

Supporting Information

Organocatalytic Asymmetric Synthesis of Fluorinated Pyranopyrazoles

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1. General Information

All solvents and catalysts (C19–C20) were obtained from commercial sources and used without further purification unless otherwise noted. The chromatographic column adopts 200-300 mesh silica gel. The melting points were determined by a Micro Melting Point Analyzer Model XT-4 without correction. ^1H and ^{13}C NMR spectra were acquired with a Bruker Avance II spectrometer at 600 and 151 MHz. ^{19}F NMR spectra were acquired with a Bruker Avance II spectrometer at 565 MHz. HRMS was measured by ESI-TOF on the Bruker APEX IV mass spectrometer. HPLC analysis was performed using Chiralpak IA, IC on a Shimadzu SPD-20A detector (eluent = *n*-hexane/*i*-propanol). X-ray diffraction analysis of a single crystal was analyzed on the D8 Venture X-ray single crystal diffractometer to determine absolute configuration of the product. The specific rotations were measured with an Autopol III automatic polarimeter in a 1 dm cell at 20 °C. The concentration (c) is given in g/100 mL.

2. Experimental procedures

2.1 Synthetic routes of organocatalysts C10–C15, C18.

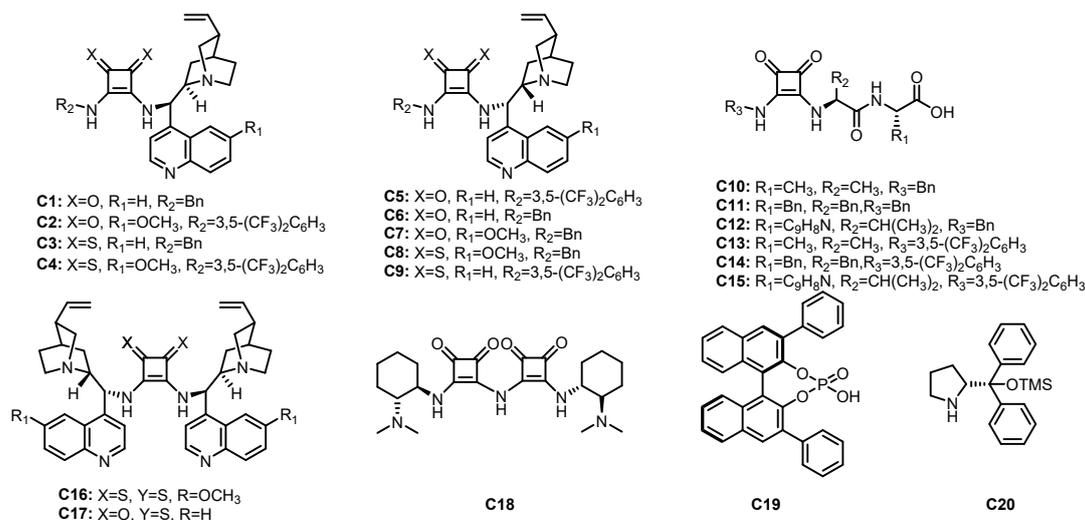
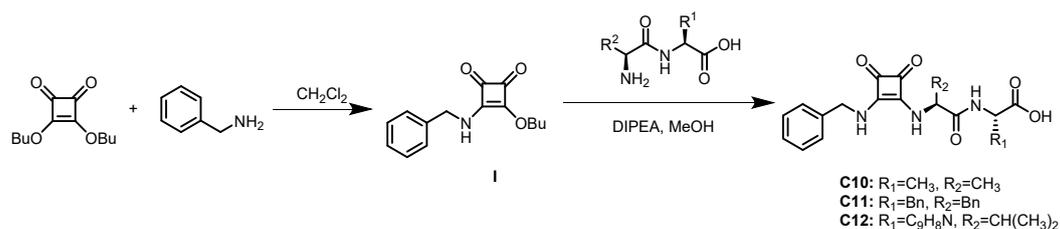


Figure S1. Structure of C1–C20.

Organocatalysts C1–C9, C16–C17 according to the literature procedures.¹⁻⁴

Organocatalysts C10–C15, C18 were prepared following the synthetic routes shown below.

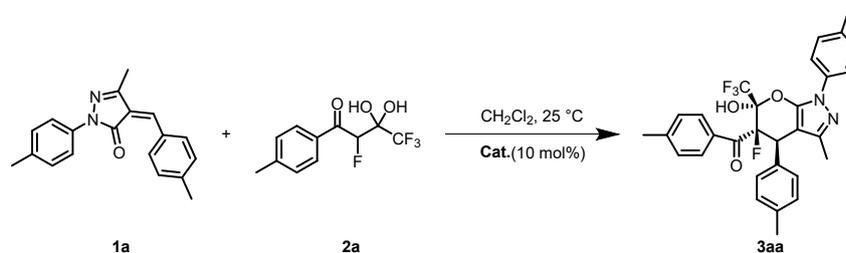


Step 1: A solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione (1.5 mmol, 1.0 eq) in CH₂Cl₂ was

(0.32 mmol, 2.0 eq) in MeOH was stirred at room temperature for 48 h. Upon complete conversion, the residue was purified by flash column chromatography on silica gel to give the product **C18**.

2.2 Optimization of Reaction Conditions

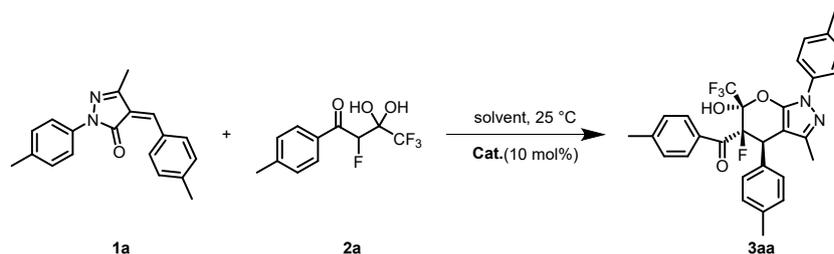
Table S1 Screening of catalysts^a



entry	catalyst	time (h)	yield ^b (%)	ee ^c (%)	dr ^d (%)
1	C1	24	23	-53	>20:1
2	C2	24	13	-57	>20:1
3	C3	24	17	-25	>20:1
4	C4	24	20	-55	>20:1
5	C5	24	37	67	>20:1
6	C6	24	30	47	>20:1
7	C7	24	16	45	>20:1
8	C8	24	22	63	>20:1
9	C9	24	20	55	>20:1
10	C10	120	14	3	>20:1
11	C11	120	9	0	>20:1
12	C12	120	11	4	>20:1
13	C13	120	9	0	>20:1
14	C14	120	11	3	>20:1
15	C15	120	13	6	>20:1
16	C16	24	9	11	>20:1
17	C17	24	7	-31	>20:1
18	C18	24	11	3	>20:1
19	C19	24	11	10	>20:1
20	C20	24	9	-3	>20:1

^aReaction conditions: **1a** (0.12 mmol, 1.2 eq), **2a** (0.1 mmol, 1.0 eq), Cat. (10 mol%). ^bIsolated yield.

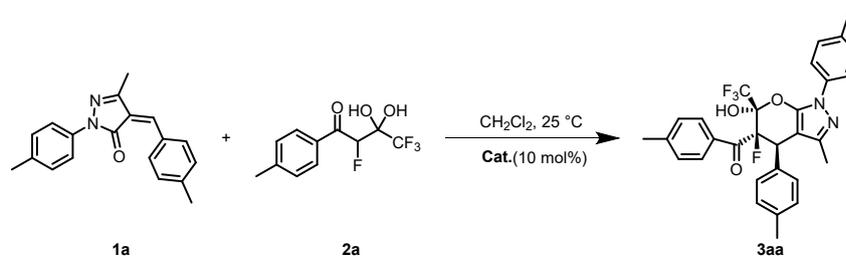
^cThe ee was determined by chiral HPLC analysis. ^dThe dr was determined by chiral HPLC analysis.

Table S2 Screening of solvent^a

entry	solvent	yield ^b (%)	ee ^c (%)	dr ^d (%)
1	CH ₂ Cl ₂	37	67	>20:1
2	MeOH	9	59	>20:1
3	CHCl ₃	2	85	>20:1
4	THF	13	63	>20:1
5	DMF	28	11	>20:1
6	DMSO	13	7	>20:1
7	Toluene	21	71	>20:1
8	EA	26	82	>20:1

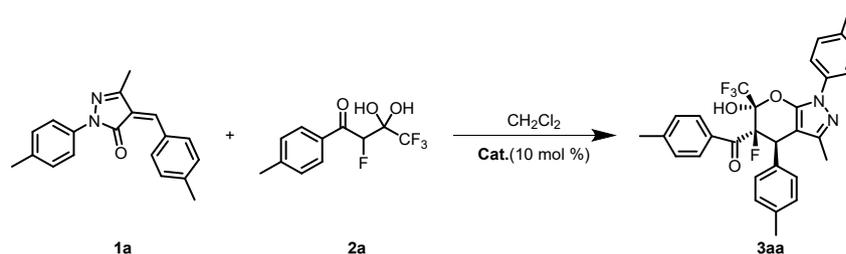
^aReaction conditions: **1a** (0.12 mmol, 1.2 eq), **2a** (0.1 mmol, 1.0 eq), **C5** (10 mol%). ^bIsolated yield.

^cThe ee was determined by chiral HPLC analysis. ^dThe dr was determined by chiral HPLC analysis.

Table S3 Screening equivalents of **1a**^a

entry	solvent	1a:2a	yield ^b (%)	ee ^c (%)	dr ^d (%)
1	CHCl ₃	2:1	7	87	>20:1
2	CH ₂ Cl ₂	2:1	68	90	>20:1
3	CH ₂ Cl ₂	1:2	30	79	>20:1
4	CH ₂ Cl ₂	1:1	37	67	>20:1
5	CH ₂ Cl ₂	4:1	58	79	>20:1

^aReaction conditions: **1a**, **2a**, **C5** (10 mol%). ^bIsolated yield. ^cThe ee was determined by chiral HPLC analysis. ^dThe dr was determined by chiral HPLC analysis.

Table S4 Screening of temperature^a

entry	temperature(°C)	time(h)	yield ^b (%)	ee ^c (%)	dr ^d (%)
1	0	120	14	87	>20:1
2	25	24	68	90	>20:1
3	35	24	67	85	>20:1

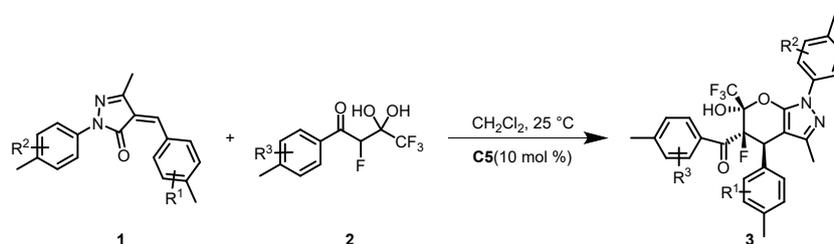
^aReaction conditions: **1a** (0.2 mmol, 2.0 eq), **2a** (0.1 mmol, 1.0 eq), **C5** (10 mol%). ^bIsolated yield.

^cThe ee was determined by chiral HPLC analysis. ^dThe dr was determined by chiral HPLC analysis.

2.3 General procedure synthesis of pyrazolopyran compounds **3**.

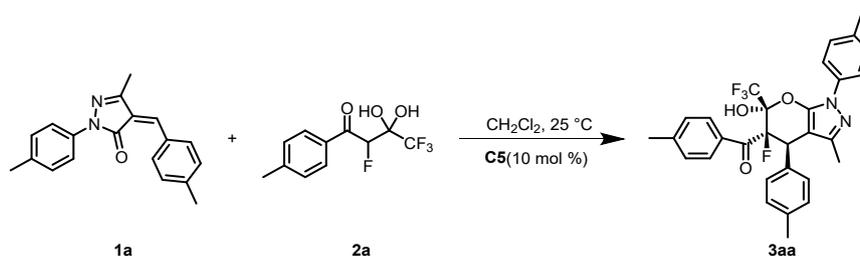
The α -trifluoromethyl β -fluorinated *gem*-diols **2** were prepared according to the reported procedures.^{5, 6}

The α , β -unsaturated pyrazolones **1** were prepared according to the reported procedure.⁷ The *Z*-configuration of α , β -unsaturated pyrazolone **1** was determined based on NOESY spectroscopy, as described in section 12.



The mixture of α -trifluoromethyl β -fluorinated *gem*-diols (**2**, 0.1 mmol, 1.0 eq), α , β -unsaturated pyrazolones (**1**, 0.2 mmol, 2.0 eq) and **C5** (6 mg, 0.01 mmol, 10 mol%) were stirred at 25 °C for 24 h and monitored by TLC. After full conversion, the reaction mixture was concentrated and purified by silica gel column chromatography with petroleum ether and EtOAc.

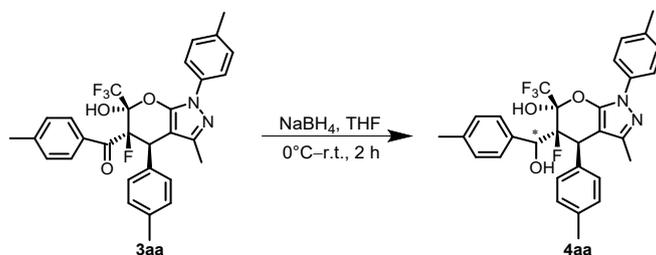
2.4 Large-Scale Experiment



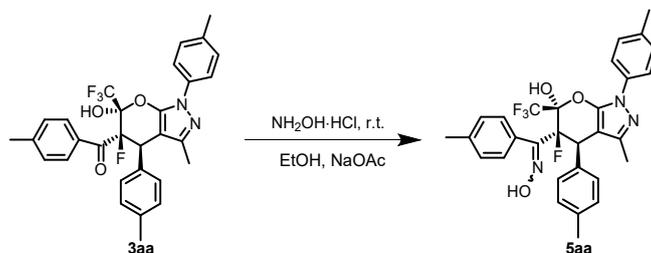
The mixture of α -trifluoromethyl β -fluorinated *gem*-diols (**2a**, 1.0 mmol, 1.0 eq), α , β -unsaturated

pyrazolones (**1a**, 2.0 mmol, 2.0 eq) and **C5** (60 mg, 0.1 mmol, 10 mol%) were stirred at 25 °C for 24 h and monitored by TLC. After full conversion, the reaction mixture was concentrated and purified by silica gel column chromatography with petroleum ether and EtOAc.

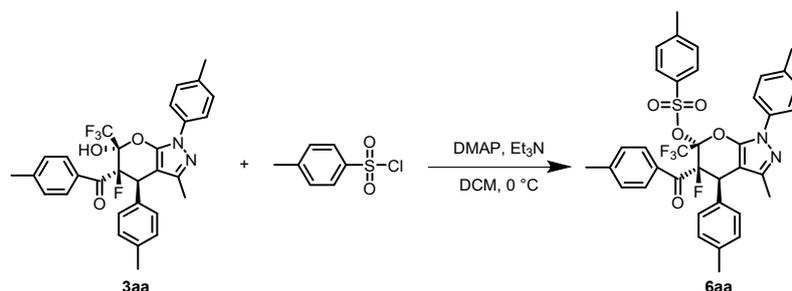
2.5 Derivatizations of product **3aa**.



The product **3aa** (0.1 mmol, 1.0 eq) in THF was added NaBH₄ (1.5 mmol, 15 eq) in the 0 °C and the resulting mixture was stirred at 25 °C for 2 h. After full conversion, the mixture was quenched by 1N HCl, extracted with CH₂Cl₂. The residue was concentrated and the was purified by silica gel column chromatography with petroleum ether and EtOAc.



Hydroxylamine hydrochloride (0.5 mmol, 1.0 eq) was dissolved in EtOH. Sodium acetate (0.7 mmol, 7.0 eq) was dissolved in water and added to the reaction mixture. A solution of **3aa** (0.1 mmol, 1.0 eq) in EtOH was then introduced. The resulting suspension was stirred at room temperature for 18 h. After full conversion, the mixture was concentrated, extracted with EtOAc, dried over anhydrous Na₂SO₄. The residue was concentrated and the was purified by silica gel column chromatography with petroleum ether and EtOAc.

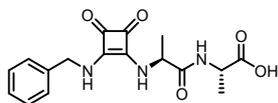


The product **3aa** (0.05 mmol, 1.0 eq) in CH₂Cl₂ was added Et₃N (2.5 mmol, 50.0 eq) slowly. *p*-Toluenesulfonyl Chloride (0.06 mmol, 1.2 eq) and DMAP (0.1 mmol, 2.0 eq) were then added and the temperature was maintained at 0 °C for 30 min. After full conversion, the reaction mixture was diluted with CH₂Cl₂, washed with saturated sodium bicarbonate solution. The residue was concentrated and the was purified by silica gel column chromatography with petroleum ether and EtOAc.

3. References

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4. Characterization data of catalysts C10–C15, C18.



C10: (2-(benzylamino)-3,4-dioxocyclobut-1-en-1-yl)-L-alanyl-L-alanine

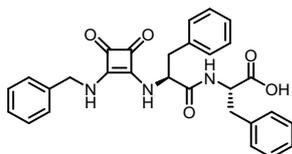
According to the synthetic routes, C10 was obtained in 70% yield as a white solid.

M. p. 236 – 237 °C; $[\alpha]_D^{25} = -5$ (c = 0.2, MeOH).

¹H NMR (600 MHz, DMSO-*d*₆) δ 8.54 (s, 1H), 8.09 (s, 1H), 7.82 (s, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.35 – 7.29 (m, 3H), 4.73 (d, *J* = 6.8 Hz, 2H), 4.21 (q, *J* = 7.2 Hz, 1H), 3.17 (s, 1H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.28 (d, *J* = 7.3 Hz, 3H).

¹³C NMR (150 MHz, DMSO-*d*₆) δ 183.2, 182.6, 174.3, 170.8, 168.1, 167.2, 139.3, 129.1, 128.0, 127.9, 60.2, 55.3, 47.3, 17.5, 14.5.

HRMS (ESI) *m/z* calcd. for C₁₇H₂₀N₃O₅ (M+H)⁺:346.1397, found 346.1399.



C11: (2-(benzylamino)-3,4-dioxocyclobut-1-en-1-yl)-L-phenylalanyl-L-phenylalanine

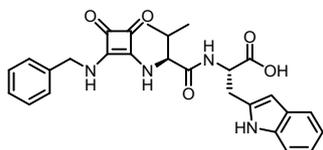
According to the synthetic routes, C11 was obtained in 80% yield as a white solid.

M. p. 223 – 224 °C; $[\alpha]_D^{25} = -48$ (c = 0.1, MeOH).

¹H NMR (600 MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 7.94 (s, 1H), 7.63 (s, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.33 – 7.26 (m, 3H), 7.22 (d, *J* = 4.8 Hz, 4H), 7.20 (s, 1H), 7.17 (t, *J* = 8.5 Hz, 5H), 4.93 (s, 1H), 4.68 (t, *J* = 6.1 Hz, 1H), 4.47 (td, *J* = 8.6, 4.8 Hz, 1H), 3.18 (s, 1H), 3.13 (d, *J* = 4.5 Hz, 1H), 3.12 – 3.10 (m, 1H), 2.91 (dd, *J* = 13.9, 9.4 Hz, 1H), 2.83 (dd, *J* = 13.8, 8.2 Hz, 1H).

¹³C NMR (150 MHz, DMSO-*d*₆) δ 183.3, 182.5, 173.2, 170.8, 167.9, 167.4, 139.3, 138.0, 130.1, 129.5, 129.1, 128.6, 128.5, 127.9, 126.9, 126.8, 60.2, 55.3, 47.2, 37.2.

HRMS (ESI) *m/z* calcd. for C₃₀H₂₇F₄N₂O₃ (M+H)⁺:498.2023, found 498.2037.



C12: (2-(benzylamino)-3,4-dioxocyclobut-1-en-1-yl)-L-valyl-L-tryptophan

According to the synthetic routes, C12 was obtained in 88% yield as a white solid.

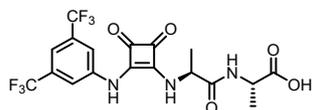
M. p. 167 – 168 °C; $[\alpha]_D^{25} = -30$ (c = 0.2, MeOH).

¹H NMR (600 MHz, DMSO-*d*₆) δ 10.84 (s, 1H), 8.64 (s, 1H), 8.00 (s, 1H), 7.68 (s, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.33 (dd, *J* = 11.8, 7.7 Hz, 3H), 7.14 (s, 1H), 7.04 (t, *J* = 7.6 Hz, 1H),

6.94 (t, $J = 7.5$ Hz, 1H), 4.76 (dd, $J = 14.6, 6.5$ Hz, 1H), 4.69 (dd, $J = 14.7, 5.8$ Hz, 1H), 4.62 (dd, $J = 9.8, 5.3$ Hz, 1H), 4.47 (q, $J = 7.1$ Hz, 1H), 3.22 (d, $J = 4.9$ Hz, 1H), 3.18 (s, 1H), 3.04 (dd, $J = 14.8, 8.9$ Hz, 1H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.82 (d, $J = 6.9$ Hz, 3H).

^{13}C NMR (150 MHz, $\text{DMSO-}d_6$) δ 183.2, 182.5, 173.6, 170.7, 167.9, 167.7, 139.2, 136.5, 129.2, 128.1, 128.0, 127.6, 123.9, 121.4, 118.8, 118.6, 111.8, 110.5, 61.0, 53.7, 47.3, 32.9, 27.4, 19.1, 17.3.

HRMS (ESI) m/z calcd. for $\text{C}_{27}\text{H}_{29}\text{N}_4\text{O}_5$ ($\text{M}+\text{H}$) $^+$:489.2132, found 489.2137.



C13: (2-((3,5-bis(trifluoromethyl)phenyl)amino)-3,4-dioxocyclobut-1-en-1-yl)-L-alanyl-L-alanine

According to the synthetic routes, **C13** was obtained in 75% yield as a white solid.

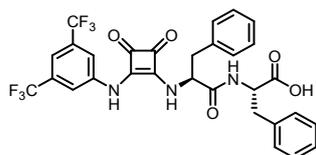
M. p. 156 – 157 °C; $[\alpha]_D^{25} = -5$ ($c = 0.2$, MeOH).

^1H NMR (600 MHz, CD_3OD) δ 8.00 (s, 2H), 7.44 (s, 1H), 4.32 (q, $J = 7.3$ Hz, 1H), 1.46 (d, $J = 7.0$ Hz, 3H), 1.34 (d, $J = 7.3$ Hz, 3H).

^{13}C NMR (150 MHz, CD_3OD) δ 184.2, 181.0, 174.7, 172.0, 168.9, 163.3, 141.0, 132.5 (q, $J = 33.4$ Hz), 123.2 (q, $J = 272.0$ Hz), 117.9, 115.2, 115.2, 115.1, 52.8, 19.8, 16.2.

^{19}F NMR (565 MHz, CD_3OD) δ -64.63.

HRMS (ESI) m/z calcd. for $\text{C}_{18}\text{H}_{16}\text{F}_6\text{N}_3\text{O}_5$ ($\text{M}+\text{H}$) $^+$:468.0989, found 468.0996.



C14: (2-((3,5-bis(trifluoromethyl)phenyl)amino)-3,4-dioxocyclobut-1-en-1-yl)-L-phenylalanyl-L-phenylalanine

According to the synthetic routes, **C14** was obtained in 88% yield as a white solid.

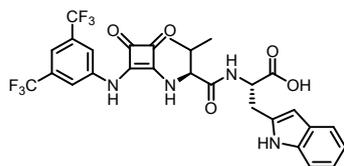
M. p. 229 – 230 °C; $[\alpha]_D^{25} = -75$ ($c = 0.2$, MeOH).

^1H NMR (600 MHz, CD_3OD) δ 7.94 (s, 2H), 7.44 (s, 1H), 7.11 (d, $J = 6.1$ Hz, 4H), 7.09 (s, 3H), 7.08 (s, 1H), 7.06 (d, $J = 6.3$ Hz, 1H), 6.97 (t, $J = 7.0$ Hz, 1H), 4.96 – 4.92 (m, 1H), 4.65 (dd, $J = 9.6, 4.9$ Hz, 1H), 3.16 (d, $J = 5.3$ Hz, 1H), 3.14 (t, $J = 4.5$ Hz, 1H), 2.85 (td, $J = 12.8, 9.0$ Hz, 2H).

^{13}C NMR (150 MHz, CD_3OD) δ 183.9, 180.8, 173.1, 170.6, 168.7, 162.8, 140.9, 136.9, 135.7, 132.5 (q, $J = 33.6$ Hz), 129.4, 128.9, 128.1, 128.0, 126.7, 126.3, 123.2 (q, $J = 271.9$ Hz), 117.8, 115.2, 58.1, 53.8, 39.8, 37.1.

^{19}F NMR (565 MHz, CD_3OD) δ -64.66.

HRMS (ESI) m/z calcd. for $\text{C}_{30}\text{H}_{24}\text{F}_6\text{N}_3\text{O}_5$ ($\text{M}+\text{H}$) $^+$:620.1615, found 620.1633.



C15: (2-((3,5-bis(trifluoromethyl)phenyl)amino)-3,4-dioxocyclobut-1-en-1-yl)-L-valyl-L-tryptophan

According to the synthetic routes, **C15** was obtained in 87% yield as a white solid.

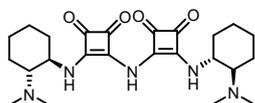
M. p. 167 - 168 °C; $[\alpha]_D^{25} = -98$ (c = 0.2, MeOH).

¹H NMR (600 MHz, CD₃OD) δ 8.01 (s, 2H), 7.48 (s, 1H), 7.43 (d, $J = 8.9$ Hz, 1H), 7.06 (d, $J = 8.9$ Hz, 1H), 6.99 (s, 1H), 6.84 – 6.74 (m, 2H), 4.71 (d, $J = 4.6$ Hz, 1H), 4.38 (s, 1H), 3.33 (dd, $J = 14.7, 4.6$ Hz, 1H), 3.04 (dd, $J = 14.7, 9.1$ Hz, 1H), 1.97 (q, $J = 6.8$ Hz, 1H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H).

¹³C NMR (150 MHz, CD₃OD) δ 183.9, 180.9, 170.6, 169.0, 162.7, 141.0, 136.5, 132.5 (q, $J = 34.3$ Hz), 132.4, 127.6, 126.0, 124.2, 123.3 (q, $J = 271.9$ Hz), 122.4, 120.7, 120.6, 118.4, 117.9, 115.1, 110.7, 109.8, 62.8, 53.8, 32.0, 27.3, 17.9, 16.6.

¹⁹F NMR (565 MHz, CD₃OD) δ -64.66.

HRMS (ESI) m/z calcd. for C₂₈H₂₅F₆N₄O₅ (M+H)⁺:611.1724, found 611.1738.



C18: 3-(((1R,2R)-2-(dimethylamino)cyclohexyl)amino)-4-(((1R,2S)-2-(dimethylamino)cyclohexyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)cyclobut-3-ene-1,2-dione

According to the synthetic routes, **C18** was obtained in 92% yield as a yellow solid.

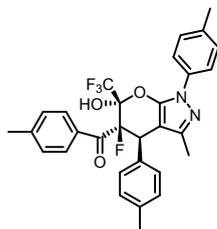
M. p. 242 – 243 °C; $[\alpha]_D^{25} = -88$ (c = 0.2, CH₂Cl₂).

¹H NMR (600 MHz, CD₃OD) δ 4.14 (s, 1H), 3.28 (s, 1H), 3.13 – 2.97 (m, 2H), 2.73 (s, 1H), 2.65 (s, 1H), 2.57 (s, 9H), 2.10 – 2.00 (m, 4H), 1.84 (s, 1H), 1.82 (s, 3H), 1.72 (s, 2H), 1.54 – 1.47 (m, 2H), 1.32 (s, 4H), 1.25 – 1.18 (m, 1H).

¹³C NMR (150 MHz, CD₃OD) δ 188.5, 186.0, 178.1, 174.4, 171.6, 169.4, 131.0, 128.5, 67.8, 53.6, 48.5, 46.3, 39.2, 34.2, 33.9, 24.1, 24.0, 22.4, 22.3, 21.2.

HRMS (ESI) m/z calcd. for C₂₄H₃₆N₅O₄ (M+H)⁺:458.2762, found 458.2768.

5. Characterization data of products 3 and 4aa–6aa.



3aa: ((4*R*,5*S*,6*S*)-5-fluoro-6-hydroxy-3-methyl-1,4-di-*p*-tolyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3aa** was obtained in 68% yield with 90% ee and >20:1 dr as a white solid.

M. p. 131 – 132 °C; $[\alpha]_D^{25} = -7$ ($c = 0.3$, CH₂Cl₂).

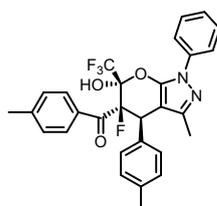
¹H NMR (600 MHz, CDCl₃) δ 7.62 (d, $J = 8.1$ Hz, 2H), 7.32 (s, 1H), 7.26 (s, 5H), 7.20 (d, $J = 9.1$ Hz, 1H), 7.02 (d, $J = 8.1$ Hz, 2H), 6.92 (s, 1H), 4.75 (d, $J = 29.6$ Hz, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H), 1.72 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 202.5 (d, $J = 23.9$ Hz), 146.3, 145.6, 144.8, 138.5, 136.0, 135.5, 132.2, 132.1, 130.3, 130.1, 130.1, 129.7, 129.4, 128.9, 121.6 (q, $J = 288.5$ Hz), 120.6, 97.9 (q, $J = 23.7$ Hz), 95.6, 95.2 (d, $J = 216.4$ Hz), 46.3 (d, $J = 19.4$ Hz), 21.8, 21.1, 21.0, 13.7.

¹⁹F NMR (565 MHz, CDCl₃) δ -79.03 (d, $J = 14.3$ Hz), -180.45 (q, $J = 14.5$ Hz).

HRMS (ESI) m/z calcd. for C₃₀H₂₇F₄N₂O₃ (M+H)⁺: 539.1952, found 539.1967.

Enantiomeric excess is 90% determined by HPLC (Chiralpak IC, Hexane/Isopropanol 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $tr = 4.53$ min; minor isomer: $tr = 3.97$ min.



3ba: ((4*R*,5*S*,6*S*)-5-fluoro-6-hydroxy-3-methyl-1-phenyl-4-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3ba** was obtained in 80% yield with 89% ee and >20:1 dr as a white solid.

M. p. 127 – 128 °C; $[\alpha]_D^{25} = -13$ ($c = 0.2$, CH₂Cl₂).

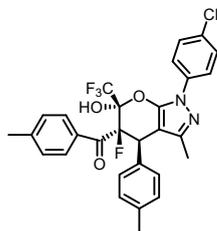
¹H NMR (600 MHz, CDCl₃) δ 7.76 (d, $J = 7.8$ Hz, 2H), 7.46 – 7.42 (m, 2H), 7.32 (s, 1H), 7.27 – 7.23 (m, 3H), 7.19 (s, 1H), 7.02 (d, $J = 8.1$ Hz, 2H), 6.92 (s, 2H), 4.76 (d, $J = 29.5$ Hz, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 1.73 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 202.5 (d, $J = 24.1$ Hz), 146.6, 145.6, 145.0, 138.5, 138.0, 132.2, 132.1, 130.3, 130.1, 130.1, 129.4, 129.1, 128.9, 126.2, 121.4 (q, $J = 288.7$ Hz), 120.5, 97.9 (q, $J = 24.6$ Hz), 95.9, 95.2 (d, $J = 216.7$ Hz), 46.3 (d, $J = 19.3$ Hz), 21.7, 21.1, 13.7.

¹⁹F NMR (565 MHz, CDCl₃) δ -79.02 (d, $J = 14.6$ Hz), -180.39 (q, $J = 14.6$ Hz).

HRMS (ESI) m/z calcd. for $C_{29}H_{25}F_4N_2O_3$ (M+H)⁺:525.1796, found.525.1807

Enantiomeric excess is 89% determined by HPLC (Chiralpak IC, Hexane/Isopropanol 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: t_r = 6.68 min; minor isomer: t_r = 5.68 min.



3ca: ((4R,5S,6S)-1-(4-chlorophenyl)-5-fluoro-6-hydroxy-3-methyl-4-(p-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-5-yl)(p-tolyl)methanone

According to the general procedure, **3ca** was obtained in 70% yield with 88% ee and >20:1 dr as a white solid.

M. p. 91 – 92 °C; $[\alpha]_D^{25} = -22$ (c = 0.1, CH_2Cl_2).

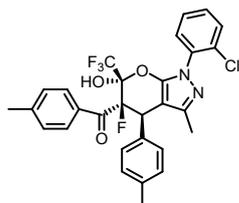
¹H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, J = 8.9 Hz, 2H), 7.41 (d, J = 8.9 Hz, 2H), 7.30 (s, 1H), 7.26 – 7.23 (m, 2H), 7.19 (s, 1H), 7.02 (d, J = 8.4 Hz, 2H), 6.92 (s, 1H), 6.44 (s, 1H), 4.74 (d, J = 29.8 Hz 1H), 2.32 (s, 3H), 2.29 (s, 3H), 1.72 (s, 3H).

¹³C NMR (150 MHz, $CDCl_3$) δ 202.3 (d, J = 24.1 Hz), 147.0, 145.7, 145.0, 138.6, 136.5, 132.1, 132.1, 131.6, 130.5, 130.3, 130.2, 130.1, 129.4, 129.2, 129.2, 128.9, 121.4 (q, J = 288.6 Hz), 121.5, 98.0 (q, J = 24.5 Hz), 96.2, 95.1 (d, J = 216.8 Hz), 46.3 (d, J = 19.1 Hz), 21.7, 21.1, 13.7.

¹⁹F NMR (565 MHz, $CDCl_3$) δ -79.04 (d, J = 14.1 Hz), -180.37 (q, J = 15.3 Hz).

HRMS (ESI) m/z calcd. for $C_{29}H_{24}ClF_4N_2O_3$ (M+H)⁺:559.1406, found 559.1418.

Enantiomeric excess is 88% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: t_r = 6.22 min; minor isomer: t_r = 5.02 min.



3da: ((4R,5S,6S)-1-(2-chlorophenyl)-5-fluoro-6-hydroxy-3-methyl-4-(p-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-5-yl)(p-tolyl)methanone

According to the general procedure, **3da** was obtained in 52% yield with 62% ee and >20:1 dr as a white solid.

M. p. 138 – 139 °C; $[\alpha]_D^{25} = -3$ (c = 0.2, CH_2Cl_2).

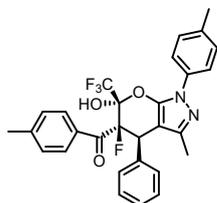
¹H NMR (600 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H), 7.40 – 7.37 (m, 2H), 7.24 (d, J = 8.4 Hz, 3H), 7.02 (d, J = 8.4 Hz, 2H), 6.93 (s, 2H), 6.23 (s, 1H), 4.78 (d, J = 29.1 Hz, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 1.75 (s, 3H).

¹³C NMR (150 MHz, $CDCl_3$) δ 202.7 (d, J = 24.0 Hz), 147.2, 146.3, 145.6, 138.5, 134.8, 132.1, 131.5, 130.4, 130.3, 130.1, 130.1, 130.0, 129.4, 129.2, 128.9, 127.4, 121.3 (q, J = 288.6 Hz), 98.0 (q, J = 24.6), 95.3 (d, J = 216.3 Hz), 94.5, 46.5 (d, J = 19.1 Hz), 21.8, 21.1, 13.8.

¹⁹F NMR (565 MHz, CDCl₃) δ -78.98 (d, *J* = 14.1 Hz), -180.72 (q, *J* = 14.2 Hz).

HRMS (ESI) *m/z* calcd. for C₂₉H₂₄ClF₄N₂O₃ (M+H)⁺:559.1406, found 559.1426.

Enantiomeric excess is 62% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: *tr* = 13.24 min; minor isomer: *tr* = 6.38 min.



3ea: ((4*R*,5*S*,6*S*)-5-fluoro-6-hydroxy-3-methyl-4-phenyl-1-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3ea** was obtained in 62% yield with 82% ee and >20:1 dr as a white solid.

M. p. 94 – 95 °C; $[\alpha]_D^{25} = -6$ (*c* = 0.3, CH₂Cl₂).

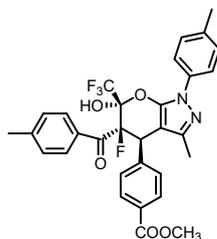
¹H NMR (600 MHz, CDCl₃) δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.48 – 7.35 (m, 2H), 7.26 (s, 2H), 7.24 (d, *J* = 9.4 Hz, 3H), 7.13 (d, *J* = 8.5 Hz, 1H), 7.05 (s, 1H), 7.01 (d, *J* = 8.3 Hz, 2H), 4.79 (d, *J* = 30.0 Hz, 1H), 2.38 (s, 3H), 2.31 (s, 3H), 1.72 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 202.4 (d, *J* = 24.4 Hz), 146.2, 145.7, 144.9, 136.0, 135.5, 132.6, 132.1, 130.5, 130.1, 130.0, 129.7, 128.9, 128.7, 121.4 (q, *J* = 288.5 Hz), 120.6, 97.8 (q, *J* = 24.5 Hz), 95.5, 95.2 (d, *J* = 217.4 Hz), 46.7 (d, *J* = 19.1 Hz), 21.8, 21.0, 13.7.

¹⁹F NMR (565 MHz, CDCl₃) δ -79.03 (d, *J* = 14.2 Hz), -180.42 (q, *J* = 14.1 Hz).

HRMS (ESI) *m/z* calcd. for C₂₉H₂₅F₄N₂O₃ (M+H)⁺:525.1796, found 525.1805.

Enantiomeric excess is 82% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: *tr* = 6.44 min; minor isomer: *tr* = 4.87 min.



3fa: methyl 4-((4*R*,5*S*,6*S*)-5-fluoro-6-hydroxy-3-methyl-5-(4-methylbenzoyl)-1-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-4-yl)benzoate

According to the general procedure, **3fa** was obtained in 77% yield with 88% ee and >20:1 dr as a white solid.

M. p. 125 – 126 °C; $[\alpha]_D^{25} = -25$ (*c* = 0.6, CH₂Cl₂).

¹H NMR (600 MHz, CDCl₃) δ 8.01 (s, 1H), 7.85 (s, 1H), 7.57 (d, *J* = 6.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 3H), 7.03 (d, *J* = 8.0 Hz, 2H), 4.89 (d, *J* = 30.0 Hz, 1H), 3.88 (s, 3H), 2.36 (s, 3H), 2.29 (s, 3H), 1.61 (s, 3H).

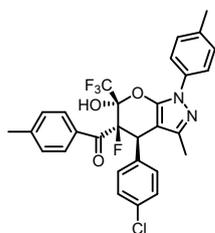
¹³C NMR (151 MHz, CDCl₃) δ 199.6 (d, *J* = 24.5 Hz), 166.6, 146.1, 145.4, 144.9, 138.4, 136.1, 135.1, 132.5, 132.5, 130.7, 130.2, 130.2, 129.8, 129.8, 129.6, 129.5, 129.0, 128.5, 128.5, 121.4 (q, *J* = 288.4 Hz), 120.6, 98.0 (q, *J* = 25.2 Hz), 95.8 (d, *J* = 215.9 Hz), 95.5, 52.2, 46.0 (d, *J* = 18.7 Hz), 21.7, 21.0,

13.5.

^{19}F NMR (565 MHz, CDCl_3) δ -78.78 (d, J = 13.3 Hz), -180.36 (q, J = 15.8 Hz).

HRMS (ESI) m/z calcd. for $\text{C}_{31}\text{H}_{27}\text{F}_4\text{N}_2\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 583.1851, found 583.1858.

Enantiomeric excess is 88% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: t_r = 9.42 min; minor isomer: t_r = 8.42 min.



3ga: ((4R,5S,6S)-4-(4-chlorophenyl)-5-fluoro-6-hydroxy-3-methyl-1-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3ga** was obtained in 85% yield with 76% ee and > 20:1 dr as a white solid.

M. p. 127 – 128 °C; $[\alpha]_D^{25} = -19$ (c = 0.3, CH_2Cl_2).

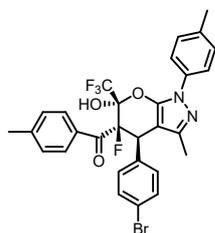
^1H NMR (600 MHz, CDCl_3) δ 7.60 (d, J = 6.4 Hz, 2H), 7.33 (d, J = 6.6 Hz, 4H), 7.24 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 7.1 Hz, 1H), 7.06 (d, J = 8.5 Hz, 2H), 6.99 (s, 1H), 4.77 (d, J = 29.8 Hz, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 1.69 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3) δ 201.4 (d, J = 24.0 Hz), 146.1, 146.0, 144.9, 136.2, 135.4, 134.7, 132.1, 132.1, 131.7, 131.4, 130.1, 130.0, 129.7, 129.2, 129.1, 121.4 (q, J = 288.3 Hz), 120.6, 97.8 (q, J = 25.1 Hz), 95.3 (d, J = 217.0 Hz), 95.2, 46.1 (d, J = 19.1 Hz), 21.8, 21.0, 13.7.

^{19}F NMR (565 MHz, CDCl_3) δ -79.01 (d, J = 13.9 Hz), -180.67 (q, J = 14.3 Hz).

HRMS (ESI) m/z calcd. for $\text{C}_{29}\text{H}_{24}\text{ClF}_4\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 559.1406, found 559.1408.

Enantiomeric excess is 76% determined by HPLC (Chiralpak IC, Hexane/Isopropanol 80/20, flow rate = 1.0 mL/min, 254 nm): major pair of diastereoisomers: major isomer: t_r = 4.08 min; minor isomer: t_r = 3.84 min; minor pair of diastereoisomers: major isomer: t_r = 5.08 min; minor isomer: t_r = 4.89 min;



3ha: ((4R,5S,6S)-4-(4-bromophenyl)-5-fluoro-6-hydroxy-3-methyl-1-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3ha** was obtained in 78% yield with 79% ee and >20:1 dr as a white solid.

M. p. 121 – 122 °C; $[\alpha]_D^{25} = -35$ (c = 0.3, CH_2Cl_2).

^1H NMR (600 MHz, CDCl_3) δ 7.62 (s, 2H), 7.52 (s, 1H), 7.33 (d, J = 8.4 Hz, 3H), 7.25 (d, J = 8.5 Hz,

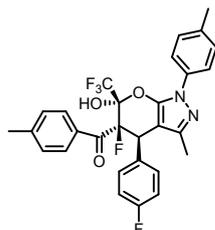
2H), 7.07 (d, $J = 8.3$ Hz, 2H), 6.94 (s, 1H), 6.40 (s, 1H), 4.77 (d, $J = 29.2$ Hz, 1H), 2.38 (s, 3H), 2.35 (s, 3H), 1.71 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3) δ 201.5 (d, $J = 23.5$ Hz), 146.1, 146.0, 144.8, 136.2, 135.4, 132.0, 131.9, 130.1, 130.0, 129.7, 129.1, 122.9, 121.3 (q, $J = 288.6$ Hz), 120.6, 97.8 (q, $J = 25.3$ Hz), 95.2 (d, $J = 217.0$ Hz), 95.1, 46.2 (d, $J = 19.1$ Hz), 21.8, 21.0, 13.8.

^{19}F NMR (565 MHz, CDCl_3) δ -79.03 (d, $J = 14.0$ Hz), -180.68 (q, $J = 14.0$ Hz).

HRMS (ESI) m/z calcd. for $\text{C}_{29}\text{H}_{24}\text{BrF}_4\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 603.0901, found 603.0902.

Enantiomeric excess is 79% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_r = 5.51$ min; minor isomer: $t_r = 4.57$.



3ia: ((4R,5S,6S)-5-fluoro-4-(4-fluorophenyl)-6-hydroxy-3-methyl-1-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3ia** was obtained in 78% yield and 90% ee and >20:1 dr as a white solid.

M. p. 123 – 124 °C; $[\alpha]_D^{25} = -28$ ($c = 0.3$, CH_2Cl_2).

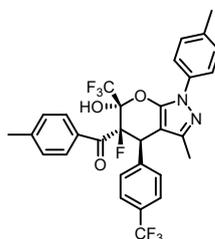
^1H NMR (600 MHz, CDCl_3) δ 7.60 (d, $J = 8.5$ Hz, 2H), 7.41 (s, 1H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.24 (d, $J = 8.5$ Hz, 2H), 7.05 (d, $J = 8.4$ Hz, 3H), 6.82 (s, 1H), 6.55 (s, 1H), 4.78 (d, $J = 30.0$ Hz, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 1.70 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3) δ 201.7 (d, $J = 23.6$ Hz), 162.9 (d, $J = 248.0$ Hz) 146.0, 146.0, 144.8, 136.1, 135.4, 132.1, 132.1, 130.1, 130.0, 129.7, 129.1, 128.6, 121.4 (q, $J = 288.5$ Hz), 120.6, 116.1, 115.9, 115.4, 97.9 (q, $J = 25.2$ Hz), 95.4, 95.3 (d, $J = 216.5$ Hz), 46.0 (d, $J = 19.1$ Hz), 21.7, 21.0, 13.7.

^{19}F NMR (565 MHz, CDCl_3) δ -79.03 (d, $J = 14.1$ Hz), -112.84, -180.79 (q, $J = 14.1$ Hz).

HRMS (ESI) m/z calcd. for $\text{C}_{29}\text{H}_{24}\text{F}_5\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 543.1702, found 543.1713.

Enantiomeric excess is 90% determined by HPLC (Chiralpak IC, Hexane/Isopropanol 95/5, flow rate = 1.0 mL/min, 254 nm): major pair of diastereoisomers: major isomer: $t_r = 8.40$ min; minor isomer: $t_r = 6.03$ min.; minor pair of diastereoisomers: major isomer: $t_r = 6.73$ min; minor isomer: $t_r = 7.12$ min;



3ja: ((4R,5S,6S)-5-fluoro-6-hydroxy-3-methyl-1-(*p*-tolyl)-6-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3ja** was obtained in 66% yield with 87% ee and >20:1 dr as a white solid.

M. p. 109 – 110 °C; $[\alpha]_D^{25} = -16$ ($c = 0.3$, CH_2Cl_2).

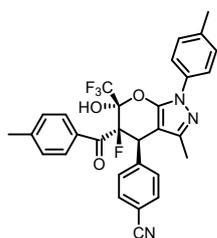
¹H NMR (600 MHz, CDCl₃) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.55 – 7.39 (m, 3H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.22 – 7.13 (m, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.89 (d, *J* = 30.0 Hz, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 1.64 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 199.7 (d, *J* = 24.0 Hz), 146.1, 145.7, 145.1, 137.3, 136.3, 135.0, 132.5, 132.5, 131.0, 131.0, 130.8, 129.8, 129.7, 129.7, 129.0, 125.5 (q, *J* = 3.9 Hz), 123.9 (q, *J* = 272.2 Hz), 121.4 (q, *J* = 288.1 Hz), 120.8, 98.0 (q, *J* = 25.4 Hz), 95.7 (d, *J* = 216.1 Hz), 45.9 (d, *J* = 18.7 Hz), 21.6, 20.9, 13.5.

¹⁹F NMR (565 MHz, CDCl₃) δ -62.72, -78.77 (d, *J* = 13.9 Hz), -180.45 (q, *J* = 14.4 Hz).

HRMS (ESI) *m/z* calcd. for C₃₀H₂₄F₇N₂O₃ (M+H)⁺: 593.1670, found 593.1682.

Enantiomeric excess is 87% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: *tr* = 6.59 min; minor isomer: *tr* = 4.81 min.



3ka: 4-((4R,5S,6S)-5-fluoro-6-hydroxy-3-methyl-5-(4-methylbenzoyl)-1-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-4-yl)benzonitrile

According to the general procedure, **3ka** was obtained in 70% yield with 84% ee and >20:1 dr as a white solid.

M. p. 114 – 115 °C; [α]_D²⁵ = -33 (c = 0.4, CH₂Cl₂).

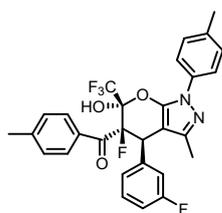
¹H NMR (600 MHz, CDCl₃) δ 7.72 – 7.64 (m, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.55 (s, 1H), 7.43 (s, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.25 (s, 1H), 7.21 (d, *J* = 12.5 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.45 (s, 1H), 4.86 (d, *J* = 29.0 Hz, 1H), 2.39 (s, 3H), 2.35 (s, 3H), 1.67 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 200.5 (d, *J* = 23.2 Hz), 146.5, 145.7, 144.9, 138.6, 136.4, 135.2, 132.4, 131.9, 131.2, 130.0, 129.9, 129.8, 129.3, 121.3 (q, *J* = 288.7 Hz), 120.7, 118.2, 112.7, 97.8 (q, *J* = 25.2 Hz), 95.3 (d, *J* = 216.0 Hz), 46.7 (d, *J* = 18.8 Hz), 21.8, 21.0, 13.7.

¹⁹F NMR (565 MHz, CDCl₃) δ -78.98 (d, *J* = 13.7 Hz), -180.51 (q, *J* = 14.2 Hz).

HRMS (ESI) *m/z* calcd. for C₃₀H₂₄F₄N₃O₃ (M+H)⁺: 550.1748, found 550.1757.

Enantiomeric excess is 84% determined by HPLC (Chiralpak IC, Hexane/Isopropanol 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: *tr* = 20.15 min; minor isomer: *tr* = 17.18 min.



3la: ((4R,5S,6S)-5-fluoro-4-(3-fluorophenyl)-6-hydroxy-3-methyl-1-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3la** was obtained in 78% yield with 75% ee and >20:1 dr as a white

solid.

M. p. 104 – 105 °C; $[\alpha]_D^{25} = -19$ (c = 0.3, CH₂Cl₂).

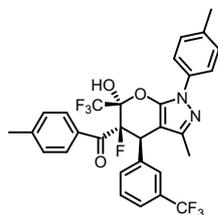
¹H NMR (600 MHz, CDCl₃) δ 7.62 (d, *J* = 6.8 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.25 (s, 2H), 7.17 – 7.09 (m, 1H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.97 (t, *J* = 8.9 Hz, 1H), 6.89 – 6.74 (m, 1H), 6.38 (s, 1H), 4.87 – 4.71 (m, 1H), 2.38 (s, 3H), 2.33 (s, 3H), 1.73 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 201.6 (d, *J* = 23.9 Hz), 146.1, 146.0, 144.8, 136.2, 135.4, 132.0, 130.2, 130.1, 130.0, 129.7, 129.1, 126.2, 121.4 (q, *J* = 287.9 Hz), 120.7, 117.6, 117.2, 116.0, 115.6, 97.9 (q, *J* = 25.0 Hz), 95.1 (d, *J* = 216.8 Hz), 95.0, 46.4 (d, *J* = 14.8 Hz), 21.8, 21.0, 13.7.

¹⁹F NMR (565 MHz, CDCl₃) δ -79.04 (d, *J* = 14.0 Hz), -111.64, -112.56, -180.46 (q, *J* = 13.3 Hz).

HRMS (ESI) *m/z* calcd. for C₂₉H₂₄F₅N₂O₃ (M+H)⁺: 543.1702, found 543.1713.

Enantiomeric excess is 75% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major pair of diastereoisomers: major isomer: tr = 5.65 min; minor isomer: tr = 4.50 min.



3ma: ((4*R*,5*S*,6*S*)-5-fluoro-6-hydroxy-3-methyl-1-(*p*-tolyl)-6-(trifluoromethyl)-4-(3-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3ma** was obtained in 75% yield with 83% ee and >20:1 dr as a white solid.

M. p. 111 – 112 °C; $[\alpha]_D^{25} = -32$ (c = 0.4, CH₂Cl₂).

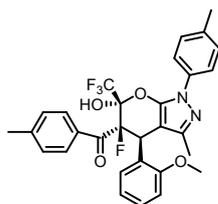
¹H NMR (600 MHz, CDCl₃) δ 7.77 – 7.59 (m, 3H), 7.53 (s, 1H), 7.38 (s, 3H), 7.26 (d, *J* = 8.1 Hz, 3H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.89 (d, *J* = 29.0 Hz, 1H), 2.40 (s, 3H), 2.33 (s, 3H), 1.68 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 200.5 (d, *J* = 23.8 Hz), 146.0, 145.9, 145.0, 136.3, 135.2, 133.8, 132.1, 130.0, 129.9, 129.7, 129.3, 129.2, 129.1, 128.4, 127.2, 125.5 (q, *J* = 3.3 Hz), 123.8 (q, *J* = 280.3 Hz), 121.4 (q, *J* = 290.4 Hz), 120.7, 97.9 (q, *J* = 25.0 Hz), 95.4 (d, *J* = 216.8 Hz), 94.9, 46.4 (d, *J* = 14.8 Hz), 21.7, 21.0, 13.6.

¹⁹F NMR (565 MHz, CDCl₃) δ -62.82 (d, *J* = 78.4 Hz), -78.95 (d, *J* = 13.8 Hz), -180.81.

HRMS (ESI) *m/z* calcd. for C₃₀H₂₄F₇N₂O₃ (M+H)⁺: 593.1670, found 593.1677.

Enantiomeric excess is 83% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 5.45 min; minor isomer: tr = 4.92 min.



3na: ((4*R*,5*S*,6*S*)-5-fluoro-6-hydroxy-4-(2-methoxyphenyl)-3-methyl-1-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3na** was obtained in 58% yield with 70% ee and >20:1 dr as a white solid.

M. p. 67 – 68 °C; $[\alpha]_D^{25} = -39$ (c = 0.4, CH₂Cl₂).

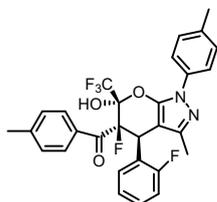
¹H NMR (600 MHz, CDCl₃) δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.34 (m, 1H), 7.28 – 7.27 (m, 2H), 7.25 (s, 2H), 7.03 – 6.97 (m, 3H), 6.89 (s, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 5.38 (d, *J* = 29.6 Hz, 1H), 3.36 (s, 3H), 2.38 (s, 3H), 2.32 (s, 3H), 1.74 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 200.9 (d, *J* = 24.1 Hz), 157.2, 146.1, 145.6, 145.3, 135.9, 135.6, 132.2, 131.7, 130.2, 130.1, 129.7, 129.7, 128.8, 121.6 (q, *J* = 288.5 Hz), 121.3, 120.5, 110.5, 98.6 (q, *J* = 25.4 Hz), 95.8, 94.3 (d, *J* = 215.8 Hz), 54.9, 38.0 (d, *J* = 19.3 Hz), 21.8, 21.0, 13.7.

¹⁹F NMR (565 MHz, CDCl₃) δ -78.70 (d, *J* = 14.9 Hz), -177.54 (q, *J* = 15.0 Hz).

HRMS (ESI) *m/z* calcd. for C₃₀H₂₇F₄N₂O₄ (M+H)⁺:555.1901, found 555.1913.

Enantiomeric excess is 70% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: *tr* = 7.71min; minor isomer: *tr* = 5.32min.



30a: ((4*R*,5*S*,6*S*)-5-fluoro-4-(2-fluorophenyl)-6-hydroxy-3-methyl-1-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **30a** was obtained in 61% yield with 77% ee and >20:1 dr as a white solid.

M. p. 97 – 98 °C; $[\alpha]_D^{25} = -8$ (c = 0.4, CH₂Cl₂).

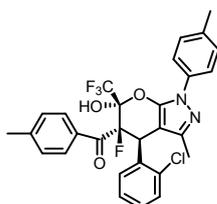
¹H NMR (600 MHz, CDCl₃) δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.45 – 7.41 (m, 1H), 7.38 (d, *J* = 6.6 Hz, 2H), 7.27 – 7.23 (m, 3H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.86 (t, *J* = 9.1 Hz, 1H), 5.27 (d, *J* = 29.3 Hz, 1H), 2.37 (s, 3H), 2.31 (s, 3H), 1.69 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 200.8 (d, *J* = 24.4 Hz), 160.6 (d, *J* = 248.0 Hz), 145.9, 145.8, 145.2, 136.2, 135.4, 132.5, 131.7, 131.7, 130.5, 130.4, 130.1, 130.1, 129.7, 129.0, 124.4, 121.4 (q, *J* = 288.2 Hz), 120.7, 120.2, 120.1, 115.6, 115.5, 98.2 (q, *J* = 25.3 Hz), 94.9, 94.6 (d, *J* = 217.1 Hz), 37.8 (d, *J* = 18.8 Hz), 21.8, 21.0, 13.4.

¹⁹F NMR (565 MHz, CDCl₃) δ -78.84 (d, *J* = 14.7 Hz), -116.59, -179.55 (q, *J* = 14.4 Hz).

HRMS (ESI) *m/z* calcd. for C₂₉H₂₄F₅N₂O₃ (M+H)⁺:543.1702, found 543.1710.

Enantiomeric excess is 77% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: *tr* = 5.84 min; minor isomer: *tr* = 5.02 min.



3pa: ((4*R*,5*S*,6*S*)-4-(2-chlorophenyl)-5-fluoro-6-hydroxy-3-methyl-1-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3pa** was obtained in 55% yield with 83% ee and >20:1 dr as a white solid.

M. p. 100 – 101 °C; $[\alpha]_D^{25} = -17$ (c = 0.3, CH₂Cl₂).

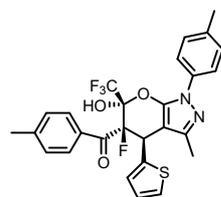
¹H NMR (600 MHz, CDCl₃) δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.48 (dd, *J* = 7.2, 3.9 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.24 (m, 2H), 7.24 (s, 1H), 7.19 (d, *J* = 7.4 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 5.52 (d, *J* = 29.1 Hz, 1H), 2.37 (s, 3H), 2.31 (s, 3H), 1.62 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 200.4 (d, *J* = 24.0 Hz), 146.0, 145.9, 145.0, 136.1, 135.4, 134.7, 133.0, 133.0, 131.8, 131.7, 131.3, 130.1, 130.1, 129.9, 129.7, 129.0, 127.0, 121.5 (q, *J* = 289.7 Hz), 120.5, 98.4 (q, *J* = 25.1 Hz), 95.8, 94.3 (d, *J* = 217.7 Hz), 41.2 (d, *J* = 18.1 Hz), 21.8, 21.0, 13.2.

¹⁹F NMR (565 MHz, CDCl₃) δ -78.66 (d, *J* = 14.5 Hz), -179.47 (q, *J* = 14.9 Hz).

HRMS (ESI) *m/z* calcd. for C₂₉H₂₄ClF₄N₂O₃ (M+H)⁺:559.1406, found 559.1413.

Enantiomeric excess is 83% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major pair of diastereoisomers: major isomer: tr = 5.45 min; minor isomer: tr = 4.62 min; minor pair of diastereoisomers: major isomer: tr = 6.37 min; minor isomer: tr = 5.76 min;



3qa: ((4*R*,5*S*,6*S*)-5-fluoro-6-hydroxy-3-methyl-4-(thiophen-2-yl)-1-(*p*-tolyl)-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3qa** was obtained in 53% yield with 84% ee and >20:1 dr as a white solid.

