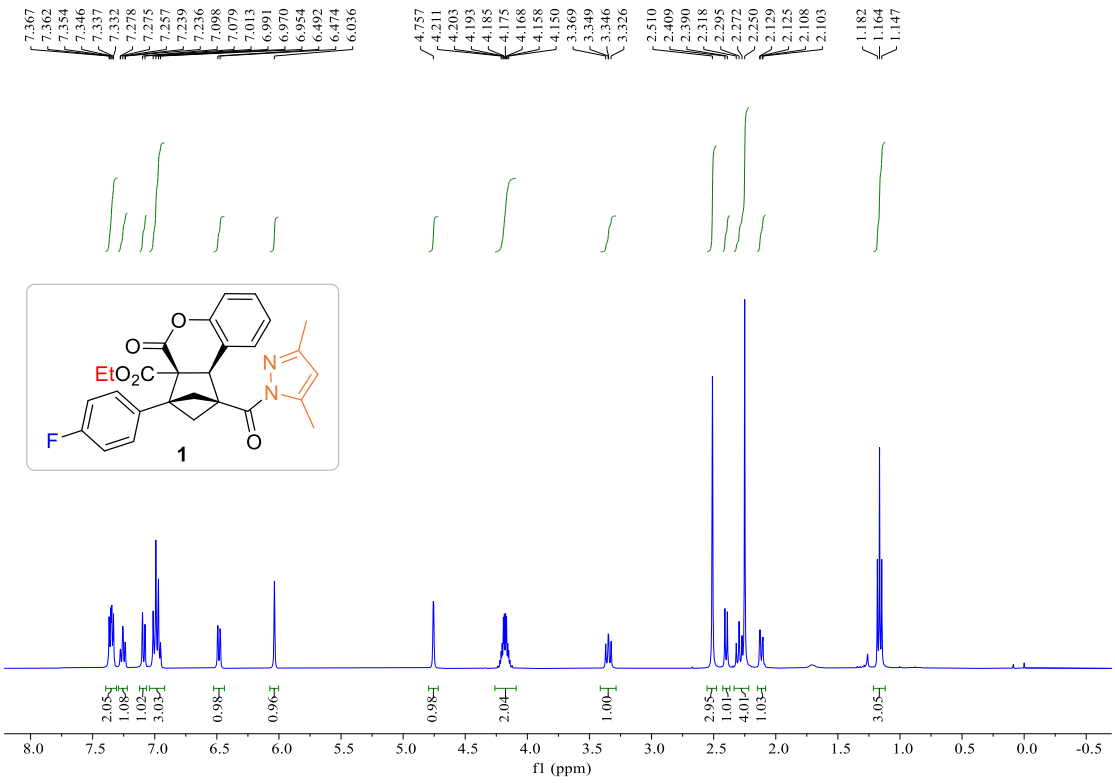
1AA, ^{13}C NMR (101 MHz, $CDCl_3$)



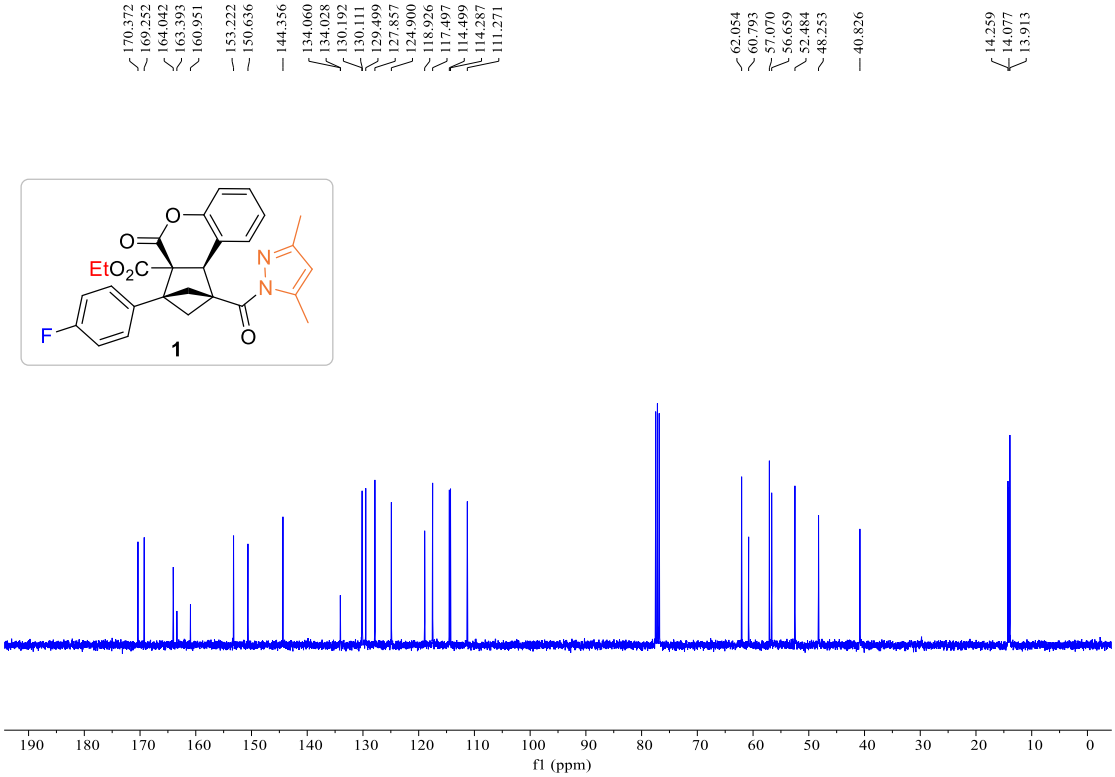
1AA, ^{19}F NMR (376 MHz, $CDCl_3$)



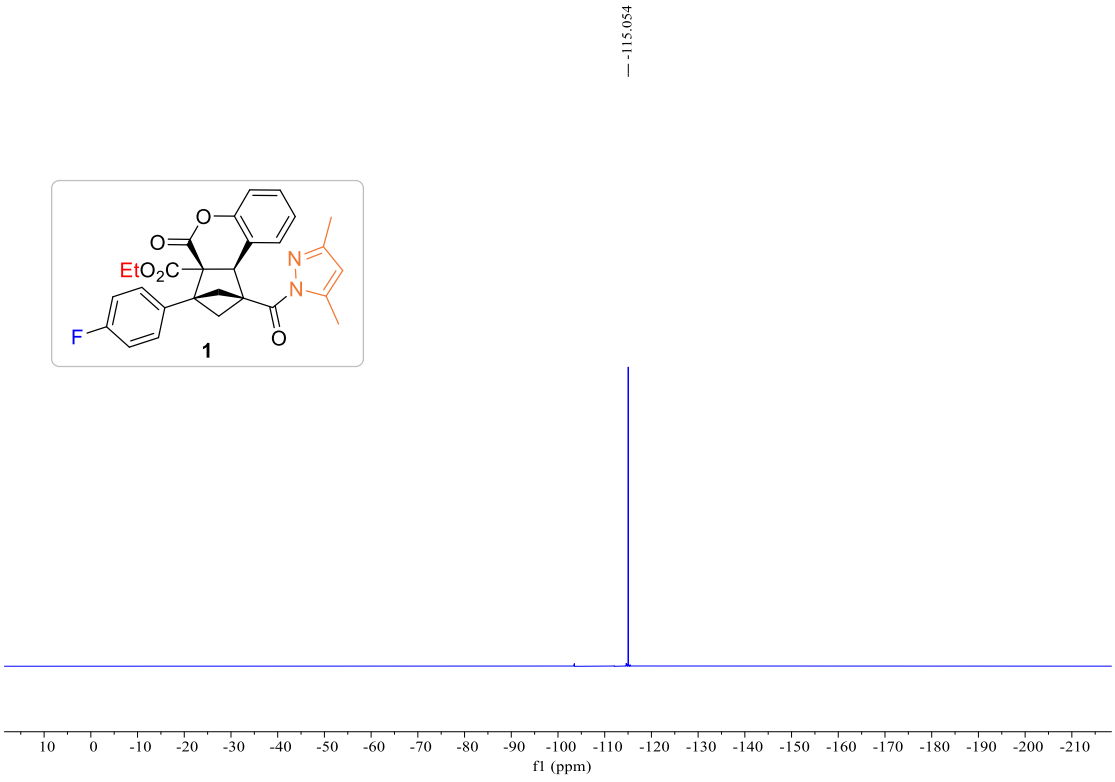
1, ^{1}H NMR (400 MHz, $CDCl_3$)



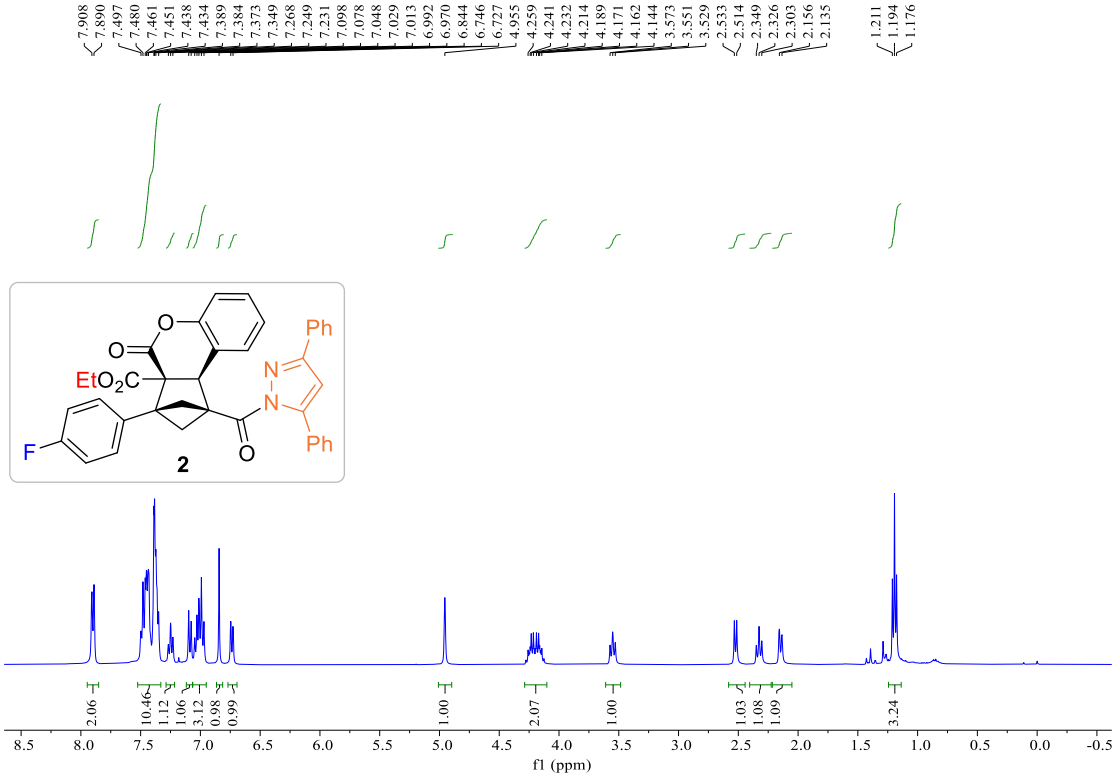
1, ^{13}C NMR (101 MHz, $CDCl_3$)



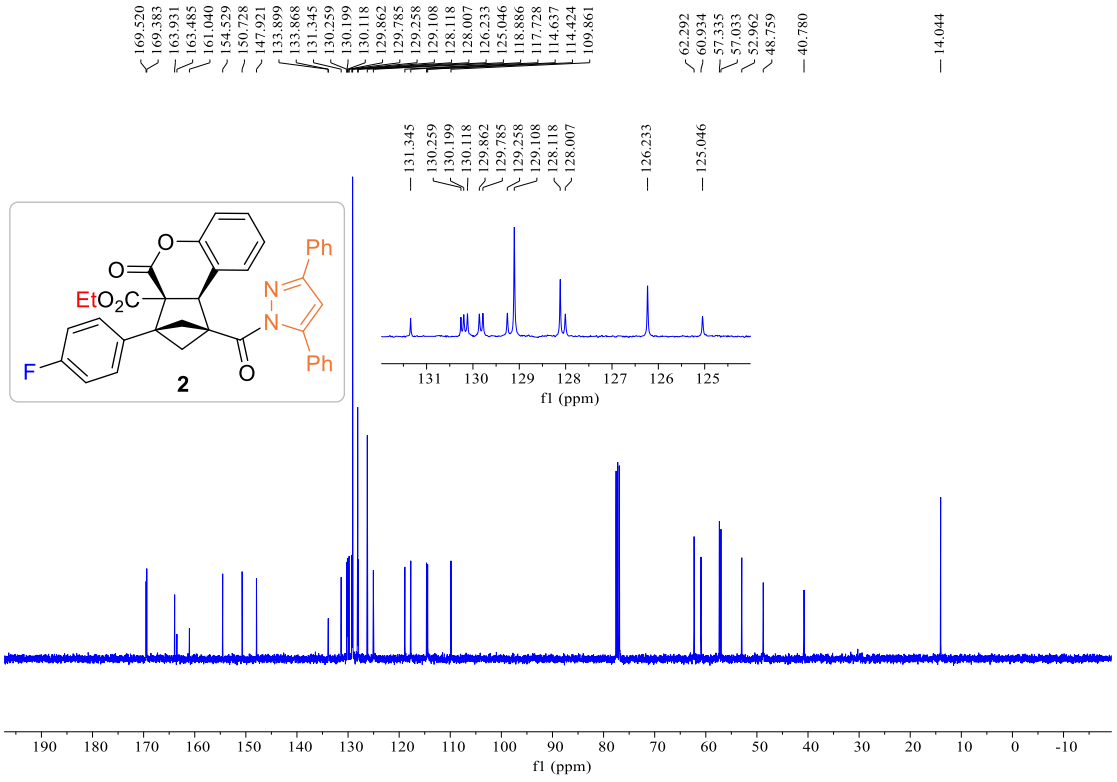
1, ^{19}F NMR (376 MHz, $CDCl_3$)



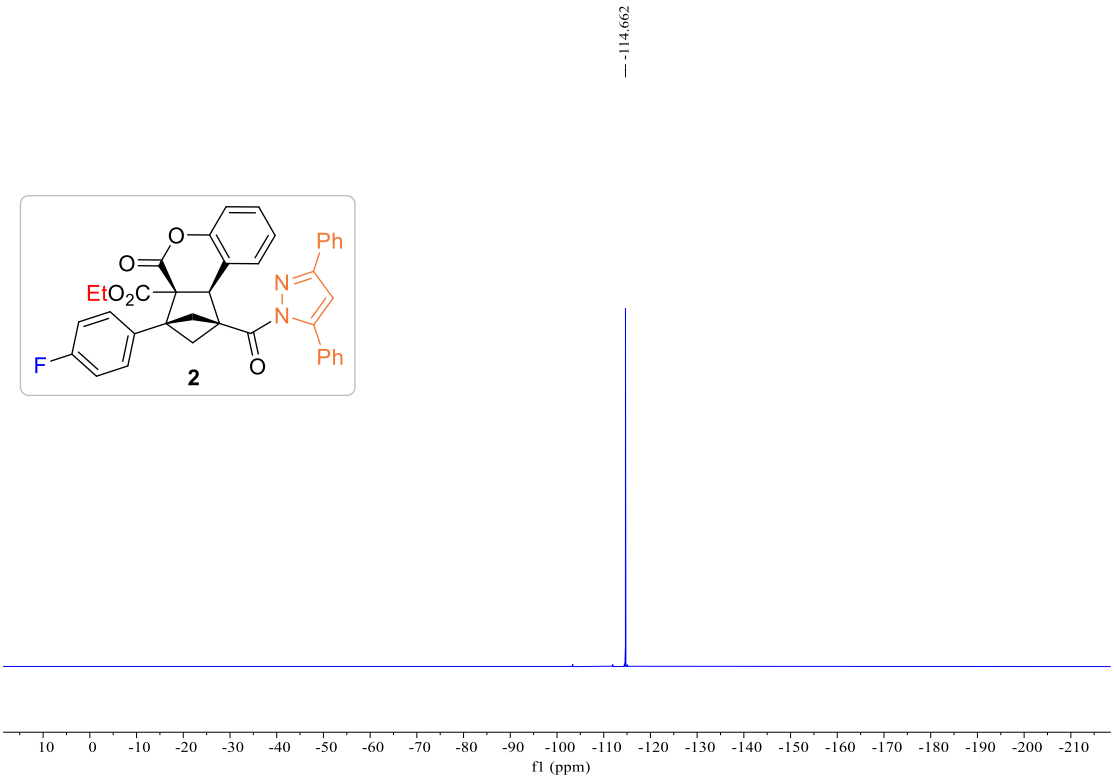
2, ^{1}H NMR (400 MHz, $CDCl_3$)



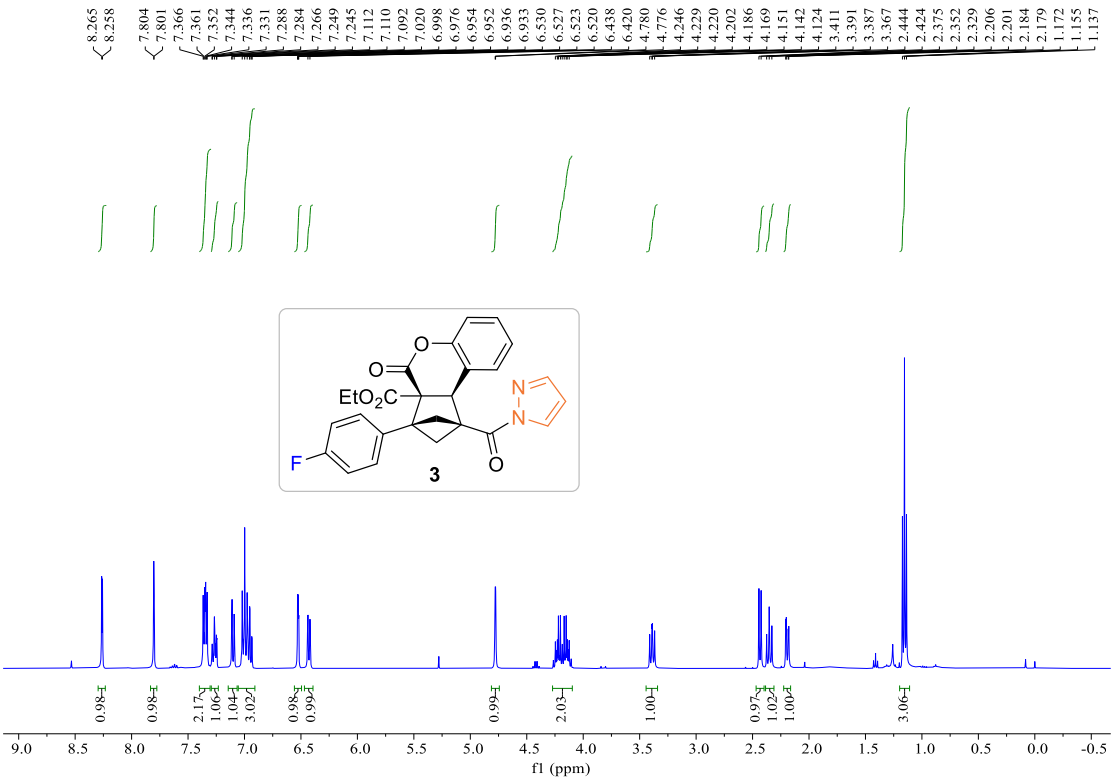
2, ^{13}C NMR (101 MHz, $CDCl_3$)



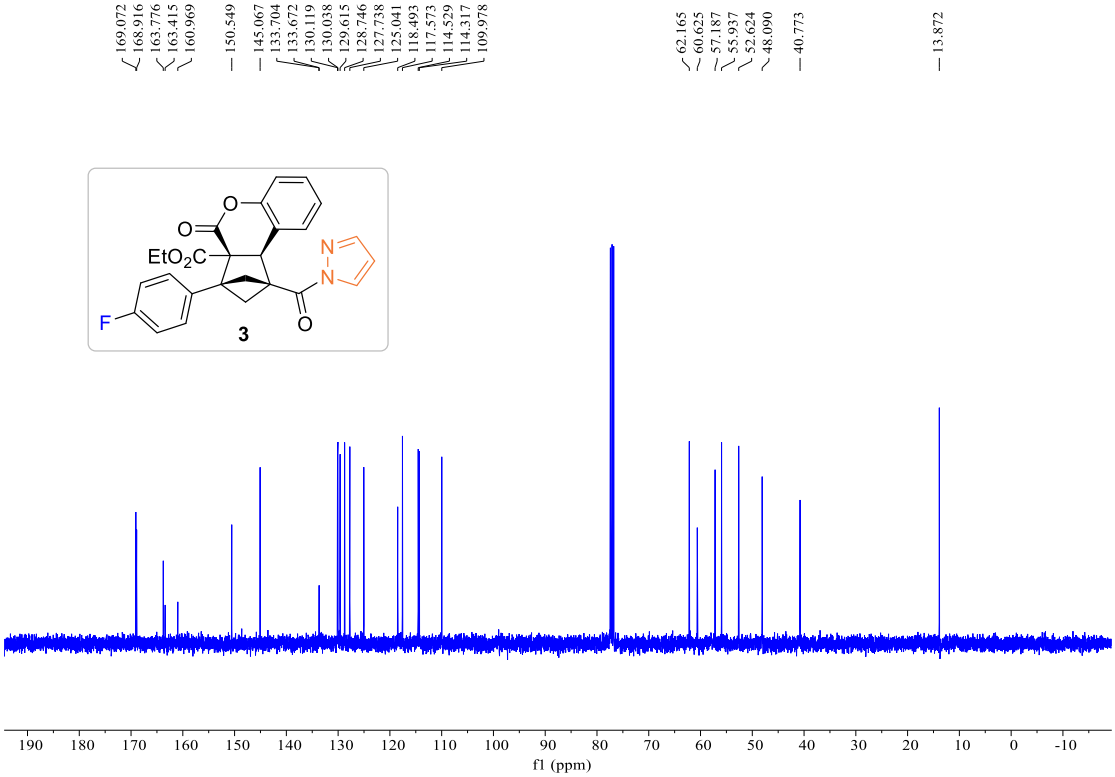
2, ^{19}F NMR (376 MHz, $CDCl_3$)



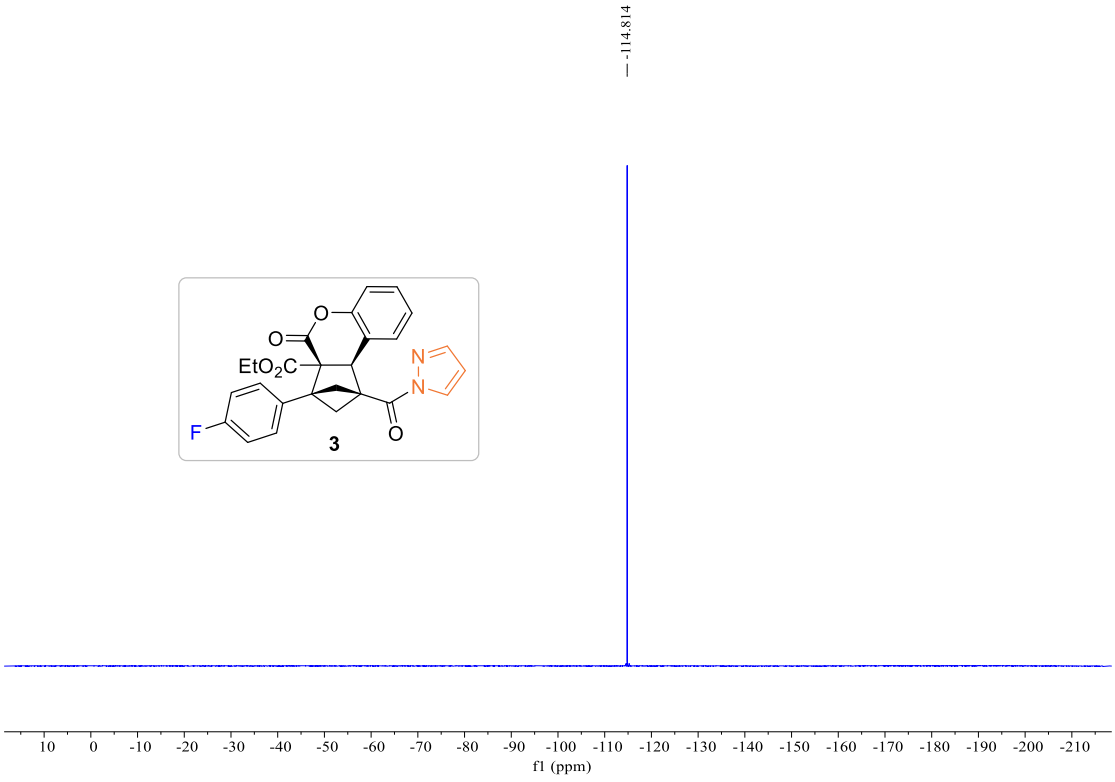
3, ^{1}H NMR (400 MHz, $CDCl_3$)



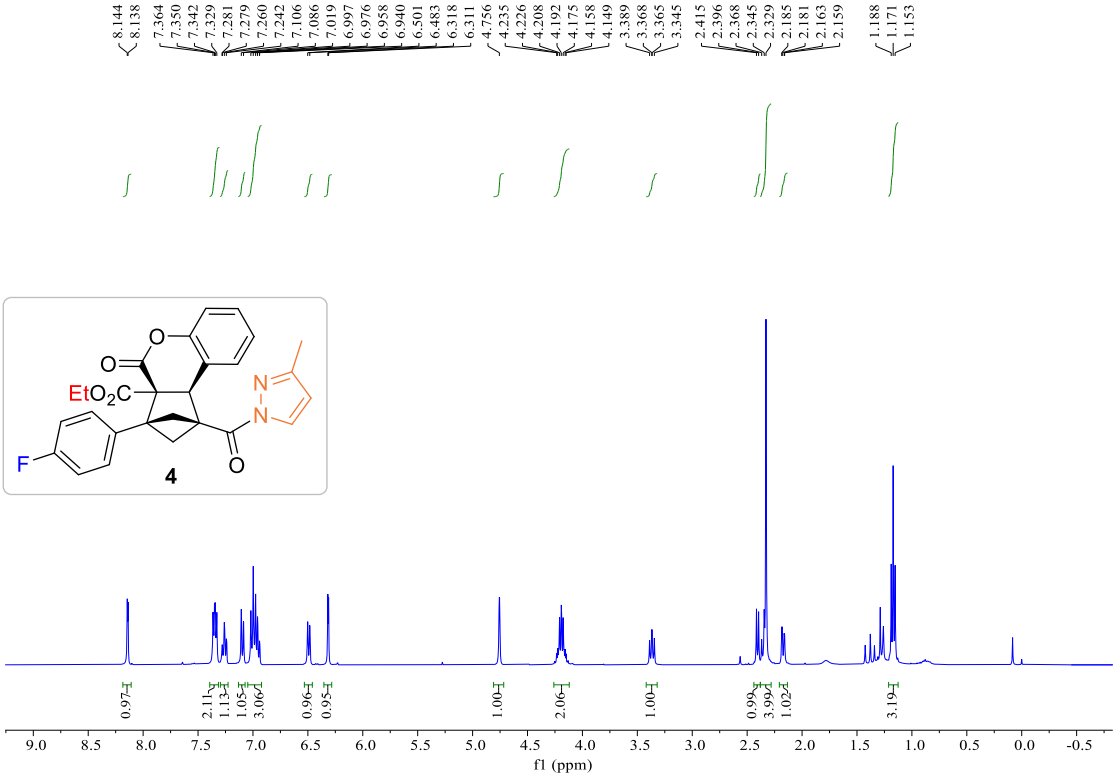
3, ^{13}C NMR (101 MHz, $CDCl_3$)



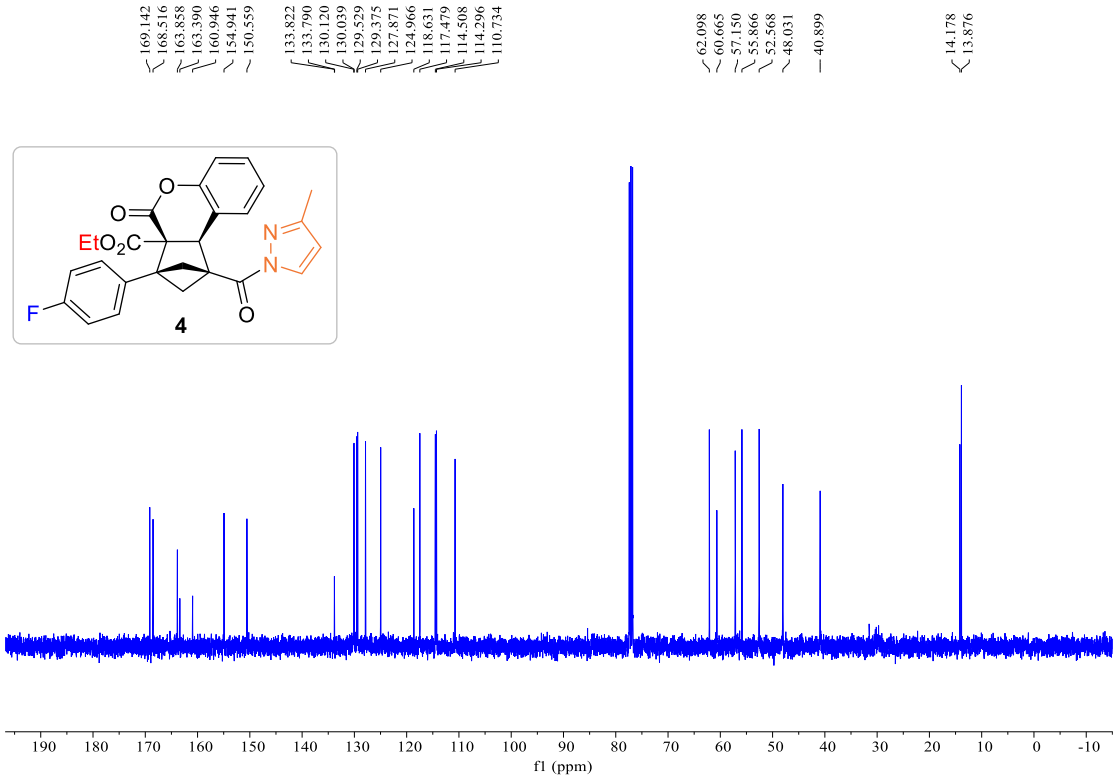
3, ^{19}F NMR (376 MHz, $CDCl_3$)



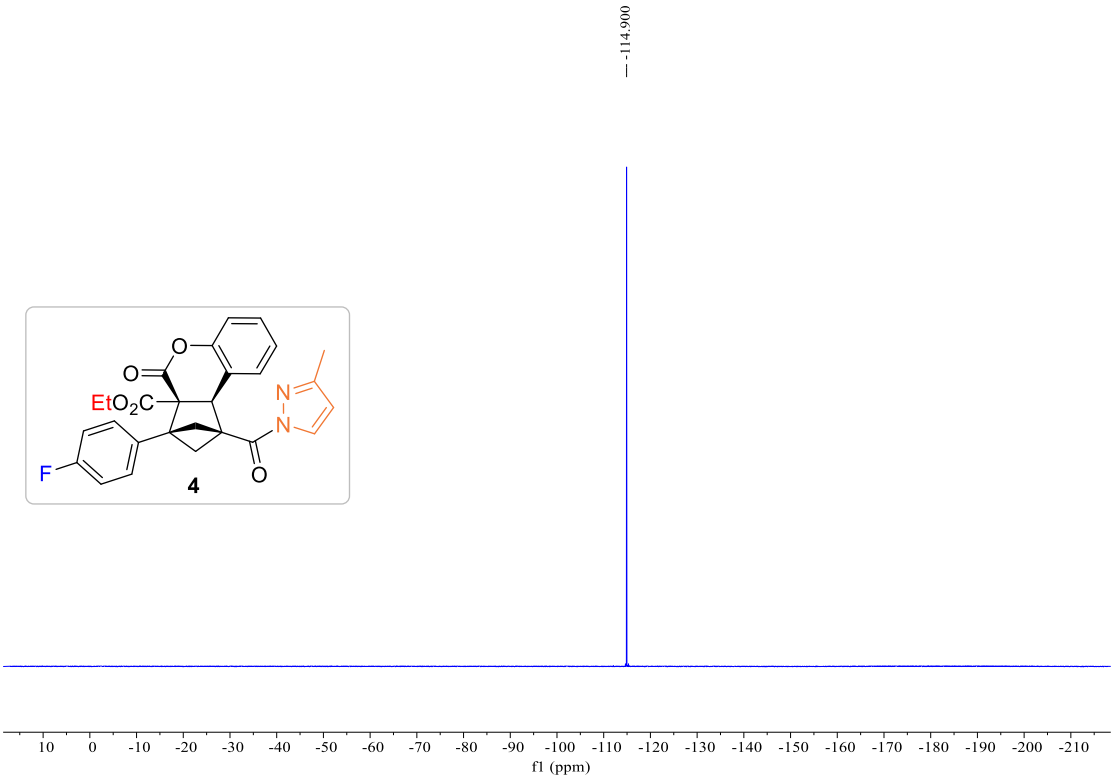
4, ^{1}H NMR (400 MHz, $CDCl_3$)



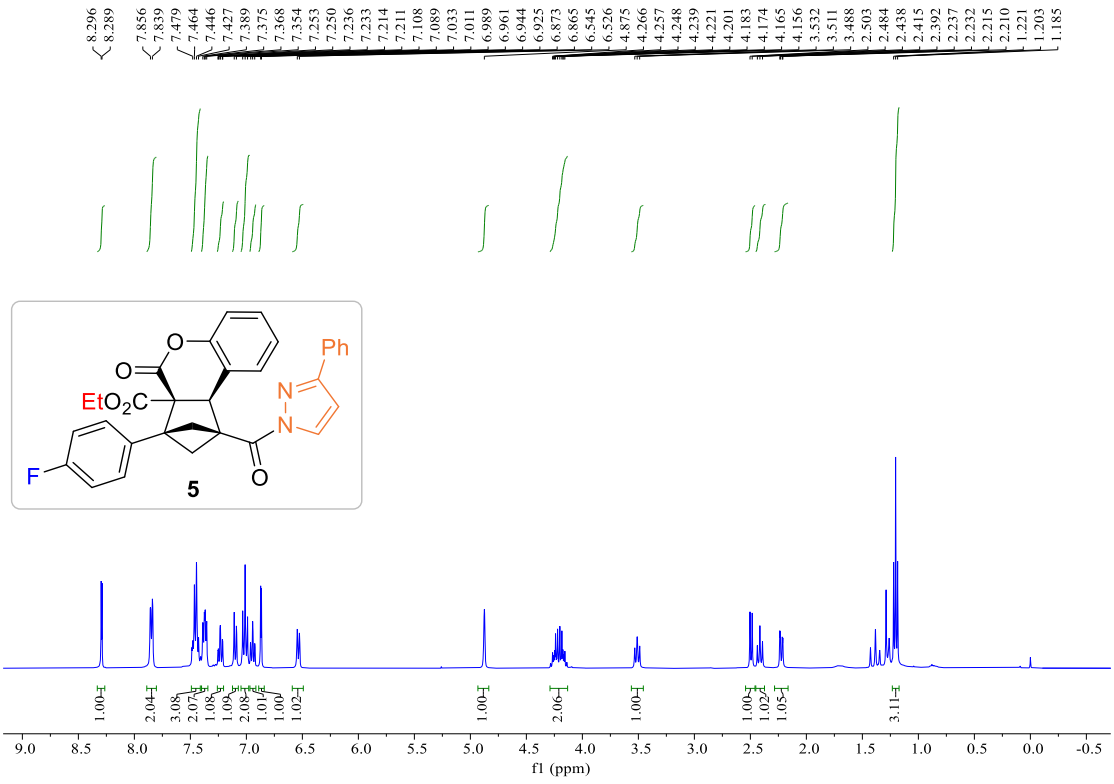
4, ^{13}C NMR (101 MHz, $CDCl_3$)



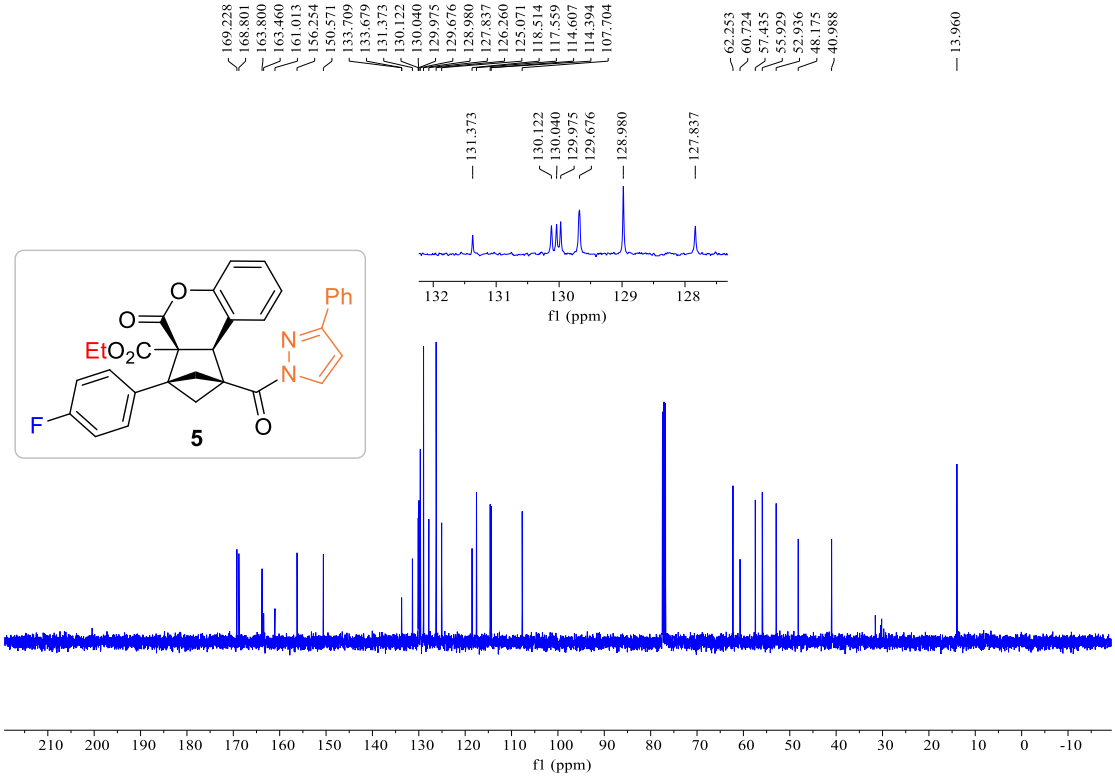
4, ^{19}F NMR (376 MHz, $CDCl_3$)



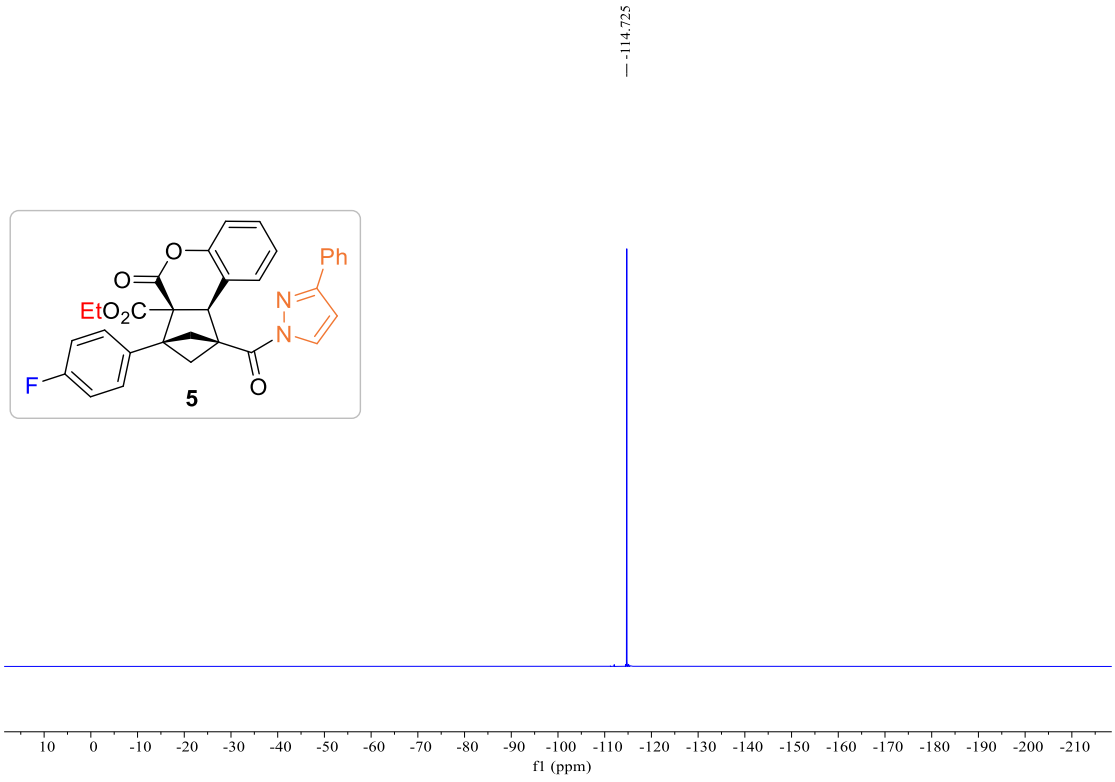
5, ^{1}H NMR (400 MHz, $CDCl_3$)



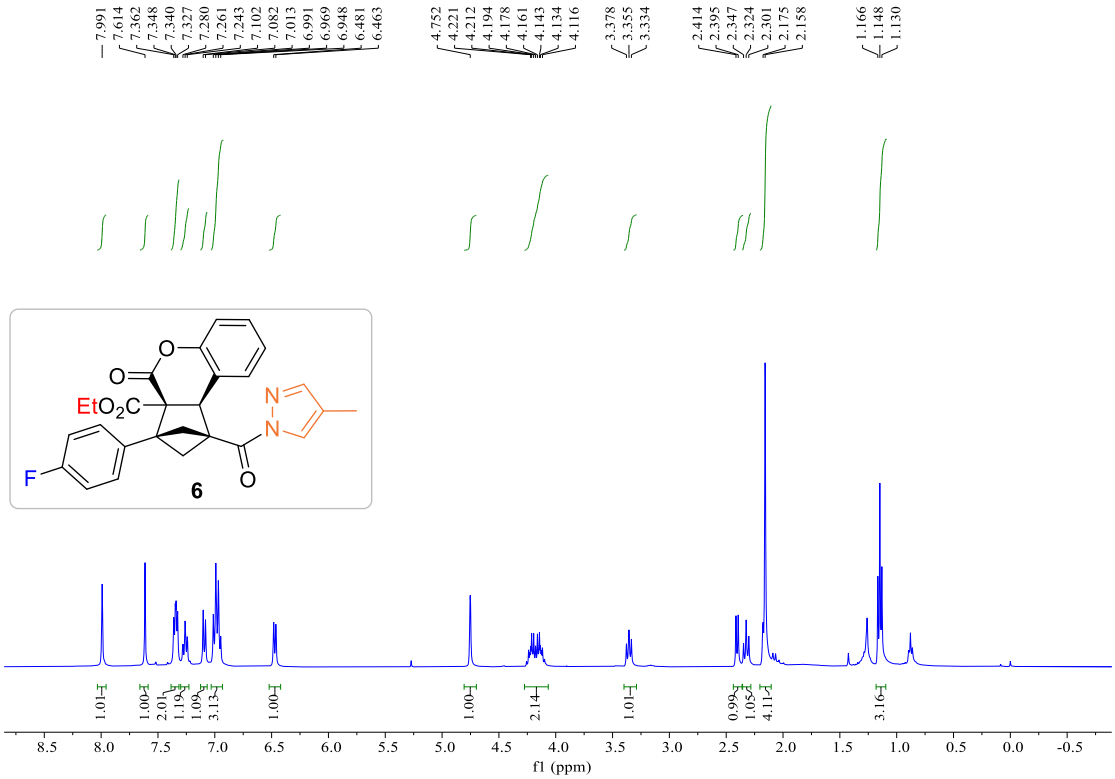
5, ^{13}C NMR (101 MHz, $CDCl_3$)



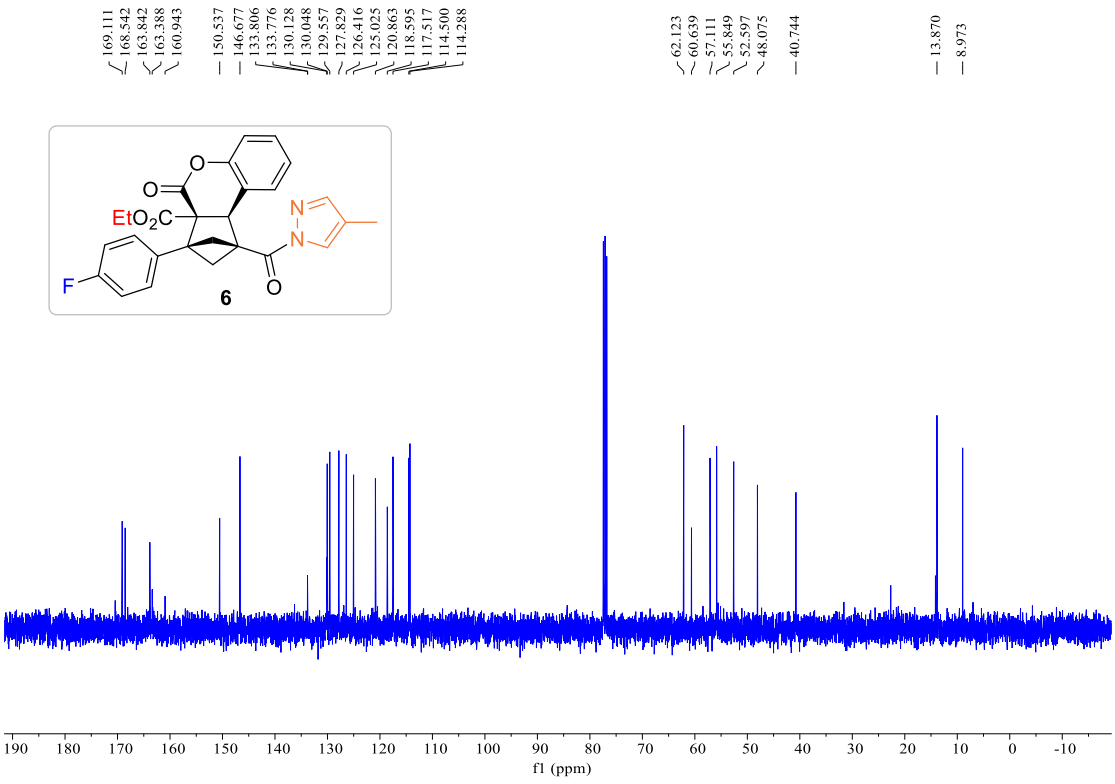
5, ^{19}F NMR (376 MHz, $CDCl_3$)



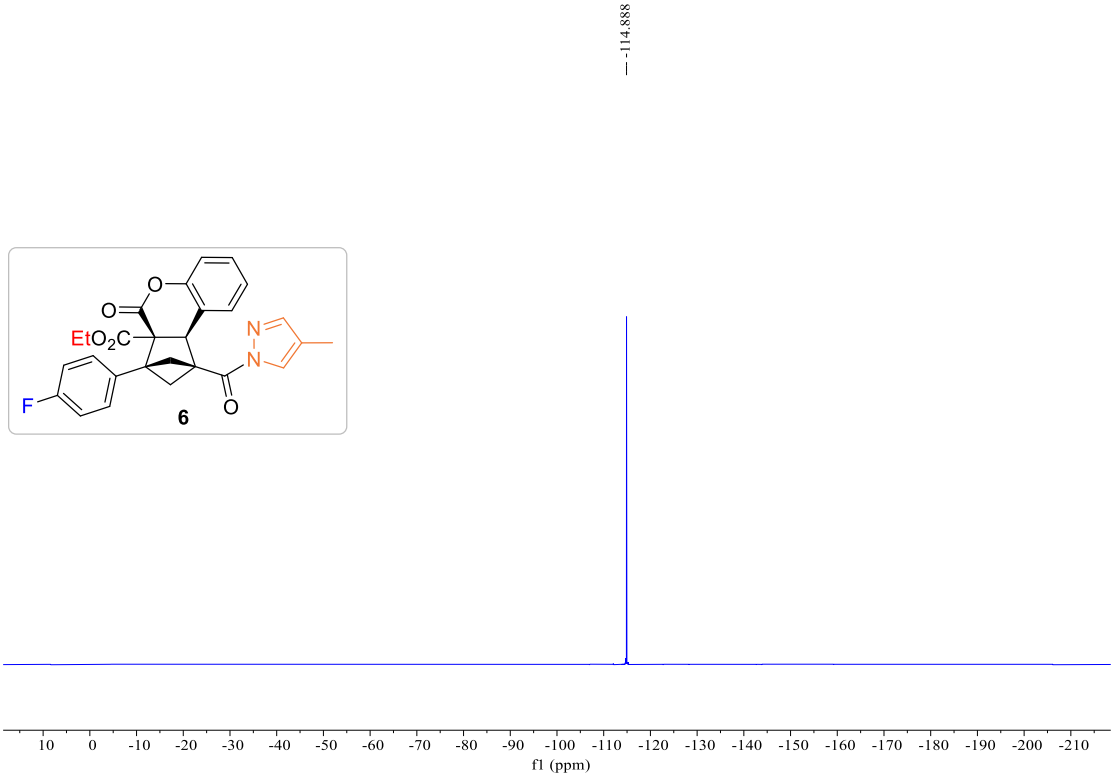
6, ^{1}H NMR (400 MHz, $CDCl_3$)



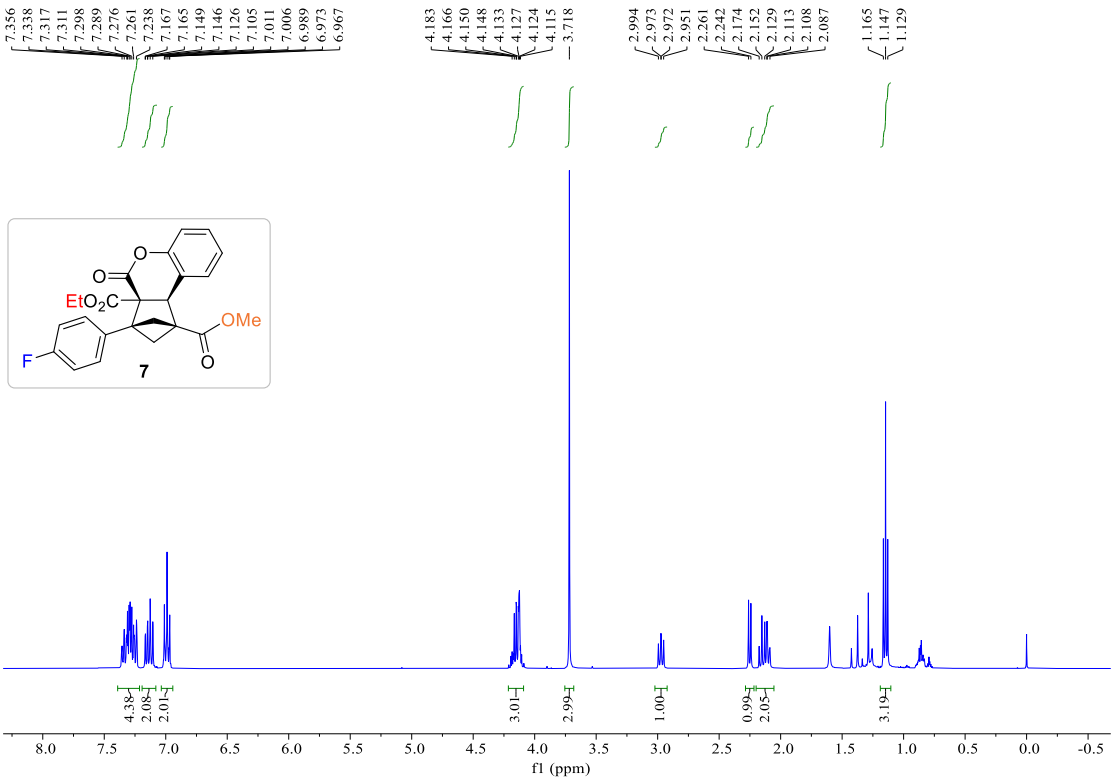
6, ^{13}C NMR (101 MHz, $CDCl_3$)



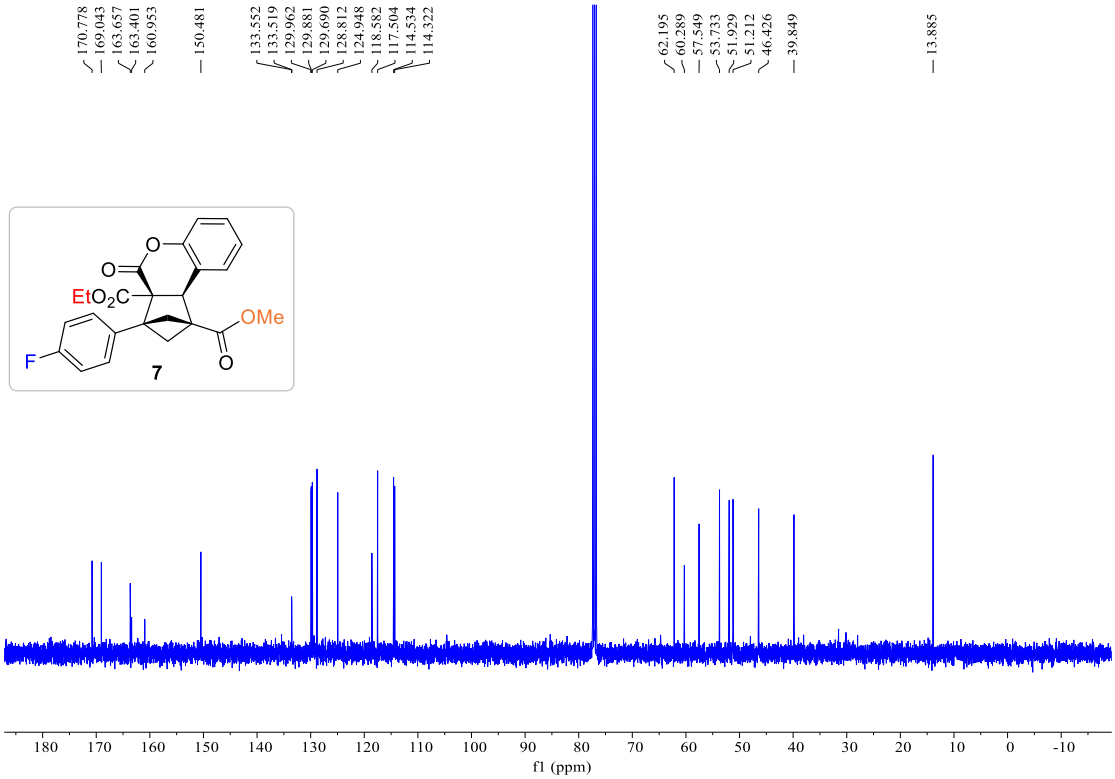
6, ^{19}F NMR (376 MHz, $CDCl_3$)



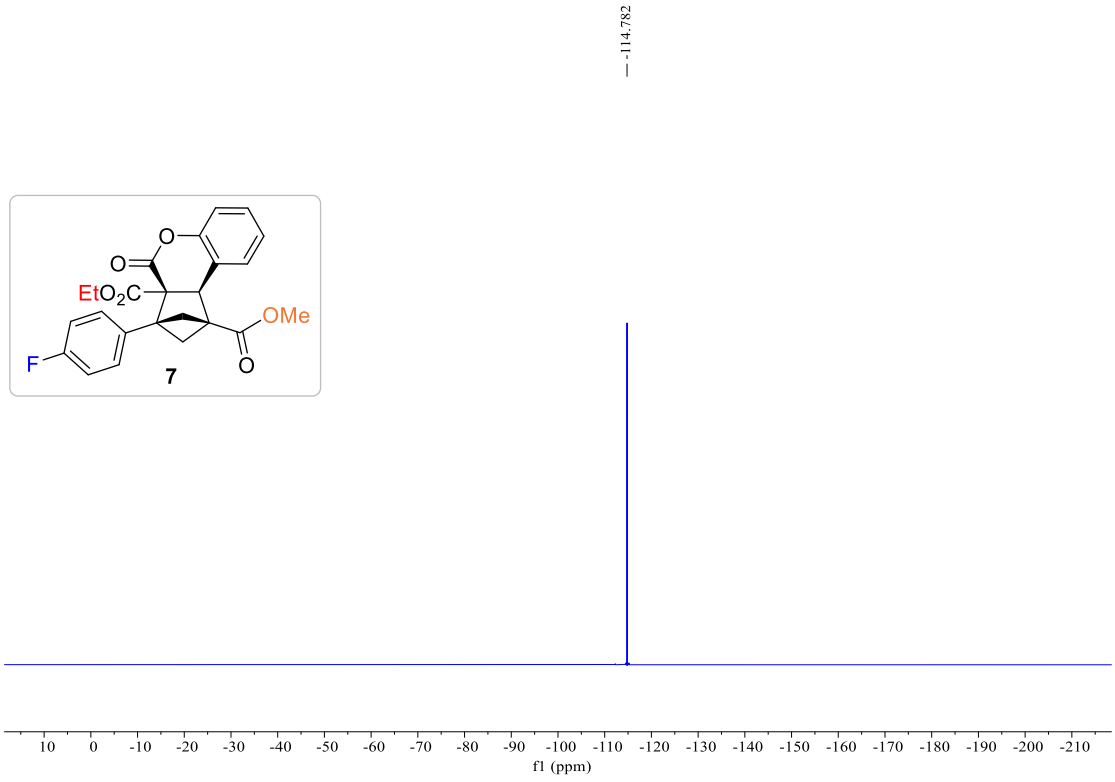
7, ^{1}H NMR (400 MHz, $CDCl_3$)



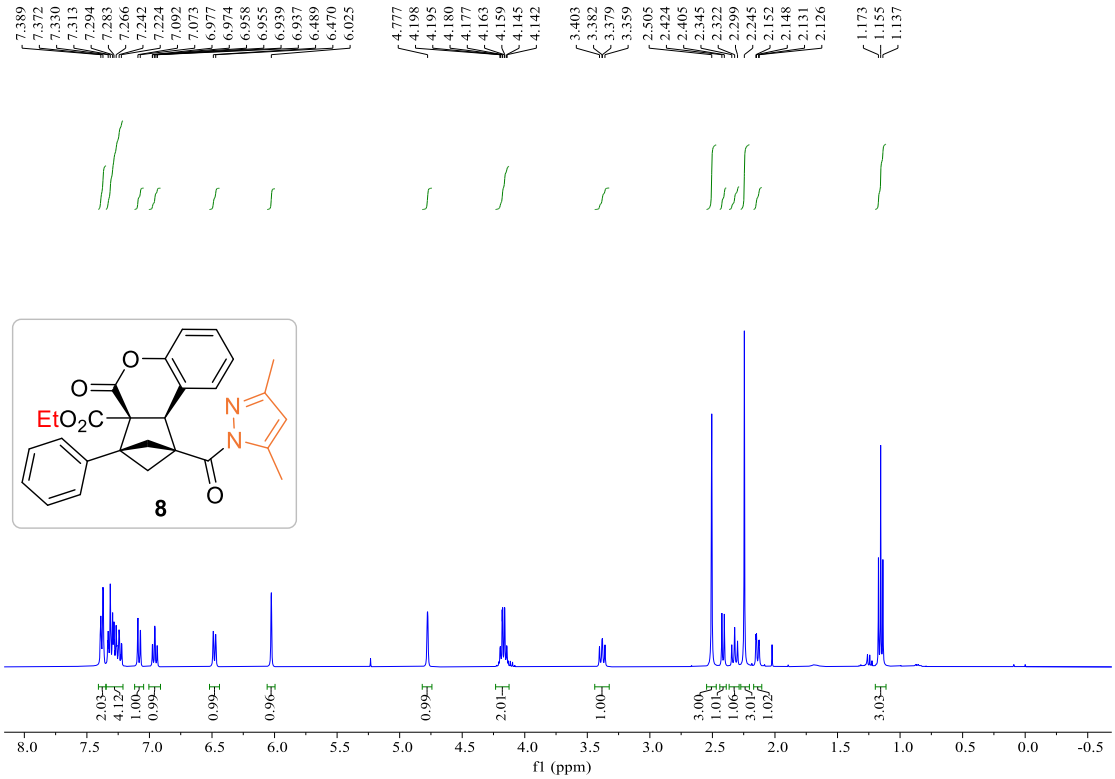
7, ^{13}C NMR (101 MHz, $CDCl_3$)



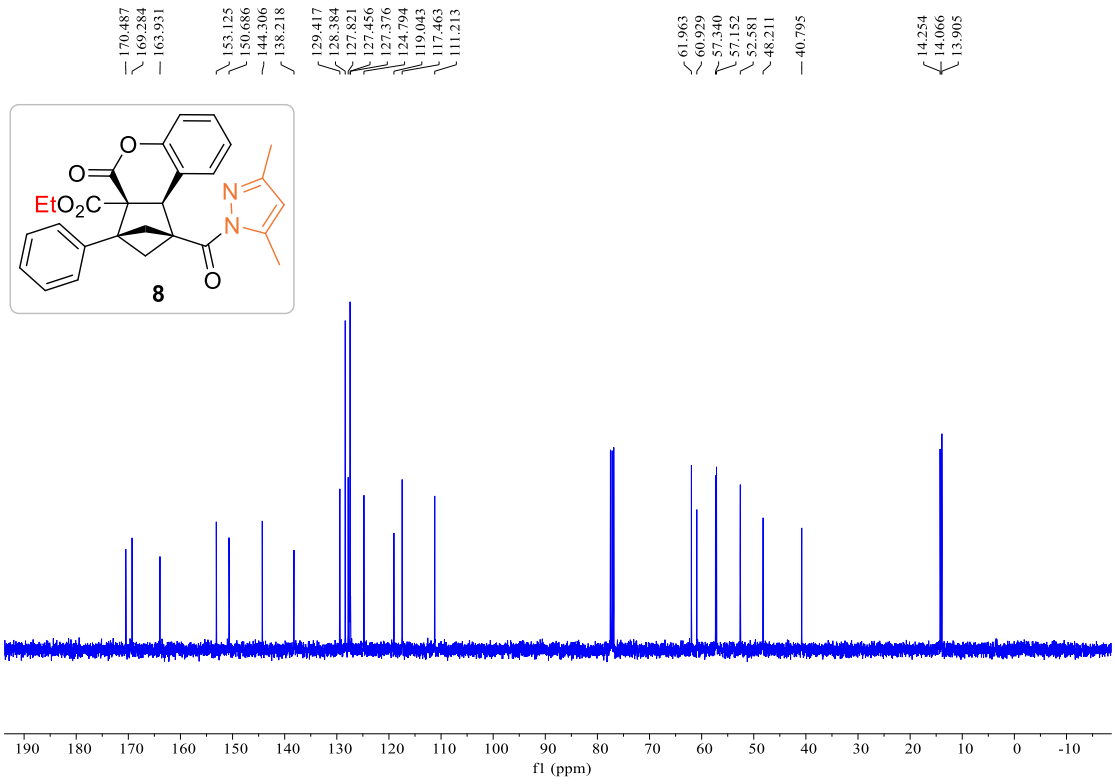
7, ^{19}F NMR (376 MHz, $CDCl_3$)



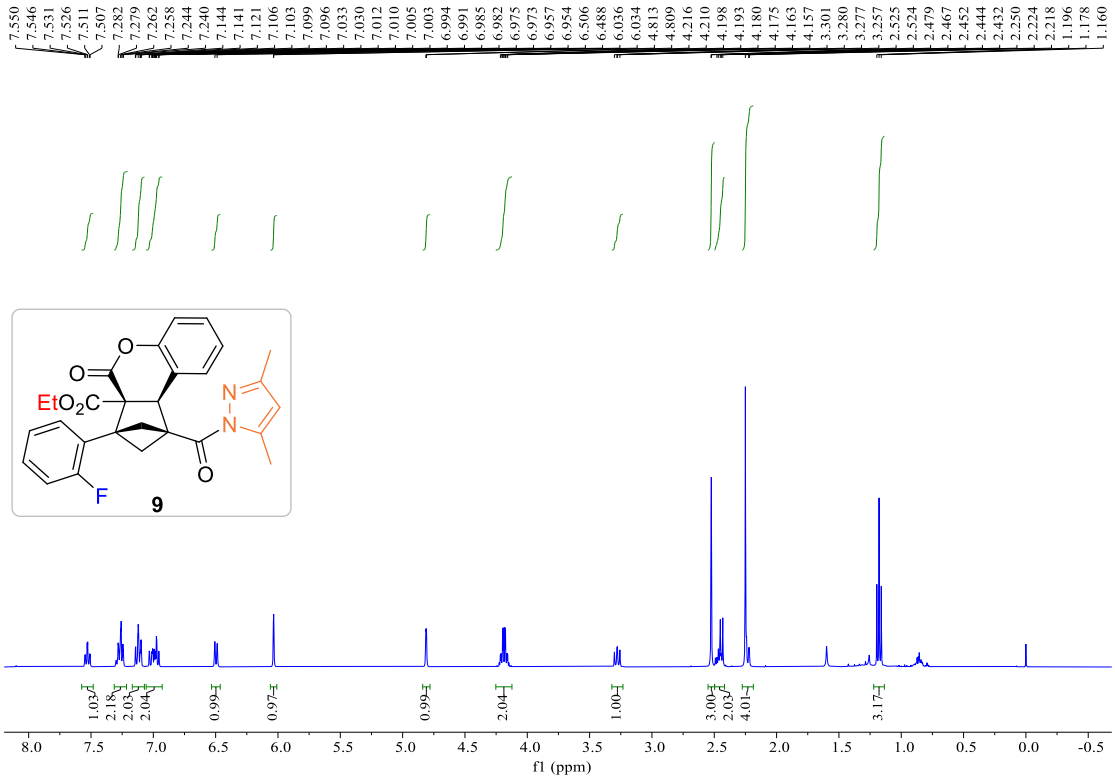
8, ^{1}H NMR (400 MHz, $CDCl_3$)



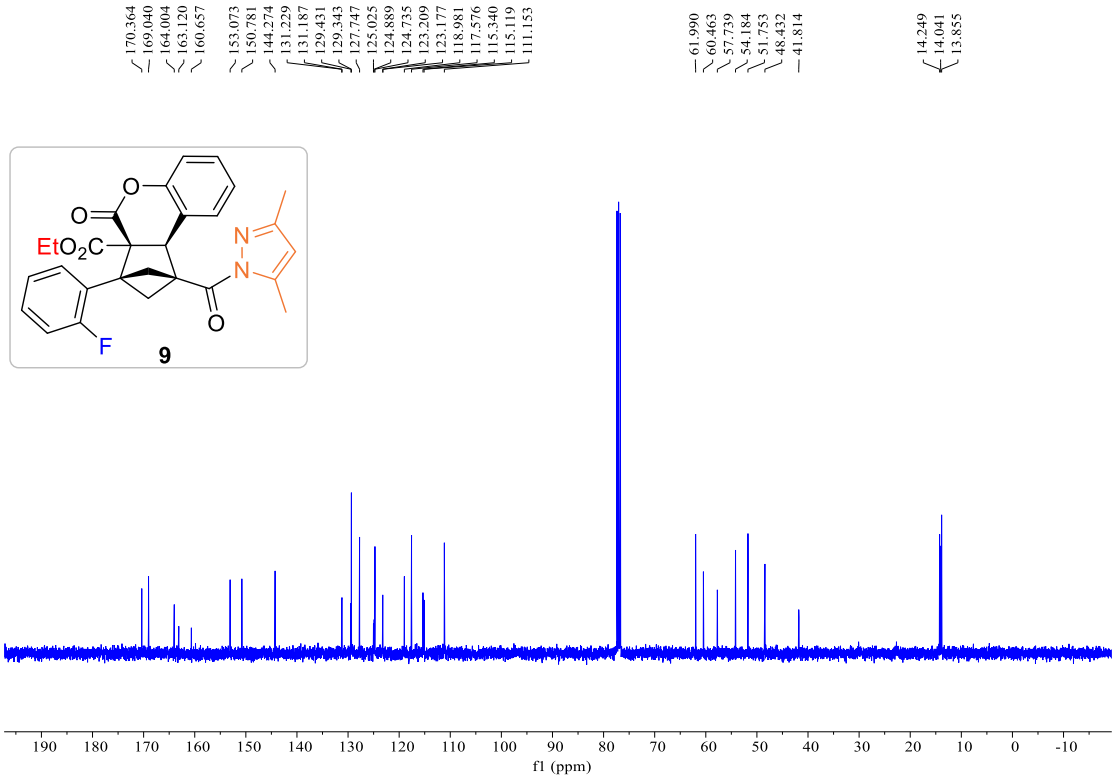
8, ^{13}C NMR (101 MHz, $CDCl_3$)



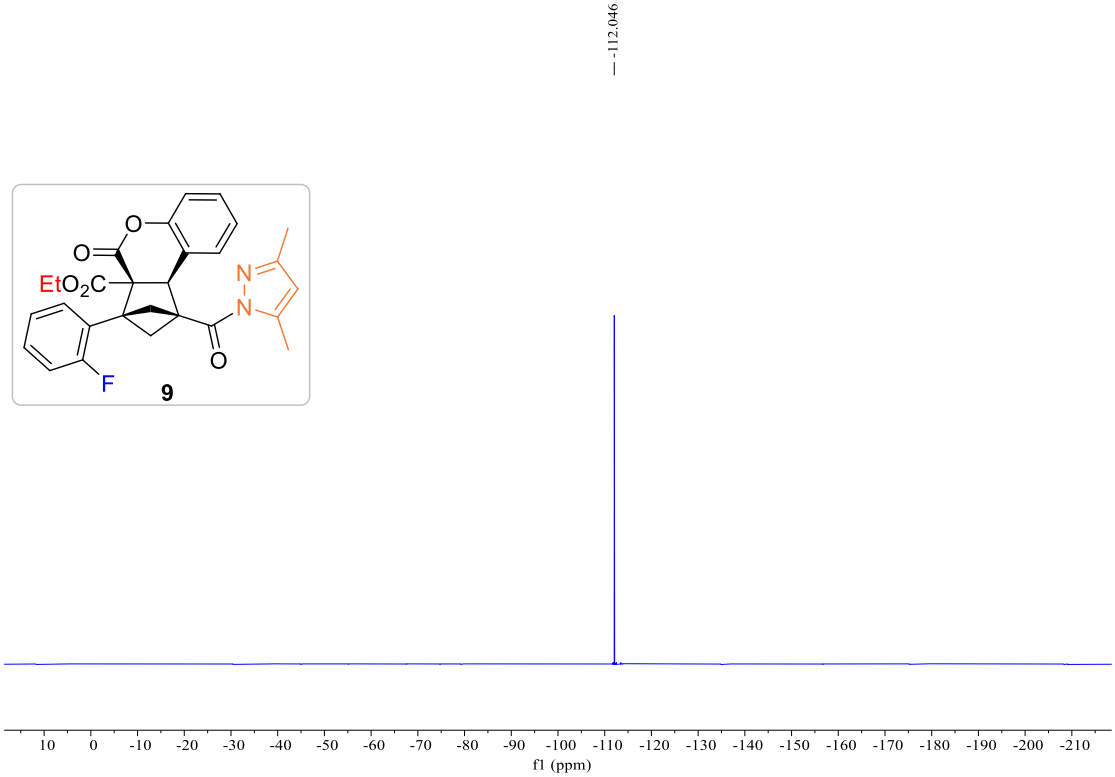
9, ^{1}H NMR (400 MHz, $CDCl_3$)



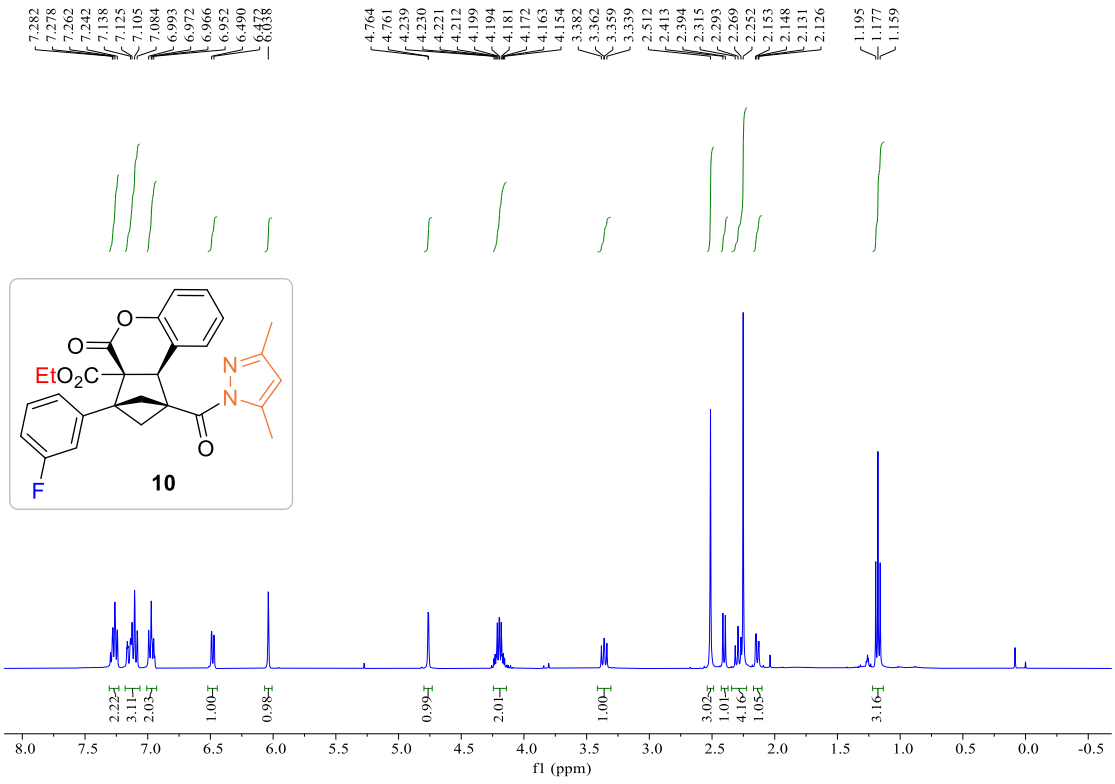
9, ^{13}C NMR (101 MHz, $CDCl_3$)



