

Supporting Information

Asymmetric Synthesis of 1H-pyrazolo[3,4-b]pyridine Analogues Catalyzed by Chiral-at-Metal Rh(III) Complexes

Xiang Ji^a, Shijie Zhu^a, Yongsheng Li^{a,*}, Zhifei Zhao^a, Shi-Wu Li^{a,*}

^aSchool of Chemistry and Chemical Engineering/State Key Laboratory Incubation Base for Green Processing of Chemical Engineering, Shihezi University, Shihezi, Xinjiang 832003, China.

E-mail: lishiwu@shzu.edu.cn.

Table of Contents

I. General Information.....	S-1
II. Experimental Section.....	S-2
III. References.....	S-21
IV. NMR Spectrum.....	S-22
V. Chiral HPLC analysis trace.....	S-52
VI. Single Crystal X-Ray Diffraction of 4g.....	S-80

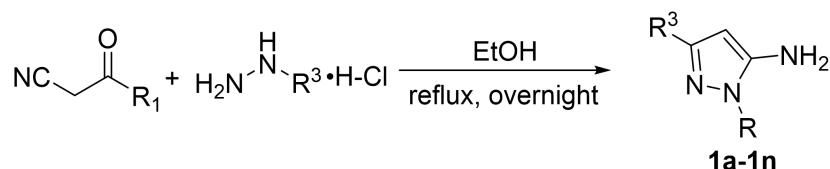
I General Information

Commercially available materials were used as received, unless otherwise noted, all reactions and manipulations involving air- or moisture-sensitive compounds were performed using standard Schlenk technique. Without special instructions, the heating reactions used are all using an oil bath. Reactions were checked by TLC analysis and plates were visualized with short-wave UV light (254 nm). The ^1H , ^{13}C NMR and ^{19}F spectra were obtained in CDCl_3 using a Bruker-BioSpin AVANCE III HD NMR spectrometer at 400 MHz, 100 MHz and 376 MHz respectively. Chemical shifts are reported in parts per million (δ value) calibrated against the residual solvent peak. The determination of e.e. was performed via chiral HPLC analysis using Shimadzu LC-20A HPLC workstation. HPLC analysis of the compounds was done using chiralcel IC column using hexane and isopropanol as eluent, and the column temperature is 40 °C. The Rudolph Autopol V polarimeter was employed to gauge the optical rotation. The melting point was measured by Shanghai Instrument electrooptical SGW X-4A micro melting point instrument. High resolution mass spectra(HRMS) were recorded on Thermo Scientific Q Exactive mass spectrometry equipped with an APCI source. Crystal structure data was collected on a SuperNova, Dual, Cu at zero, Atlas diffractometer. The following abbreviations are used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

II Experimental Section

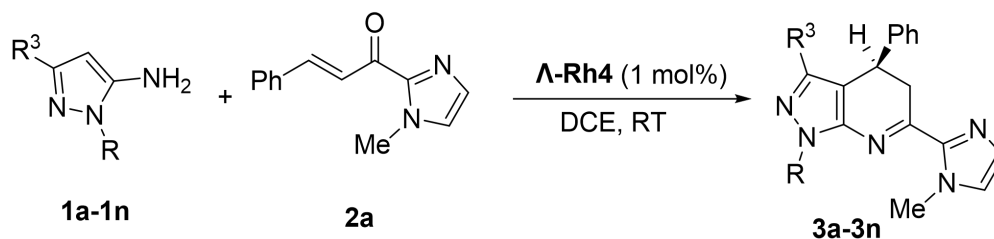
Λ -Rh was prepared according to reported procedure.^[1] 5-Aminopyrazoles and β,γ -unsaturated α -keto esters were synthesized according to reported procedures.^[2-3]

1. General procedure for pyrazol-amine.



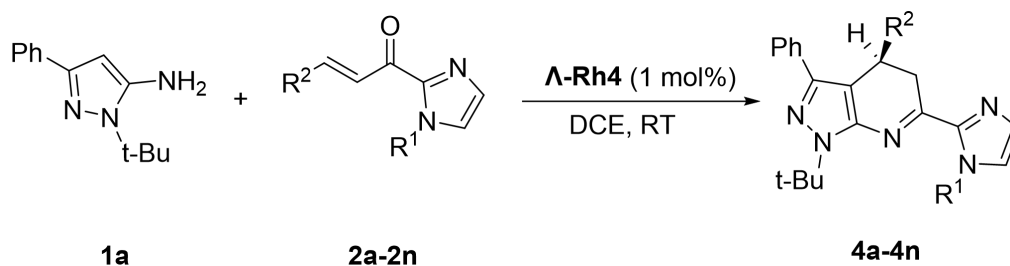
Aryl formyl acetonitrile (1 equiv) was dissolved into EtOH (0.3 M relative to aryl formyl acetonitrile), then Hydrazine monohydrochloride (2 equiv) was added. The reaction was heated to reflux overnight until consumption of the Aryl formyl acetonitrile (monitored by TLC). A saturated solution of NaHCO₃ (aq.) was added and the aqueous phase was extracted with CH₂Cl₂. The organic mixture was dried by Na₂SO₄ and concentrated under reduced pressure. The concentrate was purified by silica gel flash chromatography (PE/EtOAc=6:1-2:1) to afford **1**.

2. General procedure for synthesis of Compounds **3**.



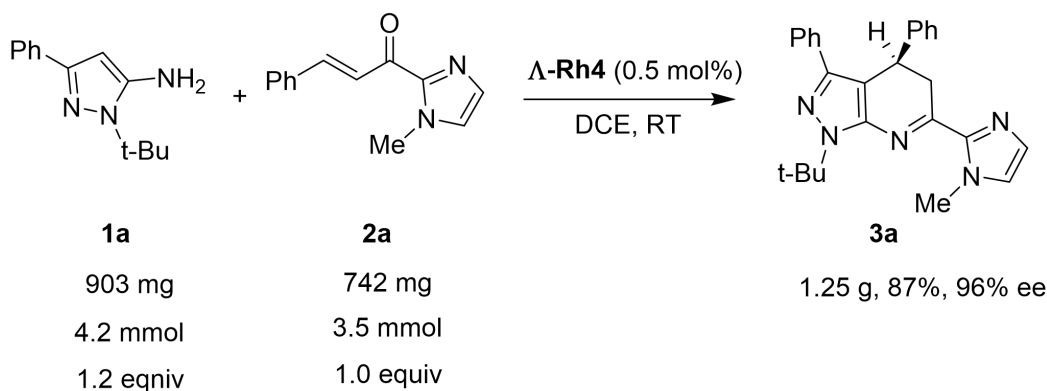
To an oven-dried 10 mL Schlenk tube equipped with a stir bar, **Λ -Rh4** (1 mol%) was added along with α,β -unsaturated 2-acyl imidazole **2** (21.2 mg, 0.10 mmol, 1.0 equiv) and pyrazol-amine **1** (0.12 mmol, 1.2 equiv) in DCE (0.5 mL). The reaction was stirring at room temperature until consumption of the 2-acyl imidazole (monitored by TLC). The solution was directly purified by silica gel column chromatography (PE/EtOAc=4:1-1:1) to afford **3**.