M. p. 86 – 87 °C; $[\alpha]_D^{25} = -5$ (c = 0.4, CH₂Cl₂).

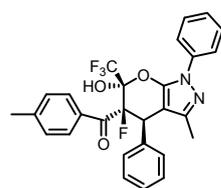
¹H NMR (600 MHz, CDCl₃) δ 7.61 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 3H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.98 (s, 1H), 6.89 (t, *J* = 4.4 Hz, 1H), 5.14 (d, *J* = 28.8 Hz, 1H), 2.38 (s, 3H), 2.35 (s, 3H), 1.81 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 201.7 (d, *J* = 23.9 Hz), 146.4, 145.9, 144.3, 136.2, 135.3, 134.6, 132.2, 130.1, 130.0, 129.8, 129.8, 129.7, 129.2, 129.1, 126.8, 121.4 (q, *J* = 288.3 Hz), 120.7, 97.8 (q, *J* = 24.6 Hz), 95.8, 94.8 (d, *J* = 217.1 Hz), 42.3 (d, *J* = 20.2 Hz), 21.8, 21.0, 13.3.

¹⁹F NMR (565 MHz, CDCl₃) δ -79.12 (d, *J* = 13.9 Hz), -178.82 (d, *J* = 13.0 Hz).

HRMS (ESI) *m/z* calcd. for C₂₇H₂₃F₄N₂O₃S (M+H)⁺:531.1360, found 531.1378.

Enantiomeric excess is 84% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 7.07 min; minor isomer: tr = 5.88 min.



3ra: ((4*R*,5*S*,6*S*)-5-fluoro-6-hydroxy-3-methyl-1,4-diphenyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(*p*-tolyl)methanone

According to the general procedure, **3ra** was obtained in 60% yield with 80% ee and >20:1 dr as a white solid.

M. p. 95 – 96 °C; $[\alpha]_D^{25} = -2$ (c = 0.3, CH₂Cl₂).

¹H NMR (600 MHz, CDCl₃) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 3H), 7.39 (s, 1H), 7.28 (s, 1H), 7.26 – 7.22 (m, 3H), 7.12 (s, 1H), 7.06 (s, 1H), 7.01 (d, *J* = 8.3 Hz, 2H), 4.79 (d, *J* = 29.5 Hz, 1H), 2.31 (s, 3H), 1.72 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 202.2 (d, *J* = 24.0 Hz), 146.6, 145.7, 145.1, 137.9, 132.5, 132.1, 132.1, 130.5, 130.1, 130.0, 129.2, 128.9, 128.7, 126.2, 121.4 (q, *J* = 289.1 Hz), 120.6, 98.0 (q, *J* = 25.6 Hz), 95.7, 95.2 (d, *J* = 216.9 Hz), 46.7 (d, *J* = 19.1 Hz), 21.8, 13.7.

¹⁹F NMR (565 MHz, CDCl₃) δ -79.00 (d, *J* = 14.2 Hz), -180.38 (q, *J* = 14.2 Hz).

HRMS (ESI) m/z calcd. for C₂₈H₂₃F₄N₂O₃ (M+H)⁺:511.1639, found 511.1653.

Enantiomeric excess is 80% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 5.09 min; minor isomer: tr = 4.42 min.



3ab: ((4*R*,5*S*,6*S*)-5-fluoro-6-hydroxy-3-methyl-1,4-di-*p*-tolyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(phenyl)methanone

According to the general procedure, **3ab** was obtained in 70% yield with 87% ee and >20:1 dr as a white solid.

M. p. 87 – 88 °C; $[\alpha]_D^{25} = -5$ (c = 0.4, CH₂Cl₂).

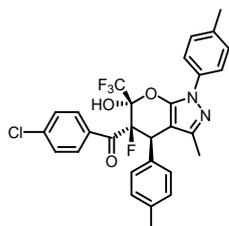
¹H NMR (600 MHz, CDCl₃) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 3H), 7.25 – 7.20 (m, 4H), 6.92 (s, 2H), 6.35 (s, 1H), 4.76 (d, *J* = 29.6 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H), 1.72 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 203.1 (d, *J* = 24.3 Hz), 146.3, 144.8, 138.6, 136.0, 135.5, 134.7, 134.7, 134.1, 130.3, 129.9, 129.8, 129.7, 129.3, 128.1, 121.5 (q, *J* = 288.7 Hz), 120.6, 97.9 (q, *J* = 24.7 Hz), 95.6, 95.3 (d, *J* = 216.3 Hz), 46.4 (d, *J* = 19.0 Hz), 21.1, 21.0, 13.7.

¹⁹F NMR (565 MHz, CDCl₃) δ -78.96 (d, *J* = 14.1 Hz), -180.60 (q, *J* = 14.0 Hz).

HRMS (ESI) m/z calcd. for C₂₉H₂₅F₄N₂O₃ (M+H)⁺:525.1796, found 525.1816.

Enantiomeric excess is 87% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major pair of diastereoisomers: major isomer: tr = 5.82 min; minor isomer: tr = 4.60 min; minor pair of diastereoisomers: major isomer: tr = 3.72 min; minor isomer: tr = 4.07 min;



3ac: (4-chlorophenyl)((4*R*,5*S*,6*S*)-5-fluoro-6-hydroxy-3-methyl-1,4-di-*p*-tolyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)methanone

According to the general procedure, **3ac** was obtained in 65% yield with 72% ee and >20:1 dr as a white solid.

M. p. 123 – 124 °C; $[\alpha]_D^{25} = -9$ (c = 0.1, CH₂Cl₂).

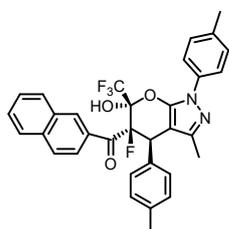
¹H NMR (600 MHz, CDCl₃) δ 7.61 (d, *J* = 8.4 Hz, 2H), 7.32 (s, 1H), 7.24 (d, *J* = 8.4 Hz, 4H), 7.20 (d, *J* = 8.9 Hz, 3H), 6.93 (s, 2H), 4.75 (d, *J* = 29.7 Hz, 1H), 2.38 (s, 3H), 2.30 (s, 3H), 1.72 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 201.9 (d, *J* = 25.0 Hz), 146.3, 144.8, 141.0, 138.8, 136.1, 135.4, 133.0, 131.3, 131.2, 130.3, 129.7, 129.4, 129.2, 129.1, 128.6, 121.4 (q, *J* = 288.8 Hz), 120.7, 97.8 (q, *J* = 25.9 Hz), 95.5, 95.4 (d, *J* = 215.8 Hz), 46.3 (d, *J* = 19.1 Hz), 21.1, 21.0, 13.7.

¹⁹F NMR (565 MHz, CDCl₃) δ -78.94 (d, *J* = 13.9 Hz), -180.34 (q, *J* = 14.1 Hz).

HRMS (ESI) *m/z* calcd. for C₂₉H₂₄ClF₄N₂O₃ (M+H)⁺:559.1406, found 559.1416.

Enantiomeric excess is 72% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 6.19 min; minor isomer: tr = 5.02 min;



3ad: ((4*R*,5*S*,6*S*)-5-fluoro-6-hydroxy-3-methyl-1,4-di-*p*-tolyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)(naphthalen-2-yl)methanone

According to the general procedure, **3ad** was obtained in 70% yield with 84% ee and >20:1 dr as a white solid.

M. p. 76 – 77 °C; $[\alpha]_D^{25} = -22$ (c = 0.1, CH₂Cl₂).

¹H NMR (600 MHz, CDCl₃) δ 7.78 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.61 – 7.55 (m, 3H), 7.54 – 7.47 (m, 2H), 7.46 (d, *J* = 12.7 Hz, 1H), 7.29 (s, 2H), 6.94 (s, 1H), 6.84 (s, 1H), 6.32 (s, 1H), 4.82 (d, *J* = 29.3 Hz, 1H), 2.39 (s, 3H), 2.24 (s, 3H), 1.79 (s, 3H).

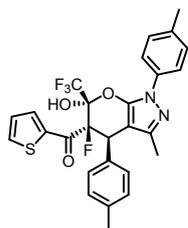
¹³C NMR (150 MHz, CDCl₃) δ 203.1 (d, *J* = 25.8 Hz), 146.3, 144.9, 138.8, 136.0, 135.7, 135.5, 133.4, 133.3, 131.8, 130.5, 130.2, 129.7, 129.5, 128.0, 127.6, 126.8, 124.5, 121.5 (q, *J* = 288.9 Hz), 120.6, 98.1 (q, *J* = 24.4 Hz), 95.5, 95.3 (d, *J* = 217.2 Hz), 46.5 (d, *J* = 19.2 Hz), 21.1, 21.0, 13.8.

¹⁹F NMR (565 MHz, CDCl₃) δ -78.91 (d, *J* = 14.3 Hz), -179.48 (q, *J* = 14.3 Hz).

HRMS (ESI) *m/z* calcd. for C₃₃H₂₇F₄N₂O₃ (M+H)⁺:575.1952, found 575.1965.

Enantiomeric excess is 84% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major pair of diastereoisomers: major isomer: tr = 6.73 min; minor

isomer: tr = 5.03 min; minor pair of diastereoisomers: major isomer: tr = 7.53 min; minor isomer: tr = 7.06 min;



3ae: ((4R,5S,6S)-5-fluoro-6-hydroxy-3-methyl-1,4-di-p-tolyl-6-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrano[2,3-c]pyrazol-5-yl)(thiophen-2-yl)methanone

According to the general procedure, **3ae** was obtained in 82% yield with 72% ee and >20:1 dr as a white solid.

M. p. 95 – 96 °C; $[\alpha]_D^{25} = -39$ (c = 0.1, CH₂Cl₂).

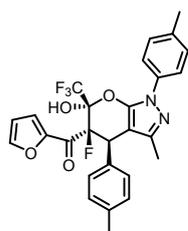
¹H NMR (600 MHz, CDCl₃) δ 7.71 (d, *J* = 4.9 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.52 (s, 1H), 7.26 (s, 1H), 7.25 (s, 1H), 7.13 (s, 1H), 6.94 (t, *J* = 4.5 Hz, 1H), 6.92 – 6.82 (m, 2H), 6.32 (s, 1H), 4.72 (d, *J* = 29.8 Hz, 1H), 2.39 (s, 3H), 2.24 (s, 3H), 1.72 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 192.8 (d, *J* = 24.4 Hz), 146.3, 144.8, 139.5, 138.3, 138.3, 137.4, 137.4, 136.0, 135.5, 130.2, 129.7, 129.3, 129.1, 128.7, 121.4 (q, *J* = 289.4 Hz), 120.6, 97.8 (q, *J* = 24.6 Hz), 95.4, 94.3 (d, *J* = 214.7 Hz), 46.1 (d, *J* = 19.1 Hz), 21.1, 21.0, 13.7.

¹⁹F NMR (565 MHz, CDCl₃) δ -79.24 (d, *J* = 14.8 Hz), -180.44 (q, *J* = 14.5 Hz).

HRMS (ESI) m/z calcd. for C₂₇H₂₃F₄N₂O₃S (M+H)⁺:531.1360, found 531.1371.

Enantiomeric excess is 72% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 95/5, flow rate = 1.0 mL/min, 254 nm): major pair of diastereoisomers: major isomer: tr = 10.69 min; minor isomer: tr = 7.29 min; minor pair of diastereoisomers: major isomer: tr = 7.97 min; minor isomer: tr = 9.26 min;



3af: ((4R,5S,6S)-5-fluoro-6-hydroxy-3-methyl-1,4-di-p-tolyl-6-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrano[2,3-c]pyrazol-5-yl)(furan-2-yl)methanone

According to the general procedure, **3af** was obtained in 74% yield with 93% ee and >20:1 dr as a white solid.

M. p. 117 – 118 °C; $[\alpha]_D^{25} = -94$ (c = 0.3, CH₂Cl₂).

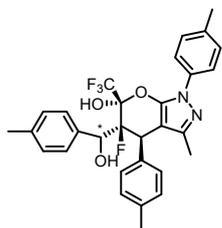
¹H NMR (600 MHz, CDCl₃) δ 7.63 – 7.59 (m, 3H), 7.24 (d, *J* = 8.4 Hz, 3H), 7.11 (s, 1H), 6.97 – 6.86 (m, 3H), 6.34 (d, *J* = 3.9 Hz, 1H), 4.72 (d, *J* = 30.1 Hz, 1H), 2.38 (s, 3H), 2.25 (s, 3H), 1.68 (s, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 186.2 (d, *J* = 24.4 Hz), 149.5, 149.3, 146.4, 144.7, 138.3, 136.1, 135.4, 130.2, 129.8, 129.7, 129.3, 129.1, 129.1, 128.9, 125.8, 125.7, 121.4 (q, *J* = 288.5 Hz), 120.6, 118.5, 113.1, 113.1, 97.7 (q, *J* = 25.0 Hz), 95.4, 93.5 (d, *J* = 213.6 Hz), 45.7 (d, *J* = 19.0 Hz), 21.1, 21.0, 13.6.

^{19}F NMR (565 MHz, CDCl_3) δ -79.24 (d, J = 14.4 Hz), -183.56 (q, J = 14.6 Hz).

HRMS (ESI) m/z calcd. for $\text{C}_{27}\text{H}_{23}\text{F}_4\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 515.1588, found 515.1602.

Enantiomeric excess is 93% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 98/2, flow rate = 1.0 mL/min, 254 nm): major isomer: t_r = 40.68 min; minor isomer: t_r = 52.91 min.



4aa: ((4R,5S,6S)-5-fluoro-5-((S)-hydroxy(*p*-tolyl)methyl)-3-methyl-1,4-di-*p*-tolyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyranopyrazol-6-ol

According to the general procedure, **4aa** was obtained in 67% yield with 83% ee and >20:1 dr as a white solid.

M. p. 95 – 96 °C; $[\alpha]_D^{25} = -22$ (c = 0.6, CH_2Cl_2).

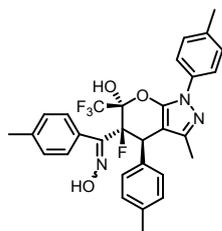
^1H NMR (600 MHz, CDCl_3) δ 7.30 (d, J = 9.0 Hz, 1H), 7.25 (s, 1H), 7.19 (q, J = 8.6 Hz, 3H), 7.07 (d, J = 7.4 Hz, 2H), 7.04 – 7.00 (m, 4H), 6.96 (d, J = 6.2 Hz, 2H), 5.15 – 4.97 (m, 1H), 4.62 – 4.45 (m, 1H), 2.28 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 1.85 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3) δ 148.3, 138.1, 136.5, 136.4, 135.4, 134.8, 130.6, 130.0, 129.7, 129.5, 128.9, 128.5, 128.3, 127.7, 122.6 (q, J = 287.9 Hz), 121.2, 105.1, 96.9 (q, J = 22.6 Hz), 91.8 (d, J = 178.0 Hz), 75.0 (d, J = 21.1 Hz), 70.6, 41.9 (d, J = 23.1 Hz), 21.1, 21.0, 20.9, 11.7.

^{19}F NMR (565 MHz, CDCl_3) δ -70.35, -173.53 (q, J = 17.4 Hz).

HRMS (ESI) m/z calcd. for $\text{C}_{30}\text{H}_{29}\text{F}_4\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 541.2109, found 541.2115.

Enantiomeric excess is 83% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: t_r = 3.13 min; minor isomer: t_r = 4.14 min.



5aa: (((4R,5S,6S)-5-fluoro-6-hydroxy-3-methyl-1,4-di-*p*-tolyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyranopyrazol-5-yl)(*p*-tolyl)methanone oxime

According to the general procedure, **5aa** was obtained in 58% yield with 93% ee and >20:1 dr as a white solid.

M. p. 99 – 100 °C; $[\alpha]_D^{25} = -35$ (c = 0.5, CH_2Cl_2).

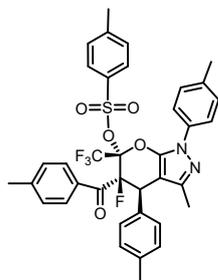
^1H NMR (600 MHz, CDCl_3) δ 9.55 (s, 1H), 7.59 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.1 Hz, 3H), 7.20 – 7.16 (m, 1H), 7.12 (d, J = 10.1 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 6.33 – 6.30 (m, 2H), 4.55 (d, J = 30.5 Hz, 1H), 2.38 (s, 3H), 2.35 (s, 3H), 2.24 (s, 3H), 1.70 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3) δ 157.5 (d, $J = 32.5$ Hz), 146.4, 145.2, 139.7, 138.3, 136.2, 135.2, 131.2, 131.0, 130.5, 130.2, 129.7, 129.6, 129.3, 129.2, 128.6, 128.2, 124.1, 121.7 (q, $J = 287.4$ Hz), 120.8, 97.9 (q, $J = 25.0$ Hz), 97.0, 90.9 (d, $J = 204.0$ Hz), 48.5 (d, $J = 19.3$ Hz), 21.3, 21.2, 21.0, 13.6.

^{19}F NMR (565 MHz, CDCl_3) δ -78.44 (d, $J = 14.0$ Hz), -180.02 (q, $J = 13.8$ Hz).

HRMS (ESI) m/z calcd. for $\text{C}_{30}\text{H}_{28}\text{F}_4\text{N}_3\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 554.2061, found 554.2081.

Enantiomeric excess is 93% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: $t_r = 5.24$ min; minor isomer: $t_r = 4.37$ min.



6aa: (4*R*,5*S*,6*R*)-5-fluoro-3-methyl-5-(4-methylbenzoyl)-1,4-di-*p*-tolyl-6-(trifluoromethyl)-1,4,5,6-tetrahydropyran[2,3-*c*]pyrazol-6-yl 4-methylbenzenesulfonate

According to the general procedure, **6aa** was obtained in 70% yield with 83% ee and >20:1 dr as a white solid.

M. p. 59 – 60 °C; $[\alpha]_D^{25} = -106$ ($c = 0.7$, CH_2Cl_2).

^1H NMR (600 MHz, CDCl_3) δ 7.77 (d, $J = 8.5$ Hz, 2H), 7.63 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.23 (d, $J = 8.3$ Hz, 2H), 7.20 (dd, $J = 8.4, 2.2$ Hz, 2H), 7.00 (d, $J = 8.3$ Hz, 6H), 4.43 (d, $J = 30.5$ Hz, 1H), 2.41 (s, 3H), 2.39 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H), 1.50 (s, 3H).

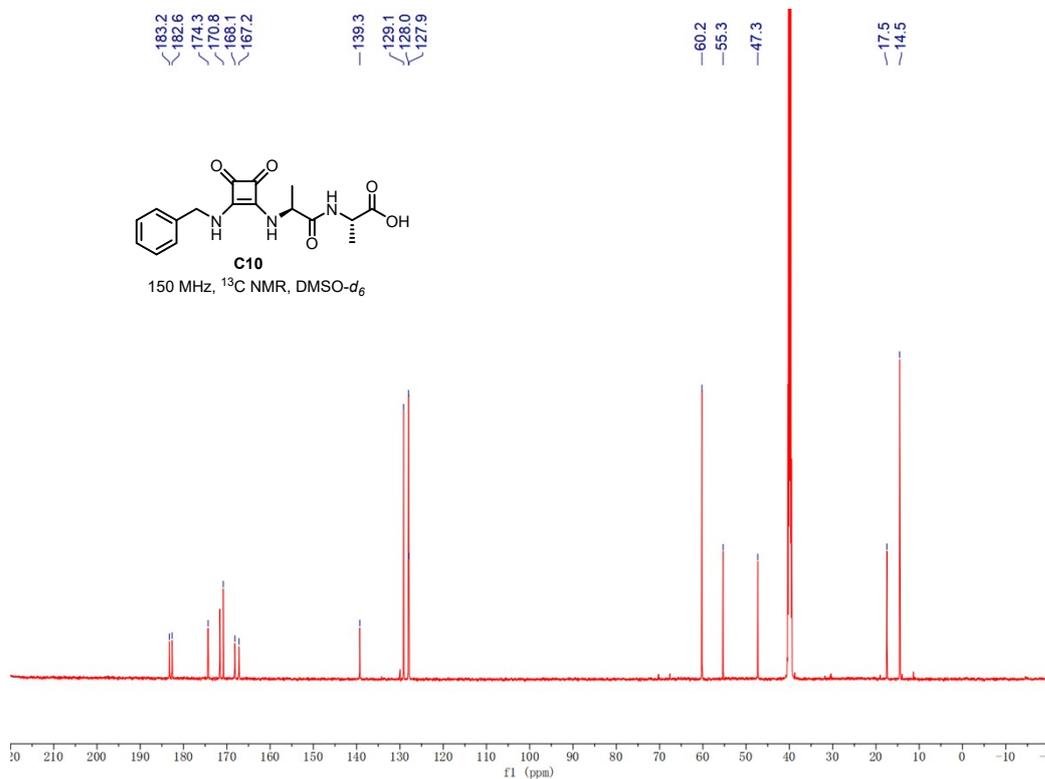
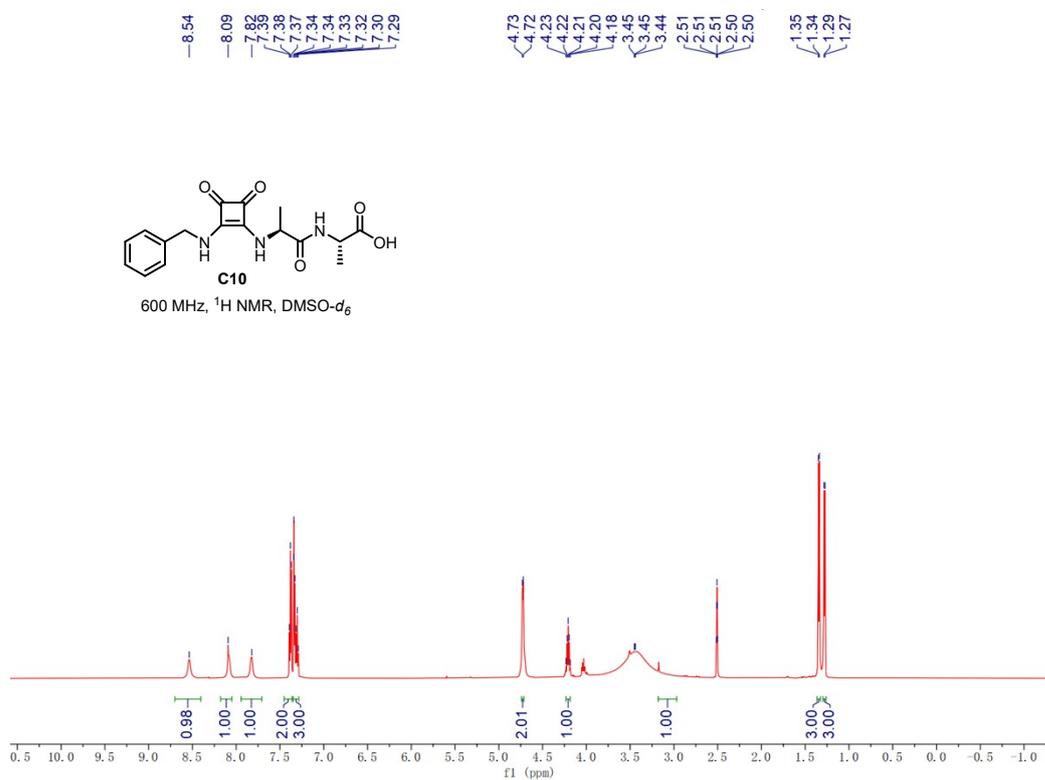
^{13}C NMR (150 MHz, CDCl_3) δ 194.4 (d, $J = 25.5$ Hz), 146.0, 145.5, 143.7, 143.6, 138.2, 136.2, 134.0, 133.7, 129.8, 129.6, 129.3, 129.2, 129.2, 128.9, 128.6, 127.3, 127.1, 120.3, 119.9 (q, $J = 290.1$ Hz), 100.9 (q, $J = 28.8$ Hz), 97.4, 95.8 (d, $J = 214.5$ Hz), 44.3 (d, $J = 18.4$ Hz), 21.7, 21.6, 21.1, 21.0, 13.4.

^{19}F NMR (565 MHz, CDCl_3) δ -74.99 (d, $J = 14.4$ Hz), -179.98.

HRMS (ESI) m/z calcd. for $\text{C}_{37}\text{H}_{33}\text{F}_4\text{N}_2\text{O}_5\text{S}$ ($\text{M}+\text{H}$) $^+$: 693.2041, found 693.2049.

Enantiomeric excess is 83% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 80/20, flow rate = 1.0 mL/min, 254 nm): major pair of diastereoisomers: major isomer: $t_r = 3.72$ min; minor isomer: $t_r = 3.10$ min; minor pair of diastereoisomers: major isomer: $t_r = 5.25$ min; minor isomer: $t_r = 4.75$ min;

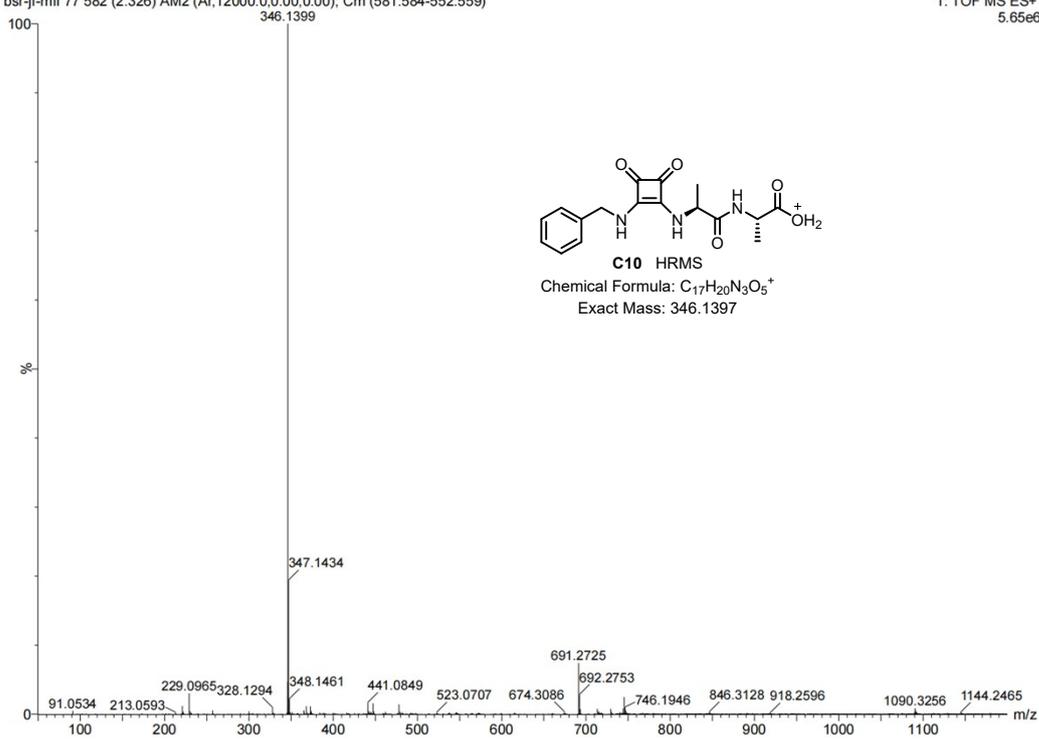
6. Copies of ^1H NMR, ^{13}C NMR, ^{19}F NMR, HRMS spectra of catalysts.



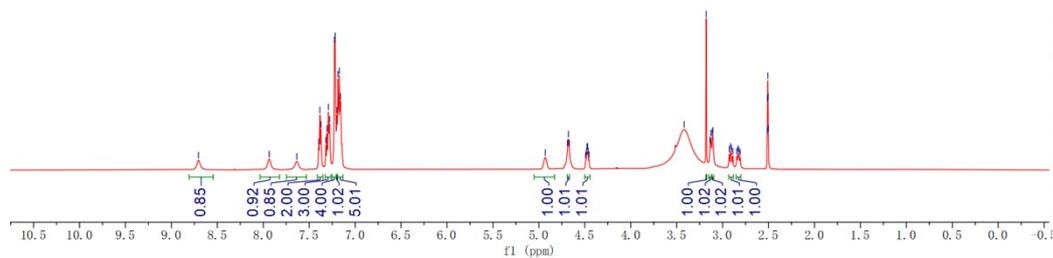
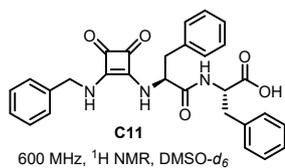
24-Oct-2025 13:36:30

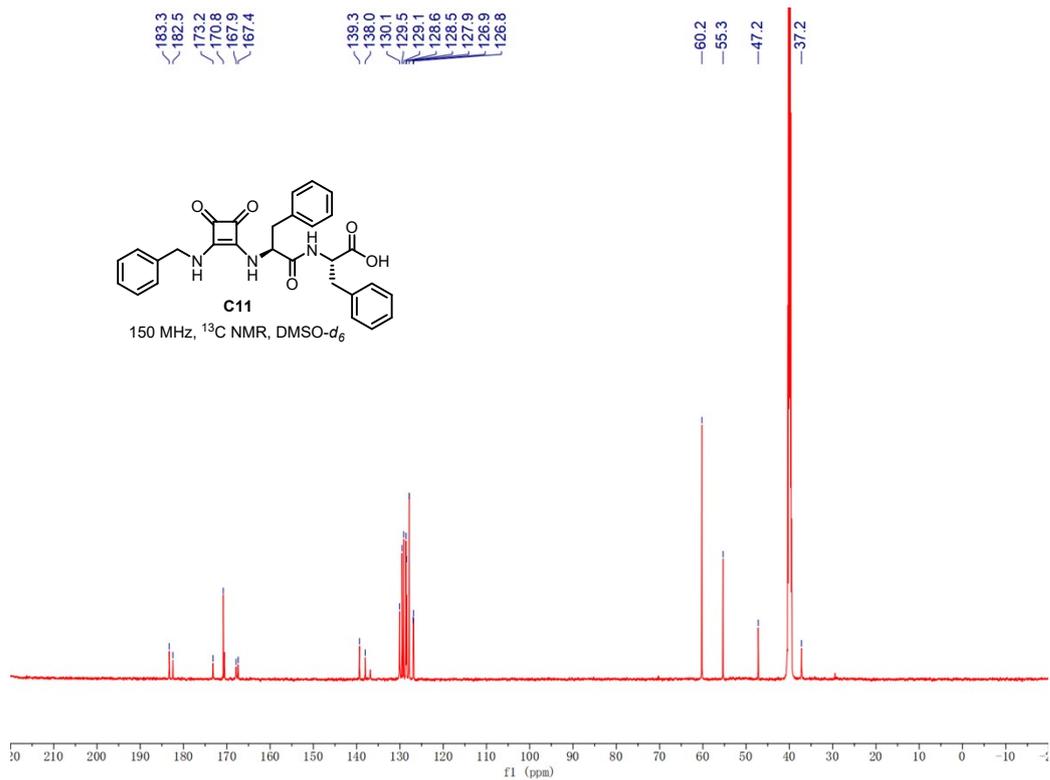
bsr-jf-mif 77 582 (2.326) AM2 (Ar,12000.0,0.00,0.00); Cm (581:584-552:559)

1: TOF MS ES+
5.65e6



7.94, 7.63, 7.40, 7.38, 7.37, 7.32, 7.31, 7.28, 7.28, 7.23, 7.22, 7.20, 7.19, 7.17, 7.16, 4.93, 4.69, 4.68, 4.67, 4.49, 4.48, 4.48, 4.47, 4.46, 4.45, 3.42, 3.18, 3.14, 3.13, 3.11, 3.11, 2.93, 2.91, 2.90, 2.89, 2.85, 2.85, 2.82, 2.81, 2.51, 2.51, 2.50, 2.50

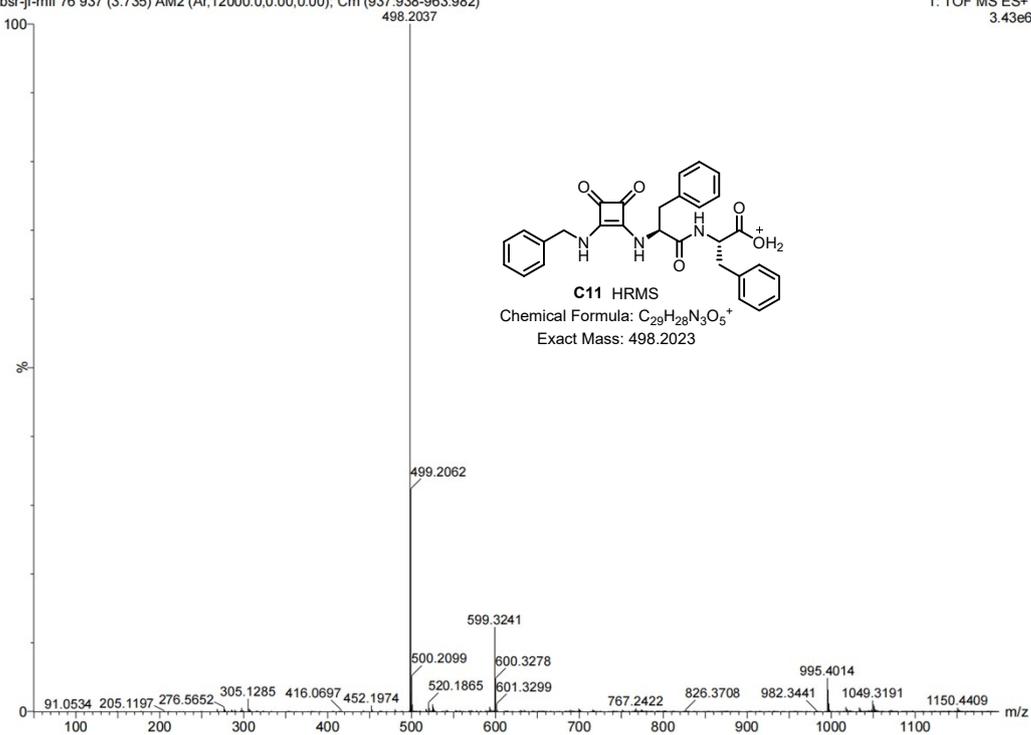




24-Oct-2025 13:25:44

bsr-jf-mif 76 937 (3.735) AM2 (Ar,12000.0,0.00,0.00); Cm (937-938-963-982)

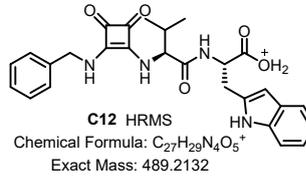
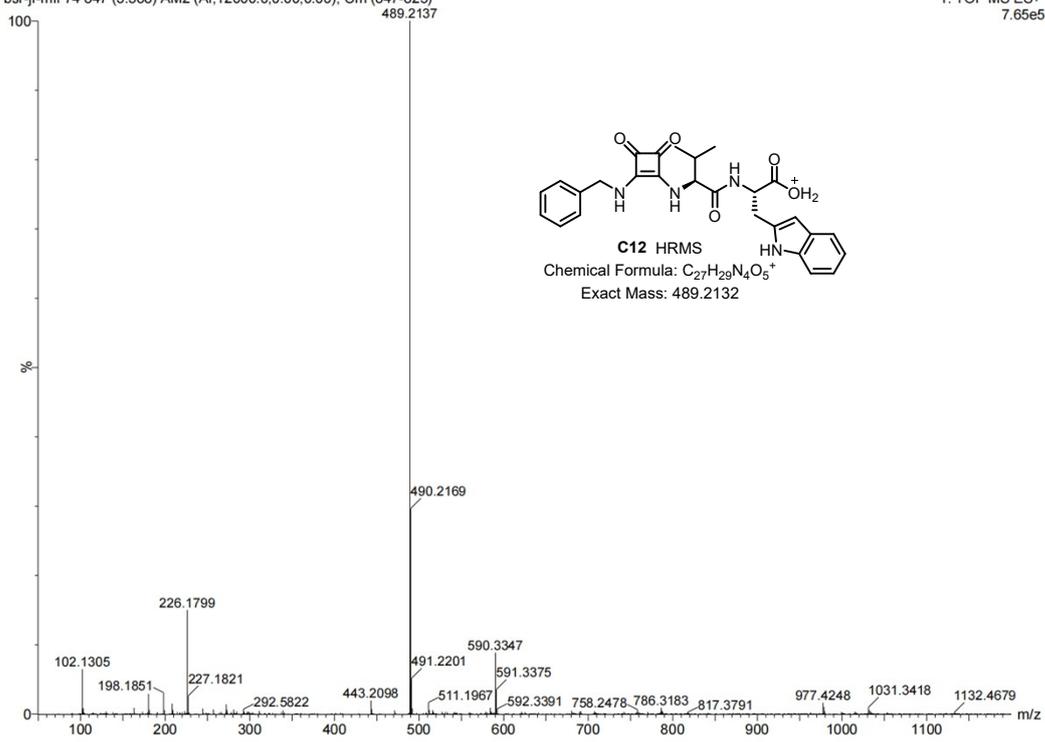
1: TOF MS ES+
3.43e6



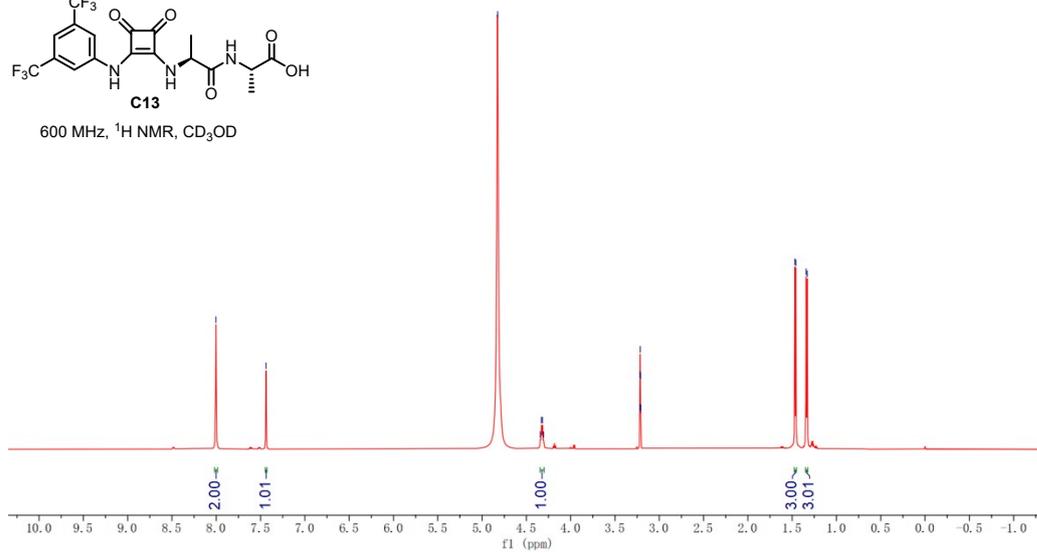
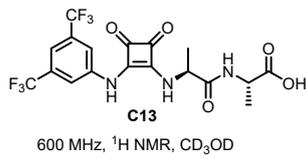
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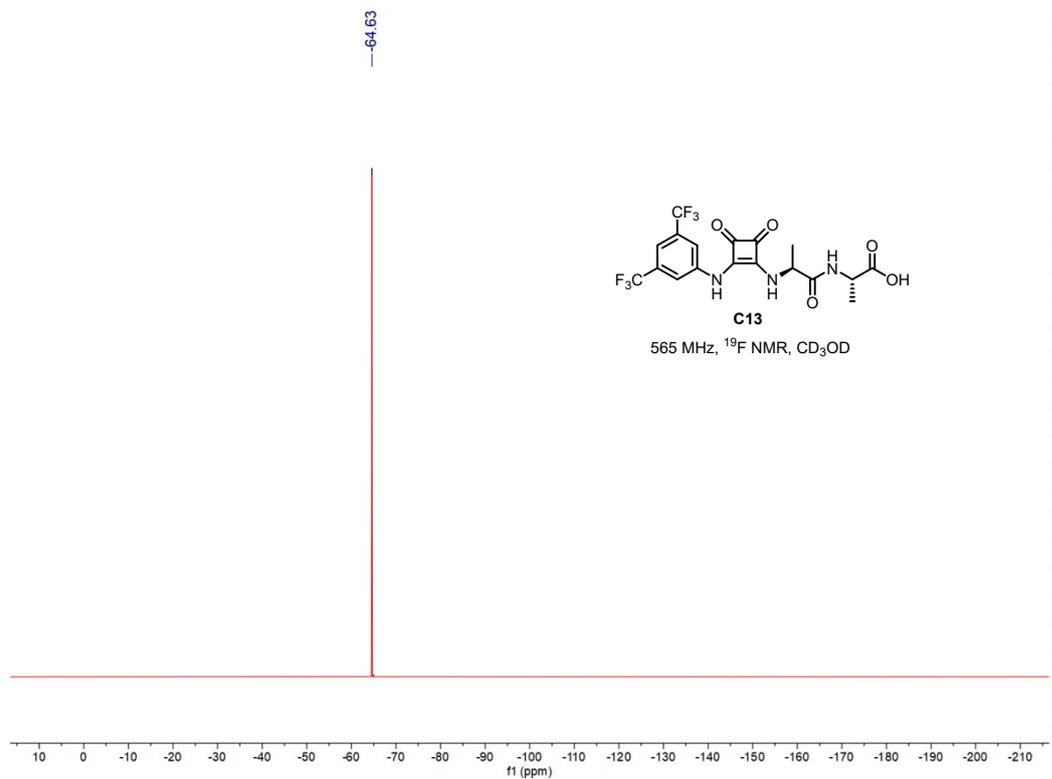
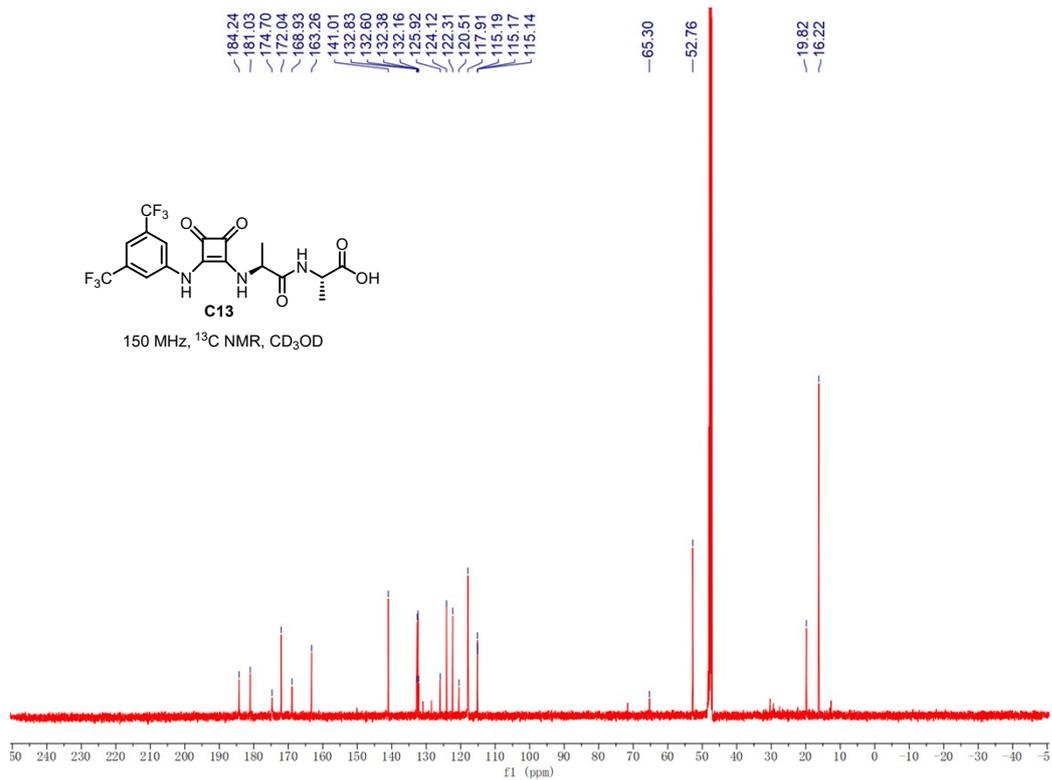
bsr-ji-mif 74 847 (3.388) AM2 (Ar,12000.0,0.00,0.00); Cm (847-825)

1: TOF MS ES+
7.65e5



8.00 7.44 4.82 4.34 4.33 4.32 4.31 3.22 3.21 3.21 3.21 1.47 1.46 1.34 1.33

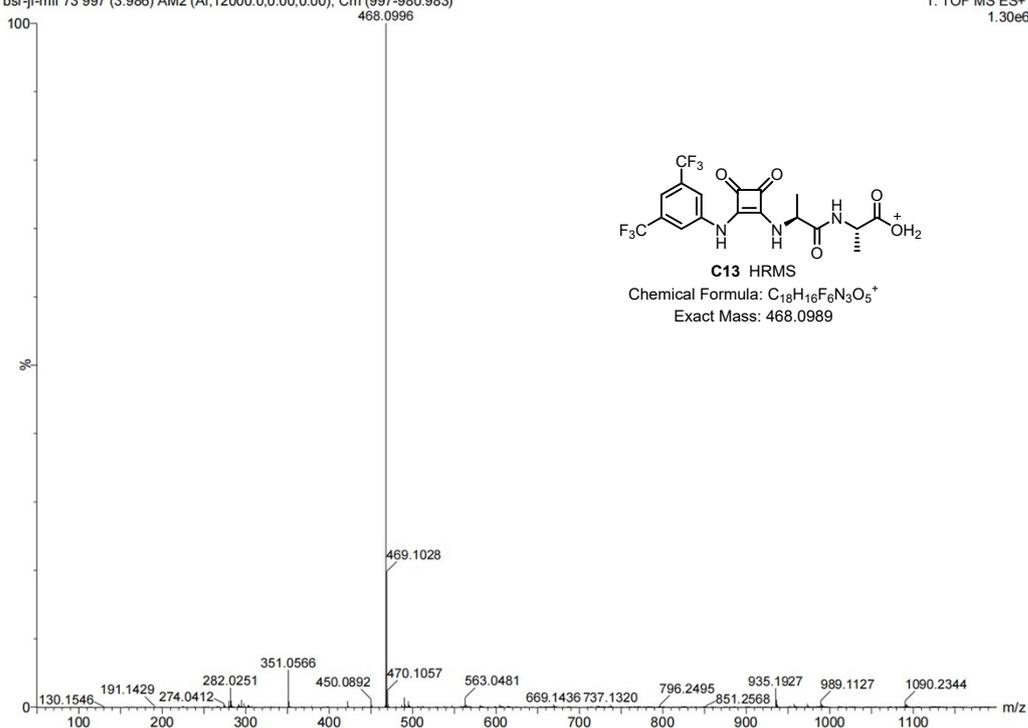




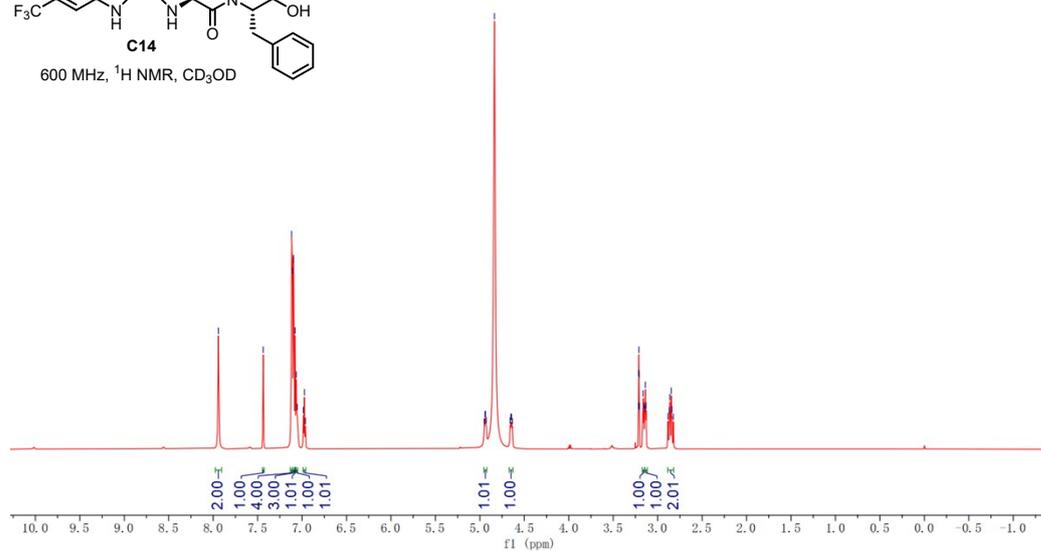
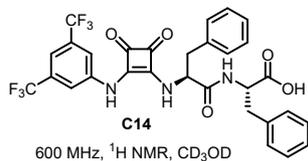
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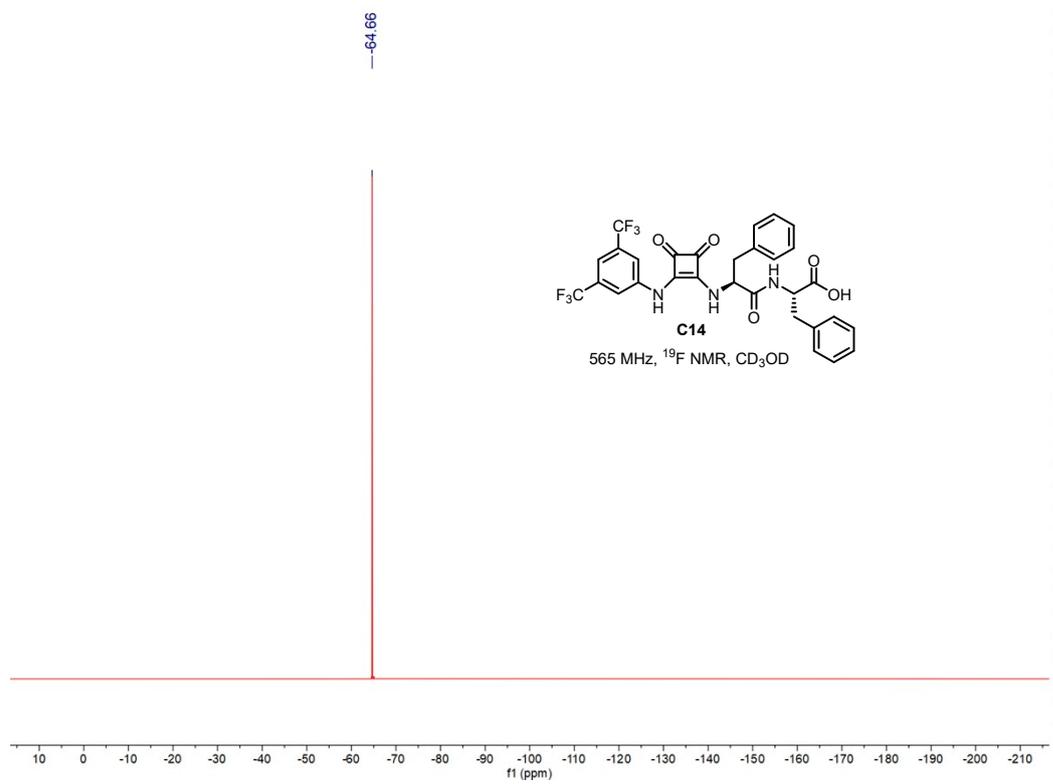
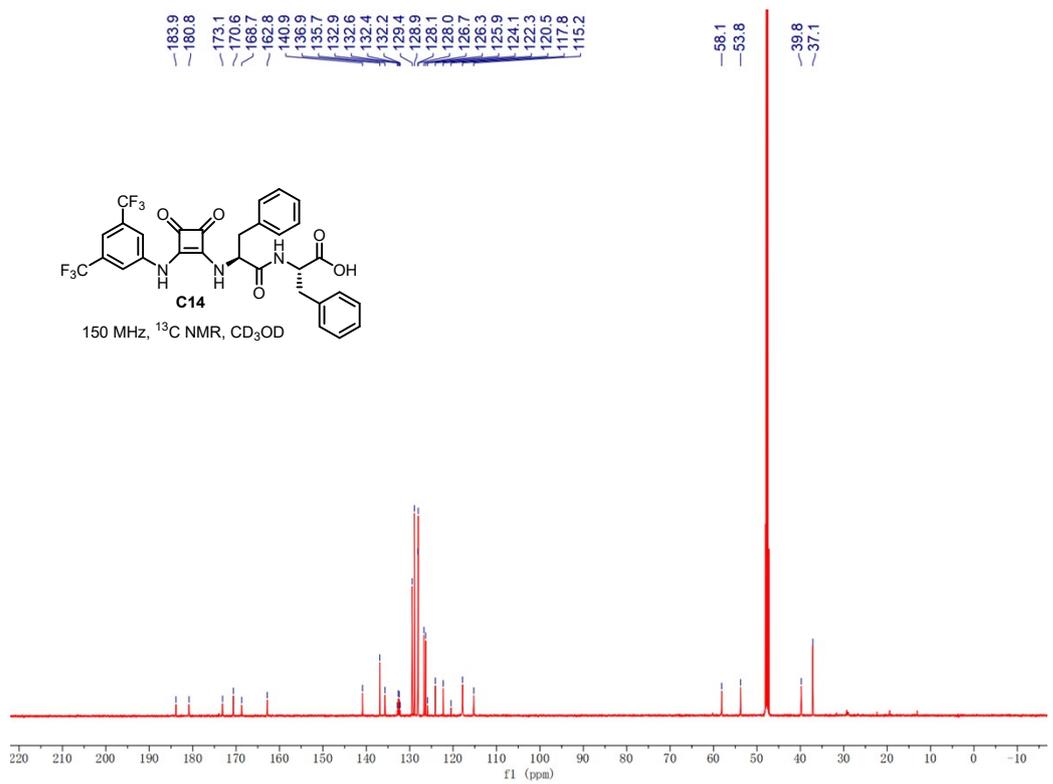
bsr-jf-mif 73 997 (3.986) AM2 (Ar,12000.0,0.00,0.00); Cm (997-980.983)

1: TOF MS ES+
1.30e6



7.94
7.44
7.12
7.11
7.09
7.08
7.07
7.05
6.99
6.97
6.96
4.95
4.94
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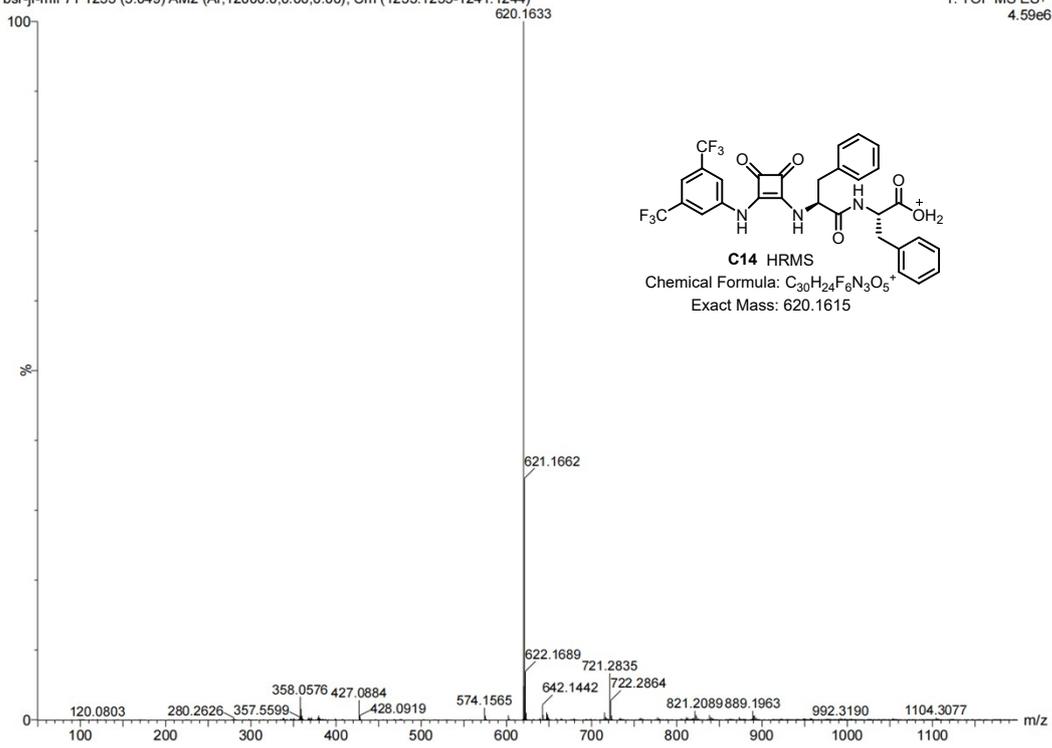