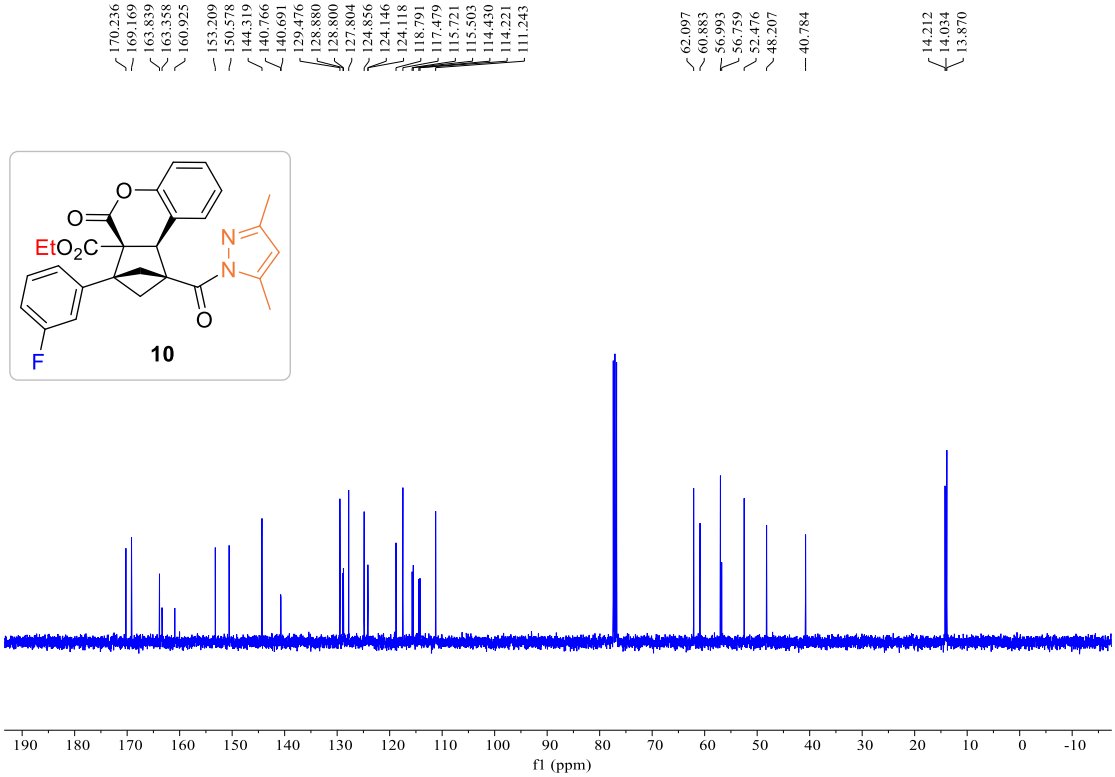
9, ^{19}F NMR (376 MHz, $CDCl_3$)



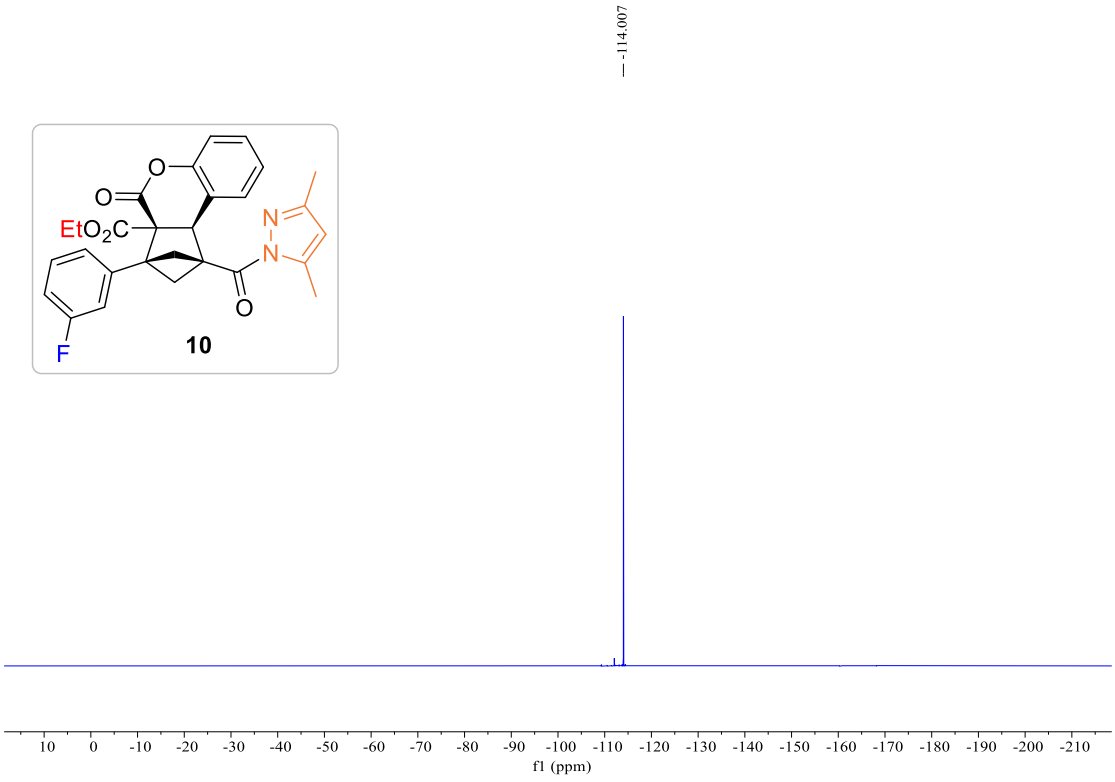
10, ^{1}H NMR (400 MHz, $CDCl_3$)



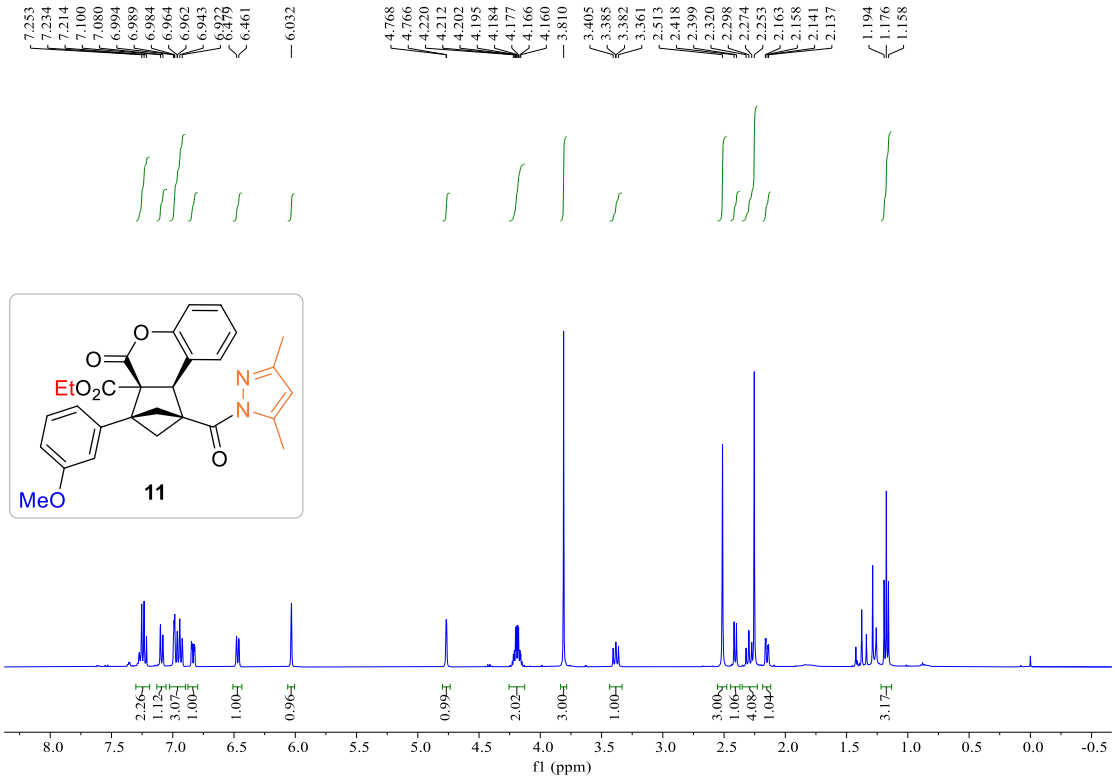
10, ^{13}C NMR (101 MHz, $CDCl_3$)



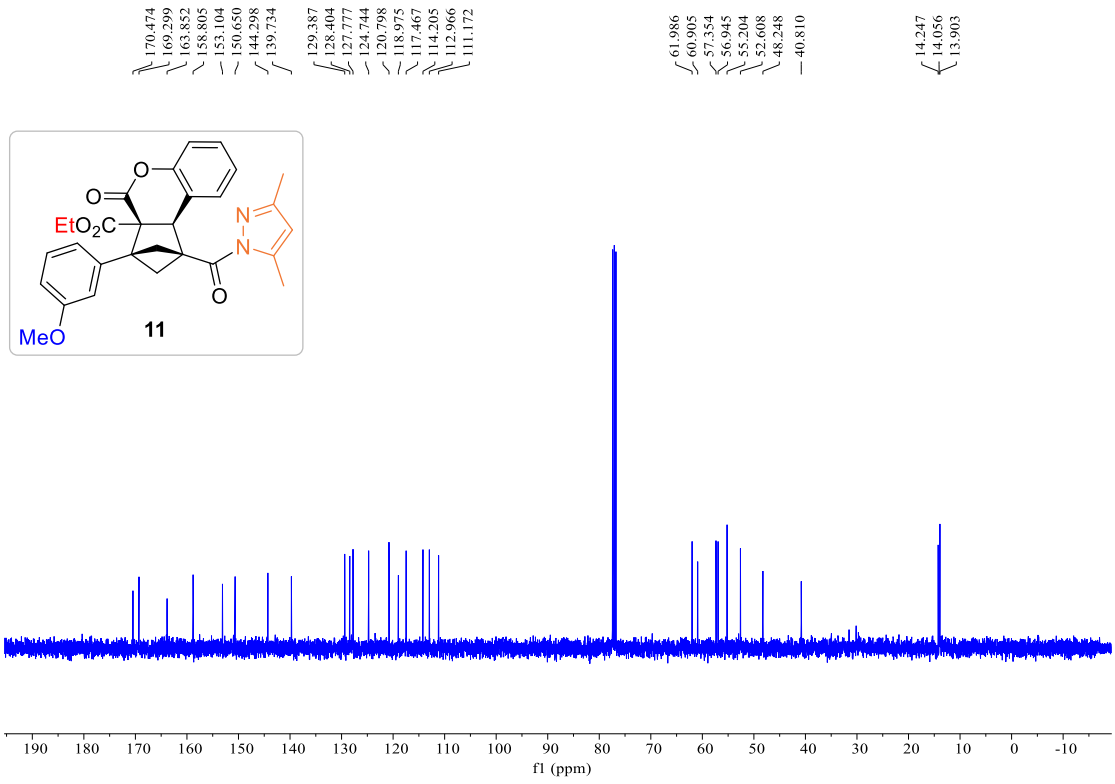
10, ^{19}F NMR (376 MHz, CDCl3)



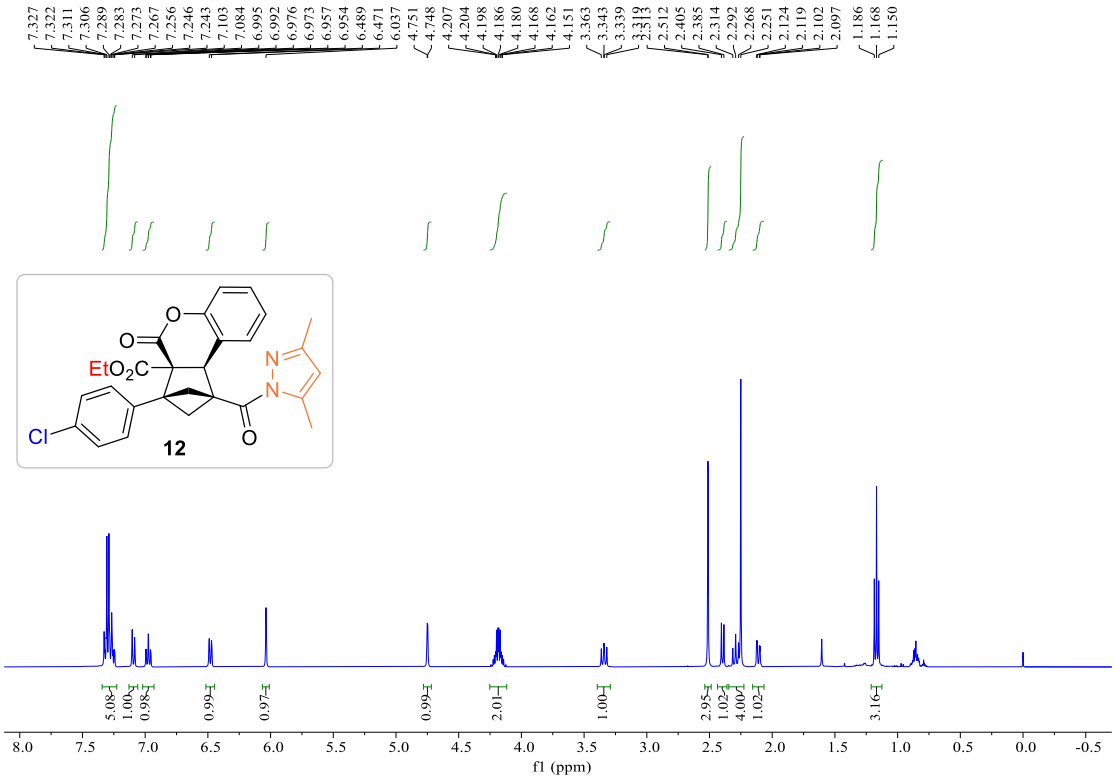
11, ^{1}H NMR (400 MHz, $CDCl_3$)



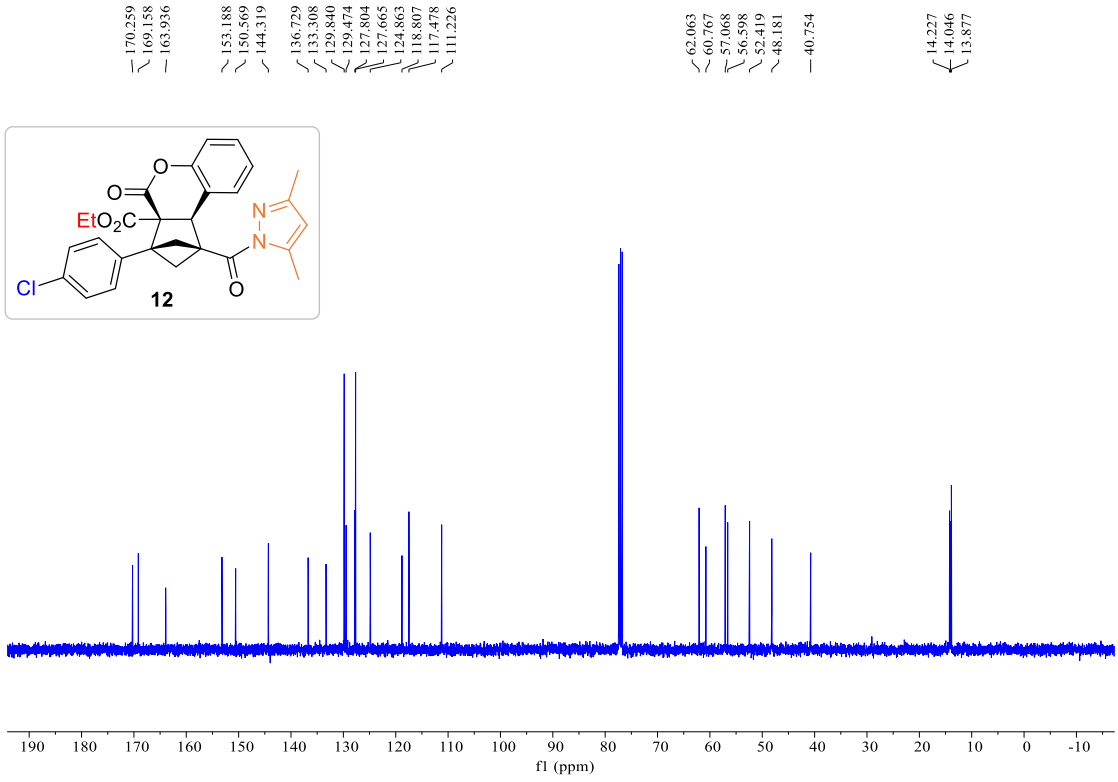
11, ^{13}C NMR (101 MHz, $CDCl_3$)



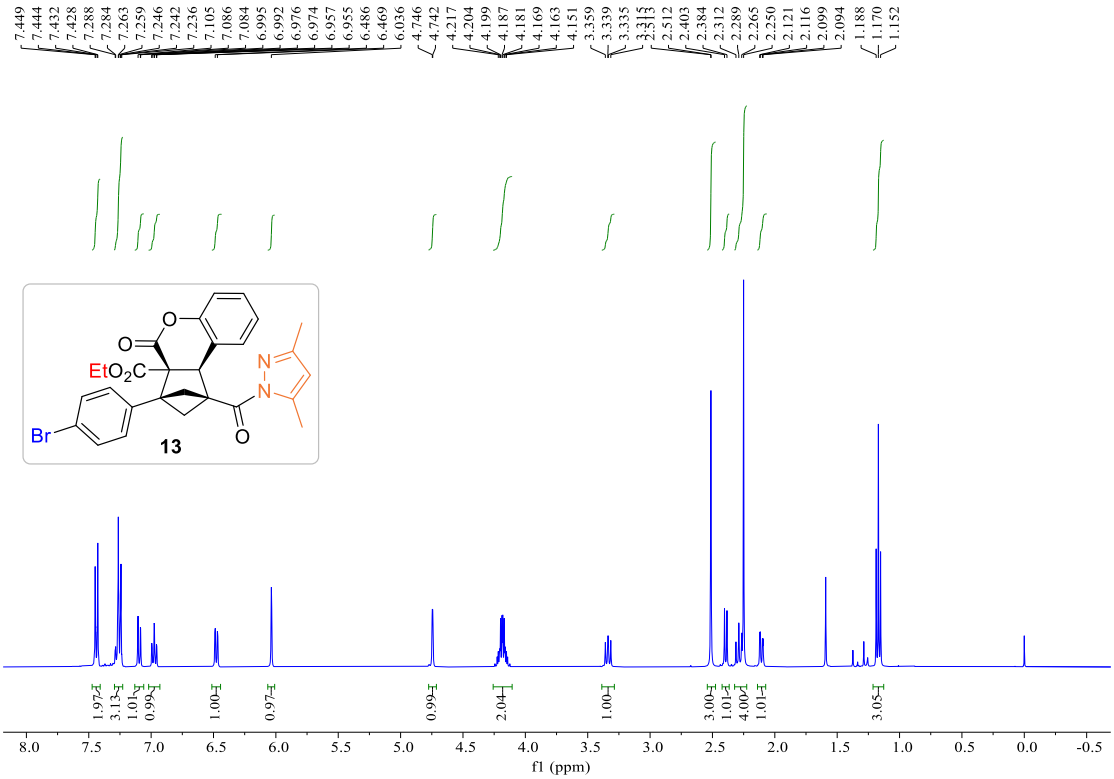
12, ^{1}H NMR (400 MHz, $CDCl_3$)



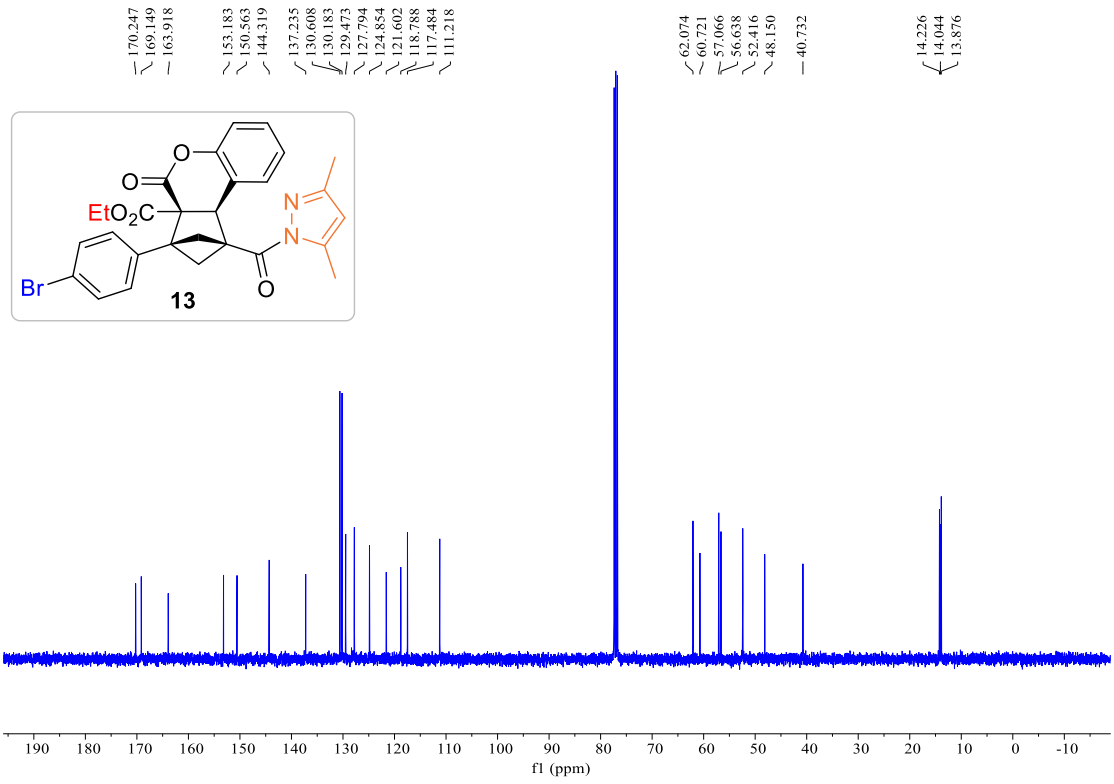
12, ^{13}C NMR (101 MHz, $CDCl_3$)



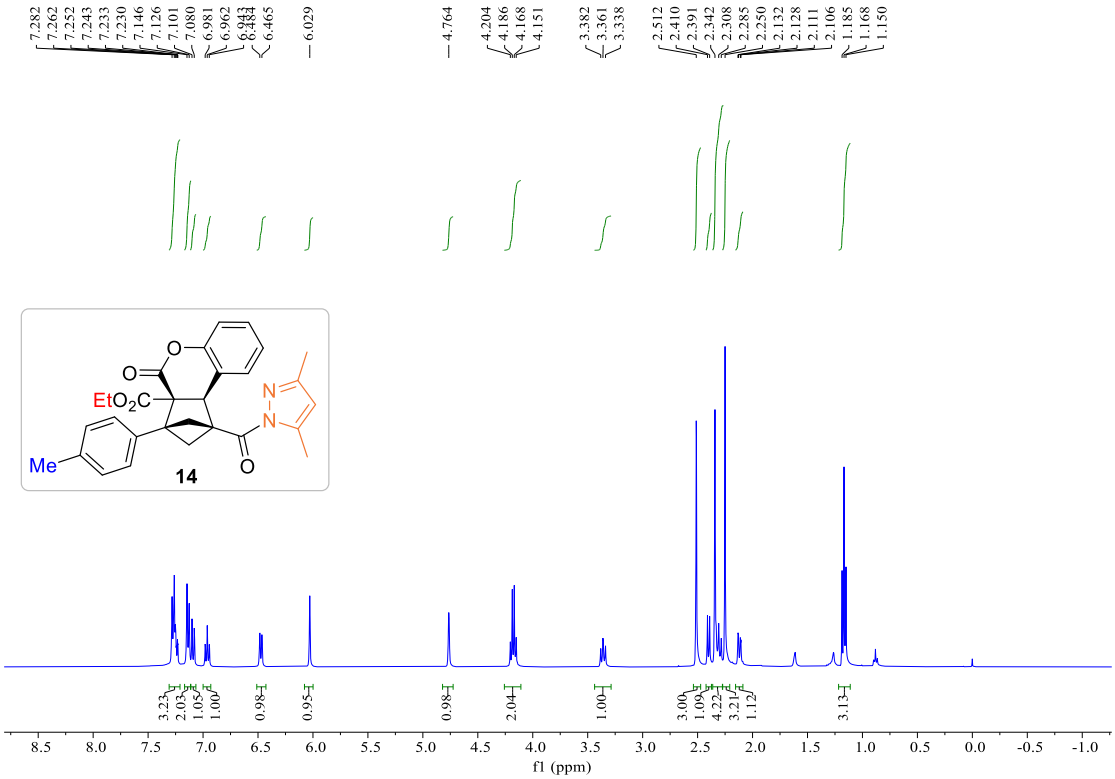
13, ^{1}H NMR (400 MHz, $CDCl_3$)



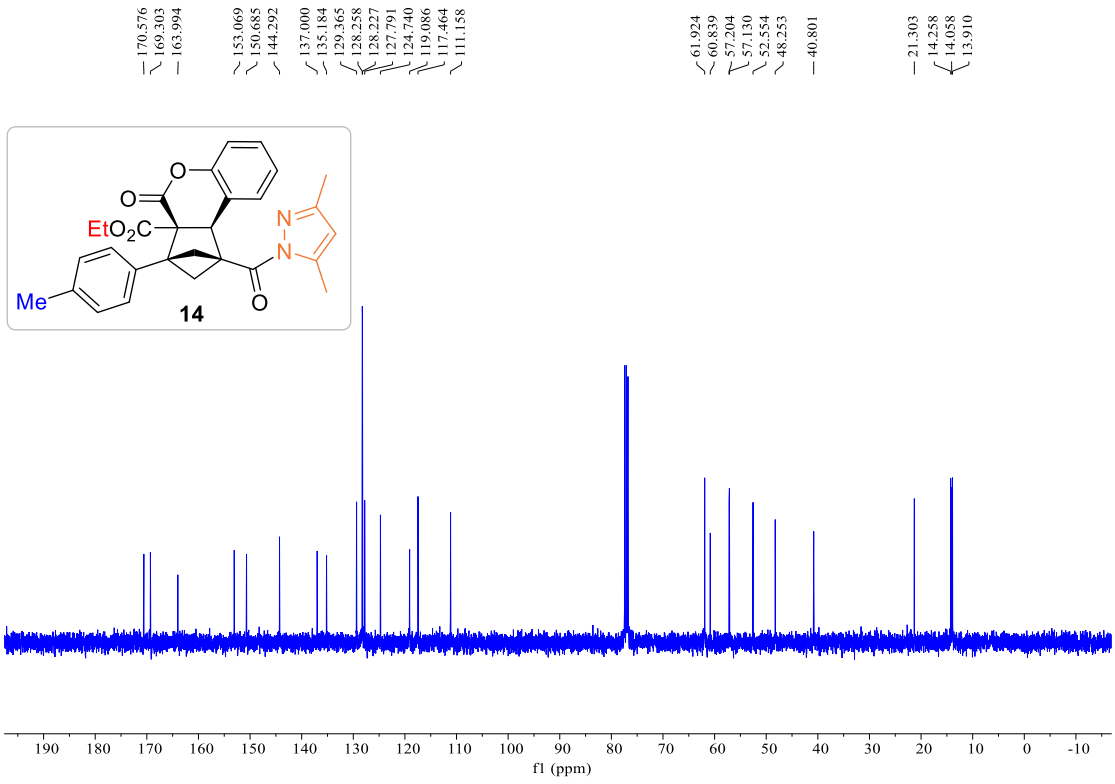
13, ^{13}C NMR (101 MHz, $CDCl_3$)



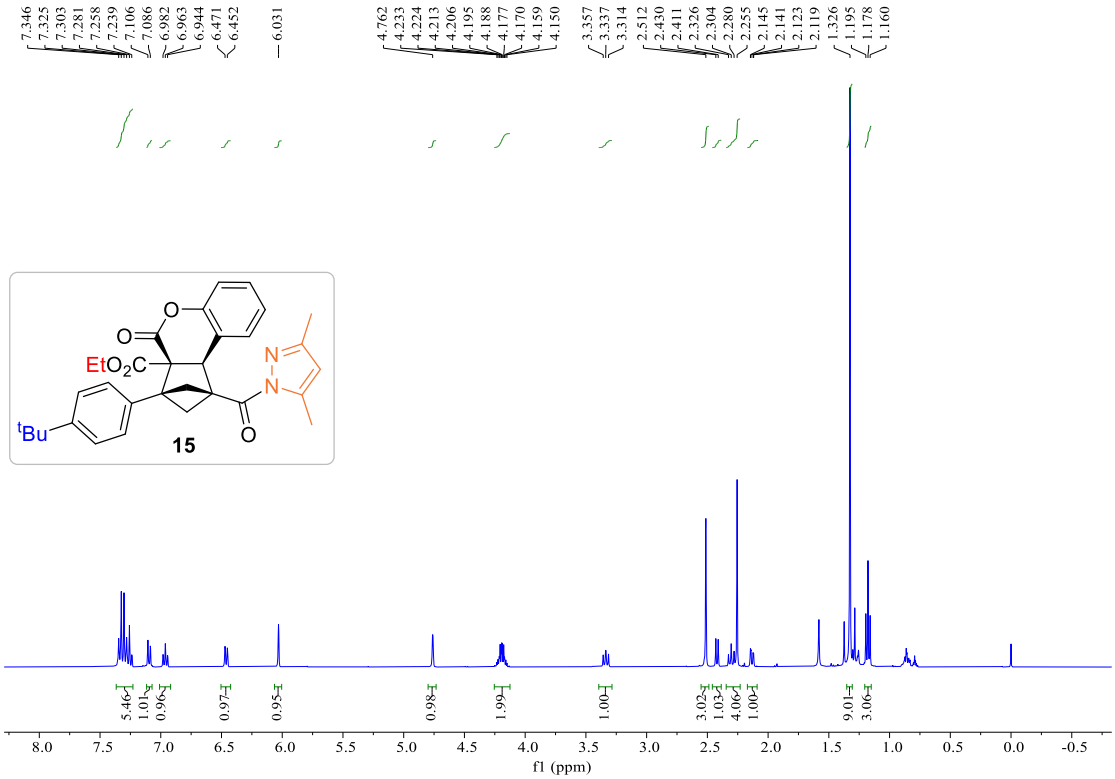
14, ^{1}H NMR (400 MHz, $CDCl_3$)



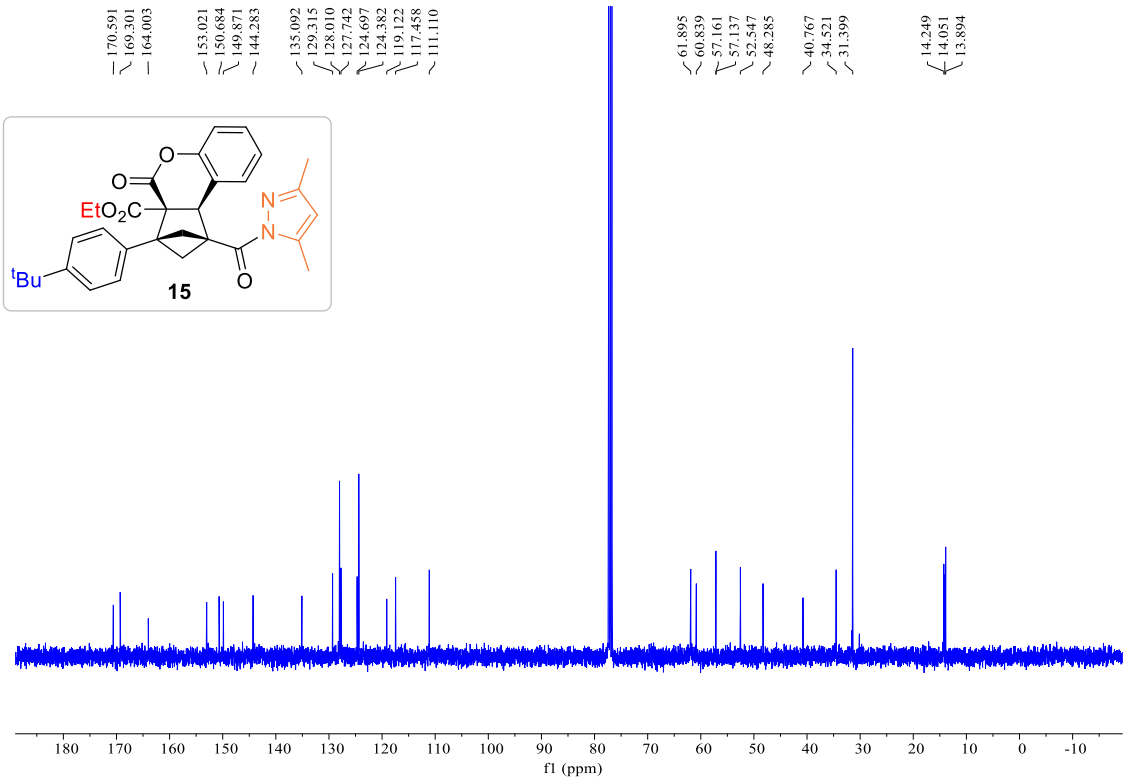
14, ^{13}C NMR (101 MHz, $CDCl_3$)



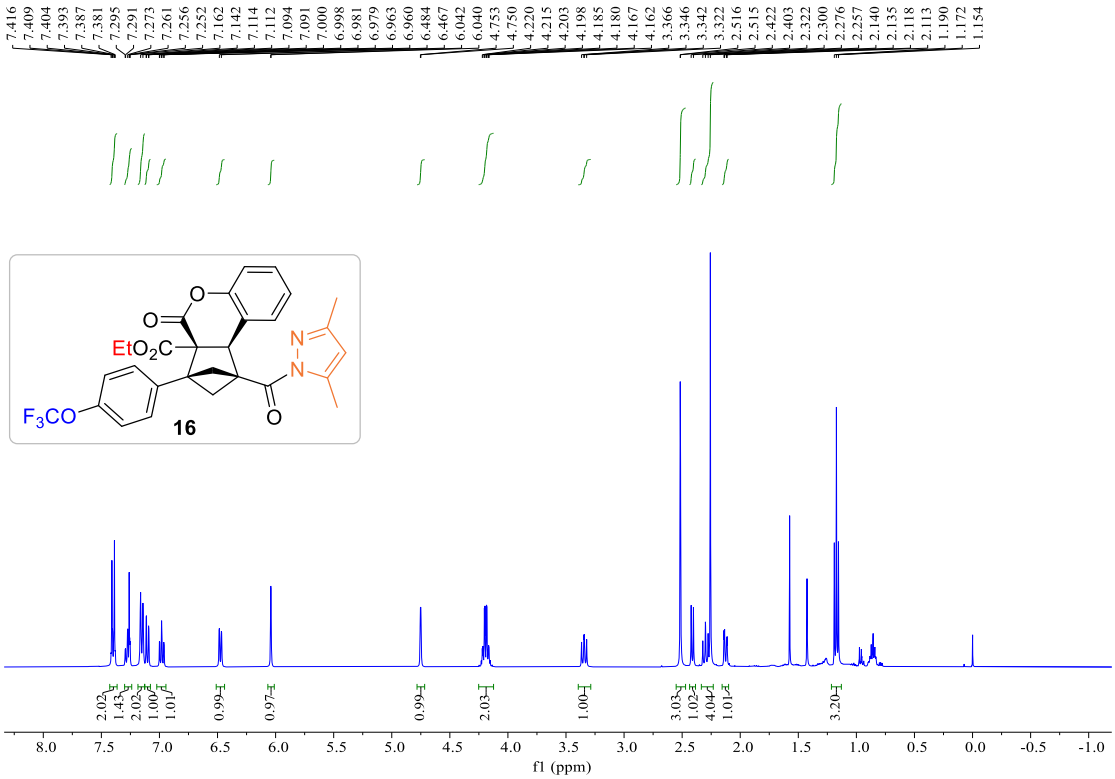
15, ^{1}H NMR (400 MHz, $CDCl_3$)



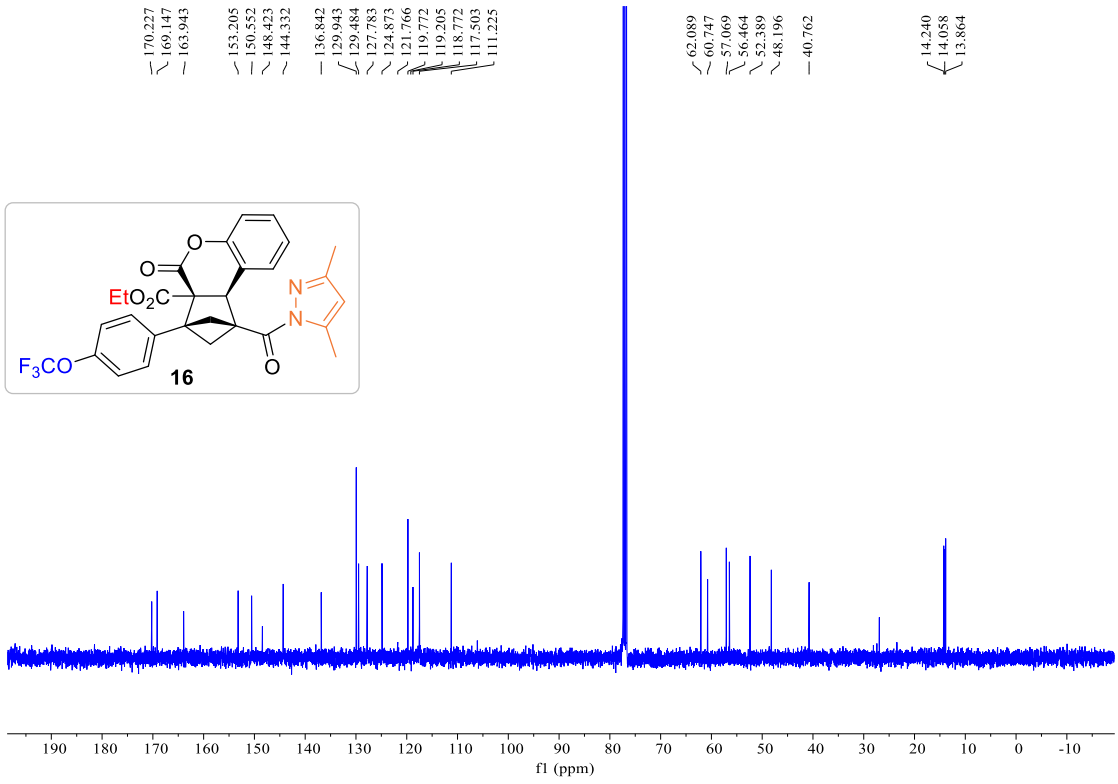
15, ^{13}C NMR (101 MHz, $CDCl_3$)



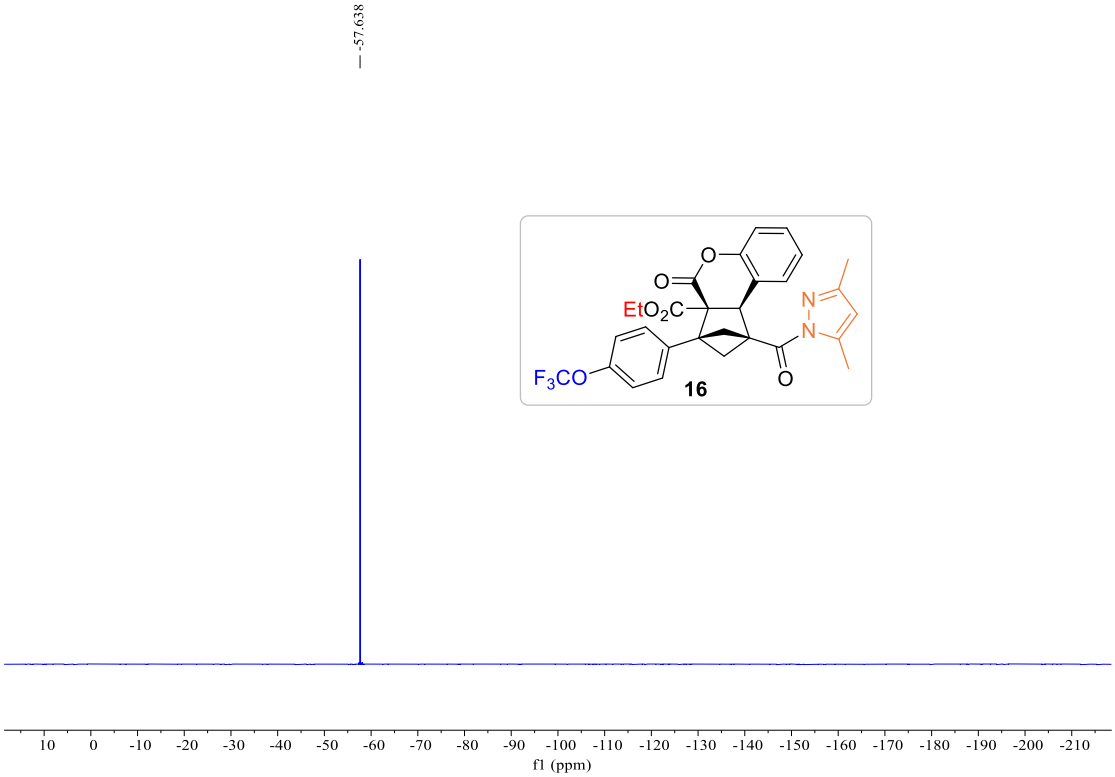
16, ^{1}H NMR (400 MHz, $CDCl_3$)



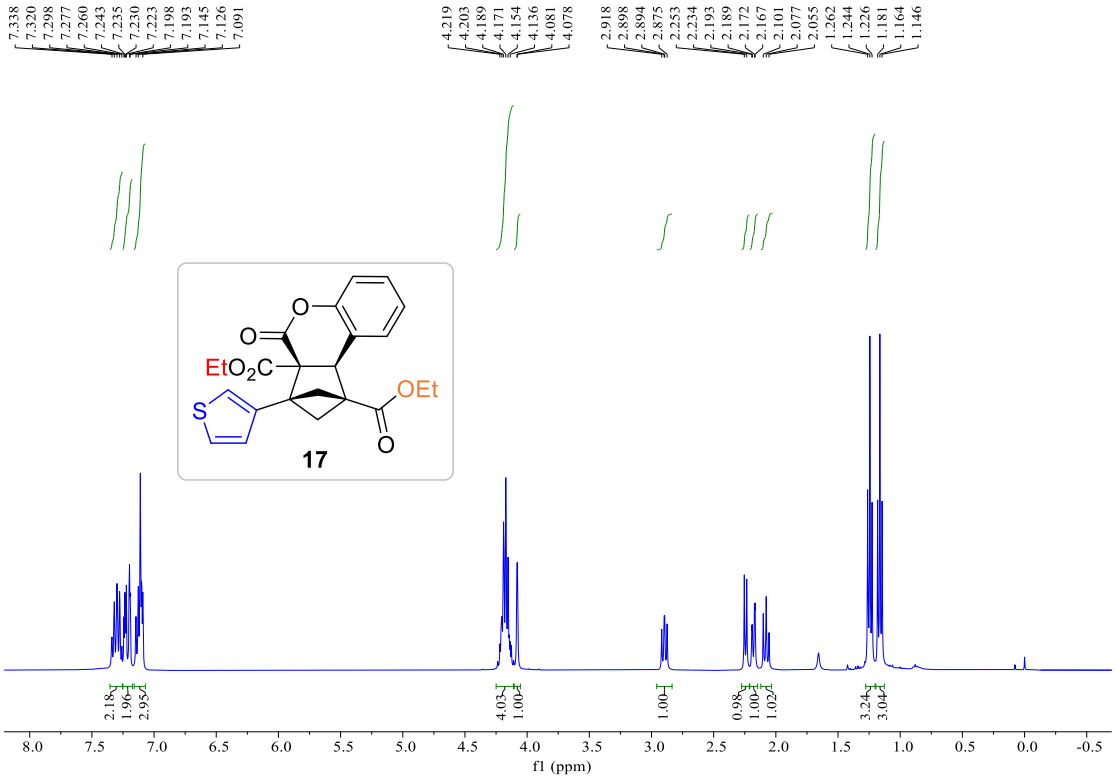
16, ^{13}C NMR (101 MHz, CDCl3)



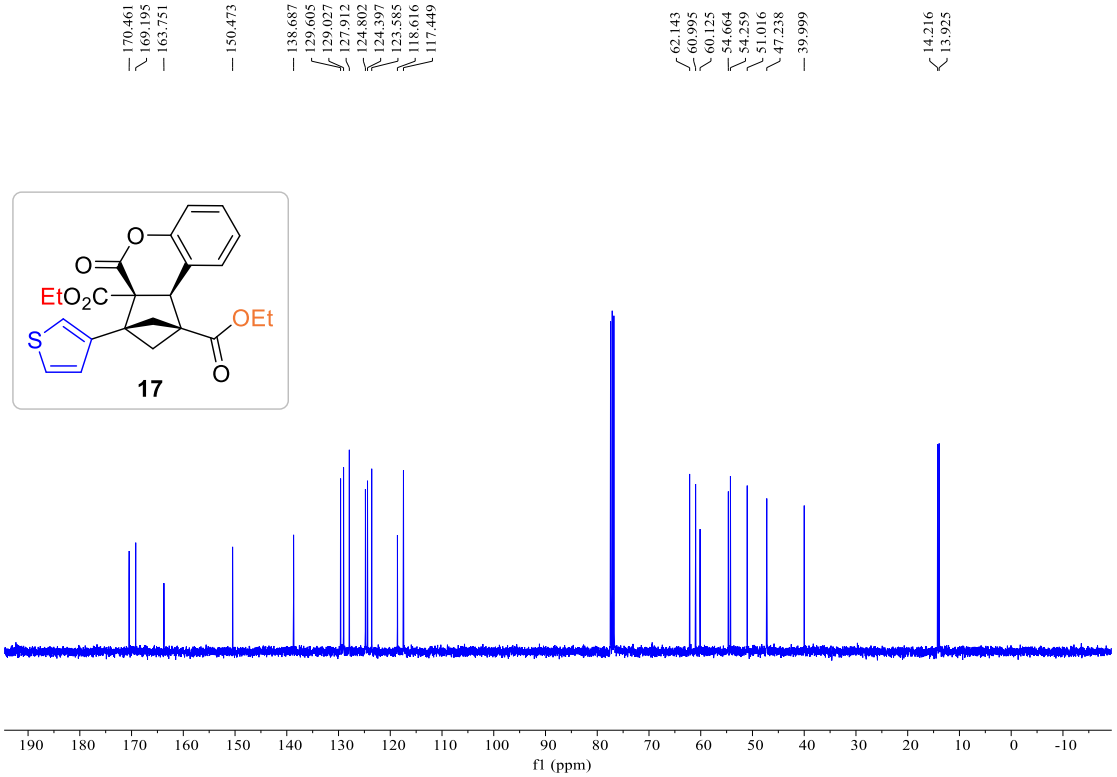
16, ^{19}F NMR (376 MHz, $CDCl_3$)



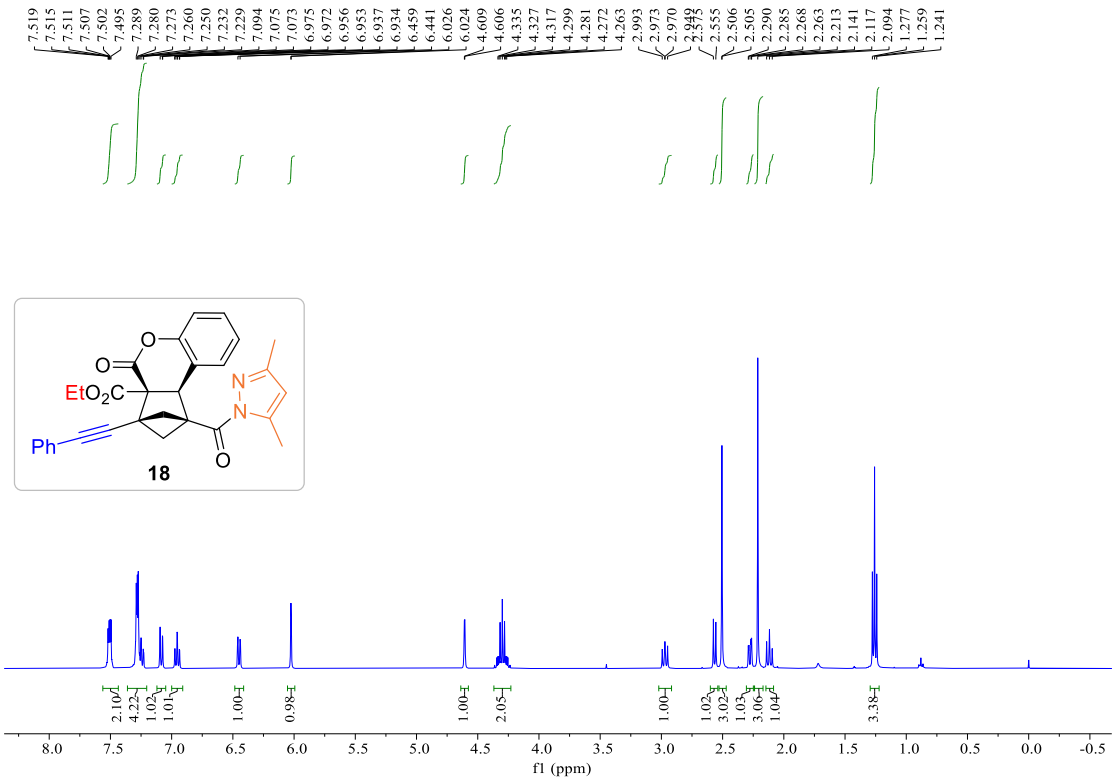
17, ^{1}H NMR (400 MHz, $CDCl_3$)



17, ^{13}C NMR (101 MHz, $CDCl_3$)



18, ^{1}H NMR (400 MHz, $CDCl_3$)



18, ^{13}C NMR (101 MHz, $CDCl_3$)

169.799
168.477
163.419
153.251
150.506
144.290
132.027
129.512
128.090
127.826
124.840
123.135
118.390
117.533
111.294
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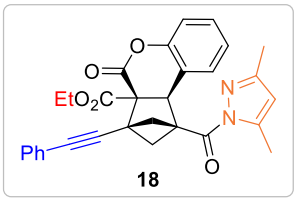
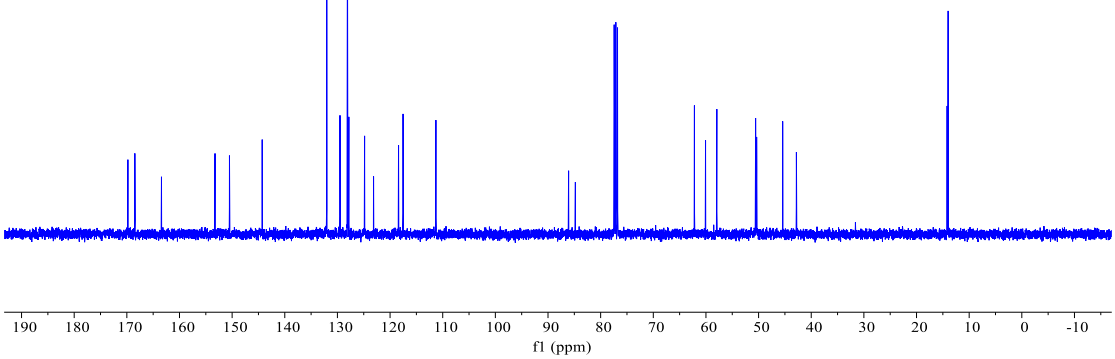
50.566
50.369
45.422
42.818
14.191
13.997

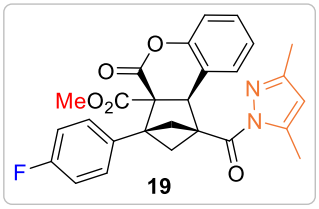


18



19, ^{1}H NMR (400 MHz, $CDCl_3$)

7.366
7.362
7.352
7.345
7.336
7.331
7.282
7.279
7.261
7.251
7.243
7.240
7.097
7.079
7.017
7.013
6.996
6.974
6.958
6.956
6.491
6.472
6.038
4.743
3.689
3.375
3.354
3.351
3.331
2.506
2.414
2.394
2.318
2.295
2.272
2.257
2.135
2.131
2.113
2.109



19

2.03
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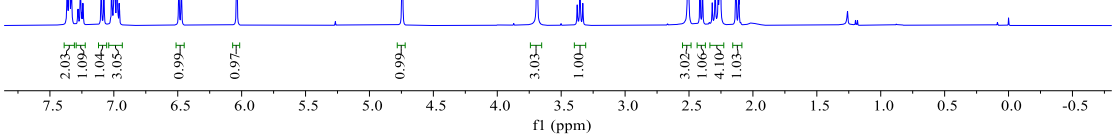
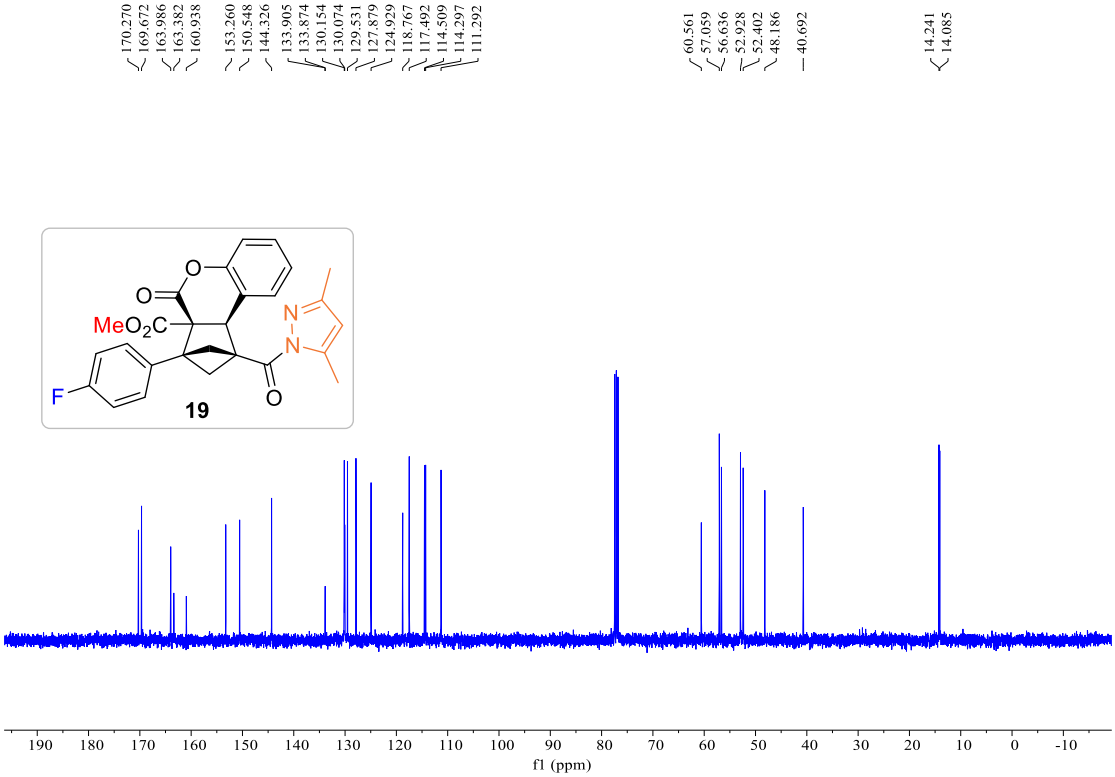
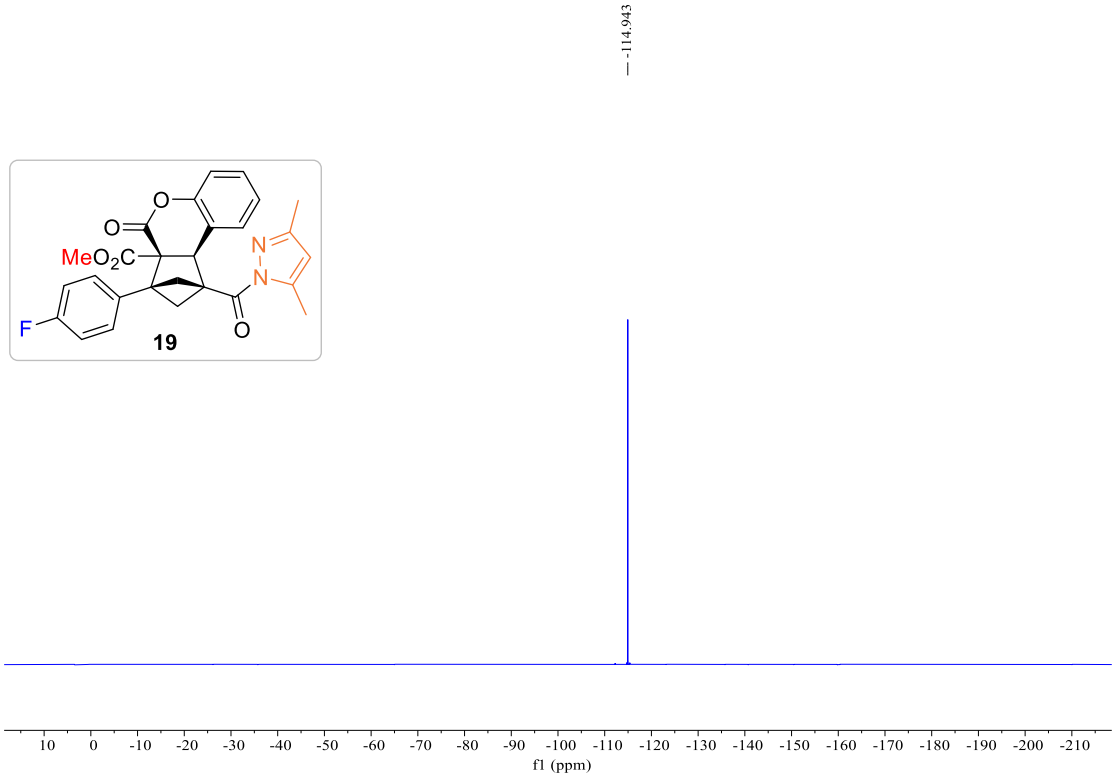
1.04
3.05
0.99
0.97
0.99
3.03
1.00
3.02
1.06
4.10
1.03



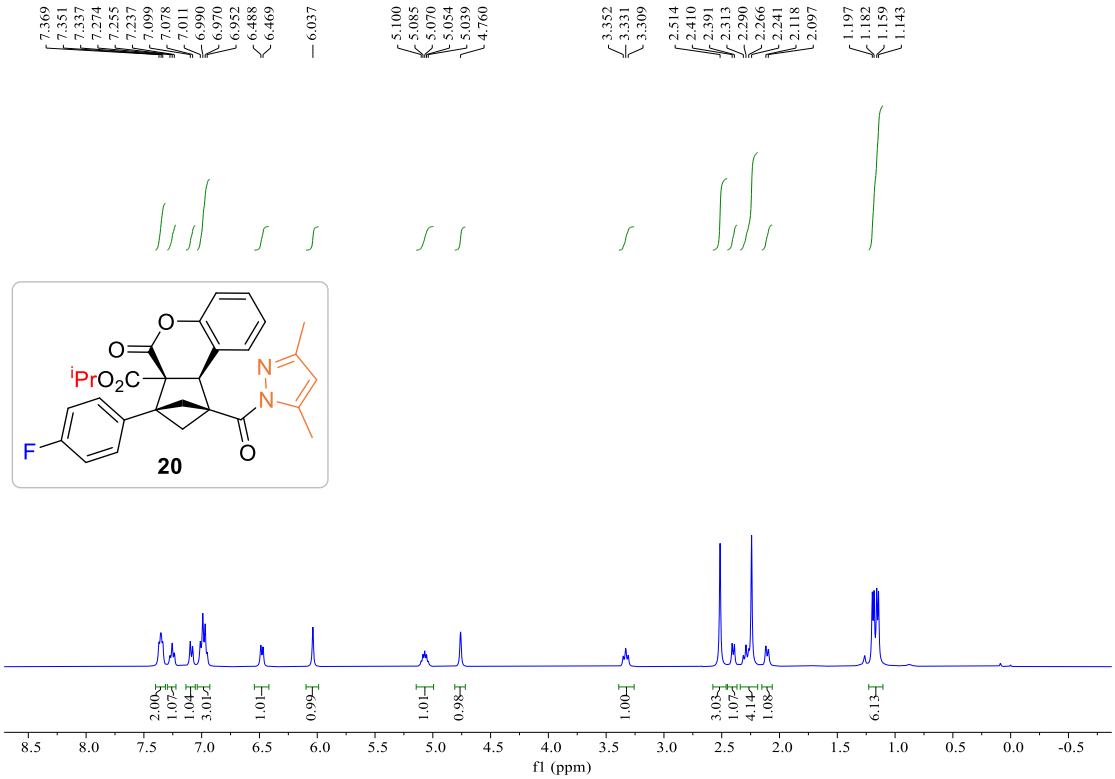
19, ^{13}C NMR (101 MHz, $CDCl_3$)



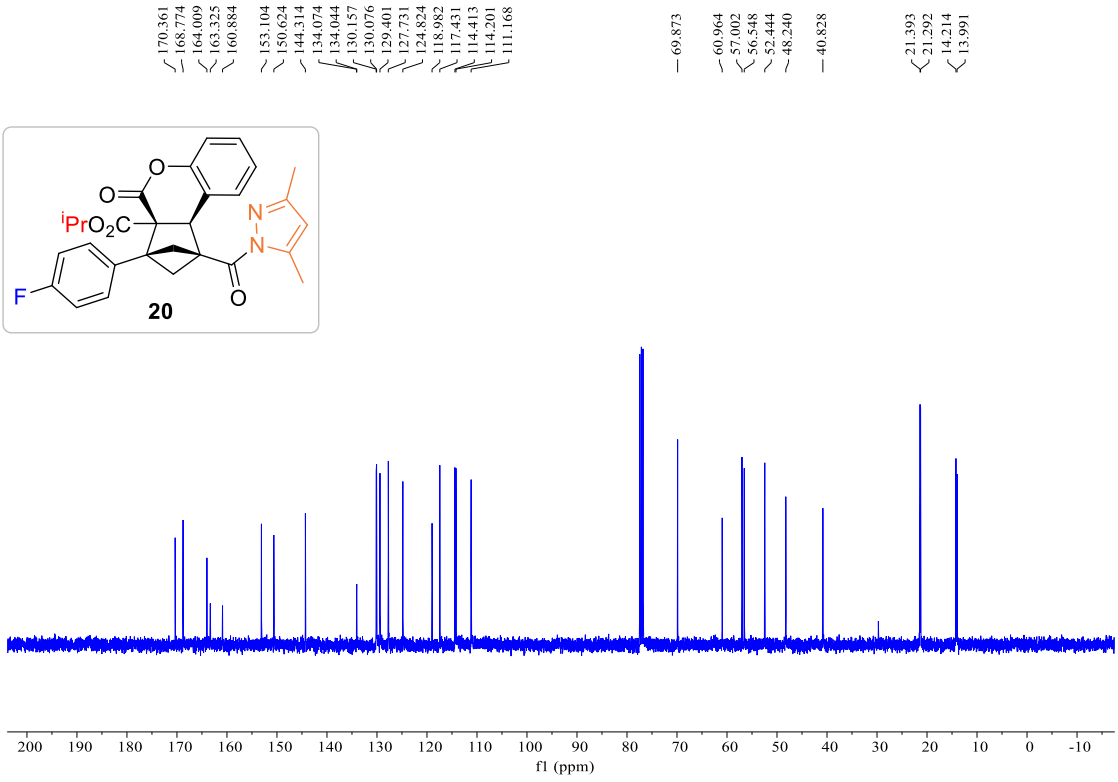
19, ^{19}F NMR (376 MHz, $CDCl_3$)



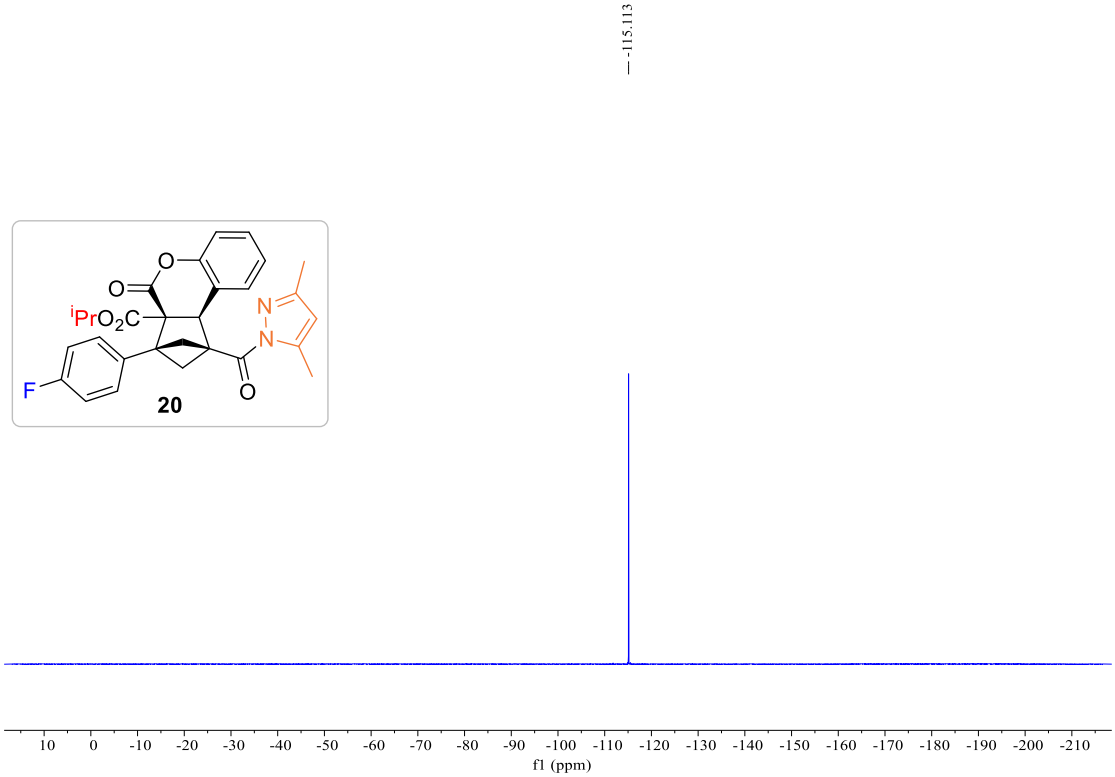
20, ^{1}H NMR (400 MHz, $CDCl_3$)



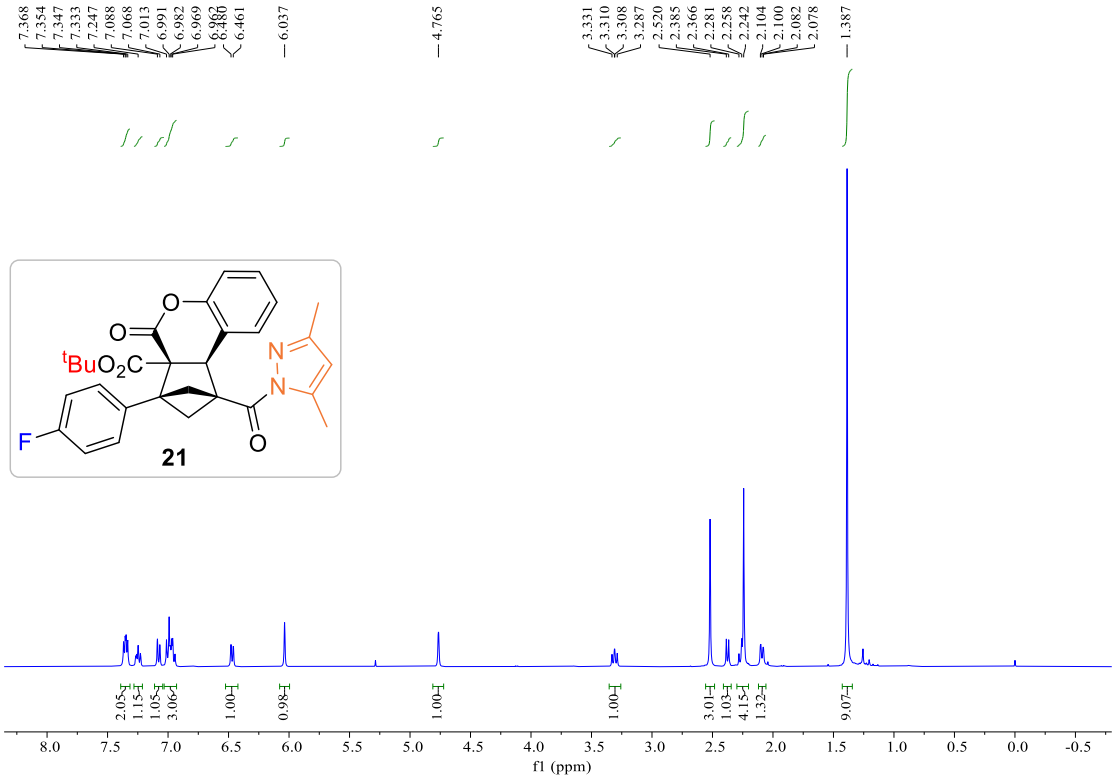
20, ^{13}C NMR (101 MHz, $CDCl_3$)



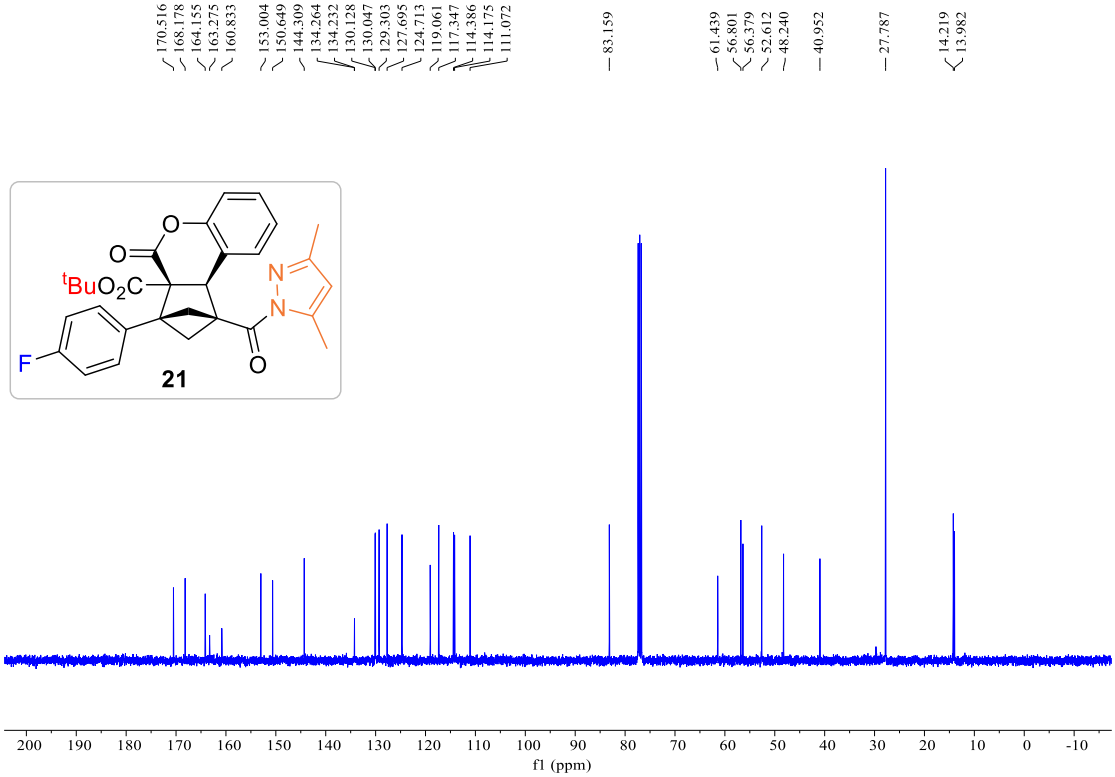
20, ^{19}F NMR (376 MHz, $CDCl_3$)



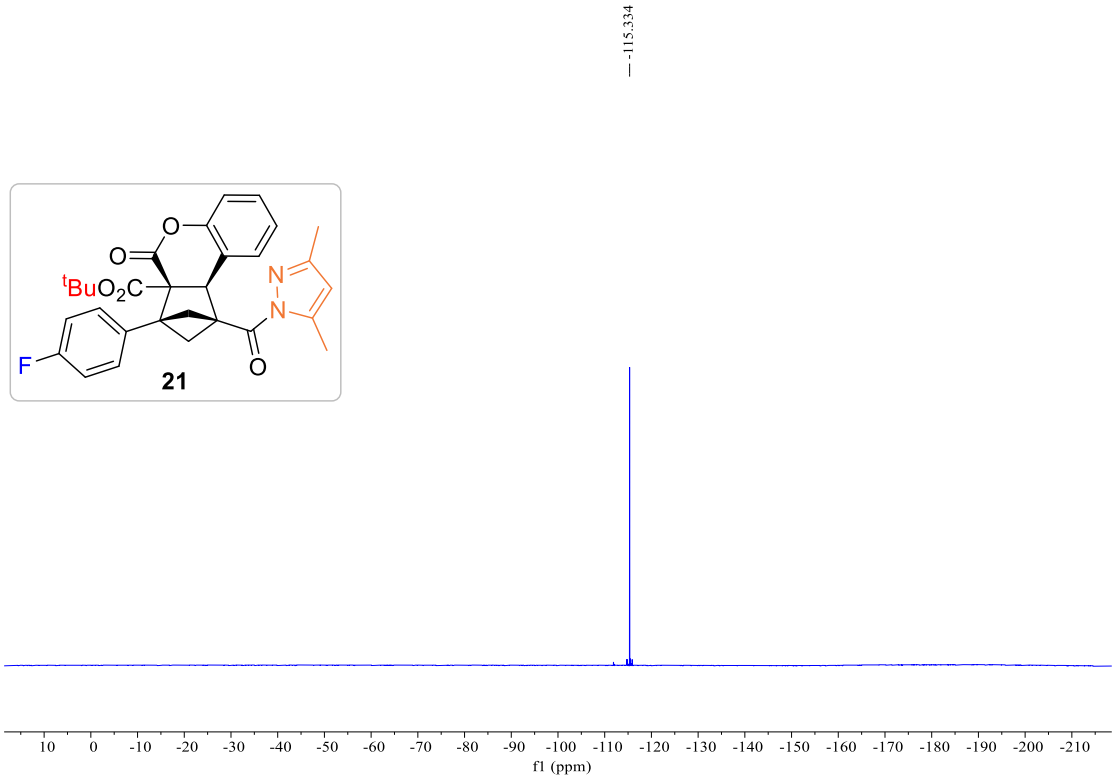
21, ^{1}H NMR (400 MHz, $CDCl_3$)



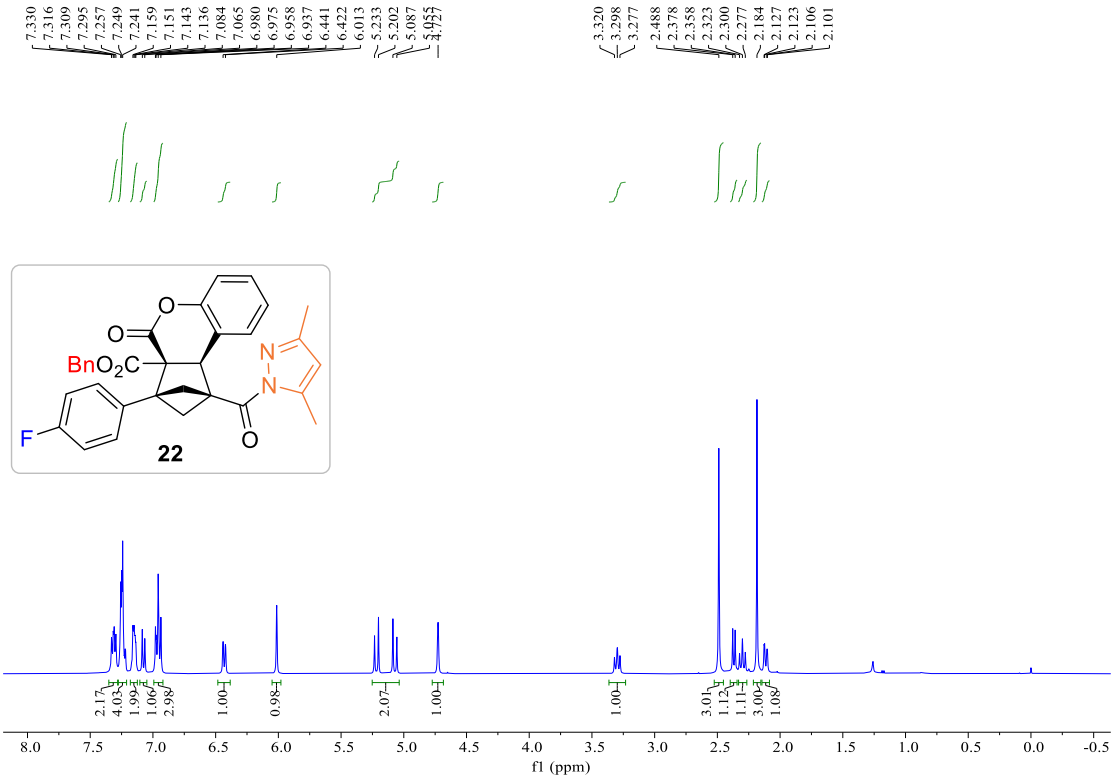
21, ^{13}C NMR (101 MHz, $CDCl_3$)