3. General procedure for synthesis of Compounds **4**.



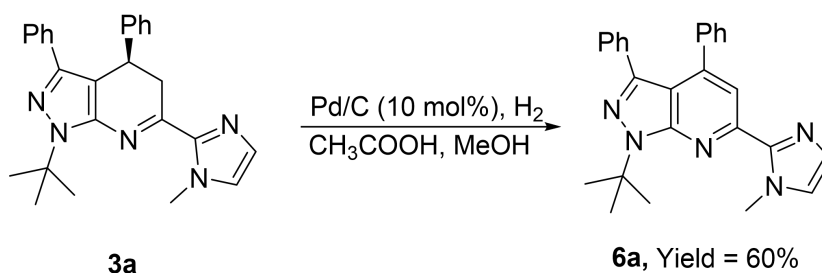
To an oven-dried 10 mL Schlenk tube equipped with a stir bar, $\Lambda\text{-Rh4}$ (1 mol%) was added along with α,β -unsaturated 2-acyl imidazole **2** (0.10 mmol, 1.0 equiv) and pyrazol-amine **1** (25.8 mg, 0.12 mmol, 1.2 equiv) in DCE (0.5 mL). The reaction was stirring at room temperature until consumption of the 2-acyl imidazole (monitored by TLC). The solution was directly purified by silica gel column chromatography (PE/EtOAc=4:1-1:1) to afford **4**.

4. General procedure for gram-scale experiments of product **3a**.



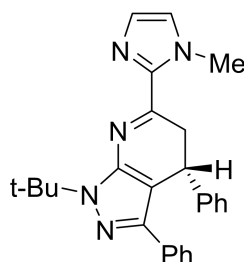
To an oven-dried 25 mL Schlenk tube equipped with a stir bar, $\Lambda\text{-Rh4}$ (0.5 mol%) was added along with α,β -unsaturated 2-acyl imidazole **2a** (1.0 equiv, 3.5 mmol, 742 mg) and pyrazol-amine **1a** (1.2 equiv, 4.2 mmol, 903 mg) in DCE (3.0 mL). The reaction was stirring at room temperature until consumption of the 2-acyl imidazole **2a** (monitored by TLC). The solution was directly purified by silica gel column chromatography (PE/EtOAc=3:1) to afford **3a** (light yellow solid, 1.25 g, 87% yield, 96% ee).

5. General procedure for synthetic transformation of the product **6a**.

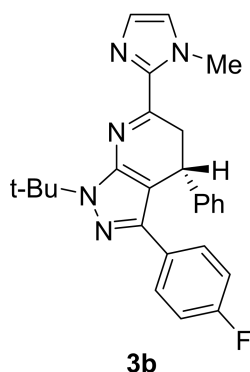


To an oven-dried 250 mL round bottom flask equipped, **3a** (0.2 mmol) was added along with Pd/C (10 mol%) and CH₃COOH in MeOH (20 ml). Use H₂ to displace the air in the round bottom flask three times, then the reaction was stirring at 50 °C until consumption of the **3a** (monitored by TLC). The solution was directly purified by silica gel column chromatography (PE/EtOAc=4:1) to afford **6a** (49 mg, 60% yield).

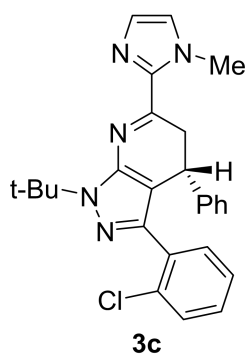
6. Characterization data of product.



(R)-1-(tert-butyl)-6-(1-methyl-1H-imidazol-2-yl)-3,4-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (**3a**). Light yellow solid (39 mg, 95% yield). Mp: 150.9-152.4 °C. HPLC: 96% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 8.533 min, tr (minor) = 9.967 min. $[\alpha]_{\text{D}}^{20} = +17.0$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) $\delta = 7.50\text{-}7.45$ (m, 2H), 7.21-7.17 (m, 2H), 7.17-7.14 (m, 1H), 7.14-7.12 (m, 1H), 7.12-7.10 (m, 1H), 7.08-7.02 (m, 3H), 7.01 (d, $J = 0.92$ Hz, 1H), 6.90-6.87 (m, 1H), 4.41-4.35 (m, 1H), 4.04 (s, 3H), 3.93-3.85 (m, 1H), 3.08-3.00 (m, 1H), 1.77 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) $\delta = 156.5, 146.7, 144.2, 143.6, 142.7, 134.0, 128.8, 128.7, 128.4, 127.2, 127.0, 126.6, 126.5, 126.1, 104.8, 59.9, 37.4, 34.8, 34.2, 29.9$. HRMS (APCI) m/z calcd for C₂₆H₂₈N₅⁺ (M+H)⁺ 410.2339, found 410.2333.

