

# Benzylidene Succinimides as 3C Synthons for the Asymmetric Tandem Mannich Reaction/Transamidation of Cyclic Trifluoromethyl Ketimines to Access CF<sub>3</sub>-Containing Polycyclic Dihydroquinazolinones

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## Supporting Information

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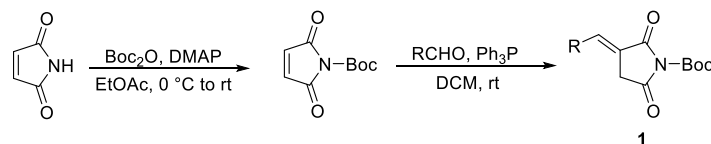
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## 1. General experimental information

Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by TLC.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  or  $\text{DMSO-}d_6$ .  $^1\text{H}$  NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ( $\text{CDCl}_3$  at 7.26 ppm,  $\text{DMSO-}d_6$  at 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration.  $^{13}\text{C}$  NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ( $\text{CDCl}_3$  at 77.16 ppm,  $\text{DMSO-}d_6$  at 39.52 ppm). Melting points products were recorded on a Büchi Melting Point B-545. The HRMS were recorded by Bruker micro TOF-Q II mass spectrometer (Bremen, Germany)

## 2. General experimental procedures for synthesis of compounds 1.

Benzylidene succinimides **1** were prepared according to literatures protocol.<sup>1</sup>

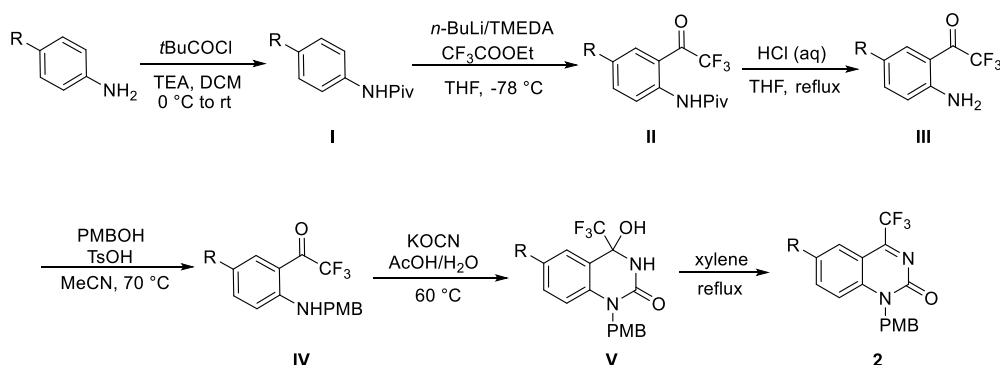


To a solution of maleimide (20 mmol) in ethyl acetate (100 mL), then 0.1 equivalent dimethylaminopyridine (DMAP, 2 mmol) was added. And the reaction mixture cooled to 0 °C, di-*tert*-butyl dicarbonate ( $\text{Boc}_2\text{O}$ , 30 mmol) was added dropwise into solution. After being stirred at room temperature for 20 h, the reaction mixture was quenched by addition of water. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After filtration, the solution was concentrated under reduced pressure and the resulting crude mixture was purified by silica gel column chromatography to afford compound *N*-Boc protected maleimide.

To a solution of *N*-Boc protected maleimide (6 mmol), triphenylphosphine ( $\text{Ph}_3\text{P}$ , 6.6 mmol) in dichloromethane (10 mL), and then 1.2 equivalent corresponding aldehyde was added. After stirring the mixture for 24 h, the solvent was removed under reduced pressure and the resulting crude mixture was purified by silica gel column chromatography to afford compound **1**.

## 3. General experimental procedures for synthesis of cyclic trifluoromethyl ketimines 2.

Cyclic trifluoromethyl ketimines **2** were prepared according to literatures protocol.<sup>2</sup>



To a solution of corresponding aniline (50 mmol), triethylamine ( $\text{Et}_3\text{N}$ , 50 mmol) in dichloromethane (200 mL) under 0 °C, the pivaloyl chloride ( $\text{PivCl}$ , 50 mmol) was added

dropwise into solution. Stirring the mixture for 3-6 h, after about 150 mL solvent was removed under reduced pressure, white solid product was appeared. And then 100 mL petroleum ether was added, then filtration to afford the products **I**.

To a dried round-bottom flask was added amide **I** (20 mmol), then the device was evacuated and backfilled with argon for 3 times. Anhydrous THF (60 mL) and TMEDA (20 mmol) was added under argon protected atmosphere and the solution was cooled to -78 °C. Then the solution of *n*-BuLi (40 mmol, 1 mol/L) was added dropwise. After the solution was warmed to 0 °C for 4 h, and cooled to -78 °C, CF<sub>3</sub>COOEt (40 mmol) was added. Stirring the mixture at room temperature for another 6 h, the reaction mixture was quenched by addition of water. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solution was concentrated under reduced pressure and the resulting crude mixture was purified by silica gel column chromatography (MTBE/EA=50/1) to afford products **II**.

To a solution of **II** was treated with aqueous of HCl solution (6 mol/L, 40 mL), and stirred for 6 h at 80 °C. After that, the reaction mixture was neutralized (pH = 6-7) with a solution of Na<sub>2</sub>CO<sub>3</sub> and extracted with MTBE. The combined organic layers were washed with a saturated aqueous solution of NaCl and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Filtration, evaporation, and column chromatography on silica gel (MTBE/EA=50/1) to afford products **III**.

To a solution of compounds **III** (10 mmol), *p*-toluenesulfonic acid (1.5 mmol) with 50 mL acetonitrile, the mixture was stirred at 70 °C, and then the *p*-methoxybenzyl alcohol (11 mmol) was added dropwise. After the completion of the reaction which was monitored by TLC, the solvent was removed under reduced pressure and crude products **IV** were obtained, which were used without further purification.

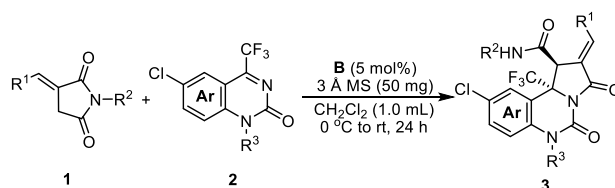
To a solution of the crude compounds **IV** (8 mmol), potassium cyanate (24 mmol) with the mixture of AcOH/H<sub>2</sub>O (14/1.4 mL). The mixture was heated to 60 °C till completion. The mixture was cooled to 0 °C and 20 mL H<sub>2</sub>O was added, the products **V** isolated by filtration as a bright yellow solid, which could be washed by water twice.

A round-bottom flask equipped with a condenser with a Dean-Stark trap, was charged with products **V** and xylene (100 mL). The heterogeneous mixture was heated under reflux (137-140 °C) for 24 h. After removed 80 mL solvent, the mixture was cooled to room temperature. The resulting slurry was filtered and the product dried in vacuo at 30 °C to give **2** as a yellow powder.

#### References:

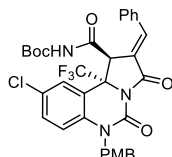
- (a) L. Yan, W. Yang, L. Li, Y. Shen and Z. Jiang, *Chin. J. Chem.*, 2011, **29**, 1906; (b) W.-L. Yang, Y.-Z. Liu, S. Luo, X. Yu, J. S. Fossey and W.-P. Deng, *Chem. Commun.*, 2015, **51**, 9212; (c) B.-L. Zhao and D.-M. Du, *Chem. Commun.*, 2016, **52**, 6162.
- (a) J. W. Corbett, S. S. Ko, J. D. Rodgers, L. A. Gearhart, N. A. Magnus, L. T. Bacheler, S. Diamond, S. Jeffrey, R. M. Klabe, P. S. Anderson, S. K. Erickson-Viitanen, *J. Med. Chem.* 2000, **43**, 2019; (b) N. A. Magnus, P. N. Confalone, L. Storace, M. Patel, C. C. Wood, W. P. Davis, Jr. R. L. Parsons, *J. Org. Chem.* 2003, **68**, 754.

#### 4. General experimental procedures for asymmetric synthesis of compounds **3**.



To a solution of catalyst **B** (3.2 mg, 5 mol%) and benzylidene succinimides **1** (0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was added cyclic trifluoromethyl ketimine **2** (0.12 mmol) and 3Å molecular sieve (50 mg). Then the mixture was stirred for 12 h at 0 °C, and then continued to run for another 12 h at room temperature. After completion, the reaction mixture was directly purified by flash chromatography on silica gel (dichloromethane/petroleum ether/ ethyl acetate = 8:1:0.5) to give the corresponding product **3**.

**Tert-butyl ((1*S*,10*bR*)-2-((*E*)-benzylidene)-9-chloro-6-(4-methoxybenzyl)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl)carbamate (**3aa**).**



White solid; 62.0 mg, 95% yield; >20:1 *dr*, 98% *ee*;  $[\alpha]_{\text{D}}^{20} = +148.7$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 163.5-166.2 °C.

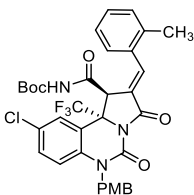
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta$  7.75 (s, 1H), 7.57 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.49 (d, *J* = 14.7 Hz, 2H), 7.44-7.35 (m, 3H), 7.22-7.15 (m, 3H), 6.87 (d, *J* = 8.9 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.49 (s, 1H), 5.23 (d, *J* = 16.3 Hz, 1H), 5.07 (d, *J* = 16.3 Hz, 1H), 3.75 (s, 3H), 1.58 (s, 9H).

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)**  $\delta$  166.3, 159.1, 150.9, 146.8, 137.3, 136.6, 133.3, 131.6, 131.0, 130.4, 129.7, 129.1, 128.3, 128.0, 127.3, 126.9, 126.3, 124.5 (q, *J* = 289.6 Hz, 1C), 118.0, 117.2, 114.4, 84.8, 67.3 (q, *J* = 30.0 Hz, 1C), 55.3, 46.2, 45.1, 28.1.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 7.00 min,  $t_{\text{major}}$  = 9.71 min).

**HRMS (ESI)** Calcd. for C<sub>33</sub>H<sub>30</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 656.1775; found: 656.1771.

**Tert-butyl ((1*S*,10*bR*)-9-chloro-6-(4-methoxybenzyl)-2-((*E*)-2-methylbenzylidene)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl)carbamate (**3ba**).**



White solid; 63.7 mg, 95% yield; >20:1 *dr*, 98% *ee*;  $[\alpha]_{\text{D}}^{20} = +138.1$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 130.6-133.2 °C.

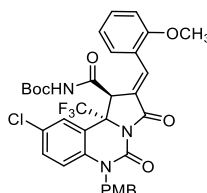
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta$  7.91 (s, 1H), 7.47-7.34 (m, 2H), 7.29 (dd, *J* = 16.2, 7.4 Hz, 2H), 7.22 (d, *J* = 6.5 Hz, 1H), 7.21-7.13 (m, 4H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.21 (s, 1H), 5.20 (d, *J* = 16.3 Hz, 1H), 5.08 (d, *J* = 16.2 Hz, 1H), 3.74 (s, 3H), 2.29 (s, 3H), 1.47 (s, 9H).

**<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)**  $\delta$  165.5, 159.0, 150.3, 146.8, 142.6, 137.6, 136.9, 136.5, 132.9, 130.9, 130.6, 129.7, 129.0, 128.3, 128.0, 127.4, 127.3, 126.8, 126.2, 124.5 (q, *J* = 289.3 Hz, 1C), 118.0, 117.1, 114.4, 84.4, 67.1 (q, *J* = 29.2 Hz, 1C), 55.3, 46.2, 44.7, 27.9, 19.8.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 5.51 min,  $t_{\text{major}}$  = 7.02 min).

**HRMS (ESI)** Calcd. for  $\text{C}_{34}\text{H}_{32}\text{ClF}_3\text{N}_3\text{O}_6$   $[\text{M}+\text{H}]^+$ : 670.1932; found: 670.1925.

**Tert-butyl ((1*S*,10*B**R*)-9-chloro-6-(4-methoxybenzyl)-2-((*E*)-2-methoxybenzylidene)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl carbamate (3ca).**



White solid; 60.2 mg, 88% yield; >20:1 *dr*, 98% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +174.4 (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 153.8-155.2 °C.

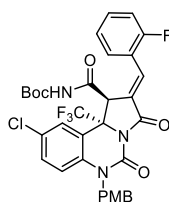
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.96 (s, 1H), 7.46-7.40 (m, 2H), 7.39-7.31 (m, 2H), 7.17 (dd,  $J$  = 8.8, 2.5 Hz, 3H), 6.93 (dd,  $J$  = 9.9, 8.0 Hz, 2H), 6.83 (dd,  $J$  = 14.6, 8.8 Hz, 3H), 6.35 (s, 1H), 5.23 (d,  $J$  = 16.3 Hz, 1H), 5.06 (d,  $J$  = 16.3 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 1.49 (s, 9H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )**  $\delta$  166.0, 159.0, 157.7, 150.5, 146.9, 140.7, 136.5, 133.3, 131.6, 130.8, 129.3, 128.3, 128.0, 127.4, 127.3, 126.8, 124.5 (q,  $J$  = 289.4 Hz, 1C), 122.4, 120.5, 118.2, 117.1, 114.4, 111.3, 84.3, 67.0 (q,  $J$  = 29.5 Hz, 1C), 55.5, 55.3, 46.1, 45.5, 28.0.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 5.66 min,  $t_{\text{major}}$  = 7.37 min).

**HRMS (ESI)** Calcd. for  $\text{C}_{34}\text{H}_{32}\text{ClF}_3\text{N}_3\text{O}_7$   $[\text{M}+\text{H}]^+$ : 686.1881; found: 686.1884.

**Tert-butyl ((1*S*,10*B**R*)-9-chloro-2-((*E*)-2-fluorobenzylidene)-6-(4-methoxybenzyl)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl carbamate (3da).**



White solid; 67.9 mg, 99% yield; >20:1 *dr*, 97% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +154.4 (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 146.5-149.8 °C.

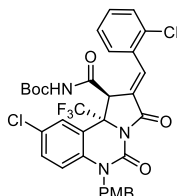
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.83 (s, 1H), 7.59-7.42 (m, 3H), 7.42-7.34 (m, 1H), 7.22-7.07 (m, 5H), 6.87 (d,  $J$  = 8.9 Hz, 1H), 6.82 (d,  $J$  = 8.6 Hz, 2H), 6.37 (s, 1H), 5.22 (d,  $J$  = 16.2 Hz, 1H), 5.06 (d,  $J$  = 16.2 Hz, 1H), 3.74 (s, 3H), 1.52 (s, 9H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )**  $\delta$  165.6, 160.6 (d,  $J$  = 252.8 Hz, 1C), 159.1, 150.7 (d,  $J$  = 4.6 Hz, 1C), 146.7, 136.5, 132.1 (d,  $J$  = 8.5 Hz, 1C), 130.9, 129.8, 129.7, 129.6, 129.4, 128.4, 128.0, 127.3, 126.9, 124.5 (d,  $J$  = 3.6 Hz, 1C), 124.4 (q,  $J$  = 289.9 Hz, 1C), 121.4 (d,  $J$  = 13.4 Hz, 1C), 117.9, 117.2, 116.4 (d,  $J$  = 21.8 Hz, 1C), 114.4, 84.7, 67.23 (q,  $J$  = 29.8 Hz, 1C), 55.3, 46.2, 45.3, 28.0.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 5.60 min,  $t_{\text{major}}$  = 8.16 min).

**HRMS (ESI)** Calcd. for  $\text{C}_{33}\text{H}_{29}\text{ClF}_4\text{N}_3\text{O}_6$   $[\text{M}+\text{H}]^+$ : 674.1681; found: 674.1674.

***Tert*-butyl ((1*S*,10*bR*)-9-chloro-2-((*E*)-2-chlorobenzylidene)-6-(4-methoxybenzyl)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl carbamate (3ea).**



White solid; 70.1 mg, 99% yield; >20:1 *dr*, 96% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +118.0 (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 151.4-154.3 °C.

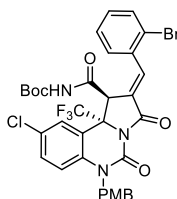
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.94 (s, 1H), 7.49-7.35 (m, 4H), 7.35-7.27 (m, 2H), 7.20-7.13 (m, 3H), 6.86 (d,  $J$  = 9.0 Hz, 1H), 6.82 (d,  $J$  = 8.7 Hz, 2H), 6.28 (s, 1H), 5.20 (d,  $J$  = 16.3 Hz, 1H), 5.09 (d,  $J$  = 16.3 Hz, 1H), 3.74 (s, 3H), 1.47 (s, 9H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )**  $\delta$  169.3, 165.2, 159.1, 150.4, 146.7, 136.5, 134.7, 134.4, 132.3, 131.0, 130.9, 130.2, 130.1, 129.1, 128.4, 128.0, 127.2, 127.1, 126.8, 124.4 (q,  $J$  = 289.7 Hz, 1C), 117.9, 117.2, 114.4, 84.6, 67.2 (q,  $J$  = 29.4 Hz, 1C), 55.3, 46.2, 44.7, 28.0.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 5.51 min,  $t_{\text{major}}$  = 7.54 min).

**HRMS (ESI)** Calcd. for  $\text{C}_{33}\text{H}_{29}\text{Cl}_2\text{F}_3\text{N}_3\text{O}_6$   $[\text{M}+\text{H}]^+$ : 690.1386; found: 690.1404.

***Tert*-butyl ((1*S*,10*bR*)-2-((*E*)-2-bromobenzylidene)-9-chloro-6-(4-methoxybenzyl)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl carbamate (3fa).**



White solid; 72.1 mg, 98% yield; >20:1 *dr*, 97% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +109.3 (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 150.2-152.7 °C.

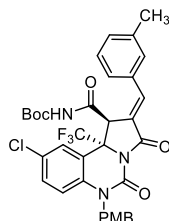
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.88 (s, 1H), 7.63 (d,  $J$  = 7.9 Hz, 1H), 7.44-7.29 (m, 4H), 7.25-7.09 (m, 4H), 6.86 (d,  $J$  = 9.0 Hz, 1H), 6.83 (d,  $J$  = 8.6 Hz, 2H), 6.22 (s, 1H), 5.19 (d,  $J$  = 16.3 Hz, 1H), 5.10 (d,  $J$  = 16.3 Hz, 1H), 3.75 (s, 3H), 1.46 (s, 9H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )**  $\delta$  169.3, 165.1, 159.1, 150.4, 146.7, 136.7, 136.5, 134.4, 133.3, 131.0, 130.9, 130.2, 129.2, 128.4, 128.0, 127.7, 127.3, 126.8, 124.4 (q,  $J$  = 289.3 Hz, 1C), 124.3, 117.9, 117.3, 114.5, 84.7, 67.2 (q,  $J$  = 29.6 Hz, 1C), 55.4, 46.3, 44.6, 28.1, 28.0.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 80/20; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 7.51 min,  $t_{\text{major}}$  = 10.54 min).

**HRMS (ESI)** Calcd. for C<sub>33</sub>H<sub>29</sub>BrClF<sub>3</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 734.0880; found: 734.0884.

***Tert*-butyl ((1*S*,10*bR*)-9-chloro-6-(4-methoxybenzyl)-2-((*E*)-3-methylbenzylidene)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl) carbamate (3ga).**



White solid; 66.8 mg, 99% yield; >20:1 *dr*, 98% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +142.8 (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 159.2-162.9 °C.

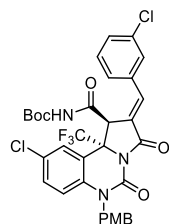
**<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)**  $\delta$  11.39 (s, 1H), 7.77 (s, 1H), 7.63 (s, 1H), 7.59-7.46 (m, 3H), 7.46-7.32 (m, 2H), 7.20 (m, 3H), 6.91 (d, *J* = 8.3 Hz, 2H), 5.18 (dd, *J* = 34.5, 16.4 Hz, 3H), 3.71 (s, 3H), 2.41 (s, 3H), 1.41 (s, 9H).

**<sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)**  $\delta$  165.7, 158.6, 151.1, 148.0, 145.8, 138.6, 136.4, 136.0, 133.9, 132.5, 131.6, 131.3, 130.1, 129.1, 127.9, 127.4, 127.0, 126.6, 125.8, 124.1 (q, *J* = 240.8 Hz, 1C), 118.0, 116.8, 114.2, 81.8, 66.2 (q, *J* = 27.9 Hz, 1C), 55.1, 47.8, 44.8, 27.5, 20.9.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 6.37 min,  $t_{\text{major}}$  = 7.89 min).

**HRMS (ESI)** Calcd. for C<sub>34</sub>H<sub>32</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 670.1932; found: 670.1926.

***Tert*-butyl ((1*S*,10*bR*)-9-chloro-2-((*E*)-3-chlorobenzylidene)-6-(4-methoxybenzyl)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl) carbamate (3ha).**



White solid; 65.8 mg, 95% yield; >20:1 *dr*, 96% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +130.6 (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 145.2-147.5 °C.

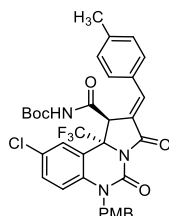
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta$  7.61 (s, 1H), 7.42 (s, 1H), 7.41-7.35 (m, 2H), 7.33-6.99 (m, 6H), 6.81 (d, *J* = 8.9 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 2H), 6.35 (s, 1H), 5.15 (d, *J* = 16.3 Hz, 1H), 5.00 (d, *J* = 16.3 Hz, 1H), 3.68 (s, 3H), 1.49 (s, 9H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)**  $\delta$  165.9, 159.2, 150.8, 146.7, 136.6, 135.8, 135.2, 135.1, 131.1, 130.4, 130.3, 129.7, 129.6, 128.4, 128.0, 127.3, 127.2, 126.8, 124.4 (q, *J* = 289.1 Hz, 1C), 117.8, 117.3, 114.5, 114.4, 85.3, 67.5 (q, *J* = 28.2 Hz, 1C), 55.4, 46.4, 44.8, 28.1.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 6.94 min,  $t_{\text{major}}$  = 9.56 min).

**HRMS (ESI)** Calcd. for  $\text{C}_{33}\text{H}_{29}\text{Cl}_2\text{F}_3\text{N}_3\text{O}_6$   $[\text{M}+\text{H}]^+$ : 690.1386; found: 690.1380.

***Tert*-butyl ((1*S*,10*bR*)-9-chloro-6-(4-methoxybenzyl)-2-((*E*)-4-methylbenzylidene)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl) carbamate (3ia).**



White solid; 54.2 mg, 81% yield; >20:1 *dr*, 98% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +195.5 (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 167.6-169.2 °C.

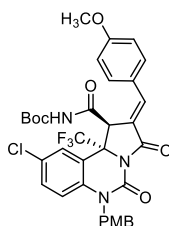
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.72 (s, 1H), 7.58-7.37 (m, 4H), 7.24-7.08 (m, 5H), 6.86 (d,  $J$  = 8.9 Hz, 1H), 6.82 (d,  $J$  = 8.7 Hz, 2H), 6.46 (s, 1H), 5.23 (d,  $J$  = 16.3 Hz, 1H), 5.07 (d,  $J$  = 16.3 Hz, 1H), 3.75 (s, 3H), 2.38 (s, 3H), 1.60 (s, 9H).

**$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )**  $\delta$  166.5, 159.1, 151.0, 146.8, 141.0, 137.5, 136.6, 131.5, 130.9, 130.5, 129.9, 129.8, 128.3, 128.0, 127.4, 127.0, 125.1, 124.5 (q,  $J$  = 288.6 Hz, 1C), 118.0, 117.2, 114.4, 84.8, 67.3 (q,  $J$  = 29.0 Hz, 1C), 60.5, 55.4, 46.2, 28.1, 21.7.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 6.83 min,  $t_{\text{major}}$  = 9.90 min).

**HRMS (ESI)** Calcd. for  $\text{C}_{34}\text{H}_{32}\text{ClF}_3\text{N}_3\text{O}_6$   $[\text{M}+\text{H}]^+$ : 670.1932; found: 670.1927.

***Tert*-butyl ((1*S*,10*bR*)-9-chloro-6-(4-methoxybenzyl)-2-((*E*)-4-methoxybenzylidene)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl) carbamate (3ja).**



White solid; 67.4 mg, 98% yield; >20:1 *dr*, 97% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +167.8 (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 188.8-191.0 °C.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.68 (s, 1H), 7.63-7.39 (m, 4H), 7.19 (dd,  $J$  = 8.0, 7.7 Hz, 3H), 6.95-6.78 (m, 5H), 6.44 (s, 1H), 5.23 (d,  $J$  = 16.3 Hz, 1H), 5.07 (d,  $J$  = 16.3 Hz, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 1.61 (s, 9H).

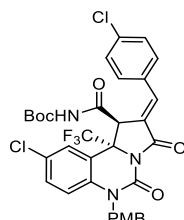
**$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )**  $\delta$  166.8, 161.5, 159.1, 151.1, 146.9, 137.1, 136.6, 134.1, 131.9, 130.9, 128.3, 128.0, 127.4, 126.9, 125.8, 124.5 (q,  $J$  = 289.9 Hz, 1C), 123.1, 118.1, 117.2, 114.6, 114.4, 84.8, 67.3 (q,  $J$  = 29.7 Hz, 1C), 60.5, 55.5, 55.3, 46.2, 28.1.



**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 8.45 min,  $t_{\text{major}}$  = 11.46 min).

**HRMS (ESI)** Calcd. for  $\text{C}_{34}\text{H}_{32}\text{ClF}_3\text{N}_3\text{O}_7$   $[\text{M}+\text{H}]^+$ : 686.1881; found: 686.1876.

***Tert*-butyl ((1*S*,10*bR*)-9-chloro-2-((*E*)-4-chlorobenzylidene)-6-(4-methoxybenzyl)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl) carbamate (3ka).**



White solid; 70.1 mg, 99% yield; >20:1 *dr*, 97% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +168.4 (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 156.7-158.9 °C.

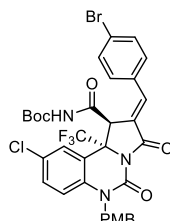
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.69 (s, 1H), 7.59-7.40 (m, 4H), 7.39-7.33 (m, 2H), 7.22-7.13 (m, 3H), 6.87 (d,  $J$  = 8.9 Hz, 1H), 6.83 (d,  $J$  = 8.7 Hz, 2H), 6.46 (s, 1H), 5.23 (d,  $J$  = 16.3 Hz, 1H), 5.06 (d,  $J$  = 16.3 Hz, 1H), 3.75 (s, 3H), 1.58 (s, 9H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )**  $\delta$  169.2, 166.0, 159.1, 150.9, 146.7, 136.6, 136.4, 135.9, 131.8, 131.0, 130.8, 129.4, 128.4, 128.0, 127.3, 127.2, 126.8, 124.4 (q,  $J$  = 289.6 Hz, 1C), 117.9, 117.3, 114.5, 85.1, 67.3 (q,  $J$  = 30.0 Hz, 1C), 55.4, 46.3, 44.9, 28.0.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 70/30; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 6.05 min,  $t_{\text{major}}$  = 9.34 min).

**HRMS (ESI)** Calcd. for  $\text{C}_{33}\text{H}_{29}\text{Cl}_2\text{F}_3\text{N}_3\text{O}_6$   $[\text{M}+\text{H}]^+$ : 690.1386; found: 690.1389.

***Tert*-butyl ((1*S*,10*bR*)-2-((*E*)-4-bromobenzylidene)-9-chloro-6-(4-methoxybenzyl)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl) carbamate (3la).**



White solid; 73.1 mg, 99% yield; >20:1 *dr*, 96% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +171.9 (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 197.7-200.3 °C.

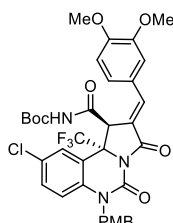
**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**  $\delta$  7.67 (s, 1H), 7.52 (d,  $J$  = 8.4 Hz, 2H), 7.50-7.38 (m, 4H), 7.23-7.12 (m, 3H), 6.87 (d,  $J$  = 8.9 Hz, 1H), 6.82 (d,  $J$  = 8.6 Hz, 2H), 6.44 (s, 1H), 5.23 (d,  $J$  = 16.3 Hz, 1H), 5.06 (d,  $J$  = 16.3 Hz, 1H), 3.75 (s, 3H), 1.58 (s, 9H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )**  $\delta$  169.2, 166.0, 159.1, 150.9, 146.7, 136.5, 136.0, 132.4, 132.2, 131.0, 130.9, 128.4, 128.0, 127.4, 127.3, 126.8, 124.8, 124.4 (q,  $J$  = 289.6 Hz, 1C), 117.9, 117.3, 114.5, 85.1, 67.3 (q,  $J$  = 29.5 Hz, 1C), 55.4, 46.3, 44.8, 28.0.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 7.76 min,  $t_{\text{major}}$  = 12.68 min).

**HRMS (ESI)** Calcd. for C<sub>33</sub>H<sub>29</sub>BrClF<sub>3</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 734.0880; found: 734.0873.

***Tert*-butyl ((1*S*,10*bR*)-9-chloro-2-((*E*)-3,4-dimethoxybenzylidene)-6-(4-methoxybenzyl)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl) carbamate (3ma).**



White solid; 58.1 mg, 81% yield; >20:1 *dr*, 99% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +167.5 (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 139.2-141.8 °C.

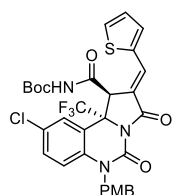
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta$  7.68 (s, 1H), 7.50 (s, 1H), 7.32-7.26 (m, 1H), 7.24-7.06 (m, 4H), 7.00 (s, 1H), 6.88-6.84 (m, 2H), 6.84-6.79 (m, 2H), 6.46 (s, 1H), 5.22 (d, *J* = 16.4 Hz, 1H), 5.05 (d, *J* = 16.2 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.74 (s, 3H), 1.55 (s, 9H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)**  $\delta$  168.8, 166.6, 159.1, 151.1, 149.3, 146.9, 139.0, 137.6, 136.6, 136.2, 131.0, 128.8, 128.4, 128.0, 127.3, 126.9, 126.1, 124.5 (q, *J* = 289.4 Hz, 1C), 118.0, 117.2, 114.4, 114.1, 111.2, 84.7, 67.2 (q, *J* = 29.8 Hz, 1C), 56.2, 56.0, 55.3, 46.2, 31.3, 28.0.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 80/20; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 11.03 min,  $t_{\text{major}}$  = 16.32 min).

**HRMS (ESI)** Calcd. for C<sub>35</sub>H<sub>34</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>8</sub> [M+H]<sup>+</sup>: 716.1987; found: 716.2018.

***Tert*-butyl ((1*S*,10*bR*,*E*)-9-chloro-6-(4-methoxybenzyl)-3,5-dioxo-2-(thiophen-2-ylmethylene)-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl) carbamate (3na).**



White solid; 60.3 mg, 91% yield; >20:1 *dr*, 97% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +143.5 (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 178.3-181.2 °C.

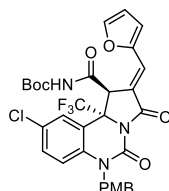
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta$  7.80-7.76 (m, 1H), 7.73 (s, 1H), 7.54 (s, 1H), 7.49-7.39 (m, 2H), 7.36 (dd, *J* = 5.1, 2.9 Hz, 1H), 7.23-7.14 (m, 3H), 6.87 (d, *J* = 8.9 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.40 (s, 1H), 5.23 (d, *J* = 16.3 Hz, 1H), 5.09 (d, *J* = 16.3 Hz, 1H), 3.76 (s, 3H), 1.62 (s, 9H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)**  $\delta$  166.6, 159.1, 151.4, 146.8, 136.6, 135.1, 131.0, 130.5, 130.2, 128.9, 128.3, 128.0, 127.6, 127.4, 127.1, 127.0, 124.4 (q, *J* = 290.2 Hz, 1C), 124.1, 118.0, 117.2, 114.4, 85.0, 67.3 (q, *J* = 29.0 Hz, 1C), 60.5, 55.4, 46.2, 28.0.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 7.64 min,  $t_{\text{major}}$  = 10.72 min).

**HRMS (ESI)** Calcd. for  $\text{C}_{31}\text{H}_{28}\text{ClF}_3\text{N}_3\text{O}_6\text{S}$   $[\text{M}+\text{H}]^+$ : 662.1339; found: 662.1346.

**Tert-butyl ((1*S*,10*bR*,*E*)-9-chloro-2-(furan-2-ylmethylene)-6-(4-methoxybenzyl)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl) carbamate (30a).**



White solid; 62.2 mg, 96% yield; >20:1 *dr*, 97% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +247.3 (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 166.4-168.2 °C.

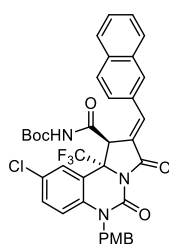
**$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )**  $\delta$  11.35 (s, 1H), 7.94 (s, 1H), 7.81 (s, 1H), 7.59-7.46 (m, 2H), 7.28-7.12 (m, 4H), 6.91 (d,  $J$  = 8.0 Hz, 2H), 6.82-6.74 (m, 1H), 5.17 (q,  $J$  = 16.6 Hz, 3H), 3.71 (s, 3H), 1.42 (s, 9H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )**  $\delta$  165.5, 158.5, 154.3, 149.2, 146.8, 145.9, 136.0, 131.1, 127.8, 127.4, 127.0, 126.6, 125.8, 124.7 (q,  $J$  = 288.0 Hz, 1C), 122.9, 121.8, 119.7, 117.7, 117.0, 114.1, 113.5, 81.4, 66.2 (q,  $J$  = 31.8 Hz, 1C), 55.0, 48.1, 44.8, 27.5.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 7.11 min,  $t_{\text{major}}$  = 17.95 min).

**HRMS (ESI)** Calcd. for  $\text{C}_{31}\text{H}_{28}\text{ClF}_3\text{N}_3\text{O}_7$   $[\text{M}+\text{H}]^+$ : 646.1568; found: 646.1558.

**Tert-butyl ((1*S*,10*bR*,*E*)-9-chloro-6-(4-methoxybenzyl)-2-(naphthalen-2-ylmethylene)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl) carbamate (3pa).**



Light yellow solid; 67.2 mg, 95% yield; >20:1 *dr*, 97% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +204.5 (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 176.8-177.2 °C.

**$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )**  $\delta$  11.40 (s, 1H), 8.27 (s, 1H), 8.04 (dd,  $J$  = 12.4, 7.9 Hz, 3H), 7.92-7.70 (m, 3H), 7.70-7.60 (m, 2H), 7.54 (dd,  $J$  = 8.9, 2.4 Hz, 1H), 7.21 (dd,  $J$  = 8.9 Hz, 3H), 6.91 (d,  $J$  = 8.3 Hz, 2H), 5.35 (s, 1H), 5.25 (d,  $J$  = 16.2 Hz, 1H), 5.13 (d,  $J$  = 16.2 Hz, 1H), 3.71 (s, 3H), 1.34 (s, 9H).

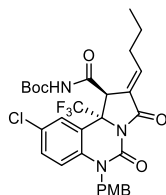
**$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )**  $\delta$  171.4, 166.4, 159.1, 150.9, 146.9, 137.6, 136.6, 133.9, 133.2, 131.1, 131.0, 130.7, 129.0, 128.8, 128.3, 128.0, 127.8, 127.7, 127.3, 126.9, 126.8, 126.3, 125.3,

124.5 (q,  $J = 289.6$  Hz, 1C), 118.0, 117.2, 114.4, 84.9, 67.4 (q,  $J = 28.0$  Hz, 1C), 60.5, 55.3, 46.3, 28.0.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{minor}} = 8.44$  min,  $t_{\text{major}} = 13.40$  min).

**HRMS (ESI)** Calcd. for  $\text{C}_{37}\text{H}_{32}\text{ClF}_3\text{N}_3\text{O}_6$   $[\text{M}+\text{H}]^+$ : 706.1932; found: 706.1940.

**Tert-butyl** ((1*S*,10*bR*,*E*)-9-chloro-6-(4-methoxybenzyl)-3,5-dioxo-2-pentylidene-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl)carbamate (**3qa**).



White solid; 46.1 mg, 74% yield; >20:1 *dr*, 99% *ee*;  $[\alpha]_{\text{D}}^{20} = +92.1$  ( $c$  1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 138.7-140.4 °C.

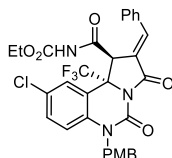
**$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )**  $\delta$  11.26 (s, 1H), 7.51 (dd,  $J = 8.9, 2.3$  Hz, 1H), 7.42 (s, 1H), 7.18 (dd,  $J = 8.7, 5.8$  Hz, 3H), 6.90 (d,  $J = 8.2$  Hz, 2H), 6.81 (dd,  $J = 11.0, 7.8$  Hz, 1H), 5.21 (d,  $J = 16.4$  Hz, 1H), 5.10 (d,  $J = 16.4$  Hz, 1H), 4.90 (s, 1H), 3.71 (s, 3H), 2.36-2.13 (m, 2H), 1.55-1.46 (m, 2H), 1.45 (s, 9H), 0.89 (t,  $J = 7.3$  Hz, 3H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )**  $\delta$  164.2, 158.5, 148.3, 145.9, 140.7, 136.0, 131.0, 130.8, 128.1, 127.8, 127.4, 127.0, 125.7, 124.3 (q,  $J = 288.9$  Hz, 1C), 117.8, 117.4, 114.1, 81.8, 65.7 (q,  $J = 28.2$  Hz, 1C), 55.0, 46.4, 44.7, 31.0, 27.5, 21.0, 13.4.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{minor}} = 5.83$  min,  $t_{\text{major}} = 7.00$  min);

**HRMS (ESI)** Calcd. for  $\text{C}_{30}\text{H}_{32}\text{ClF}_3\text{N}_3\text{O}_6$   $[\text{M}+\text{H}]^+$ : 622.1932; found: 622.1927.

**Ethyl** ((1*S*,10*bR*)-2-((*E*)-benzylidene)-9-chloro-6-(4-methoxybenzyl)-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl)carbamate (**3ra**).



White solid; 62.2 mg, 99% yield; >20:1 *dr*, 97% *ee*;  $[\alpha]_{\text{D}}^{20} = +146.2$  ( $c$  1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 146.8-148.7 °C.

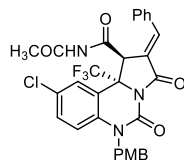
**$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )**  $\delta$  11.63 (s, 1H), 7.79-7.63 (m, 4H), 7.60-7.41 (m, 4H), 7.20 (dd,  $J = 8.7, 8.2$  Hz, 3H), 6.91 (d,  $J = 8.2$  Hz, 2H), 5.34 (s, 1H), 5.24 (d,  $J = 16.5$  Hz, 1H), 5.12 (d,  $J = 16.5$  Hz, 1H), 4.25-3.96 (m, 2H), 3.71 (s, 3H), 1.20 (t,  $J = 7.2$  Hz, 3H).