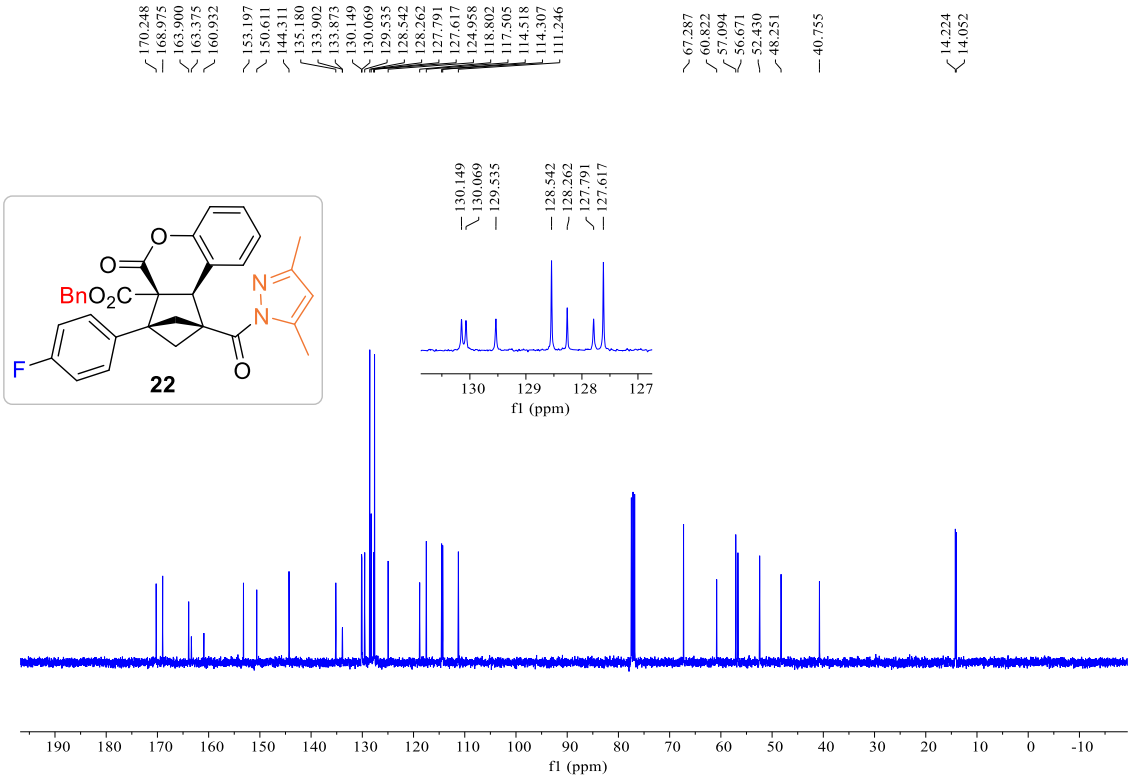
21, ^{19}F NMR (376 MHz, $CDCl_3$)



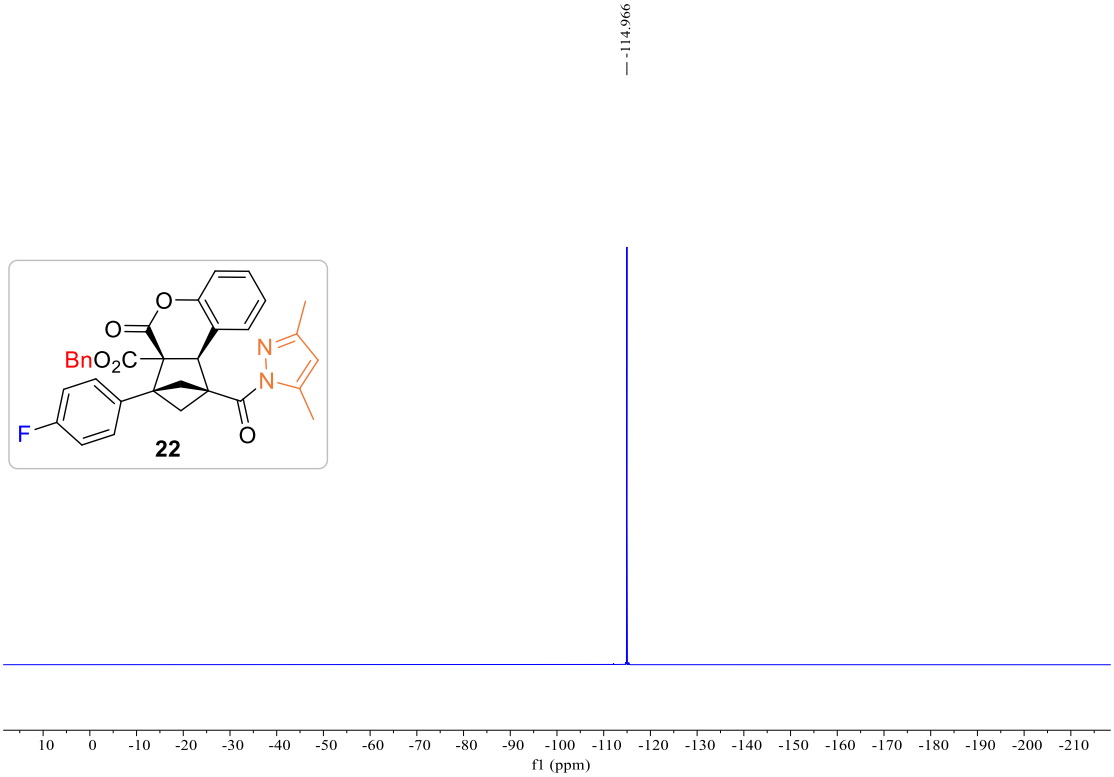
22, ^{1}H NMR (400 MHz, $CDCl_3$)



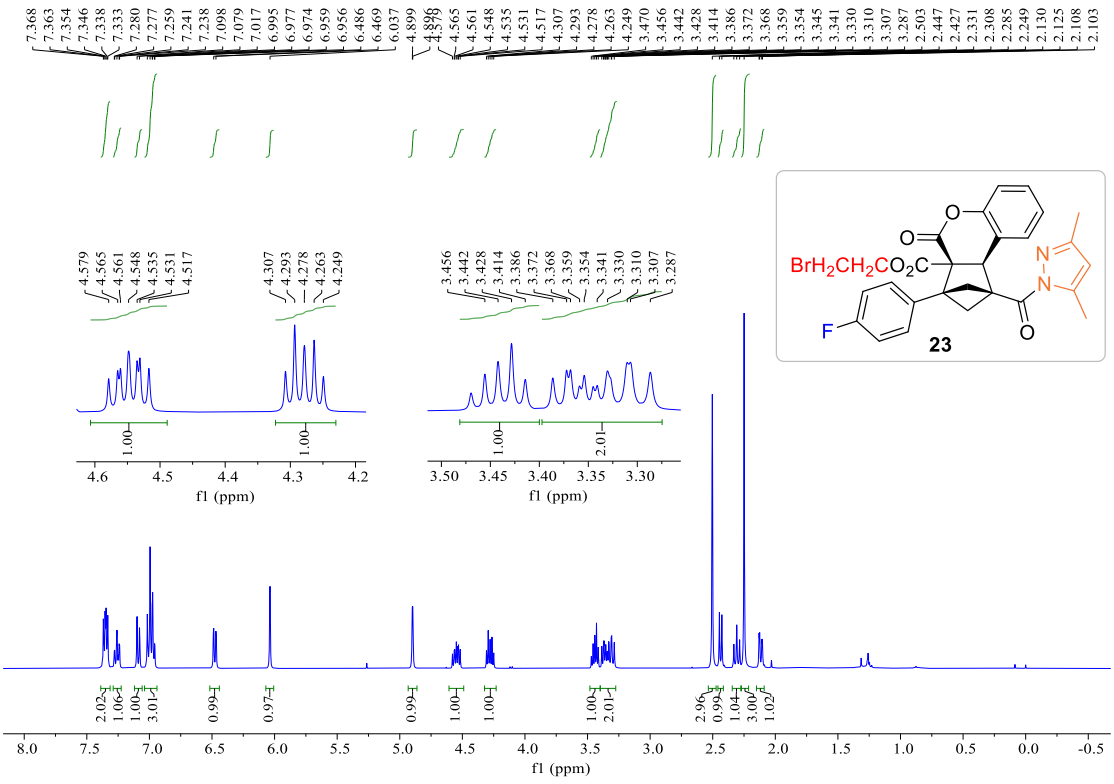
22, ^{13}C NMR (101 MHz, $CDCl_3$)



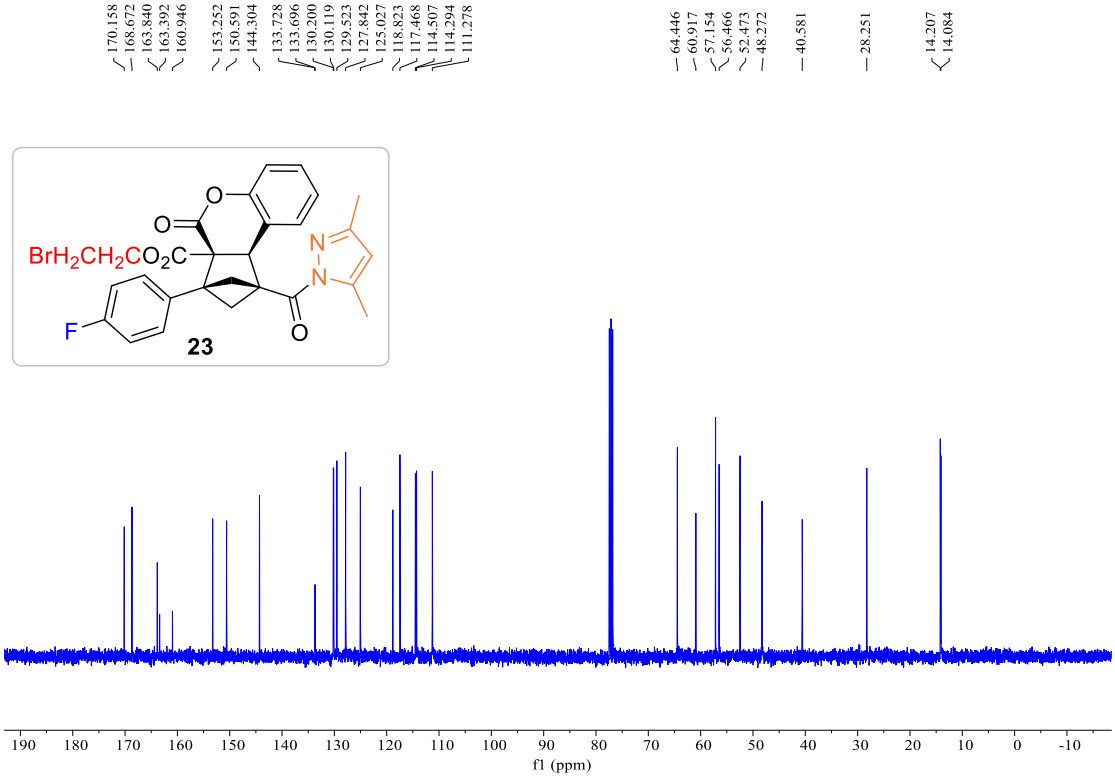
22, ^{19}F NMR (376 MHz, $CDCl_3$)



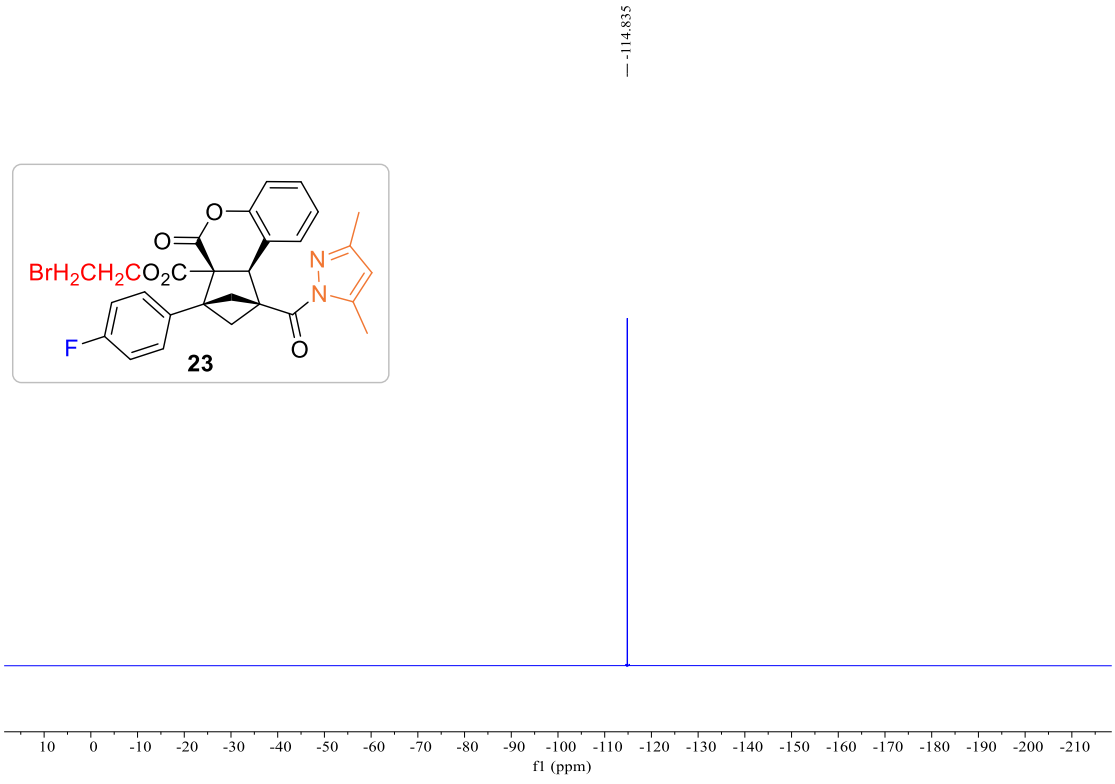
23, ^{1}H NMR (400 MHz, $CDCl_3$)



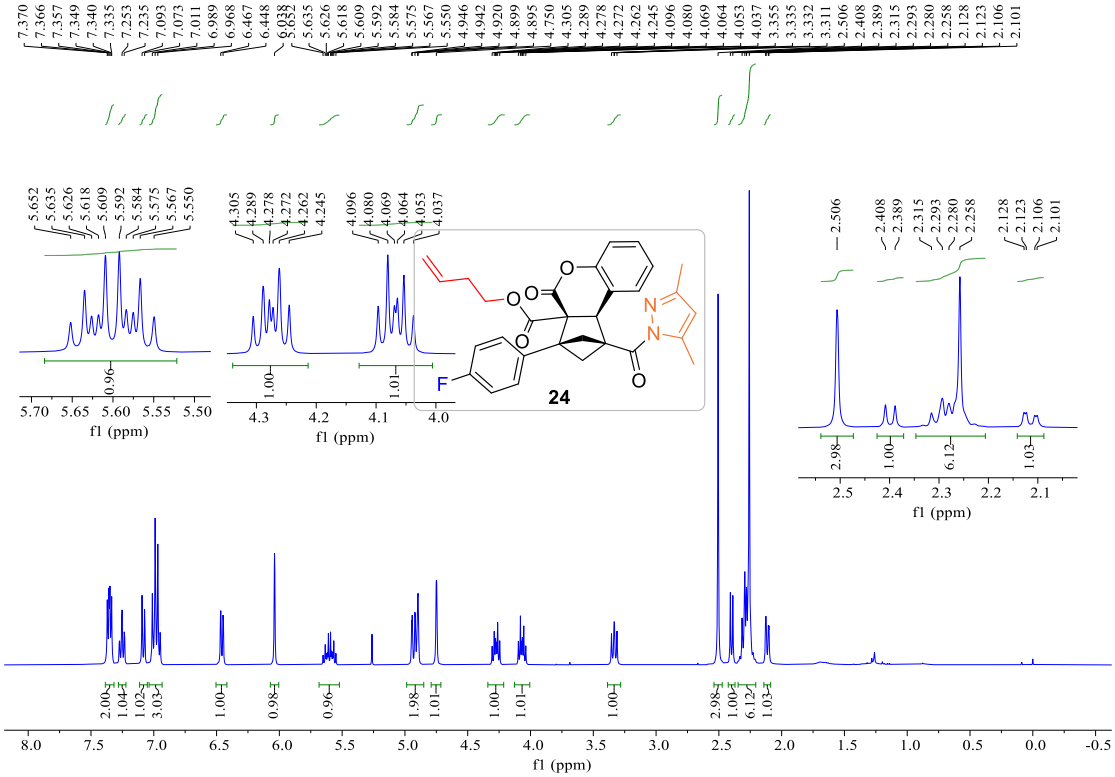
23, ^{13}C NMR (101 MHz, $CDCl_3$)



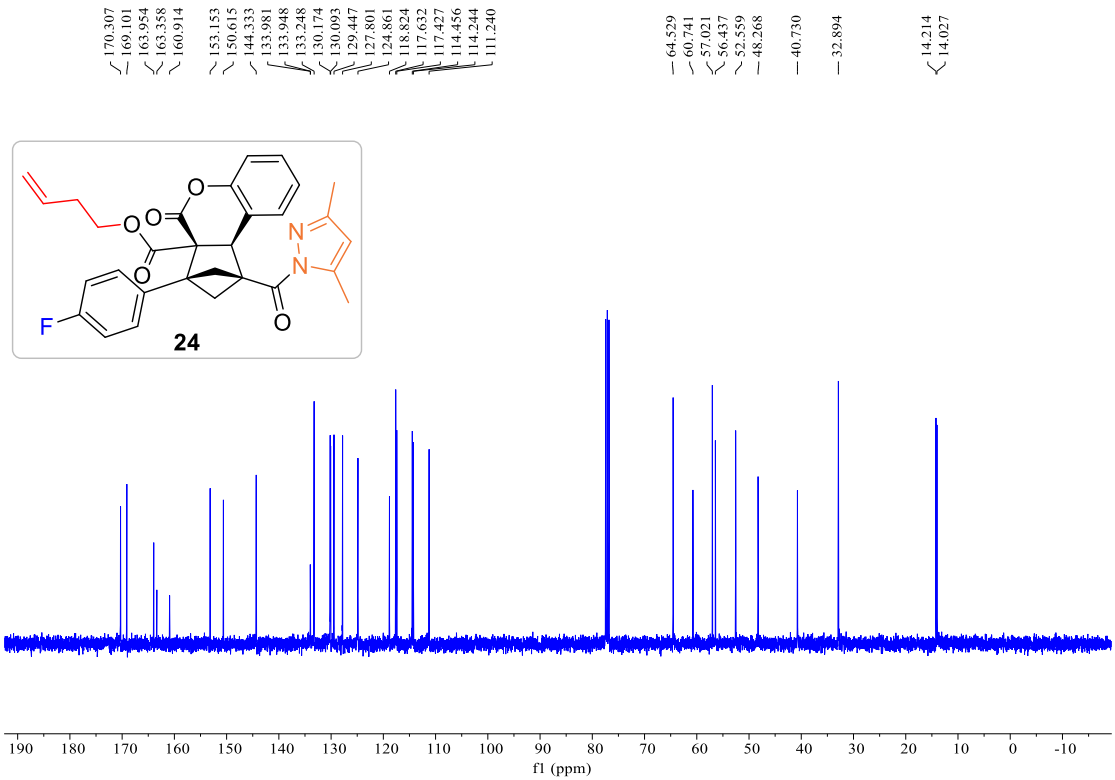
23, ^{19}F NMR (376 MHz, $CDCl_3$)



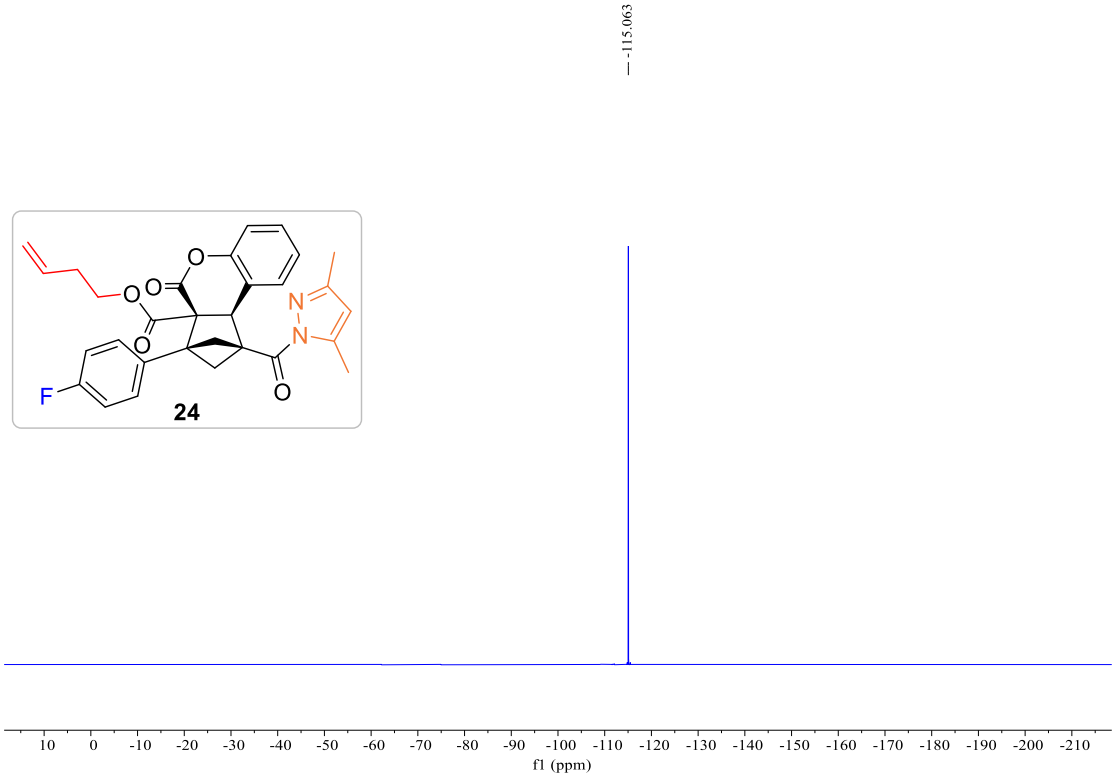
24, ^{1}H NMR (400 MHz, $CDCl_3$)



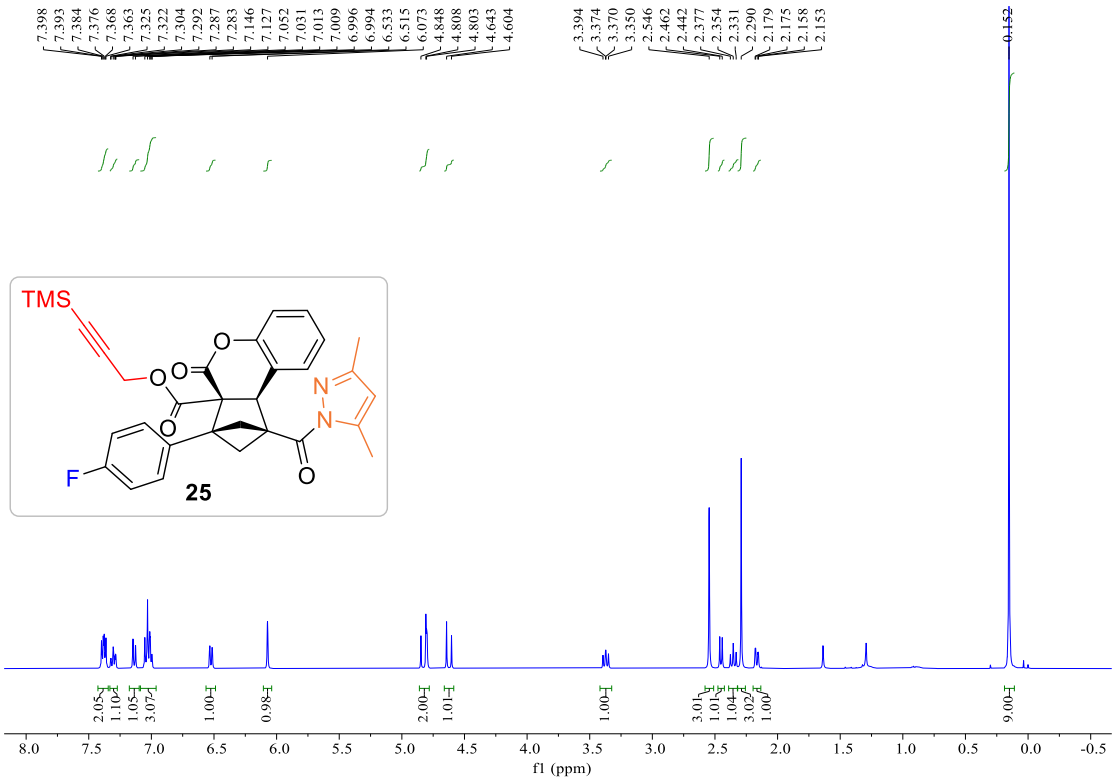
24, ^{13}C NMR (101 MHz, $CDCl_3$)



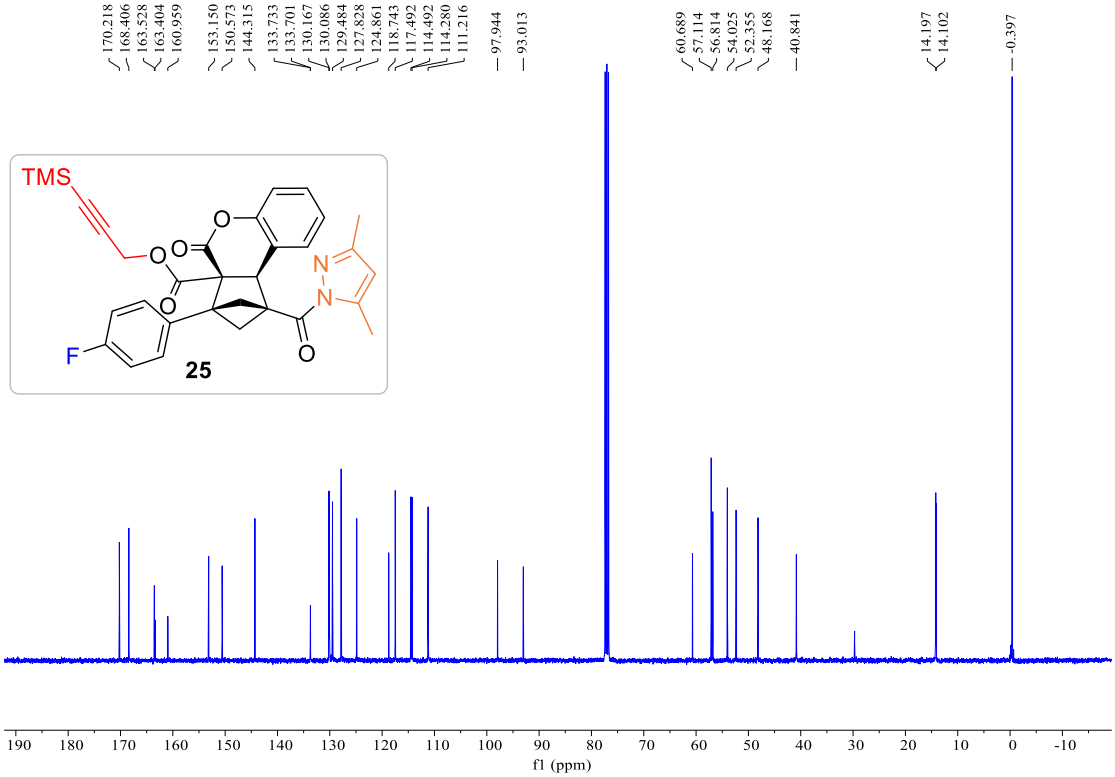
24, ^{19}F NMR (376 MHz, $CDCl_3$)



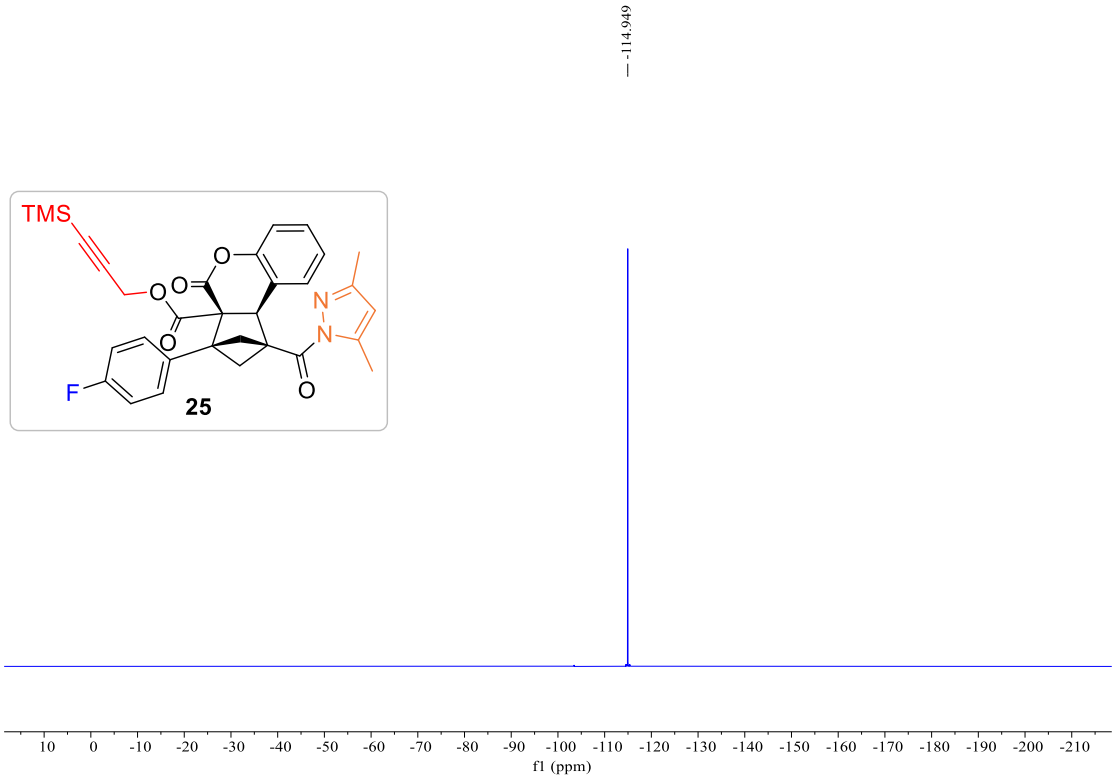
25, ^{1}H NMR (400 MHz, $CDCl_3$)



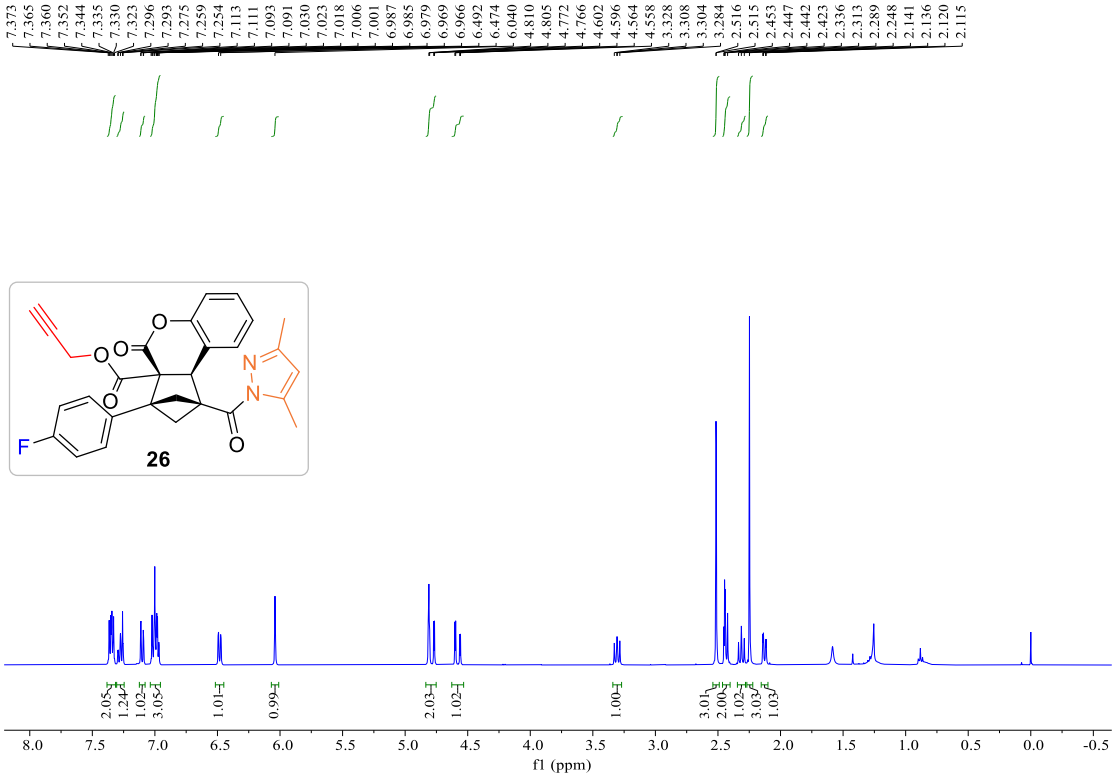
25, ^{13}C NMR (101 MHz, $CDCl_3$)



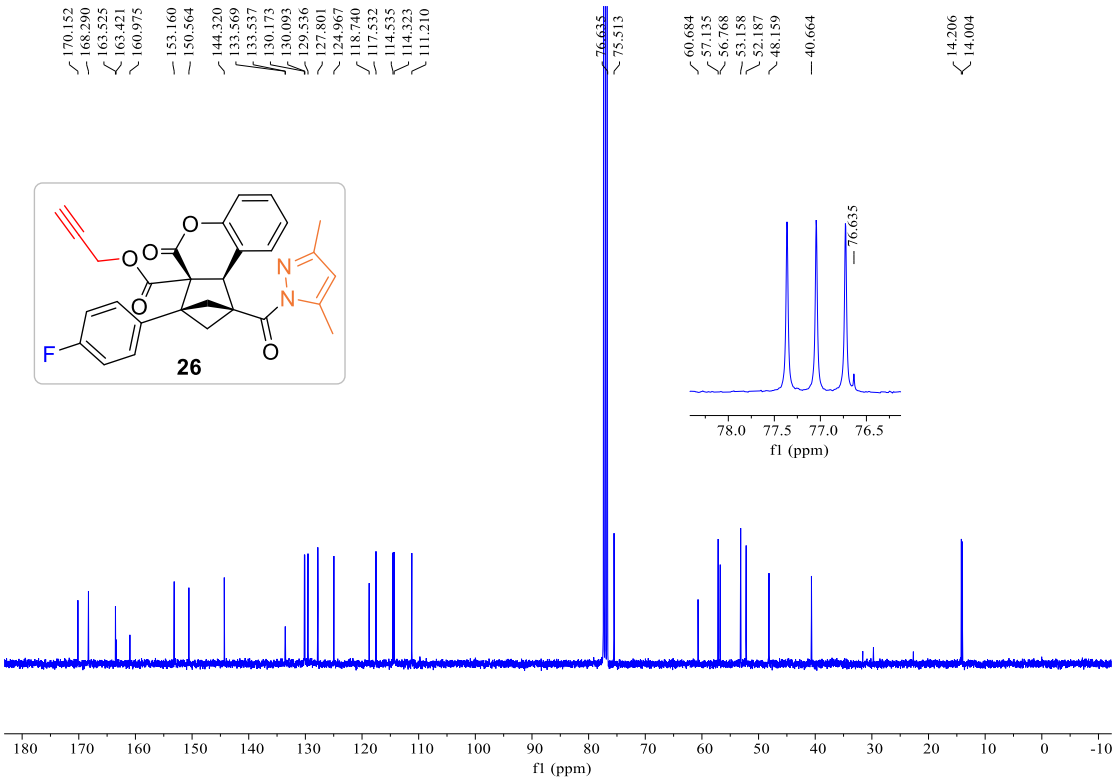
25, ^{19}F NMR (376 MHz, $CDCl_3$)



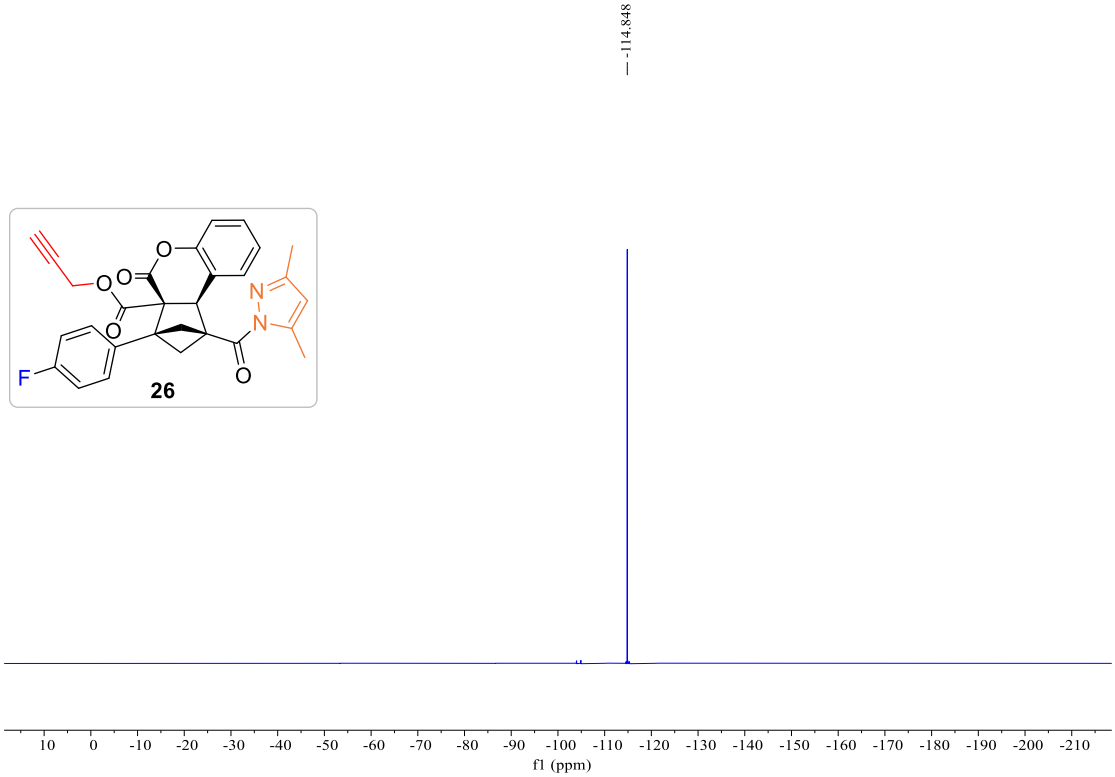
26, ^{1}H NMR (400 MHz, $CDCl_3$)



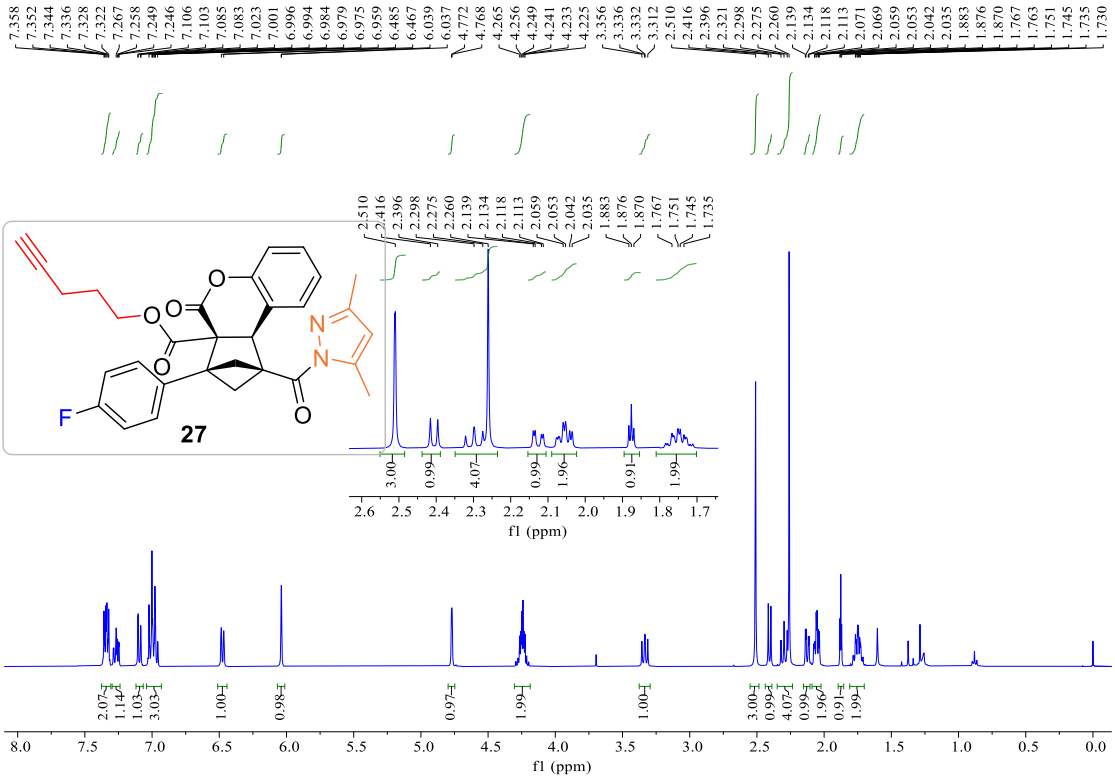
26, ^{13}C NMR (101 MHz, $CDCl_3$)



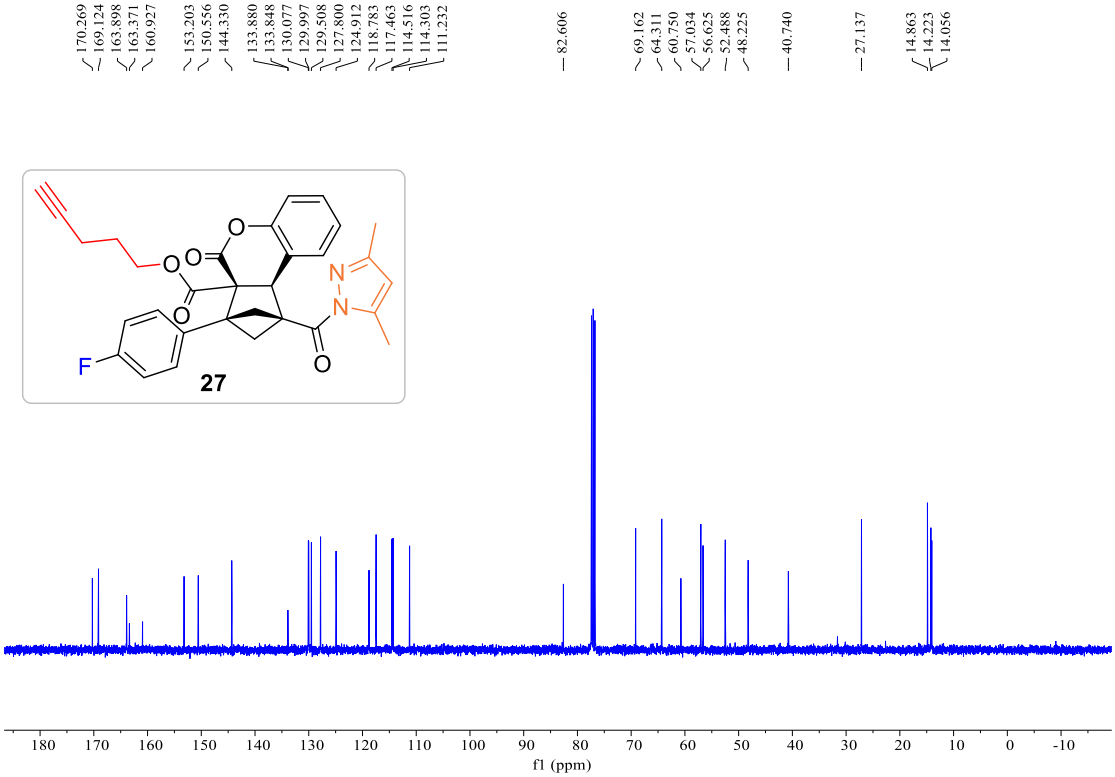
26, ^{19}F NMR (376 MHz, $CDCl_3$)



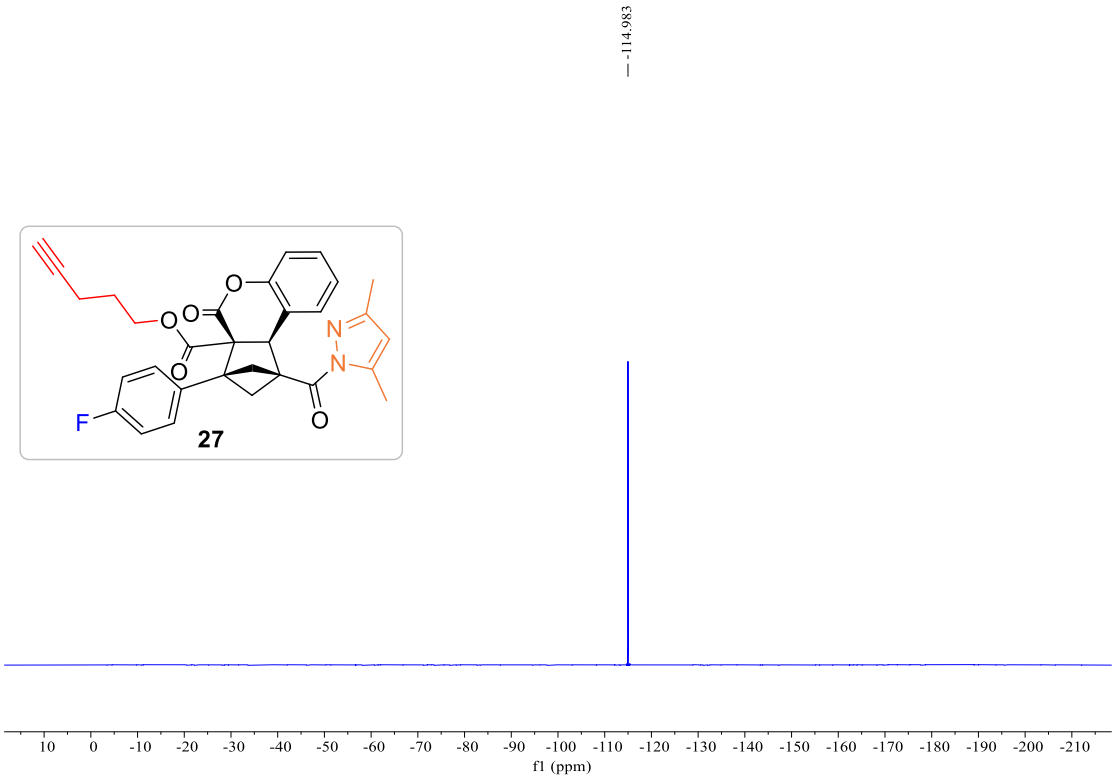
27, ^{1}H NMR (400 MHz, $CDCl_3$)



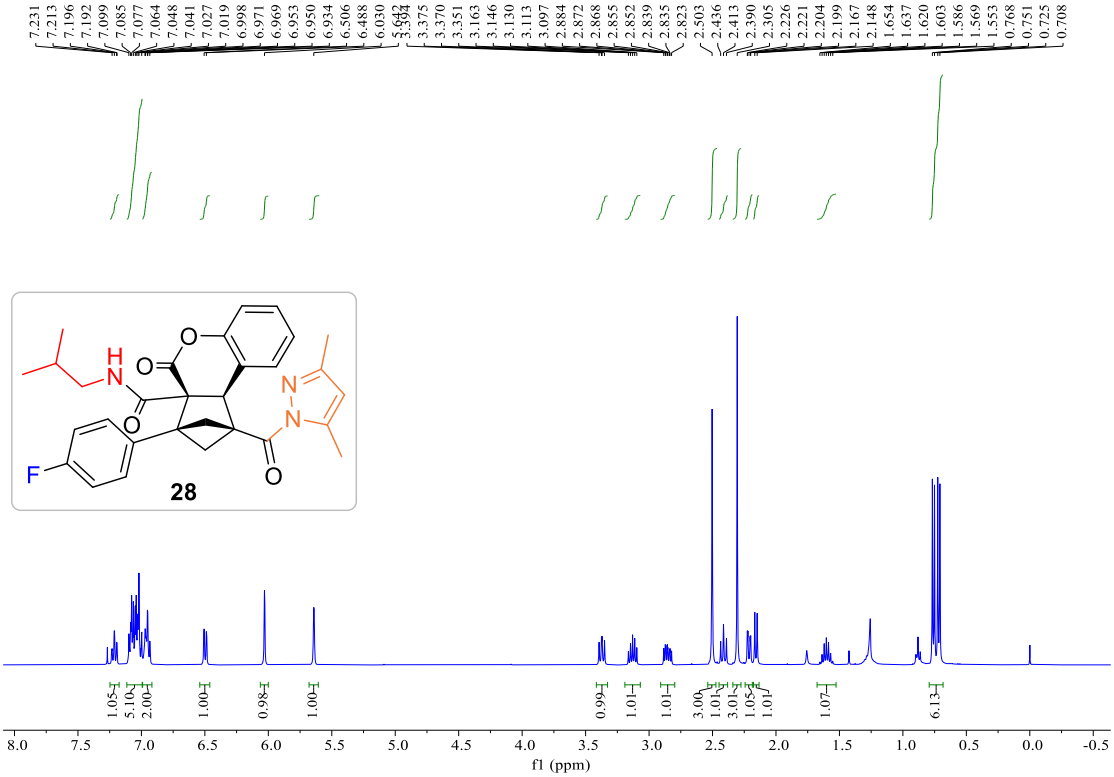
27, ^{13}C NMR (101 MHz, $CDCl_3$)



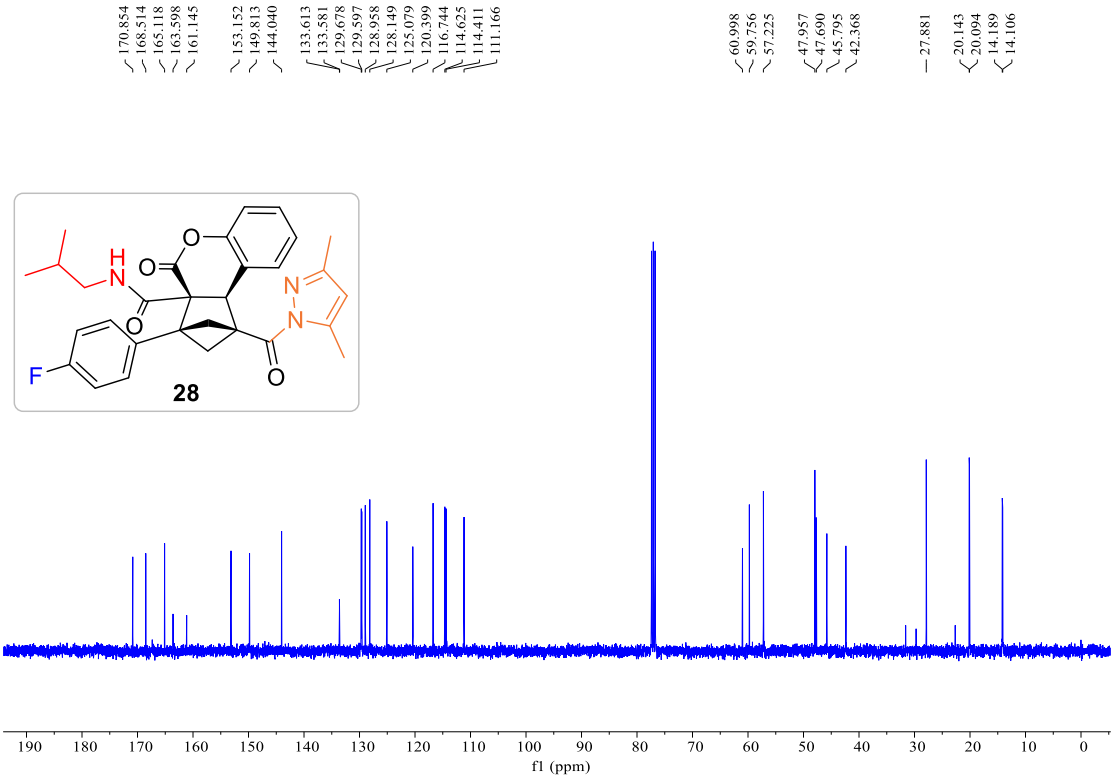
27, ^{19}F NMR (376 MHz, $CDCl_3$)



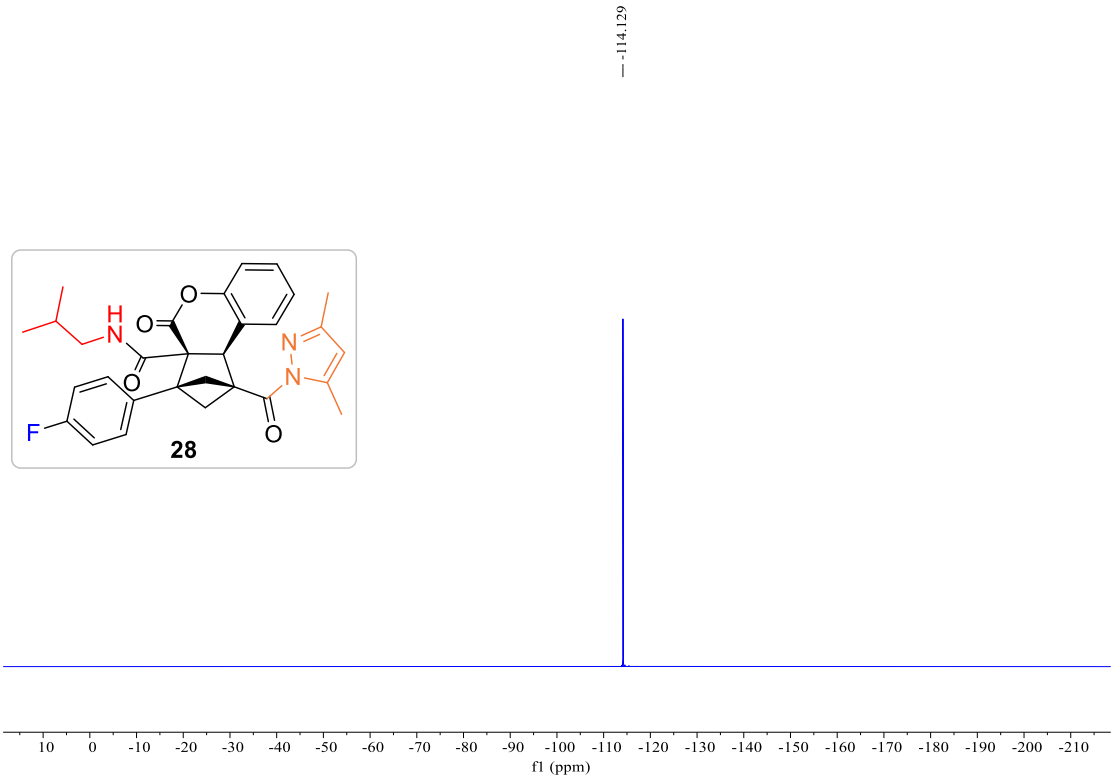
28, ^{1}H NMR (400 MHz, $CDCl_3$)



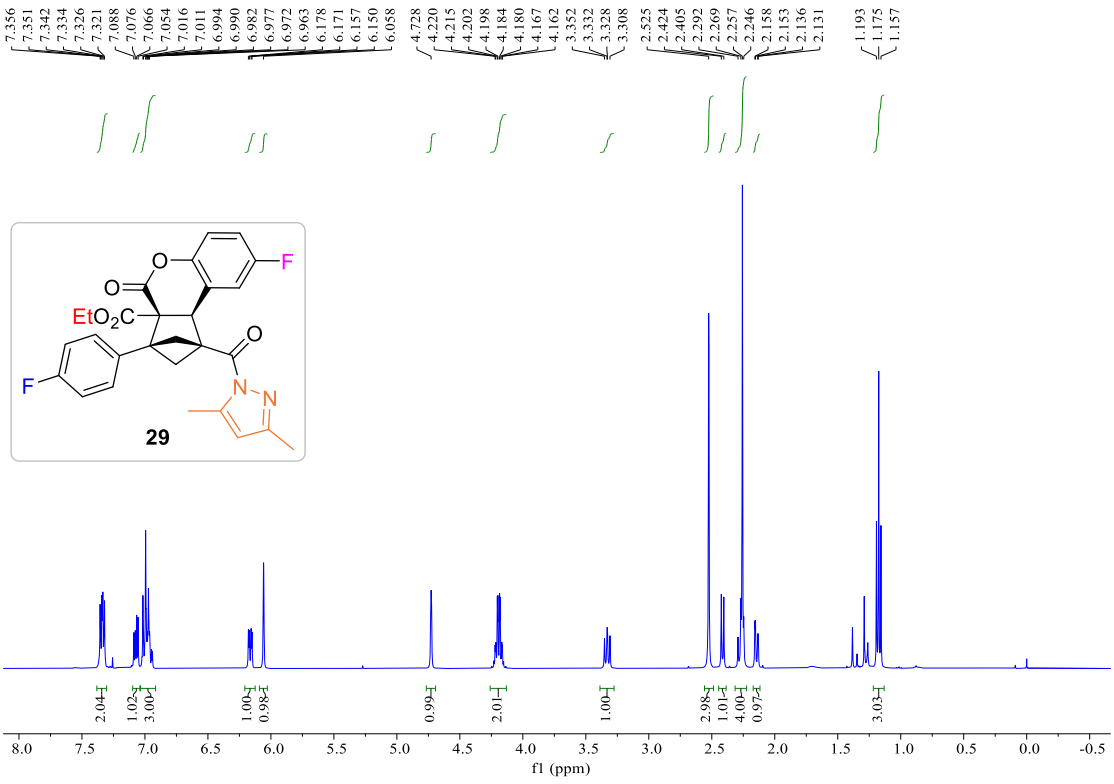
28, ^{13}C NMR (101 MHz, $CDCl_3$)



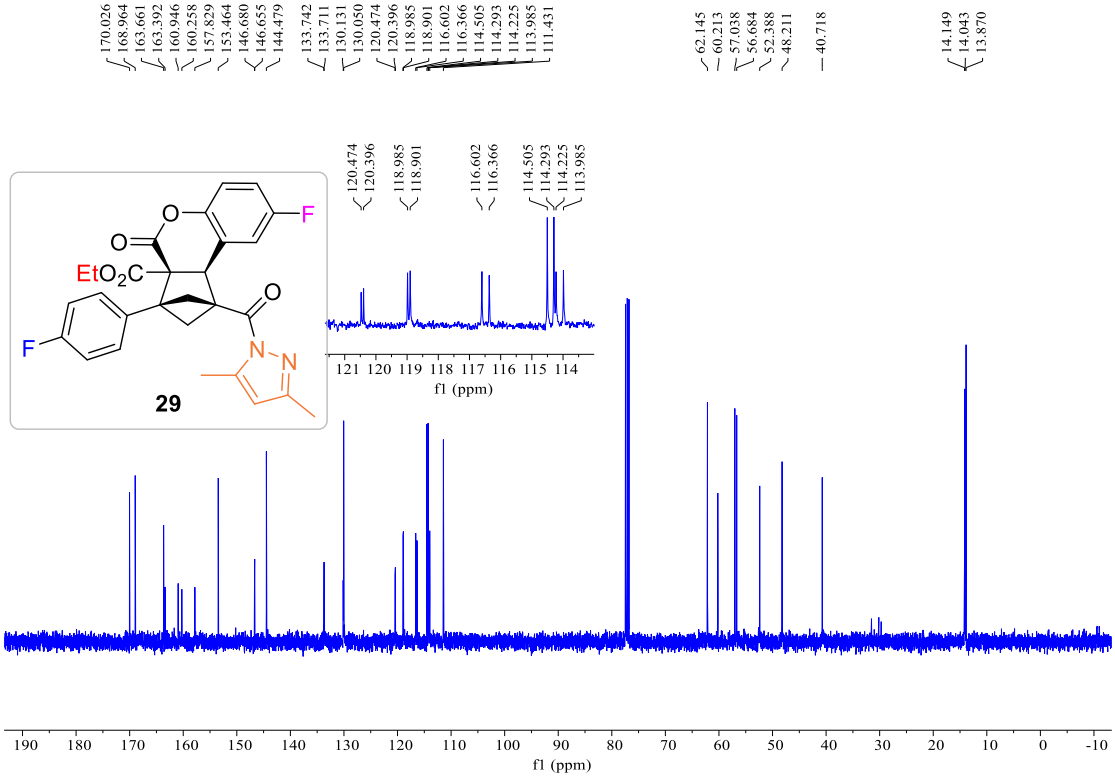
28, ^{19}F NMR (376 MHz, $CDCl_3$)



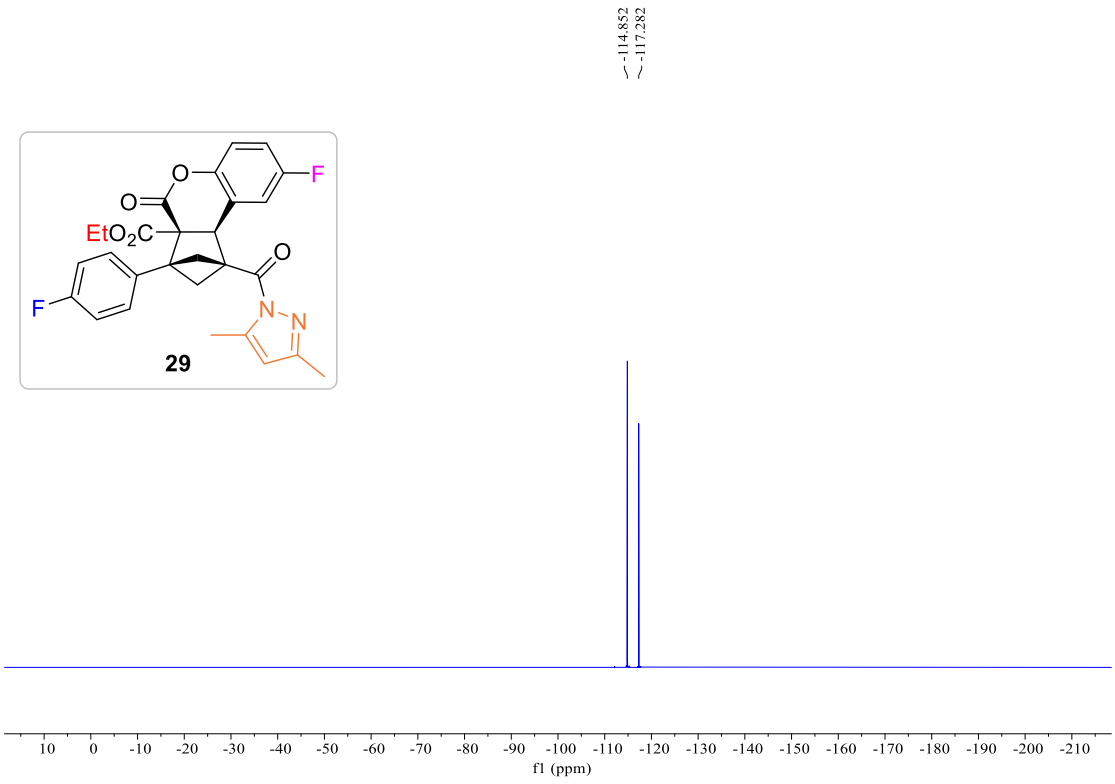
29, ^{1}H NMR (400 MHz, $CDCl_3$)



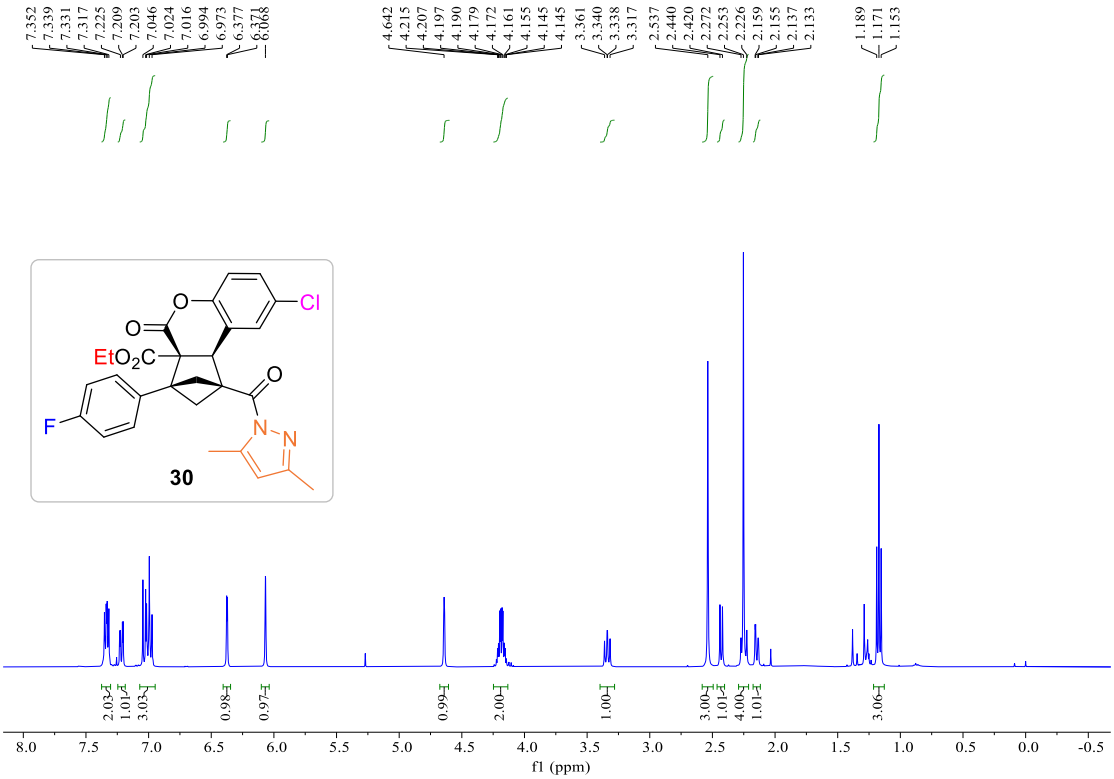
29, ^{13}C NMR (101 MHz, $CDCl_3$)



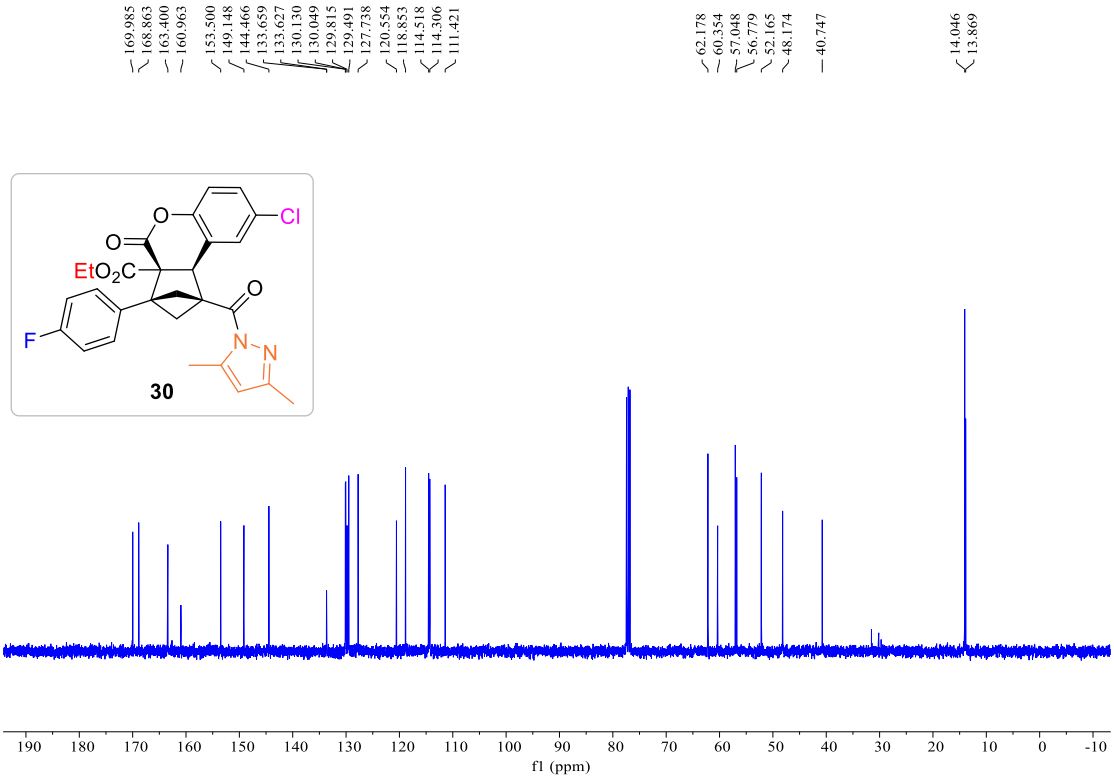
29, ^{19}F NMR (376 MHz, $CDCl_3$)



30, ^{1}H NMR (400 MHz, $CDCl_3$)

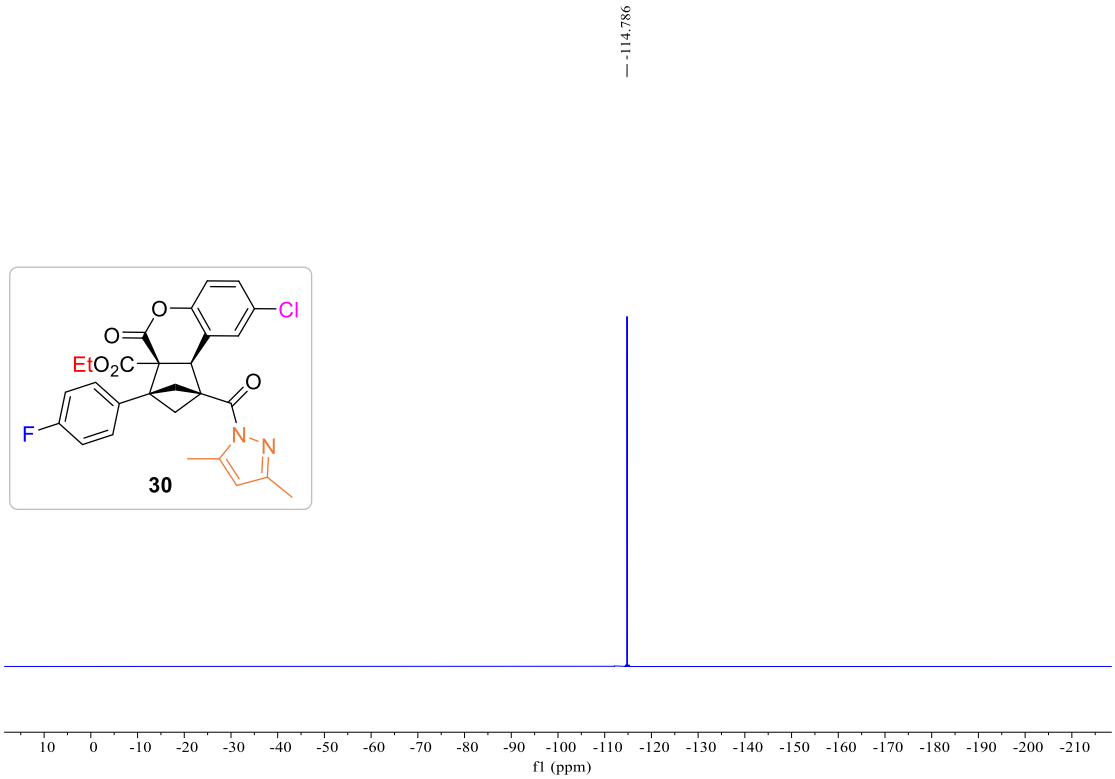


30, ^{13}C NMR (101 MHz, $CDCl_3$)