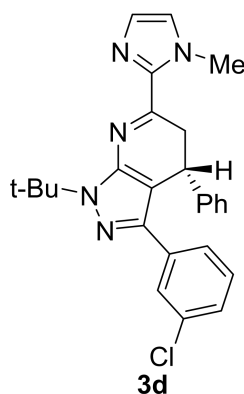


(R)-1-(tert-butyl)-3-(4-fluorophenyl)-6-(1-methyl-1H-imidazol-2-yl)-4-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3b). Light yellow solid (40 mg, 93% yield). Mp: 165.2-167.7 °C. HPLC: 94% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 7.485 min, tr (minor) = 8.358 min. $[\alpha]_D^{20} = +42.5$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.54-7.45 (m, 2H), 7.23-7.16 (m, 2H), 7.15-7.11 (m, 1H), 7.08 (d, *J* = 8.44 Hz, 3H), 6.97-6.88 (m, 3H), 4.40 (d, *J* = 7.84 Hz, 1H), 4.09 (s, 3H), 3.94 (d, *J* = 16.28 Hz, 1H), 3.20-3.06 (m, 1H), 1.83 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ = 163.3, 160.9, 156.6, 146.7, 144.1, 142.8, 142.6, 130.2, 128.9, 128.7, 128.2, 128.1, 127.2, 126.8, 126.2, 115.3, 115.1, 104.6, 59.9, 37.4, 34.8, 34.2, 29.9. ¹⁹F NMR (376 MHz, CDCl₃) δ = 115.3. HRMS (APCI) *m/z* calcd for C₂₆H₂₇FN₅⁺ (M+H)⁺ 428.2245, found 428.2239.

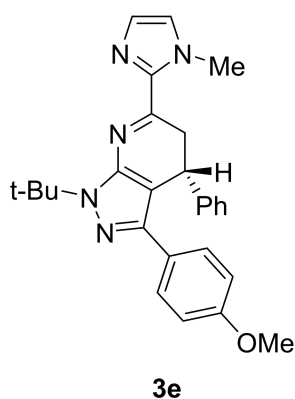


(R)-1-(tert-butyl)-3-(2-chlorophenyl)-6-(1-methyl-1H-imidazol-2-yl)-4-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3c) Light yellow solid (42 mg, 95% yield). Mp: 72.1-73.8 °C. HPLC: 99% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 11.140 min, tr (minor) = 16.680 min. $[\alpha]_D^{20} = +13.0$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.16-7.10 (m, 2H),

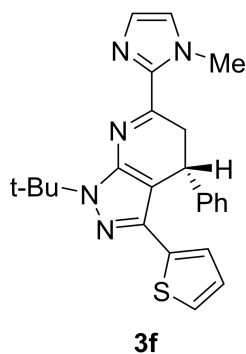
7.07-7.02 (m, 1H), 7.02-6.98 (m, 2H), 6.98-6.95 (m, 1H), 6.94 (s, 1H), 6.93-6.87 (m, 4H), 4.21 (t, $J = 7.92$ Hz, 1H), 4.06 (s, 3H), 3.37 (d, $J = 7.96$ Hz, 2H), 1.74 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 157.2, 145.7, 144.1, 143.0, 142.7, 133.5, 133.4, 131.7, 129.4, 128.9, 128.7, 128.0, 127.4, 126.3, 126.2, 107.4, 59.8, 37.5, 35.4, 34.7, 30.0$. HRMS (APCI) m/z calcd for $\text{C}_{26}\text{H}_{27}\text{ClN}_5^+$ ($\text{M}+\text{H}$) $^+$ 444.1950, found 444.1942.



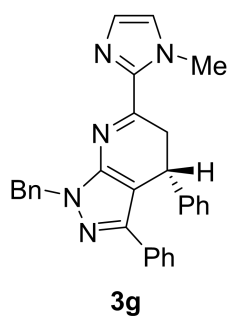
(R)-1-(tert-butyl)-3-(3-chlorophenyl)-6-(1-methyl-1H-imidazol-2-yl)-4-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3d). Light yellow solid (43 mg, 96% yield). Mp: 78.0-81.1 °C. HPLC: 99% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, t_r (major) = 7.532 min, t_r (minor) = 8.182 min. $[\alpha]_{\text{D}}^{20} = +32.5$ ($c = 0.2, \text{CH}_2\text{Cl}_2$). ^1H NMR (400 MHz, CDCl_3) $\delta = 7.62$ (s, 1H), 7.37-7.30 (m, 1H), 7.26-7.16 (m, 2H), 7.16-7.05 (m, 6H), 6.94 (s, 1H), 4.45-4.39 (m, 1H), 4.09 (s, 3H), 3.93 (d, $J = 16.28$ Hz, 1H), 3.23-3.07 (m, 1H), 1.83 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 156.7, 146.8, 144.1, 142.5, 142.3, 135.8, 134.3, 129.6, 128.9, 128.8, 127.2, 127.0, 126.8, 126.5, 126.2, 124.5, 105.2, 60.1, 37.4, 34.8, 34.3, 29.9$. HRMS (APCI) m/z calcd for $\text{C}_{26}\text{H}_{27}\text{ClN}_5^+$ ($\text{M}+\text{H}$) $^+$ 444.1950, found 444.1942.



(R)-1-(tert-butyl)-3-(4-methoxyphenyl)-6-(1-methyl-1H-imidazol-2-yl)-4-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3e). White solid (38 mg, 87% yield). Mp: 85.1-87.6 °C. HPLC: 85% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 12.840 min, tr (minor) = 19.261 min. $[\alpha]_D^{20} = +22.5$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) $\delta = 7.47$ (d, *J* = 8.8 Hz, 2H), 7.23-7.16 (m, 2H), 7.15-7.05 (m, 4H), 6.94 (s, 1H), 6.82-6.76 (m, 2H), 4.44-4.38 (m, 1H), 4.09 (s, 3H), 3.96 (d, *J* = 17.16 Hz, 1H), 3.75 (s, 3H), 3.16-3.05 (m, 1H), 1.83 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) $\delta = 158.8, 156.4, 146.4, 144.3, 143.5, 142.8, 128.8, 128.7, 127.7, 127.2, 126.8, 126.6, 126.1, 113.8, 104.2, 59.7, 55.2, 37.4, 34.8, 34.1, 29.9$. HRMS (APCI) *m/z* calcd for C₂₇H₃₀N₅O⁺ (M+H)⁺ 440.2445, found 440.2437.