**$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )**  $\delta$  165.6, 158.6, 145.9, 136.3, 136.0, 132.5, 131.4, 131.0, 130.1, 130.0, 129.3, 128.3, 128.0, 127.4, 127.2, 126.5, 125.5, 124.3 (q,  $J = 289.8$  Hz, 1C), 118.0, 116.7, 114.2, 66.3 (q,  $J = 29.7$ , 1C), 61.9, 55.1, 47.6, 44.9, 14.0.

**HPLC analysis:** Chiralpak AS-H column (*n*-hexane/ *i*-PrOH = 70/30; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{major}}$  = 6.87 min,  $t_{\text{minor}}$  = 16.28 min).

**HRMS (ESI)** Calcd. for C<sub>31</sub>H<sub>26</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 628.1462; found: 628.1451.

**(1*S*,10*bR*)-*N*-acetyl-2-((*E*)-benzylidene)-9-chloro-6-(4-methoxybenzyl)-3,5-dioxo-10b-(trifluoromethyl)-1,2,3,5,6,10b-hexahydropyrrolo[1,2-*c*]quinazoline-1-carboxamide (3sa).**



White solid; 59.6 mg, 99% yield; >20:1 *dr*, 95% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +164.5 (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 151.6-154.2 °C.

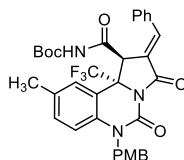
**<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)**  $\delta$  11.62 (s, 1H), 7.77-7.65 (m, 4H), 7.59-7.49 (m, 4H), 7.23 (d, *J* = 9.0 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.52 (s, 1H), 5.27 (d, *J* = 16.4 Hz, 1H), 5.11 (d, *J* = 16.4 Hz, 1H), 3.71 (s, 3H), 1.99 (s, 3H).

**<sup>13</sup>C NMR (151 MHz, DMSO-*d*<sub>6</sub>)**  $\delta$  165.6, 158.6, 145.8, 136.5, 136.0, 132.5, 131.3, 131.0, 130.9, 130.0, 129.3, 128.3, 128.0, 127.4, 127.1, 126.6, 125.5, 124.3 (q, *J* = 289.9 Hz, 1C), 118.0, 116.8, 114.2, 66.3 (q, *J* = 29.4 Hz, 1C), 55.1, 47.3, 44.8, 24.8.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 9.08 min,  $t_{\text{major}}$  = 12.04 min).

**HRMS (ESI)** Calcd. for C<sub>30</sub>H<sub>24</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 598.1357; found: 598.1351.

***Tert*-butyl ((1*S*,10*bR*)-2-((*E*)-benzylidene)-6-(4-methoxybenzyl)-9-methyl-3,5-dioxo-10b-(trifluoromethyl)-1,2,3,5,6,10b-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl)carbamate (3ab).**



Light yellow solid; 56.6 mg, 89% yield; >20:1 *dr*, 93% *ee*;  $[\alpha]_{\text{D}}^{20}$  = +163.6 (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 134.5-137.9 °C.

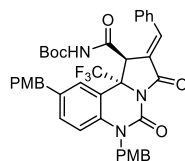
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta$  7.75 (s, 1H), 7.59 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.44-7.37 (m, 3H), 7.34 (s, 1H), 7.28 (s, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.04 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 3H), 6.43 (s, 1H), 5.23 (d, *J* = 16.2 Hz, 1H), 5.09 (d, *J* = 16.2 Hz, 1H), 3.75 (s, 3H), 2.22 (s, 3H), 1.56 (s, 9H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)**  $\delta$  166.5, 158.9, 150.7, 147.2, 139.8, 137.0, 135.5, 133.4, 132.5, 131.6, 130.3, 129.7, 129.1, 128.1, 128.0, 127.2, 126.8, 124.7 (q, *J* = 290.2 Hz, 1C), 116.3, 115.8, 114.3, 84.4, 67.6 (q, *J* = 28.1 Hz, 1C), 55.4, 46.1, 32.1, 28.1, 20.7.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm;  $t_{\text{minor}}$  = 6.74 min,  $t_{\text{major}}$  = 8.88 min).

**HRMS (ESI)** Calcd. for C<sub>34</sub>H<sub>33</sub>F<sub>3</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 636.2321; found: 636.2304.

**Tert-butyl ((1S,10bR)-2-((E)-benzylidene)-6,9-bis(4-methoxybenzyl)-3,5-dioxo-10b-(trifluoromethyl)-1,2,3,5,6,10b-hexahydropyrrolo[1,2-c]quinazoline-1-carbonyl)carbamate (3ac).**



White solid; 60.1 mg, 81% yield; >20:1 *dr*, 97% *ee*;  $[\alpha]_D^{20} = +144.8$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 133.4-136.2 °C.

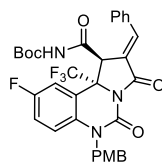
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta$  7.77 (s, 1H), 7.63-7.54 (m, 2H), 7.40 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.36 (s, 1H), 7.25-7.16 (m, 3H), 7.00 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.96-6.85 (m, 3H), 6.85-6.75 (m, 4H), 6.43 (s, 1H), 5.15 (s, 2H), 3.80 (d, *J* = 3.7 Hz, 2H), 3.75 (s, 3H), 3.75 (s, 3H), 1.44 (s, 9H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)**  $\delta$  166.5, 159.0, 158.3, 150.6, 147.2, 137.2, 136.2, 135.9, 133.5, 132.4, 131.6, 130.3, 129.7, 129.4, 129.1, 128.1, 128.0, 127.4, 126.8, 124.8 (q, *J* = 289.6 Hz, 1C), 116.4, 116.2, 114.4, 114.3, 114.1, 84.4, 67.6 (q, *J* = 31.0 Hz, 1C), 55.4, 46.3, 45.3, 40.1, 29.8, 27.9.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 70/30; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm; *t*<sub>major</sub> = 6.58 min, *t*<sub>minor</sub> = 15.33 min).

**HRMS (ESI)** Calcd. for C<sub>41</sub>H<sub>39</sub>F<sub>3</sub>N<sub>3</sub>O<sub>7</sub> [M+H]<sup>+</sup>: 742.2740; found: 742.2730.

**Tert-butyl ((1S,10bR)-2-((E)-benzylidene)-9-fluoro-6-(4-methoxybenzyl)-3,5-dioxo-10b-(trifluoromethyl)-1,2,3,5,6,10b-hexahydropyrrolo[1,2-c]quinazoline-1-carbonyl)carbamate (3ad).**



White solid; 62.5 mg, 98% yield; >20:1 *dr*, 96% *ee*;  $[\alpha]_D^{20} = +167.6$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 147.5-151.2 °C.

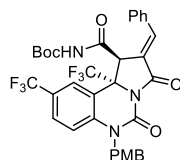
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**  $\delta$  7.75 (s, 1H), 7.63-7.53 (m, 2H), 7.46-7.35 (m, 4H), 7.29-7.23 (m, 1H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.03-6.84 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.44 (s, 1H), 5.21 (d, *J* = 16.4 Hz, 1H), 5.11 (d, *J* = 16.4 Hz, 1H), 3.76 (s, 3H), 1.57 (s, 9H).

**<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)**  $\delta$  166.3, 159.1, 158.8, 157.2, 151.0, 146.9, 137.3, 134.4 (d, *J* = 2.4 Hz, 1C), 133.3, 131.7, 130.5, 129.1, 128.9 (d, *J* = 251.1 Hz, 1C), 127.5, 126.3, 124.5 (q, *J* = 289.8 Hz, 1C), 117.9 (d, *J* = 22.2 Hz, 1C), 117.8 (d, *J* = 6.9 Hz, 1C), 117.5 (d, *J* = 7.7 Hz, 1C), 114.5, 114.0 (d, *J* = 25.5 Hz, 1C), 84.9, 67.5 (q, *J* = 29.1 Hz, 1C), 55.4, 46.5, 45.2, 28.0.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm; *t*<sub>minor</sub> = 6.62 min, *t*<sub>major</sub> = 10.95 min).

**HRMS (ESI)** Calcd. for C<sub>33</sub>H<sub>30</sub>F<sub>4</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 640.2071; found: 640.2066.

**Tert-butyl ((1S,10bR)-2-((E)-benzylidene)-6-(4-methoxybenzyl)-3,5-dioxo-9,10b-bis(trifluoromethyl)-1,2,3,5,6,10b-hexahydropyrrolo[1,2-c]quinazoline-1-carbonyl)carbamate (3ae).**



White solid; 67.1 mg, 97% yield; >20:1 *dr*, 98% *ee*;  $[\alpha]_D^{20} = +186.5$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 136.7-139.4 °C.

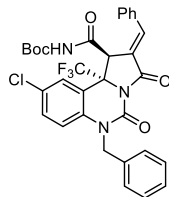
<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  11.39 (s, 1H), 8.04 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.80-7.63 (m, 3H), 7.62-7.48 (m, 3H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 5.37 (s, 1H), 5.30 (d, *J* = 16.3 Hz, 1H), 5.19 (d, *J* = 16.3 Hz, 1H), 3.71 (s, 3H), 1.35 (s, 9H).

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  166.2, 159.2, 150.9, 146.8, 140.8, 137.7, 133.2, 130.5, 129.6, 129.2, 128.1, 128.0, 127.0, 126.1, 125.0 (q, *J* = 33.5 Hz, 1C), 124.5, 124.4 (q, *J* = 289.4 Hz, 1C), 123.6 (q, *J* = 275.8 Hz, 1C), 122.7, 117.1, 116.0, 114.5, 85.1, 67.4 (q, *J* = 30.3 Hz, 1C), 60.5, 55.4, 46.3, 27.9.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 80/20; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm; *t*<sub>minor</sub> = 7.71 min, *t*<sub>major</sub> = 9.26 min).

**HRMS (ESI)** Calcd. for C<sub>34</sub>H<sub>30</sub>F<sub>6</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 690.2039; found: 690.2043.

**Tert-butyl ((1*S*,10*bR*)-6-benzyl-2-((*E*)-benzylidene)-9-chloro-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl)carbamate (3af).**



White solid; 61.1 mg, 98% yield; >20:1 *dr*, 97% *ee*;  $[\alpha]_D^{20} = +163.4$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 152.3-154.6 °C.

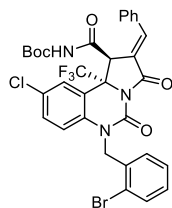
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.76 (s, 1H), 7.58 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.52 (s, 1H), 7.45-7.37 (m, 4H), 7.35-7.27 (m, 2H), 7.27-7.15 (m, 4H), 6.83 (d, *J* = 8.9 Hz, 1H), 6.49 (s, 1H), 5.27 (d, *J* = 16.6 Hz, 1H), 5.17 (d, *J* = 16.6 Hz, 1H), 1.59 (s, 9H).

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  166.3, 161.0, 151.0, 146.8, 137.4, 136.6, 135.4, 133.3, 131.0, 130.5, 129.7, 129.1, 129.0, 128.4, 127.7, 127.0, 126.6, 126.2, 124.5 (q, *J* = 289.6 Hz, 1C), 117.9, 117.2, 84.8, 67.4 (q, *J* = 29.9 Hz, 1C), 46.8, 45.0, 28.1.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 70/30; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm; *t*<sub>minor</sub> = 5.16 min, *t*<sub>major</sub> = 8.72 min).

**HRMS (ESI)** Calcd. for C<sub>32</sub>H<sub>28</sub>ClF<sub>3</sub>N<sub>3</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 626.1670; found: 626.1663.

**Tert-butyl ((1*S*,10*bR*)-2-((*E*)-benzylidene)-6-(2-bromobenzyl)-9-chloro-3,5-dioxo-10*b*-(trifluoromethyl)-1,2,3,5,6,10*b*-hexahydropyrrolo[1,2-*c*]quinazoline-1-carbonyl)carbamate (3ag).**



White solid; 70.1 mg, 99% yield; >20:1 *dr*, 98% *ee*;  $[\alpha]_D^{20} = +153.3$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 154.8-156.5 °C.

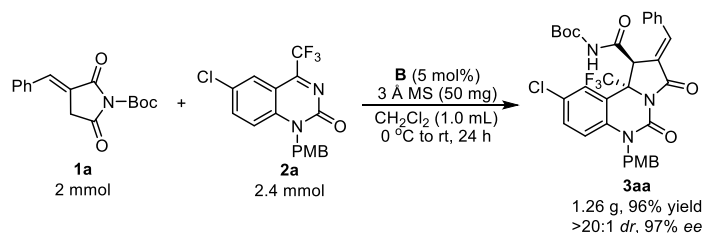
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (s, 1H), 7.65-7.52 (m, 4H), 7.52-7.28 (m, 4H), 7.20 (t, *J* = 7.2 Hz, 2H), 7.12 (t, *J* = 7.0 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 8.9 Hz, 1H), 6.51 (s, 1H), 5.34 (d, *J* = 17.4 Hz, 1H), 5.16 (d, *J* = 17.4 Hz, 1H), 1.59 (s, 9H).

<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  166.3, 150.9, 146.7, 137.6, 136.4, 133.9, 133.2, 133.1, 131.6, 131.3, 130.6, 129.7, 129.2, 129.1, 128.7, 128.2, 127.4, 127.2, 126.1, 124.4 (q, *J* = 289.2 Hz, 1C), 122.4, 117.8, 117.0, 85.0, 67.4 (q, *J* = 29.6 Hz, 1C), 47.3, 45.1, 28.1.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 75/25; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm; *t*<sub>minor</sub> = 4.56 min, *t*<sub>major</sub> = 6.44 min).

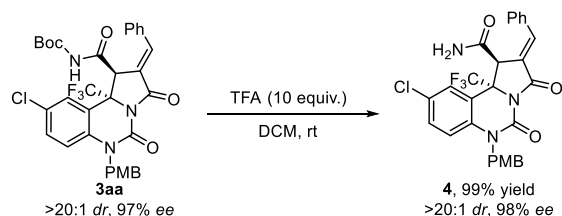
**HRMS (ESI)** Calcd. for C<sub>32</sub>H<sub>27</sub>BrClF<sub>3</sub>N<sub>3</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 704.0775; found: 704.0773.

## 5. Scale-up experiment



To a solution of catalyst **B** (64 mg, 5 mol %) and  $\alpha$ -arylidene succinimide **1a** (2.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20.0 mL) was added cyclic trifluoromethyl ketimine **2a** (2.4 mmol) and 3 Å molecular sieve (1.0 g). Then the mixture was stirred for 12 h at 0 °C, and then 12 h at 25 °C. After completion, the reaction mixture was directly purified by flash chromatography on silica gel (dichloromethane/petroleum ether/ ethyl acetate = 8:1:0.5) to give the corresponding product **3aa**.

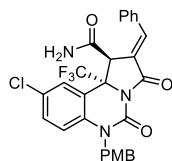
## 6. Experimental procedures for synthesis of compound 4.



To compound **3aa** (65.5 mg, 0.1 mmol) in 1.0 mL CH<sub>2</sub>Cl<sub>2</sub> were added trifluoroacetic acid (1 mmol) at room temperature. After being stirred at room temperature for 1 h, After completion, the reaction mixture was quenched by addition of water. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solution was concentrated under reduced pressure and the resulting crude mixture was purified by silica gel column chromatography (petroleum ether/AcOEt=1:1) to afford compound **4**.



**(1S,10bR)-2-((E)-benzylidene)-9-chloro-6-(4-methoxybenzyl)-3,5-dioxo-10b-(trifluoromethyl)-1,2,3,5,6,10b-hexahydropyrrolo[1,2-c]quinazoline-1-carboxamide (4).**



White solid; 54.8 mg, 99% yield; >20:1 *dr*, 98% *ee*;  $[\alpha]_D^{20} = +152.1$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 231.2-233.0 °C.

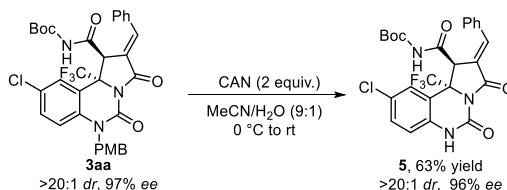
<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.37 (s, 1H), 7.91-1.80 (m, 3H), 7.72 (s, 1H), 7.61-7.51 (m, 4H), 7.49 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.18 (dd, *J* = 9.3, 8.7 Hz, 3H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.24 (d, *J* = 16.4 Hz, 1H), 5.13 (d, *J* = 16.4 Hz, 1H), 5.12 (s, 1H), 3.71 (s, 3H).

<sup>13</sup>C NMR (151 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  168.0, 166.2, 158.5, 146.1, 135.9, 134.6, 132.9, 130.9, 130.6, 130.5, 129.1, 127.9, 127.5, 127.0, 126.8, 126.7, 124.6 (q, *J* = 289.9 Hz, 1C), 117.3, 117.2, 114.1, 66.1 (q, *J* = 27.9 Hz, 1C), 55.1, 47.0, 44.7.

**HPLC analysis:** Chiralpak AD-H column (*n*-hexane/ *i*-PrOH = 80/20; flow rate: 1.0 mL/min;  $\lambda$  = 254 nm; *t*<sub>minor</sub> = 16.73 min, *t*<sub>major</sub> = 30.09 min).

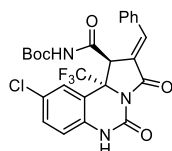
**HRMS (ESI)** Calcd. for C<sub>28</sub>H<sub>21</sub>ClF<sub>3</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 578.1070; found: 578.1047.

## 7. Experimental procedure for synthesis of compound 5.



To compound **3aa** (65.5 mg, 0.1 mmol) in 0.9 mL MeCN and 0.1 mL water were stirred at 0 °C, and then 2.0 equivalent ceric ammonium nitrate was added portionwise. And the reaction mixture returns to room temperature. After being stirred at room temperature for 24 h, the reaction mixture was quenched by addition of water. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solution was concentrated under reduced pressure and the resulting crude mixture was purified by silica gel column chromatography (petroleum ether/AcOEt=1:2) to afford compound **4**.

***Tert*-butyl ((1S,10bR)-2-((E)-benzylidene)-9-chloro-3,5-dioxo-10b-(trifluoromethyl)-1,2,3,5,6,10b-hexahydropyrrolo[1,2-c]quinazoline-1-carbonyl)carbamate (5).**



Light yellow solid; 33.9 mg, 63% yield; >20:1 *dr*, 98% *ee*;  $[\alpha]_D^{20} = +130.2$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 149.8-151.4 °C.

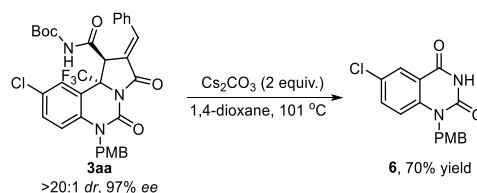
<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  11.37 (s, 1H), 10.91 (s, 1H), 7.87-7.65 (m, 3H), 7.62 (s, 1H), 7.58-7.49 (m, 4H), 7.03 (d, *J* = 8.7 Hz, 1H), 5.25 (s, 1H), 1.38 (s, 9H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ )  $\delta$  165.8, 148.2, 145.1, 135.8, 135.7, 132.6, 131.4, 130.8, 130.3, 130.0, 129.2, 126.4, 126.2, 124.5 (q,  $J = 289.2$  Hz, 1C), 117.1, 114.5, 81.9, 67.4 (q,  $J = 28.5$  Hz, 1C), 54.9, 27.5.

**HPLC analysis:** Chiralpak OD-H column (*n*-hexane/ *i*-PrOH = 85/15; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{minor}} = 7.55$  min,  $t_{\text{major}} = 9.51$  min).

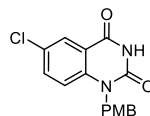
**HRMS (ESI)** Calcd. for  $\text{C}_{25}\text{H}_{21}\text{ClF}_3\text{N}_3\text{NaO}_5$   $[\text{M}+\text{Na}]^+$ : 558.1020; found: 558.1007.

## 8. Experimental procedure for synthesis of compound 6.



To the mixture of compound **3aa** (65.5 mg, 0.1 mmol) and 2.0 equivalent cesium carbonate was added 1,4-dioxane (1.0 mL), which was stirred in the reflux 1,4-dioxane at  $101^\circ\text{C}$  for 2 h. After the completion of the reaction which was monitored by TLC, the solvent was removed under reduced pressure and the resulting crude mixture was purified by silica gel column chromatography (petroleum ether/AcOEt=1:1) to afford compound **6**.

### 6-Chloro-1-(4-methoxybenzyl)quinazoline-2,4(1H,3H)-dione (6).



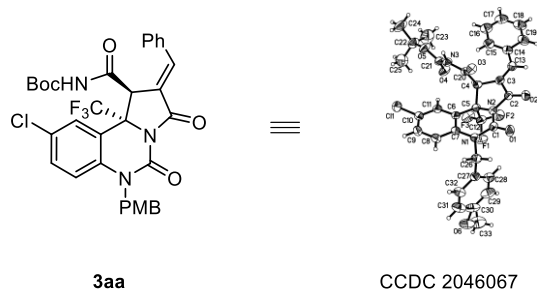
White solid; 22.3 mg, 70% yield; m.p.  $192.9$ - $194.4^\circ\text{C}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.88 (s, 1H), 7.92 (d,  $J = 2.3$  Hz, 1H), 7.69 (dd,  $J = 9.0, 2.3$  Hz, 1H), 7.30 (d,  $J = 9.0$  Hz, 1H), 7.23 (d,  $J = 8.5$  Hz, 2H), 6.88 (d,  $J = 8.5$  Hz, 2H), 5.22 (s, 2H), 3.70 (s, 3H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  160.8, 158.5, 150.5, 139.8, 134.8, 127.9, 127.8, 127.0, 126.5, 117.5, 114.1, 55.1, 44.8.

**HRMS (ESI)** Calcd. for  $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{NaO}_3$   $[\text{M}+\text{Na}]^+$ : 339.0512; found: 339.0509.

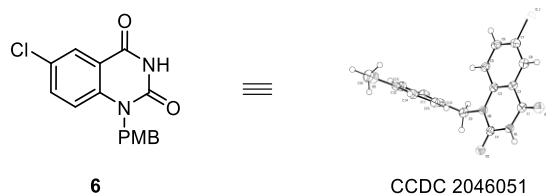
## 9. X-ray crystal structure of compound **3aa**



Crystal data and structure refinement for **3aa** (CCDC 2046067)

Identification code	20200529
Empirical formula	C <sub>33</sub> H <sub>29</sub> ClF <sub>3</sub> N <sub>3</sub> O <sub>6</sub>
Formula weight	656.04
Temperature/K	293(2)
Crystal system	monoclinic
Space group	P2 <sub>1</sub>
a/Å	9.5411(3)
b/Å	13.6581(5)
c/Å	12.6050(4)
α/°	90
β/°	89.913(3)
γ/°	90
Volume/Å <sup>3</sup>	1642.60(10)
Z	2
ρ <sub>calc</sub> /g/cm <sup>3</sup>	1.326
μ/mm <sup>-1</sup>	1.590
F(000)	680.0
Crystal size/mm <sup>3</sup>	0.18 × 0.1 × 0.08
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	7.012 to 134.12
Index ranges	-11 ≤ h ≤ 10, -14 ≤ k ≤ 16, -14 ≤ l ≤ 15
Reflections collected	21371
Independent reflections	5348 [R <sub>int</sub> = 0.0417, R <sub>sigma</sub> = 0.0363]
Data/restraints/parameters	5348/15/431
Goodness-of-fit on F <sup>2</sup>	1.030
Final R indexes [I ≥ 2σ (I)]	R <sub>1</sub> = 0.0481, wR <sub>2</sub> = 0.1274
Final R indexes [all data]	R <sub>1</sub> = 0.0578, wR <sub>2</sub> = 0.1360
Largest diff. peak/hole / e Å <sup>-3</sup>	0.16/-0.16
Flack parameter	-0.01(2)

## 10. X-ray crystal structure of compound 6

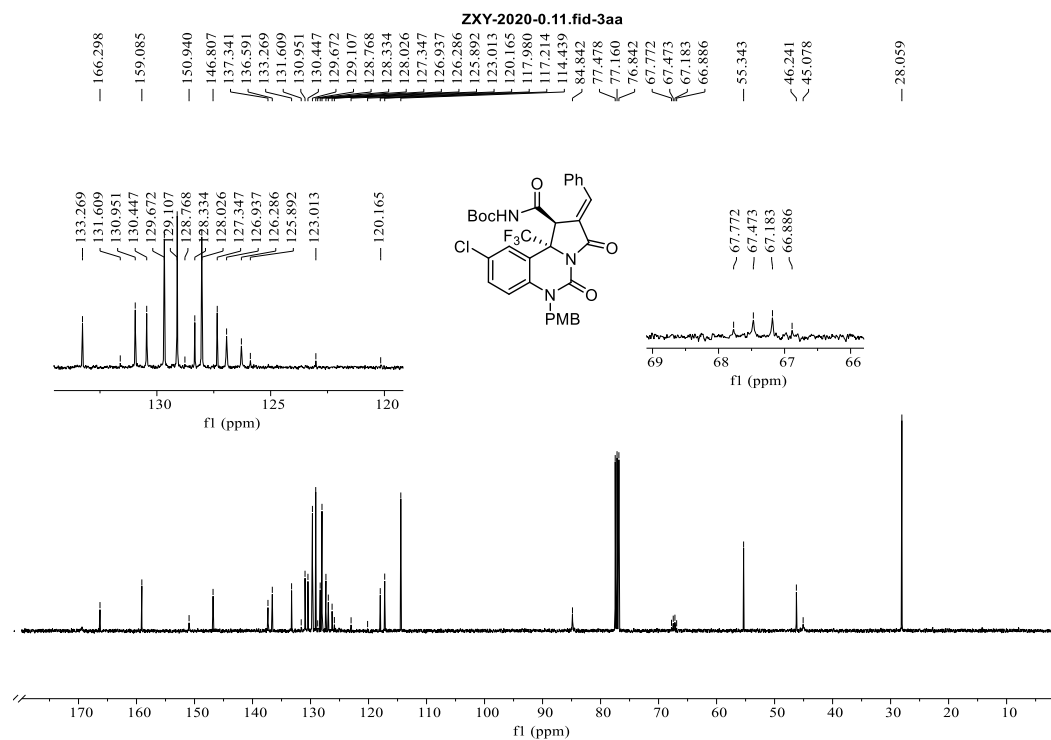
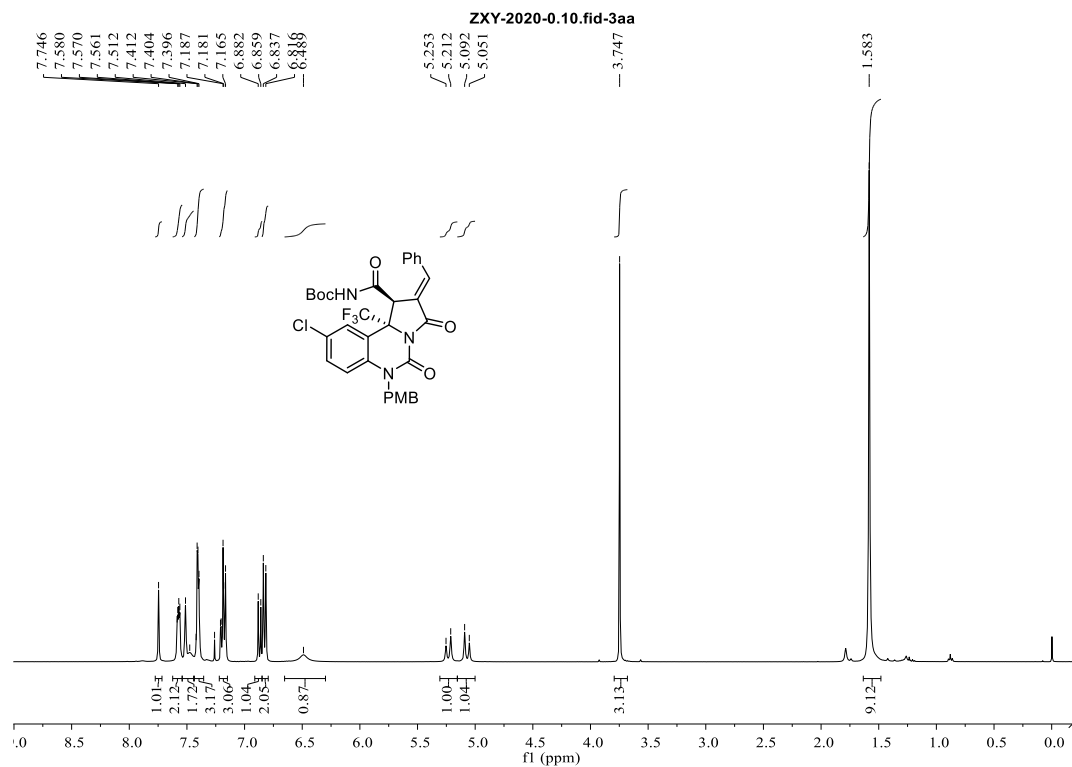


Crystal data and structure refinement for **6** (CCDC 2046051)

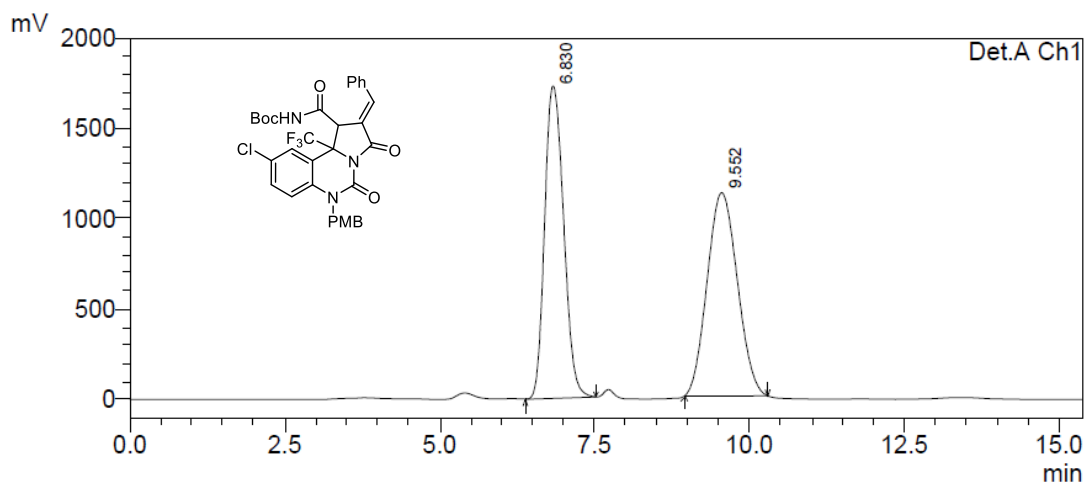
Identification code	2009239899_0m
Empirical formula	C <sub>16</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>3</sub>
Formula weight	316.73
Temperature/K	173.0
Crystal system	triclinic
Space group	P-1
a/Å	7.9537(4)
b/Å	9.3223(4)
c/Å	10.8300(5)
α/°	84.687(3)
β/°	74.704(3)
γ/°	69.975(2)
Volume/Å <sup>3</sup>	727.73(6)
Z	2
ρ <sub>calc</sub> /cm <sup>3</sup>	1.445
μ/mm <sup>-1</sup>	1.600
F(000)	328.0
Crystal size/mm <sup>3</sup>	0.18 × 0.12 × 0.1
Radiation	GaKα (λ = 1.34139)
2θ range for data collection/°	8.784 to 109.936
Index ranges	-9 ≤ h ≤ 9, -11 ≤ k ≤ 11, -13 ≤ l ≤ 13
Reflections collected	8824
Independent reflections	2767 [R <sub>int</sub> = 0.0538, R <sub>sigma</sub> = 0.0524]
Data/restraints/parameters	2767/0/200
Goodness-of-fit on F <sup>2</sup>	1.066
Final R indexes [I >= 2σ (I)]	R <sub>1</sub> = 0.0476, wR <sub>2</sub> = 0.1171
Final R indexes [all data]	R <sub>1</sub> = 0.0577, wR <sub>2</sub> = 0.1265
Largest diff. peak/hole / e Å <sup>-3</sup>	0.27/-0.40

# 11. $^1\text{H}$ , $^{13}\text{C}$ NMR, and HPLC spectra for compounds 3, 4, 5, 6

## $^1\text{H}$ and $^{13}\text{C}$ NMR of 3aa



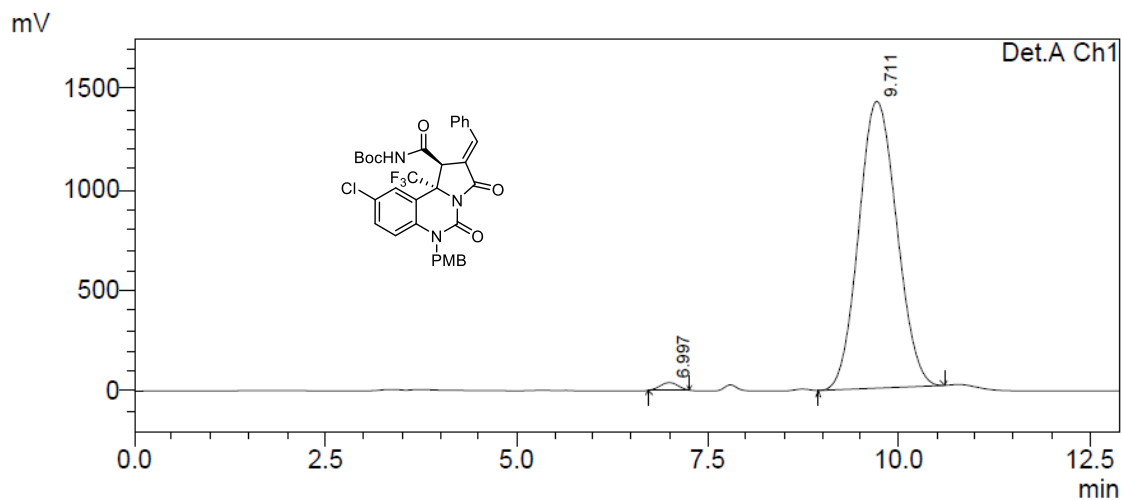
### HPLC of 3aa



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.830	36856644	1726537	49.107
2	9.552	38196948	1124417	50.893
Total		75053592		100.000

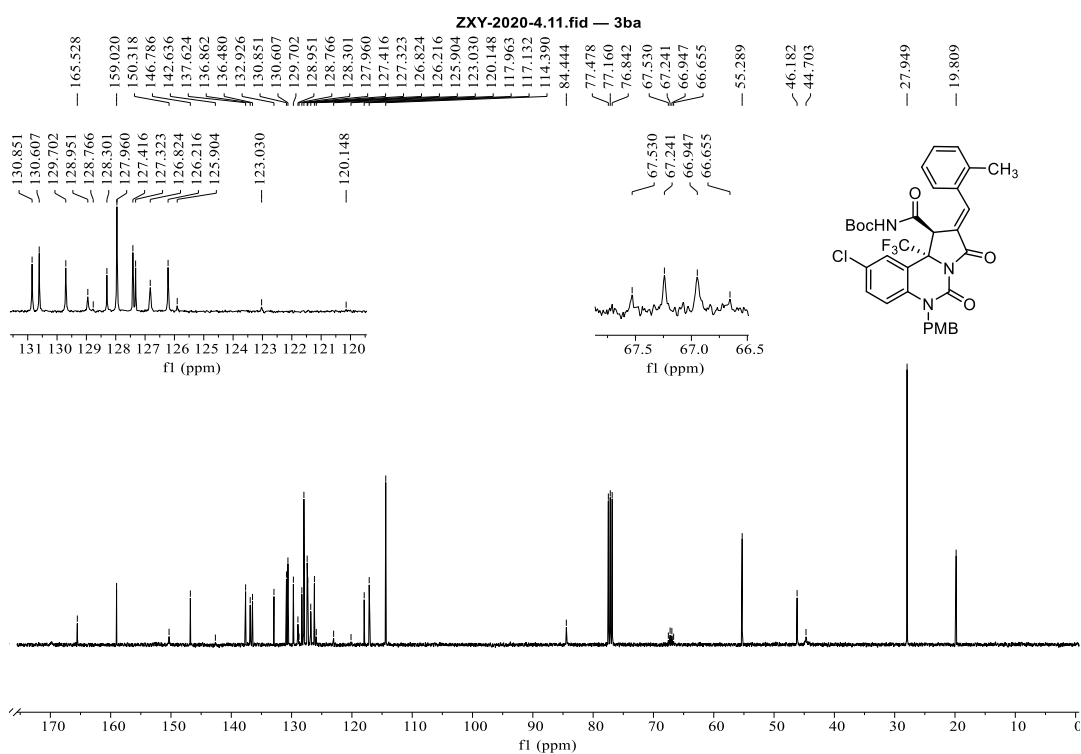
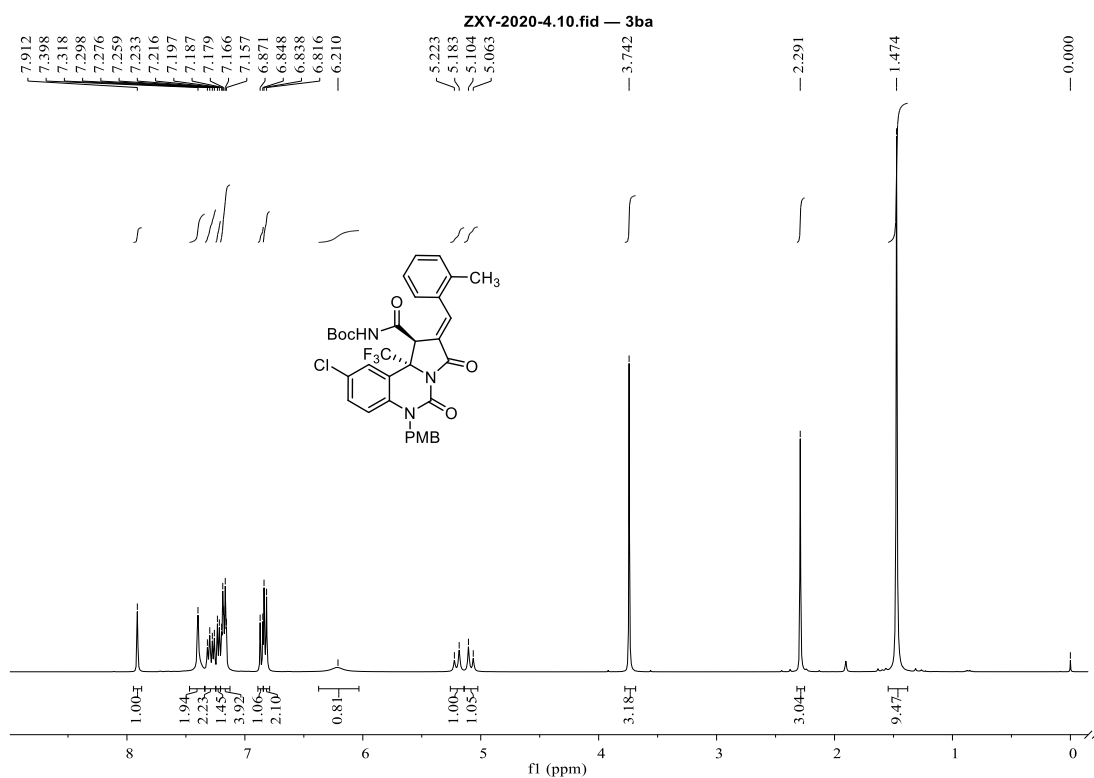