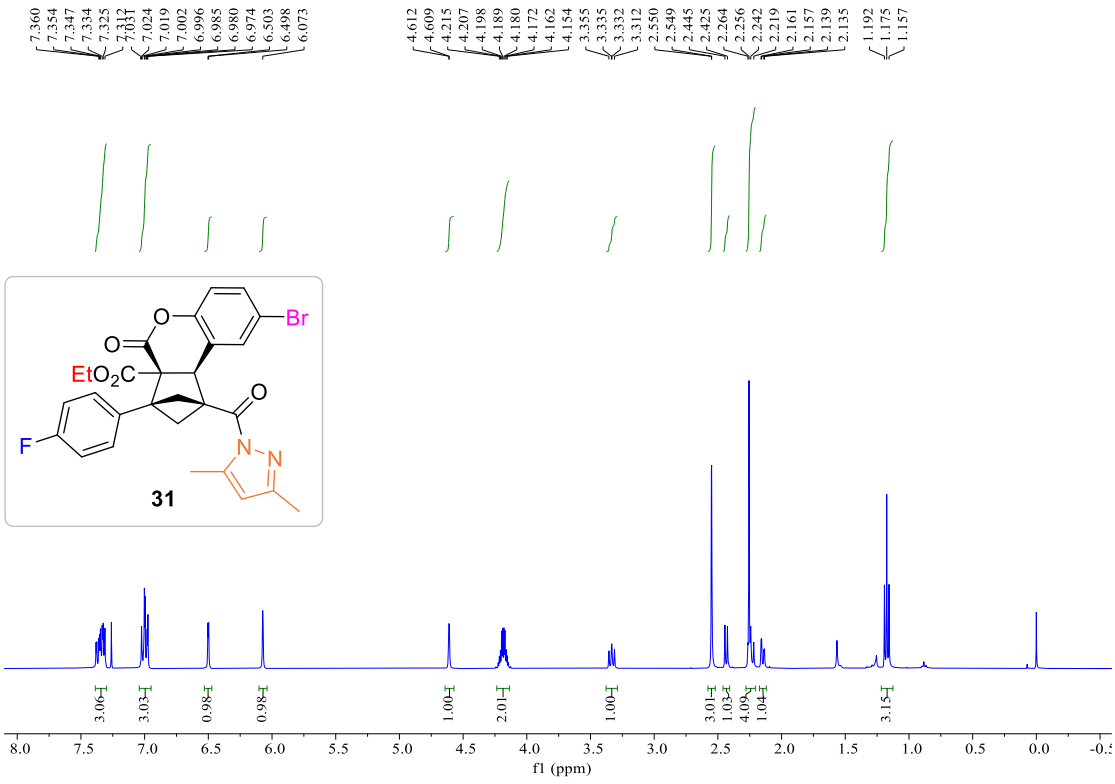


cc

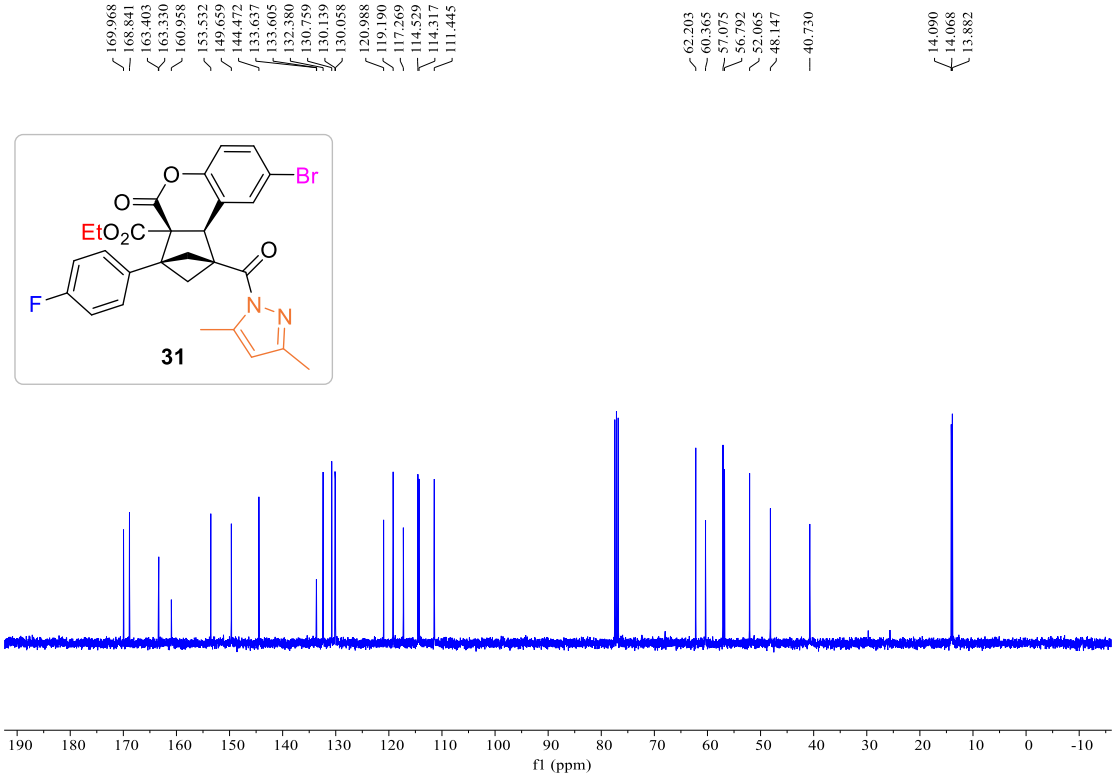
30, ^{19}F NMR (376 MHz, $CDCl_3$)



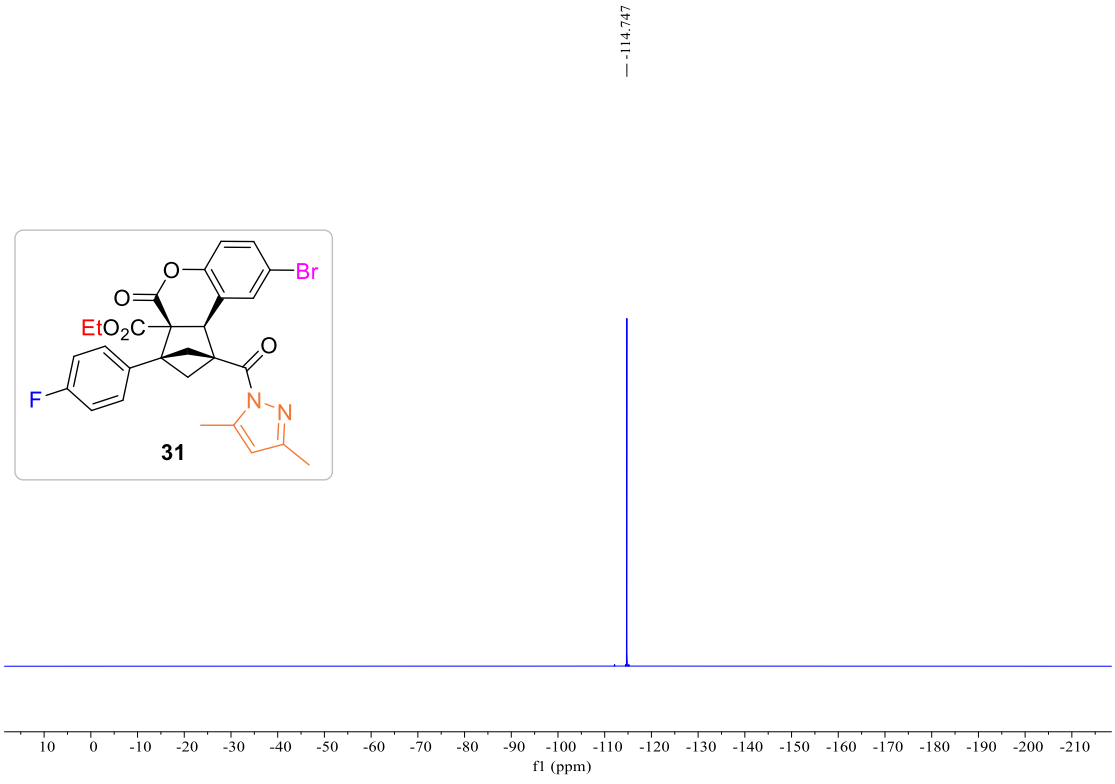
31, ^{1}H NMR (400 MHz, $CDCl_3$)



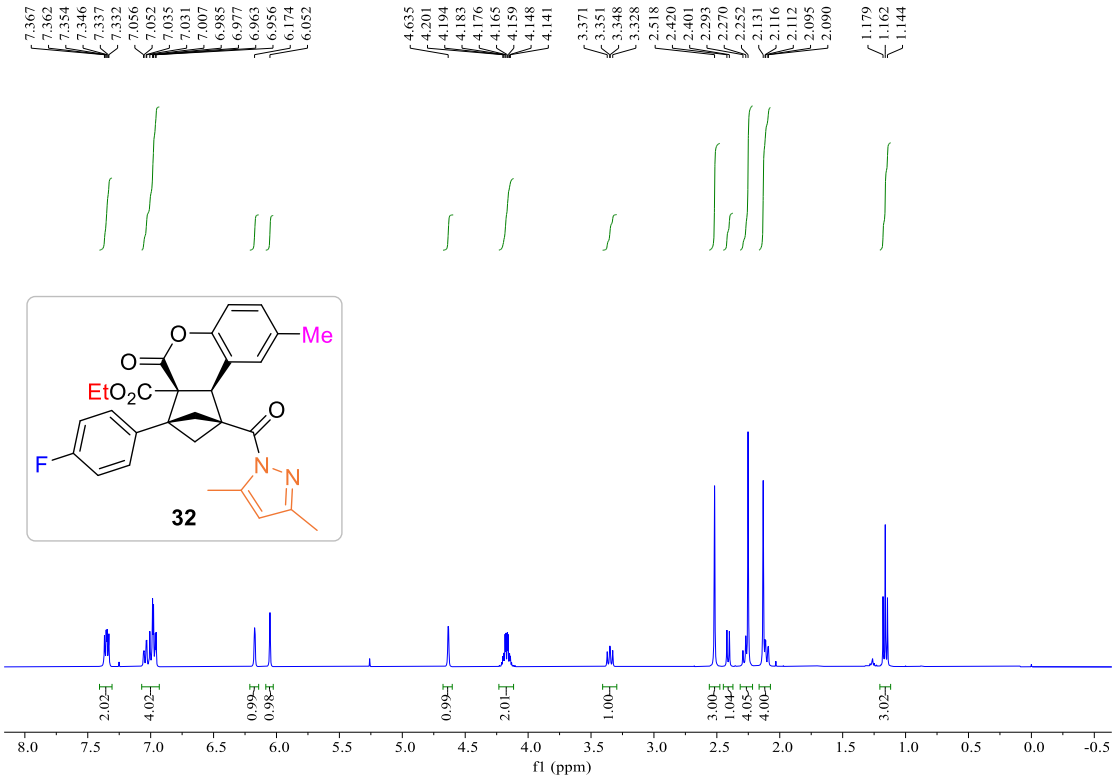
31, ^{13}C NMR (101 MHz, $CDCl_3$)



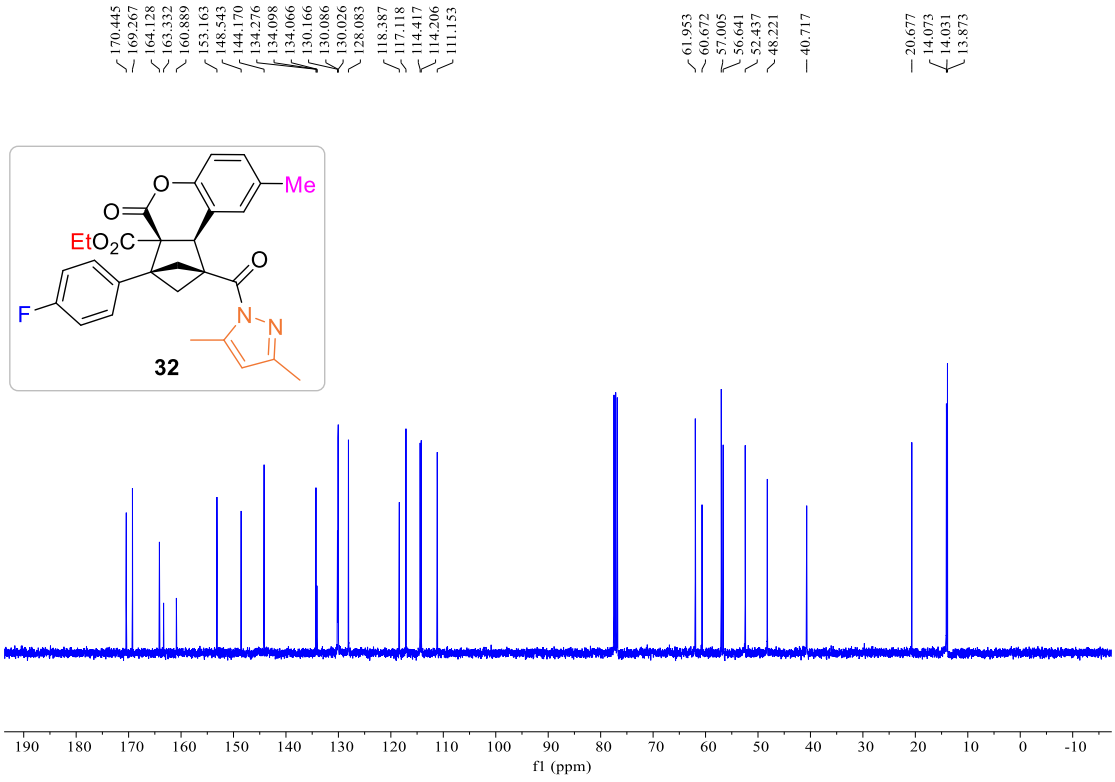
31, ^{19}F NMR (376 MHz, $CDCl_3$)



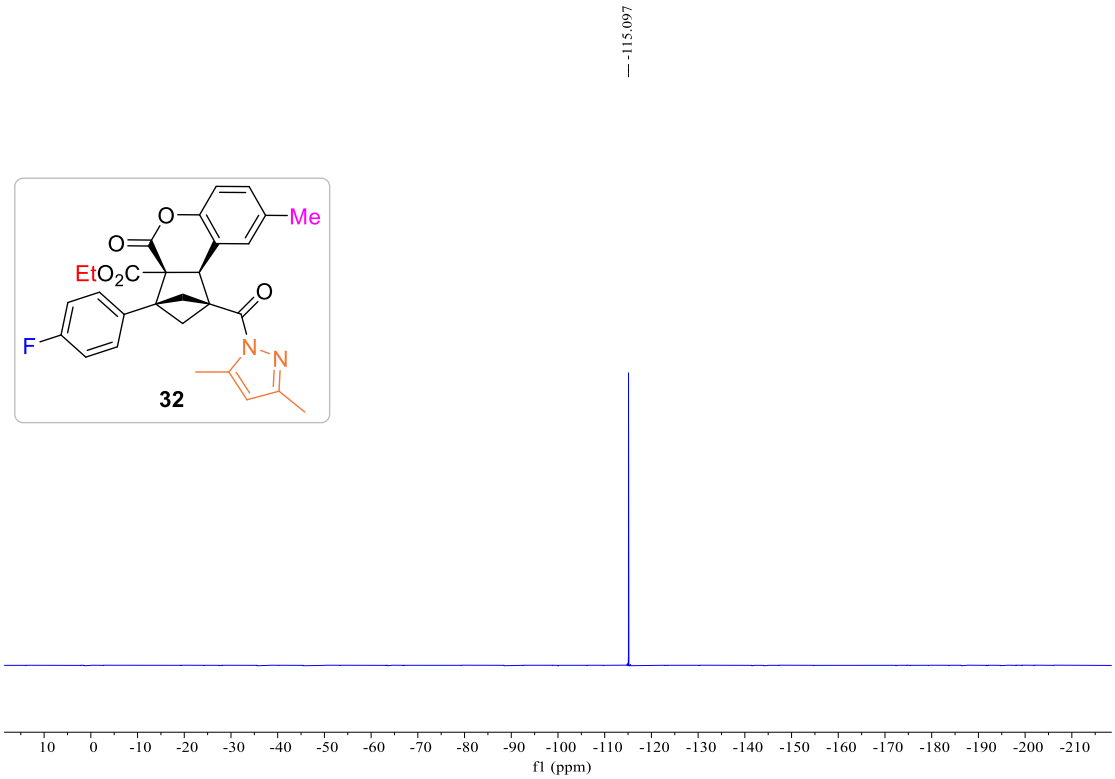
32, ^{1}H NMR (400 MHz, $CDCl_3$)



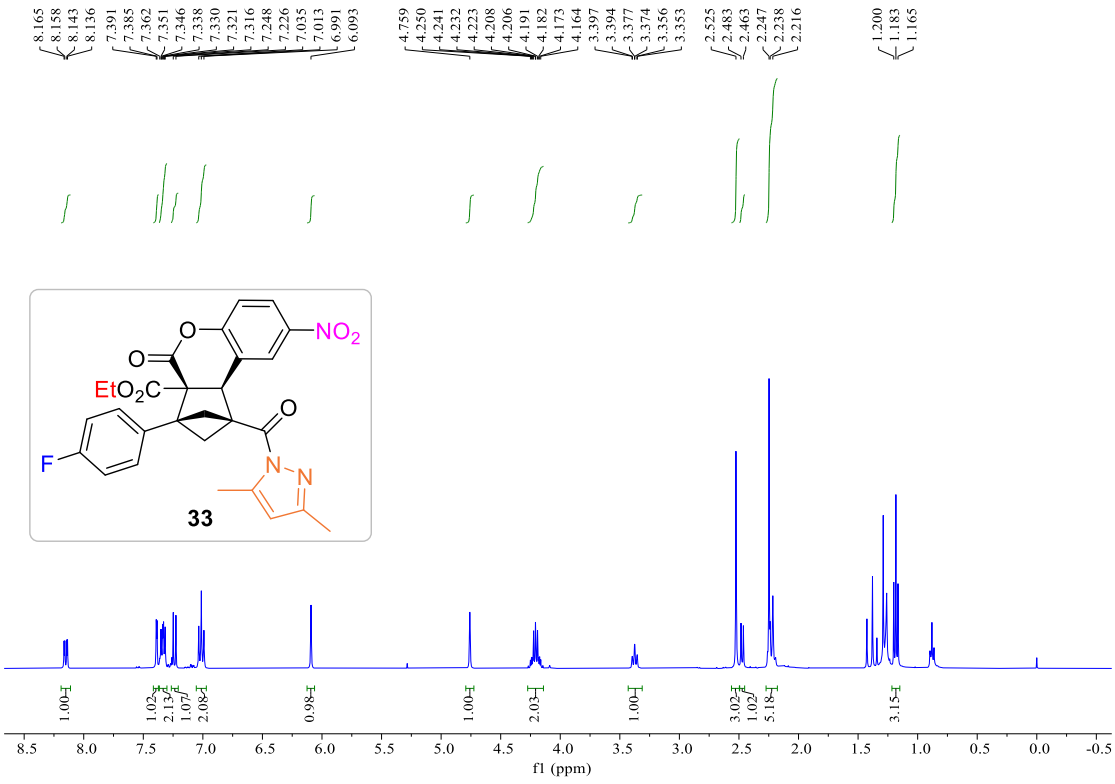
32, ^{13}C NMR (101 MHz, $CDCl_3$)



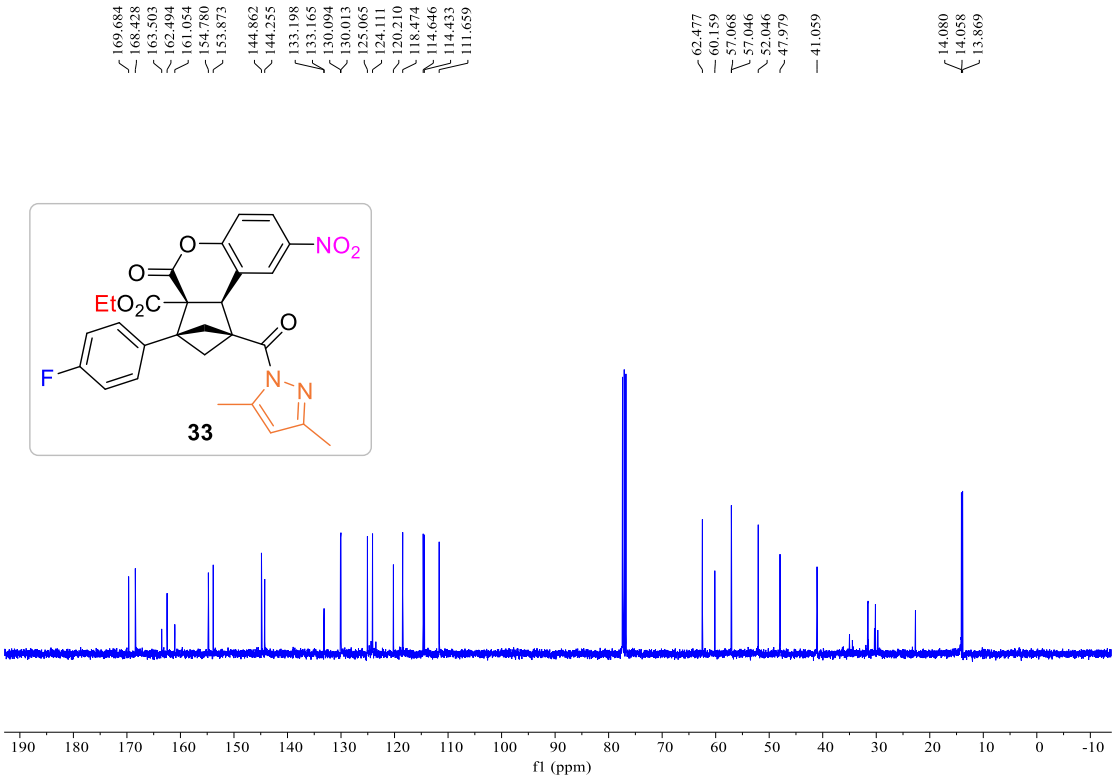
32, ^{19}F NMR (376 MHz, $CDCl_3$)



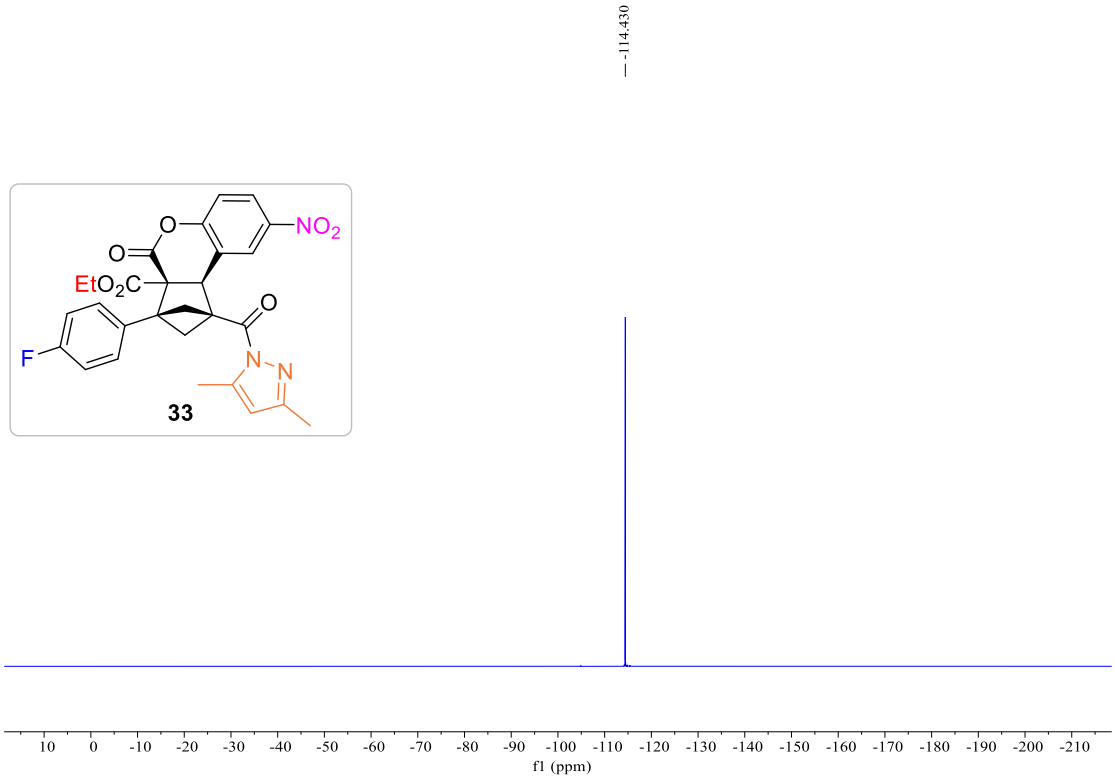
33, ^{1}H NMR (400 MHz, $CDCl_3$)



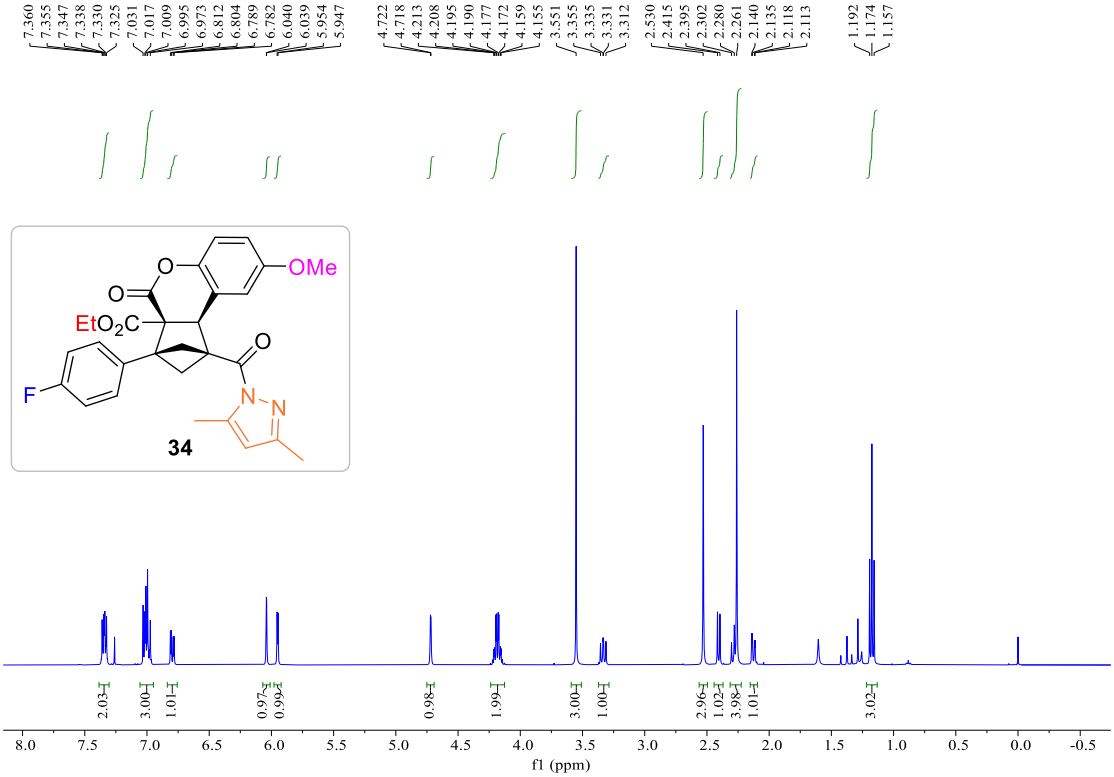
33, ^{13}C NMR (101 MHz, $CDCl_3$)



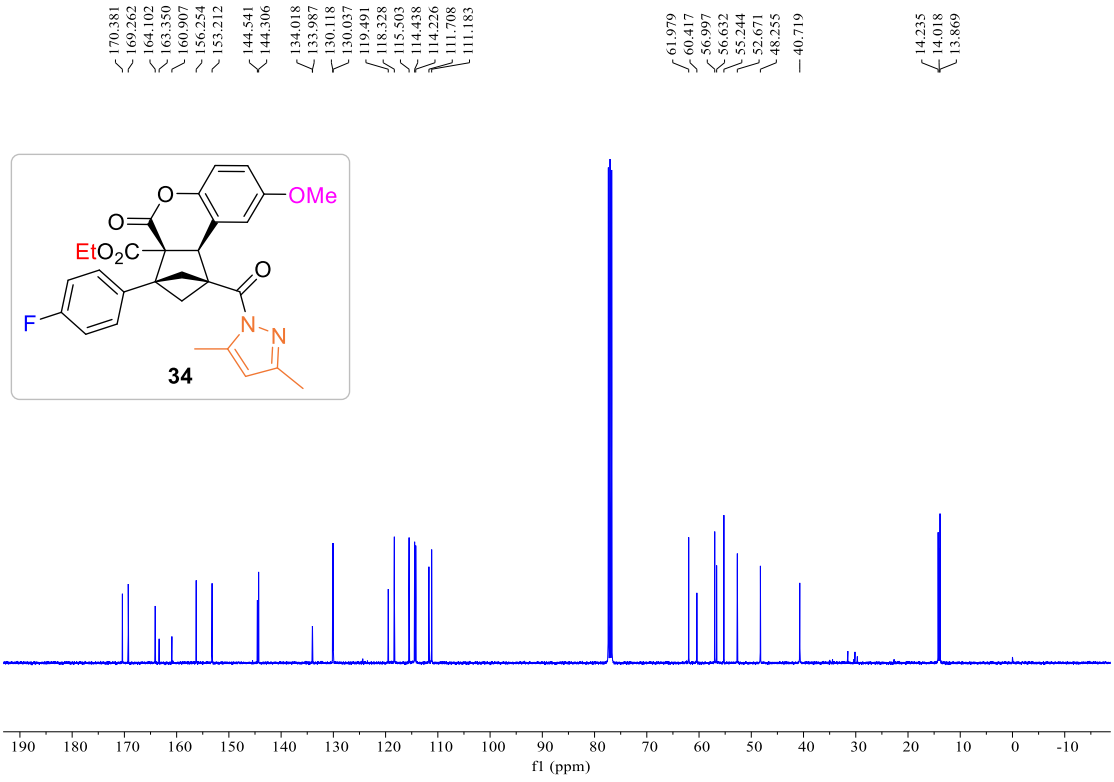
33, ^{19}F NMR (376 MHz, $CDCl_3$)



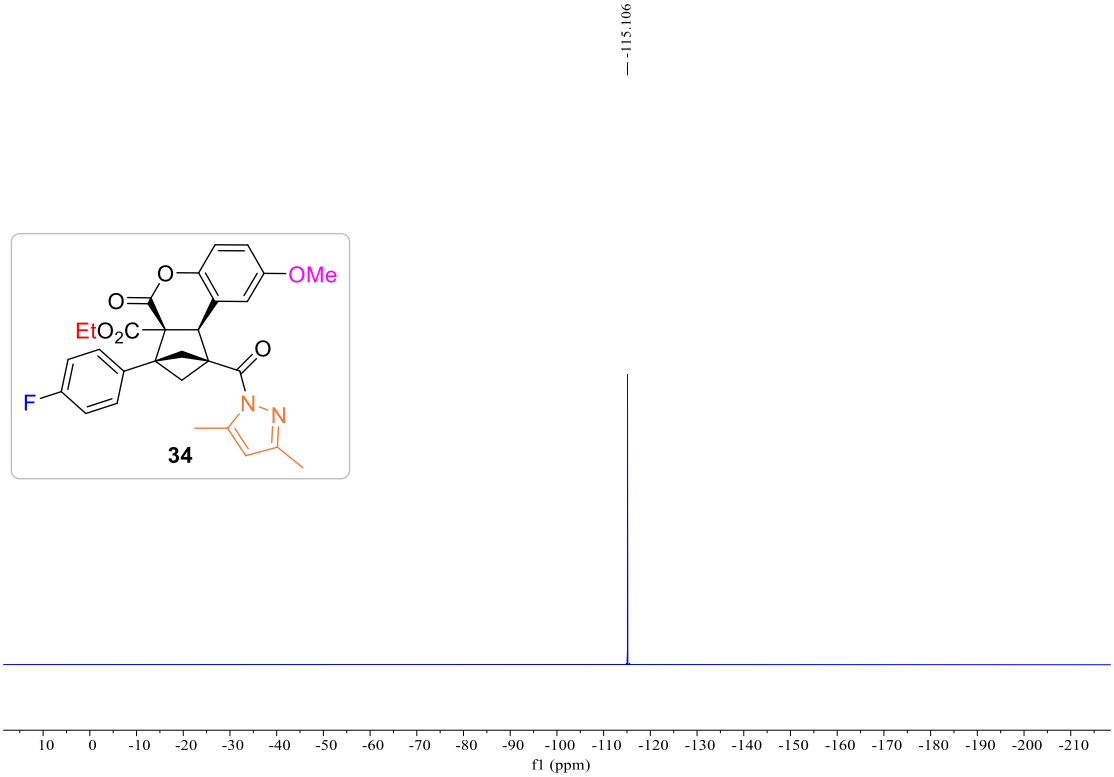
34, ^{1}H NMR (400 MHz, $CDCl_3$)



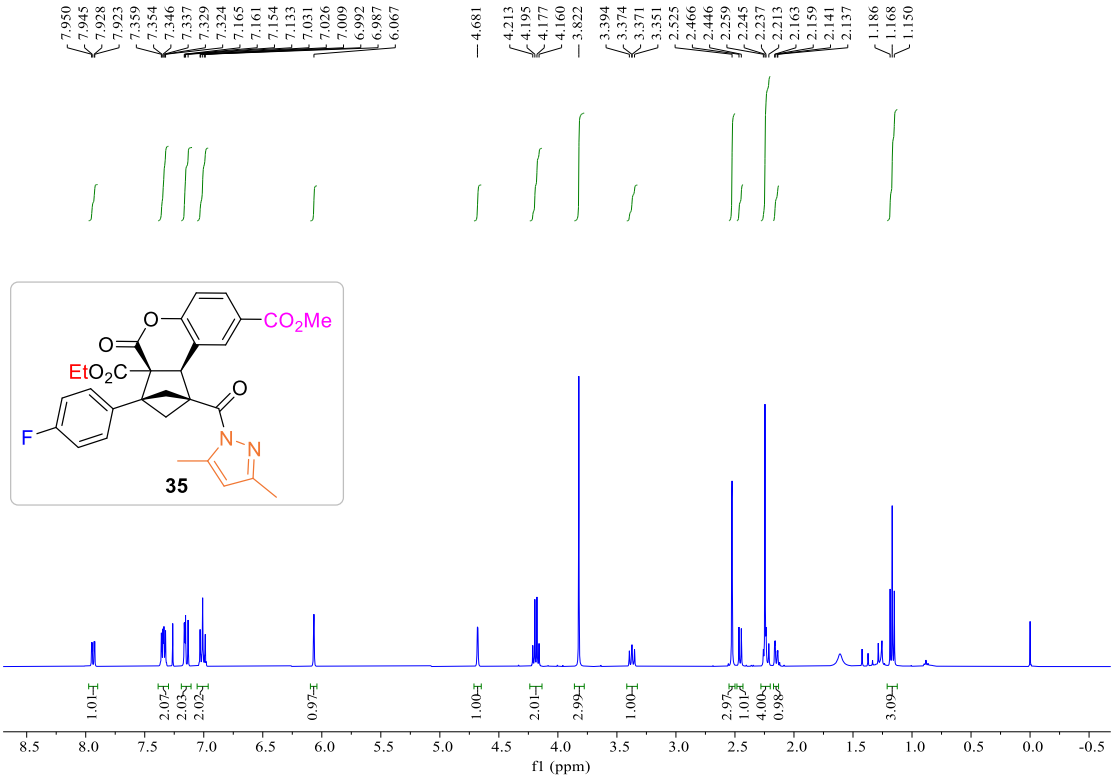
34, ^{13}C NMR (101 MHz, $CDCl_3$)



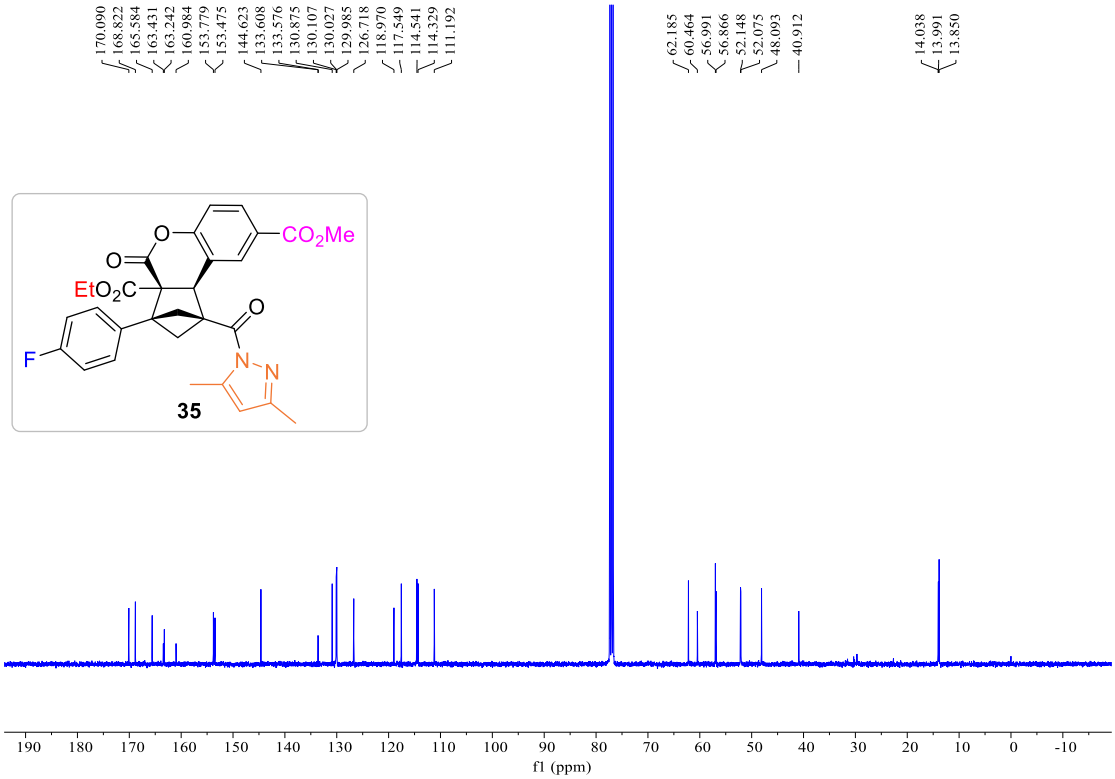
34, ^{19}F NMR (376 MHz, $CDCl_3$)



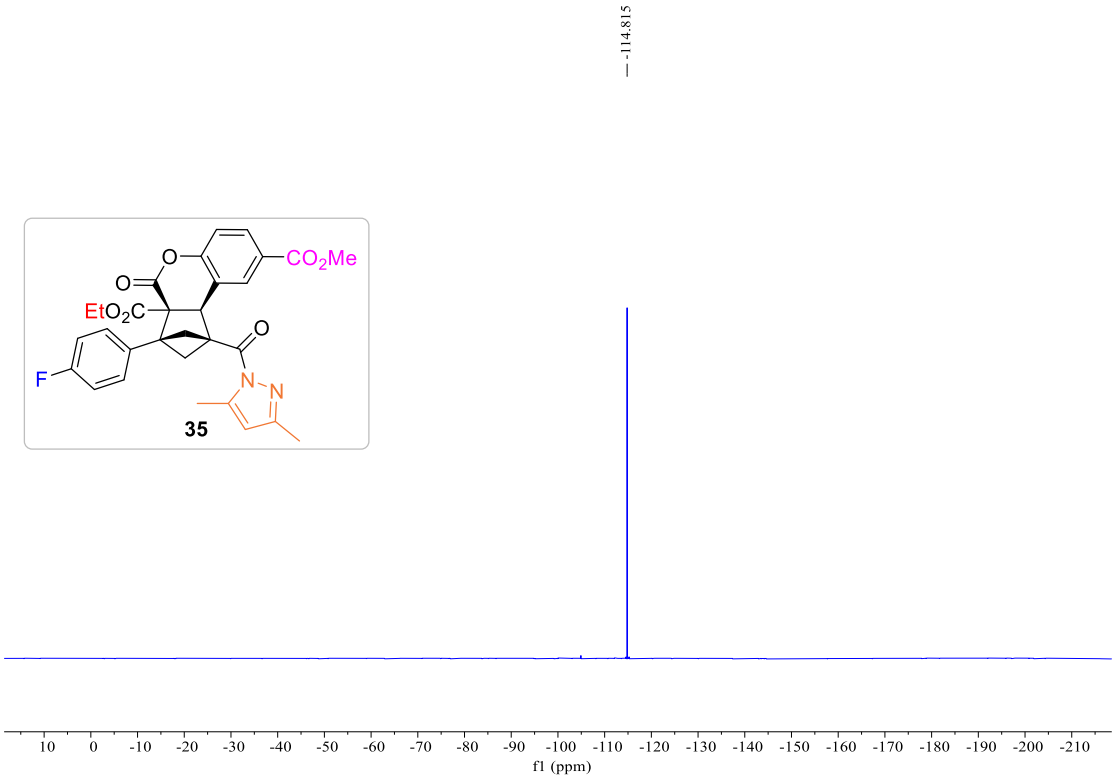
35, ^{1}H NMR (400 MHz, $CDCl_3$)



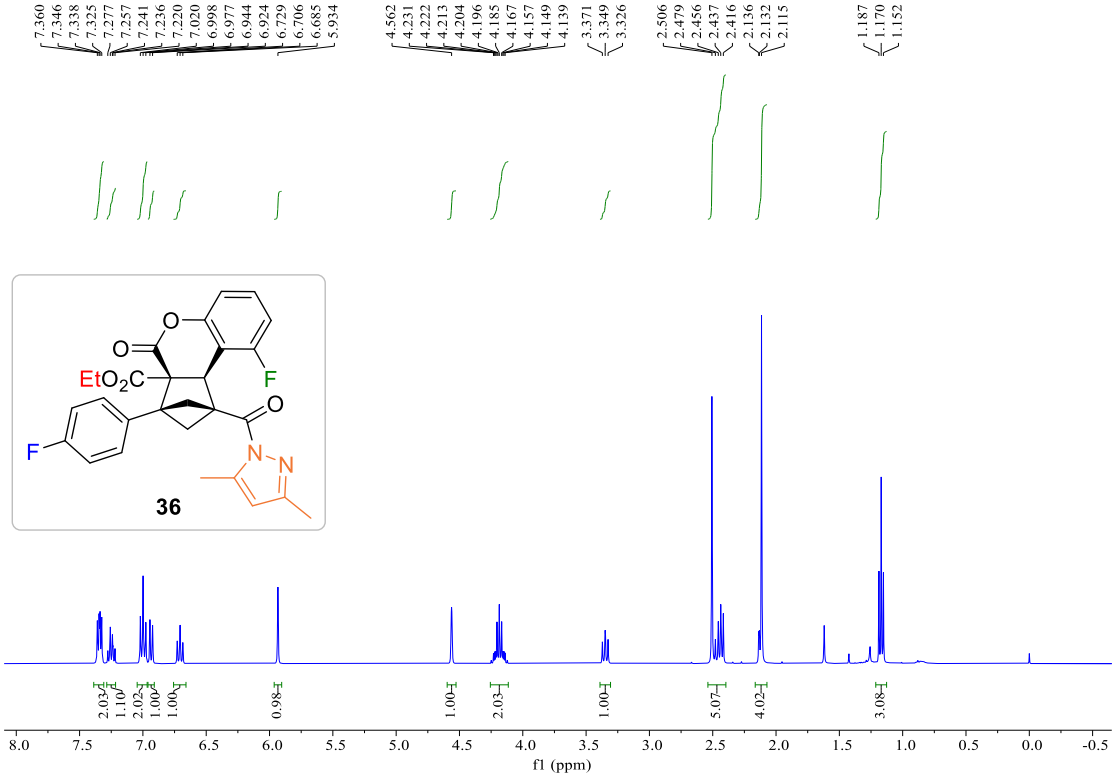
35, ^{13}C NMR (101 MHz, $CDCl_3$)



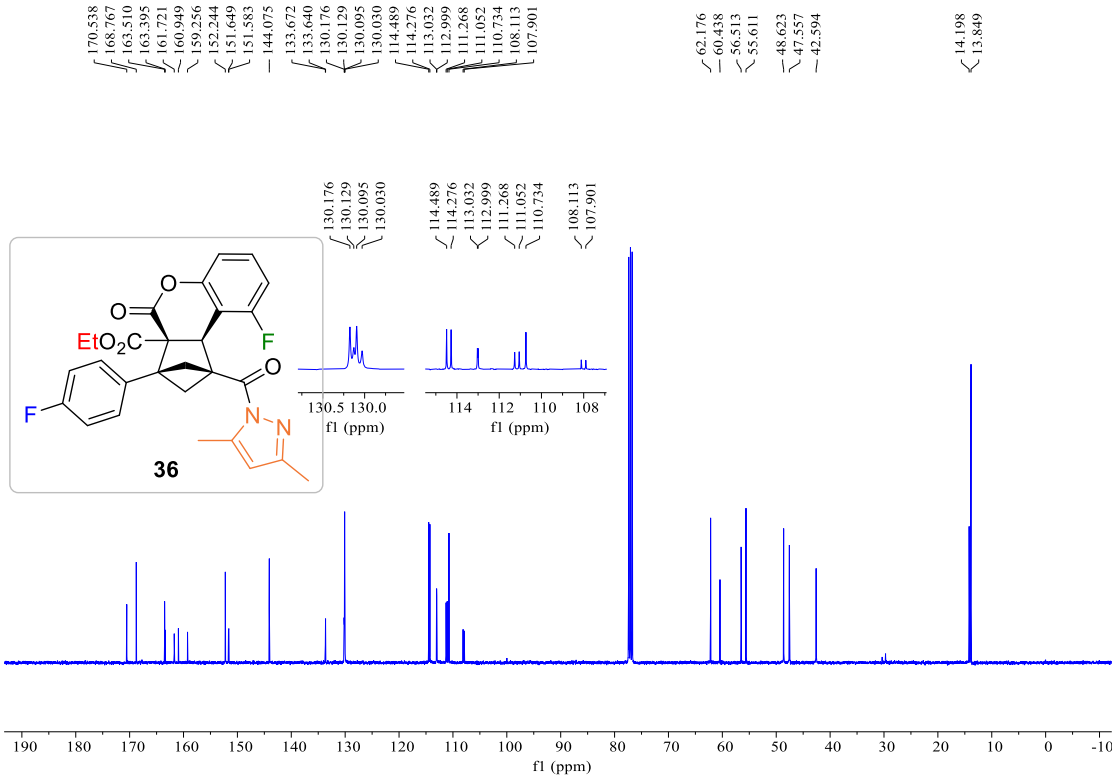
35, ^{19}F NMR (376 MHz, $CDCl_3$)



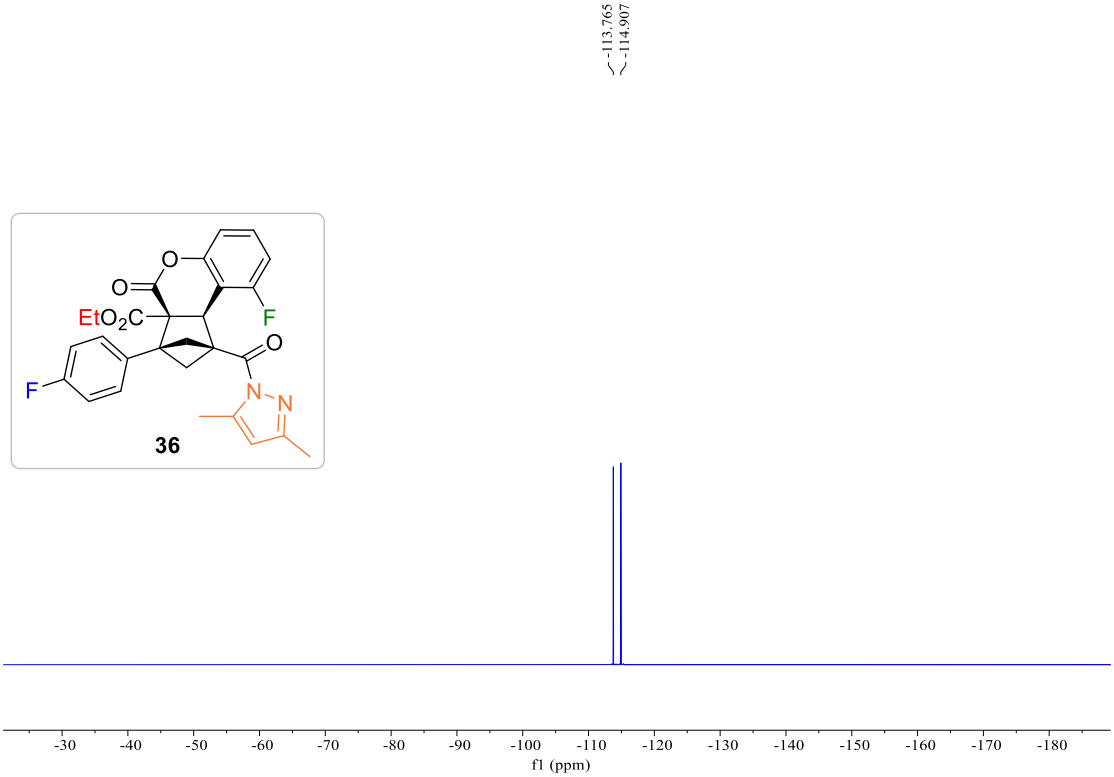
36, ^{1}H NMR (400 MHz, $CDCl_3$)



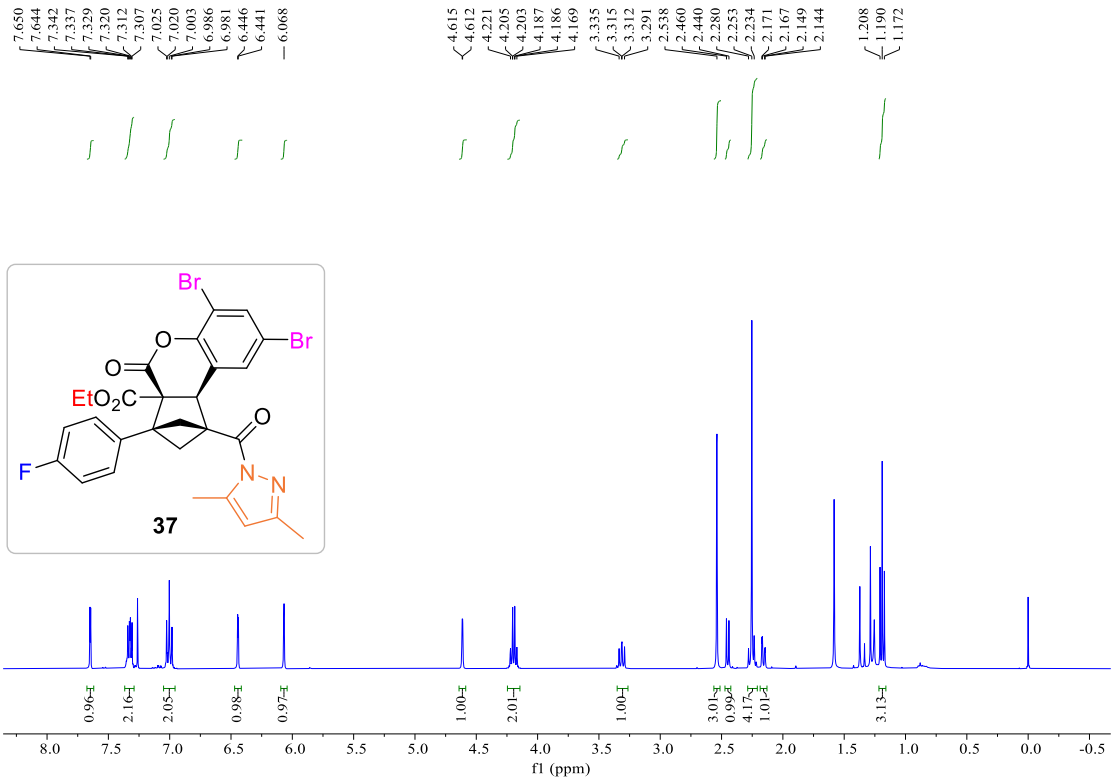
36, ^{13}C NMR (101 MHz, $CDCl_3$)



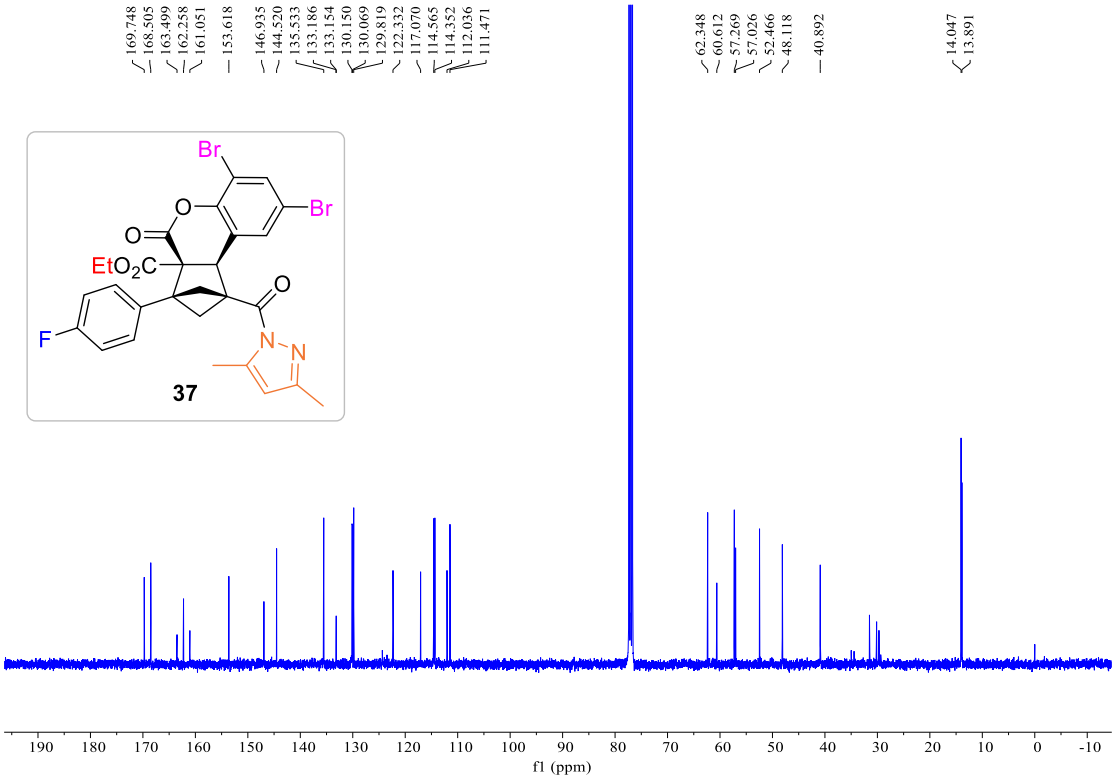
36, ^{19}F NMR (376 MHz, $CDCl_3$)



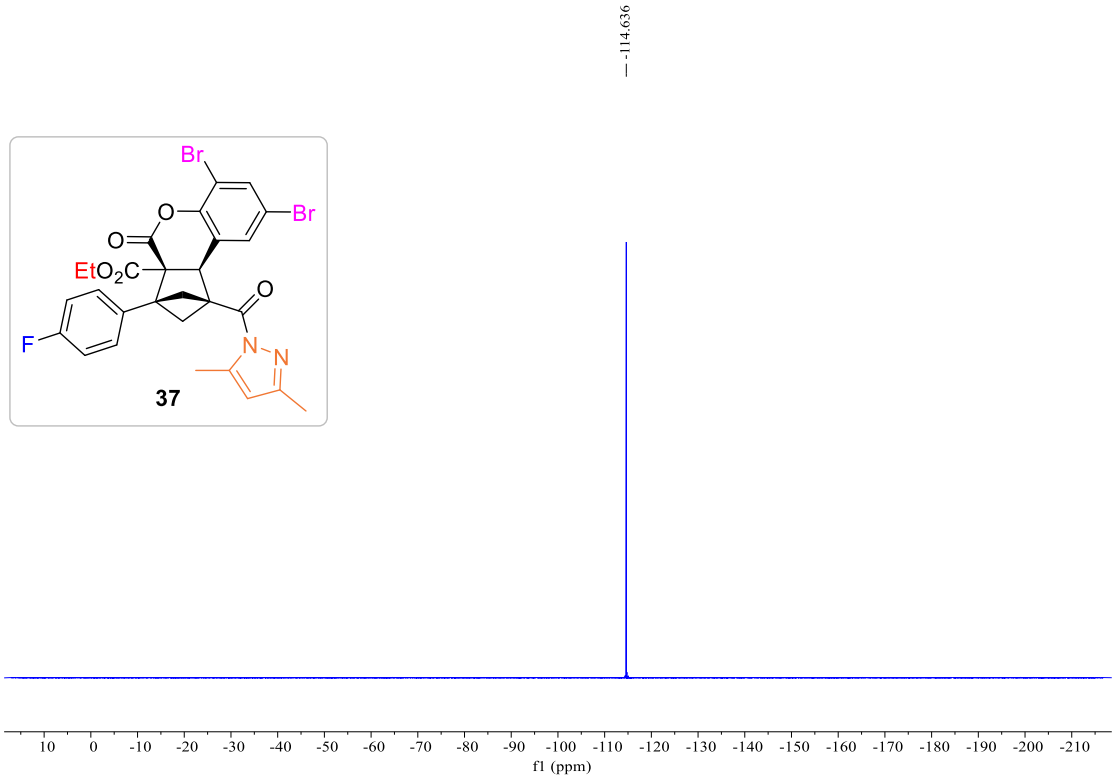
37, ^{1}H NMR (400 MHz, $CDCl_3$)



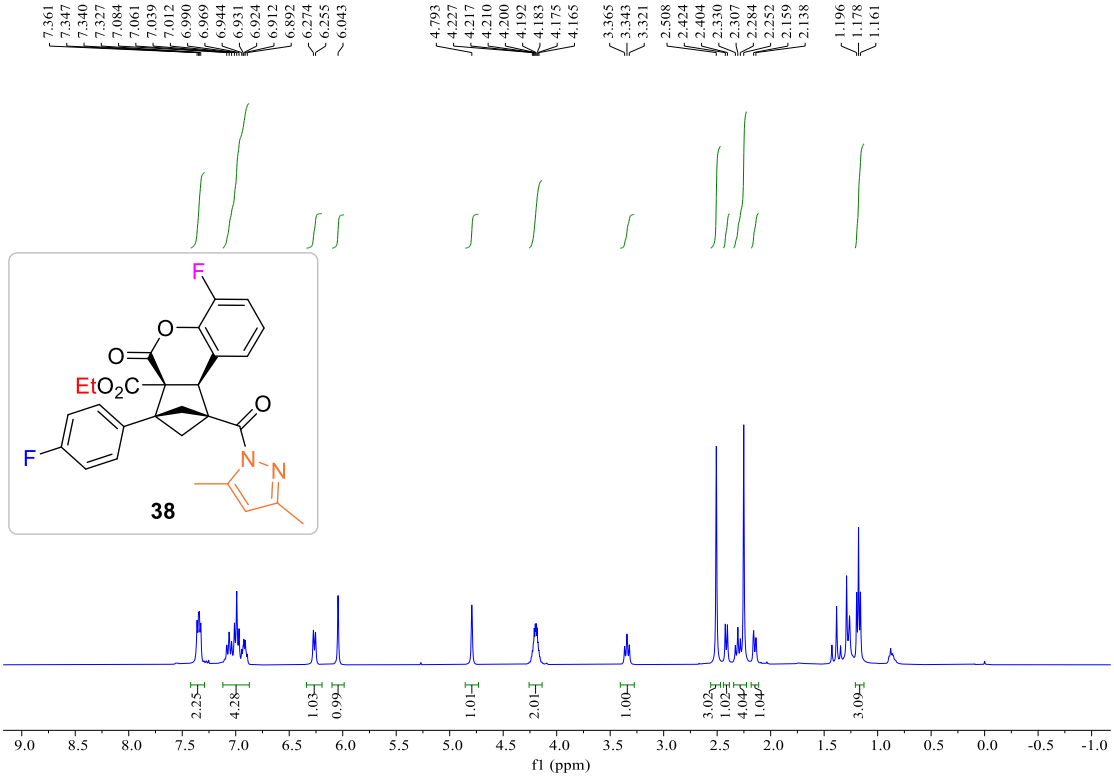
37, ^{13}C NMR (101 MHz, $CDCl_3$)



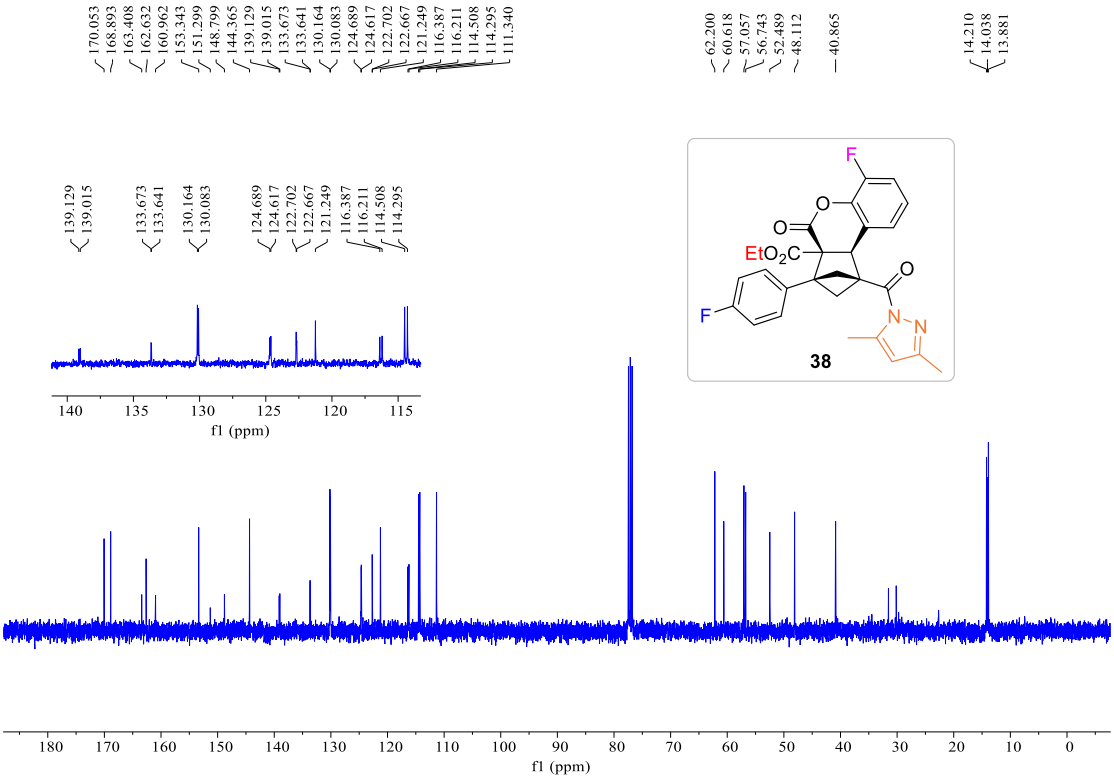
37, ^{19}F NMR (376 MHz, $CDCl_3$)



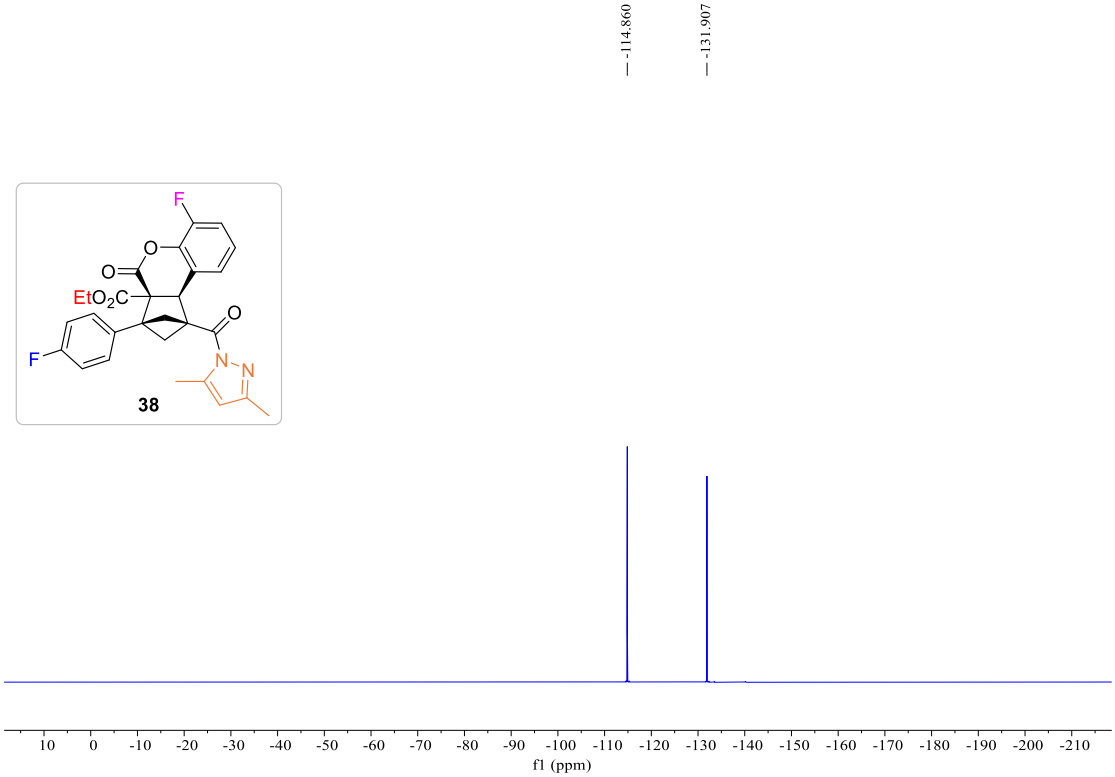
38, ^{1}H NMR (400 MHz, $CDCl_3$)



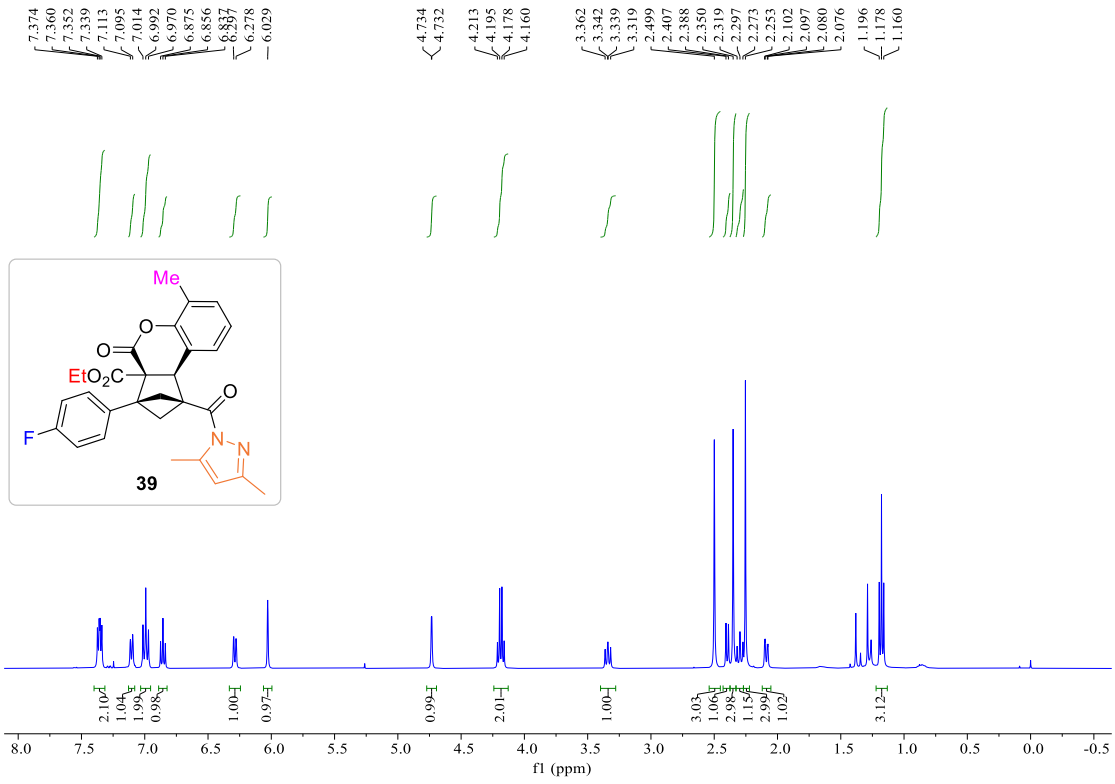
38, ^{13}C NMR (101 MHz, $CDCl_3$)



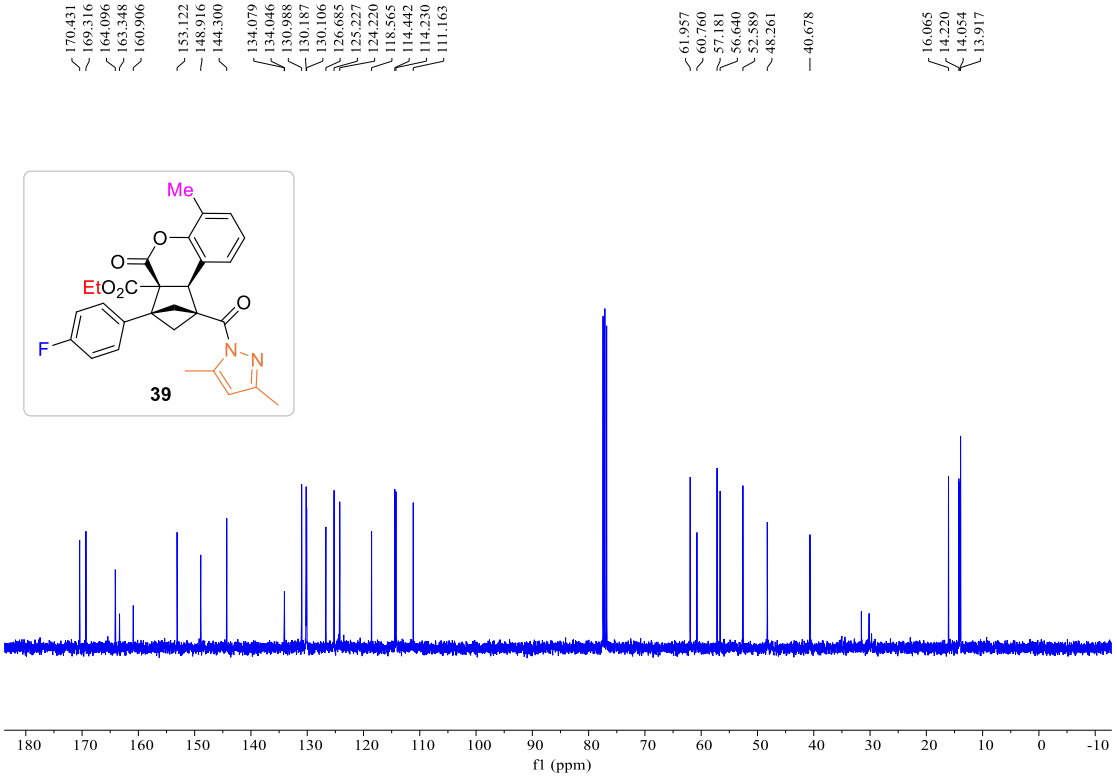
38, ^{19}F NMR (376 MHz, $CDCl_3$)



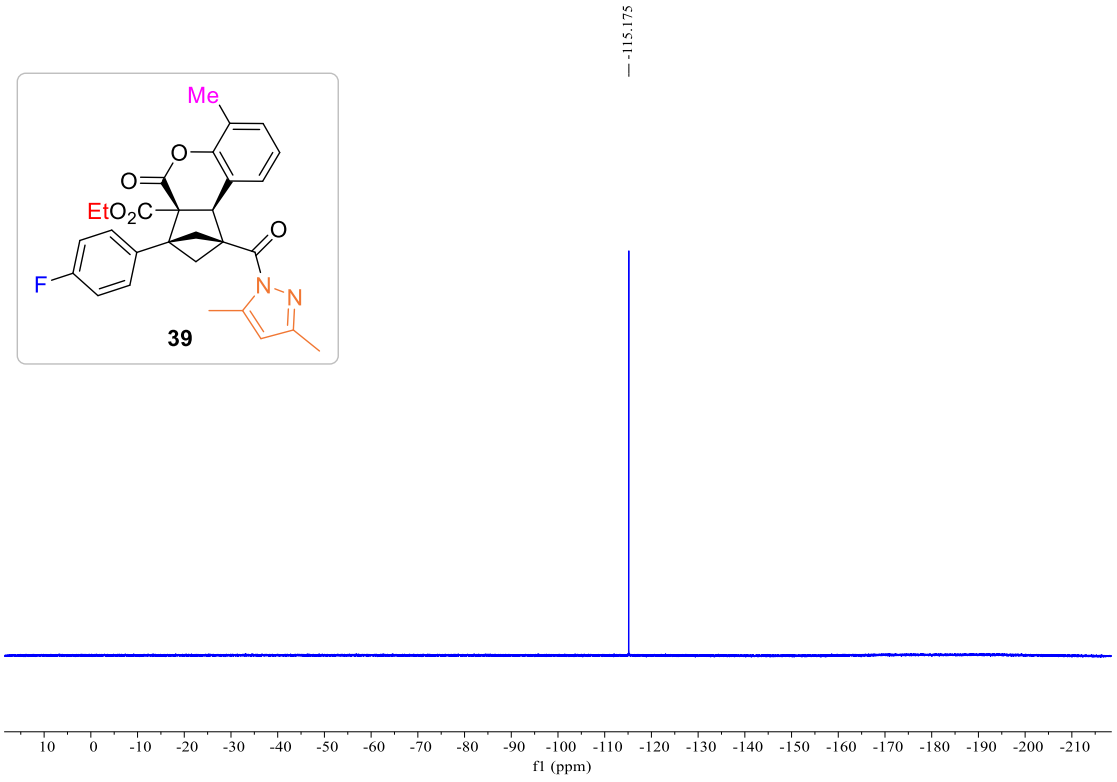
39, ^{1}H NMR (400 MHz, $CDCl_3$)



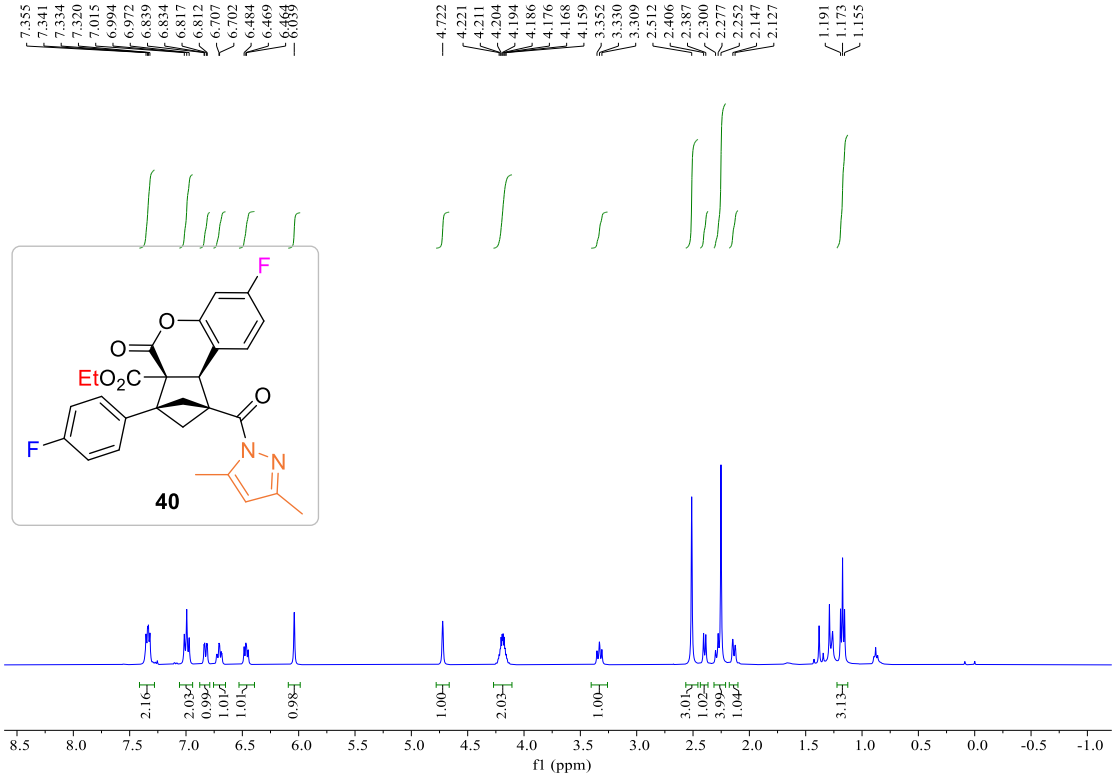
39, ^{13}C NMR (101 MHz, $CDCl_3$)