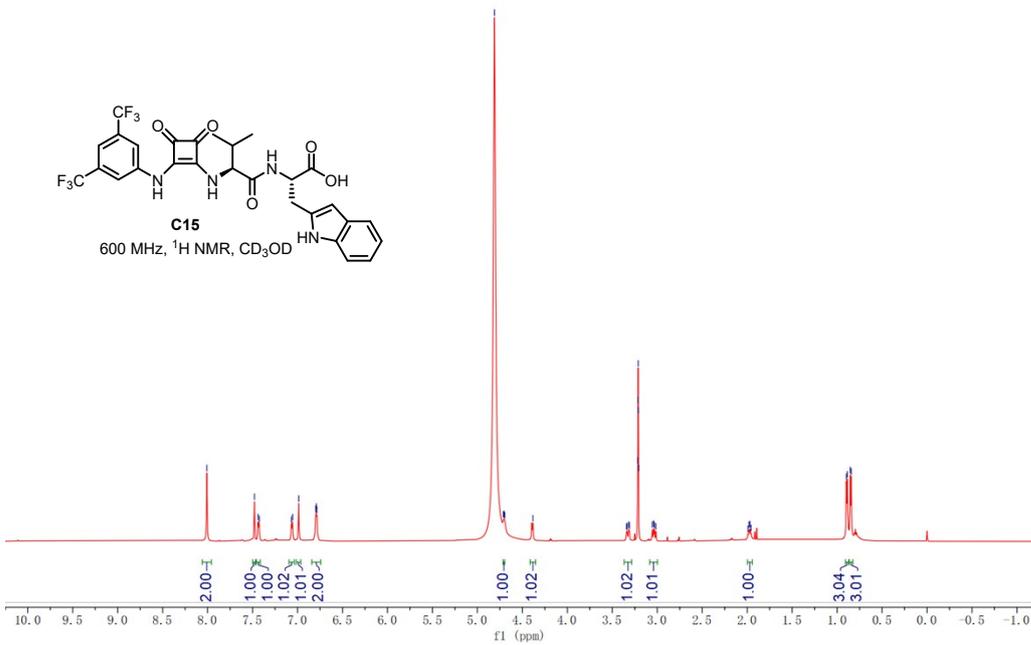
24-Oct-2025 12:42:06

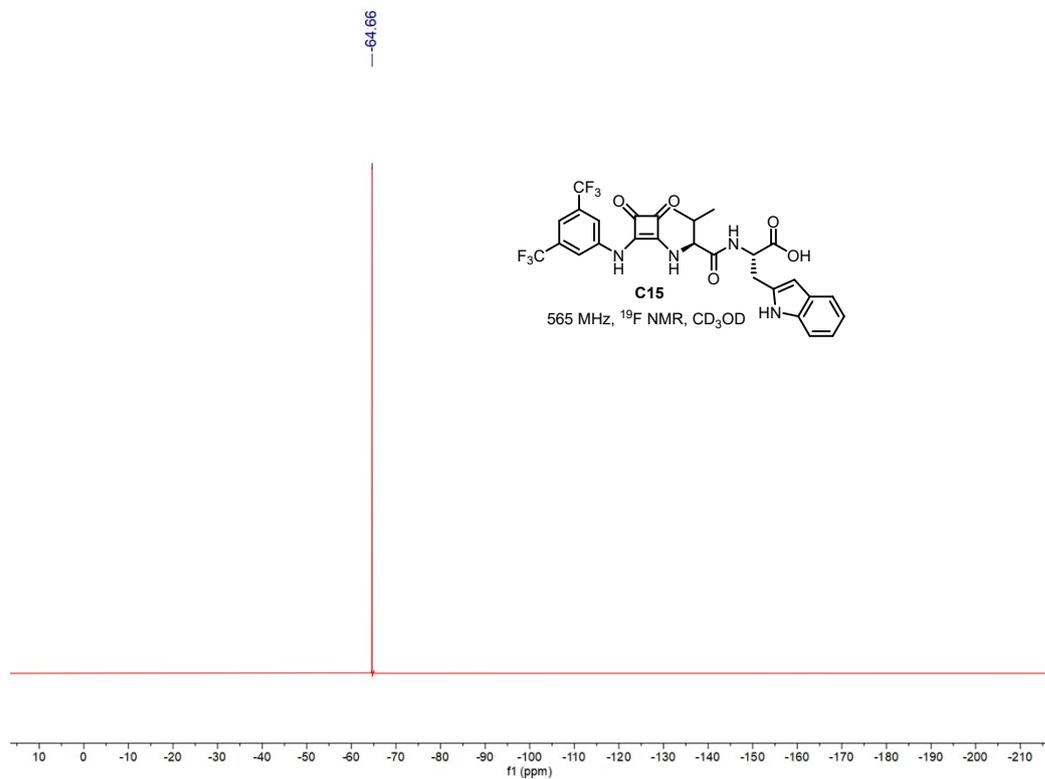
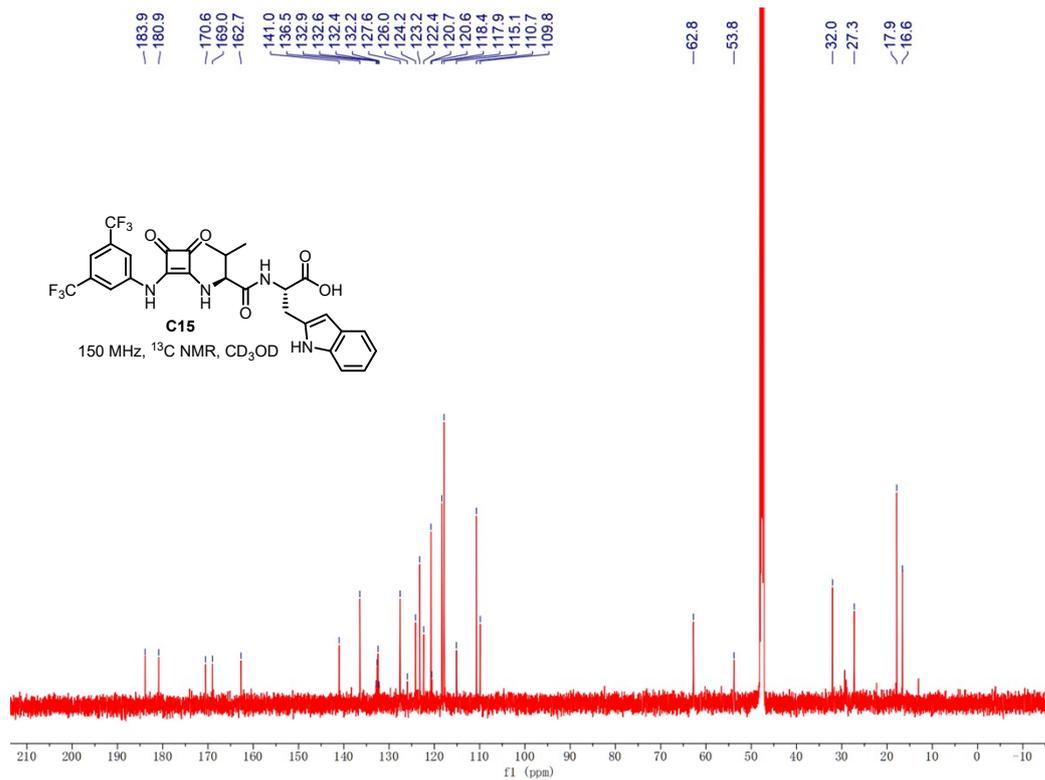
bsr-jl-mif 71 1255 (5.049) AM2 (Ar,12000.0,0.00,0.00); Cm (1253:1255-1241:1244)

1: TOF MS ES+
4.59e6



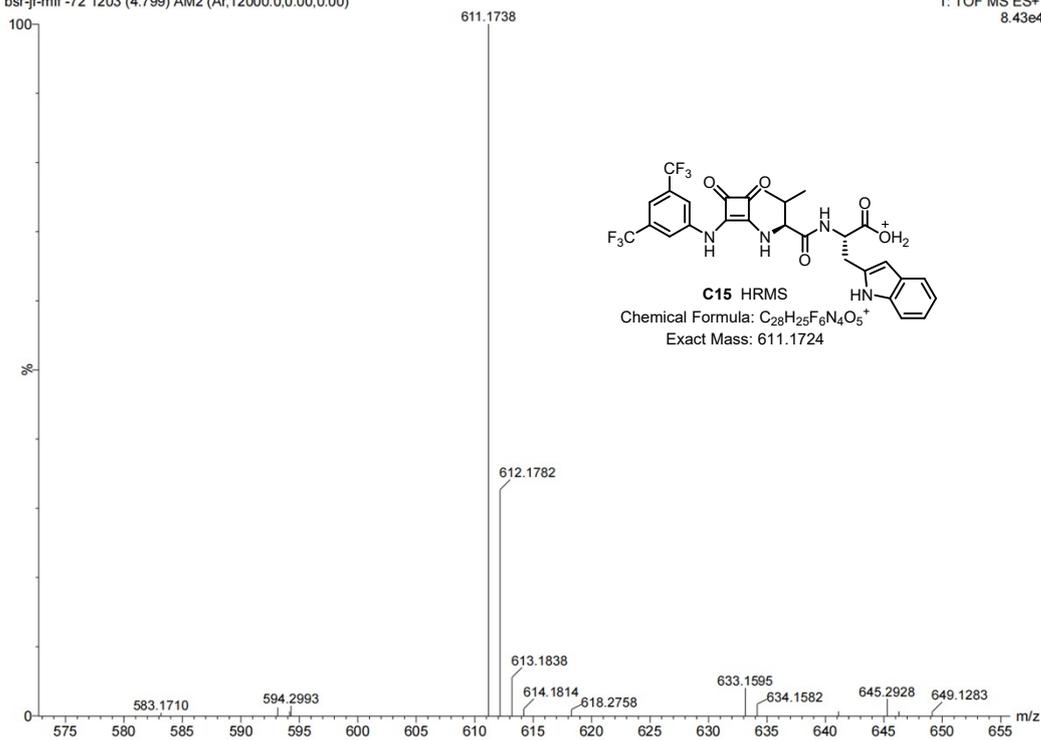
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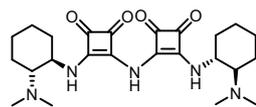


24-Oct-2025 14:44:06
bsr-jf-mif -72 1203 (4.799) AM2 (Ar,12000.0,0.00,0.00)

1: TOF MS ES+
8.43e4

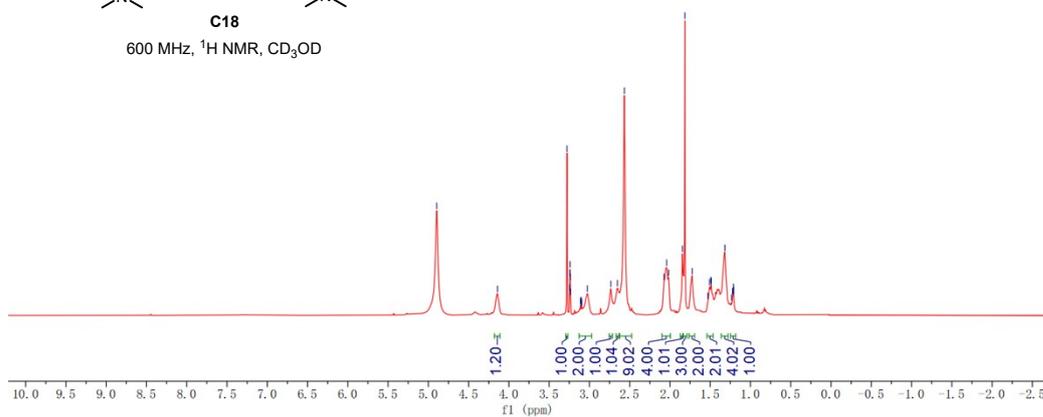


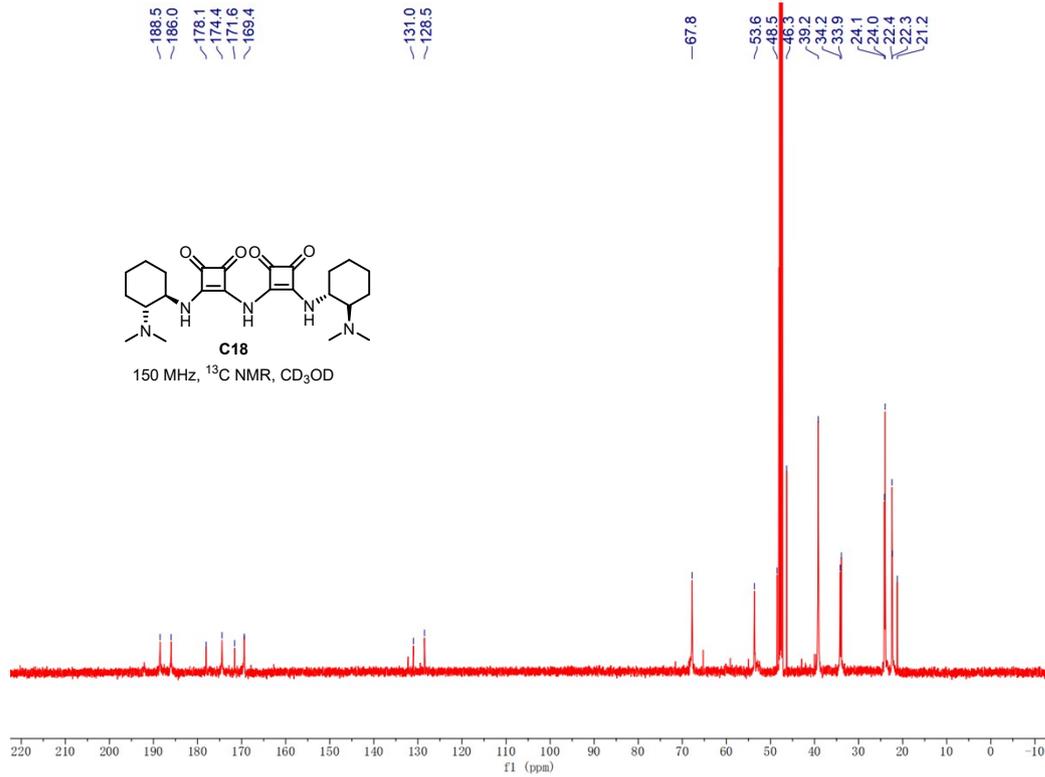
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1.21



C18

600 MHz, 1H NMR, CD_3OD

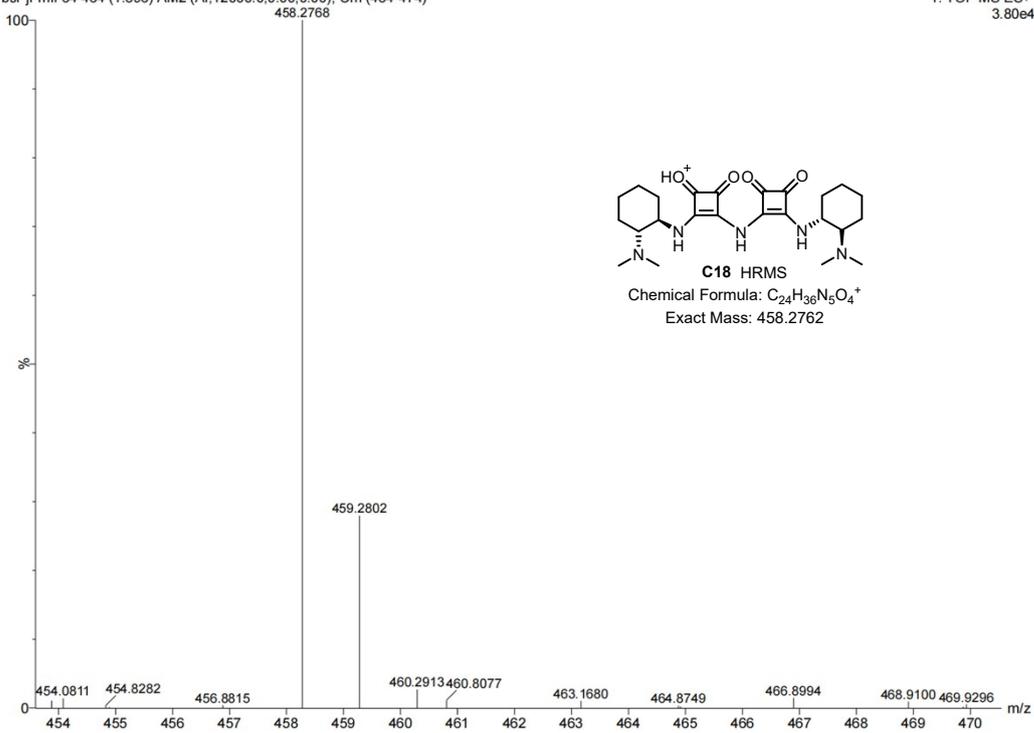




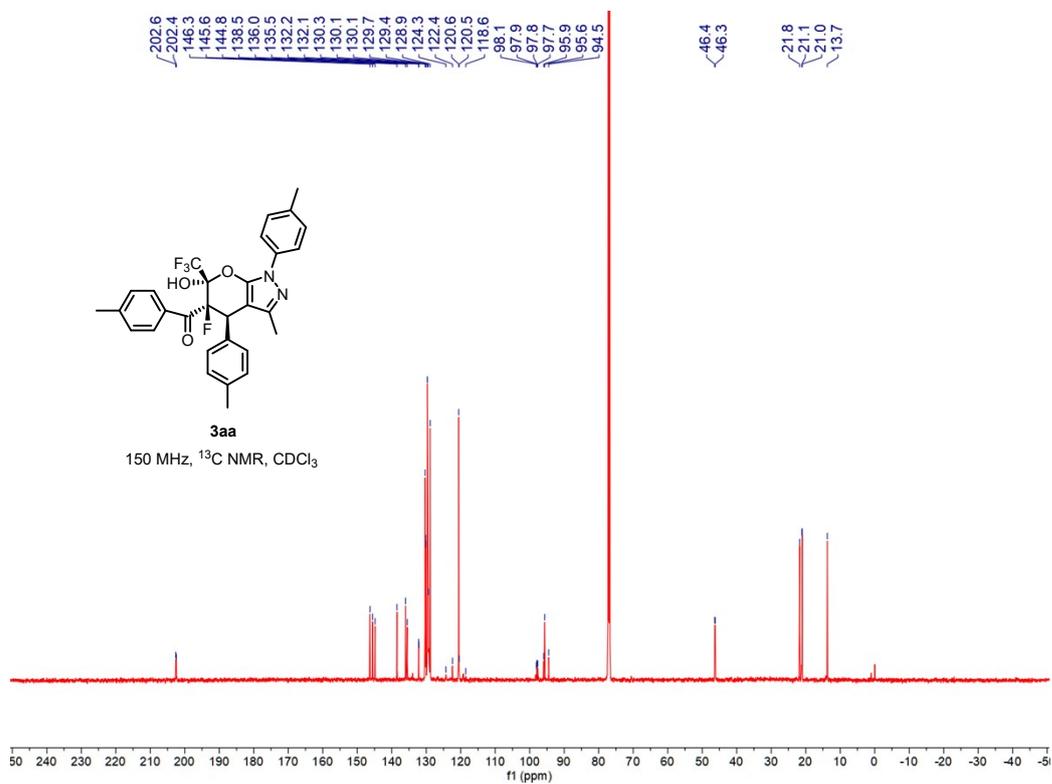
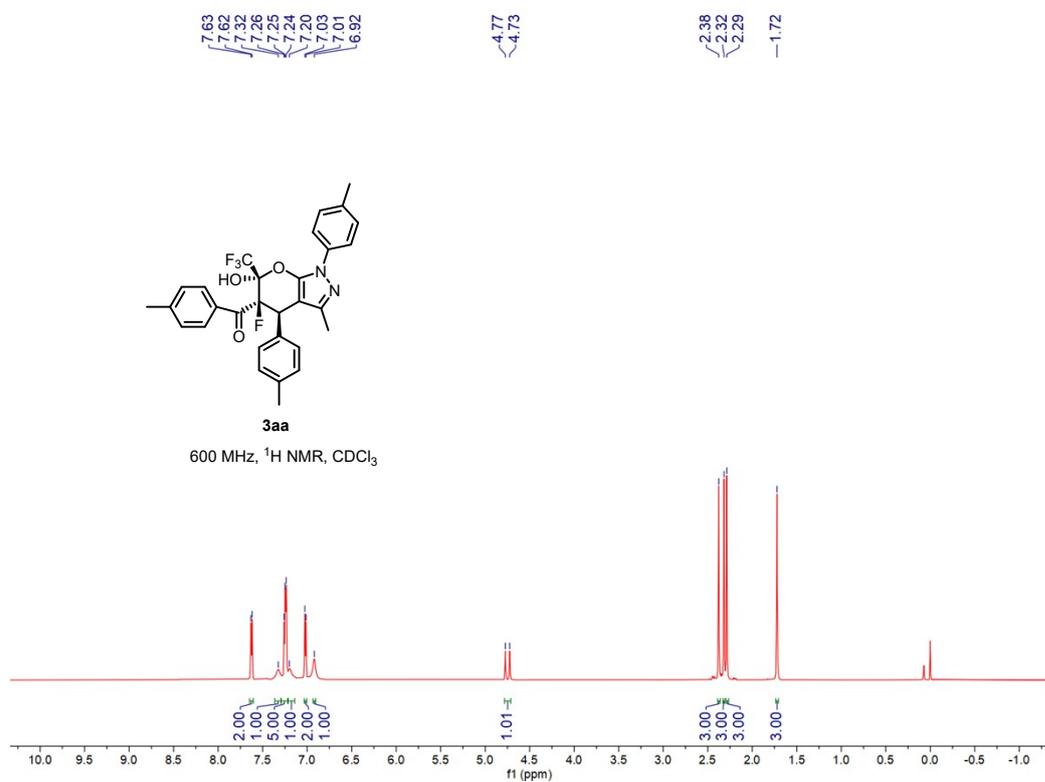
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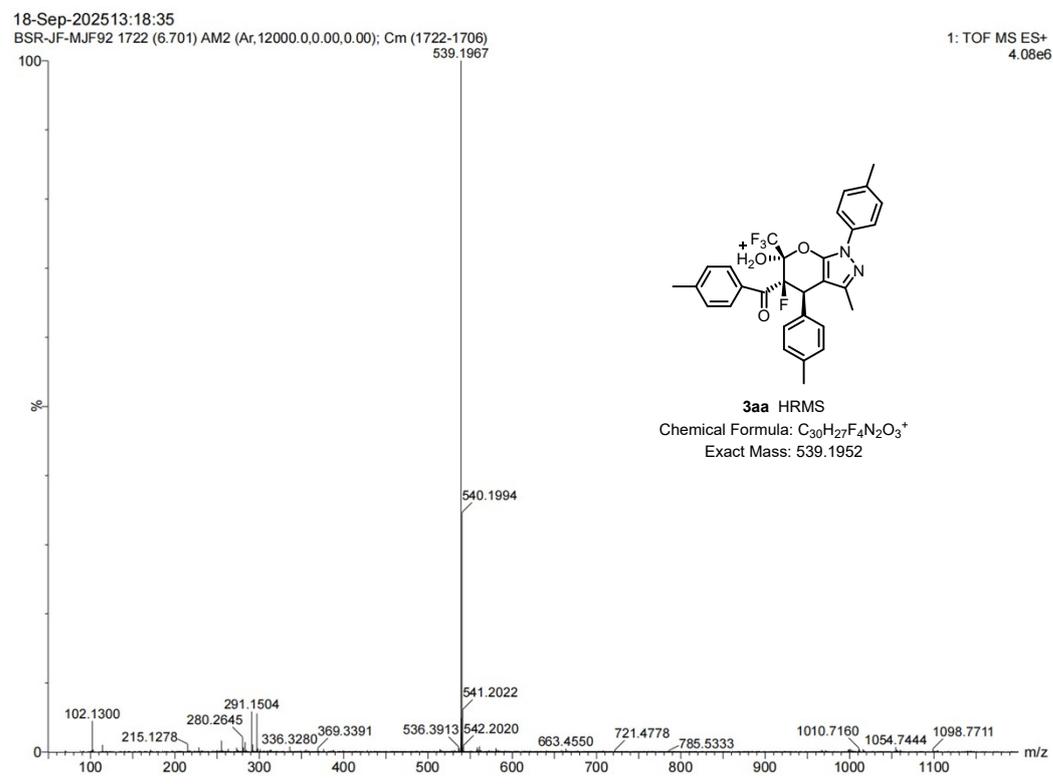
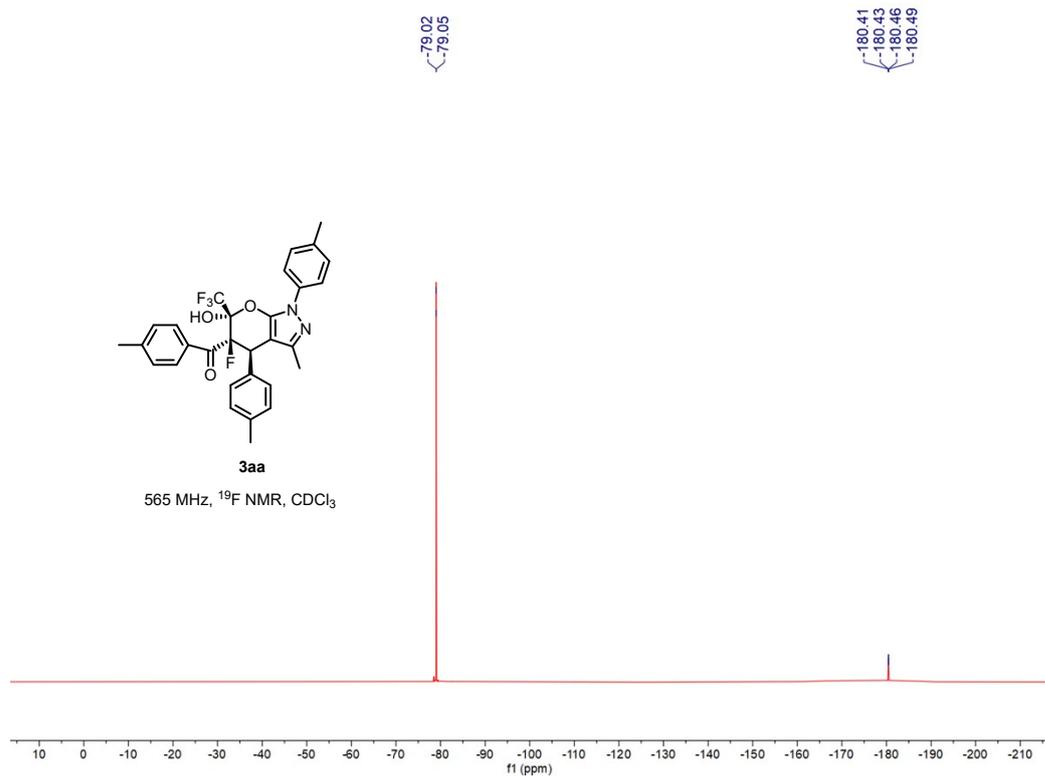
bsr-jf-mif 64 464 (1.896) AM2 (Ar,12000.0,0.00,0.00); Cm (464-474)

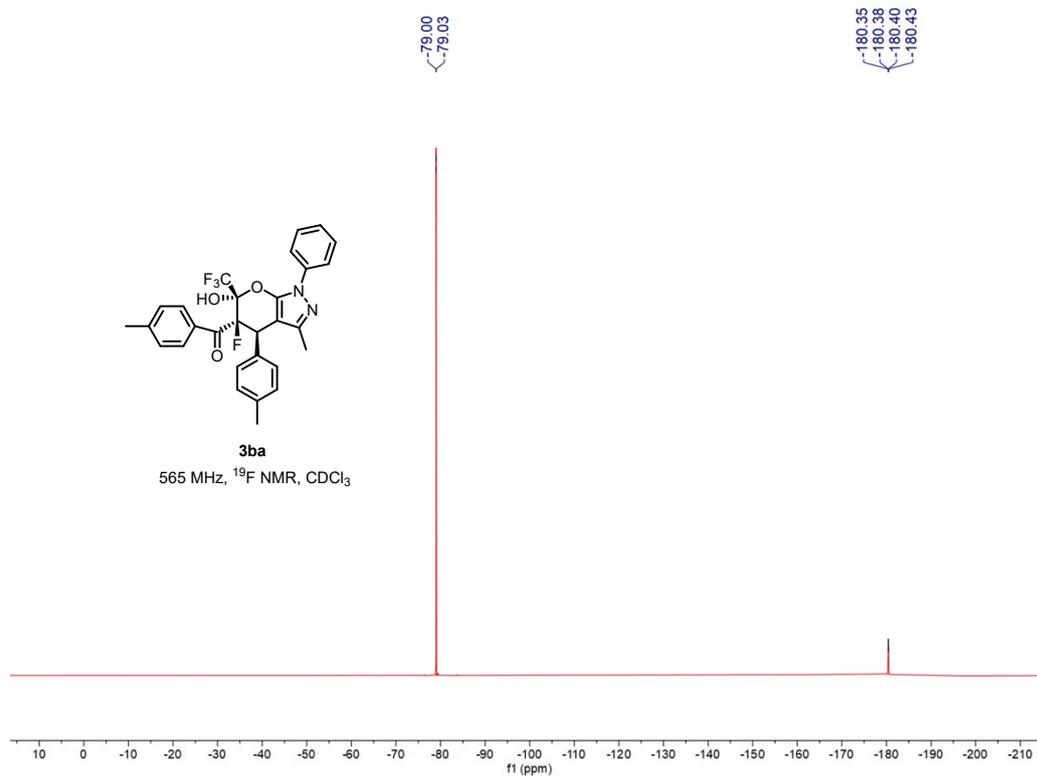
1: TOF MS ES+
3.80e4



7. Copies of ^1H NMR, ^{13}C NMR, ^{19}F NMR, HRMS spectra of products.



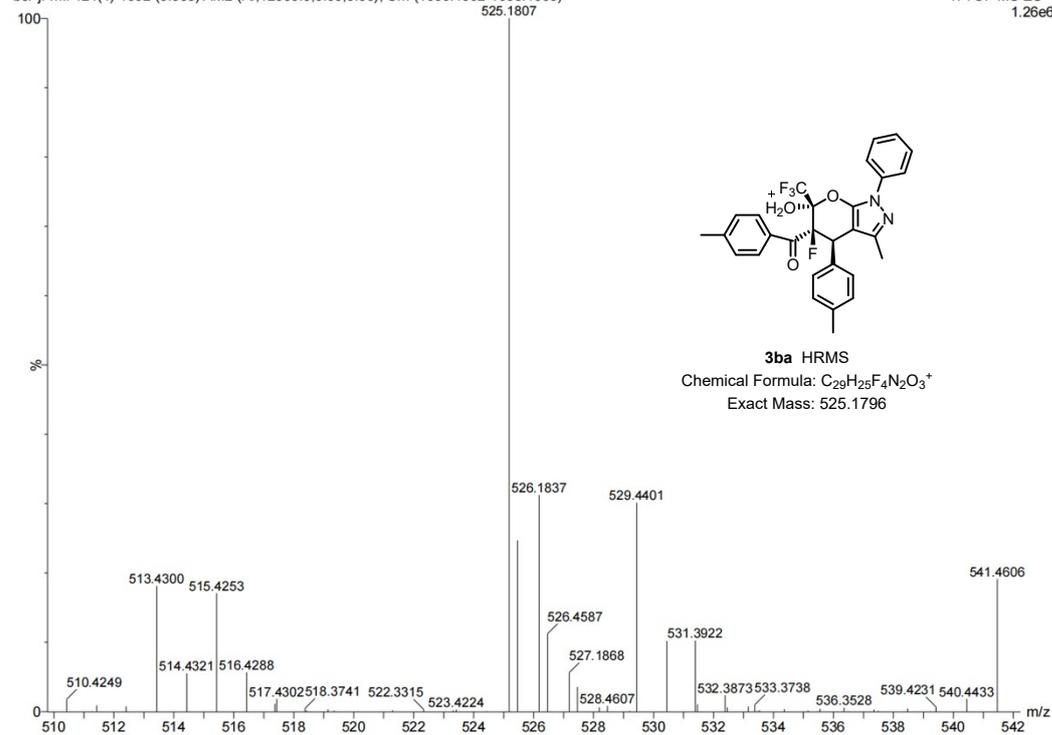


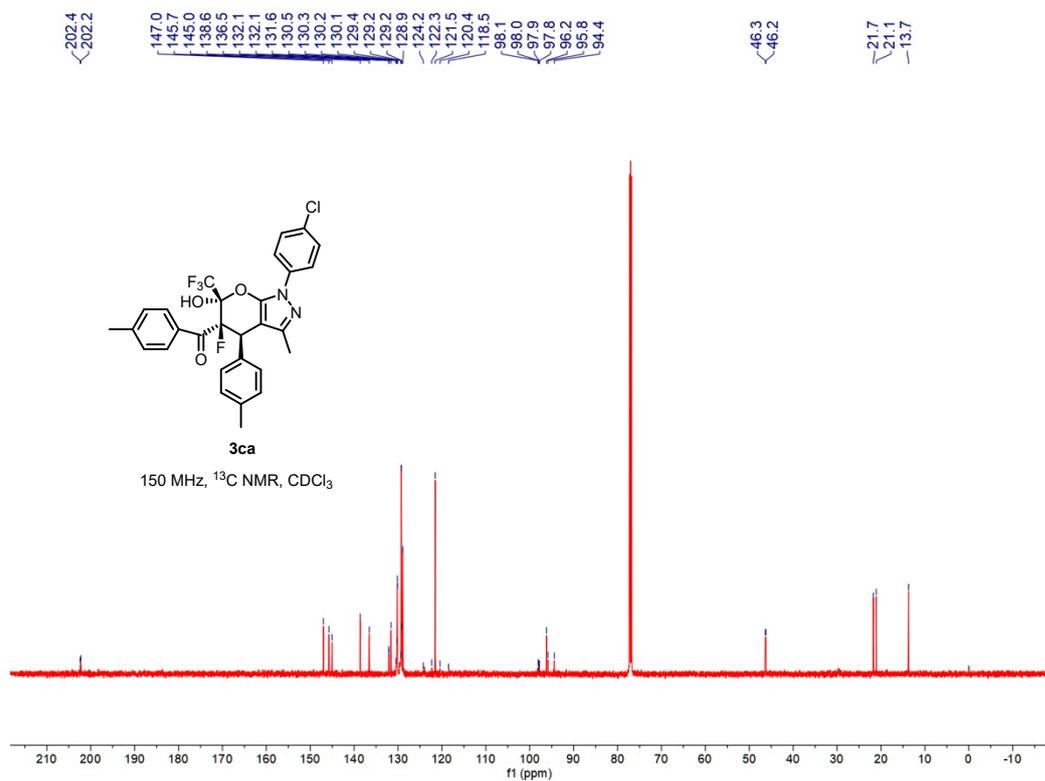
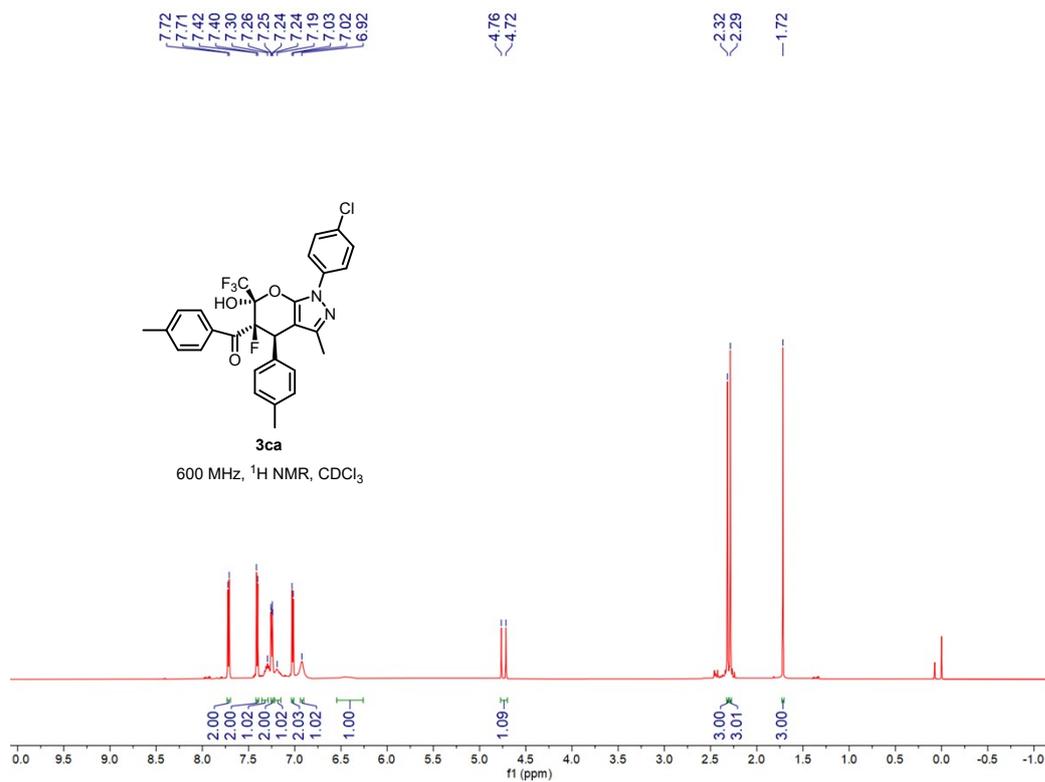


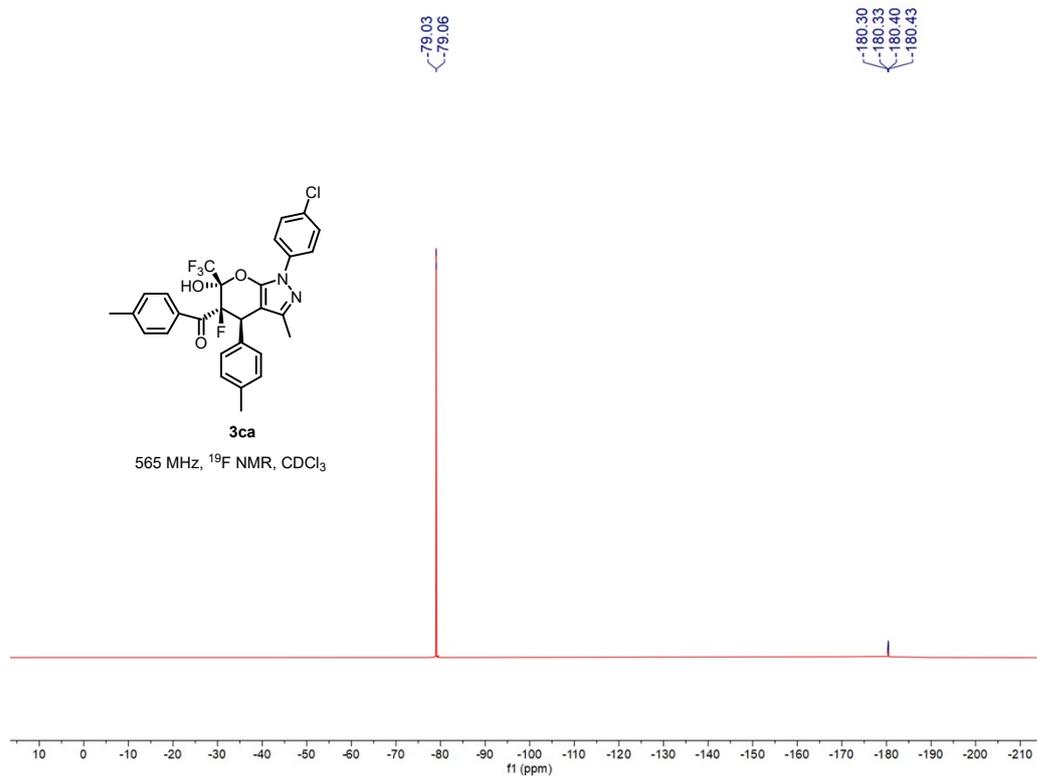
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bsr-jf-mif 121(1) 1592 (6.383) AM2 (Ar,12000.0.0.0.0.0); Cm (1569:1592-1638:1653)

1: TOF MS ES+
1.26e6



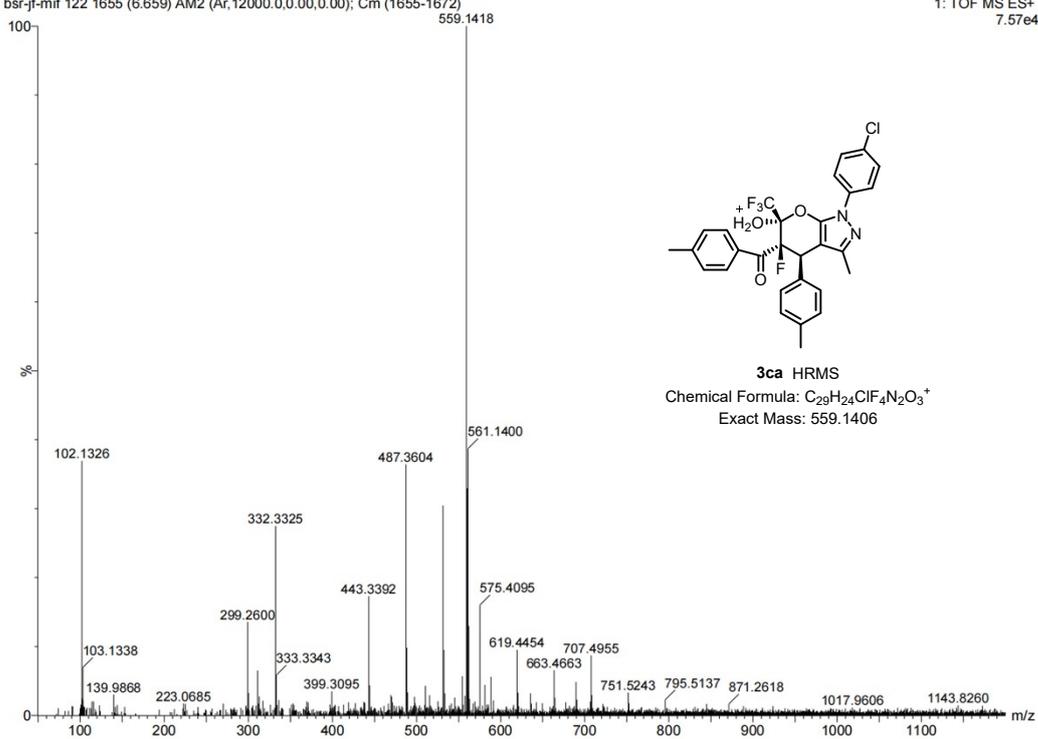


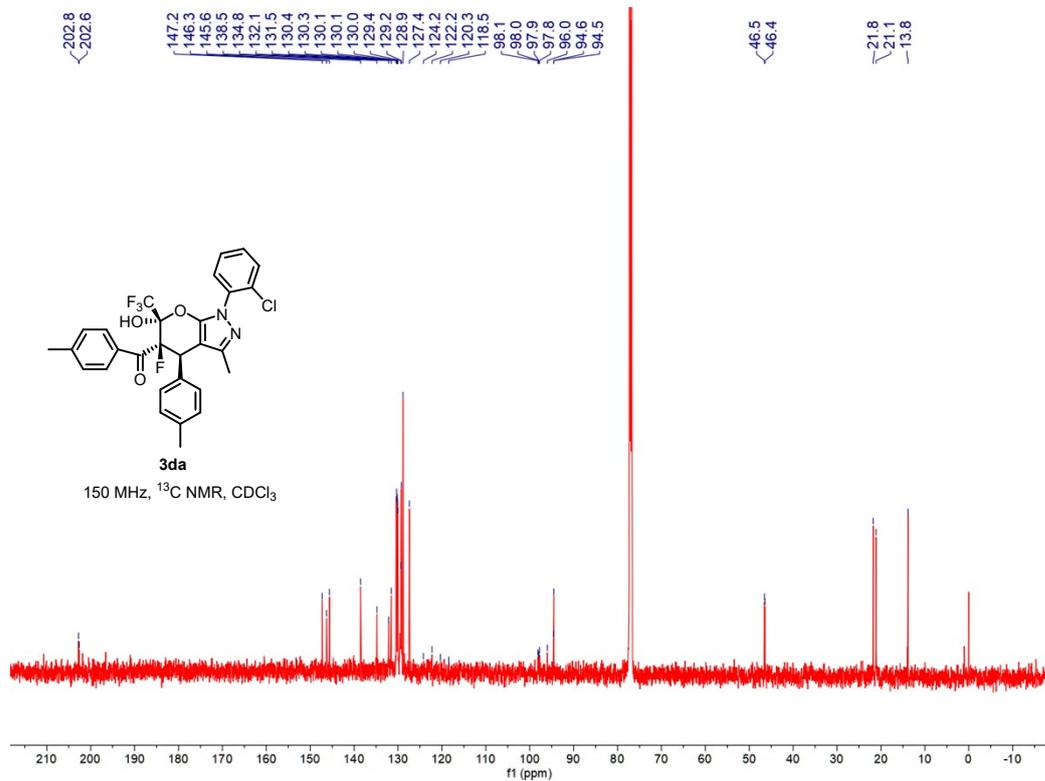
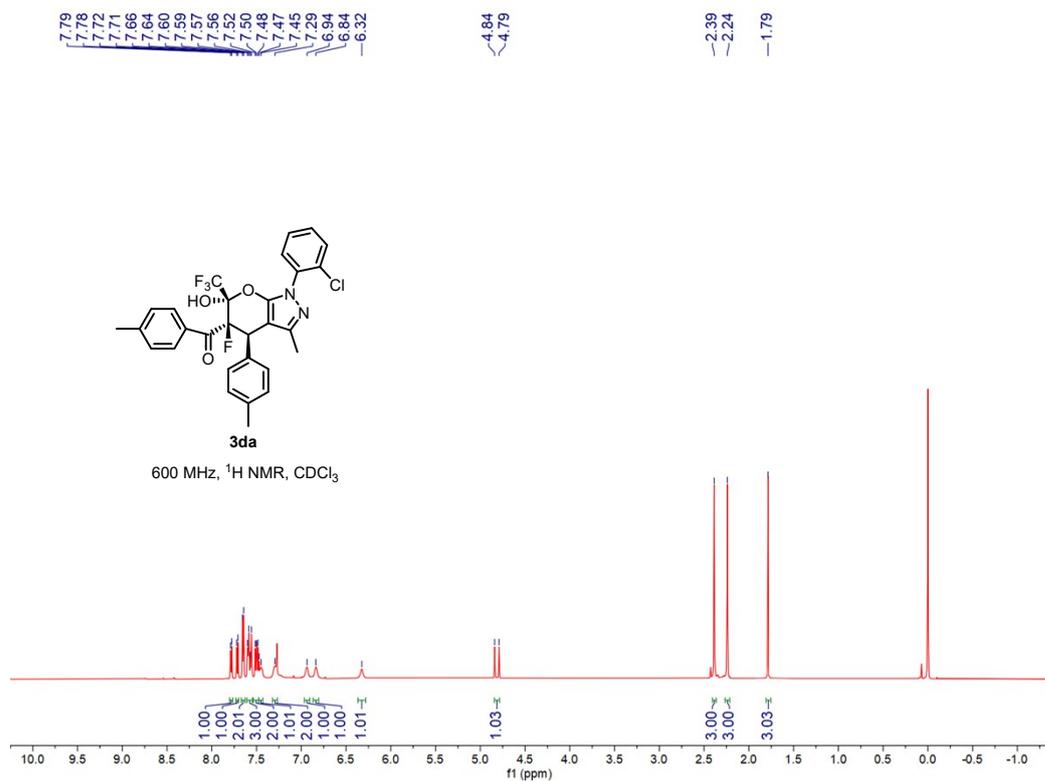


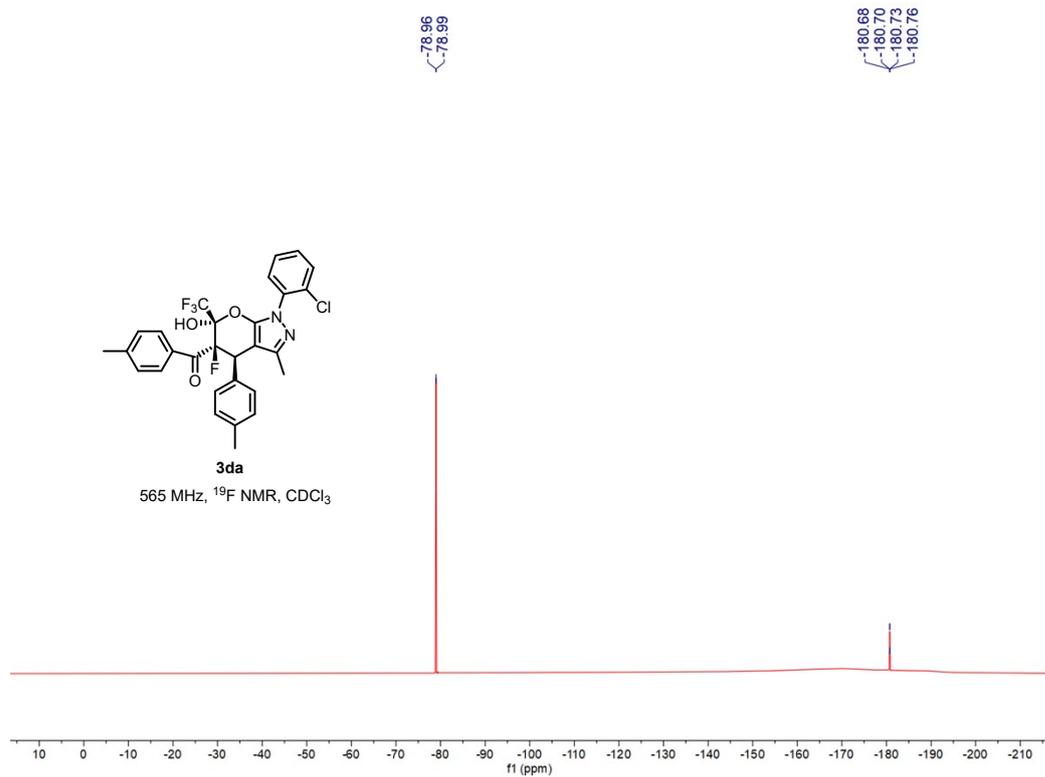
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bsr-jf-mif 122 1655 (6.659) AM2 (Ar, 12000.0, 0.00, 0.00); Cm (1655-1672)

1: TOF MS ES+
7.57e4



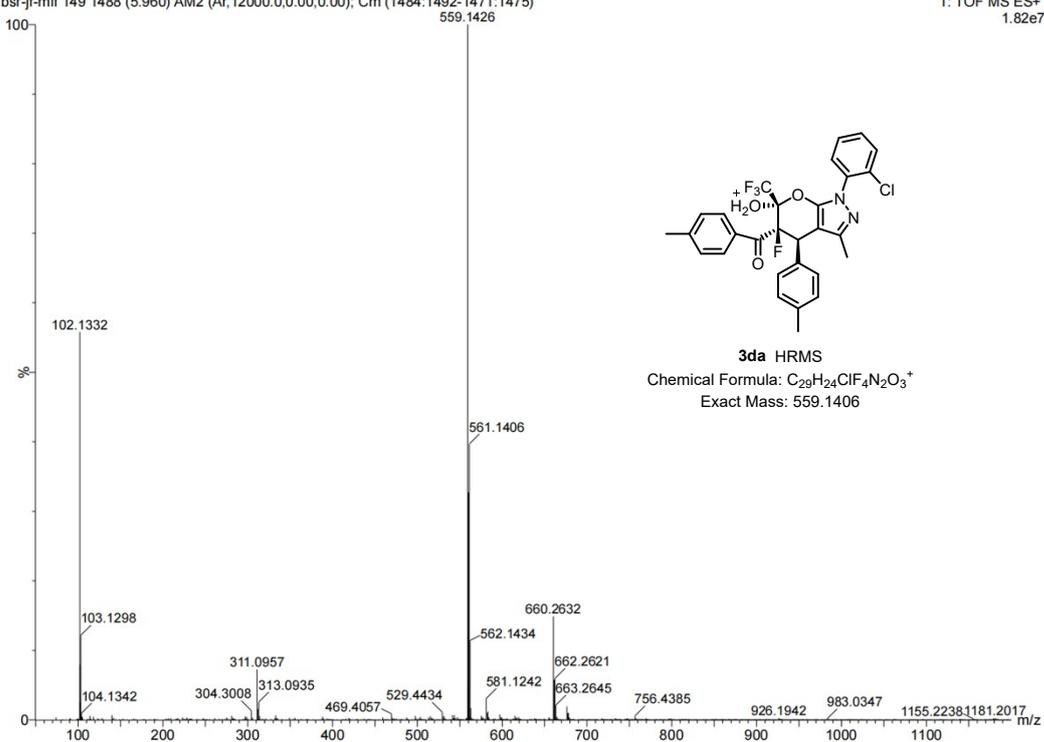


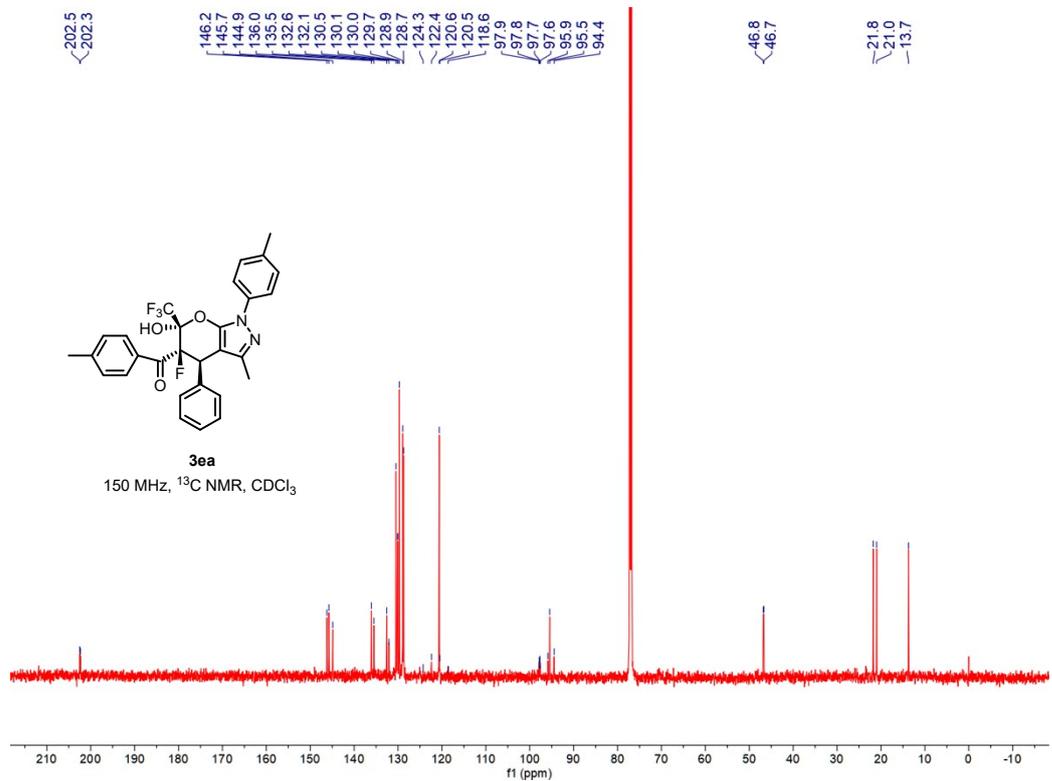
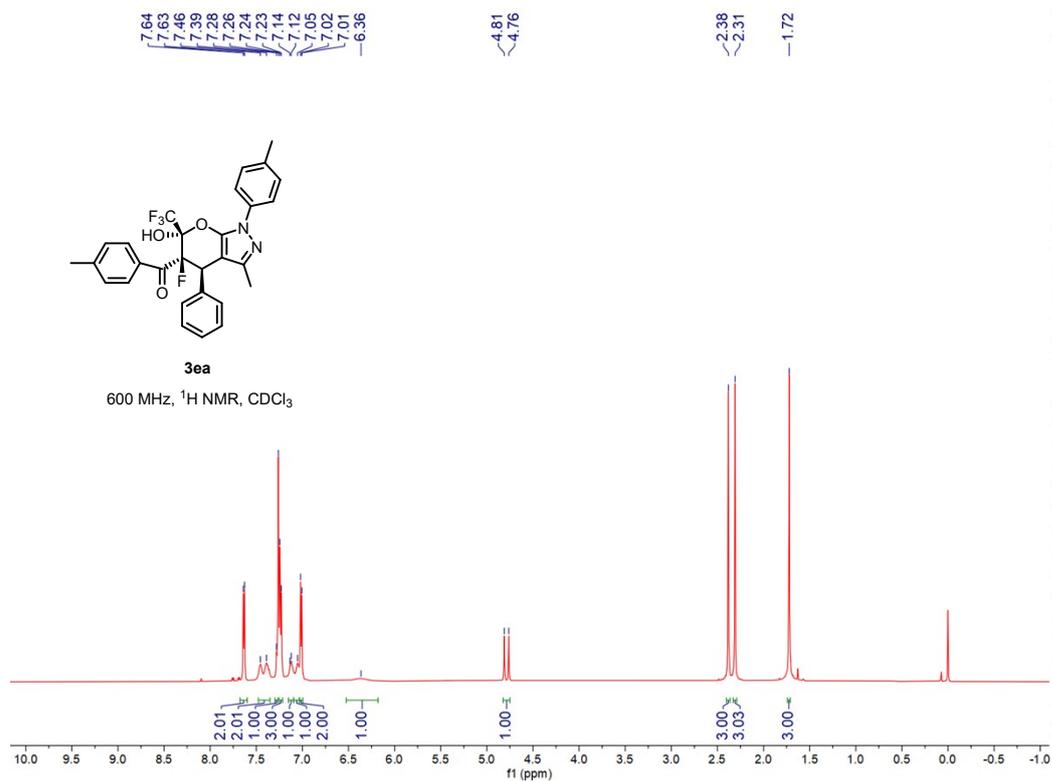