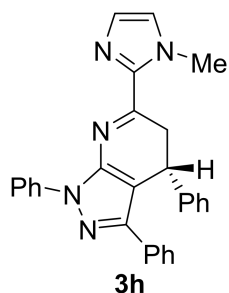


(R)-1-(tert-butyl)-6-(1-methyl-1H-imidazol-2-yl)-4-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3f). Light yellow solid (38 mg, 92% yield). Mp: 170.1-173.5 °C. HPLC: 95% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 9.375 min, tr (minor) = 11.132 min. $[\alpha]_D^{20} = -36.0$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) $\delta = 7.23$ -7.16 (m, 2H), 7.15-7.06 (m, 5H), 6.95 (s, 1H), 6.91-6.84 (m, 2H), 4.43 (dd, *J* = 9.5, 2.1 Hz, 1H), 4.08 (s, 3H), 4.04-3.93 (m, 1H), 3.19 (d, *J* = 12.8 Hz, 1H), 1.81 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) $\delta = 156.6, 146.6, 144.0, 142.4, 139.6, 136.7, 128.7, 127.3, 127.2, 126.7, 126.3, 124.0, 123.8, 104.2, 60.0, 37.5, 34.6, 33.8, 29.8$. HRMS (APCI) *m/z* calcd for C₂₄H₂₆N₅S⁺ (M+H)⁺ 416.1903, found 416.1898.



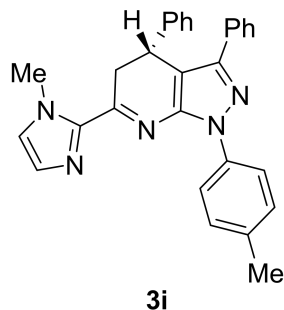
(R)-1-benzyl-6-(1-methyl-1H-imidazol-2-yl)-3,4-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3g). Light yellow solid (38 mg, 85% yield). Mp: 88.2-89.8 °C.

HPLC: 87% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 7.743 min, tr (minor) = 9.378 min. $[\alpha]_D^{20} = +24.0$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.58-7.53 (m, 2H), 7.32 (d, $J = 4.36$ Hz, 4H), 7.29-7.23 (m, 3H), 7.23-7.16 (m, 3H), 7.15-7.09 (m, 3H), 7.06 (s, 1H), 6.91 (s, 1H), 5.65-5.52 (m, 2H), 4.53-4.48 (m, 1H), 3.98-3.90 (m, 1H), 3.94 (s, 3H), 3.21-3.11 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ = 158.7, 147.1, 146.6, 143.7, 142.8, 137.7, 133.5, 129.0, 128.8, 128.7, 128.4, 127.6, 127.4, 127.2, 126.8, 126.6, 126.4, 103.5, 51.7, 37.3, 35.3, 34.6. HRMS (APCI) m/z calcd for C₂₉H₂₆N₅⁺ (M+H)⁺ 444.2183, found 444.2174.

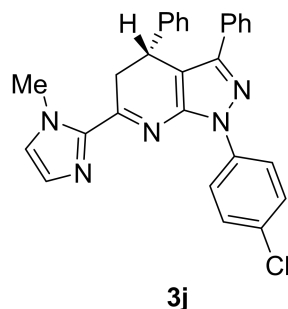


(R)-6-(1-methyl-1H-imidazol-2-yl)-1,3,4-triphenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3h). Light yellow solid (40 mg, 92% yield). Mp: 221.3-225.1 °C. HPLC: 97% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 80:20, flow rate 0.7 mL/min, tr (major) = 14.200 min, tr (minor) = 14.763 min. $[\alpha]_D^{20} = +32.0$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 8.05-7.95 (m, 2H), 7.68-7.60 (m, 2H), 7.53-7.43 (m, 2H), 7.36-7.13 (m, 9H), 7.09 (d, $J = 1.0$ Hz, 1H), 6.95 (s, 1H), 4.56 (dd, $J = 9.3, 2.2$ Hz, 1H), 4.08-4.00 (m, 1H), 4.00 (s, 3H), 3.20 (dd, $J = 17.2, 9.3$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ = 159.3, 147.7, 147.2, 143.8, 142.3, 139.3, 133.2, 129.2, 128.9, 128.8, 128.5, 127.9, 127.2, 126.9, 126.7, 123.1, 105.2, 37.4, 34.9, 34.4. HRMS (APCI) m/z calcd for $\text{C}_{28}\text{H}_{24}\text{N}_5^+$ ($\text{M}+\text{H}$) $^+$ 430.2026, found 430.2020.

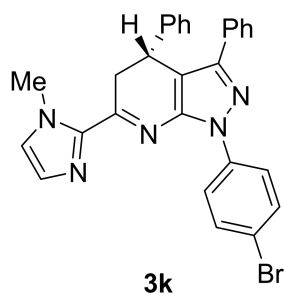


(R)-6-(1-methyl-1H-imidazol-2-yl)-3,4-diphenyl-1-(p-tolyl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3i). Light yellow solid (41 mg, 93% yield). Mp: 199.8-201.4 °C. HPLC: 98% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 80:20, flow rate 0.7 mL/min, tr (major) = 16.777 min, tr (minor) = 17.488 min. $[\alpha]_{\text{D}}^{20}$ = +28.0 (c = 0.2, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ = 7.82-7.75 (m, 2H), 7.59-7.53 (m, 2H), 7.23-7.05 (m, 10H), 7.02 (s, 1H), 6.87 (s, 1H), 4.47 (dd, J = 9.4, 2.2 Hz, 1H), 3.99-3.89 (m, 4H), 3.12 (dd, J = 17.2, 9.3 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 159.1, 147.5, 147.1, 143.9, 142.5, 136.9, 136.6, 133.3, 129.4, 129.2, 128.9, 128.6, 127.8, 127.3, 126.9, 126.7, 123.1, 105.1, 37.5, 34.9, 34.4, 21.2. HRMS (APCI) m/z calcd for $\text{C}_{29}\text{H}_{26}\text{N}_5^+$ ($\text{M}+\text{H}$) $^+$ 444.2183, found 444.2176.