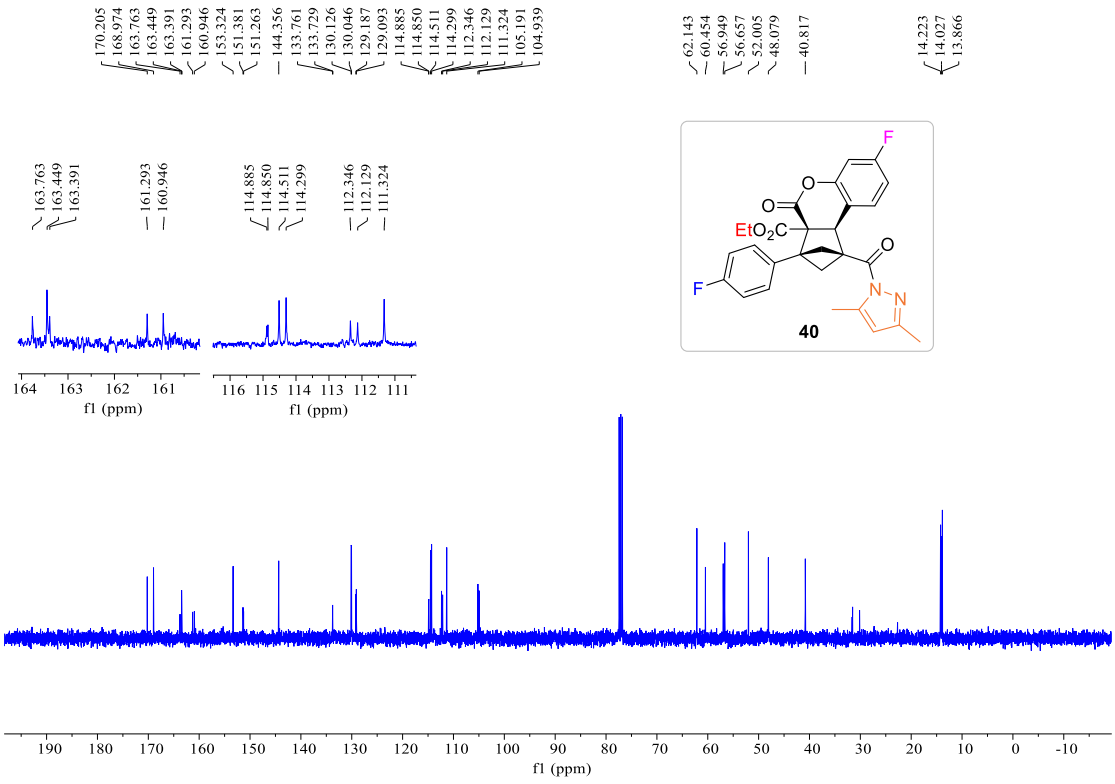
39, ^{19}F NMR (376 MHz, $CDCl_3$)



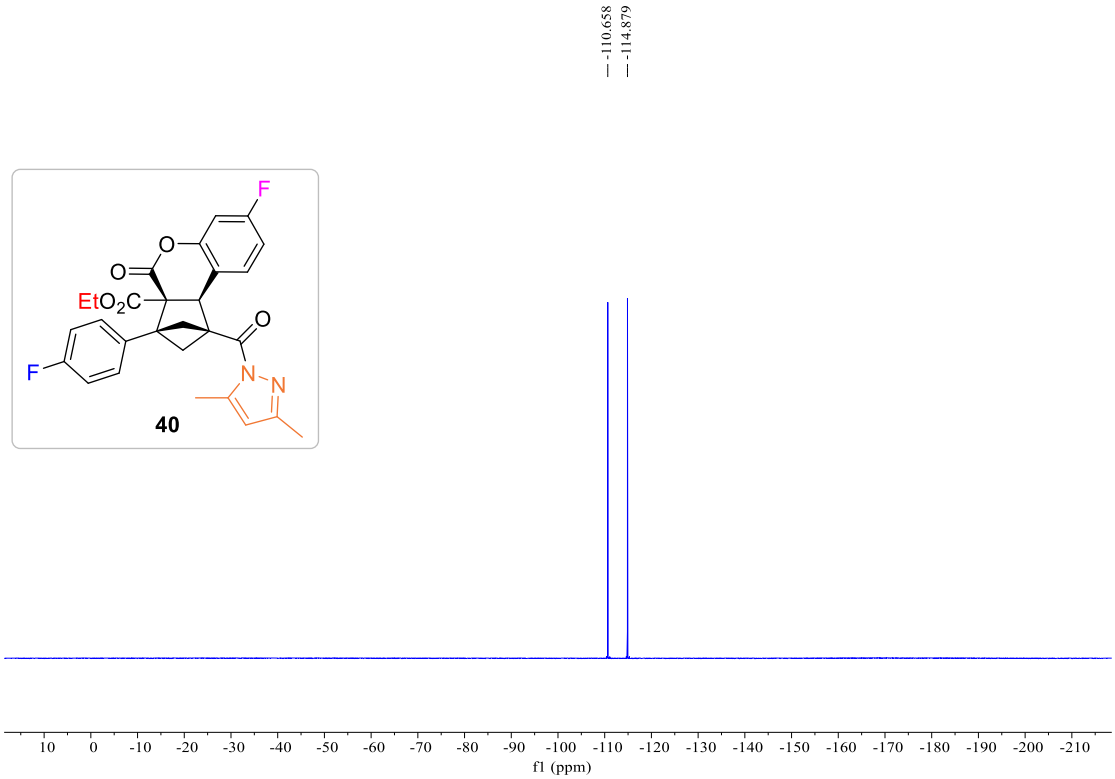
40, ^{1}H NMR (400 MHz, $CDCl_3$)



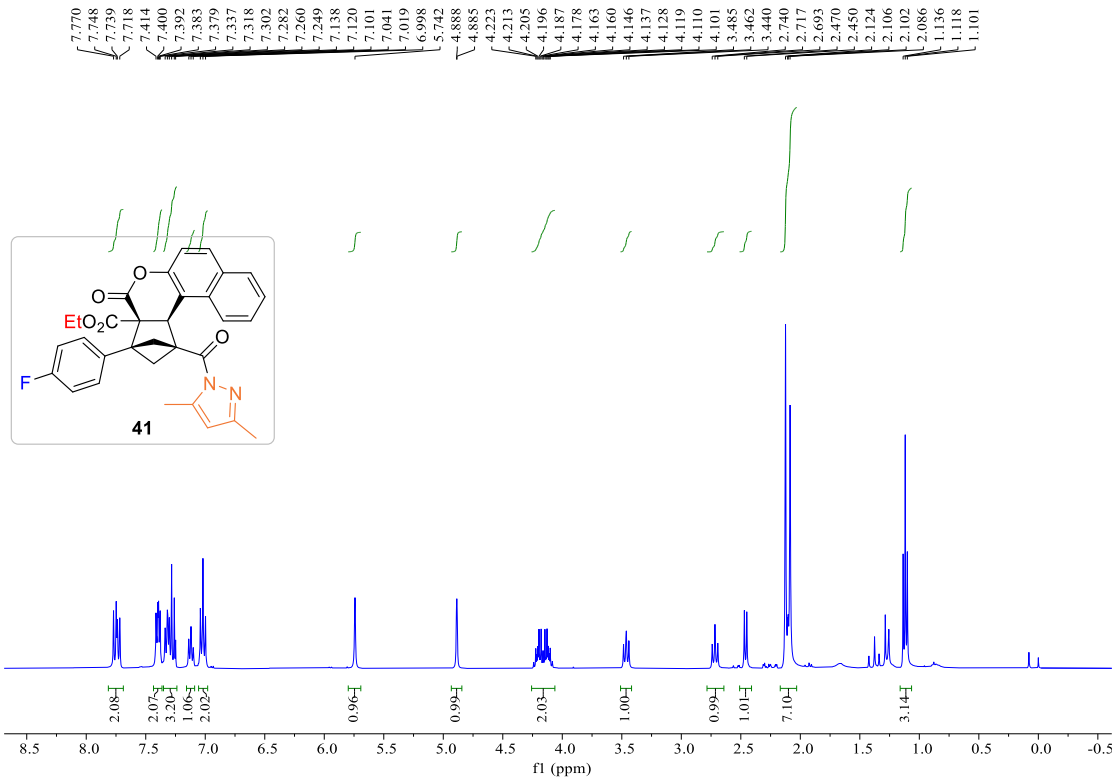
40, ^{13}C NMR (101 MHz, $CDCl_3$)



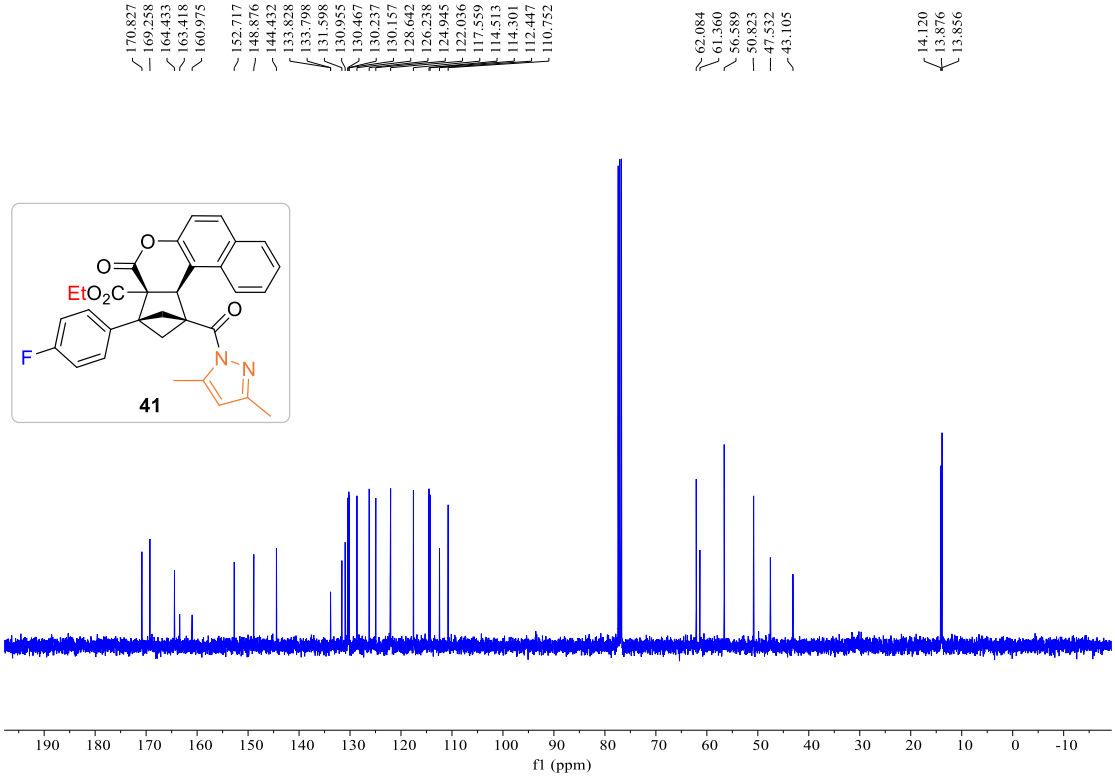
40, ^{19}F NMR (376 MHz, $CDCl_3$)



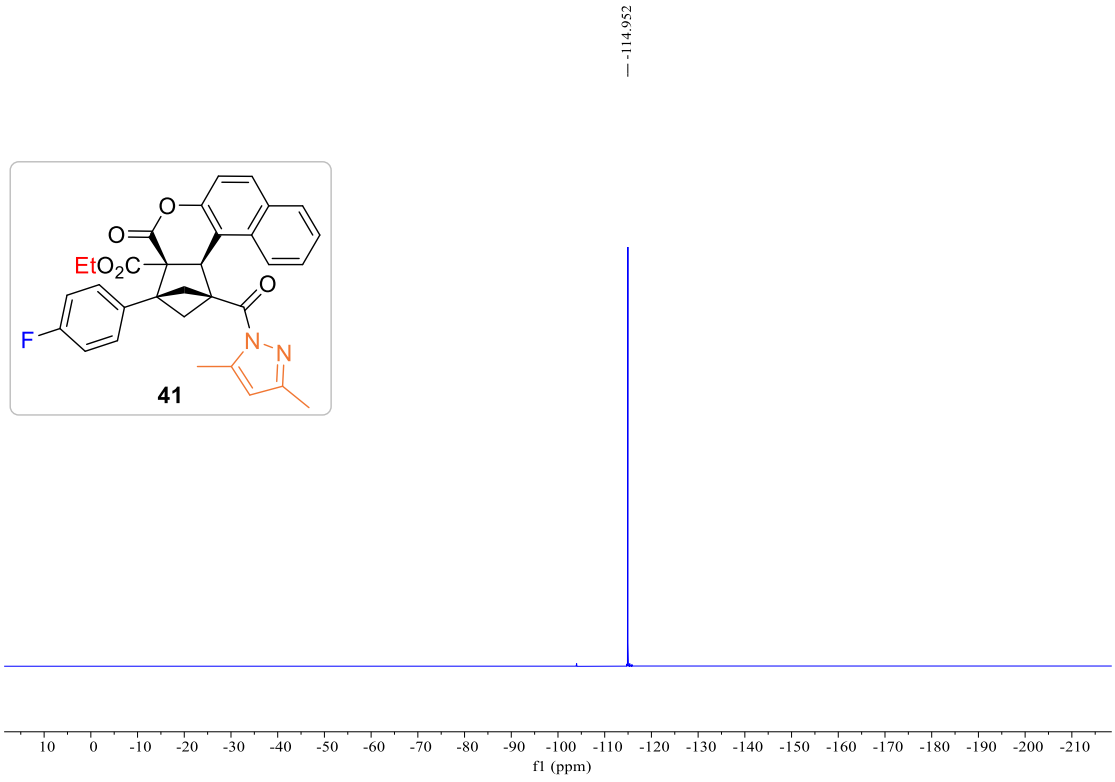
41, ^{1}H NMR (400 MHz, $CDCl_3$)



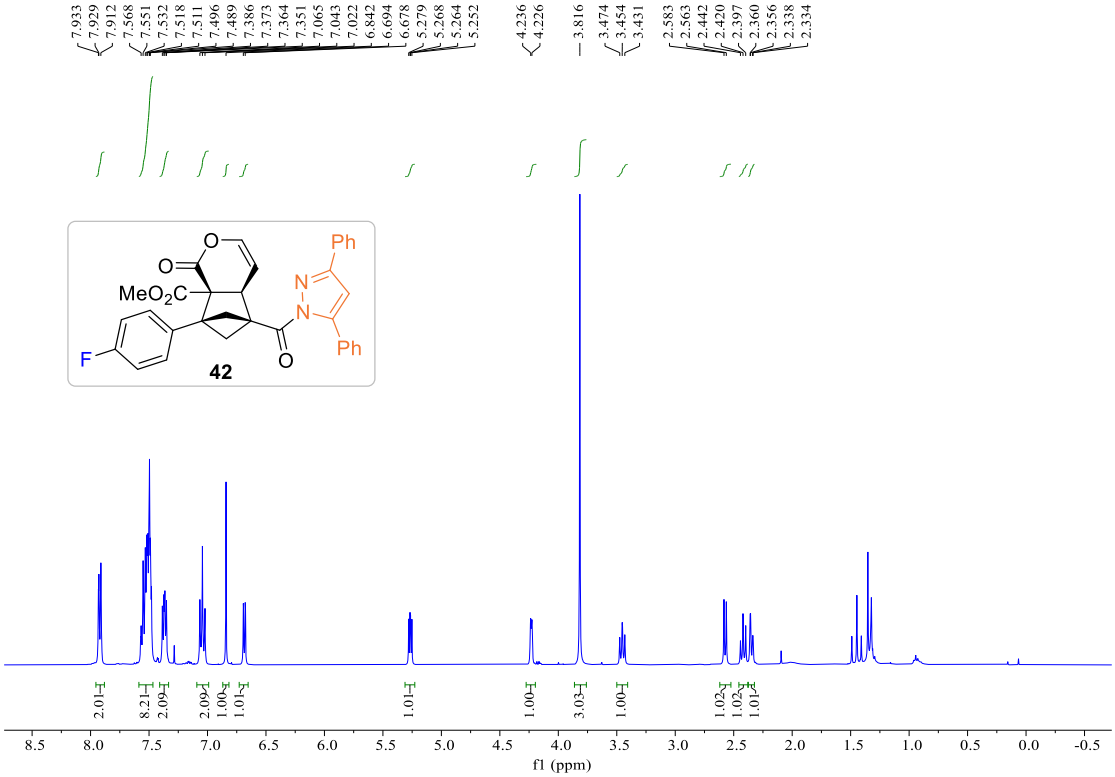
41, ^{13}C NMR (101 MHz, $CDCl_3$)



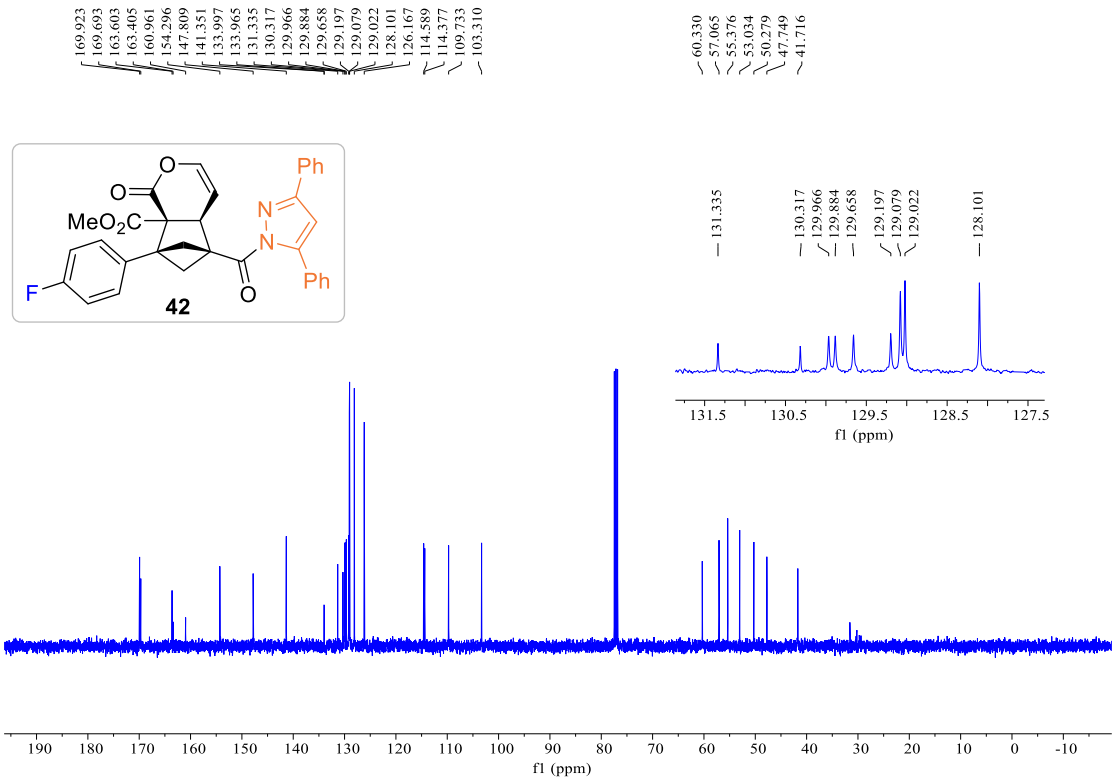
41, ^{19}F NMR (376 MHz, $CDCl_3$)



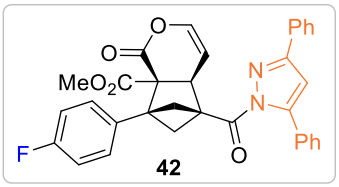
42, ^{1}H NMR (400 MHz, $CDCl_3$)



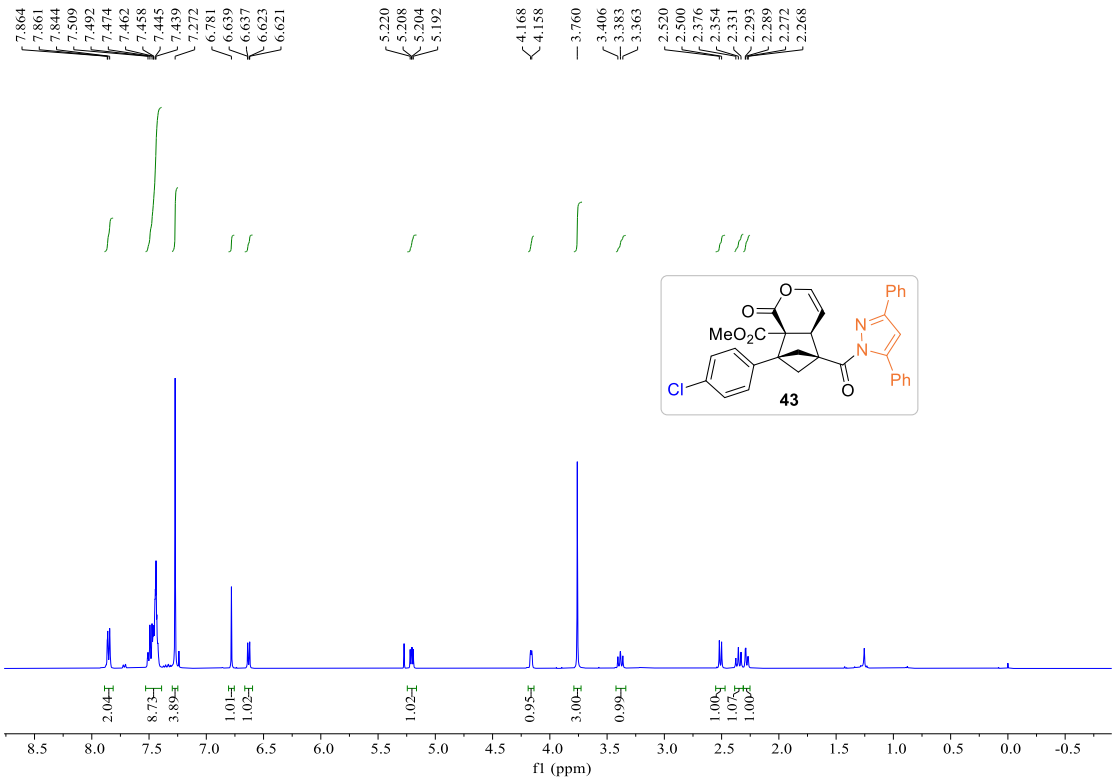
42, ^{13}C NMR (101 MHz, $CDCl_3$)



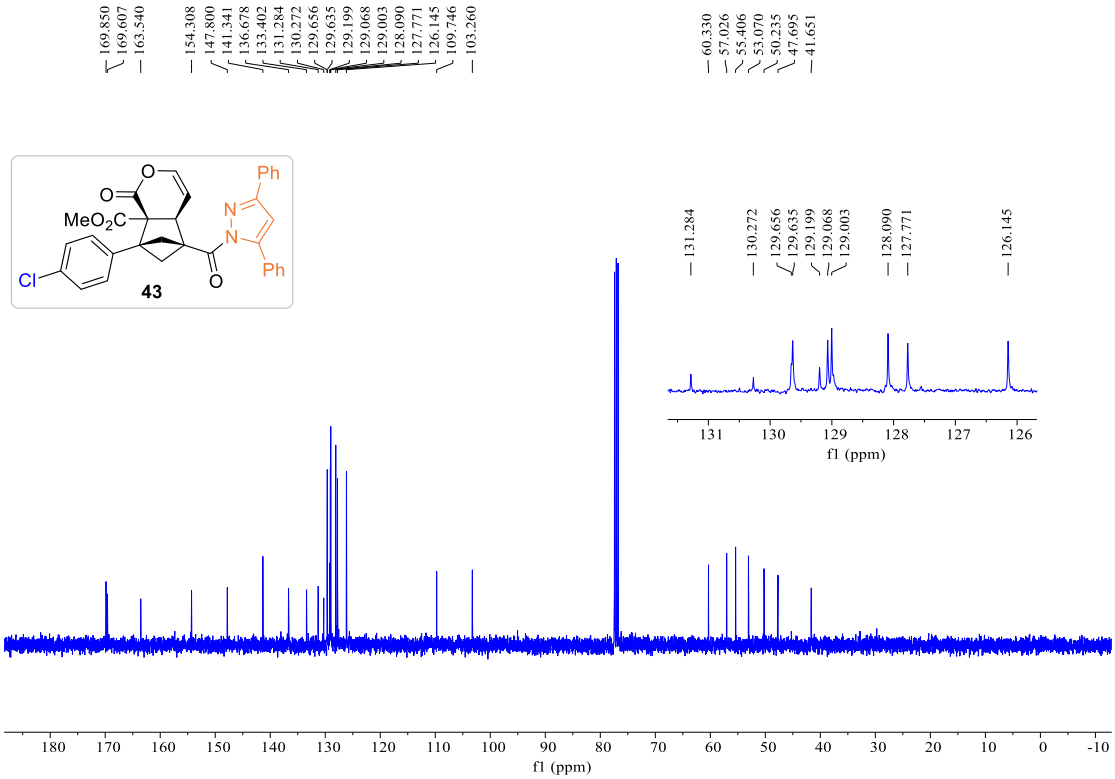
42, ^{19}F NMR (376 MHz, $CDCl_3$)



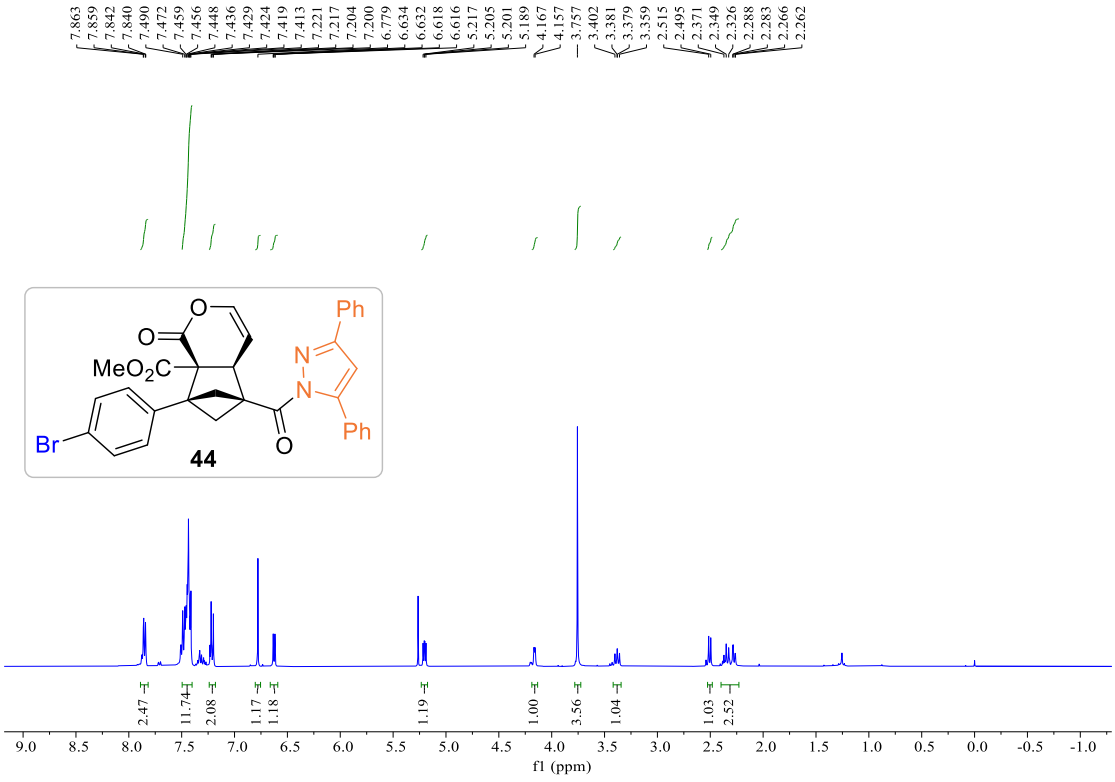
43, ^{1}H NMR (400 MHz, $CDCl_3$)



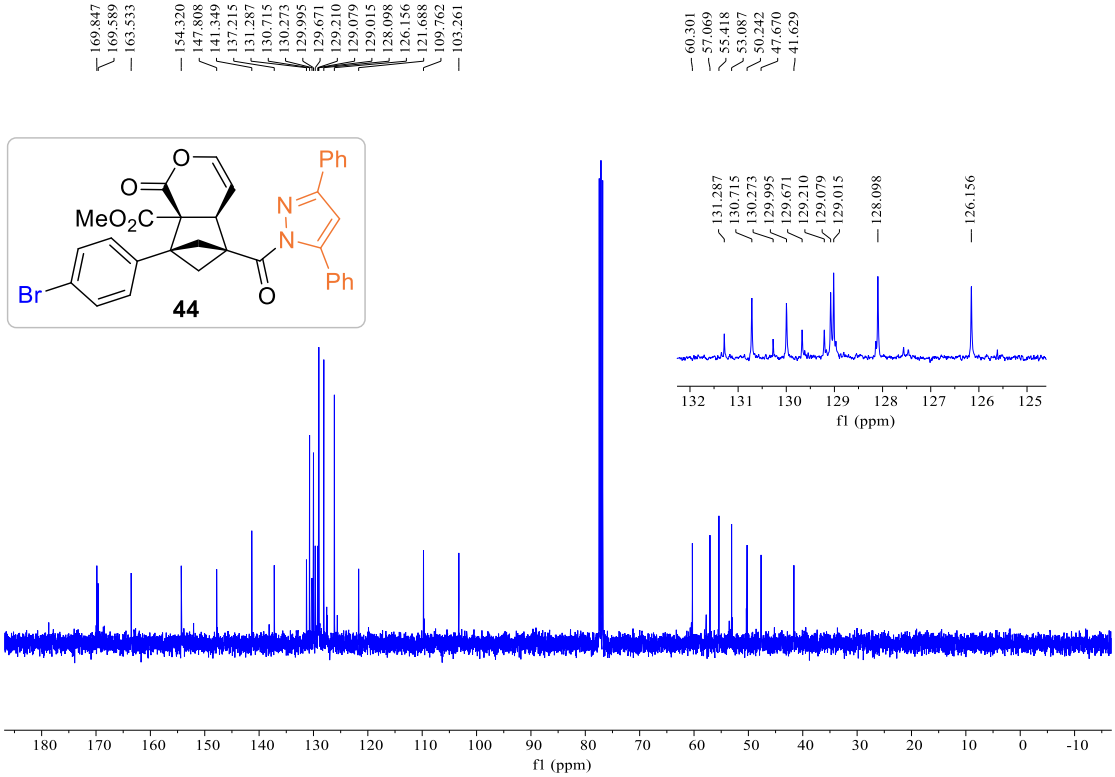
43, ^{13}C NMR (101 MHz, $CDCl_3$)



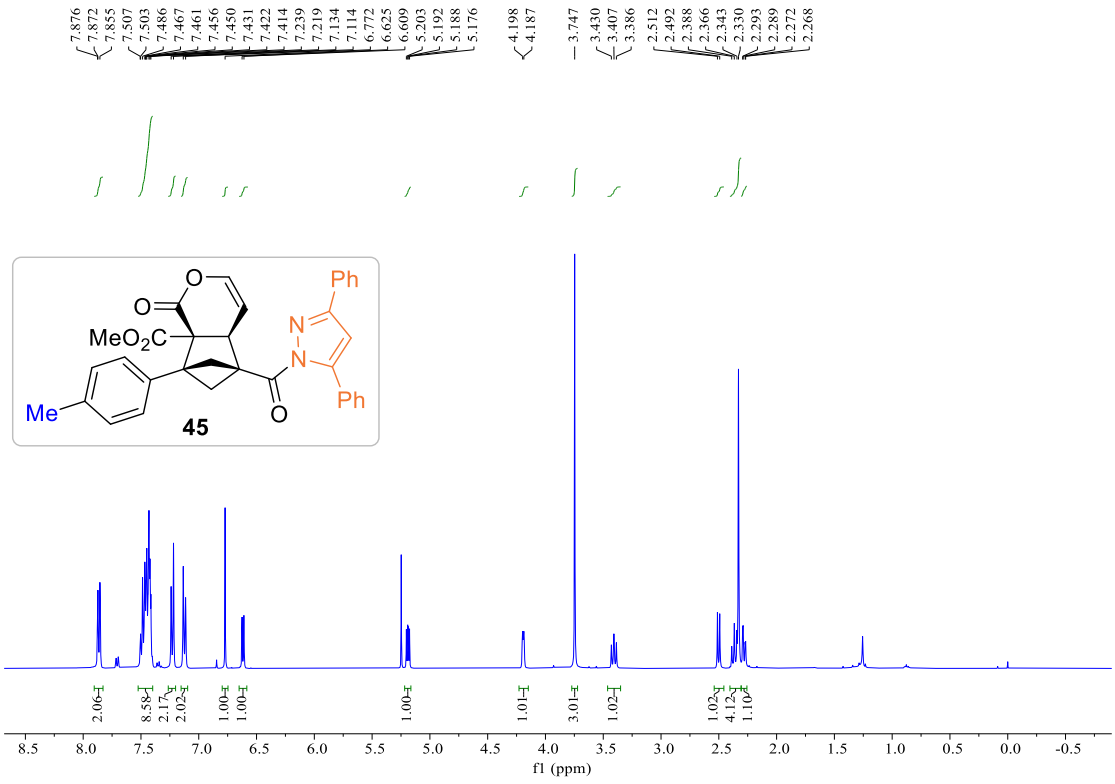
44, ^{1}H NMR (400 MHz, $CDCl_3$)



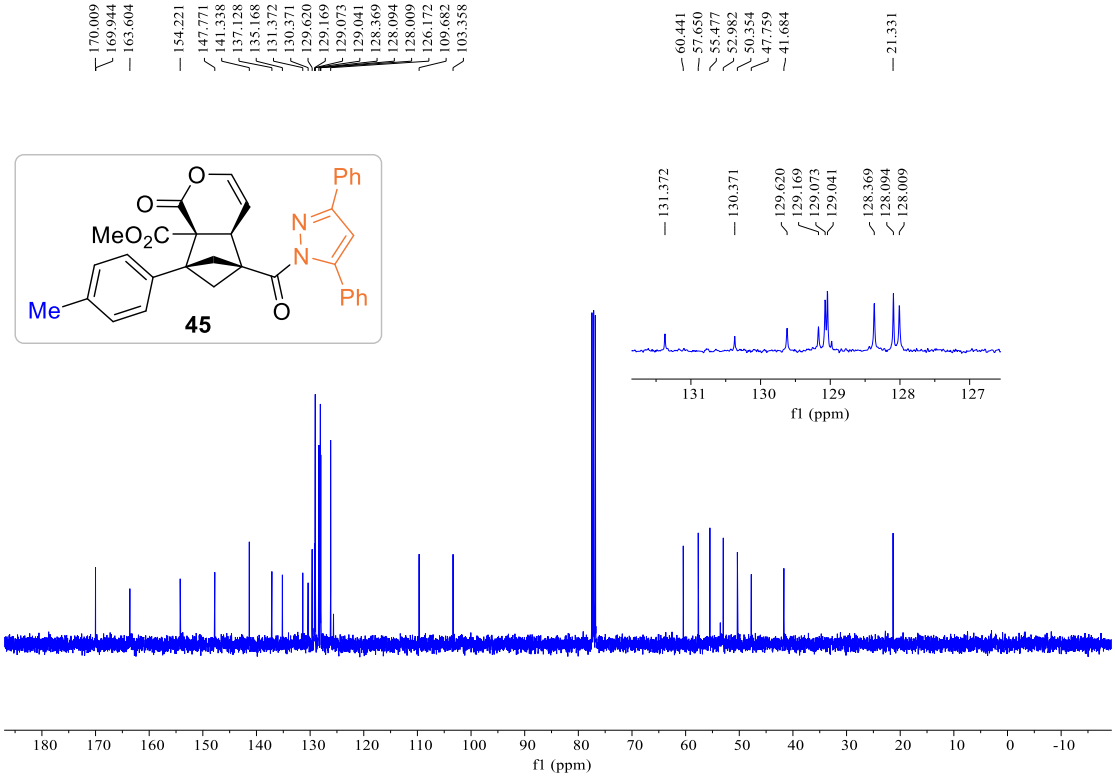
44, ^{13}C NMR (101 MHz, $CDCl_3$)



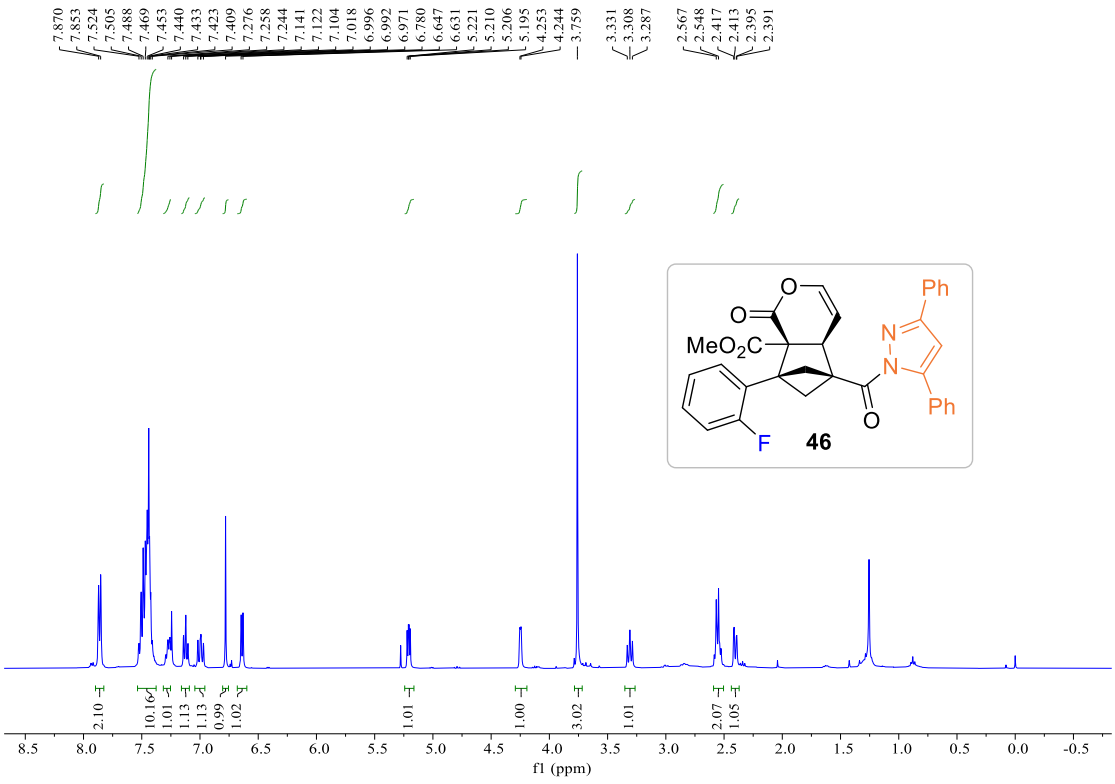
45, ^{1}H NMR (400 MHz, $CDCl_3$)



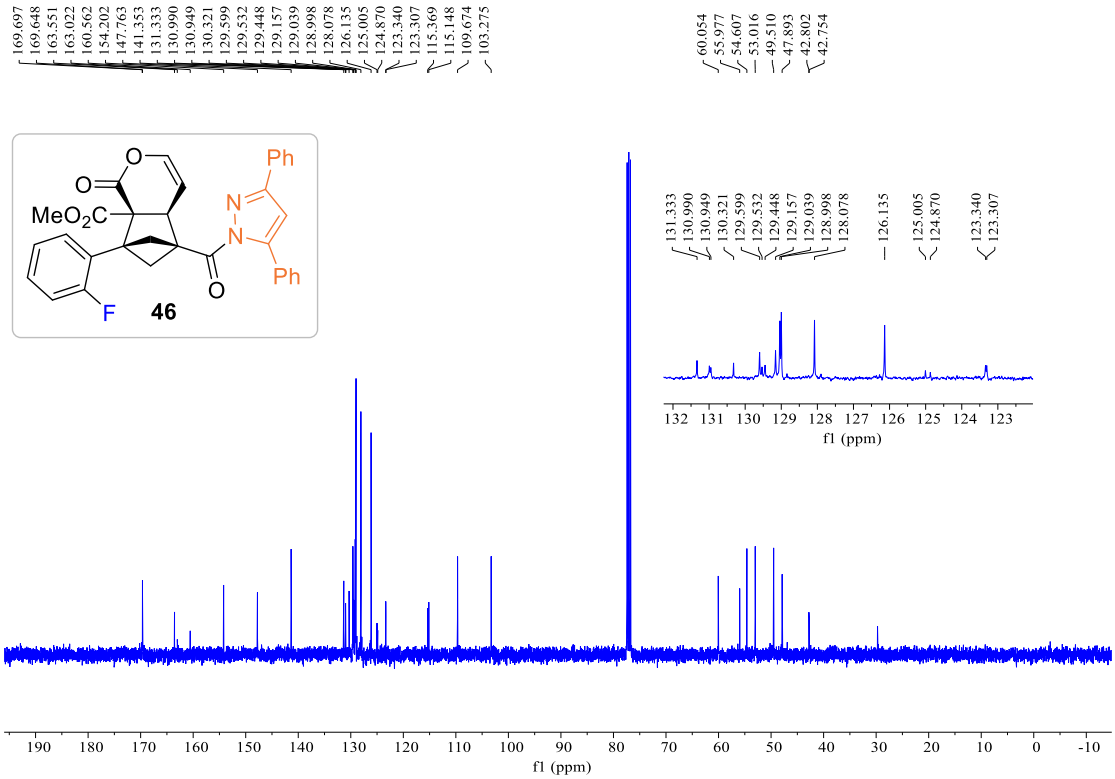
45, ^{13}C NMR (101 MHz, $CDCl_3$)



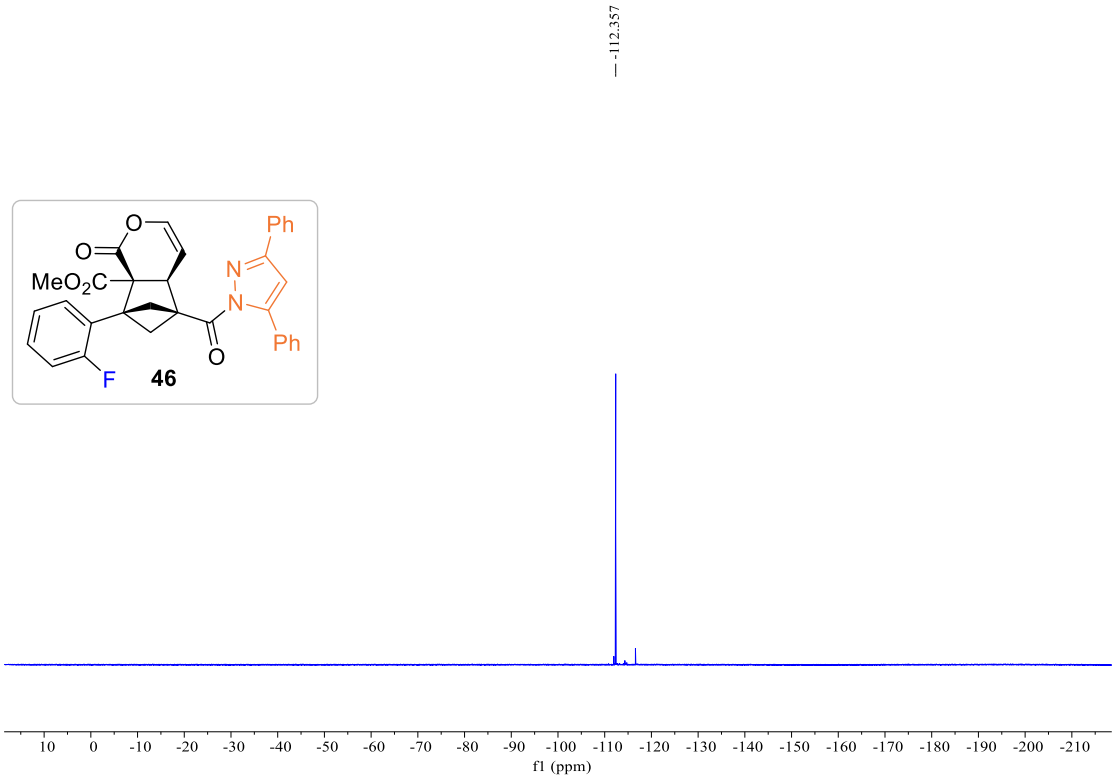
46, ^{1}H NMR (400 MHz, $CDCl_3$)



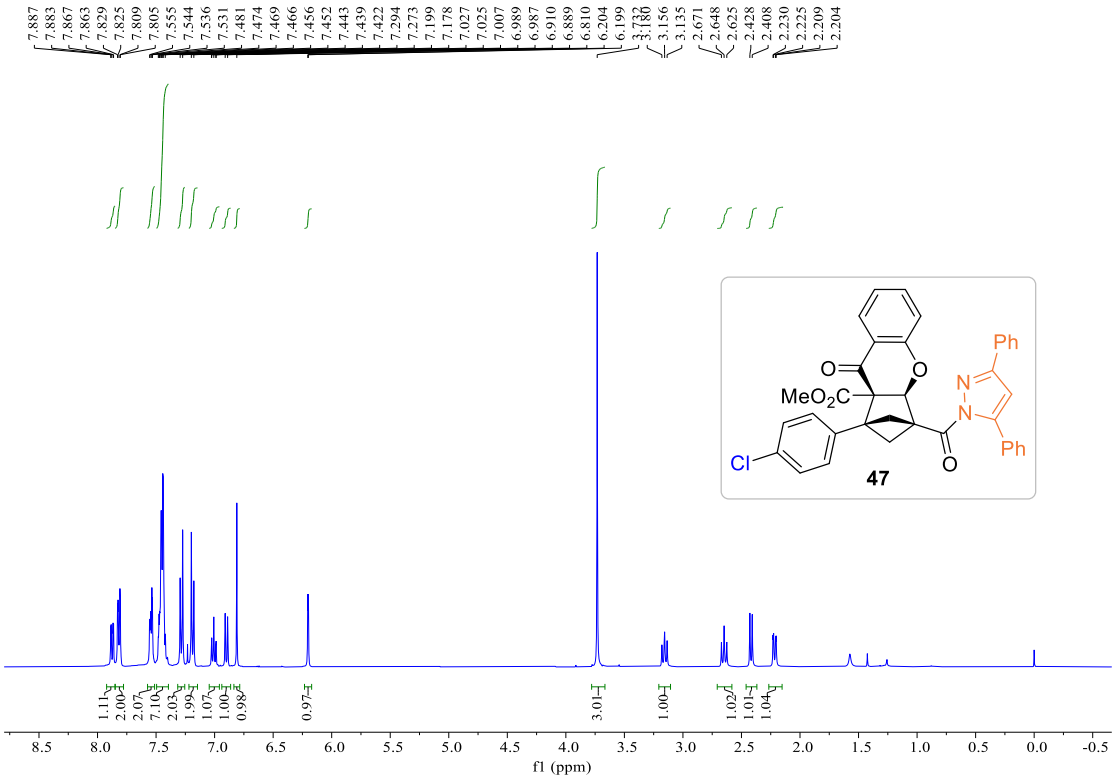
46, ^{13}C NMR (101 MHz, $CDCl_3$)



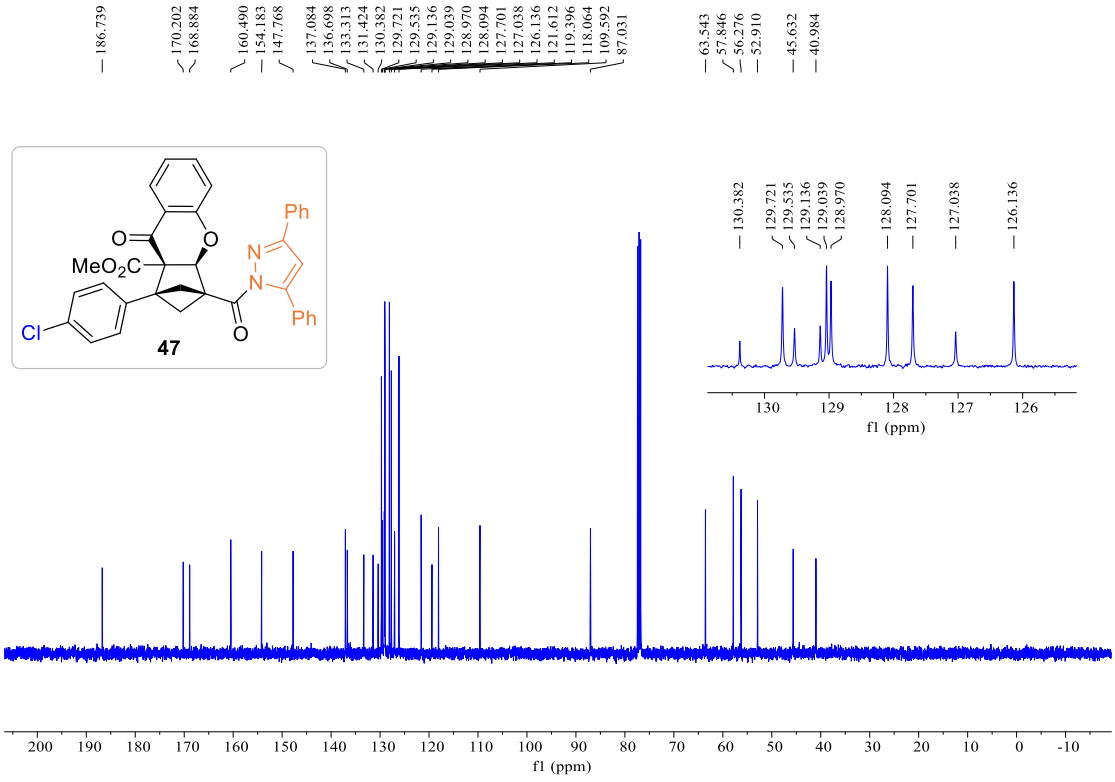
46, ^{19}F NMR (376 MHz, $CDCl_3$)



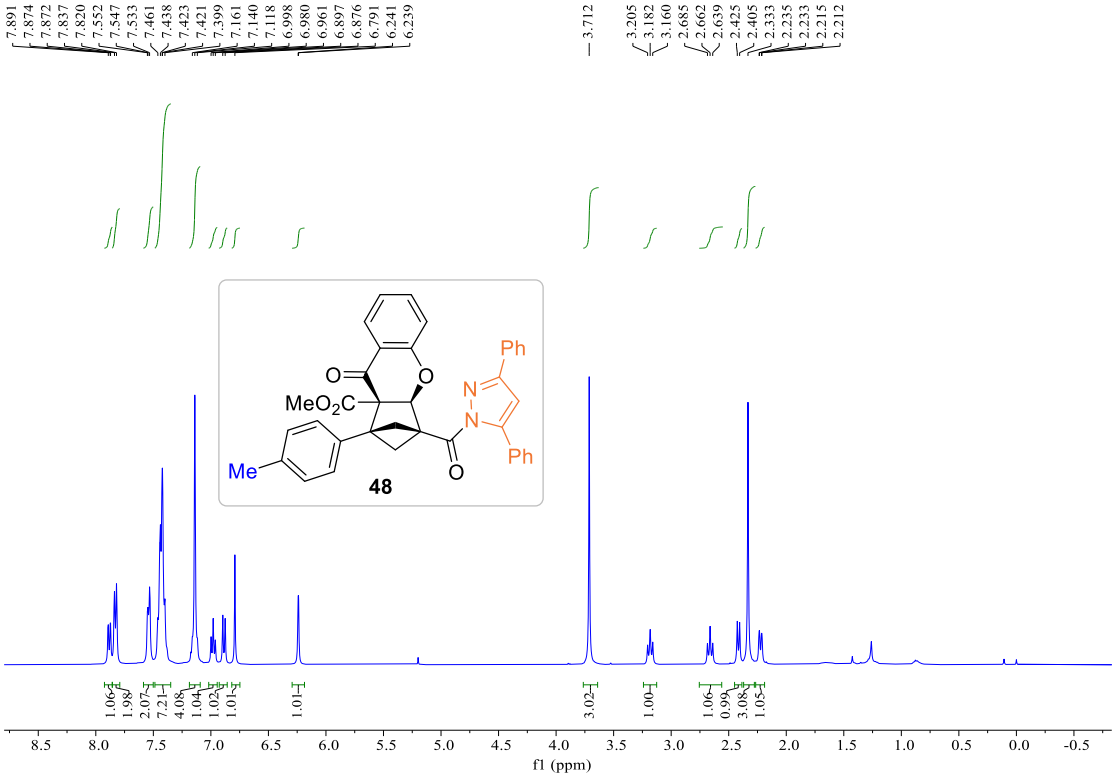
47, ^{1}H NMR (400 MHz, $CDCl_3$)



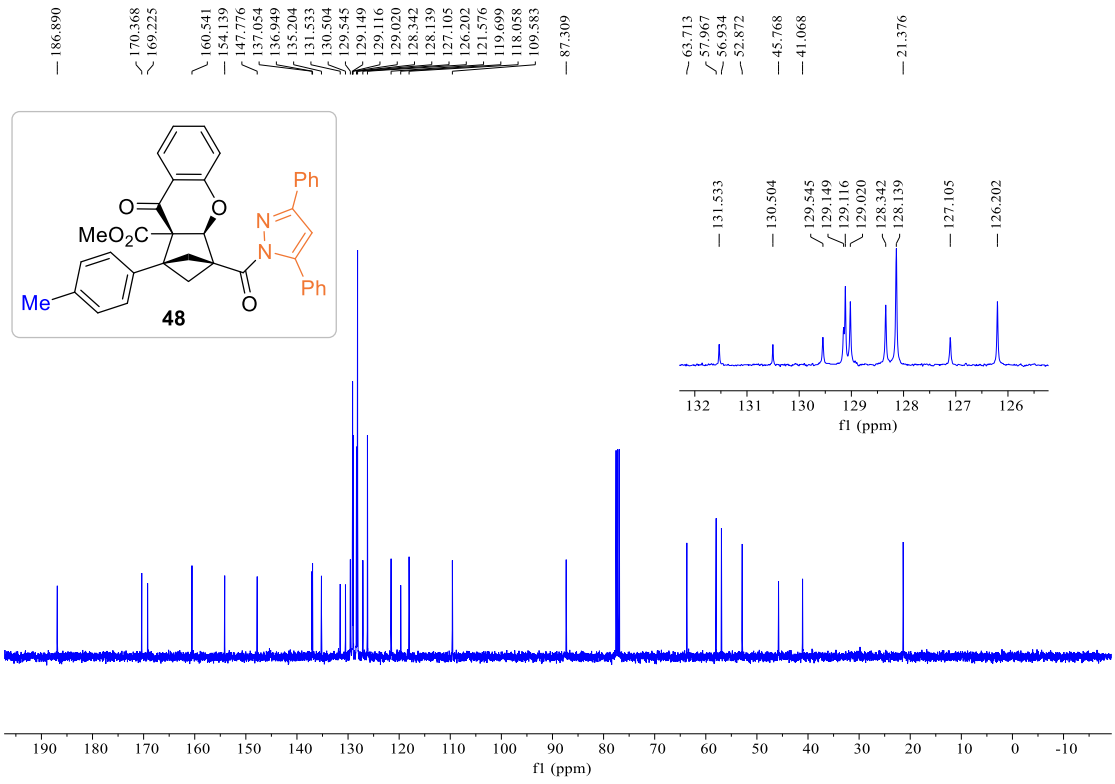
47, ^{13}C NMR (101 MHz, $CDCl_3$)



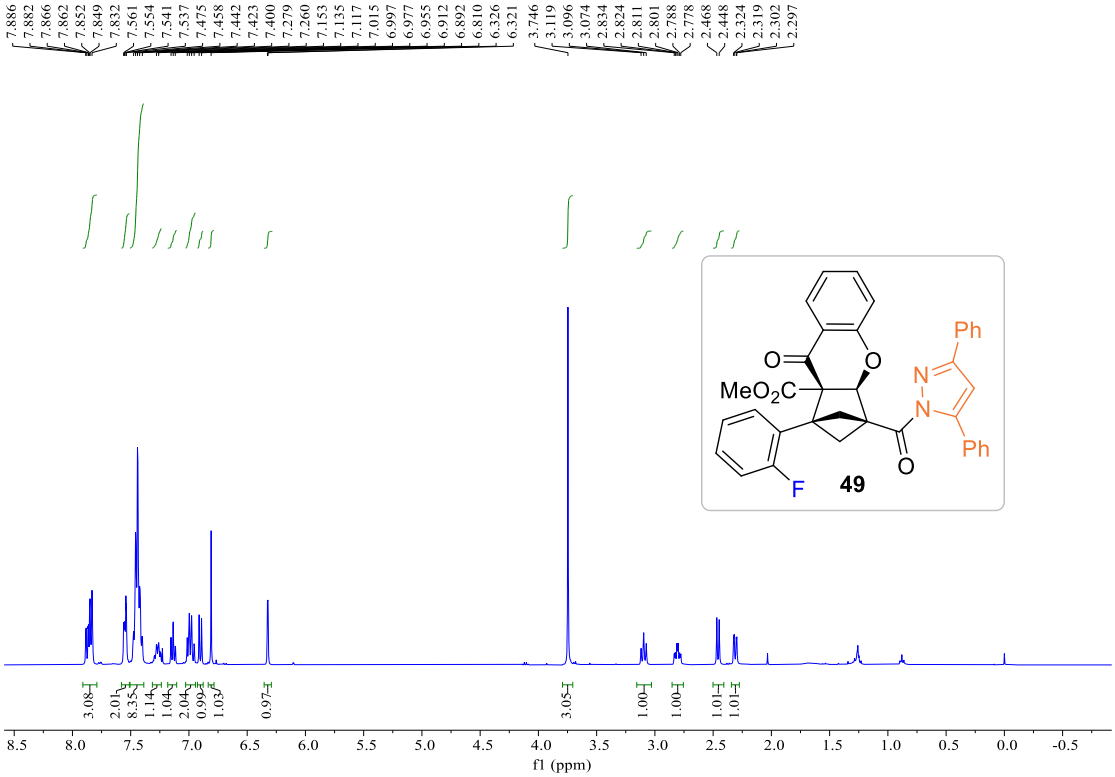
48, ^{1}H NMR (400 MHz, $CDCl_3$)



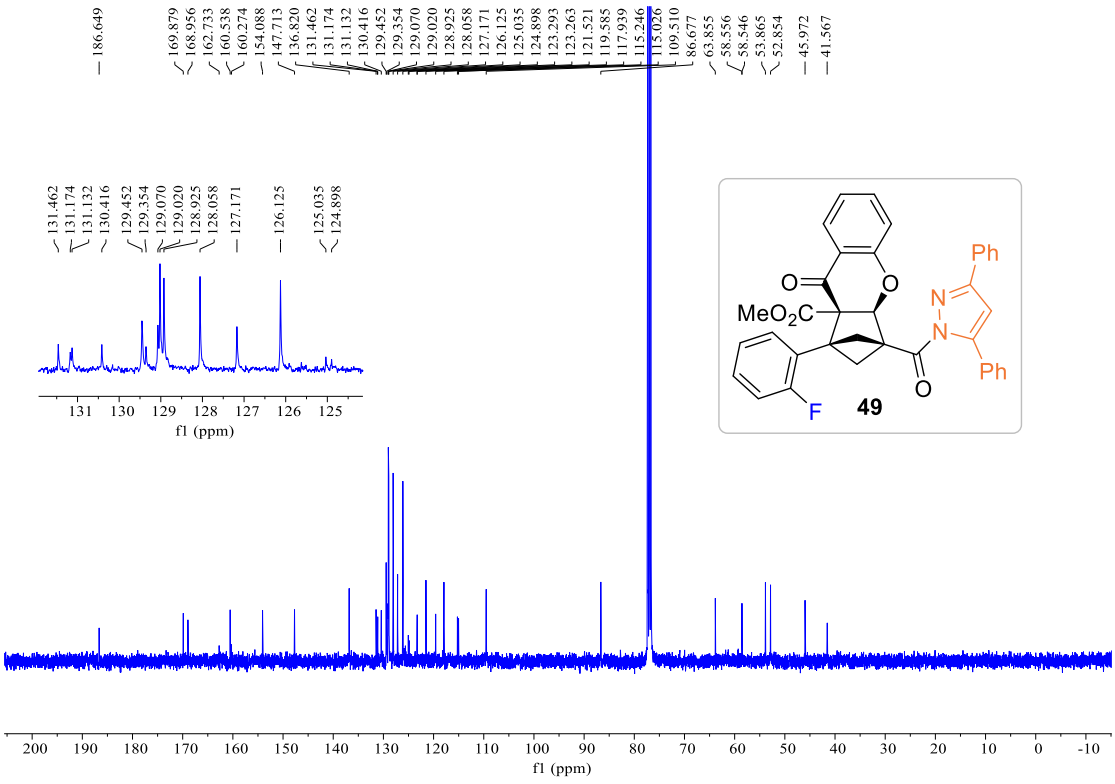
48, ^{13}C NMR (101 MHz, $CDCl_3$)



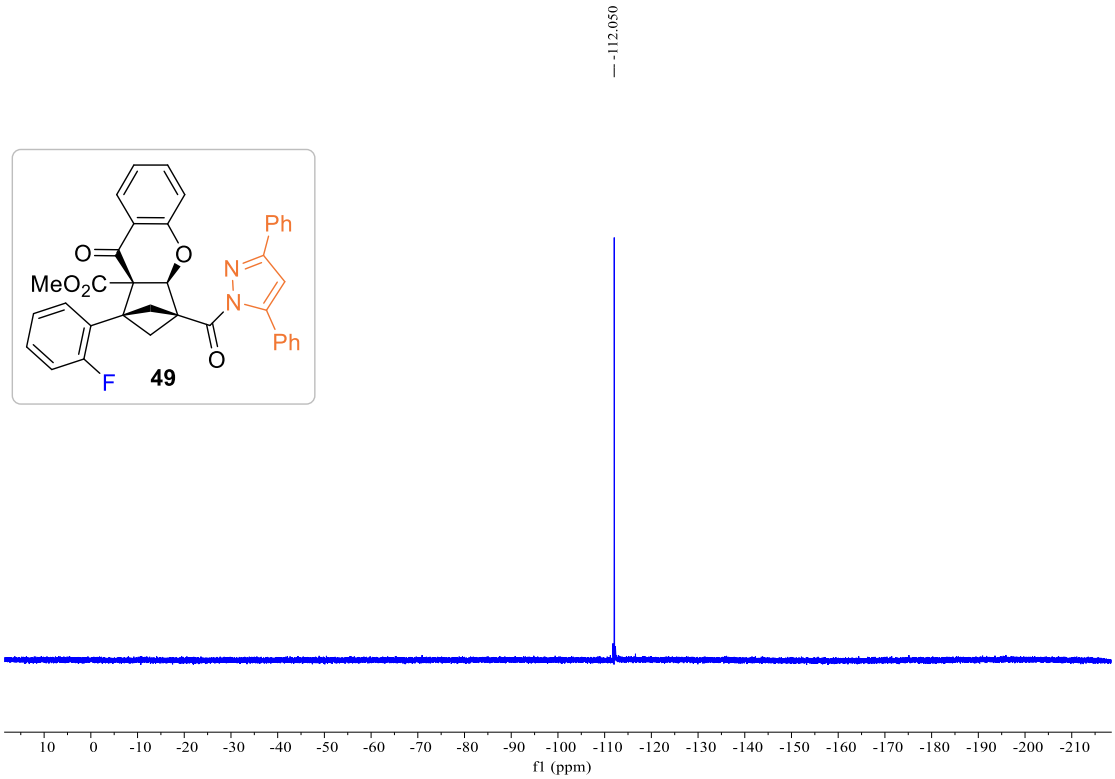
49, ^{1}H NMR (400 MHz, $CDCl_3$)



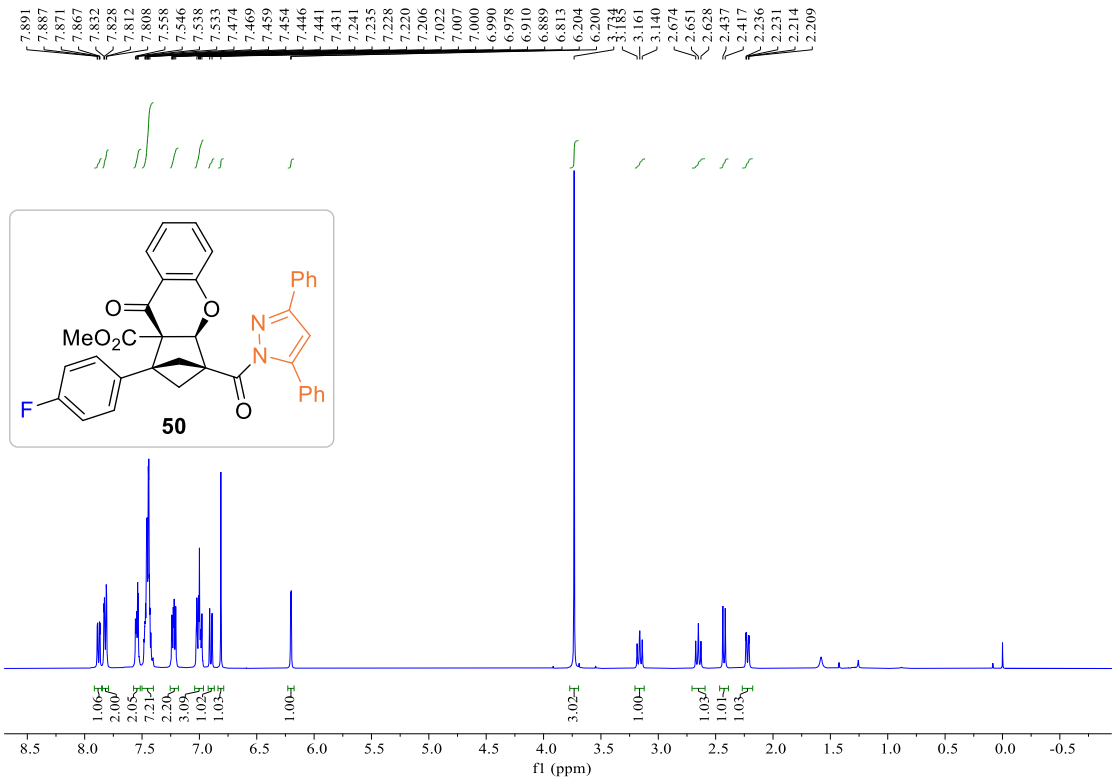
49, ^{13}C NMR (101 MHz, $CDCl_3$)



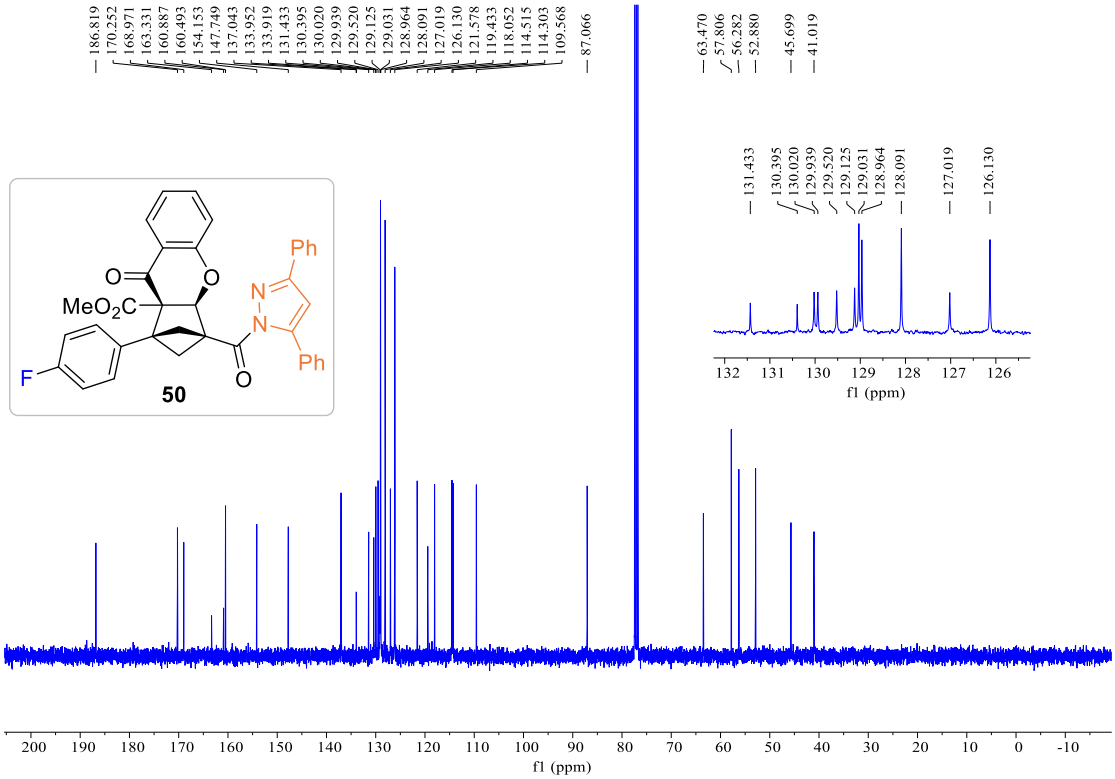
49, ^{19}F NMR (376 MHz, $CDCl_3$)



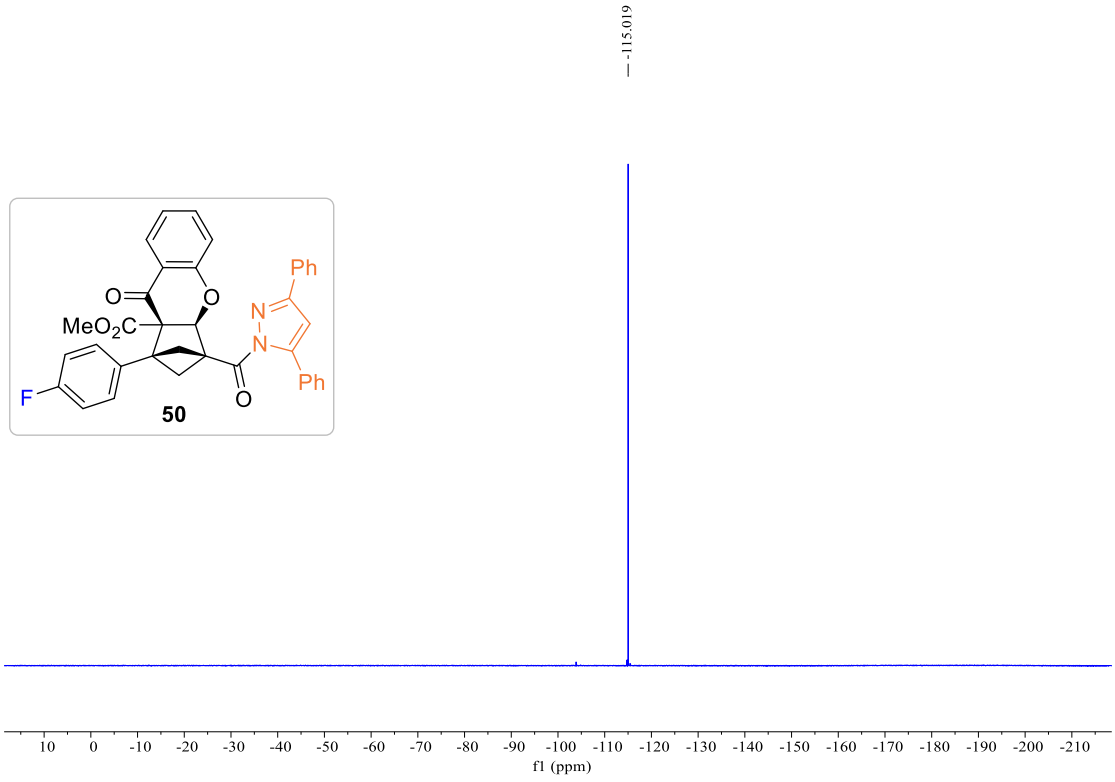
50, ^{1}H NMR (400 MHz, $CDCl_3$)



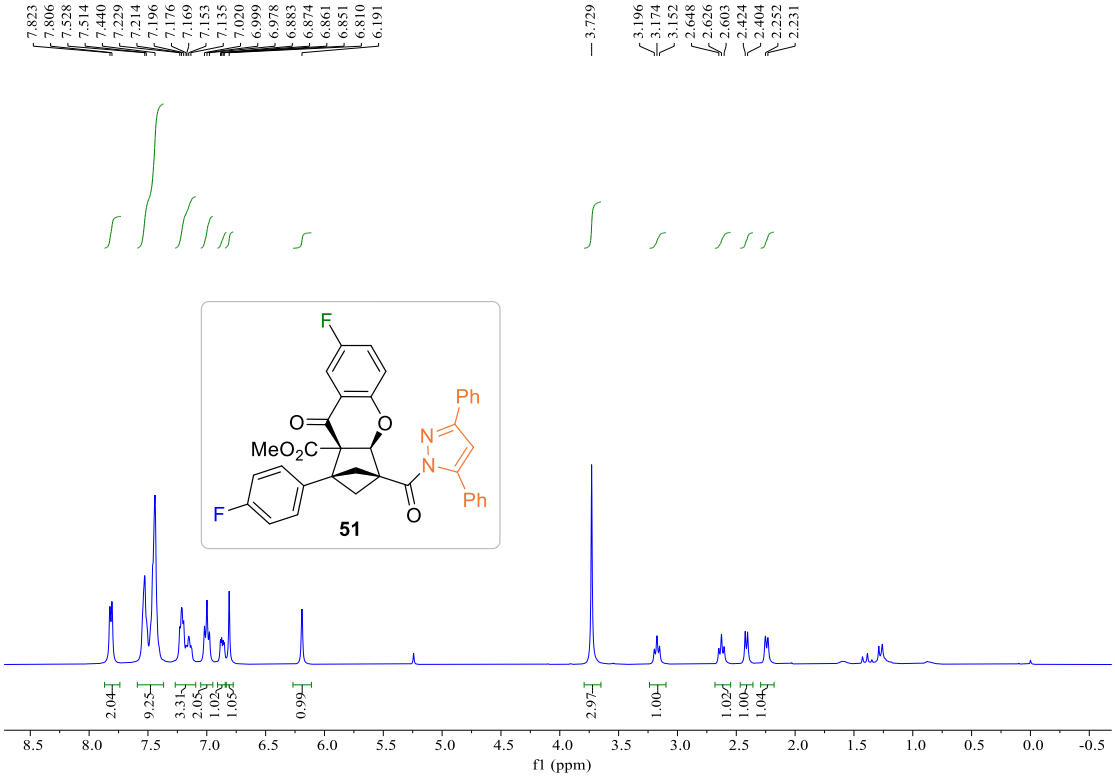
50, ^{13}C NMR (101 MHz, $CDCl_3$)



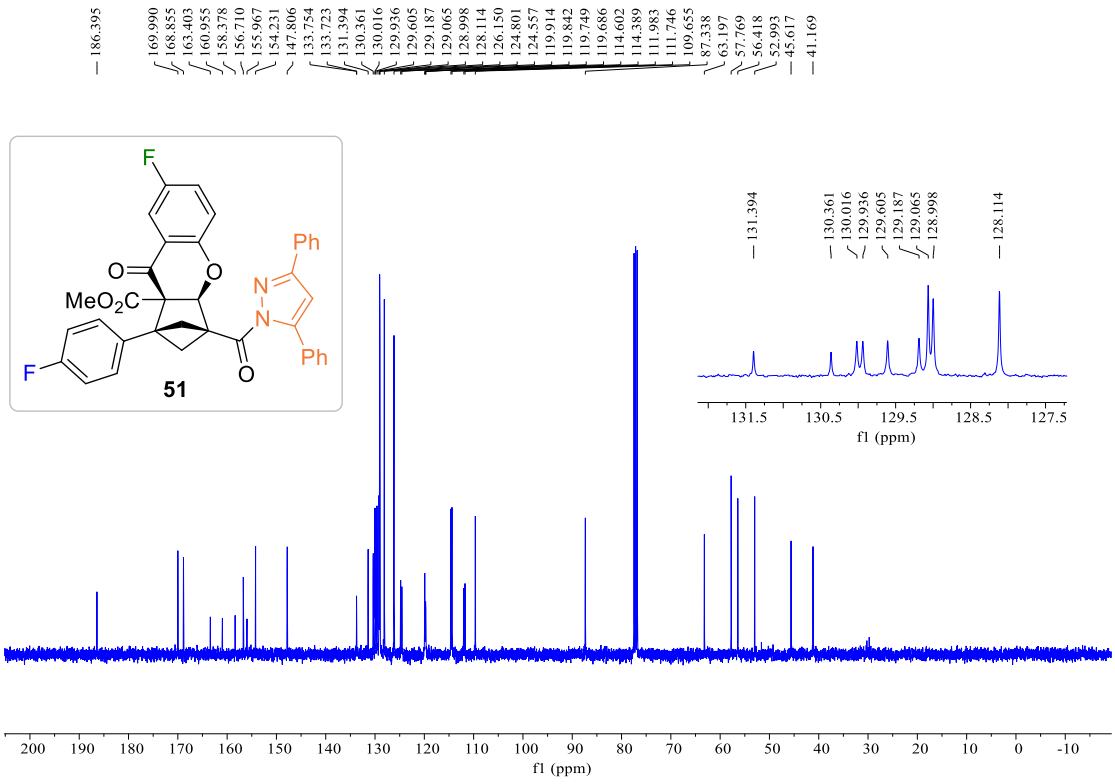
50, ^{19}F NMR (376 MHz, $CDCl_3$)