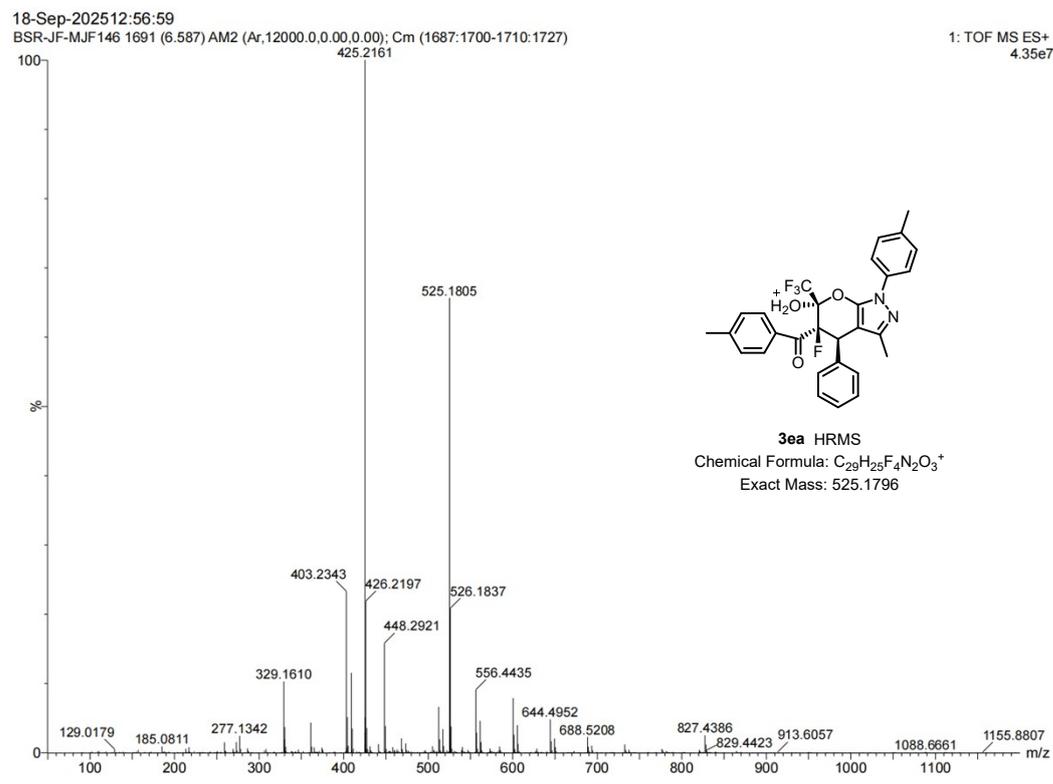
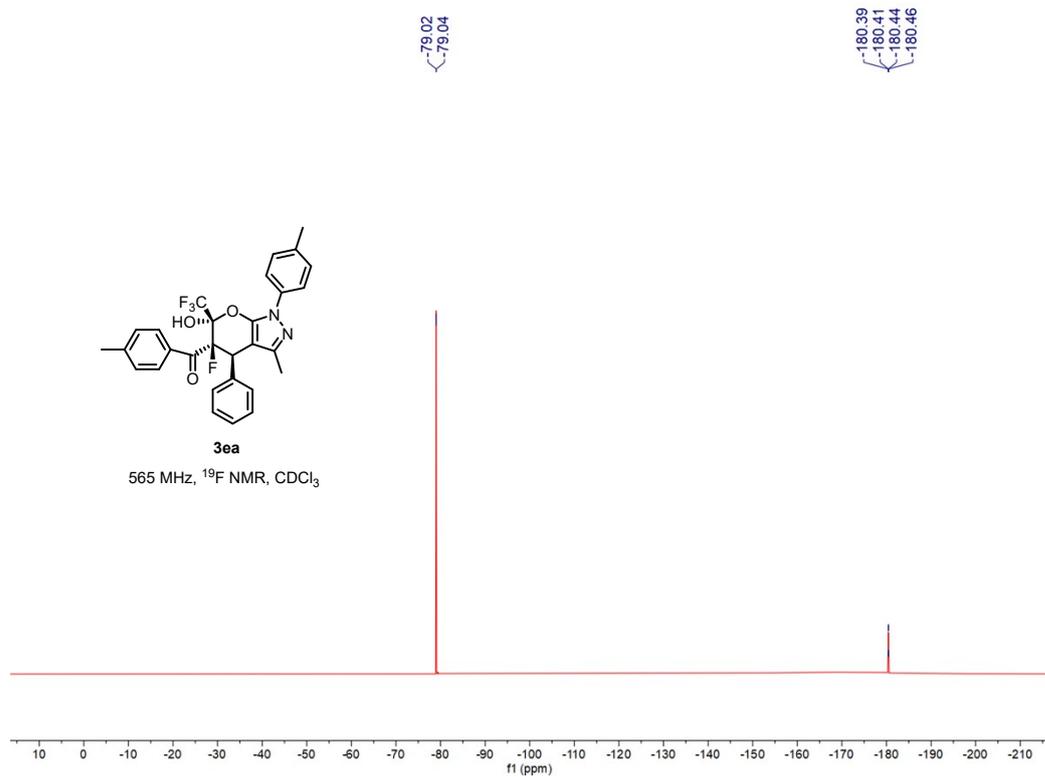
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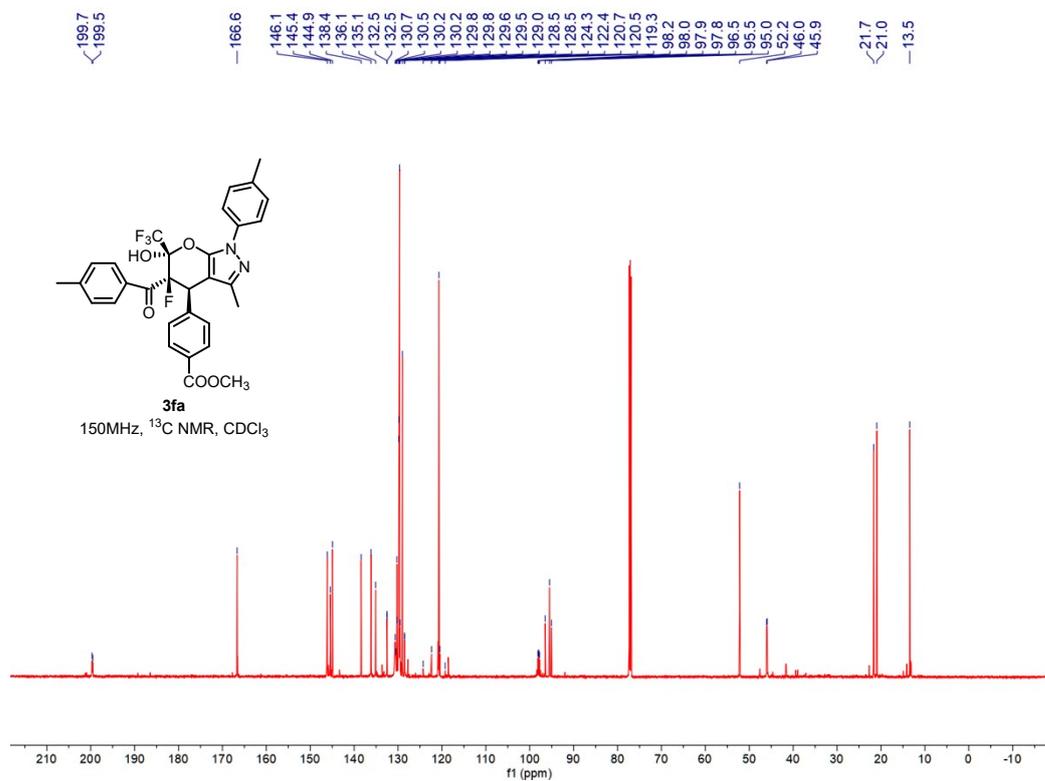
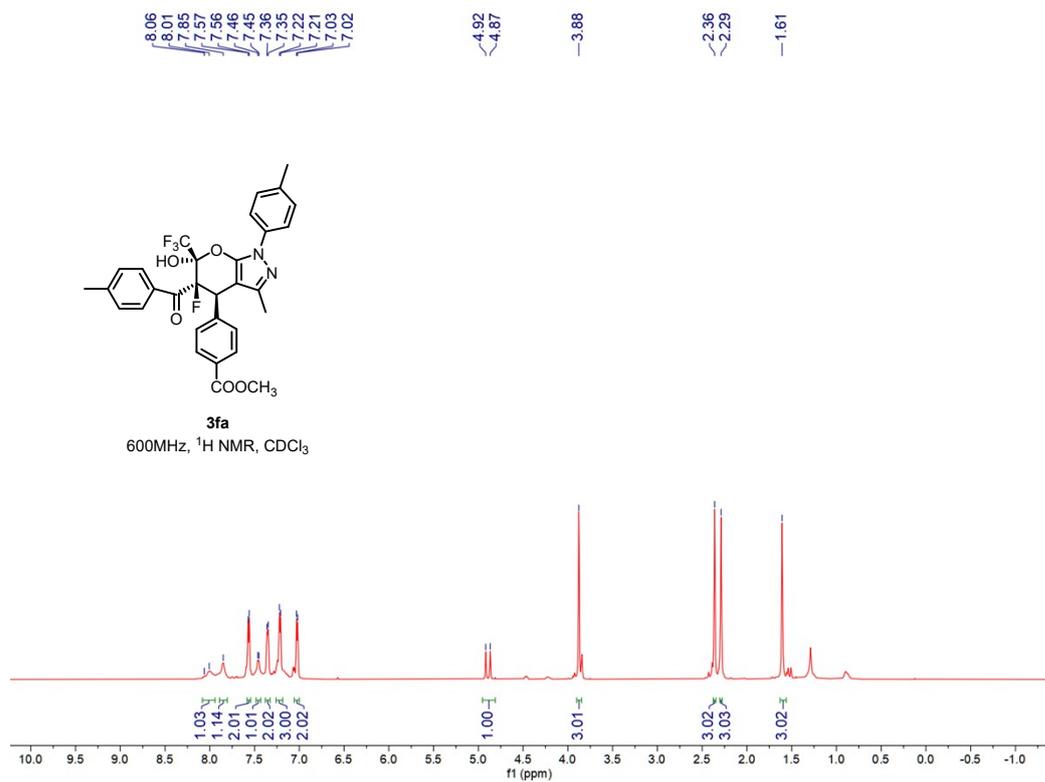
bsr-jf-mif 149 1488 (5.960) AM2 (Ar,12000.0,0.00,0.00); Cm (1484:1492-1471:1475)

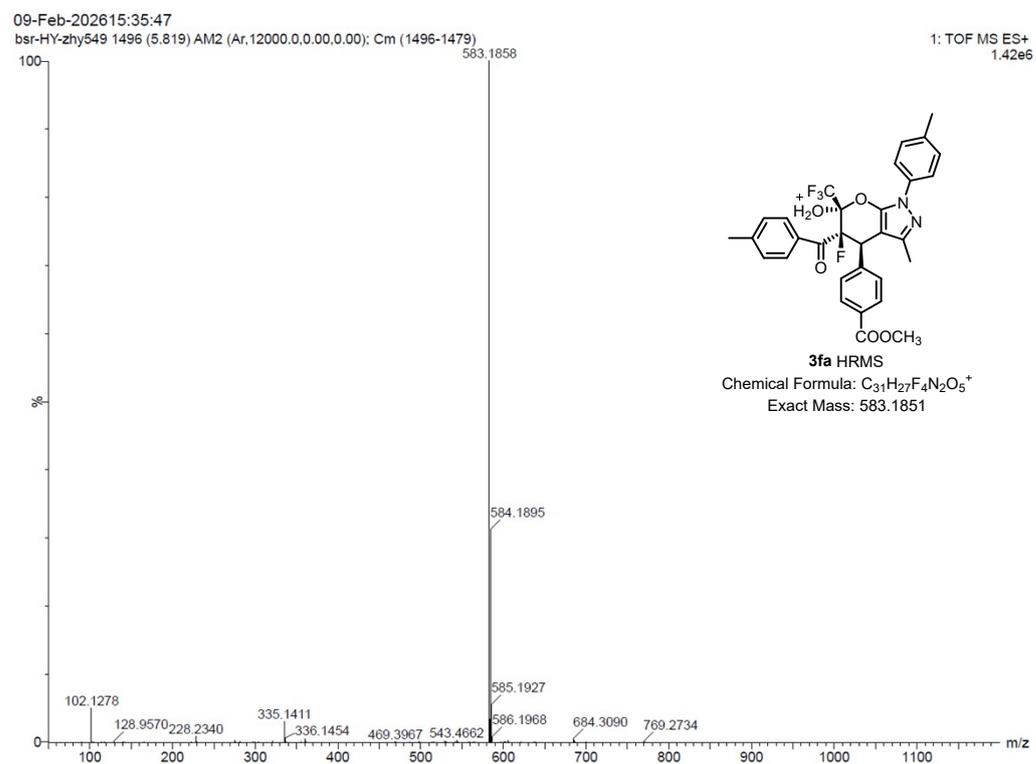
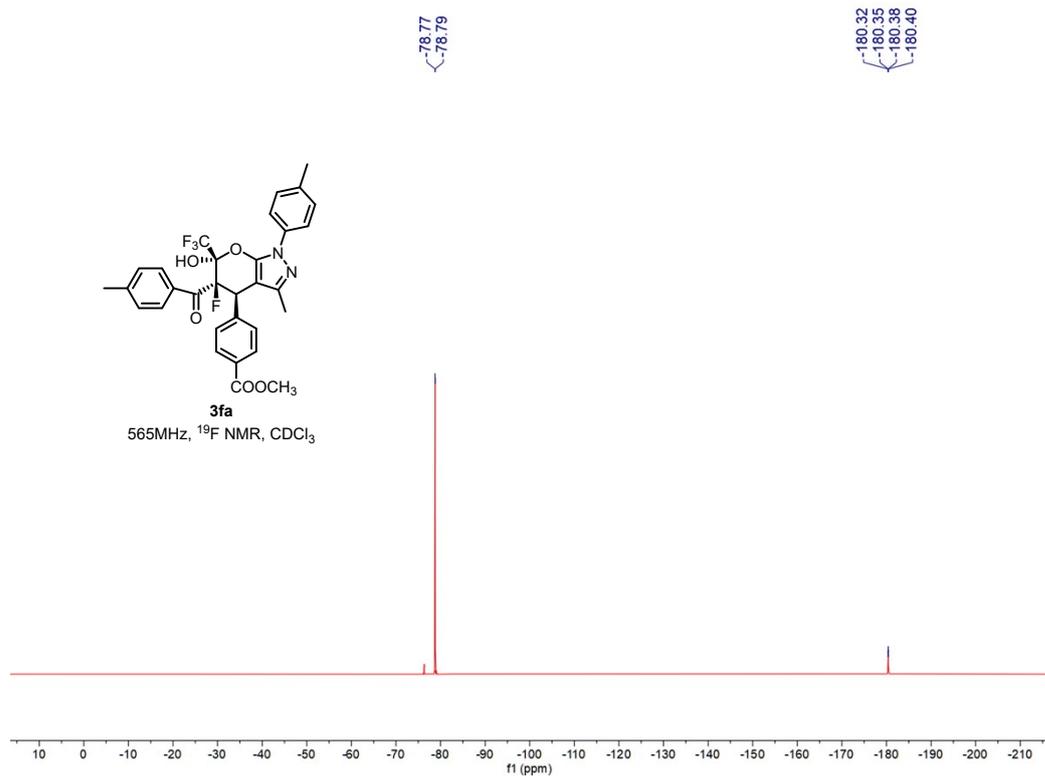
1: TOF MS ES+
1.82e7

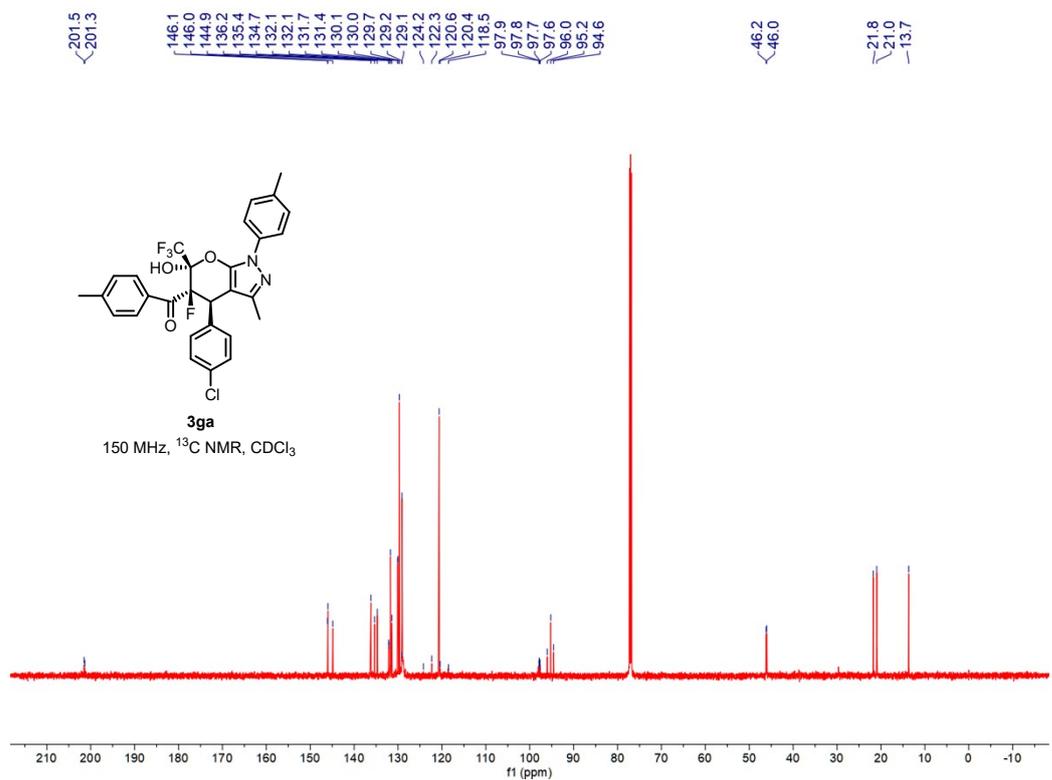
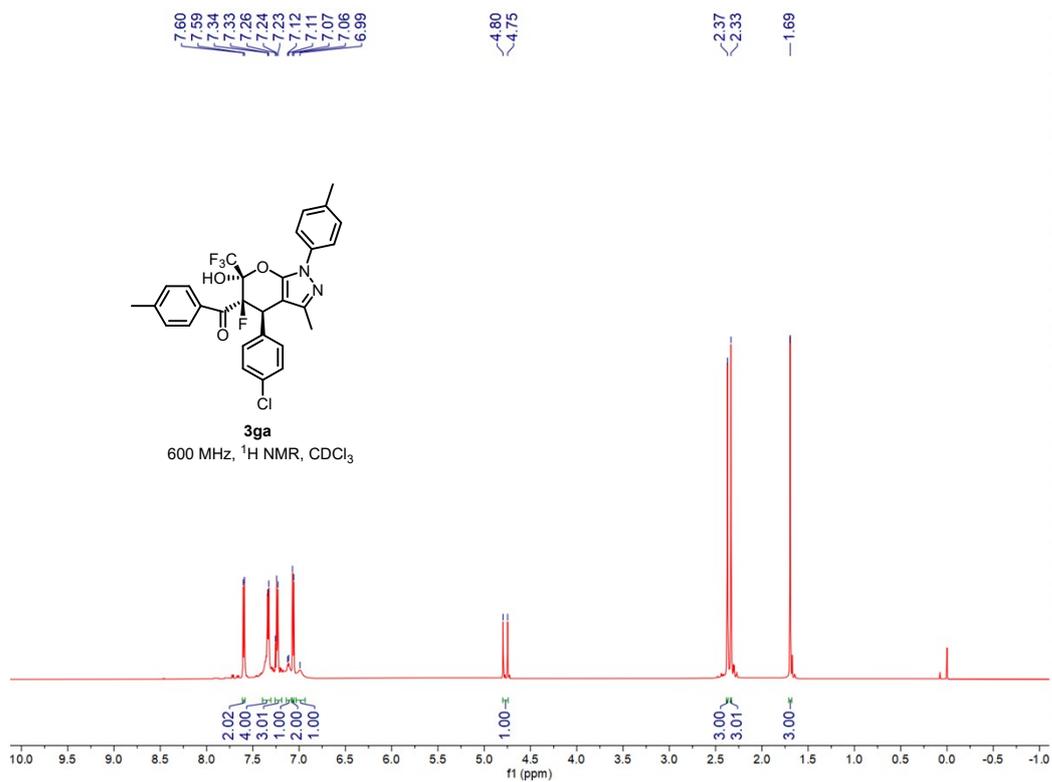


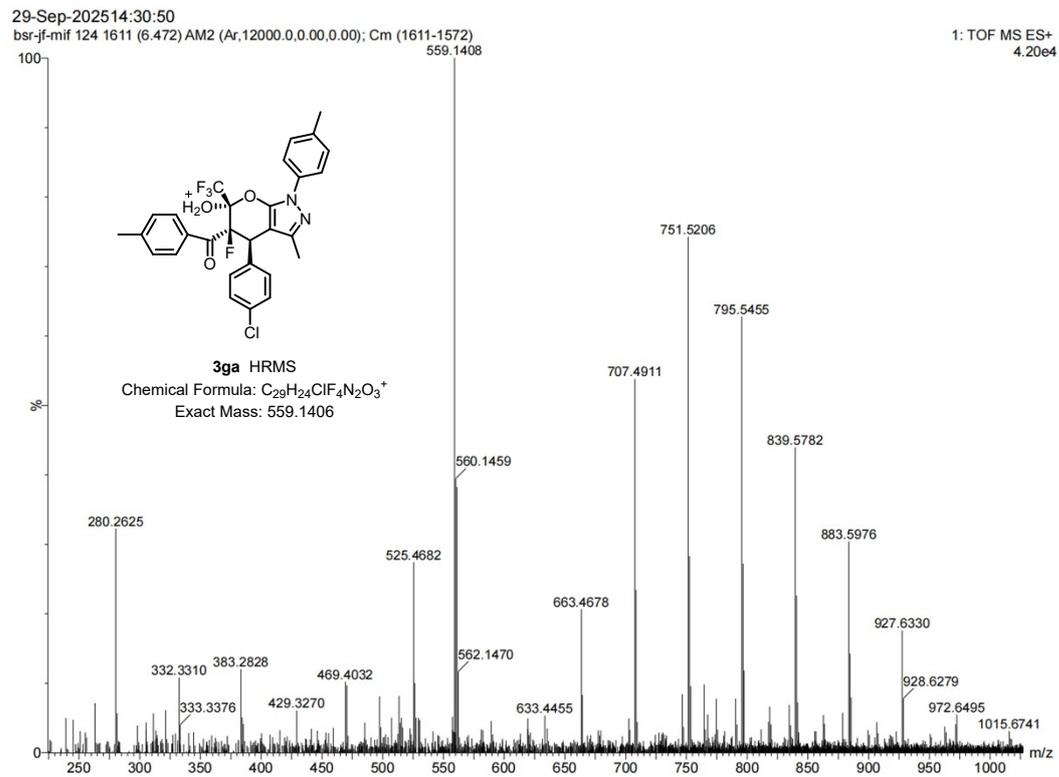
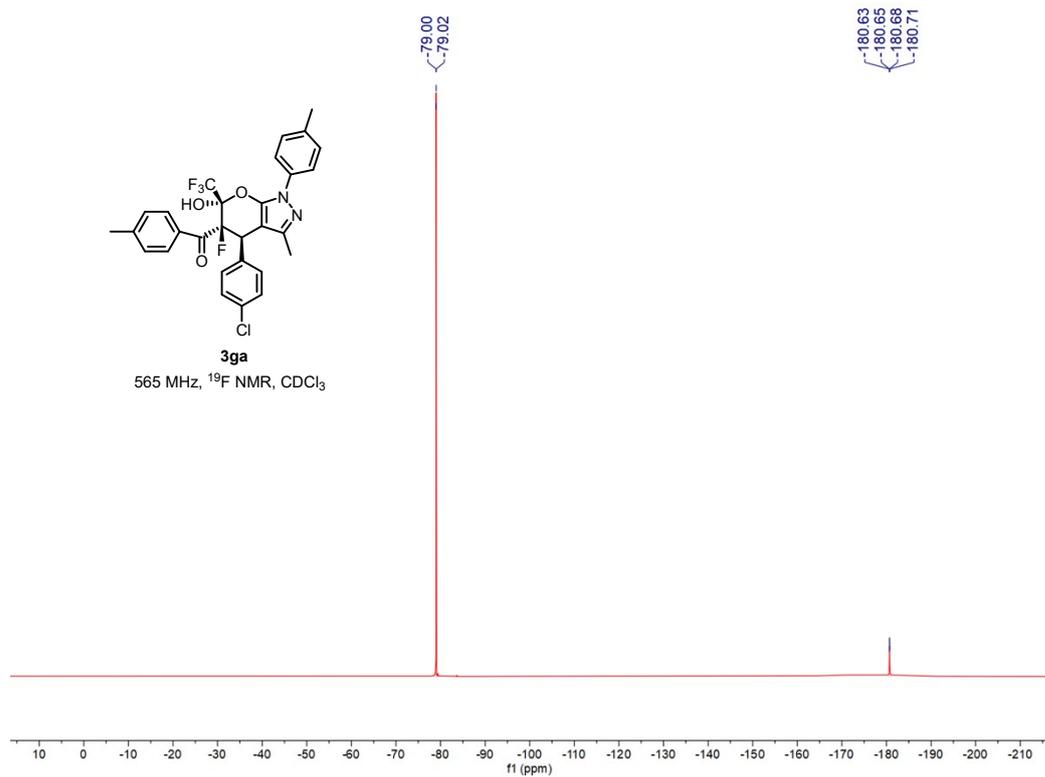


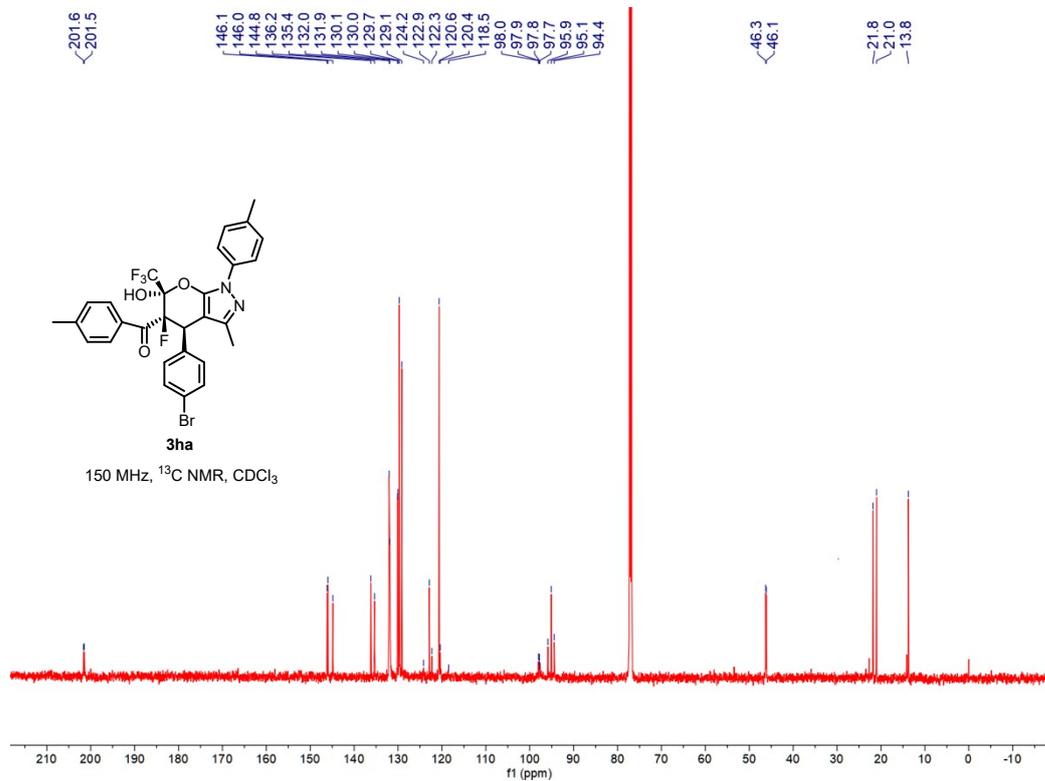
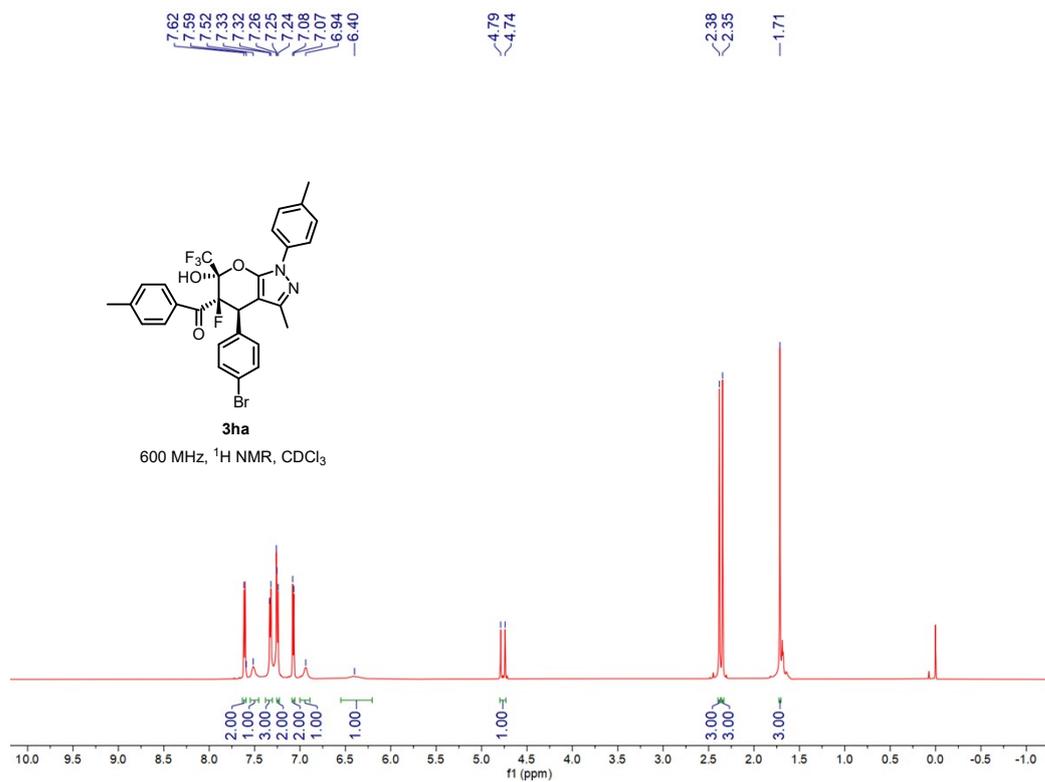


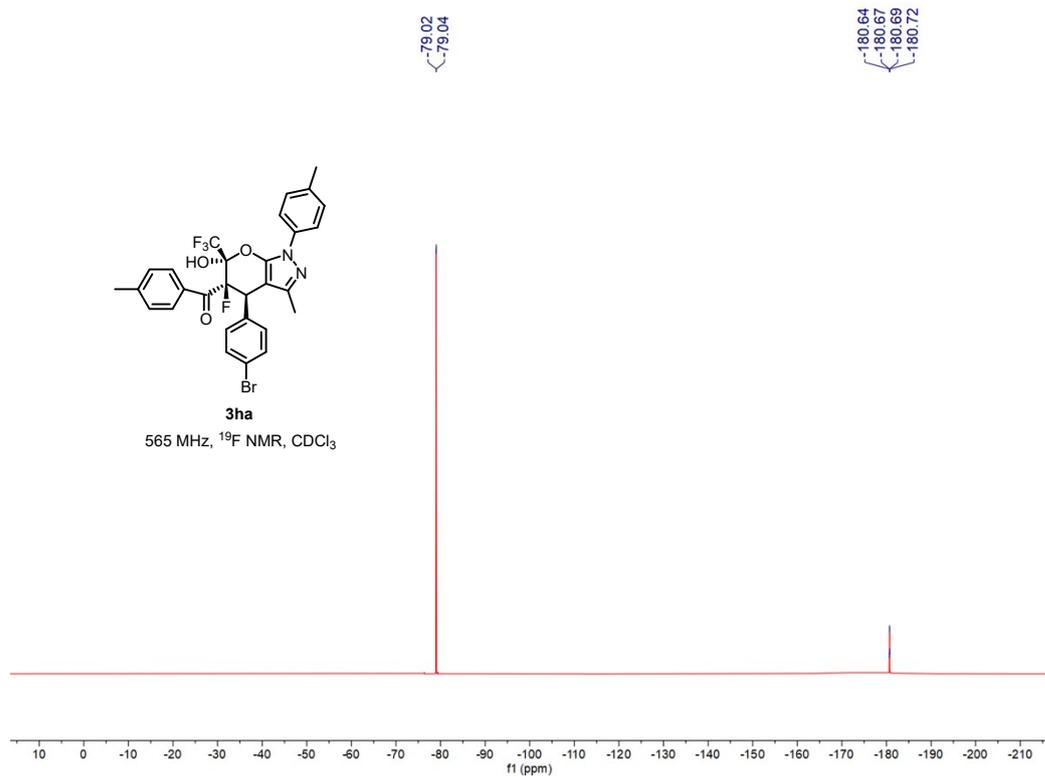








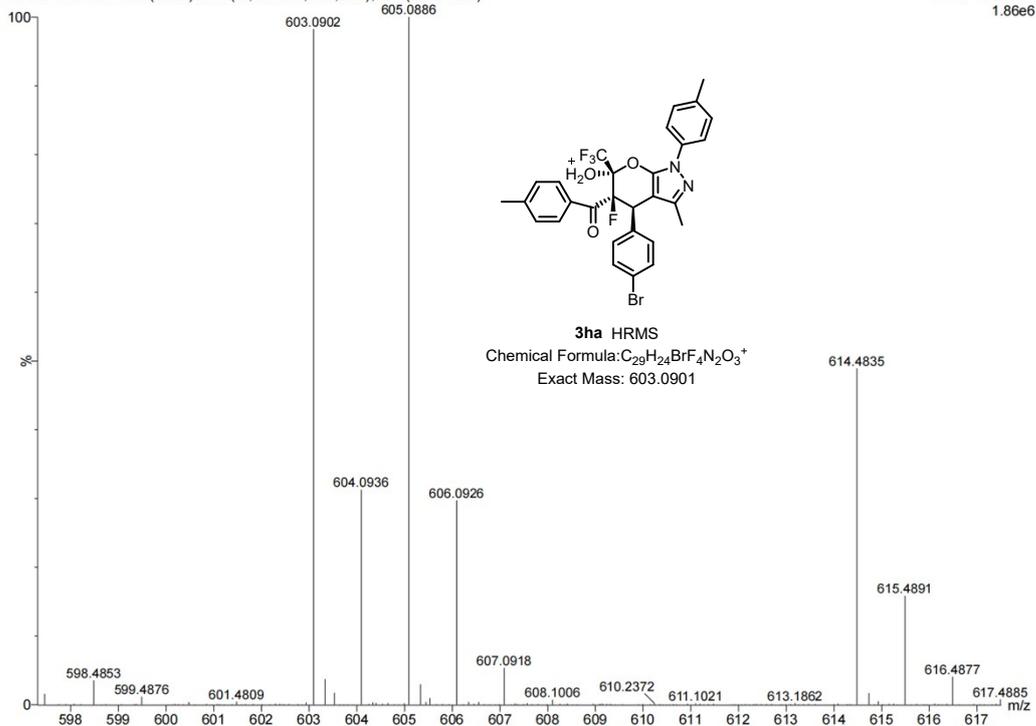


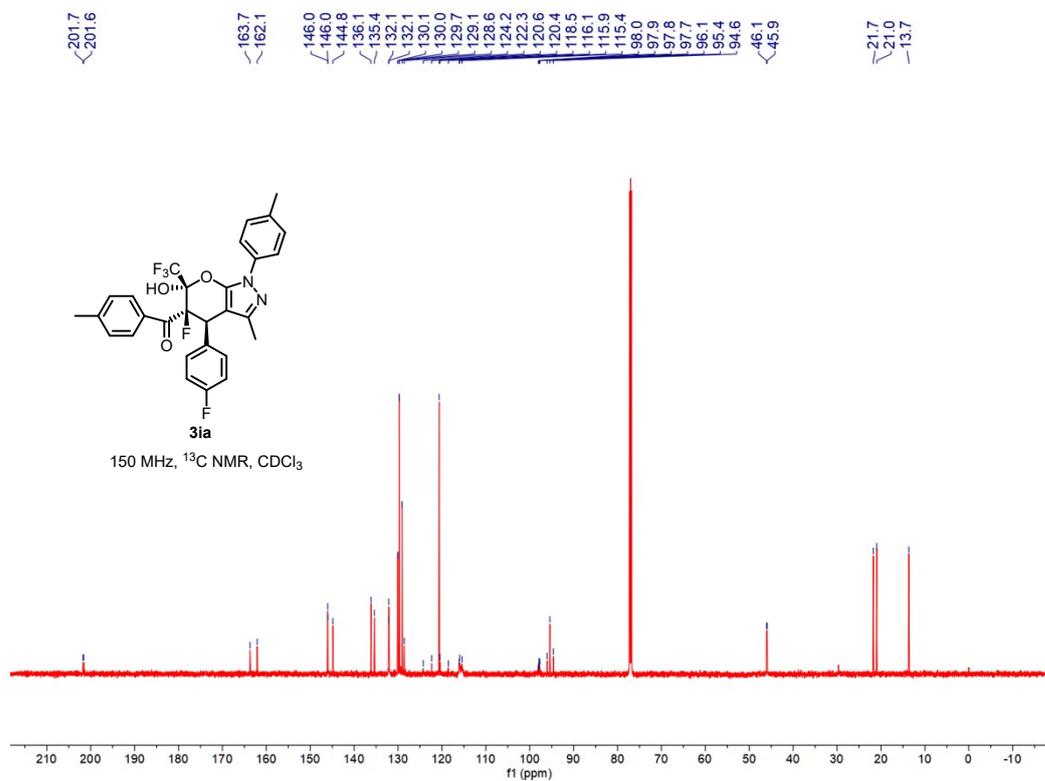
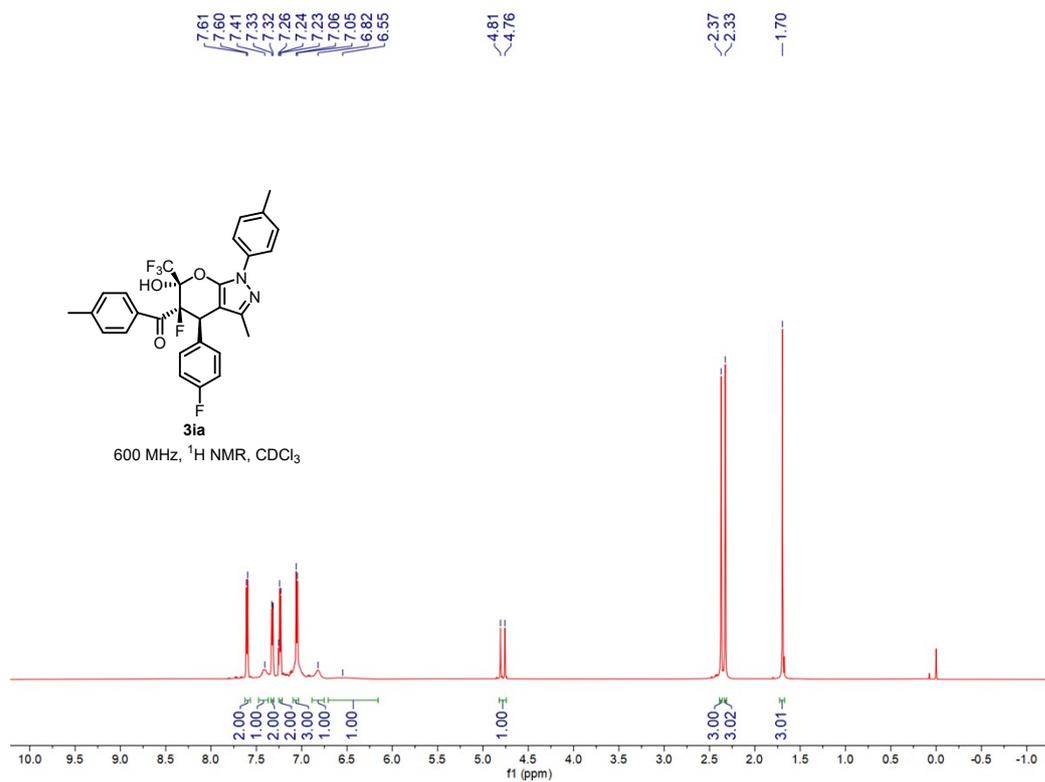


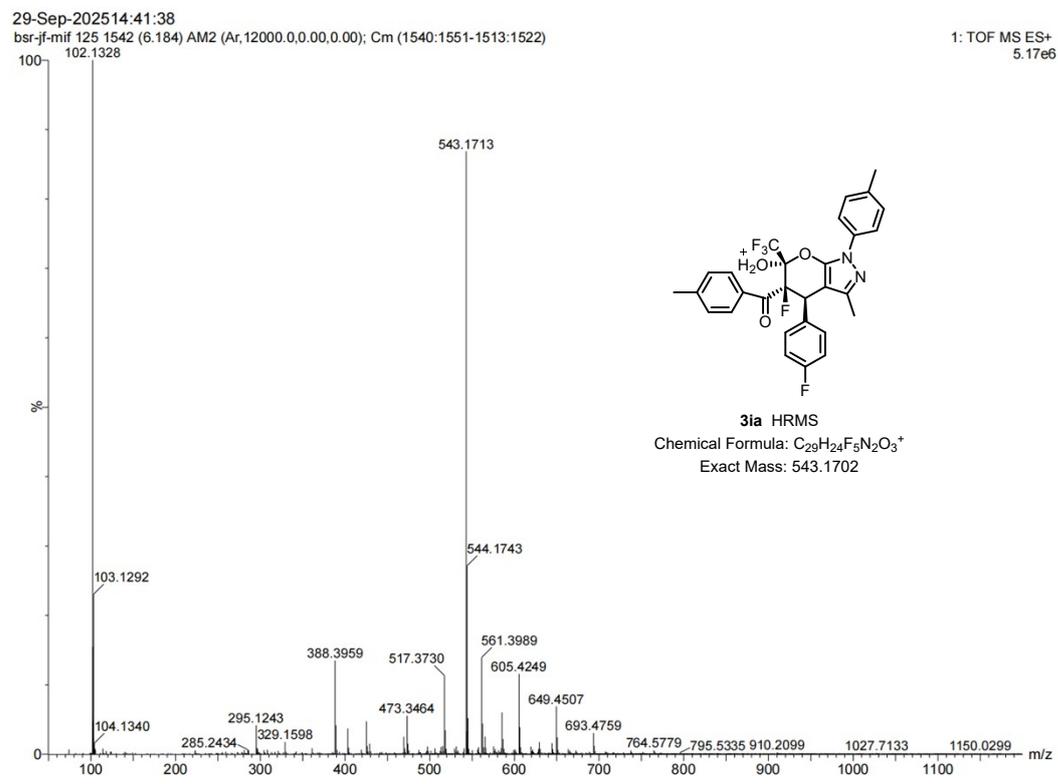
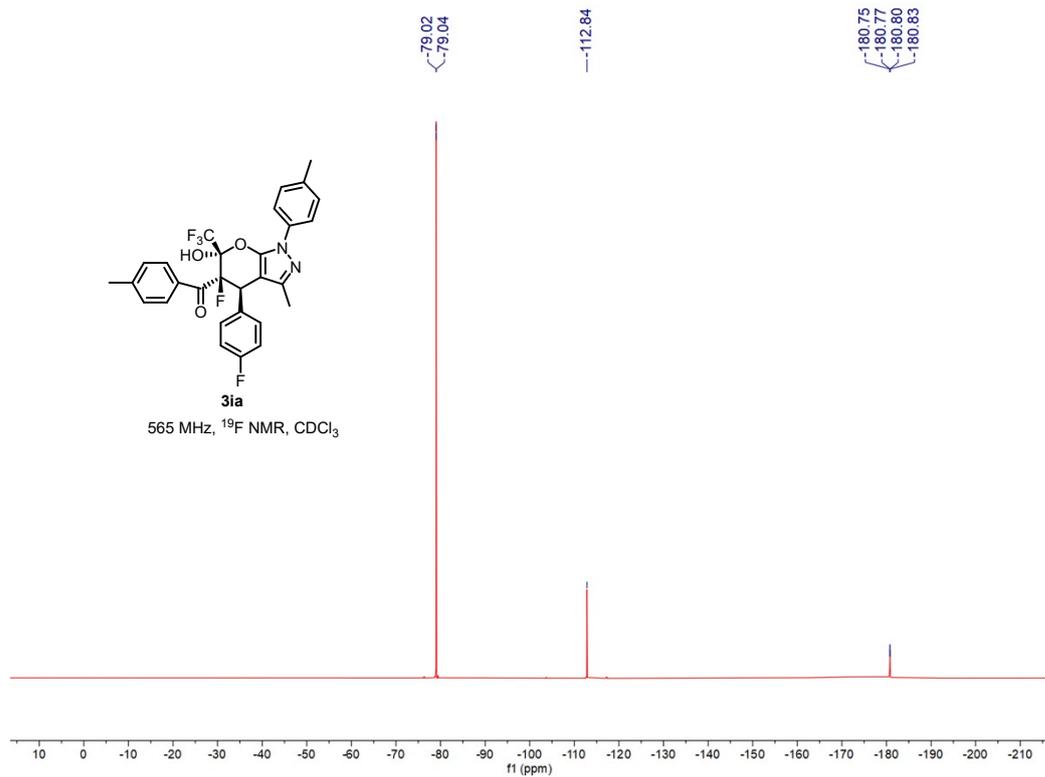
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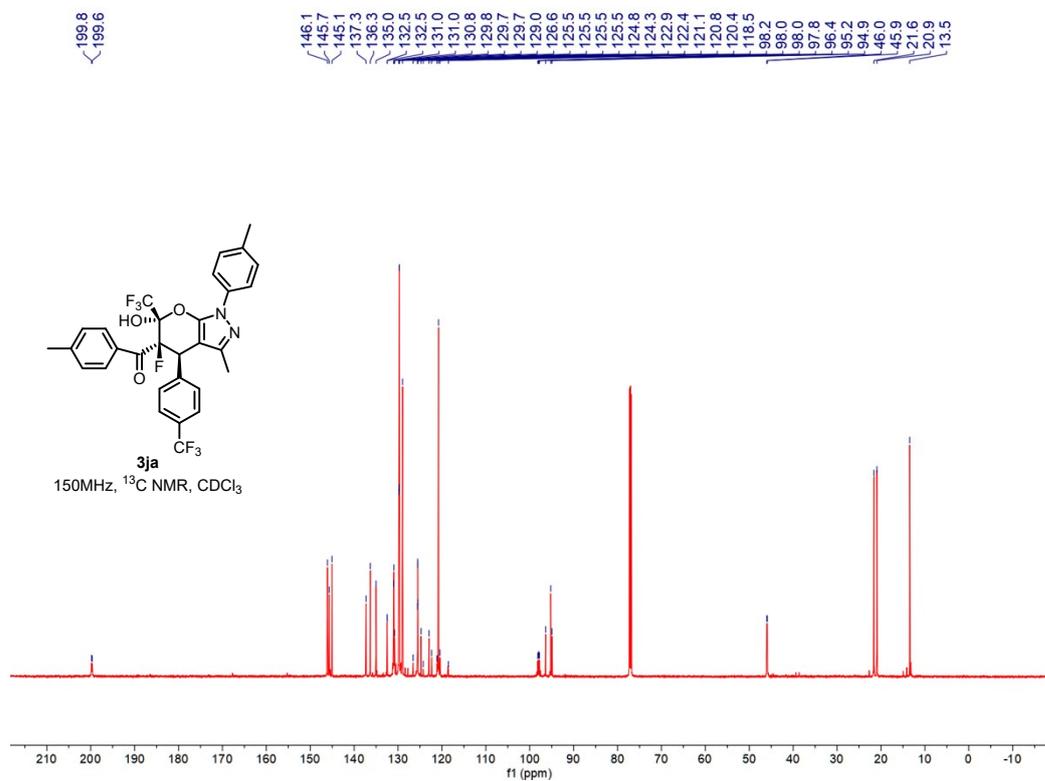
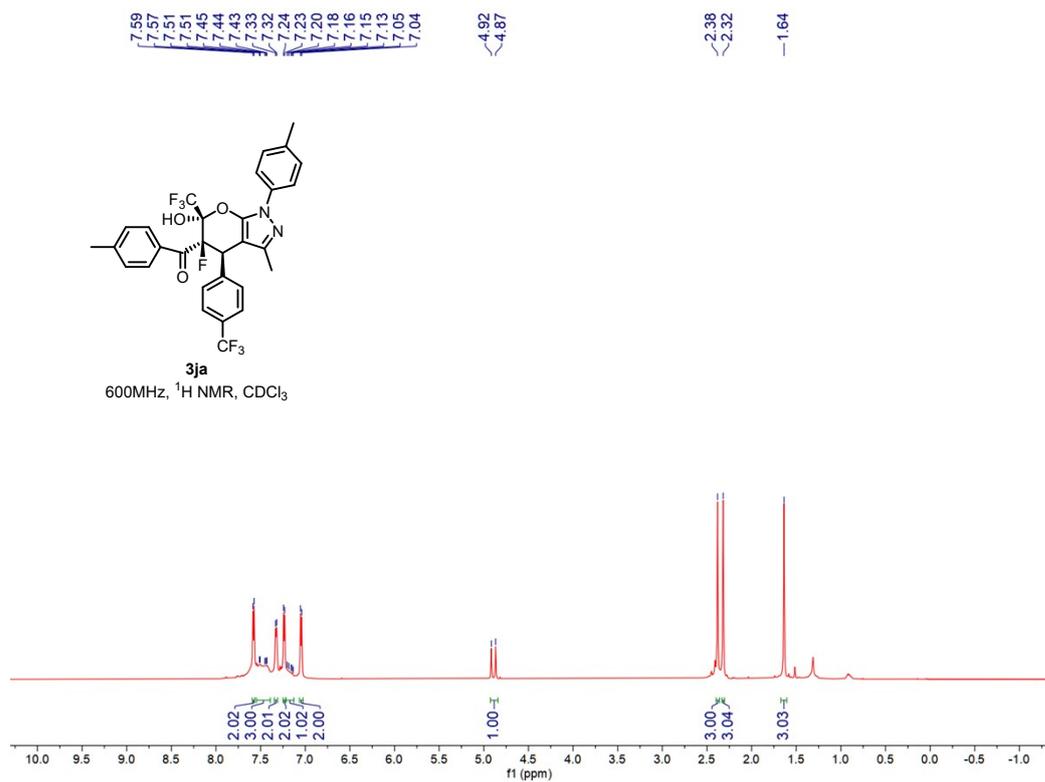
BSR-JF-MJF 137 1783 (6.939) AM2 (Ar, 12000.0, 0.00, 0.00); Cm (1783-1805)

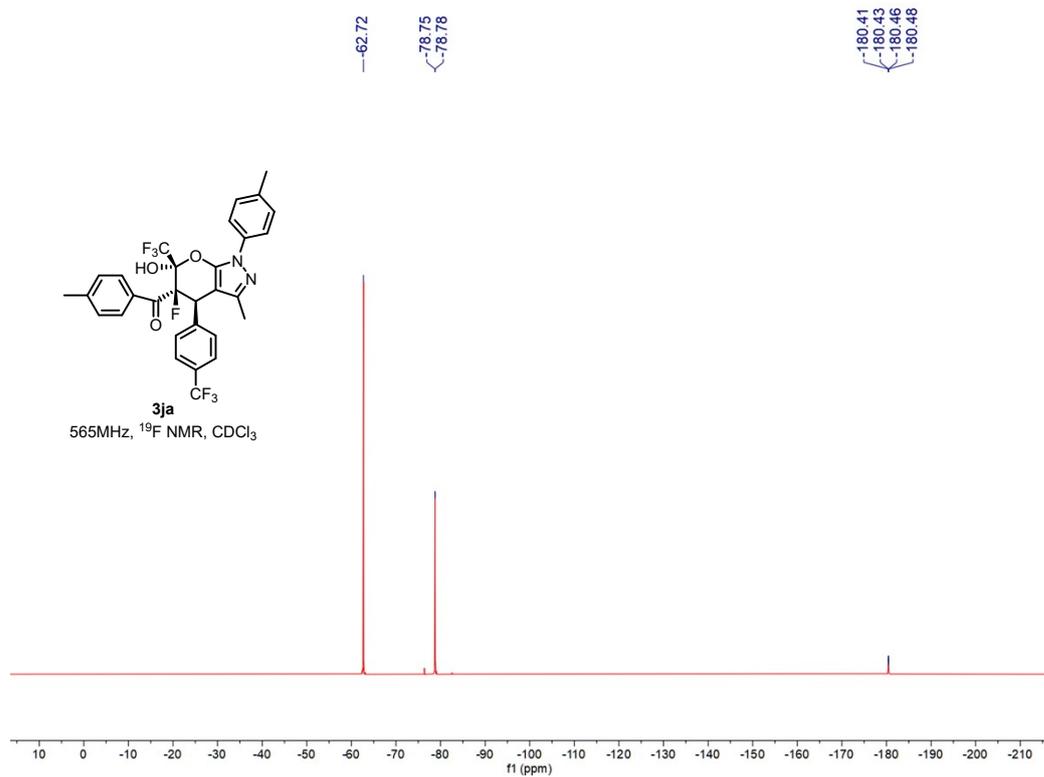
1: TOF MS ES+
1.86e6







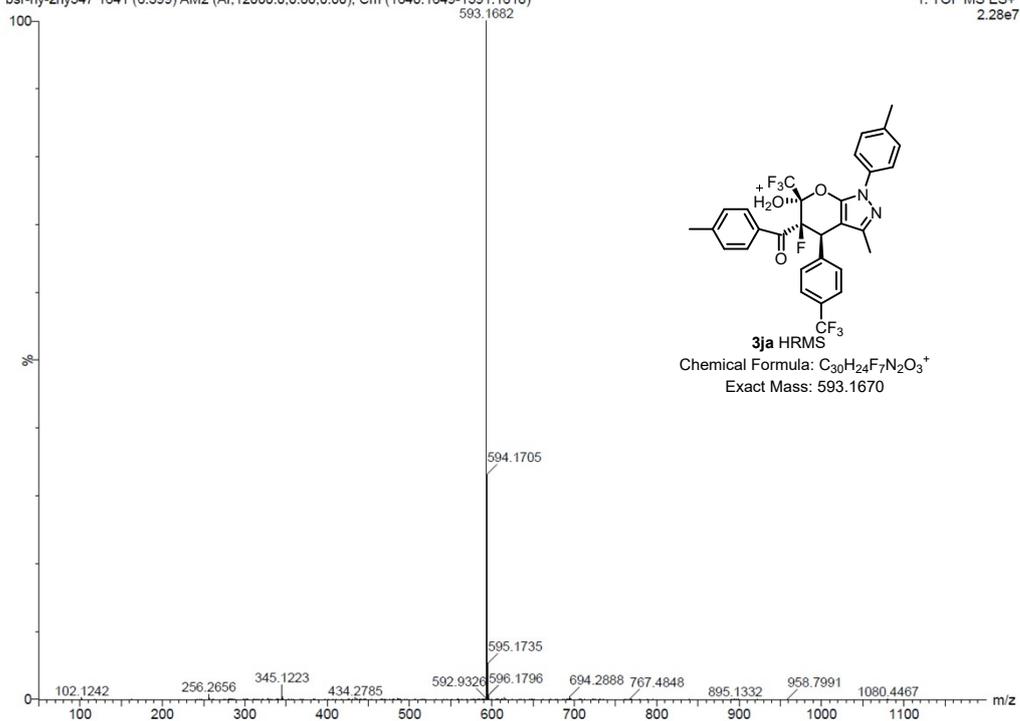


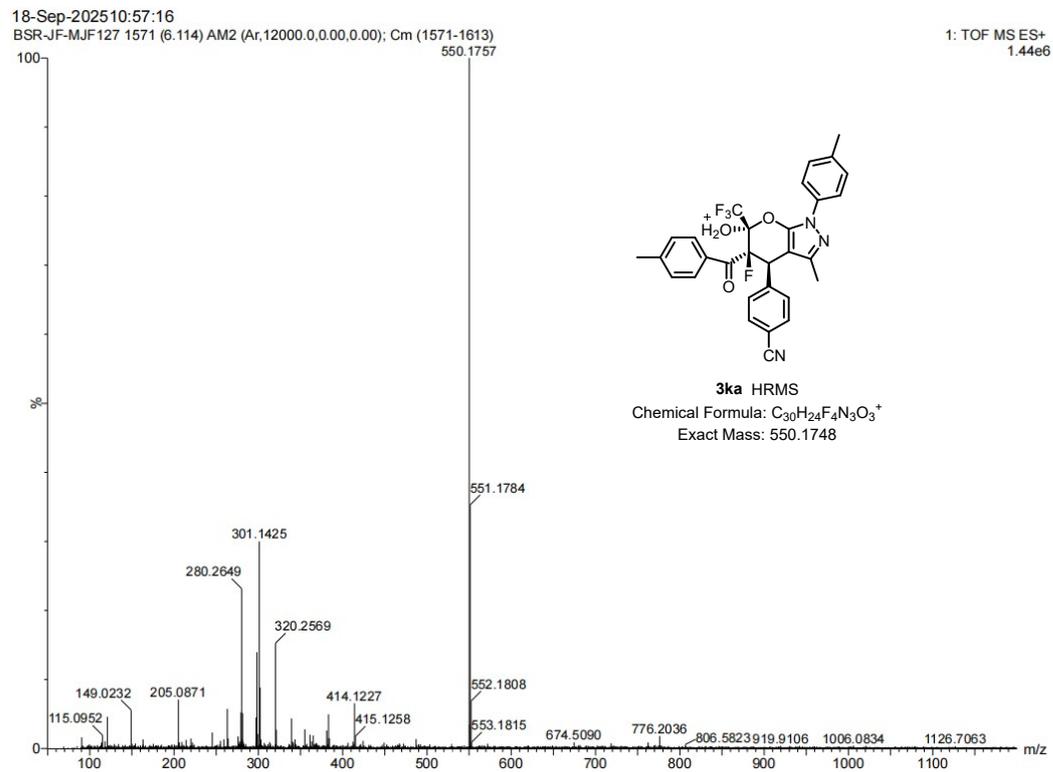
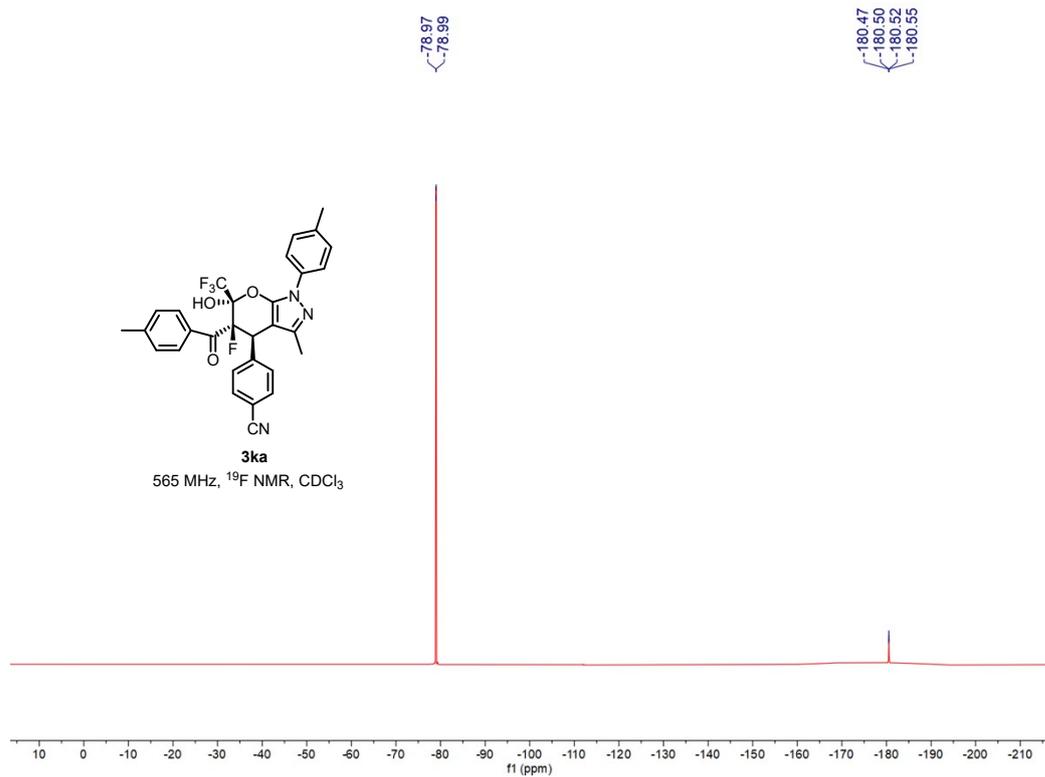