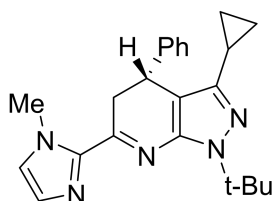


(R)-1-(4-chlorophenyl)-6-(1-methyl-1H-imidazol-2-yl)-3,4-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3j). Light yellow solid (42 mg, 91% yield). Mp: 137.6-139.8 °C. HPLC: 97% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 80:20, flow rate 0.7 mL/min, tr (major) = 12.418 min, tr (minor) = 13.095 min. $[\alpha]_{\text{D}}^{20}$ = +32.0 (c = 0.2, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ = 8.02-7.93 (m, 2H),

7.65-7.58 (m, 2H), 7.49-7.41 (m, 2H), 7.32-7.20 (m, 5H), 7.18-7.11 (m, 3H), 7.10 (d, $J = 1.0$ Hz, 1H), 6.97 (s, 1H), 4.54 (dd, $J = 9.4, 2.2$ Hz, 1H), 4.09-3.95 (m, 1H), 4.01 (s, 3H), 3.20 (dd, $J = 17.2, 9.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 159.6, 148.0, 147.2, 143.7, 142.2, 137.8, 132.9, 132.1, 129.3, 128.9, 128.6, 128.0, 127.2, 127.0, 126.8, 124.0, 105.5, 37.4, 34.9, 34.3$. HRMS (APCI) m/z calcd for $\text{C}_{28}\text{H}_{23}\text{ClN}_5^+$ ($\text{M}+\text{H}$) $^+$ 464.1637, found 464.1631.

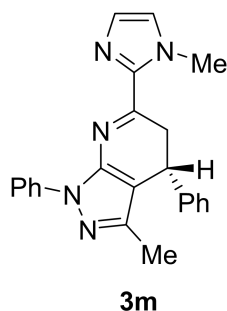


(*R*)-1-(4-bromophenyl)-6-(1-methyl-1H-imidazol-2-yl)-3,4-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3k). Light yellow solid (48 mg, 94% yield). Mp: 227.9-230.7 °C. HPLC: 99% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 80:20, flow rate 0.7 mL/min, t_r (major) = 12.812 min, t_r (minor) = 13.648 min. $[\alpha]_{\text{D}}^{20} = +42.0$ ($c = 0.2, \text{CH}_2\text{Cl}_2$). ^1H NMR (400 MHz, CDCl_3) $\delta = 7.99-7.87$ (m, 2H), 7.68-7.55 (m, 4H), 7.31-7.20 (m, 5H), 7.16 (d, $J = 7.3$ Hz, 2H), 7.11 (d, $J = 1.0$ Hz, 1H), 6.98 (s, 1H), 4.54 (dd, $J = 9.4, 2.2$ Hz, 1H), 4.10-3.99 (m, 4H), 3.20 (dd, $J = 17.2, 9.3$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 159.6, 148.0, 147.2, 143.6, 142.1, 138.3, 132.9, 131.8, 129.3, 128.9, 128.6, 128.0, 127.2, 127.0, 126.9, 126.8, 124.3, 120.0, 105.6, 37.4, 34.9, 34.3$. HRMS (APCI) m/z calcd for $\text{C}_{28}\text{H}_{23}\text{BrN}_5^+$ ($\text{M}+\text{H}$) $^+$ 508.1131, found 508.1125.

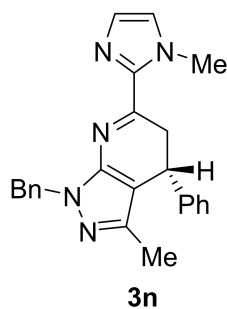


(*R*)-1-(tert-butyl)-3-cyclopropyl-6-(1-methyl-1H-imidazol-2-yl)-4-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3l). Light yellow solid (35 mg, 95% yield). Mp:

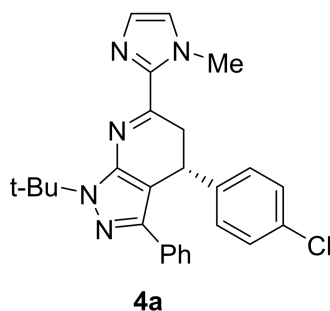
178.2-180.6 °C. HPLC: 99% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 6.179 min, tr (minor) = 6.488 min. $[\alpha]_D^{20} = +36.0$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.25-7.19 (m, 2H), 7.18-7.12 (m, 3H), 7.08 (s, 1H), 6.96 (s, 1H), 4.20 (dd, *J* = 8.9, 5.9 Hz, 1H), 4.09 (s, 3H), 3.56 (dd, *J* = 17.3, 5.9 Hz, 1H), 3.31 (dd, *J* = 17.3, 8.9 Hz, 1H), 1.72 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ = 156.2, 146.1, 145.7, 144.3, 143.7, 128.7, 128.5, 127.4, 126.5, 126.0, 105.4, 59.2, 37.5, 34.4, 29.9, 8.5, 6.5, 6.1. HRMS (APCI) *m/z* calcd for C₂₃H₂₈N₅⁺ (M+H)⁺ 374.2339, found 374.2332.



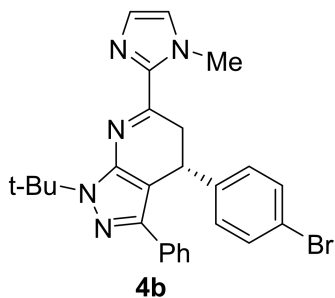
(R)-3-methyl-6-(1-methyl-1H-imidazol-2-yl)-1,4-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3m). Light yellow solid (35 mg, 95% yield). Mp: 120.8-122.1 °C. HPLC: 99% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 14.998 min, tr (minor) = 15.779 min. $[\alpha]_D^{20} = +42.0$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.90-7.81 (m, 2H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.28-7.23 (m, 3H), 7.21-7.15 (m, 3H), 7.08 (s, 1H), 6.93 (s, 1H), 4.22 (t, *J* = 8.0 Hz, 1H), 3.97 (s, 3H), 3.58-3.42 (m, 2H), 2.02 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ = 159.2, 146.1, 143.7, 143.0, 139.2, 129.4, 129.0, 128.7, 127.4, 126.9, 126.6, 126.3, 122.6, 106.4, 37.4, 34.7, 12.7. HRMS (APCI) *m/z* calcd for C₂₃H₂₂N₅⁺ (M+H)⁺ 368.1870, found 368.1863.