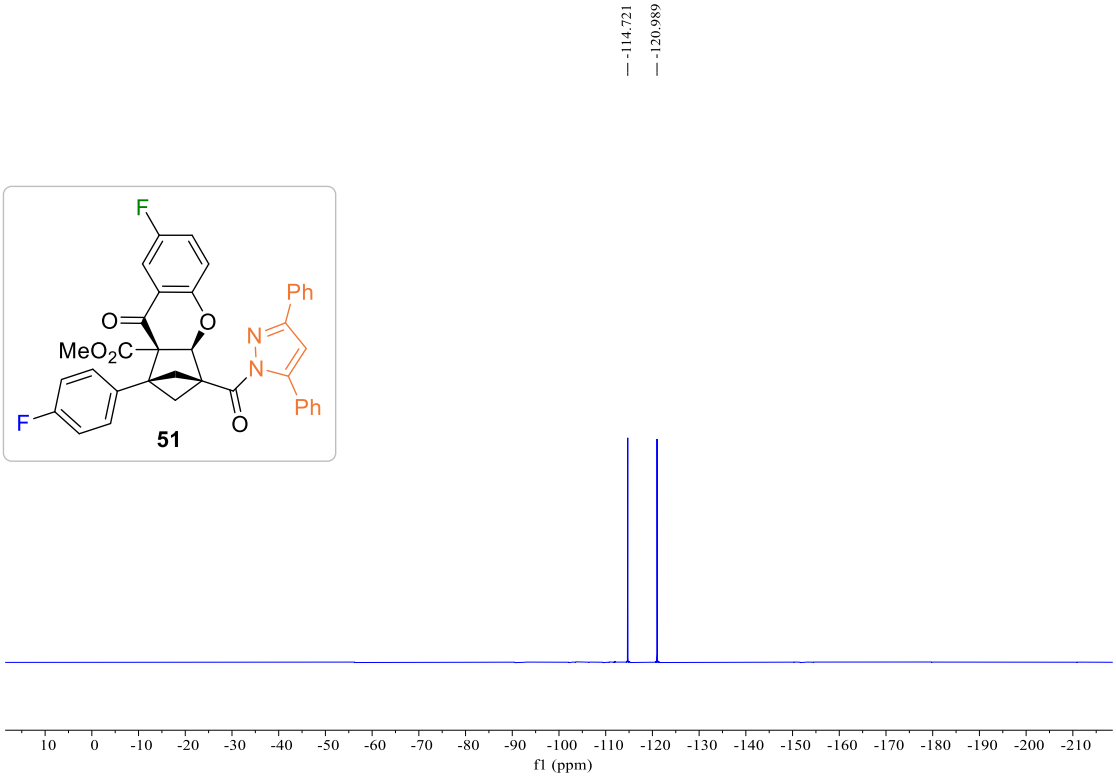
51, ^{1}H NMR (400 MHz, $CDCl_3$)



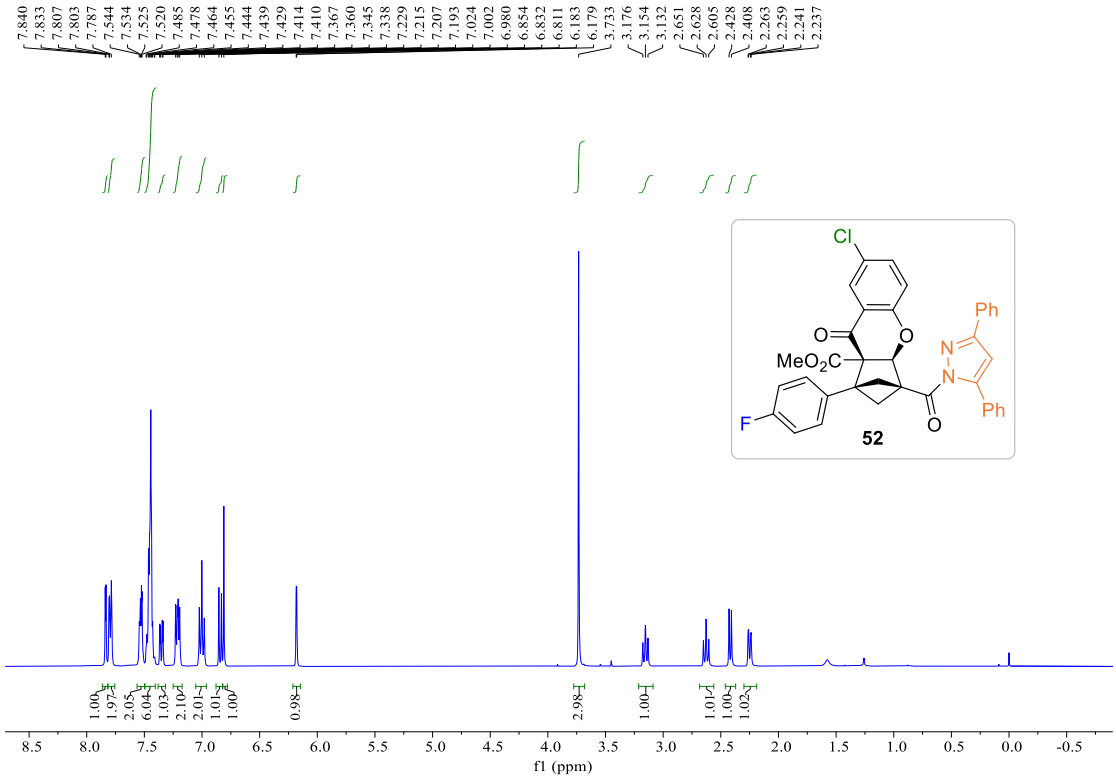
51, ^{13}C NMR (101 MHz, $CDCl_3$)



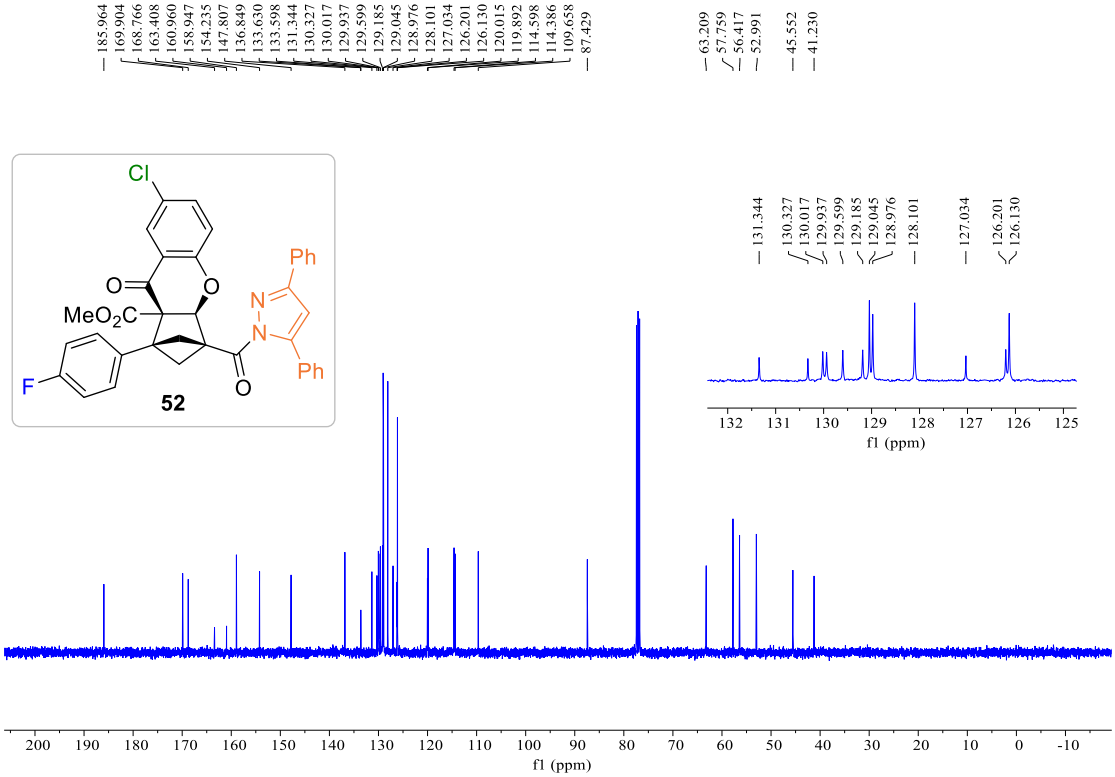
51, ^{19}F NMR (376 MHz, $CDCl_3$)



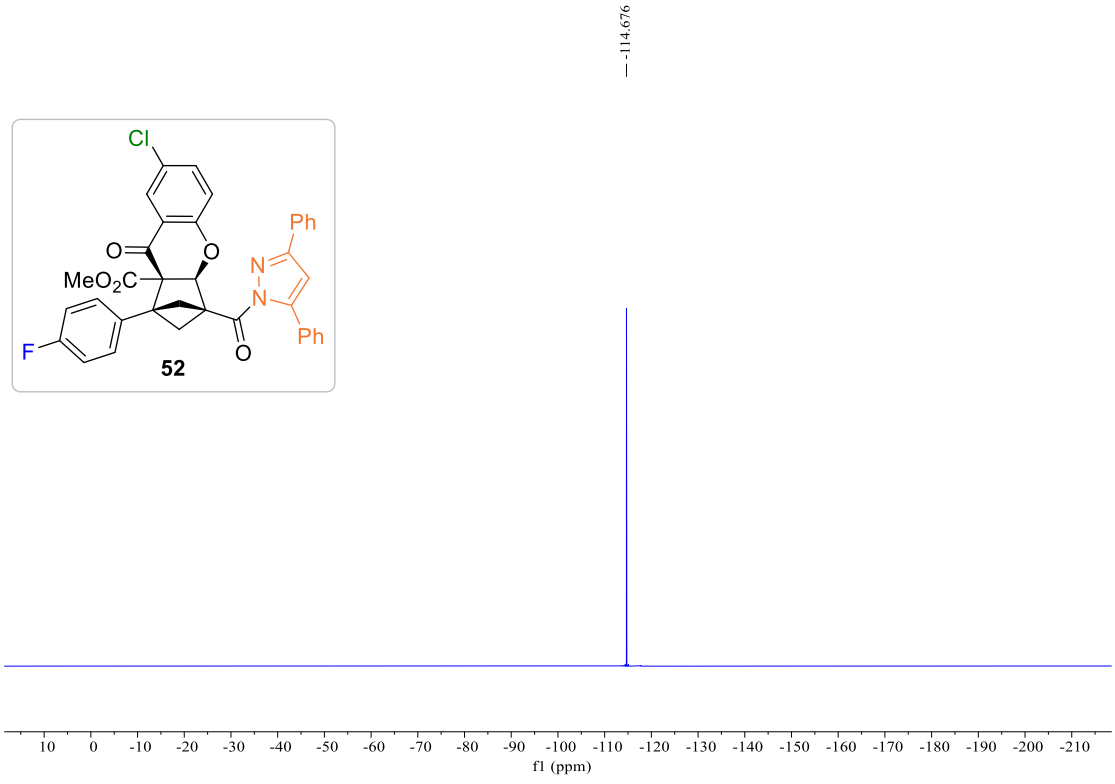
52, ^{1}H NMR (400 MHz, $CDCl_3$)



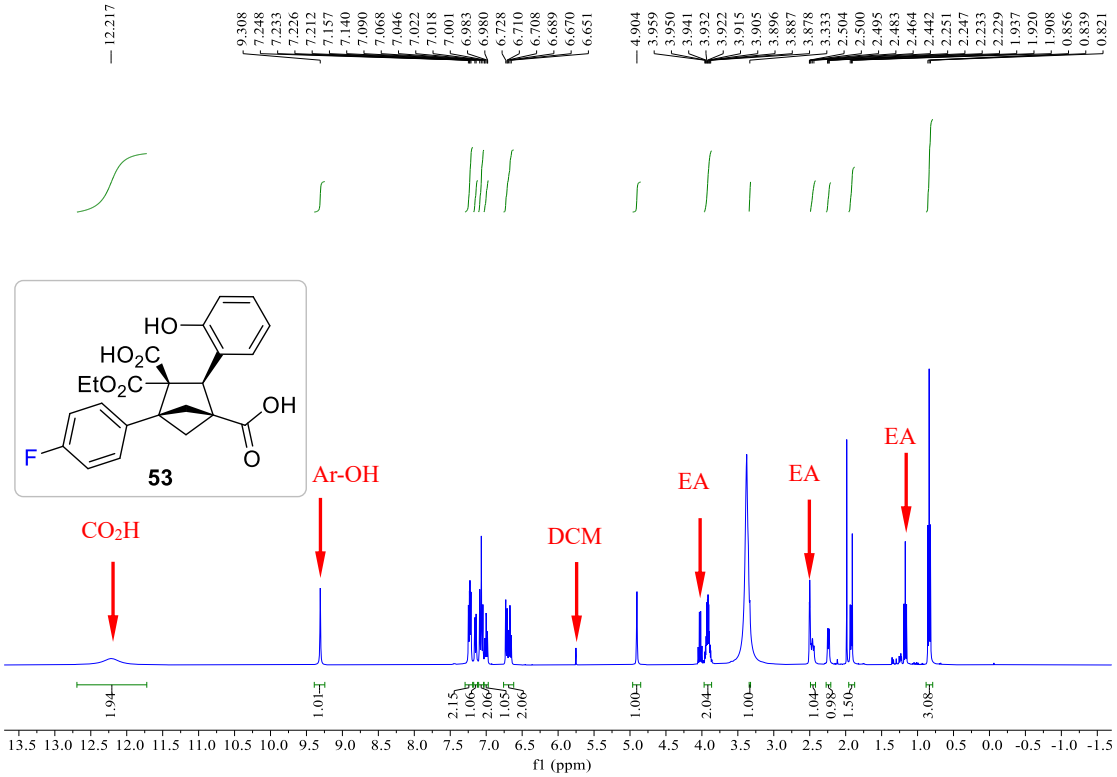
52, ^{13}C NMR (101 MHz, $CDCl_3$)



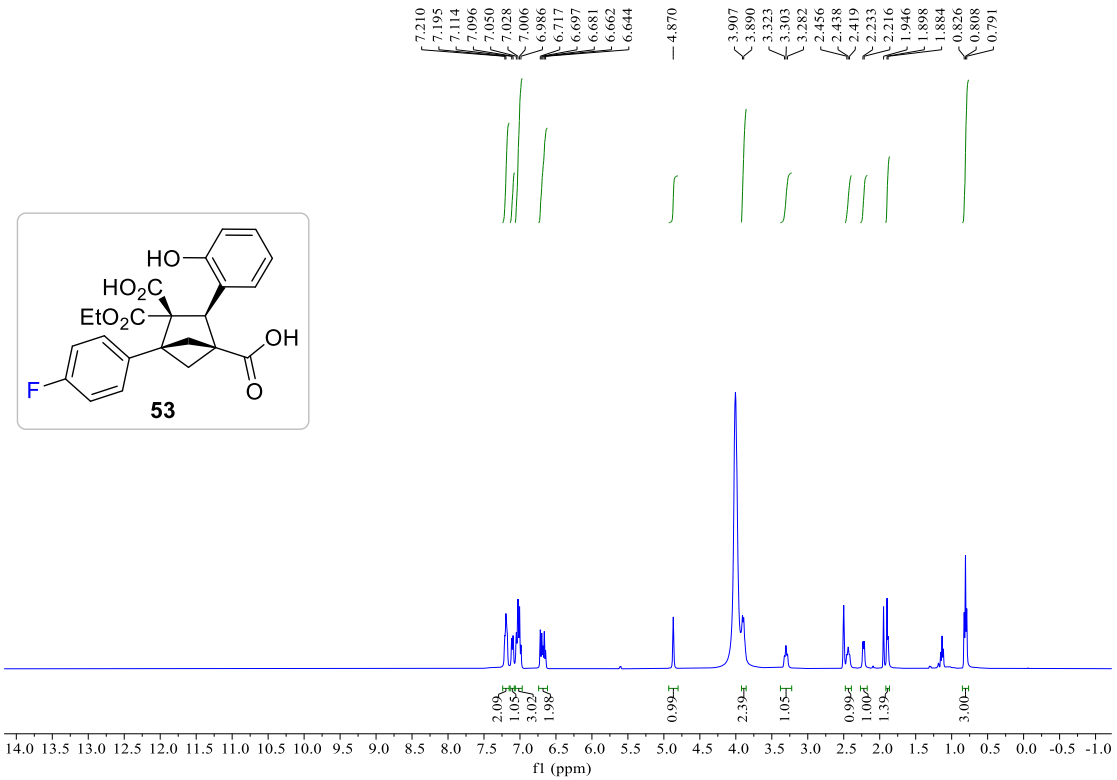
52, ^{19}F NMR (376 MHz, $CDCl_3$)



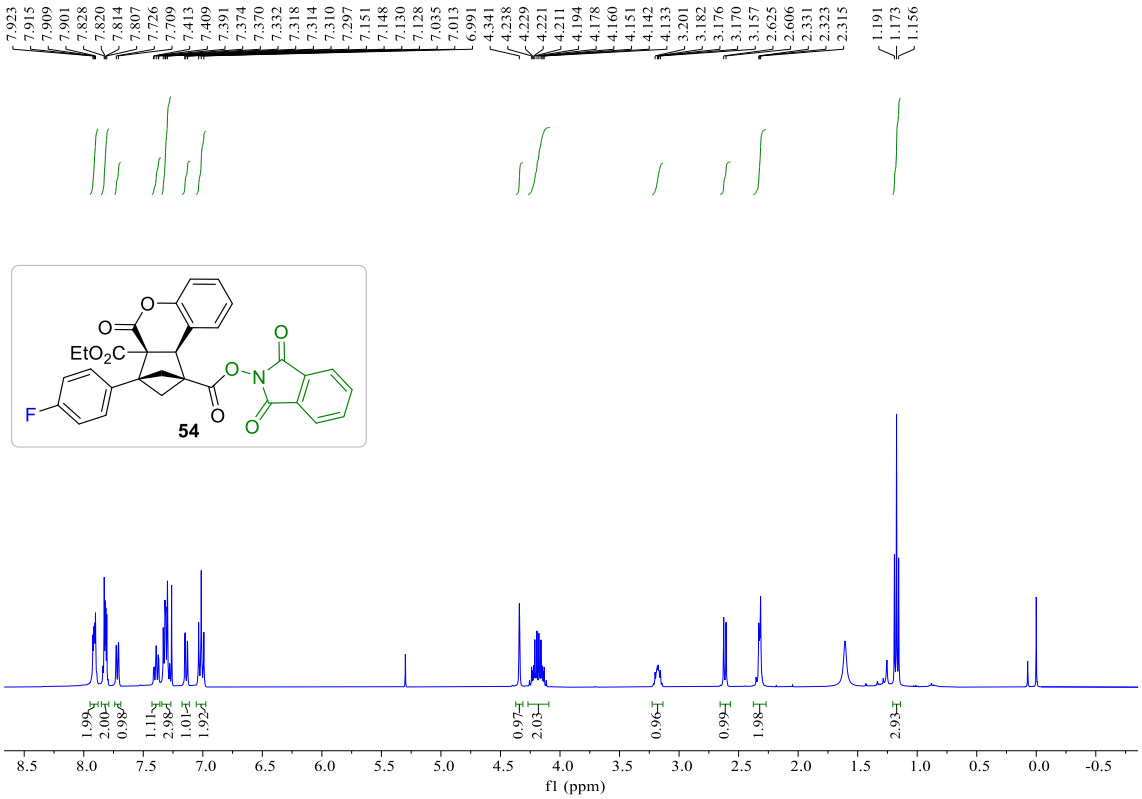
53, ^{1}H NMR (400 MHz, $CDCl_3$)



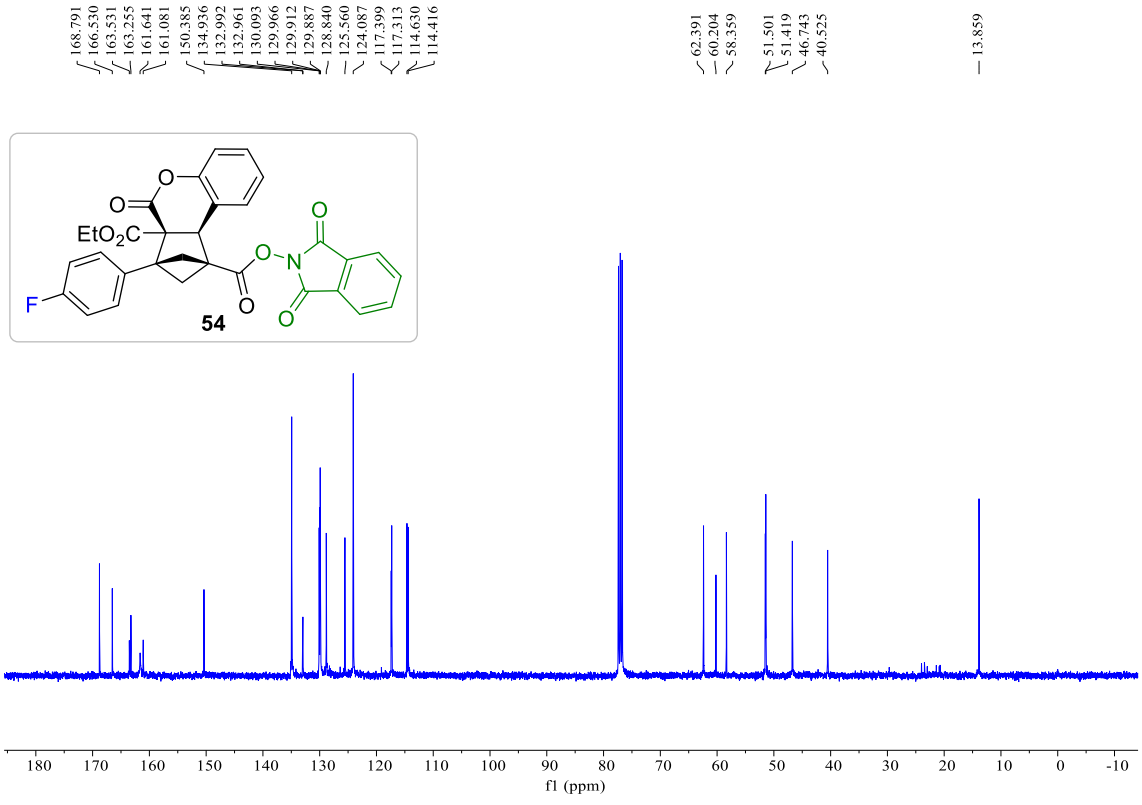
53, ^{1}H NMR (400 MHz, $CDCl_3$) After D_2O exchange:



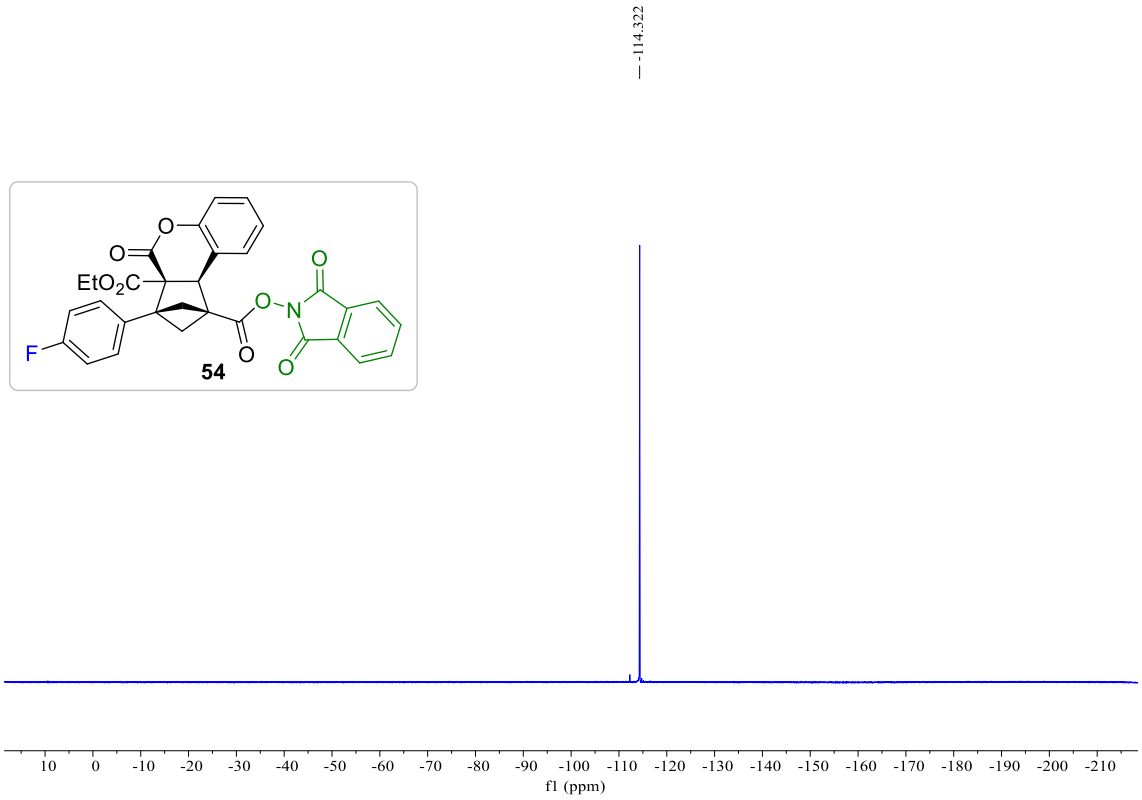
54, ^{1}H NMR (400 MHz, $CDCl_3$)



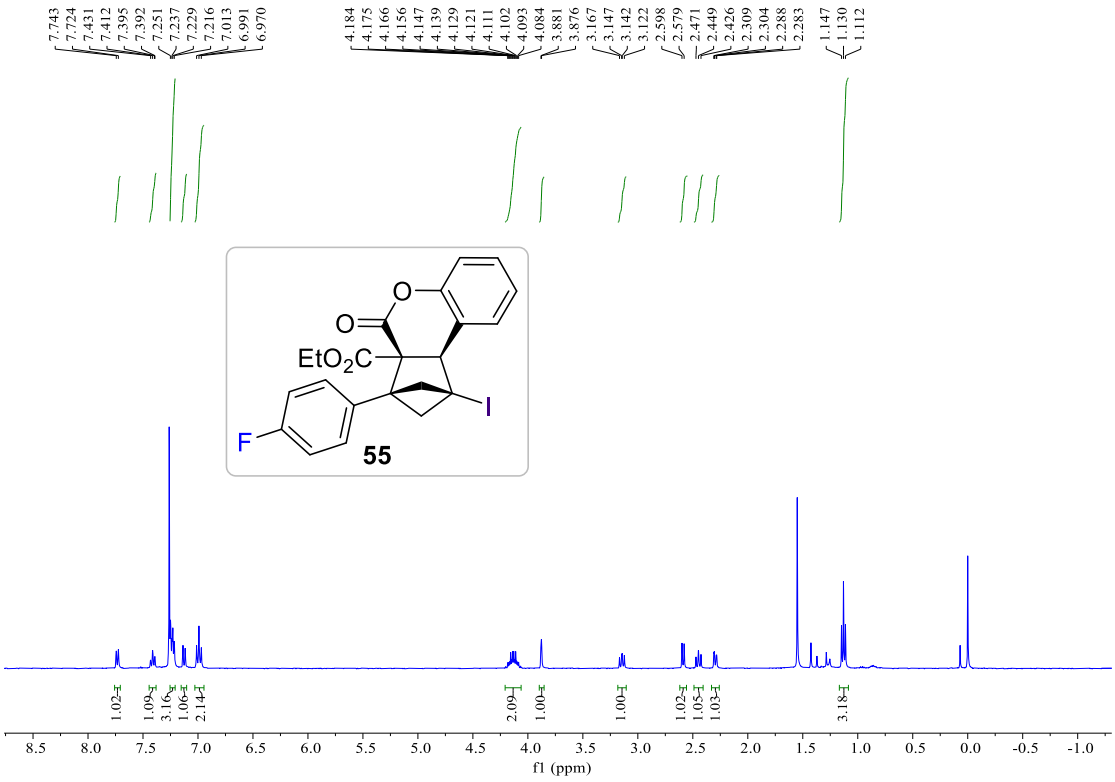
54, ^{13}C NMR (101 MHz, $CDCl_3$)



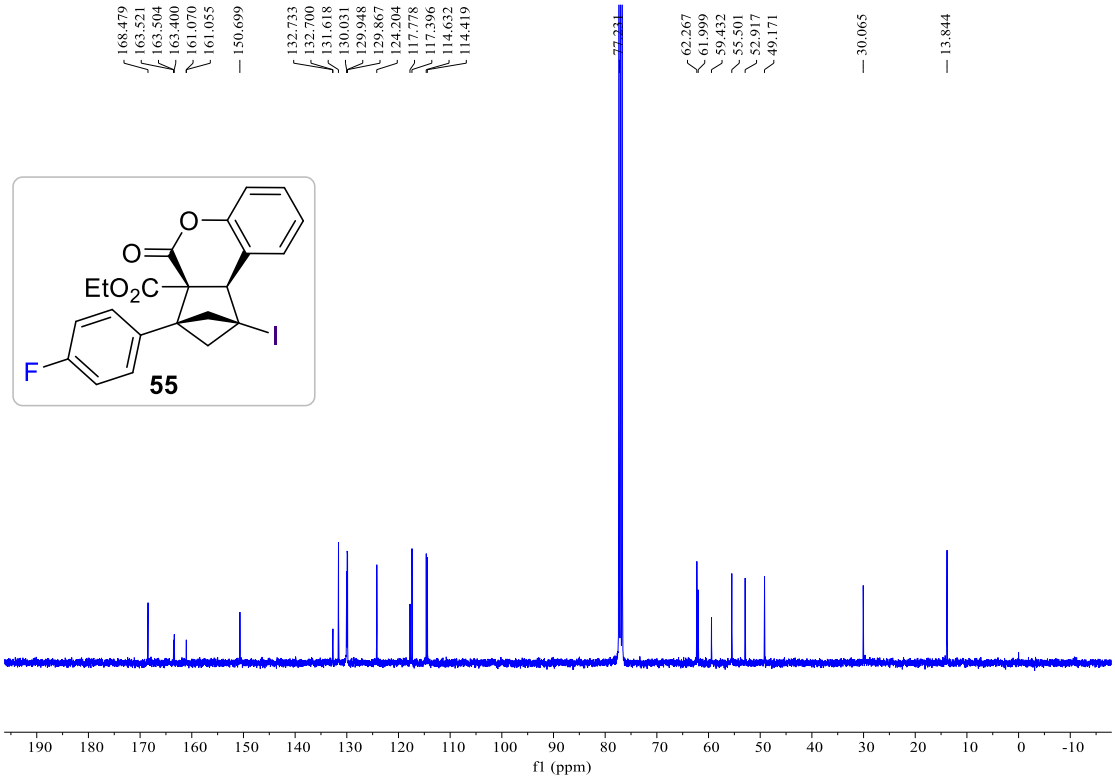
54, ^{19}F NMR (376 MHz, $CDCl_3$)



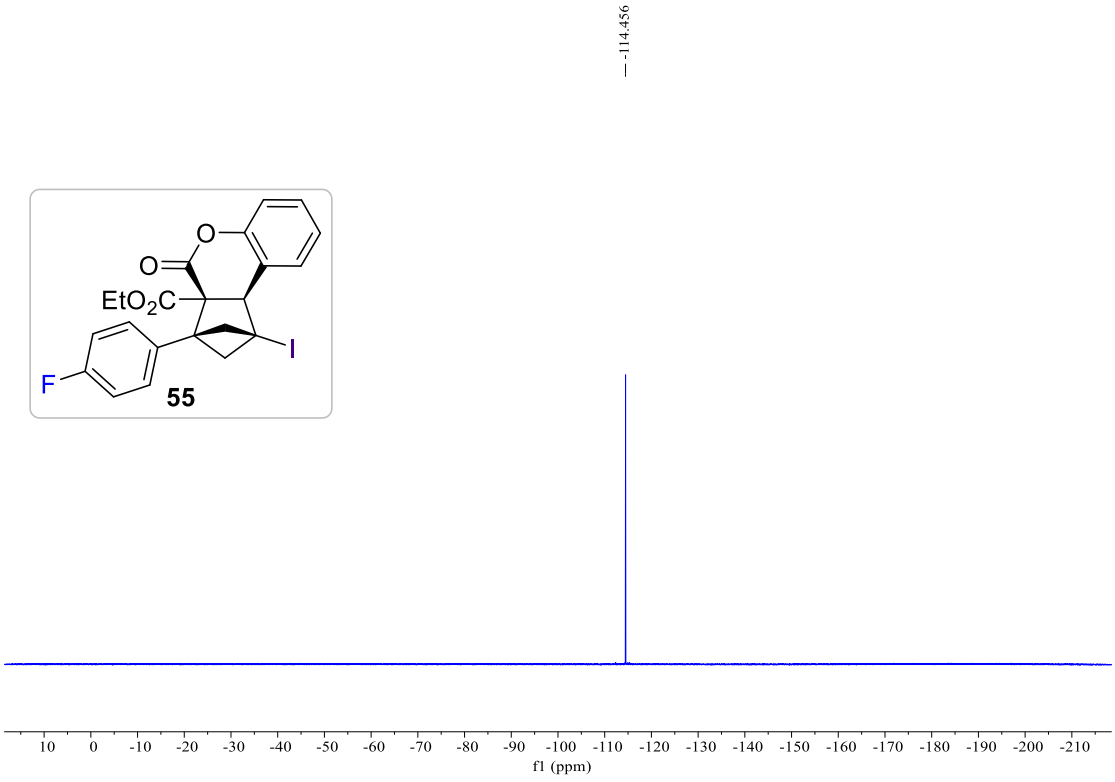
55, ^{1}H NMR (400 MHz, $CDCl_3$)



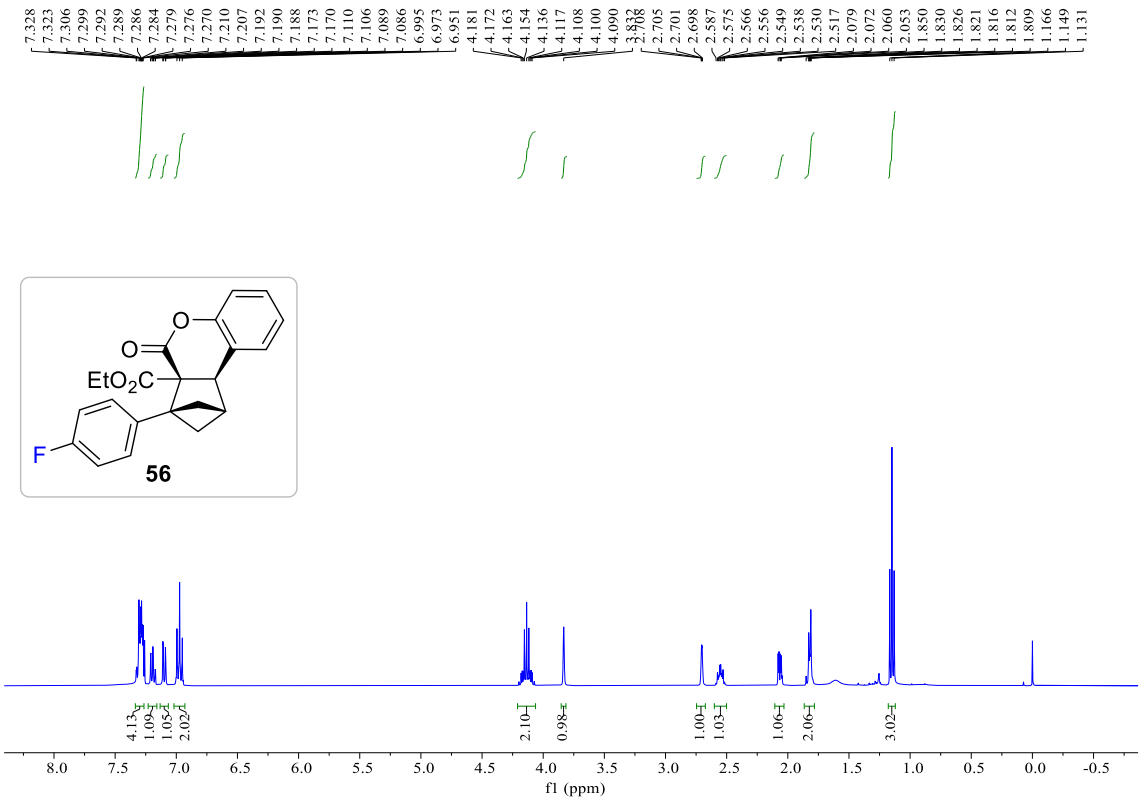
55, ^{13}C NMR (101 MHz, $CDCl_3$)



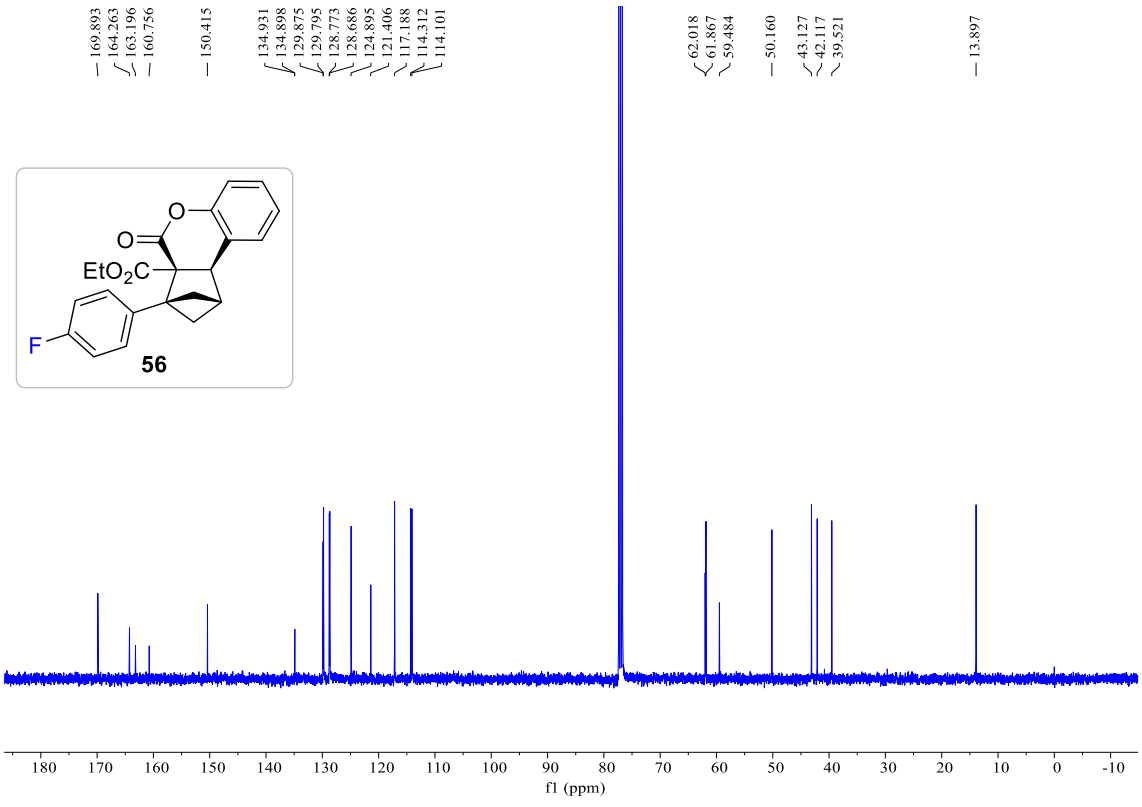
55, ^{19}F NMR (376 MHz, $CDCl_3$)



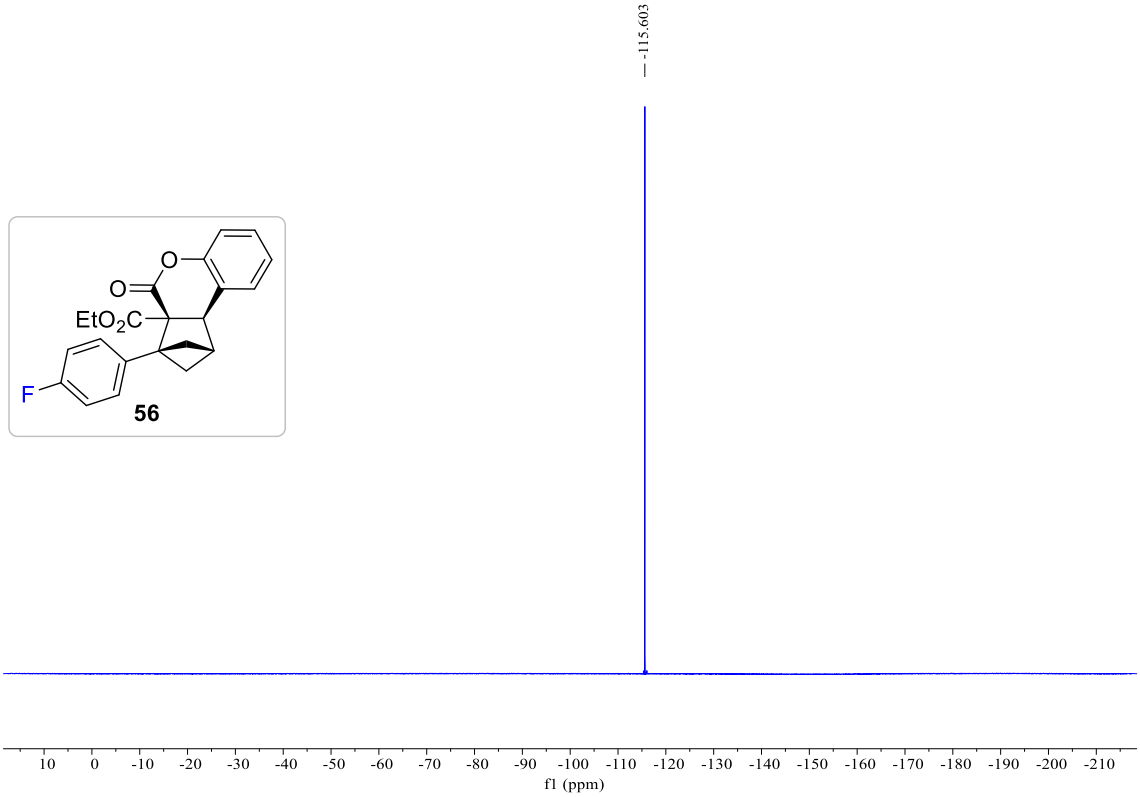
56, ^{1}H NMR (400 MHz, $CDCl_3$)



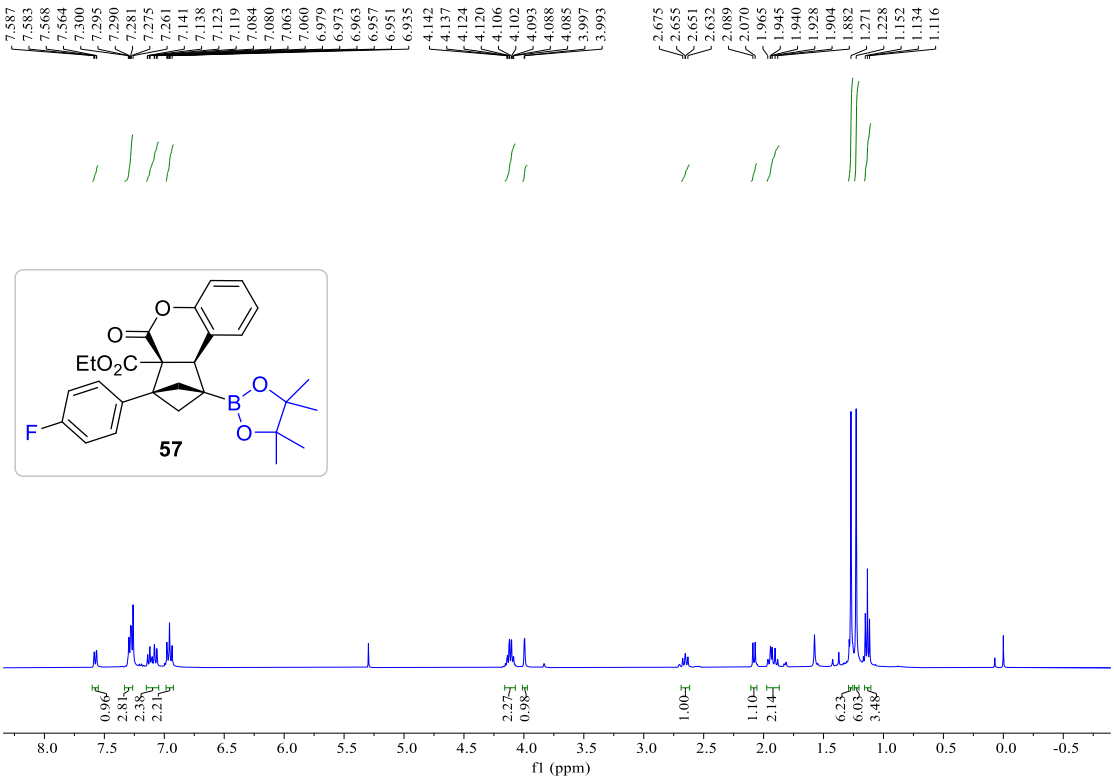
56, ^{13}C NMR (101 MHz, $CDCl_3$)



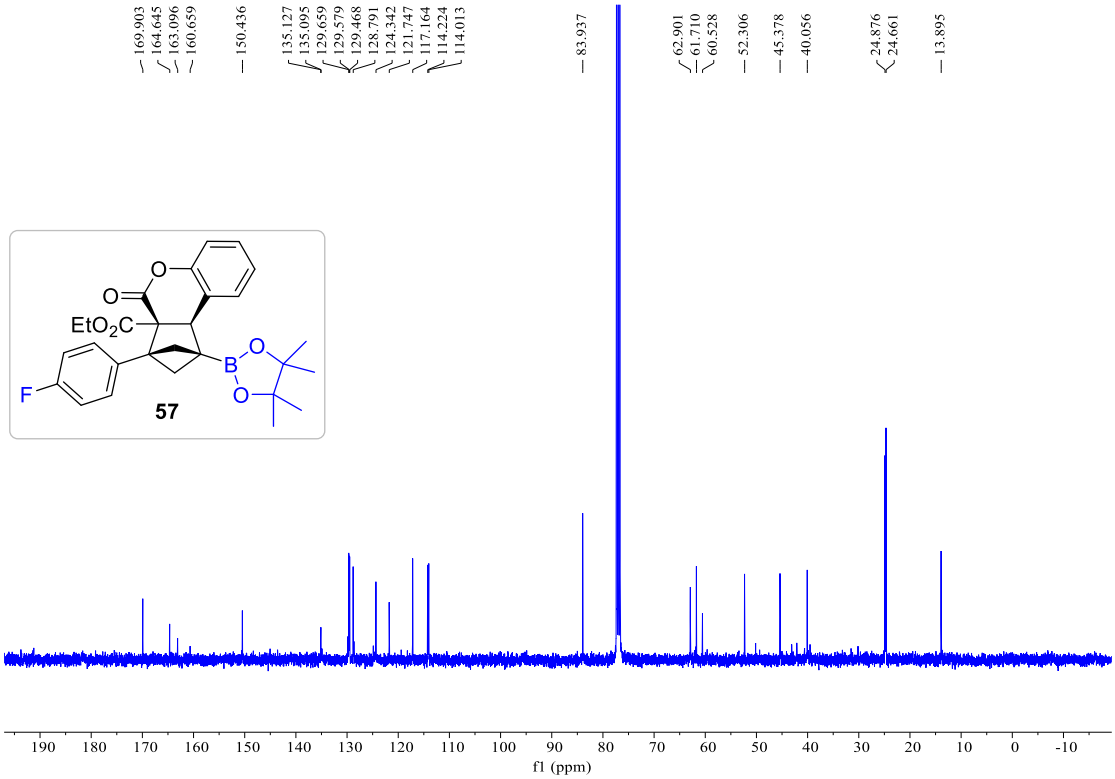
56, ^{19}F NMR (376 MHz, $CDCl_3$)



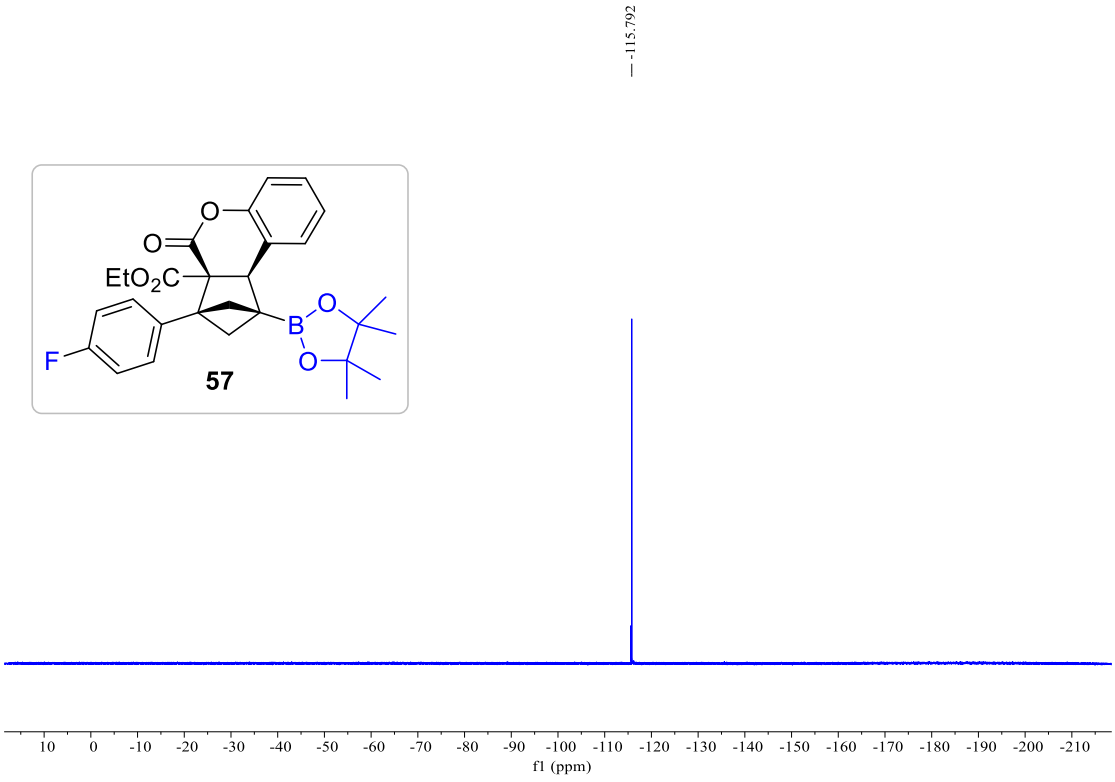
57, ^{1}H NMR (400 MHz, $CDCl_3$)



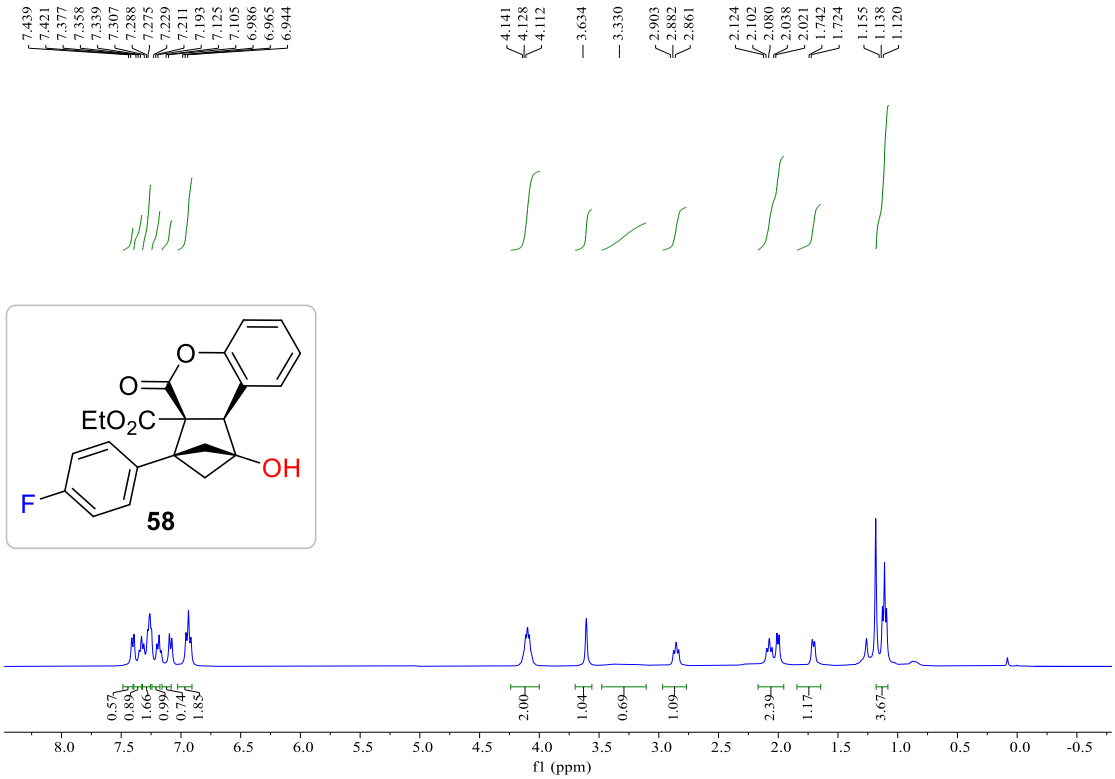
57, ^{13}C NMR (101 MHz, $CDCl_3$)



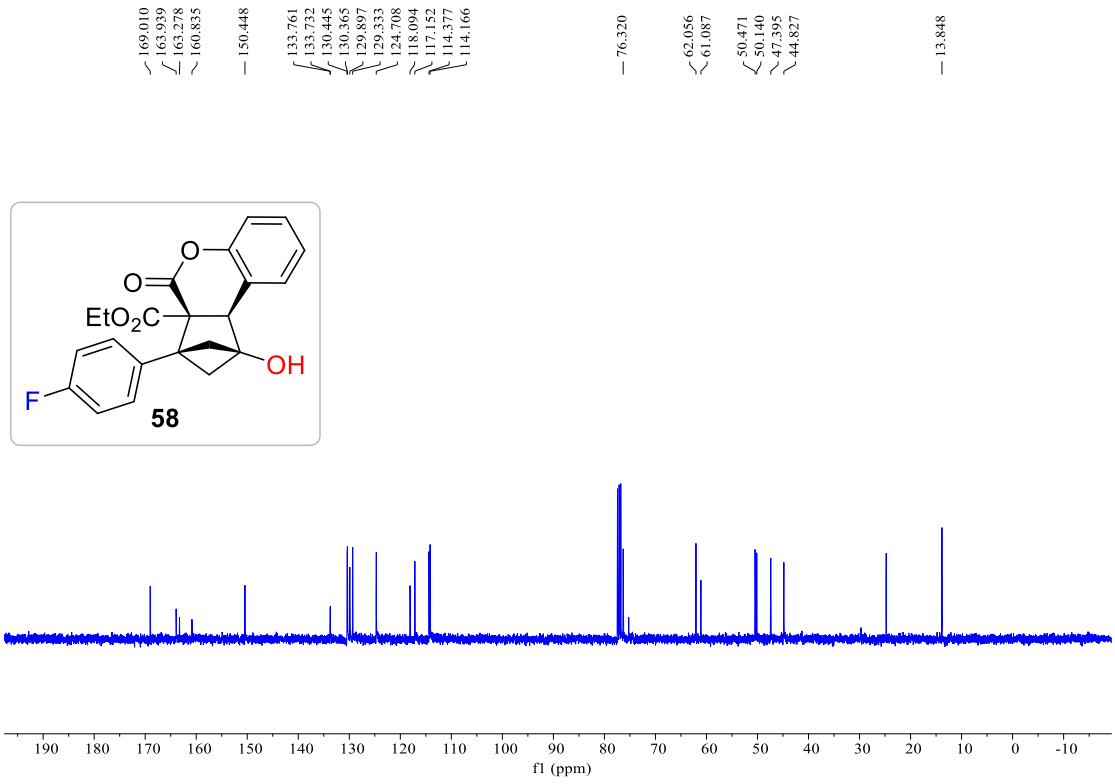
57, ^{19}F NMR (376 MHz, $CDCl_3$)



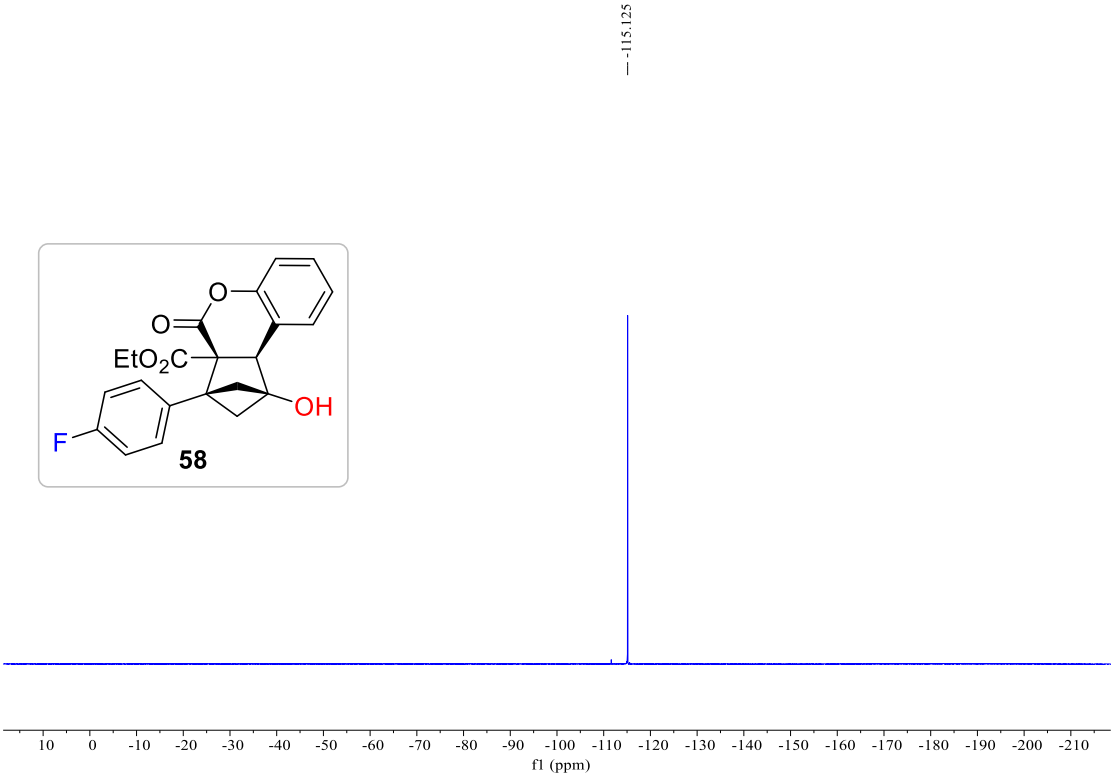
58, ^{1}H NMR (400 MHz, $CDCl_3$)



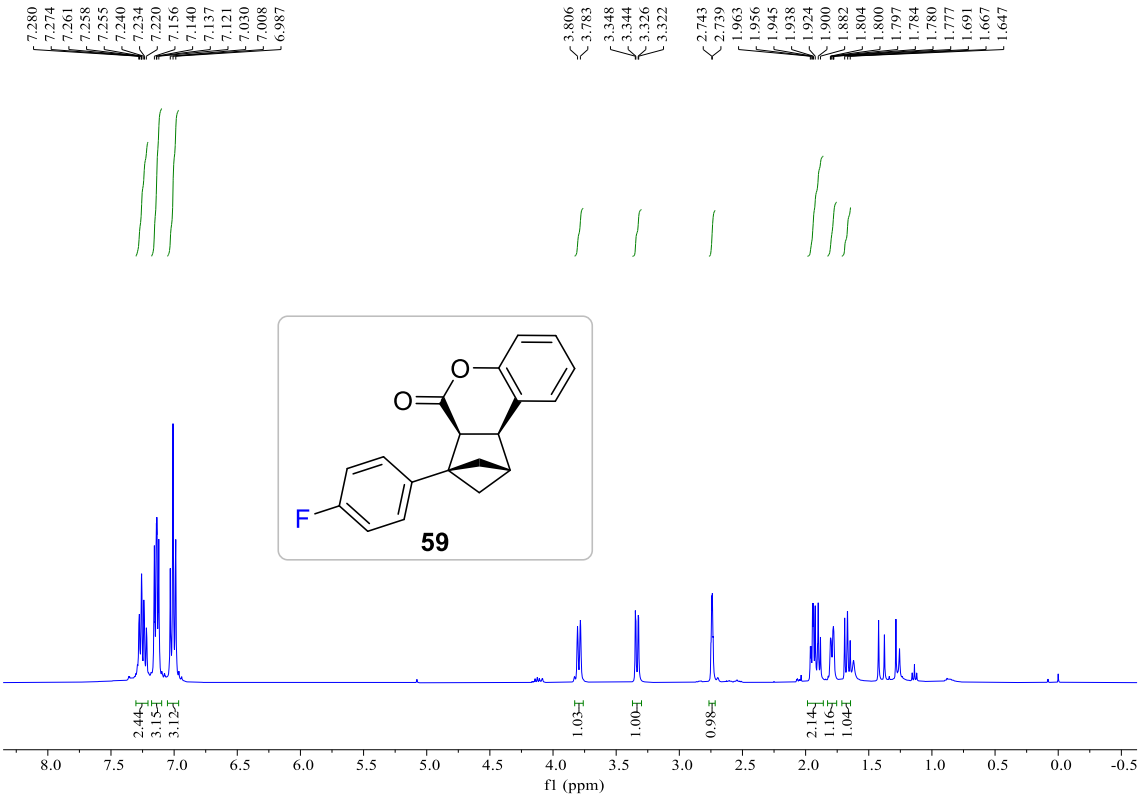
58, ^{13}C NMR (101 MHz, $CDCl_3$)



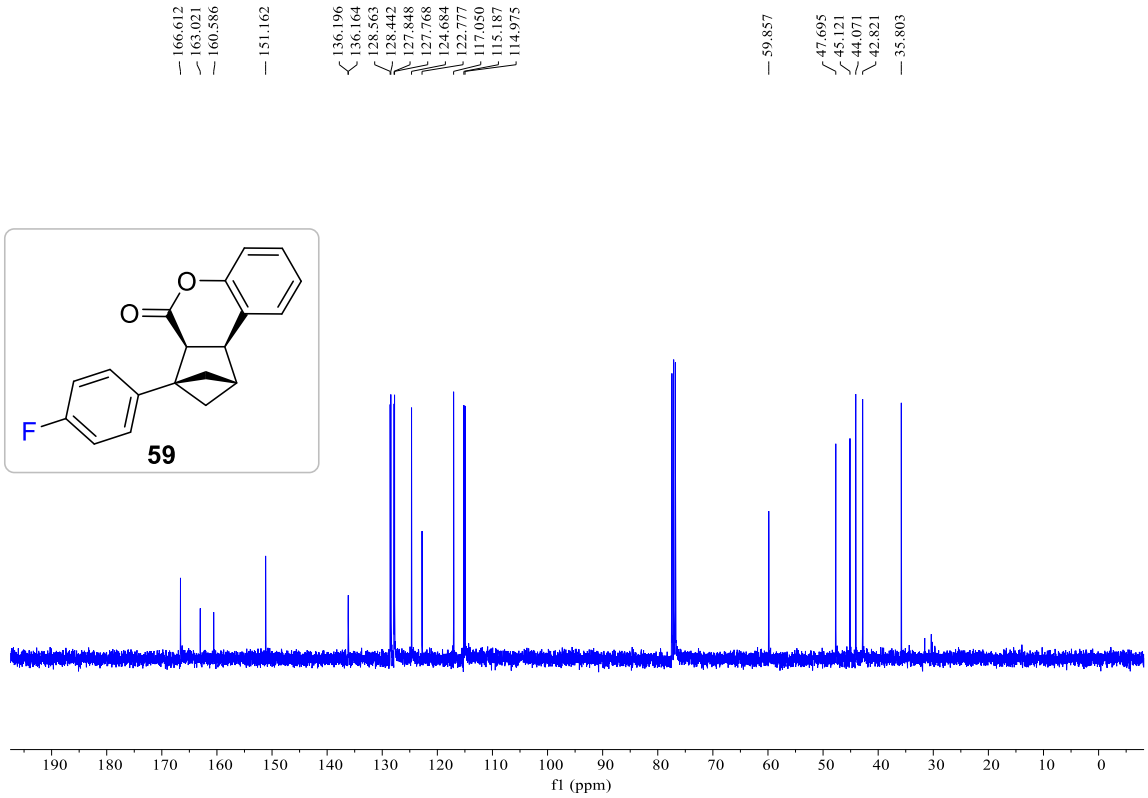
58, ^{19}F NMR (376 MHz, $CDCl_3$)



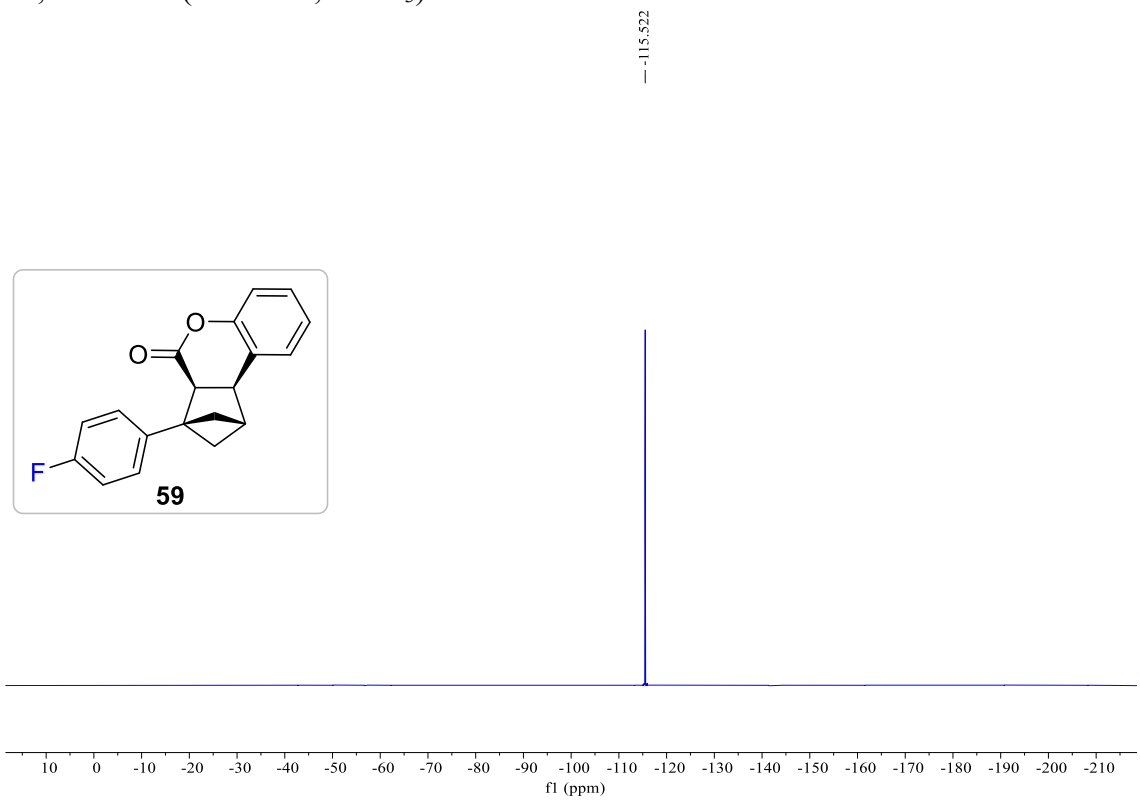
59, ^{1}H NMR (400 MHz, $CDCl_3$)



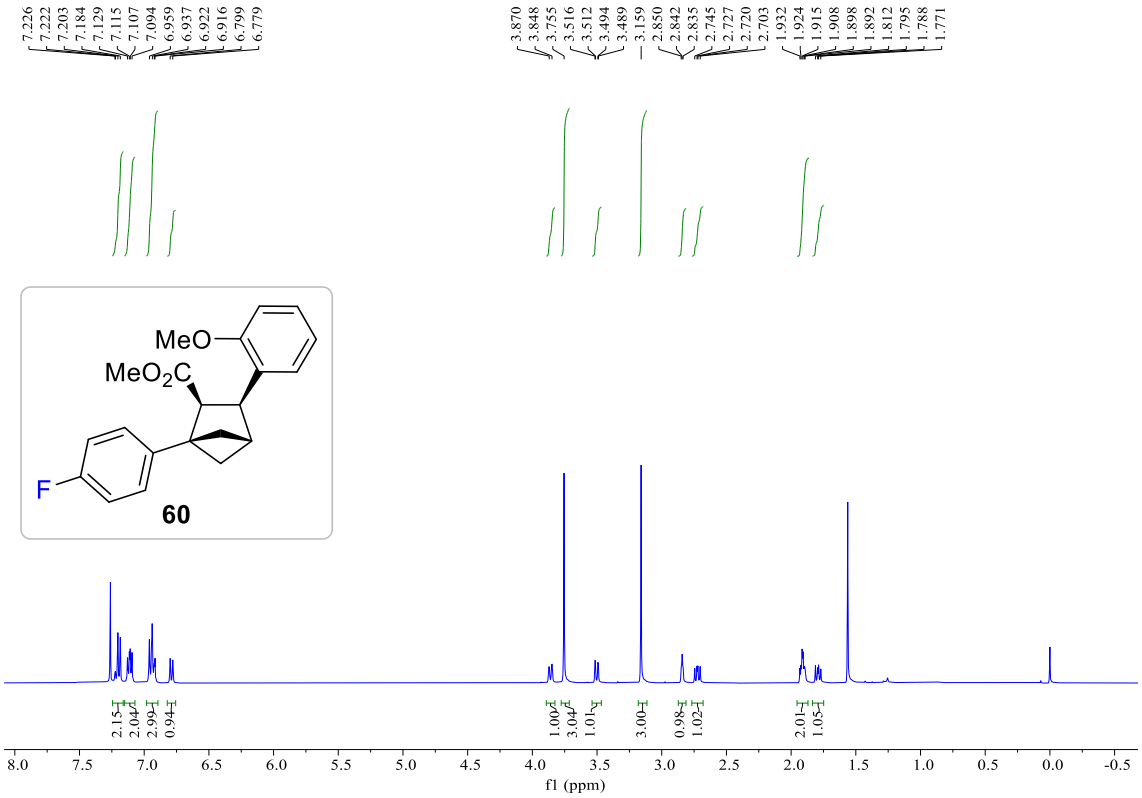
59, ^{13}C NMR (101 MHz, $CDCl_3$)



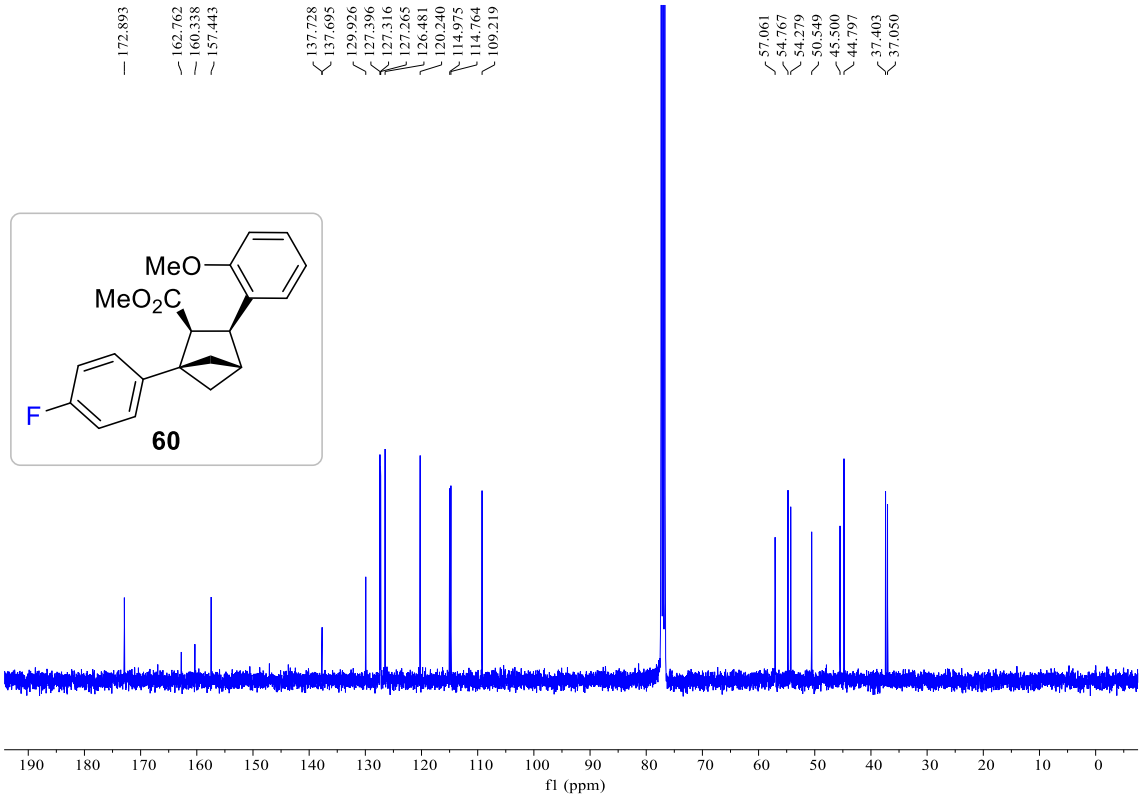
59, ^{19}F NMR (376 MHz, $CDCl_3$)