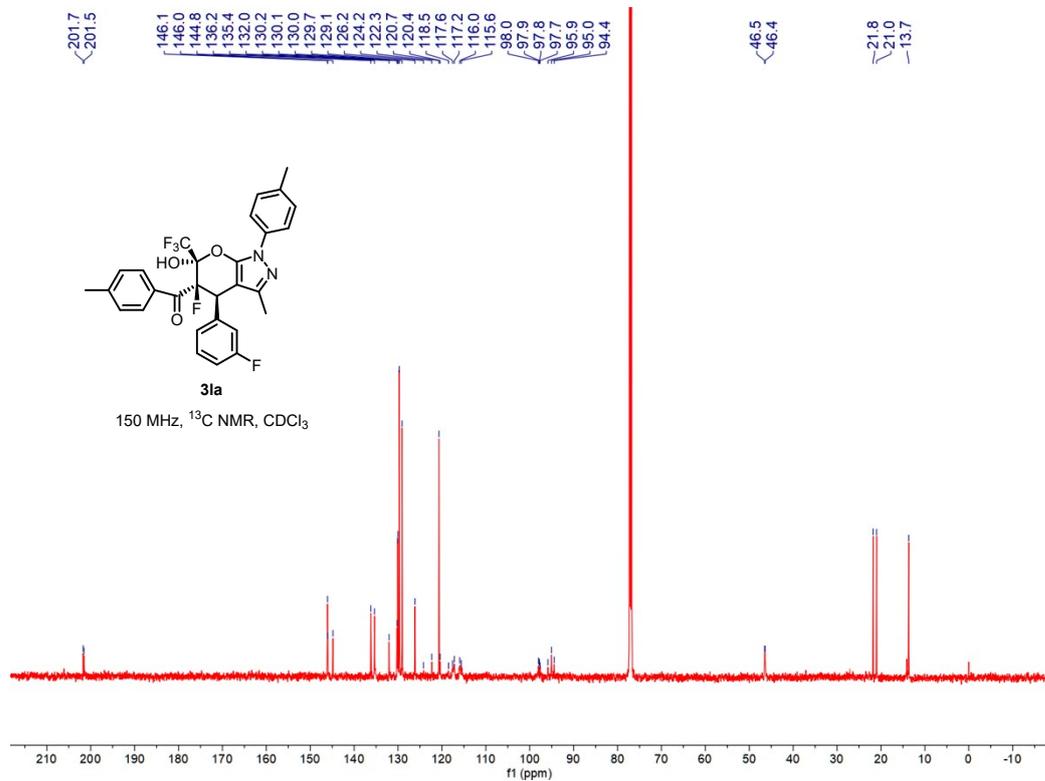
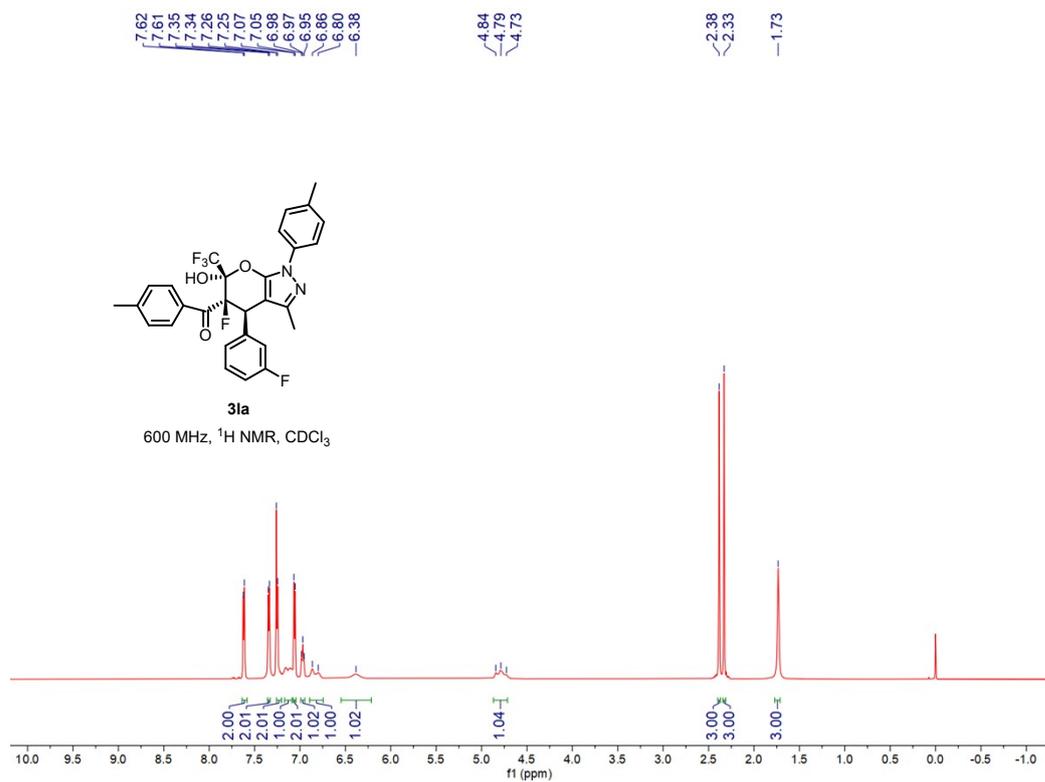
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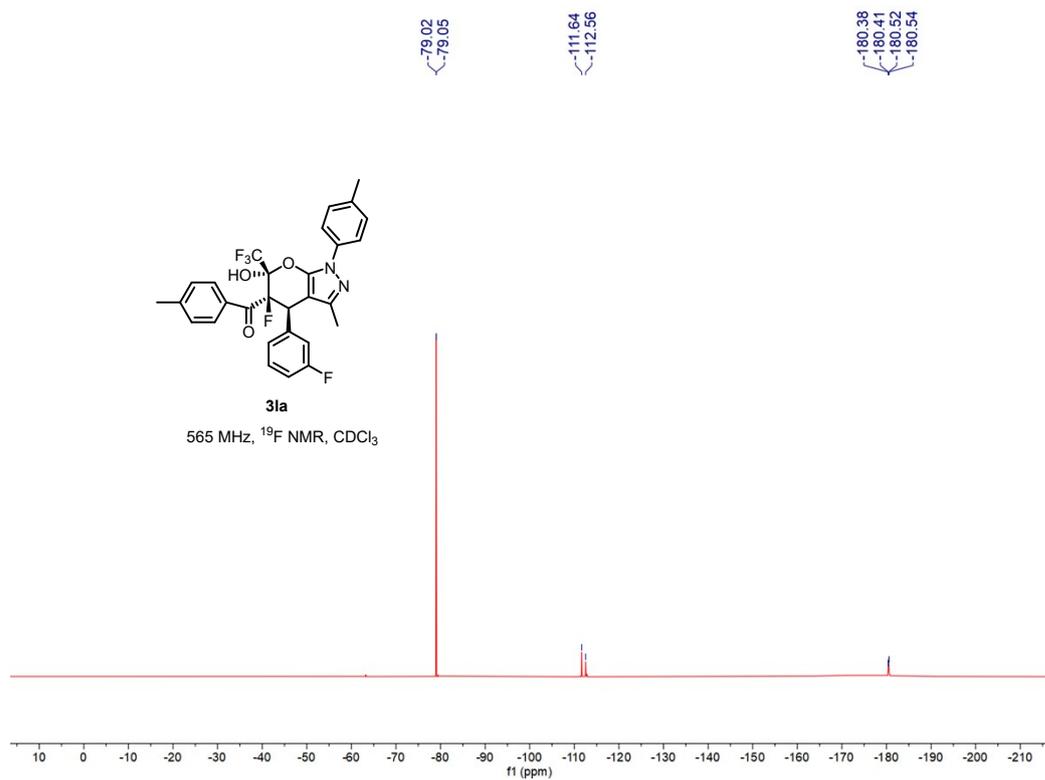
bsr-hy-zhy547 1641 (6.399) AM2 (Ar, 12000.0.0.00.0.00); Cm (1640:1649-1591:1618)

1: TOF MS ES+
2.28e7





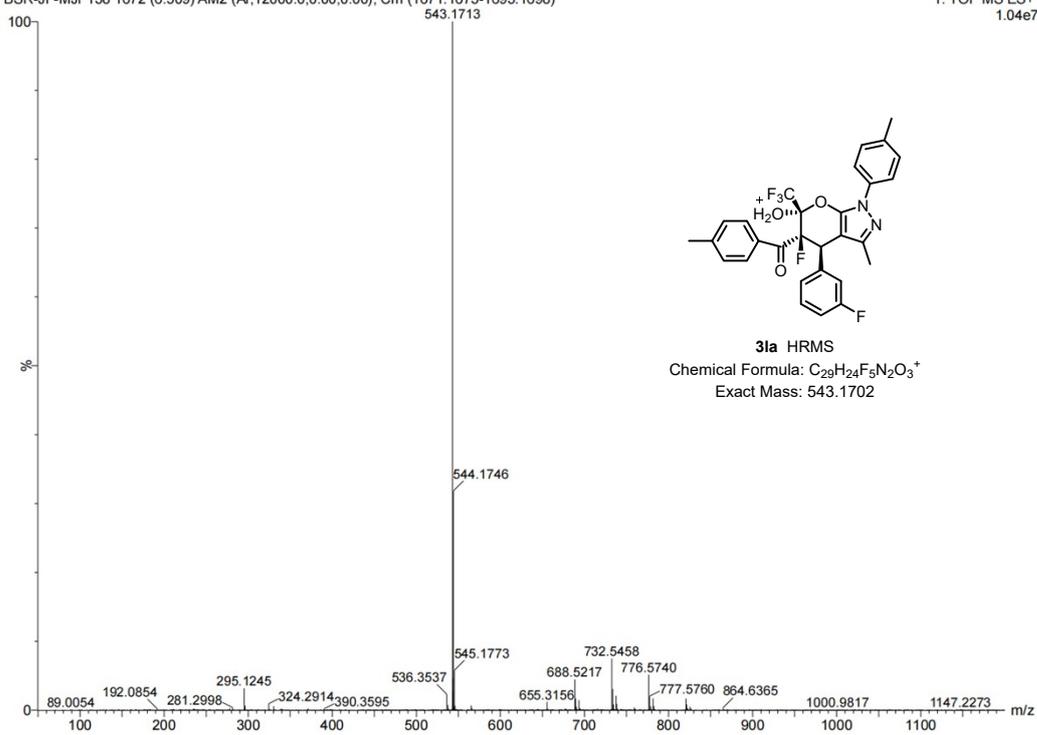


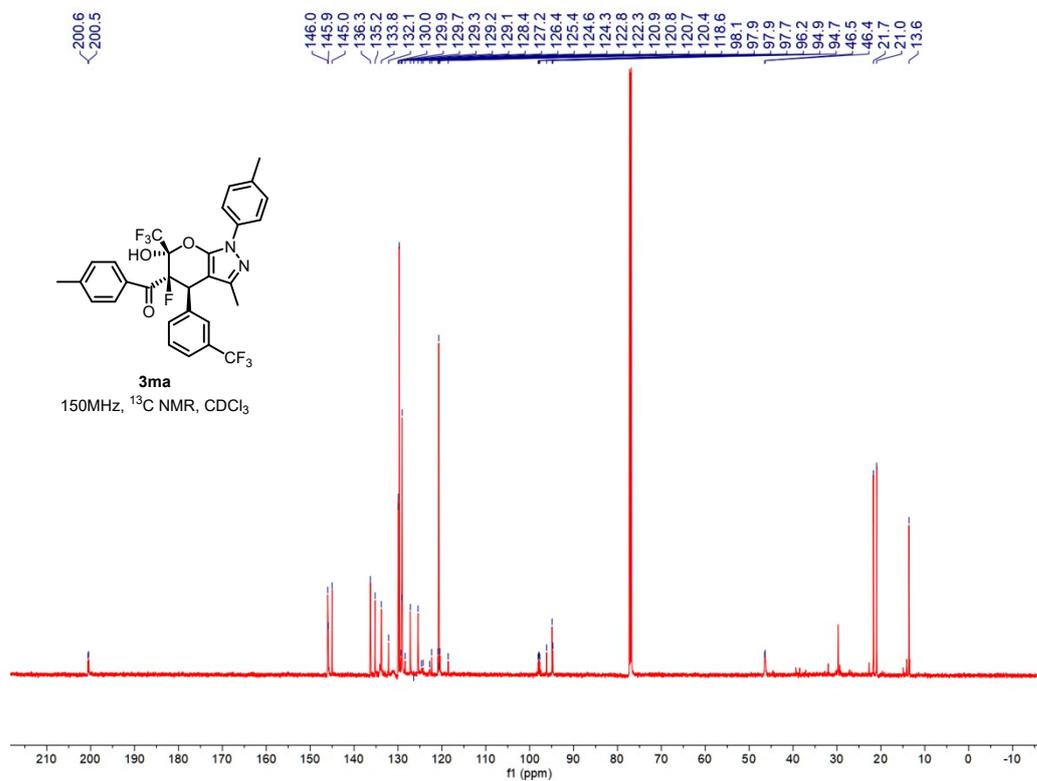
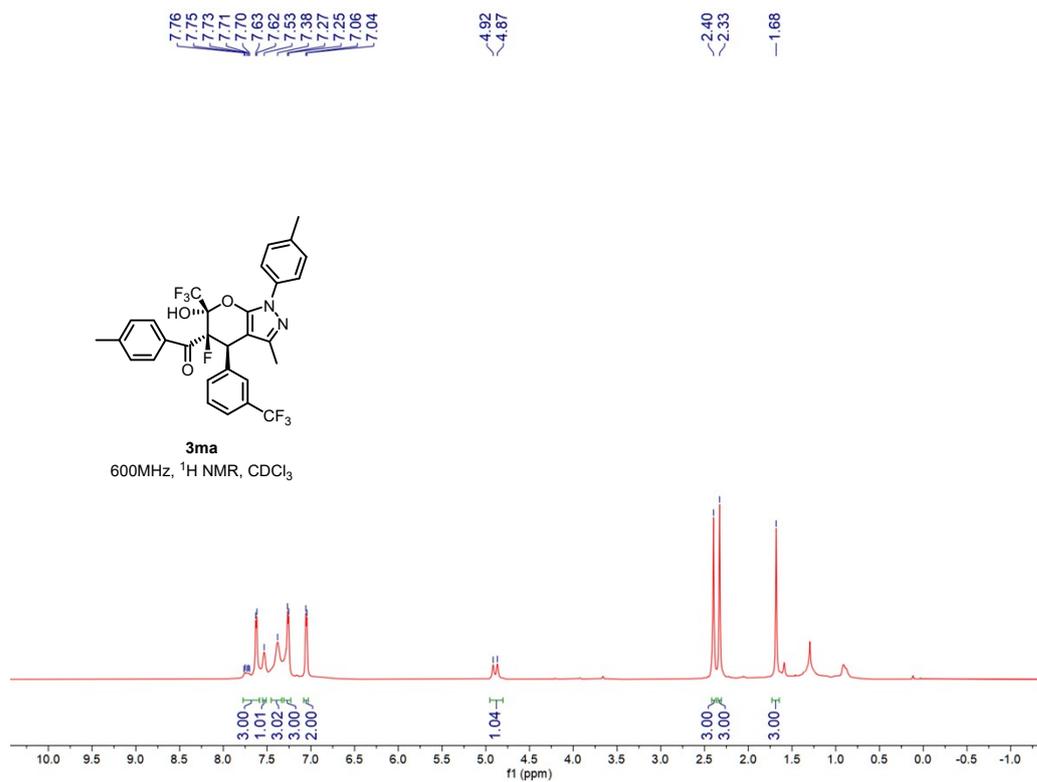


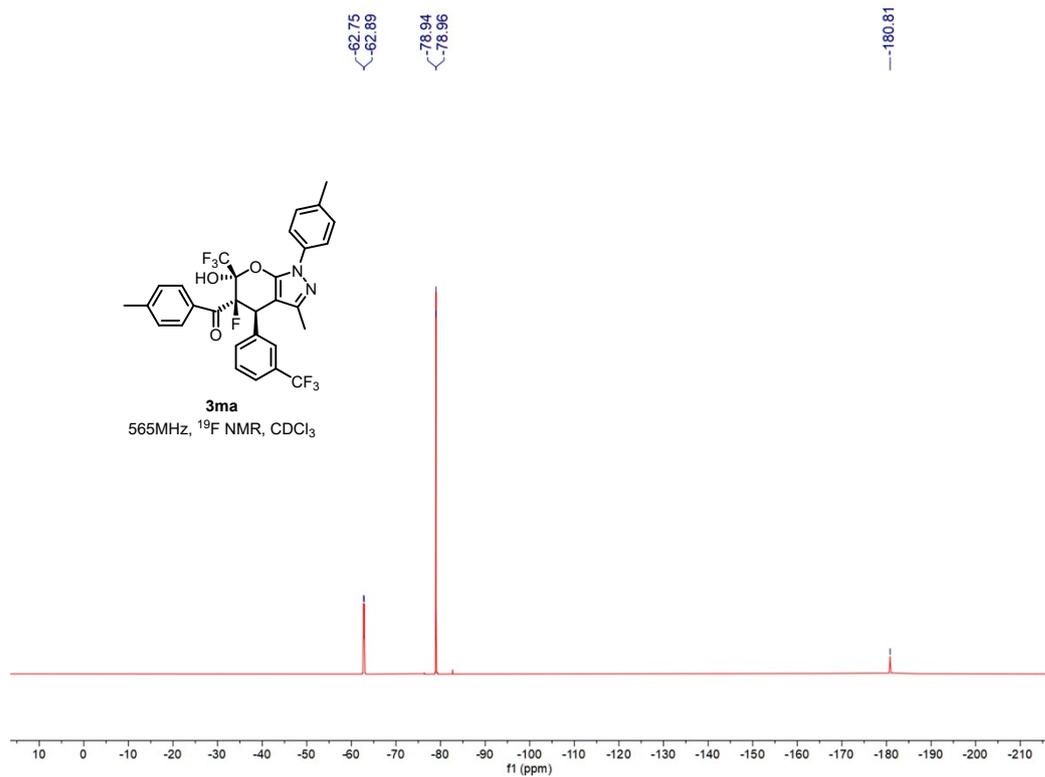
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BSR-JF-MJF138 1672 (6.509) AM2 (Ar,12000.0,0.00,0.00); Cm (1671.1673-1693.1698)

1: TOF MS ES+
1.04e7



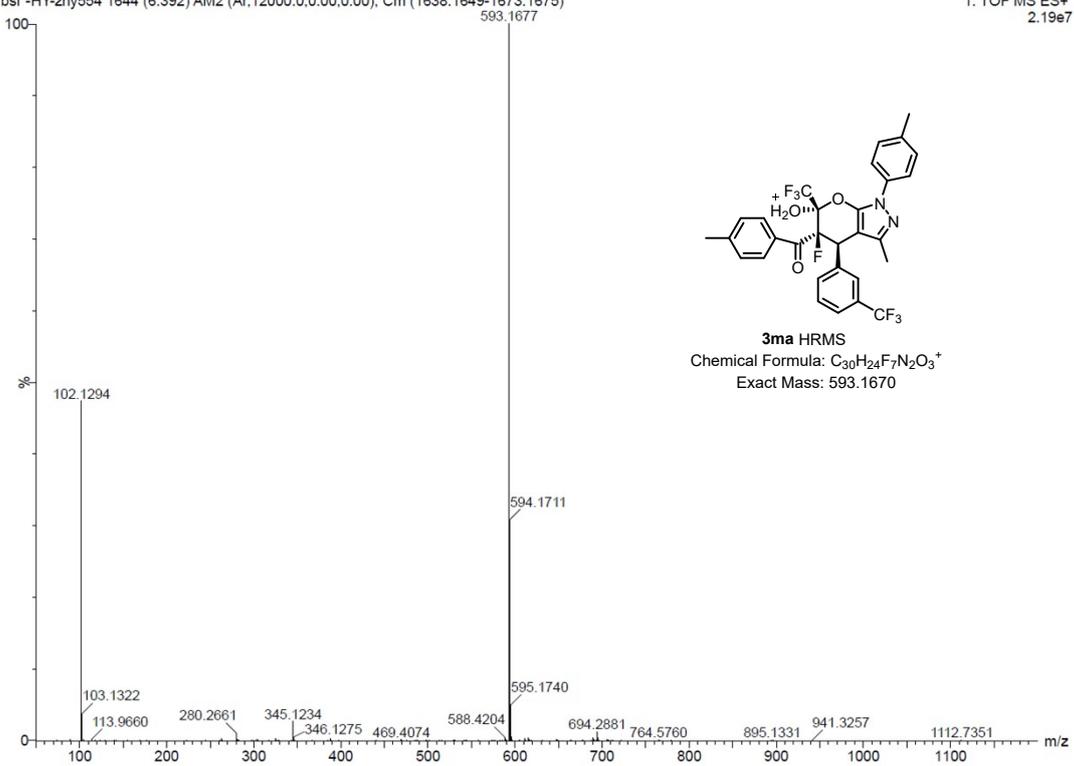


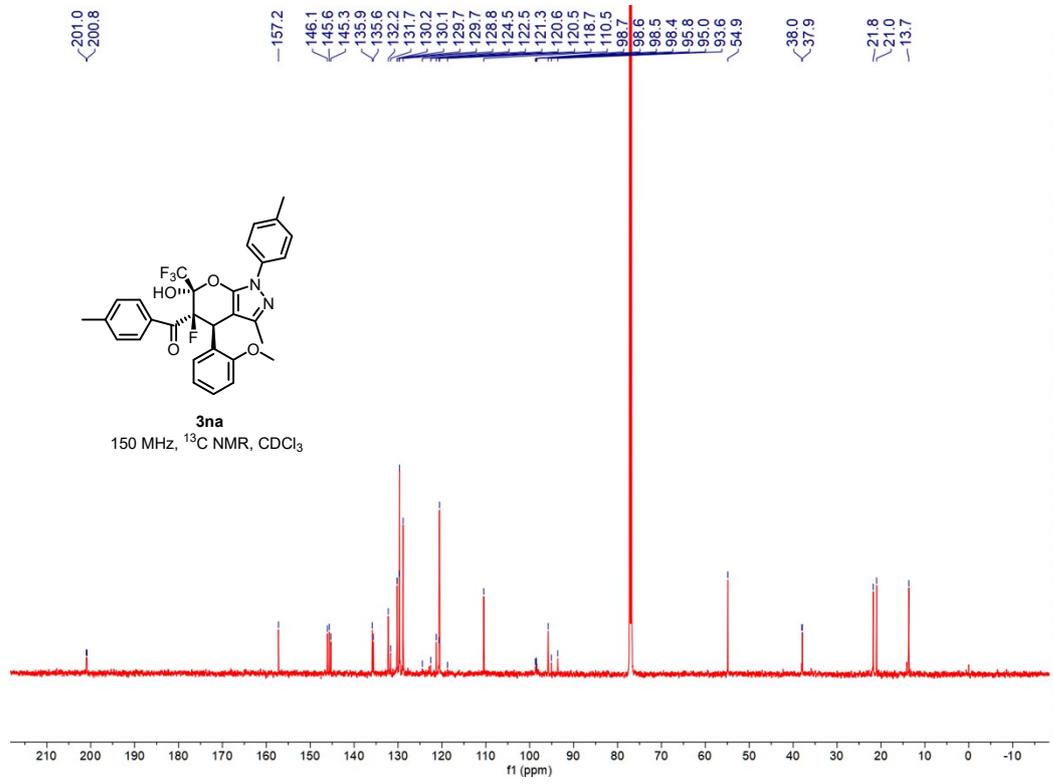
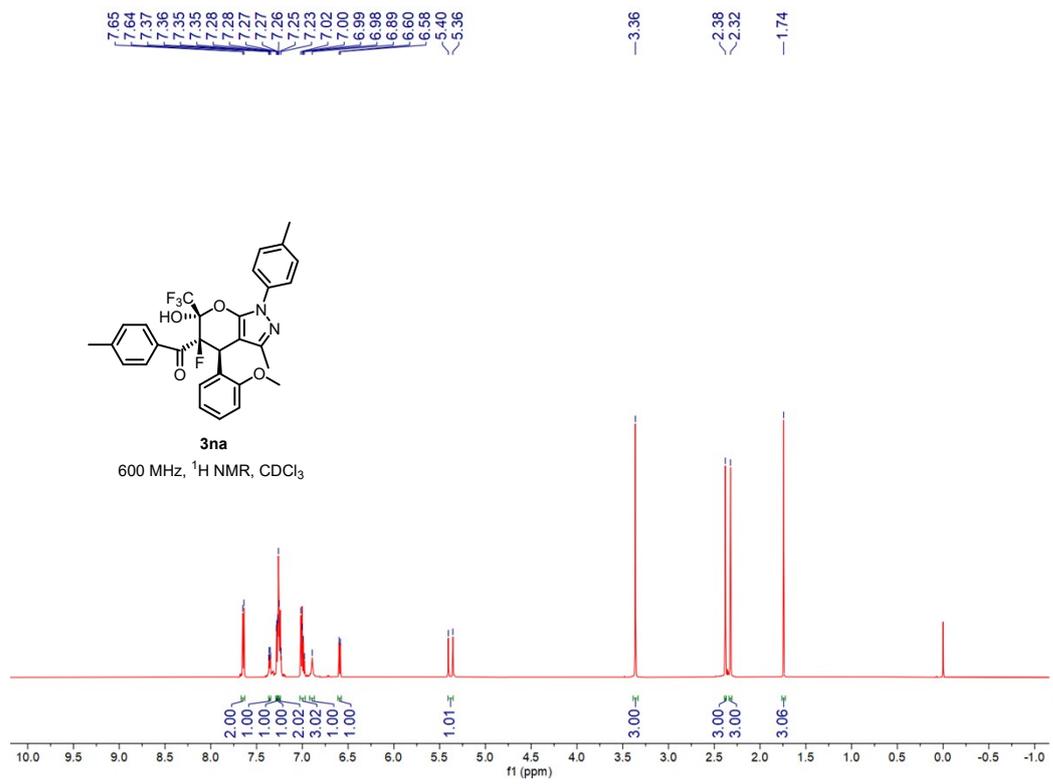


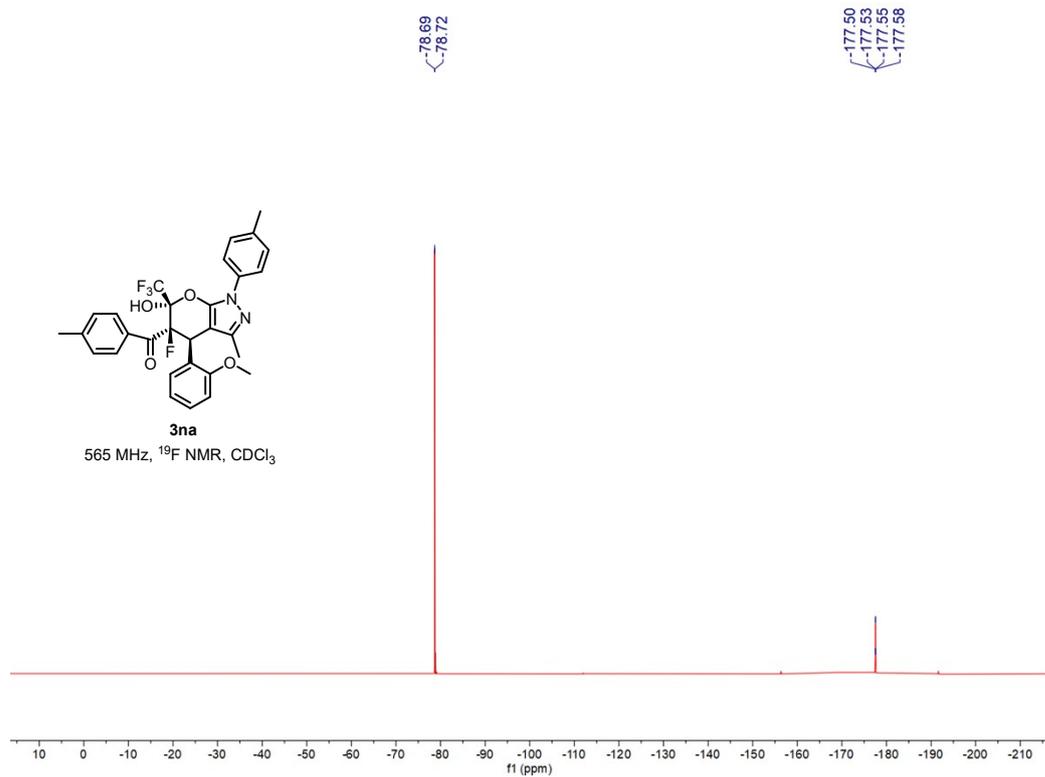
09-Feb-2026 16:28:41

bsr -HY-zhy554 1644 (6.392) AM2 (Ar,12000.0.0.00.0.00); Cm (1638:1649-1673:1675)

1: TOF MS ES+
2.19e7



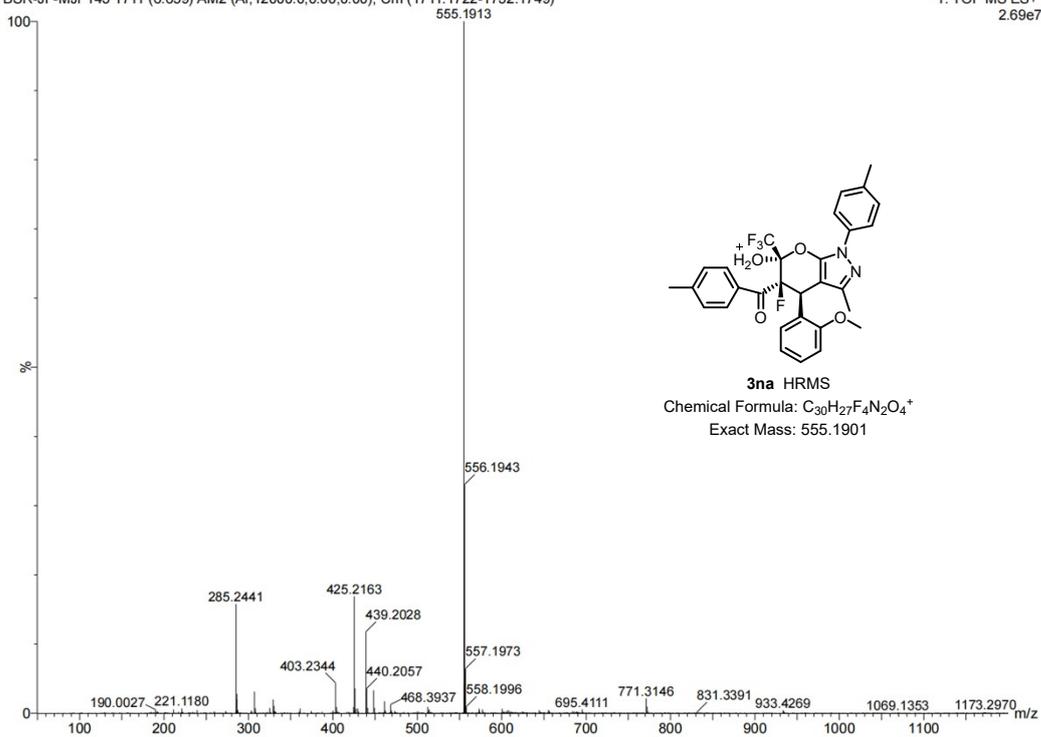


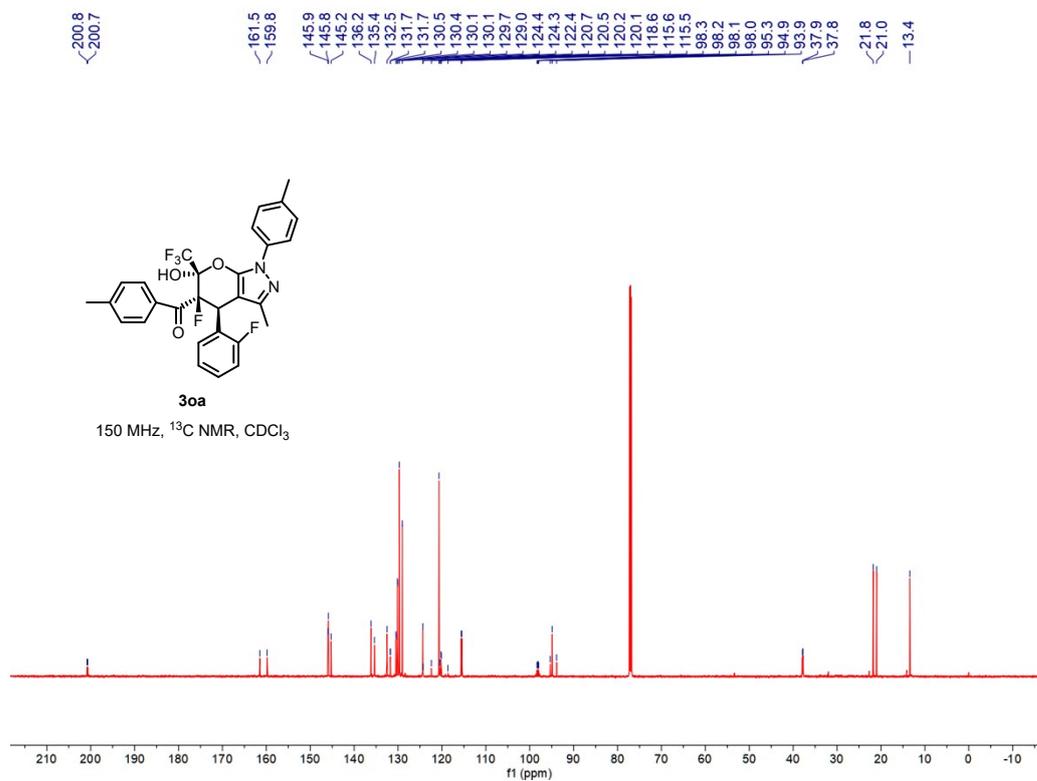
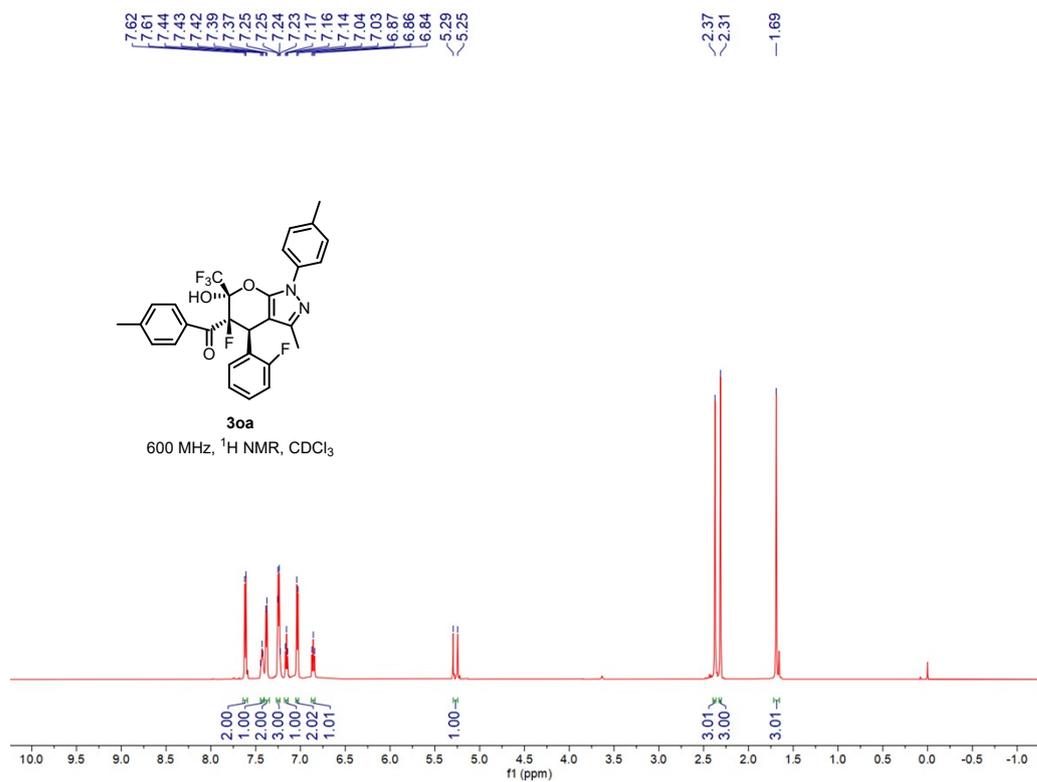


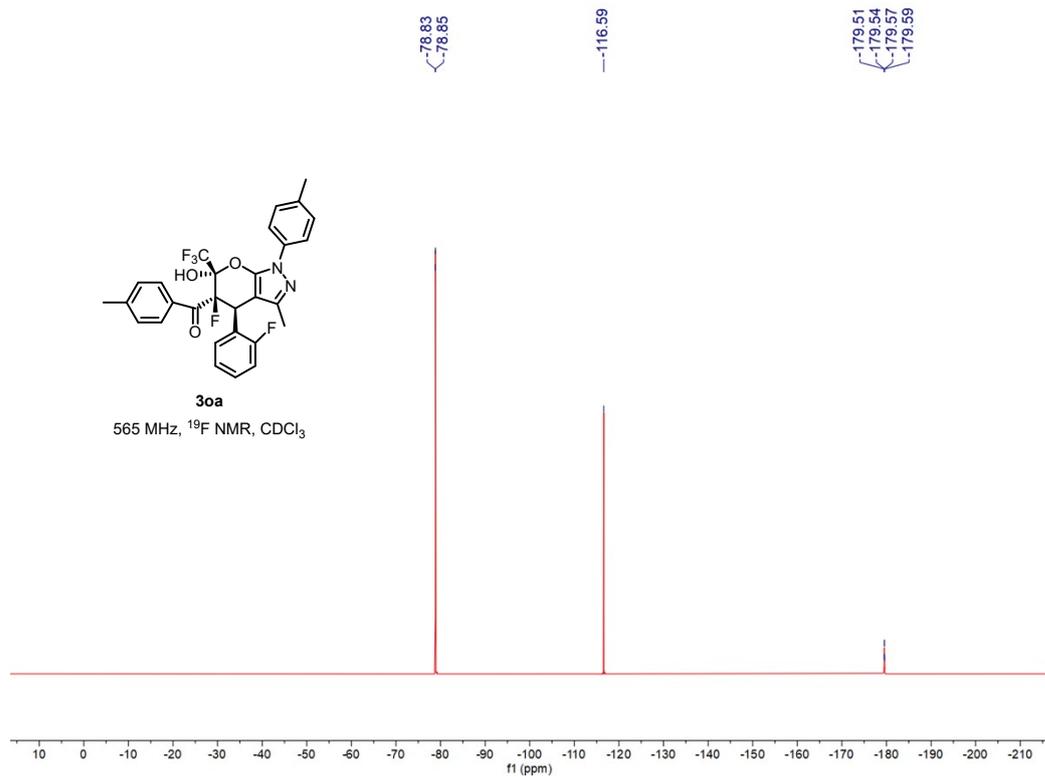
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BSR-JF-MJF143 1711 (6.659) AM2 (Ar, 12000.0,0.00,0.00); Cm (1711:1722-1732:1749)

1: TOF MS ES+
2.69e7



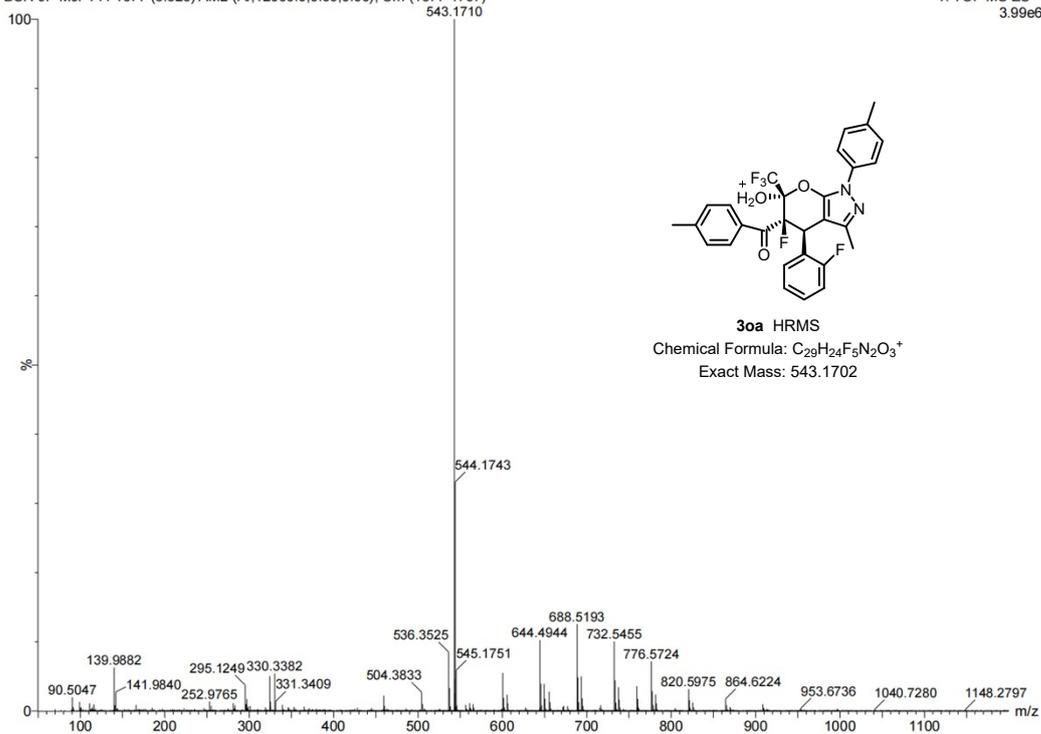


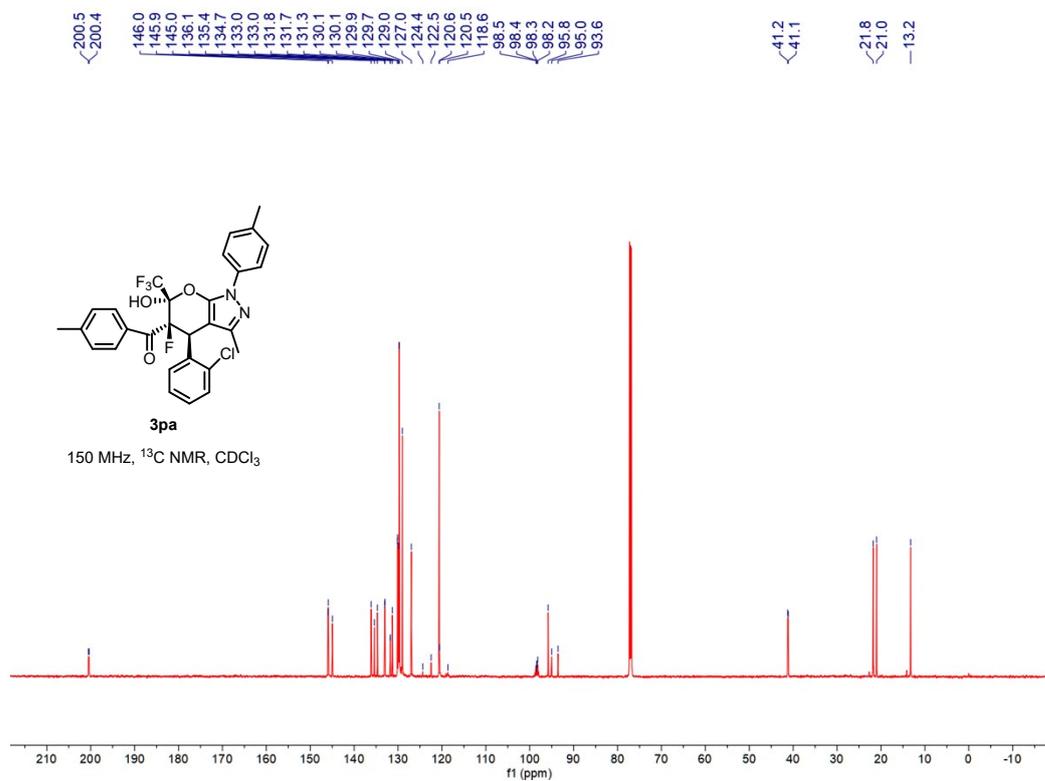
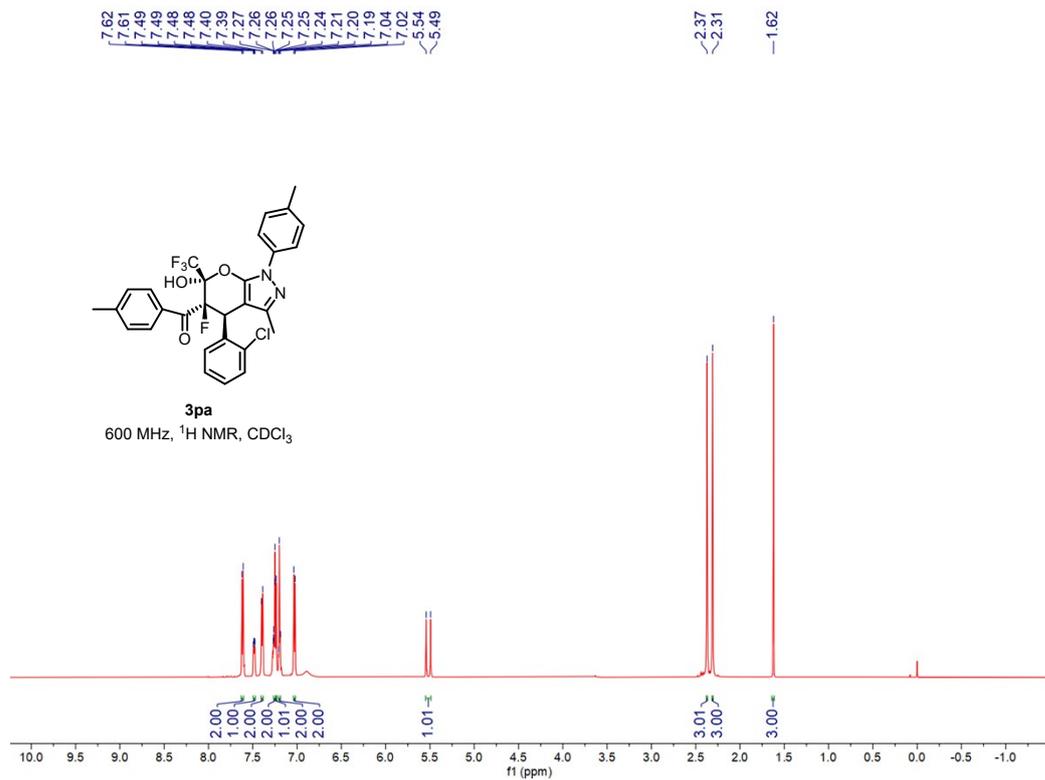


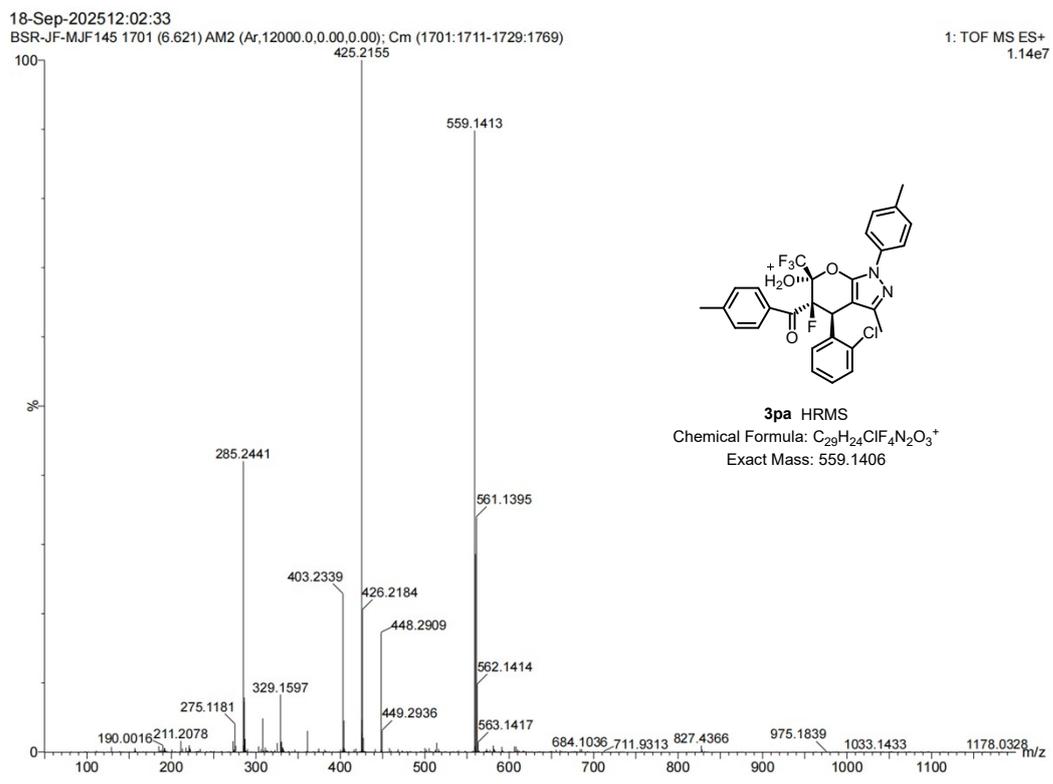
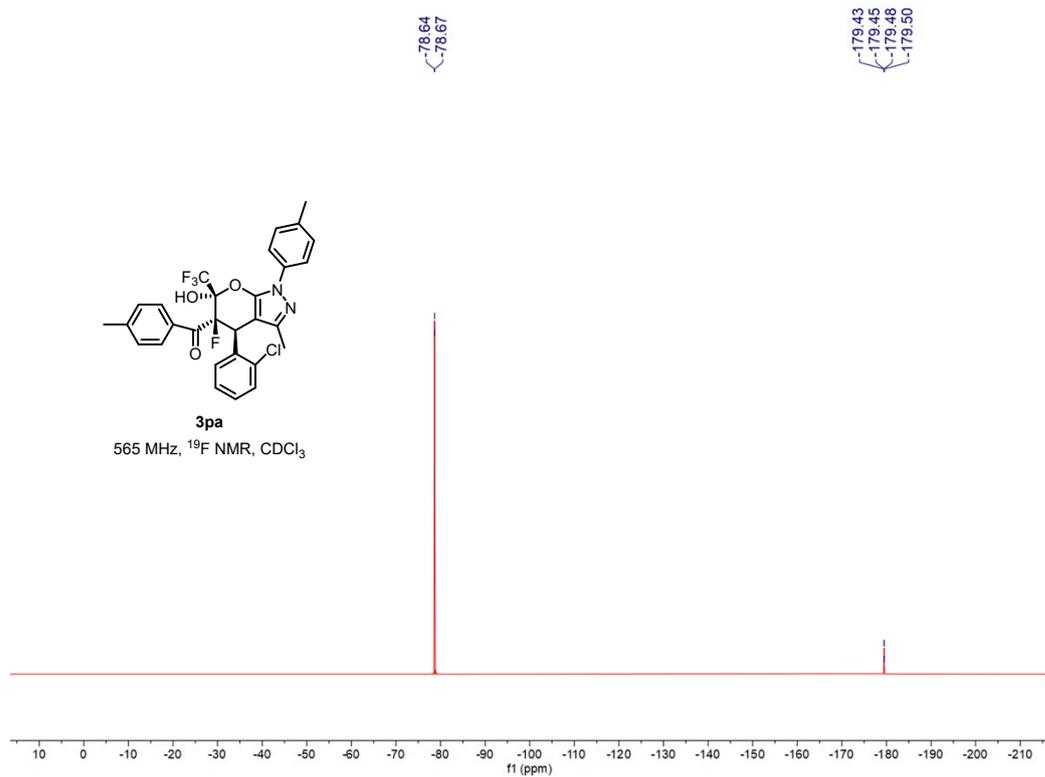
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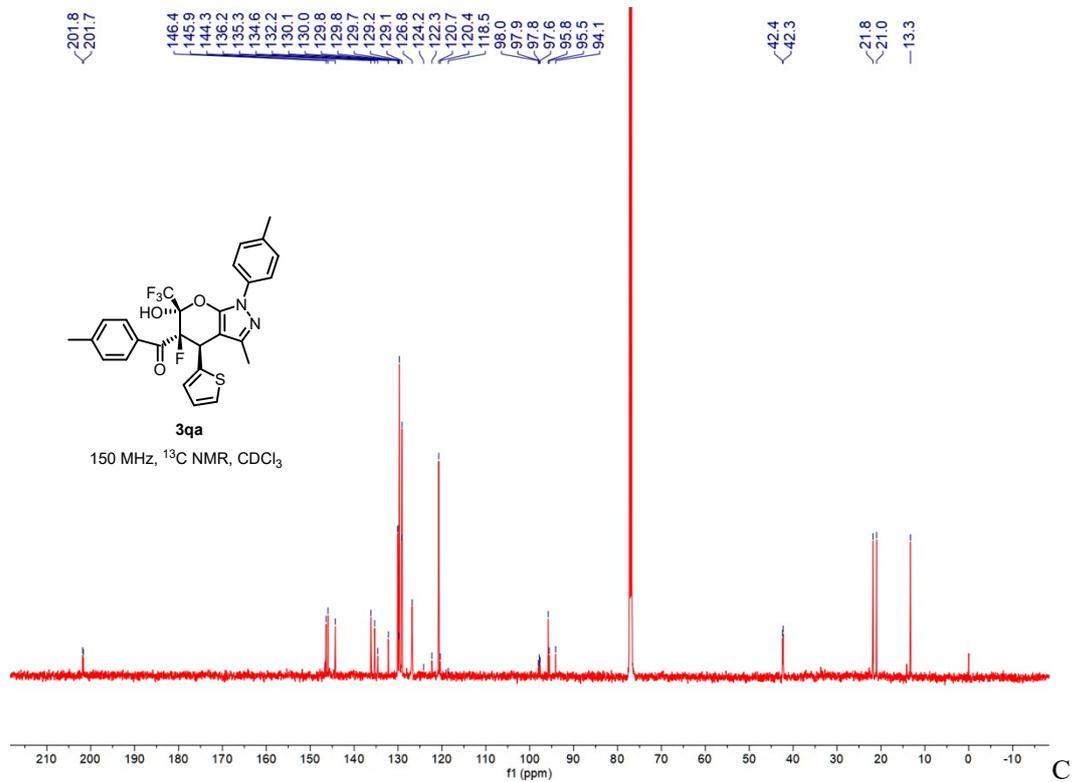
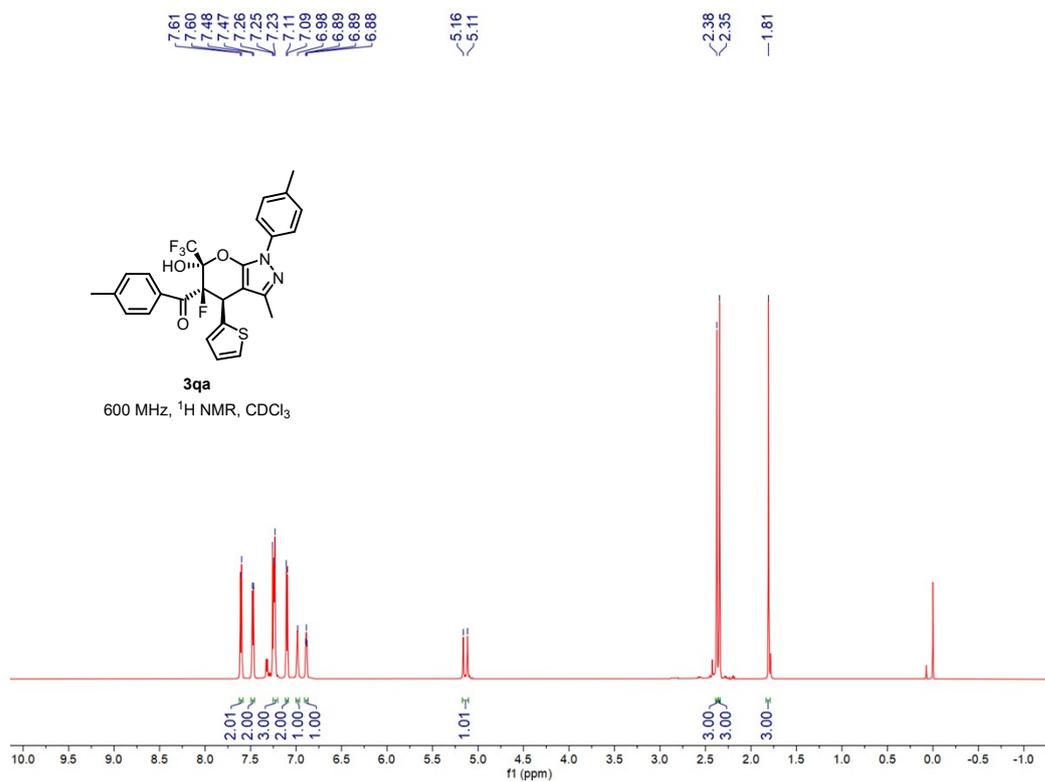
BSR-JF-MJF144 1677 (6.526) AM2 (Ar,12000.0,0.00,0.00); Cm (1677-1797)

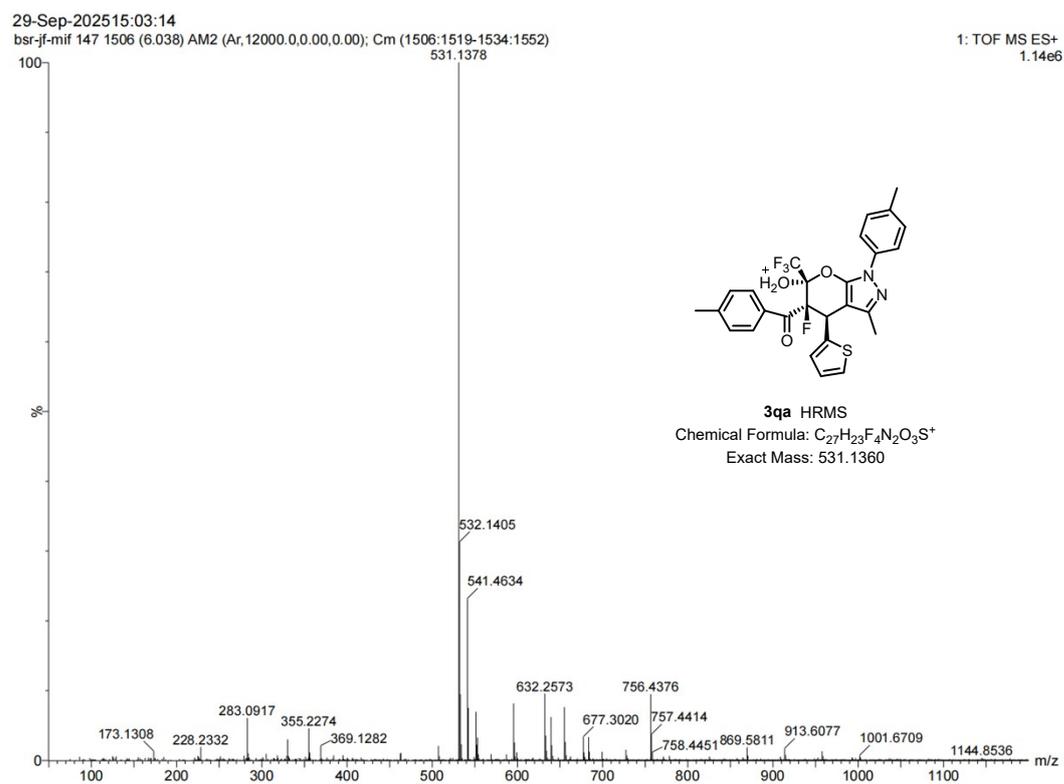
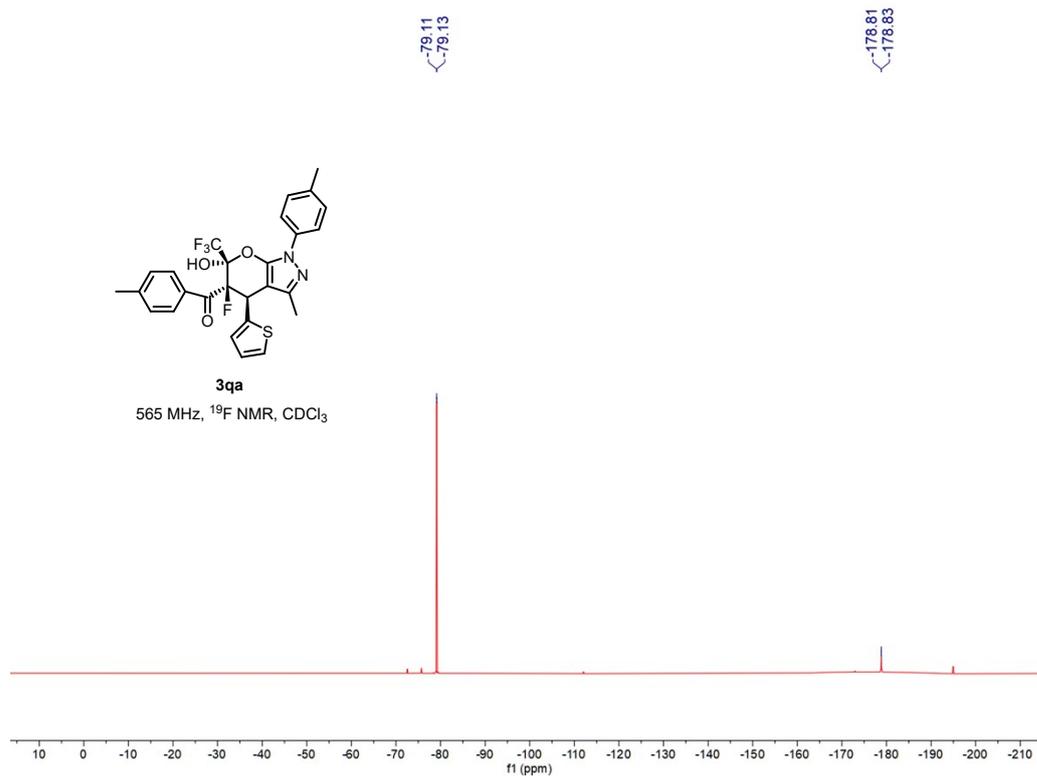
1: TOF MS ES+
3.99e6

