

# Asymmetric dearomatization of 2-nitrobenzofurans by organocatalyzed one-step Michael addition to access 3,3'-disubstituted oxindoles

Zhen-Zhen Ge,<sup>a,d,§</sup> Lei Yang,<sup>a,d,§</sup> Yong You,<sup>b</sup> Zhen-Hua Wang,<sup>b</sup> Ke-Xin Xie,<sup>c</sup> Ming-Qiang Zhou,<sup>a</sup>  
Jian-Qiang Zhao,<sup>b,\*</sup> and Wei-Cheng Yuan<sup>a,b,\*</sup>

<sup>a</sup>National Engineering Research Center of Chiral Drugs, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, 610041, China.

<sup>b</sup>Institute for Advanced Study, Chengdu University, Chengdu 610106, China.

<sup>c</sup>Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China

<sup>d</sup>University of Chinese Academy of Sciences, Beijing, 100049, China

yuanwc@cioc.ac.cn

zhaojianqiang@cdu.edu.cn

## Supporting Information

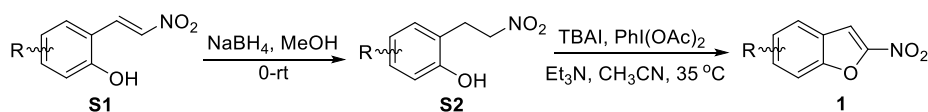
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## 1. General experimental information

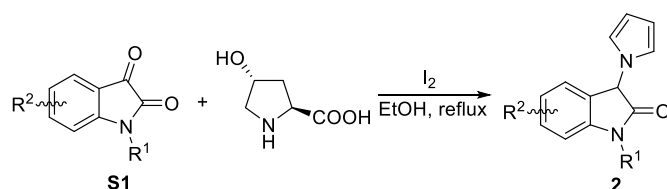
Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by TLC. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub>. <sup>1</sup>H NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard (CDCl<sub>3</sub> at 7.26 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. <sup>13</sup>C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard (CDCl<sub>3</sub> at 77.20 ppm). Melting points were recorded on a melting point apparatus.

## 2. General experimental procedures for synthesis of 2-nitrobenzofurans. 2-Nitrobenzofurans **1** were synthesized following known procedure.<sup>1,2</sup>



A solution of **S1** (1.0 equiv) in MeOH (0.1 M) was slowly added NaBH<sub>4</sub> (2.0 equiv) at 0 °C. Then the reaction was warmed to room temperature for completion (monitored by TLC). After quenched with water, the mixture was concentrated by rotary evaporation to remove MeOH, extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated by rotary evaporation to afford the crude **S2**. To a 100 mL flask were added crude **S2**, Bu<sub>4</sub>NI (2.5 equiv), NEt<sub>3</sub> (2.0 equiv), PhI(OAc)<sub>2</sub> (3.0 equiv) and acetonitrile (0.1 M). The mixture was stirred at 35 °C for 1-2 h. Upon completion as shown by TLC, the reaction mixture was washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted using EtOAc. The organic layer was dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 20/1) to afford the desired product **1**.

## 3. General experimental procedures for synthesis of 3-pyrrolyl-oxindoles. Compounds **2** were synthesized following known procedure.<sup>3</sup>



To isatin **S1** (10 mmol), hydroxyproline (10 mmol), and iodine (200 mg) was added ethanol (20 mL) and the mixture was heated under reflux for 1 h. Then the mixture was diluted with water (6 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×50mL), and the extract was washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (10%, 50 mL), saturated Na<sub>2</sub>CO<sub>3</sub> (50 mL), and dried (Na<sub>2</sub>SO<sub>4</sub>). Pure product **2** was isolated by silica gel column chromatography eluting with ethyl acetate/hexane (30/70).

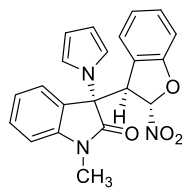
### Reference:

- (1) S.-C. Lu, P.-R. Zheng and G. Liu, *J. Org. Chem.*, **2012**, *77*, 7711.
- (2) Q. Cheng, H.-J. Zhang, W.-J. Yue and S.-L. You, *Chem.*, 2017, **3**, 428.
- (3) B.-D. Cui, Y. You, J. -Q. Zhao, J. Zuo, Z. -J. Wu, X. -Y. Xu, X. -M. Zhang and W. -C. Yuan, *Chem. Commun.*, 2015, **51**, 757.

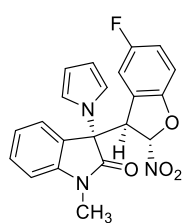
## 4. General experimental procedures for asymmetric synthesis of compounds **3**

To a solution of catalyst **D** (7.1 mg, 0.01 mmol, 10 mol %) and 2-nitrobenzofurans **1** (0.12 mmol) in xylene (1.0 mL) was added 3-pyrrolyl-oxindoles **2** (0.1 mmol) at -20 °C. Then the

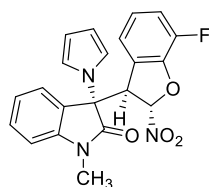
mixture was stirred continuously for specific time at -20 °C. After completion, the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 3:1~6:1) to give the corresponding products **3**.



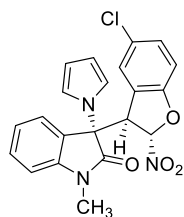
**(S)-1-methyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3a)**. Light yellow solid; 37.4 mg, 99% yield; >20:1 dr, 96% ee;  $[\alpha]_{\text{D}}^{20} = -52.7$  (*c* 1.83, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 172.8-173.9 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 21.34$  min,  $t_{\text{minor}} = 14.15$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.23 (s, 3H), 4.86-4.95 (m, 1H), 5.48 (d, *J* = 1.9 Hz, 1H), 5.91-6.05 (m, 1H), 6.27 (t, *J* = 2.3 Hz, 2H), 6.32-6.44 (m, 1H), 6.85-6.96 (m, 2H), 6.95-7.02 (m, 2H), 7.04 (t, *J* = 2.2 Hz, 2H), 7.28-7.37 (m, 1H), 7.40-7.48 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  26.7, 56.0, 66.1, 106.2, 109.3, 109.6, 110.3, 119.4, 120.4, 122.6, 123.2, 123.4, 125.6, 126.0, 130.8, 131.4, 144.0, 159.1, 171.8; HRMS (ESI-TOF) Calcd. for C<sub>21</sub>H<sub>17</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 398.1111; found: 398.1100.



**(S)-3-((2S,3R)-5-fluoro-2-nitro-2,3-dihydrobenzofuran-3-yl)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (3b)**. Light yellow solid; 36.1 mg, 92% yield; >20:1 dr, 95% ee;  $[\alpha]_{\text{D}}^{20} = -100.9$  (*c* 1.63, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 93.5-94.7 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 26.61$  min,  $t_{\text{minor}} = 15.61$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.25 (s, 3H), 4.83-4.94 (m, 1H), 5.46 (d, *J* = 1.9 Hz, 1H), 5.58-5.69 (m, 1H), 6.29 (t, *J* = 2.2 Hz, 2H), 6.42-6.55 (m, 1H), 6.91-6.99 (m, 2H), 6.99-7.07 (m, 4H), 7.42-7.50 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  26.7, 56.2 (*J* = 2.1 Hz), 65.8, 106.6, 109.4, 109.9, 110.8 (*J* = 8.5 Hz), 113.0 (*J* = 26.3 Hz), 117.4 (*J* = 24.6 Hz), 119.3, 122.0, 122.2, 123.3, 125.9, 131.6, 144.0, 156.2 (*J* = 168.6 Hz), 160.4, 171.6; HRMS (ESI-TOF) Calcd. for C<sub>21</sub>H<sub>16</sub>FN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 416.1017; found: 416.1023.

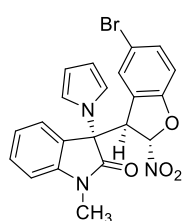


**(S)-3-((2S,3R)-7-fluoro-2-nitro-2,3-dihydrobenzofuran-3-yl)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (3c)**. Light yellow solid; 35.7 mg, 91% yield; >20:1 dr, 88% ee;  $[\alpha]_{\text{D}}^{20} = -68.6$  (*c* 1.45, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 176.3-177.5 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (90/10 hexane/EtOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 11.20$  min,  $t_{\text{minor}} = 12.71$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.26 (s, 3H), 4.95 (d, *J* = 2.1 Hz, 1H), 5.51 (d, *J* = 2.1 Hz, 1H), 5.76 (dd, 1H), 6.27 (t, *J* = 2.2 Hz, 2H), 6.35-6.45 (m, 1H), 6.78-6.92 (m, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.99-7.08 (m, 3H), 7.08-7.18 (m, 1H), 7.46 (td, *J* = 7.8, 1.2 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  26.7, 56.4 (*J* = 7.5 Hz), 65.9, 106.4, 109.5, 109.8, 118.1 (*J* = 16.1 Hz), 119.4, 120.9 (*J* = 4.0 Hz), 122.1, 123.5, 124.0, 124.3 (*J* = 5.4 Hz), 125.8, 131.6, 144.0, 145.7 (*J* = 11.3 Hz), 146.8 (*J* = 258.3 Hz), 171.6; HRMS (ESI-TOF) Calcd. for C<sub>21</sub>H<sub>16</sub>FN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 416.1017; found: 416.1018.

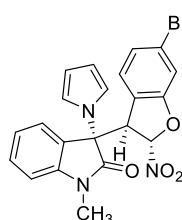


**(S)-3-((2S,3R)-5-chloro-2-nitro-2,3-dihydrobenzofuran-3-yl)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (3d)**. Light yellow solid; 40.5 mg, 99% yield; >20:1 dr, 95% ee;  $[\alpha]_{\text{D}}^{20} = -136.4$  (*c* 1.73, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 163.1-164.3 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 20.60$  min,  $t_{\text{minor}} = 15.51$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.25 (s, 3H), 4.88 (d, *J* = 1.9 Hz, 1H), 5.48 (d, *J* = 1.9 Hz, 1H), 5.83 (d, *J* = 2.3 Hz, 1H), 6.30 (t, *J* = 2.2 Hz, 2H), 6.46-6.58 (m, 1H), 6.95 (t, *J* = 7.9 Hz, 2H), 7.00-7.08 (m, 3H), 7.30 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.42-7.53 (m, 1H);

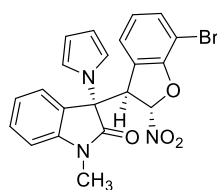
$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  26.7, 56.2, 65.9, 106.4, 109.4, 110.0, 111.3, 119.4, 122.3, 122.5, 123.4, 125.9, 128.6, 130.8, 131.6, 144.0, 157.6, 171.6; HRMS (ESI-TOF) Calcd. for  $\text{C}_{21}\text{H}_{16}^{35}\text{ClN}_3\text{NaO}_4$   $[\text{M}+\text{Na}]^+$ : 432.0722; found:432.0726; Calcd. for  $\text{C}_{21}\text{H}_{16}^{37}\text{ClN}_3\text{NaO}_4$   $[\text{M}+\text{Na}]^+$ : 434.0692; found:434.0707.



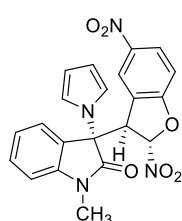
**(S)-3-((2S,3R)-5-bromo-2-nitro-2,3-dihydrobenzofuran-3-yl)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (3e).** Light yellow solid; 43.2 mg, 95% yield; >20:1 dr, 96% ee;  $[\alpha]_{\text{D}}^{20} = -118.1$  (*c* 1.75,  $\text{CH}_2\text{Cl}_2$ ); m.p. 101.4-102.6 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 20.03$  min,  $t_{\text{minor}} = 16.10$  min);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.24 (s, 3H), 4.88 (d, *J* = 2.7 Hz, 1H), 5.48 (d, *J* = 1.9 Hz, 1H), 5.87-5.98 (m, 1H), 6.30 (t, *J* = 2.3 Hz, 2H), 6.44-6.57 (m, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.94-6.99 (m, 1H), 7.00-7.09 (m, 3H), 7.36-7.55 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  26.7, 56.2, 65.9, 106.3, 109.4, 110.0, 111.8, 115.7, 119.4, 122.3, 122.9, 123.4, 125.9, 128.8, 131.6, 133.6, 144.0, 158.2, 171.5; HRMS (ESI-TOF) Calcd. for  $\text{C}_{21}\text{H}_{16}^{79}\text{BrN}_3\text{NaO}_4$   $[\text{M}+\text{Na}]^+$ : 476.0216; found: 476.0222; Calcd. for  $\text{C}_{21}\text{H}_{16}^{81}\text{BrN}_3\text{NaO}_4$   $[\text{M}+\text{Na}]^+$ : 478.0196; found: 478.0195.



**(S)-3-((2S,3R)-6-bromo-2-nitro-2,3-dihydrobenzofuran-3-yl)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (3f).** Light yellow solid; 45.0 mg, 99% yield; >20:1 dr, 95% ee;  $[\alpha]_{\text{D}}^{20} = -104.2$  (*c* 2.15,  $\text{CH}_2\text{Cl}_2$ ); m.p. 108.1-109.4 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (95/5 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 22.34$  min,  $t_{\text{minor}} = 19.84$  min);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.25 (s, 3H), 4.84 (d, *J* = 2.0 Hz, 1H), 5.46 (d, *J* = 2.0 Hz, 1H), 5.73-5.83 (m, 1H), 6.26 (t, *J* = 2.2 Hz, 2H), 6.42-6.56 (m, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 7.00-7.08 (m, 4H), 7.18 (d, *J* = 1.7 Hz, 1H), 7.39-7.58 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  26.7, 55.8, 65.8, 106.3, 109.4, 109.8, 114.1, 119.4, 119.9, 122.3, 123.4, 124.1, 125.9, 126.6, 126.7, 131.5, 144.0, 159.7, 171.6; HRMS (ESI-TOF) Calcd. for  $\text{C}_{21}\text{H}_{16}^{79}\text{BrN}_3\text{NaO}_4$   $[\text{M}+\text{Na}]^+$ : 476.0216; found: 476.0221; Calcd. for  $\text{C}_{21}\text{H}_{16}^{81}\text{BrN}_3\text{NaO}_4$   $[\text{M}+\text{Na}]^+$ : 478.0196; found: 478.0190.

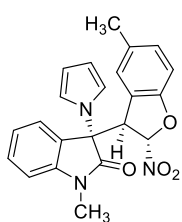


**(S)-3-((2S,3R)-7-bromo-2-nitro-2,3-dihydrobenzofuran-3-yl)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (3g).** Light yellow solid; 41.3 mg, 91% yield; >20:1 dr, 87% ee;  $[\alpha]_{\text{D}}^{20} = -14.0$  (*c* 1.40,  $\text{CH}_2\text{Cl}_2$ ); m.p. 208.3-209.7 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 17.72$  min,  $t_{\text{minor}} = 15.86$  min);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.26 (s, 3H), 4.98 (d, *J* = 2.2 Hz, 1H), 5.45 (d, *J* = 2.0 Hz, 1H), 5.90 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.26 (t, *J* = 2.2 Hz, 2H), 6.29-6.36 (m, 1H), 6.80 (t, *J* = 7.8 Hz, 1H), 6.92-7.06 (m, 4H), 7.39-7.57 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  26.8, 56.9, 65.9, 102.9, 105.4, 109.5, 109.8, 119.4, 121.9, 122.1, 123.4, 124.6, 124.8, 126.0, 131.7, 133.9, 144.0, 156.5, 171.6; HRMS (ESI-TOF) Calcd. for  $\text{C}_{21}\text{H}_{16}^{79}\text{BrN}_3\text{NaO}_4$   $[\text{M}+\text{Na}]^+$ : 476.0216; found: 476.0231; Calcd. for  $\text{C}_{21}\text{H}_{16}^{81}\text{BrN}_3\text{NaO}_4$   $[\text{M}+\text{Na}]^+$ : 478.0196; found: 478.0195.



**(S)-3-((2S,3R)-2,5-dinitro-2,3-dihydrobenzofuran-3-yl)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (3h).** Light yellow solid; 41.5 mg, 99% yield; >20:1 dr, 90% ee;  $[\alpha]_{\text{D}}^{20} = -130.9$  (*c* 1.83,  $\text{CH}_2\text{Cl}_2$ ); m.p. 212.1-213.4 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 34.71$  min,  $t_{\text{minor}} =$

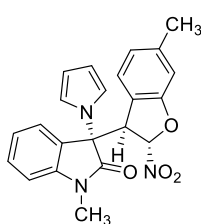
27.81 min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.24 (s, 3H), 4.94 (d, *J* = 2.0 Hz, 1H), 5.67 (d, *J* = 2.1 Hz, 1H), 6.34 (t, *J* = 2.2 Hz, 2H), 6.52-6.64 (m, 1H), 6.66-6.71 (m, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 7.03-7.17 (m, 4H), 7.42-7.54 (m, 1H), 8.29 (dd, *J* = 8.9, 2.4 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 26.8, 55.6, 65.7, 106.5, 109.7, 110.5, 110.6, 119.3, 122.1, 122.3, 122.4, 123.6, 125.5, 127.7, 131.9, 143.9, 144.1, 163.2, 171.2; HRMS (ESI-TOF) Calcd. for C<sub>21</sub>H<sub>16</sub>BrN<sub>4</sub>NaO<sub>6</sub> [M+Na]<sup>+</sup>: 443.0962; found: 443.0966.



**(S)-1-methyl-3-((2S,3R)-5-methyl-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3i).** Light yellow solid; 38.5 mg, 99% yield; >20:1 dr, 96% ee; [α]<sub>D</sub><sup>20</sup> = -106.5 (*c* 1.55, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 171.5-172.7 °C.

The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/<sup>i</sup>PrOH; flow rate: 1.0 mL/min; λ = 254 nm; *t*<sub>major</sub> = 17.26 min, *t*<sub>minor</sub> = 13.95 min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.15 (s, 3H), 3.24 (s, 3H),

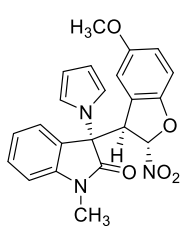
4.86 (d, *J* = 2.5 Hz, 1H), 5.42 (d, *J* = 1.8 Hz, 1H), 5.65-5.78 (m, 1H), 6.27 (t, *J* = 2.3 Hz, 2H), 6.34-6.45 (m, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.91-6.96 (m, 1H), 6.96-7.02 (m, 1H), 7.04 (t, *J* = 2.3 Hz, 2H), 7.08-7.15 (m, 1H), 7.37-7.51 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 20.7, 26.7, 56.2, 66.1, 106.4, 109.2, 109.5, 109.7, 119.4, 120.3, 122.5, 123.2, 126.1, 126.2, 131.1, 131.3, 133.0, 144.0, 157.1, 171.9; HRMS (ESI-TOF) Calcd. for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 412.1268; found: 412.1270.



**(S)-1-methyl-3-((2S,3R)-6-methyl-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3j).** Light yellow solid; 38.6 mg, 99% yield; >20:1 dr, 96% ee; [α]<sub>D</sub><sup>20</sup> = -73.1 (*c* 1.64, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 175.1-176.4 °C.

The ee was determined by HPLC analysis using a Chiralpak IA-H column (95/5 hexane/<sup>i</sup>PrOH; flow rate: 1.0 mL/min; λ = 254 nm; *t*<sub>major</sub> = 24.04 min, *t*<sub>minor</sub> = 17.87 min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.36 (s, 3H), 3.24 (s, 3H),

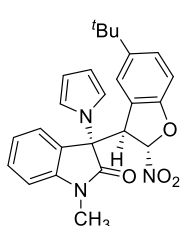
4.81-4.91 (m, 1H), 5.45 (d, *J* = 1.9 Hz, 1H), 5.86 (d, *J* = 7.7 Hz, 1H), 6.26 (t, *J* = 2.2 Hz, 2H), 6.40-6.47 (m, 1H), 6.66-6.74 (m, 1H), 6.82 (d, *J* = 1.4 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.96-7.05 (m, 3H), 7.39-7.48 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 21.6, 26.7, 55.9, 66.1, 106.4, 109.2, 109.5, 110.9, 117.3, 119.4, 122.6, 123.2, 124.3, 125.1, 126.1, 131.3, 141.5, 144.0, 159.3, 171.9; HRMS (ESI-TOF) Calcd. for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 412.1268; found: 412.1263.



**(S)-3-((2S,3R)-5-methoxy-2-nitro-2,3-dihydrobenzofuran-3-yl)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (3k).** Light yellow solid; 39.2 mg, 97% yield; >20:1 dr, 93% ee; [α]<sub>D</sub><sup>20</sup> = -105.9 (*c* 1.56, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 185.3-186.6 °C.

The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/<sup>i</sup>PrOH; flow rate: 1.0 mL/min; λ = 254 nm; *t*<sub>major</sub> = 25.48 min, *t*<sub>minor</sub> = 17.49 min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.27 (s, 3H), 3.54 (s, 3H),

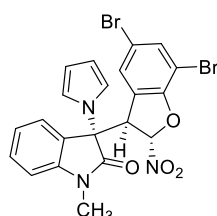
4.87 (d, *J* = 1.8 Hz, 1H), 5.37 (d, *J* = 1.8 Hz, 1H), 5.46 (d, *J* = 2.5 Hz, 1H), 6.27 (t, *J* = 2.2 Hz, 2H), 6.34-6.40 (m, 1H), 6.82-6.93 (m, 2H), 6.93-7.01 (m, 2H), 7.05 (t, *J* = 2.2 Hz, 2H), 7.40-7.49 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 26.7, 55.6, 56.5, 65.9, 106.6, 109.3, 109.5, 109.6, 117.3, 119.2, 119.5, 121.1, 122.1, 123.2, 126.3, 131.4, 144.0, 152.9, 155.9, 171.9; HRMS (ESI-TOF) Calcd. for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>NaO<sub>5</sub> [M+Na]<sup>+</sup>: 428.1217; found: 428.1216.



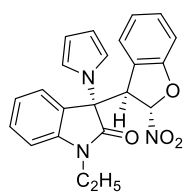
**(S)-3-((2S,3R)-5-(tert-butyl)-2-nitro-2,3-dihydrobenzofuran-3-yl)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (3l).** Light yellow solid; 42.6 mg, 99% yield; >20:1 dr, 95% ee; [α]<sub>D</sub><sup>20</sup> = -85.1 (*c* 1.65, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 198.0-199.1 °C.

The ee was determined by HPLC analysis using a Chiralpak IA-H column

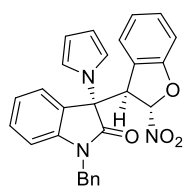
(90/10 hexane/<sup>i</sup>PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 11.82$  min,  $t_{\text{minor}} = 9.18$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.13 (s, 9H), 3.21 (s, 3H), 4.87 (d,  $J = 2.5$  Hz, 1H), 5.50 (d,  $J = 1.8$  Hz, 1H), 5.94 (d,  $J = 2.1$  Hz, 1H), 6.28 (t,  $J = 2.2$  Hz, 2H), 6.39 (d,  $J = 7.5$  Hz, 1H), 6.85-6.96 (m, 2H), 6.97-7.09 (m, 3H), 7.30-7.36 (m, 1H), 7.39-7.47 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  26.6, 31.3, 34.4, 56.2, 66.2, 106.6, 109.2, 109.3, 109.6, 119.4, 119.9, 122.7, 122.9, 123.3, 126.0, 127.4, 131.2, 143.9, 146.6, 156.8, 171.9; HRMS (ESI-TOF) Calcd. for C<sub>25</sub>H<sub>25</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 454.1737; found: 454.1739.



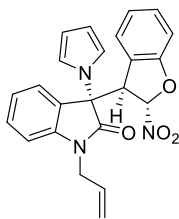
**(S)-3-((2S,3R)-5,7-dibromo-2-nitro-2,3-dihydrobenzofuran-3-yl)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (3m).** Light yellow solid; 49.2 mg, 92% yield; >20:1 dr, 91% ee;  $[\alpha]_{\text{D}}^{20} = -79.2$  (*c* 1.81, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 142.3-143.5 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/<sup>i</sup>PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 19.58$  min,  $t_{\text{minor}} = 15.90$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.27 (s, 3H), 4.94 (d,  $J = 2.1$  Hz, 1H), 5.44 (d,  $J = 2.1$  Hz, 1H), 5.79-5.90 (m, 1H), 6.30 (t,  $J = 2.2$  Hz, 2H), 6.38-6.52 (m, 1H), 6.99 (d,  $J = 7.9$  Hz, 1H), 7.01-7.10 (m, 3H), 7.43-7.55 (m, 1H), 7.64 (d,  $J = 1.9$  Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  26.8, 57.2, 65.7, 103.6, 105.5, 109.6, 110.1, 116.1, 119.3, 121.7, 123.5, 123.8, 125.9, 127.9, 131.9, 136.0, 144.0, 155.9, 171.4; HRMS (ESI-TOF) Calcd. for C<sub>21</sub>H<sub>15</sub><sup>79</sup>Br<sub>2</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 553.9314; found: 553.9322; Calcd. for C<sub>21</sub>H<sub>15</sub><sup>81</sup>Br<sub>2</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 557.9281; found: 557.929; Calcd. for C<sub>21</sub>H<sub>15</sub><sup>79</sup>Br<sup>81</sup>BrN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 555.9301; found: 555.9317.



**(S)-1-ethyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3n).** Light yellow solid; 35.8 mg, 92% yield; 17:1 dr, 89% ee;  $[\alpha]_{\text{D}}^{20} = -4.7$  (*c* 1.83, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 157.1-158.4 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (95/5 hexane/<sup>i</sup>PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 33.69$  min,  $t_{\text{minor}} = 28.42$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.08 (t,  $J = 7.1$  Hz, 3H), 3.47-3.67 (m, 1H), 3.79-3.98 (m, 1H), 4.89 (d,  $J = 1.8$  Hz, 1H), 5.67 (d,  $J = 1.8$  Hz, 1H), 5.93 (d,  $J = 7.6$  Hz, 1H), 6.29 (t,  $J = 2.2$  Hz, 2H), 6.61 (d,  $J = 7.6$  Hz, 1H), 6.80-6.89 (m, 1H), 6.92 (d,  $J = 7.9$  Hz, 1H), 6.98-7.10 (m, 4H), 7.25-7.35 (m, 1H), 7.39-7.47 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  12.2, 35.1, 56.1, 66.1, 106.3, 109.3, 109.7, 110.0, 110.4, 120.3, 123.1, 123.2, 123.6, 125.4, 125.7, 130.7, 131.1, 142.8, 159.0, 171.2; HRMS (ESI-TOF) Calcd. for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 412.1268; found: 412.1263.

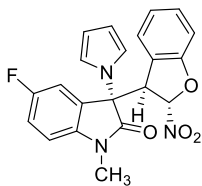


**(S)-1-benzyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3o).** Light yellow solid; 40.1 mg, 89% yield; 13:1 dr, 91% ee;  $[\alpha]_{\text{D}}^{20} = +37.9$  (*c* 1.71, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 170.2-171.3 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (95/5 hexane/EtOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 12.55$  min,  $t_{\text{minor}} = 15.85$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.58 (d,  $J = 15.4$  Hz, 1H), 4.98 (d,  $J = 1.8$  Hz, 1H), 5.19 (d,  $J = 15.4$  Hz, 1H), 5.62 (d,  $J = 1.8$  Hz, 1H), 6.01 (d,  $J = 7.5$  Hz, 1H), 6.32 (q,  $J = 2.5$  Hz, 2H), 6.54 (d,  $J = 7.5$  Hz, 1H), 6.80-6.91 (m, 2H), 6.94-7.05 (m, 2H), 7.10 (t,  $J = 2.3$  Hz, 2H), 7.16-7.22 (m, 2H), 7.27-7.35 (m, 5H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  44.4, 56.1, 66.1, 106.1, 109.8, 110.3, 119.4, 119.6, 120.3, 123.3, 123.4, 125.6, 125.7, 127.7, 128.0, 128.8, 129.0, 130.8, 131.1, 134.8, 142.9, 159.1, 171.9; HRMS (ESI-TOF) Calcd. for C<sub>27</sub>H<sub>21</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 474.1424; found: 474.1426.



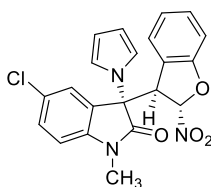
**(S)-1-allyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3p).**

Light yellow solid; 38.8 mg, 97% yield; 10:1 dr, 86% ee;  $[\alpha]_D^{20} = +12.3$  (*c* 1.95, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 161.3-162.4 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (95/5 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 29.01$  min,  $t_{\text{minor}} = 26.33$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.13-4.25 (m, 1H), 4.38-4.50 (m, 1H), 4.87-4.96 (m, 1H), 5.08-5.24 (m, 2H), 5.53-5.72 (m, 2H), 5.97 (d, *J* = 7.6 Hz, 1H), 6.29 (q, *J* = 2.1 Hz, 2H), 6.58 (d, *J* = 7.5 Hz, 1H), 6.81-6.95 (m, 2H), 6.97-7.11 (m, 4H), 7.24-7.36 (m, 1H), 7.36-7.48 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  42.7, 56.0, 66.1, 106.3, 109.8, 110.1, 110.4, 118.7, 119.4, 119.6, 120.3, 123.3, 124.2, 125.5, 125.6, 130.3, 130.8, 131.1, 142.9, 159.1, 171.4; HRMS (ESI-TOF) Calcd. for C<sub>23</sub>H<sub>19</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 424.1268; found: 424.1264.



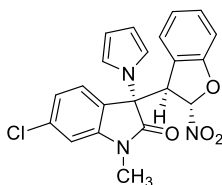
**(S)-5-fluoro-1-methyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3q).**

Light yellow solid; 38.5 mg, 98% yield; >20:1 dr, 93% ee;  $[\alpha]_D^{20} = -45.4$  (*c* 1.56, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 169.3-170.4 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 19.25$  min,  $t_{\text{minor}} = 26.56$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.22 (s, 3H), 4.87-4.97 (m, 1H), 5.49 (d, *J* = 1.8 Hz, 1H), 6.01 (d, *J* = 7.5 Hz, 1H), 6.04-6.15 (m, 1H), 6.29 (t, *J* = 2.2 Hz, 2H), 6.84-6.95 (m, 2H), 6.98-7.07 (m, 3H), 7.11-7.22 (m, 1H), 7.30-7.41 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  26.8, 55.8, 66.3, 105.9, 109.9, 110.0, 110.5, 114.2 (d, *J* = 25.6 Hz), 118.0 (d, *J* = 23.4 Hz), 119.3, 119.9, 123.6, 123.9 (d, *J* = 7.9 Hz), 125.5, 131.1, 139.9, 158.8 (d, *J* = 242.4 Hz), 159.0, 171.6; HRMS (ESI-TOF) Calcd. for C<sub>21</sub>H<sub>16</sub>FN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 416.1017; found: 416.1028.



**(S)-5-chloro-1-methyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3r).**

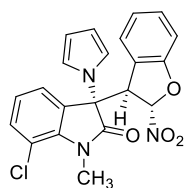
Light yellow solid; 40.5 mg, 99% yield; >20:1 dr, 92% ee;  $[\alpha]_D^{20} = -36.2$  (*c* 1.65, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 194.7-150.8 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 17.07$  min,  $t_{\text{minor}} = 23.58$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.20 (s, 3H), 4.91 (d, *J* = 2.3 Hz, 1H), 5.51 (d, *J* = 1.8 Hz, 1H), 5.96-6.06 (m, 1H), 6.24-6.38 (m, 3H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.88-6.95 (m, 1H), 7.00 (t, *J* = 2.3 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 1H), 7.32-7.39 (m, 1H), 7.39-7.45 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  26.8, 55.9, 77.4, 105.9, 110.0, 110.2, 110.5, 119.3, 119.9, 123.6, 124.3, 125.5, 126.3, 128.8, 131.1, 131.3, 142.4, 159.0, 171.4; HRMS (ESI-TOF) Calcd. for C<sub>21</sub>H<sub>16</sub><sup>35</sup>ClN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 432.0722; found: 432.0729; Calcd. for C<sub>21</sub>H<sub>16</sub><sup>37</sup>ClN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 434.0692; found: 434.0713.



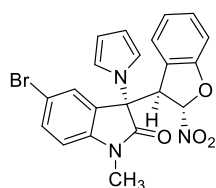
**(S)-6-chloro-1-methyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3s).**

Light yellow solid; 40.2 mg, 98% yield; >20:1 dr, 95% ee;  $[\alpha]_D^{20} = -76.3$  (*c* 1.64, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 157.3-158.9 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 15.34$  min,  $t_{\text{minor}} = 13.44$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.22 (s, 3H), 4.90 (d, *J* = 2.5 Hz, 1H), 5.45 (d, *J* = 1.8 Hz, 1H), 5.93-6.07 (m, 1H), 6.24 (d, *J* = 8.7 Hz, 1H), 6.26-6.30 (m, 2H), 6.86-6.94 (m, 1H), 6.94-7.00 (m, 4H), 7.01 (d, *J* = 8.1 Hz, 1H), 7.30-7.39 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  26.8, 55.9, 65.8, 105.9, 109.9, 110.1, 110.5, 119.3, 120.1, 120.7, 123.2, 123.6, 125.6, 127.0, 131.0, 137.5, 145.2, 159.0, 171.8; HRMS (ESI-TOF) Calcd. for

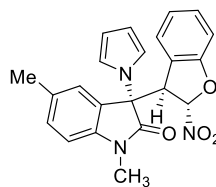
C<sub>21</sub>H<sub>16</sub><sup>35</sup>ClN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 432.0722; found:432.0724; Calcd. for C<sub>21</sub>H<sub>16</sub><sup>37</sup>ClN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 434.0692; found:434.0708.



**(S)-7-chloro-1-methyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3t).** Light yellow solid; 39.8 mg, 97% yield; >20:1 dr, 90% ee;  $[\alpha]_D^{20} = -33.3$  (*c* 1.87, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 87.2-88.3 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 14.45$  min,  $t_{\text{minor}} = 11.73$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.56 (s, 3H), 4.92 (d, *J* = 2.3 Hz, 1H), 5.60 (d, *J* = 1.8 Hz, 1H), 5.99 (d, *J* = 7.6 Hz, 1H), 6.28 (t, *J* = 2.2 Hz, 2H), 6.33 (d, *J* = 7.6 Hz, 1H), 6.86-6.94 (m, 2H), 6.97-7.04 (m, 3H), 7.30-7.40 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  30.2, 55.9, 65.7, 106.0, 110.0, 110.5, 116.7, 119.3, 120.0, 123.5, 123.9, 124.3, 125.5, 125.6, 131.0, 133.6, 139.9, 159.0, 172.1; HRMS (ESI-TOF) Calcd. for C<sub>21</sub>H<sub>16</sub><sup>35</sup>ClN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 432.0722; found:432.0738; Calcd. for C<sub>21</sub>H<sub>16</sub><sup>37</sup>ClN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 434.0692; found:434.0722.



**(S)-5-bromo-1-methyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3u).** Light yellow solid; 43.1 mg, 95% yield; >20:1 dr, 92% ee;  $[\alpha]_D^{20} = -37.3$  (*c* 1.63, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 165.3-166.5 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 17.91$  min,  $t_{\text{minor}} = 24.91$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.19 (s, 3H), 4.91 (d, *J* = 1.7 Hz, 1H), 5.52 (d, *J* = 1.7 Hz, 1H), 5.96-6.06 (m, 1H), 6.30 (t, *J* = 2.2 Hz, 2H), 6.43 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.88-6.95 (m, 1H), 7.00 (t, *J* = 2.2 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.33-7.41 (m, 1H), 7.55-7.58 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  26.8, 55.9, 66.3, 105.9, 110.0, 110.5, 110.6, 115.9, 119.3, 119.9, 123.6, 124.6, 125.5, 129.0, 131.1, 134.2, 142.9, 159.0, 171.3; HRMS (ESI-TOF) Calcd. for C<sub>21</sub>H<sub>16</sub><sup>79</sup>BrN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 476.0216; found: 476.0213; Calcd. for C<sub>21</sub>H<sub>16</sub><sup>81</sup>BrN<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 478.0196; found: 478.0195.

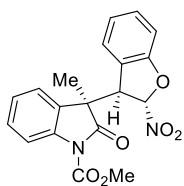


**(S)-1,5-dimethyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3v).** Light yellow solid; 38.1 mg, 98% yield; >20:1 dr, 95% ee;  $[\alpha]_D^{20} = -41.2$  (*c* 1.88, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 96.7-97.9 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 24.18$  min,  $t_{\text{minor}} = 32.61$  min); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.19 (s, 3H), 3.19 (s, 3H), 4.90 (d, *J* = 2.3 Hz, 1H), 5.50 (d, *J* = 1.8 Hz, 1H), 5.99 (d, *J* = 7.6 Hz, 1H), 6.14 (s, 1H), 6.27 (t, *J* = 2.2 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.86-6.94 (m, 1H), 6.97-7.07 (m, 3H), 7.19-7.25 (m, 1H), 7.30-7.37 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  21.0, 26.6, 56.0, 66.3, 106.1, 108.9, 109.5, 110.1, 119.4, 120.5, 122.5, 123.3, 125.6, 126.6, 130.7, 131.5, 132.9, 141.4, 159.1, 171.7; HRMS (ESI-TOF) Calcd. for C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 412.1268; found: 412.1263.

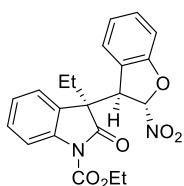
## 5. General experimental procedures for asymmetric synthesis of compounds 5

To a solution of catalyst **D** (7.1 mg, 0.01 mmol, 10 mol %) and 2-nitrobenzofuran **1a** (0.12 mmol) in xylene (1.0 mL) was added 3-monosubstituted oxindoles **4** (0.1 mmol) at -20 °C or rt. Then the mixture was stirred continuously for specific time at -20 °C or rt. After completion, the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 3:1~6:1) to give the corresponding products **5**.

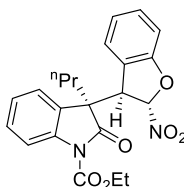




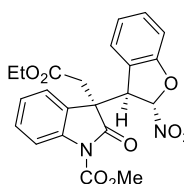
**methyl (R)-3-methyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-2-oxoindoline-1-carboxylate (5a).** Light yellow solid; 36.4 mg, 99% yield; 13:1 dr, 95% ee;  $[\alpha]_{\text{D}}^{20} = +17.2$  (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 165.0-166.1 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (70/30 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 8.27$  min,  $t_{\text{minor}} = 9.24$  min);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.83 (s, 3H), 3.91 (s, 3H), 4.10 (d, *J* = 1.6 Hz), 6.11 (d, *J* = 7.6 Hz, 1H), 6.47 (d, *J* = 1.9 Hz, 1H), 6.68-6.82 (m, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 7.11-7.16 (m, 1H), 7.21-7.33 (m, 2H), 7.41-7.48 (m, 1H), 7.91 (d, *J* = 8.1 Hz, 1H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  22.6, 50.1, 54.1, 57.3, 107.0, 111.0, 115.6, 121.3, 122.8, 122.9, 124.8, 125.4, 129.5, 129.6, 130.6, 139.2, 150.8, 158.4, 176.0; HRMS (ESI-TOF) Calcd. for  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{NaO}_6$   $[\text{M}+\text{Na}]^+$ : 391.0901; found: 391.0900.