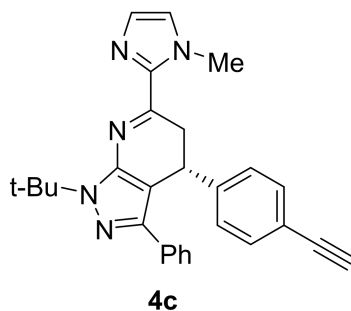
(R)-1-(tert-butyl)-3-cyclopropyl-6-(1-methyl-1H-imidazol-2-yl)-4-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (3n). Light yellow solid (31 mg, 81% yield). Mp: 129.6-131.9 °C. HPLC: 85% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 80:20, flow rate 0.7 mL/min, tr (major) = 14.451 min, tr (minor) = 15.792 min. $[\alpha]_D^{20} = +38.0$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.33-7.23 (m, 7H), 7.20-7.13 (m, 3H), 7.09 (s, 1H), 6.95 (s, 1H), 5.43 (d, *J* = 4.0 Hz, 2H), 4.20 (t, *J* = 8.0 Hz, 1H), 3.97 (s, 3H), 3.45 (d, *J* = 7.5 Hz, 2H), 1.94 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ = 158.8, 146.2, 144.7, 143.7, 143.4, 137.8, 128.9, 128.7, 128.6, 127.6, 127.3, 126.7, 126.4, 104.4, 51.2, 37.4, 35.1, 34.8, 12.7. HRMS (APCI) *m/z* calcd for C₂₄H₂₄N₅⁺ (M+H)⁺ 382.2026, found 382.2020.



(R)-1-(tert-butyl)-4-(4-chlorophenyl)-6-(1-methyl-1H-imidazol-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4a). Light yellow solid (42 mg, 95% yield). Mp: 76.5-78.1 °C. HPLC: 98% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 7.884 min, tr (minor) = 8.422 min. $[\alpha]_D^{20} = +38.0$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.56-7.50 (m, 2H), 7.29-7.23 (m, 2H), 7.22-7.18 (m, 1H), 7.18-7.16 (m, 1H), 7.16-7.14 (m, 1H), 7.09 (s, 1H), 7.06-7.00 (m, 2H), 6.95 (s, 1H), 4.45-4.40 (m, 1H), 4.09 (s, 3H), 3.94 (d, *J* = 16.96 Hz, 1H), 3.15-3.03 (m, 1H), 1.83 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ = 156.3, 146.6, 144.1, 143.6, 141.2, 133.8, 132.4, 129.0, 128.9, 128.6, 128.5, 127.2, 126.4, 126.3, 104.4, 60.0, 37.4, 34.7, 33.6, 29.9. HRMS (APCI) *m/z* calcd for C₂₆H₂₇ClN₅ (M+H)⁺ 444.1950, found 444.1942.

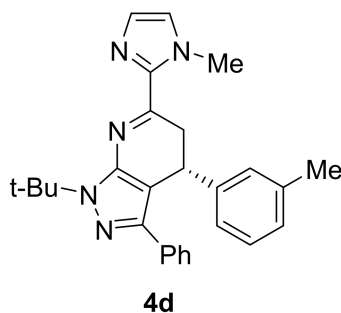


(R)-4-(4-bromophenyl)-1-(tert-butyl)-6-(1-methyl-1H-imidazol-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4b). Light yellow solid (47 mg, 96% yield). Mp: 78.7-80.3 °C. HPLC: 99% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 7.374 min, tr (minor) = 7.784 min. $[\alpha]_{\text{D}}^{20} = +34.5$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.45 (d, *J* = 7.64 Hz, 2H), 7.26-7.21 (m, 2H), 7.21-7.15 (m, 2H), 7.14-7.08 (m, 1H), 7.00 (s, 1H), 6.90 (s, 1H), 6.88 (d, *J* = 5.28 Hz, 2H), 4.33 (d, *J* = 8.04 Hz, 1H), 4.01 (s, 3H), 3.87 (d, *J* = 16.92 Hz, 1H), 3.06-2.94 (m, 1H), 1.75 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ = 156.3, 146.6, 144.0, 143.6, 141.7, 133.8, 131.8, 129.0, 128.5, 127.2, 126.4, 120.5, 104.3, 60.0, 37.5, 34.6, 33.7, 29.9. HRMS (APCI) *m/z* calcd for C₂₆H₂₇BrN₅⁺ (M+H)⁺ 488.1444, found 488.1438, 490.1417.

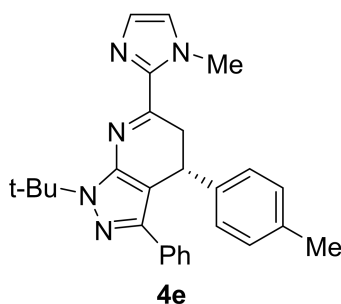


(R)-1-(tert-butyl)-4-(4-ethynylphenyl)-6-(1-methyl-1H-imidazol-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4c). Light yellow solid (42 mg, 95% yield). Mp: 92.2-94.1 °C. HPLC: 97% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 8.095 min, tr (minor) = 8.768 min. $[\alpha]_{\text{D}}^{20} = +36.0$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.53-7.50 (m, 2H), 7.35-7.31 (m, 2H), 7.28-7.22 (m, 2H), 7.22-7.16 (m, 1H), 7.10-7.03 (m, 3H), 6.95 (s, 1H), 4.47-4.41 (m, 1H), 4.09 (s, 3H), 3.95 (d, *J* = 16.96 Hz, 1H), 3.15-3.05 (m, 1H),

2.98 (s, 1H), 1.84 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ = 156.3, 146.7, 144.0, 143.7, 143.6, 133.8, 132.6, 128.9, 128.4, 127.3, 127.2, 126.4, 126.3, 120.4, 104.2, 83.6, 77.0, 60.0, 37.4, 34.6, 34.1, 29.9. HRMS (APCI) m/z calcd for $\text{C}_{28}\text{H}_{28}\text{N}_5^+$ ($\text{M}+\text{H}$) $^+$ 434.2339, found 434.2332.

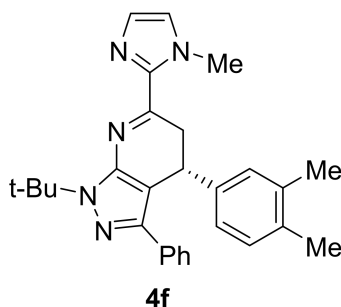


(R)-1-(tert-butyl)-6-(1-methyl-1H-imidazol-2-yl)-3-phenyl-4-(m-tolyl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4d). Light yellow solid (39 mg, 93% yield). Mp: 154.3-156.9 °C. HPLC: 96% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 7.464 min, tr (minor) = 7.918 min. $[\alpha]_{\text{D}}^{20}$ = +32.0 (c = 0.2, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ = 7.35 -7.30 (m, 2H), 7.17 -7.07 (m, 4H), 6.98-6.92 (m, 2H), 6.87-6.81 (m, 2H), 6.65-6.59 (m, 1H), 4.55-4.47 (m, 1H), 4.01 (s, 3H), 3.66 (d, J = 16.88 Hz, 1H), 3.09-2.95 (m, 1H), 2.44 (s, 3H), 1.77 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) δ = 156.4, 147.2, 144.3, 143.4, 140.6, 134.6, 133.9, 130.9, 128.7, 128.4, 127.0, 126.6, 126.3, 126.1, 105.1, 59.9, 37.4, 33.2, 30.1, 29.9, 19.6. HRMS (APCI) m/z calcd for $\text{C}_{27}\text{H}_{30}\text{N}_5^+$ ($\text{M}+\text{H}$) $^+$ 424.2496, found 424.2488.