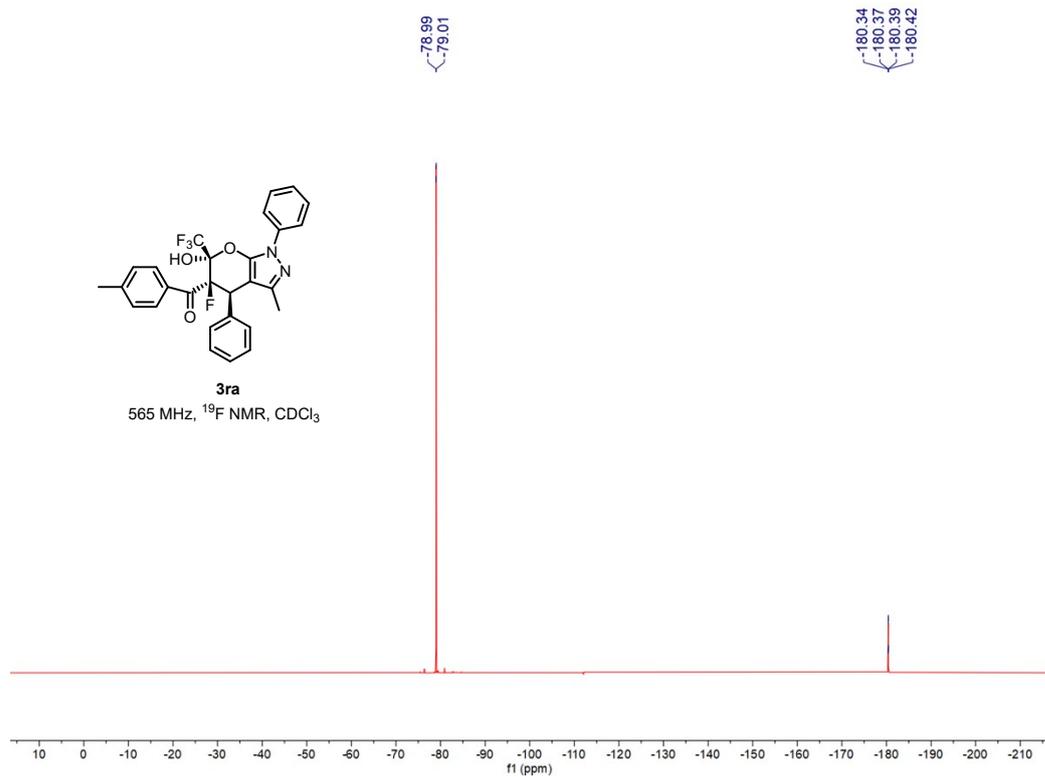








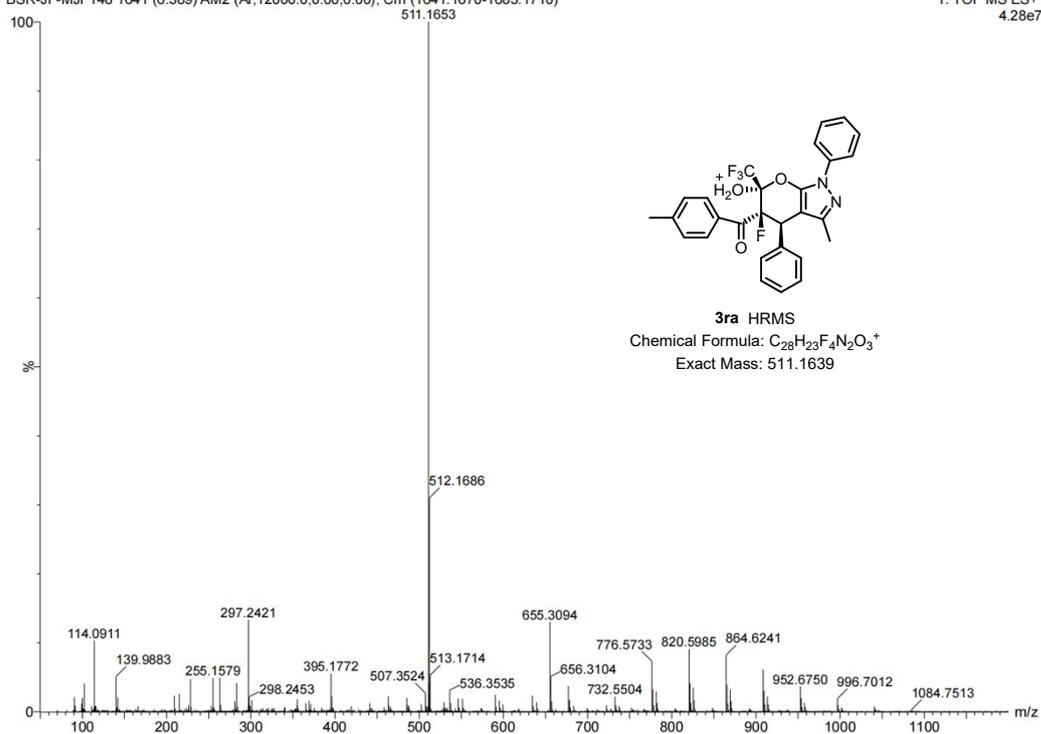


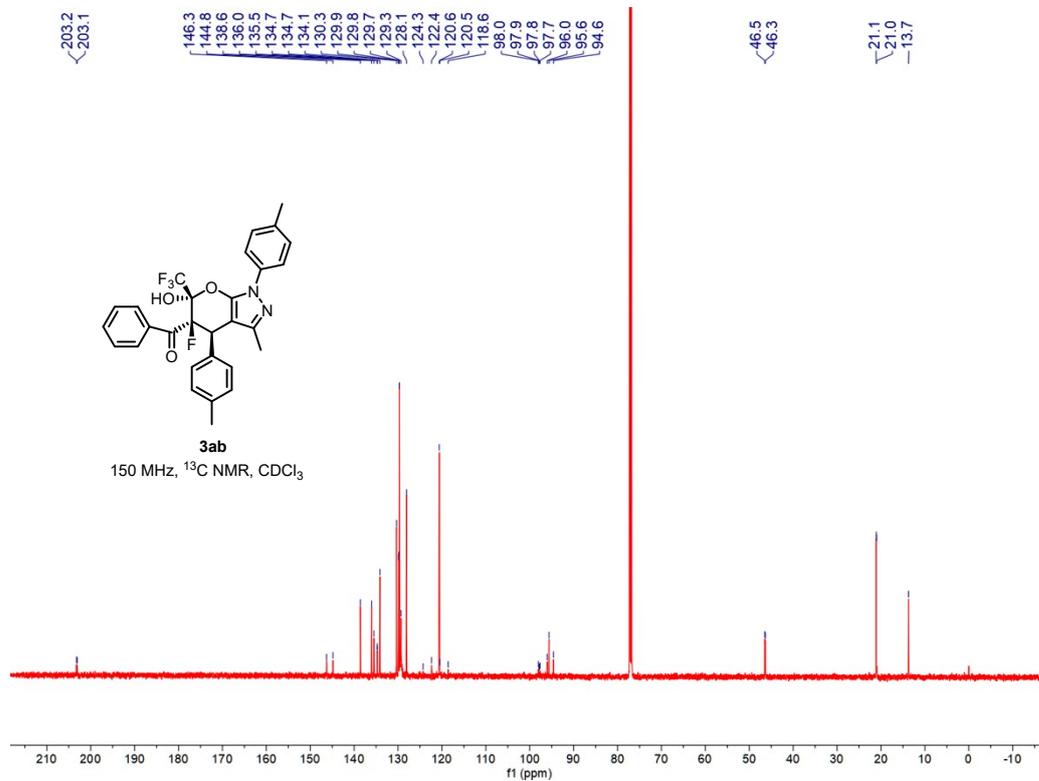
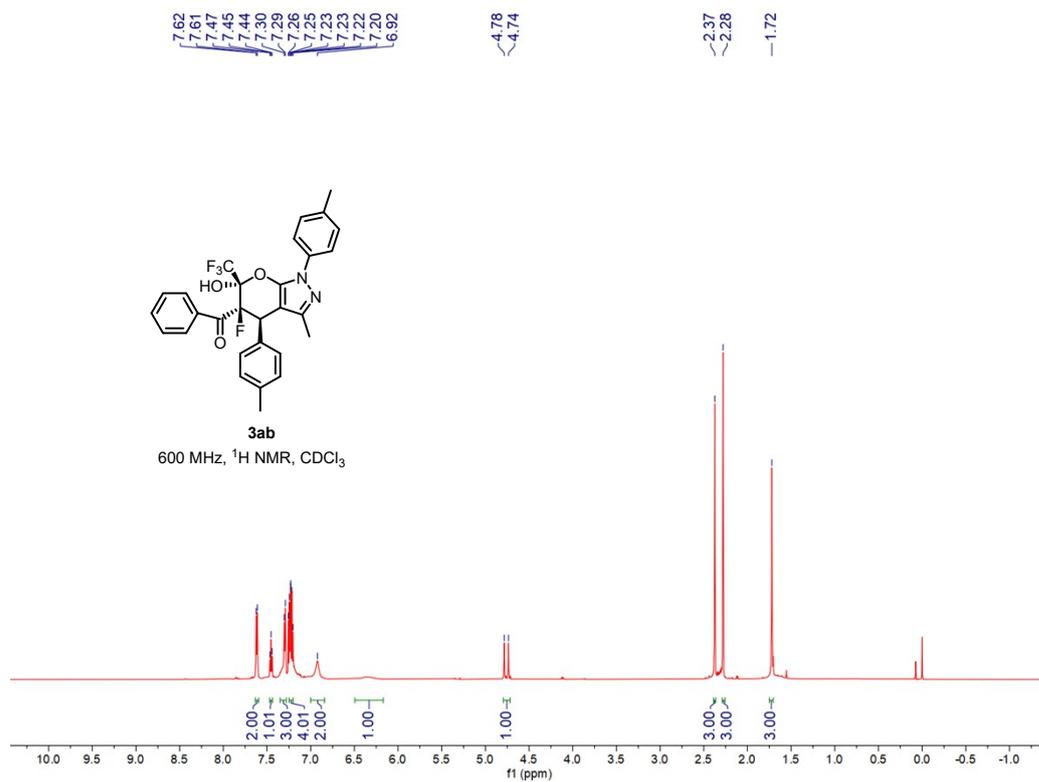


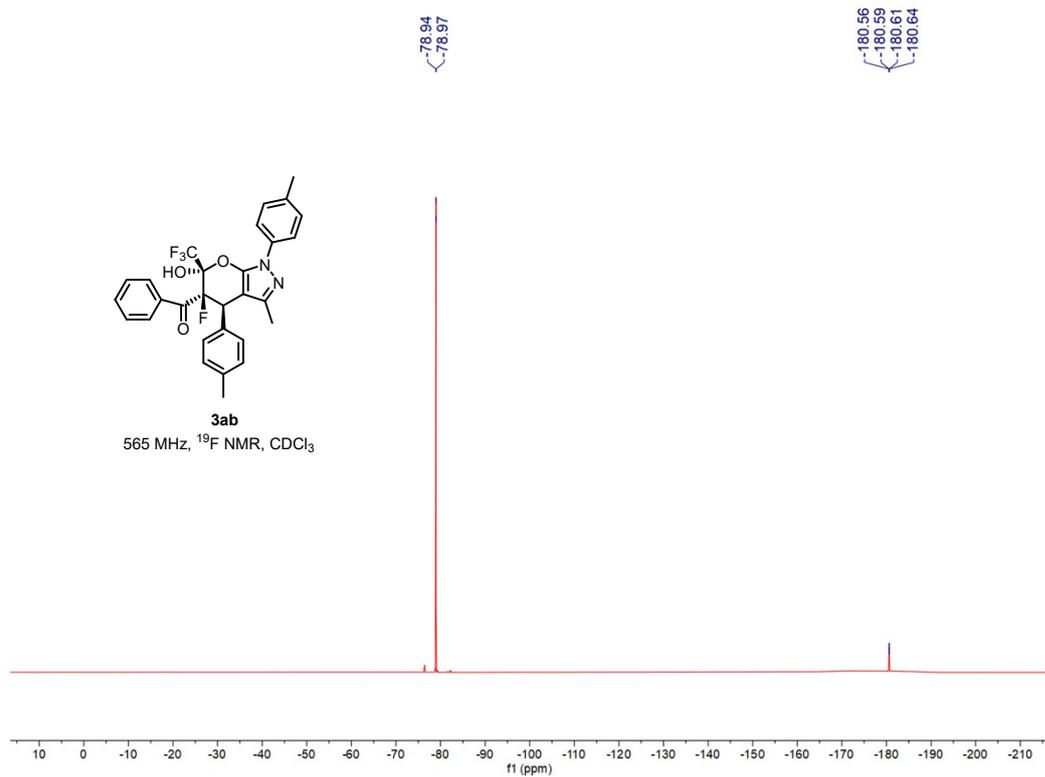
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BSR-JF-MJF148 1641 (6.389) AM2 (Ar,12000.0,0.00,0.00); Cm (1641:1670-1683:1710)

1: TOF MS ES+
4.28e7



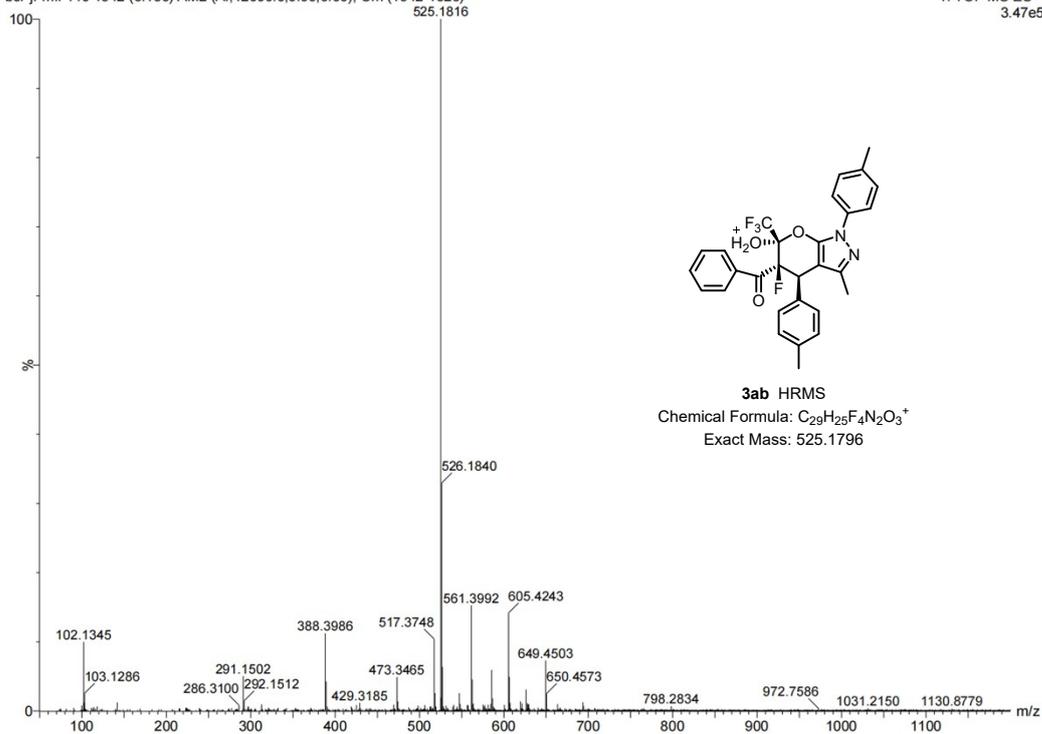


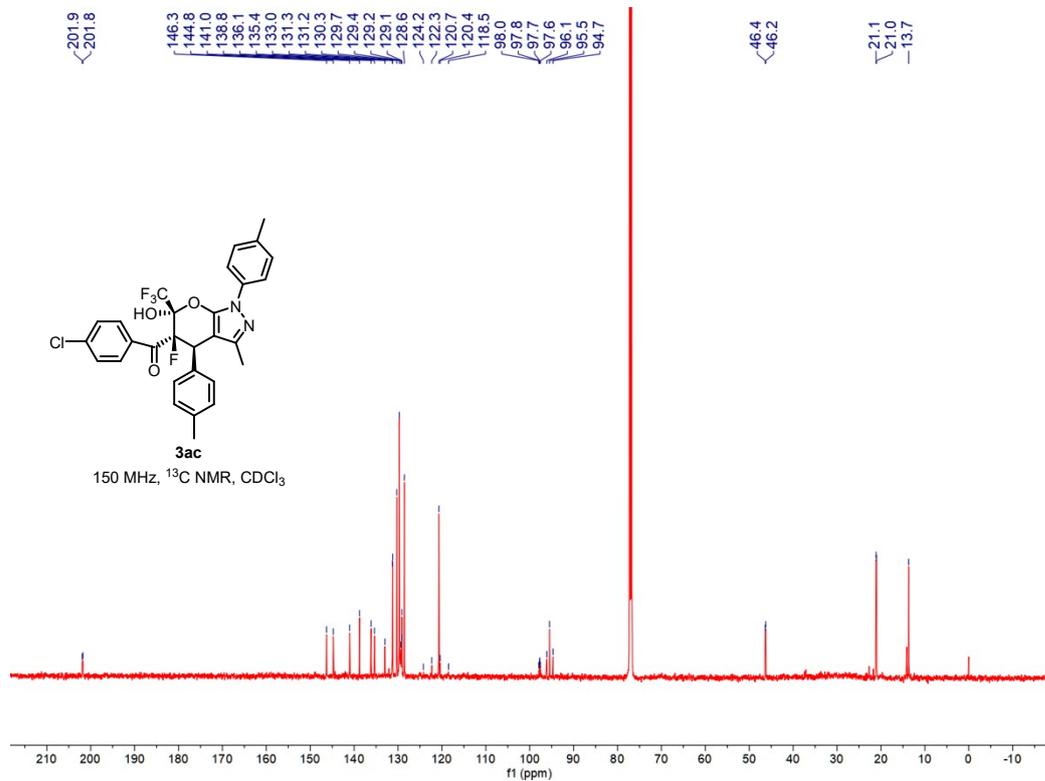
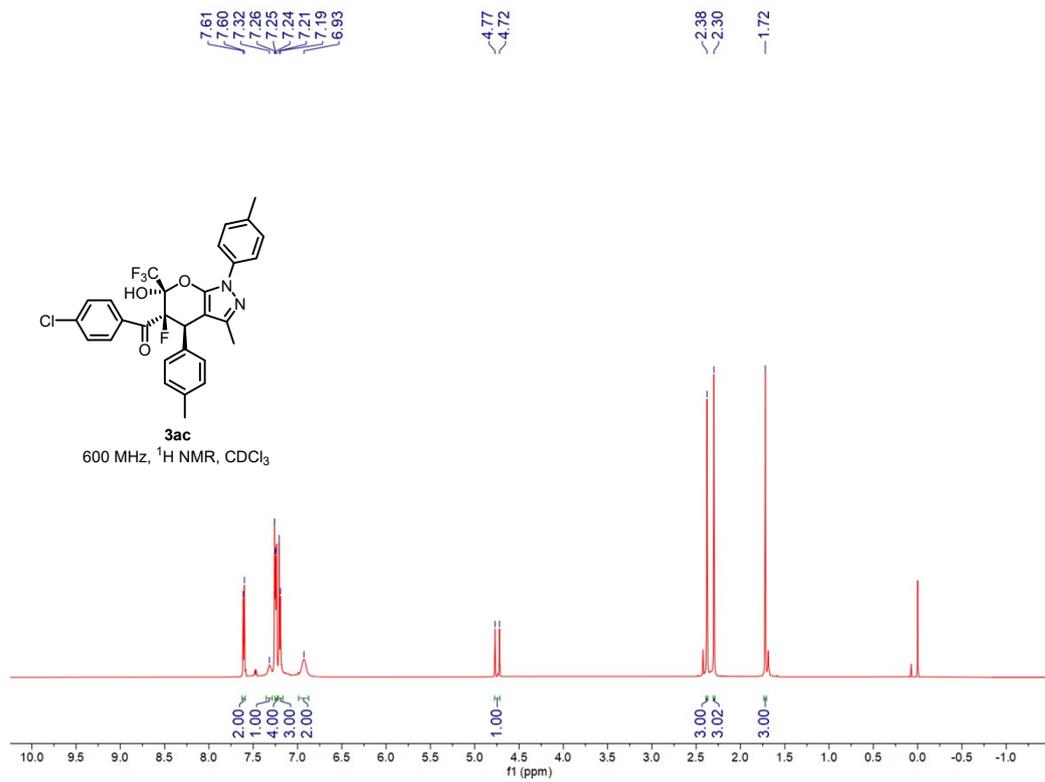


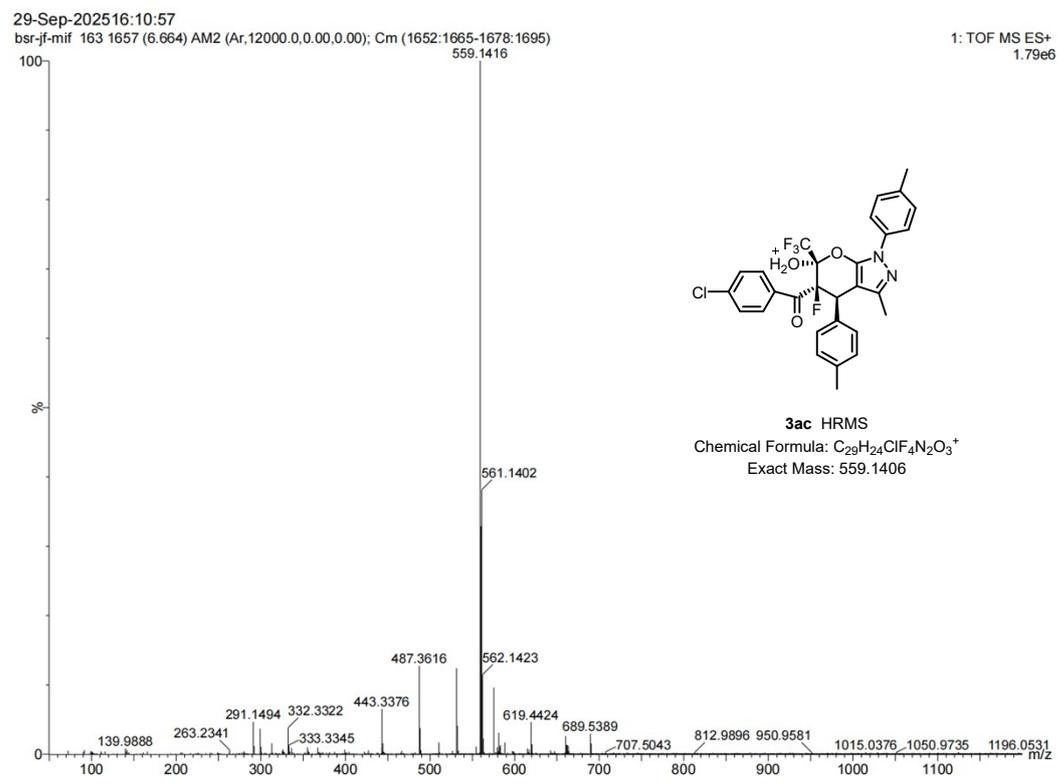
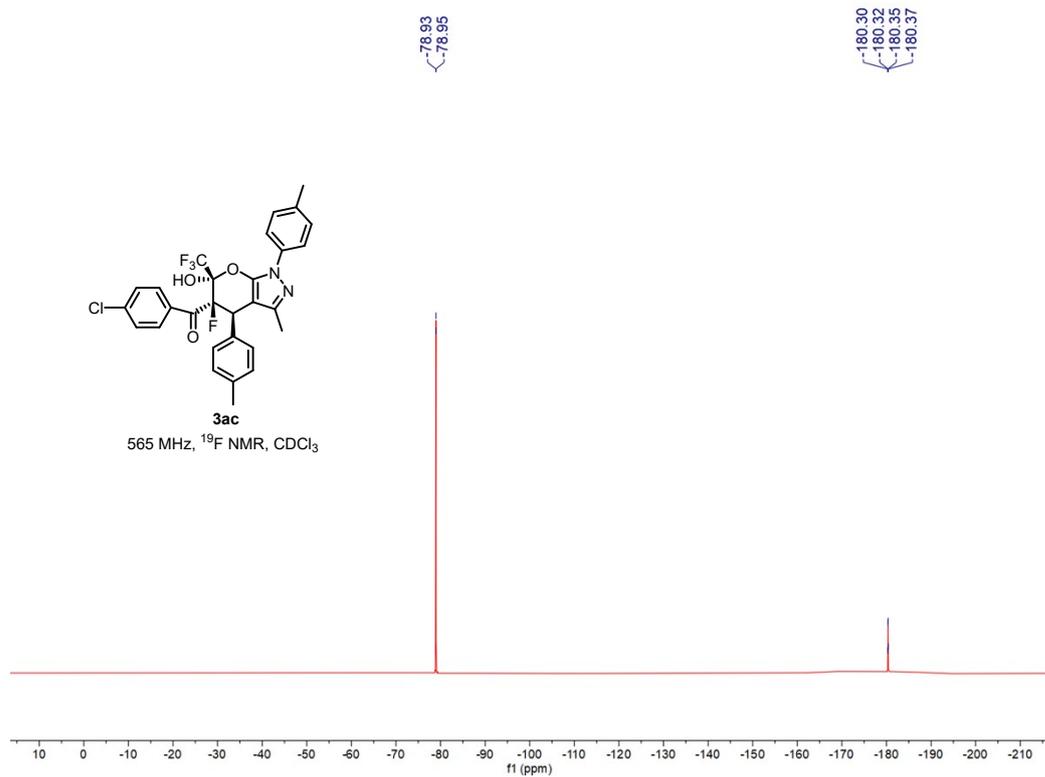
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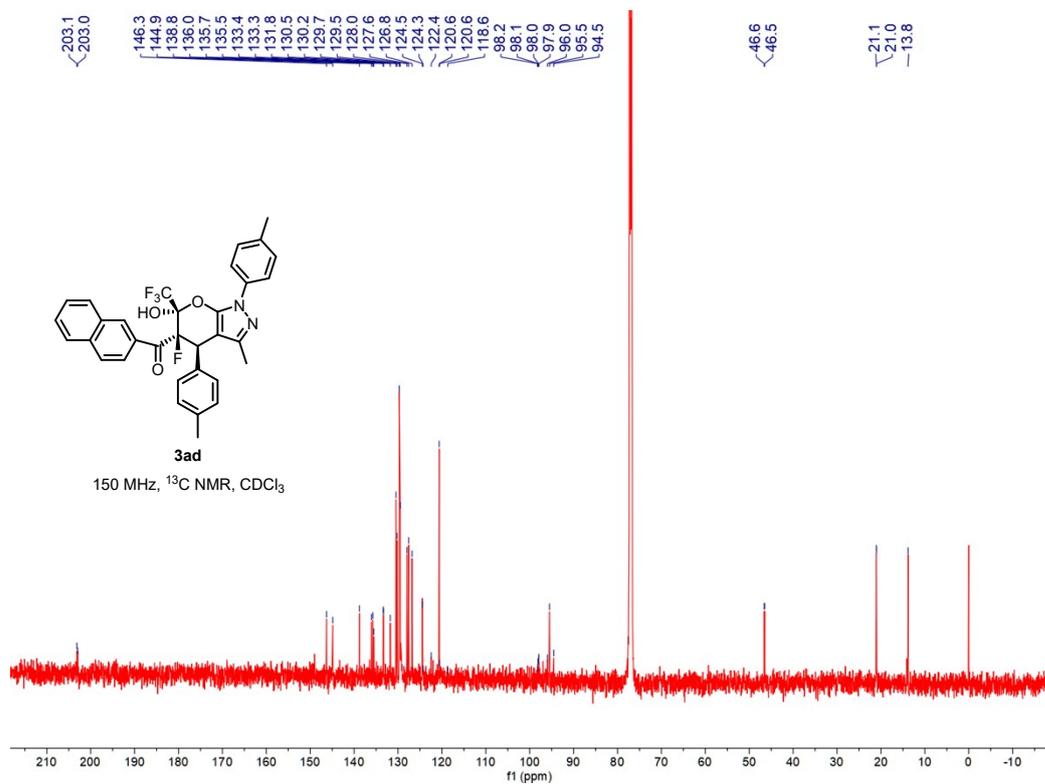
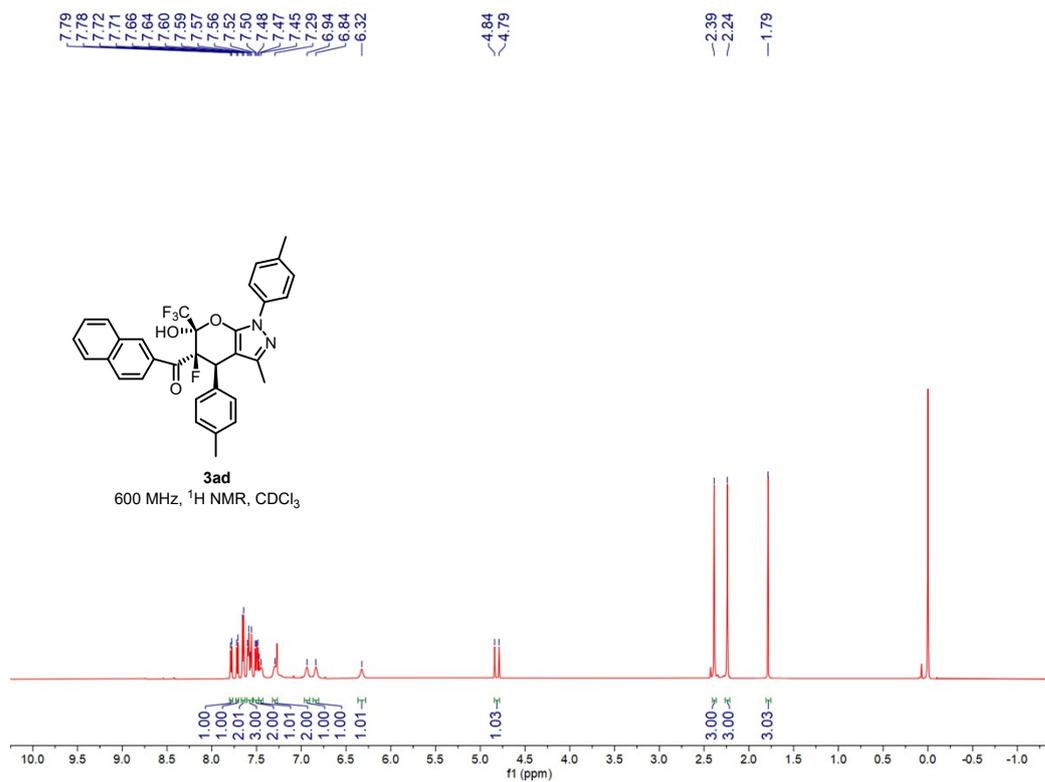
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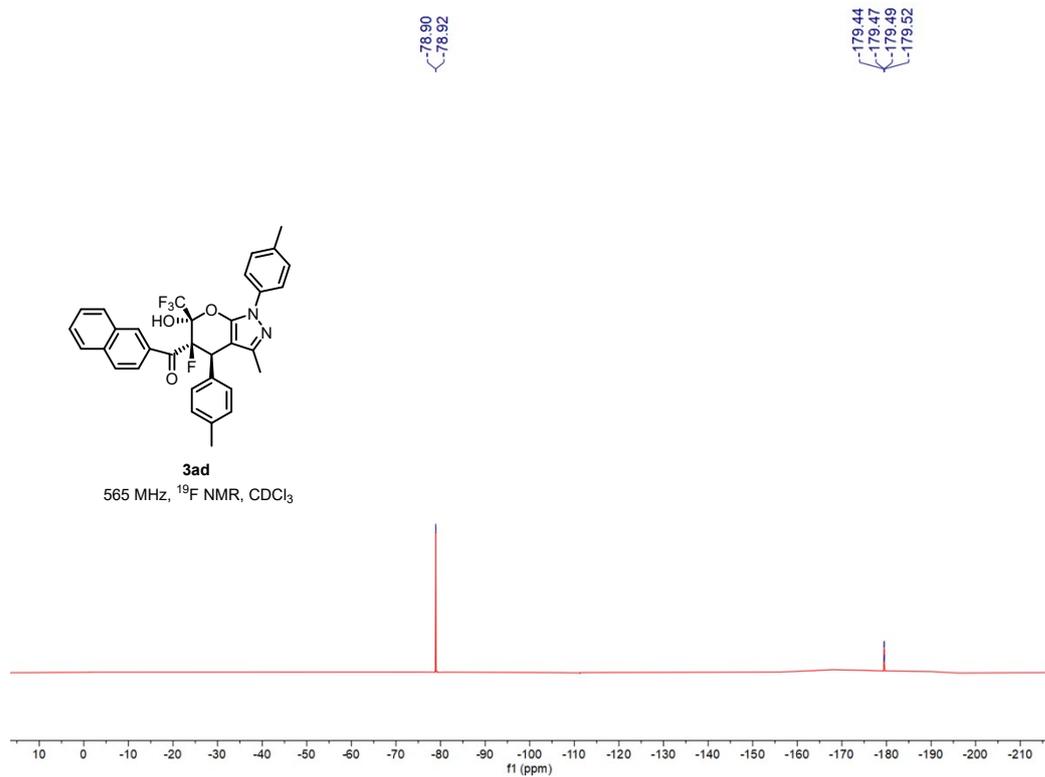
1: TOF MS ES+
3.47e5







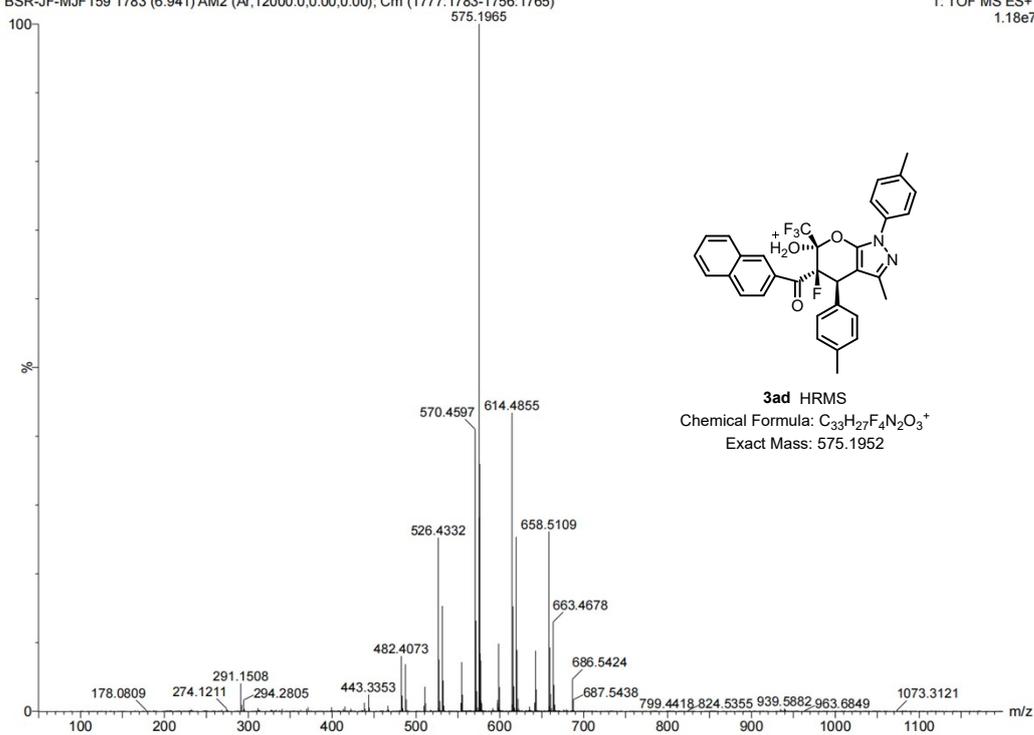


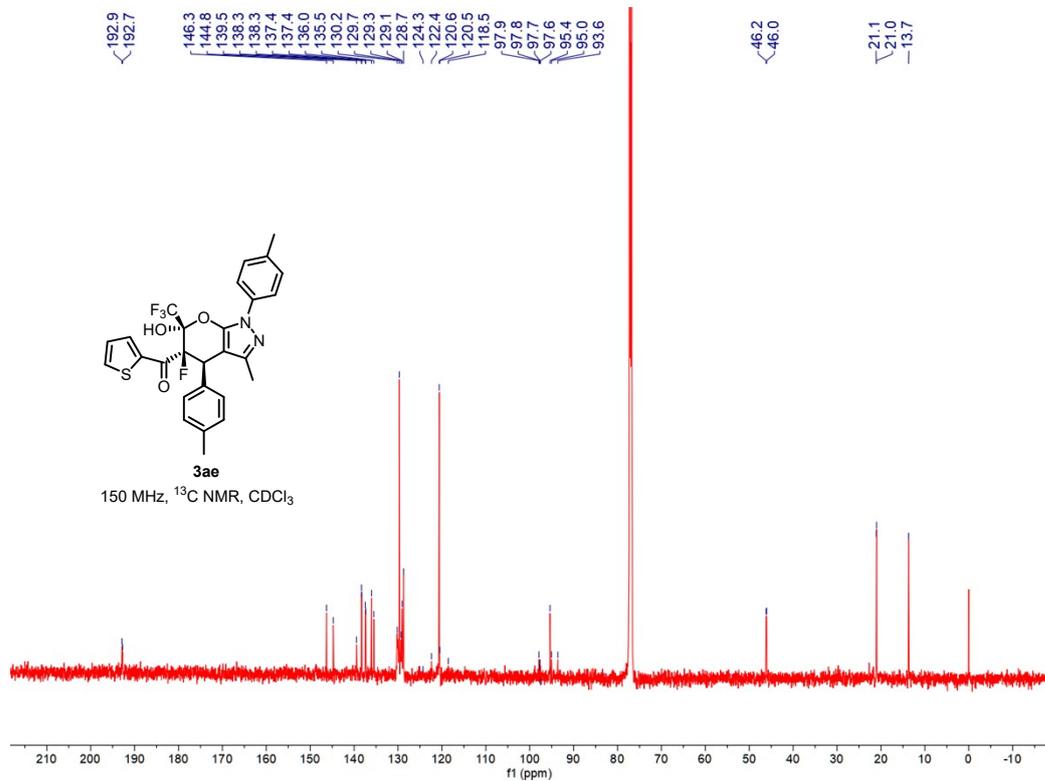
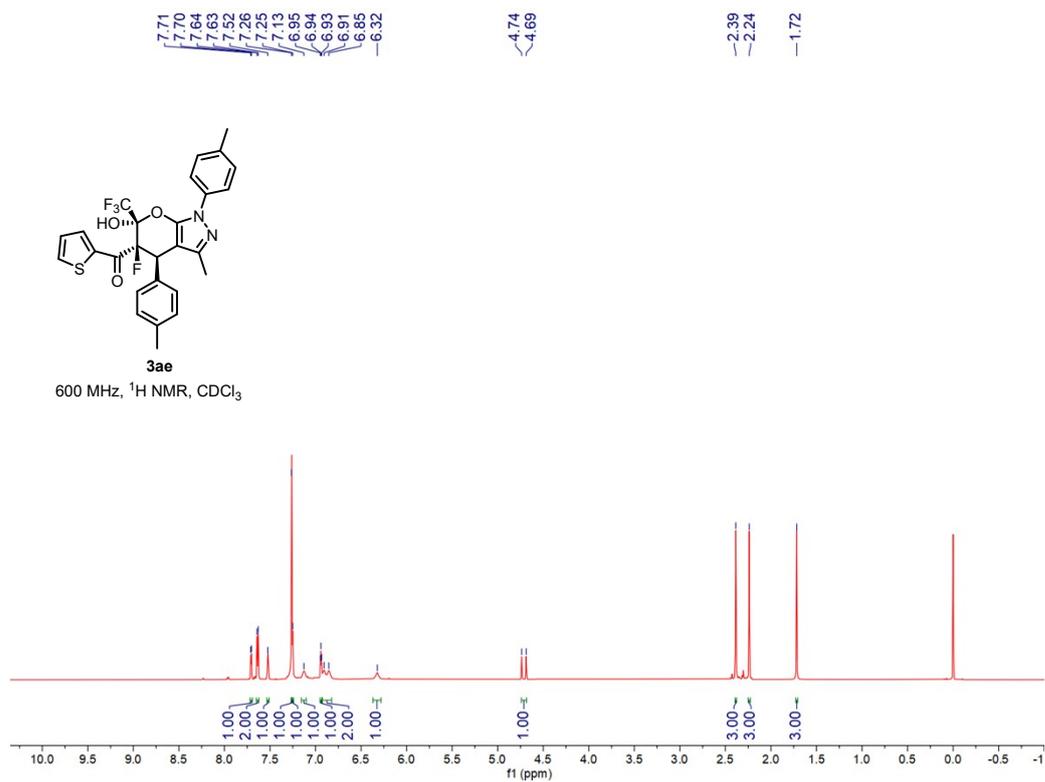


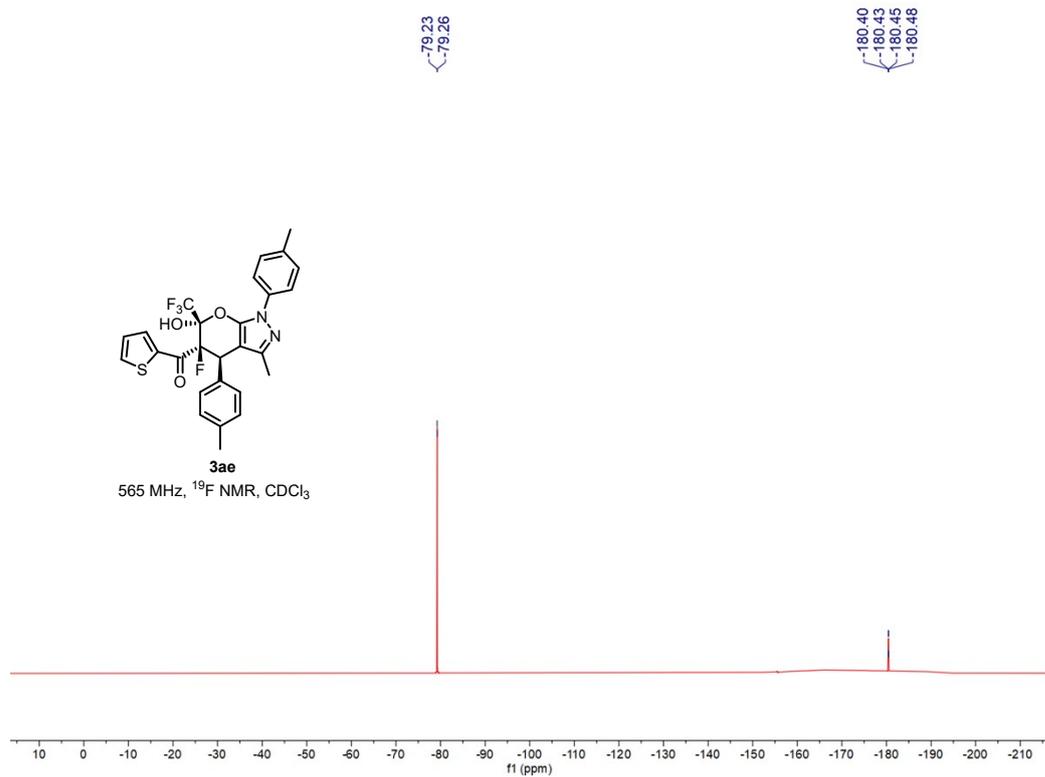
18-Sep-2025 13:07:47

BSR-JF-MJF159 1783 (6.941) AM2 (Ar, 12000.0, 0.00, 0.00); Cm (1777:1783-1756:1765)

1: TOF MS ES+
1.18e7



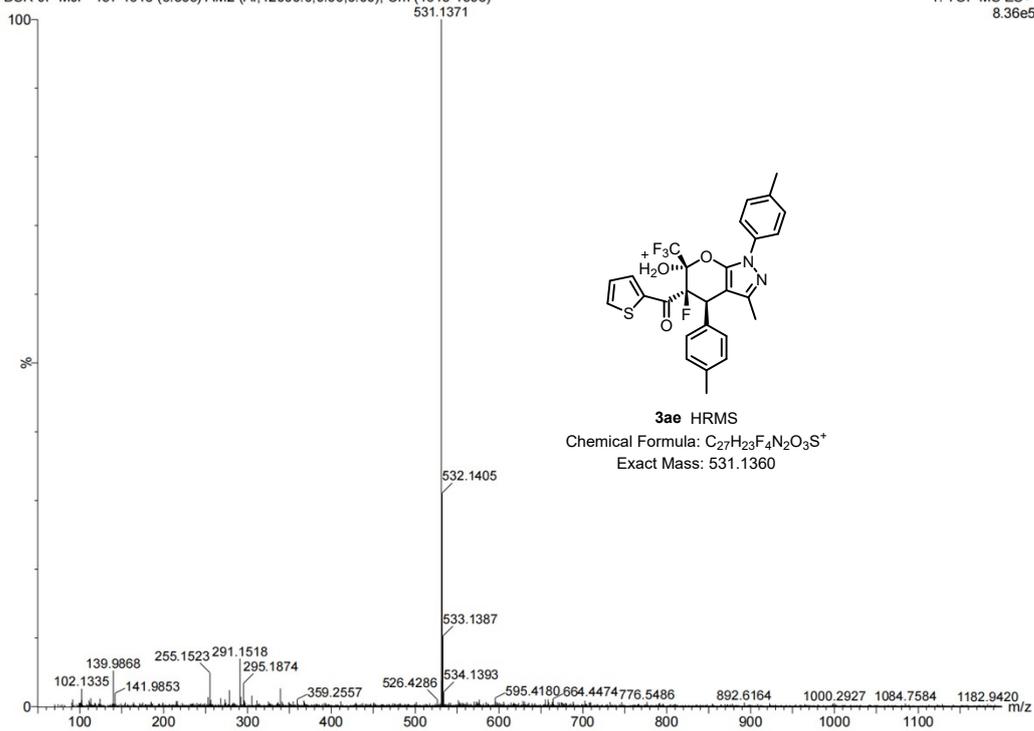


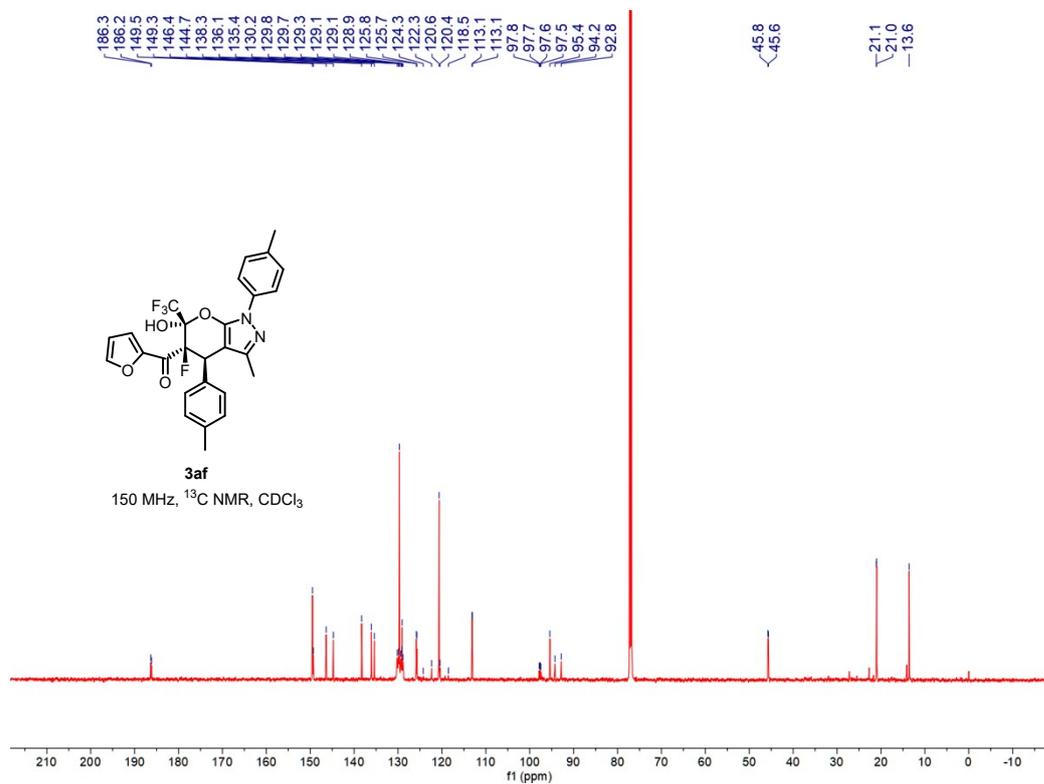
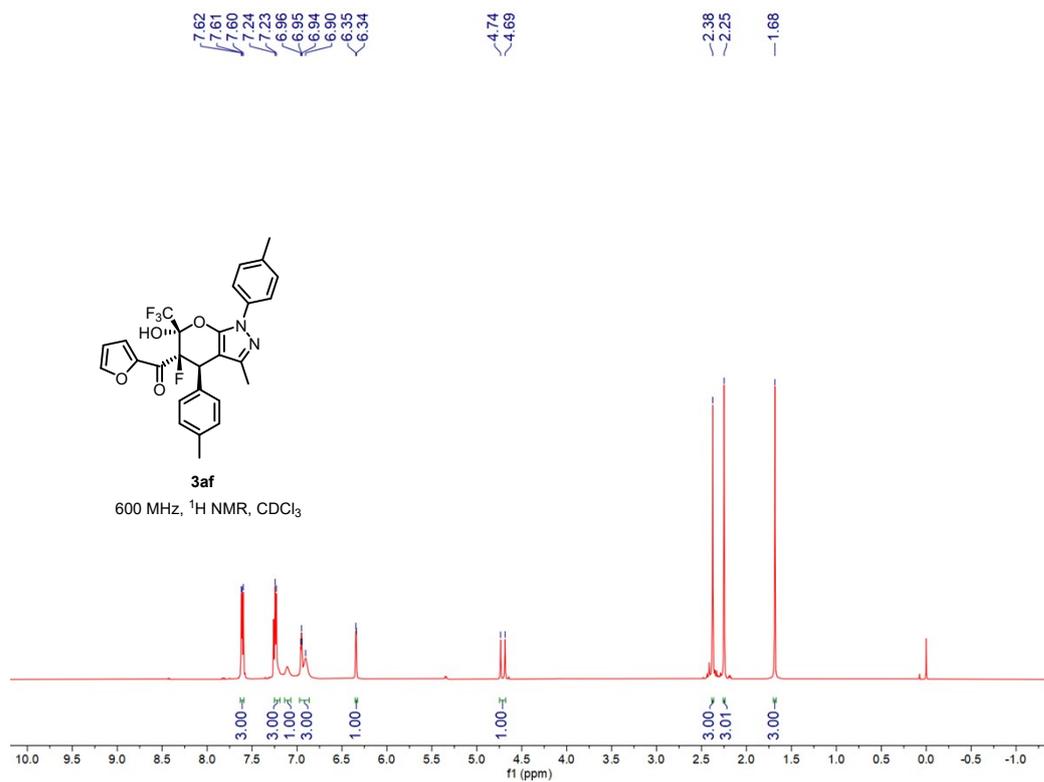


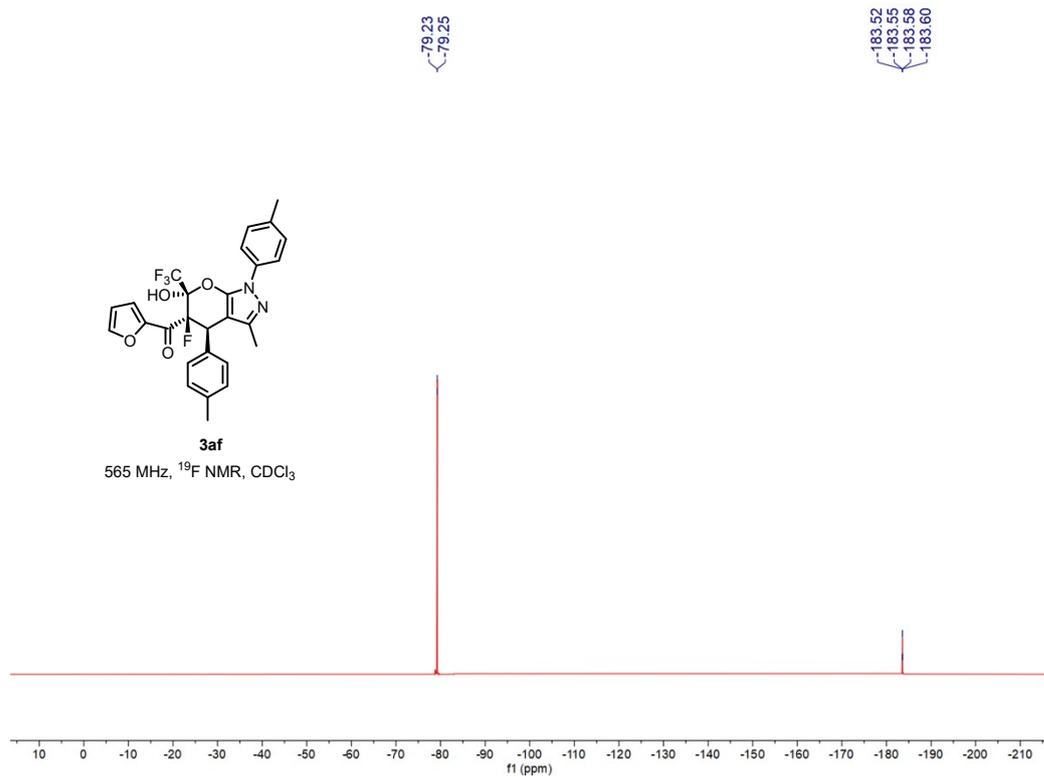
18-Sep-2025 13:29:23

BSR-JF-MJF 157 1618 (6.305) AM2 (Ar,12000.0,0.00,0.00); Cm (1618-1598)