PeakTable

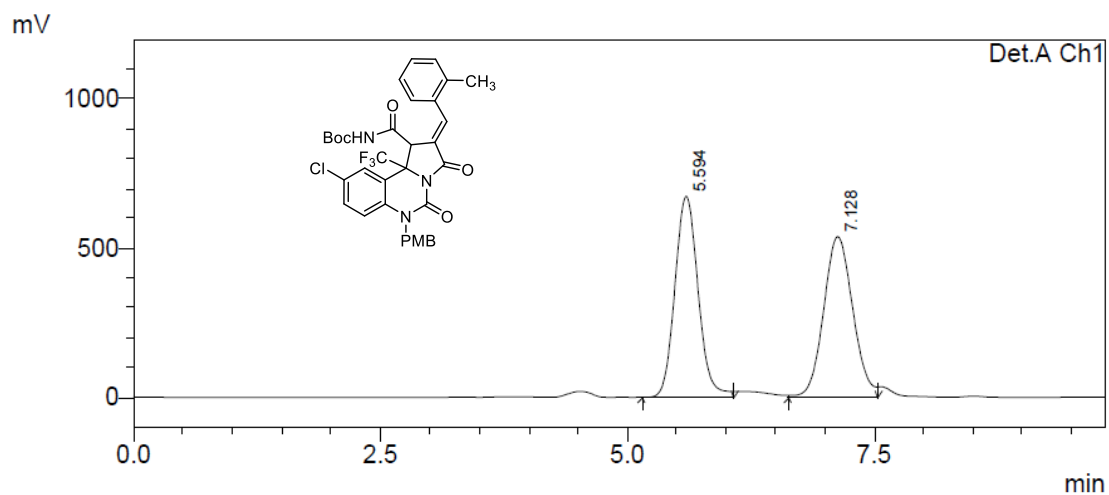
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.997	605437	37866	1.212
2	9.711	49346765	1422373	98.788
Total		49952202		100.000

# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3ba**



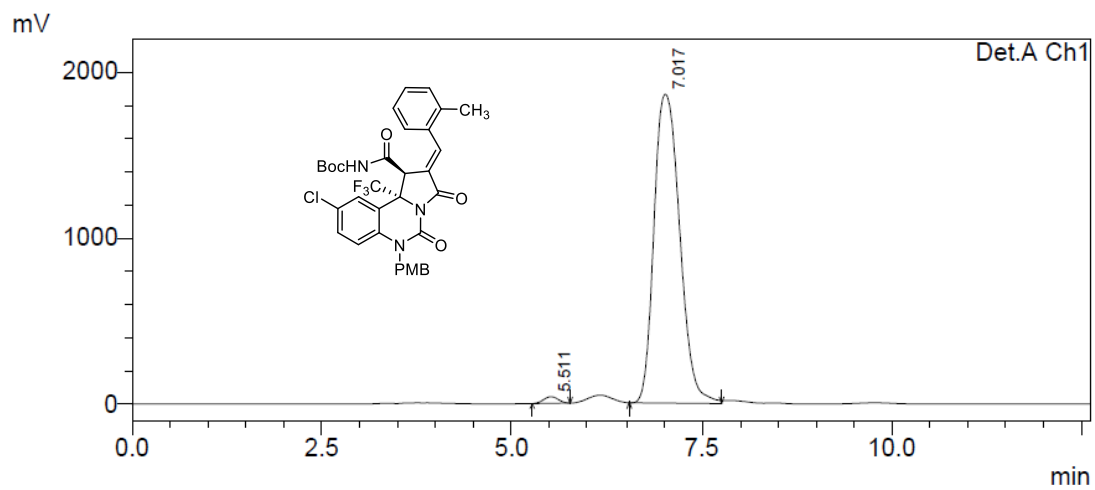
### HPLC of 3ba



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	5.594	11057317	674473	49.862
2	7.128	11118571	539292	50.138
Total		22175888		100.000



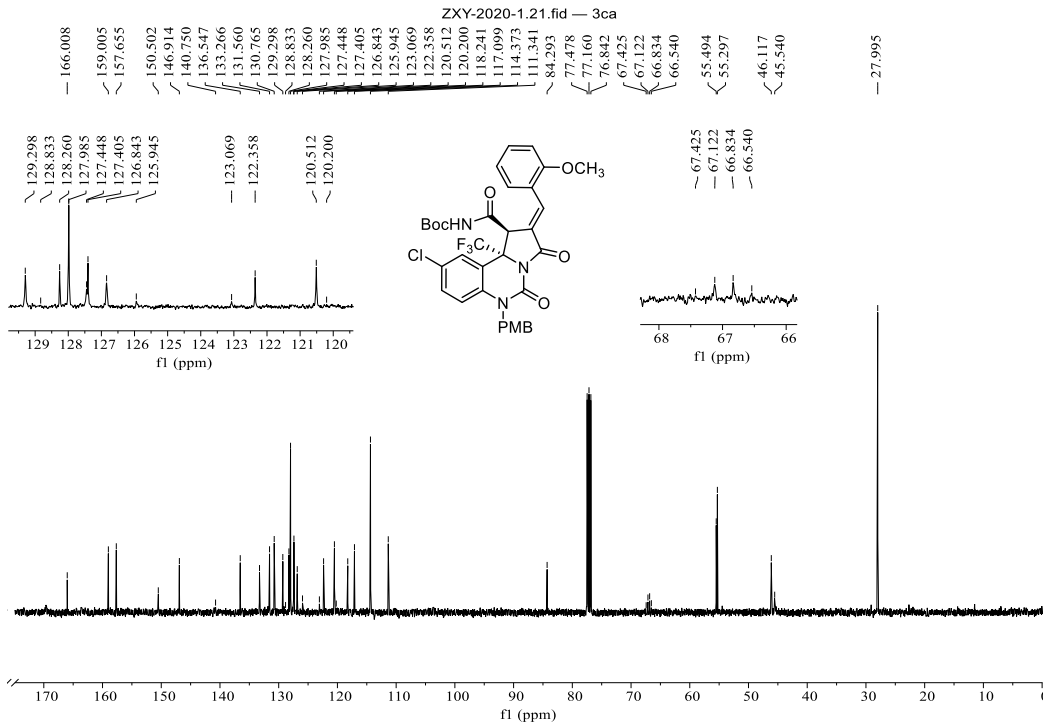
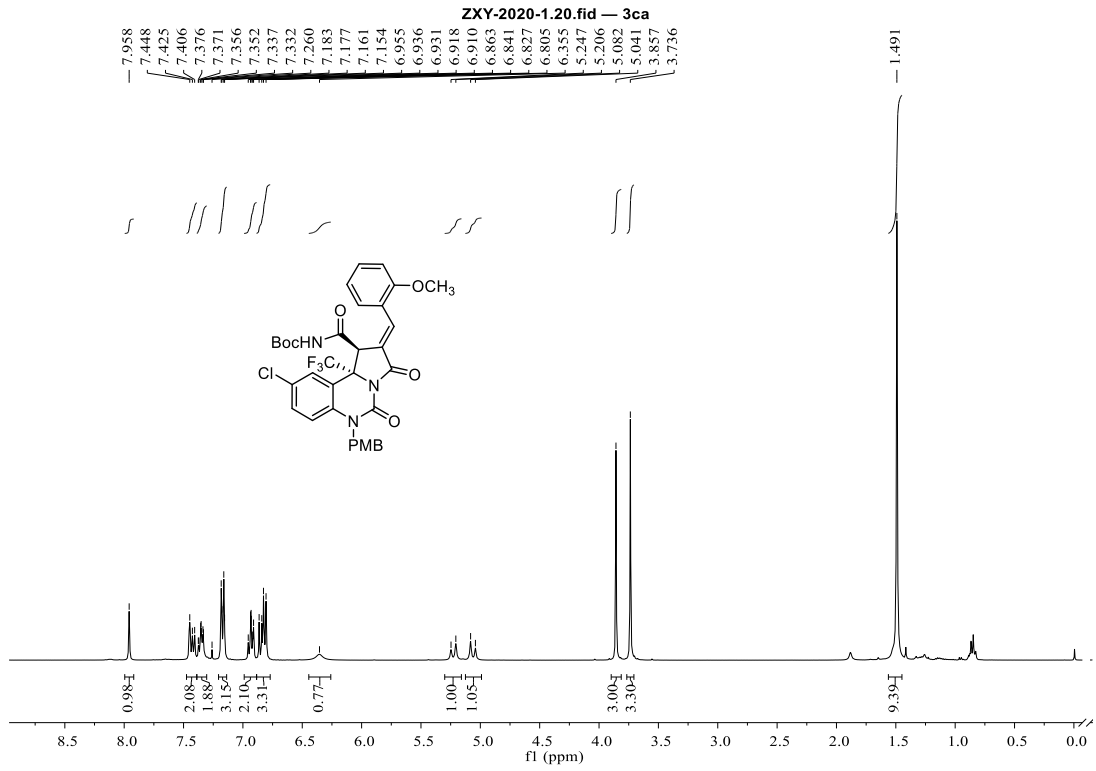
PeakTable

Detector A Ch1 254nm

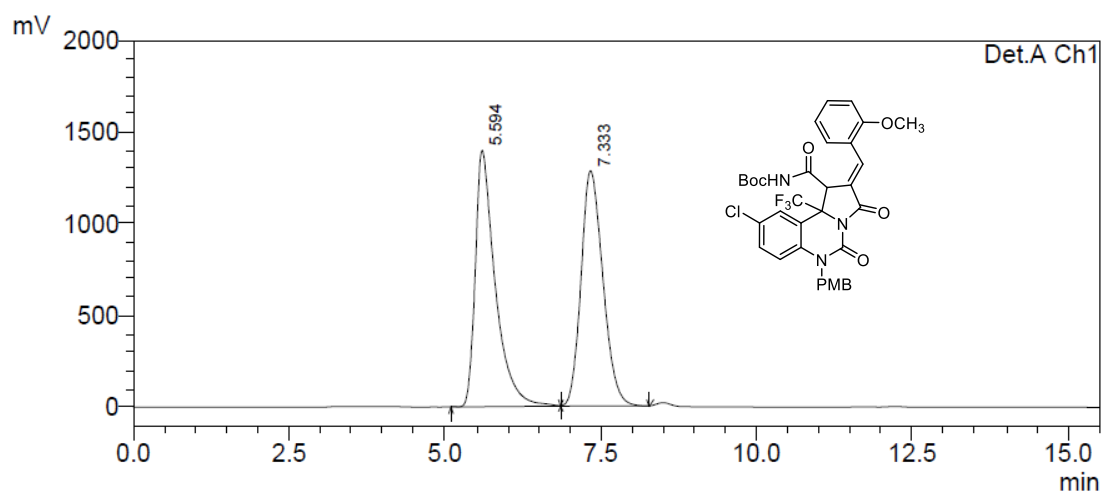
Peak#	Ret. Time	Area	Height	Area %
1	5.511	531166	40090	1.197
2	7.017	43855772	1858966	98.803
Total		44386938		100.000



# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3ca**



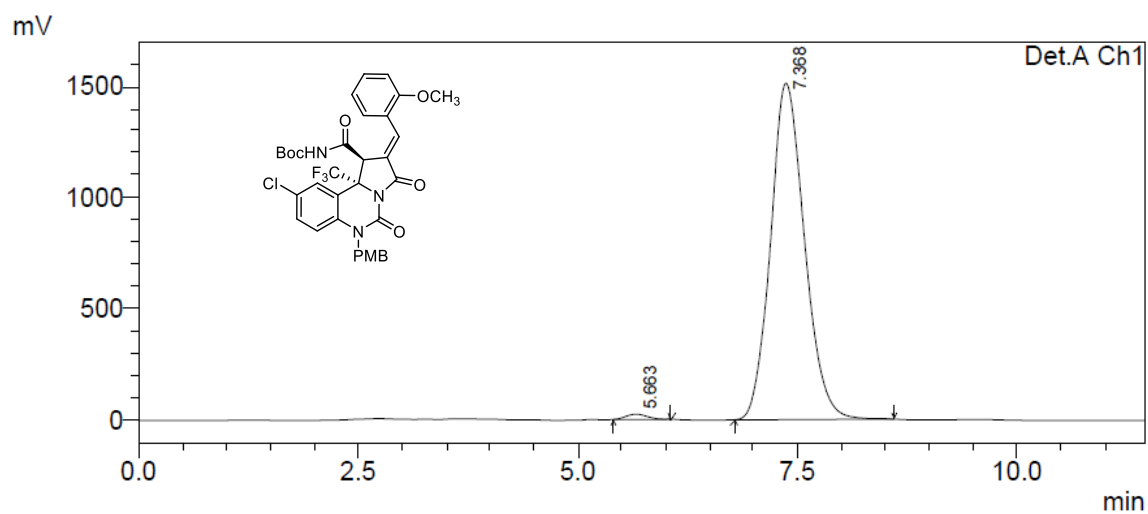
### HPLC of 3ca



1 Det.A Ch1/254nm

PeakTable

Peak#	Ret. Time	Area	Height	Area %
1	5.594	31106586	1396927	49.840
2	7.333	31306277	1281047	50.160
Total		62412864		100.000

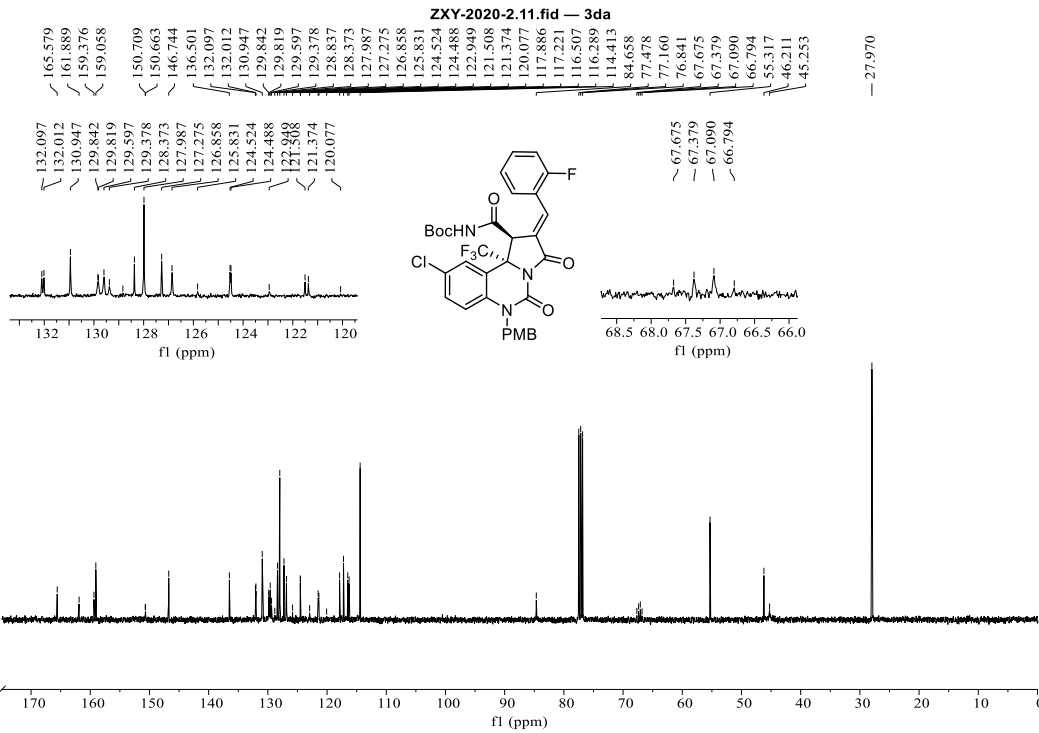
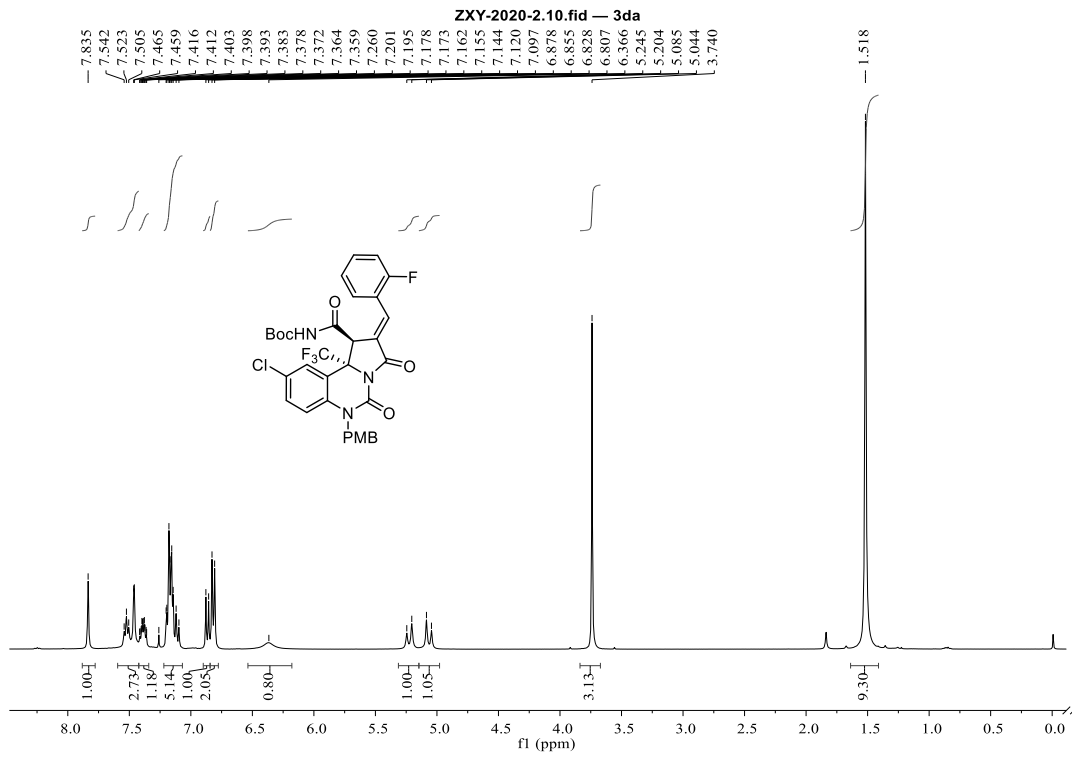


1 Det.A Ch1/254nm

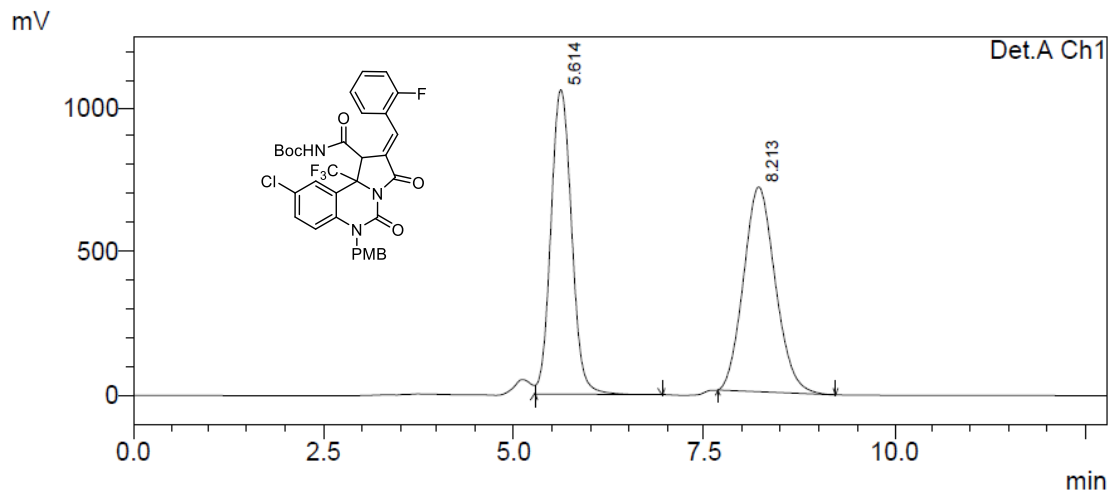
PeakTable

Peak#	Ret. Time	Area	Height	Area %
1	5.663	402138	23690	0.981
2	7.368	40574721	1508852	99.019
Total		40976859		100.000

# $^1\text{H}$ and $^{13}\text{C}$ NMR of 3da



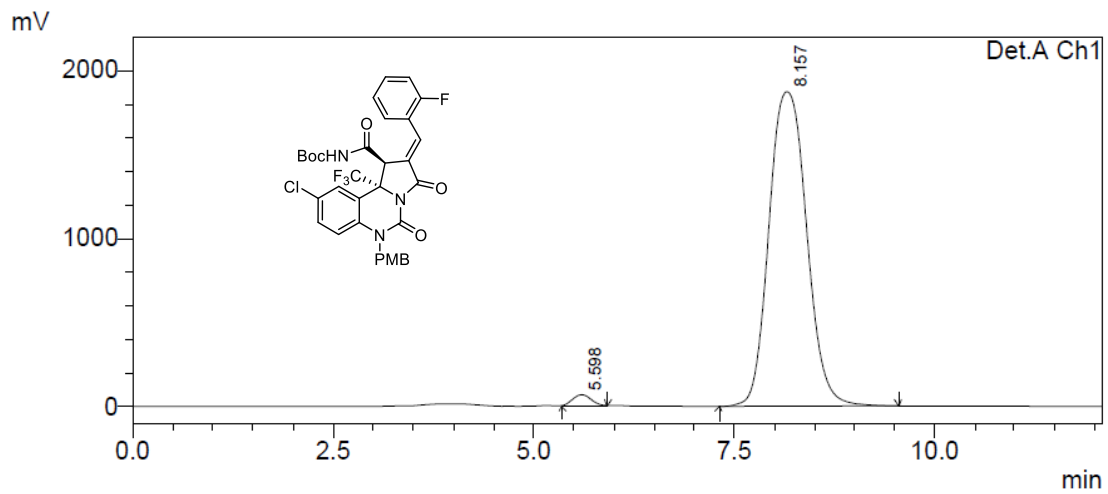
### HPLC of 3da



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	5.614	20082661	1059597	49.200
2	8.213	20735429	712113	50.800
Total		40818089		100.000

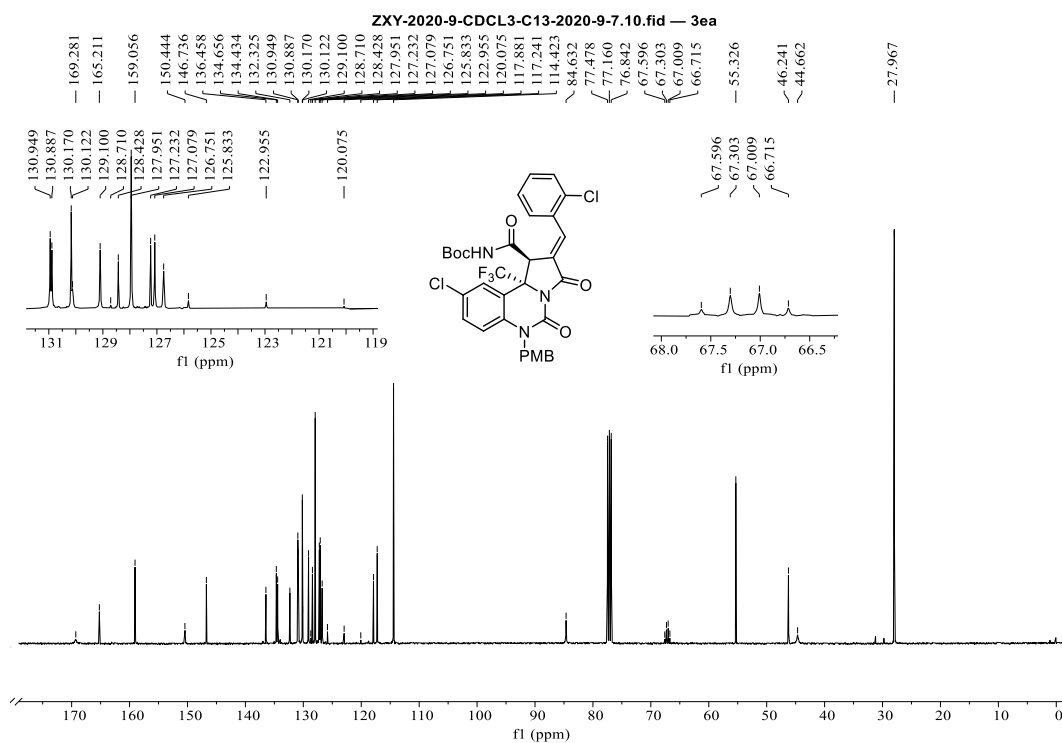
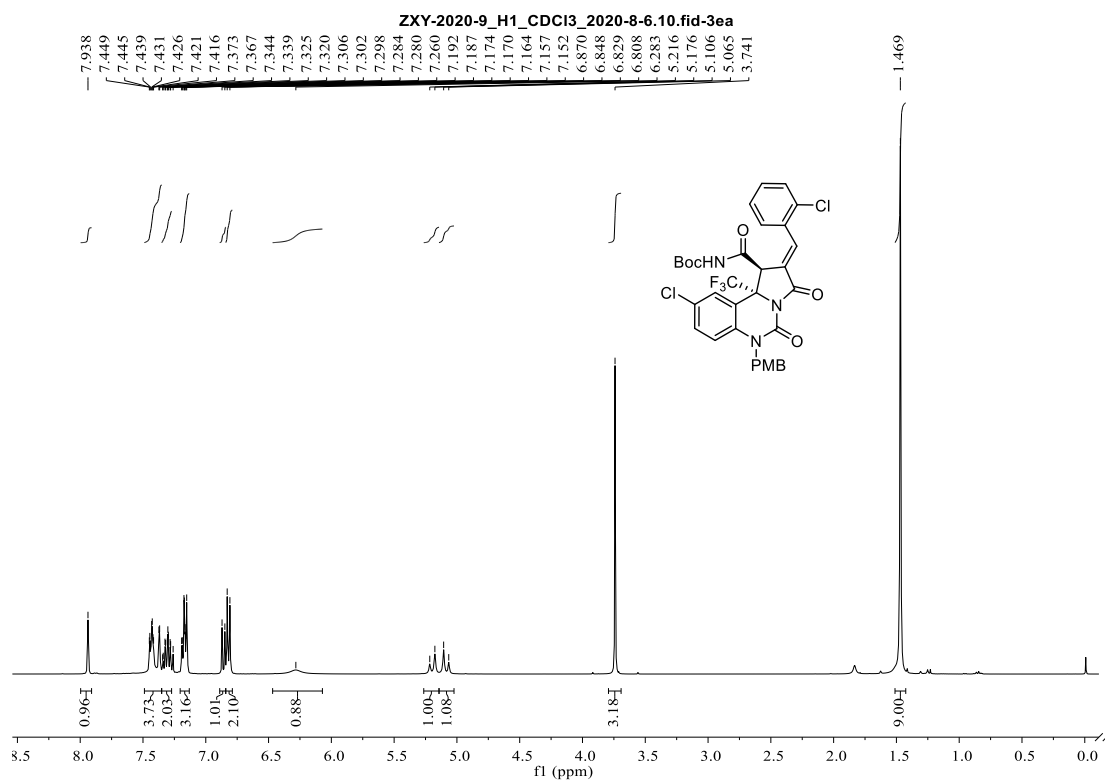


PeakTable

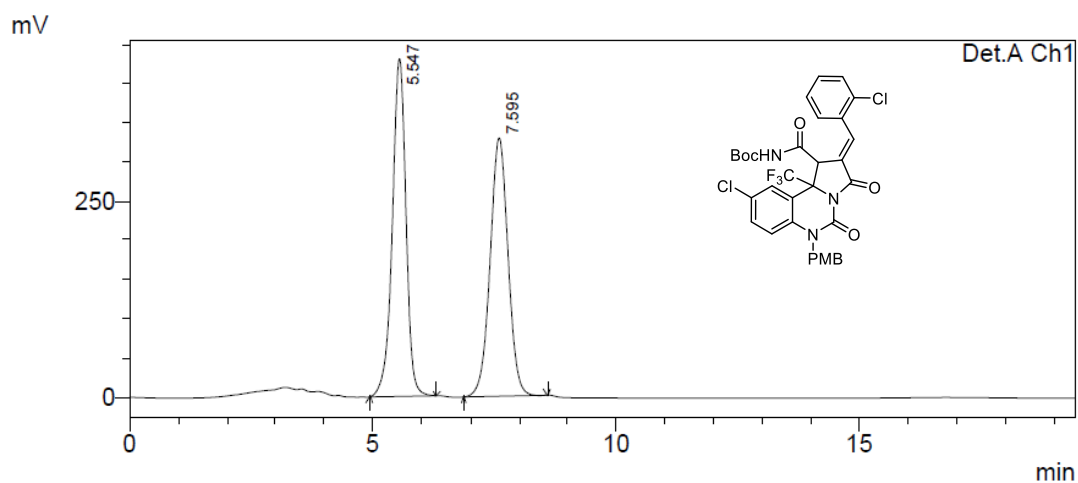
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	5.598	984756	63680	1.585
2	8.157	61160402	1870296	98.415
Total		62145157		100.000

# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3ea**



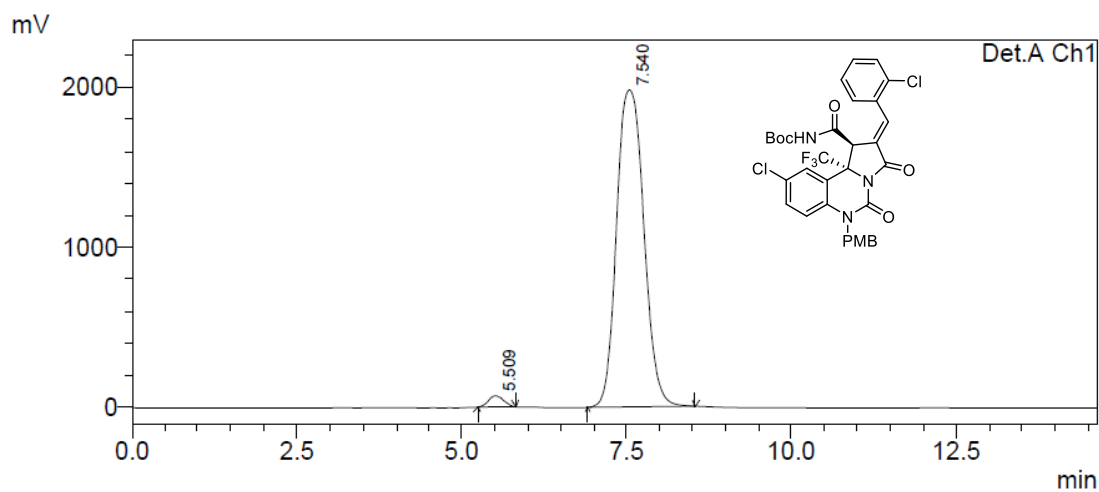
### HPLC of 3ea



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	5.547	8414164	430534	49.980
2	7.595	8420941	329018	50.020
Total		16835105		100.000

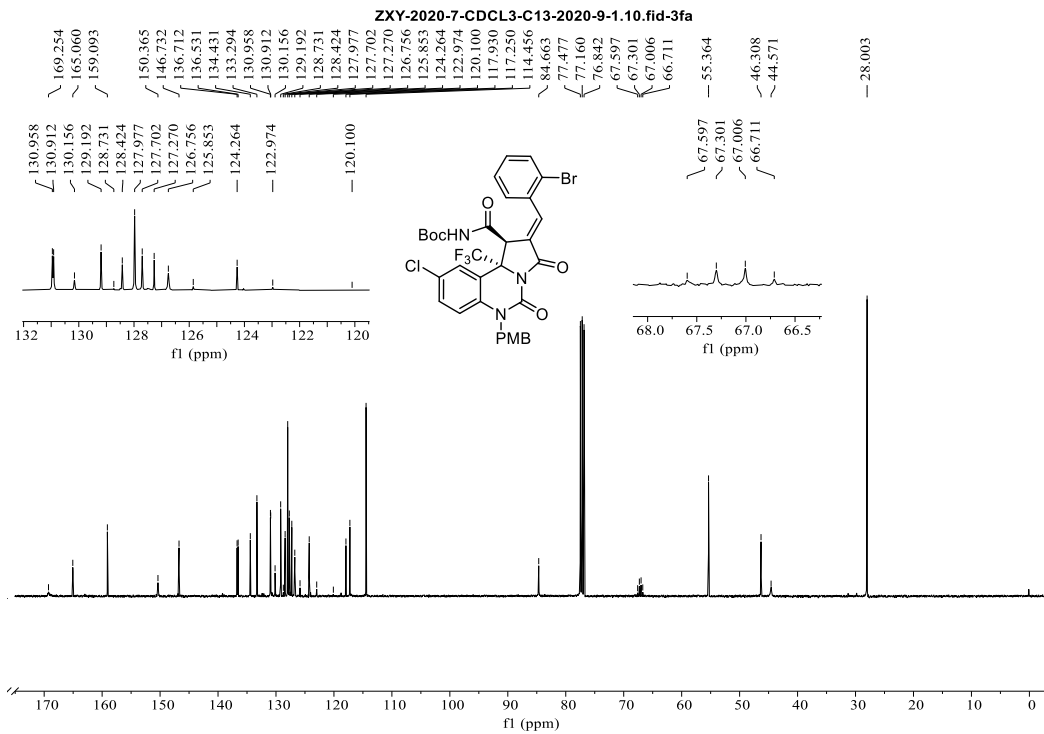
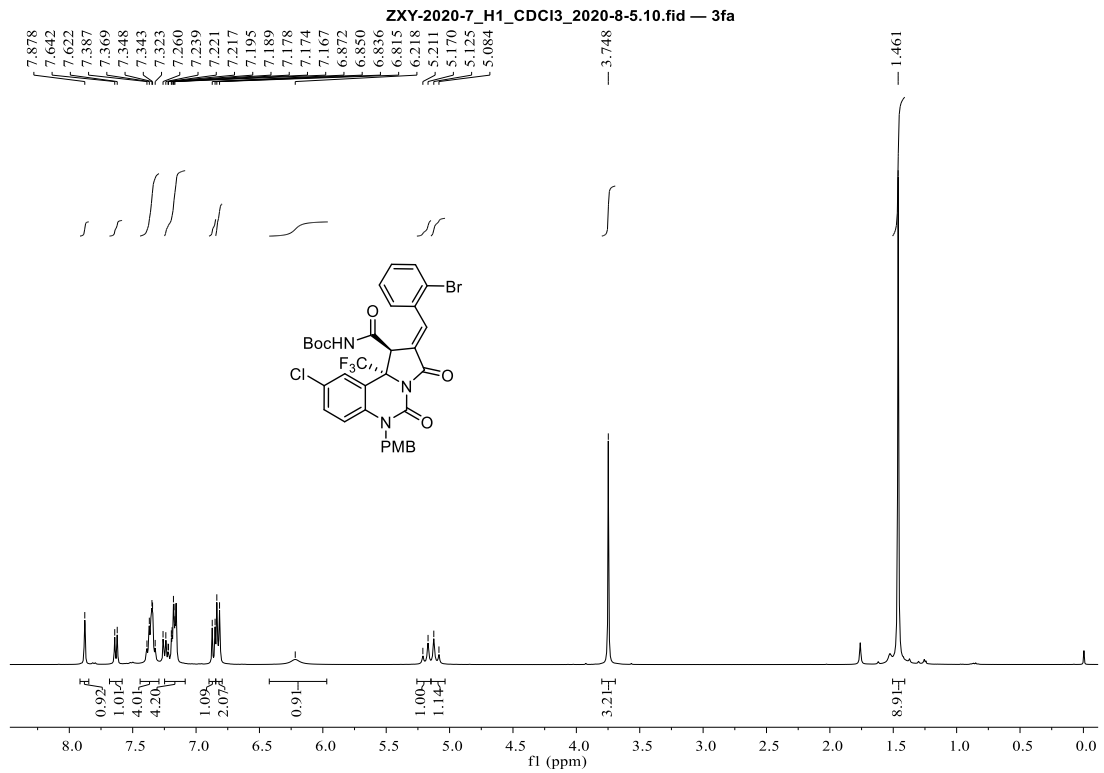


PeakTable

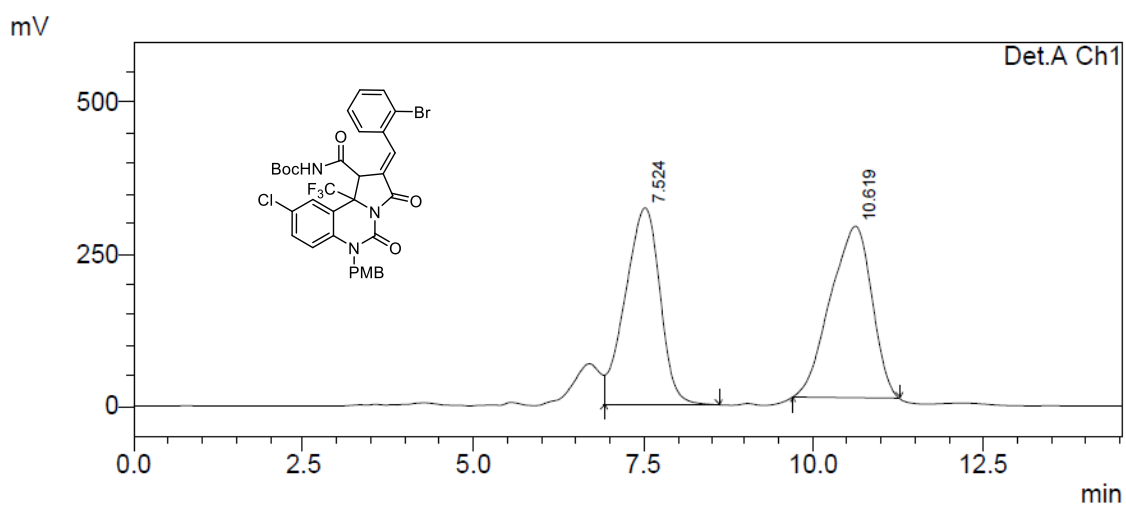
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	5.509	1124457	69650	1.938
2	7.540	56908339	1977831	98.062
Total		58032796		100.000

# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3fa**



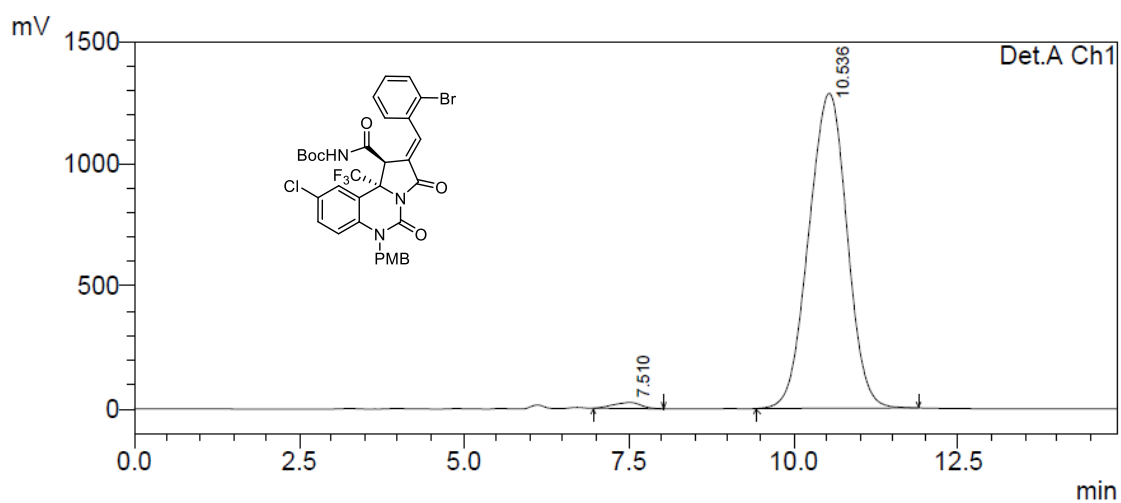
### HPLC of 3fa



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	7.524	11562434	324458	49.011
2	10.619	12029139	282762	50.989
Total		23591573		100.000



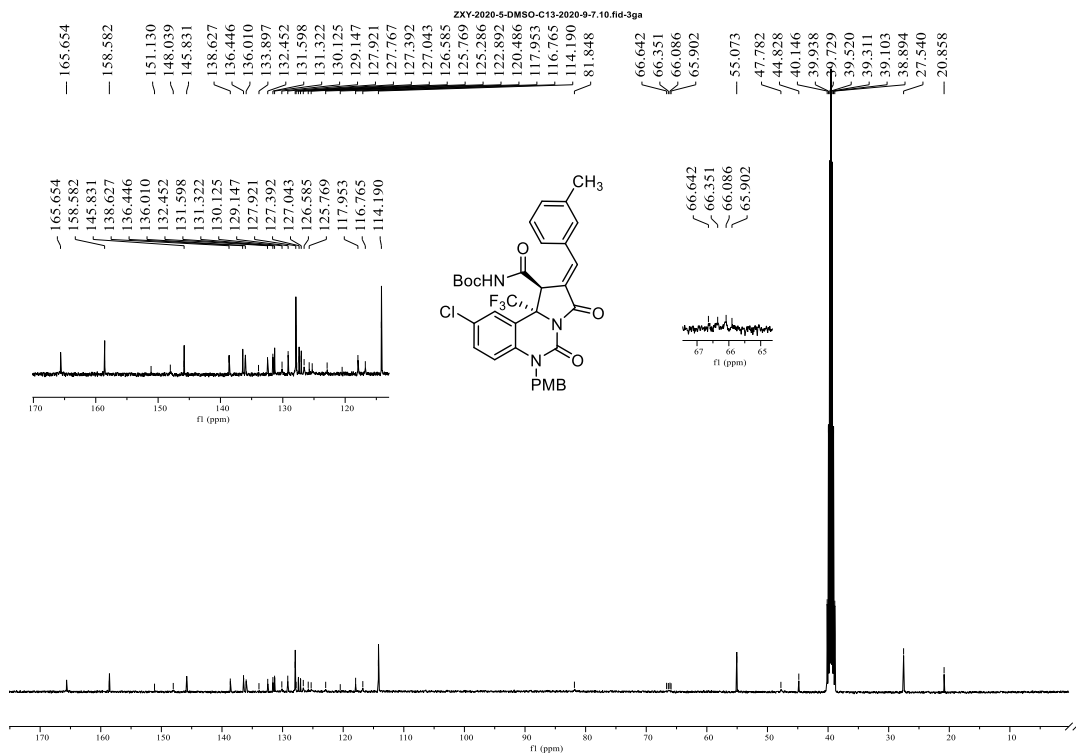
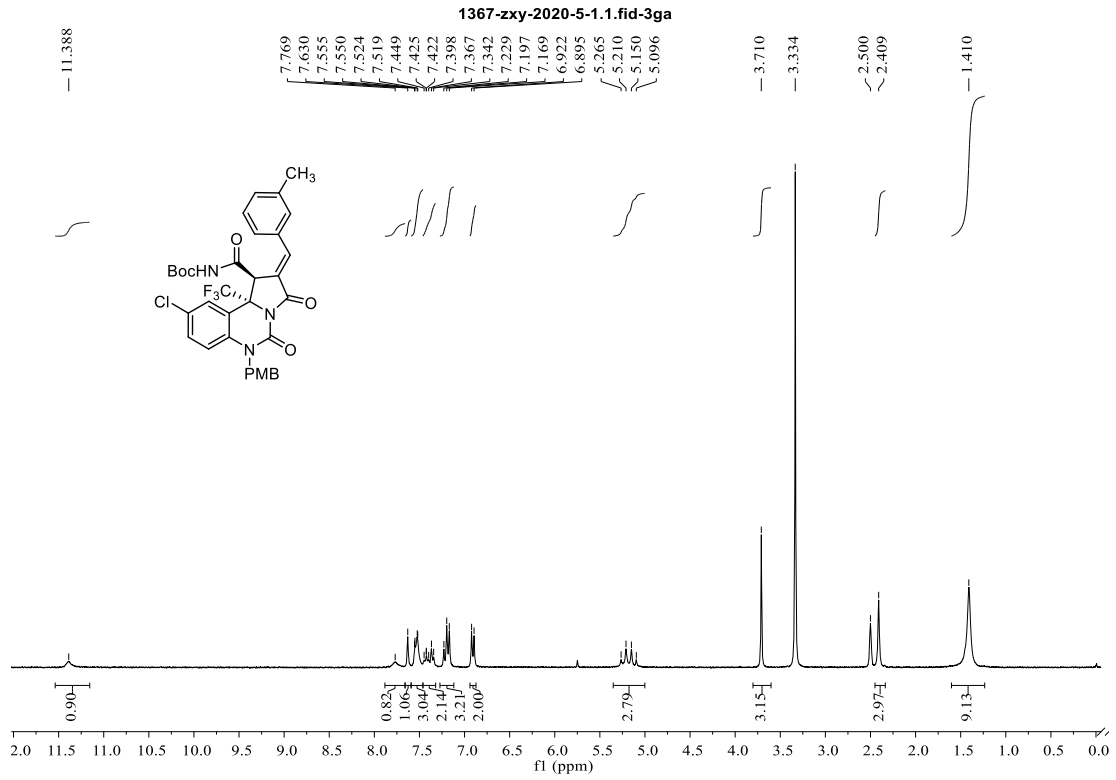
PeakTable

Detector A Ch1 254nm

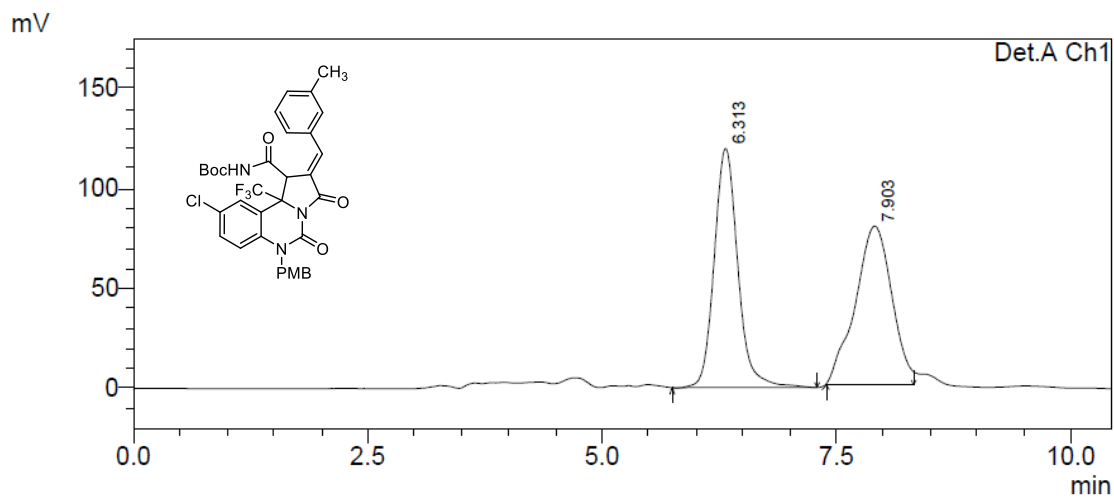
Peak#	Ret. Time	Area	Height	Area %
1	7.510	715334	25023	1.357
2	10.536	52001502	1285394	98.643
Total		52716836		100.000



# <sup>1</sup>H and <sup>13</sup>C NMR of 3ga



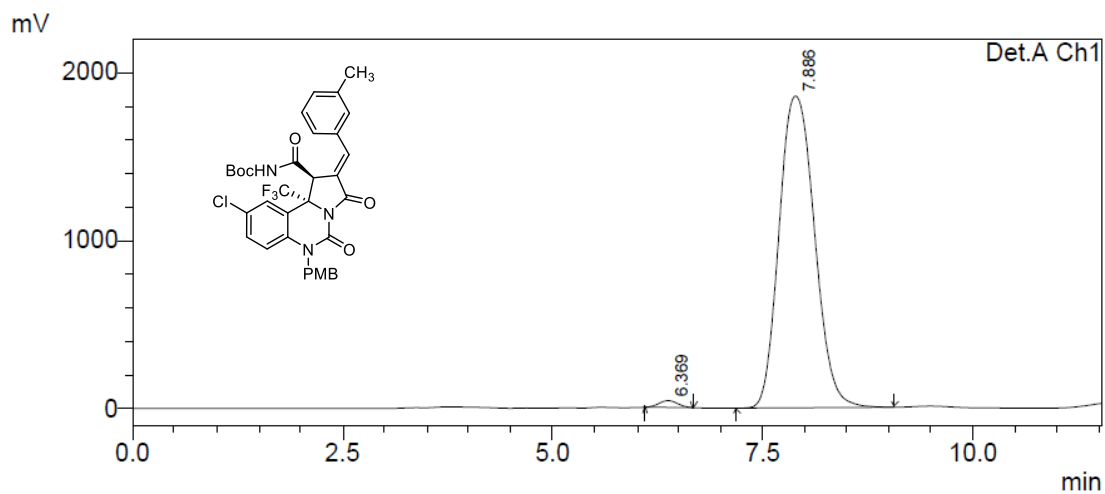
### HPLC of 3ga



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.313	2101287	119566	49.431
2	7.903	2149644	79279	50.569
Total		4250932		100.000

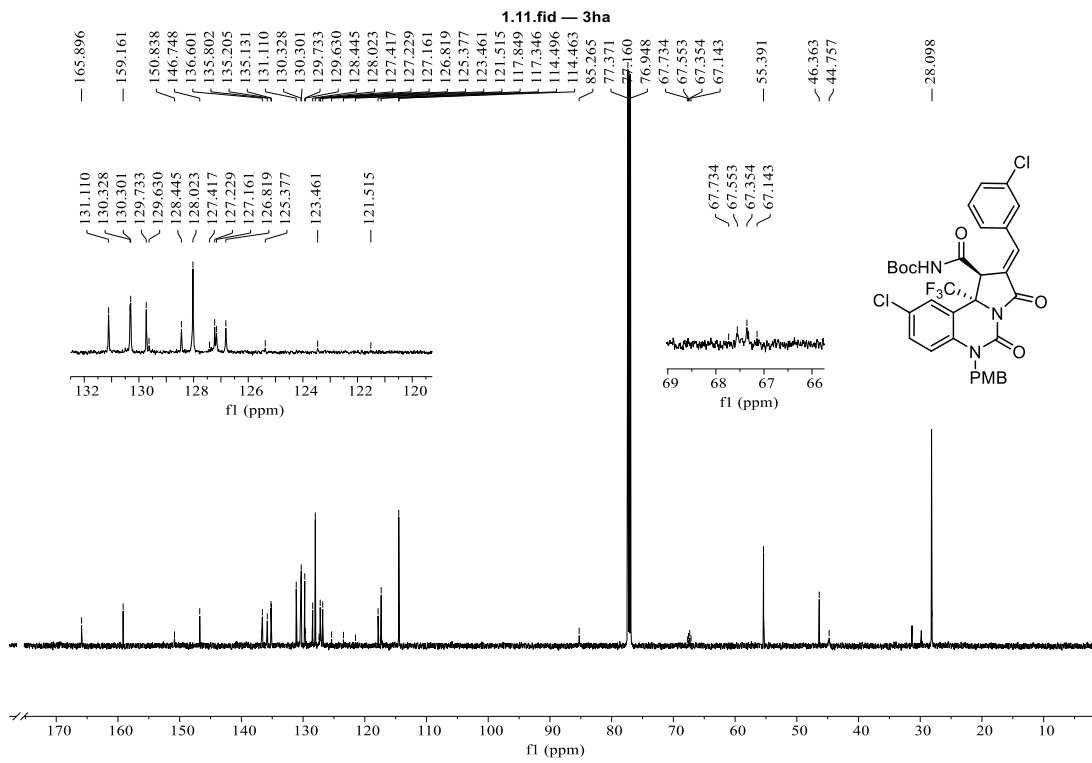
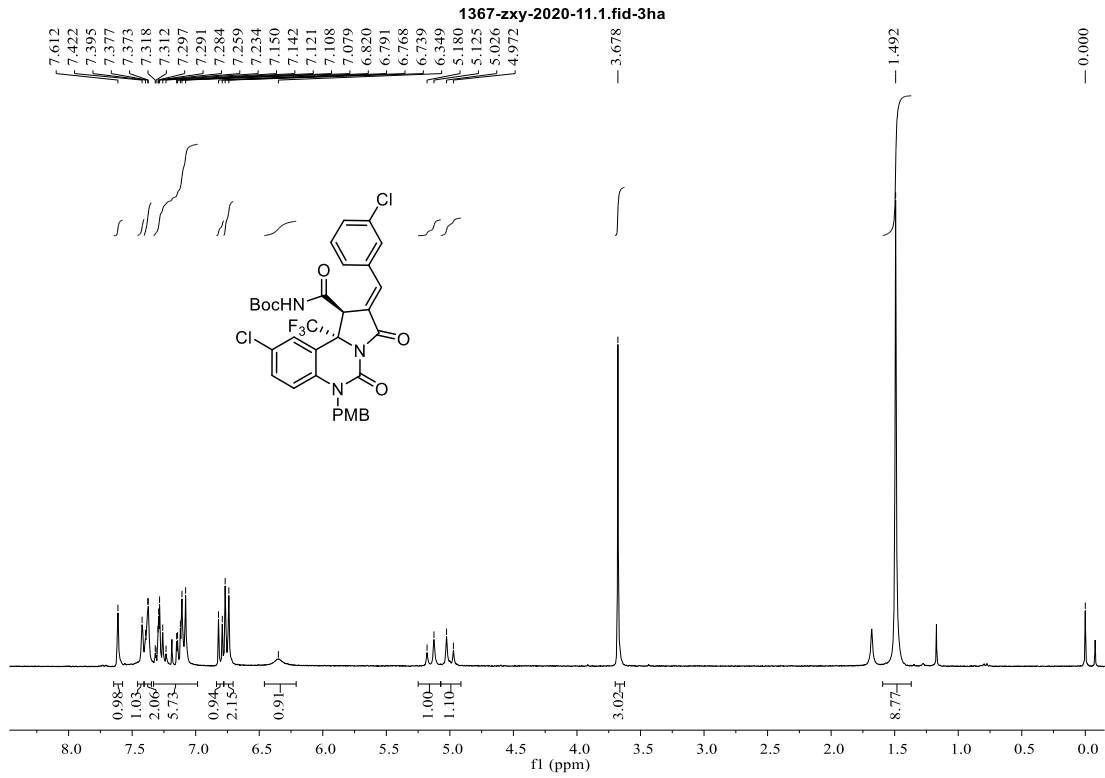


PeakTable

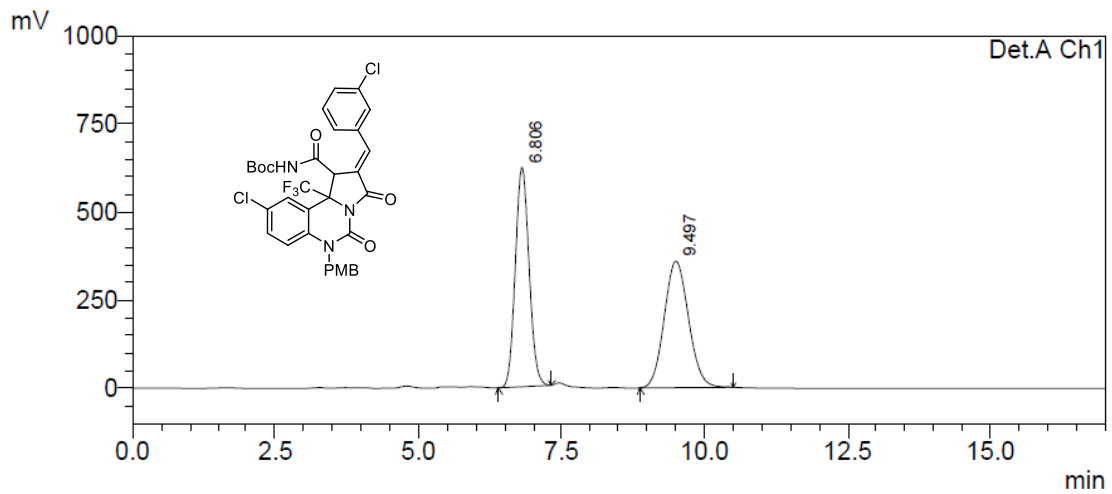
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.369	637346	40678	1.157
2	7.886	54426006	1853811	98.843
Total		55063351		100.000

# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3ha**



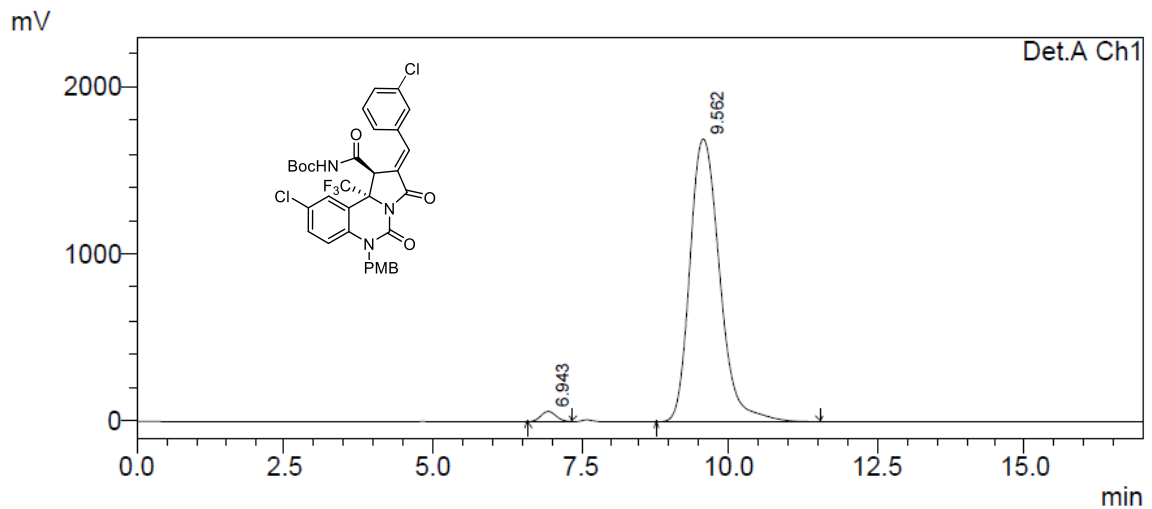
### HPLC of 3ha



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.806	10401481	621456	49.497
2	9.497	10612955	358695	50.503
Total		21014436		100.000

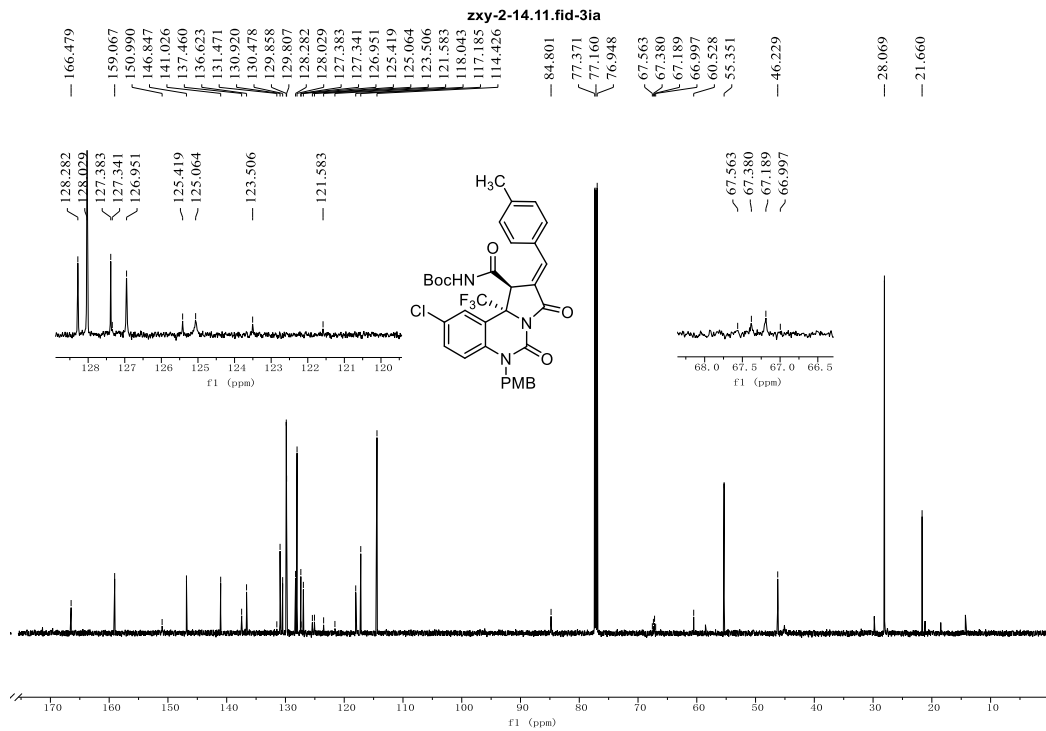
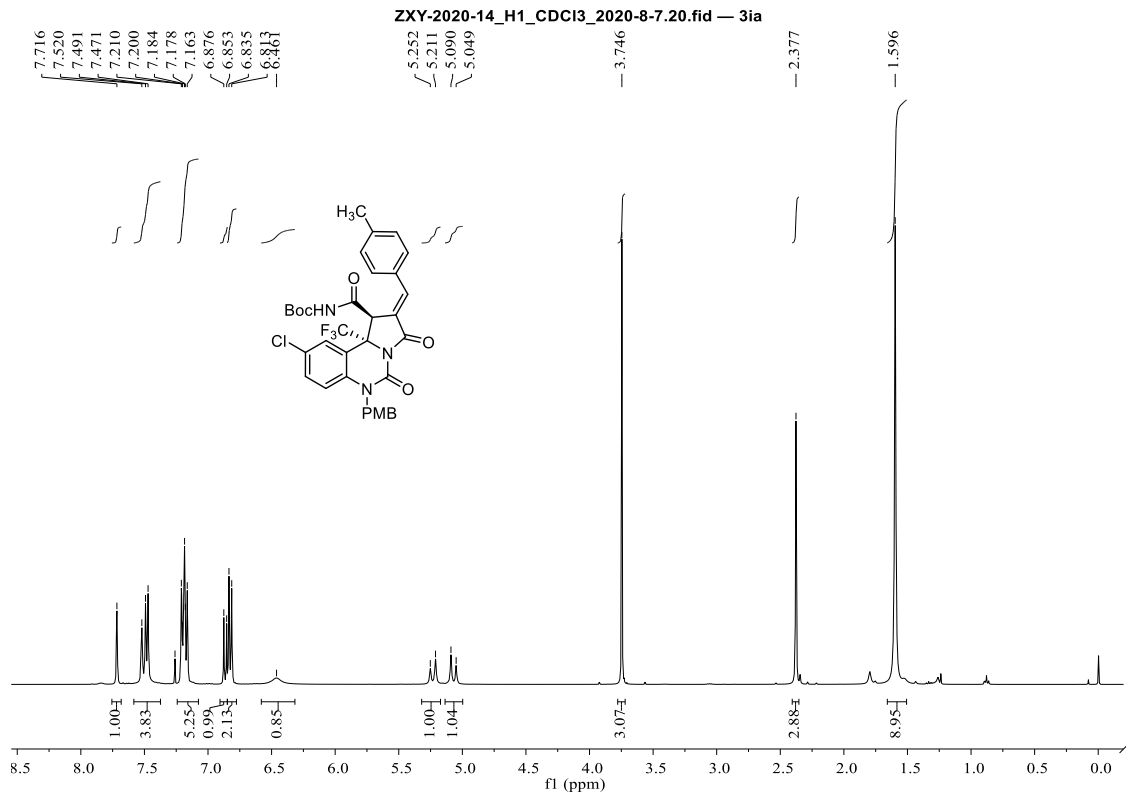


PeakTable

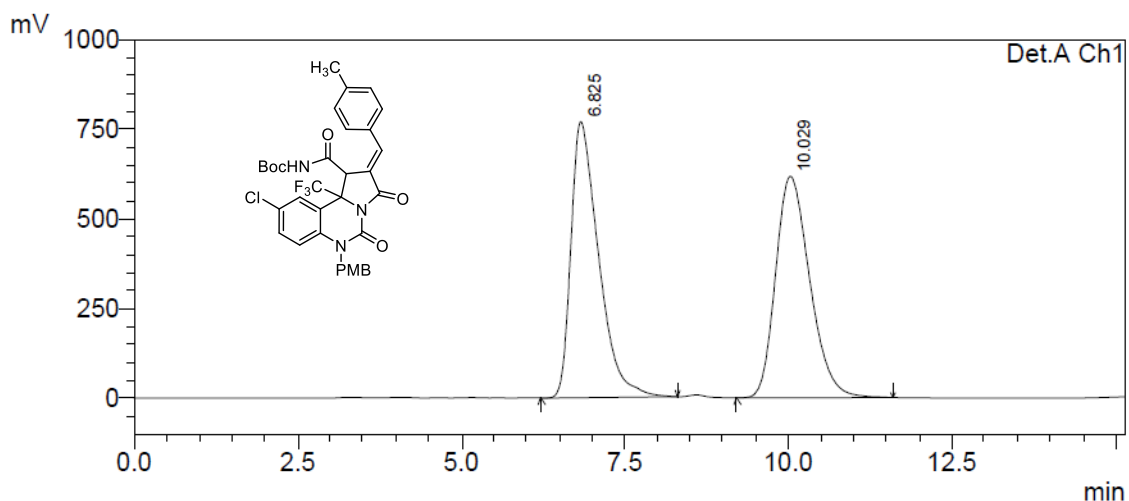
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.943	1089589	60479	1.812
2	9.562	59048095	1690038	98.188
Total		60137683		100.000

# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3ia**



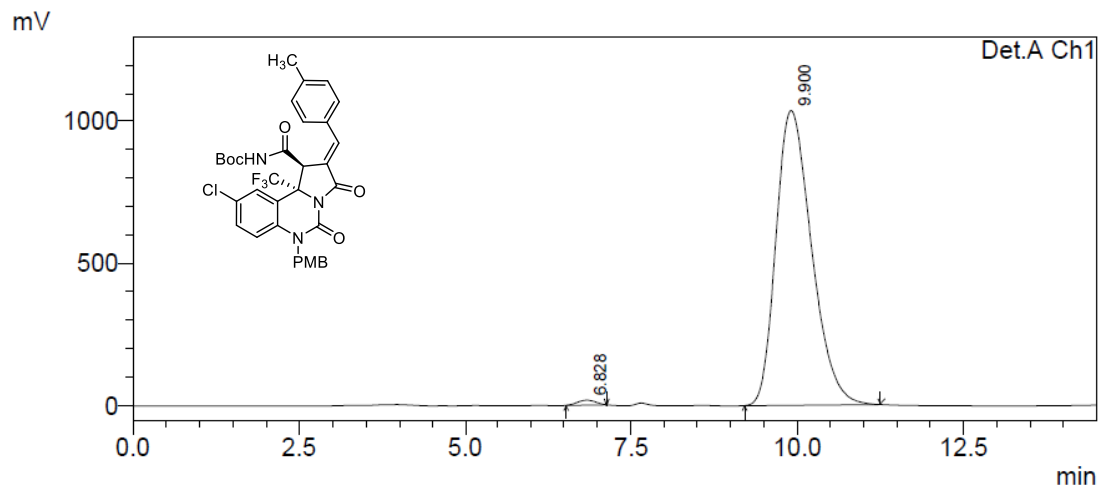
### HPLC of 3ia



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.825	22566967	769015	50.156
2	10.029	22426197	616829	49.844
Total		44993164		100.000

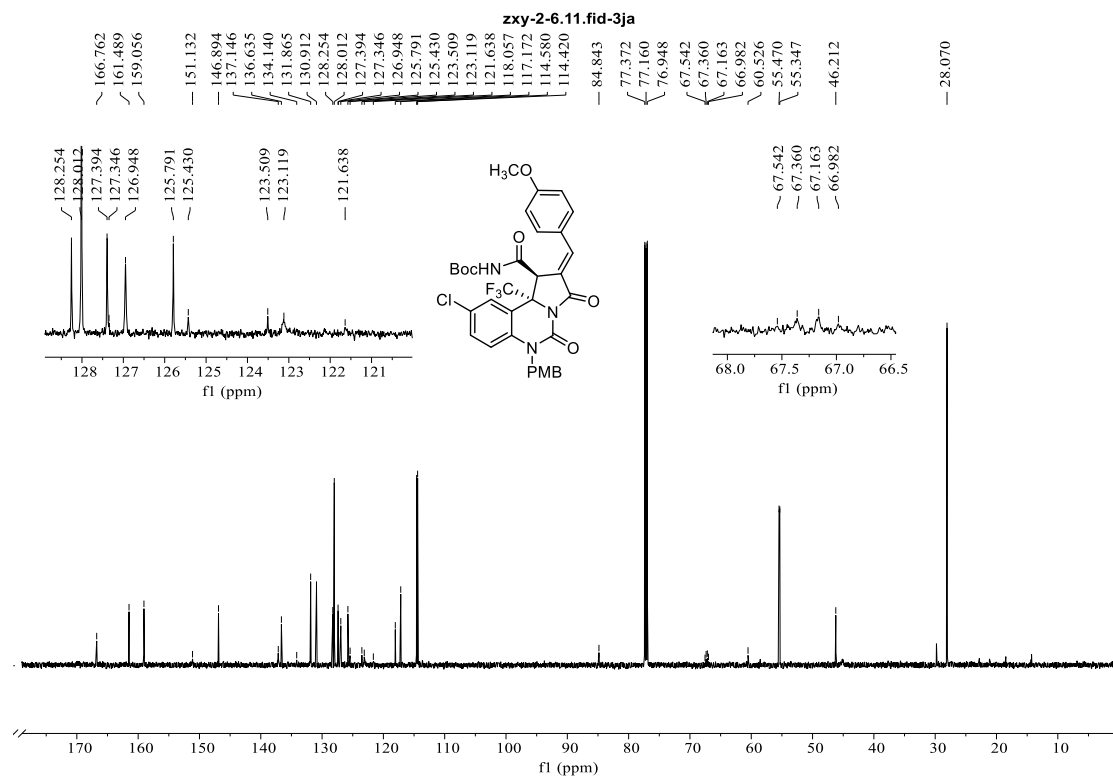
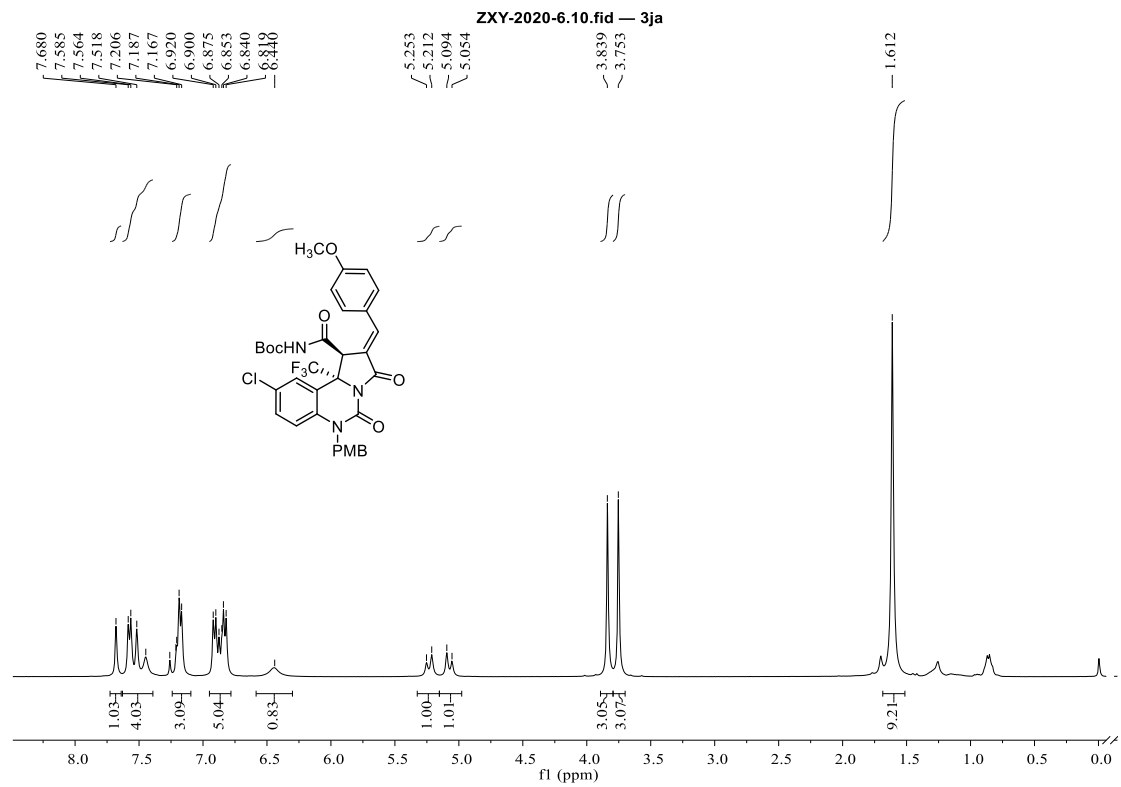


PeakTable

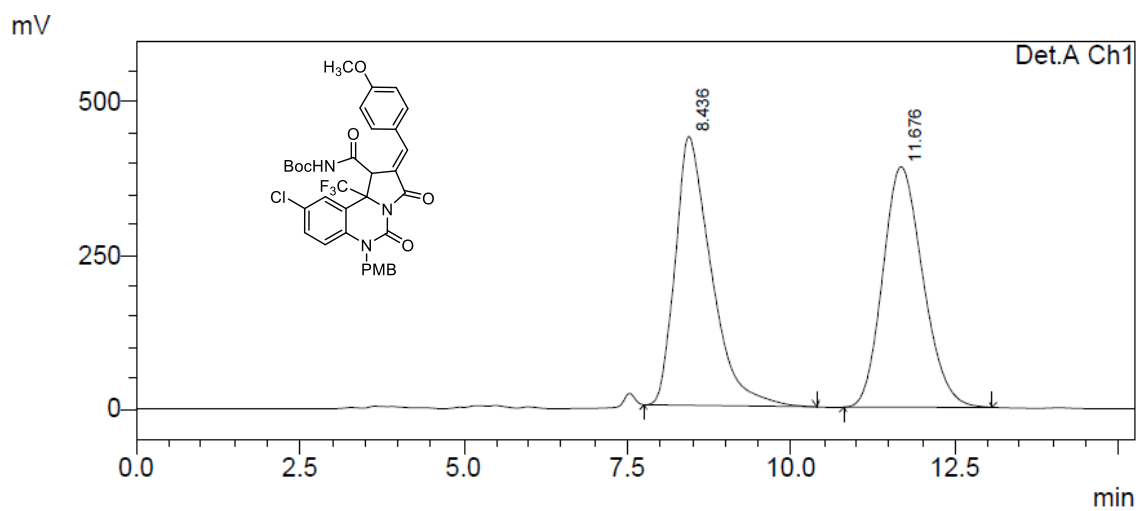
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.828	330028	17541	0.846
2	9.900	38697940	1036705	99.154
Total		39027968		100.000

# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3ja**



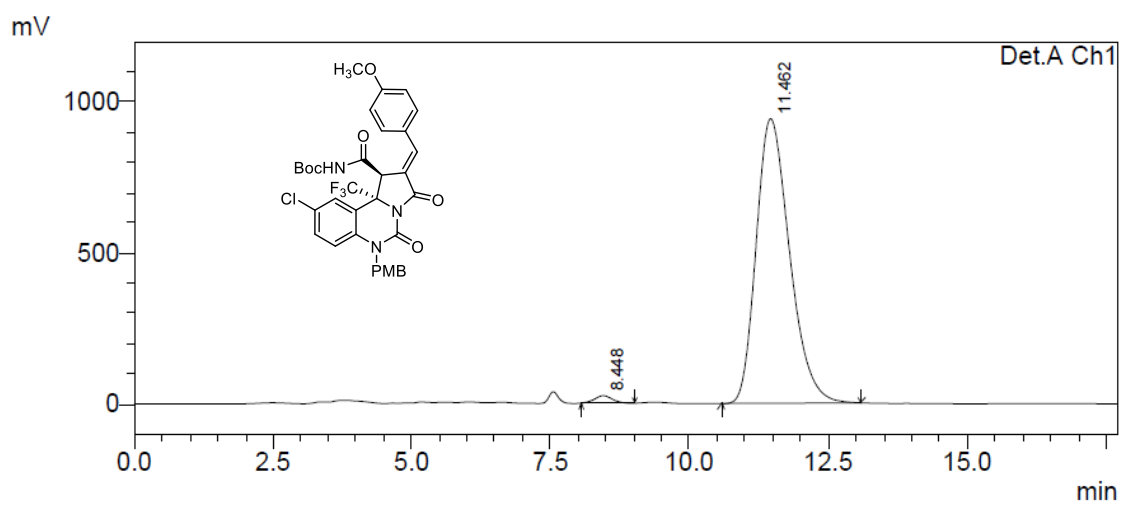
### HPLC of 3ja



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	8.436	16745927	438276	49.987
2	11.676	16754931	392243	50.013
Total		33500858		100.000