**ethyl (R)-3-ethyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-2-oxoindoline-1-carboxylate (5b).** Light yellow solid; 37.2 mg, 94% yield; 10:1 dr, 94% ee;  $[\alpha]_{\text{D}}^{20} = +22.6$  (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 116.9-118.0 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 14.74$  min,  $t_{\text{minor}} = 16.08$  min);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (major diastereomers) 0.76 (t, *J* = 7.4 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 2.12-2.28 (m, 1H), 2.43-2.59 (m, 1H), 4.11 (d, *J* = 2.4 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 6.09 (d, *J* = 7.6 Hz, 1H), 6.50 (d, *J* = 1.9 Hz, 1H), 6.70-6.78 (m, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 7.06-7.11 (m, 1H), 7.21-7.26 (m, 1H), 7.27-7.34 (m, 1H), 7.38-7.52 (m, 1H), 7.81-7.93 (m, 1H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (major diastereomers) 8.5, 14.1, 29.3, 55.5, 56.9, 63.6, 107.0, 110.9, 115.4, 121.3, 122.7, 123.0, 124.9, 125.2, 127.5, 129.6, 130.4, 140.4, 150.1, 158.4, 175.5; HRMS (ESI-TOF) Calcd. for  $\text{C}_{21}\text{H}_{20}\text{N}_2\text{NaO}_6$   $[\text{M}+\text{Na}]^+$ : 419.1214; found: 419.1200.

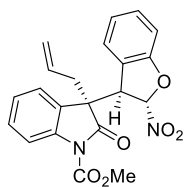


**ethyl (R)-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-2-oxo-3-propylindoline-1-carboxylate (5c).** Light yellow solid; 39.0 mg, 95% yield; >20:1 dr, 94% ee;  $[\alpha]_{\text{D}}^{20} = +71.7$  (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 202.0-203.0 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 10.68$  min,  $t_{\text{minor}} = 13.56$  min);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.91 (t, *J* = 7.1 Hz, 3H), 0.96-1.05 (m, 1H), 1.09-1.22 (m, 1H), 1.31-1.41 (m, 3H), 2.09-2.21 (m, 1H), 2.33-2.49 (m, 1H), 4.10 (d, *J* = 1.8 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 6.06 (d, *J* = 7.6 Hz, 1H), 6.52 (d, *J* = 1.9 Hz, 1H), 6.67-6.79 (m, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 7.07-7.14 (m, 1H), 7.19-7.26 (m, 1H), 7.27-7.33 (m, 1H), 7.38-7.48 (m, 1H), 7.86 (d, *J* = 8.2 Hz, 1H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.0, 14.1, 17.6, 38.2, 54.9, 57.0, 63.6, 107.0, 110.9, 115.4, 121.2, 122.6, 123.0, 124.9, 125.2, 127.9, 129.5, 130.4, 140.2, 150.1, 158.4, 175.6; HRMS (ESI-TOF) Calcd. for  $\text{C}_{22}\text{H}_{22}\text{N}_2\text{NaO}_6$   $[\text{M}+\text{Na}]^+$ : 433.1370; found: 433.1377.

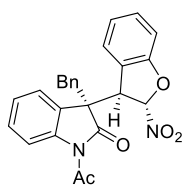


**methyl (R)-3-(2-ethoxy-2-oxoethyl)-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-2-oxoindoline-1-carboxylate (5d).** Light yellow solid; 30.8 mg, 70% yield; 16:1 dr, 94% ee;  $[\alpha]_{\text{D}}^{20} = +36.1$  (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 171.2-172.1 °C. The ee was determined by HPLC analysis using a Chiralpak IC-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 15.83$  min,  $t_{\text{minor}} = 10.70$  min);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.05 (t, *J* = 7.1 Hz, 3H), 3.31 (d, *J* = 16.5 Hz, 1H), 3.56 (d, *J* = 16.5 Hz, 1H), 3.91 (s, 3H), 3.92-3.96 (m, 1H), 3.96-4.02 (m, 1H), 4.12 (d, *J* = 2.3 Hz, 1H), 6.02 (d, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 1.9 Hz, 1H), 6.69-6.82 (m, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.23-7.30 (m, 2H), 7.42-7.49 (m, 1H), 7.88-7.97 (m, 1H);

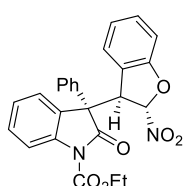
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.7, 40.4, 51.4, 54.1, 56.7, 61.4, 106.3, 111.1, 115.6, 120.2, 122.7, 122.9, 125.0, 125.2, 126.9, 130.0, 130.8, 140.7, 150.8, 158.5, 168.5, 174.8; HRMS (ESI-TOF) Calcd. for  $\text{C}_{22}\text{H}_{20}\text{N}_2\text{NaO}_8$   $[\text{M}+\text{Na}]^+$ : 463.1112; found: 463.1109.



**methyl (R)-3-allyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)-2-oxoindoline-1-carboxylate (5e).** Light yellow solid; 32.3 mg, 84% yield; 3:1 dr, 94% ee;  $[\alpha]_{\text{D}}^{20} = +8.4$  (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 176.0-177.0 °C. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 23.13$  min,  $t_{\text{minor}} = 63.01$  min);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (major diastereomers) 2.97 (dd,  $J = 13.6, 6.6$  Hz, 1H), 3.12 (dd,  $J = 13.5, 7.9$  Hz, 1H), 3.91 (s, 3H), 5.07-4.97 (m, 1H), 5.18-5.10 (m, 1H), 5.51-5.27 (m, 1H), 6.12 (d,  $J = 7.5$  Hz, 1H), 6.54 (d,  $J = 1.5$  Hz, 1H), 6.75 (t,  $J = 7.5$  Hz, 1H), 7.03 (d,  $J = 8.1$  Hz, 1H), 7.16-7.10 (m, 1H), 7.25-7.20 (m, 1H), 7.34-7.25 (m, 2H), 7.49-7.39 (m, 1H), 7.89 (d,  $J = 8.2$  Hz, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (major diastereomers) 40.4, 54.0, 54.7, 56.3, 106.9, 111.0, 115.5, 121.1, 121.2, 122.8, 123.4, 125.0, 125.2, 127.2, 129.7, 129.8, 130.6, 140.0, 150.7, 158.5, 174.9; HRMS (ESI-TOF) Calcd. for  $\text{C}_{21}\text{H}_{18}\text{N}_2\text{NaO}_6$   $[\text{M}+\text{Na}]^+$ : 417.1057; found: 417.1053.



**(R)-1-acetyl-3-benzyl-3-((2S,3R)-2-nitro-2,3-dihydrobenzofuran-3-yl)indoline-2-one (5f).** Light yellow solid; 34.2 mg, 80% yield; 10:1 dr, 71% ee;  $[\alpha]_{\text{D}}^{20} = +41.4$  (*c* 1.00,  $\text{CH}_2\text{Cl}_2$ ); m.p. 186.1-187.0 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (85/15 hexane/EtOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 9.96$  min,  $t_{\text{minor}} = 14.07$  min);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (major diastereomers) 2.34 (s, 3H), 3.45 (d,  $J = 13.0$  Hz, 1H), 3.75 (d,  $J = 13.0$  Hz, 1H), 4.35 (d,  $J = 1.9$  Hz, 1H), 6.33 (d,  $J = 7.6$  Hz, 1H), 6.52 (d,  $J = 1.9$  Hz, 1H), 6.77-6.89 (m, 3H), 7.02-7.11 (m, 4H), 7.12-7.18 (m, 1H), 7.28-7.38 (m, 3H), 7.87-8.00 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (major diastereomers) 26.1, 42.4, 56.5, 56.6, 107.1, 110.9, 116.6, 121.3, 123.0, 123.4, 125.3, 125.4, 126.9, 127.4, 128.1, 129.6, 129.7, 130.7, 133.4, 140.7, 158.6, 169.9, 177.4; HRMS (ESI-TOF) Calcd. for  $\text{C}_{25}\text{H}_{20}\text{N}_2\text{NaO}_5$   $[\text{M}+\text{Na}]^+$ : 451.1264; found: 451.1262.



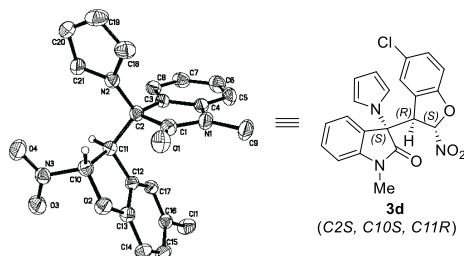
**ethyl 3-((-2-nitro-2,3-dihydrobenzofuran-3-yl)-2-oxo-3-phenylindoline-1-carboxylate (5g).** Light yellow solid; 22.2 mg, 50% yield; >20:1 dr, 0 ee; m.p. 224.0-225.1 °C. The ee was determined by HPLC analysis using a Chiralpak IA-H column (90/10 hexane/*i*PrOH; flow rate: 1.0 mL/min;  $\lambda = 254$  nm;  $t_{\text{major}} = 17.42$  min,  $t_{\text{minor}} = 18.81$  min);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.43 (t,  $J = 7.1$  Hz, 3H), 4.45 (q,  $J = 7.1$  Hz, 2H), 5.00 (d,  $J = 1.8$  Hz, 1H), 5.78 (d,  $J = 1.7$  Hz, 1H), 6.02 (d,  $J = 7.6$  Hz, 1H), 6.56 (d,  $J = 7.6$  Hz, 1H), 6.71-6.87 (m, 1H), 7.03 (d,  $J = 8.1$  Hz, 1H), 7.09-7.21 (m, 1H), 7.24-7.32 (m, 1H), 7.41-7.49 (m, 4H), 7.52-7.60 (m, 2H), 8.00 (d,  $J = 8.2$  Hz, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 56.4, 58.7, 63.8, 107.8, 110.8, 115.7, 121.8, 122.8, 125.0, 125.2, 125.3, 126.3, 127.8, 128.7, 129.2, 129.9, 130.7, 135.9, 139.5, 150.4, 159.1, 173.8; HRMS (ESI-TOF) Calcd. for  $\text{C}_{25}\text{H}_{20}\text{N}_2\text{NaO}_6$   $[\text{M}+\text{Na}]^+$ : 467.1214; found: 467.1217.

## 6. Scale-up experiment

To a solution of catalyst **E** (106.5 mg, 5 mol %) and 2-nitrobenzofuran **1a** (0.587 g, 3.6 mmol) in xylene (30.0 mL) was added 3-pyrrolyl-oxindole **2a** (0.636 g, 3.0 mmol) at -20 °C. Then the mixture was stirred continuously for 84 h at -20 °C. After completion, the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give the corresponding product **3a** in 99% yield (1.115 g).

## 7. X-Ray crystal data for compounds **3c**

Single crystals of compound **3d** were prepared from the mixture solvent of EtOH and CH<sub>2</sub>Cl<sub>2</sub>. A suitable crystal was selected for structure determination on a Xcalibur, Eos, Gemini diffractometer. The crystal was kept at 293(2) K during data collection. Using Olex2, the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXLrefinement package using Least Squares minimisation.

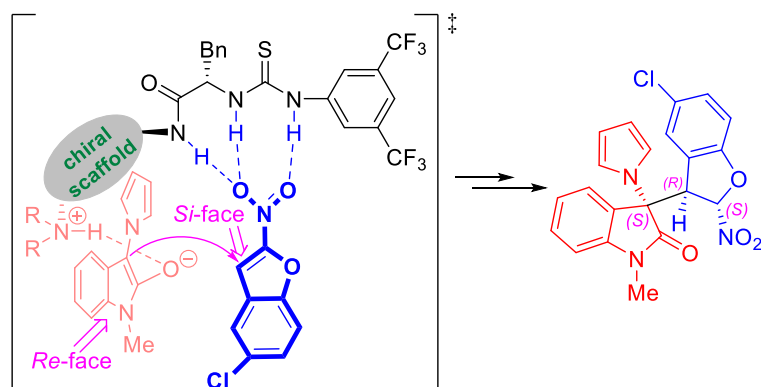


ORTEP of **3d** (at 50% level)

Crystal data and structure refinement for **3d** (1943699)

Identification code	<b>3d</b>
Empirical formula	C <sub>21</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>4</sub>
Formula weight	409.82
Temperature/K	293(2)
Crystal system	monoclinic
Space group	P2 <sub>1</sub>
a/Å	9.3140(4)
b/Å	21.8053(13)
c/Å	9.5831(5)
α/°	90
β/°	94.306(4)
γ/°	90
Volume/Å <sup>3</sup>	1940.77(17)
Z	4
ρ <sub>calc</sub> /cm <sup>3</sup>	1.403
μ/mm <sup>-1</sup>	2.035
F(000)	848.0
Crystal size/mm <sup>3</sup>	0.15 × 0.13 × 0.1
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	8.11 to 134.14
Index ranges	-11 ≤ h ≤ 11, -26 ≤ k ≤ 23, -11 ≤ l ≤ 10
Reflections collected	18941
Independent reflections	6342 [R <sub>int</sub> = 0.0369, R <sub>sigma</sub> = 0.0402]
Data/restraints/parameters	6342/1/525
Goodness-of-fit on F <sup>2</sup>	1.032
Final R indexes [I ≥ 2σ (I)]	R <sub>1</sub> = 0.0448, wR <sub>2</sub> = 0.1130
Final R indexes [all data]	R <sub>1</sub> = 0.0508, wR <sub>2</sub> = 0.1204
Largest diff. peak/hole / e Å <sup>-3</sup>	0.15/-0.18
Flack parameter	-0.011(10)

## 8. Proposed activation mode of the chiral catalyst **D** to the reaction between 3-monosubstituted oxindoles and 2-nitrobenzofurans.



In light of the multiple hydrogen-bonding bifunctional thiourea catalytic model<sup>[ref.1]</sup> and other relevant reports,<sup>[ref.2]</sup> we have proposed a possible activation mode to account for the stereochemistry of the Michael addition process between 3-monosubstituted oxindole and 2-nitrobenzofuran. The substrate 2-nitrobenzofuran is activated and oriented by the multiple hydrogen bonds of thiourea and amide moieties of the catalyst **D**, while the tertiary nitrogen of the cinchonidine would provide suitable basicity to enhance the nucleophilicity of the 3-monosubstituted oxindole. Under this dual-activation model, the C3-position of 3-monosubstituted oxindole from *Re*-face attacks the *Si*-face of C3-position of 2-nitrobenzofuran, which undergoes the Michael addition to provide the 3,3'-disubstituted oxindole product with (*C2S*, *C10S*, *C11R*) configuration.

[ref.1] For selected reviews of bifunctional thiourea catalysis, see: (a) Y. Takemoto, *Org. Biomol. Chem.* 2005, **3**, 4299. (b) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.* 2007, **107**, 5713. (c) X. Yu and W. Wang, *Chem. Asian J.* 2008, **3**, 516. (d) Z. Zhang and P. R. chreiner, *Chem. Soc. Rev.* 2009, **38**, 1187. (e) X. Fang and C.-J. Wang, *Chem. Commun.* 2015, **51**, 1185. For selected examples, see: (f) T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.* 2003, **125**, 12672. (g) J. Ye, D. J. Dixon and P. S. Hynes, *Chem. Commun.* 2005, 4481. (h) J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc.* 2008, **130**, 14416. (i) Q. Zhu, and Y. Lu, *Angew. Chem., Int. Ed.* 2010, **49**, 7753. (j) X. Dou, W. Yao, B. Zhou and Y. Lu, *Chem. Commun.* 2013, 49, 9224. (k) D.-F. Yue, J.-Q. Zhao, Y.-Z. Chen, X.-M. Zhang, X.-Y. Xu and W.-C. Yuan, *Adv. Synth. Catal.* 2018, **360**, 1420.

[ref.2] For selected examples, see: (a) Q. Cheng, H.-J. Zhang, W.-J. Yue and S.-L. You, *Chem.*, 2017, **3**, 428; (b) J.-Q. Zhao, X.-J. Zhou, Y. Zhou, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *Org. Lett.* 2018, **20**, 909; (c) L. Liang H.-Y. Niu, D.-C. Wang, X.-H. Yang, G.-R. Qu and H.-M. Guo, *Chem. Commun.*, 2019, **55**, 553; (d) J.-Q. Zhao, Y. Yang, X.-J. Zhou, Y. You, Z.-H. Wang, M.-Q. Zhou, X.-M. Zhang, X.-Y. Xu and W.-C. Yuan, *Org. Lett.*, 2019, **21**, 660; (e) X.-J. Zhou, J.-Q. Zhao, X.-M. Chen, J.-R. Zhuo, Y.-P. Zhang, Y.-Z. Chen, X.-M. Zhang, X.-Y. Xu and W.-C. Yuan, *J. Org. Chem.*, 2019, **84**, 4381; (f) X.-H. Yang, J.-P. Li, D.-C. Wang, M.-S. Xie, G.-R. Qu and H.-M. Guo, *Chem. Commun.*, 2019, **55**, 9144.

## 9. General experimental procedures for in vitro cytotoxicity assay

Three human cancer cell lines, human leukemia cells K562, human lung cancer cells A549 and human prostate cancer cells PC-3 were purchased from Chinese Academy of Sciences,

Kunming Cell Bank and Chinese Academy of Sciences, Shanghai Cell Bank respectively. All the cells were cultured in RPMI-1640 medium (GIBICO, USA), supplemented with 10% fetal bovine serum (Hyclone, USA) and Penicillin-Streptomycin (respectively 100 U/mL) in 5% CO<sub>2</sub> at 37 °C. The cytotoxicity assay was performed according to the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) method in 96-well microplates. Briefly, 5000 cells were seeded into each well of 96-well cell culture plates and allowed to grow for 24 h before the drug is added. Unless K562 tumor cell line was exposed to compounds (**3a**, **3c**, **3e**, **3h**, **3j**, **3k**, **3g**, **3m**, **3r**, **3s**, **3u** and **3v**) at the concentrations of 1, 2, 4, 8 and 20 μmol·L<sup>-1</sup>, each A549 or PC-3 tumor cell line was exposed to the test compounds (**3a**, **3c**, **3e**, **3h**, **3j**, **3k**, **3g**, **3m**, **3r**, **3s**, **3u** and **3v**) at the concentrations of 5, 10, 20, 40 and 80 μmol·L<sup>-1</sup> in triplicates for 48 h, comparable to cisplatin (Aladdin, China). Then the MTT reagent was added to reaction with the cancer cells for 4 hours. At least, measure the OD value at 490 wavelengths. The average 50% inhibitory concentration (IC<sub>50</sub>) of all the compounds is calculated by IBM SPSS Statistics (version 19). Each concentration was analyzed in triplicate at least, and the whole experiment was repeated three times.

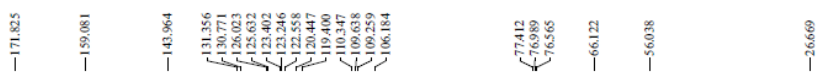
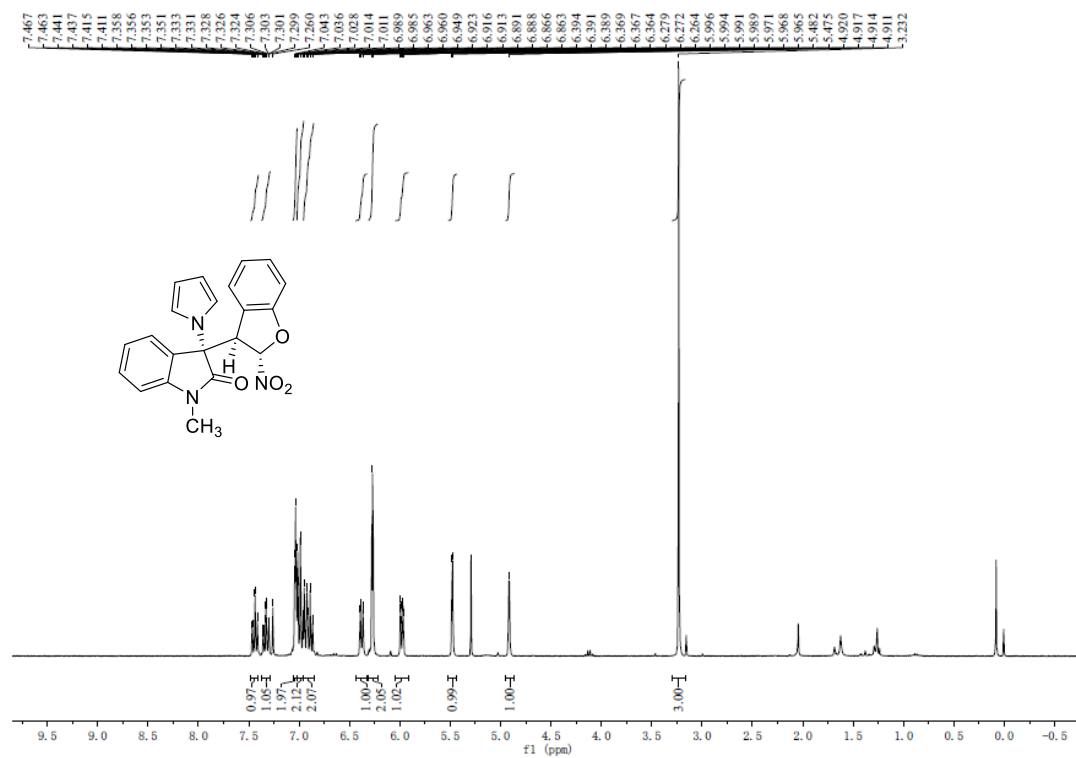
**Table 1. Cell Inhibitory Assay of target products in K562, A549, and PC-3 Cells**

compound	IC <sub>50</sub> (μM) <sup>a</sup>		
	K562	A549	PC-3
<b>3a</b>	50.39	29.75	32.55
<b>3c</b>	13.04	10.14	13.44
<b>3e</b>	35.93	52.45	19.50
<b>3h</b>	16.99	33.02	12.80
<b>3j</b>	10.36	9.04	20.93
<b>3k</b>	14.78	12.04	17.83
<b>3g</b>	29.58	23.57	25.50
<b>3m</b>	18.84	34.67	17.96
<b>3r</b>	27.93	29.25	8.52
<b>3s</b>	20.58	33.06	27.71
<b>3u</b>	20.28	29.61	29.49
<b>3v</b>	32.59	32.33	9.33
<b>cisplatin</b> <sup>b</sup>	21.77	17.40	20.33

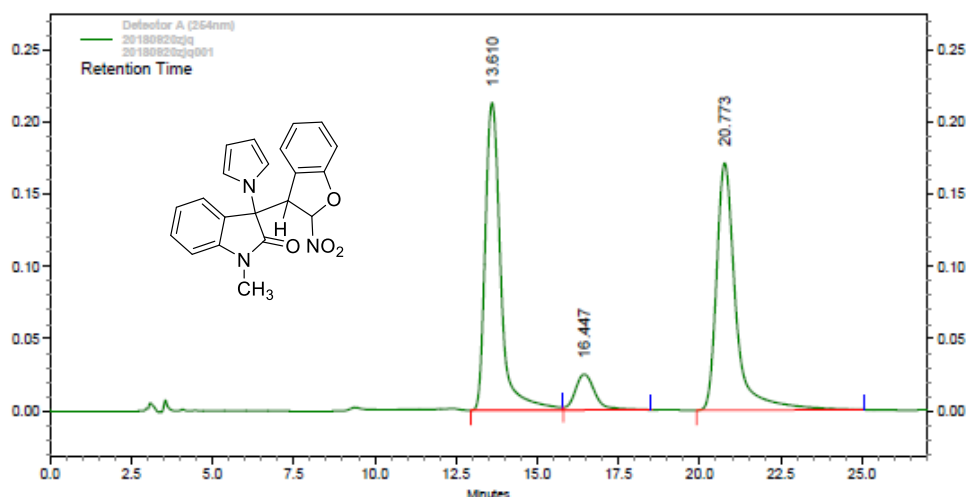
<sup>a</sup>IC<sub>50</sub> is the concentration of a compound that affords a 50% reduction in cell growth (after 48 h of incubation), expressed as the mean of triplicate experiments. <sup>b</sup>Commercially available broad-spectrum anticancer drug cisplatin as a positive control.

10.  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, and HPLC spectra for compounds 3 and 5

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

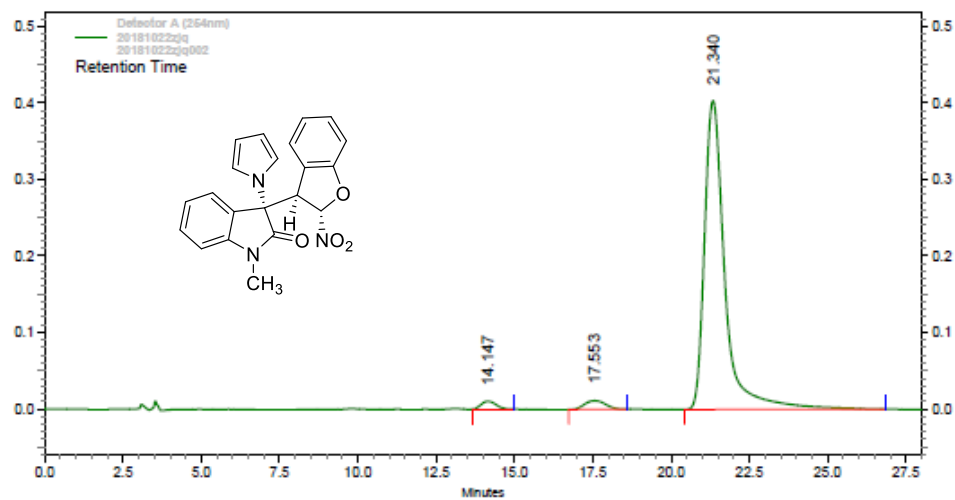


### HPLC of 3a



PK #	Retention Time	Height	Height Percent	Area	Area Percent
1	13.610	213164	52.09	7063146	46.55
2	16.447	24758	6.05	1045456	6.89
3	20.773	171291	41.86	7064170	46.56

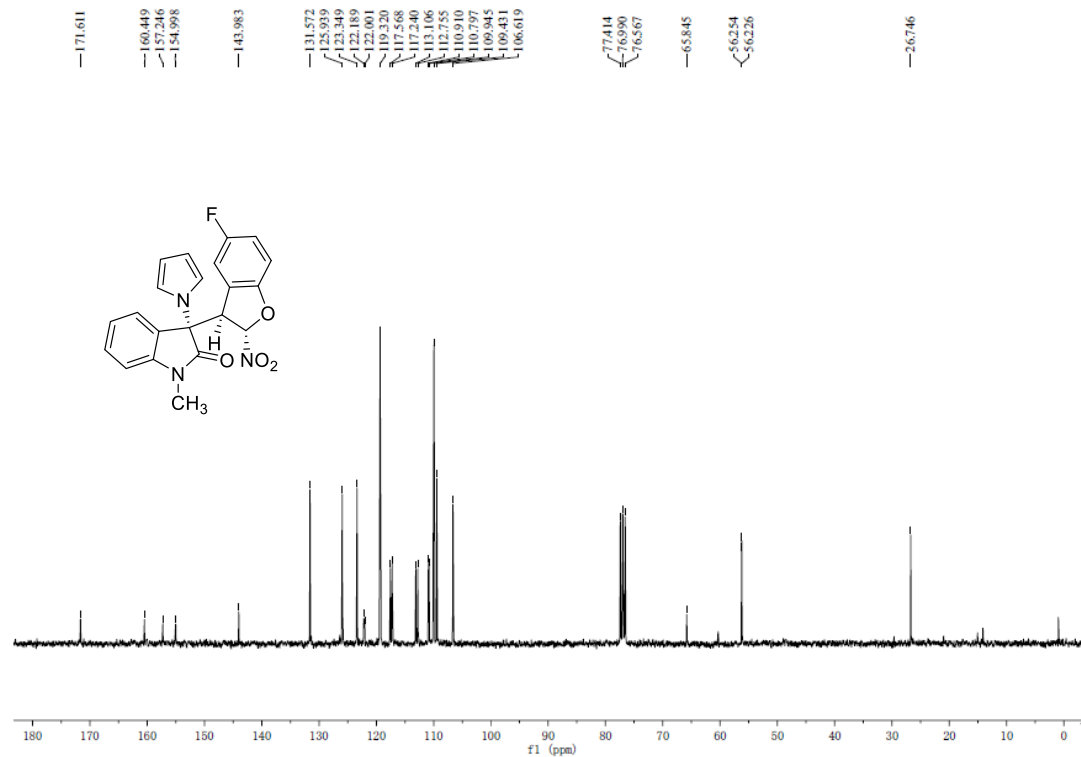
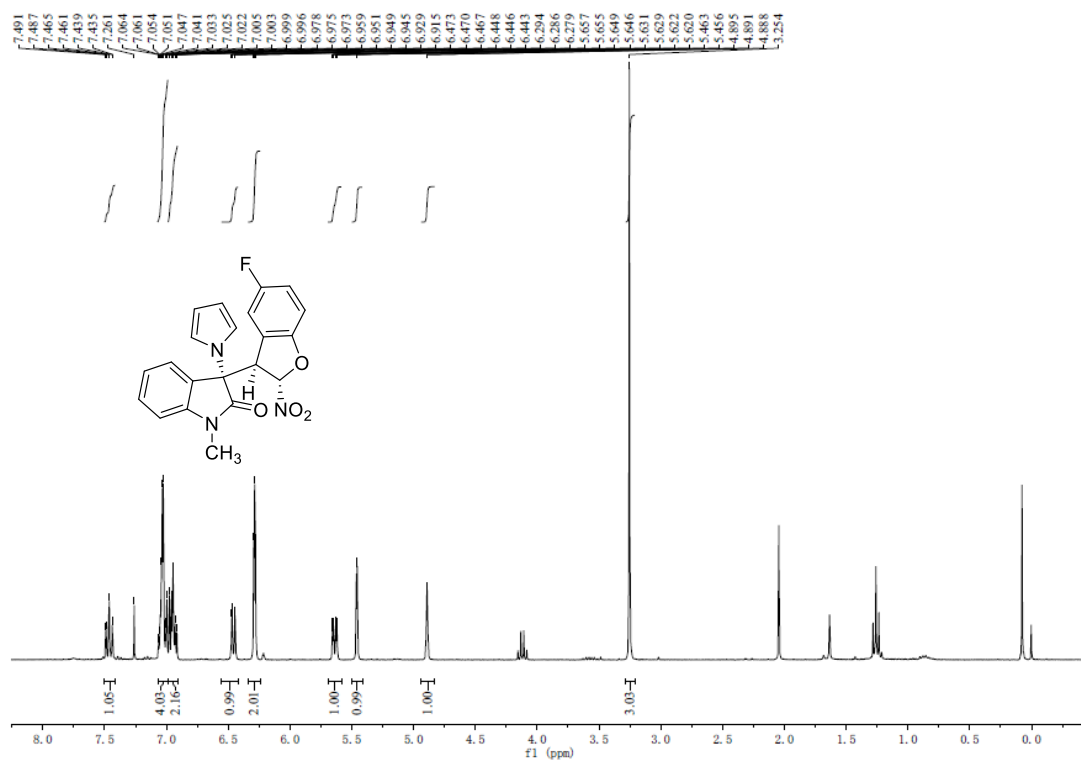
Totals	Height	Height Percent	Area	Area Percent
	409213	100.00	15172772	100.00



PK #	Retention Time	Height	Height Percent	Area	Area Percent
1	14.147	10187	2.40	344081	1.79
2	17.553	11310	2.66	527515	2.75
3	21.340	403767	94.95	18334981	95.46

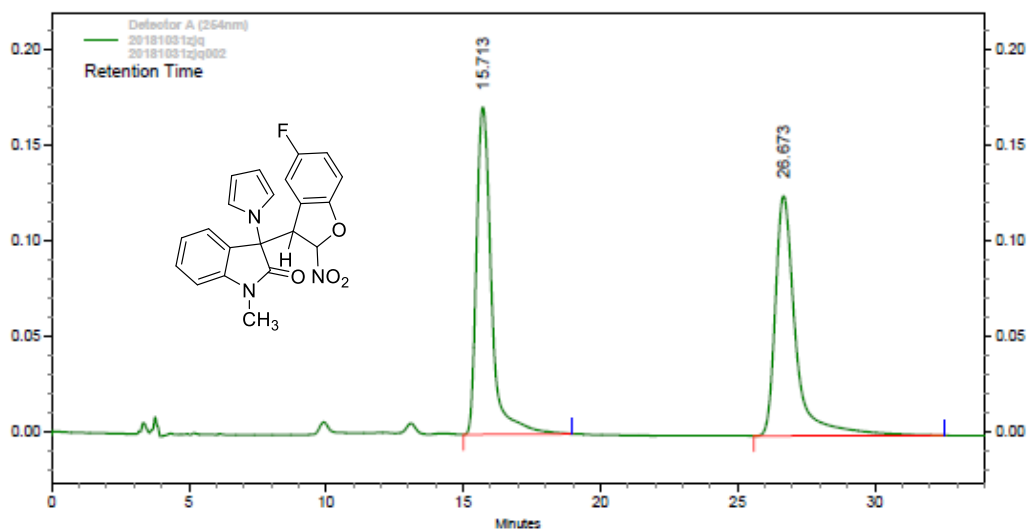
Totals	Height	Height Percent	Area	Area Percent
	425264	100.00	19206577	100.00

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

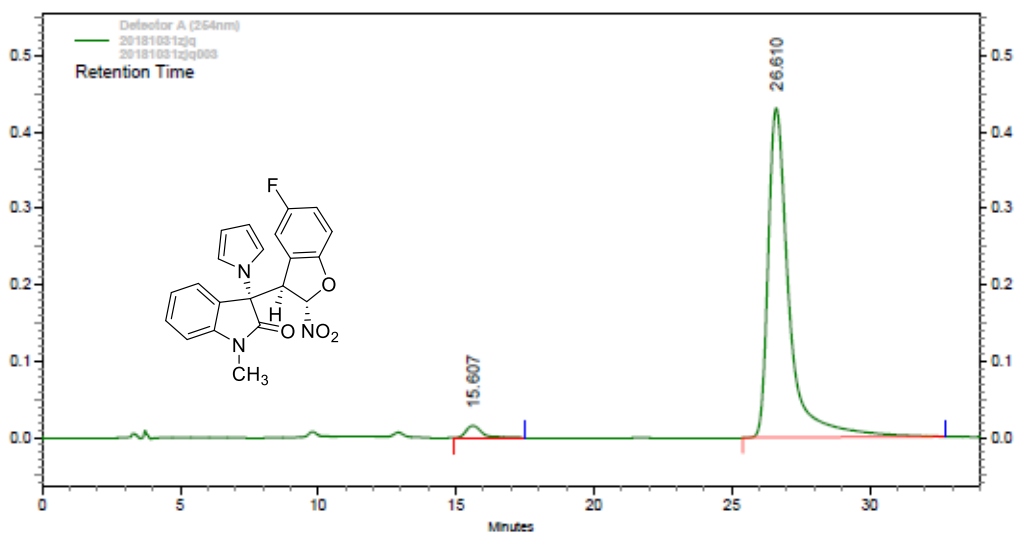




### HPLC of 3b

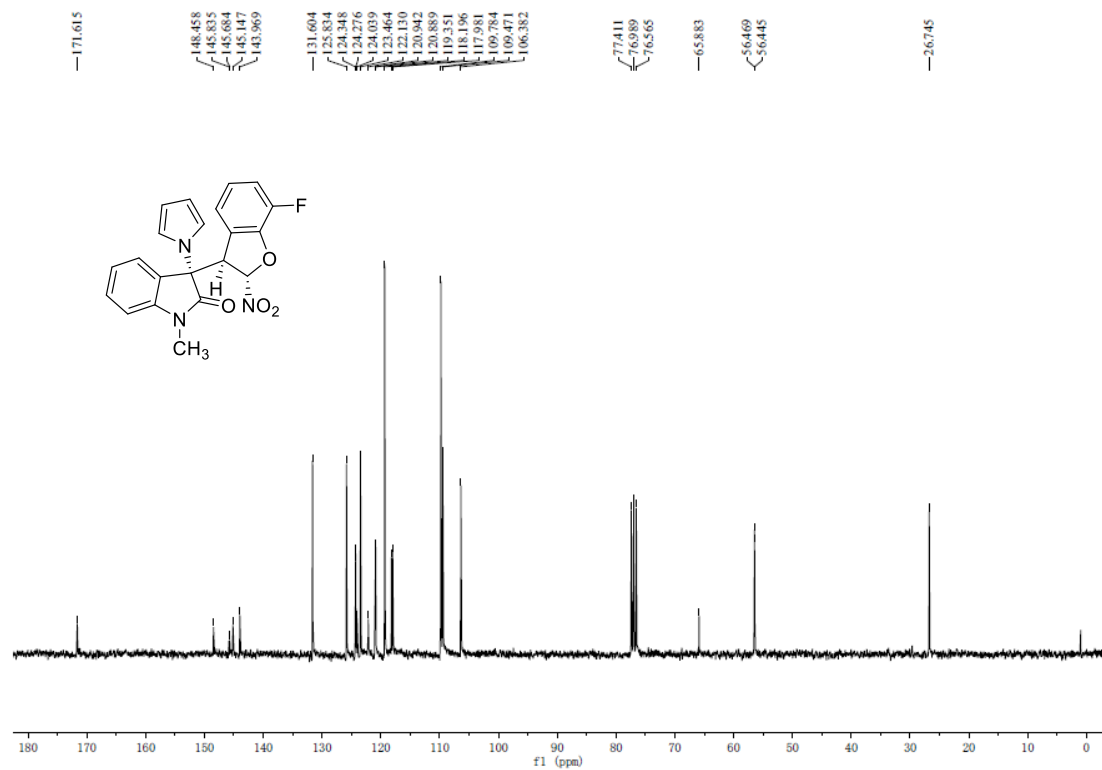
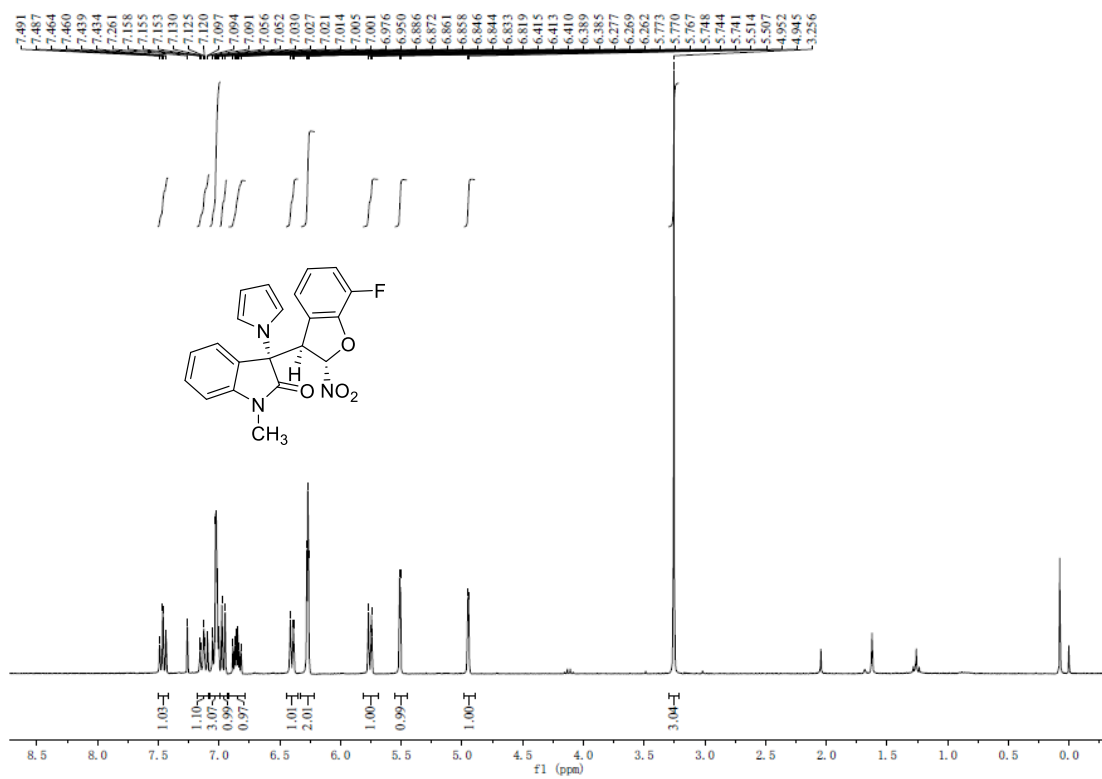