1: TOF MS ES+
8.36e5



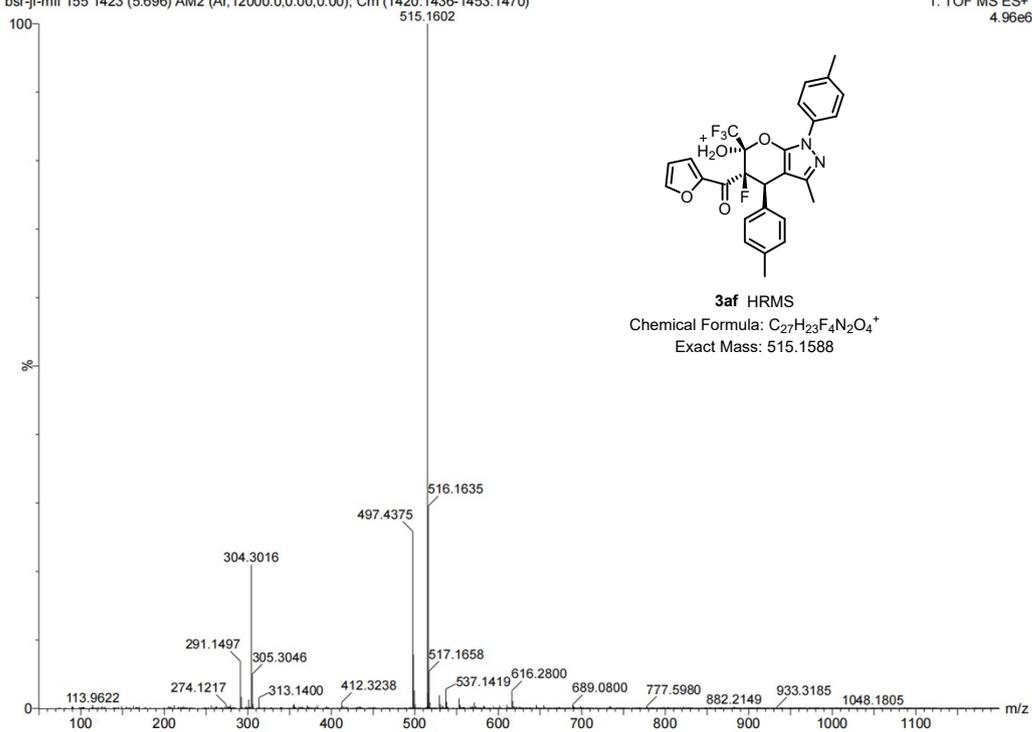


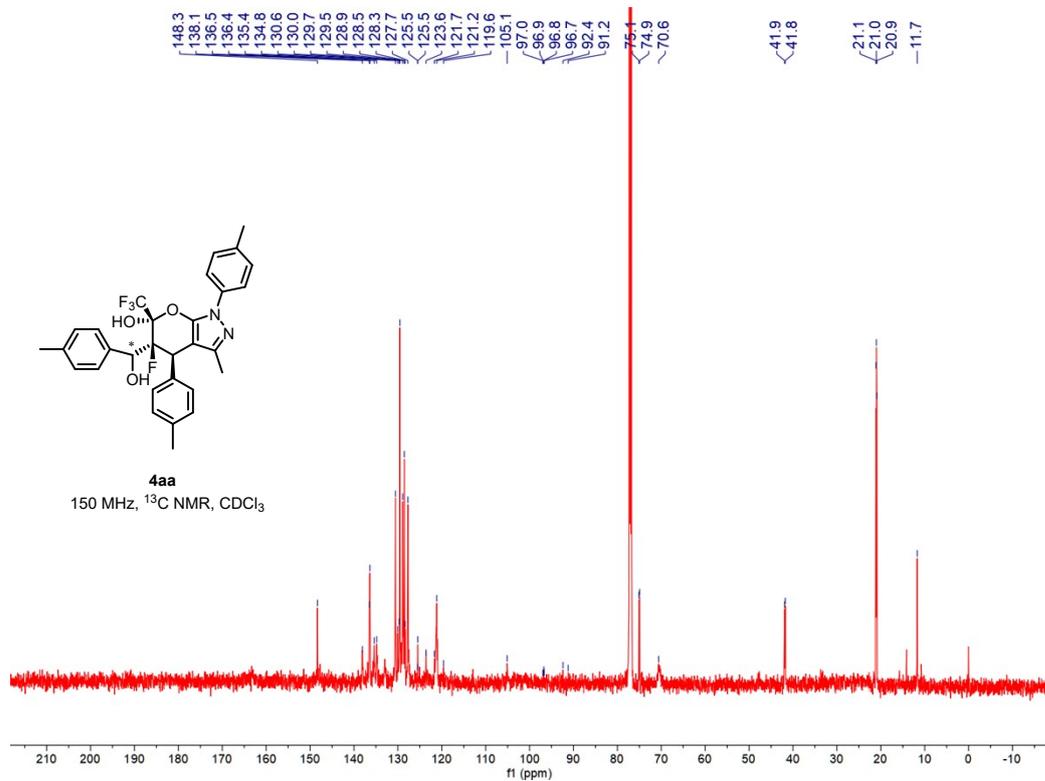
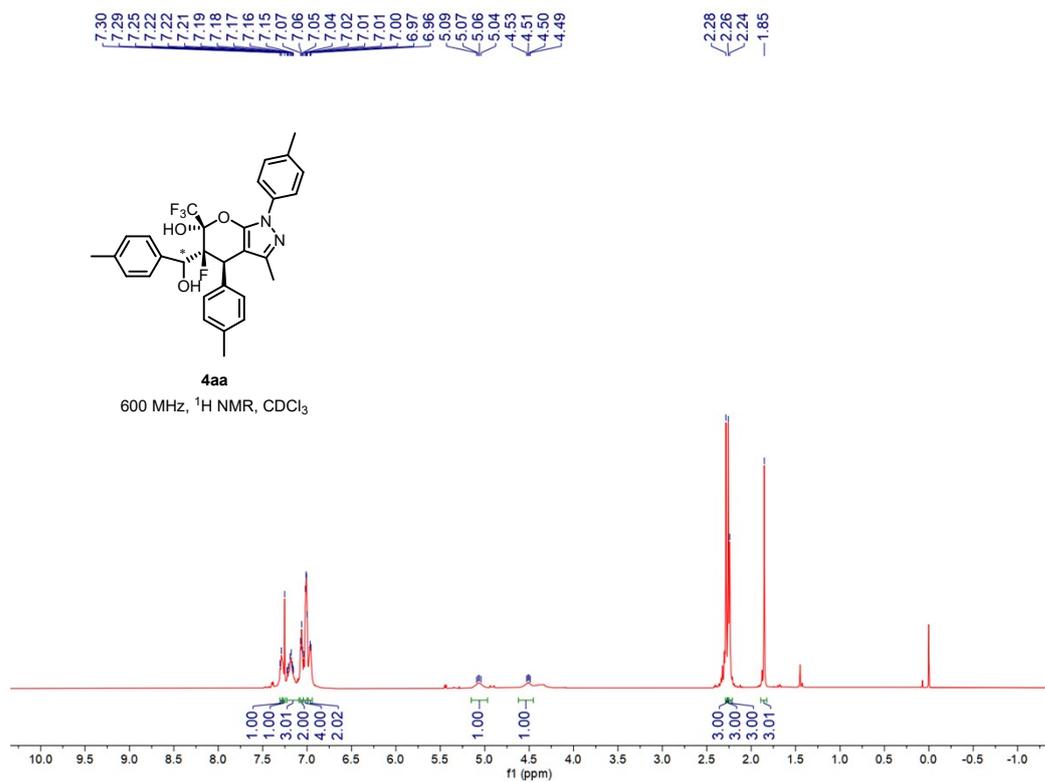


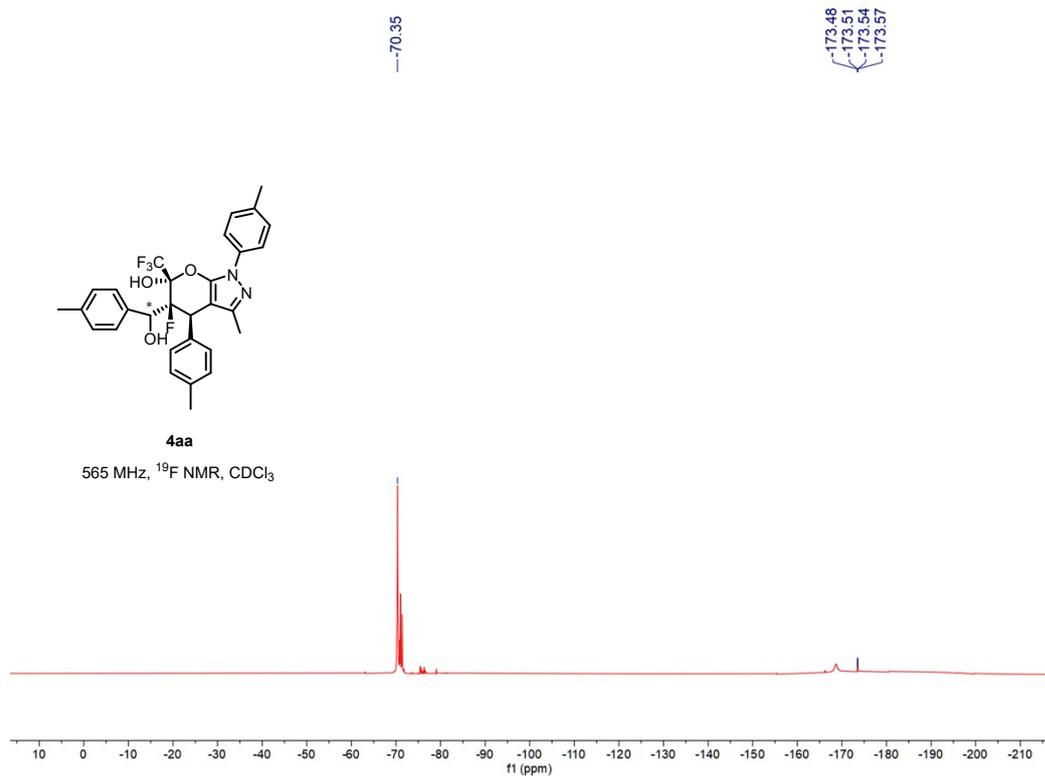
29-Sep-2025 15:24:48

bsr-jf-mif 155 1423 (5.696) AM2 (Ar,12000.0,0.00,0.00); Cm (1420:1436-1453:1470)

1: TOF MS ES+
4.96e6



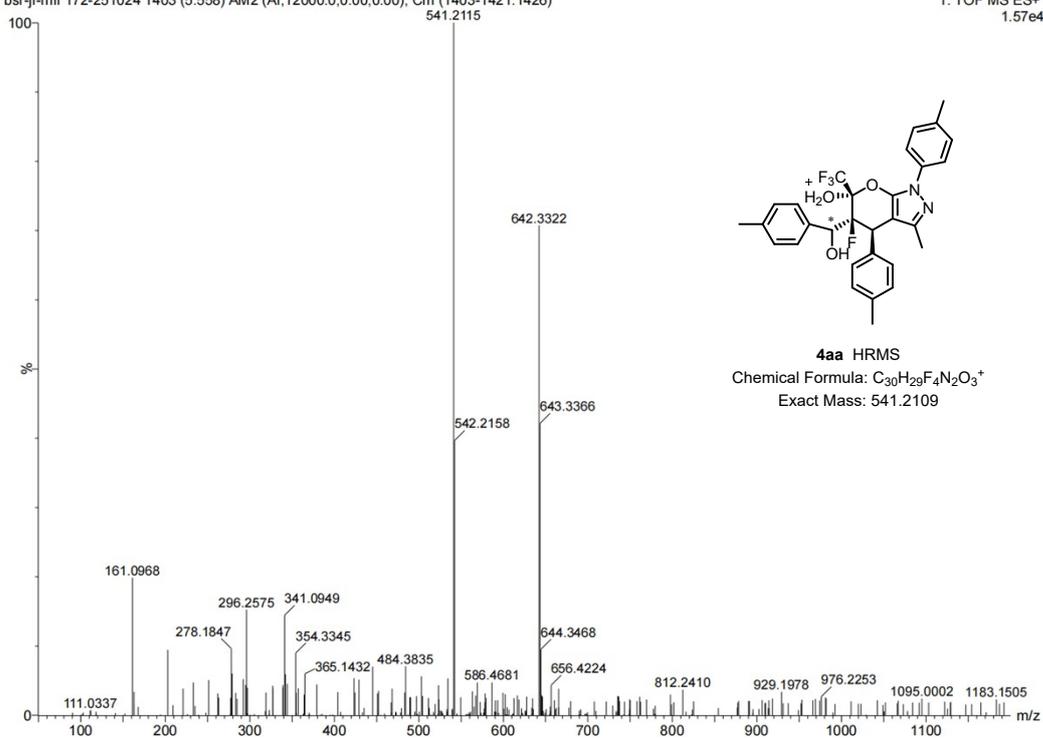


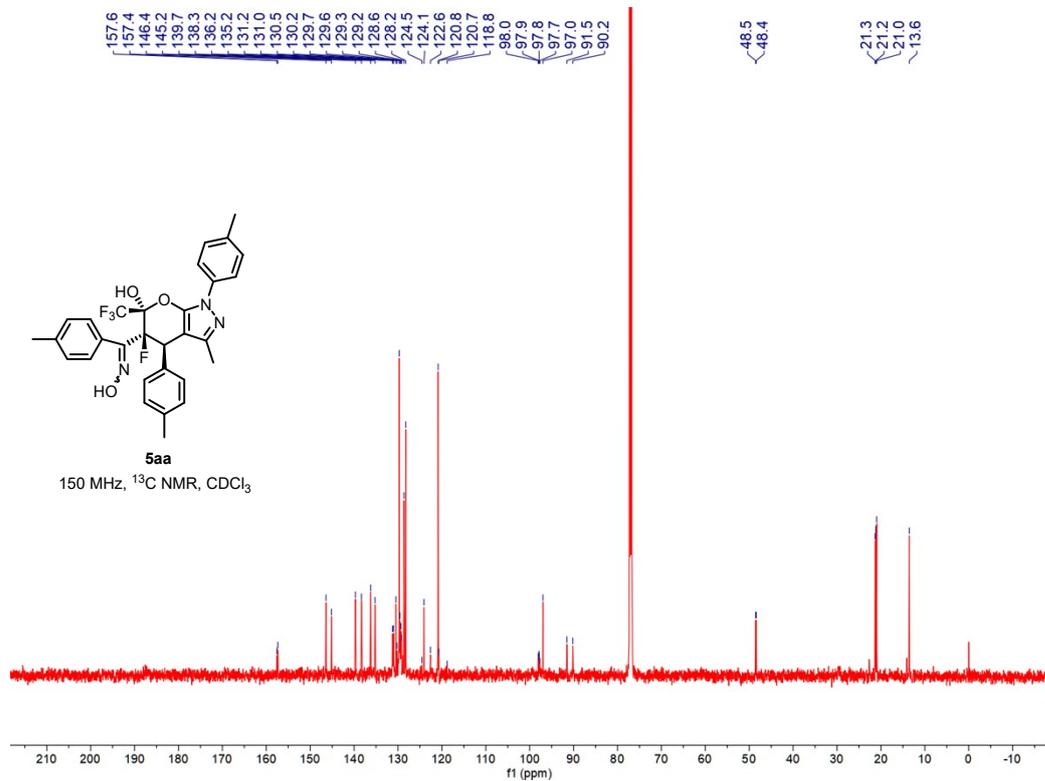
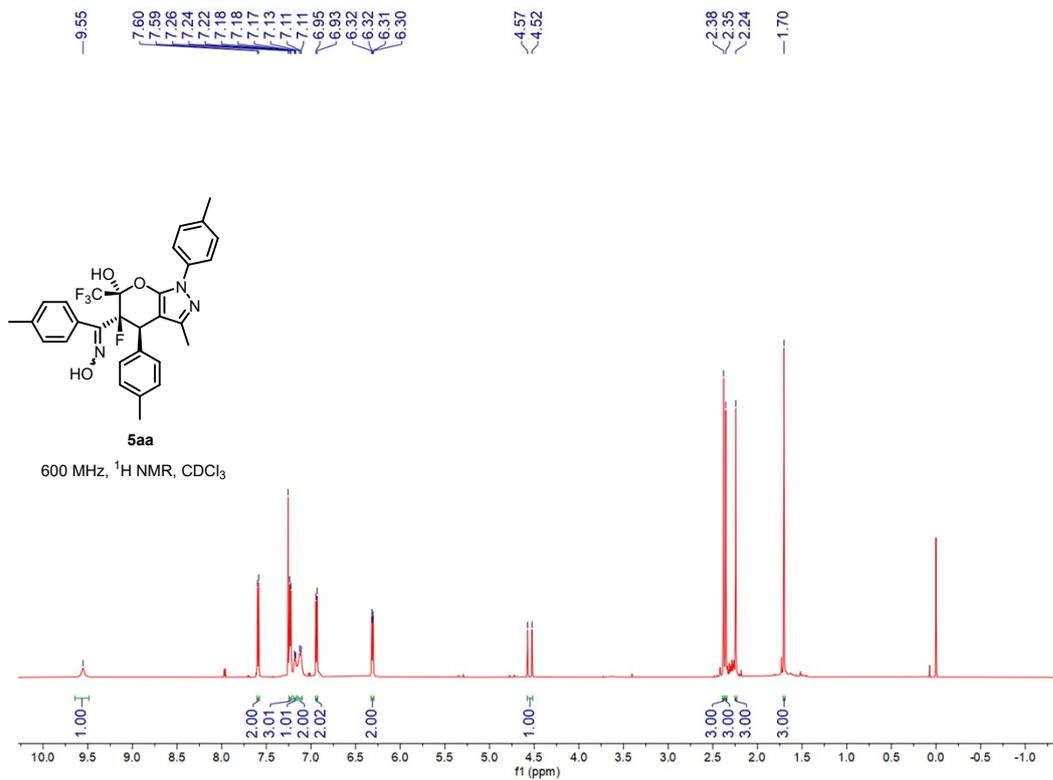


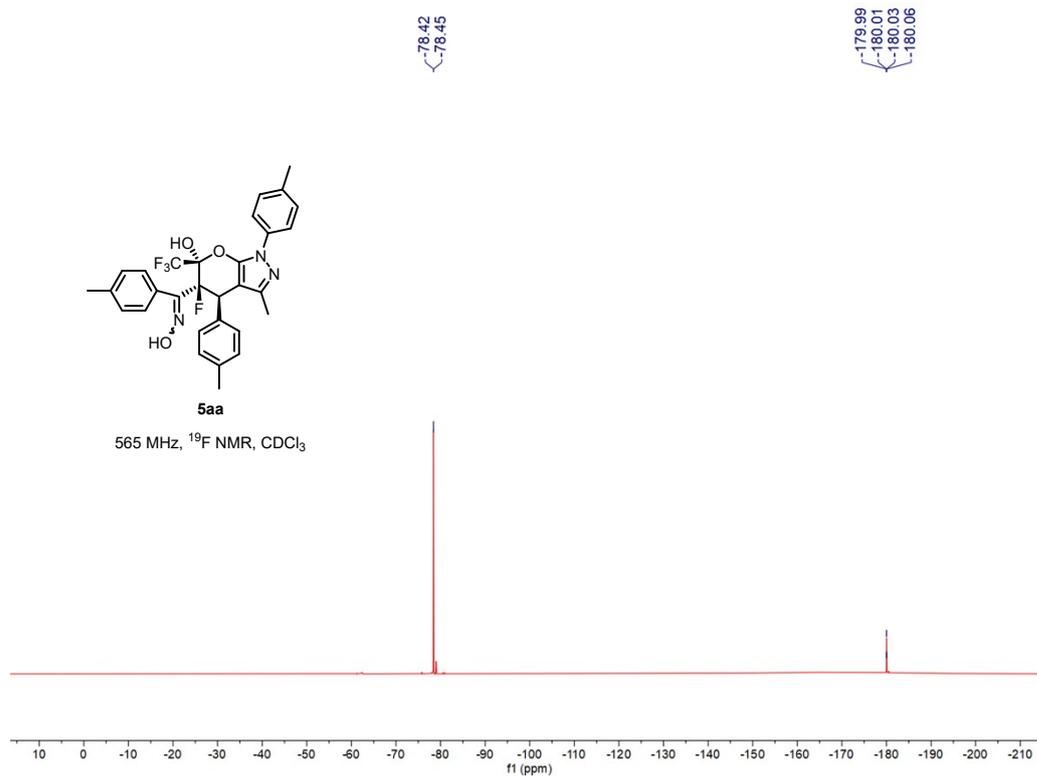
24-Oct-2025 13:47:19

bsr-jf-mif 172-251024 1403 (5.558) AM2 (Ar,12000.0,0.00,0.00); Cm (1403-1421:1426)

1: TOF MS ES+
1.57e4



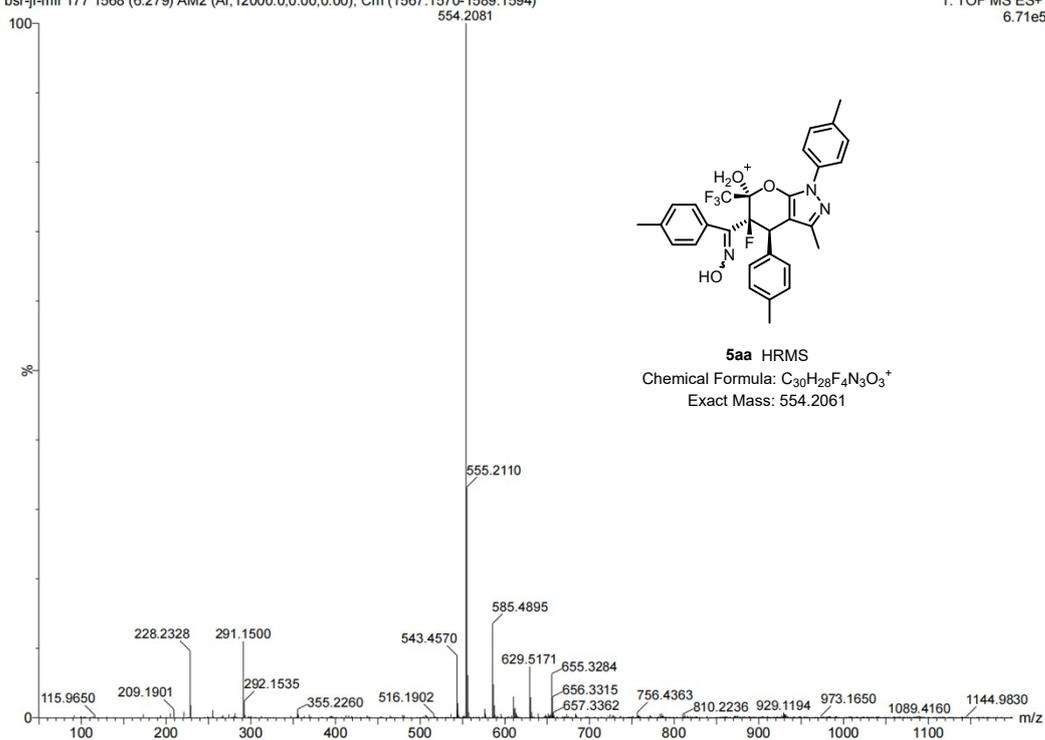


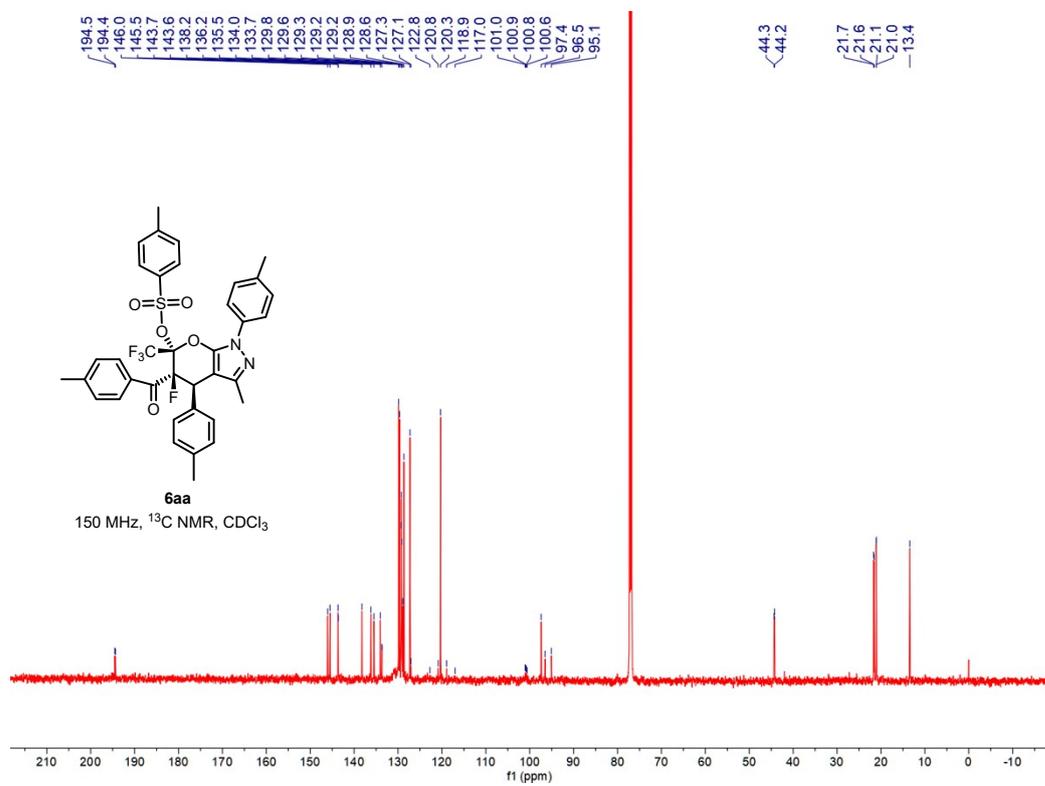
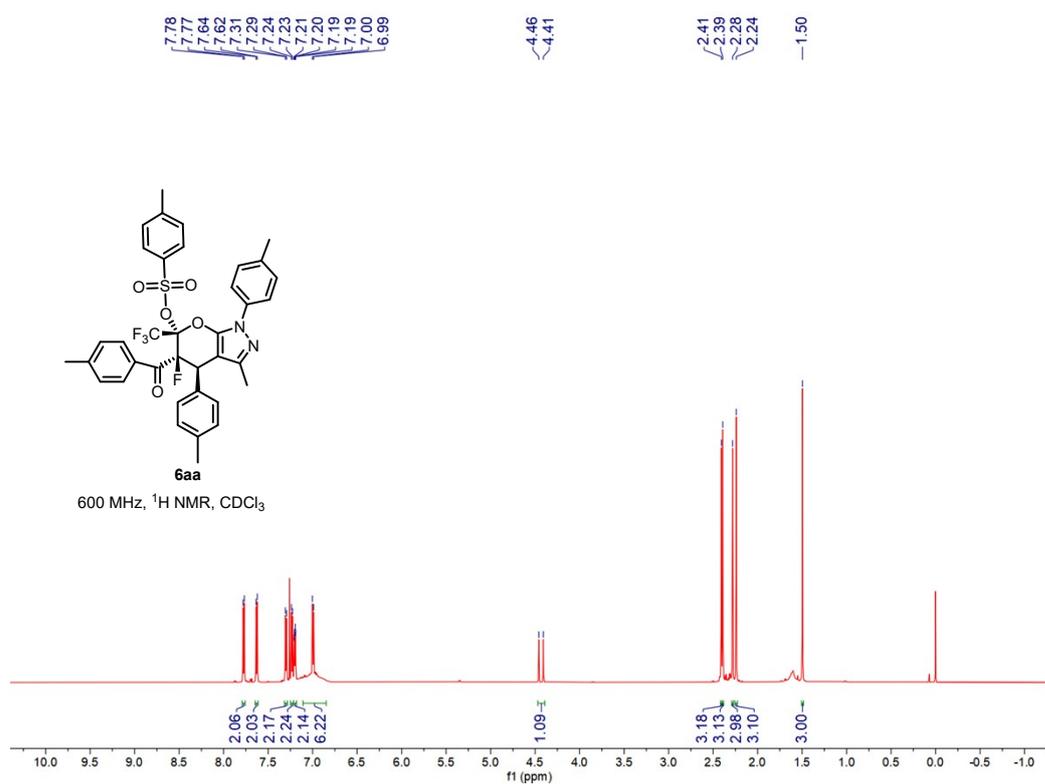


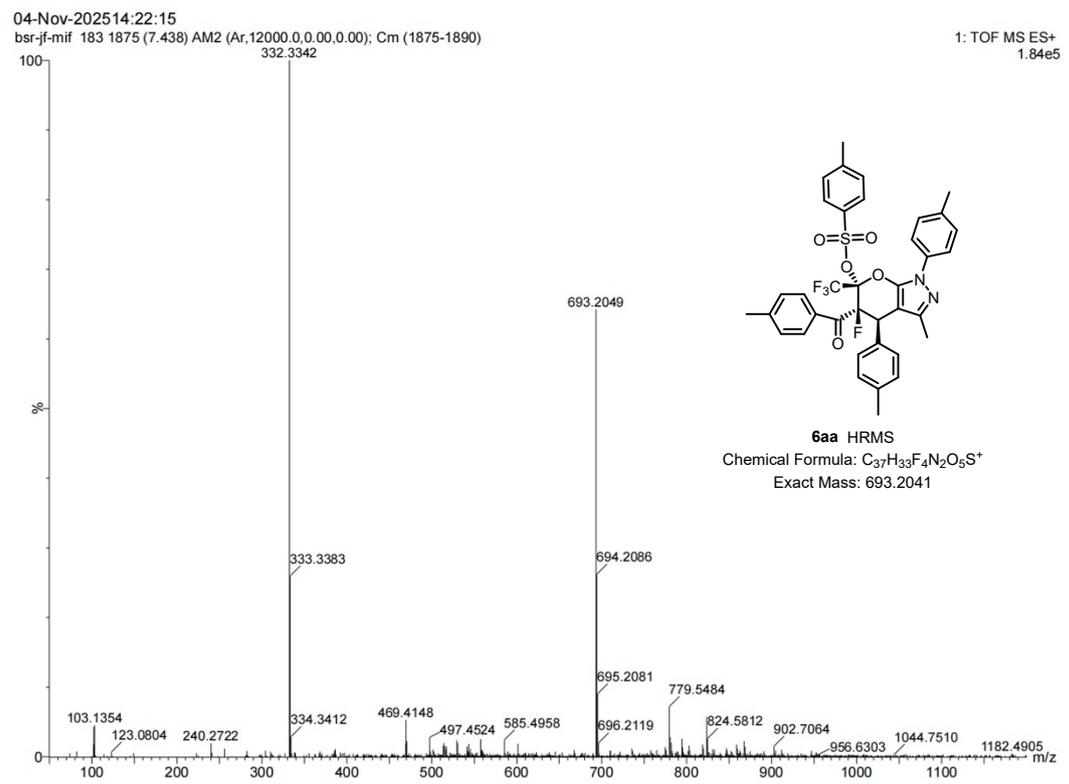
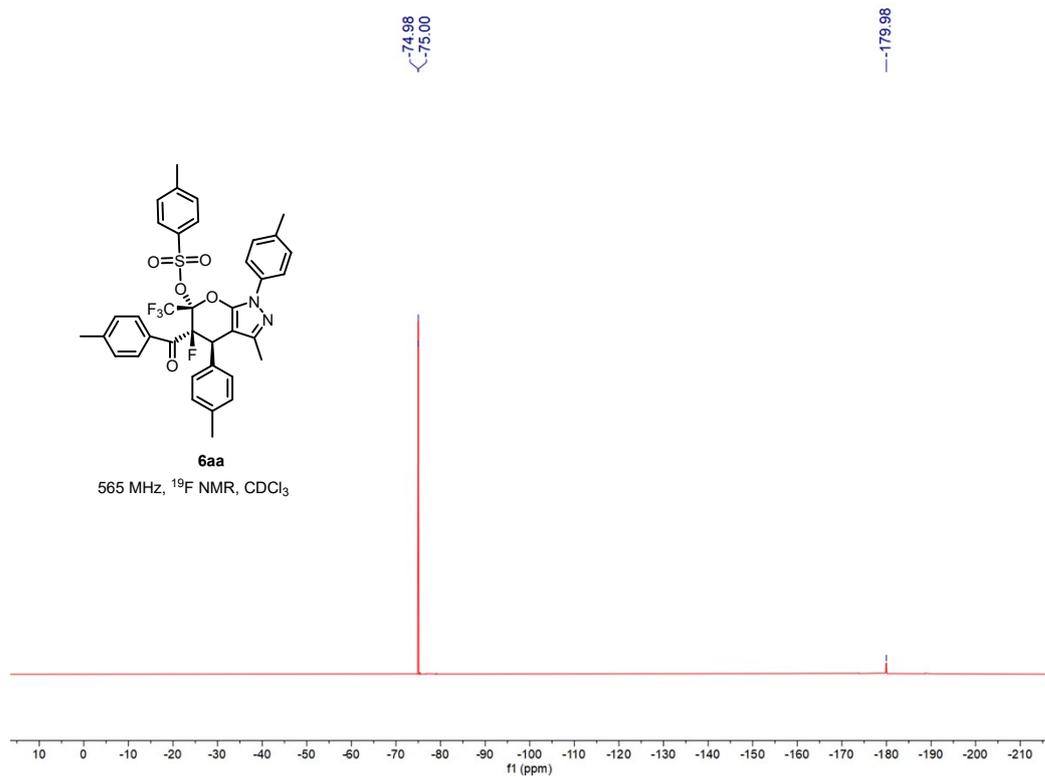
22-Oct-2025 13:39:05

bsr-jf-mif 177 1568 (6.279) AM2 (Ar, 12000.0,0.00,0.00); Cm (1567-1570-1589:1594)

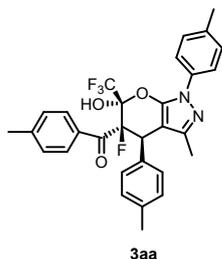
1: TOF MS ES+
6.71e5



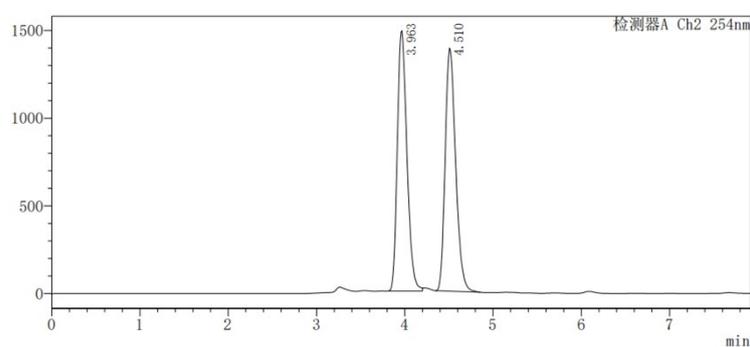




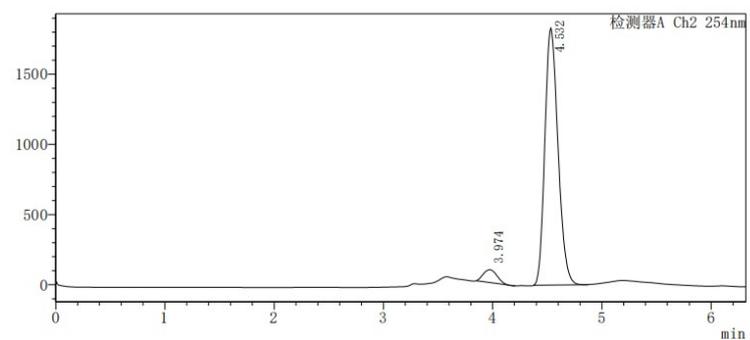
8. Copies of HPLC of products 3 and 4aa–6aa.



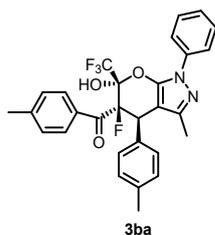
Enantiomeric excess is 90% determined by HPLC (Chiralpak IC, Hexane/Isopropanol 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 4.53 min; minor isomer: tr = 3.97 min.



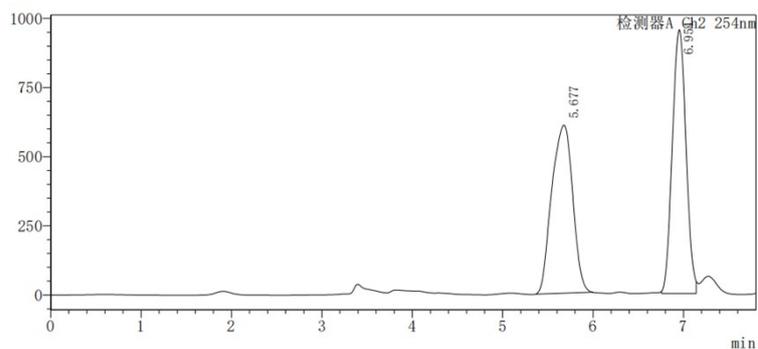
NO.	Time(min)	Area	Height	Area%
1	3.963	11200762	1483178	49.542
2	4.510	11407657	1384551	50.458



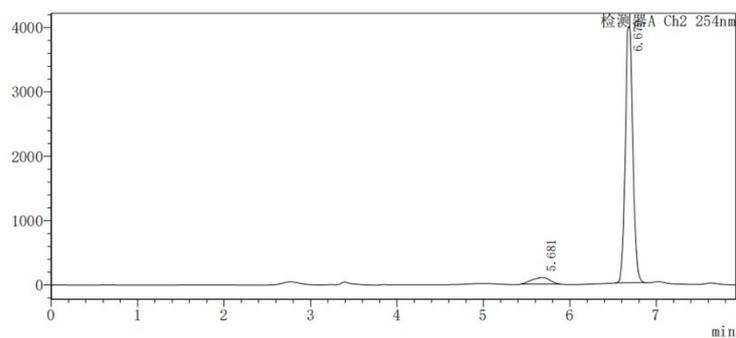
NO.	Time(min)	Area	Height	Area%
1	3.974	793546	91441	4.932
2	4.532	15296942	1829794	95.068



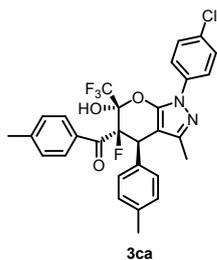
Enantiomeric excess is 89% determined by HPLC (Chiralpak IC, Hexane/Isopropanol 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 6.68 min; minor isomer: tr = 5.68 min.



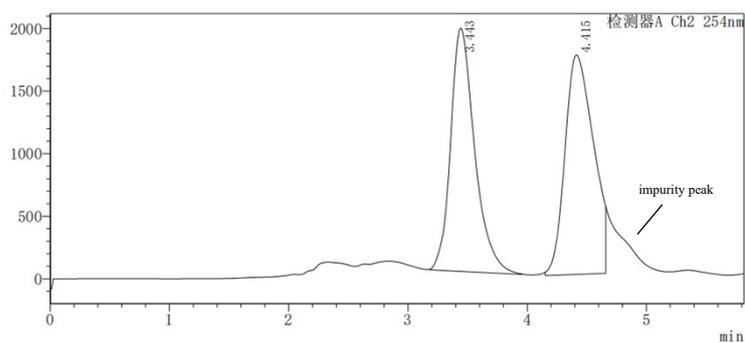
NO.	Time(min)	Area	Height	Area%
1	5.677	9802898	607780	49.407
2	6.954	10038112	953505	50.593



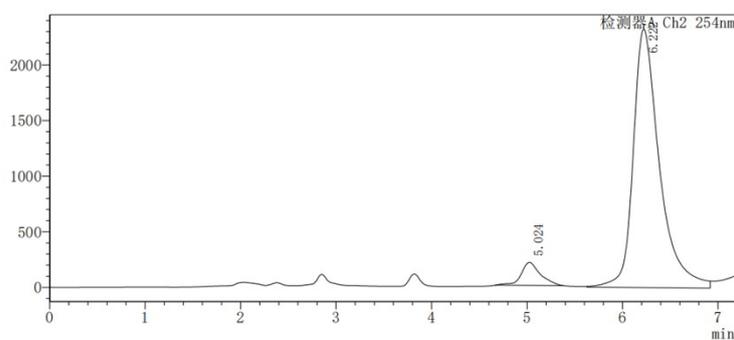
NO.	Time(min)	Area	Height	Area%
1	5.681	1466433	100364	5.737
2	6.679	24094265	3966086	94.263



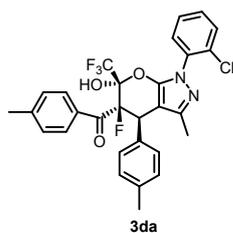
Enantiomeric excess is 88% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 6.22 min; minor isomer: tr = 5.02 min.



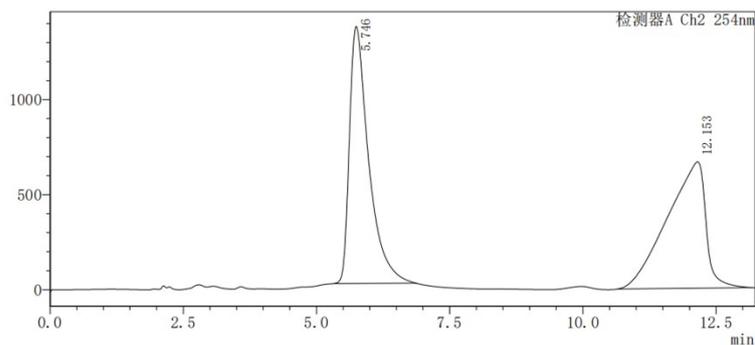
NO.	Time(min)	Area	Height	Area%
1	3.443	27323654	1944197	48.393
2	4.415	29138518	1755240	51.607



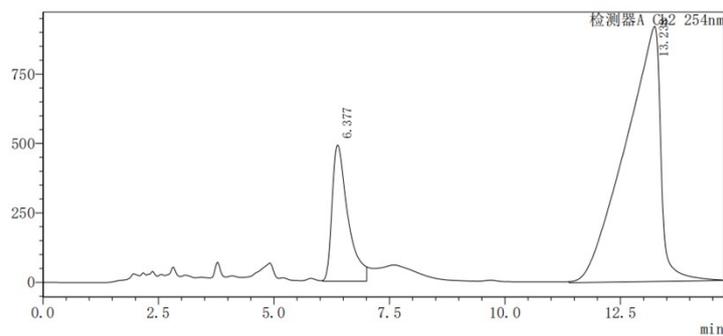
NO.	Time(min)	Area	Height	Area%
1	5.024	2884502	207140	6.081
2	6.222	44552976	2323828	93.919



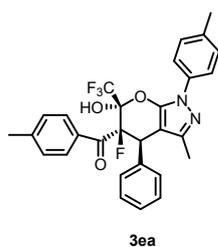
Enantiomeric excess is 62% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 13.24 min; minor isomer: tr = 6.38 min.



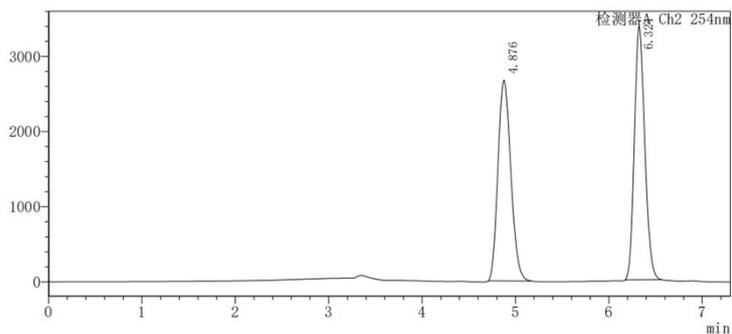
NO.	Time(min)	Area	Height	Area%
1	5.746	34036243	1352110	50.280
2	12.153	33656909	665216	49.720



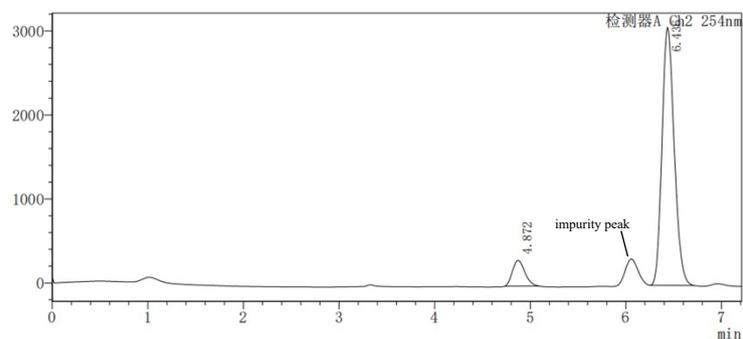
NO.	Time(min)	Area	Height	Area%
1	6.377	11725574	490511	19.190
2	13.238	49377297	918819	80.810



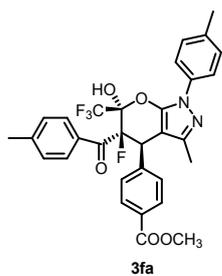
Enantiomeric excess is 82% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 6.44 min; minor isomer: tr = 4.87 min.



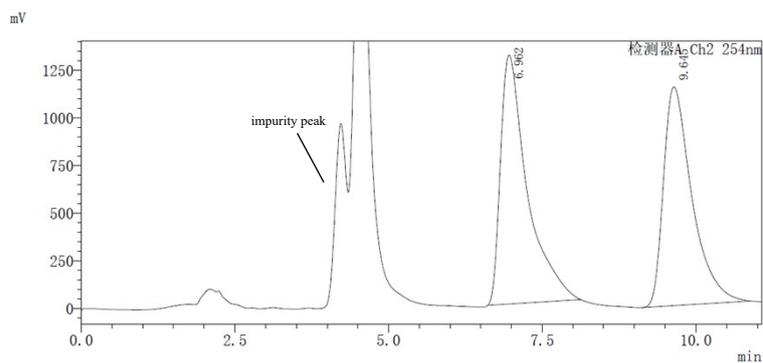
NO.	Time(min)	Area	Height	Area%
1	4.876	25586787	2671327	49.406
2	6.324	26202140	3382859	50.594



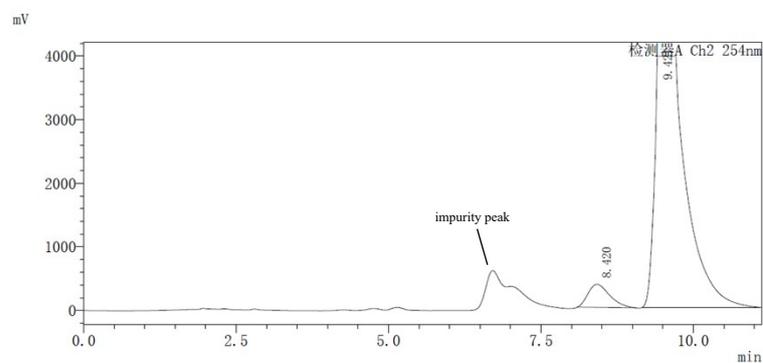
NO.	Time(min)	Area	Height	Area%
1	4.872	2763040	30733	9.201
2	6.436	27266009	3067711	90.799



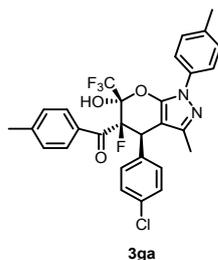
Enantiomeric excess is 88% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 9.42 min; minor isomer: tr = 8.42 min



NO.	Time(min)	Area	Height	Area%
1	6.962	39554492	1306432	51.702
2	9.645	36950610	1148039	48.298



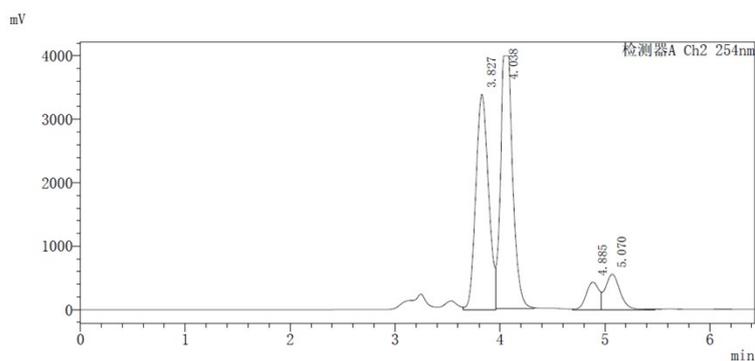
NO.	Time(min)	Area	Height	Area%
1	8.420	8970532	362818	5.882
2	9.421	143528720	3952700	94.118



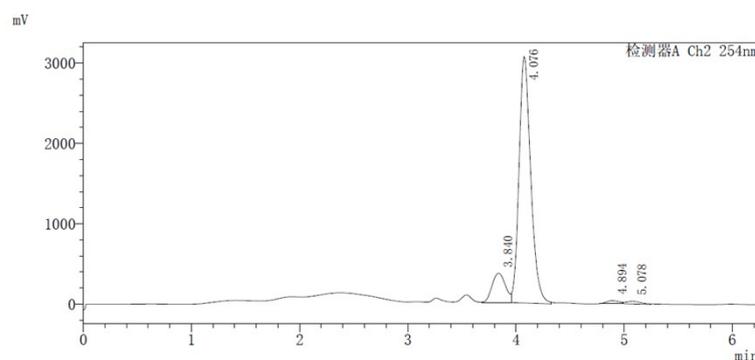
Enantiomeric excess is 76% determined by HPLC (Chiralpak IC, Hexane/Isopropanol 80/20, flow rate = 1.0 mL/min, 254 nm):

major pair of diastereoisomers: major isomer: tr = 4.08 min; minor isomer: tr = 3.84 min;

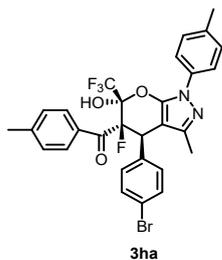
minor pair of diastereoisomers: major isomer: tr = 5.08 min; minor isomer: tr = 4.89 min.



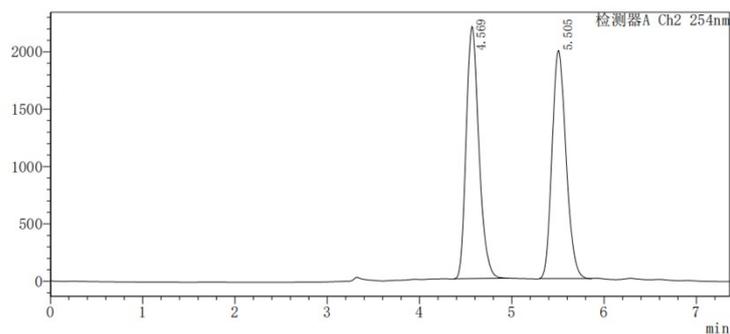
NO.	Time(min)	Area	Height	Area%
1	3.827	28764345	3396866	40.966
2	4.038	32378412	3982427	46.113
3	4.885	3692161	430726	5.258
4	5.070	5380330	555704	7.663



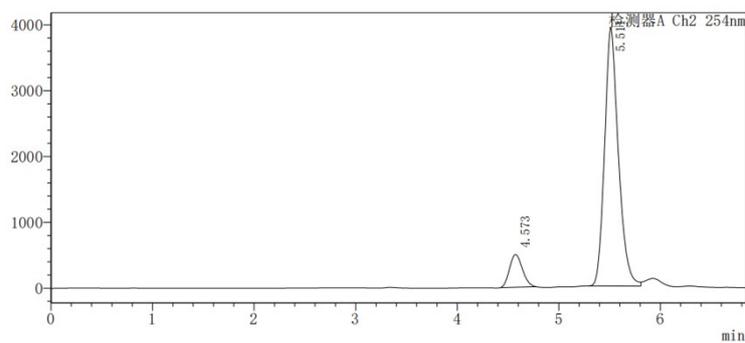
NO.	Time(min)	Area	Height	Area%
1	3.840	3188739	365176	11.899
2	4.076	22977588	3065468	85.742
3	4.894	315976	38649	1.179
4	5.078	316199	33740	1.180



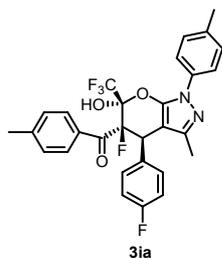
Enantiomeric excess is 79% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 5.51 min; minor isomer: tr = 4.57 min.



NO.	Time(min)	Area	Height	Area%
1	4.569	21077599	2196896	50.150
2	5.505	20951890	1987164	49.850

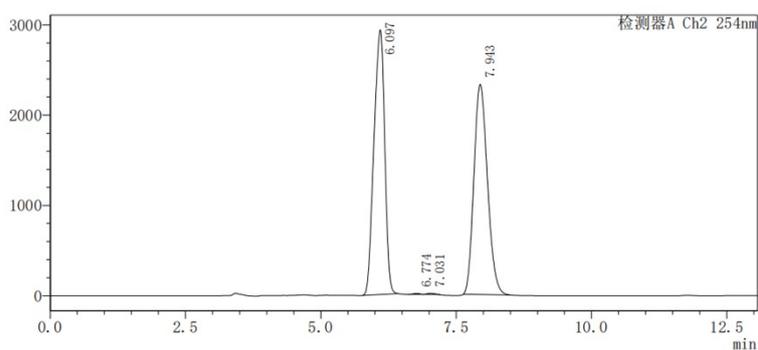


NO.	Time(min)	Area	Height	Area%
1	4.573	4376932	496697	10.548
2	5.511	37119403	3931556	89.452

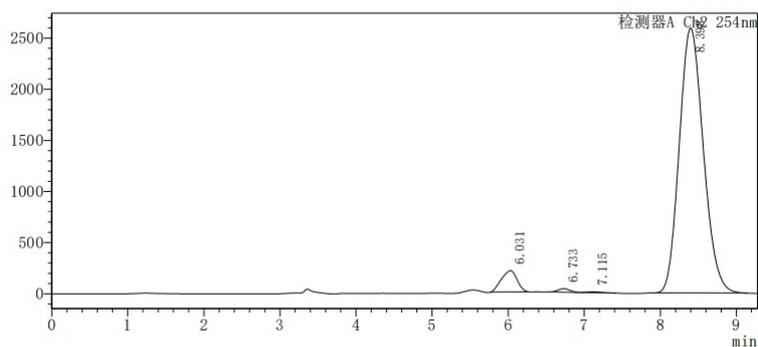


Enantiomeric excess is 90% determined by HPLC (Chiralpak IC, Hexane/Isopropanol 95/5, flow rate = 1.0 mL/min, 254 nm):

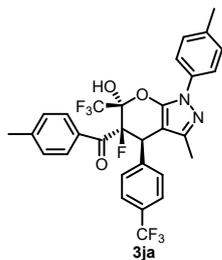
major pair of diastereoisomers: major isomer: tr = 8.40 min; minor isomer: tr = 6.03 min.;
 minor pair of diastereoisomers: major isomer: tr = 6.73 min; minor isomer: tr = 7.12 min.



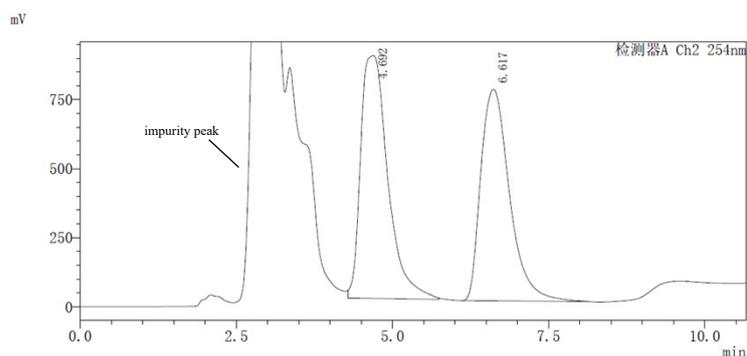
NO.	Time(min)	Area	Height	Area%
1	6.097	40443252	2929388	49.837
2	6.774	90024	10902	0.111
3	7.031	128093	12704	0.158
4	7.943	40490490	2327465	49.895



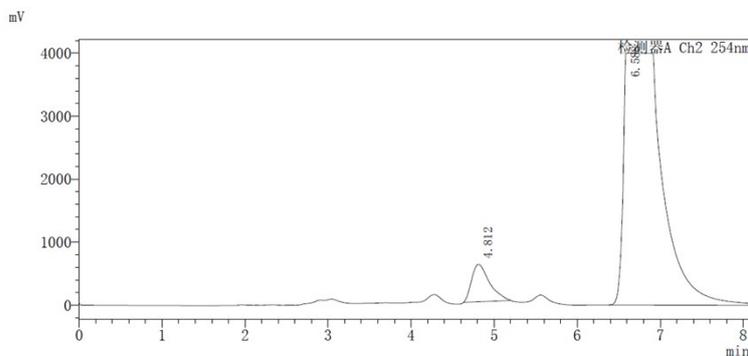
NO.	Time(min)	Area	Height	Area%
1	6.031	3010471	208925	4.982
2	6.733	362986	34183	0.601
3	7.115	100539	7372	0.166
4	8.398	56956838	2590234	94.251



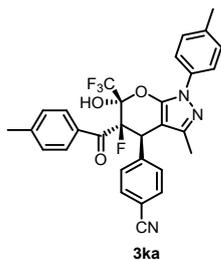
Enantiomeric excess is 87% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 6.59 min; minor isomer: tr = 4.81 min.



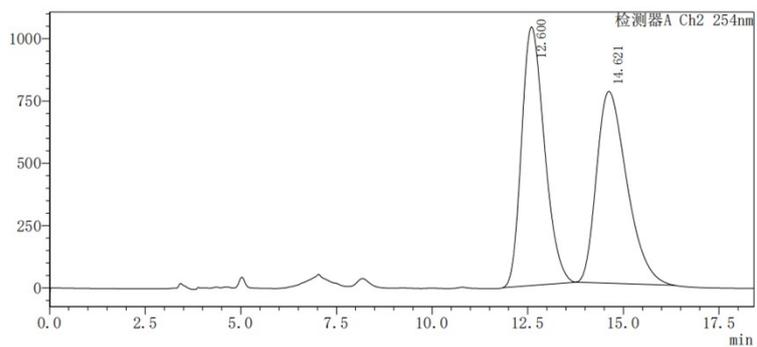
NO.	Time(min)	Area	Height	Area%
1	4.692	26657517	880199	52.020
2	6.617	24586905	767757	47.980



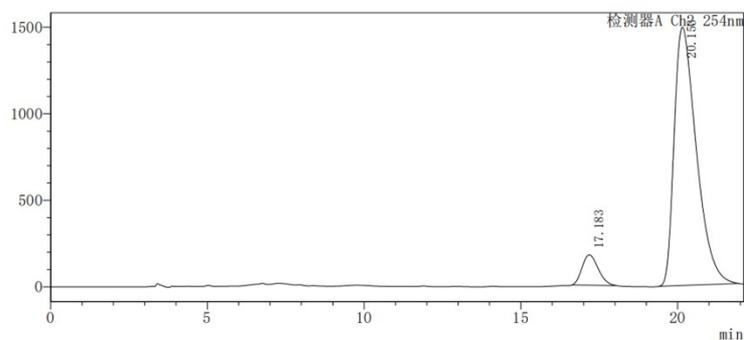
NO.	Time(min)	Area	Height	Area%
1	4.812	8845899	593545	6.368
2	6.588	130059737	3998934	93.632



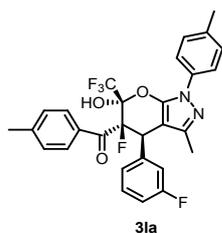
Enantiomeric excess is 84% determined by HPLC (Chiralpak IC, Hexane/Isopropanol 95/5, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 20.15 min; minor isomer: tr = 17.18 min.



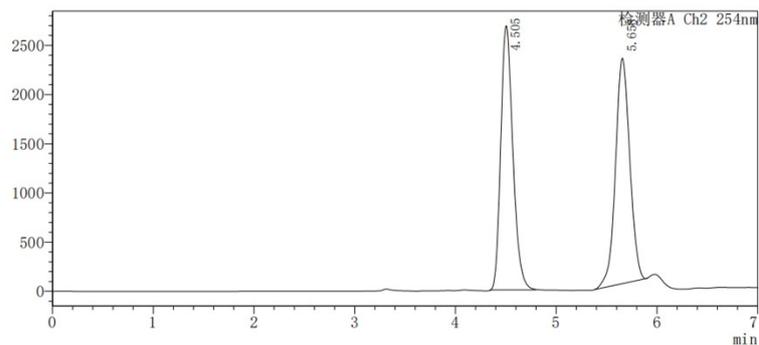
NO.	Time(min)	Area	Height	Area%
1	12.600	43189958	1037367	50.384
2	14.621	42532382	769178	49.616



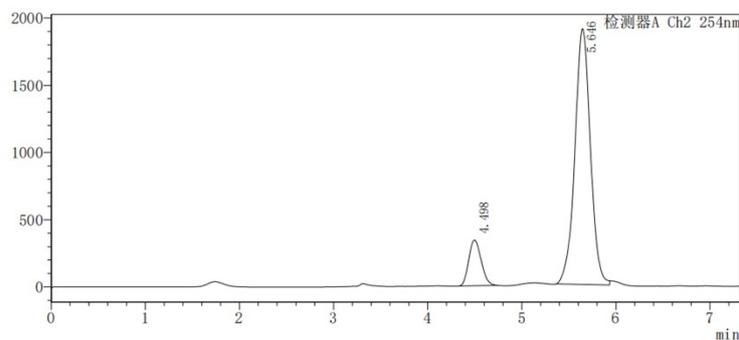
NO.	Time(min)	Area	Height	Area%
1	17.183	6295144	175986	7.880
2	20.153	73592217	1492392	92.120



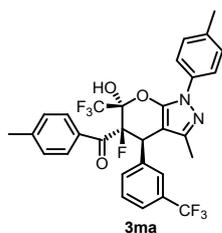
Enantiomeric excess is 75% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 5.65 min; minor isomer: tr = 4.50 min.