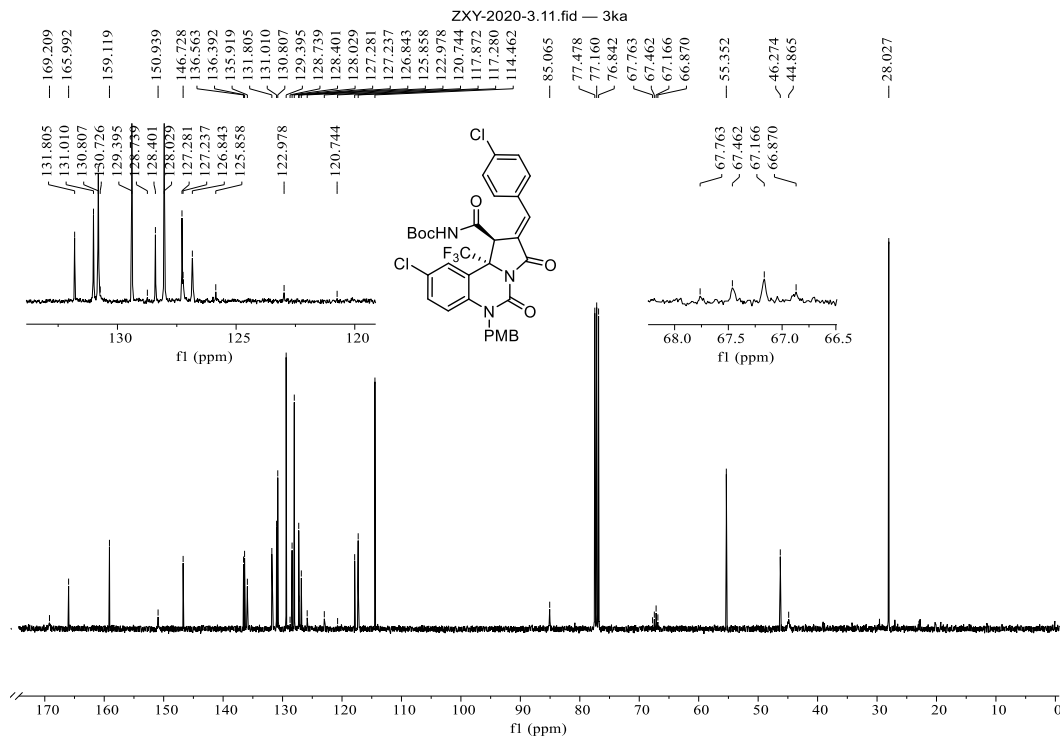
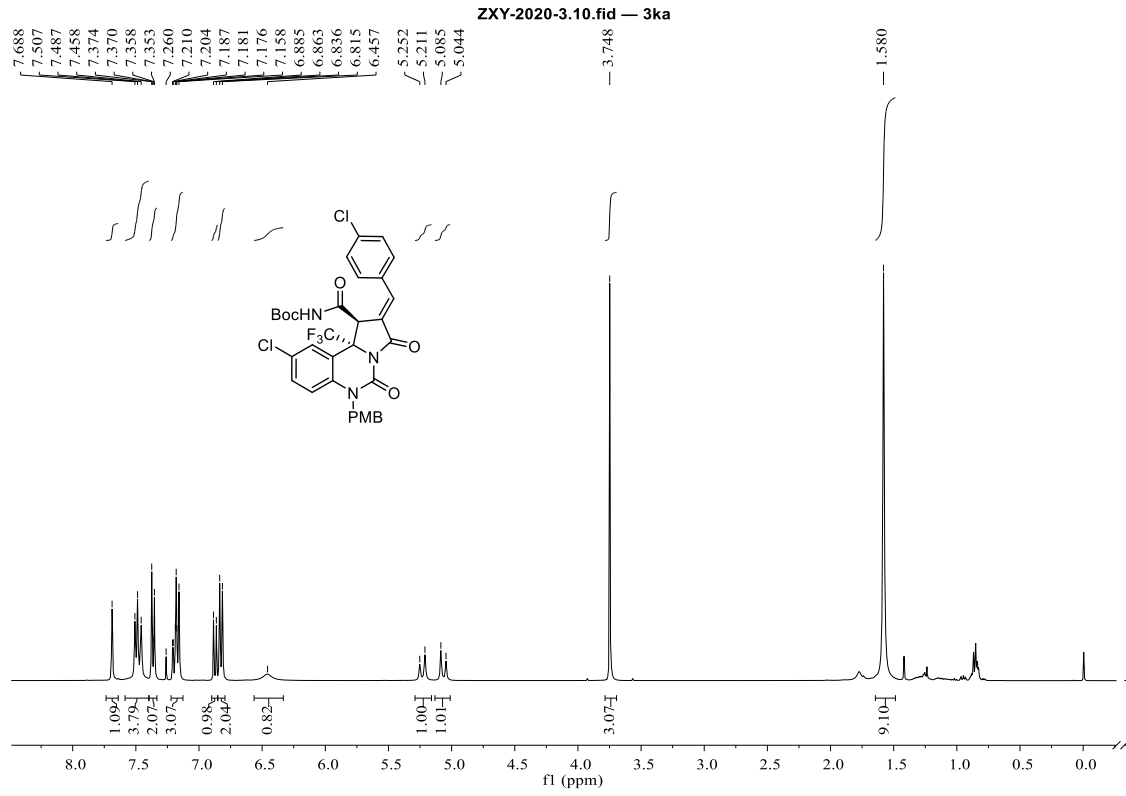
PeakTable

Detector A Ch1 254nm

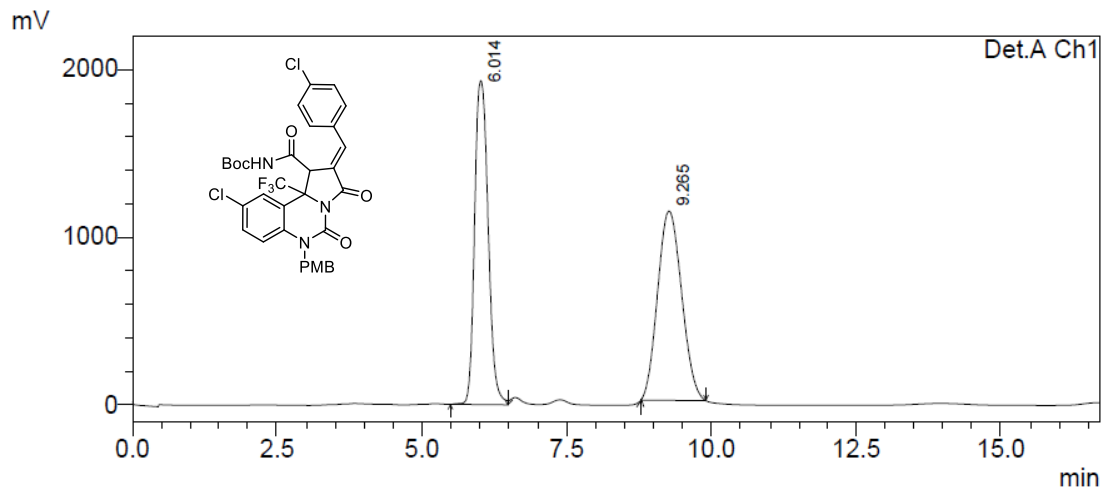
Peak#	Ret. Time	Area	Height	Area %
1	8.448	535349	24655	1.338
2	11.462	39486994	942771	98.662
Total		40022343		100.000



# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3ka**



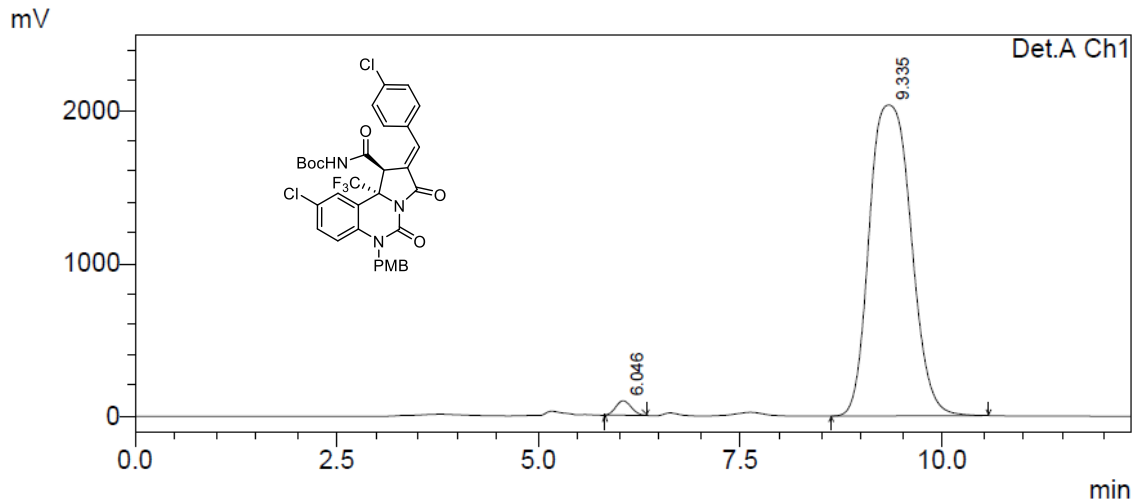
### HPLC of 3ka



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.014	31431175	1930295	49.147
2	9.265	32522799	1127785	50.853
Total		63953974		100.000

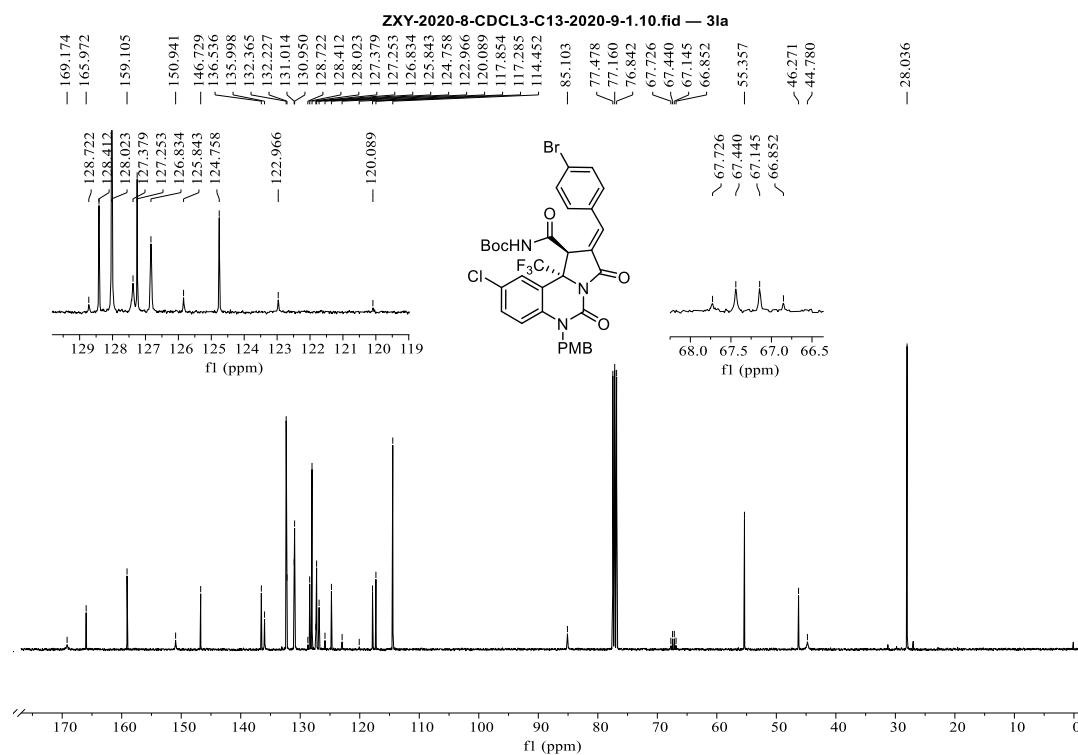
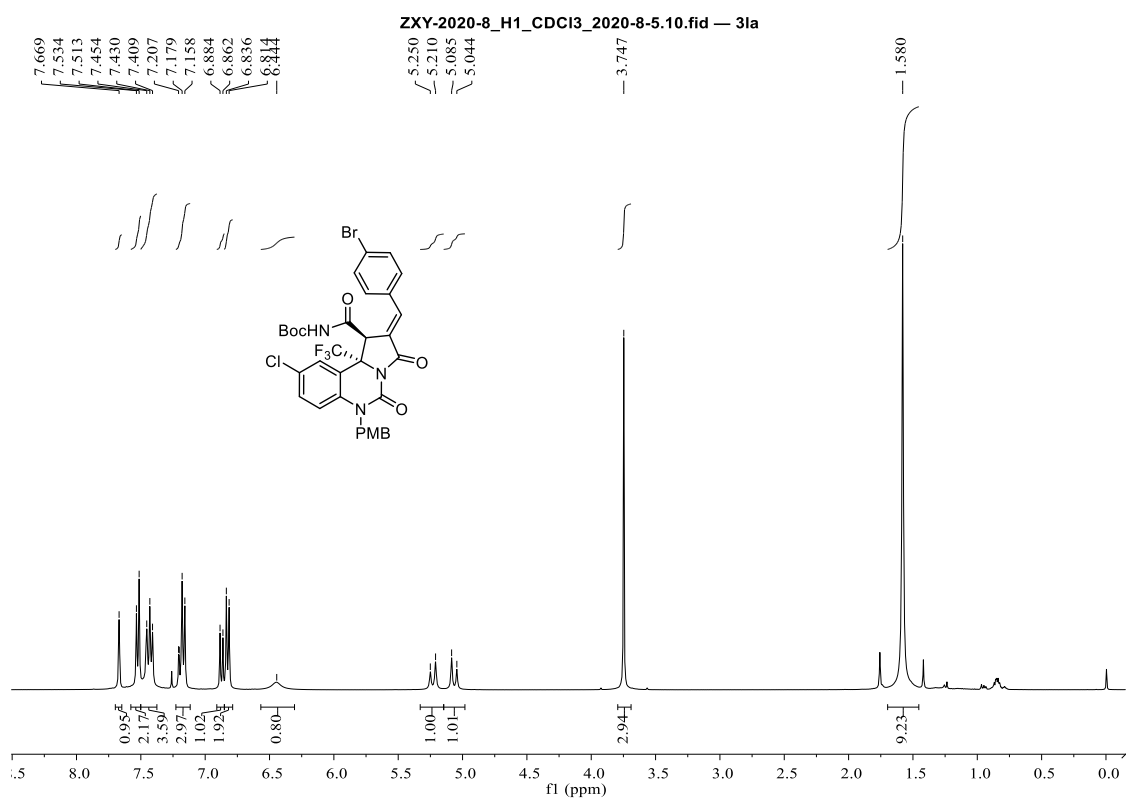


PeakTable

Detector A Ch1 254nm

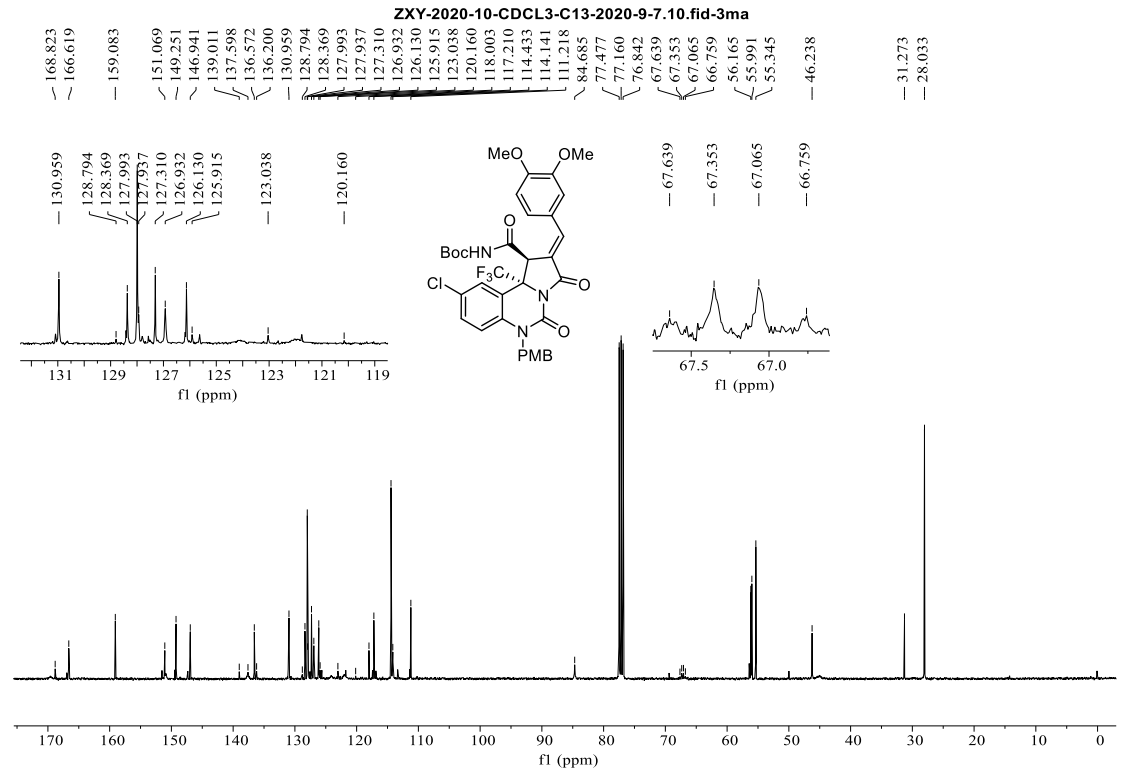
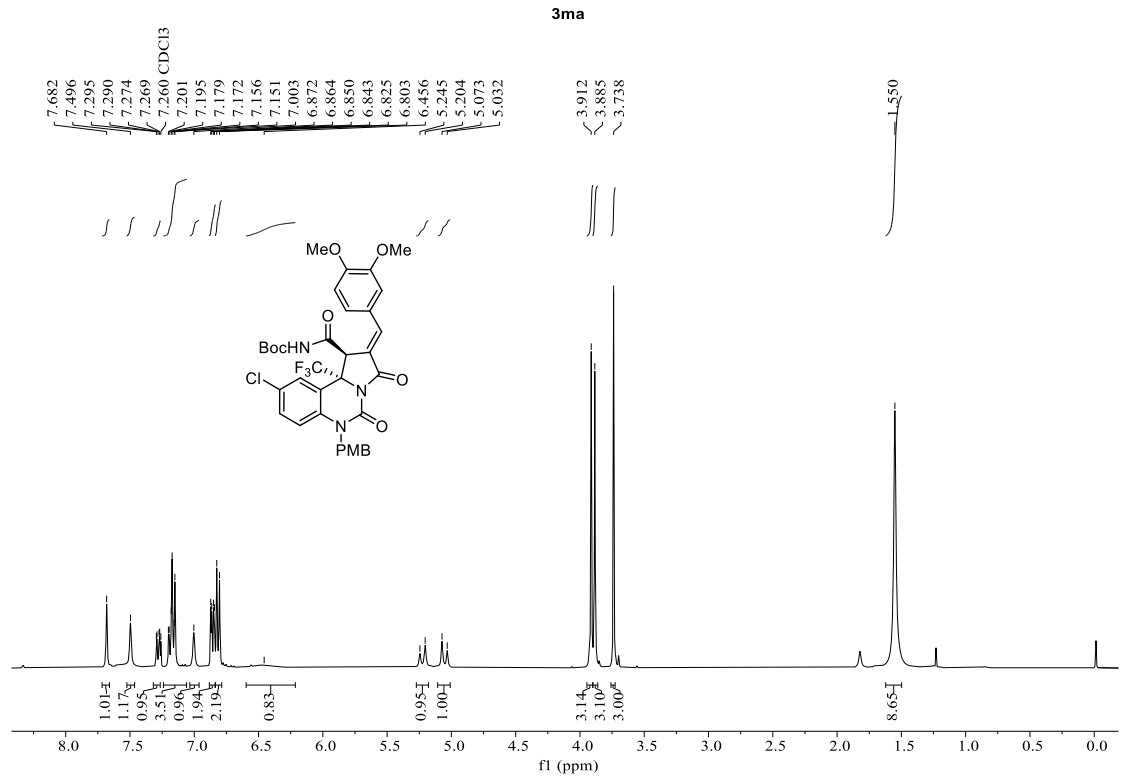
Peak#	Ret. Time	Area	Height	Area %
1	6.046	1258643	94736	1.688
2	9.335	73320637	2034579	98.312
Total		74579280		100.000

# <sup>1</sup>H and <sup>13</sup>C NMR of 3a

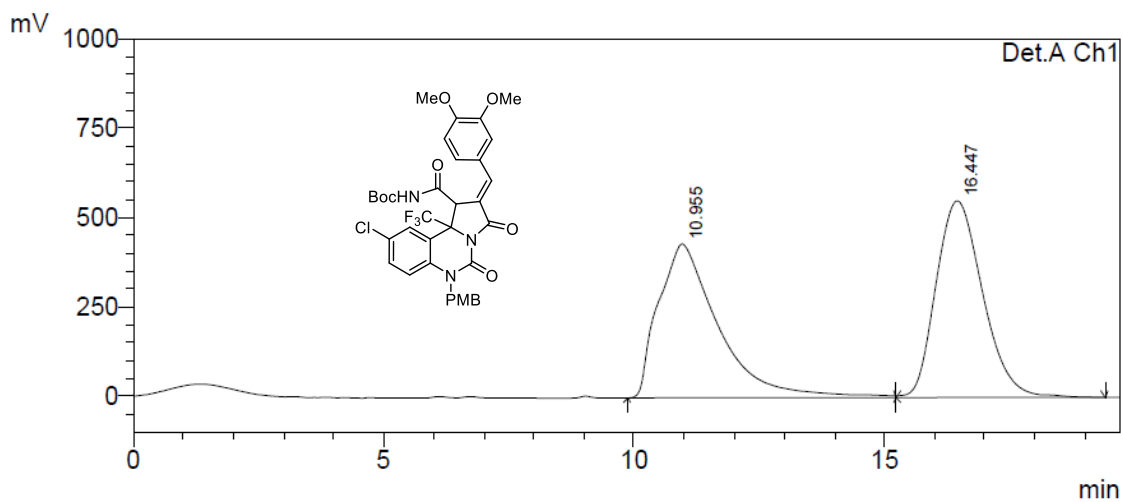




<sup>1</sup>H and <sup>13</sup>C NMR of **3ma**



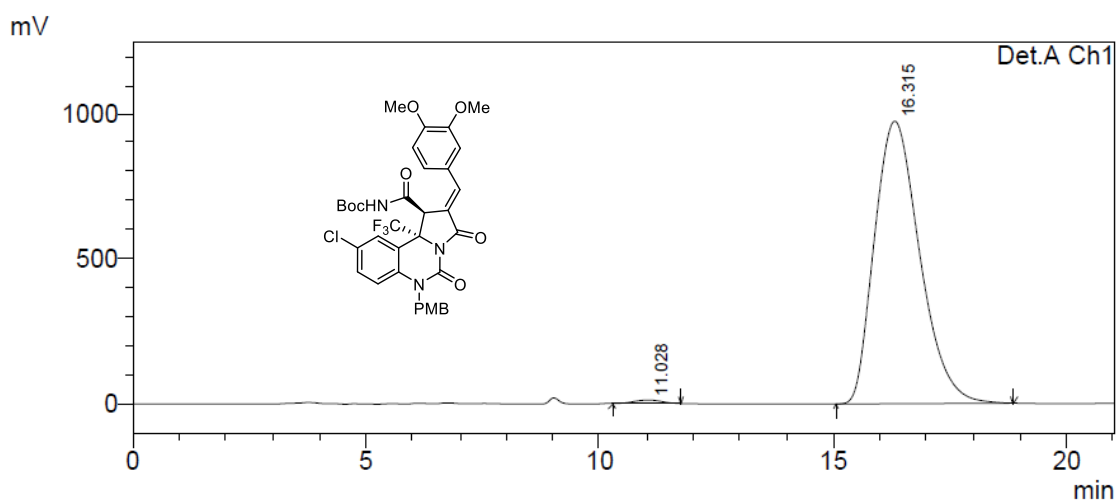
### HPLC of 3ma



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	10.955	35753396	429922	50.122
2	16.447	35579311	549598	49.878
Total		71332707		100.000

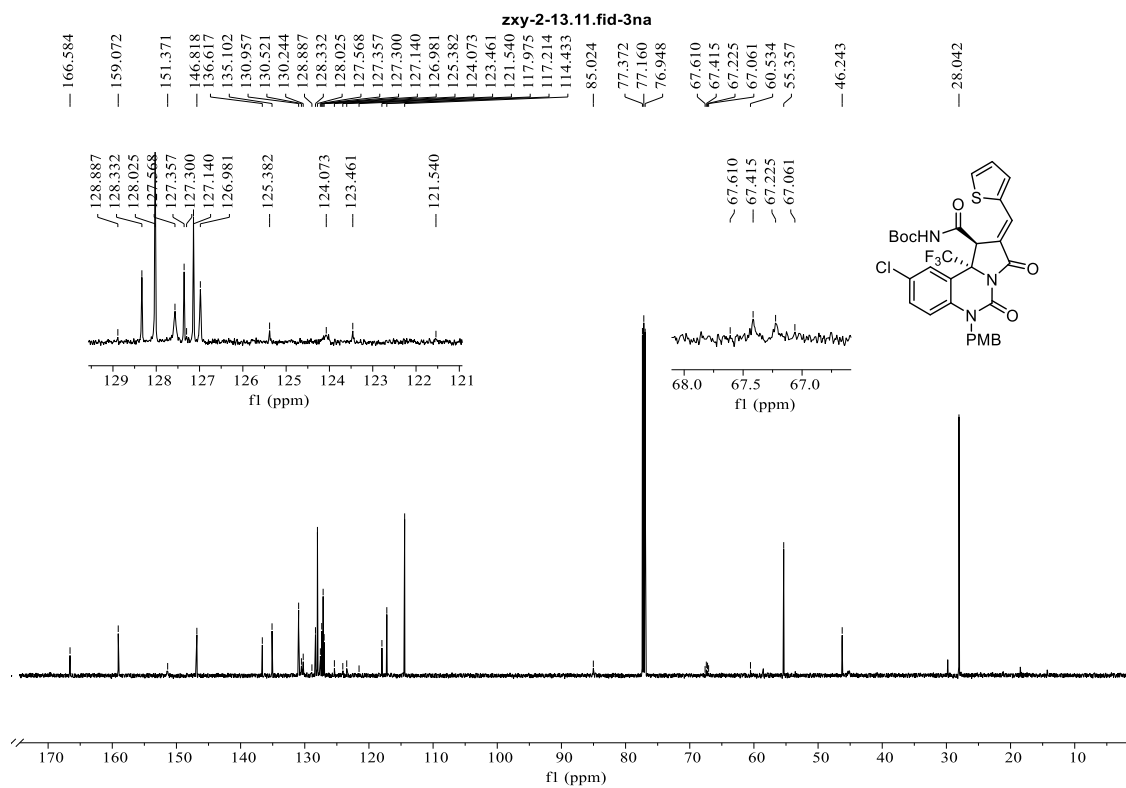
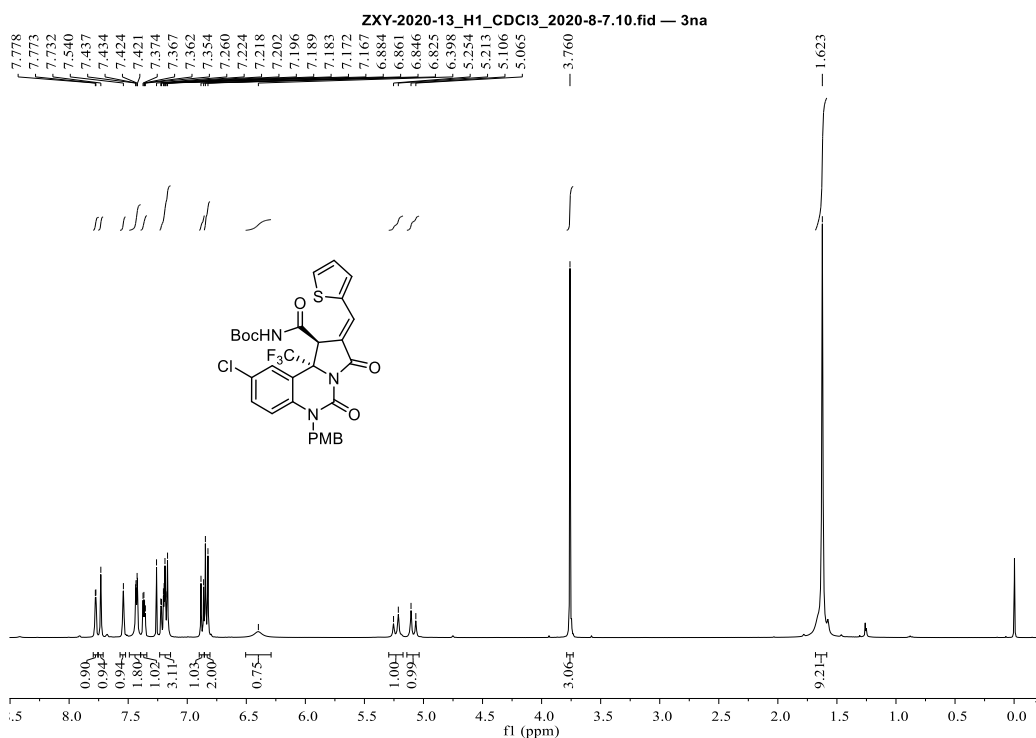


PeakTable

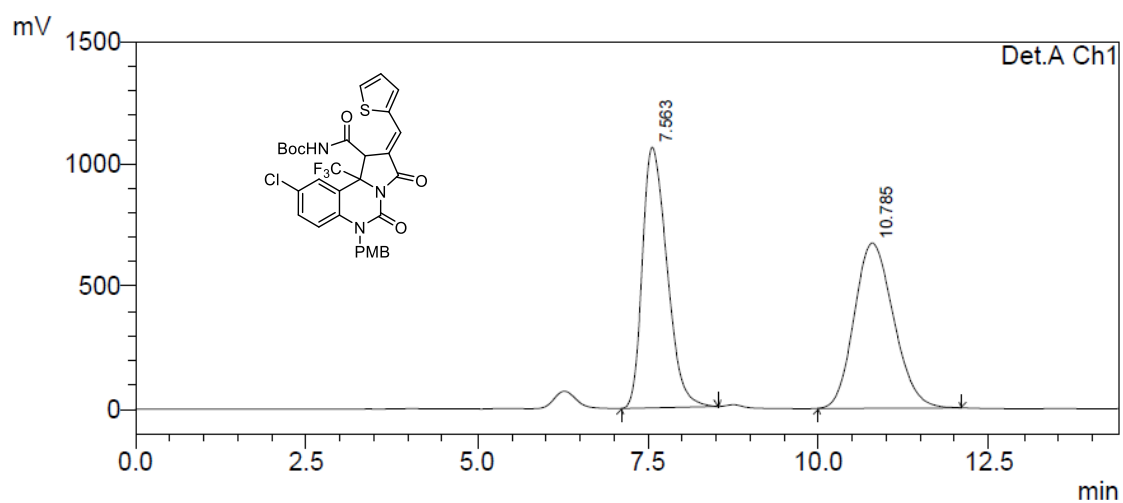
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	11.028	468367	11272	0.708
2	16.315	65663297	973900	99.292
Total		66131664		100.000

<sup>1</sup>H and <sup>13</sup>C NMR of 3na



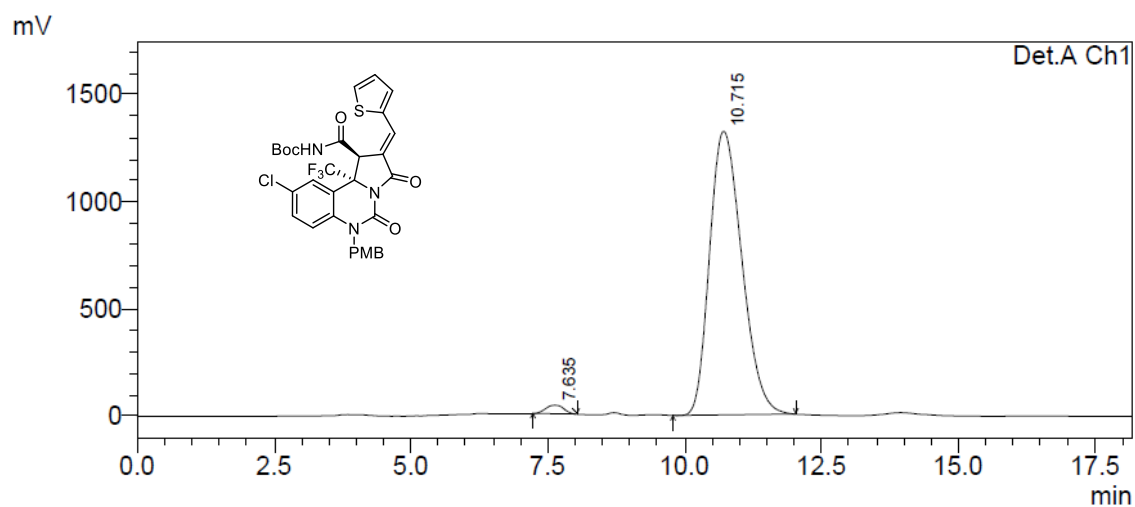
### HPLC of 3na



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	7.563	26625548	1063108	49.629
2	10.785	27023835	673502	50.371
Total		53649383		100.000



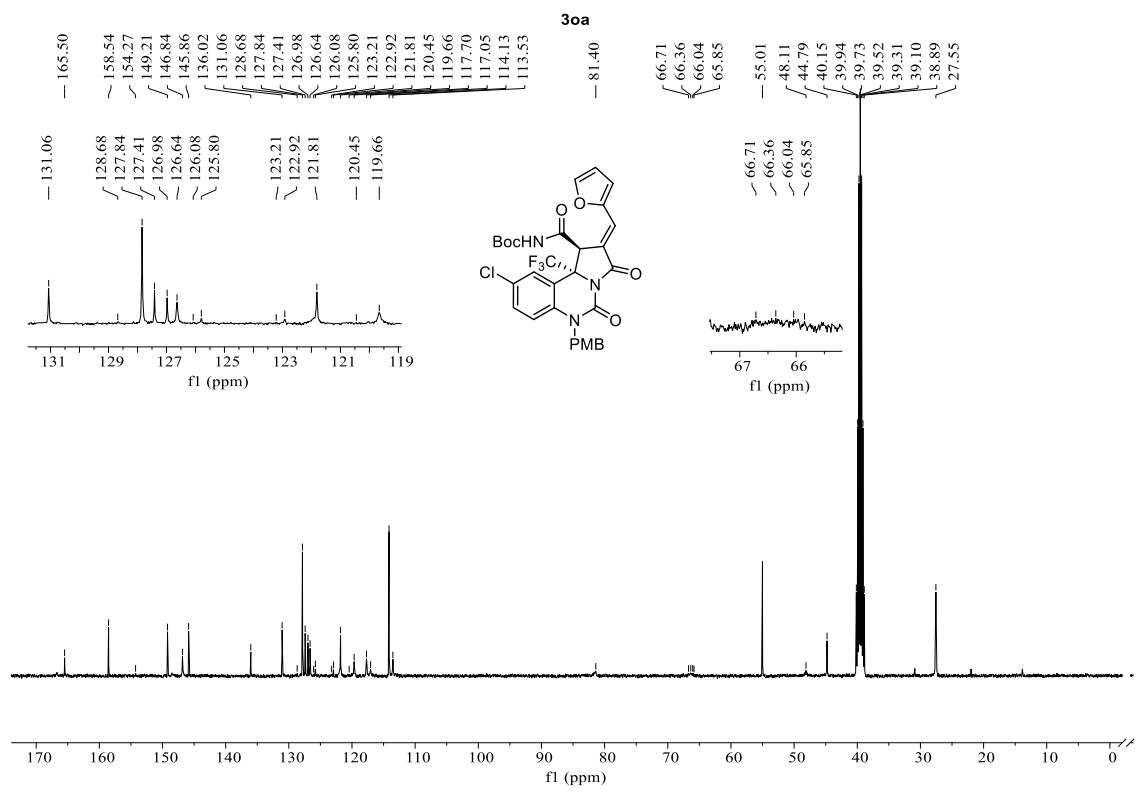
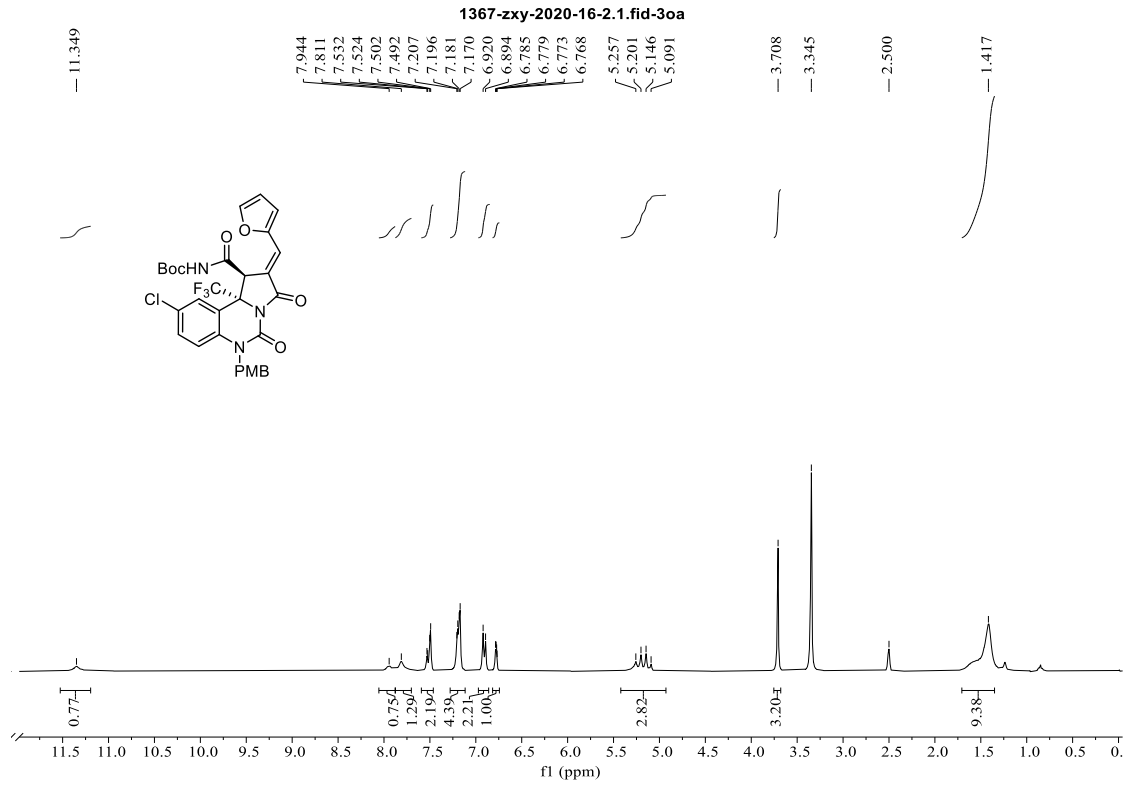
PeakTable