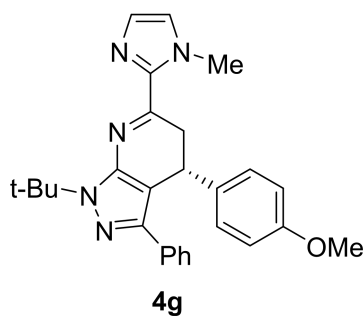


(R)-1-(tert-butyl)-6-(1-methyl-1H-imidazol-2-yl)-3-phenyl-4-(p-tolyl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4e). Light yellow solid (39 mg, 92% yield). Mp: 107.4-109.2 °C. HPLC: 94% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 7.405 min, tr (minor) = 8.224 min. $[\alpha]_{\text{D}}^{20}$ =

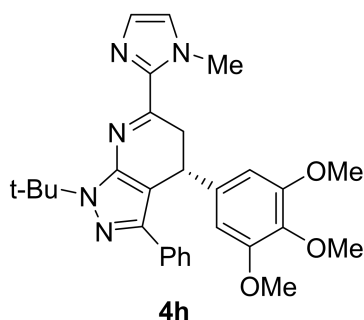
-38.5 (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.59-7.54 (m, 2H), 7.28-7.22 (m, 2H), 7.21-7.15 (m, 1H), 7.07 (s, 1H), 6.99 (s, 4H), 6.93 (s, 1H), 4.44-4.39 (m, 1H), 4.08 (s, 3H), 3.98 (d, *J* = 16.72 Hz, 1H), 3.14-3.02 (m, 1H), 2.23 (s, 3H), 1.83 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ = 156.5, 146.6, 144.2, 143.6, 139.6, 136.1, 134.0, 129.4, 128.7, 128.4, 127.1, 127.0, 126.5, 126.1, 105.1, 59.8, 37.4, 34.9, 33.7, 29.9, 21.0. HRMS (APCI) *m/z* calcd for C₂₇H₃₀N₅⁺ (M+H)⁺ 424.2496, found 424.2486.



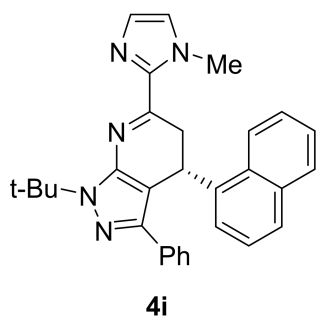
(*R*)-1-(tert-butyl)-4-(3,4-dimethylphenyl)-6-(1-methyl-1H-imidazol-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4f). Light yellow solid (39 mg, 90% yield). Mp: 89.8-91.1 °C. HPLC: 92% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, *t_r* (major) = 7.939 min, *t_r* (minor) = 8.820 min. [α]_D²⁰ = +37.0 (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.57 (d, *J* = 7.44 Hz, 2H), 7.29-7.21 (m, 2H), 7.21-7.14 (m, 1H), 7.07 (s, 1H), 6.95-6.85 (m, 3H), 6.78 (d, *J* = 7.56 Hz, 1H), 4.39 (d, *J* = 8.84 Hz, 1H), 4.07 (s, 3H), 3.95 (d, *J* = 16.76 Hz, 1H), 3.13-3.01 (m, 1H), 2.13 (s, 6H), 1.83 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ = 156.6, 146.7, 144.3, 143.6, 140.0, 136.6, 134.7, 134.1, 129.8, 128.8, 128.5, 128.4, 127.0, 126.5, 126.0, 124.5, 105.1, 59.8, 37.4, 35.0, 33.6, 29.9, 20.0, 19.4. HRMS (APCI) *m/z* calcd for C₂₈H₃₂N₅⁺ (M+H)⁺ 438.2652, found 438.2645.



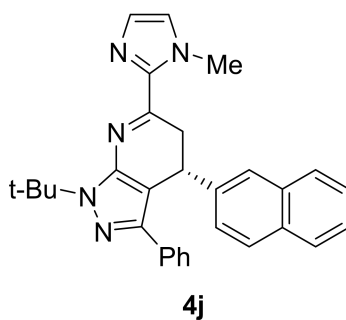
(R)-1-(tert-butyl)-4-(4-methoxyphenyl)-6-(1-methyl-1H-imidazol-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4g). Light yellow solid (39 mg, 88% yield). Mp: 74.5-76.7 °C. HPLC: 90% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 10.717 min, tr (minor) = 11.685 min. $[\alpha]_{\text{D}}^{20} = +29.0$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.59-7.53 (m, 2H), 7.29-7.22 (m, 2H), 7.21-7.15 (m, 1H), 7.08 (s, 1H), 7.04-6.97 (m, 2H), 6.94 (s, 1H), 6.75-6.70 (m, 2H), 4.43-4.37 (m, 1H), 4.09 (s, 3H), 3.95 (d, *J* = 16.68 Hz, 1H), 3.70 (s, 3H), 3.15-3.00 (m, 1H), 1.83 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ = 158.2, 156.5, 146.6, 144.3, 143.5, 134.7, 134.0, 128.8, 128.4, 128.2, 127.0, 126.5, 126.1, 114.0, 105.2, 59.9, 55.1, 37.4, 35.0, 33.3, 29.9. HRMS (APCI) *m/z* calcd for C₂₇H₃₀N₅O⁺ (M+H)⁺ 440.2445, found 440.2438.