Detector A (254nm)						
PK #	Retention Time	Height	Height Percent	Area	Area Percent	
1	15.713	171427	57.70	6495074	50.00	
2	26.673	125656	42.30	6496250	50.00	
Totals		297083	100.00	12991324	100.00	

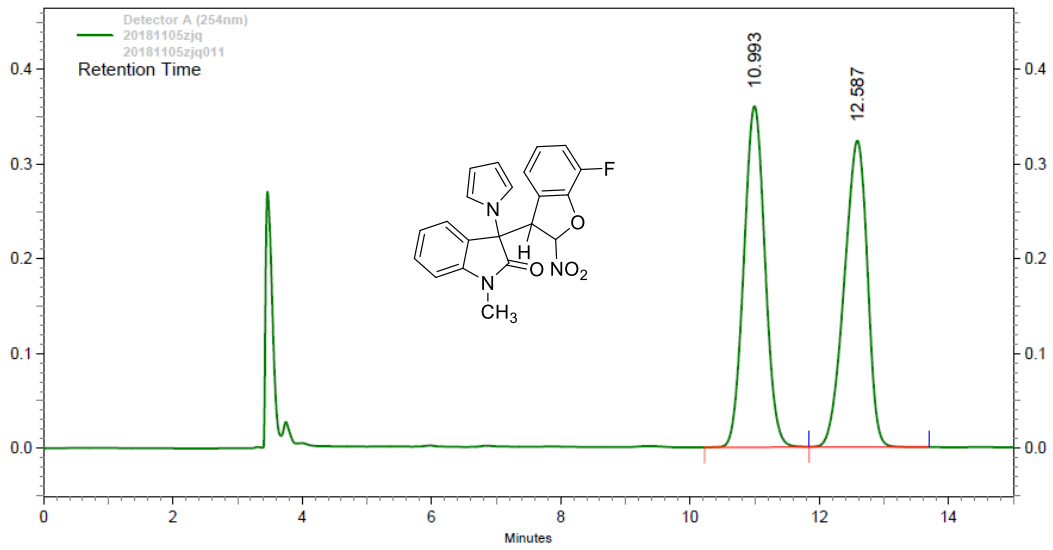


Detector A (254nm)						
PK #	Retention Time	Height	Height Percent	Area	Area Percent	
1	15.607	15245	3.41	573855	2.46	
2	26.610	431264	96.59	22713853	97.54	
Totals		446509	100.00	23287708	100.00	

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

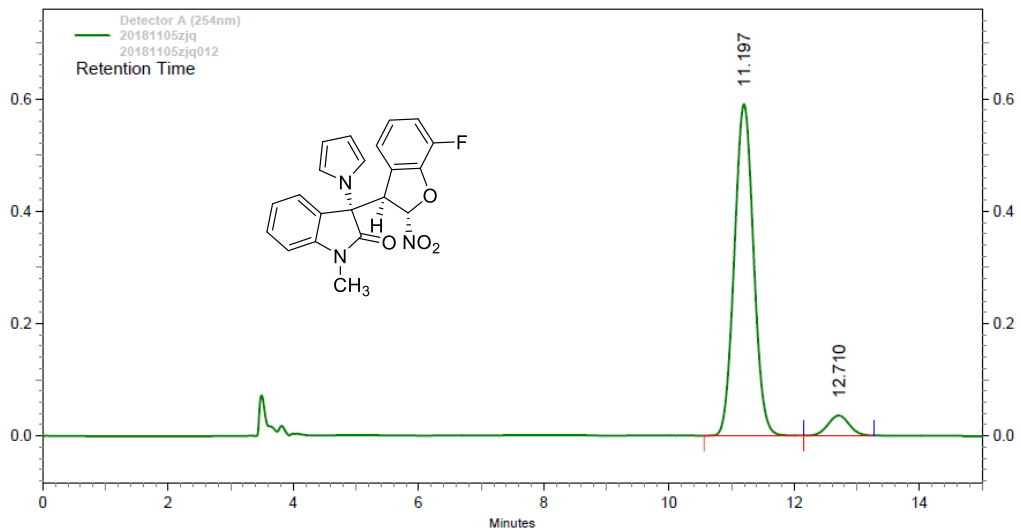


### HPLC of 3d



Detector  
A (254nm)

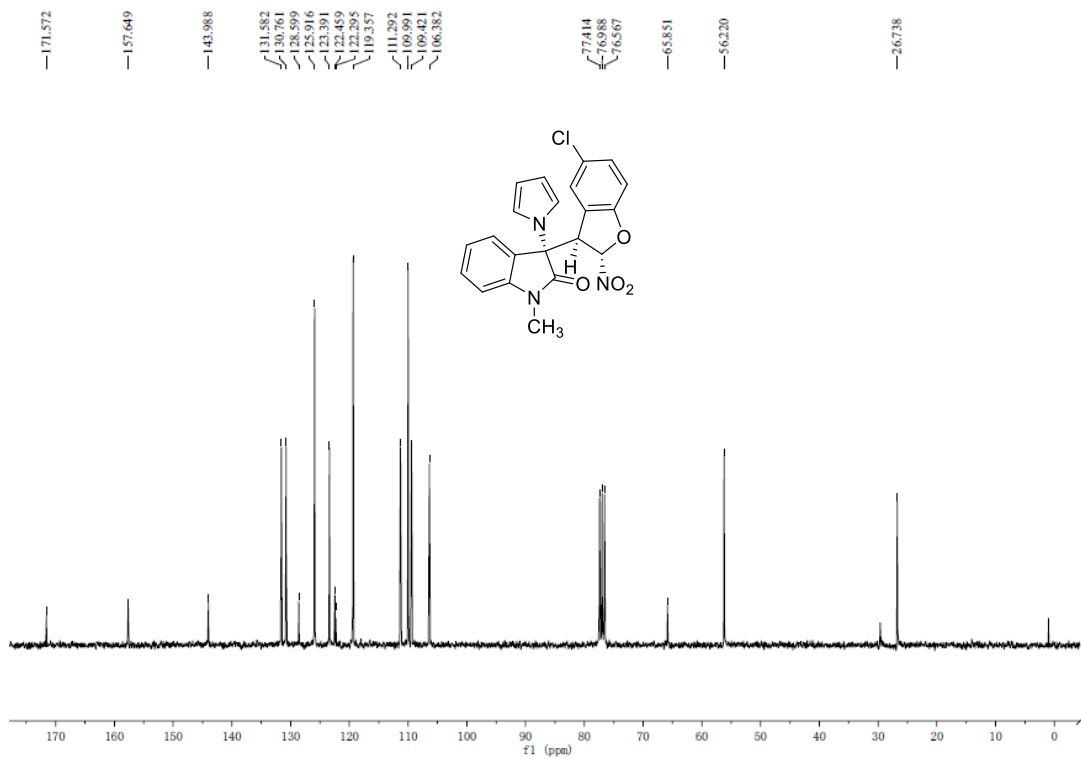
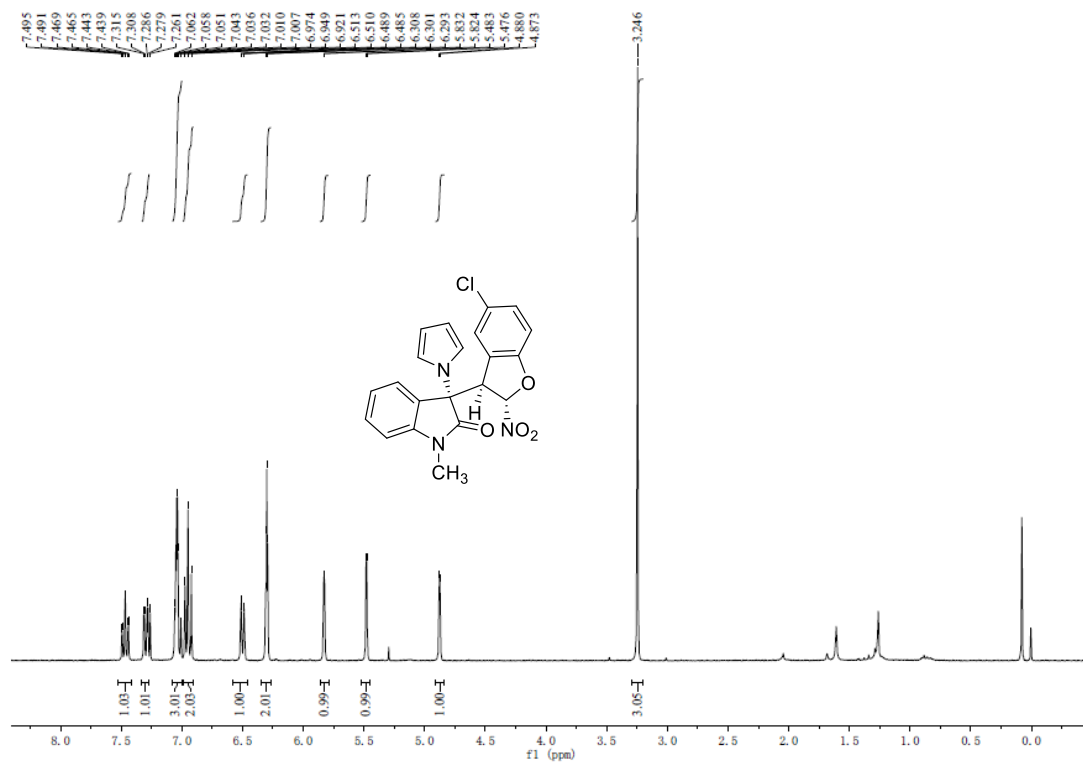
PK #	Retention Time	Height	Height Percent	Area	Area Percent
1	10.993	360180	52.66	8178156	50.45
2	12.587	323732	47.34	8032784	49.55
Totals		683912	100.00	16210940	100.00



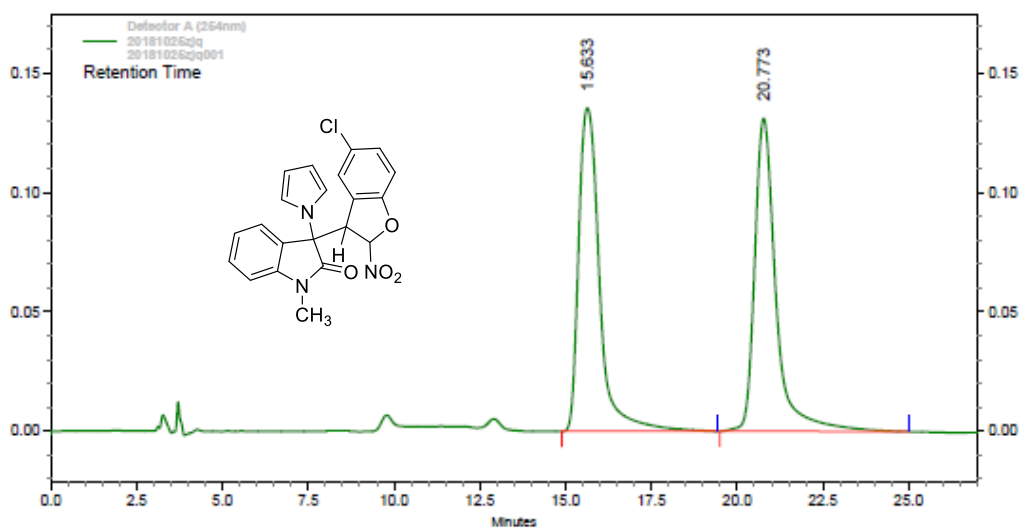
Detector  
A (254nm)

PK #	Retention Time	Height	Height Percent	Area	Area Percent
1	11.197	590034	94.31	12559009	93.76
2	12.710	35579	5.69	836294	6.24
Totals		625613	100.00	13395303	100.00

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



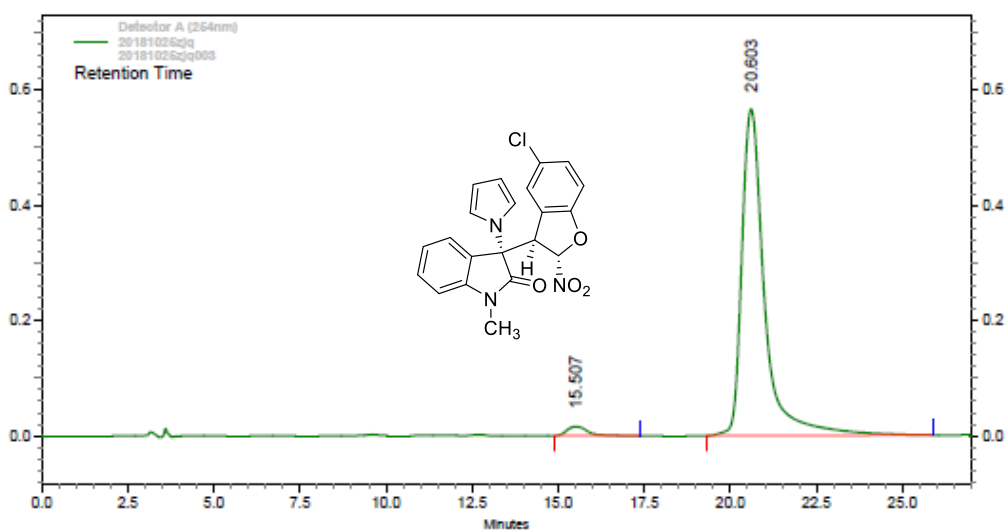
### HPLC of 3d



Detector  
A (254nm)

Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	15.633	135359	50.82	5754196	50.35
2	20.773	130997	49.18	5673688	49.65

Totals		266356	100.00	11427884	100.00
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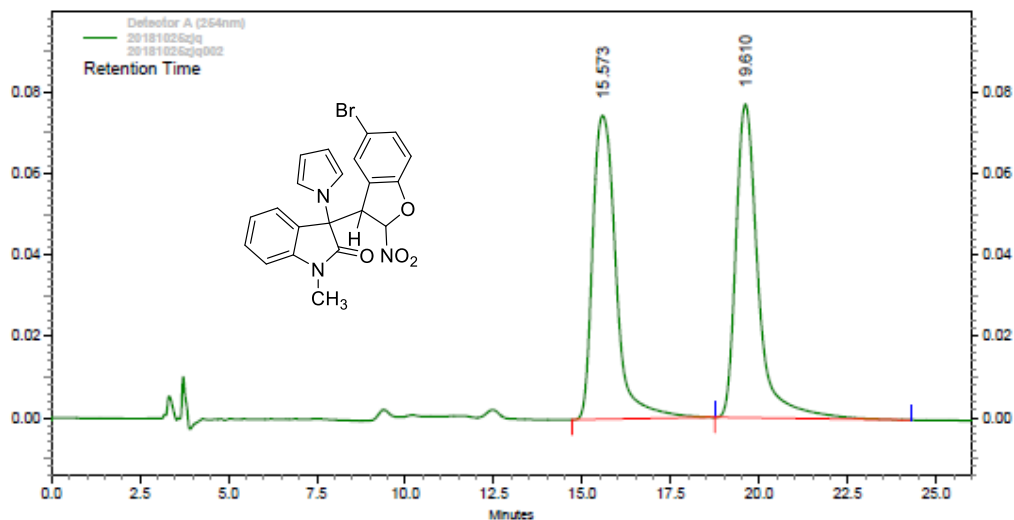
Detector  
A (254nm)

Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	15.507	15690	2.69	647036	2.42
2	20.603	566719	97.31	26106923	97.58

Totals		582409	100.00	26753959	100.00
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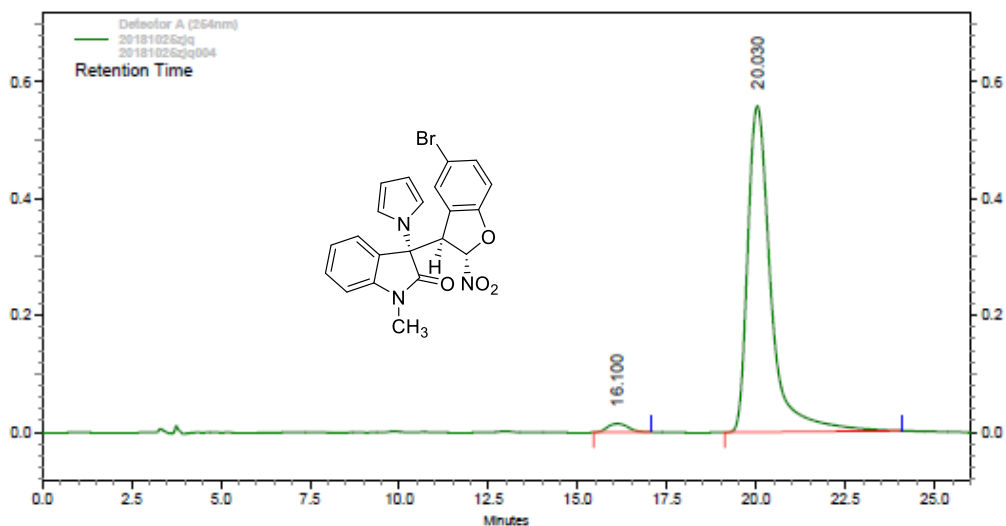


### HPLC of 3e



Detector A (254nm)					
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	15.573	74612	49.20	3420476	50.34
2	19.610	77024	50.80	3374362	49.66

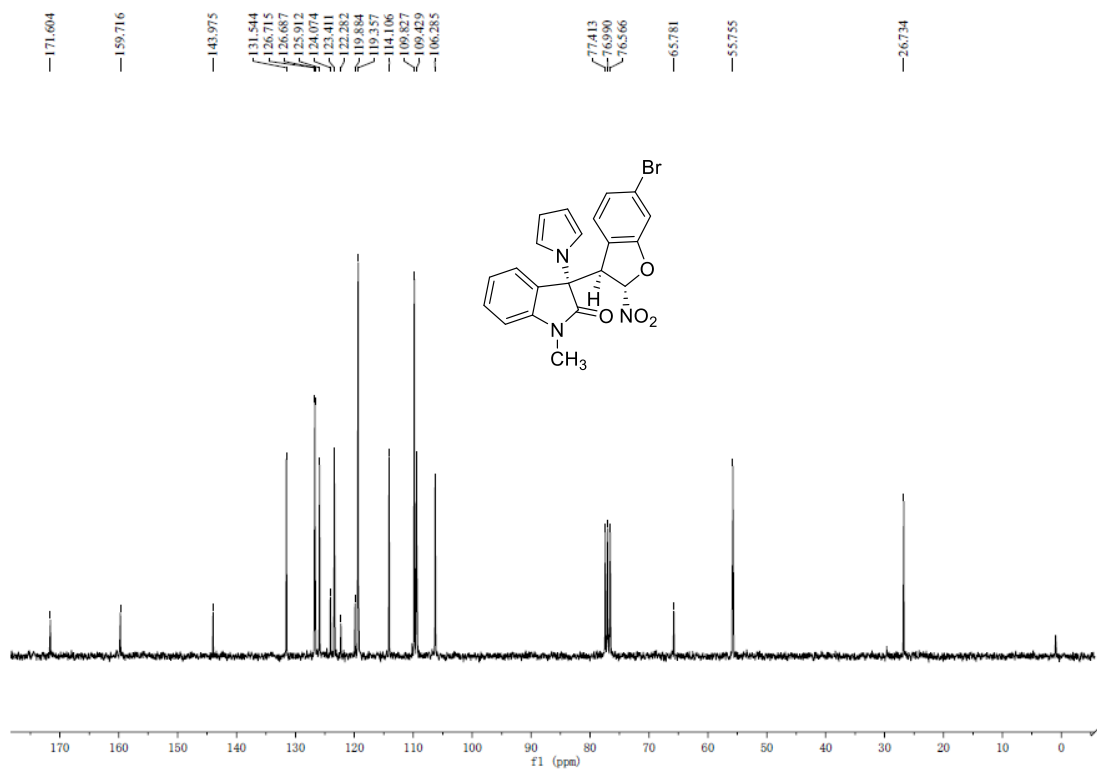
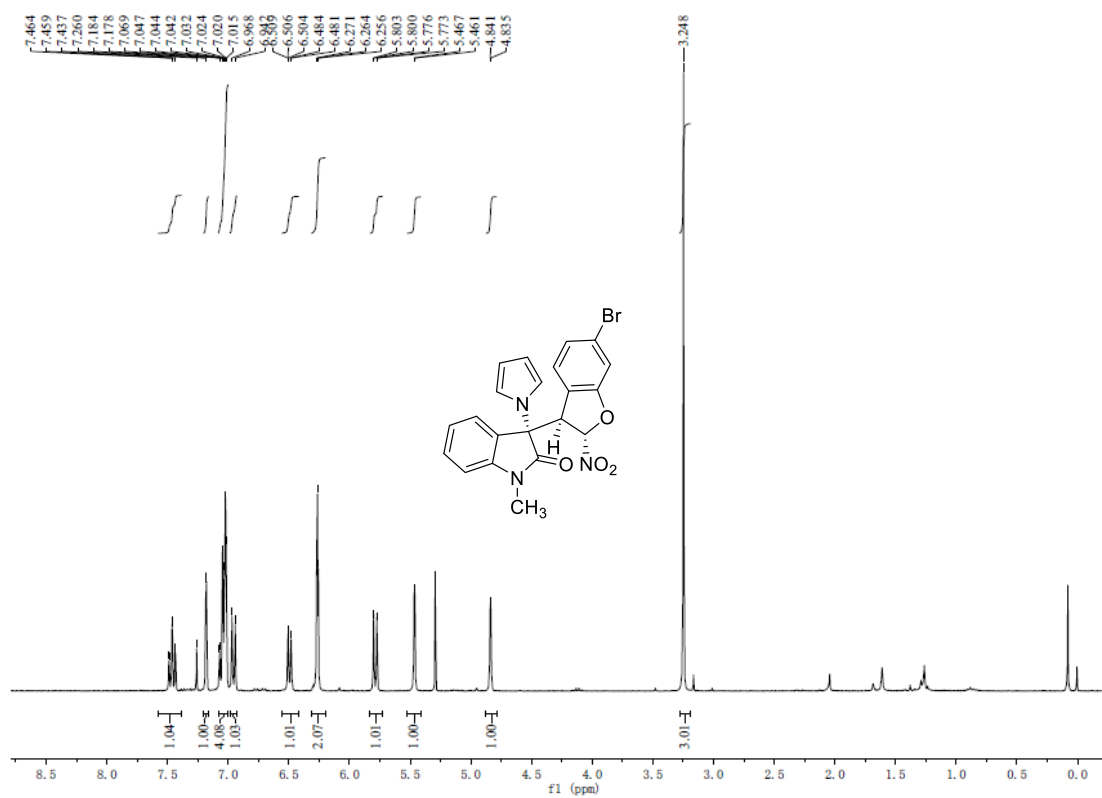
Totals		151636	100.00	6794838	100.00
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Detector A (254nm)					
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	16.100	14284	2.50	574307	2.23
2	20.030	557608	97.50	25220661	97.77

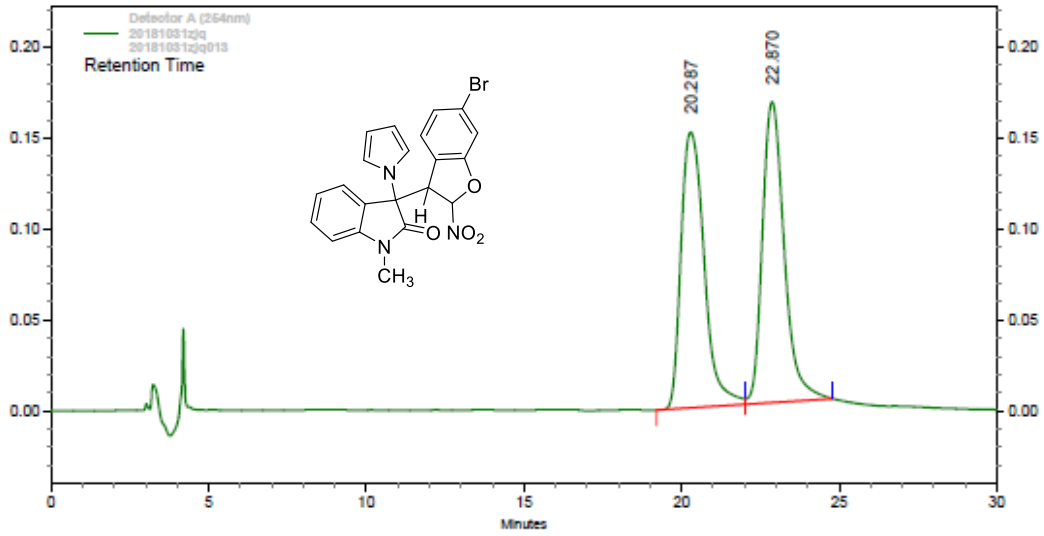
Totals		571892	100.00	25794968	100.00
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$^1\text{H}$  and  $^{13}\text{C}$  NMR of **3f**



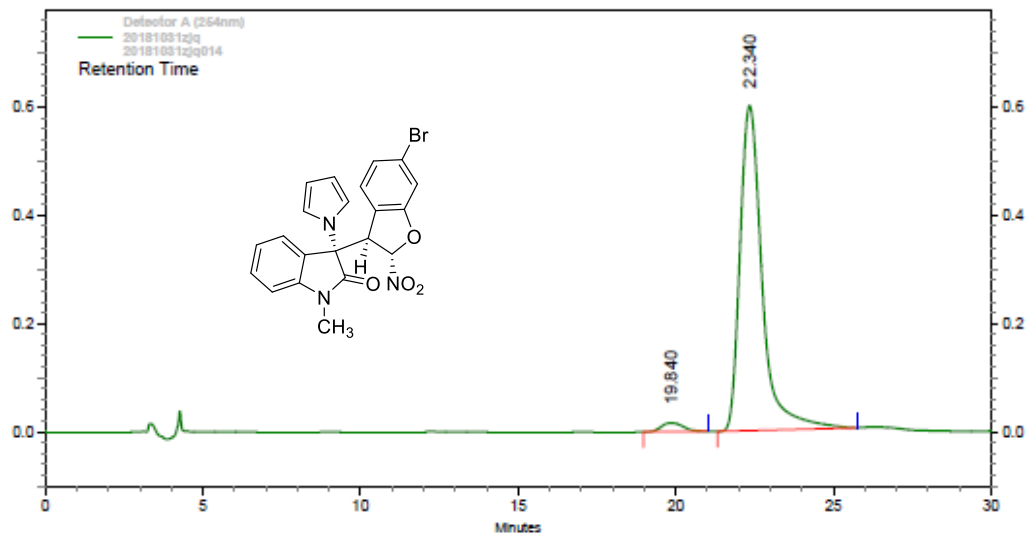


### HPLC of 3f



Detector A (254nm)						
Pk #	Retention Time	Height	Height Percent	Area	Area Percent	
1	20.287	151584	47.81	7769598	49.32	
2	22.870	165453	52.19	7982300	50.68	

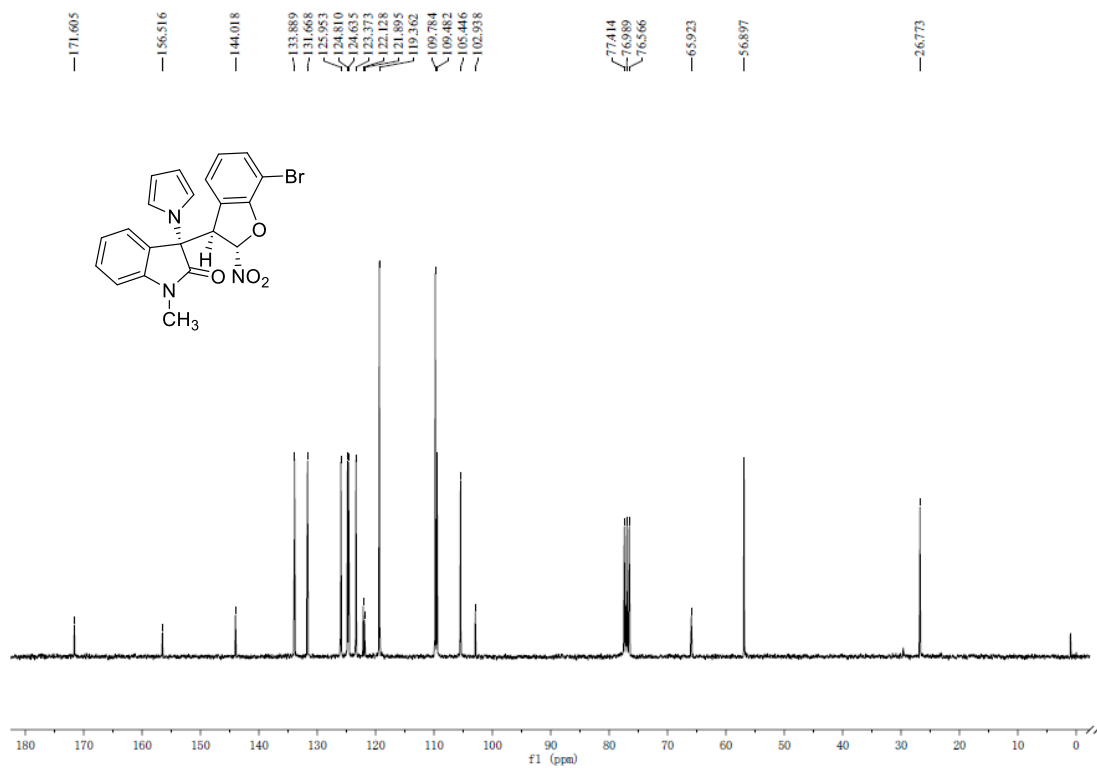
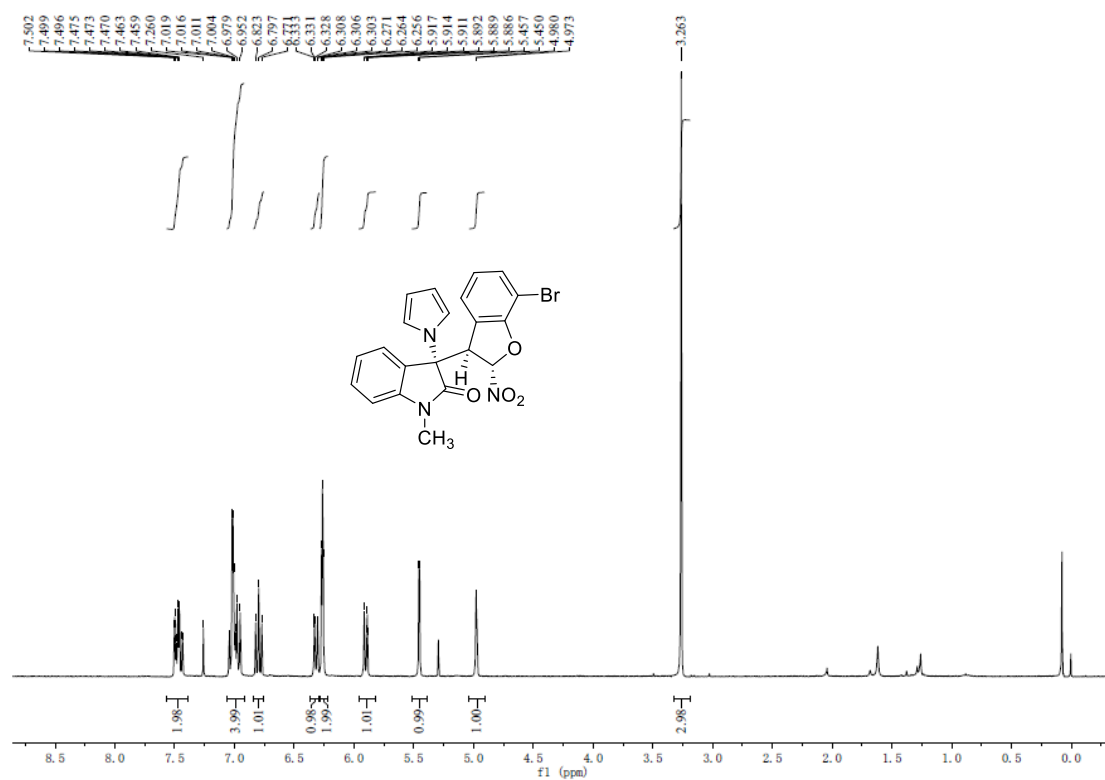
Totals					
		317037	100.00	15751898	100.00



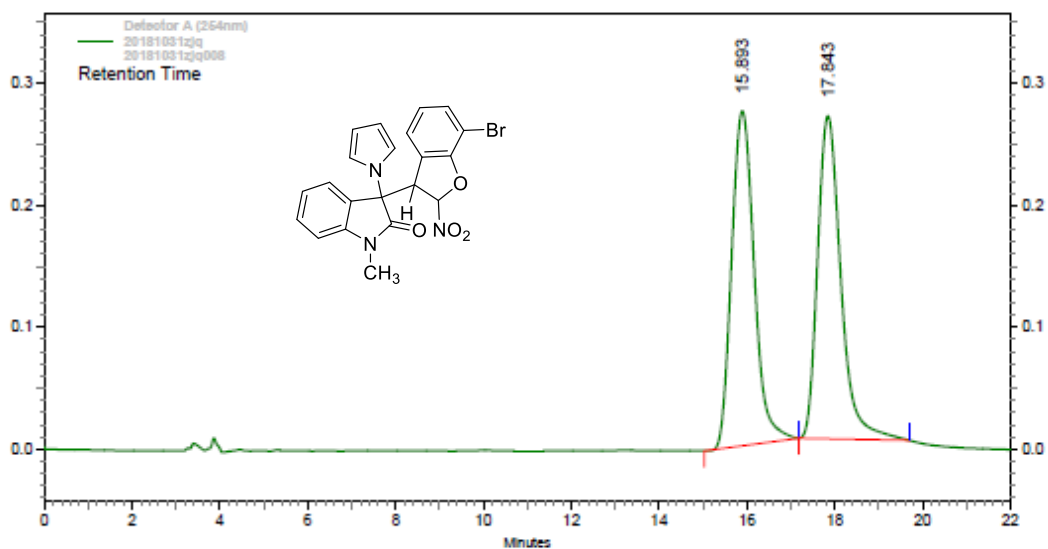
Detector A (254nm)						
Pk #	Retention Time	Height	Height Percent	Area	Area Percent	
1	19.840	16221	2.63	769633	2.55	
2	22.340	600206	97.37	29364555	97.45	

Totals					
		616427	100.00	30134188	100.00

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

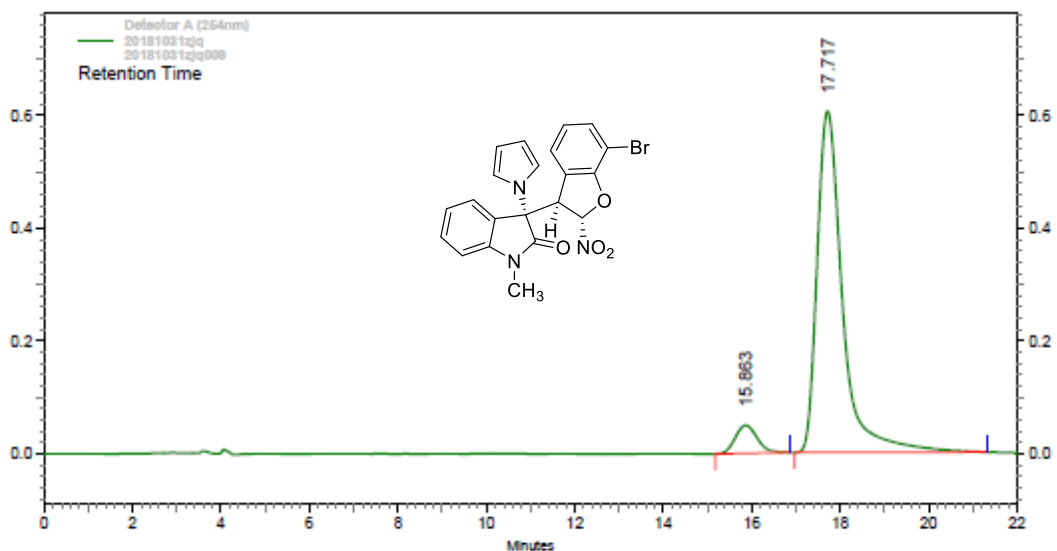


### HPLC of 3g



Detector A (254nm)