Detector A Ch1 254nm

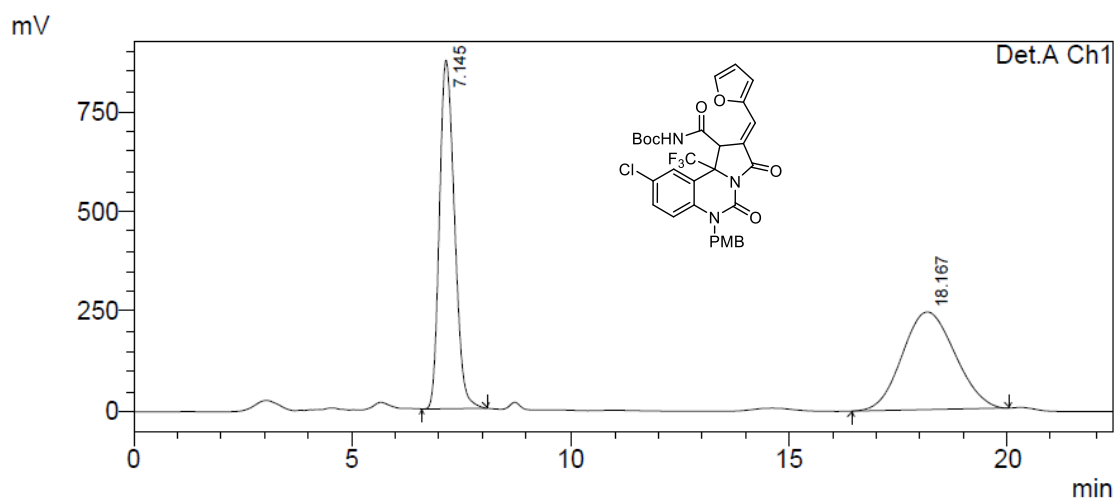
Peak#	Ret. Time	Area	Height	Area %
1	7.635	924331	39757	1.673
2	10.715	54324546	1323635	98.327
Total		55248877		100.000



# <sup>1</sup>H and <sup>13</sup>C NMR of 30a



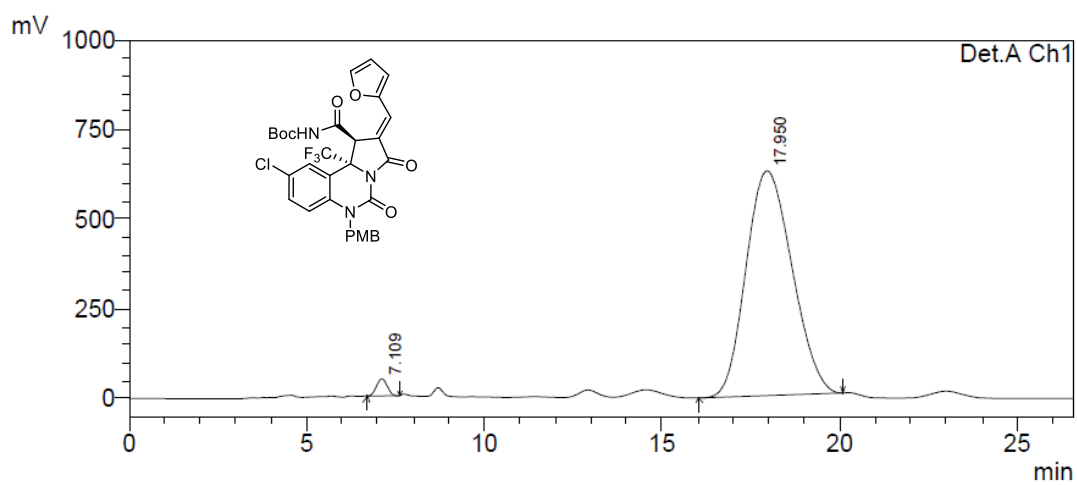
### HPLC of 30a



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	7.145	20841097	870152	50.463
2	18.167	20458464	243662	49.537
Total		41299561		100.000

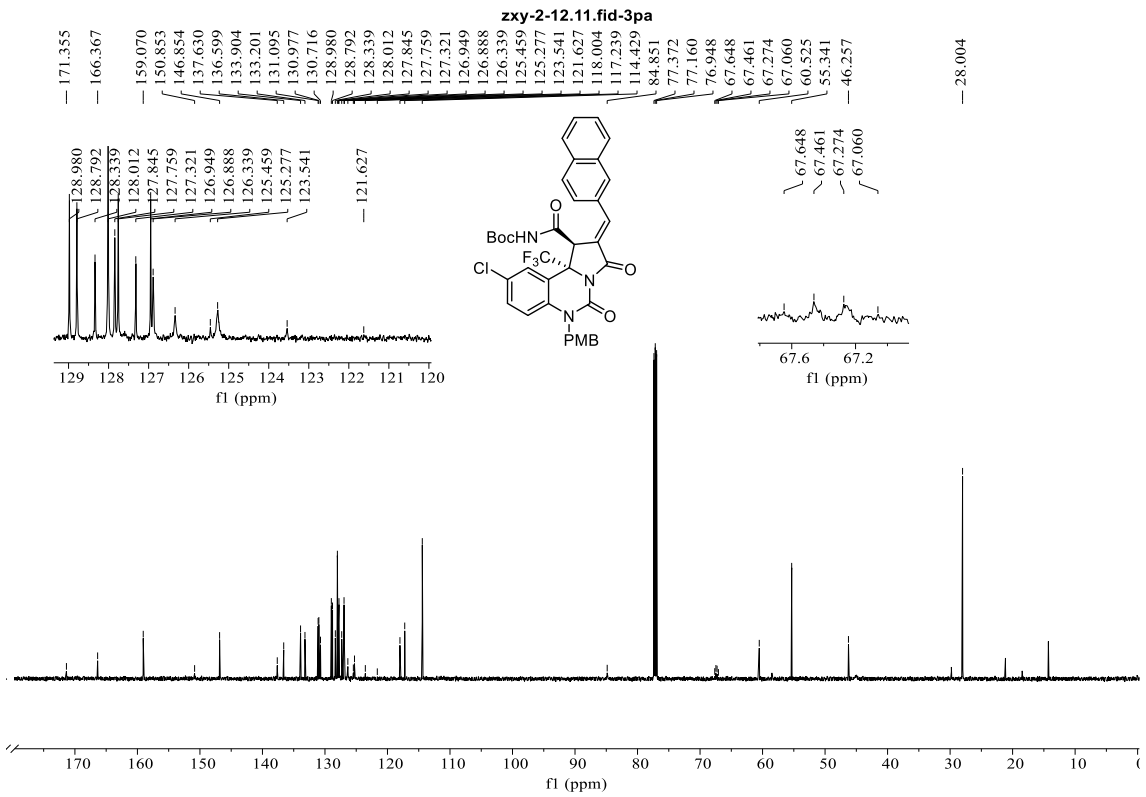
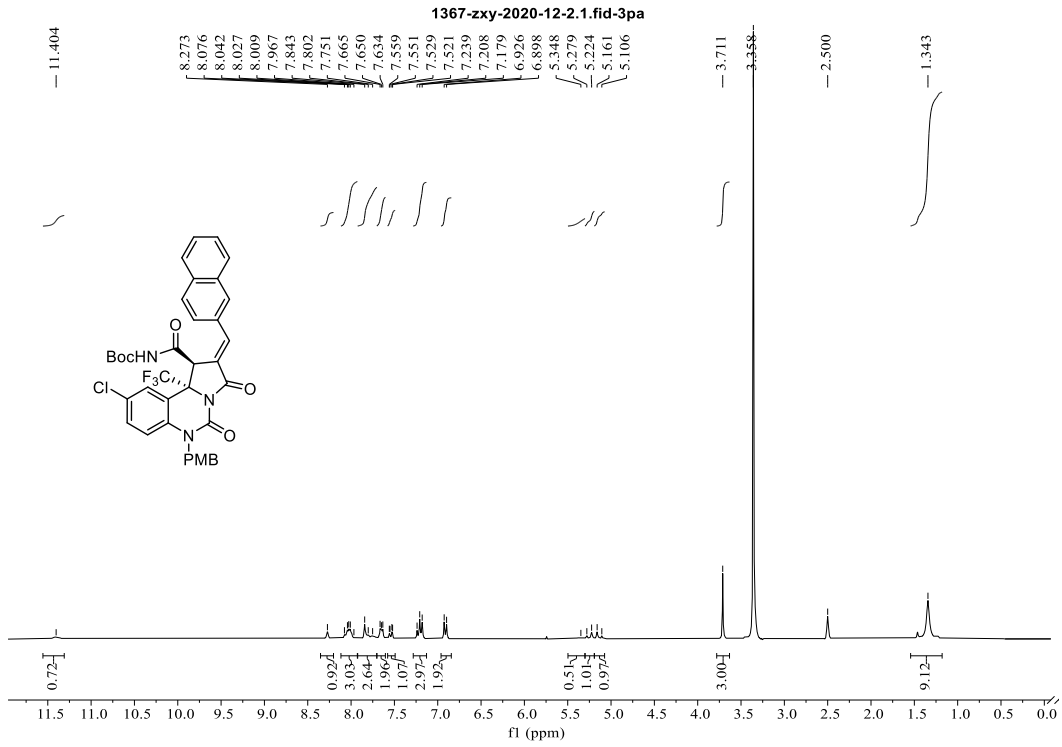


PeakTable

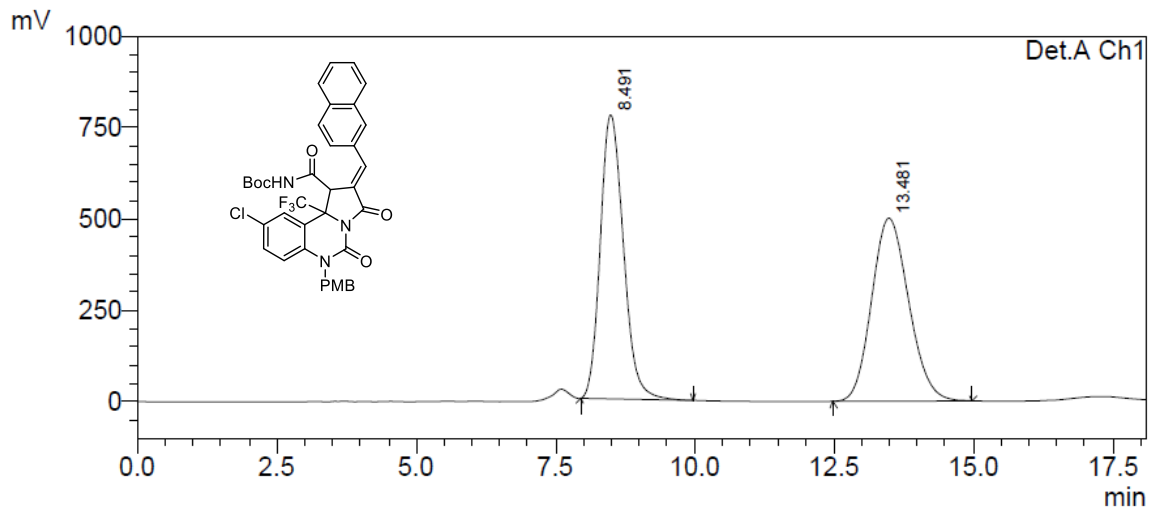
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	7.109	987435	47524	1.720
2	17.950	56408565	626373	98.280
Total		57396000		100.000

<sup>1</sup>H and <sup>13</sup>C NMR of 3pa



### HPLC of 3pa

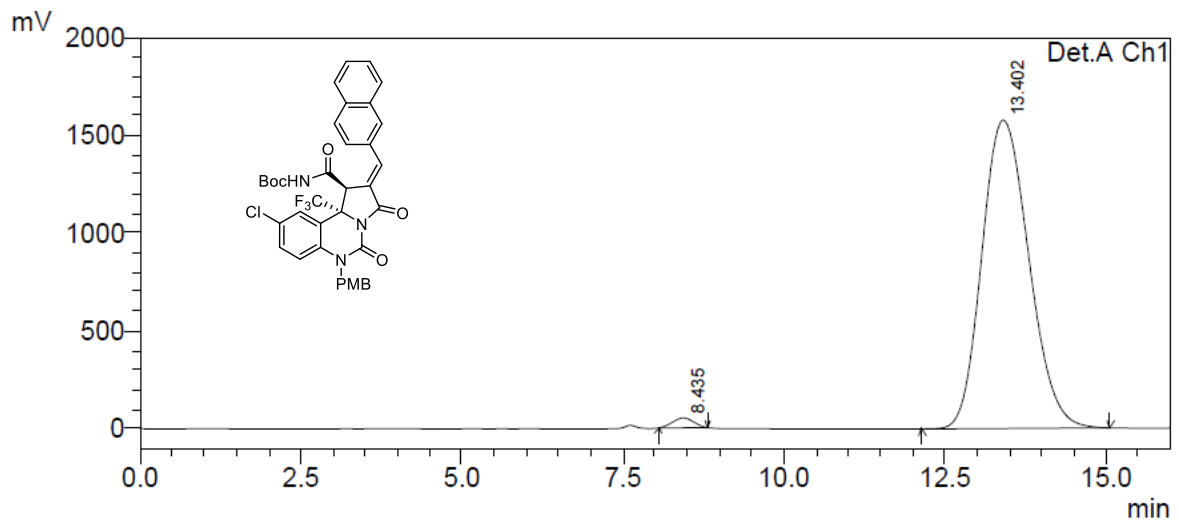


1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	8.491	22485736	776642	49.300
2	13.481	23124533	500141	50.700
Total		45610269		100.000



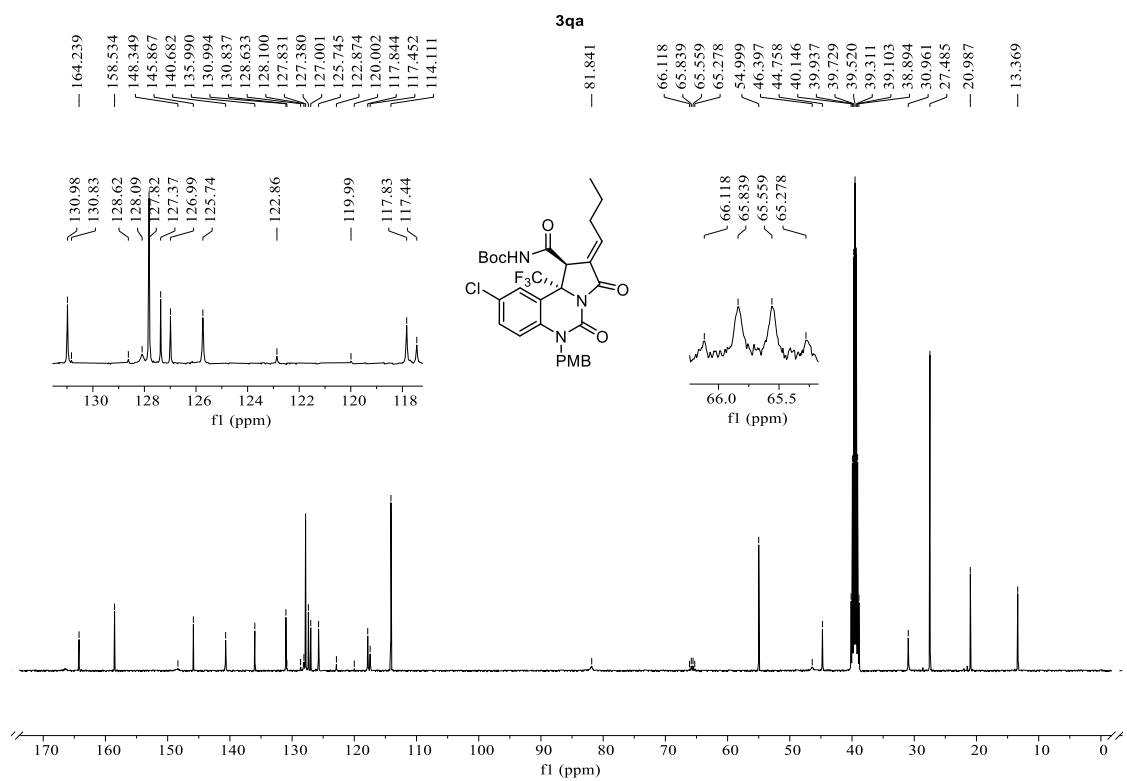
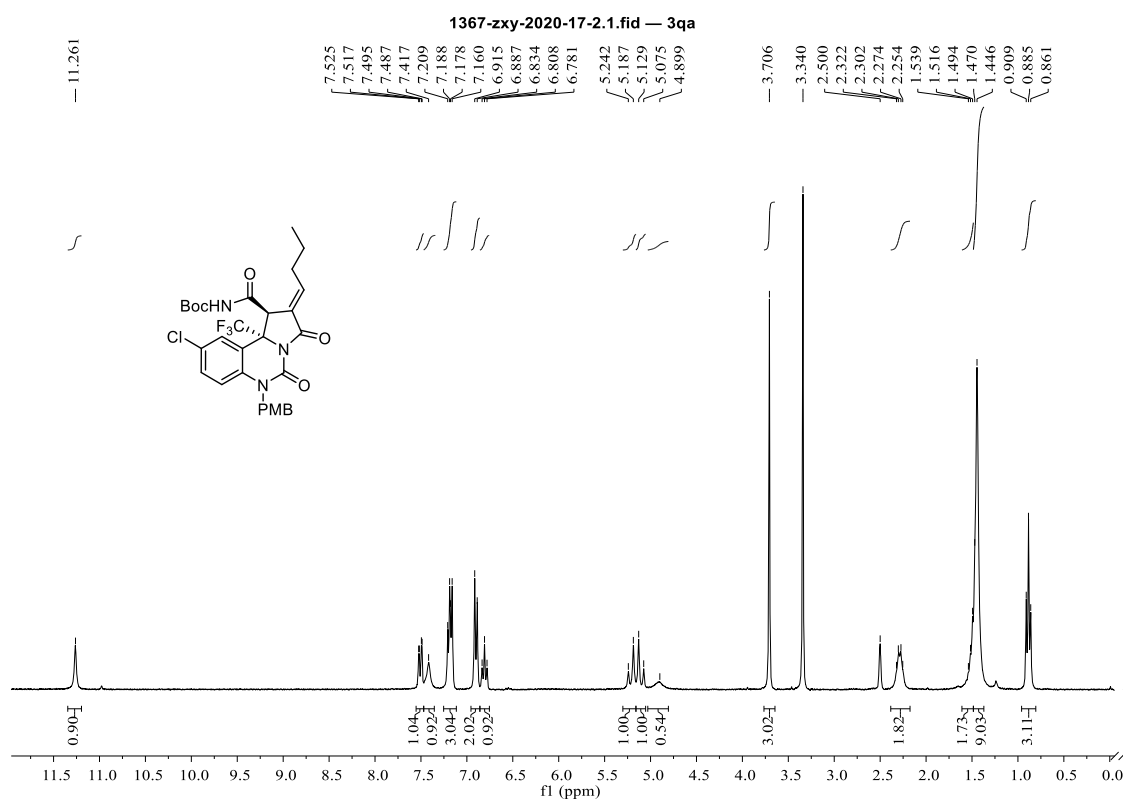
1 Det.A Ch1/254nm

PeakTable

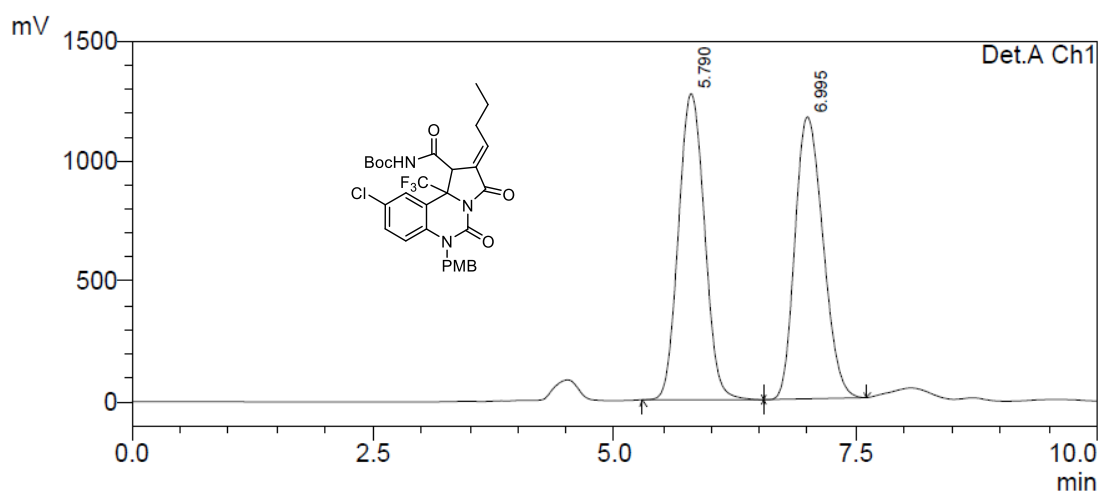
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	8.435	1149537	49850	1.416
2	13.402	80034383	1575236	98.584
Total		81183920		100.000

<sup>1</sup>H and <sup>13</sup>C NMR of 3qa



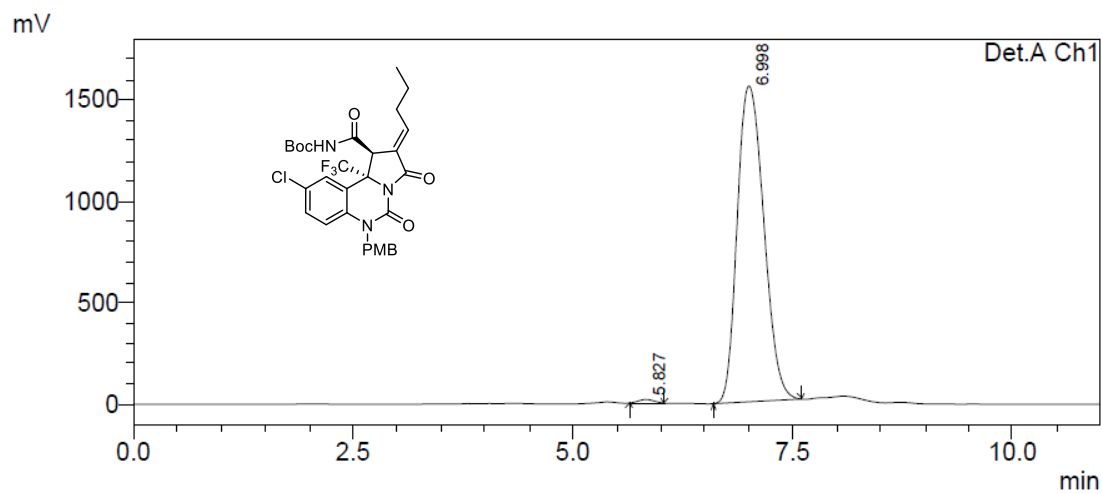
### HPLC of 3qa



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	5.790	23929126	1272271	50.175
2	6.995	23762245	1171535	49.825
Total		47691371		100.000

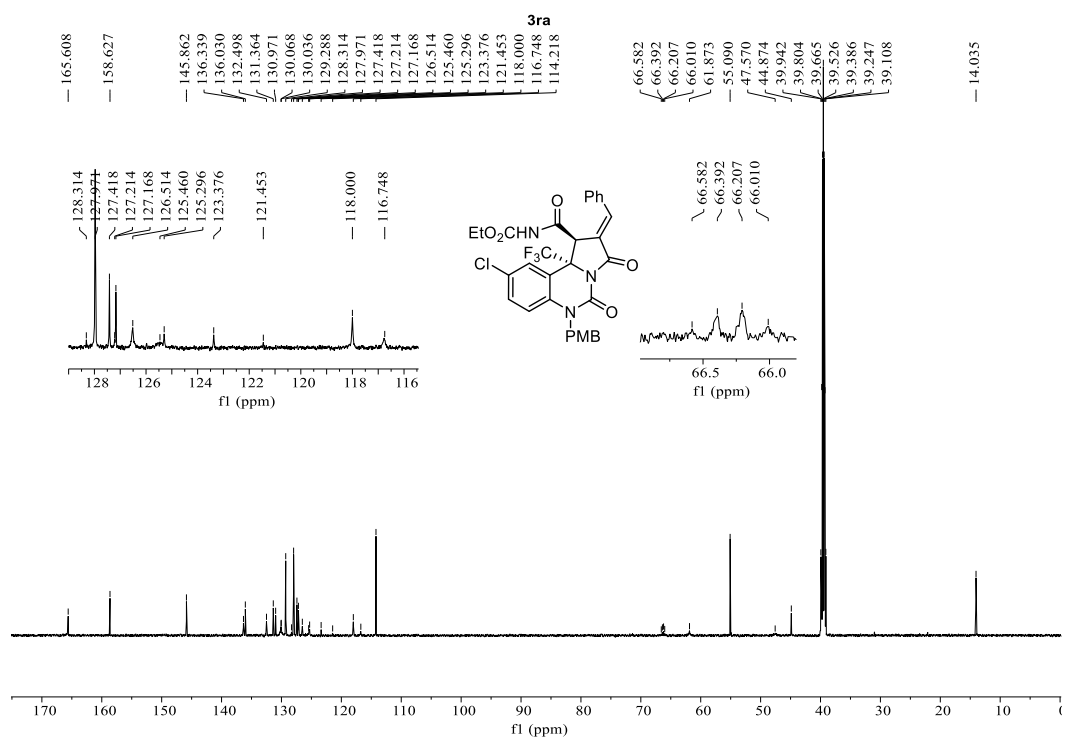
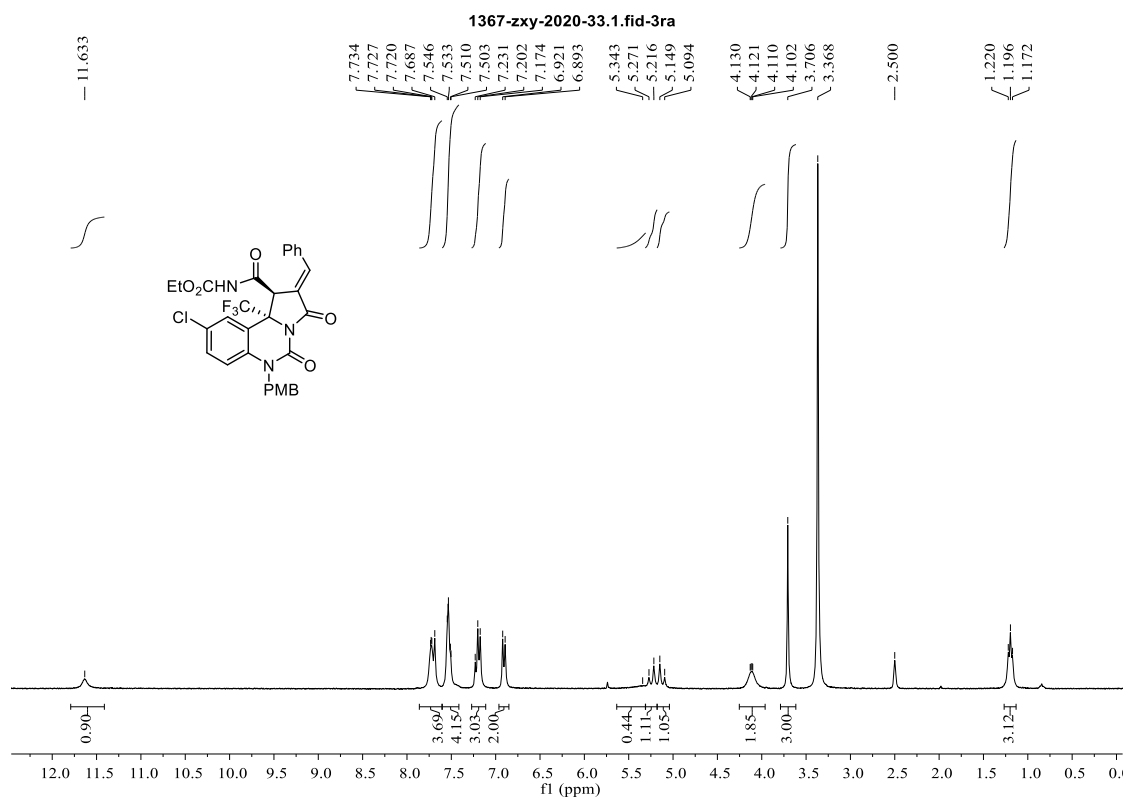


PeakTable

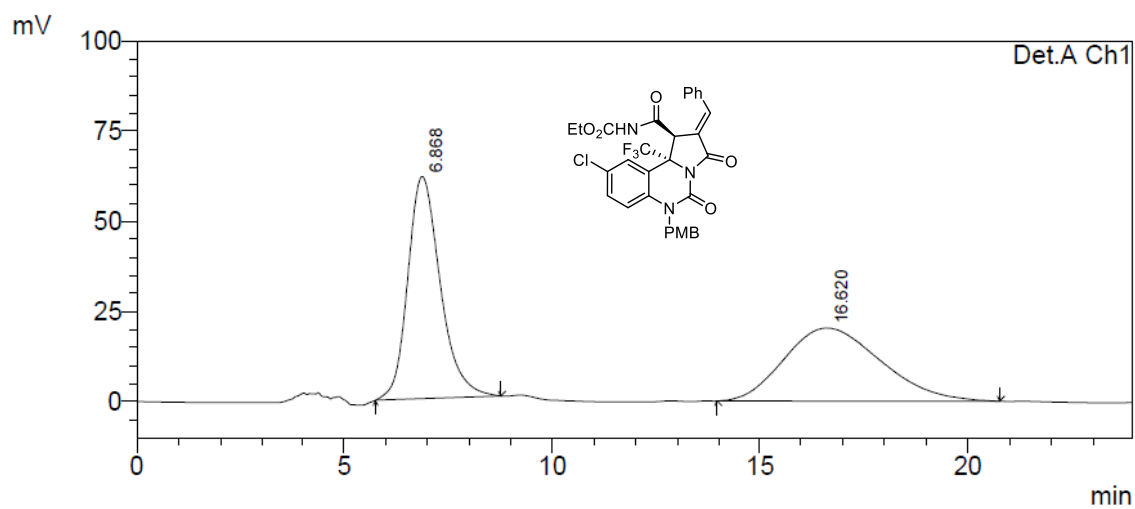
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	5.827	218947	17516	0.665
2	6.998	32729147	1555212	99.335
Total		32948094		100.000

<sup>1</sup>H and <sup>13</sup>C NMR of **3ra**



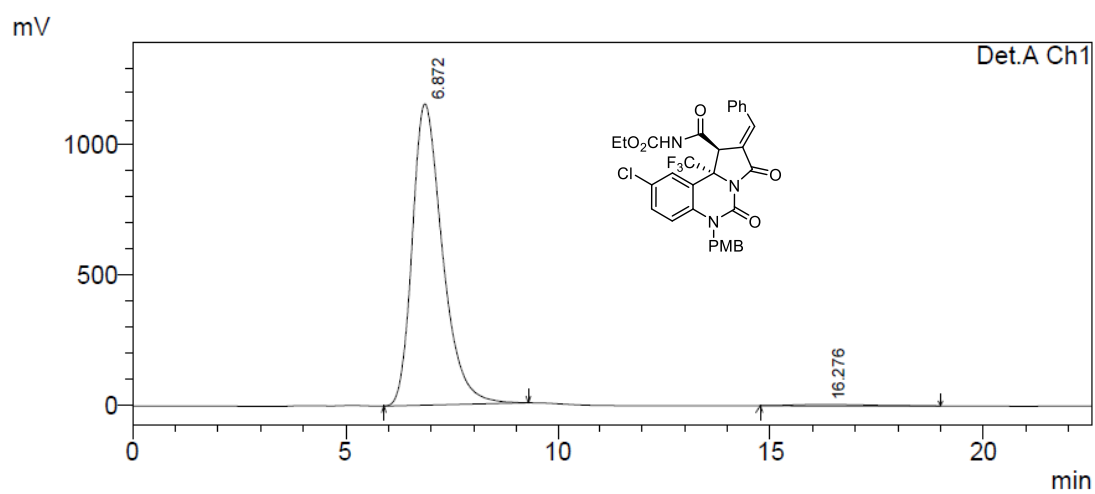
### HPLC of 3ra



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.868	3353537	61507	50.553
2	16.620	3280189	20283	49.447
Total		6633727		100.000



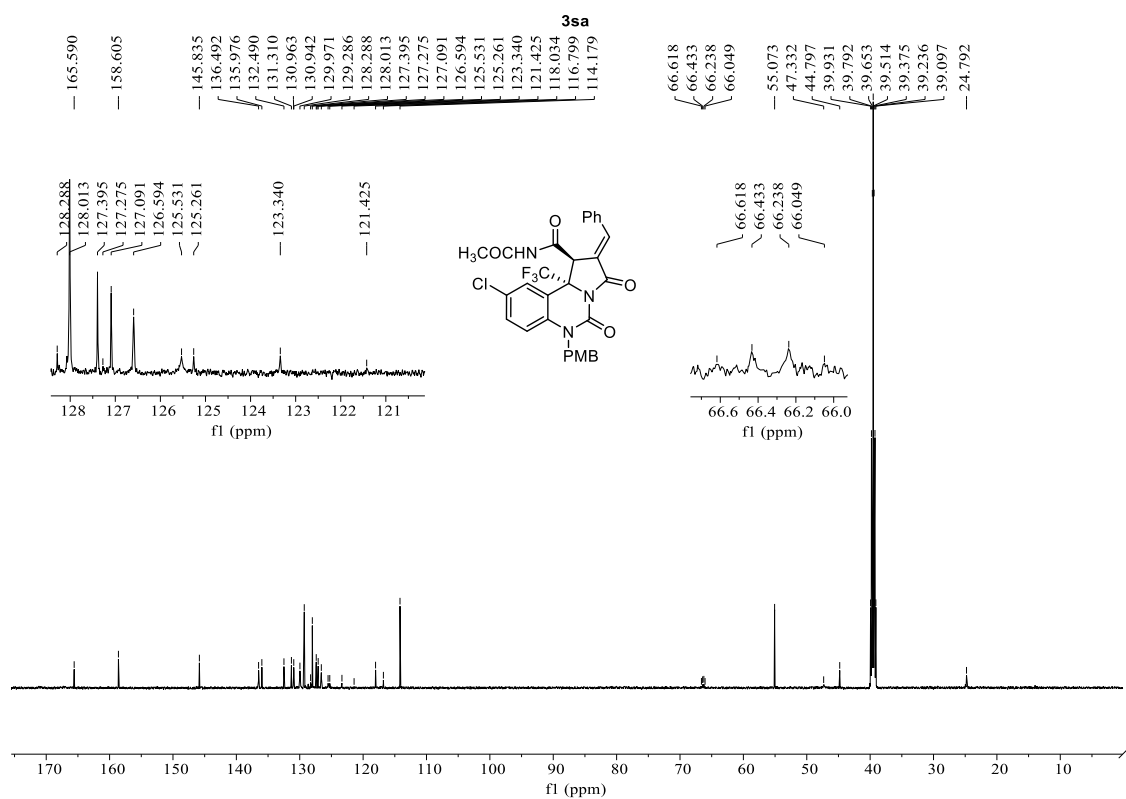
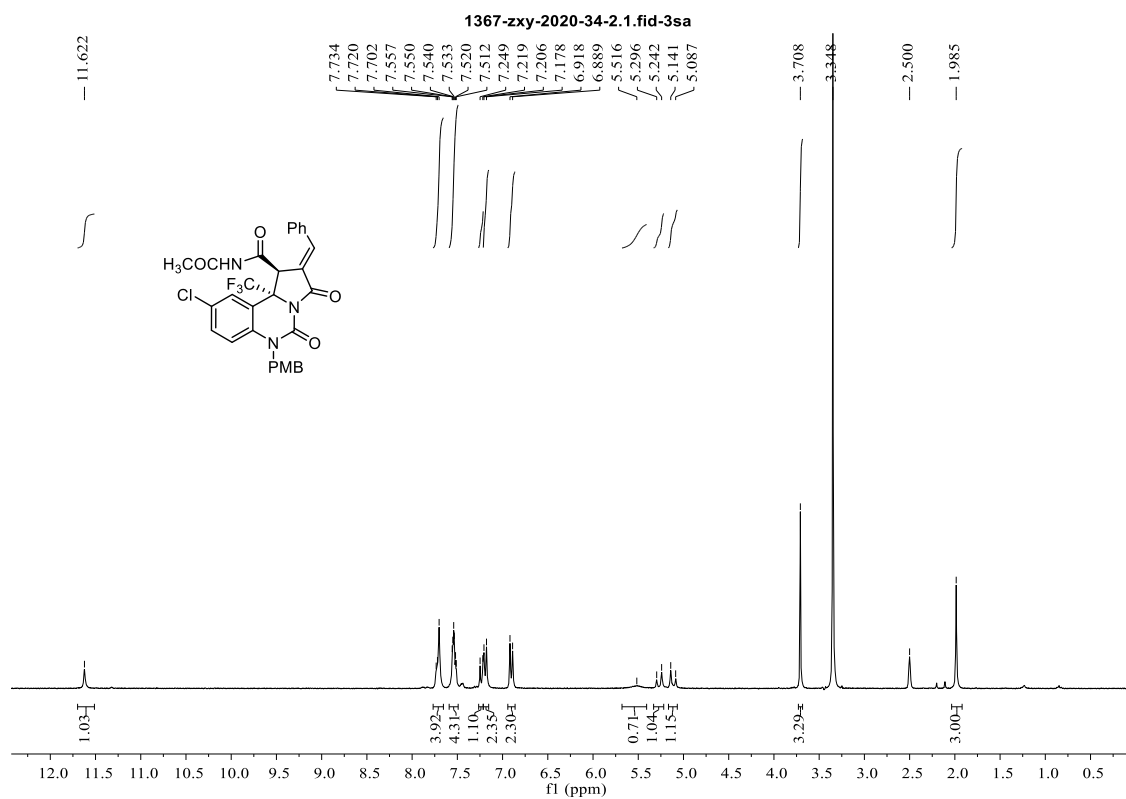
PeakTable