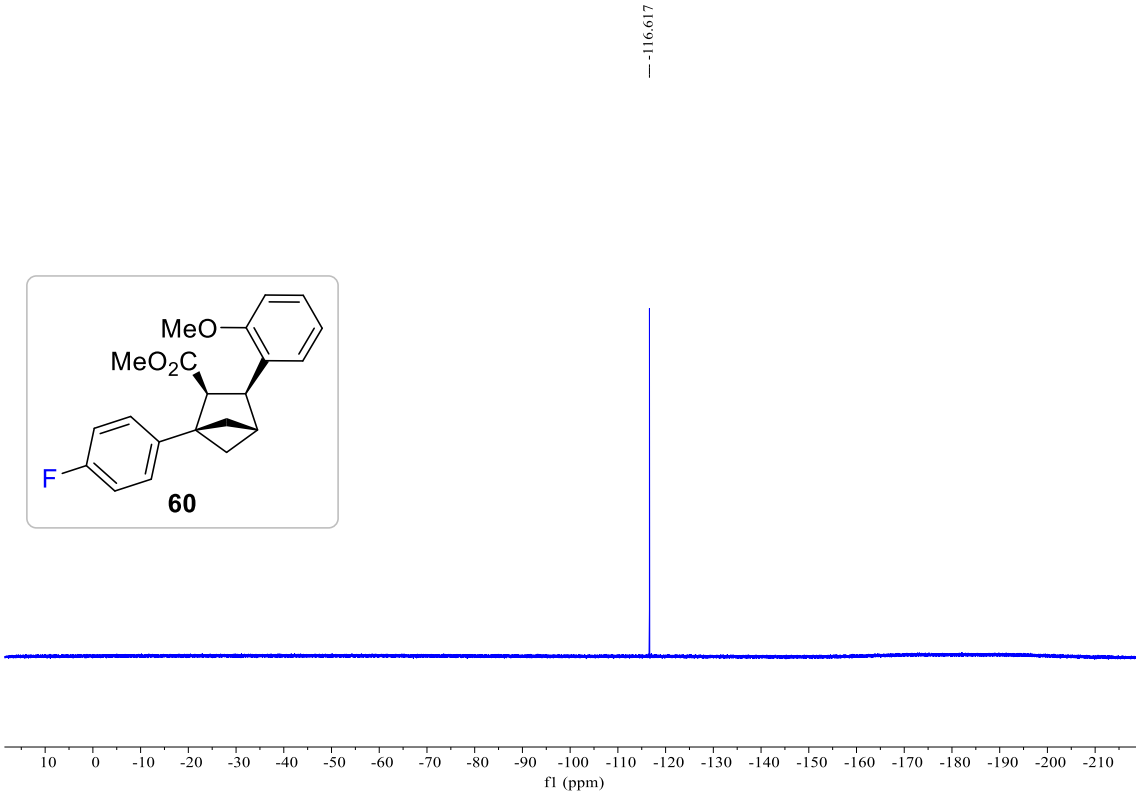
60, ^{1}H NMR (400 MHz, $CDCl_3$)



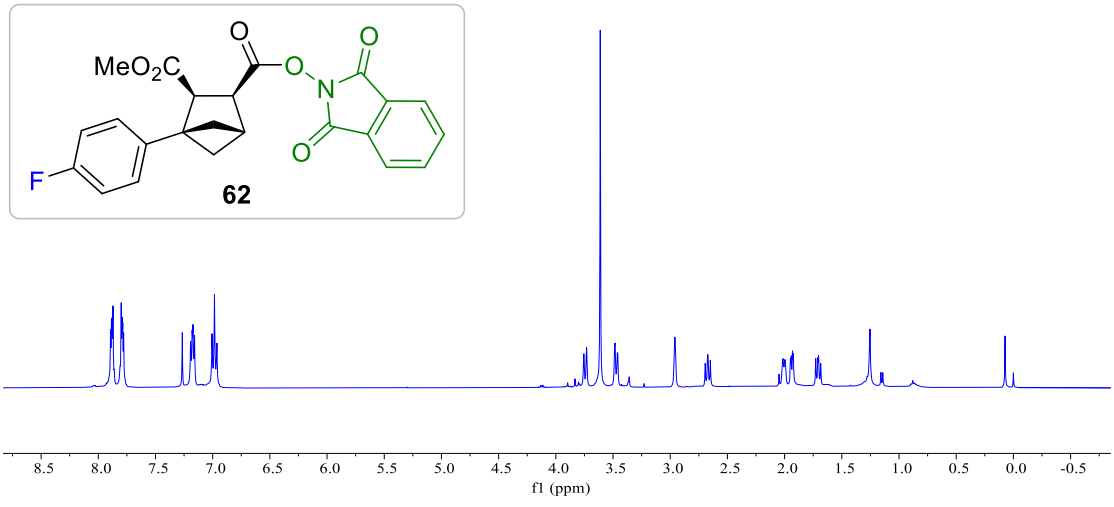
60, ^{13}C NMR (101 MHz, $CDCl_3$)



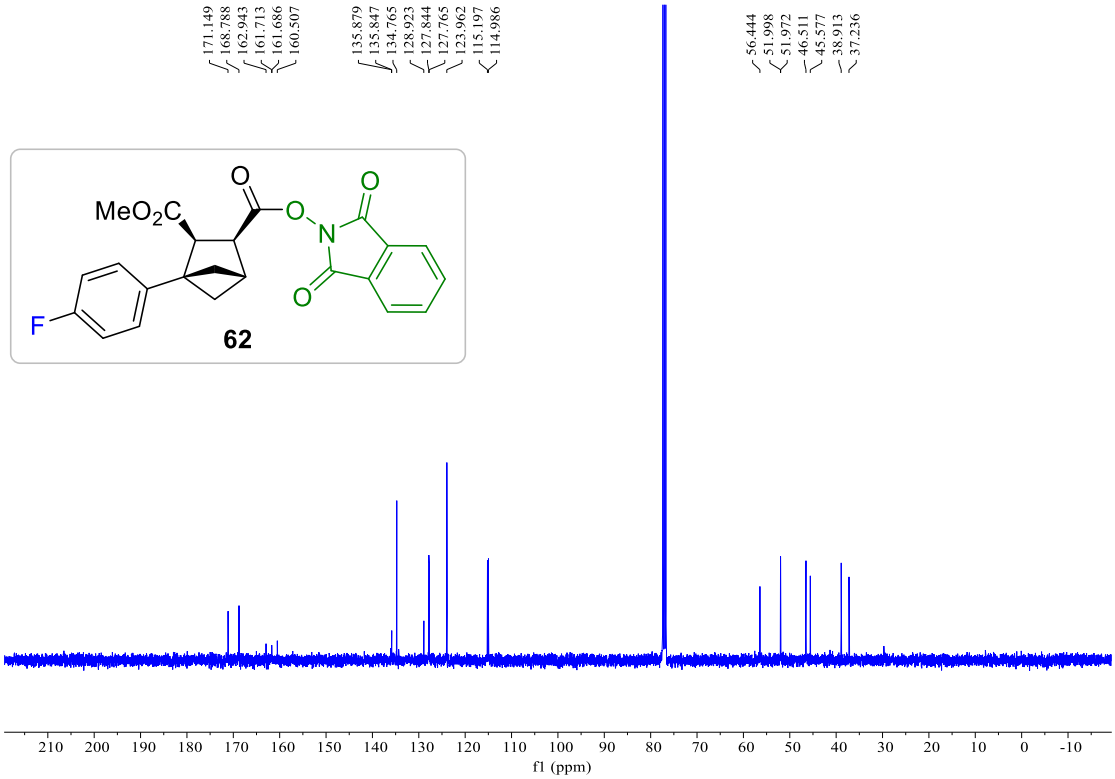
60, ^{19}F NMR (376 MHz, $CDCl_3$)



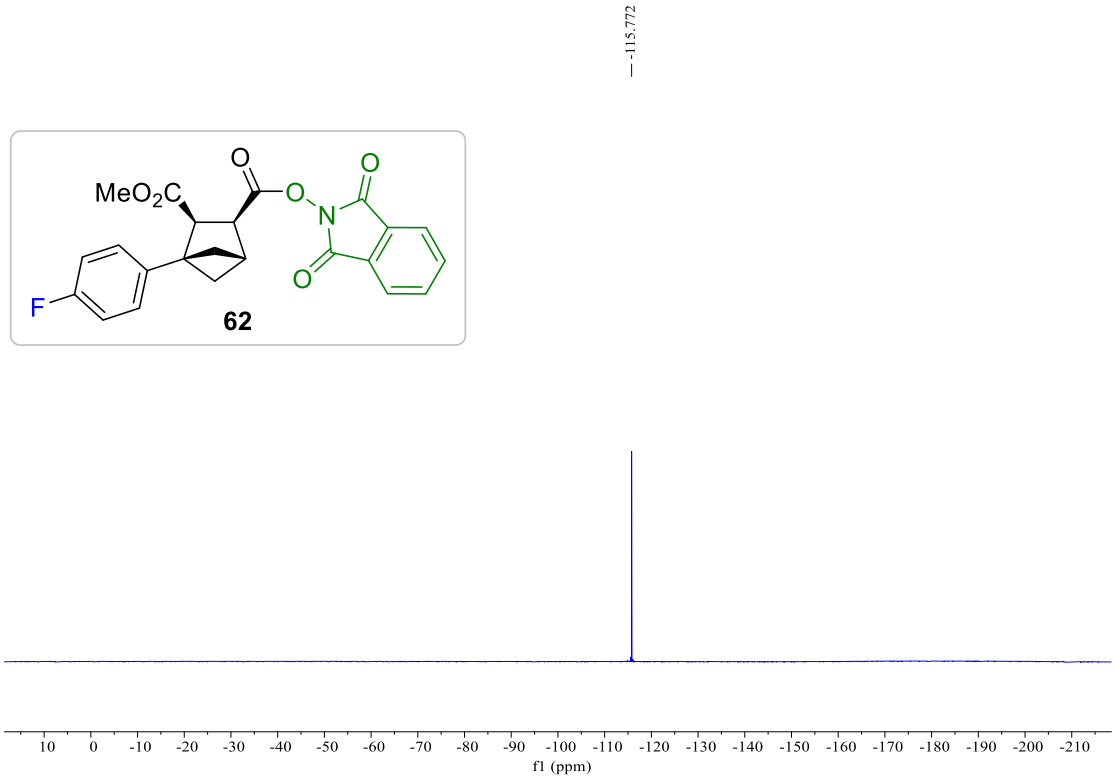
62, ^{1}H NMR (400 MHz, $CDCl_3$)



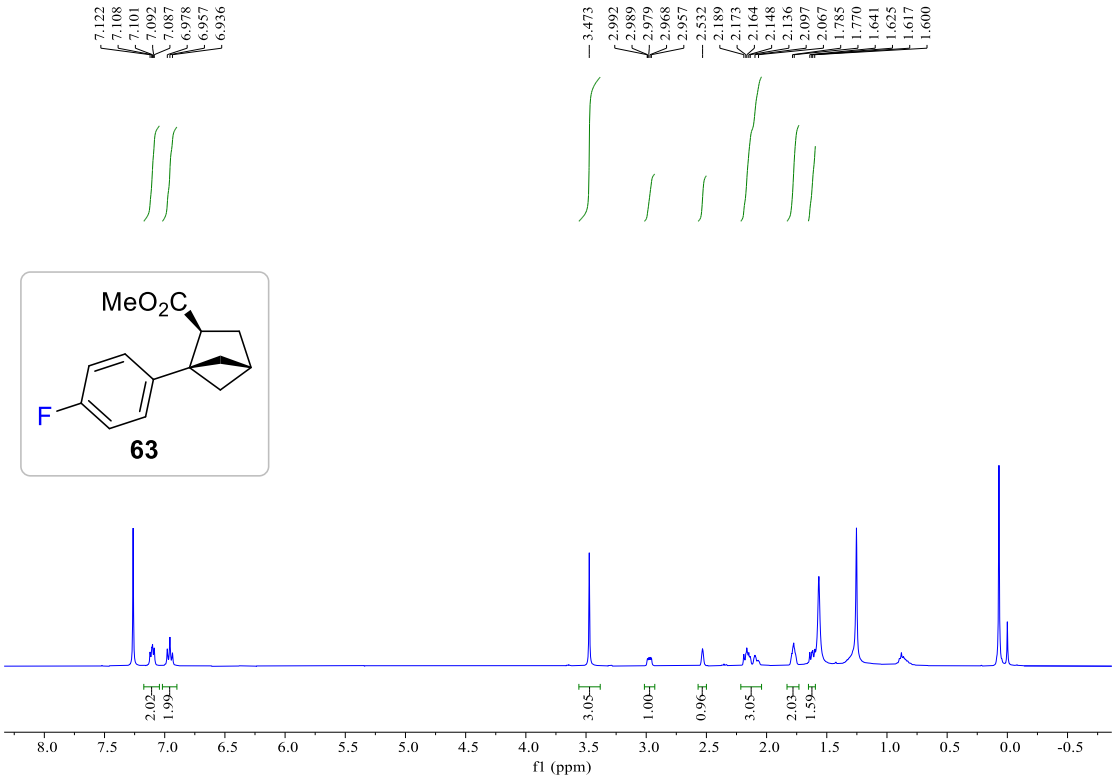
62, ^{13}C NMR (101 MHz, $CDCl_3$)



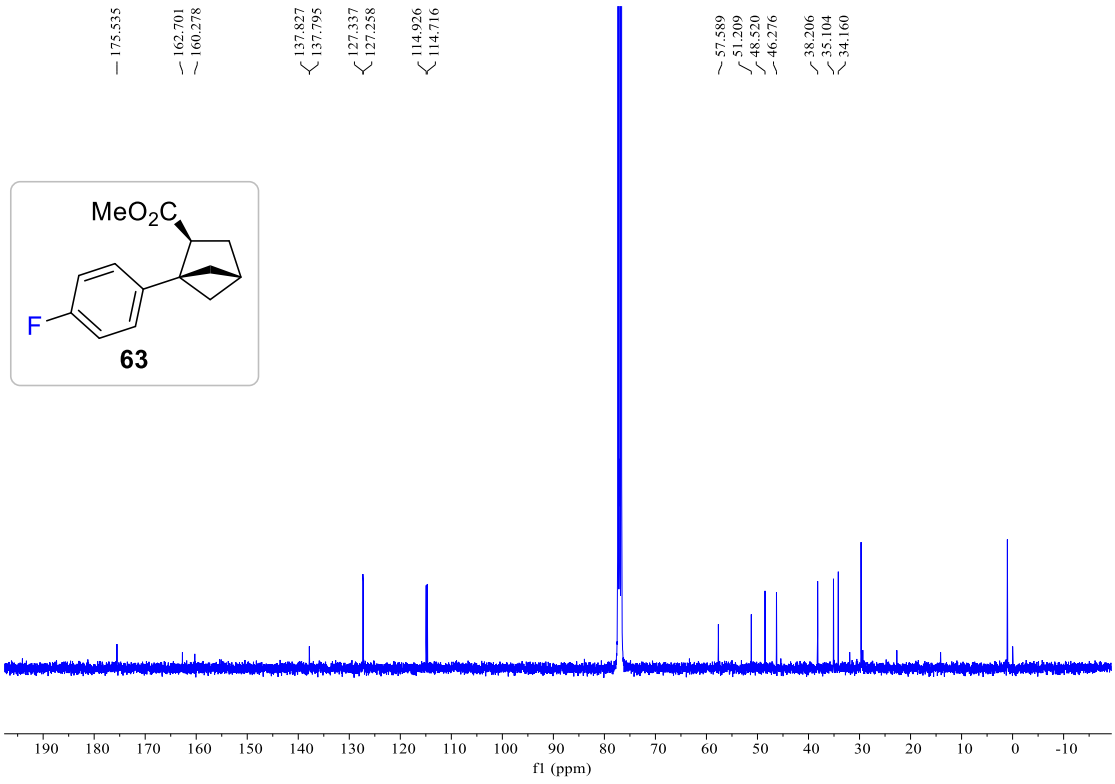
62, ^{19}F NMR (376 MHz, $CDCl_3$)



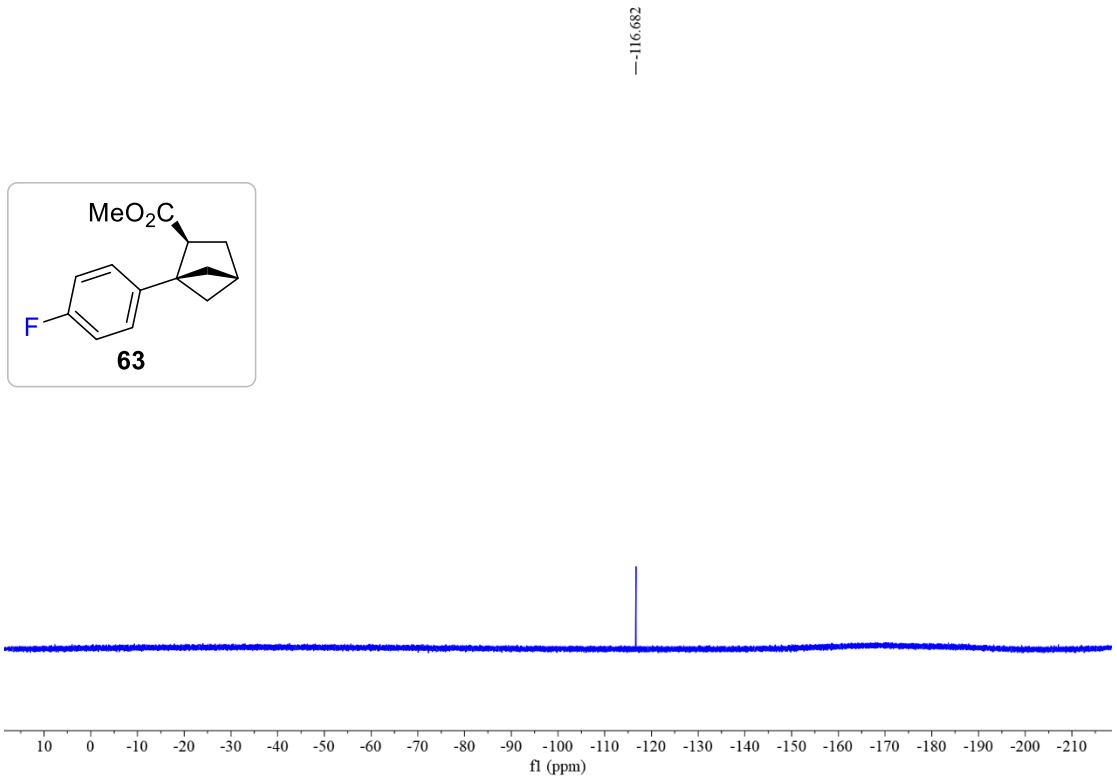
63, ^{1}H NMR (400 MHz, $CDCl_3$)



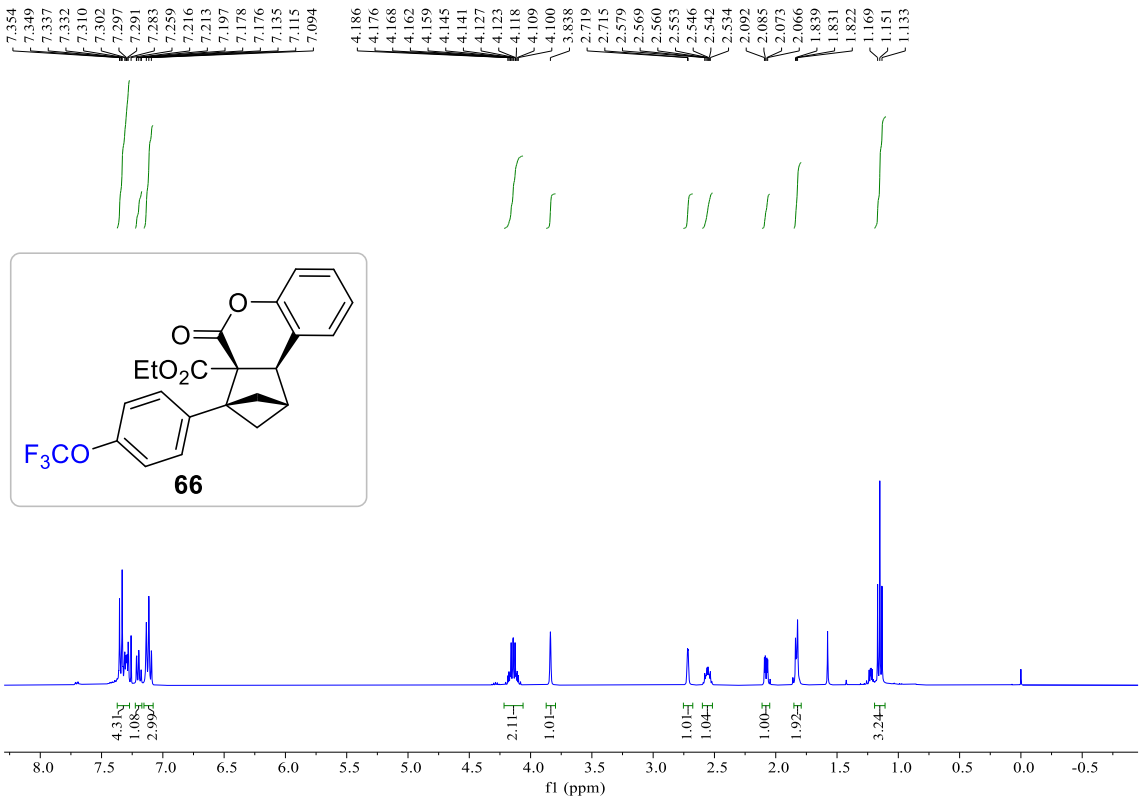
63, ^{13}C NMR (101 MHz, $CDCl_3$)



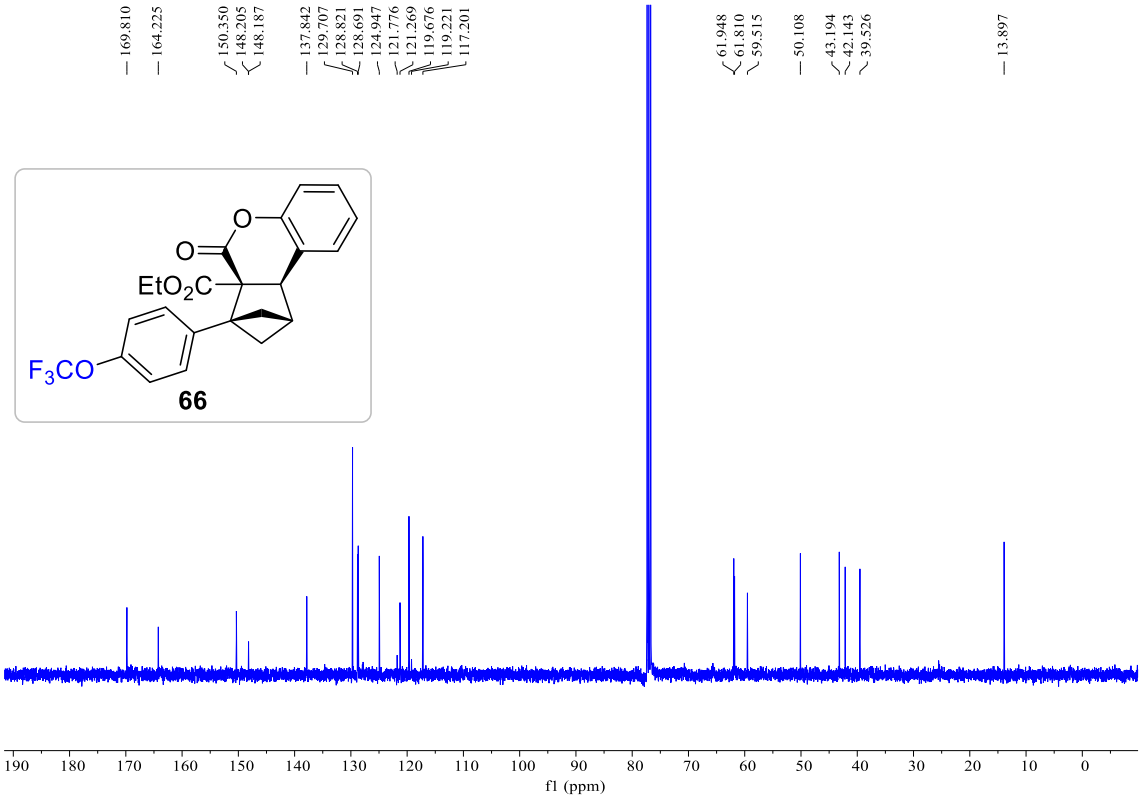
63, ^{19}F NMR (376 MHz, $CDCl_3$)



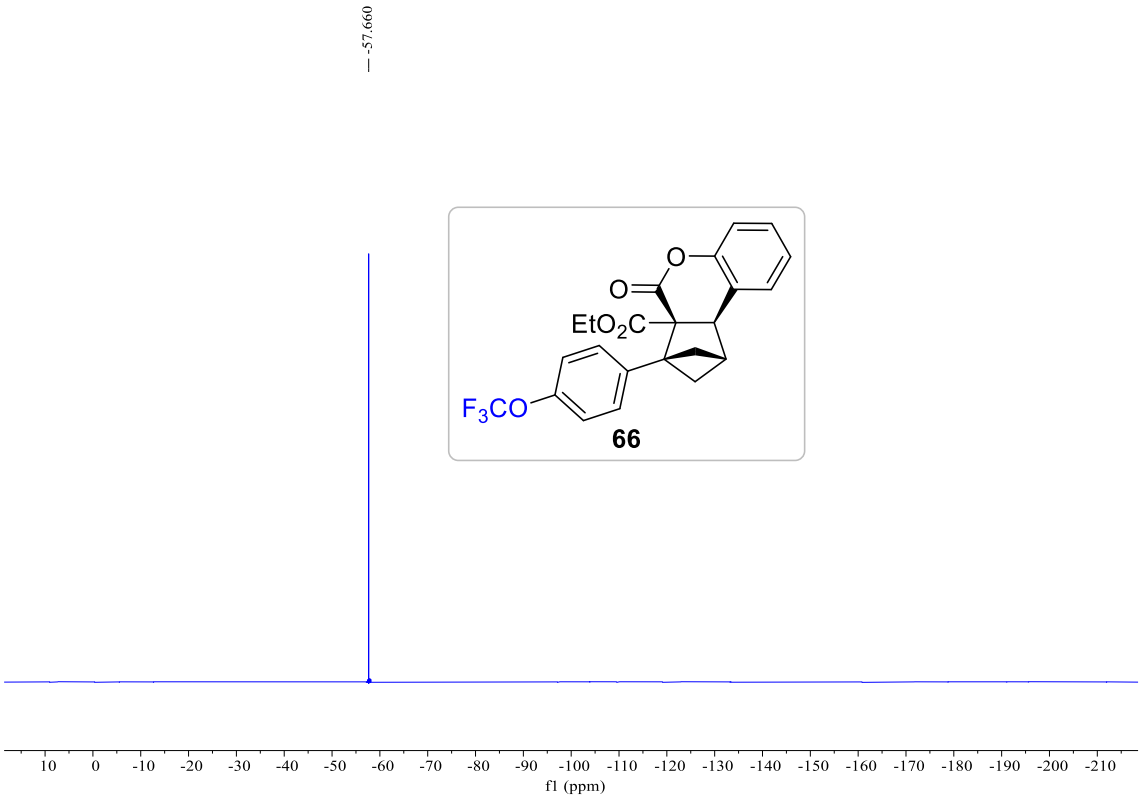
66, ^{1}H NMR (400 MHz, $CDCl_3$)



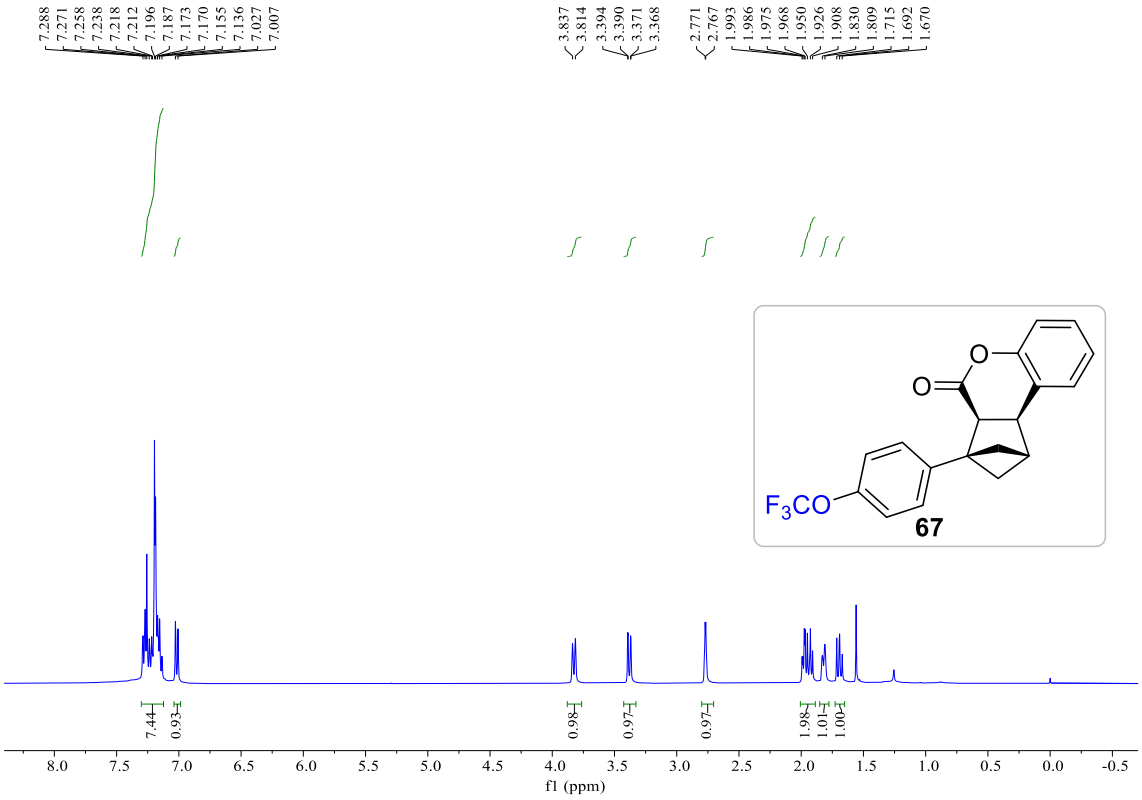
66, ^{13}C NMR (101 MHz, $CDCl_3$)



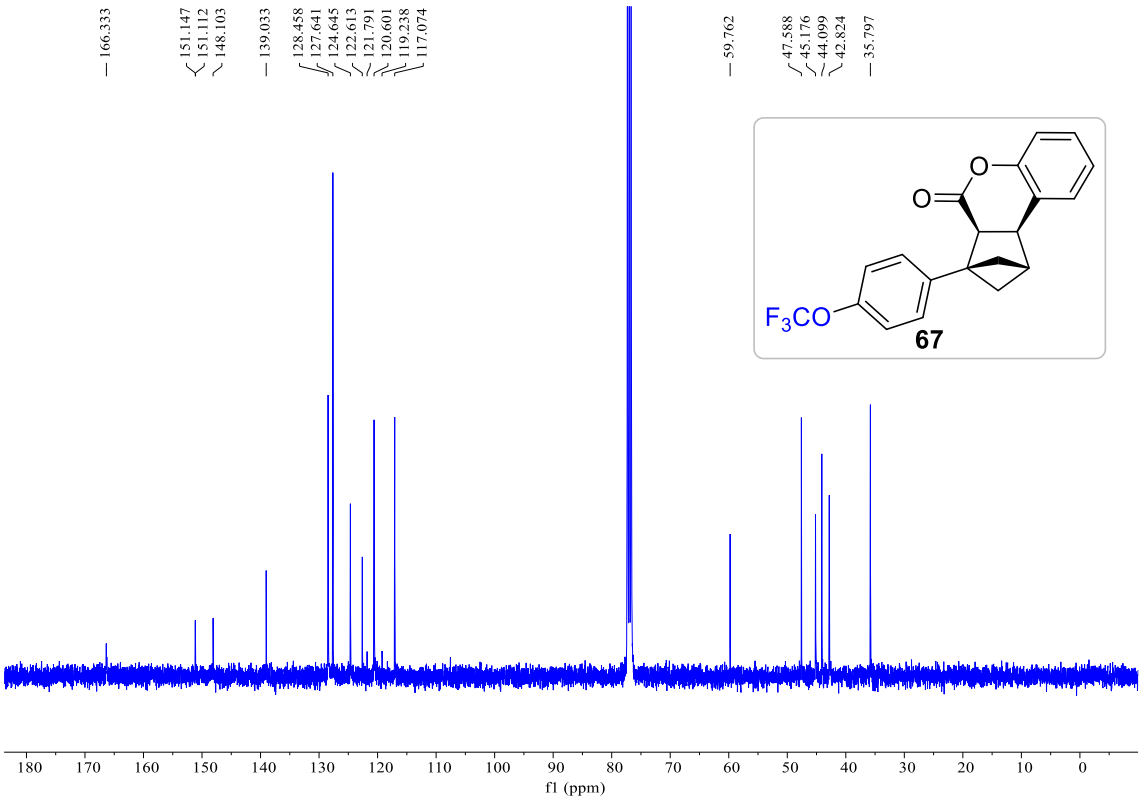
66, ^{19}F NMR (376 MHz, $CDCl_3$)



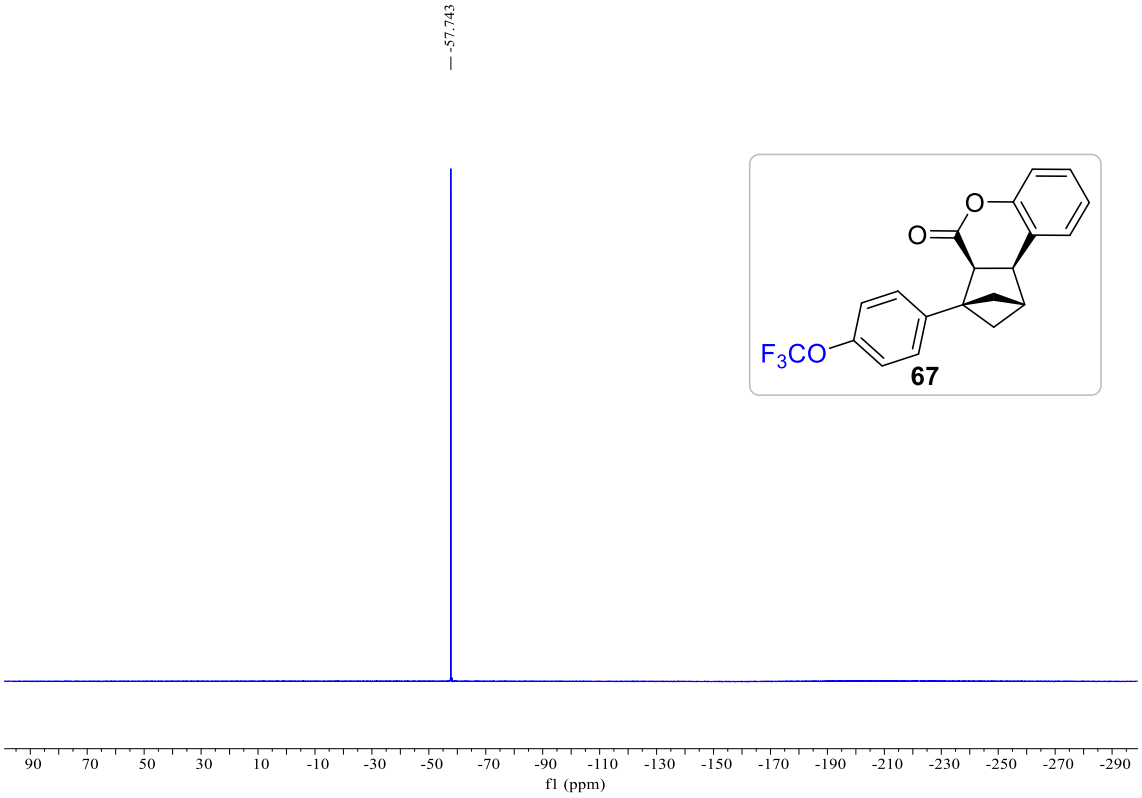
67, ^{1}H NMR (400 MHz, $CDCl_3$)



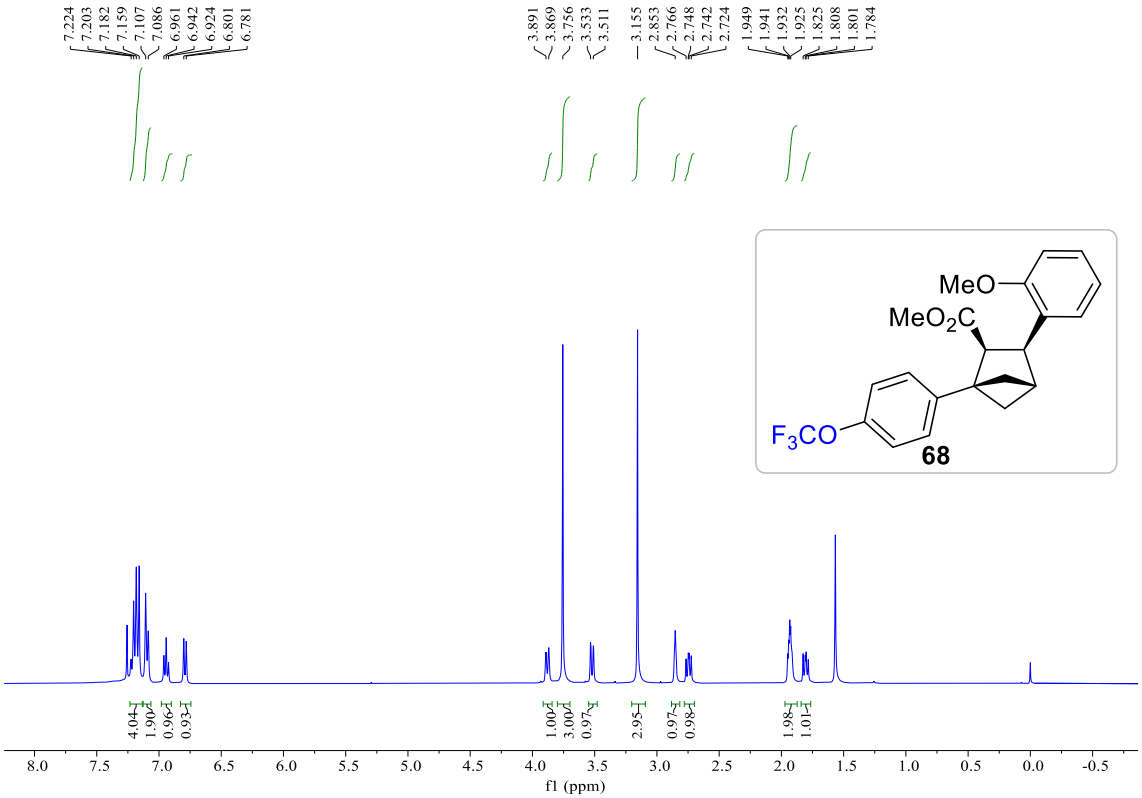
67, ^{13}C NMR (101 MHz, $CDCl_3$)



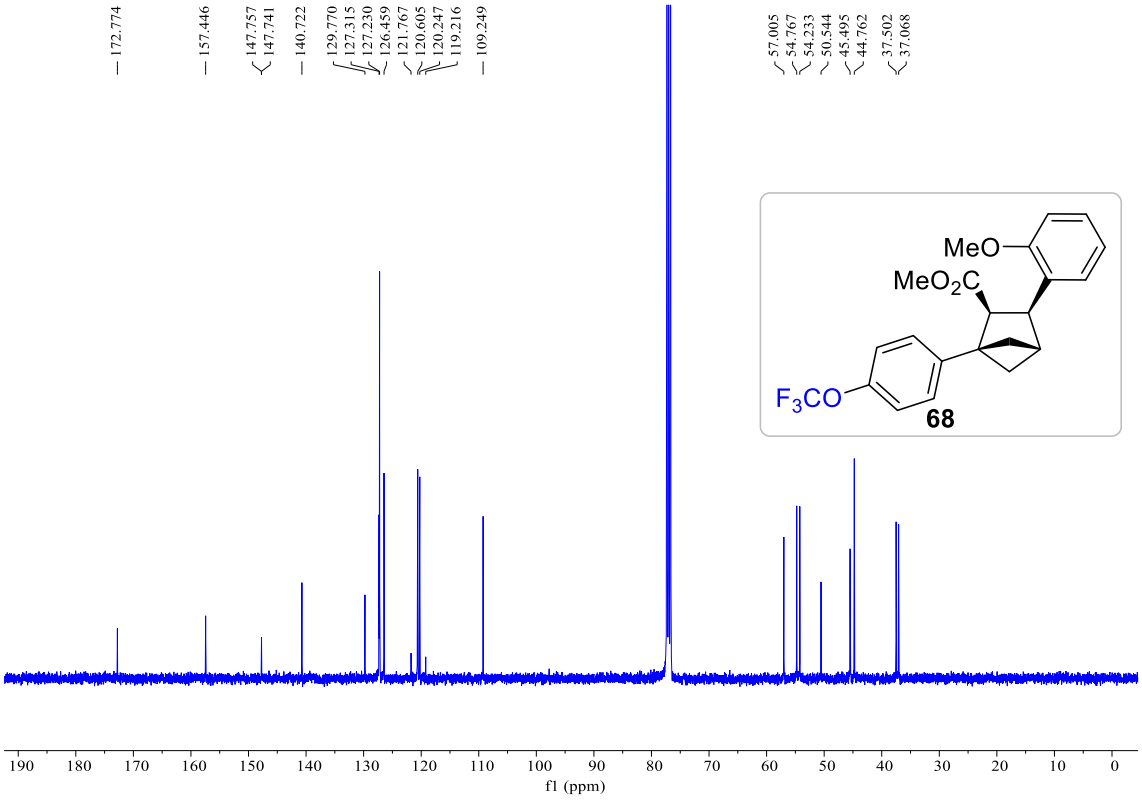
67, ^{19}F NMR (376 MHz, $CDCl_3$)



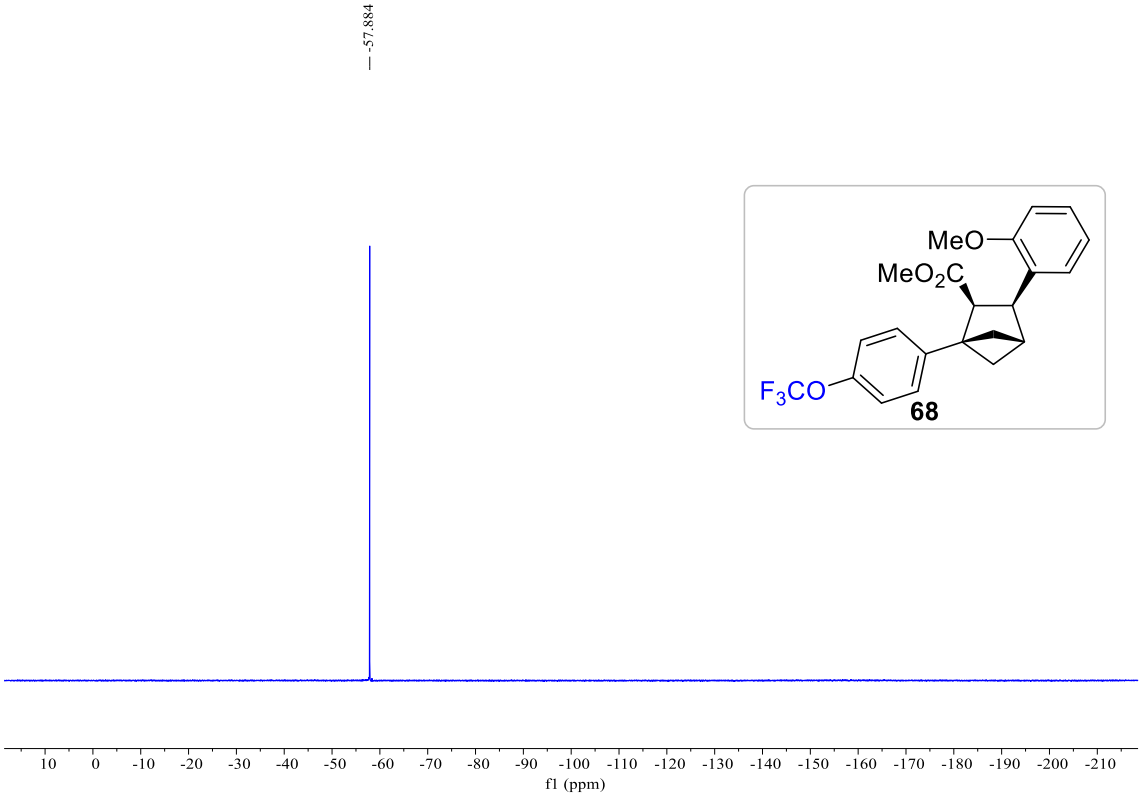
68, ^{1}H NMR (400 MHz, $CDCl_3$)



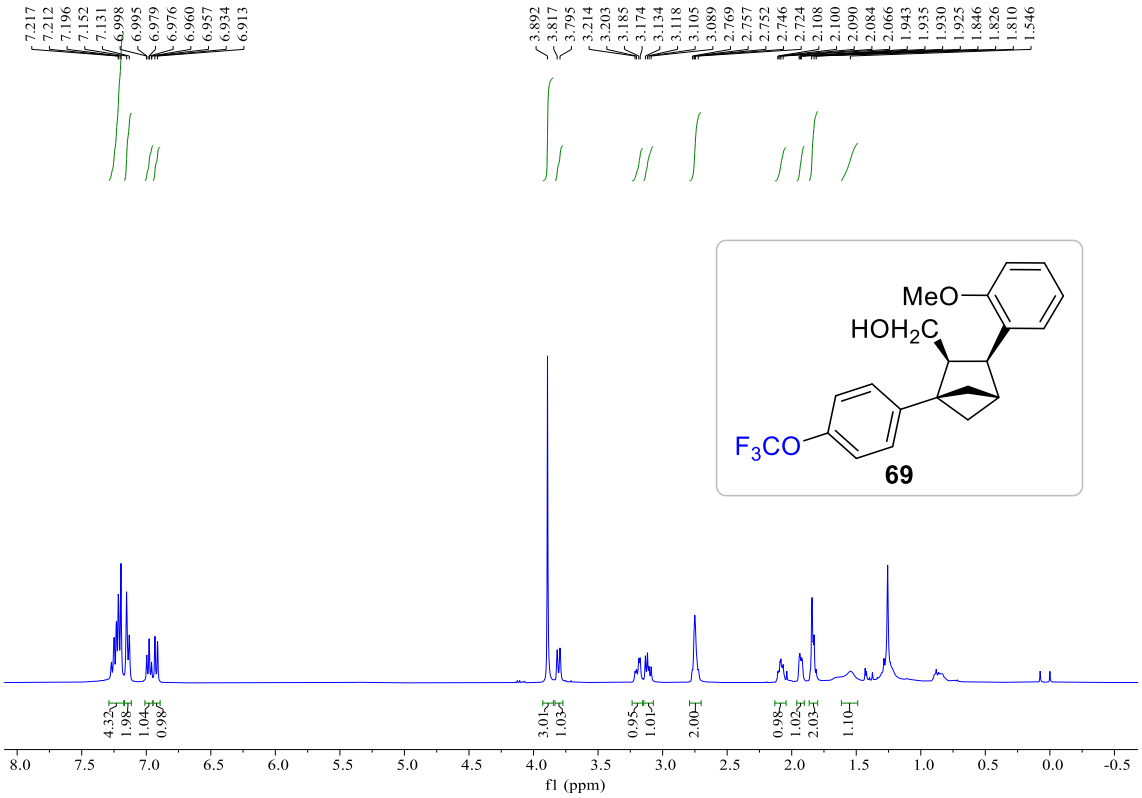
68, ^{13}C NMR (101 MHz, $CDCl_3$)



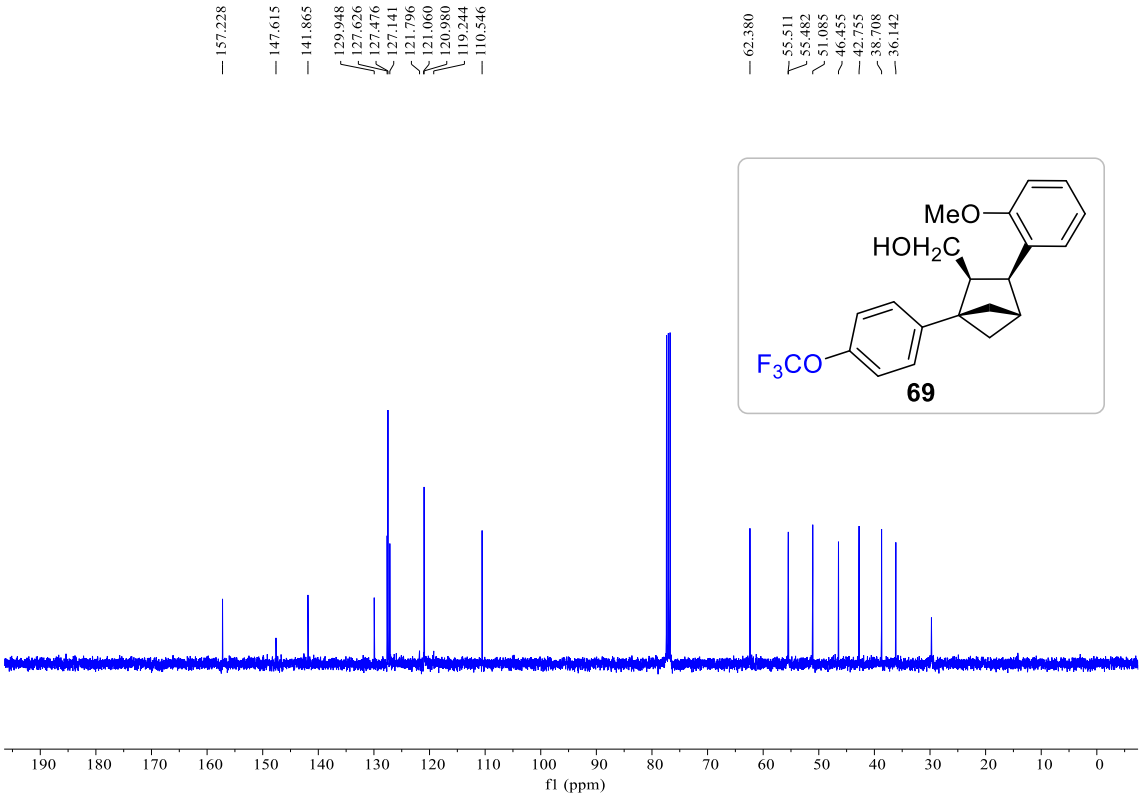
68, ^{19}F NMR (376 MHz, $CDCl_3$)



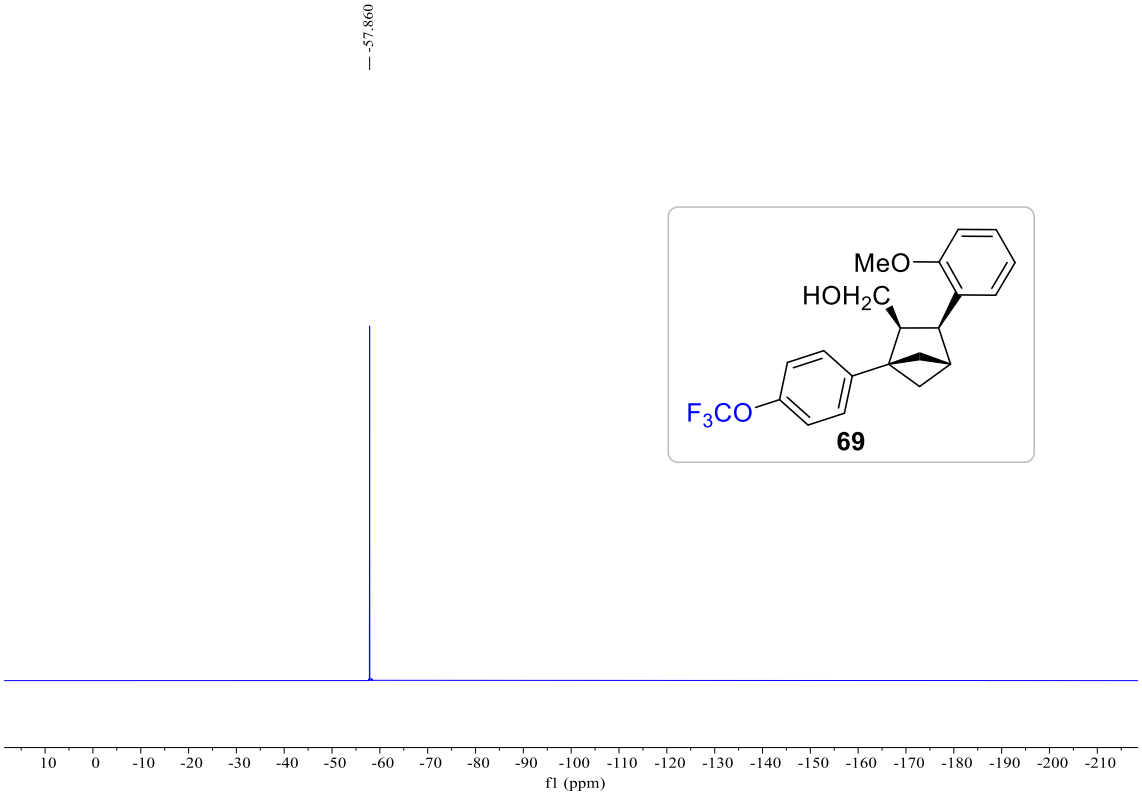
69, ^{1}H NMR (400 MHz, $CDCl_3$)



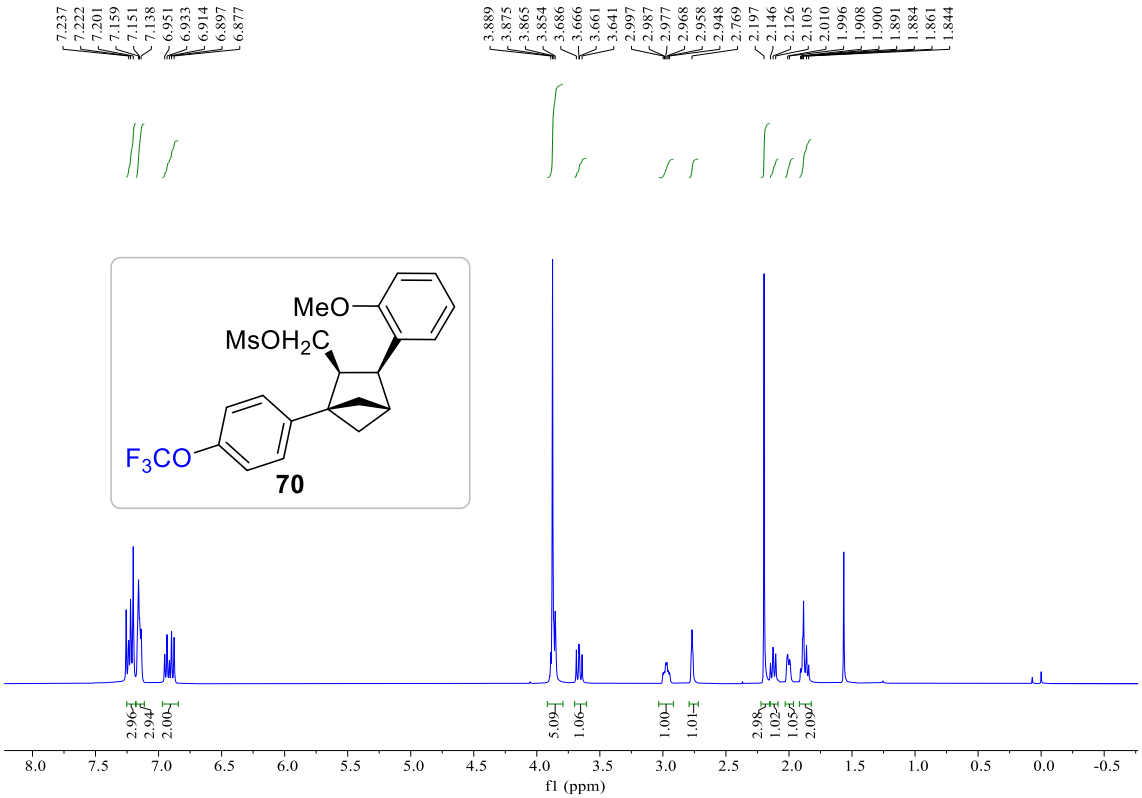
69, ^{13}C NMR (101 MHz, $CDCl_3$)



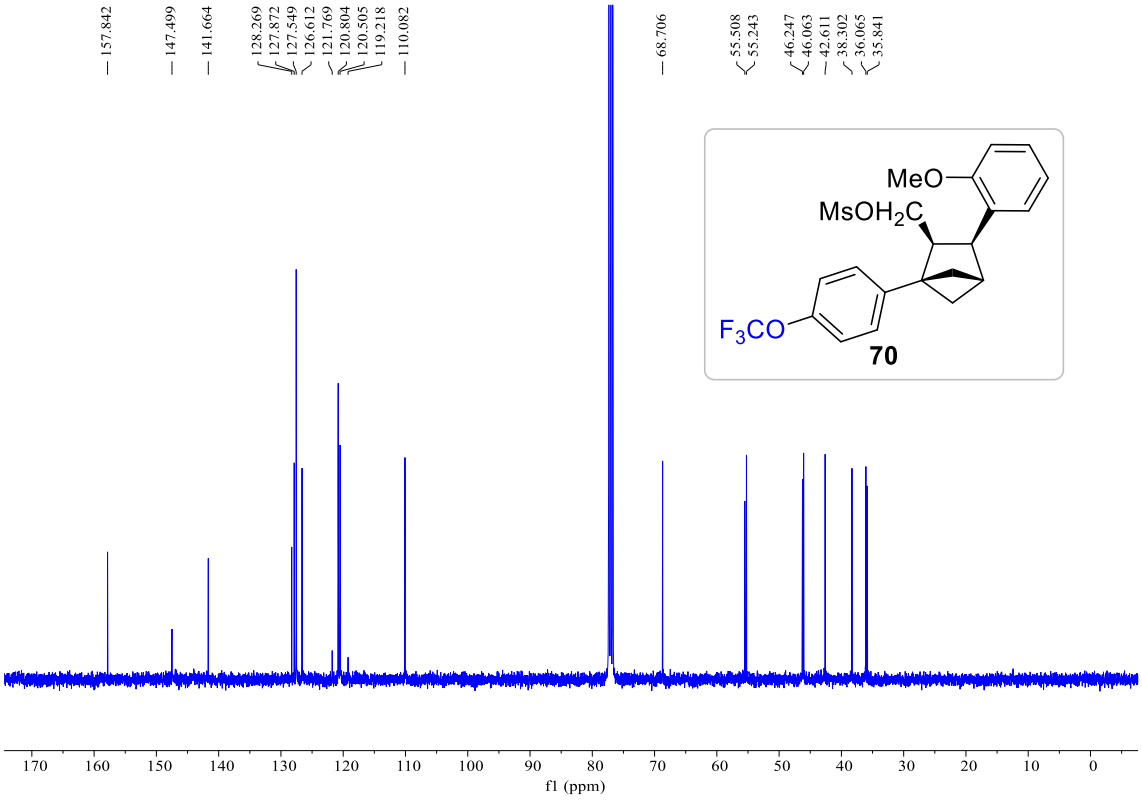
69, ^{19}F NMR (376 MHz, $CDCl_3$)



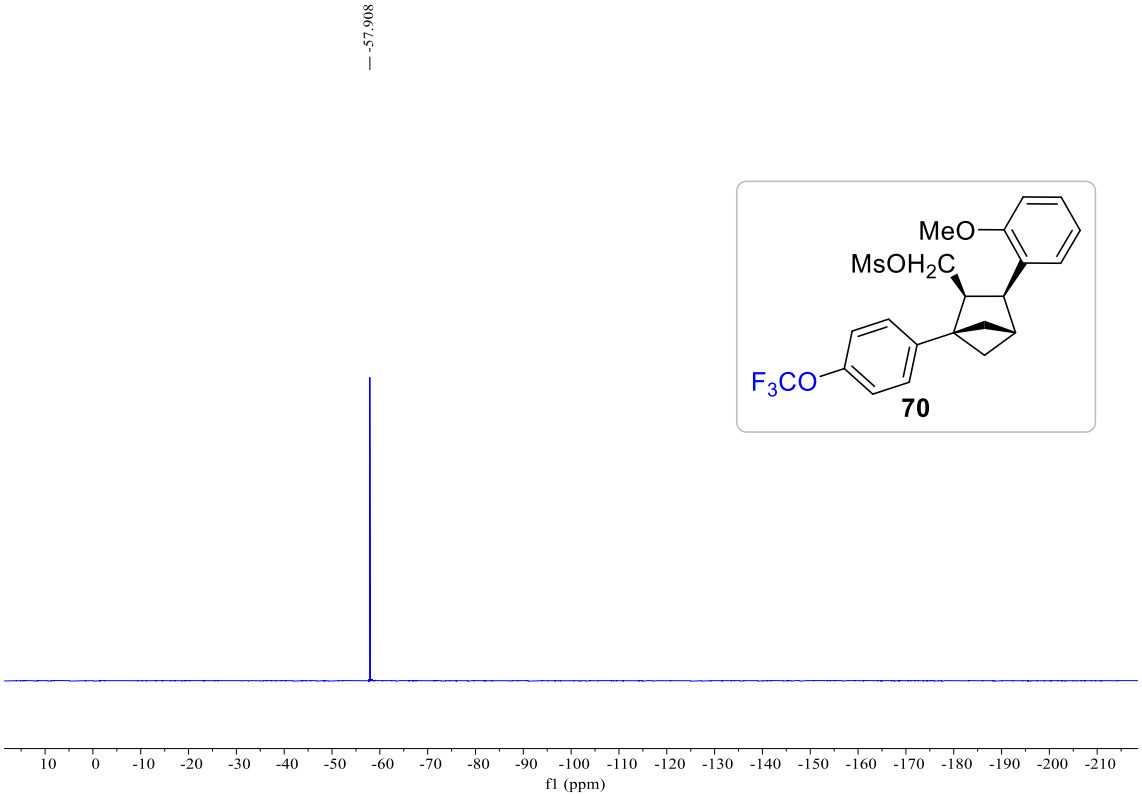
70, ^{1}H NMR (400 MHz, $CDCl_3$)



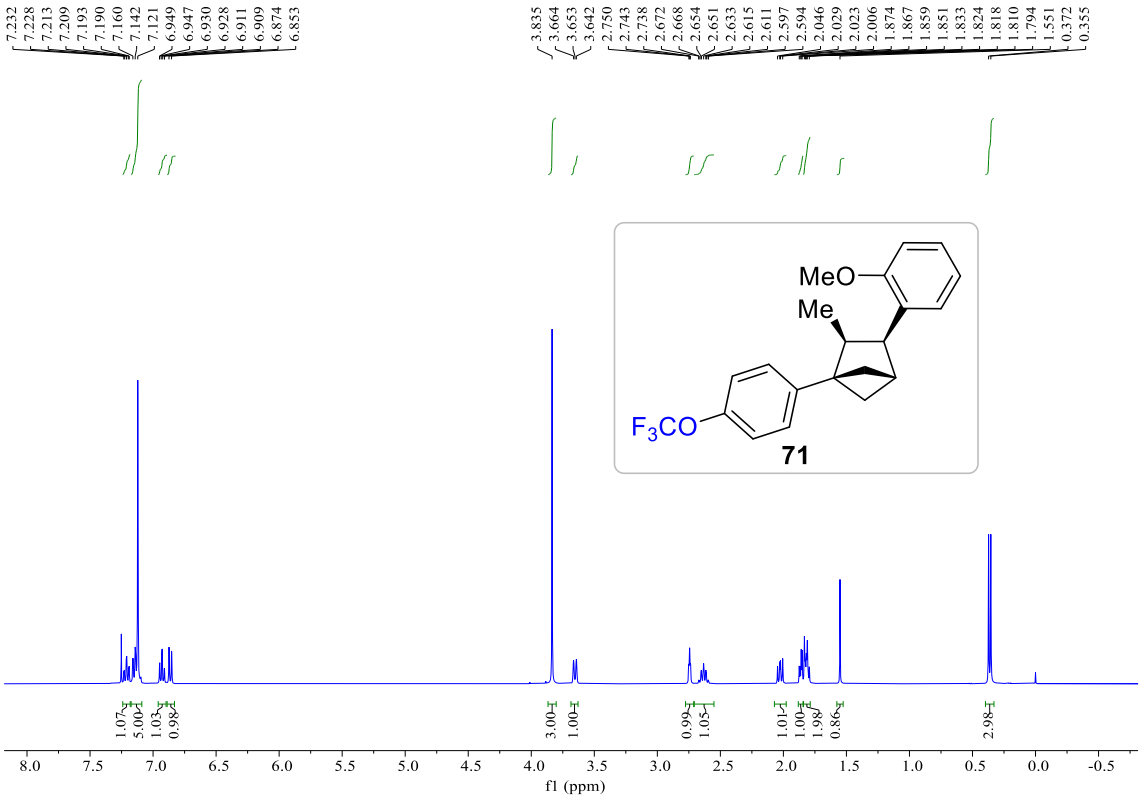
70, ^{13}C NMR (101 MHz, $CDCl_3$)



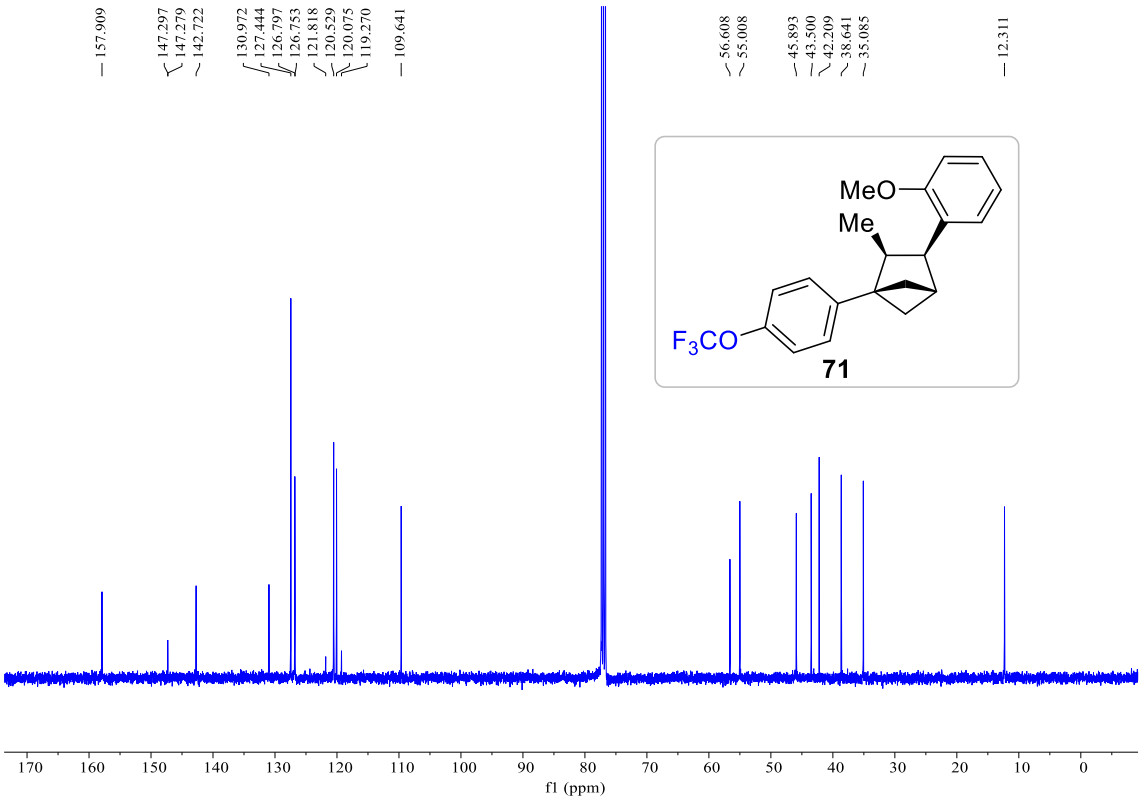
70, ^{19}F NMR (376 MHz, $CDCl_3$)



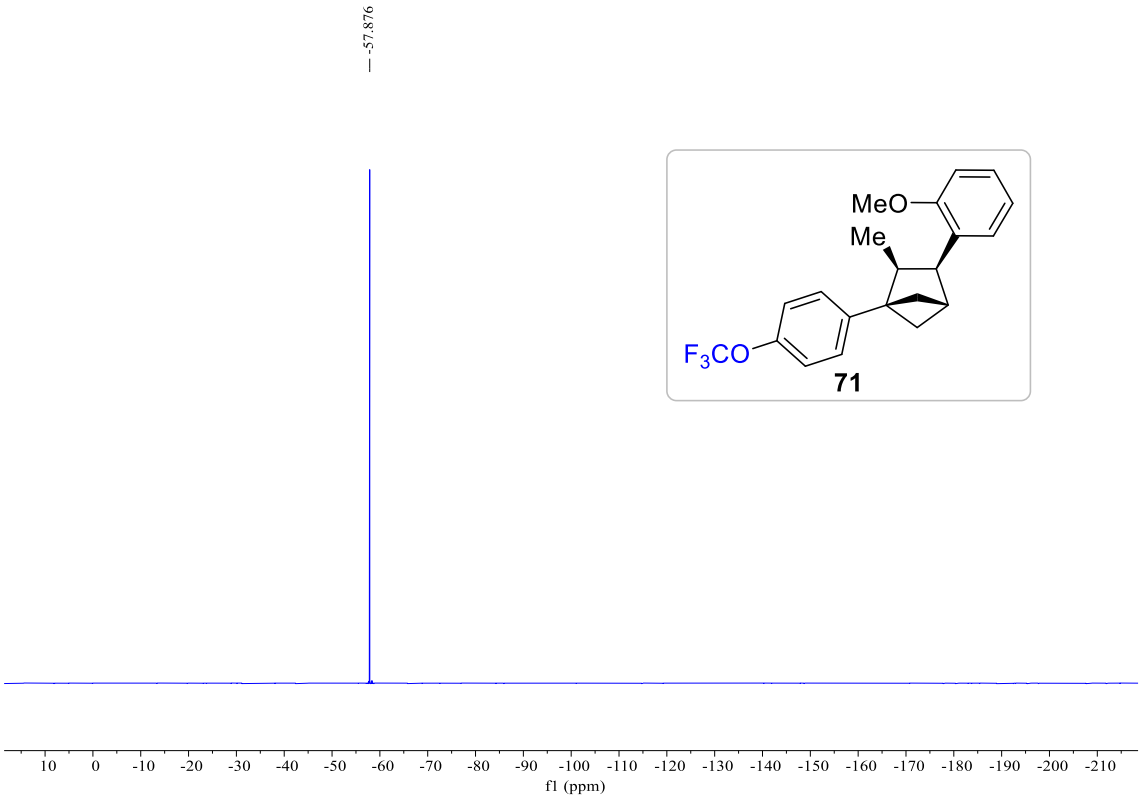
71, ^{1}H NMR (400 MHz, $CDCl_3$)



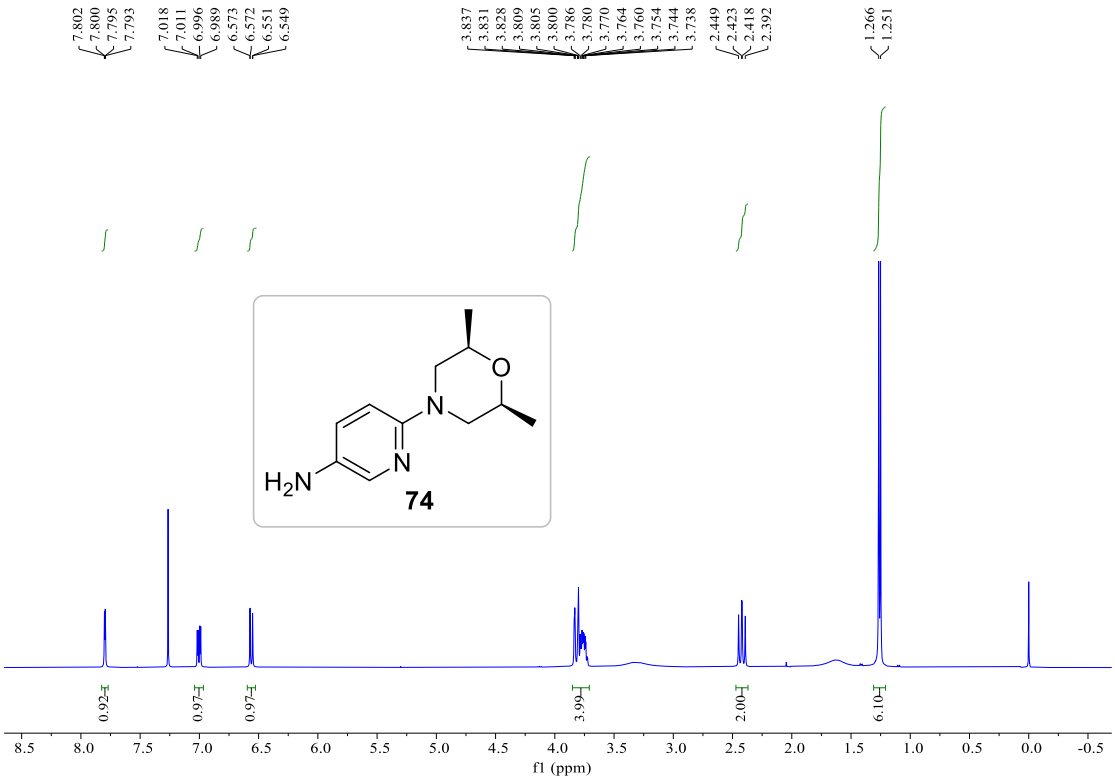
71, ^{13}C NMR (101 MHz, $CDCl_3$)



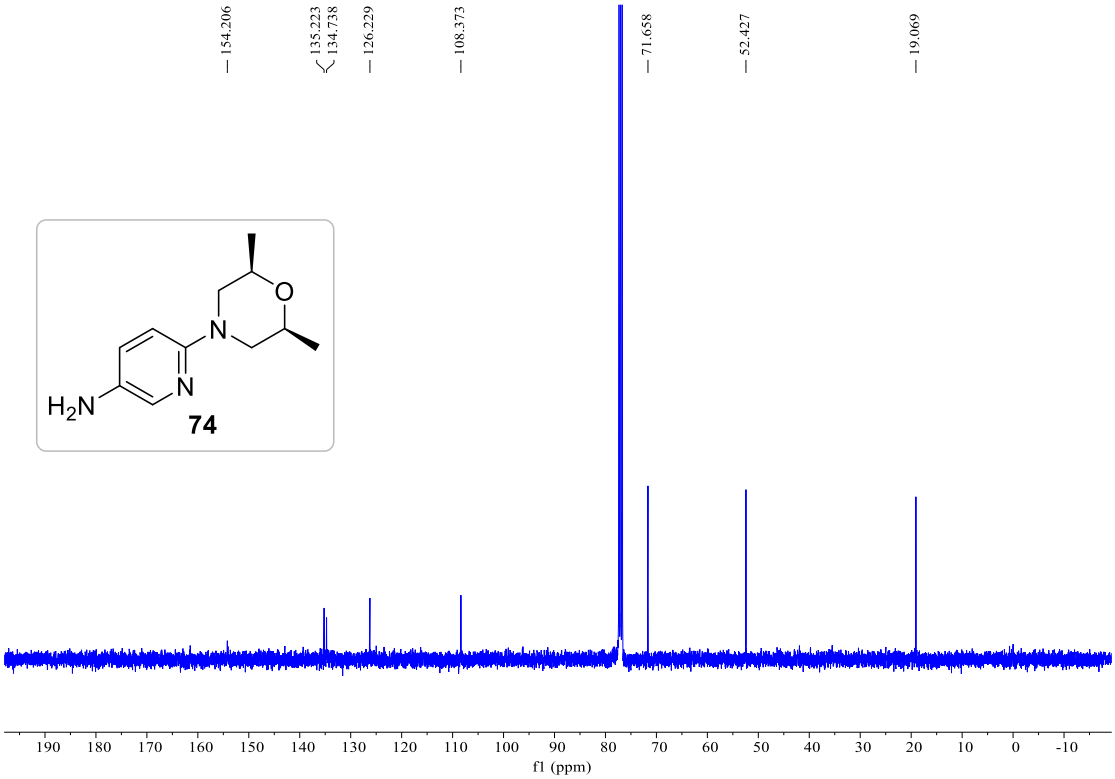
71, ^{19}F NMR (376 MHz, $CDCl_3$)