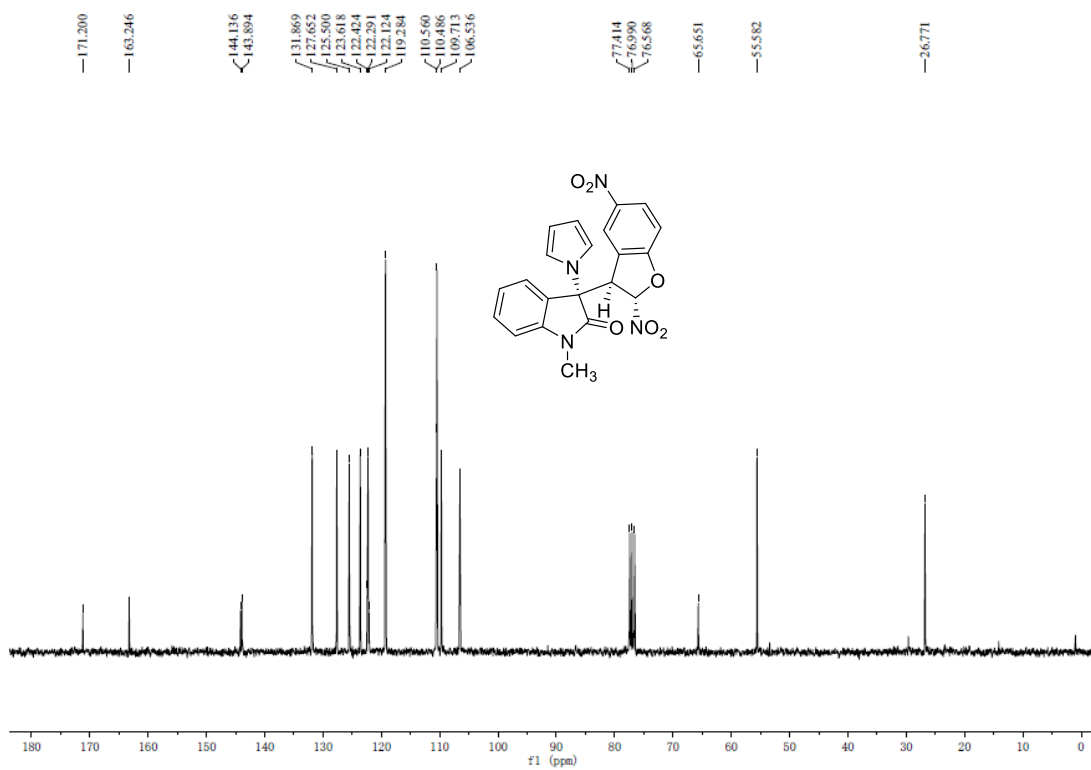
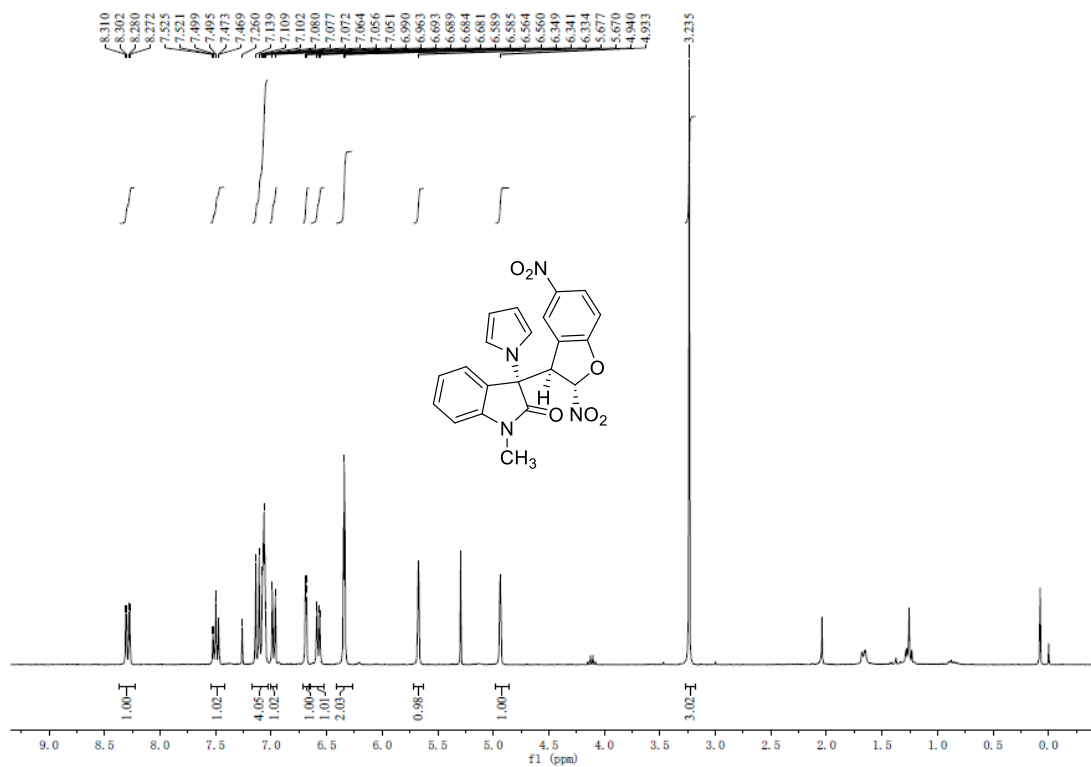
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	15.893	274660	50.90	9773357	50.08
2	17.843	264943	49.10	9742737	49.92
Totals		539603	100.00	19516094	100.00



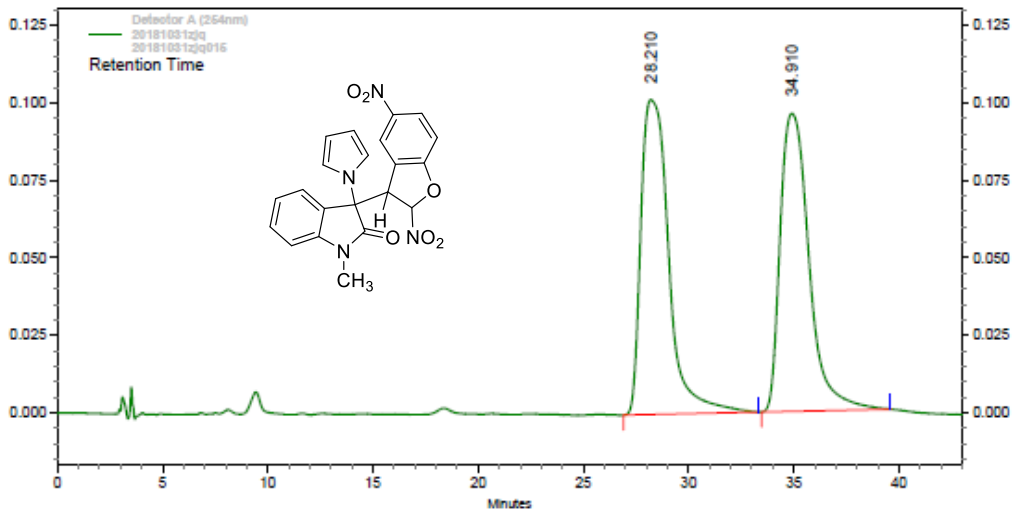
Detector A (254nm)

Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	15.863	49630	7.58	1704339	6.59
2	17.717	605170	92.42	24154495	93.41
Totals		654800	100.00	25858834	100.00

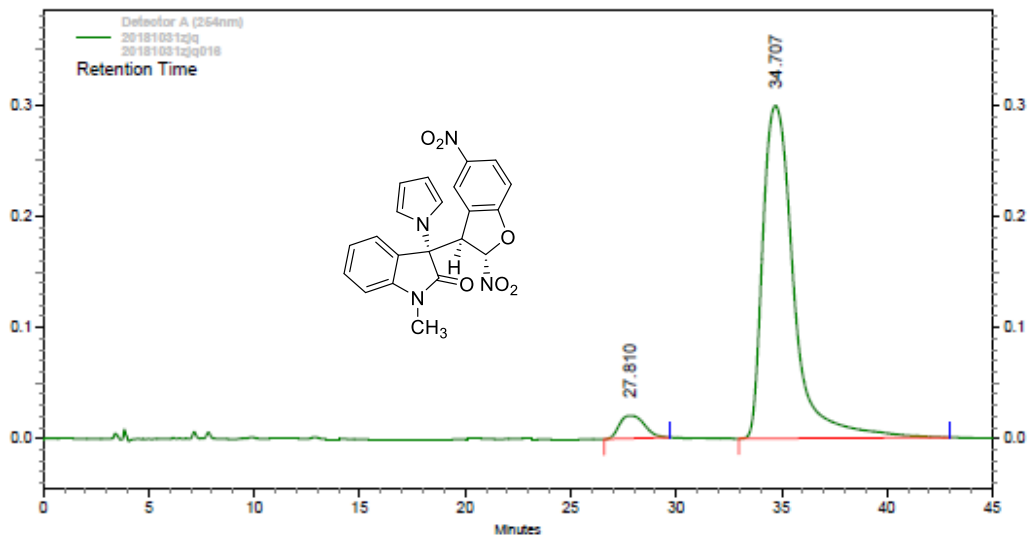
<sup>1</sup>H and <sup>13</sup>C NMR of 3h



### HPLC of 3h

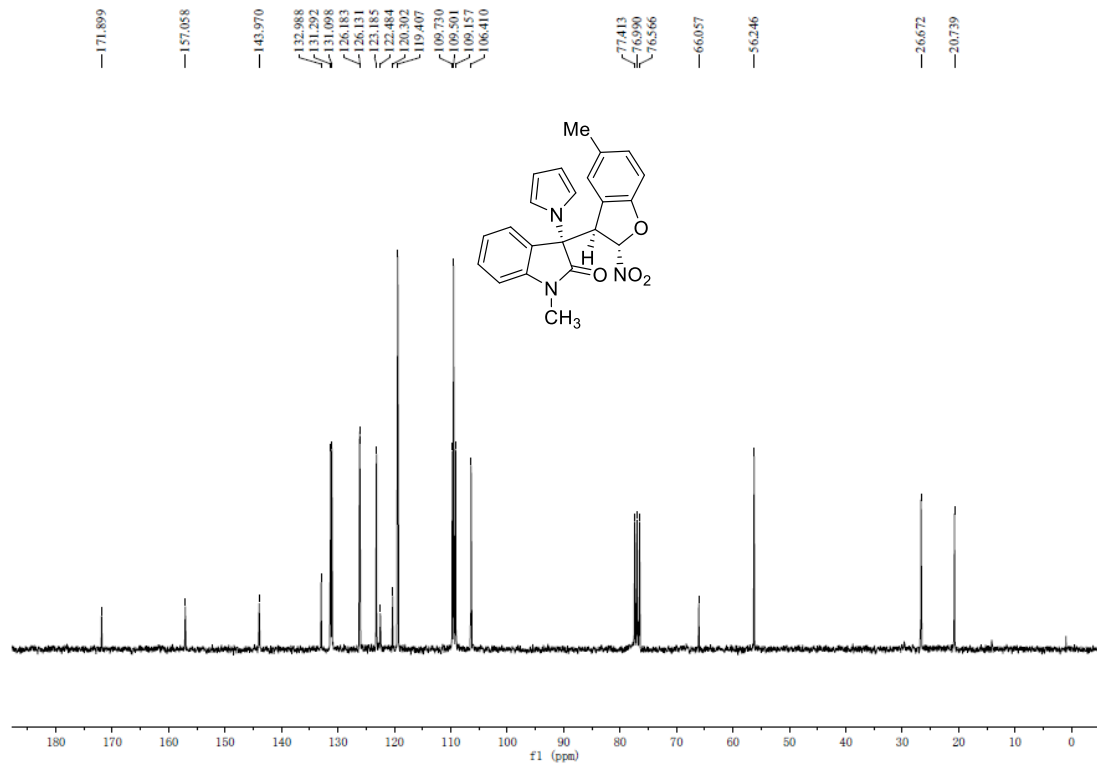
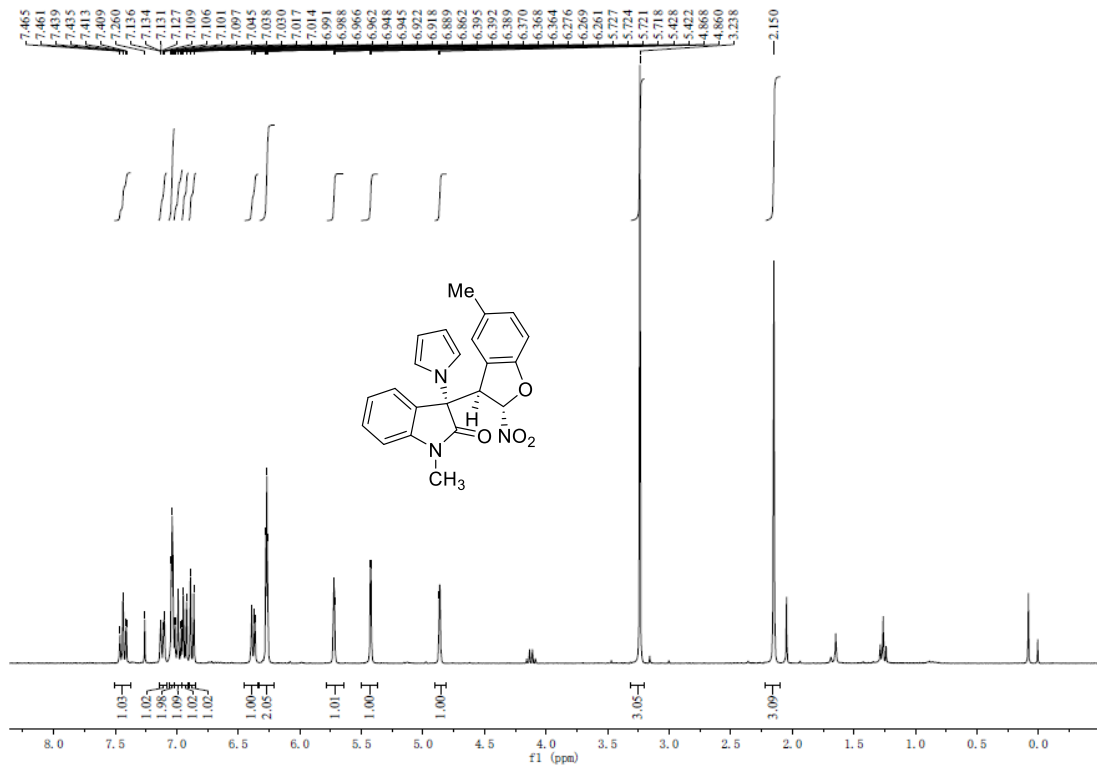


Detector A (254nm)						
Pk #	Retention Time	Height	Height Percent	Area	Area Percent	
1	28.210	101541	51.37	9347097	50.50	
2	34.910	96110	48.63	9162239	49.50	
Totals		197651	100.00	18509336	100.00	

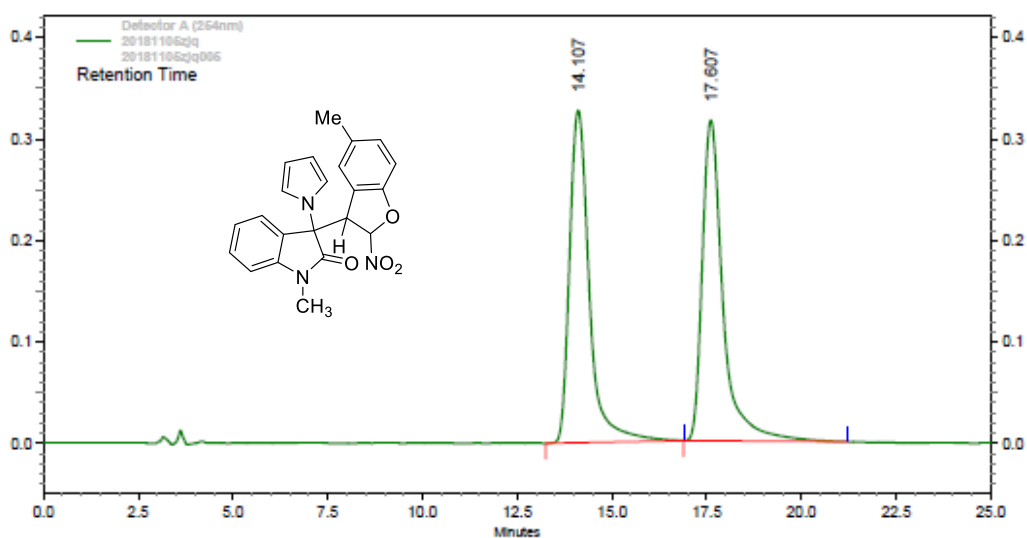


Detector A (254nm)						
Pk #	Retention Time	Height	Height Percent	Area	Area Percent	
1	27.810	20421	6.39	1690166	5.22	
2	34.707	299324	93.61	30695688	94.78	
Totals		319745	100.00	32385854	100.00	

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

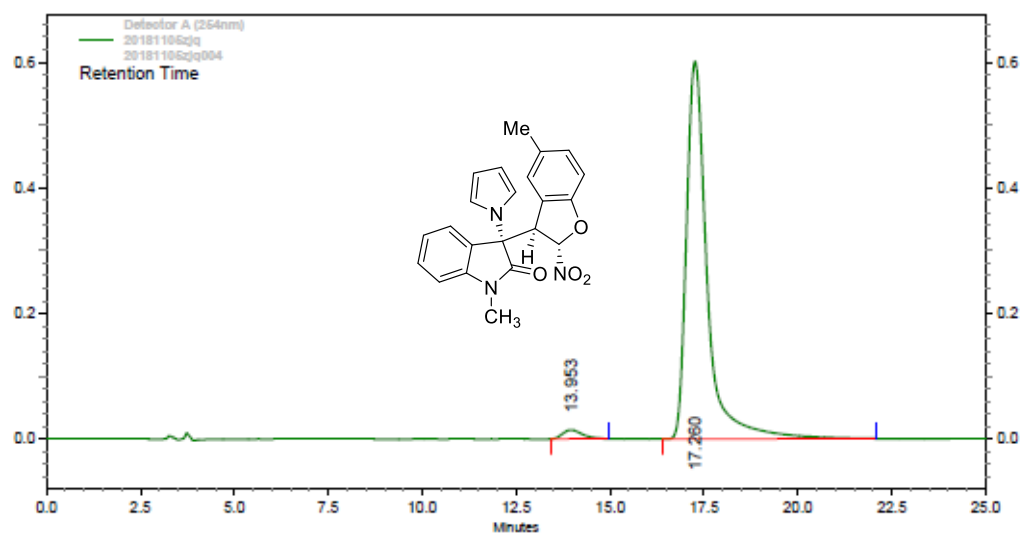


### HPLC of 3i



**Detector A (254nm)**

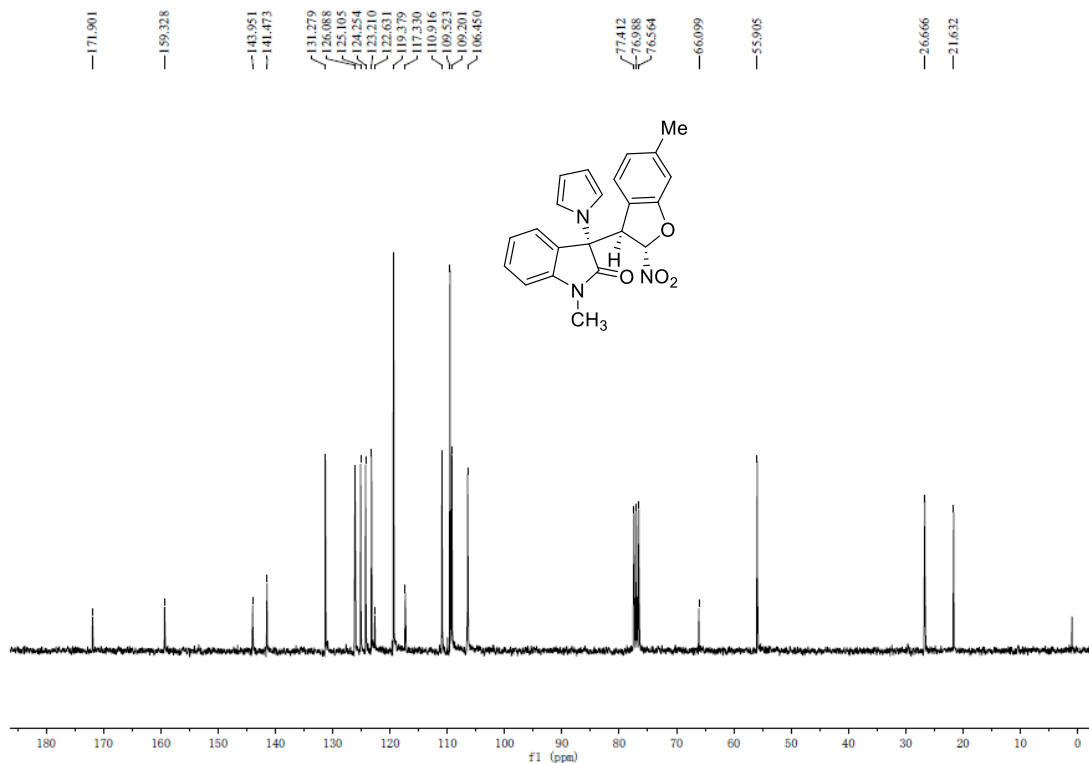
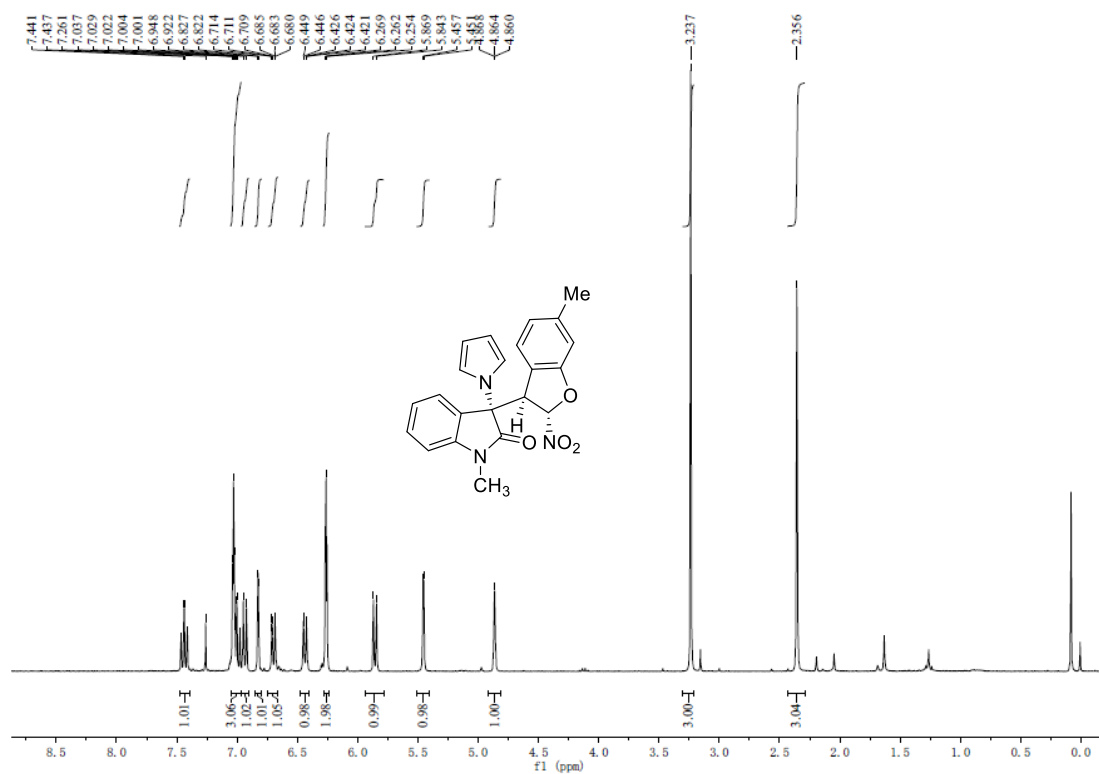
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	14.107	327637	50.90	11867576	49.64
2	17.607	316092	49.10	12038595	50.36
<b>Totals</b>		643729	100.00	23906171	100.00



**Detector A (254nm)**

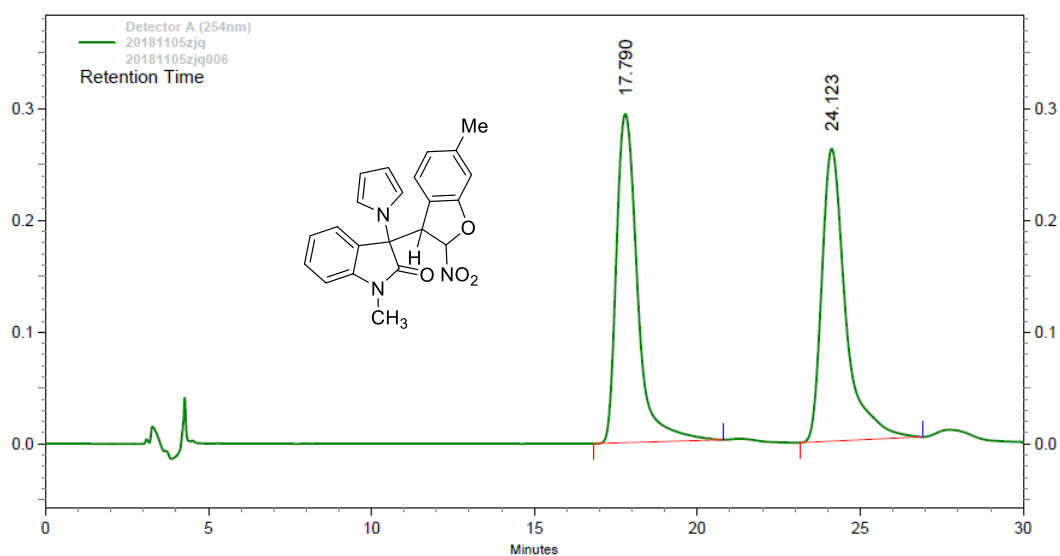
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	13.953	14096	2.29	513620	2.18
2	17.260	600771	97.71	23070048	97.82
<b>Totals</b>		614867	100.00	23583668	100.00

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





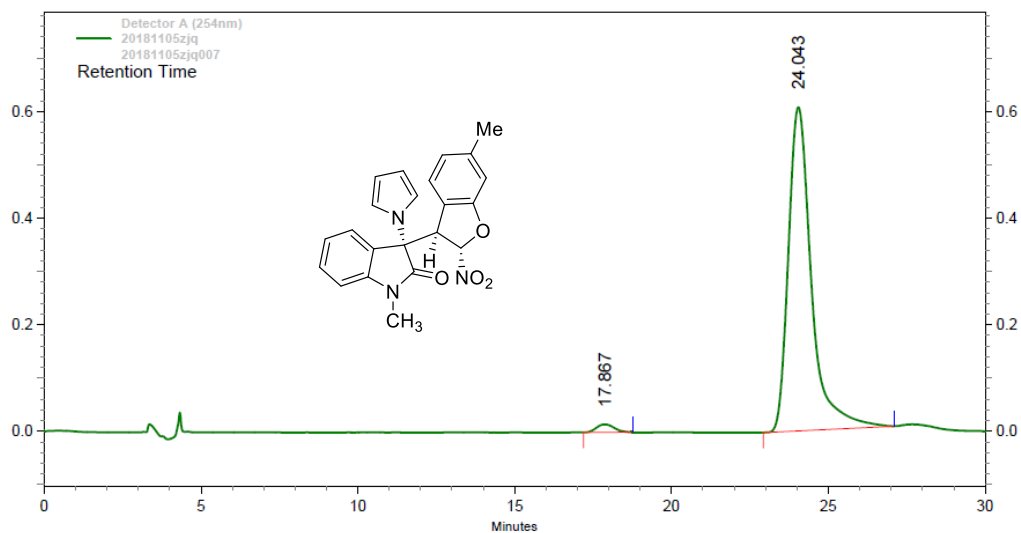
### HPLC of 3j



Detector  
A (254nm)

PK #	Retention Time	Height	Height Percent	Area	Area Percent
1	17.790	294075	52.93	13263310	49.96
2	24.123	261543	47.07	13285368	50.04

Totals		555618	100.00	26548678	100.00
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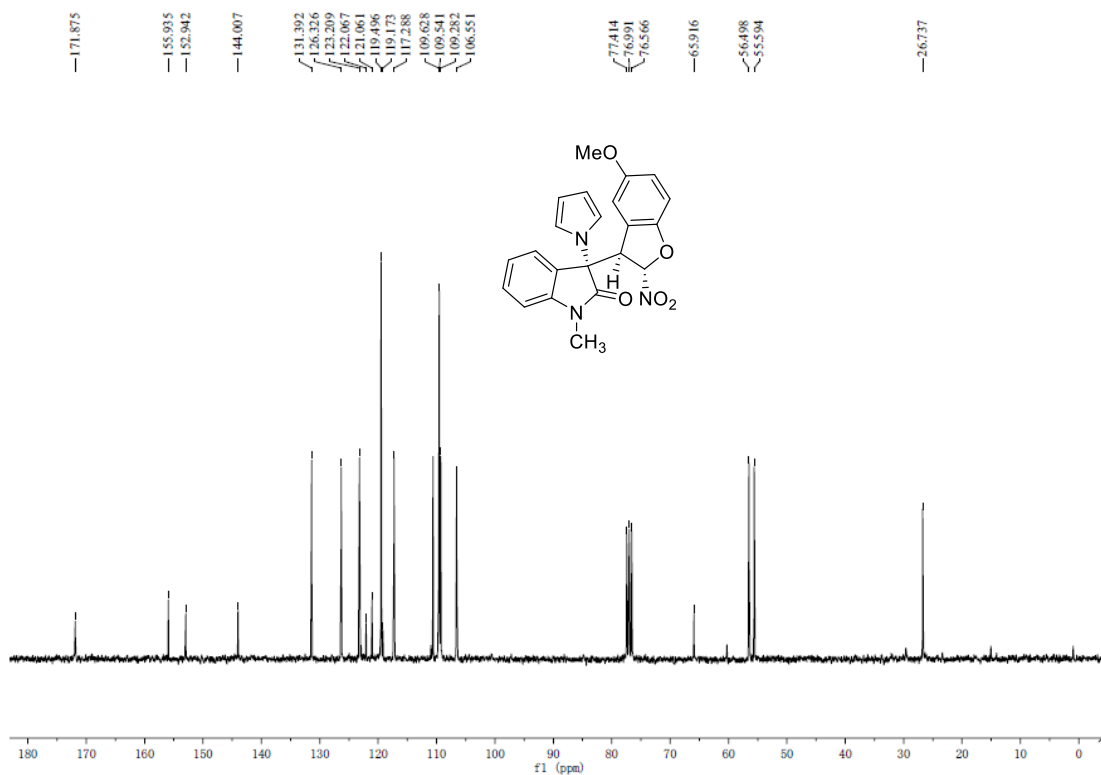
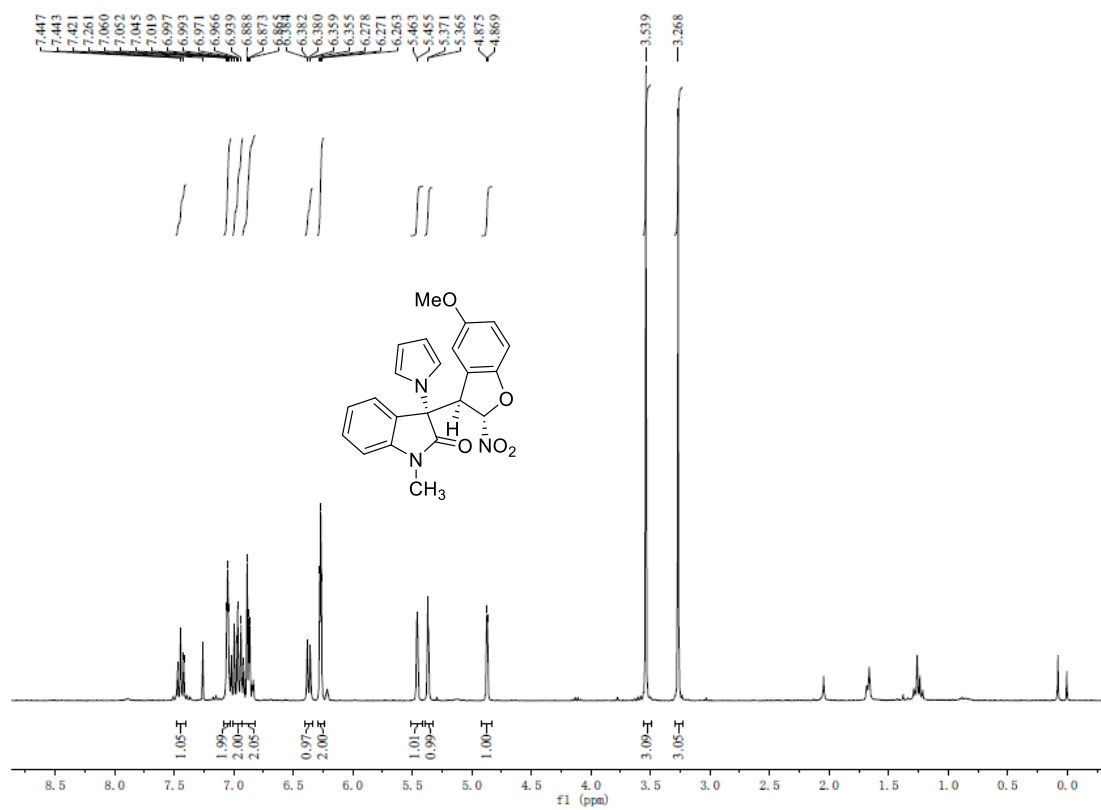


Detector  
A (254nm)

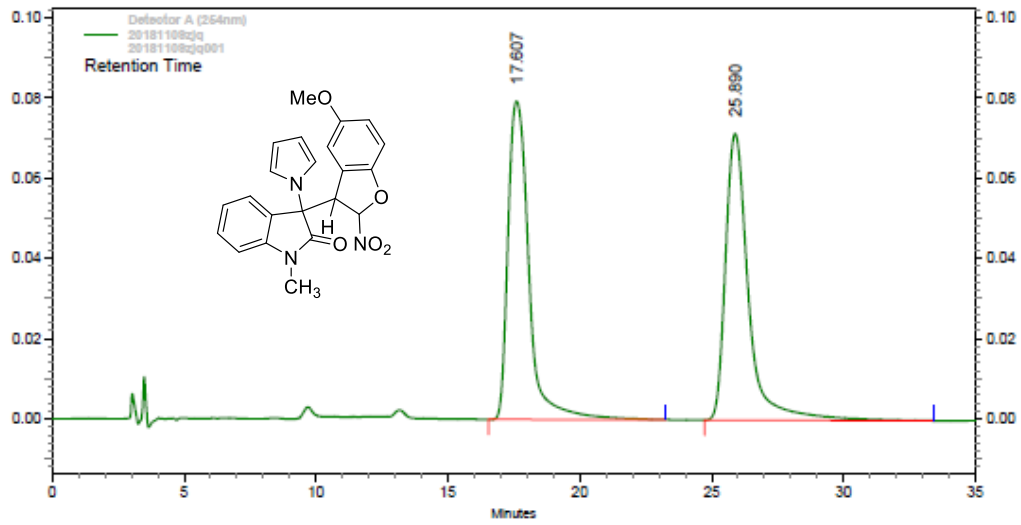
PK #	Retention Time	Height	Height Percent	Area	Area Percent
1	17.867	14862	2.39	575780	1.83
2	24.043	606899	97.61	30967105	98.17

Totals		621761	100.00	31542885	100.00
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# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3k**



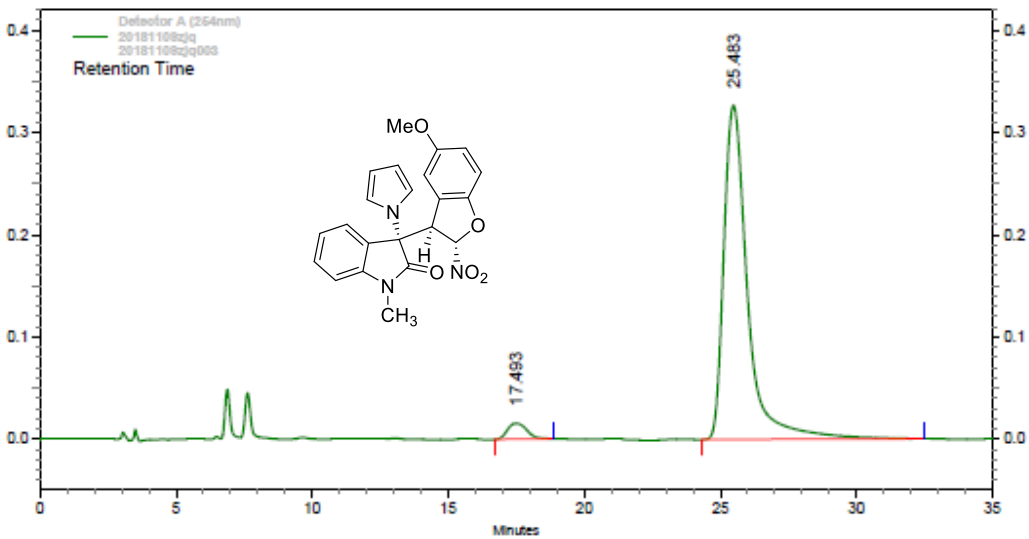
### HPLC of 3k



Detector  
A (254nm)

Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	17.607	79294	52.61	4373464	50.15
2	25.890	71439	47.39	4347276	49.85