Detector A Ch1 254nm

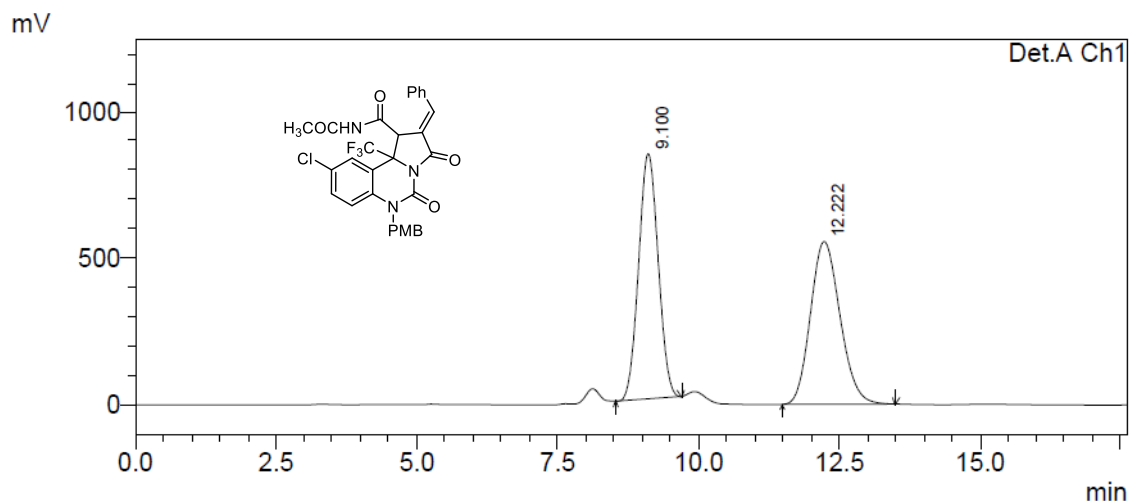
Peak#	Ret. Time	Area	Height	Area %
1	6.872	57169139	1156695	98.720
2	16.276	741002	5532	1.280
Total		57910141		100.000



# <sup>1</sup>H and <sup>13</sup>C NMR of 3sa



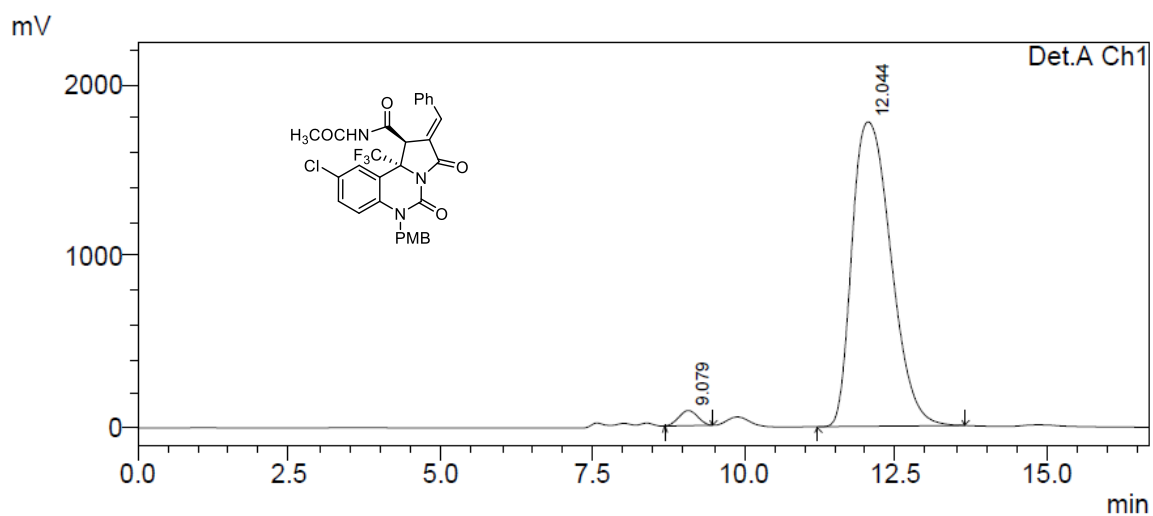
### HPLC of 3sa



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	9.100	20178066	836762	49.815
2	12.222	20328063	555841	50.185
Total		40506129		100.000

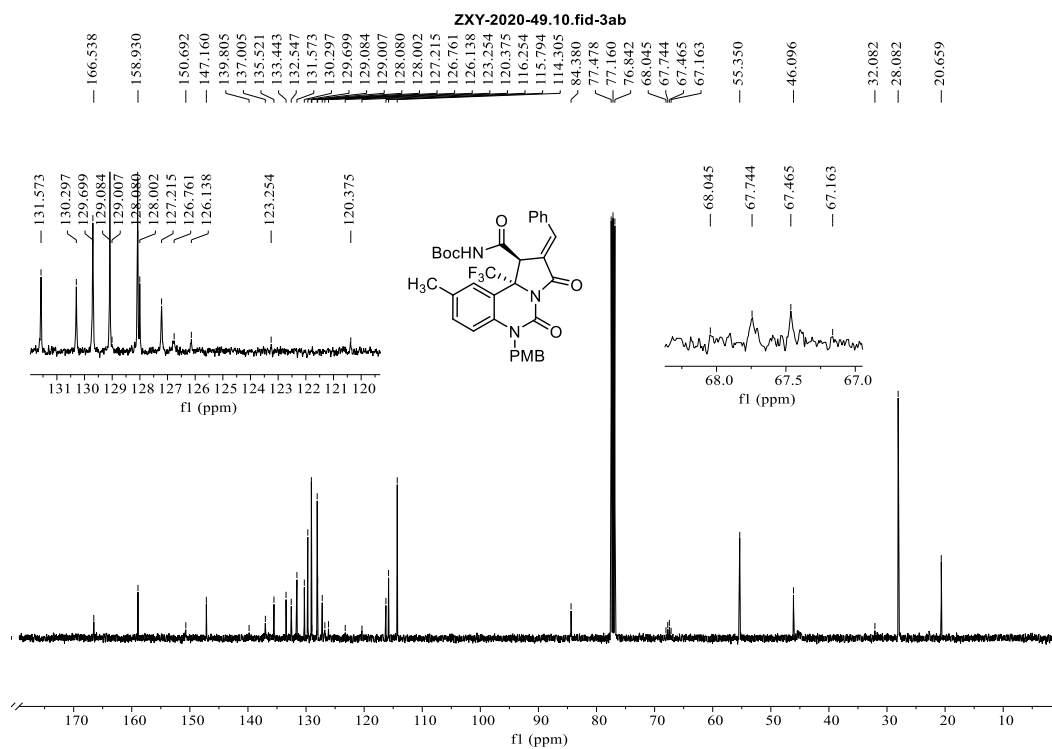
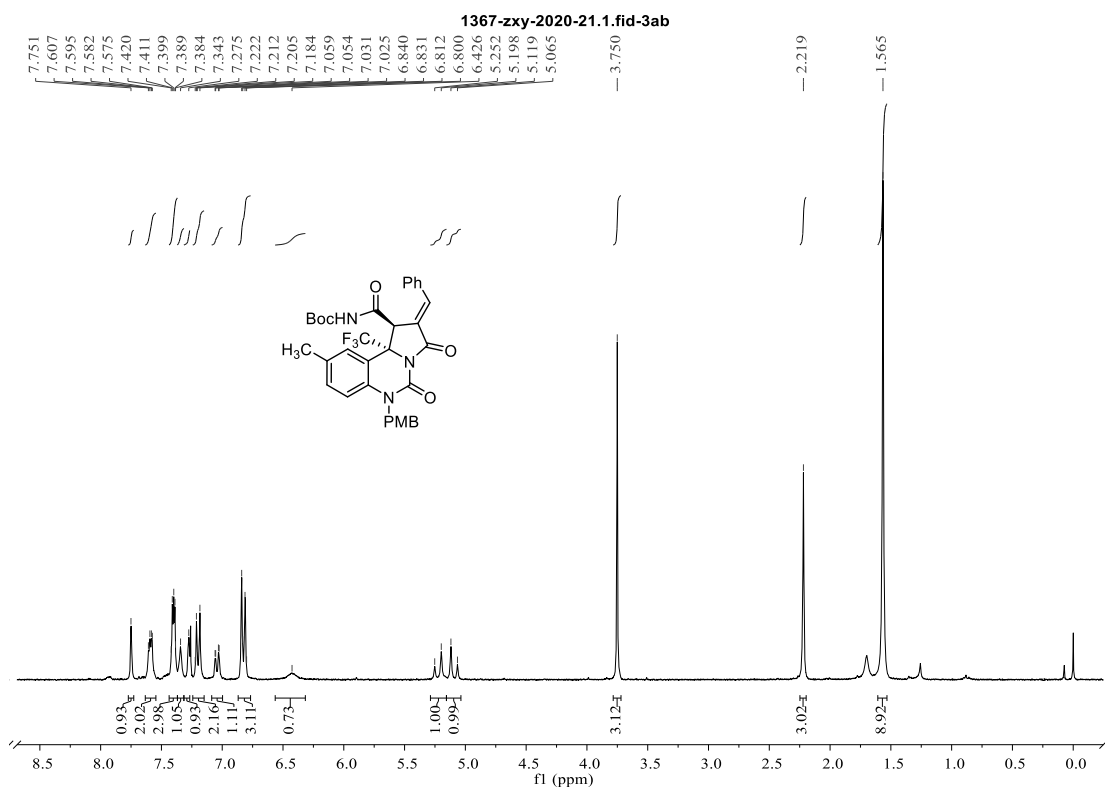


PeakTable

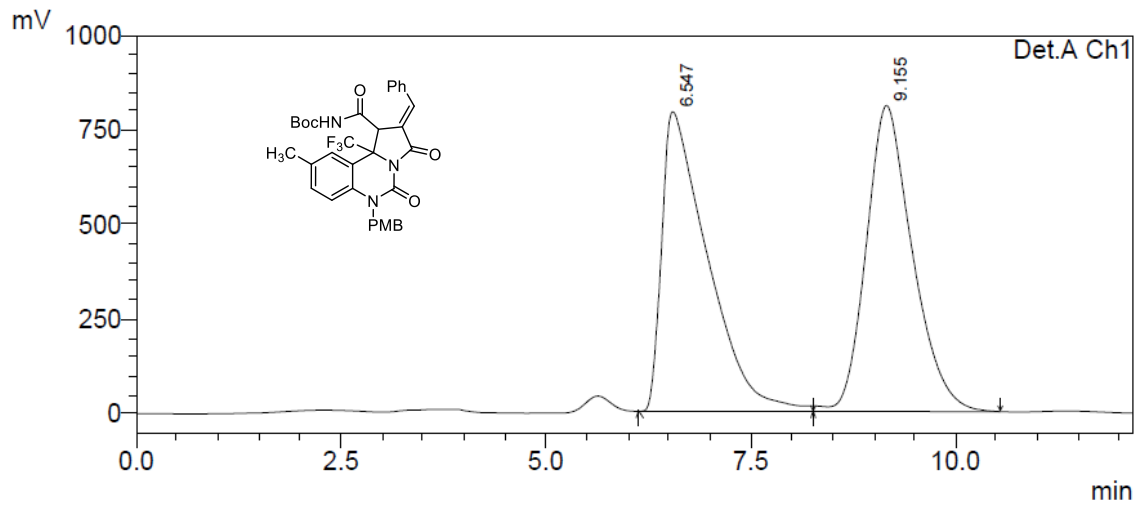
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	9.079	1902895	88057	2.338
2	12.044	79472862	1773061	97.662
Total		81375757		100.000

# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3ab**



### HPLC of 3ab

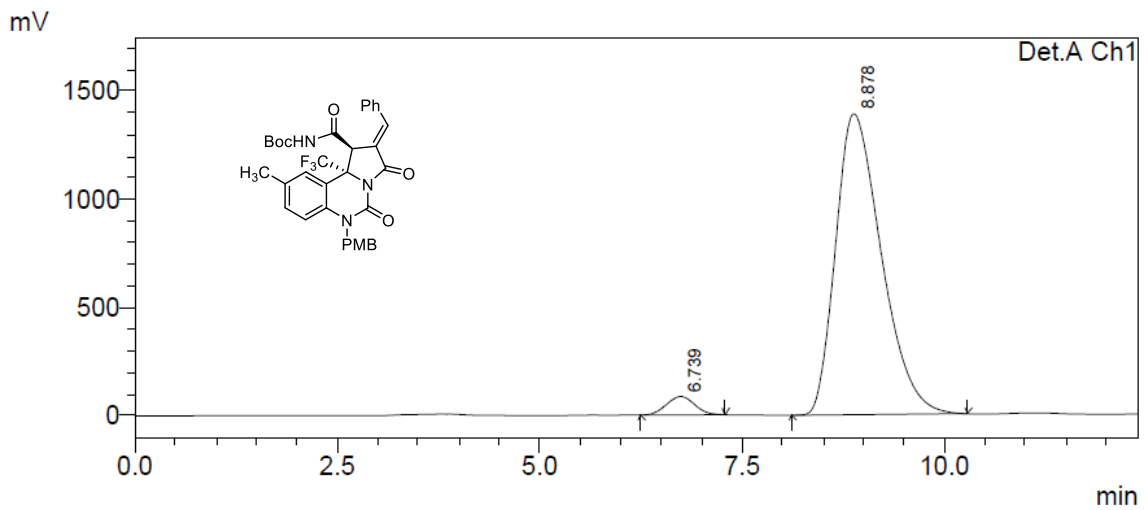


1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.547	30854080	791527	49.244
2	9.155	31800876	808615	50.756
Total		62654957		100.000



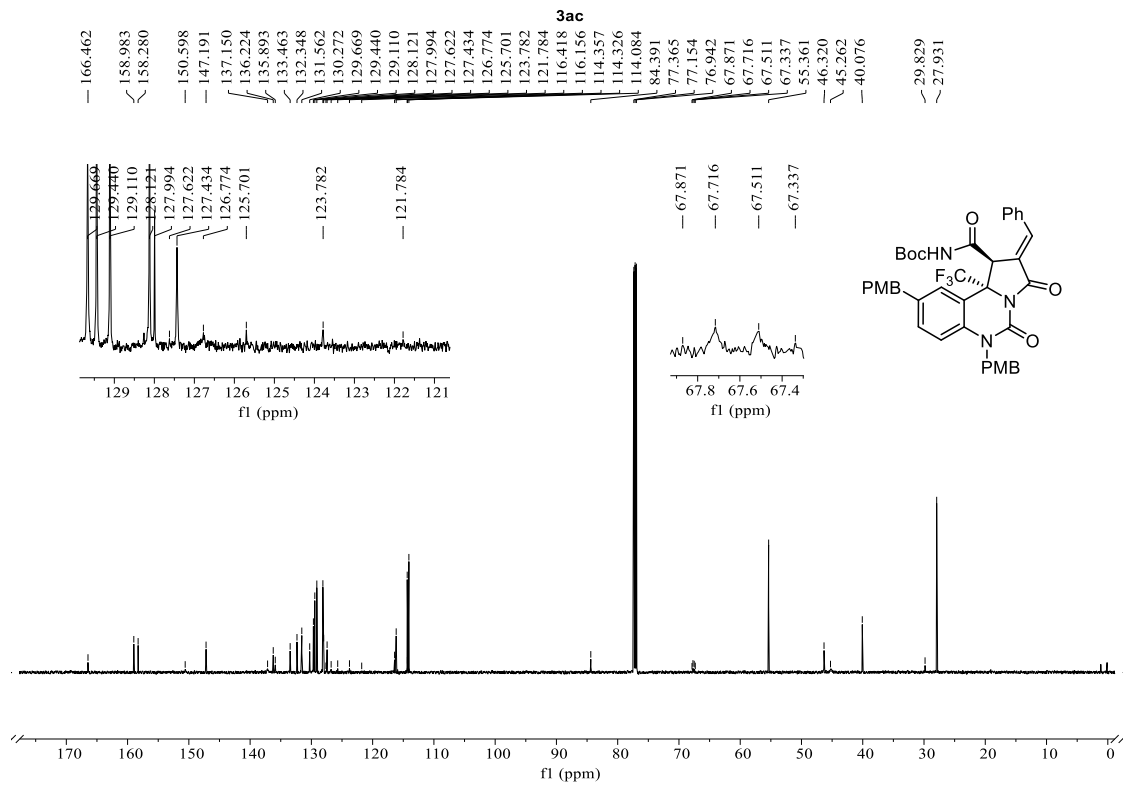
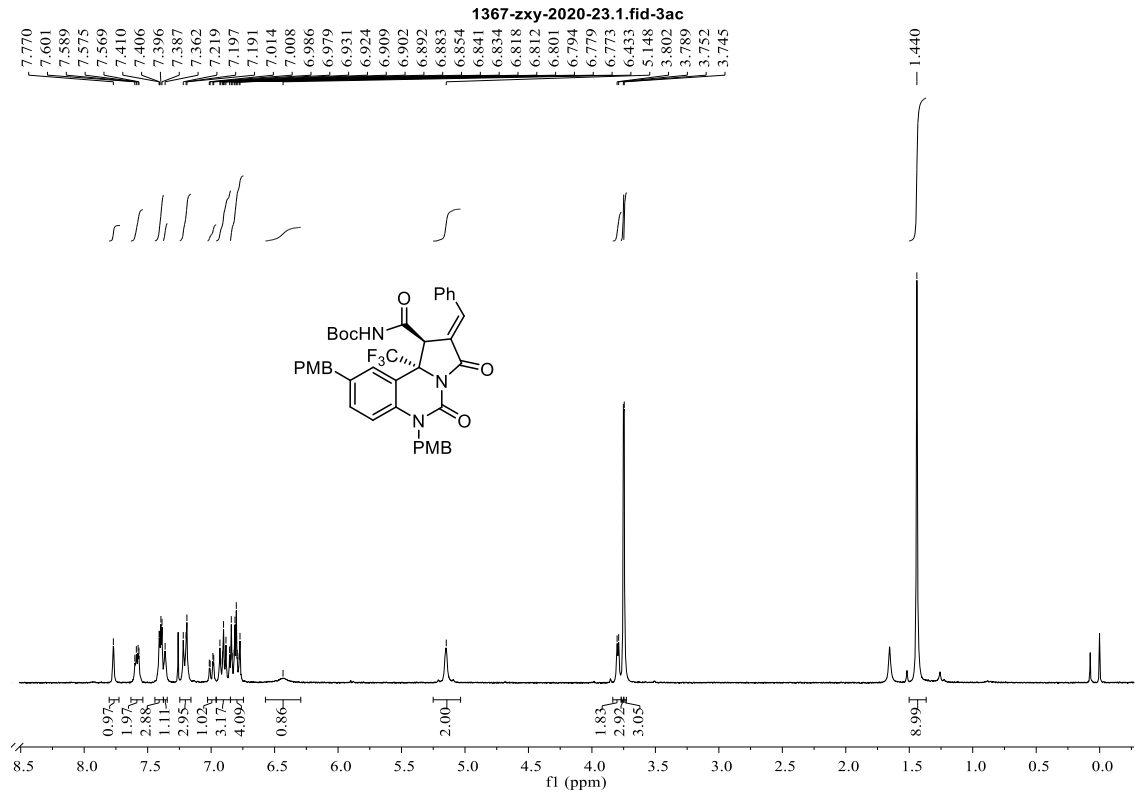
1 Det.A Ch1/254nm

PeakTable

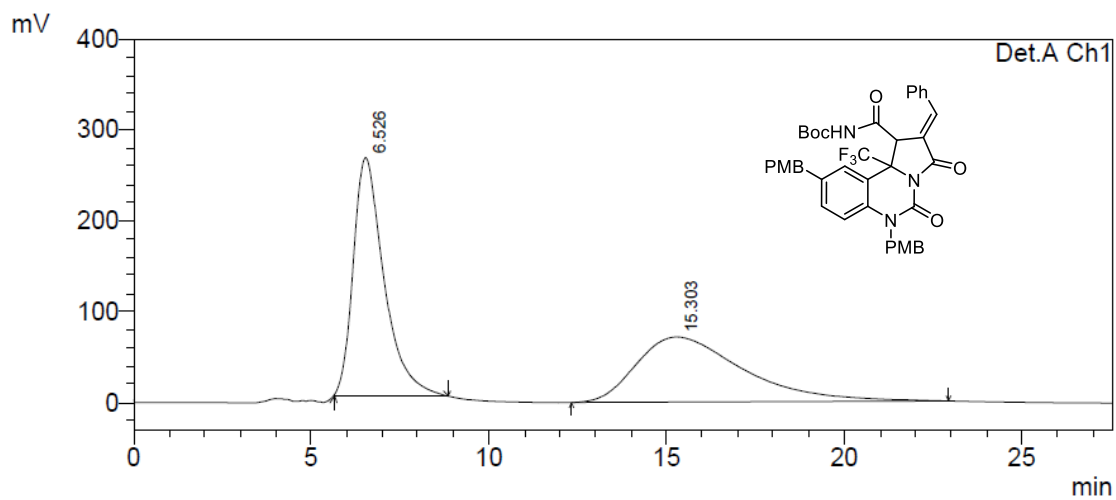
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.739	2067268	84862	3.643
2	8.878	54676537	1390544	96.357
Total		56743805		100.000

# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3ac**



### HPLC of 3ac

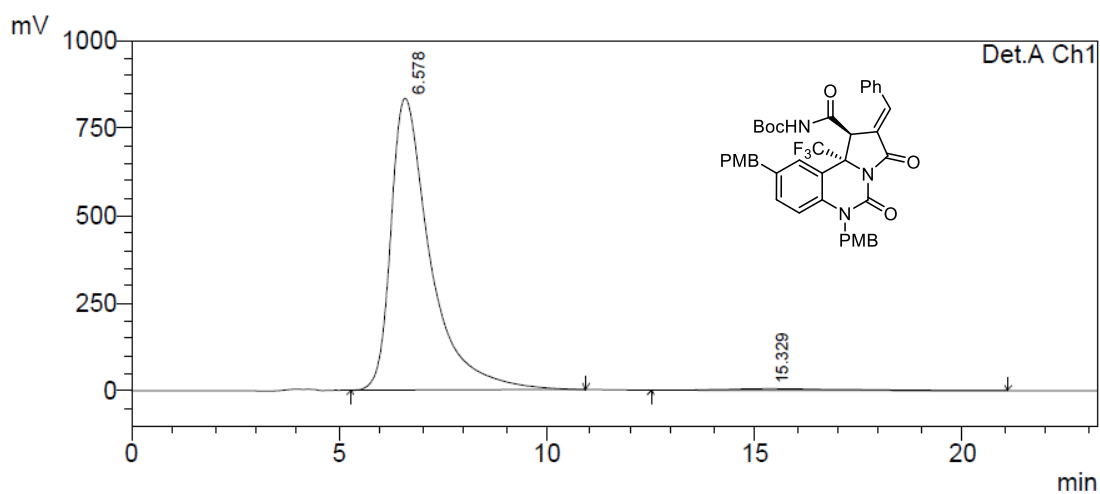


1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.526	15785128	262281	51.323
2	15.303	14971398	71524	48.677
Total		30756526		100.000



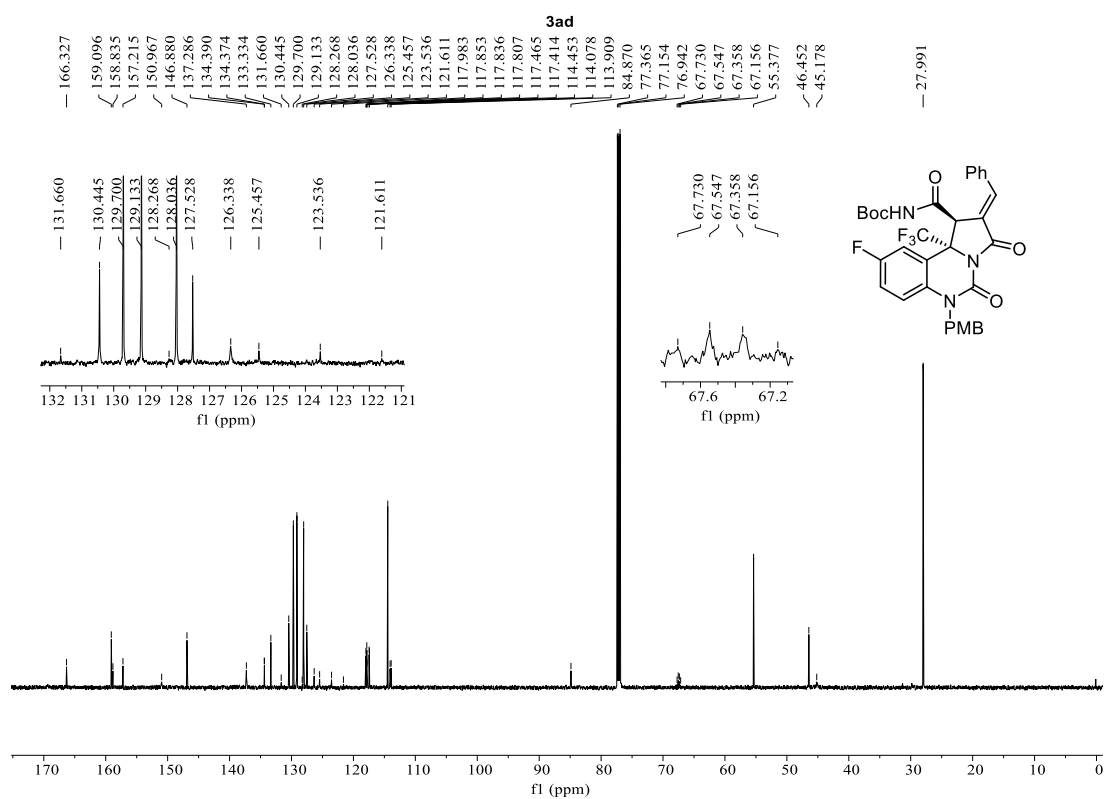
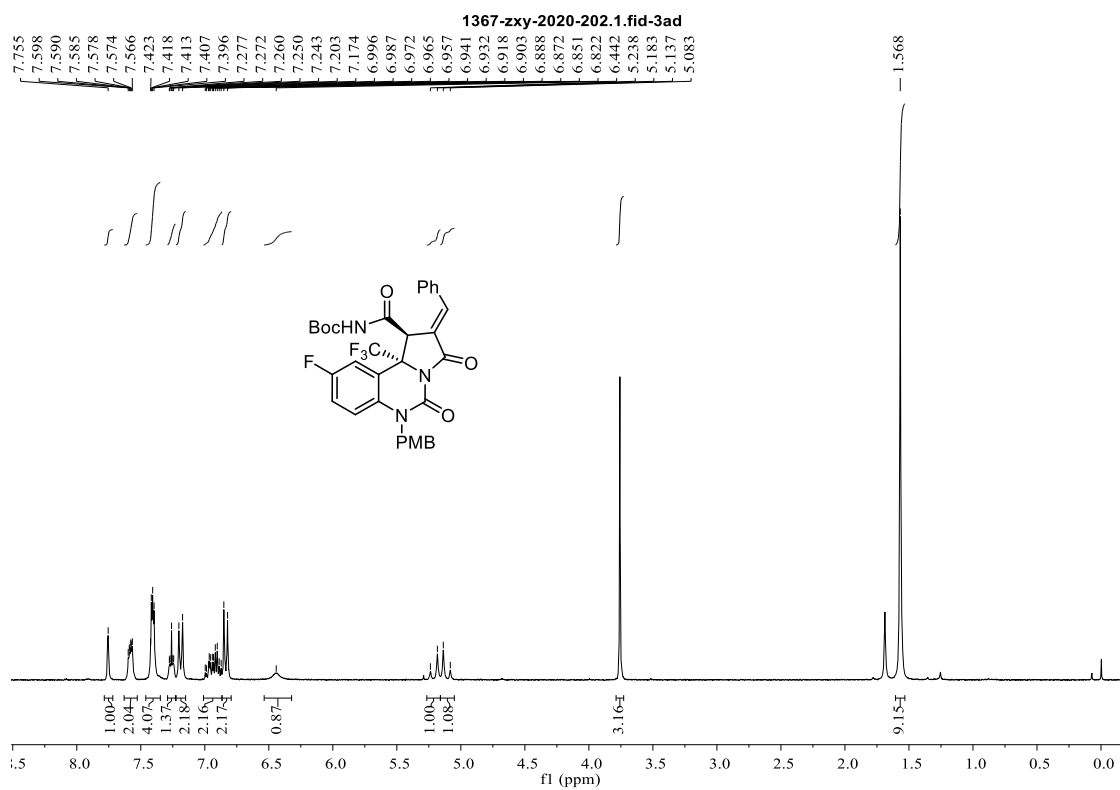
1 Det.A Ch1/254nm

PeakTable

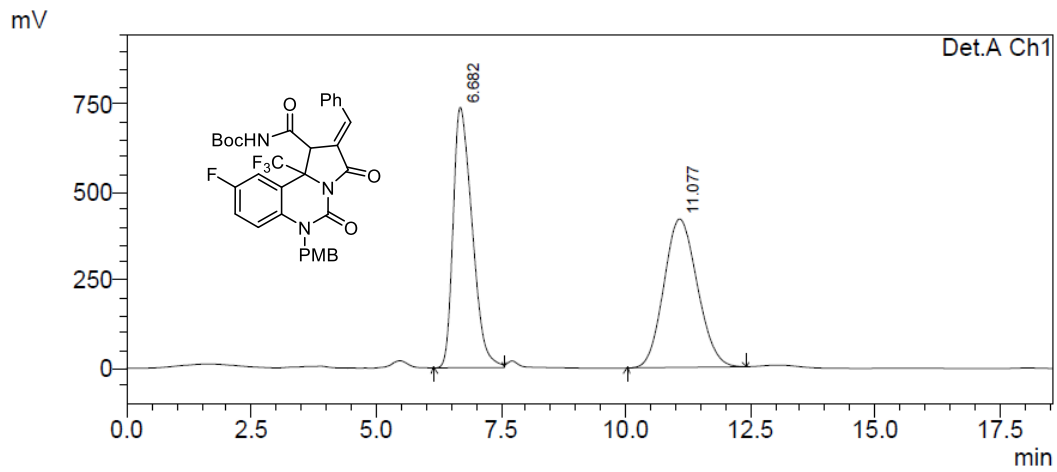
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	6.578	54961874	832476	98.256
2	15.329	975392	5009	1.744
Total		55937266		100.000

<sup>1</sup>H and <sup>13</sup>C NMR of **3ad**

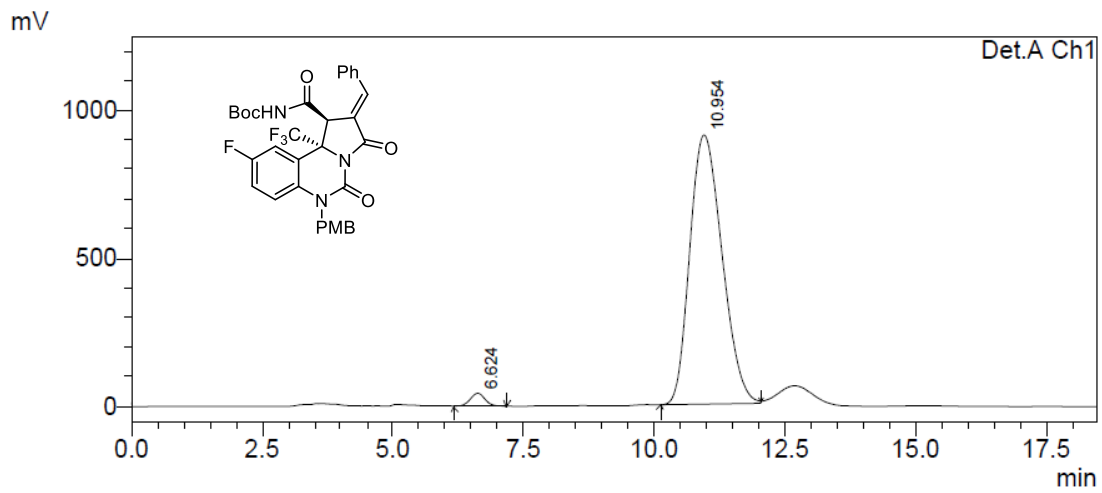


### HPLC of 3ad



PeakTable

Peak#	Ret. Time	Area	Height	Area %
1	6.682	19678153	741092	49.954
2	11.077	19714656	422226	50.046
Total		39392809		100.000

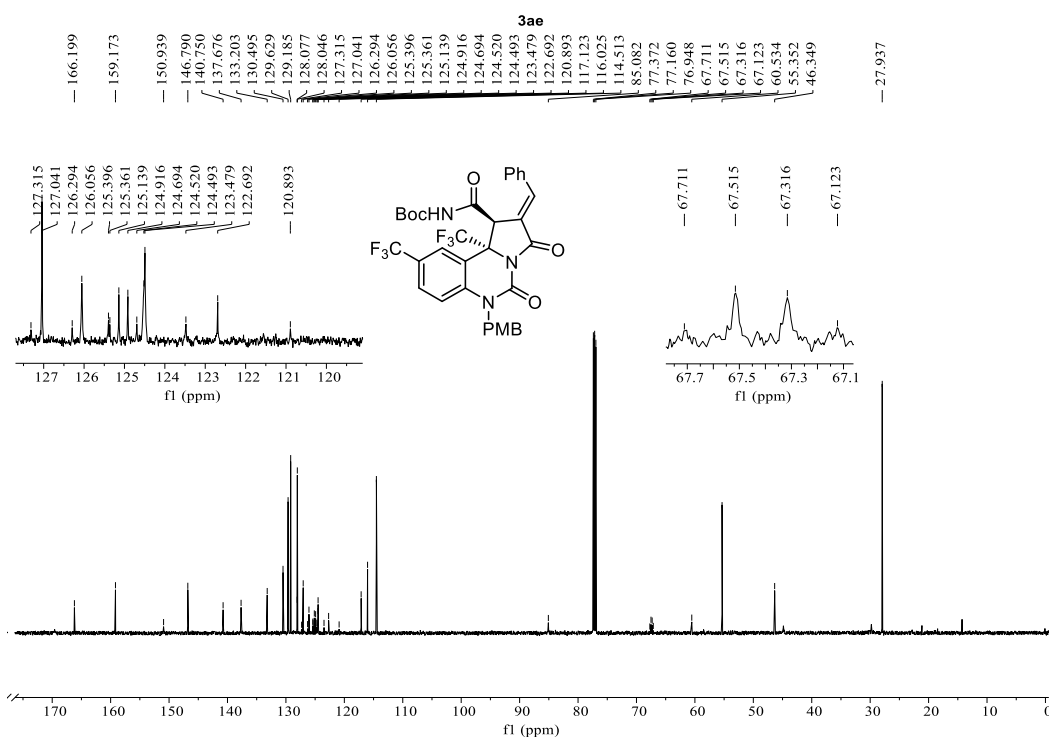
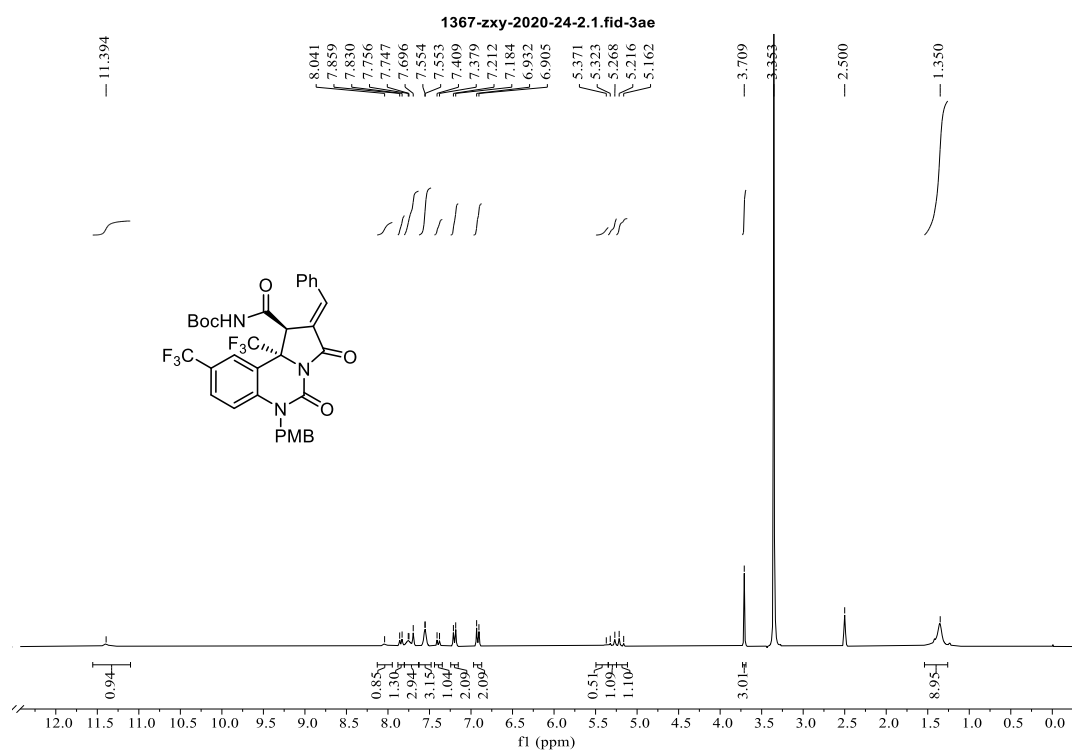


PeakTable

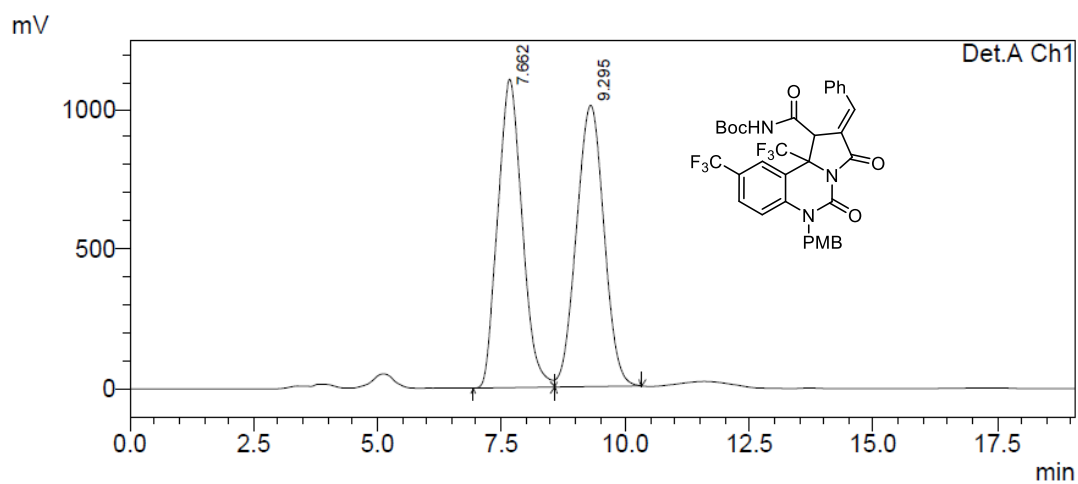
Peak#	Ret. Time	Area	Height	Area %
1	6.624	848205	43143	2.125
2	10.954	39067849	907916	97.875
Total		39916054		100.000



# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3ae**

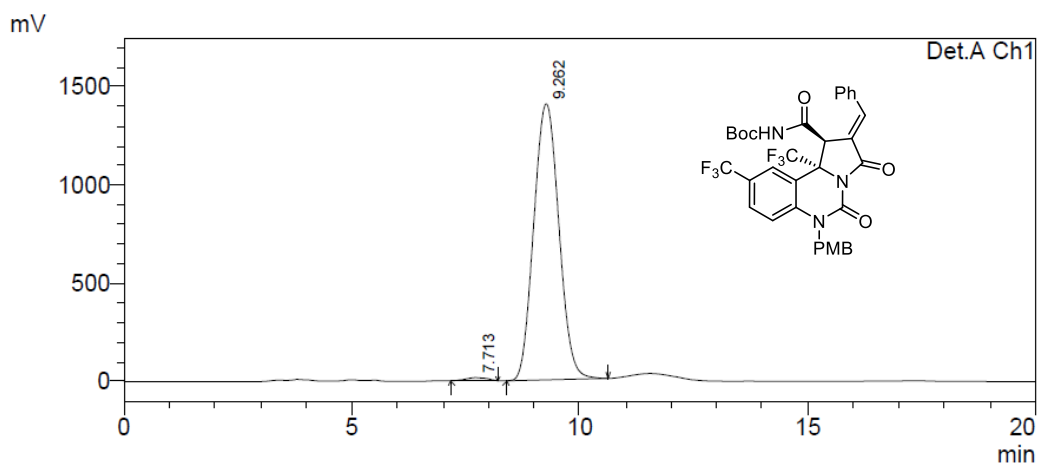


### HPLC of 3ae



PeakTable

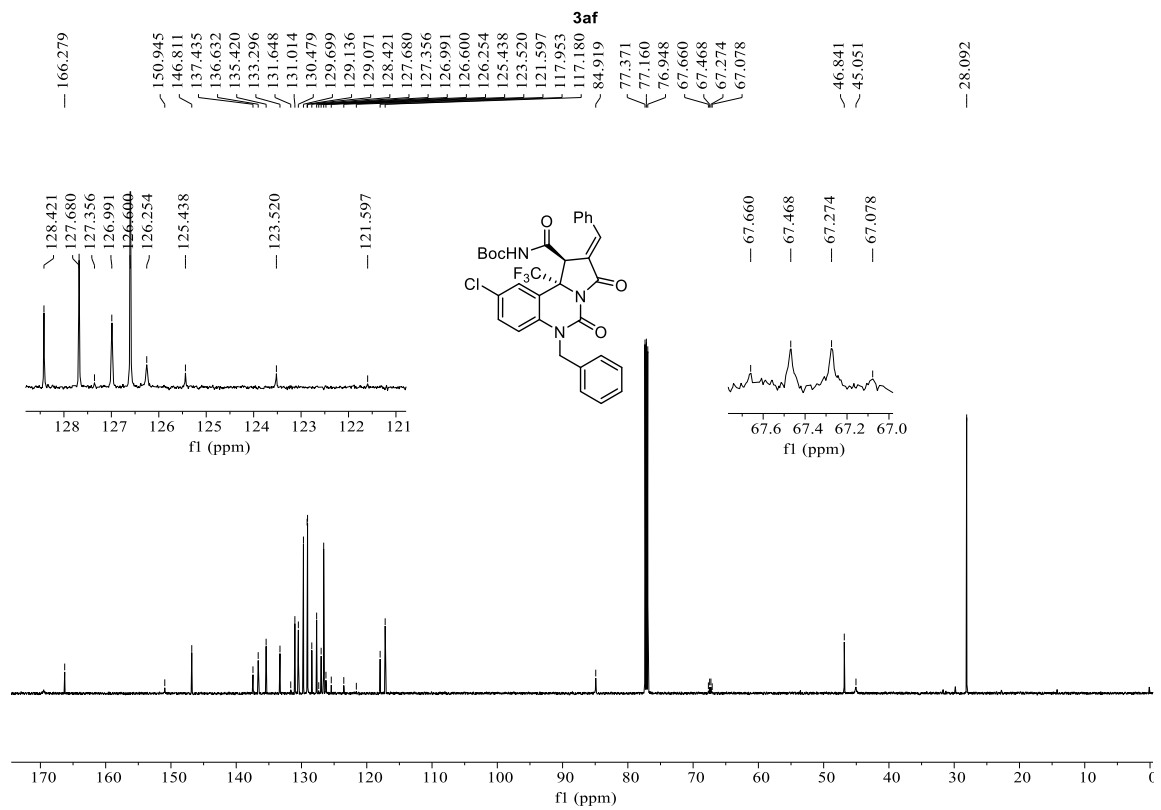
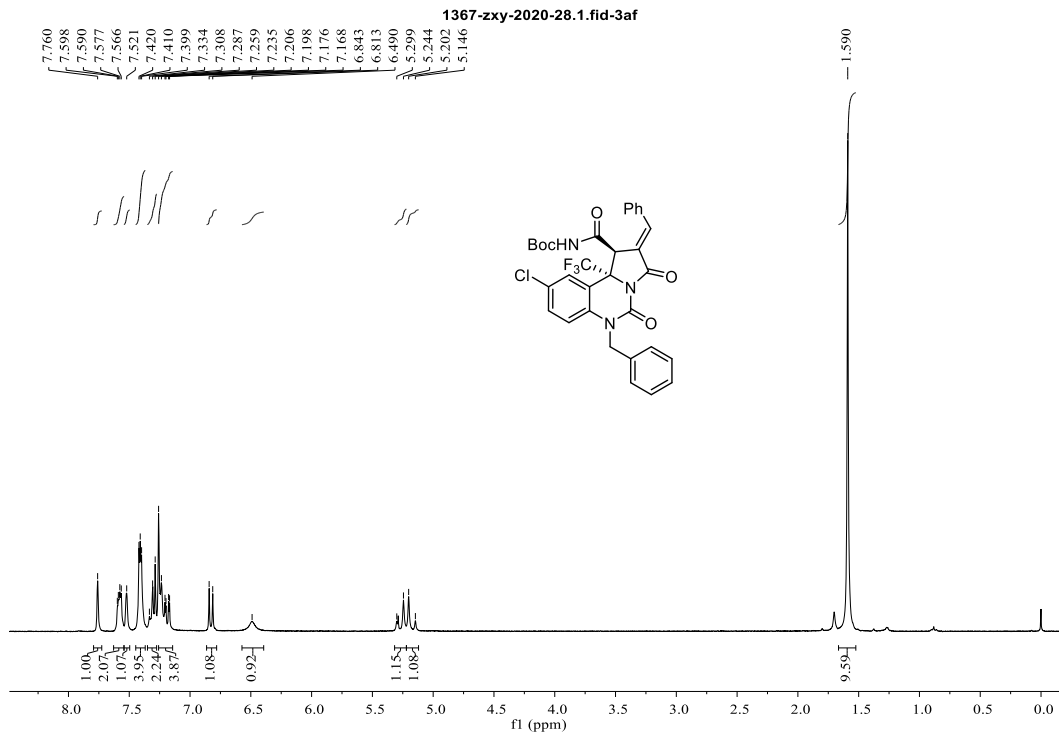
Detector A Ch1 254nm				
Peak#	Ret. Time	Area	Height	Area %
1	7.662	37892405	1104319	49.260
2	9.295	39031382	1007588	50.740
Total		76923787		100.000



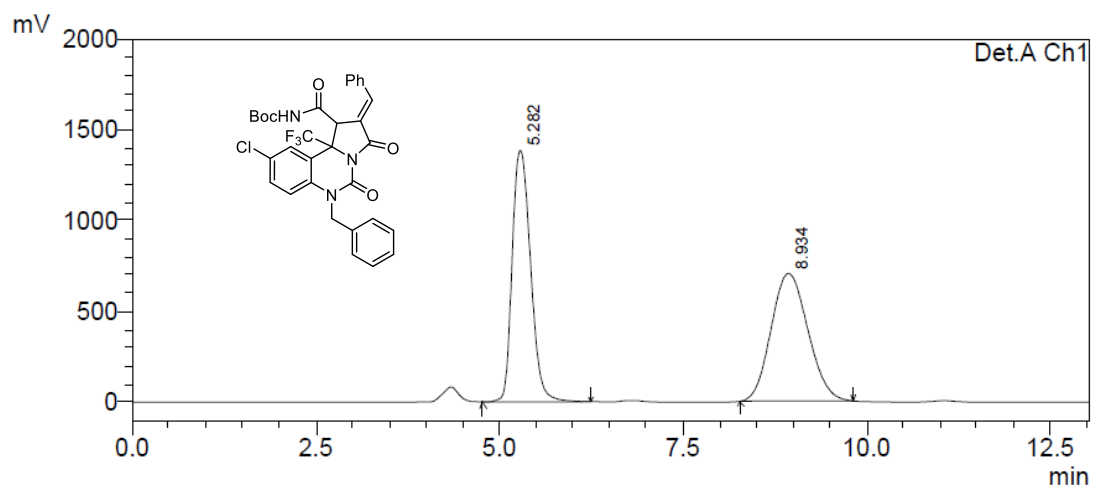
PeakTable

Detector A Ch1 254nm				
Peak#	Ret. Time	Area	Height	Area %
1	7.713	525761	15859	0.967
2	9.262	53866521	1405649	99.033
Total		54392282		100.000

# <sup>1</sup>H and <sup>13</sup>C NMR of 3af



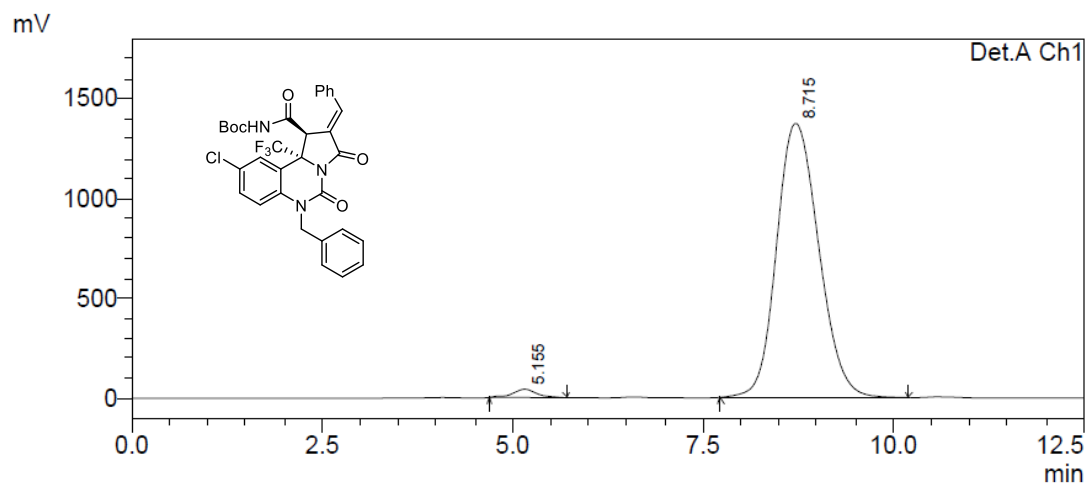
### HPLC of 3af



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	5.282	24049995	1383999	49.505
2	8.934	24531219	702742	50.495
Total		48581214		100.000

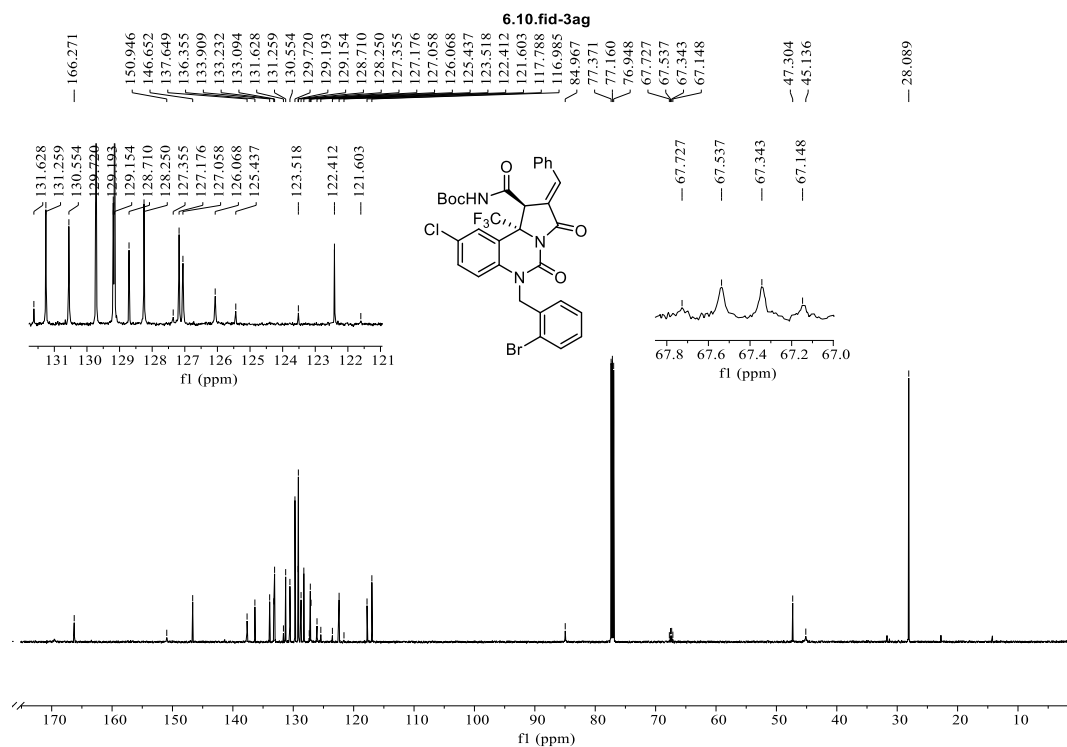
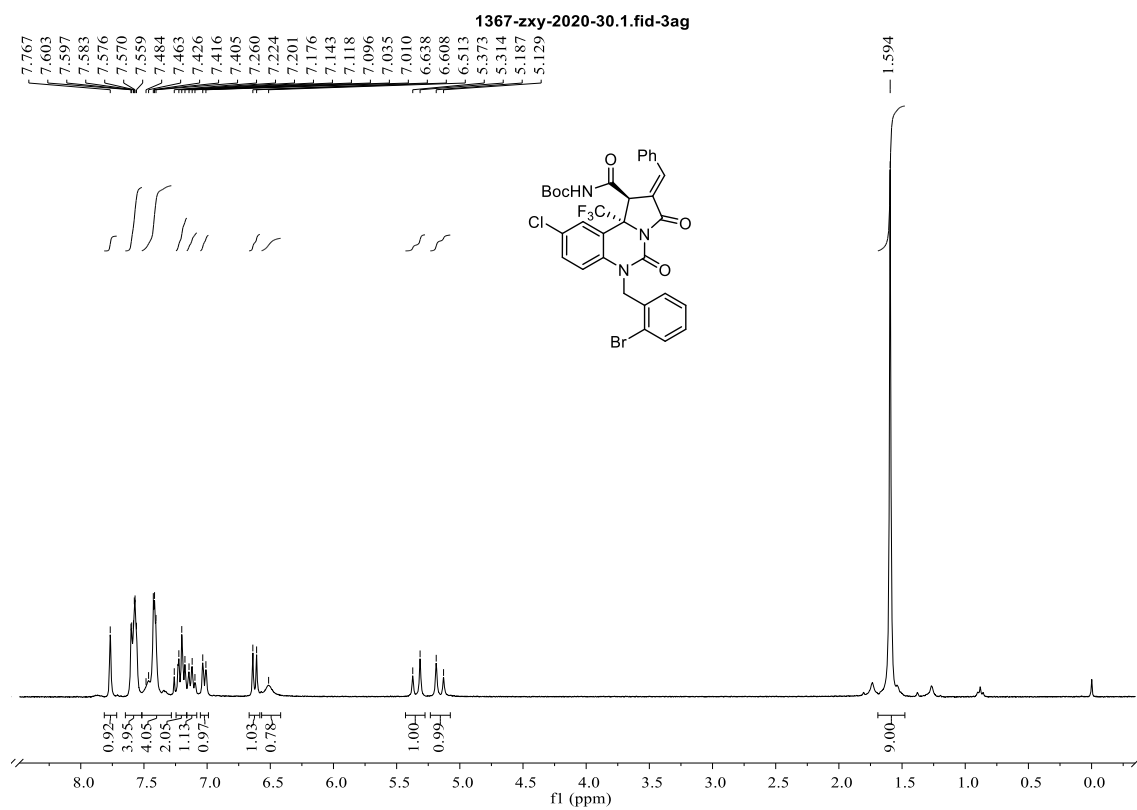


PeakTable

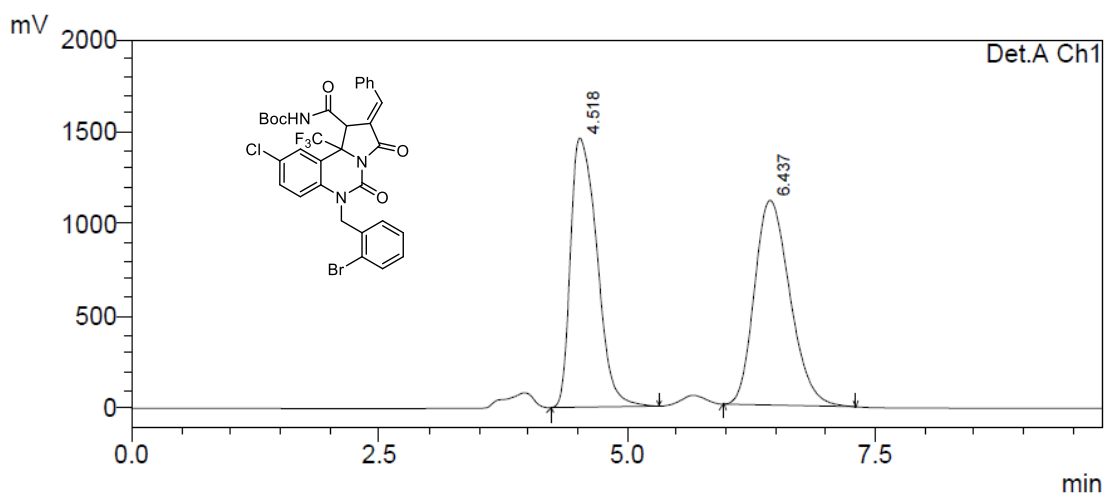
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	5.155	905870	41163	1.687
2	8.715	52777825	1370695	98.313
Total		53683695		100.000

$^1\text{H}$  and  $^{13}\text{C}$  NMR of **3ag**



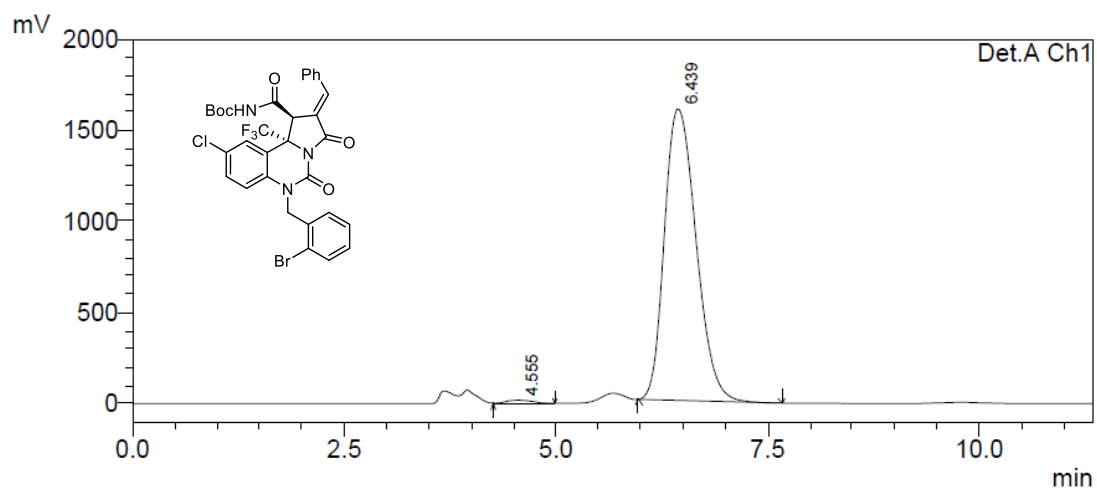
### HPLC of 3ag



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	4.518	27130999	1459424	49.510
2	6.437	27667862	1110785	50.490
Total		54798861		100.000

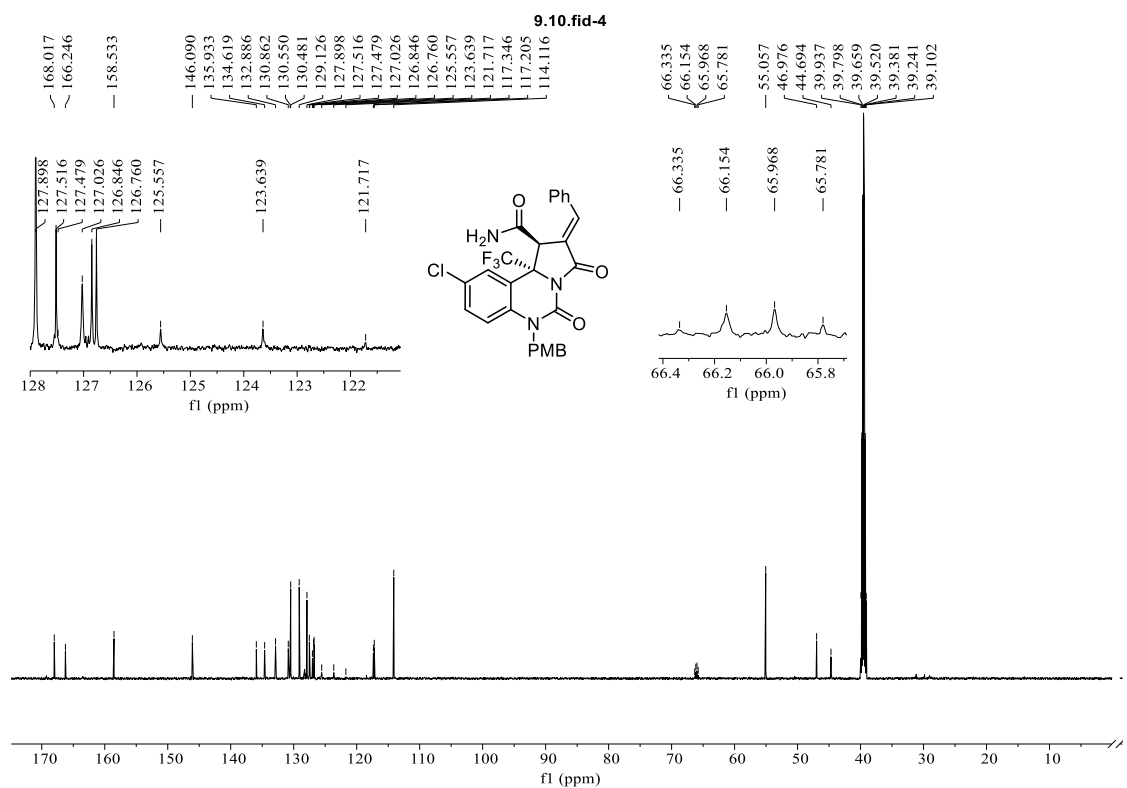
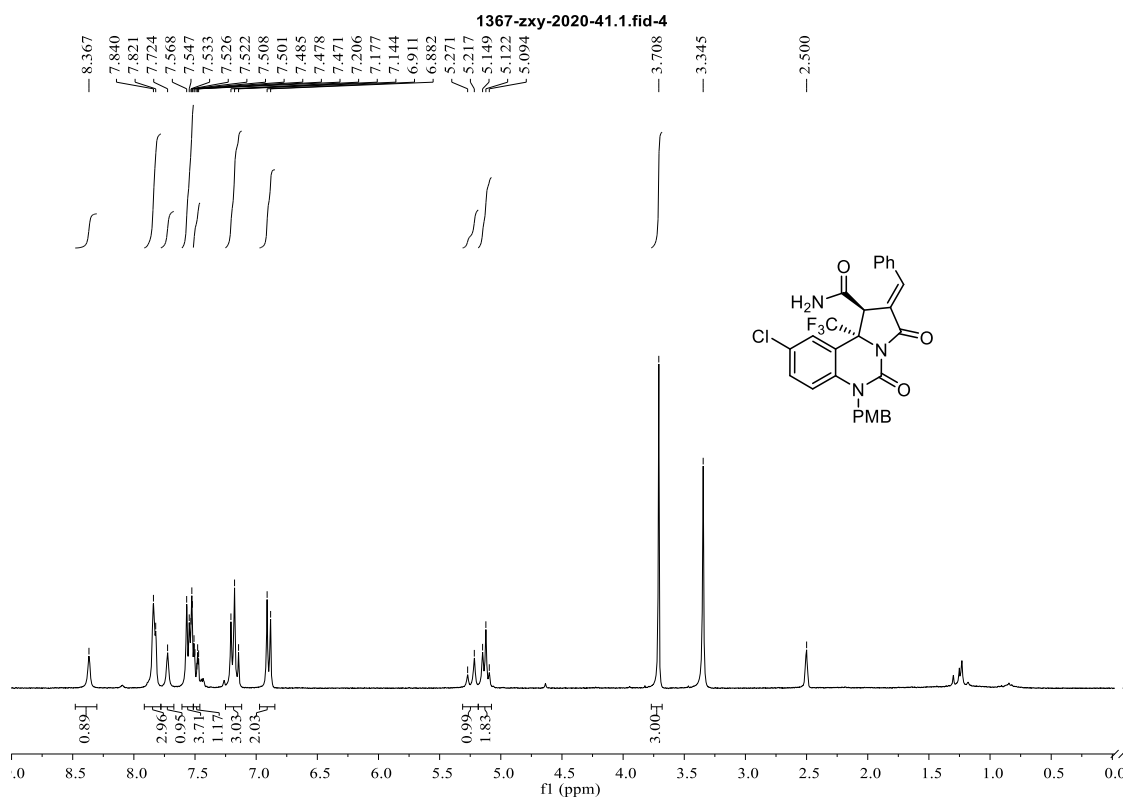


PeakTable

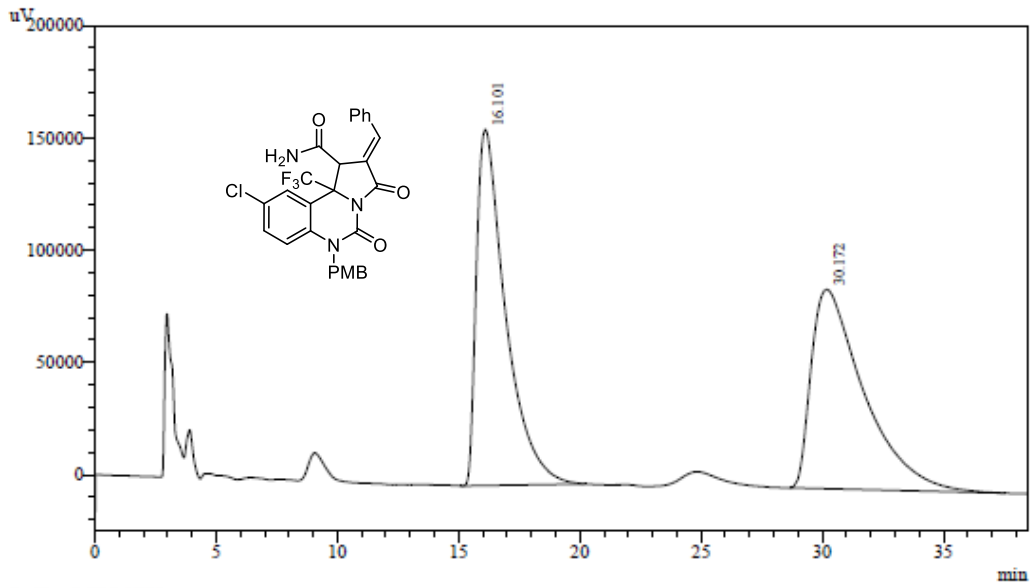
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	4.555	417899	18302	0.993
2	6.439	41674007	1599024	99.007
Total		42091906		100.000

<sup>1</sup>H and <sup>13</sup>C NMR of 4

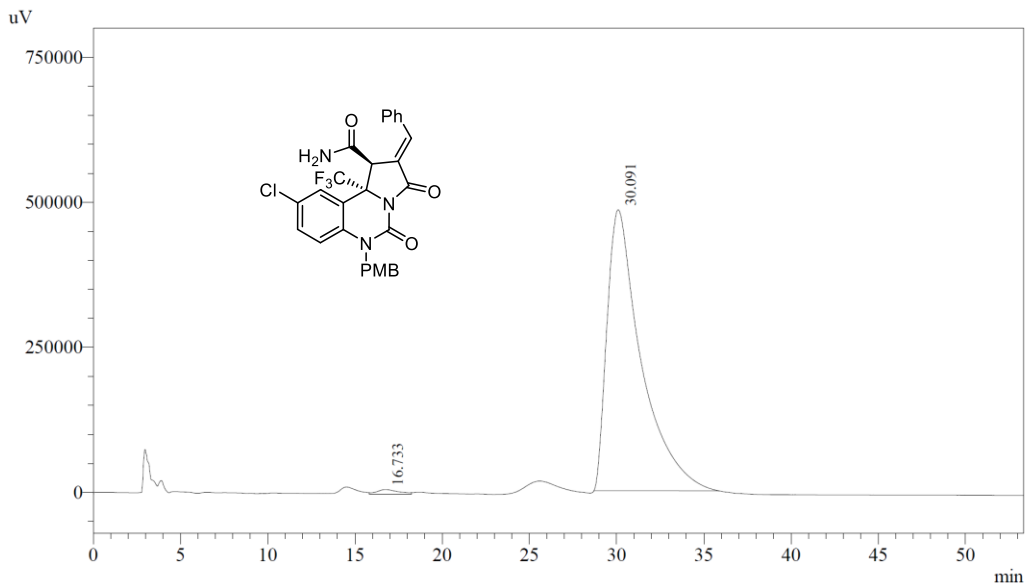


### HPLC of 4



Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.101	13275100	158512	49.743	64.116
2	30.172	13412142	88716	50.257	35.884
Total		26687242	247229	100.000	100.000

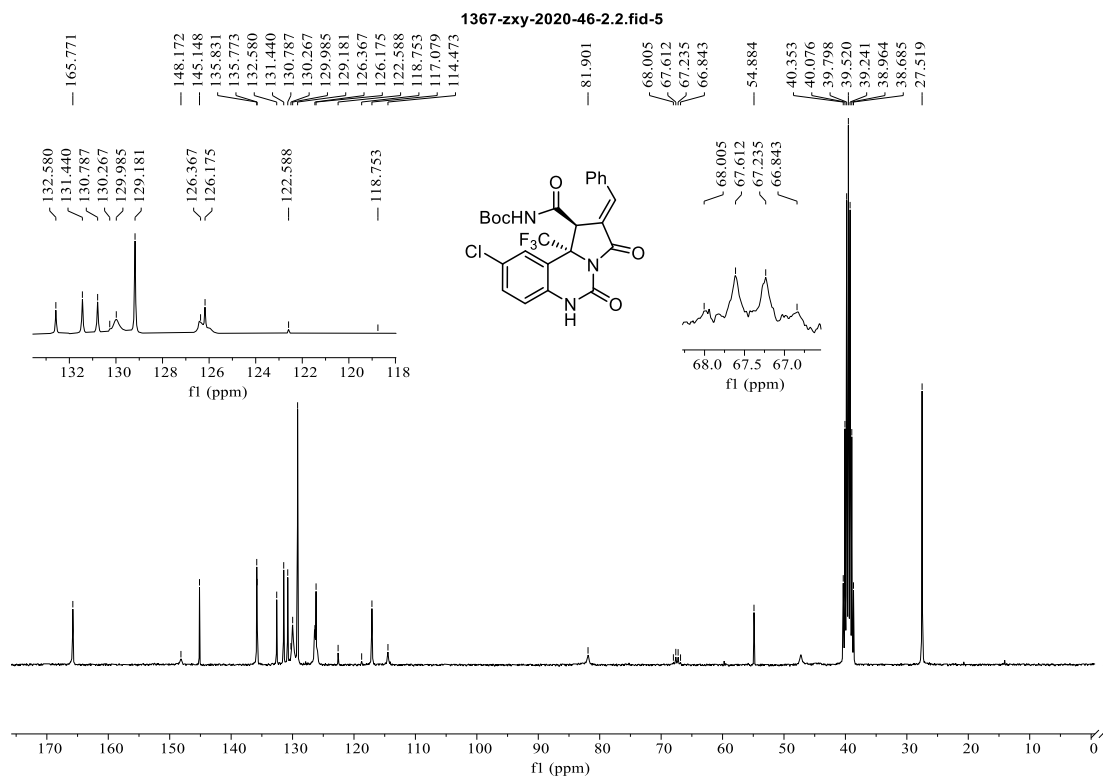
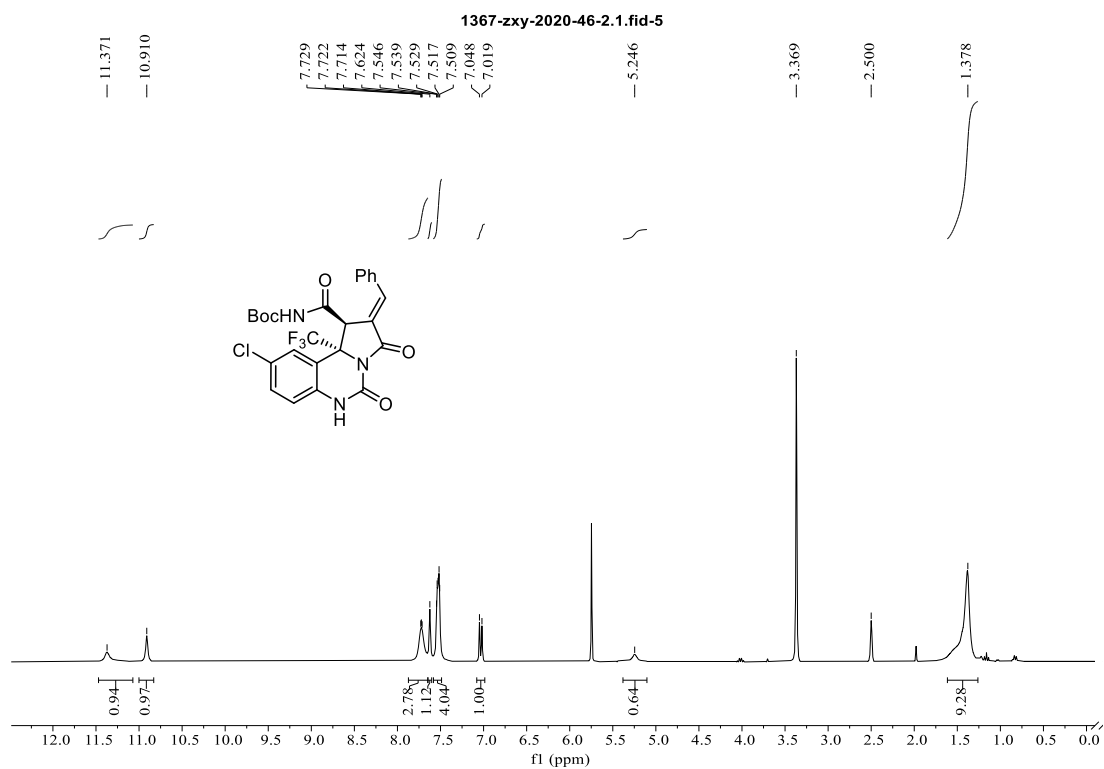


Detector A Ch1 254nm

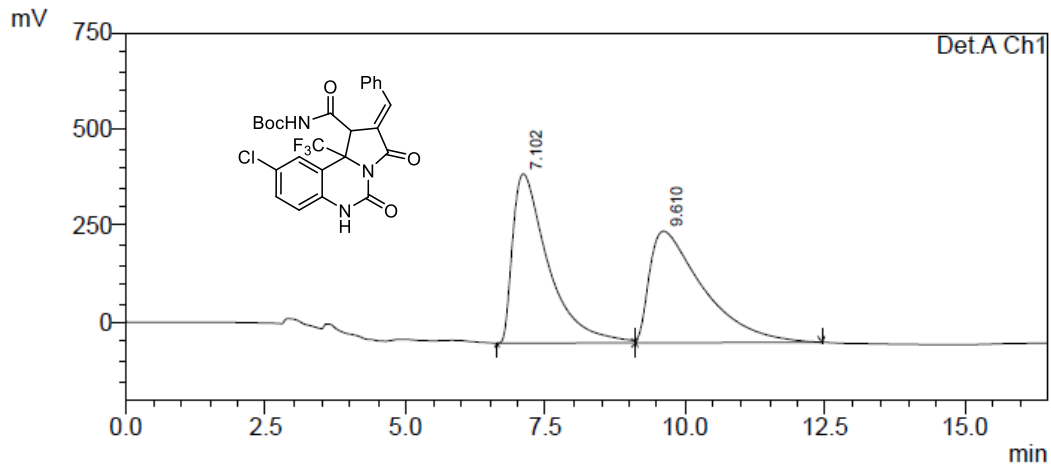
Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.733	633433	7591	0.952	1.544
2	30.091	65870916	483917	99.048	98.456
Total		66504349	491508	100.000	100.000



<sup>1</sup>H and <sup>13</sup>C NMR of 5

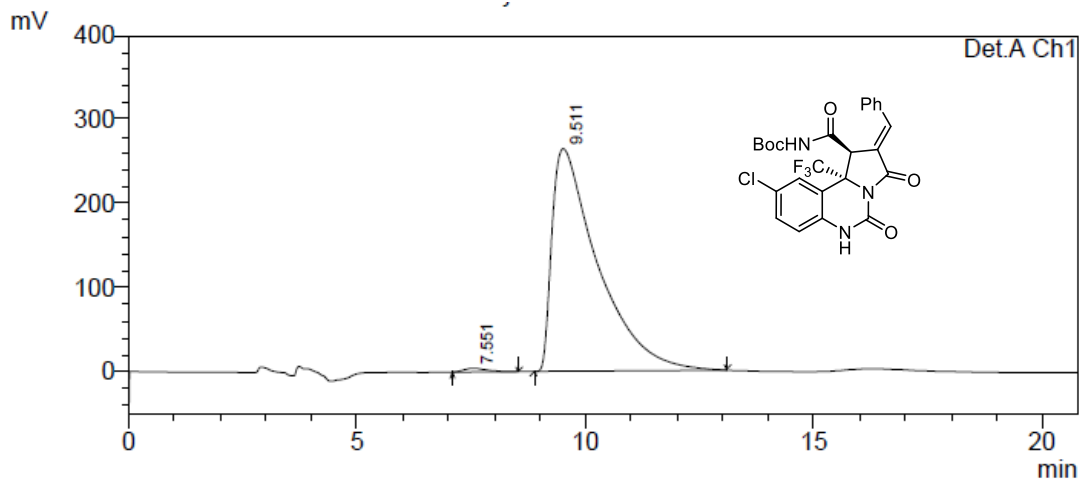


### HPLC of 5



PeakTable

Detector A Ch1 254nm				
Peak#	Ret. Time	Area	Height	Area %
1	7.102	19388878	437330	50.194
2	9.610	19239139	288258	49.806
Total		38628017		100.000



PeakTable

Detector A Ch1 254nm				
Peak#	Ret. Time	Area	Height	Area %
1	7.551	151711	4393	0.813
2	9.511	18509567	264710	99.187
Total		18661278		100.000

<sup>1</sup>H and <sup>13</sup>C NMR of 6