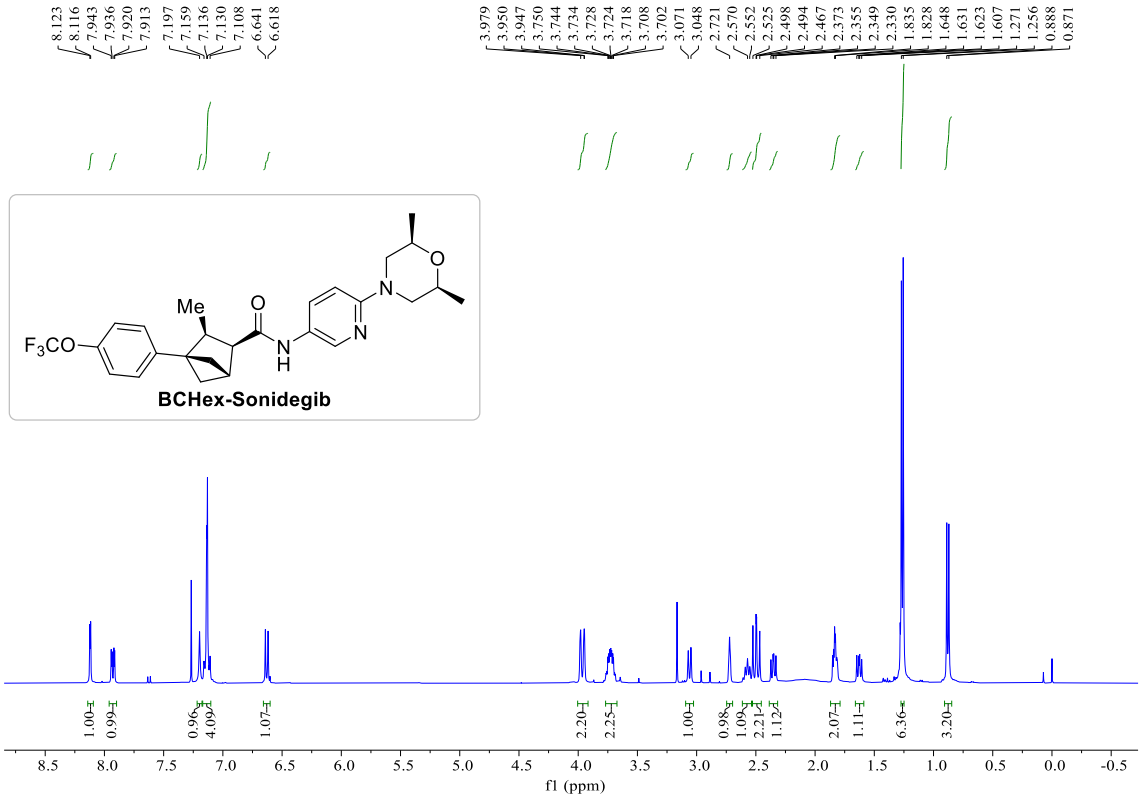
74, ^{1}H NMR (400 MHz, $CDCl_3$)



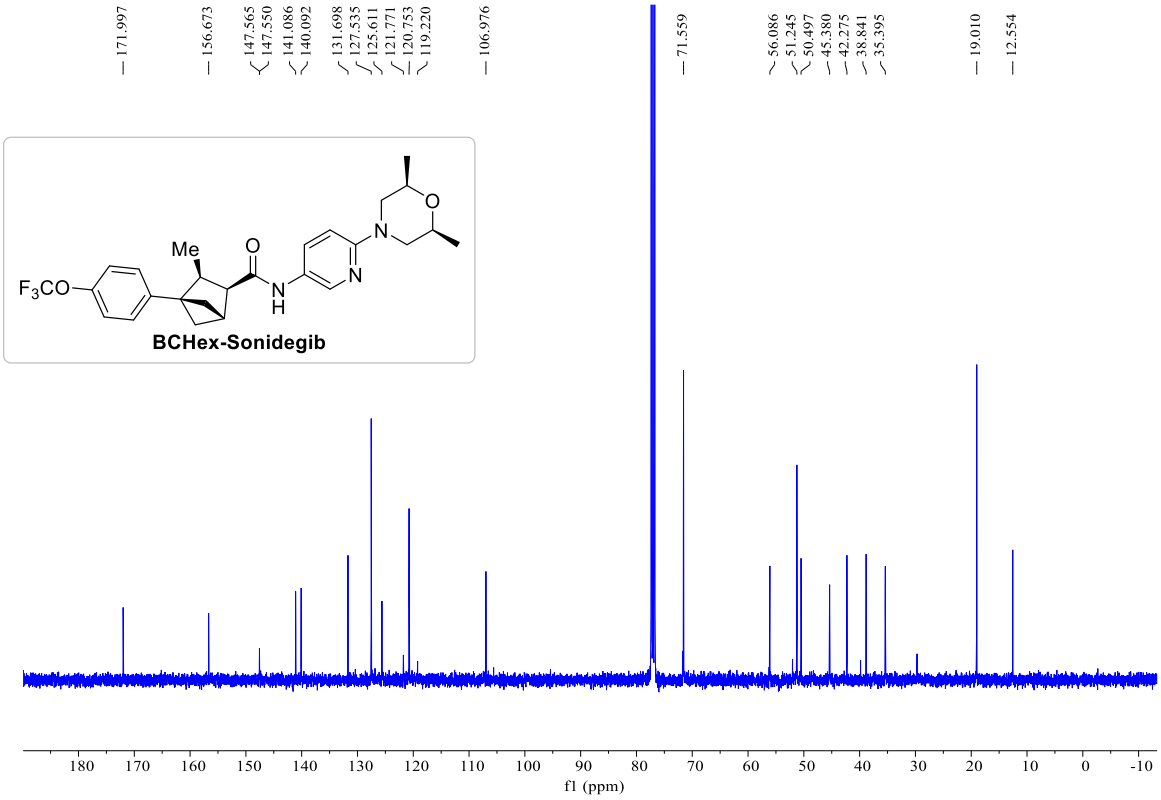
74, ^{13}C NMR (101 MHz, $CDCl_3$)



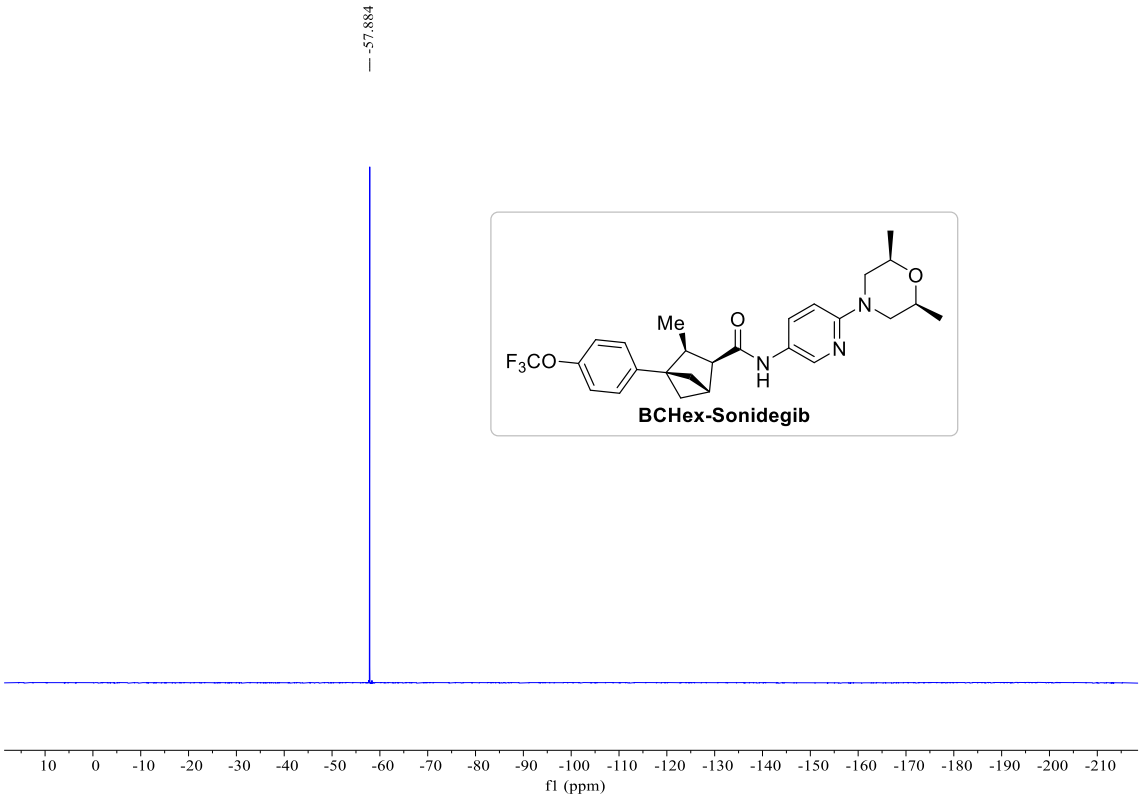
BCHex-Sonidegib, ^{1}H NMR (400 MHz, $CDCl_3$)



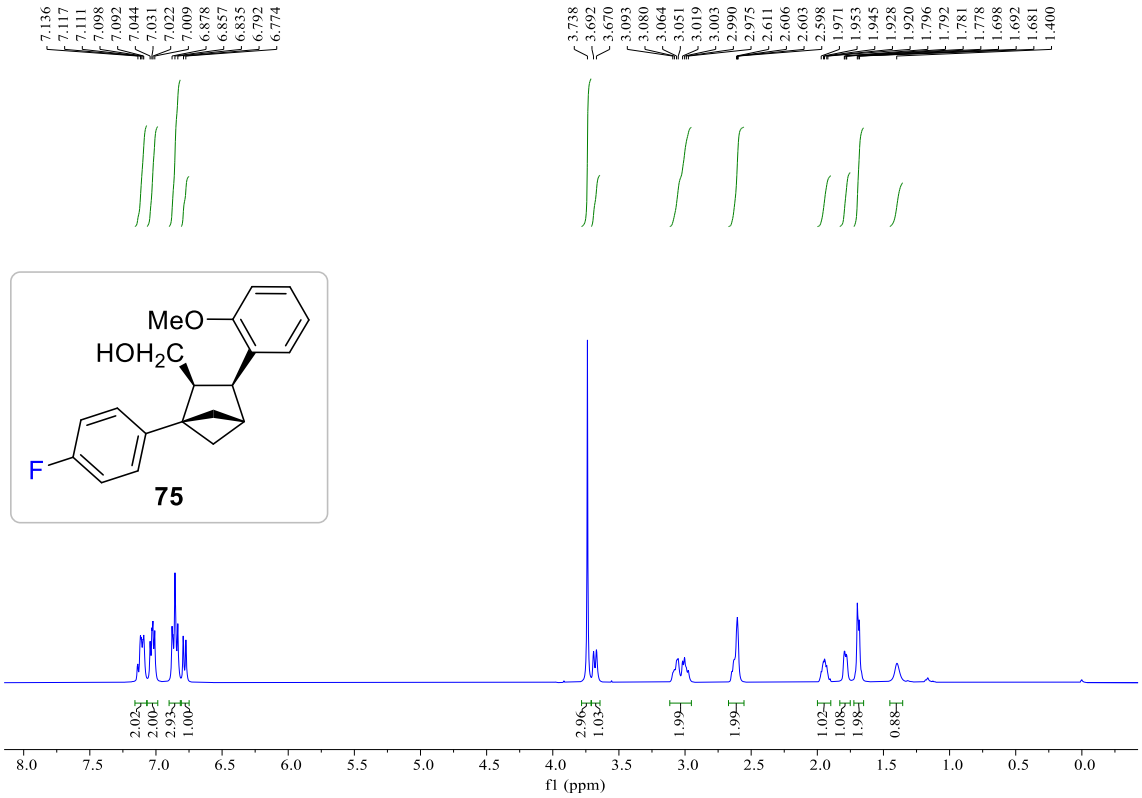
BCHex-Sonidegib, ^{13}C NMR (101 MHz, $CDCl_3$)



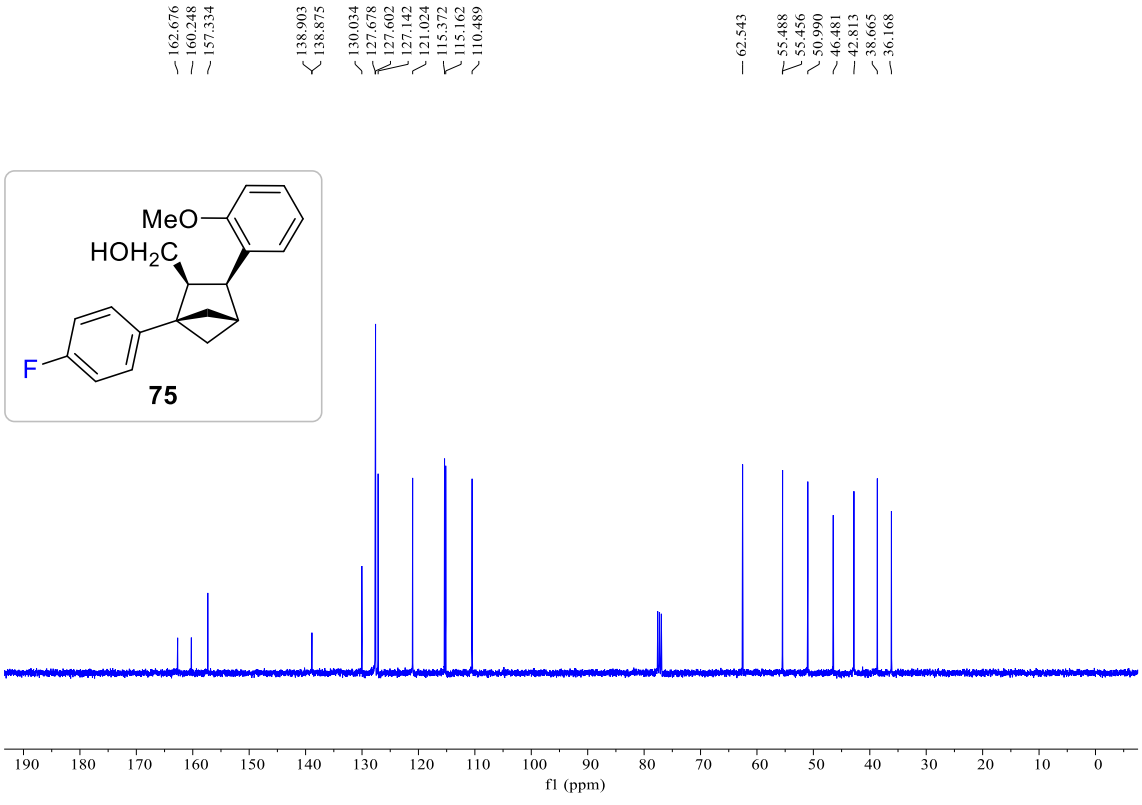
BCHex-Sonidegib, ^{19}F NMR (376 MHz, $CDCl_3$)



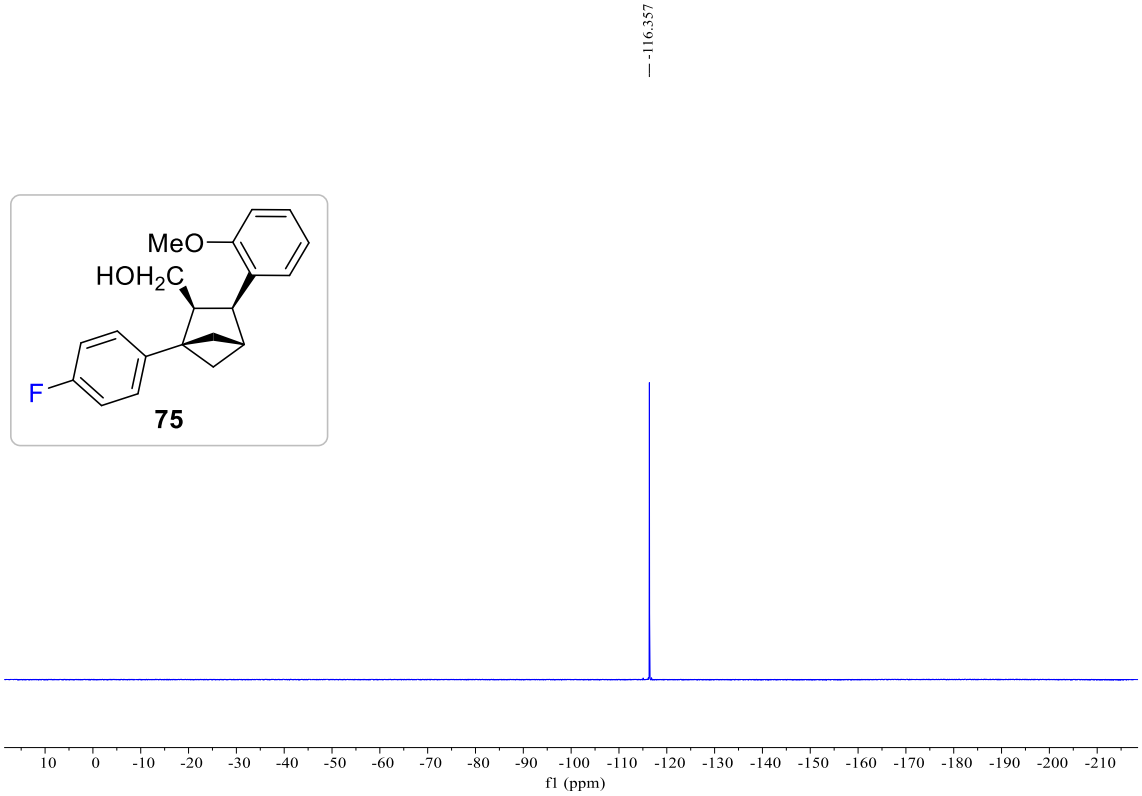
75, ^{1}H NMR (400 MHz, $CDCl_3$)



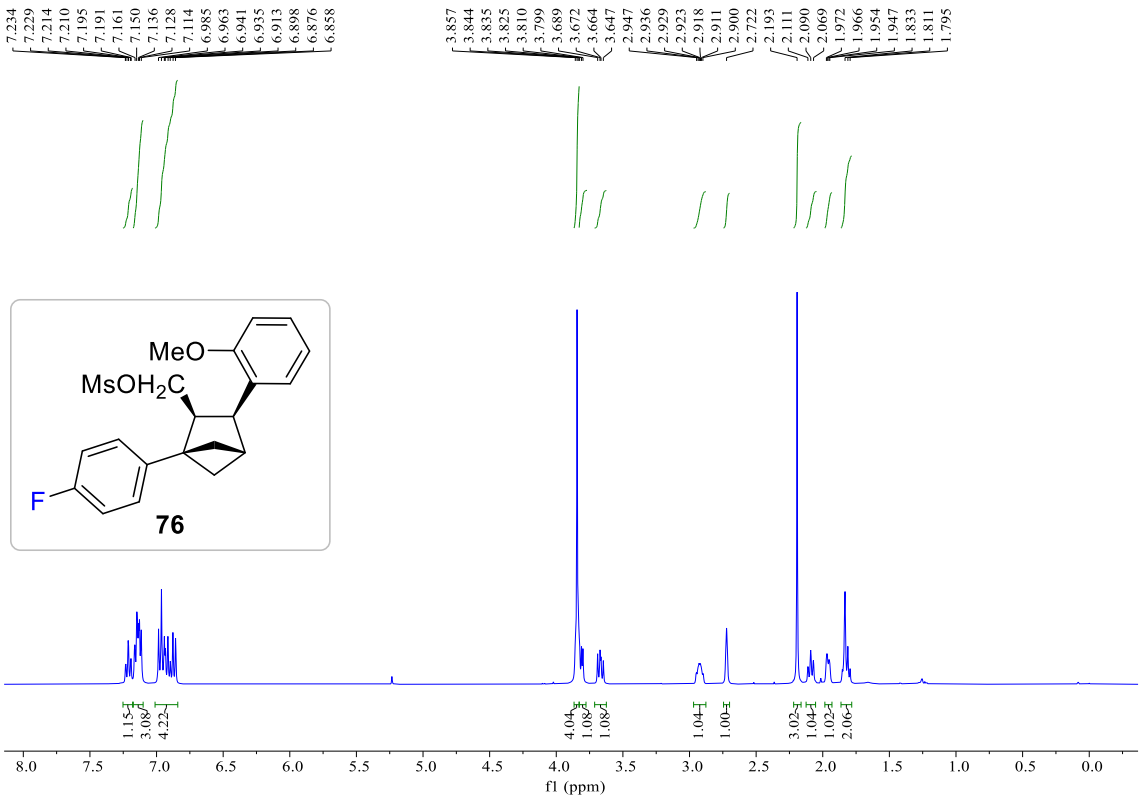
75, ^{13}C NMR (101 MHz, $CDCl_3$)



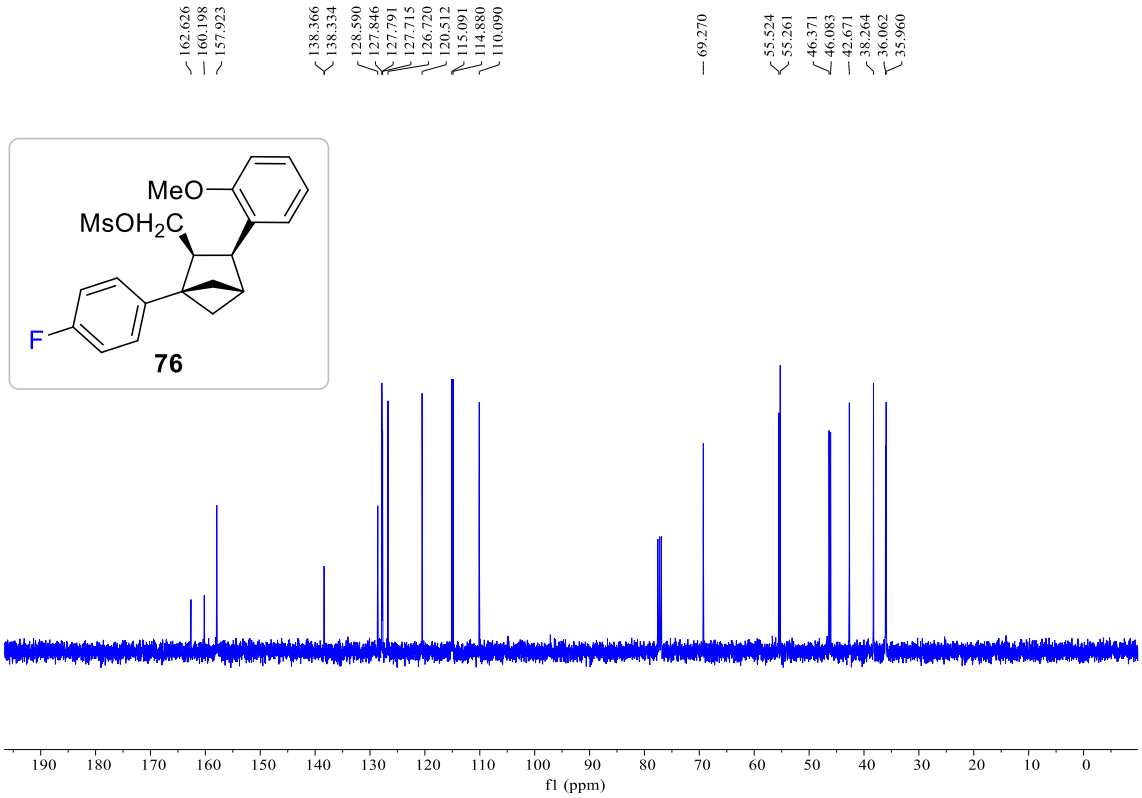
75, ^{19}F NMR (376 MHz, $CDCl_3$)



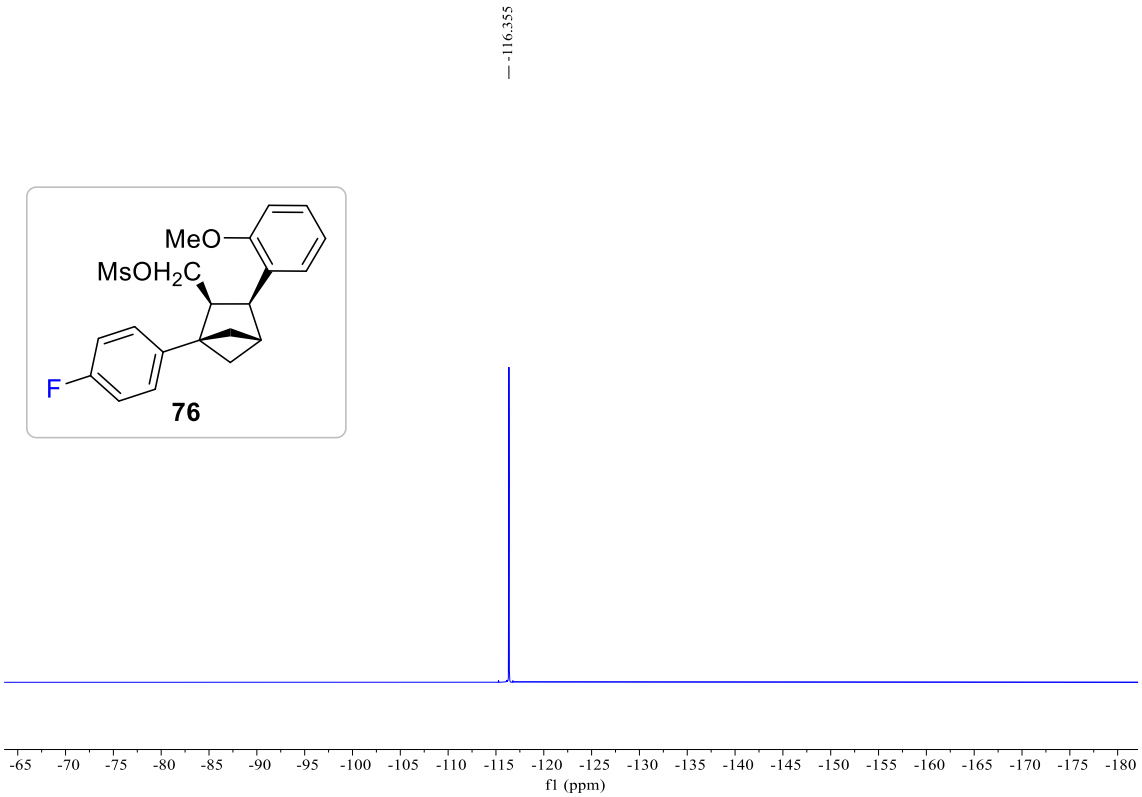
76, ^{1}H NMR (400 MHz, $CDCl_3$)



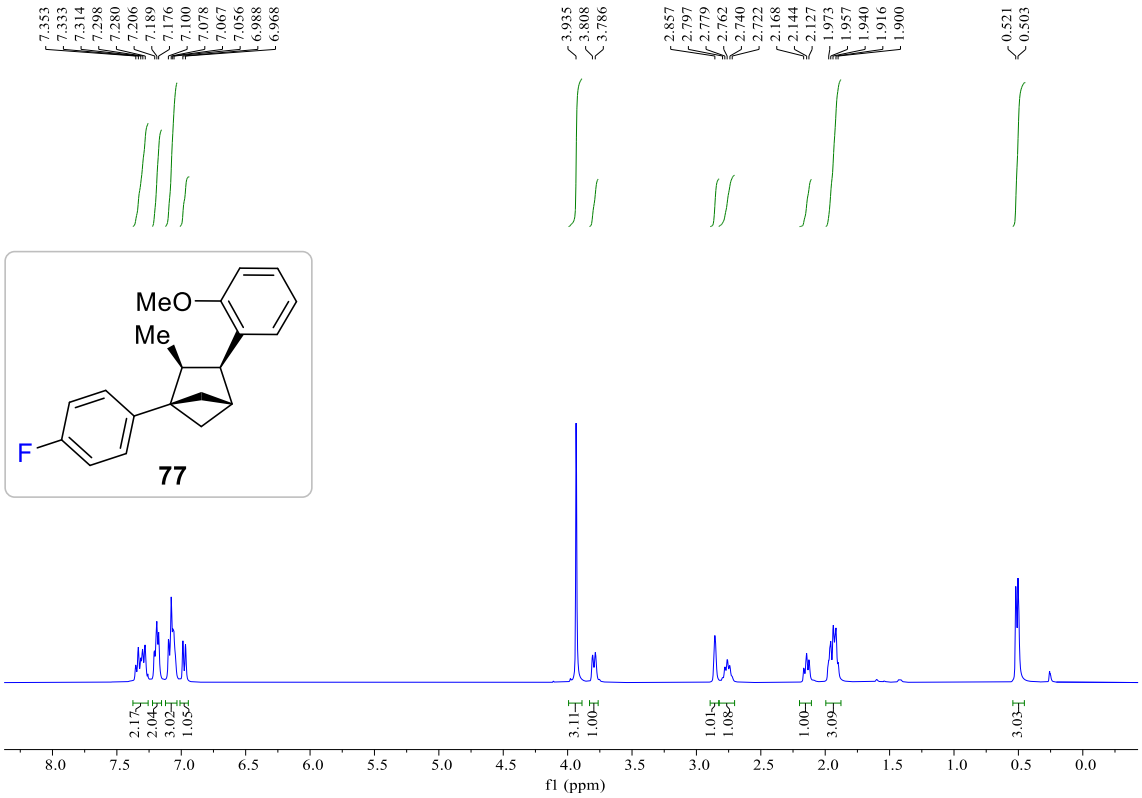
76, ^{13}C NMR (101 MHz, $CDCl_3$)



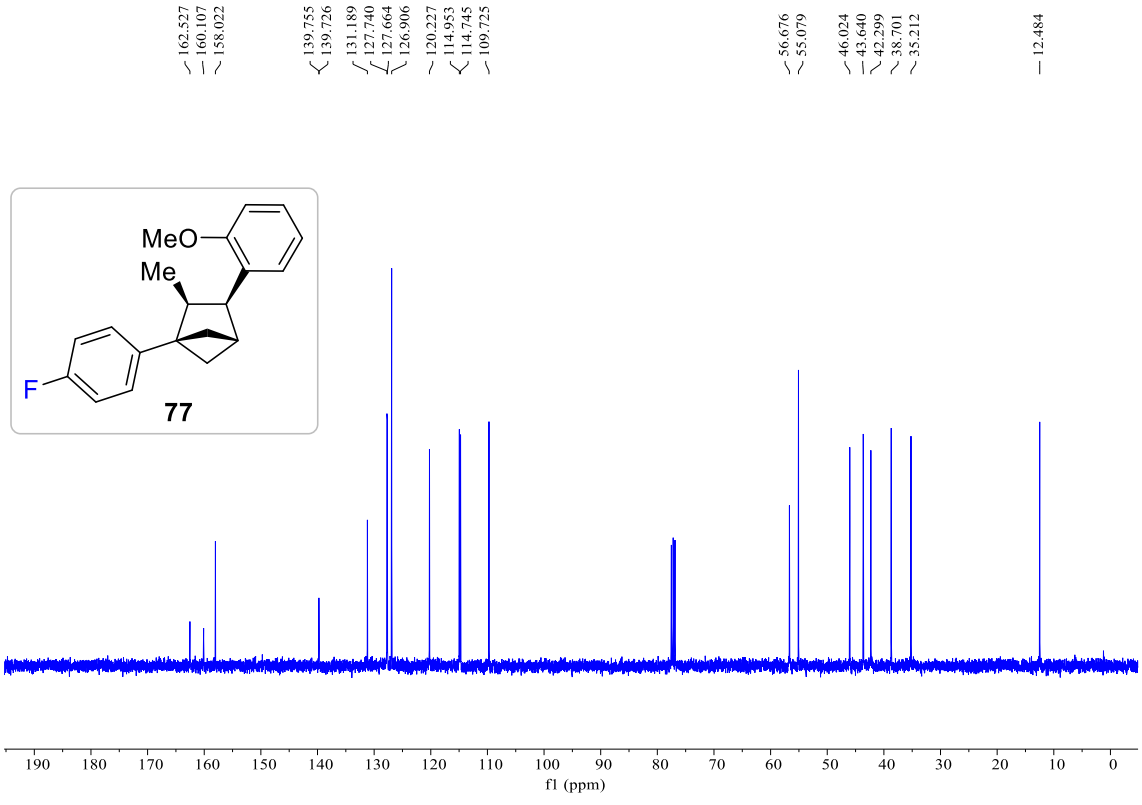
76, ^{19}F NMR (376 MHz, $CDCl_3$)



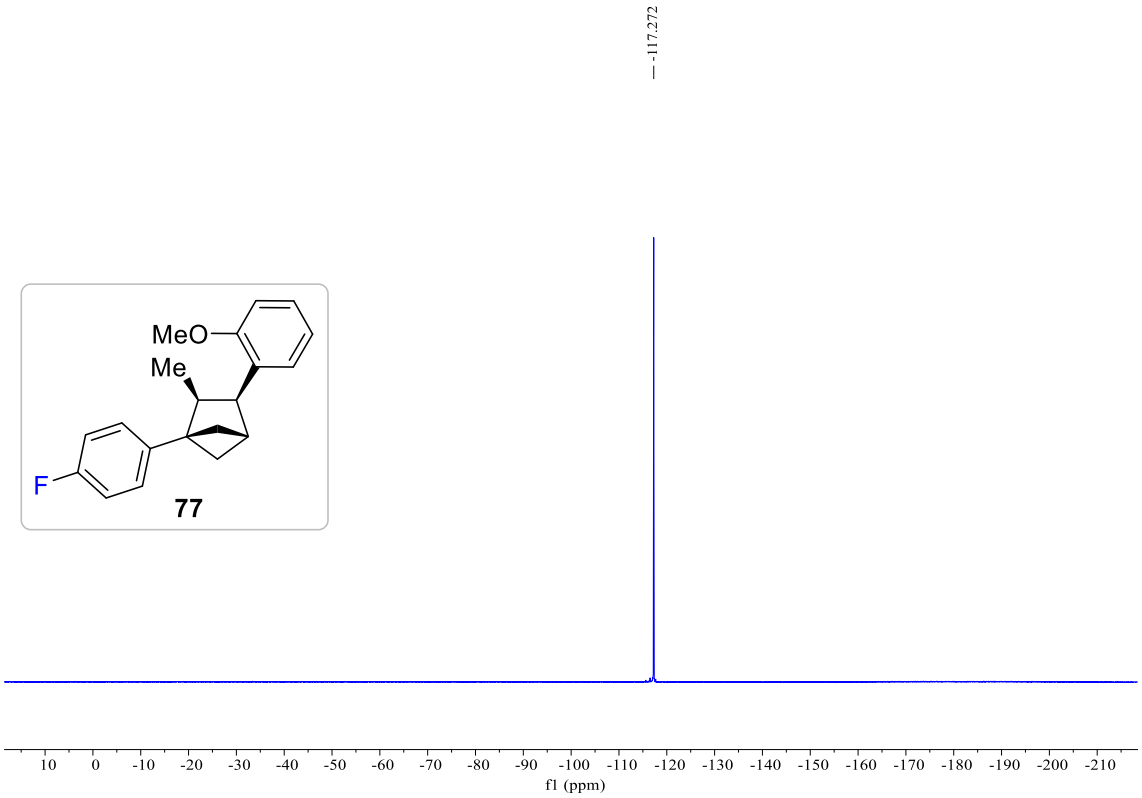
77, ^{1}H NMR (400 MHz, $CDCl_3$)



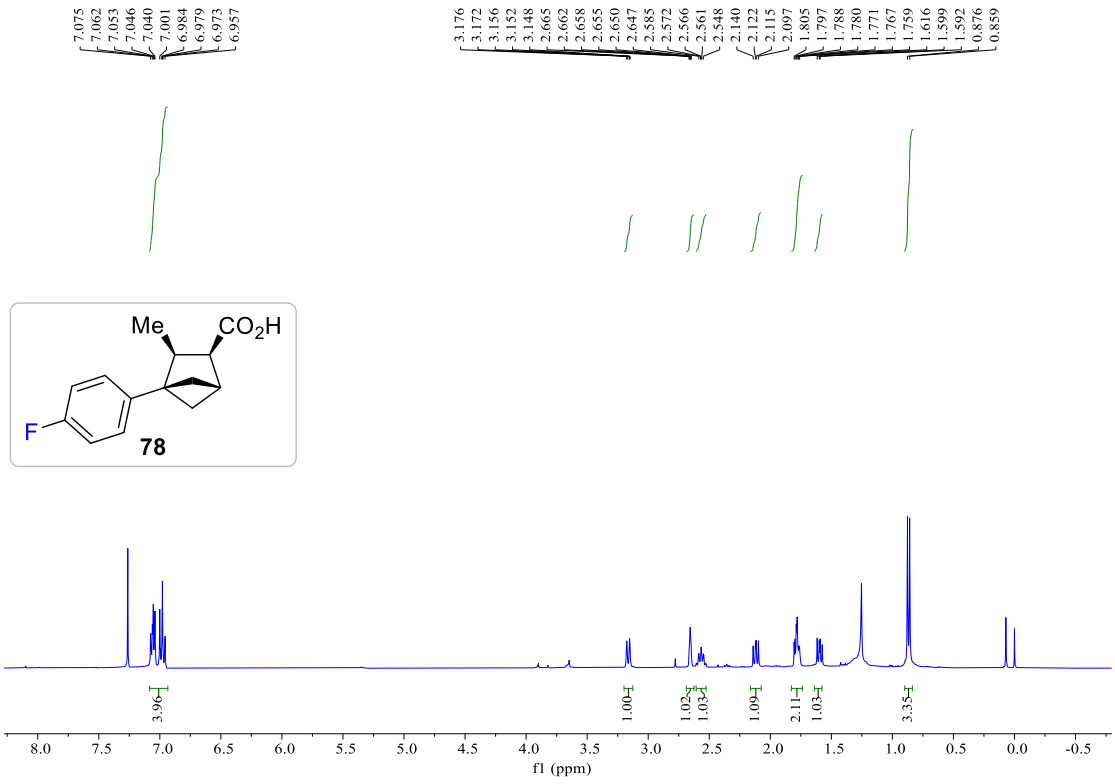
77, ^{13}C NMR (101 MHz, $CDCl_3$)



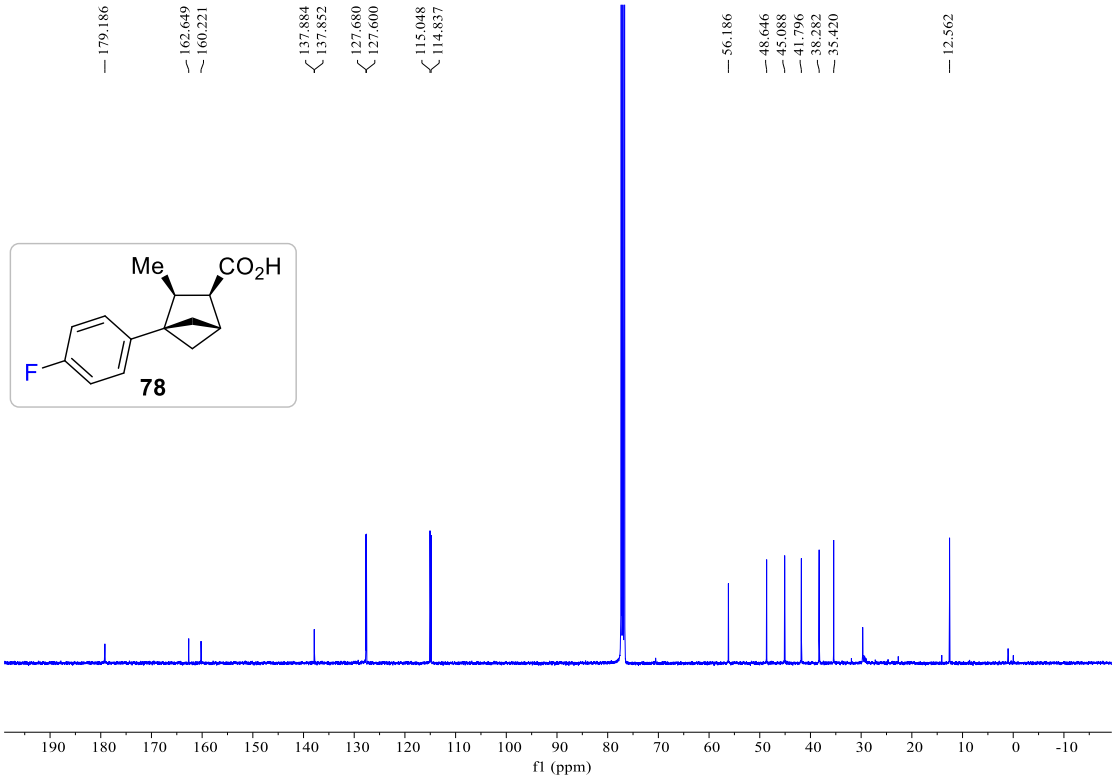
77, ^{19}F NMR (376 MHz, $CDCl_3$)



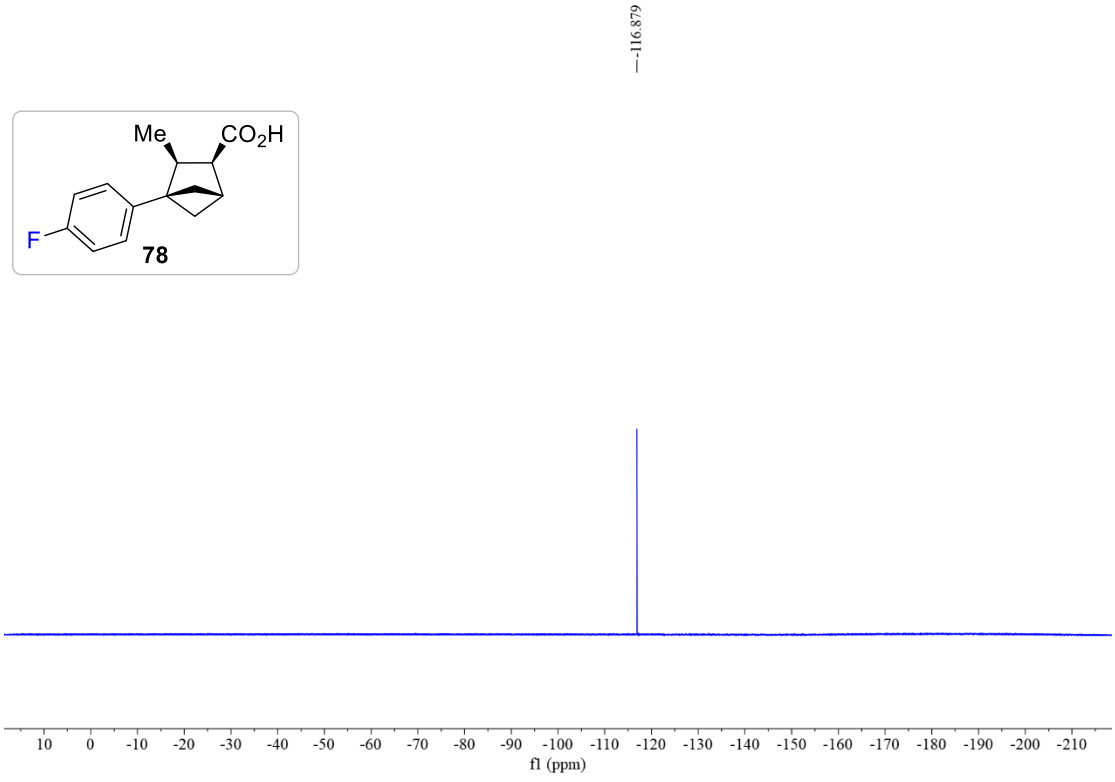
78, ^{1}H NMR (400 MHz, $CDCl_3$)



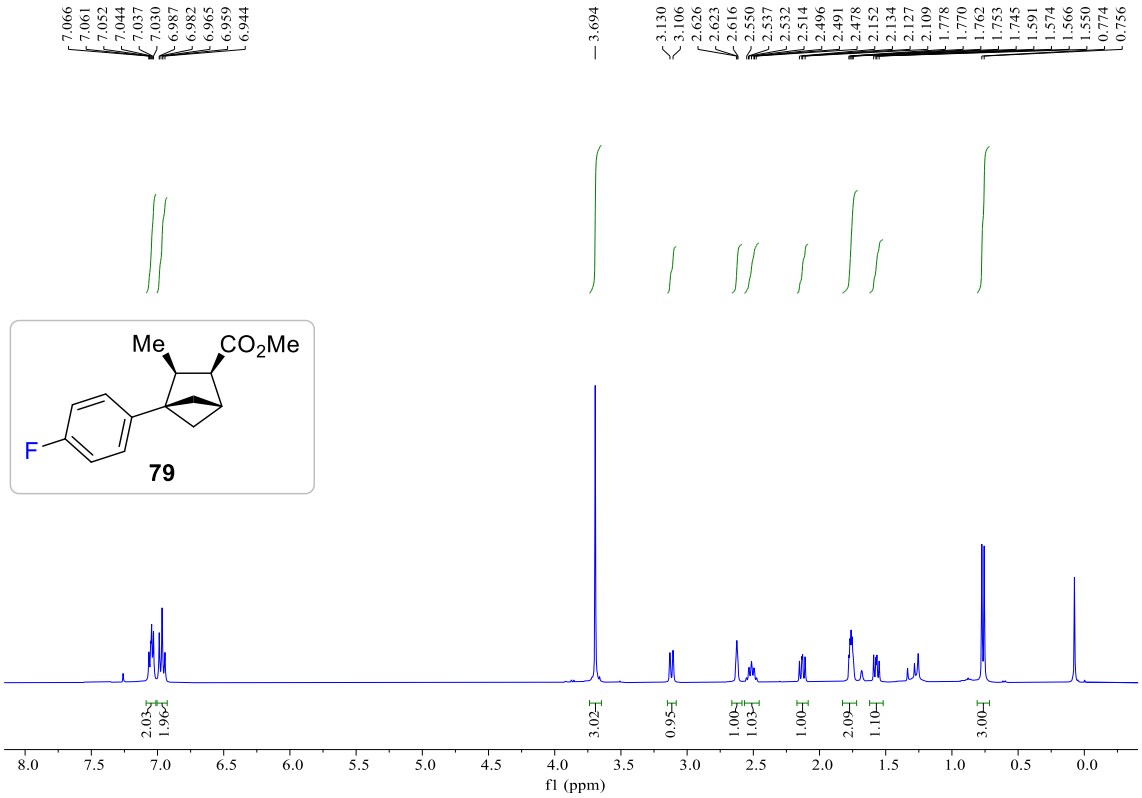
78, ^{13}C NMR (101 MHz, $CDCl_3$)



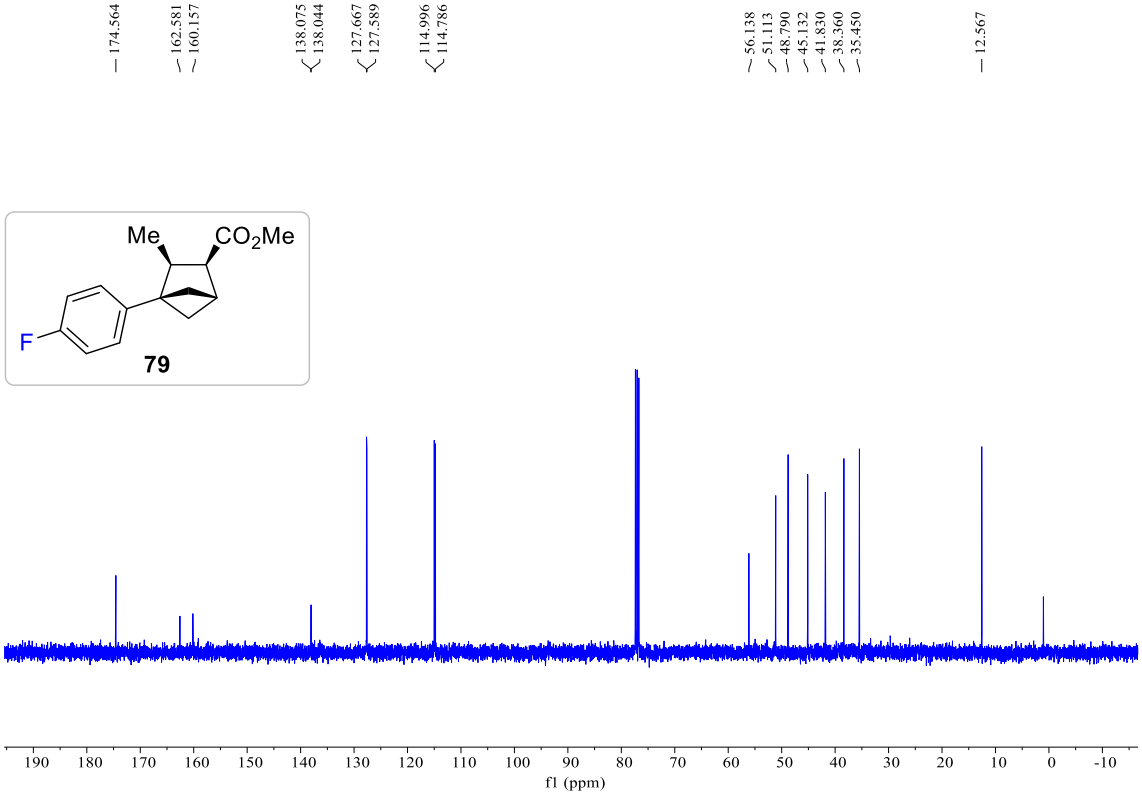
78, ^{19}F NMR (376 MHz, $CDCl_3$)



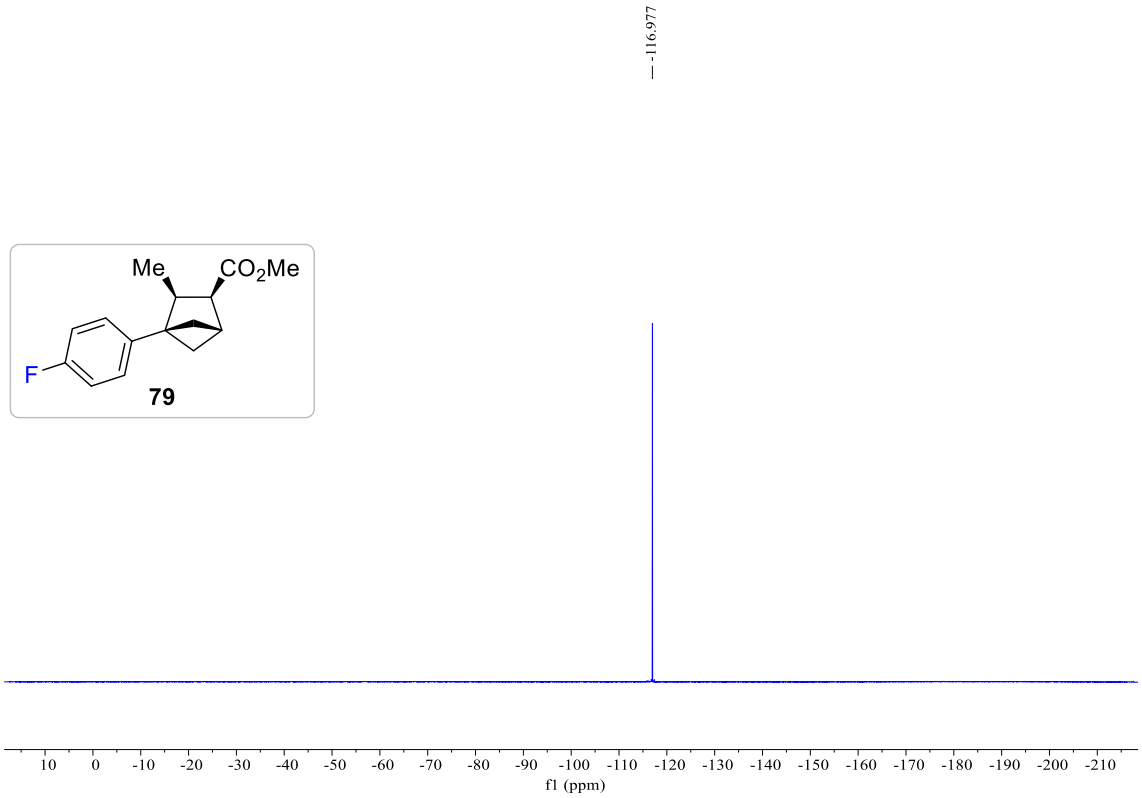
79, ^{1}H NMR (400 MHz, $CDCl_3$)



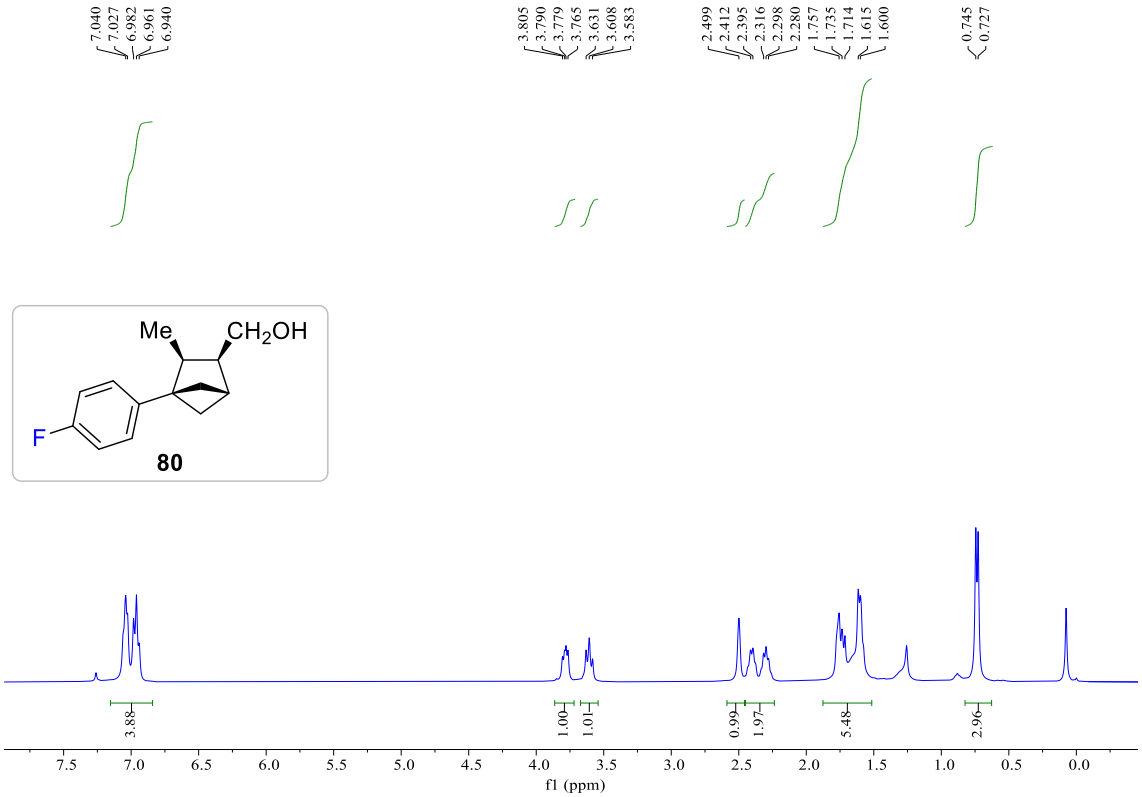
79, ^{13}C NMR (101 MHz, $CDCl_3$)



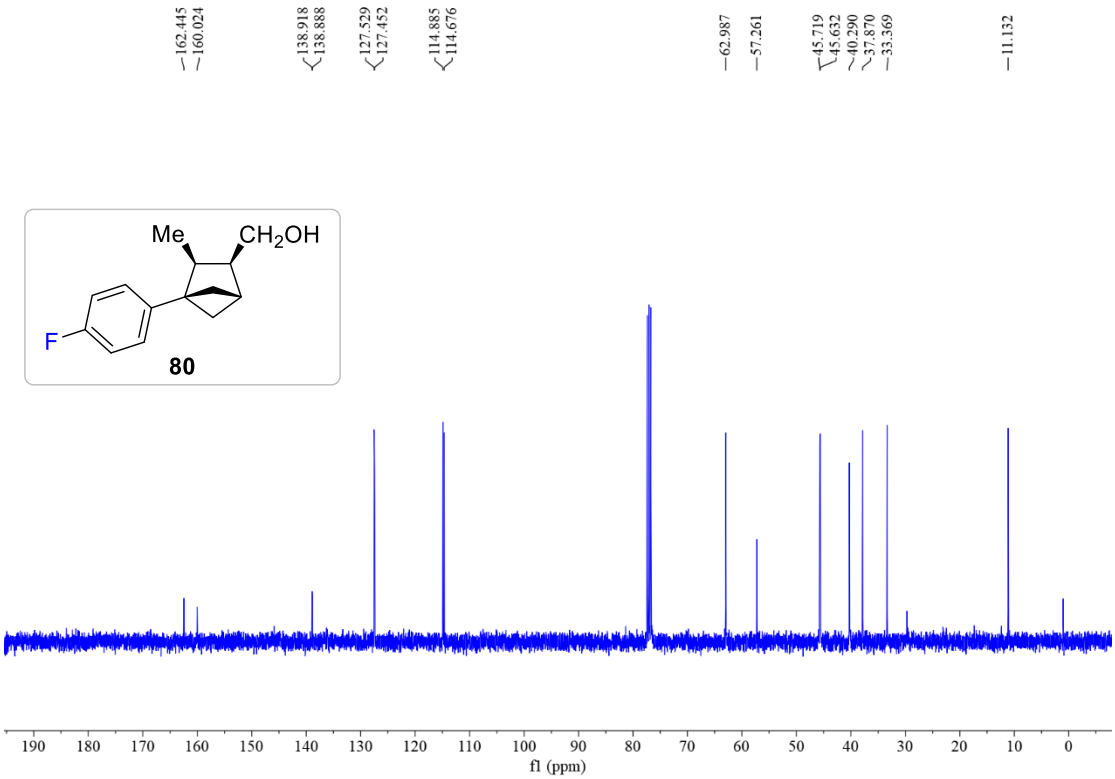
79, ^{19}F NMR (376 MHz, $CDCl_3$)



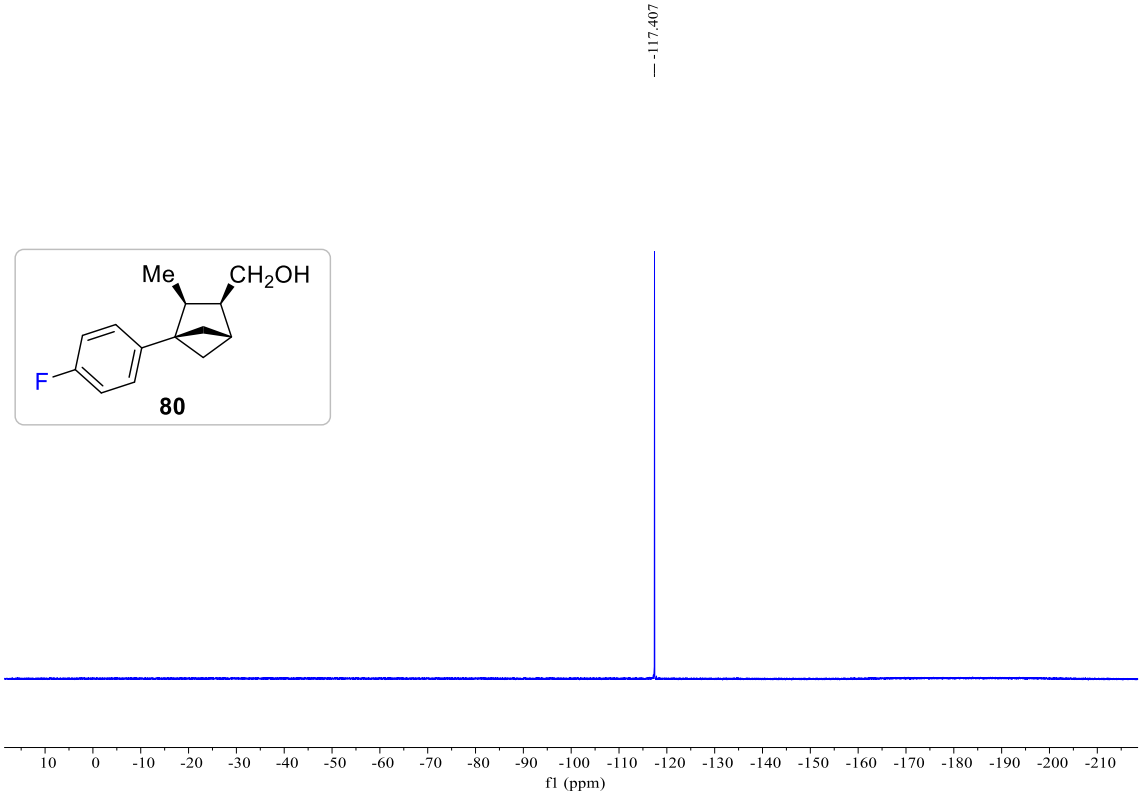
80, ^{1}H NMR (400 MHz, $CDCl_3$)



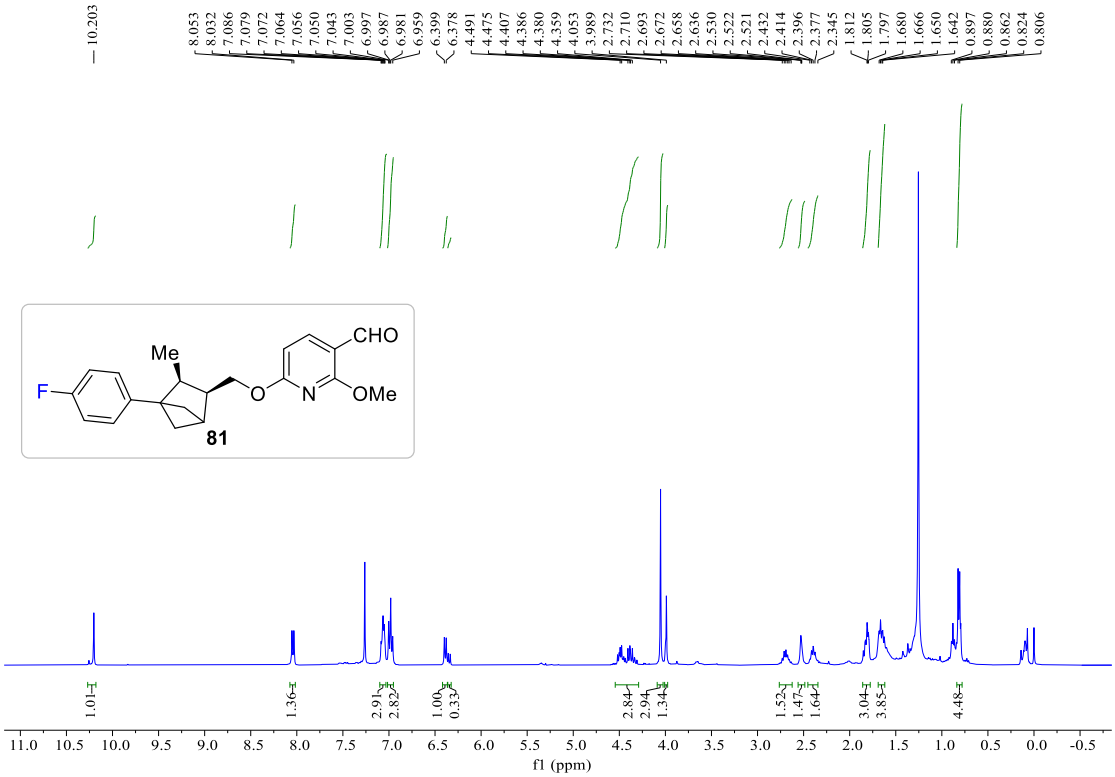
80, ^{13}C NMR (101 MHz, $CDCl_3$)



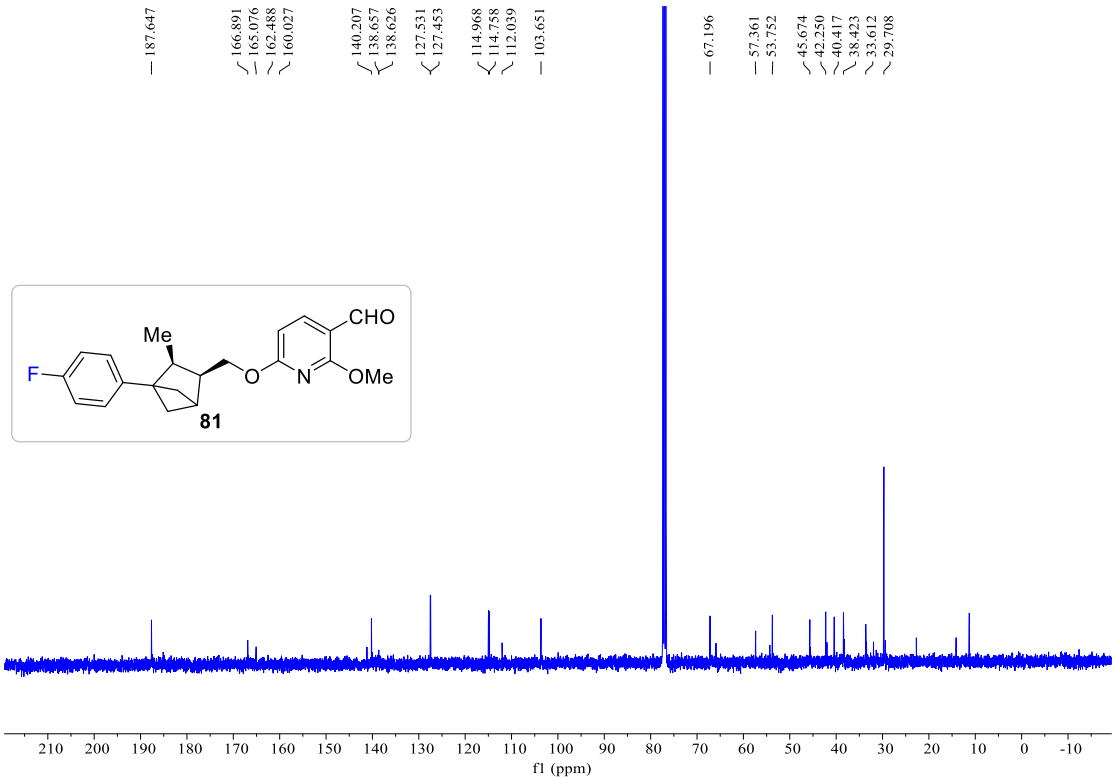
80, ^{19}F NMR (376 MHz, $CDCl_3$)



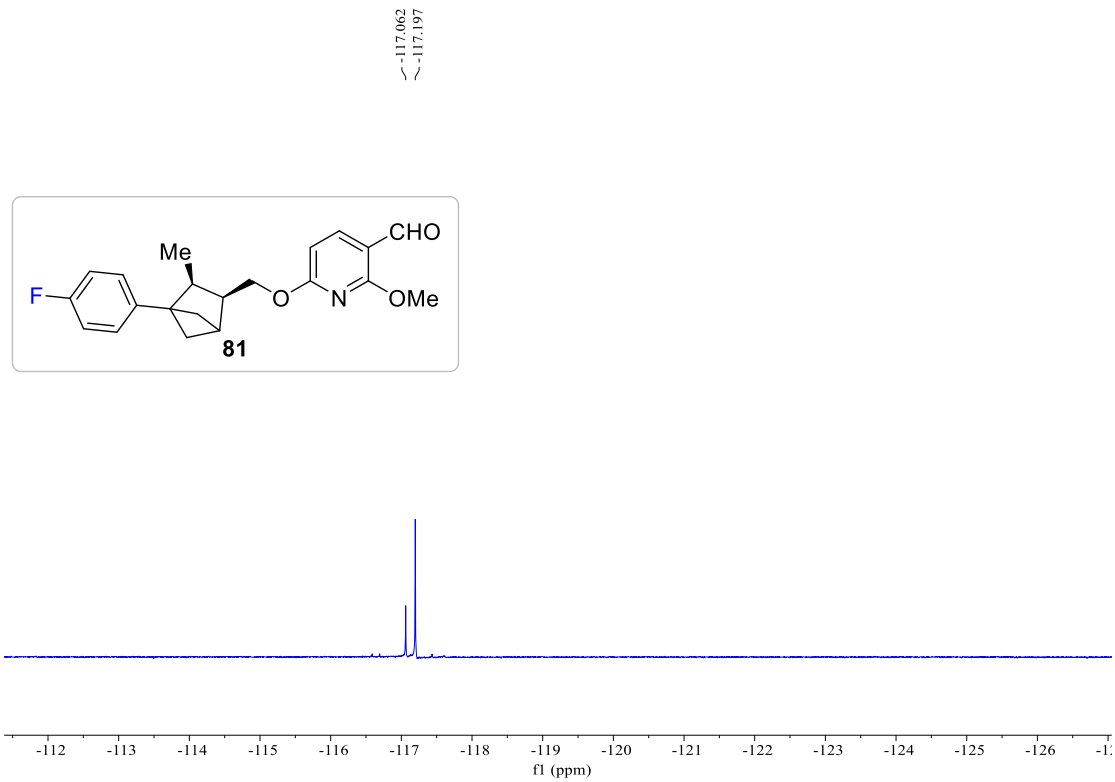
81, ^{1}H NMR (400 MHz, $CDCl_3$)



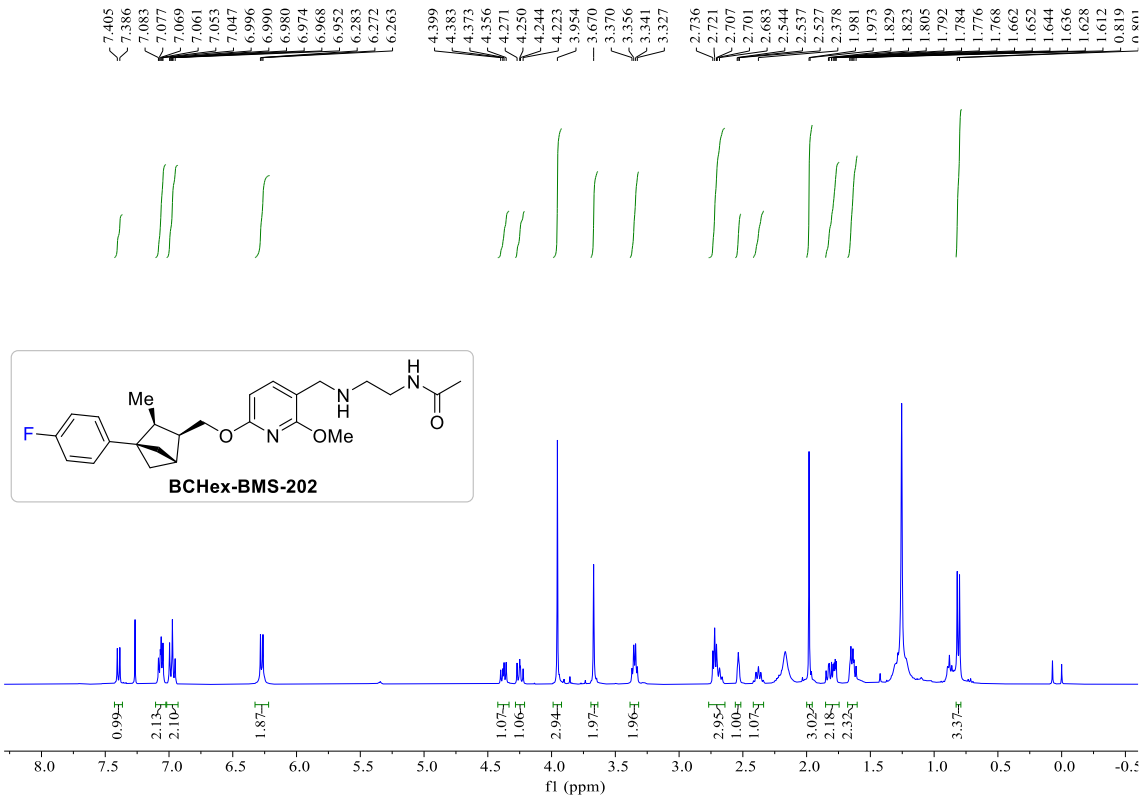
81, ^{13}C NMR (101 MHz, $CDCl_3$)



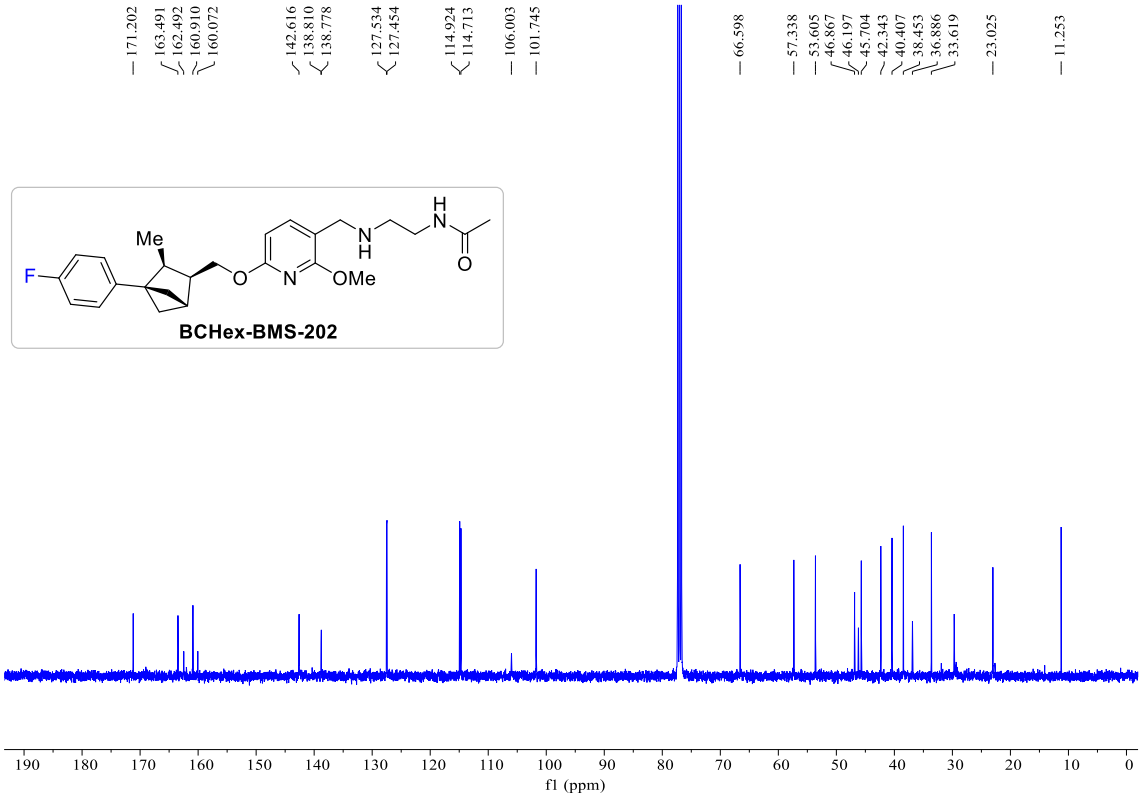
81, ^{19}F NMR (376 MHz, $CDCl_3$)



BCHex-BMS-202, ^{1}H NMR (400 MHz, $CDCl_3$)



BCHex-BMS-202, ^{13}C NMR (101 MHz, $CDCl_3$)



BCHex-BMS-202, ^{19}F NMR (376 MHz, $CDCl_3$)