Totals		150733	100.00	8720740	100.00
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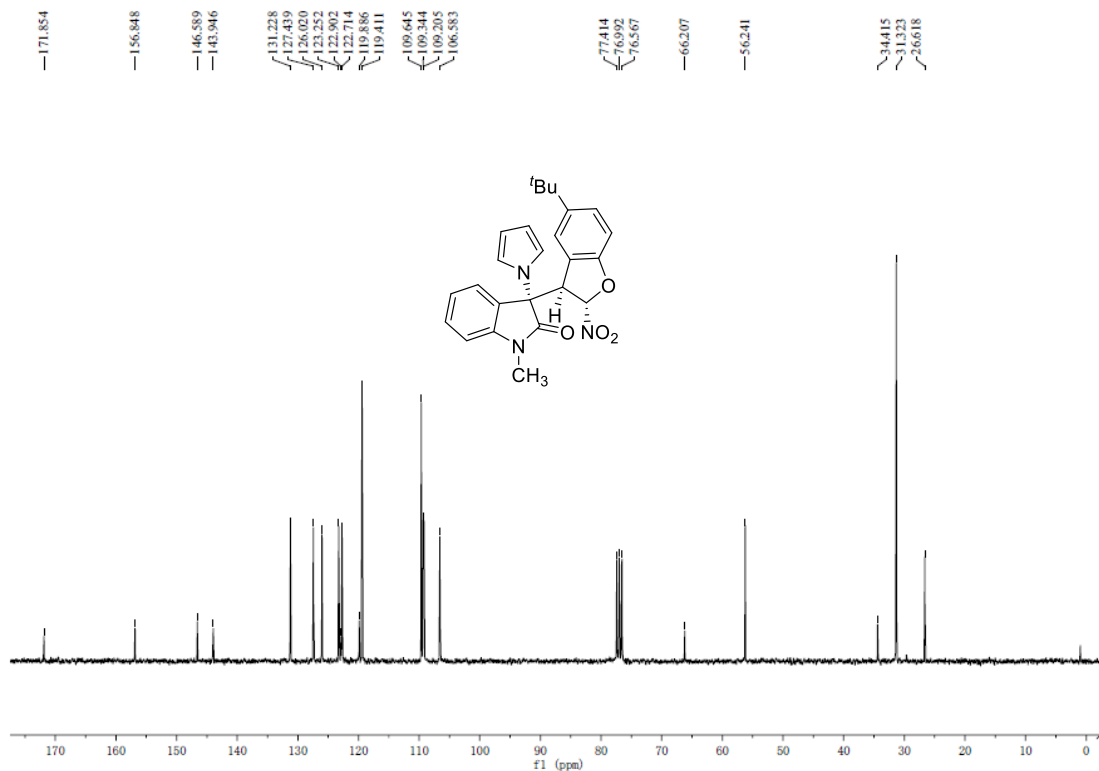
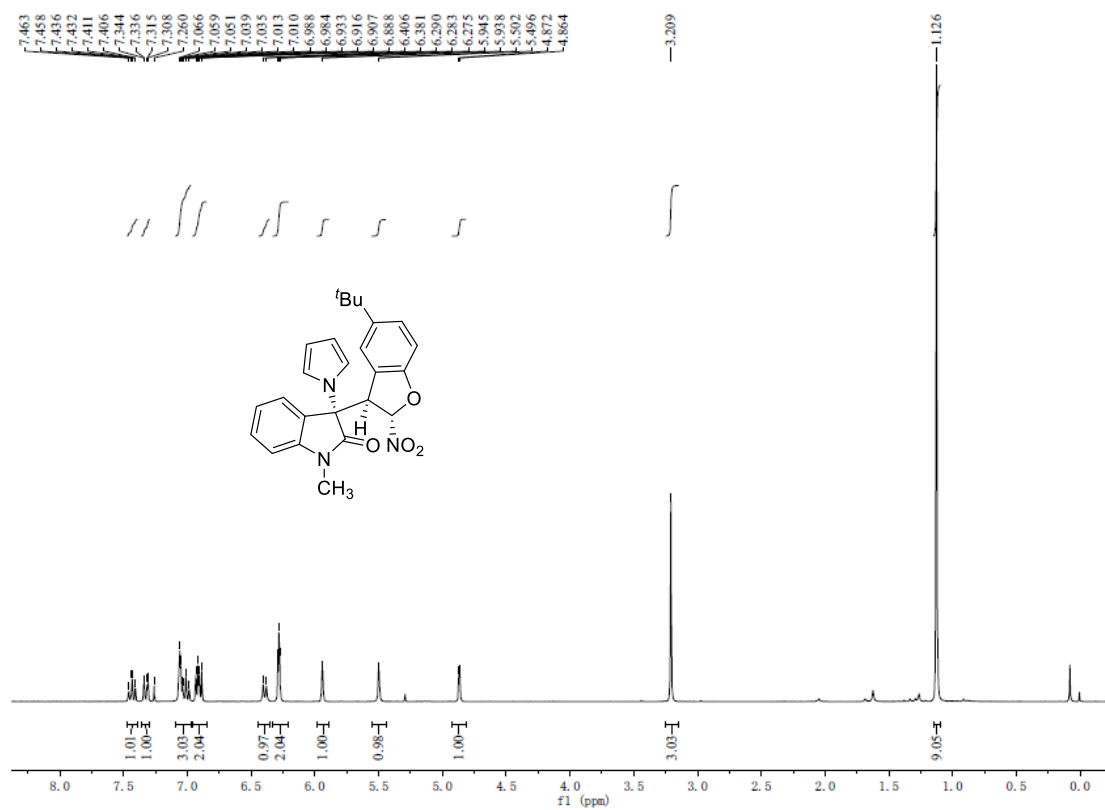


Detector  
A (254nm)

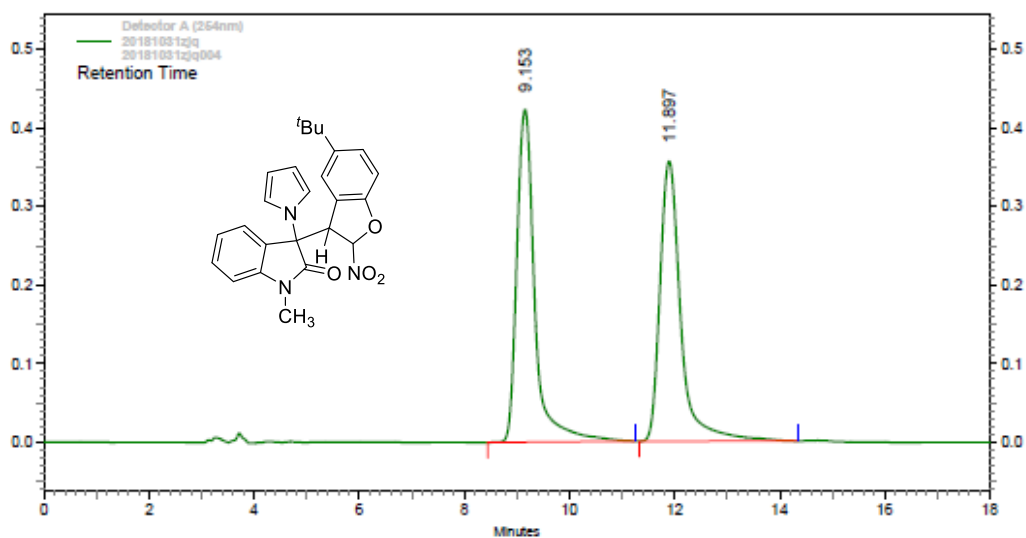
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	17.493	15457	4.52	762876	3.70
2	25.483	326706	95.48	19876254	96.30

Totals		342163	100.00	20639130	100.00
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<sup>1</sup>H and <sup>13</sup>C NMR of 3I



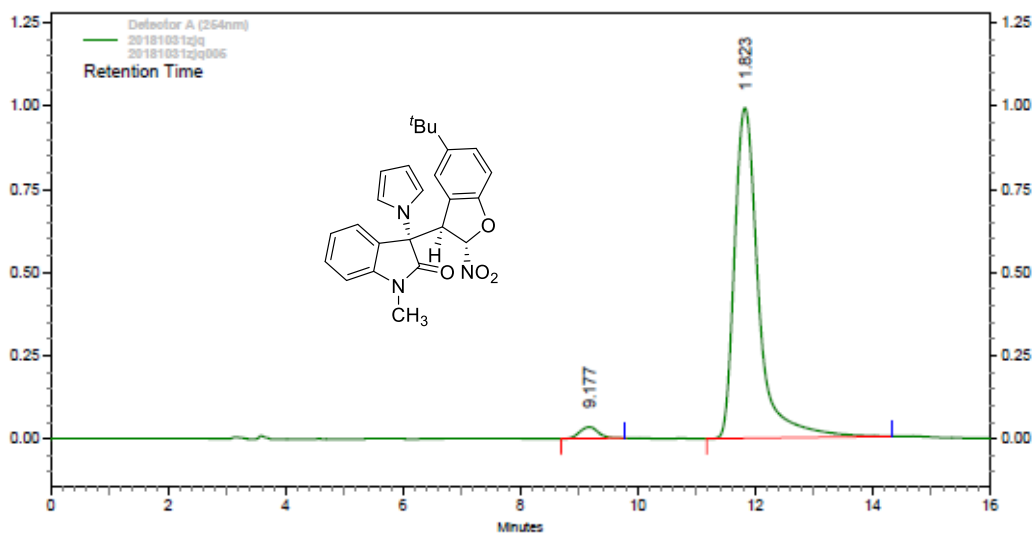
### HPLC of 3l



**Detector A (254nm)**

Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	9.153	423523	54.29	10097611	50.74
2	11.897	356535	45.71	9804774	49.26

<b>Totals</b>		780058	100.00	19902385	100.00
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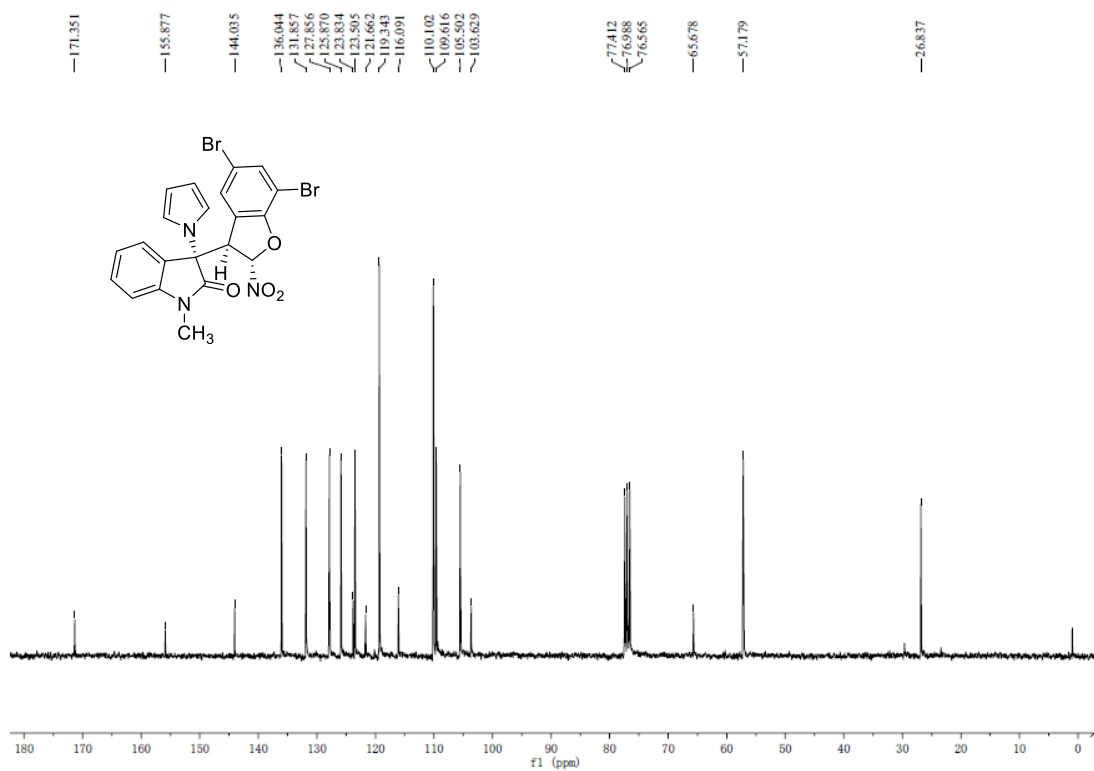
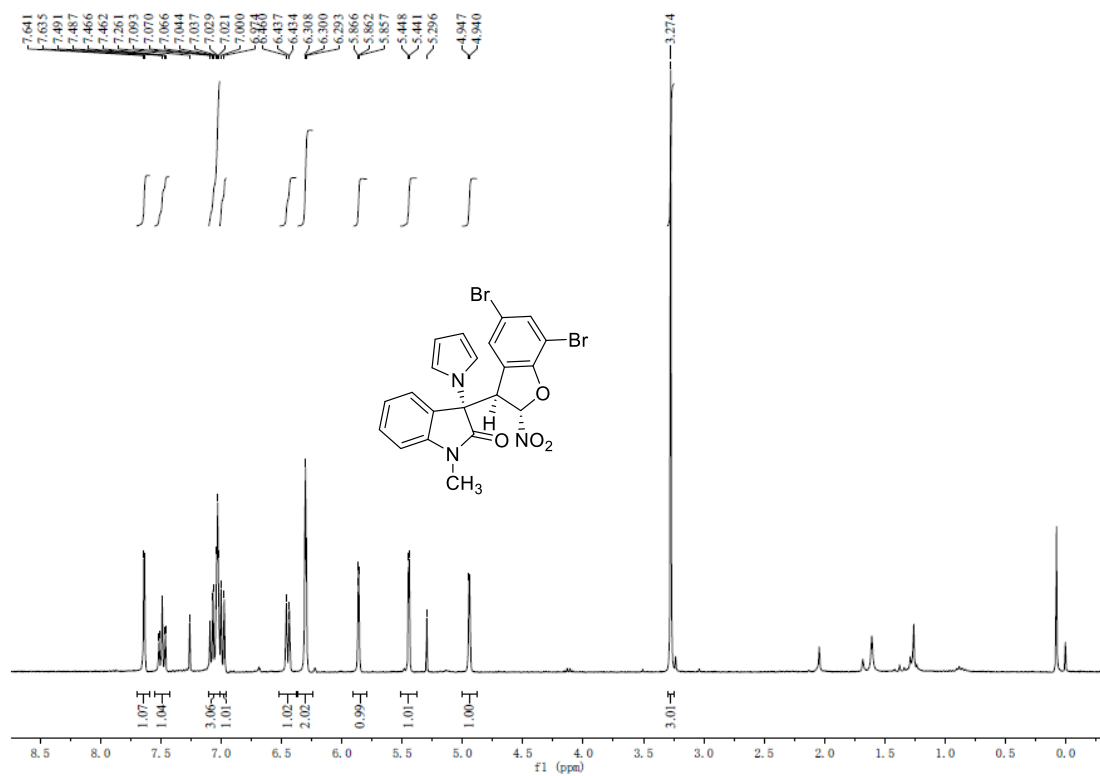


**Detector A (254nm)**

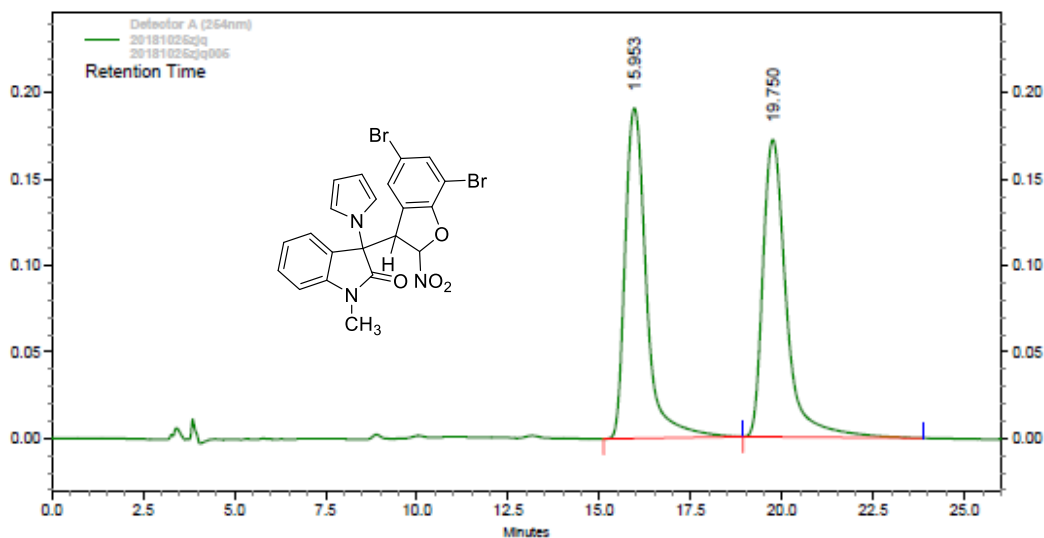
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	9.177	34742	3.38	765440	2.65
2	11.823	992645	96.62	28173253	97.35

<b>Totals</b>		1027387	100.00	28938693	100.00
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<sup>1</sup>H and <sup>13</sup>C NMR of **3m**

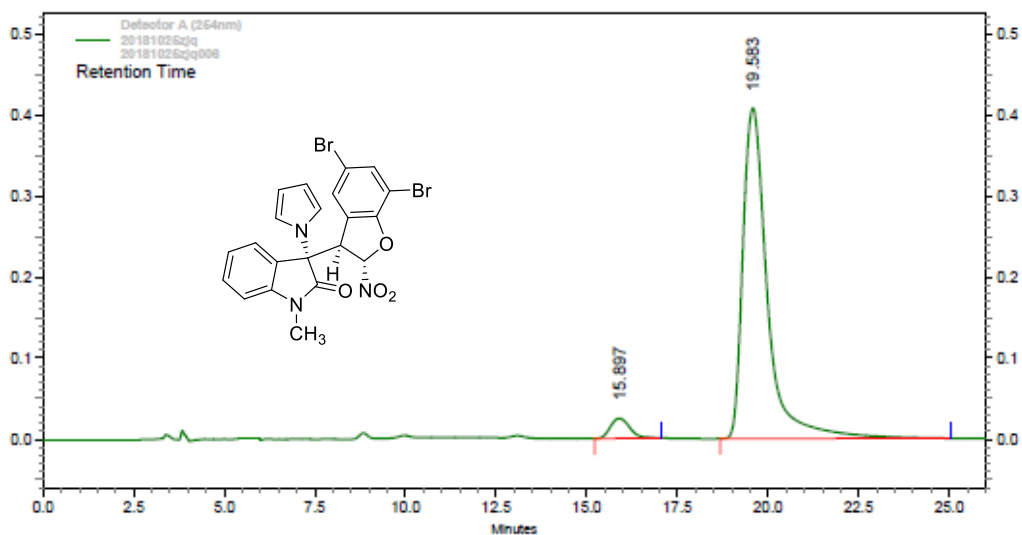


### HPLC of 3m



Detector A (254nm)	PK #	Retention Time	Height	Height Percent	Area	Area Percent
	1	15.953	191085	52.63	7732461	50.21
	2	19.750	171974	47.37	7667594	49.79

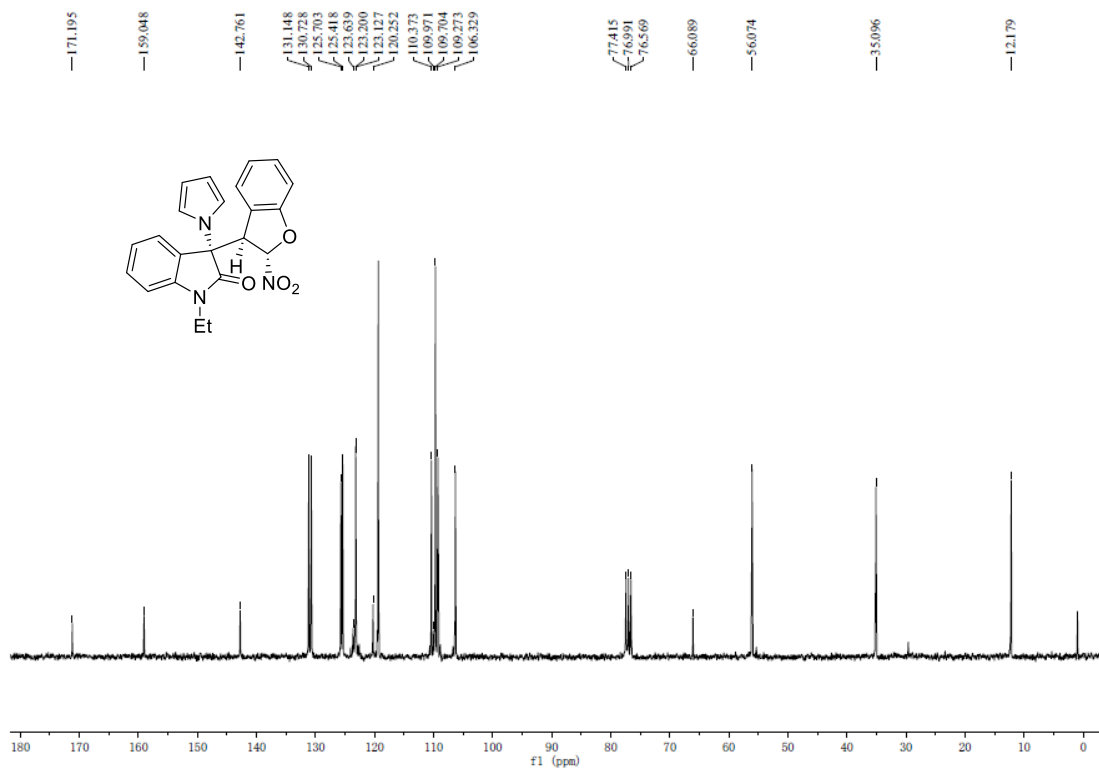
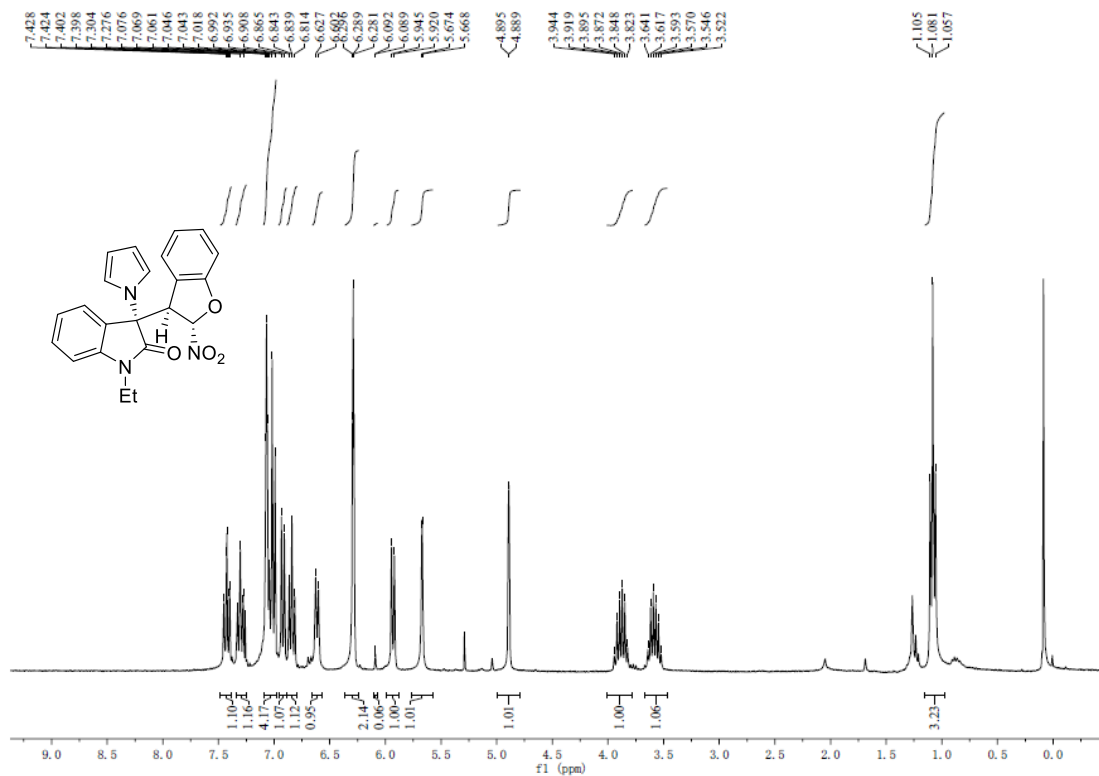
Totals	Height	Height Percent	Area	Area Percent
	363059	100.00	15400055	100.00



Detector A (254nm)	PK #	Retention Time	Height	Height Percent	Area	Area Percent
	1	15.897	24614	5.70	921624	4.57
	2	19.583	407407	94.30	19247986	95.43

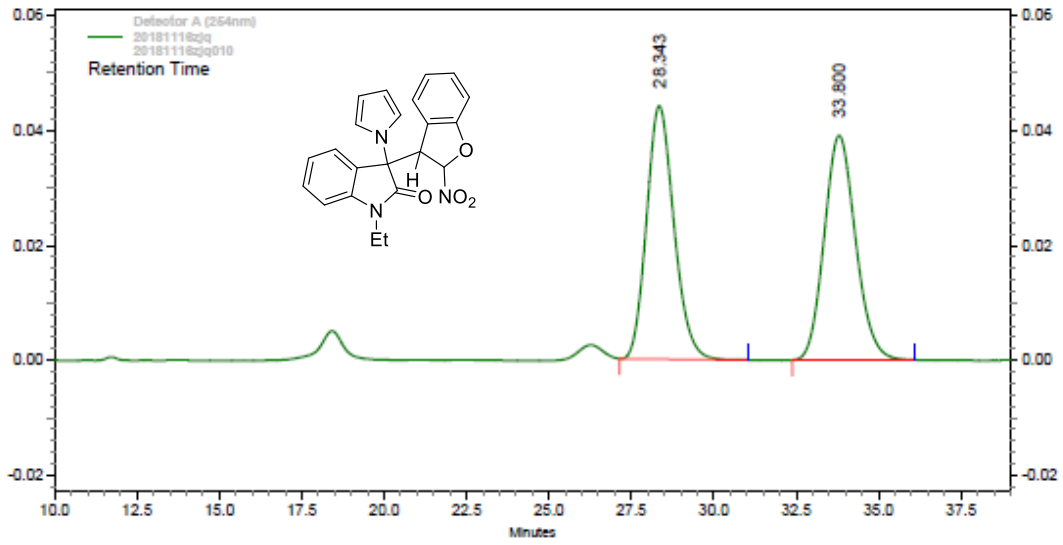
Totals	Height	Height Percent	Area	Area Percent
	432021	100.00	20169610	100.00

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

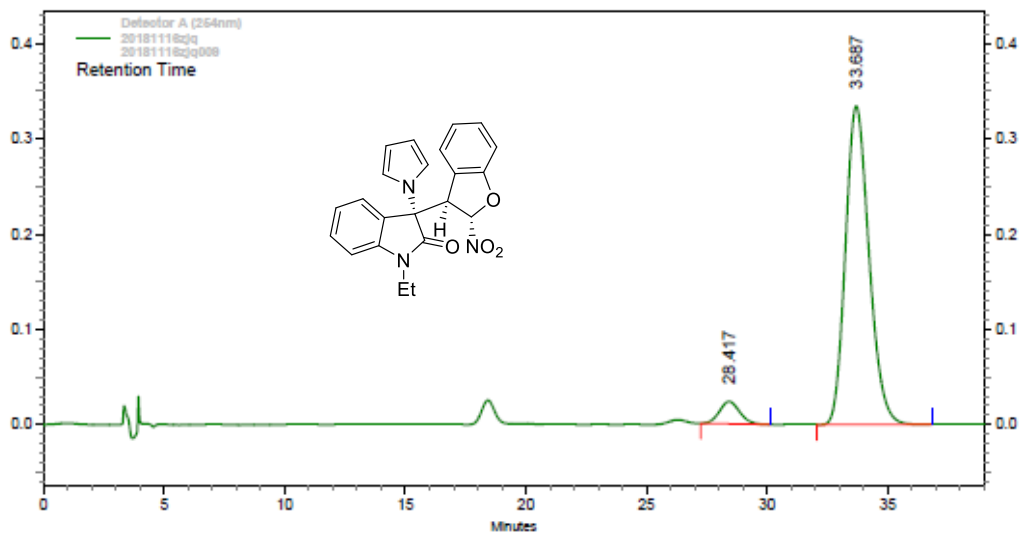




### HPLC of 3n

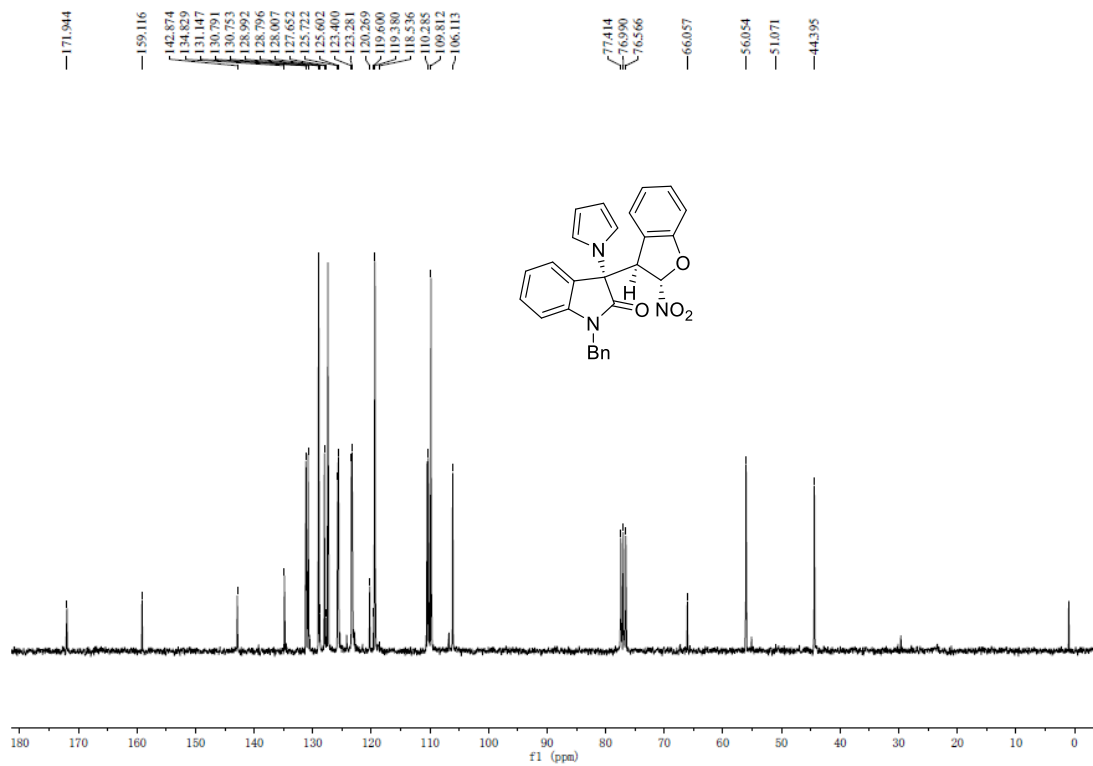
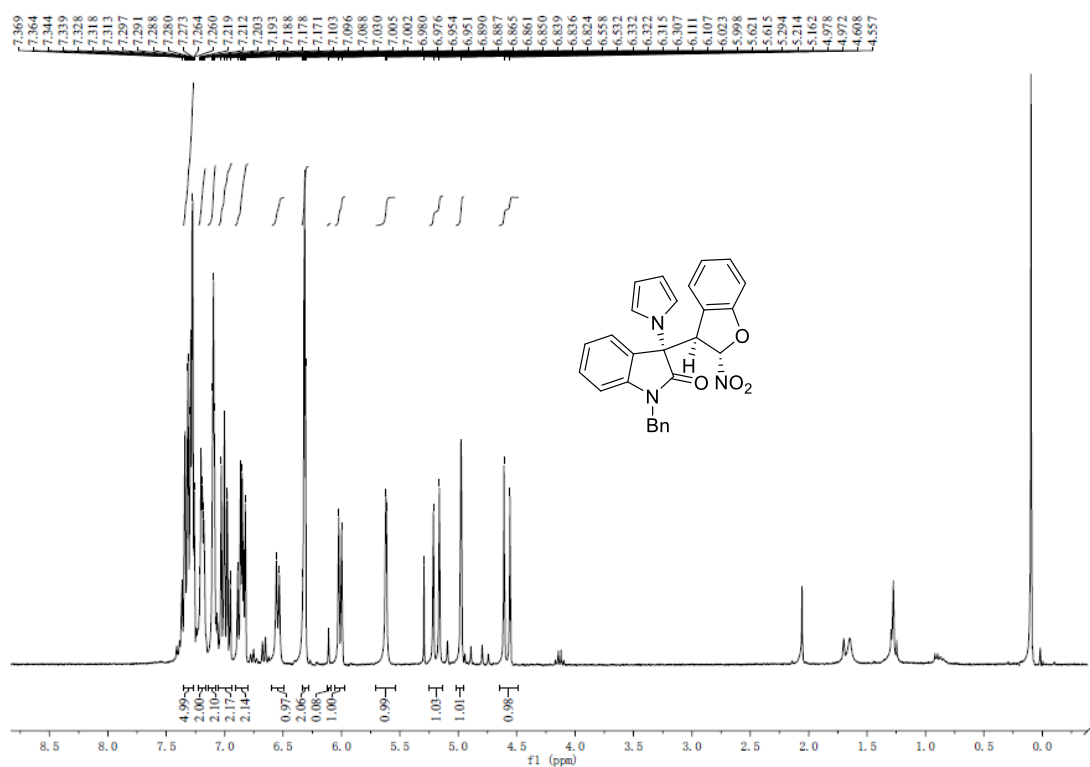


Detector A (254nm)					
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	28.343	44077	53.00	2553860	49.65
2	33.800	39081	47.00	2589583	50.35
<b>Totals</b>		83158	100.00	5143443	100.00

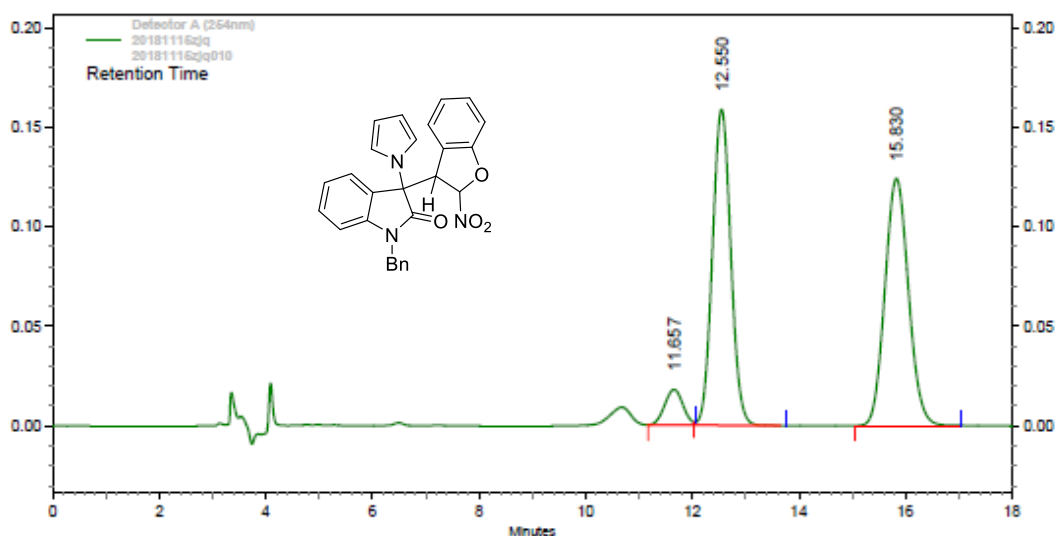


Detector A (254nm)					
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	28.417	23471	6.56	1370459	5.68
2	33.687	334246	93.44	22761653	94.32
<b>Totals</b>		357717	100.00	24132112	100.00

# $^1\text{H}$ and $^{13}\text{C}$ NMR of **30**



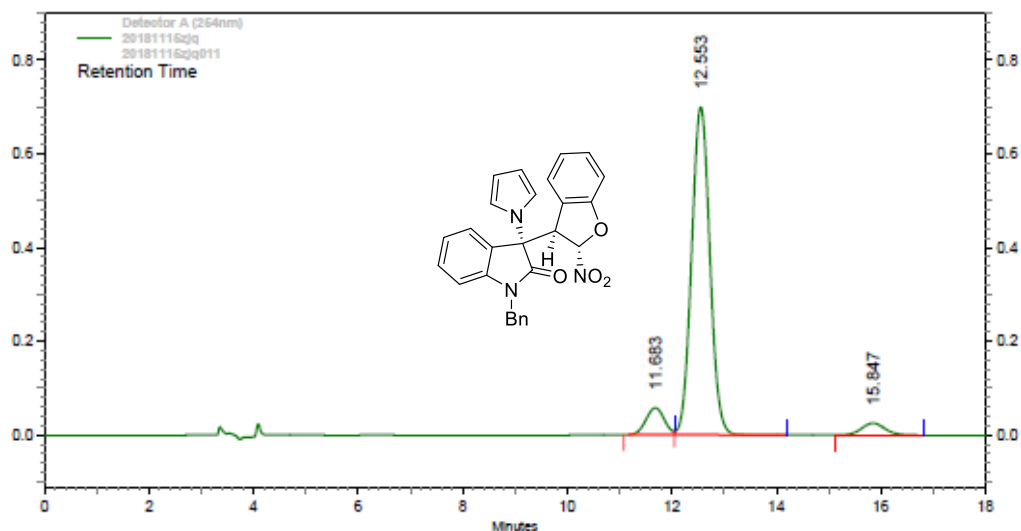
### HPLC of 3o



Detector  
A (254nm)

PK #	Retention Time	Height	Height Percent	Area	Area Percent
1	11.657	17834	5.93	426408	5.31
2	12.550	158654	52.79	3800220	47.28
3	15.830	124067	41.28	3810451	47.41

Totals		300555	100.00	8037079	100.00
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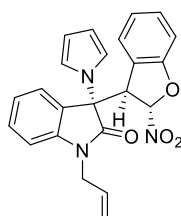
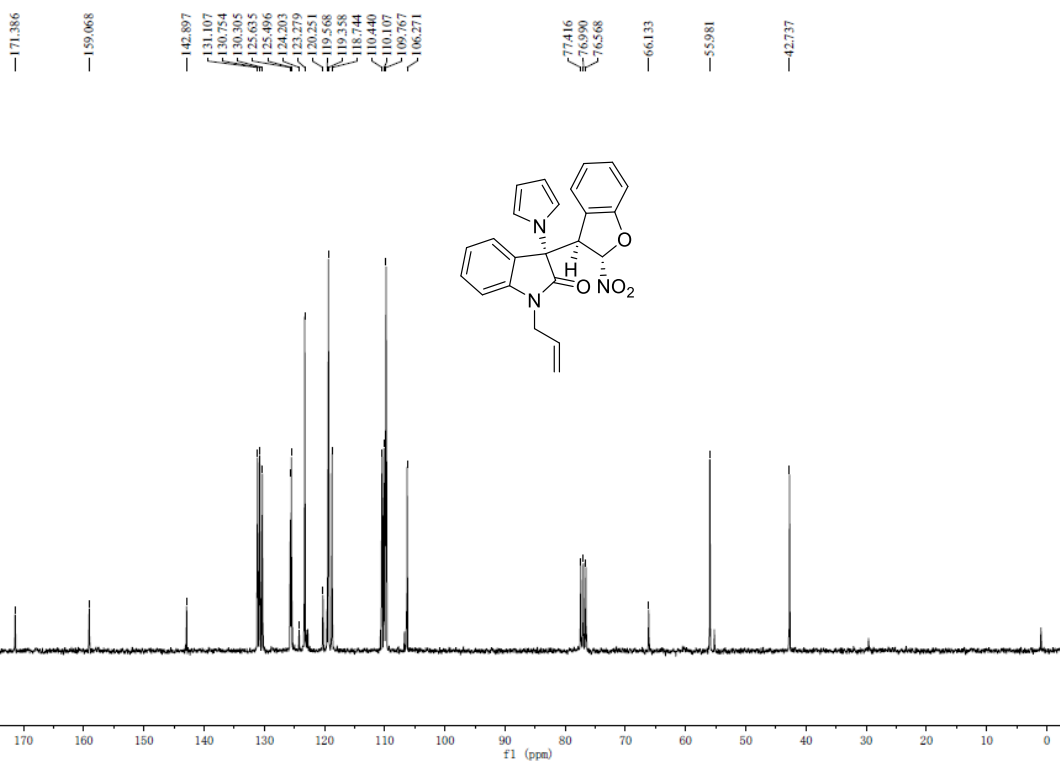
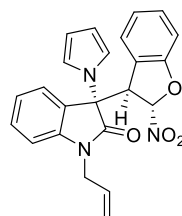
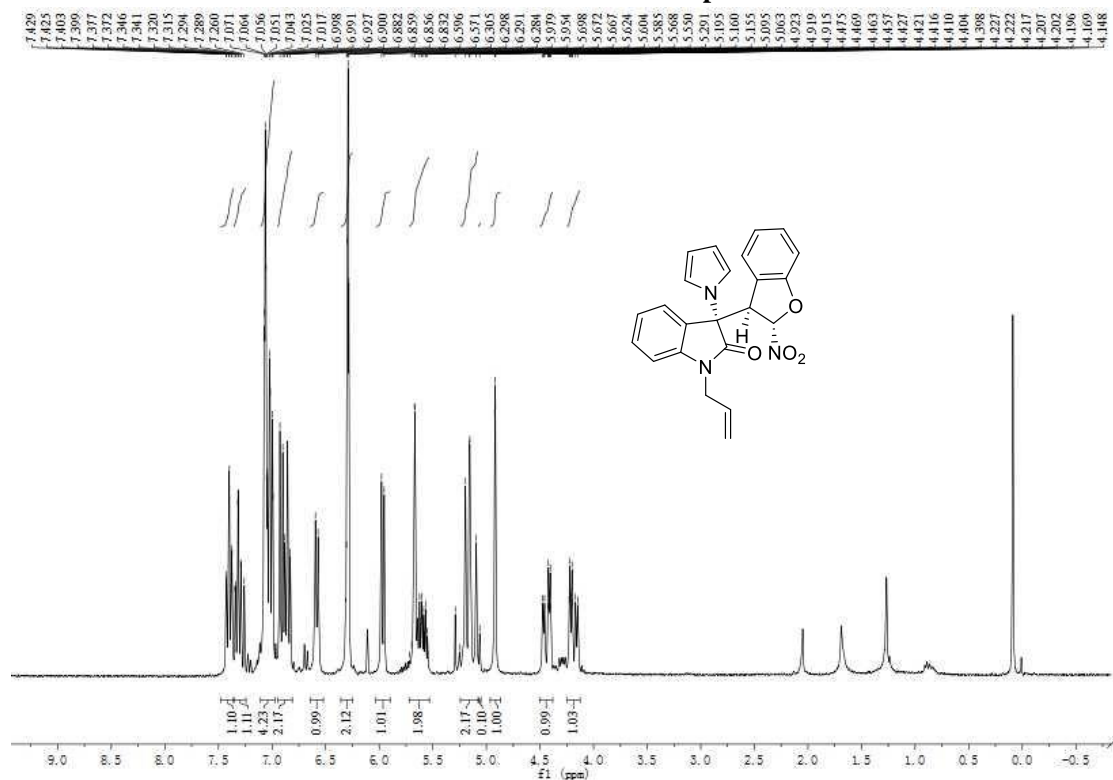