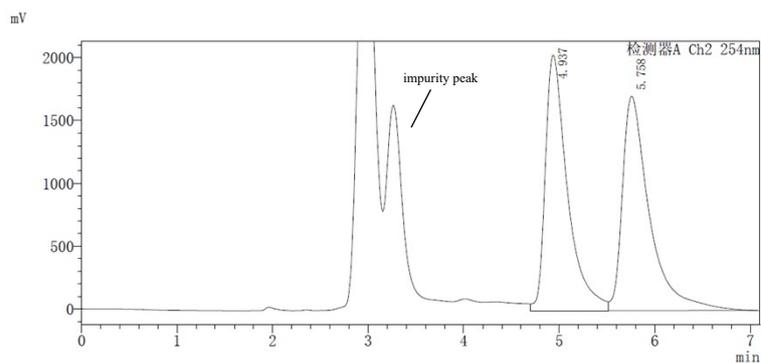
NO.	Time(min)	Area	Height	Area%
1	4.505	22452860	2682438	49.761
2	5.658	22668942	2291262	50.239



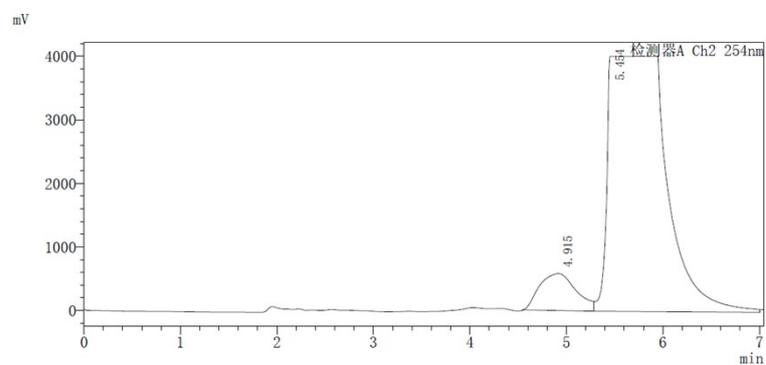
NO.	Time(min)	Area	Height	Area%
1	4.498	3127515	341053	12.521
2	5.646	21851048	1901008	87.479



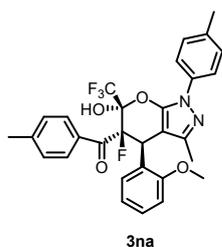
Enantiomeric excess is 83% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 5.45 min; minor isomer: tr = 4.92 min;



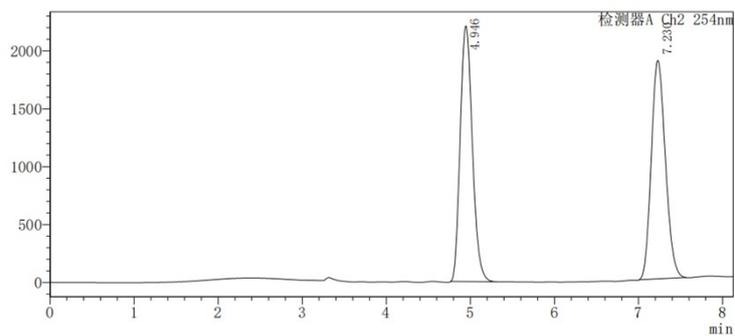
NO.	Time(min)	Area	Height	Area%
1	4.937	32832298	2032800	49.442
2	5.758	33573597	1704857	50.558



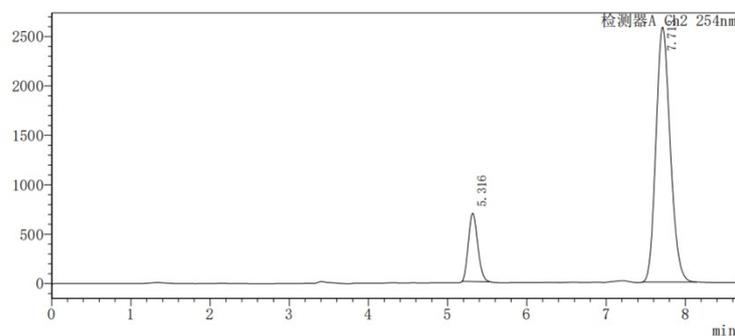
NO.	Time(min)	Area	Height	Area%
1	4.915	15338938	581528	8.322
2	5.454	168969491	4012743	91.678



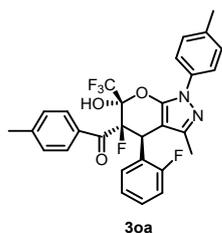
Enantiomeric excess is 70% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 7.71min; minor isomer: tr = 5.32min.



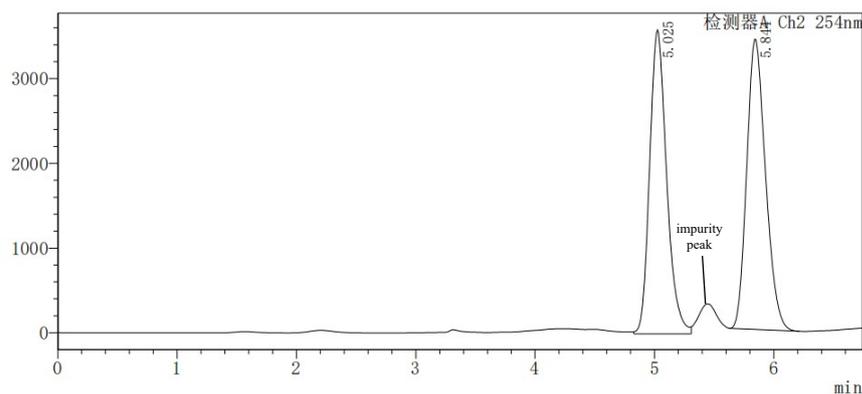
NO.	Time(min)	Area	Height	Area%
1	4.946	22197272	2206150	50.197
2	7.230	22022690	1884536	49.803



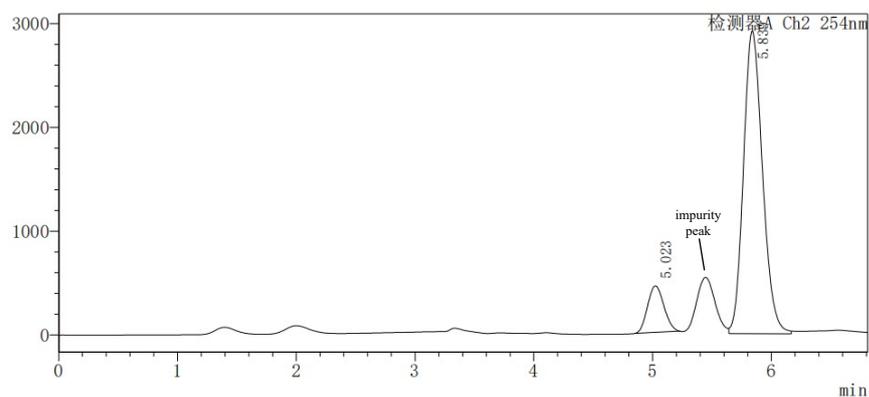
NO.	Time(min)	Area	Height	Area%
1	5.316	5685264	691154	14.940
2	7.713	32369863	2578275	85.060



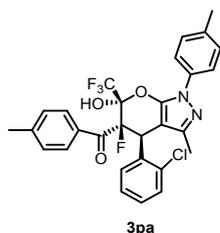
Enantiomeric excess is 77% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 5.84 min; minor isomer: tr = 5.02 min.



NO.	Time(min)	Area	Height	Area%
1	5.025	35557234	3587119	48.674
2	5.844	37493936	3426065	51.326



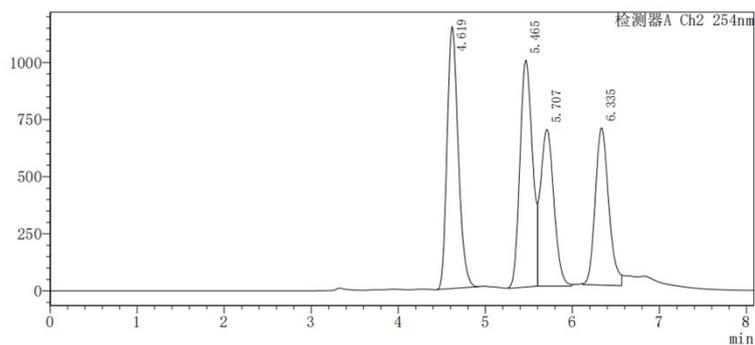
NO.	Time(min)	Area	Height	Area%
1	5.023	4295367	448706	11.673
2	5.839	32500866	2918395	88.327



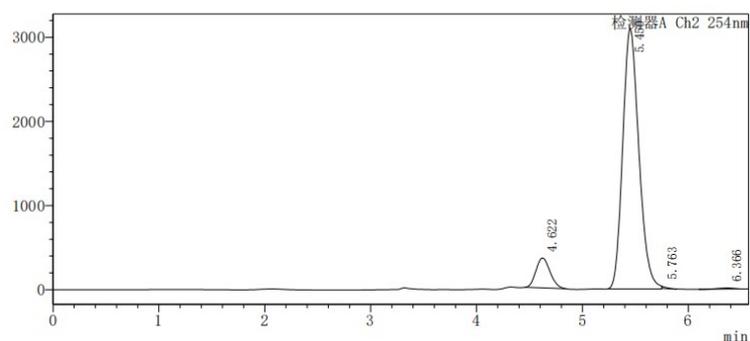
Enantiomeric excess is 83% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm):

major pair of diastereoisomers: major isomer: tr = 5.45 min; minor isomer: tr = 4.62 min;

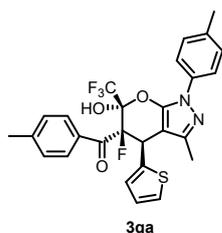
minor pair of diastereoisomers: major isomer: tr = 6.37 min; minor isomer: tr = 5.76 min;



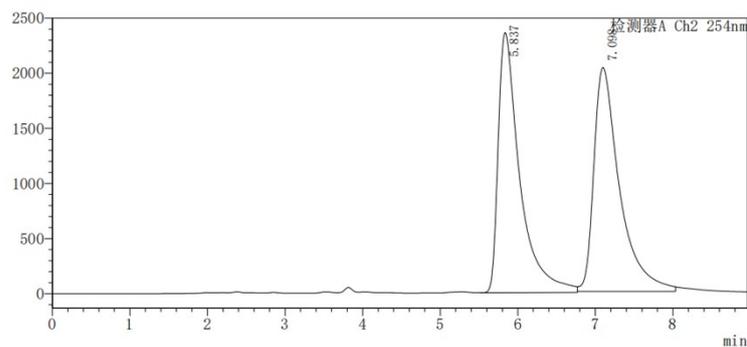
NO.	Time(min)	Area	Height	Area%
1	4.619	10206021	1144958	29.237
2	5.465	10044320	992023	28.774
3	5.707	7243280	686513	20.750
4	6.335	7414022	688179	21.239



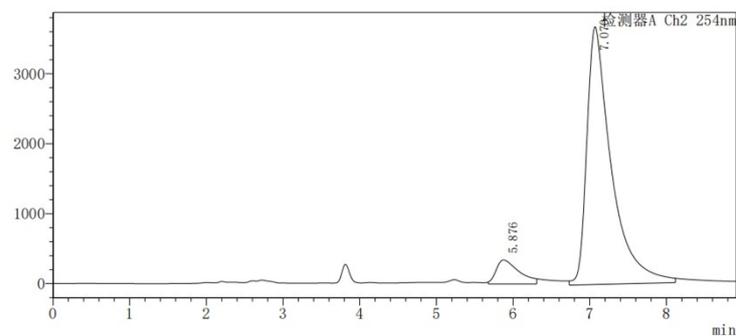
NO.	Time(min)	Area	Height	Area%
1	4.622	3123944	347781	8.696
2	5.450	32801449	3091048	91.304
3	5.763	76993	21936	0.212
4	6.366	153974	13072	0.423



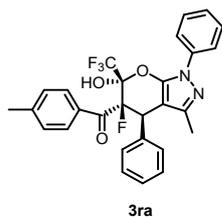
Enantiomeric excess is 84% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 7.07 min; minor isomer: tr = 5.88 min.



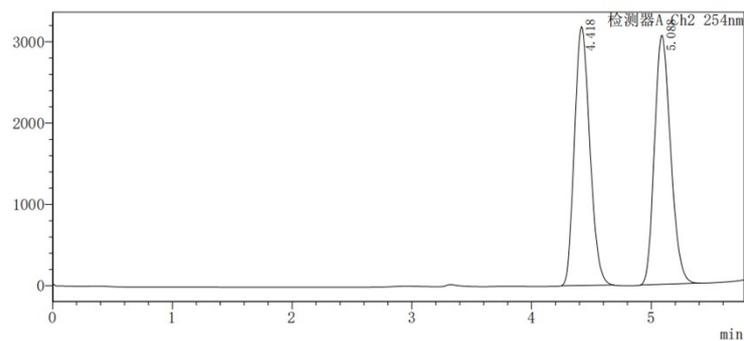
NO.	Time(min)	Area	Height	Area%
1	5.837	45568796	2359660	49.258
2	7.098	46940762	2032784	50.742



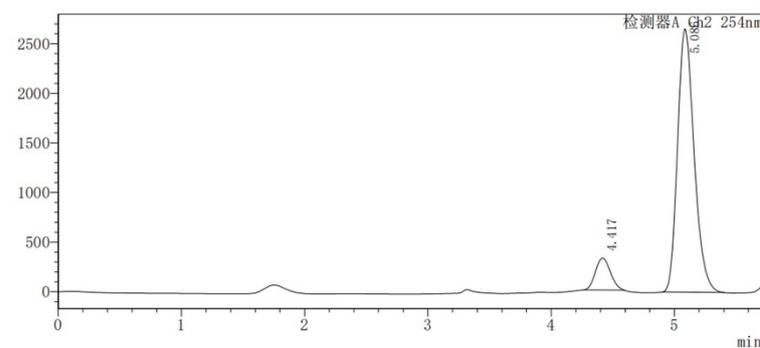
NO.	Time(min)	Area	Height	Area%
1	5.876	7069333	341105	7.941
2	7.070	81949466	3680812	92.059



Enantiomeric excess is 80% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 5.09 min; minor isomer: tr = 4.42 min.



NO.	Time(min)	Area	Height	Area%
1	4.418	28356438	3180513	49.647
2	5.088	28759408	306059	50.353

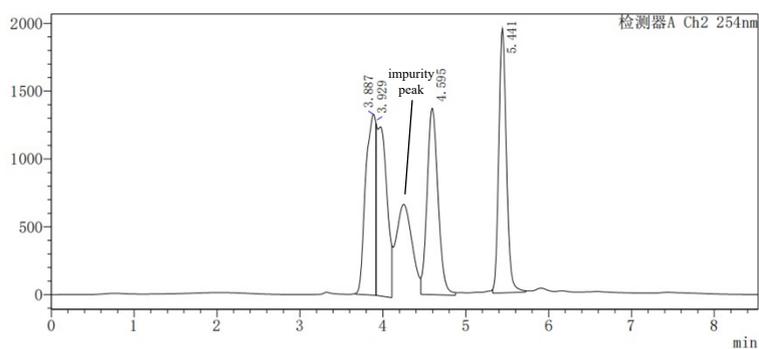


NO.	Time(min)	Area	Height	Area%
1	4.417	2726472	323563	9.908
2	5.086	24790819	2652770	90.092

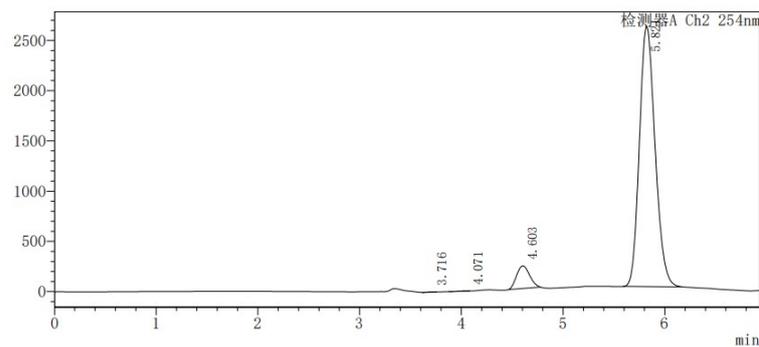


Enantiomeric excess is 87% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm):

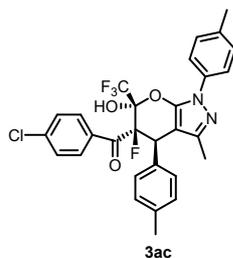
major pair of diastereoisomers: major isomer: tr = 5.82 min; minor isomer: tr = 4.60 min;
 minor pair of diastereoisomers: major isomer: tr = 3.72 min; minor isomer: tr = 4.07 min;



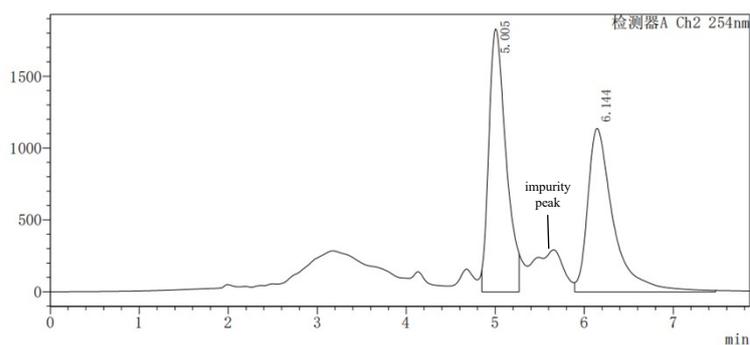
NO.	Time(min)	Area	Height	Area%
1	3.887	11168530	1332986	23.774
2	3.929	10744860	1245263	22.872
3	4.595	12615830	1374698	26.855
4	5.441	12449103	1945217	26.500



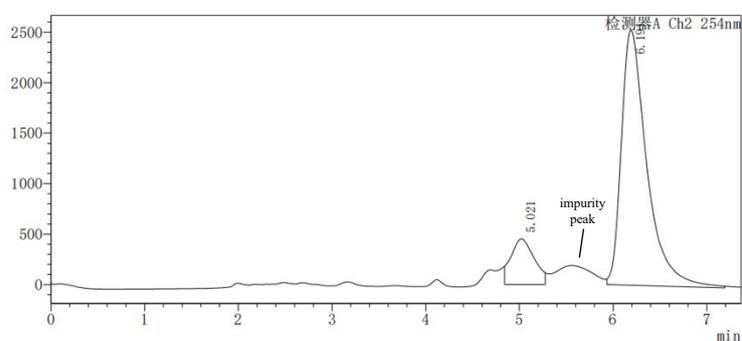
NO.	Time(min)	Area	Height	Area%
1	3.716	17991	2579	0.060
2	4.071	16757	59	0.056
3	4.603	2009454	225933	6.757
4	5.821	27729341	2587300	93.243



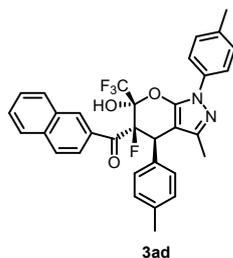
Enantiomeric excess is 72% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 6.19 min; minor isomer: tr = 5.02min.



NO.	Time(min)	Area	Height	Area%
1	5.005	24418432	1829570	51.511
2	6.144	22986148	1139003	48.489

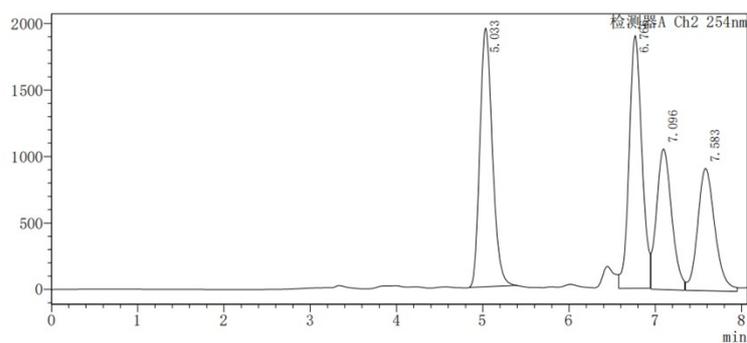


NO.	Time(min)	Area	Height	Area%
1	5.021	7745089	451379	13.944
2	6.191	47798023	2528026	86.056

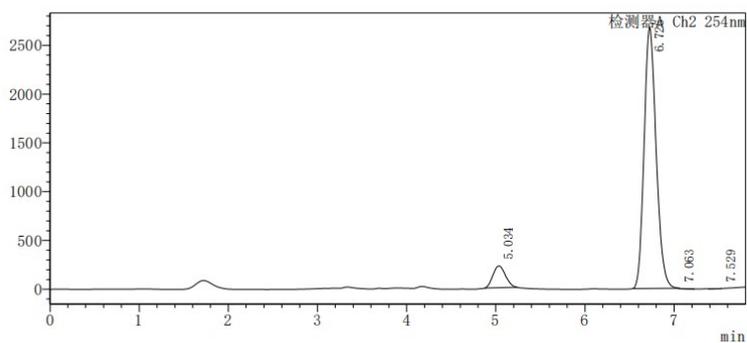


Enantiomeric excess is 84% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 90/10, flow rate = 1.0 mL/min, 254 nm):

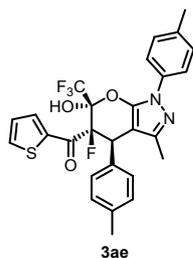
major pair of diastereoisomers: major isomer: tr = 6.73 min; minor isomer: tr = 5.03 min;
 minor pair of diastereoisomers: major isomer: tr = 7.53 min; minor isomer: tr = 7.06 min;



NO.	Time(min)	Area	Height	Area%
1	5.033	19557882	1943484	30.207
2	6.766	19531214	1898958	30.166
3	7.096	12867955	1056905	19.875
4	7.583	12788832	920112	19.752



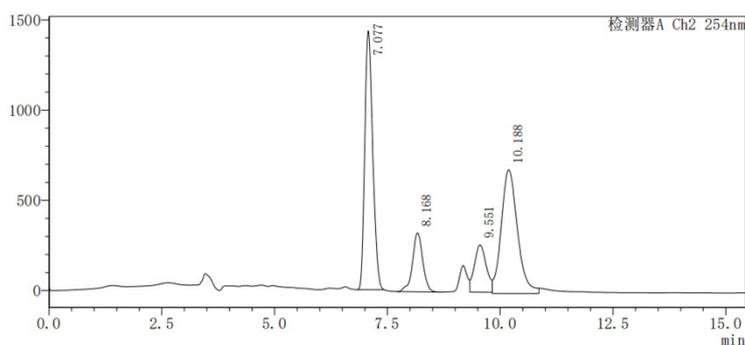
NO.	Time(min)	Area	Height	Area%
1	5.034	2178849	223960	7.960
2	6.726	25194063	2674004	92.040
3	7.063	20616	5499	0.075
4	7.529	21961	4313	0.080



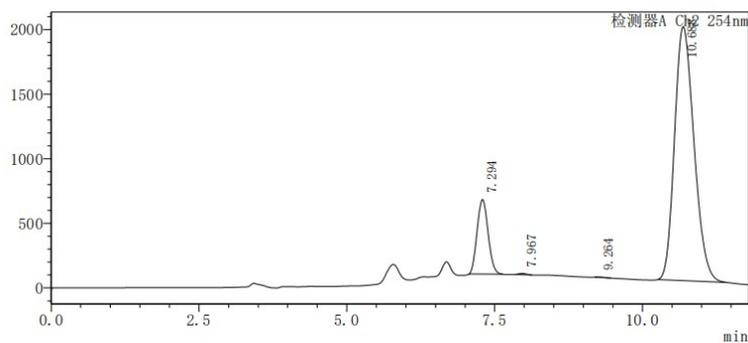
Enantiomeric excess is 72% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 95/5, flow rate = 1.0 mL/min, 254 nm):

major pair of diastereoisomers: major isomer: tr = 10.69 min; minor isomer: tr = 7.29 min;

minor pair of diastereoisomers: major isomer: tr = 7.97 min; minor isomer: tr = 9.26 min;



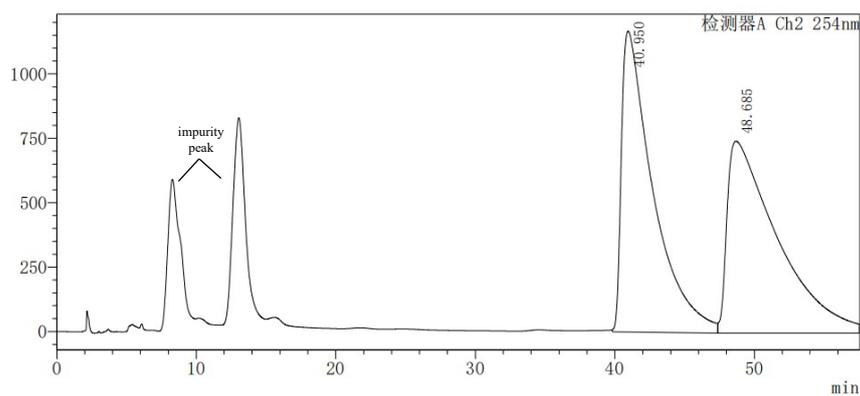
NO.	Time(min)	Area	Height	Area%
1	7.077	17544629	1431840	39.292
2	8.168	5178856	326065	11.598
3	9.551	4827479	26224	10.811
4	10.188	17101114	684551	38.299



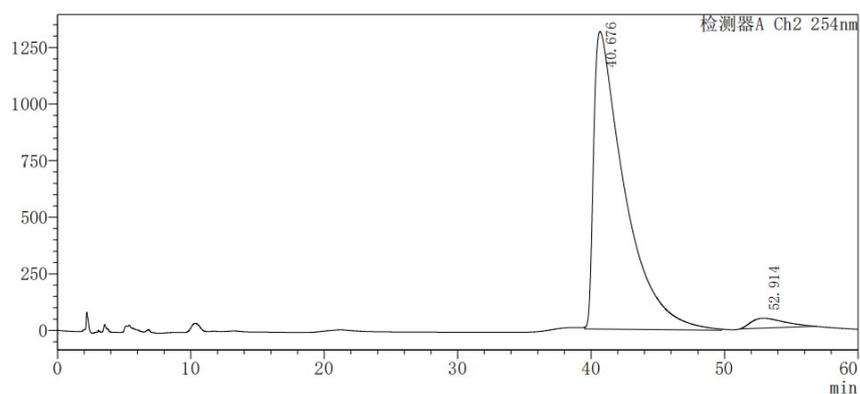
NO.	Time(min)	Area	Height	Area%
1	7.294	7499833	576959	14.255
2	7.967	92302	10236	0.175
3	9.264	30259	3304	0.057
4	10.688	45111290	1965988	85.745



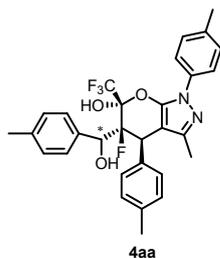
Enantiomeric excess is 93% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 98/2, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 40.68 min; minor isomer: tr = 52.91 min.



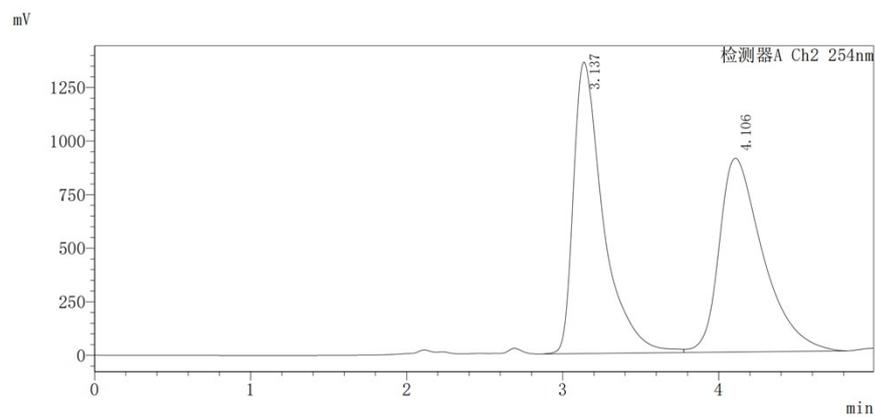
NO.	Time(min)	Area	Height	Area%
1	40.950	40.950	1167678	49.516
2	48.685	48.685	744893	50.484



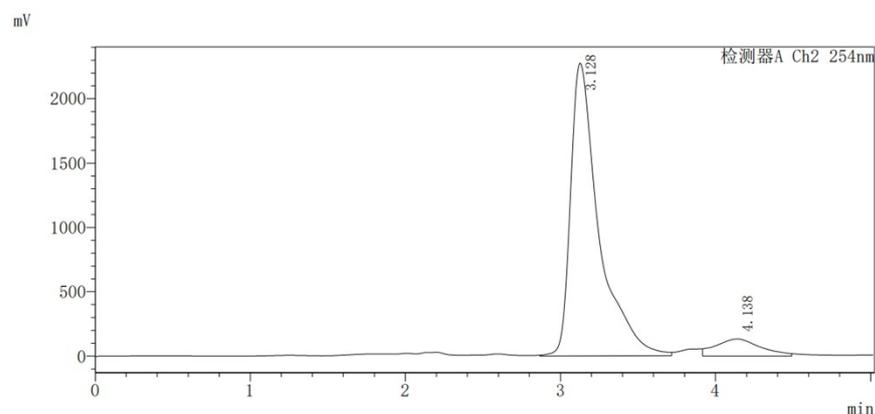
NO.	Time(min)	Area	Height	Area%
1	40.676	210660900	1314414	96.480
2	52.914	7685844	44017	3.520



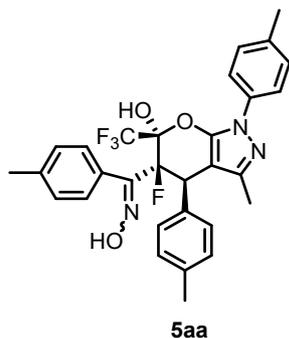
Enantiomeric excess is 83% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 80/20, flow rate = 1.0 mL/min, 254 nm): major isomer: tr = 3.13 min; minor isomer: tr = 4.14 min.



NO.	Time(min)	Area	Height	Area%
1	3.137	18055878	1360267	50.596
2	4.106	17630575	905033	49.404



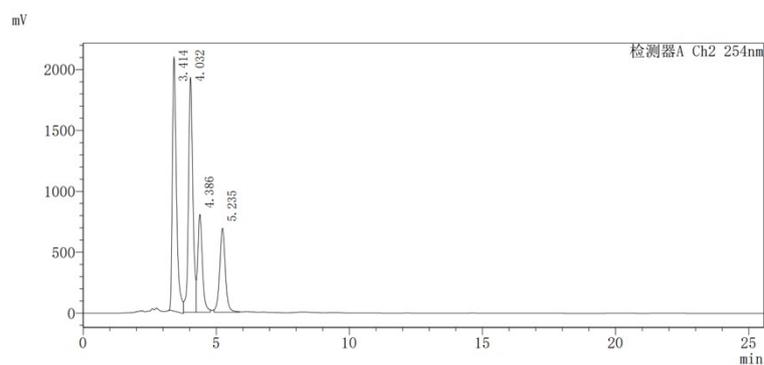
NO.	Time(min)	Area	Height	Area%
1	3.128	29000037	2275072	91.491
2	4.138	2696956	133463	8.509



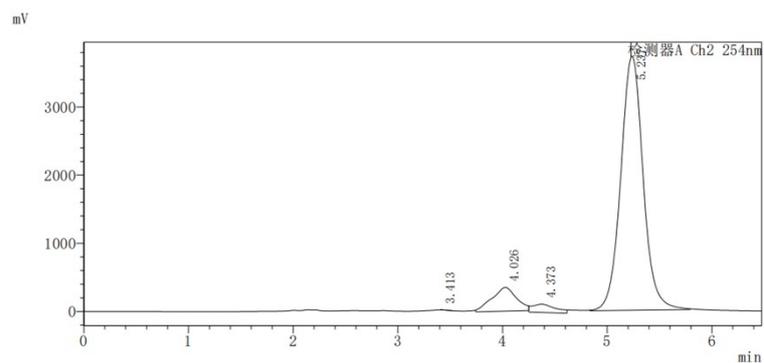
Enantiomeric excess is 93% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 80/20, flow rate = 1.0 mL/min, 254 nm):

major pair of diastereoisomers: major isomer: tr = 5.24 min; minor isomer: tr = 4.37 min.

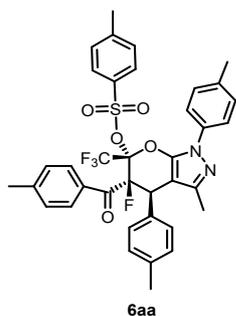
minor pair of diastereoisomers: major isomer: tr = 4.03 min; minor isomer: tr = 3.41 min;



NO.	Time(min)	Area	Height	Area%
1	3.414	22347570	2084195	34.678
2	4.032	22010791	1926358	34.155
3	4.386	9825174	803336	15.246
4	5.235	10259980	690242	15.921



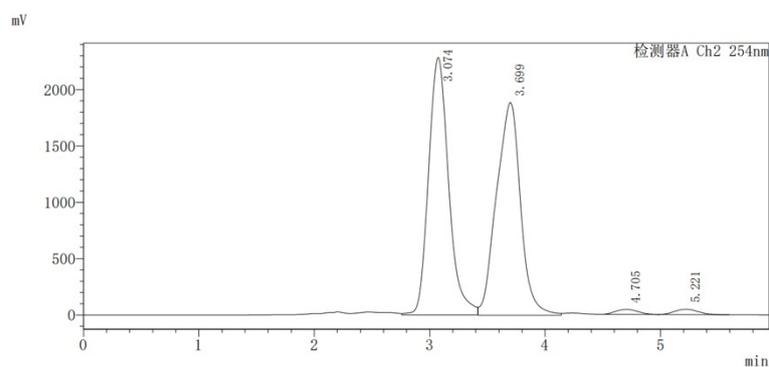
NO.	Time(min)	Area	Height	Area%
1	3.413	6102	532	0.010
2	4.026	5713718	349108	9.049
3	4.373	1867791	120430	2.958
4	5.237	55554562	3725795	87.983



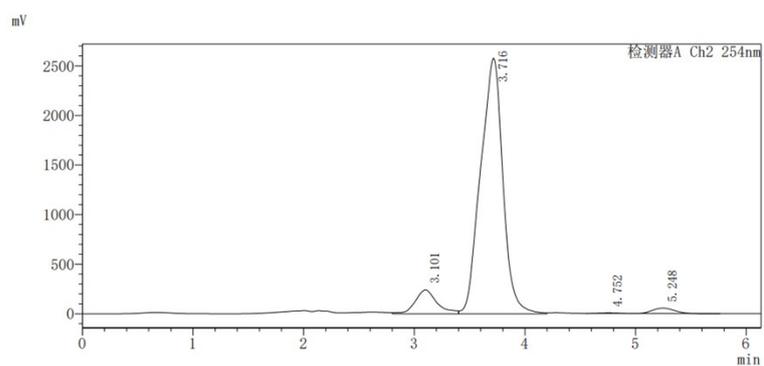
Enantiomeric excess is 83% determined by HPLC (Chiralpak IA, Hexane/Isopropanol 80/20, flow rate = 1.0 mL/min, 254 nm):

major pair of diastereoisomers: major isomer: tr = 3.72 min; minor isomer: tr = 3.10 min;

minor pair of diastereoisomers: major isomer: tr = 5.25 min; minor isomer: tr = 4.75 min;



NO.	Time(min)	Area	Height	Area%
1	3.074	27714621	2284691	49.190
2	3.699	27341653	1888404	48.528
3	4.705	606988	44584	1.077
4	5.221	679289	47182	1.206

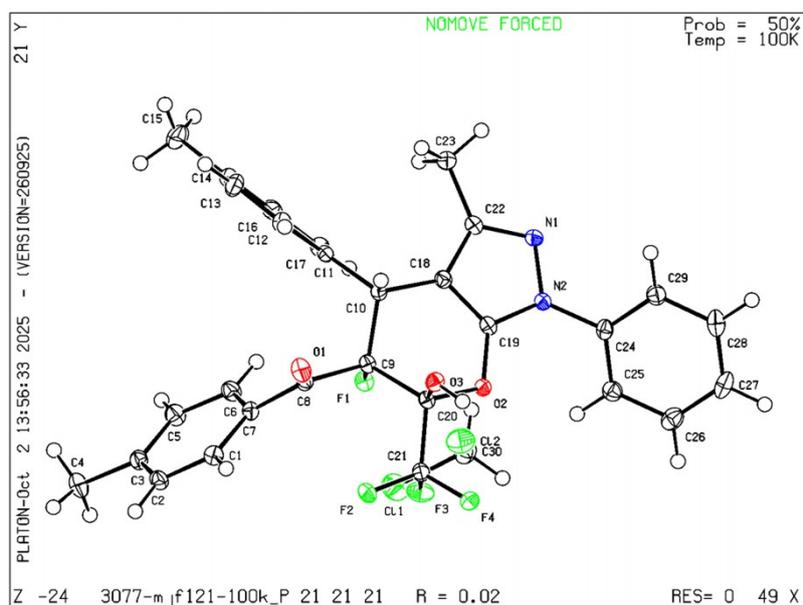
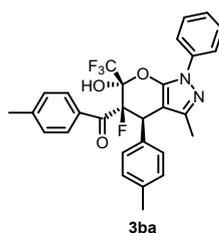


NO.	Time(min)	Area	Height	Area%
1	3.101	3286750	240224	8.183
2	3.716	36033655	2576728	89.716
3	4.752	69406	5153	0.173
4	5.248	774283	54621	1.928

9. Absolute Configuration of 3ba—X-ray Crystallography data.

Absolute configuration of 3ba (CCDC number: 2492883): The thermal ellipsoid drawn at 50% probability level.

Sample preparation method: **3ba** (15 mg) was dissolved in 4 mL of mixed solvent of chloroform and *n*-hexane, filtered, and slowly volatilized at room temperature.



checkCIF/PLATON report

Structure factors have been supplied for datablock(s) 3077-mjf121-100k_auto

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

No syntax errors found. CIF dictionary Interpreting this report

Datablock: 3077-mjf121-100k_auto

Bond precision: C-C = 0.0027 A Wavelength=1.54184

Cell: a=11.92364 (7) b=12.81775 (6) c=18.20321 (11)
 alpha=90 beta=90 gamma=90

Temperature: 100 K

	Calculated	Reported
Volume	2782.07 (3)	2782.07 (3)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C29 H24 F4 N2 O3, C H2 C12	C H2 C12, C29 H24 F4 N2 O3
Sum formula	C30 H26 Cl2 F4 N2 O3	C30 H26 Cl2 F4 N2 O3
Mr	609.43	609.43
Dx, g cm ⁻³	1.455	1.455
Z	4	4
Mu (mm ⁻¹)	2.652	2.652
F000	1256.0	1256.0
F000'	1262.95	
h, k, lmax	14, 16, 22	14, 15, 22
Nref	5703 [3207]	5657
Tmin, Tmax	0.909, 0.948	0.808, 1.000
Tmin'	0.266	

Correction method= # Reported T Limits: Tmin=0.808 Tmax=1.000

AbsCorr = MULTI-SCAN

Data completeness= 1.76/0.99 Theta(max)= 74.676

R(reflections)= 0.0230 (5596)

wR2(reflections)=
0.0645 (5657)

S = 1.033

Npar= 377

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

● **Alert level C**

PLAT042_ALERT_1_C	Calc. and Reported MoietyFormula Strings Differ	Please Check
	Calc: C29 H24 F4 N2 O3, C H2 Cl2	
	Rep.: C H2 Cl2, C29 H24 F4 N2 O3	
PLAT790_ALERT_4_C	Centre of Gravity not Within Unit-Cell: Resd. #	1 Note
	C29 H24 F4 N2 O3	
PLAT934_ALERT_3_C	Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers ..	1 Check
	1 1 0,	

● **Alert level G**

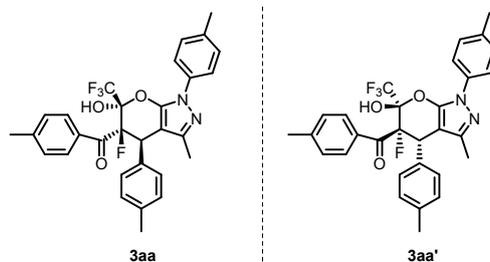
PLAT002_ALERT_2_G	Number of Distance or Angle Restraints on AtSite	2 Note
PLAT142_ALERT_4_G	s.u. on b - Axis Small or Missing	0.00006 Ang.
PLAT143_ALERT_4_G	s.u. on c - Axis Small or Missing	0.00011 Ang.
PLAT172_ALERT_4_G	The CIF-Embedded .res File Contains DFIX Records	1 Report
PLAT790_ALERT_4_G	Centre of Gravity not Within Unit-Cell: Resd. #	2 Note
	C H2 Cl2	
PLAT791_ALERT_4_G	Model has Chirality at C9 (Sohncke SpGr)	S Verify
PLAT791_ALERT_4_G	Model has Chirality at C10 (Sohncke SpGr)	R Verify
PLAT791_ALERT_4_G	Model has Chirality at C20 (Sohncke SpGr)	S Verify
PLAT860_ALERT_3_G	Number of Least-Squares Restraints	1 Note
PLAT912_ALERT_4_G	Missing # of FCF Reflections Above STh/L= 0.600	12 Note
PLAT969_ALERT_5_G	The 'Henn et al.' R-Factor-gap value	5.502 Note
	Predicted wR2: Based on SigI**2 1.17 or SHELX Weight 6.24	
PLAT978_ALERT_2_G	Number C-C Bonds with Positive Residual Density.	12 Info

- 0 **ALERT level A** = Most likely a serious problem - resolve or explain
 0 **ALERT level B** = A potentially serious problem, consider carefully
 3 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
 12 **ALERT level G** = General information/check it is not something unexpected
- 1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
 2 ALERT type 2 Indicator that the structure model may be wrong or deficient
 2 ALERT type 3 Indicator that the structure quality may be low
 9 ALERT type 4 Improvement, methodology, query or suggestion
 1 ALERT type 5 Informative message, check
-

10. Absolute Configuration of 3aa—ECD Calculation and X-ray Crystallographic Data

10.1 The calculated ECD spectra of 3aa and 3aa' and the experimental ECD of 3aa.

119



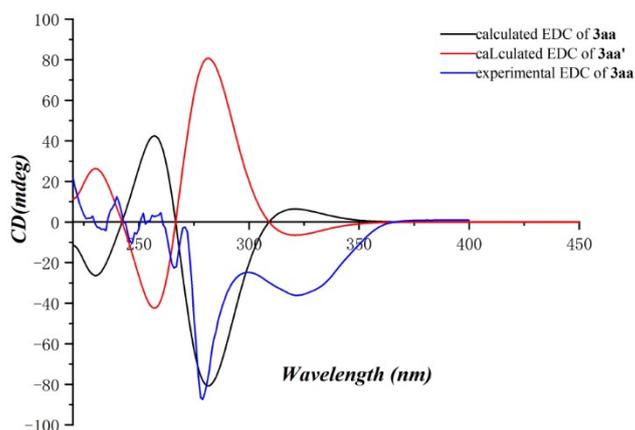


Figure1. Calculated ECD spectra of **3aa** and **3aa'** and the experimental ECD of **3aa**.

Quantum chemistry calculations

The theoretical calculations of **3aa** were performed using Gaussian 09 (Frisch et al., 2013). The possible conformations were initially obtained from the program Spartan'14 and then optimized at B3LYP/6-31G(d) level in the gas phase. Room-temperature equilibrium populations were calculated according to the Boltzmann distribution law. The ECD calculations were performed using Time Dependent Density Functional Theory (TDDFT) (Srebro-Hooper and Autschbach, 2017) at wB97xd/6-311G** level in ethanol with PCM model. The calculated ECD spectra were obtained by weighing the Boltzmann distribution rate of each geometric conformation, and the sigma/gamma value for processing the calculated ECD was 0.3 eV (Bruhn et al., 2015). All calculated curves were shifted +20 nm to better simulate experimental spectra.

Table S1. Important thermodynamic parameters and Boltzmann distributions of the optimized **3aa** at B3LYP/6-31G(d) level in gas phase.

Conformations	Energy (a.u)	$\Delta G(\text{kcal/mol})$	%
1	-1893.112041	0	100.00%
2			
3			
4			
5			

Table S2. The coordinates for the lowest energy conformers of **3aa**.

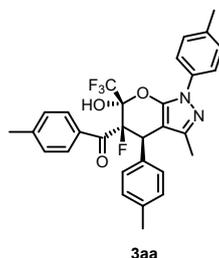
65			
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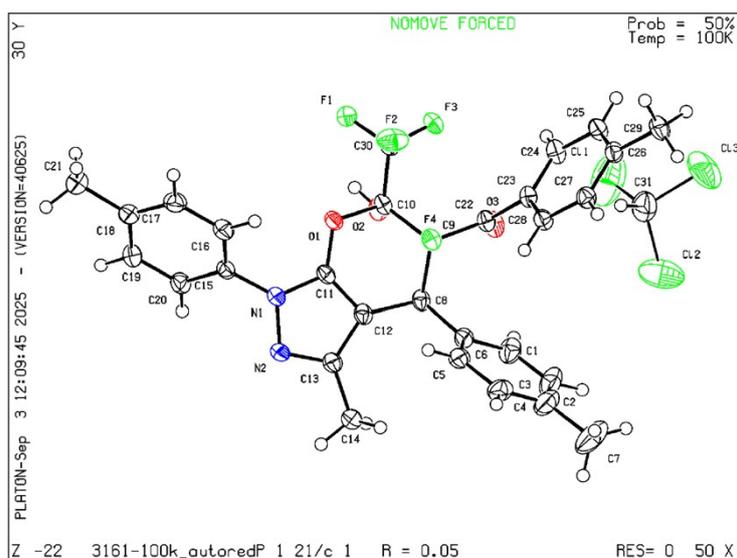
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C	-0.60523200	-0.50039300	0.47610100
C	0.62405800	-1.37808900	0.87818500
O	1.81906100	-0.87454300	0.30542400
N	3.10598500	1.13068900	0.12855200
N	2.90294300	2.48889200	0.24081800
C	1.62211700	2.64599000	0.56363800
C	4.38669200	0.62930700	-0.22171800
C	5.33135300	1.51615300	-0.74882200
C	6.59633400	1.05107400	-1.08986700
C	6.95313600	-0.29318300	-0.92365400
C	5.99002000	-1.16046400	-0.39924300
C	4.71822900	-0.71752000	-0.04111600
C	8.33759100	-0.78030900	-1.27386400
O	0.76062700	-1.42885900	2.25462800
F	-0.61898900	-0.44758400	-0.91155300
C	-1.91643800	-1.04852100	1.05798900
C	-3.09913700	-1.32473700	0.22541200
O	-1.95375100	-1.14160200	2.28736500
C	-3.03991500	-1.75142900	-1.11086700
C	-4.21563600	-2.01924500	-1.80441200
C	-5.46980100	-1.84842800	-1.20660900
C	-5.51907500	-1.42839100	0.13203500
C	-4.35504600	-1.18294300	0.84284200
C	-1.54982900	1.83762300	0.50013900
C	-6.73921000	-2.08994900	-1.98163100
C	-1.56069700	2.30736600	-0.81897900
C	-2.62686300	3.06753400	-1.28767500
C	-3.71677000	3.37843000	-0.46159300
C	-3.69790300	2.90844900	0.85425800
C	-2.62895000	2.14886100	1.32980900
C	-4.87476600	4.18965400	-0.98855300
C	1.06139300	4.01532700	0.77997700
C	0.54897300	-2.81667200	0.30489200
F	1.62183200	-3.52227600	0.68152000
F	0.47832100	-2.84019500	-1.03673000
F	-0.55513900	-3.43318400	0.78355600
H	-0.53183600	0.88107000	2.10405400
H	5.05966300	2.55597500	-0.87810200
H	7.32130900	1.74982400	-1.50050100
H	6.23577800	-2.21019900	-0.25925800
H	3.99785500	-1.41433200	0.36541000
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H	-4.15851000	-2.36588100	-2.83264800
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H	-2.61626500	3.42649800	-2.31422800
H	-4.52672300	3.14160100	1.51803100
H	-2.63613400	1.78853800	2.35531300
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H	-4.52926900	5.10390700	-1.48477700
H	-5.45339700	3.62140400	-1.72801300
H	1.86198100	4.75479800	0.69931400
H	0.28491600	4.24945900	0.04359300
H	0.59961400	4.10275700	1.77028100

10.2 X-ray Crystallography data for compound 3aa

Sample preparation method: 3aa (15 mg) was dissolved in 4 mL of mixed solvent of chloroform and *n*-hexane, filtered, and slowly volatilized at room temperature. (CCDC number: 2484936)





checkCIF/PLATON report

Structure factors have been supplied for datablock(s) 3161-100k_autored

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

No syntax errors found. CIF dictionary Interpreting this report

Datablock: 3161-100k_autored

Bond precision:	C-C = 0.0031 Å	Wavelength=1.54184	
Cell:	a=11.84022 (14)	b=11.90104 (13)	c=20.6720 (3)
	alpha=90	beta=104.8459 (14)	gamma=90
Temperature:	100 K		
	Calculated	Reported	
Volume	2815.67 (6)	2815.67 (6)	
Space group	P 21/c	P 1 21/c 1	
Hall group	-P 2ybc	-P 2ybc	
Moiety formula	2 (C30 H26 F4 N2 O3), C H	C H Cl3, 2 (C30 H26 F4 N2 O3)	
Sum formula	C61 H53 Cl3 F8 N4 O6	C61 H53 Cl3 F8 N4 O6	
Mr	1196.42	1196.42	
Dx, g cm ⁻³	1.411	1.411	
Z	2	2	
Mu (mm ⁻¹)	2.183	2.183	
F000	1236.0	1236.0	
F000'	1242.25		
h, k, lmax	14, 14, 26	14, 14, 26	
Nref	5861	5709	
Tmin, Tmax	0.877, 0.937	0.792, 1.000	
Tmin'	0.840		

Correction method= # Reported T Limits: Tmin=0.792 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 0.974

Theta(max)= 75.859

R(reflections)= 0.0502(4980)

wR2(reflections)=
0.1407(5709)

S = 1.053

Npar= 396

The following ALERTS were generated. Each ALERT has the format

test-name_ALERT_alert-type_alert-level.

Click on the hyperlinks for more details of the test.

Alert level C

PLAT042_ALERT_1_C	Calc. and Reported MoietyFormula Strings Differ	Please Check
	Calc: 2(C30 H26 F4 N2 O3), C H Cl3	
	Rep.: C H Cl3, 2(C30 H26 F4 N2 O3)	
PLAT220_ALERT_2_C	NonSolvent Resd 1 C Ueq(max)/Ueq(min) Range	3.5 Ratio
PLAT222_ALERT_3_C	NonSolvent Resd 1 H Uiso(max)/Uiso(min) Range	4.2 Ratio
PLAT906_ALERT_3_C	Large K Value in the Analysis of Variance	2.345 Check
PLAT911_ALERT_3_C	Missing FCF Refl Between Thmin & STh/L= 0.600	8 Report
	11 0 10, 9 0 12, 10 0 12, -13 4 12, 8 0 14, 9 0 14,	
	7 0 16, 8 0 16,	

Alert level G

PLAT242_ALERT_2_G	Low 'MainMol' Ueq as Compared to Neighbors of	C30 Check
PLAT299_ALERT_4_G	Atom Site Occupancy Constrained at	0.5 Check
	C11 C12 C13 C31 H31	
PLAT302_ALERT_4_G	Anion/Solvent/Minor-Residue Disorder (Resd 2)	100% Note
PLAT304_ALERT_4_G	Non-Integer Number of Atoms in (Resd 2)	2.50 Check
PLAT789_ALERT_4_G	Atoms with Negative _atom_site_disorder_group #	5 Check
PLAT793_ALERT_4_G	Model has Chirality at C8 (Centro SpGr)	S Verify
PLAT793_ALERT_4_G	Model has Chirality at C9 (Centro SpGr)	R Verify
PLAT793_ALERT_4_G	Model has Chirality at C10 (Centro SpGr)	R Verify
PLAT822_ALERT_4_G	CIF-embedded .res Contains Negative PART Numbers	1 Check
PLAT912_ALERT_4_G	Missing # of FCF Reflections Above STh/L= 0.600	143 Note
PLAT941_ALERT_3_G	Average HKL Measurement Multiplicity	3.1 Low
PLAT969_ALERT_5_G	The 'Henn et al.' R-Factor-gap value	4.427 Note
	Predicted wR2: Based on SigI**2 3.18 or SHELX Weight 13.36	
PLAT978_ALERT_2_G	Number C-C Bonds with Positive Residual Density.	17 Info

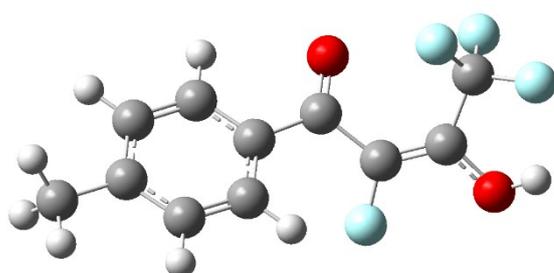
0 **ALERT level A** = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
5 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
13 **ALERT level G** = General information/check it is not something unexpected

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

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

PLATON version of 04/06/2025; check.def file version of 30/05/2025

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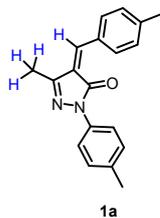


2a-B

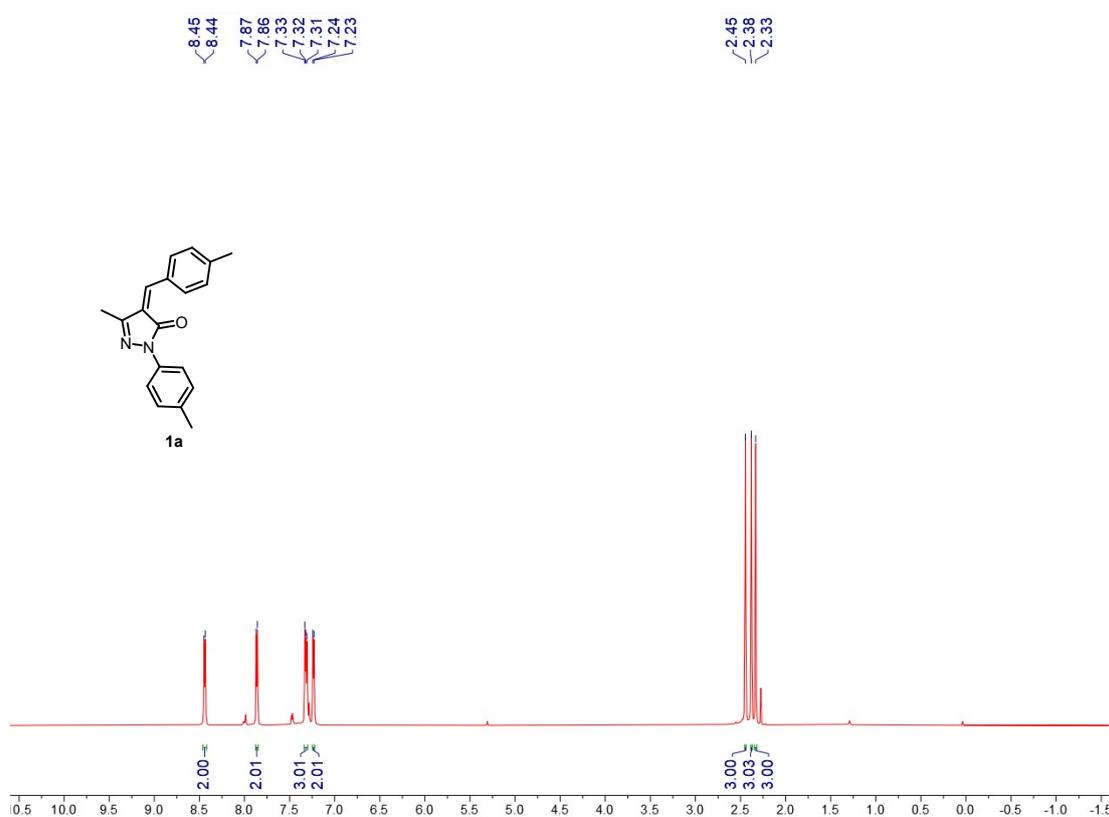
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F	4.07901300	-0.01545800	-1.05557400

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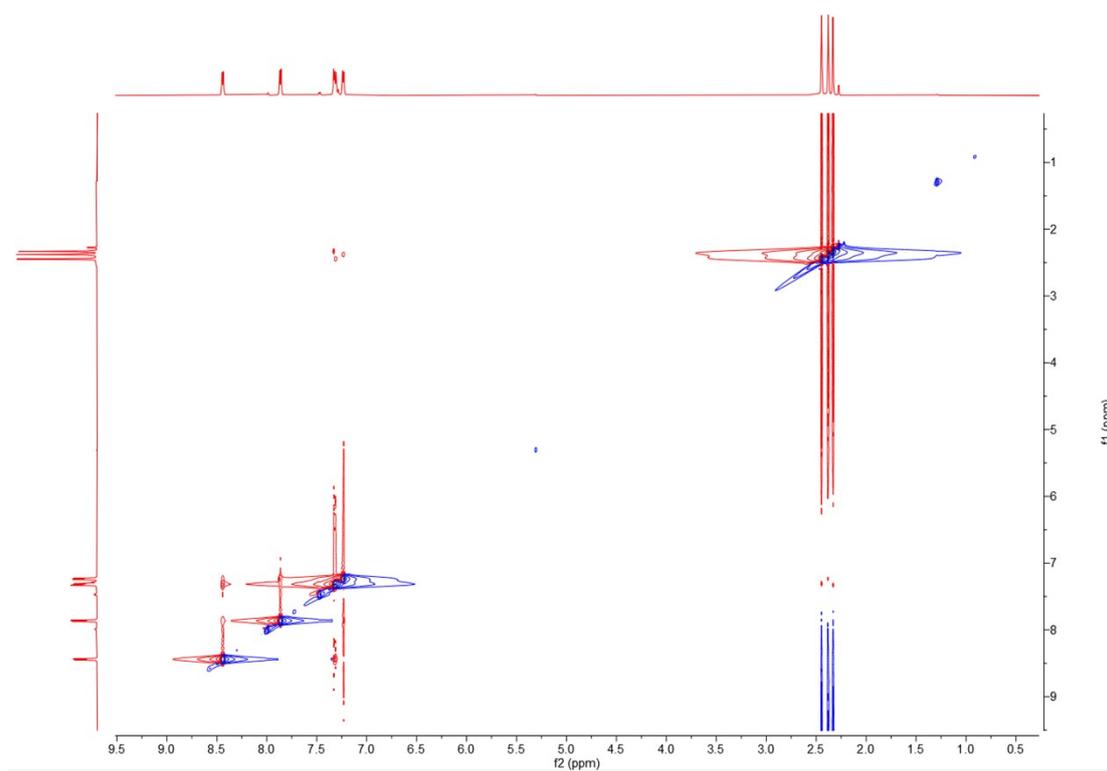
12. NOESY NMR spectra of 1a



Due to the proximity of vinylic proton with methyl proton in the space, NOE is observed between these two protons. The presence of this NOE signal indicates that the **Z-isomer** is the major configuration in these compounds **1**.



^1H NMR (600 MHz) spectrum of compound **1a** in CDCl_3



NOESY spectrum of compound **1a** in CDCl₃