Detector  
A (254nm)

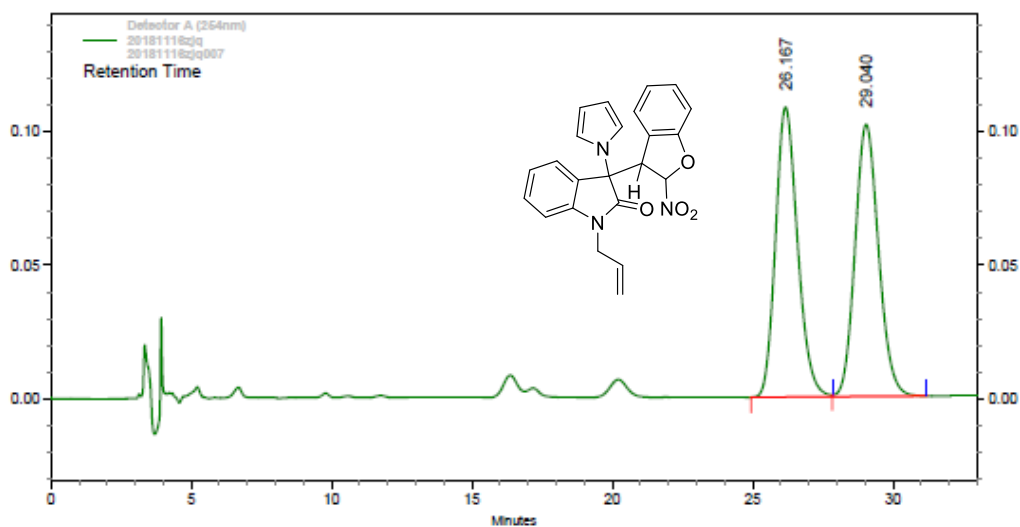
PK #	Retention Time	Height	Height Percent	Area	Area Percent
1	11.683	57399	7.34	1398149	7.30
2	12.553	699419	89.45	16985208	88.67
3	15.847	25133	3.21	771108	4.03

Totals		781951	100.00	19154465	100.00
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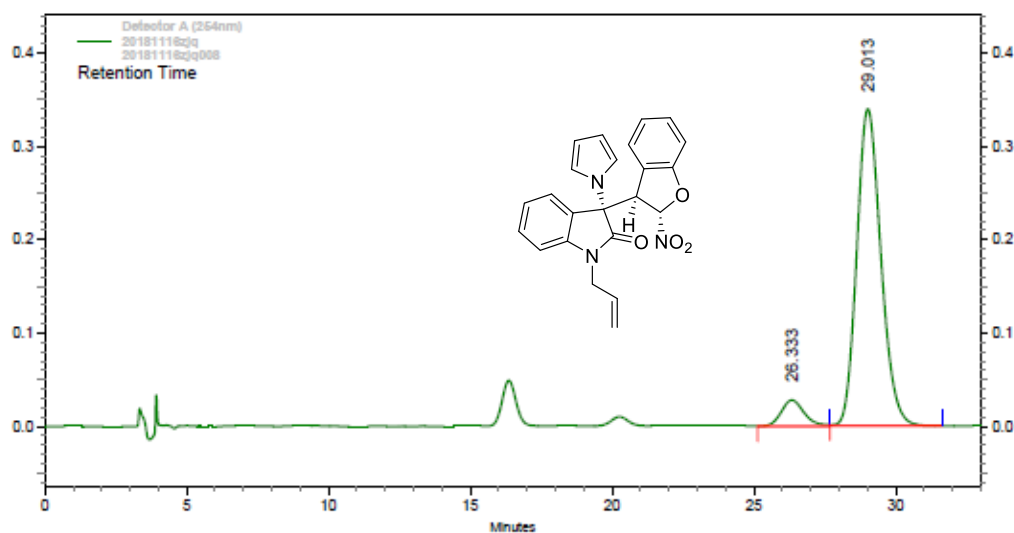
# <sup>1</sup>H and <sup>13</sup>C NMR of 3p



### HPLC of 3p

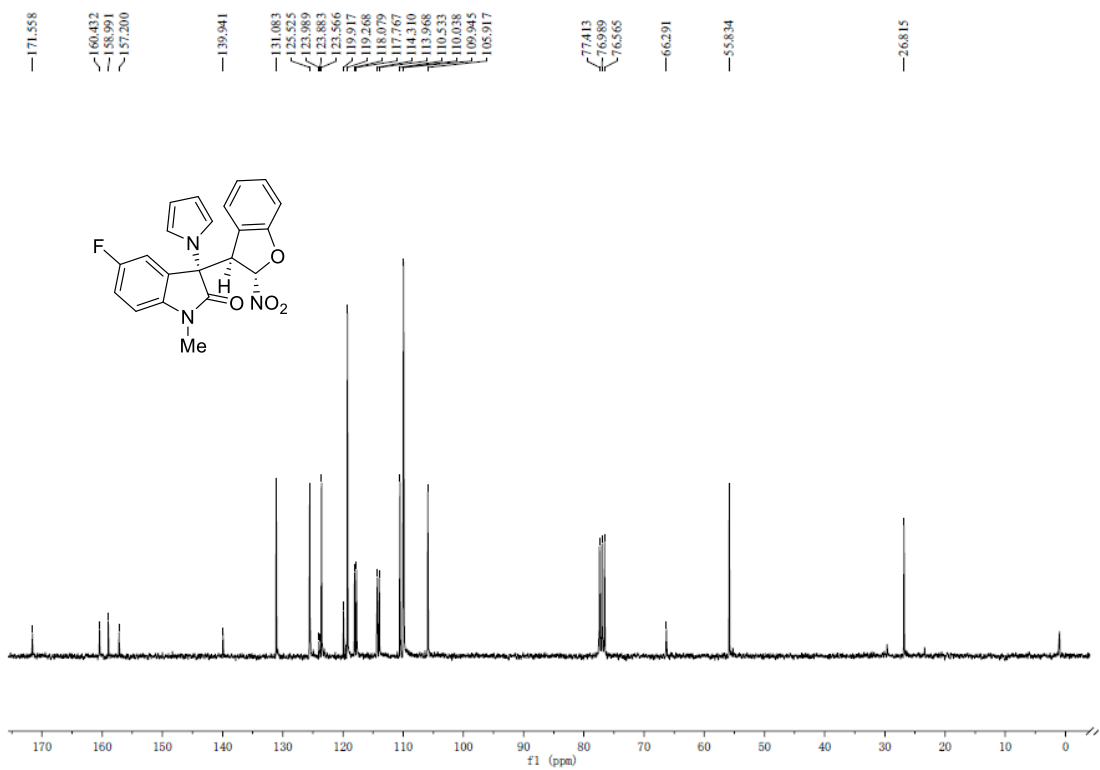
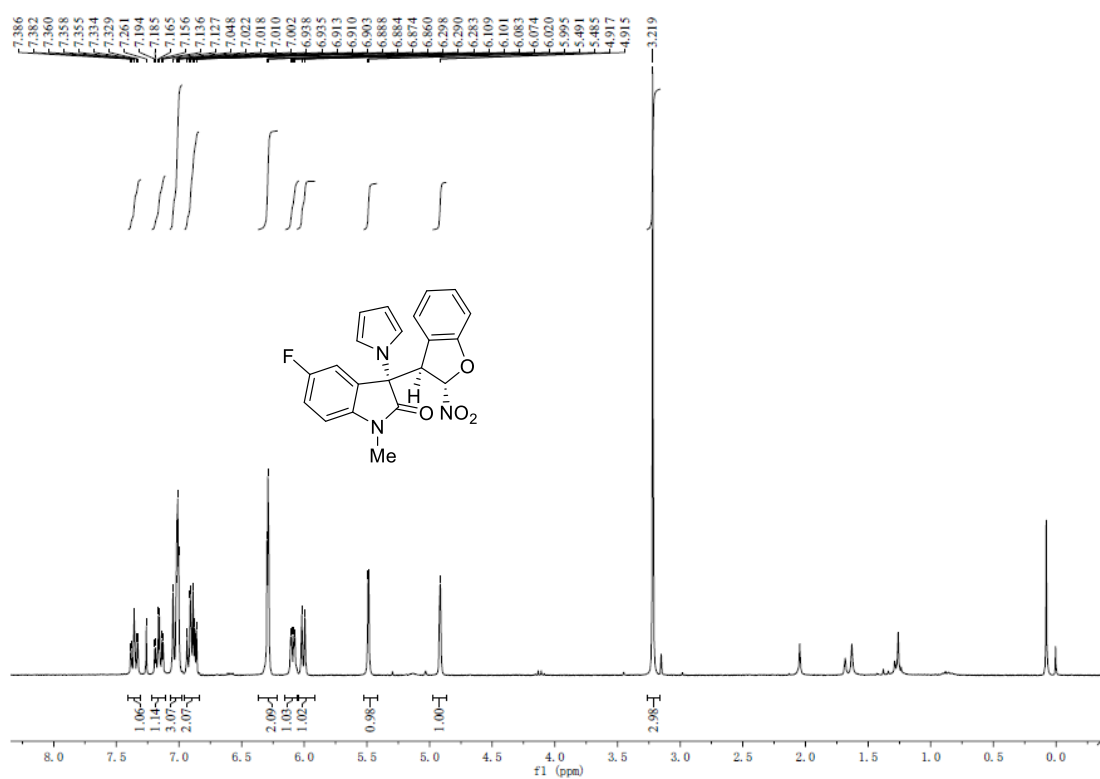


Detector A (254nm)					
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	26.167	108318	51.59	5915585	49.97
2	29.040	101633	48.41	5923586	50.03
Totals		209951	100.00	11839171	100.00

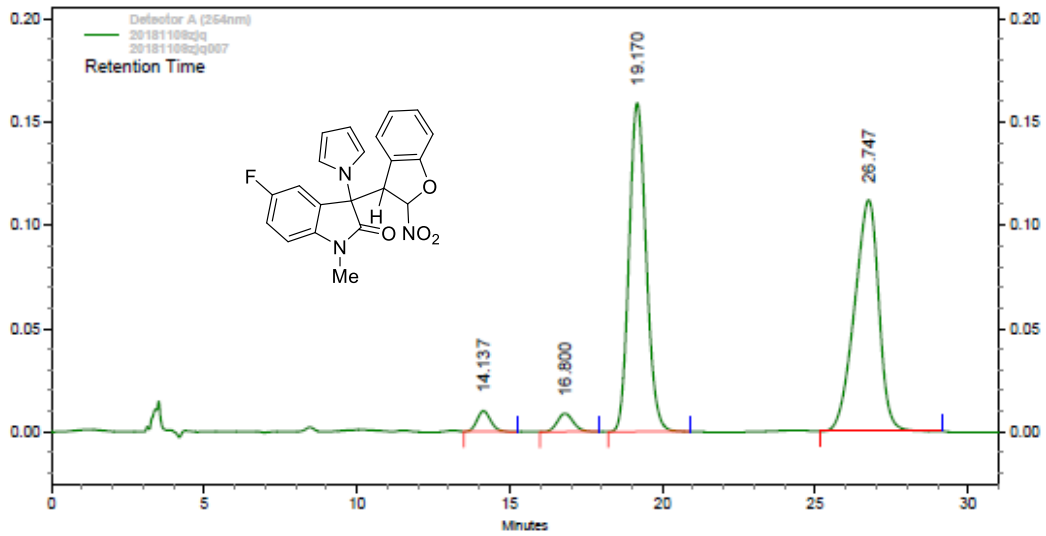


Detector A (254nm)					
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	26.333	27833	7.57	1547181	7.14
2	29.013	339613	92.43	20126573	92.86
Totals		367446	100.00	21673754	100.00

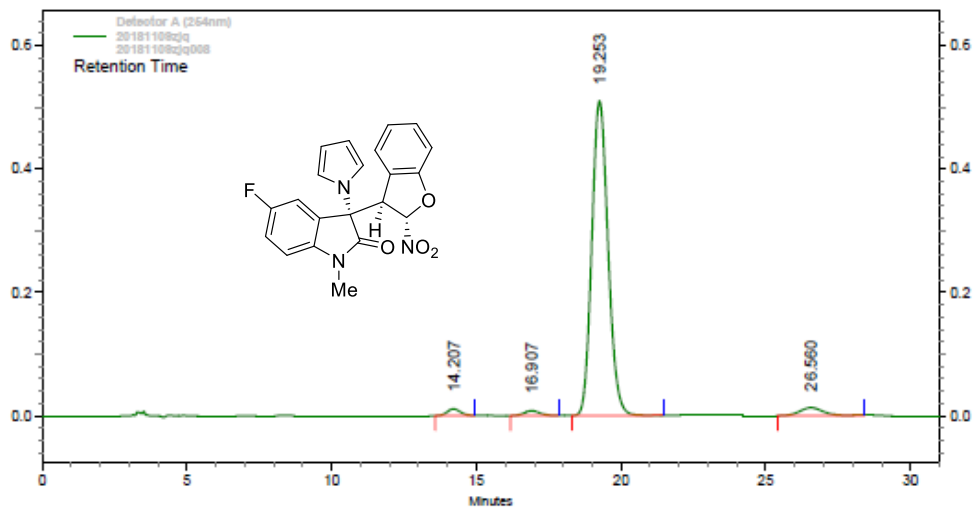
# $^1\text{H}$ and $^{13}\text{C}$ NMR of **3q**



### HPLC of 3q

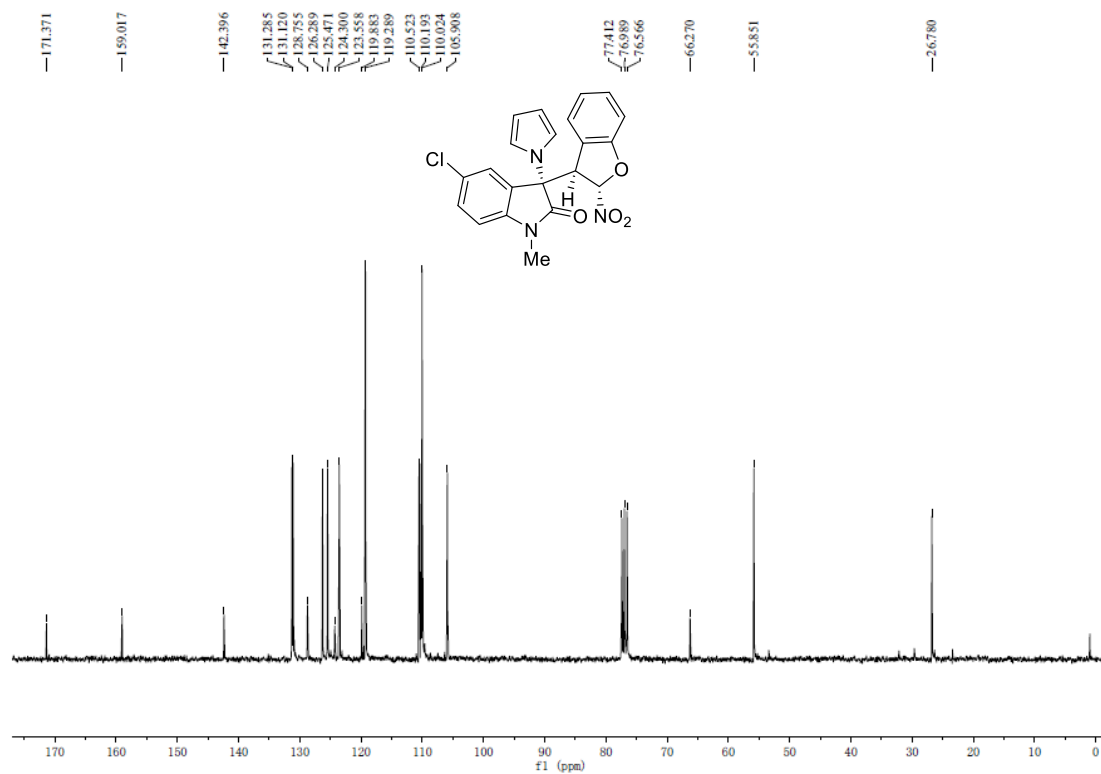
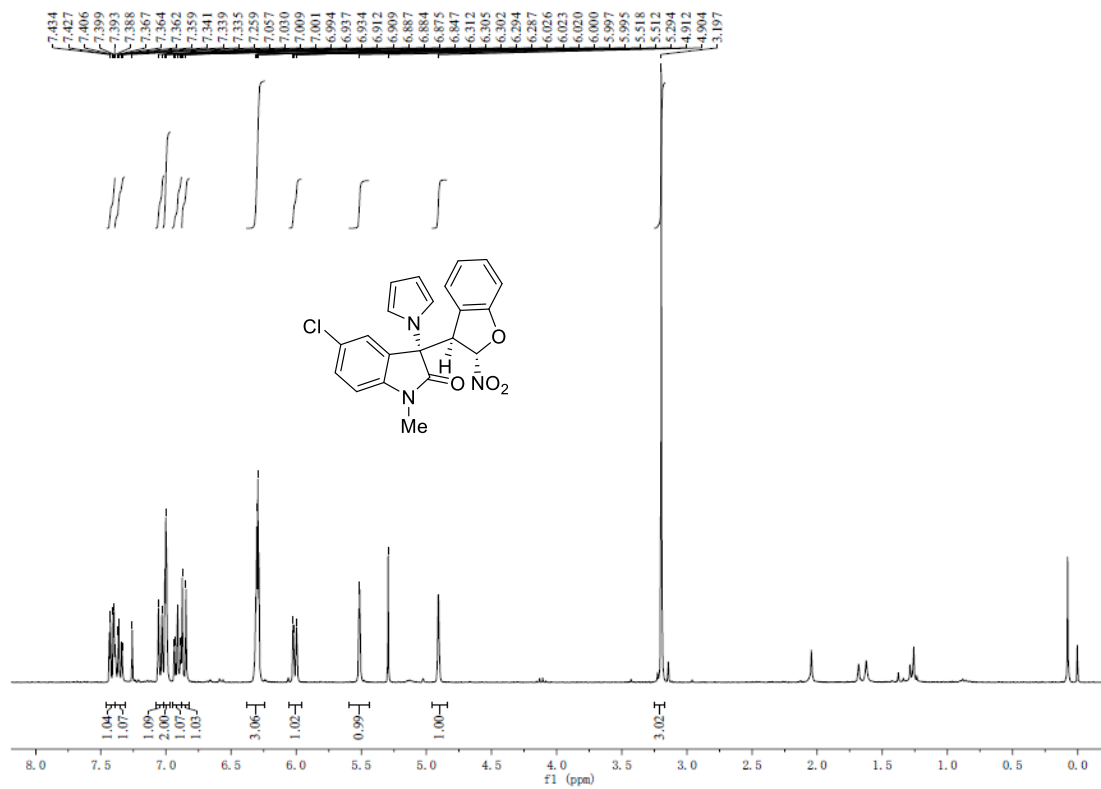


Detector A (254nm)					
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	14.137	9902	3.42	305260	2.35
2	16.800	8787	3.03	316865	2.43
3	19.170	158956	54.90	6200399	47.64
4	26.747	111880	38.64	6192809	47.58
Totals		289525	100.00	13015333	100.00



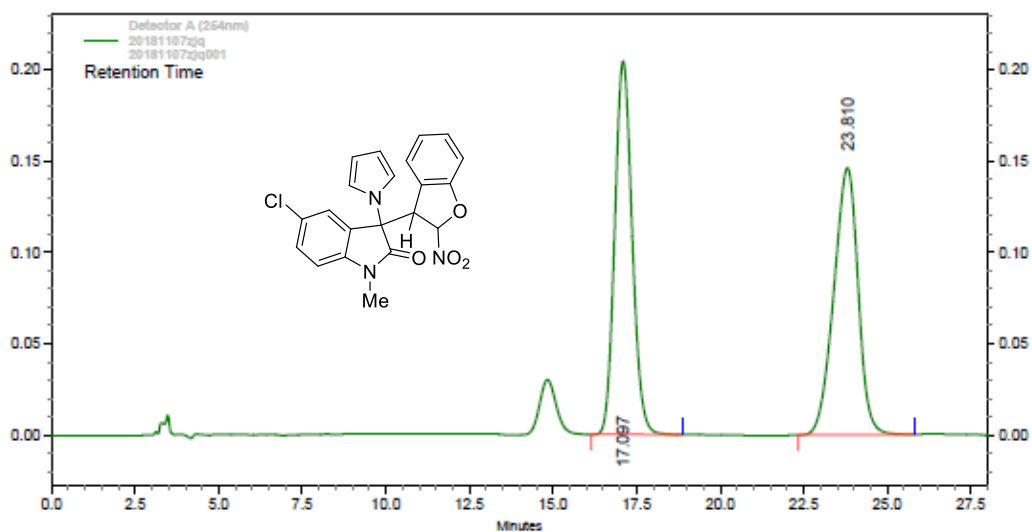
Detector A (254nm)					
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	14.207	10845	2.00	334073	1.57
2	16.907	7684	1.42	281256	1.33
3	19.253	509977	94.22	19899544	93.78
4	26.560	12767	2.36	703691	3.32
Totals		541273	100.00	21218564	100.00

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





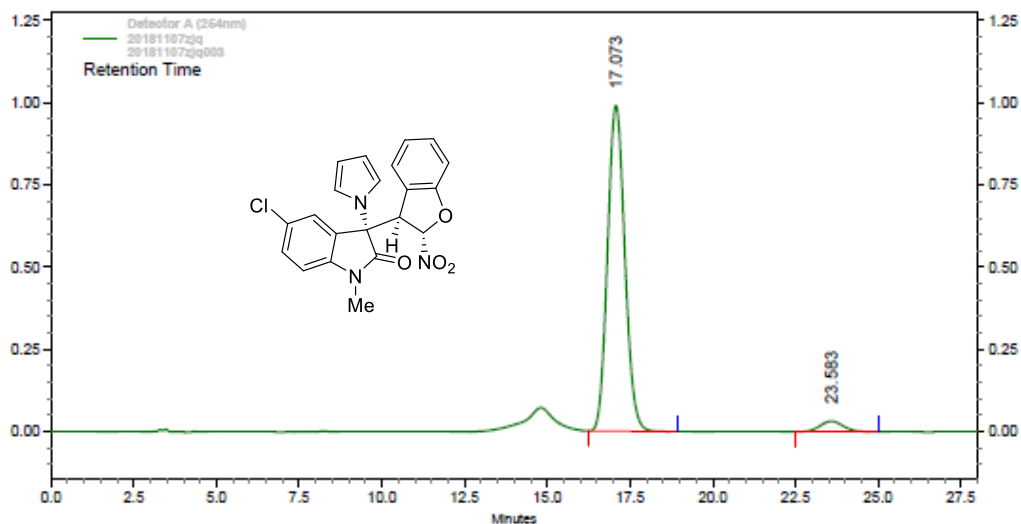
### HPLC of 3r



Detector  
A (254nm)

Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	17.097	204413	58.30	7406749	50.04
2	23.810	146185	41.70	7395857	49.96

Totals		350598	100.00	14802606	100.00
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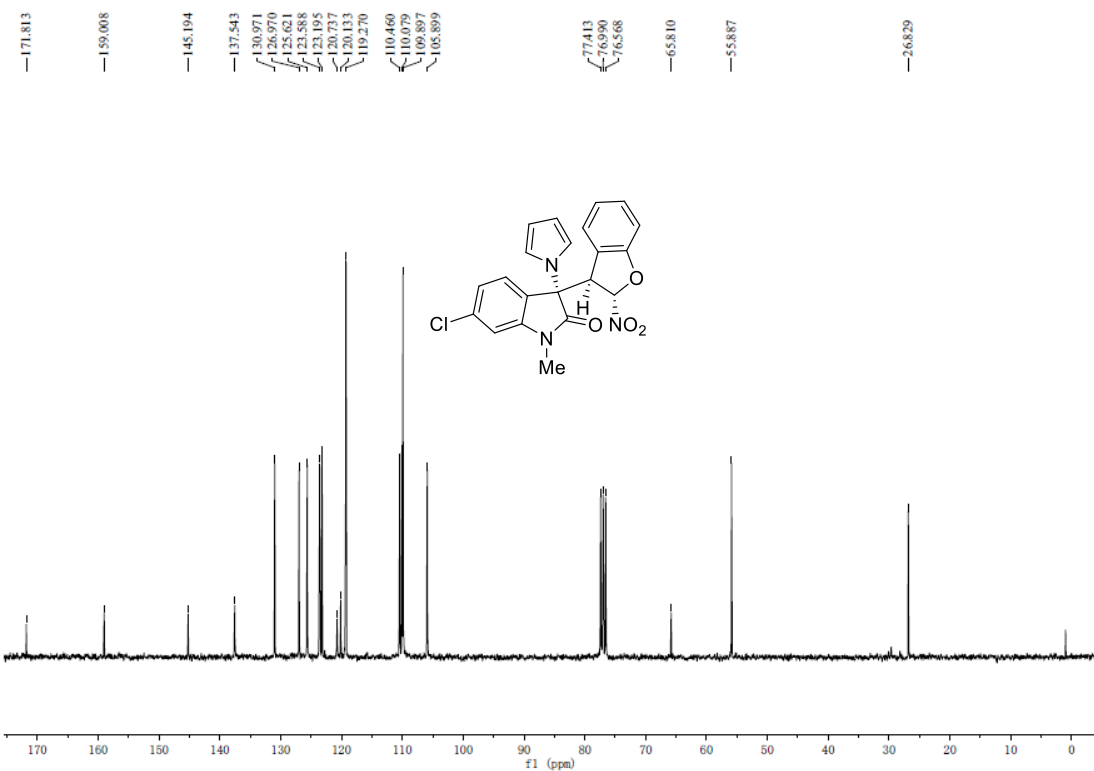
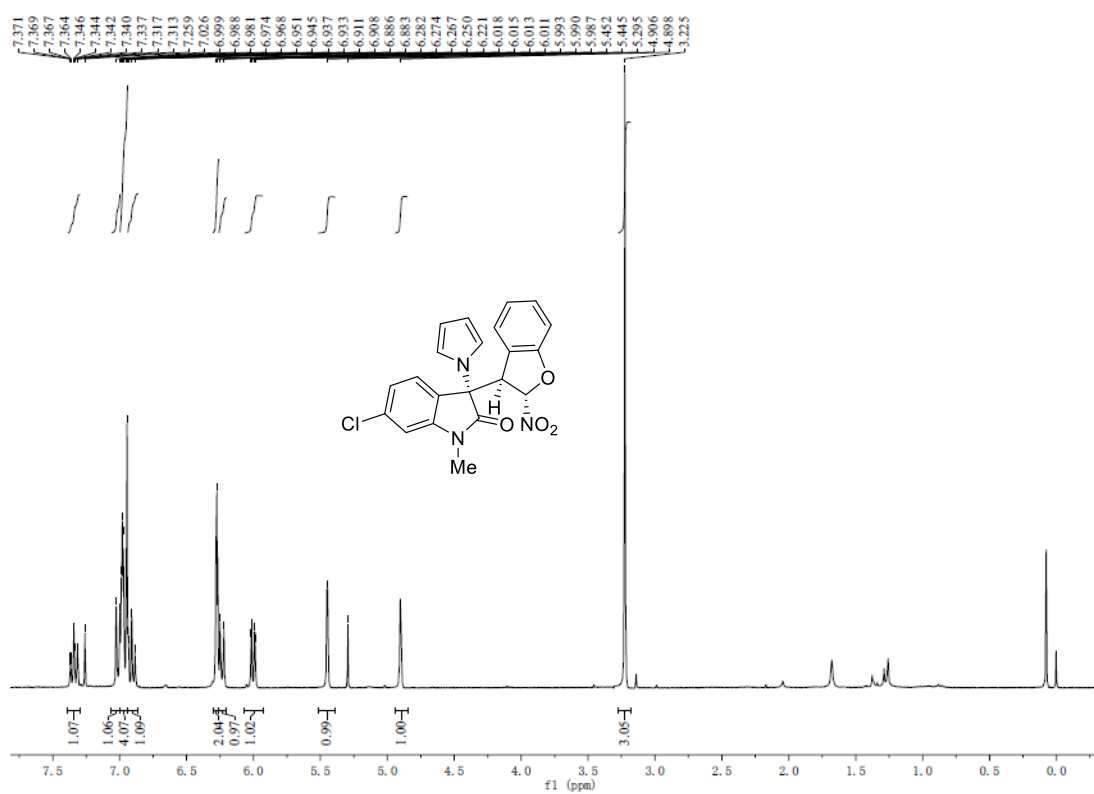


Detector  
A (254nm)

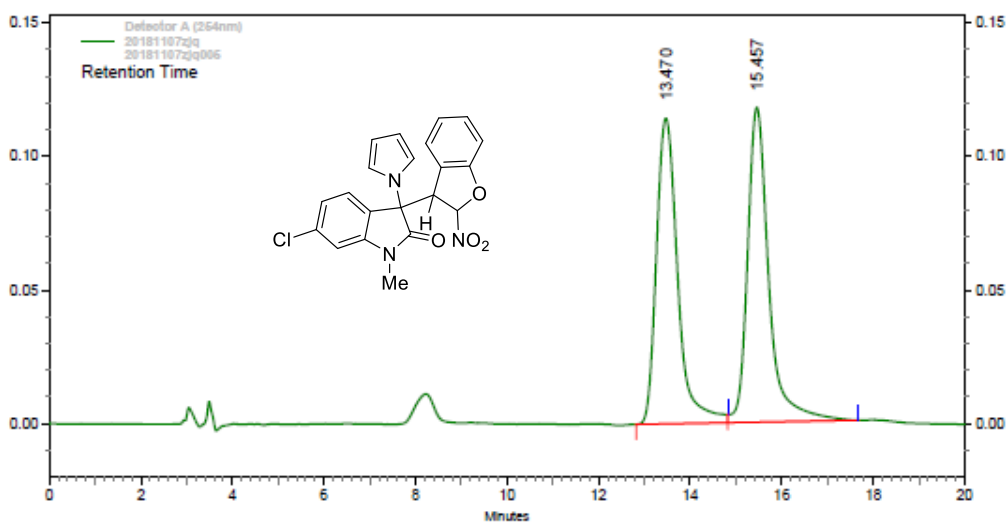
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	17.073	990277	96.86	35970524	95.76
2	23.583	32107	3.14	1591970	4.24

Totals		1022384	100.00	37562494	100.00
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$^1\text{H}$  and  $^{13}\text{C}$  NMR of **3s**

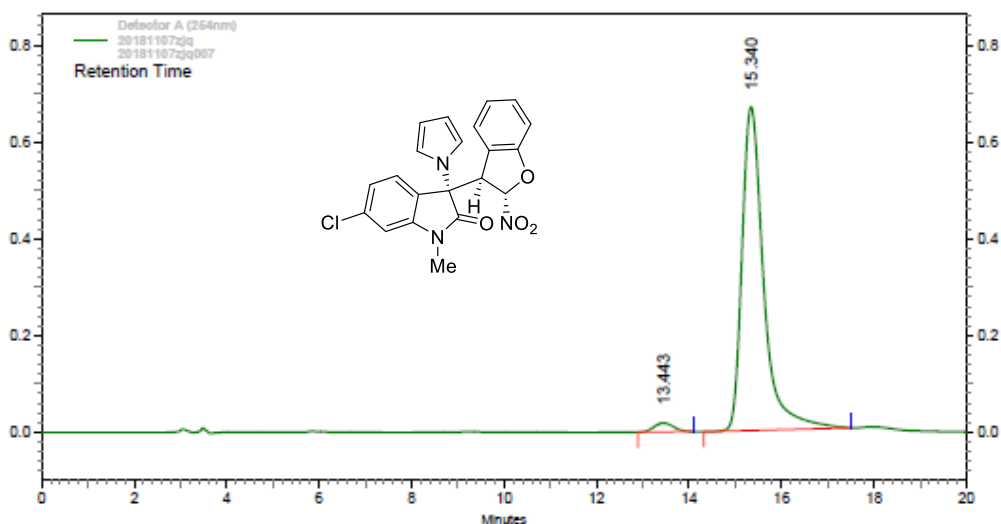


### HPLC of 3s



PK #	Retention Time	Height	Height Percent	Area	Area Percent
1	13.470	114319	49.26	3692582	49.31
2	15.457	117740	50.74	3795573	50.69

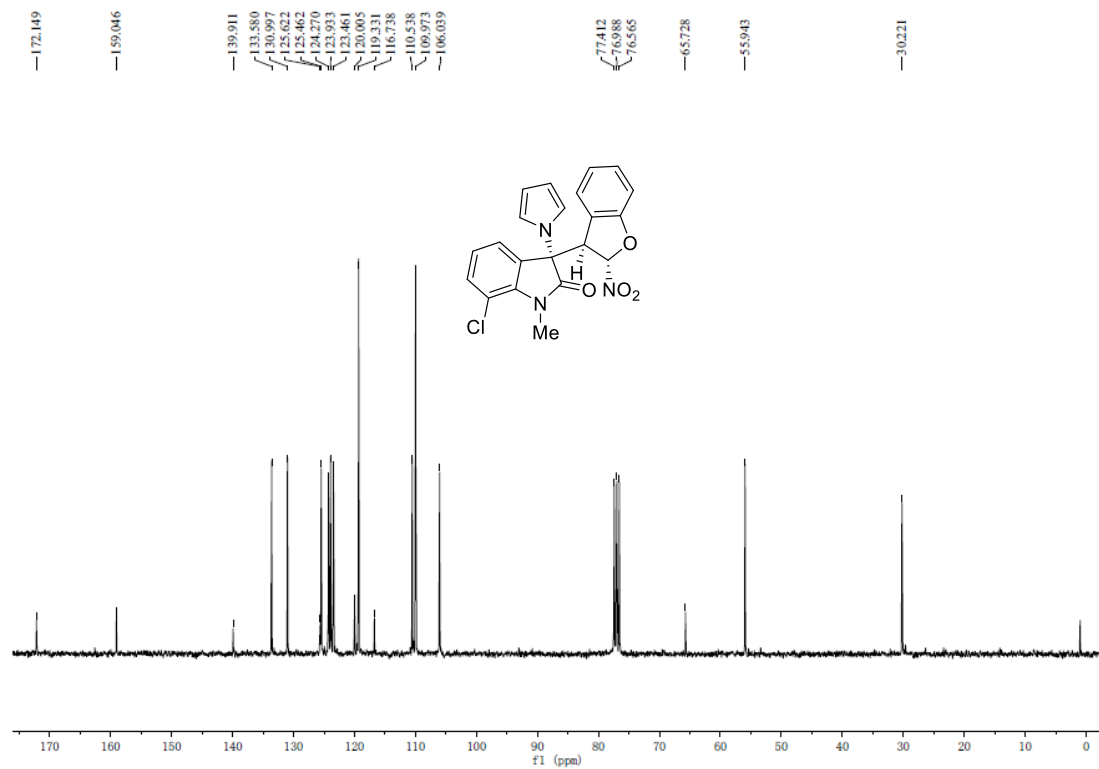
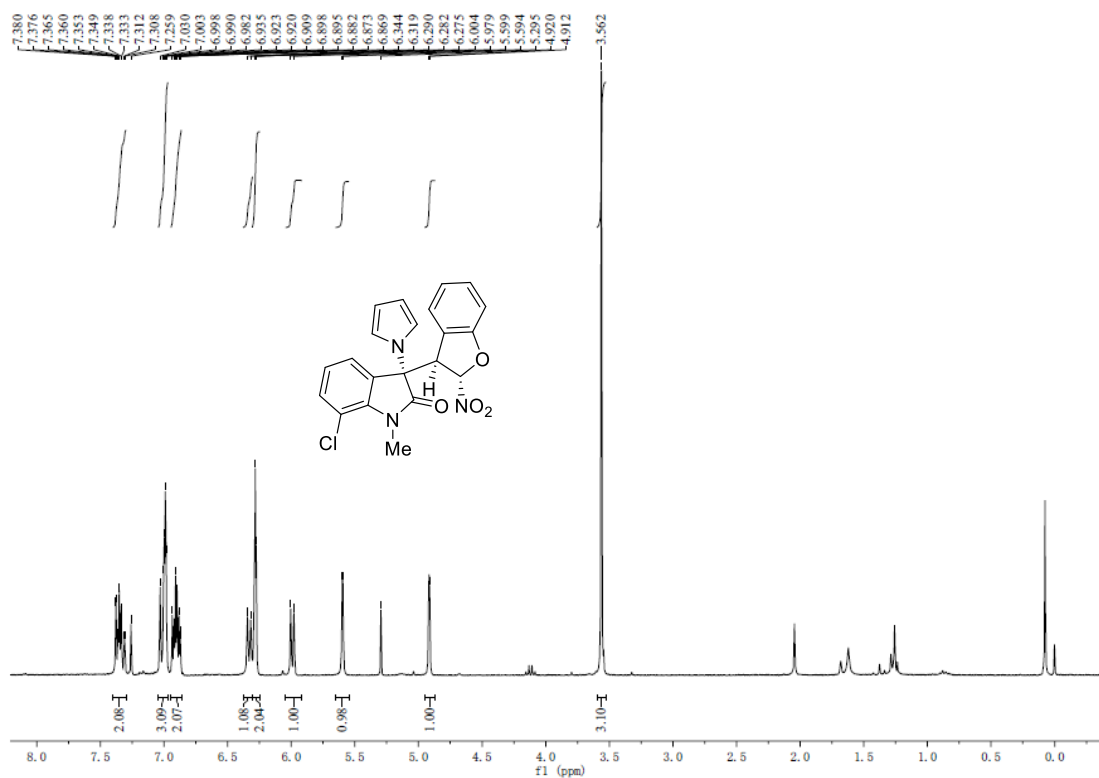
Totals	Height	Height Percent	Area	Area Percent
	232059	100.00	7488155	100.00



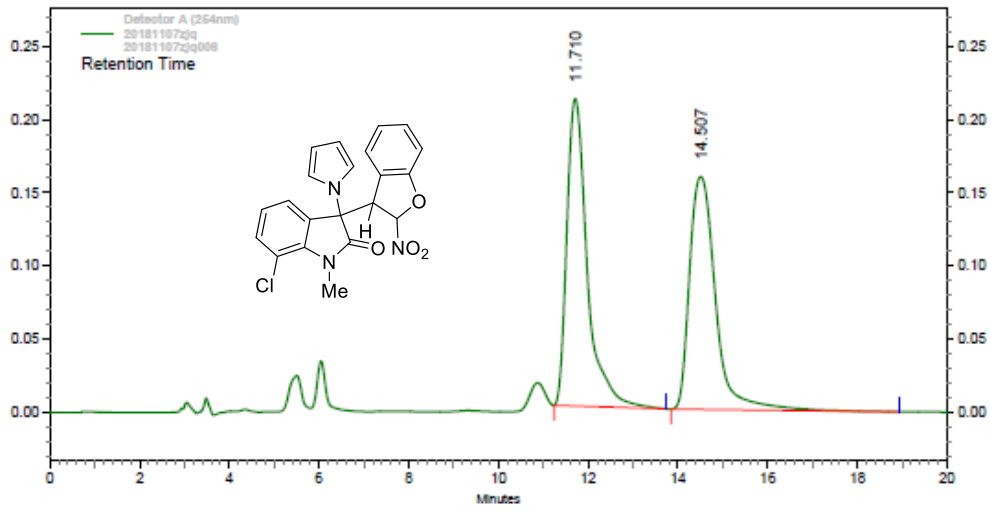
PK #	Retention Time	Height	Height Percent	Area	Area Percent
1	13.443	18230	2.65	534228	2.40
2	15.340	668763	97.35	21736443	97.60

Totals	Height	Height Percent	Area	Area Percent
	686993	100.00	22270671	100.00

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

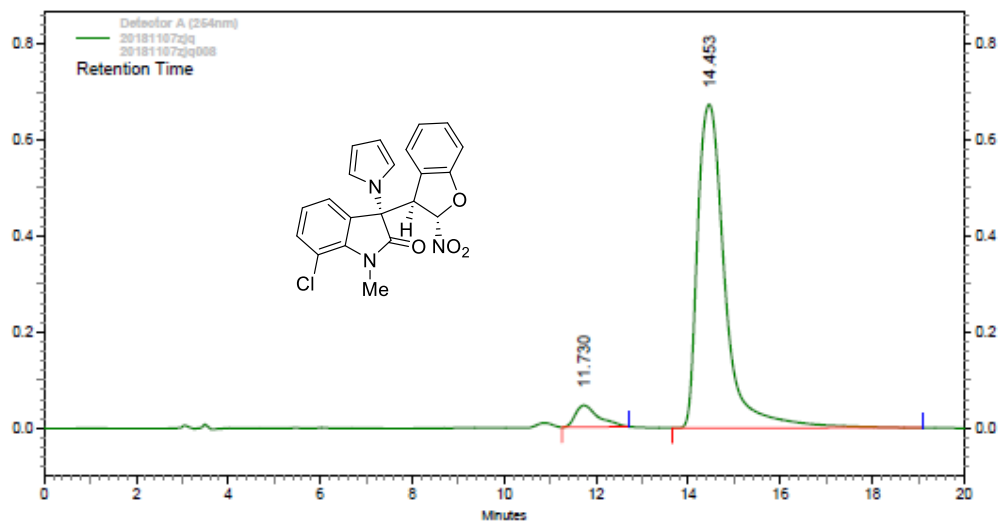


### HPLC of 3t



Detector A (254nm)

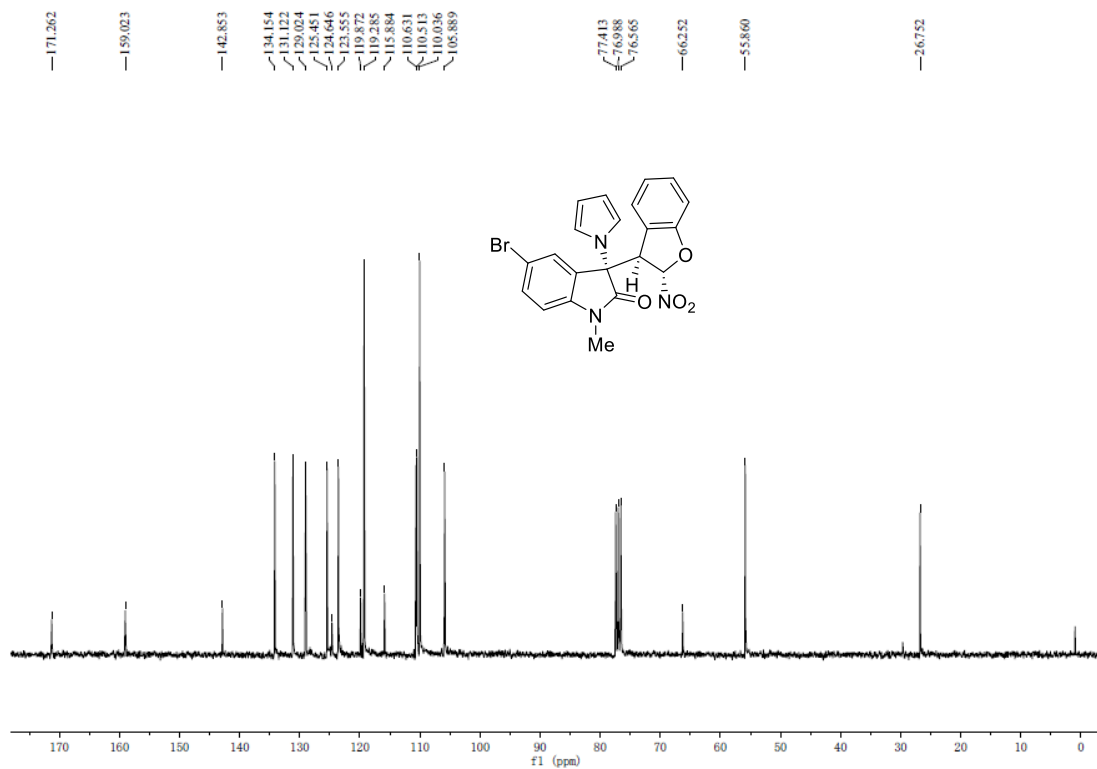
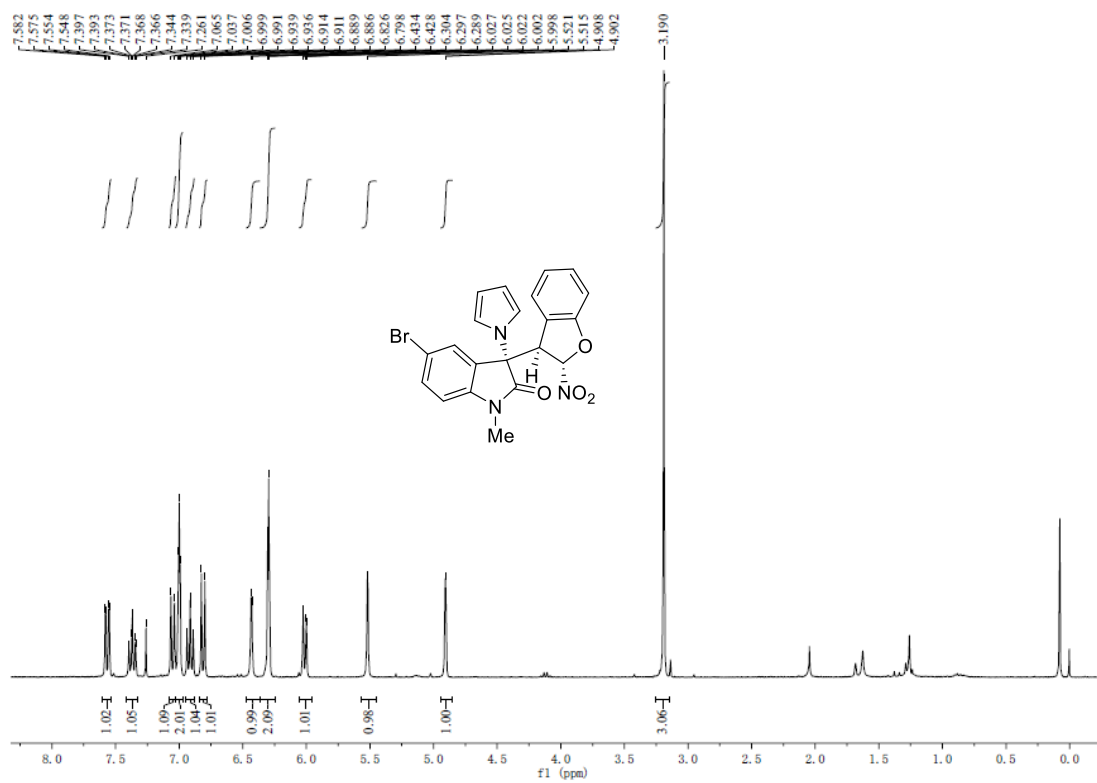
Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	11.710	210278	56.91	6631471	50.84
2	14.507	159246	43.09	6412549	49.16
<b>Totals</b>		369524	100.00	13044020	100.00



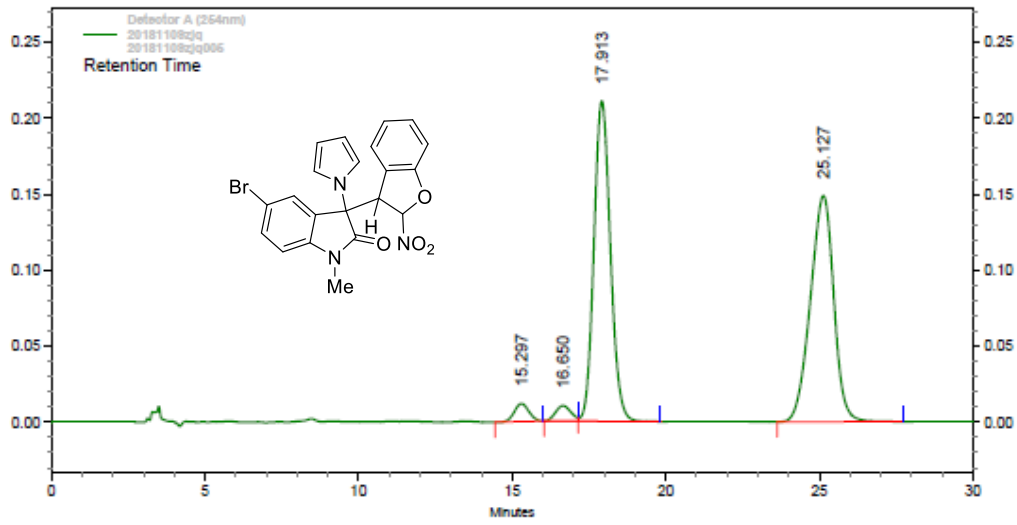
Detector A (254nm)

Pk #	Retention Time	Height	Height Percent	Area	Area Percent
1	11.730	45090	6.28	1571833	5.35
2	14.453	672963	93.72	27804589	94.65
<b>Totals</b>		718053	100.00	29376422	100.00

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

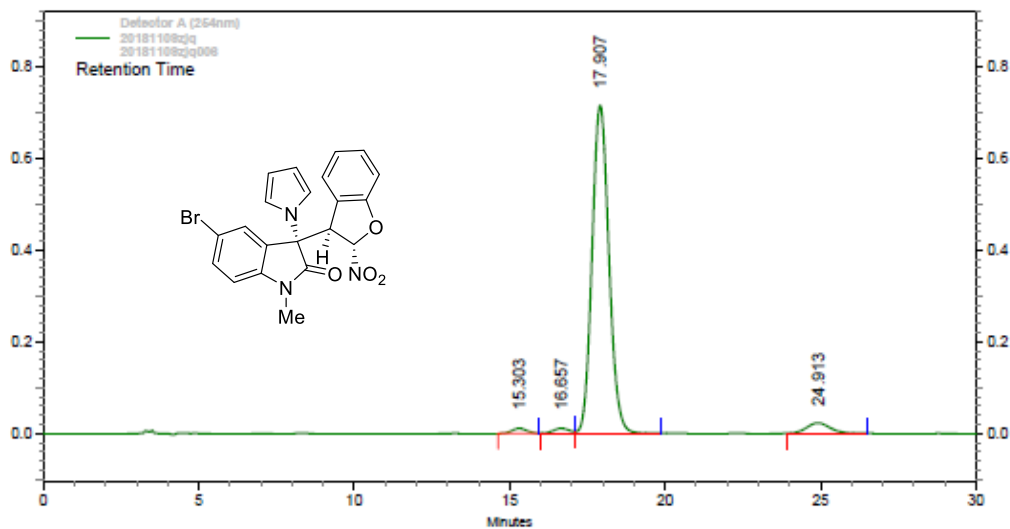


### HPLC of 3u



Detector A (254nm)	Pk #	Retention Time	Height	Height Percent	Area	Area Percent
	1	15.297	11803	3.09	386952	2.34
	2	16.650	10111	2.65	355473	2.15
	3	17.913	210791	55.25	7873439	47.70
	4	25.127	148804	39.00	7890073	47.80

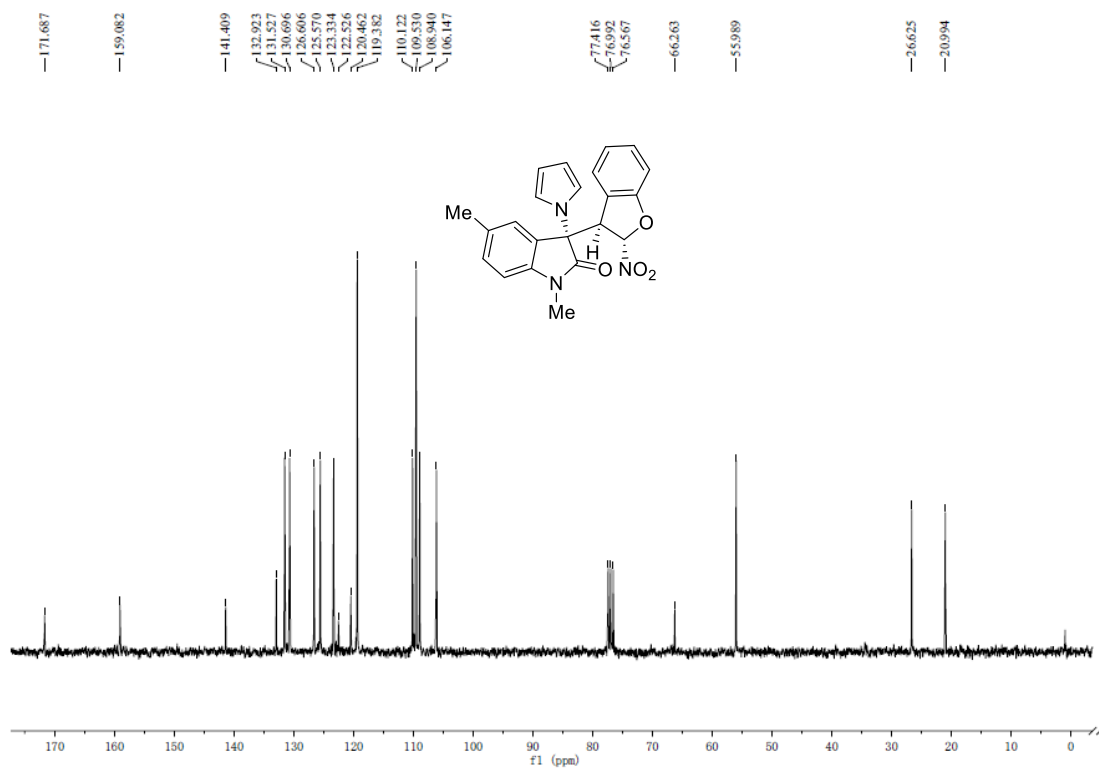
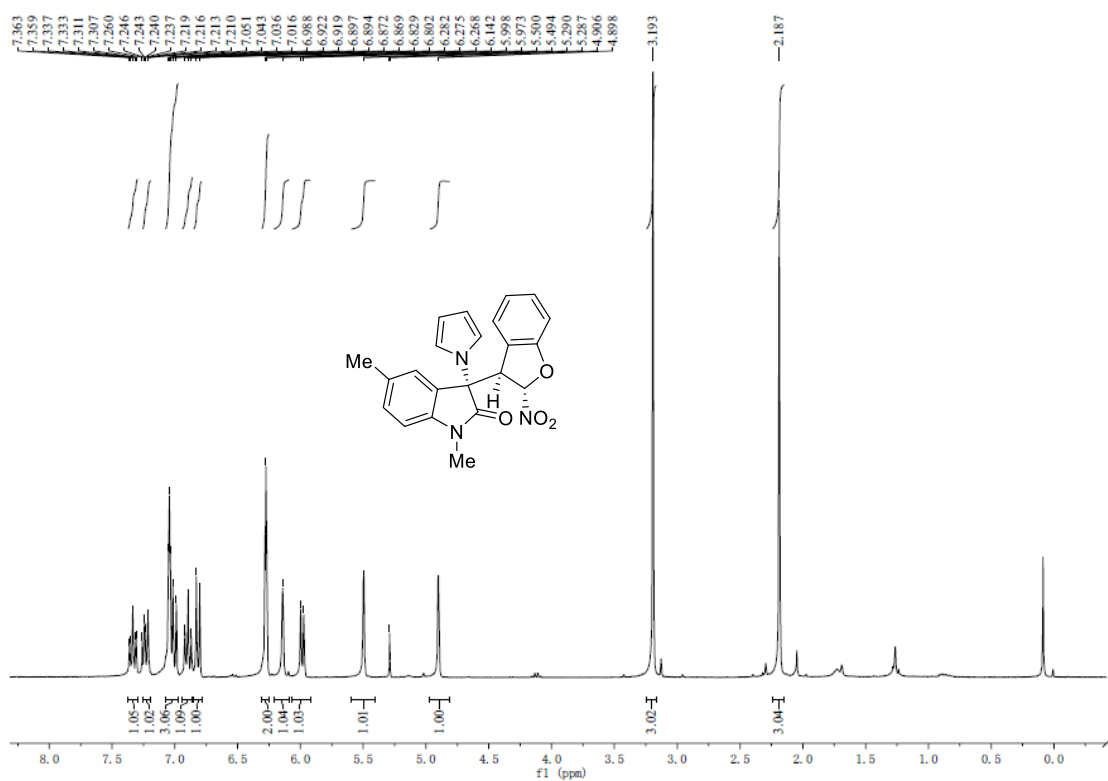
Totals						
			381509	100.00	16505937	100.00



Detector A (254nm)	Pk #	Retention Time	Height	Height Percent	Area	Area Percent
	1	15.303	10712	1.41	347173	1.21
	2	16.657	10615	1.40	367877	1.28
	3	17.907	714971	94.20	26905020	93.40
	4	24.913	22699	2.99	1186539	4.12

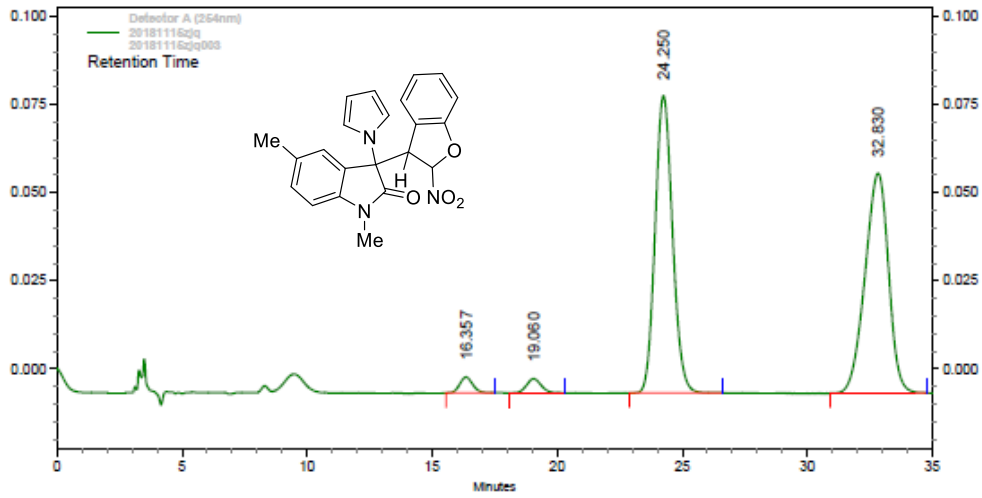
Totals						
			758997	100.00	28806609	100.00

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

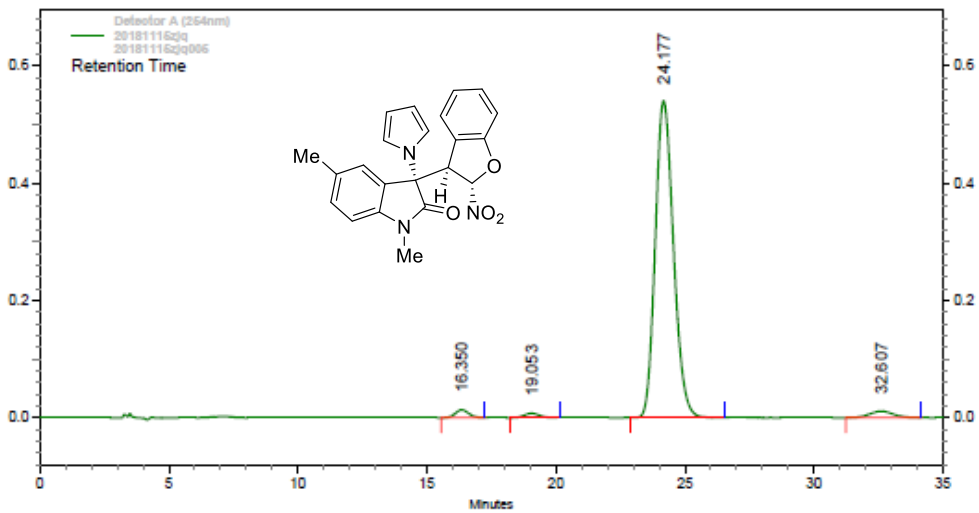




### HPLC of 3v

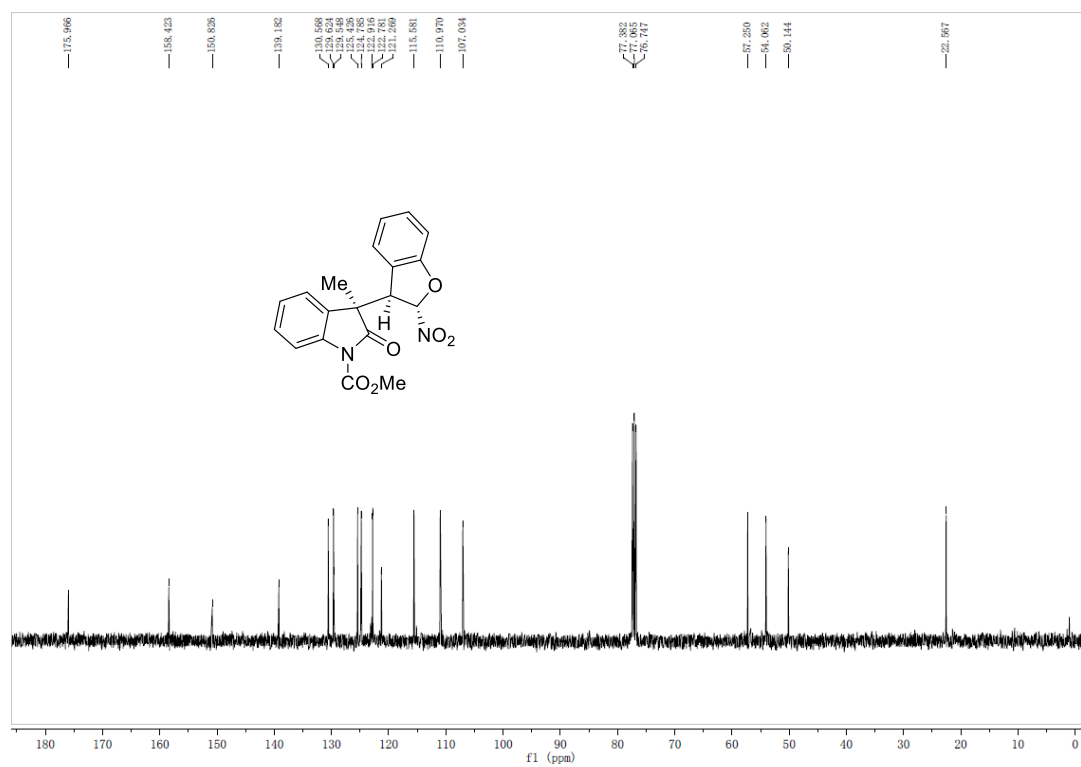
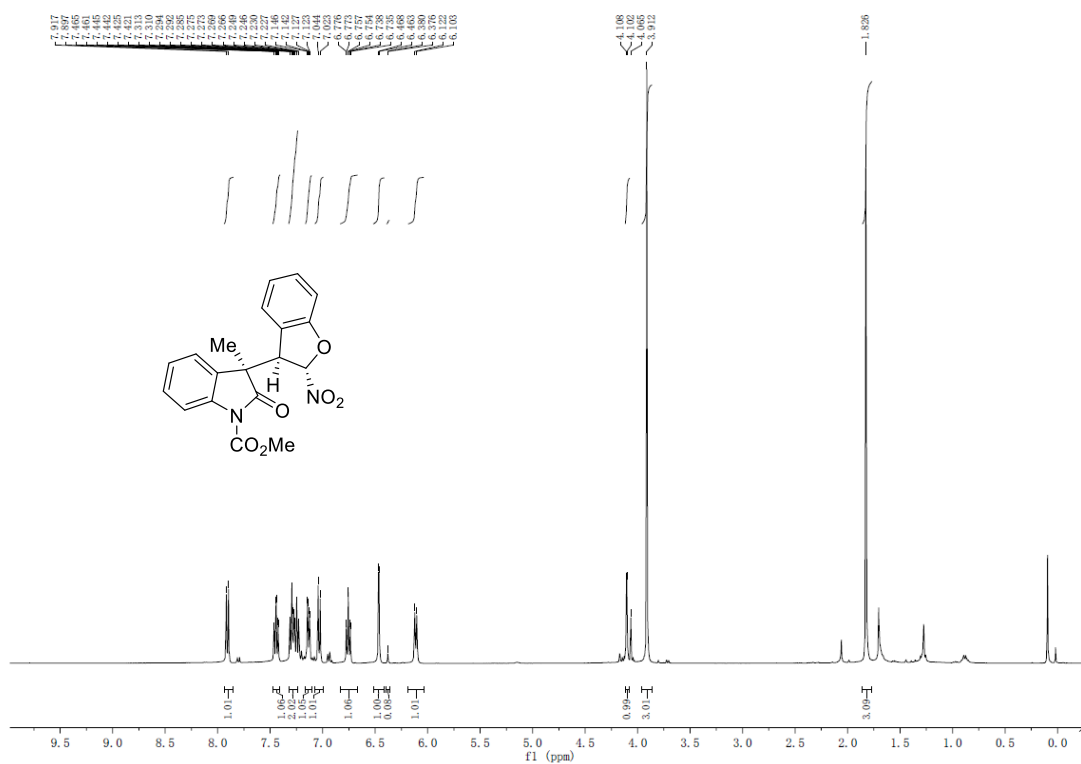


Detector A (254nm)						
PK #	Retention Time	Height	Height Percent	Area	Area Percent	
1	16.357	4475	2.88	160773	1.90	
2	19.060	4004	2.58	162441	1.91	
3	24.250	84353	54.34	4082645	48.13	
4	32.830	62405	40.20	4076913	48.06	
Totals						
		155237	100.00	8482772	100.00	

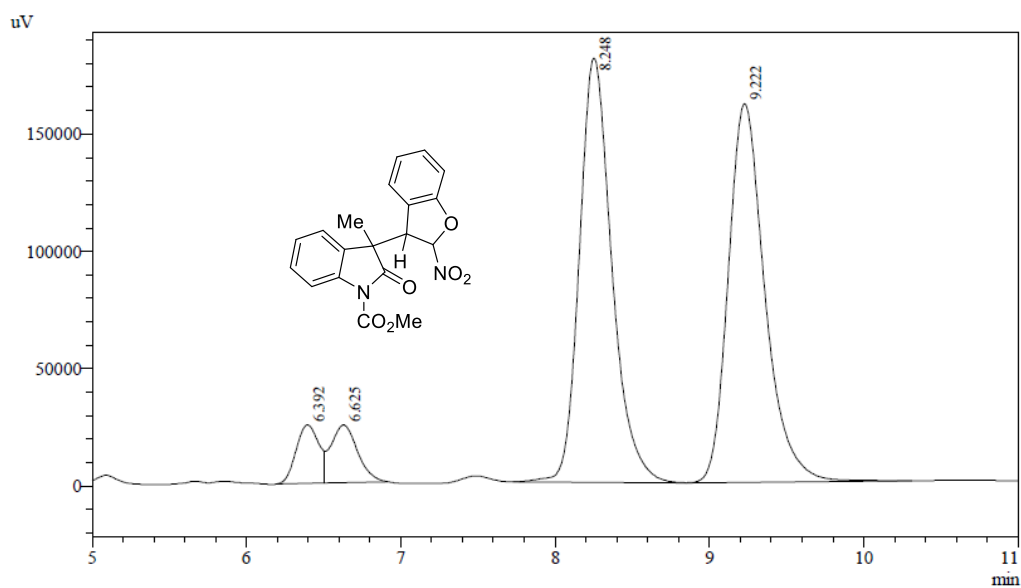


Detector A (254nm)						
PK #	Retention Time	Height	Height Percent	Area	Area Percent	
1	16.350	13321	2.33	473417	1.69	
2	19.053	7374	1.29	297306	1.06	
3	24.177	540098	94.49	26536537	94.79	
4	32.607	10804	1.89	689009	2.46	
Totals						
		571597	100.00	27996269	100.00	

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

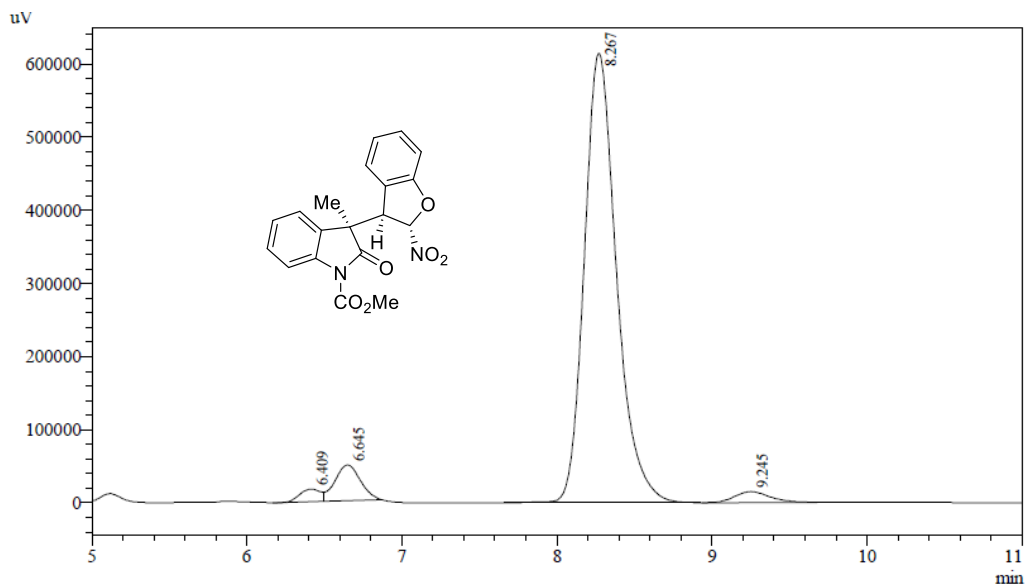


### HPLC of 5a



Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.392	260715	24996	4.449	6.379
2	6.625	293307	24620	5.005	6.283
3	8.248	2648791	180871	45.199	46.157
4	9.222	2657527	161373	45.348	41.181
Total		5860339	391860	100.000	100.000

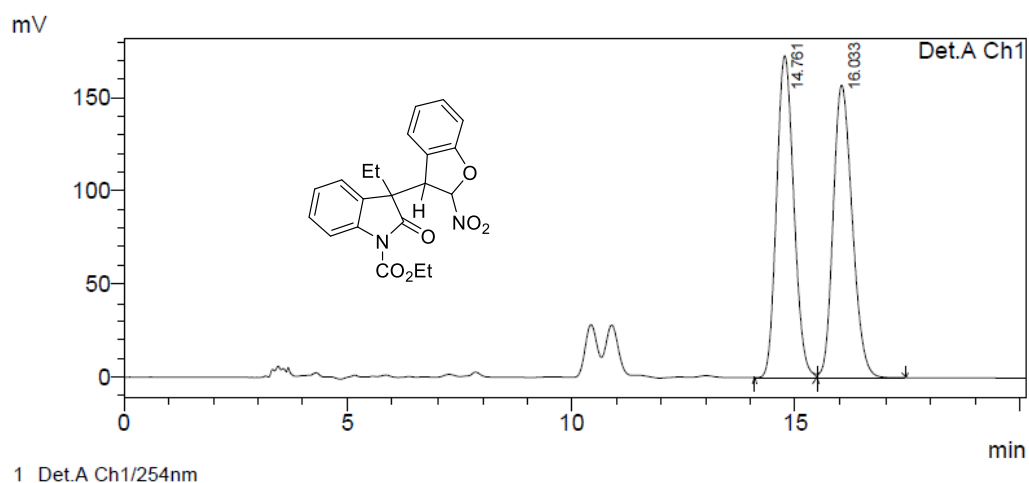


Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.409	157238	17170	1.598	2.471
2	6.645	554549	48677	5.637	7.005
3	8.267	8887906	614115	90.348	88.371
4	9.245	237699	14966	2.416	2.154
Total		9837392	694928	100.000	100.000



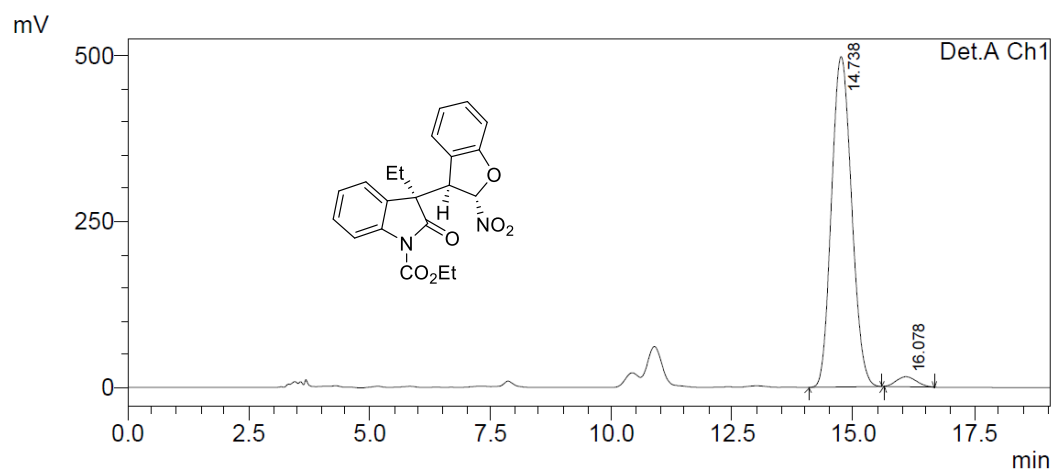
### HPLC of 5b



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	14.761	4649797	172968	49.909
2	16.033	4666710	157077	50.091
Total		9316507		100.000

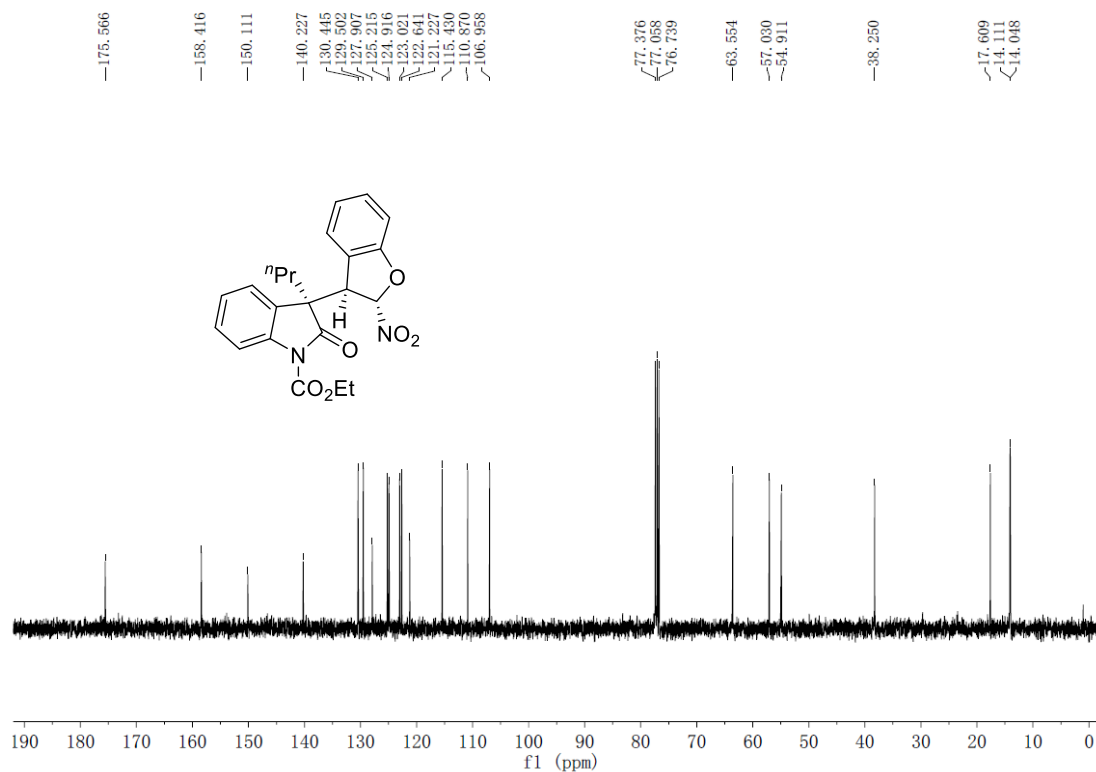
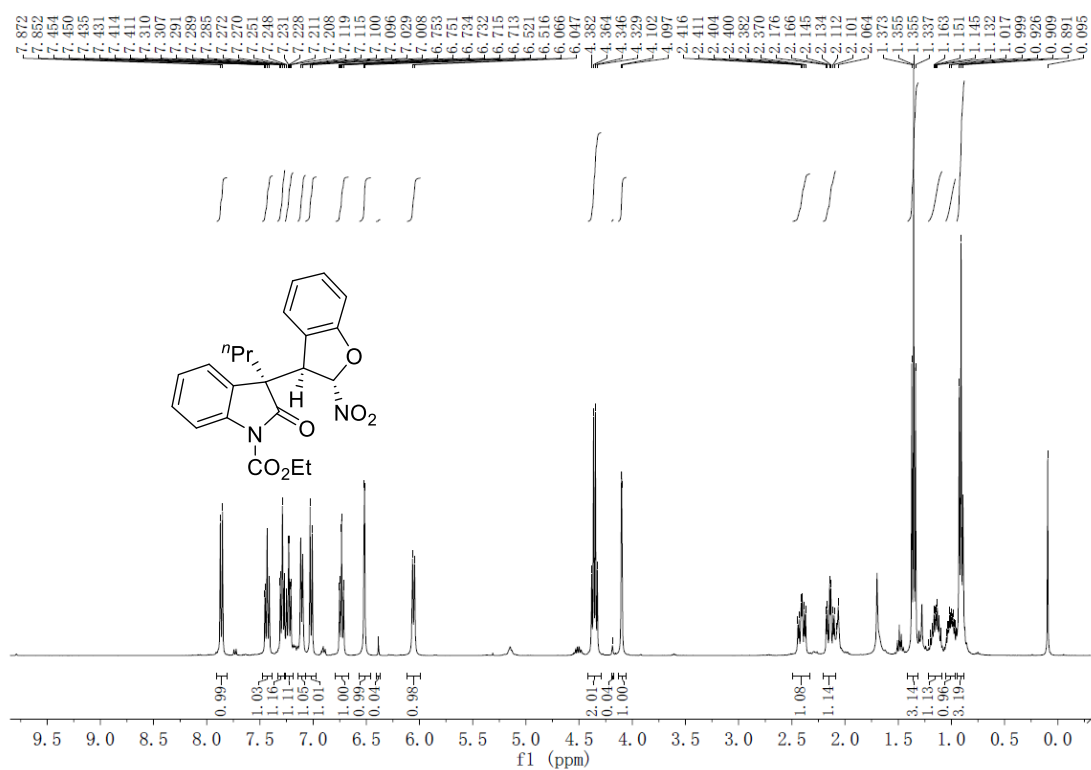


PeakTable

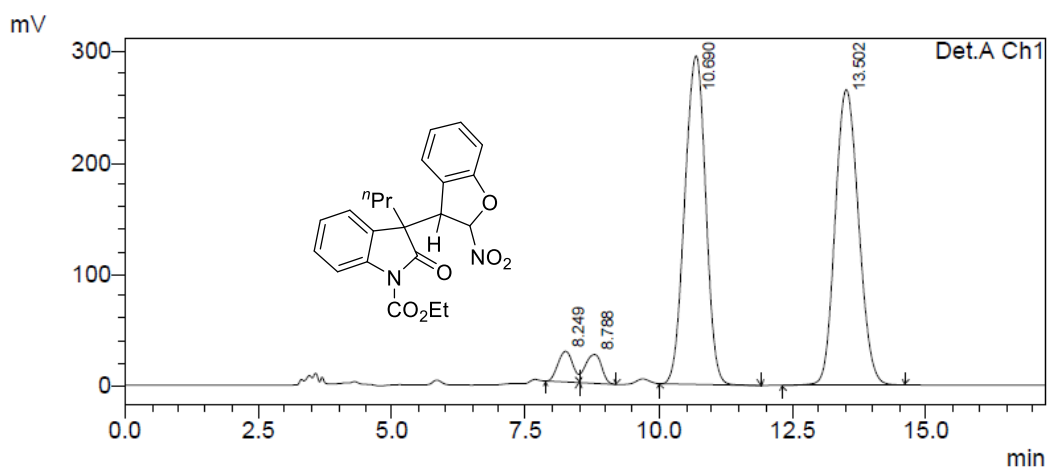
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	14.738	14422183	498098	97.074
2	16.078	434643	15095	2.926
Total		14856826		100.000

# $^1\text{H}$ and $^{13}\text{C}$ NMR of **5c**



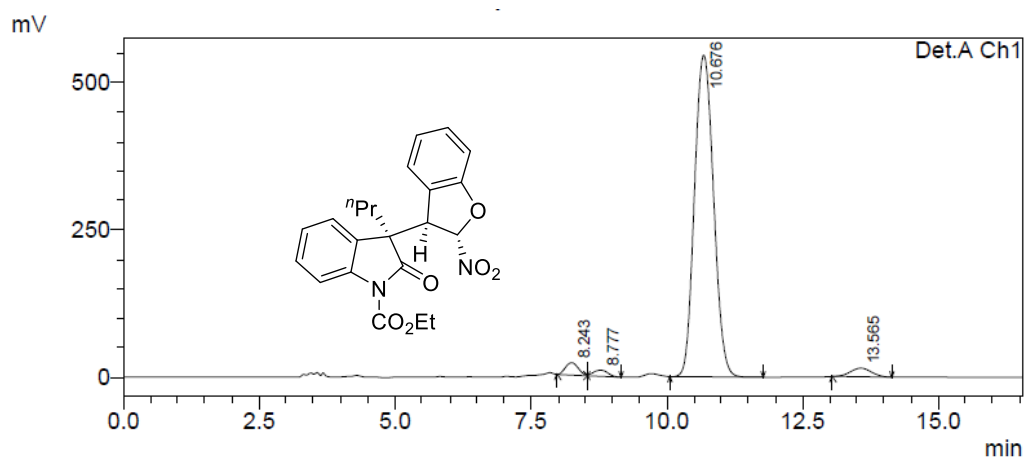
### HPLC of 5c



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	8.249	535521	27622	3.109
2	8.788	553175	25930	3.211
3	10.690	8051627	295211	46.740
4	13.502	8086125	265367	46.940
Total		17226449		100.000

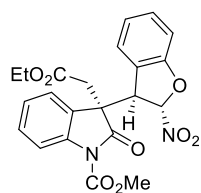
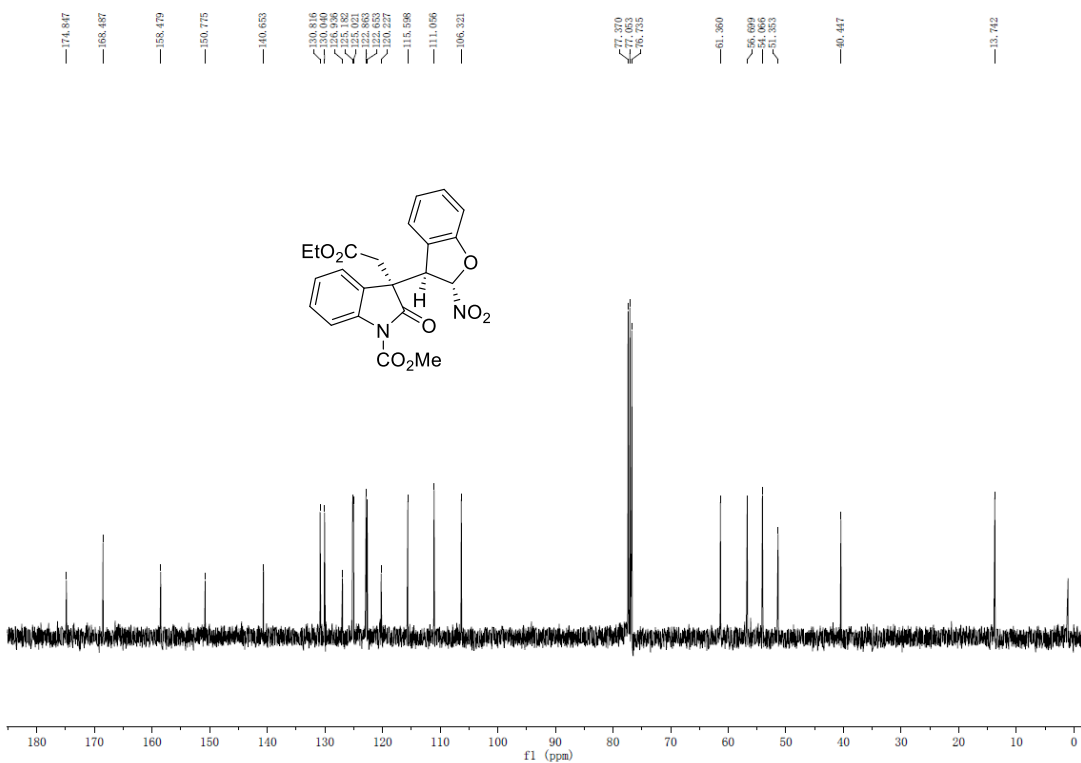
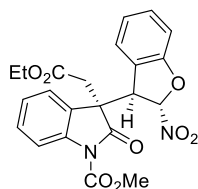
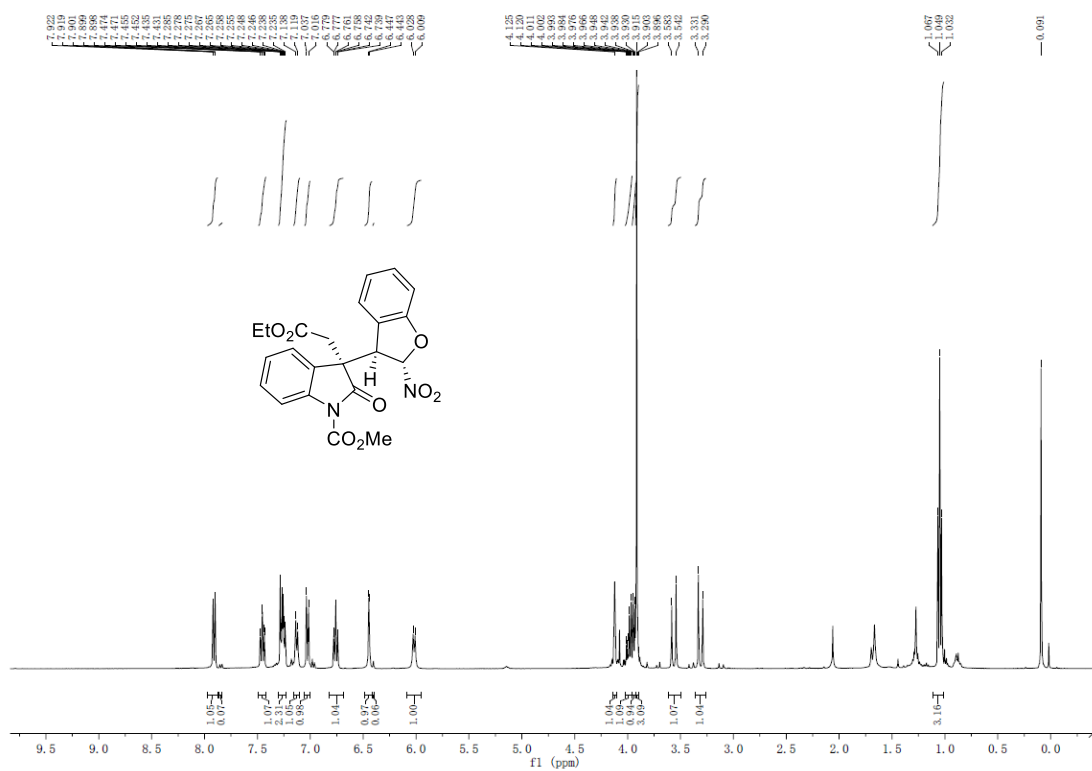


PeakTable

Detector A Ch1 254nm

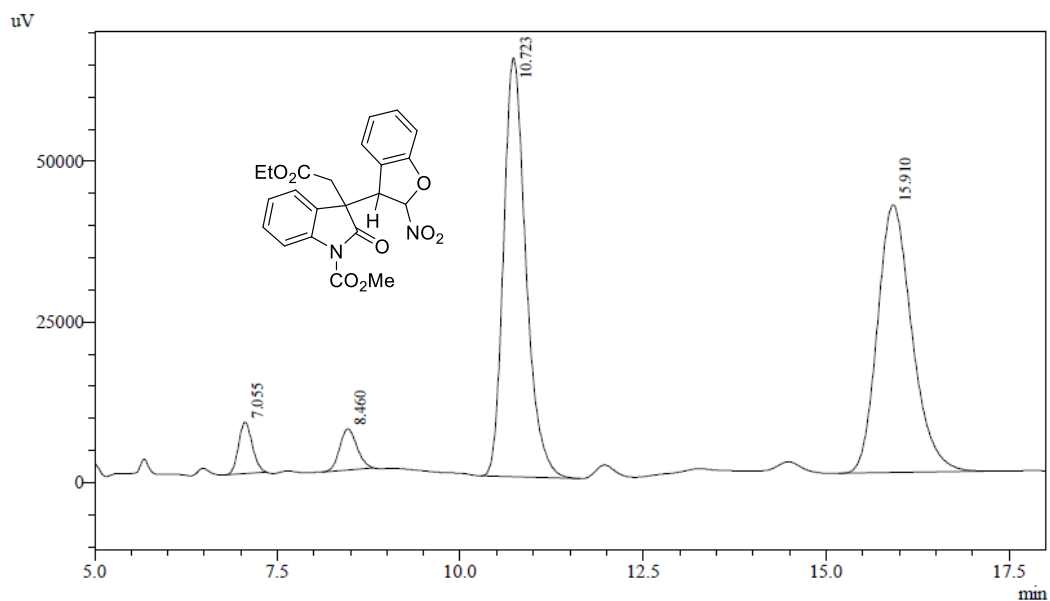
Peak#	Ret. Time	Area	Height	Area %
1	8.243	346029	20998	2.423
2	8.777	188230	10196	1.318
3	10.676	13354315	545847	93.524
4	13.565	390483	14520	2.735
Total		14279057		100.000

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



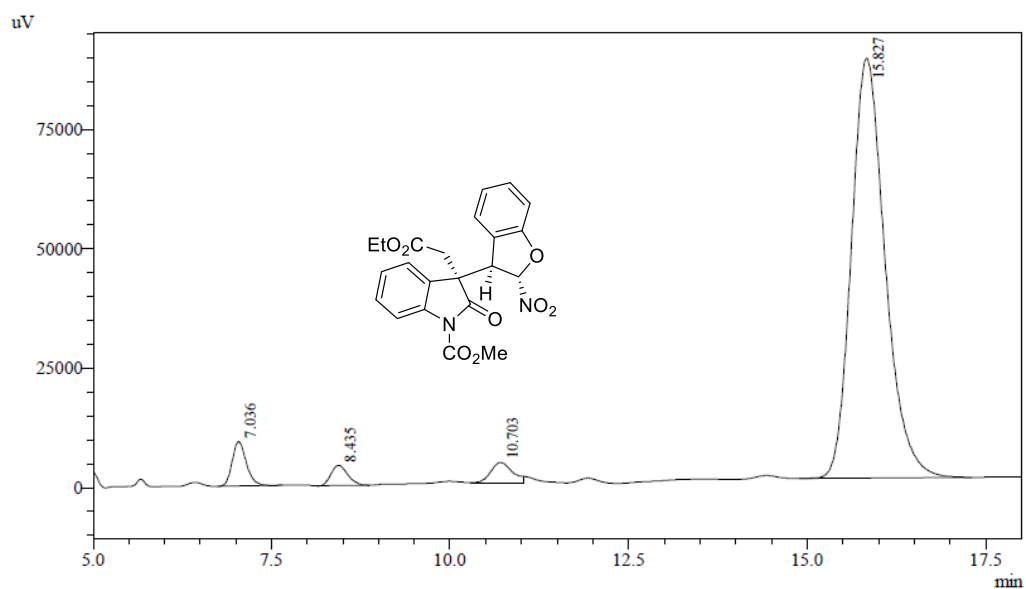


### HPLC of 5d



Detector A Ch1 254nm

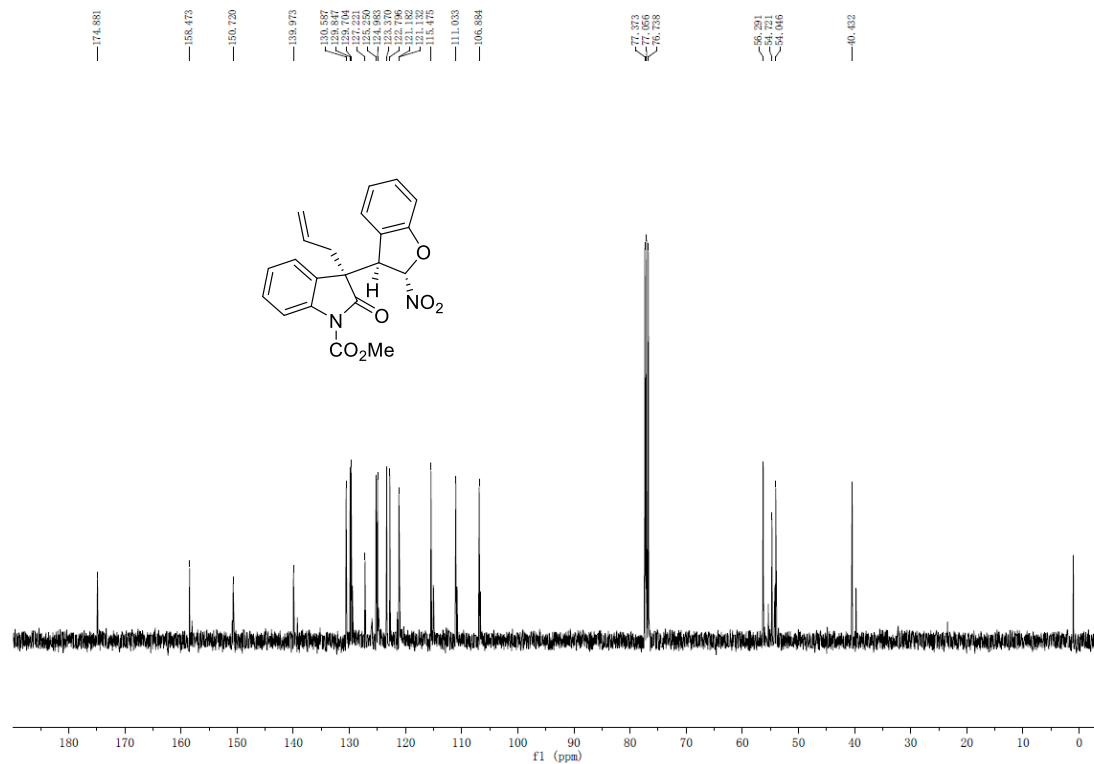
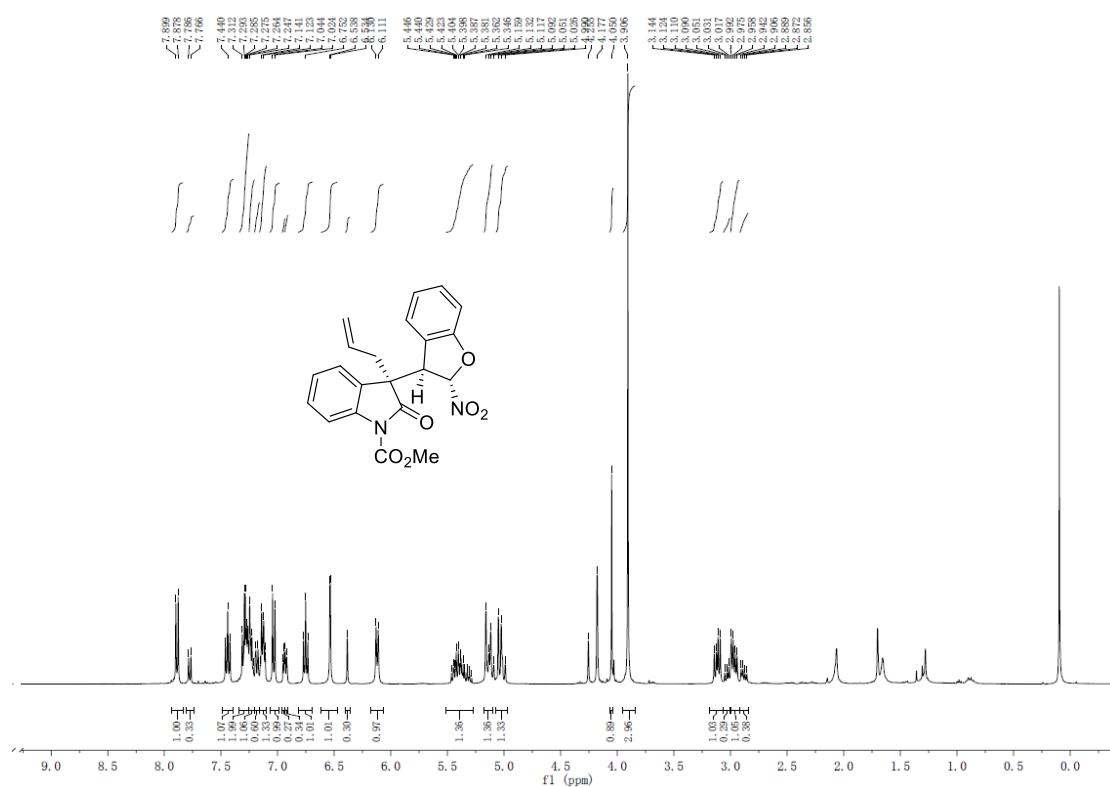
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.055	105199	7997	3.544	6.593
2	8.460	104583	6393	3.523	5.270
3	10.723	1385839	65217	46.684	53.763
4	15.910	1372943	41698	46.249	34.374
Total		2968564	121304	100.000	100.000



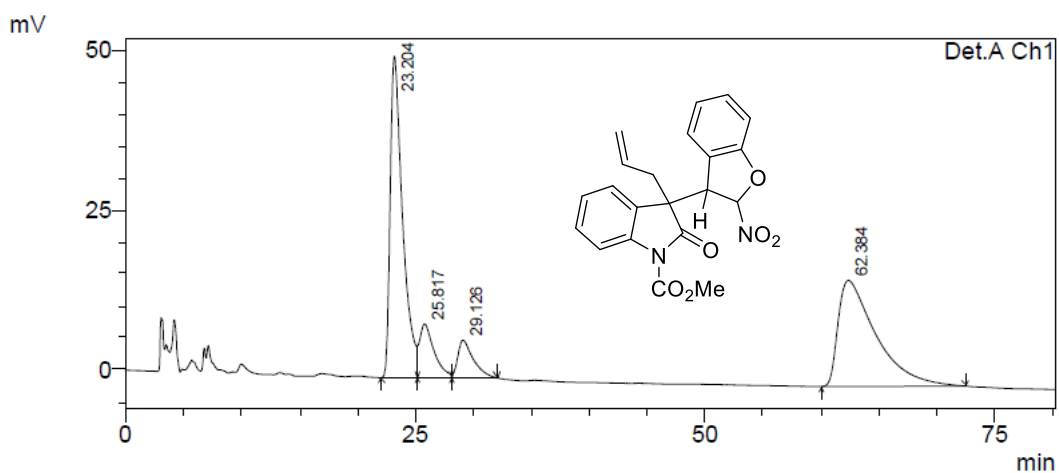
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.036	127842	9302	4.028	8.802
2	8.435	68476	4251	2.157	4.023
3	10.703	89068	4214	2.806	3.988
4	15.827	2888582	87914	91.009	83.188
Total		3173968	105682	100.000	100.000

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

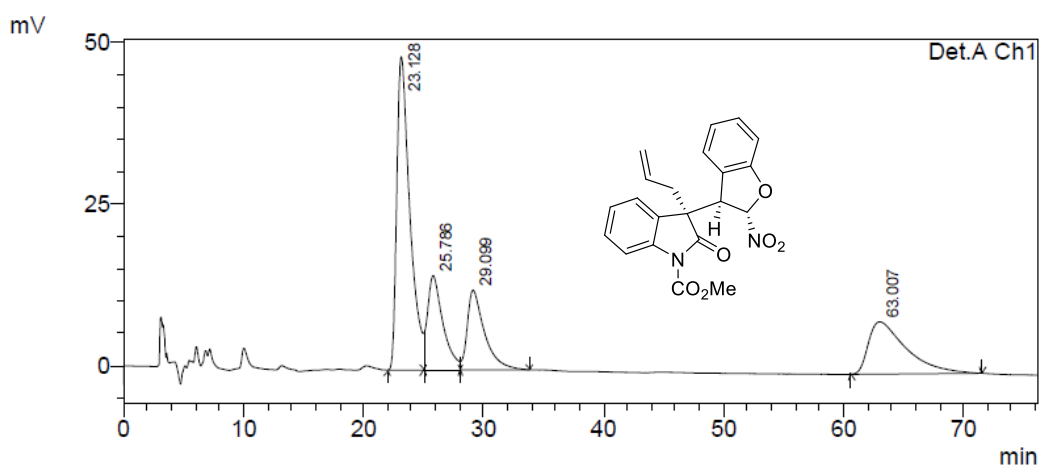


### HPLC of 5e



PeakTable

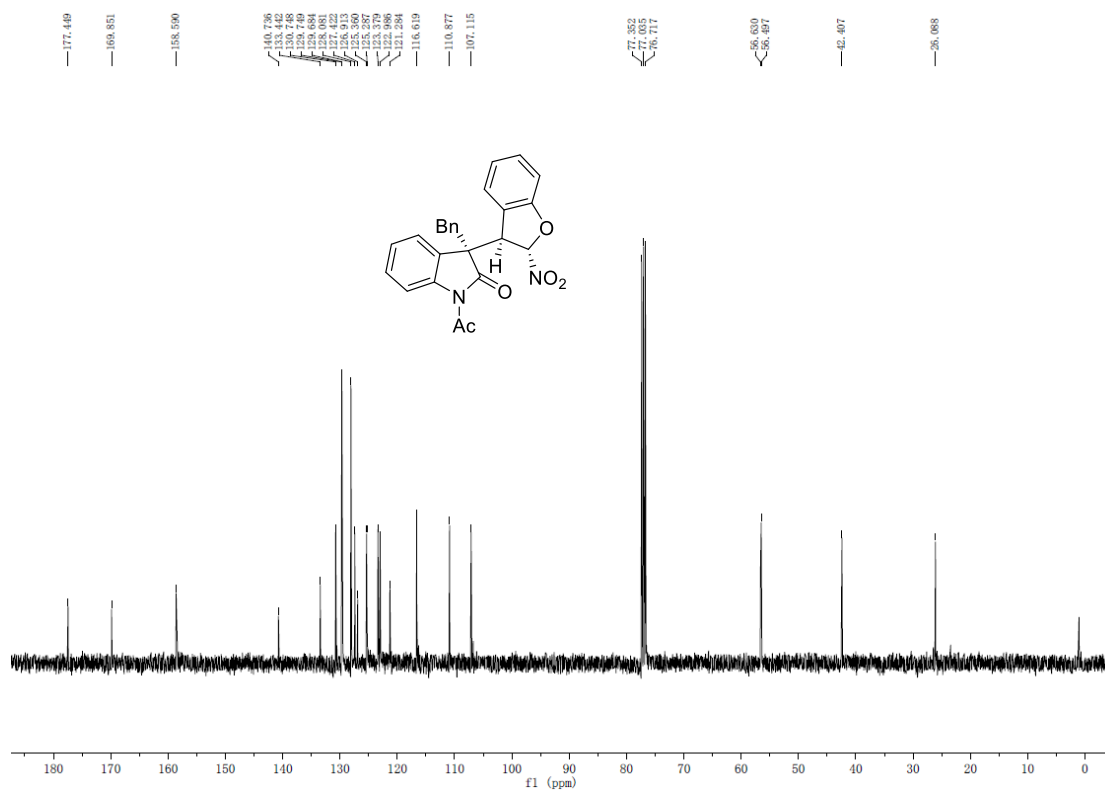
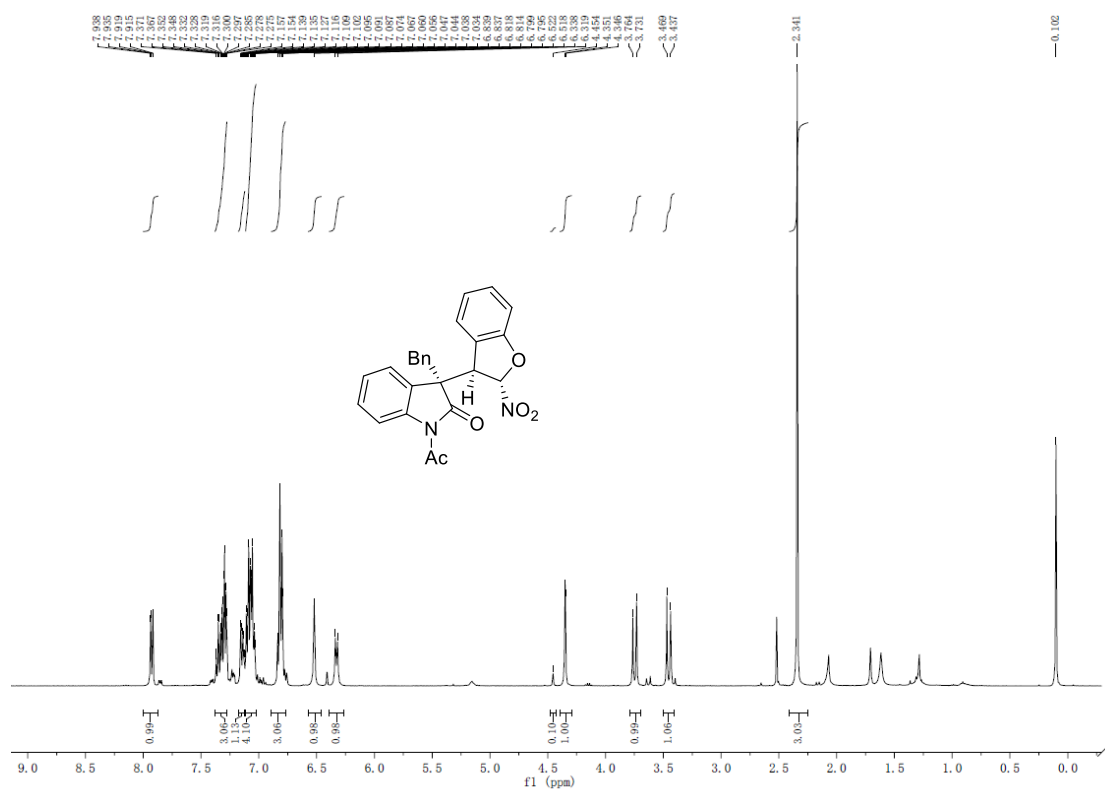
Detector A Ch1 254nm				
Peak#	Ret. Time	Area	Height	Area %
1	23.204	3718546	50052	42.410
2	25.817	739130	8375	8.430
3	29.126	546885	5859	6.237
4	62.384	3763460	16515	42.923
Total		8768022		100.000



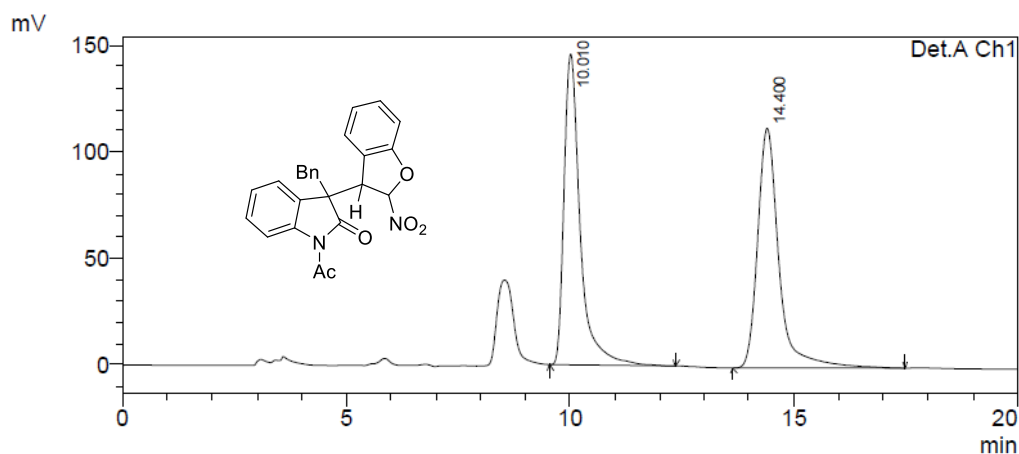
PeakTable

Detector A Ch1 254nm				
Peak#	Ret. Time	Area	Height	Area %
1	23.128	3664641	48459	45.753
2	25.786	1328417	14588	16.585
3	29.099	1238017	12330	15.457
4	63.007	1778488	8094	22.205
Total		8009564		100.000

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



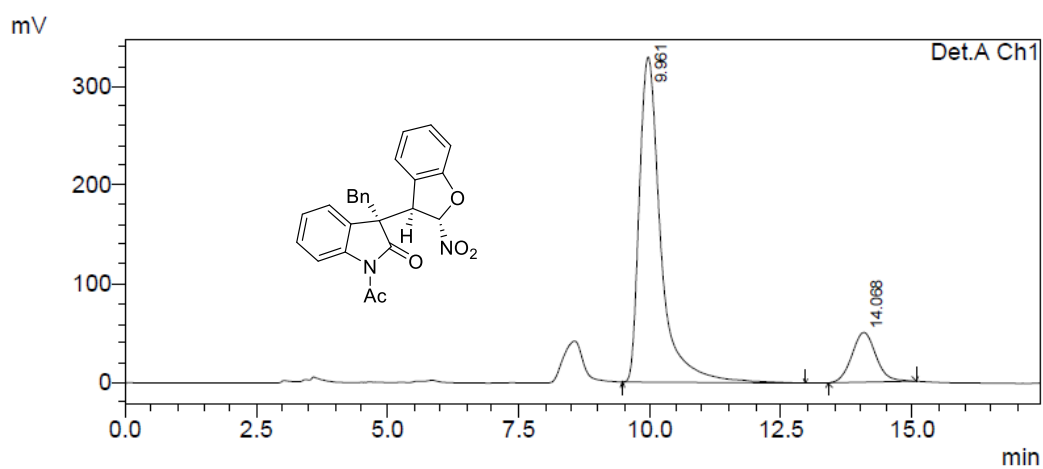
### HPLC of 5f



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	10.010	3659829	145910	49.616
2	14.400	3716482	112451	50.384
Total		7376311		100.000



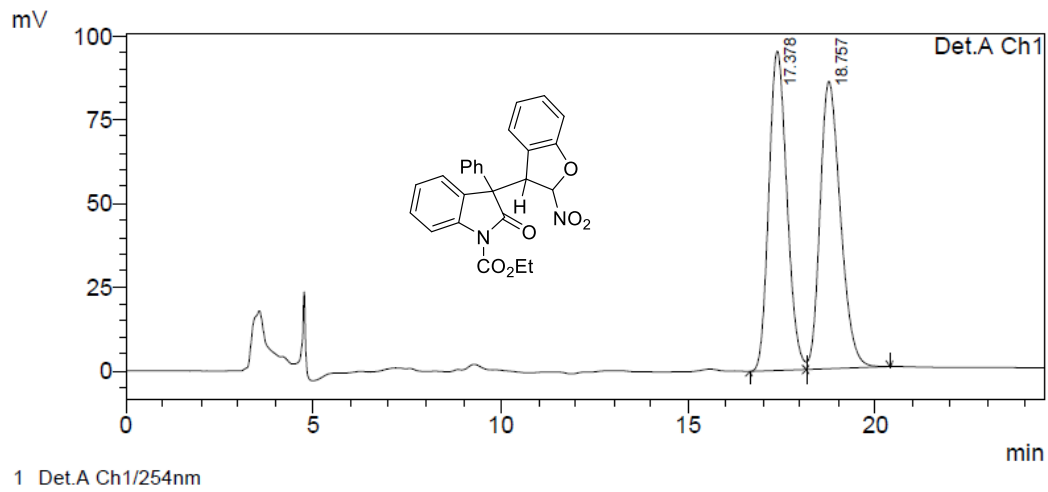
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %
1	9.961	9354308	328945	85.298
2	14.068	1612293	50295	14.702
Total		10966602		100.000

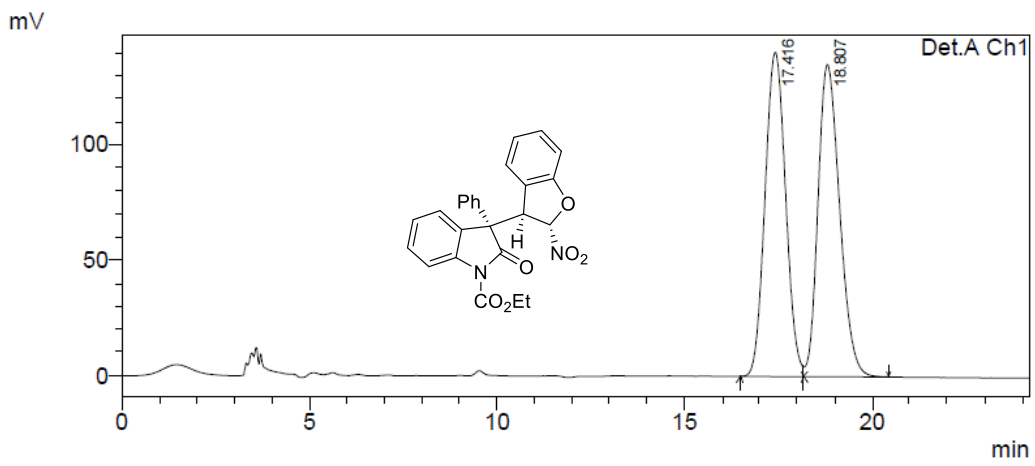


### HPLC of 5g



PeakTable

Peak#	Ret. Time	Area	Height	Area %
1	17.378	3206948	95401	49.625
2	18.757	3255448	85804	50.375
Total		6462397		100.000



PeakTable

Peak#	Ret. Time	Area	Height	Area %
1	17.416	5362148	140368	49.740
2	18.807	5418267	135087	50.260
Total		10780415		100.000