(R)-1-(tert-butyl)-6-(1-methyl-1H-imidazol-2-yl)-3-phenyl-4-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4h). Light yellow solid (43 mg, 86% yield). Mp: 61.4-63.4 °C. HPLC: 94% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 80:20, flow rate 1.0 mL/min, tr (major) = 10.686 min, tr (minor) = 12.092 min. $[\alpha]_{\text{D}}^{20} = +28.5$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.60 (d, *J* = 7.44 Hz, 2H), 7.33-7.25 (m, 2H), 7.25-7.18 (m, 1H), 7.13 (s, 1H), 6.99 (s, 1H), 6.34 (s, 2H), 4.45-4.29 (m, 1H), 4.11 (s, 3H), 3.98 (d, *J* = 16.84 Hz, 1H), 3.75 (s, 3H), 3.64 (s, 6H), 3.19-3.06 (m, 1H), 1.82 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ = 156.7, 153.1, 146.4, 144.2, 143.8, 138.2, 136.4, 134.1, 128.9, 128.4, 127.2, 126.8, 126.3, 105.3, 104.1, 60.7, 59.9, 55.8, 37.4, 34.3, 29.8. HRMS (APCI) *m/z* calcd for C₂₉H₃₄N₅O₃⁺ (M+H)⁺ 500.2656, found 500.2647.

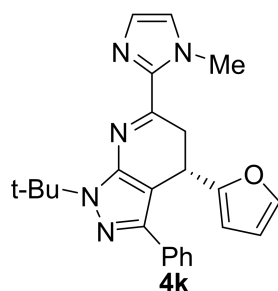


(R)-1-(tert-butyl)-6-(1-methyl-1H-imidazol-2-yl)-4-(naphthalen-1-yl)-3-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4i). Light yellow solid (38 mg, 82% yield). Mp: 221.4-222.3 °C. HPLC: 86% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 80:20, flow rate 0.7 mL/min, tr (major) = 7.318 min, tr (minor) = 8.171 min. $[\alpha]_D^{20} = +32.5$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 8.20 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.58-7.46 (m, 2H), 7.44-7.37 (m, 1H), 7.36-7.30 (m, 2H), 7.13-7.06 (m, 1H), 7.04-6.97 (m, 3H), 6.84-6.76 (m, 2H), 6.70 (s, 1H), 5.16 (d, *J* = 9.7 Hz, 1H), 3.99-3.94 (m, 1H), 3.94 (s, 3H), 3.16 (dd, *J* = 17.1, 9.8 Hz, 1H), 1.79 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ = 147.4, 144.1, 143.5, 137.6, 134.5, 133.8, 130.5, 129.2, 128.7, 128.5, 127.6, 127.0, 126.6, 126.3, 126.1, 125.6, 125.5, 124.8, 123.2, 104.5, 60.0, 37.4, 33.7, 30.0, 29.7. HRMS (APCI) *m/z* calcd for C₃₀H₃₀N₅⁺ (M+H)⁺ 460.2496, found 460.2490.

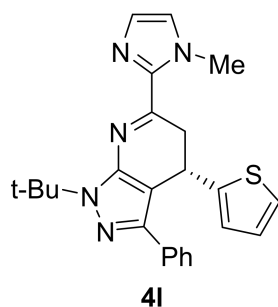


(R)-1-(tert-butyl)-6-(1-methyl-1H-imidazol-2-yl)-4-(naphthalen-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4j). Light yellow solid (44 mg, 96% yield). Mp: 93.7-95.7 °C. HPLC: 97% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 9.927 min, tr (minor) = 10.904 min. $[\alpha]_D^{20} = +45.7$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ = 7.68-7.61 (m, 2H), 7.59-7.53 (m, 1H), 7.52-7.46 (m, 2H), 7.35 (s, 1H), 7.31-7.25 (m, 3H), 7.17-7.10 (m,

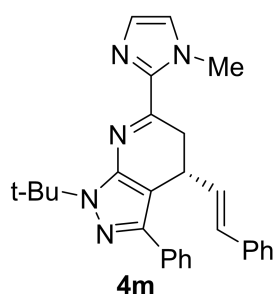
2H), 7.10-7.04 (m, 1H), 6.96 (s, 1H), 6.81 (s, 1H), 4.53 (d, $J = 8.68$ Hz, 1H), 4.03 (d, $J = 16.32$ Hz, 1H), 3.99 (s, 3H), 3.12-3.02 (m, 1H), 1.79 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) $\delta = 156.5, 146.9, 144.1, 143.8, 140.1, 133.9, 133.5, 132.5, 128.8, 128.7, 128.5, 127.9, 127.6, 127.1, 126.5, 126.2, 125.9, 125.7, 125.5, 104.6, 60.0, 54.9, 37.4, 34.8, 34.2, 29.9$. HRMS (APCI) m/z calcd for $\text{C}_{30}\text{H}_{30}\text{N}_5^+$ ($\text{M}+\text{H}$) $^+$ 460.2496, found 460.2488.



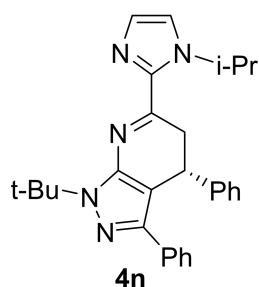
(S)-1-(tert-butyl)-4-(furan-2-yl)-6-(1-methyl-1H-imidazol-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4k). Light yellow solid (37 mg, 92% yield). Mp: 140.6-141.6 °C. HPLC: 96% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 80:20, flow rate 0.7 mL/min, t_r (major) = 6.858 min, t_r (minor) = 7.672 min. $[\alpha]_D^{20} = +24.5$ ($c = 0.2, \text{CH}_2\text{Cl}_2$). ^1H NMR (400 MHz, CDCl_3) $\delta = 7.76-7.69$ (m, 2H), 7.37-7.29 (m, 2H), 7.29-7.26 (m, 1H), 7.26-7.21 (m, 1H), 7.14 (s, 1H), 6.97 (s, 1H), 6.13 (dd, $J = 3.2, 1.8$ Hz, 1H), 5.83-5.80 (m, 1H), 4.50 (d, $J = 8.1$ Hz, 1H), 4.21 (dd, $J = 17.0, 2.0$ Hz, 1H), 4.09 (s, 3H), 2.91 (dd, $J = 17.1, 8.6$ Hz, 1H), 1.80 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 156.7, 155.2, 146.3, 144.1, 143.4, 142.1, 133.9, 129.0, 128.5, 127.2, 126.5, 126.3, 110.0, 106.4, 102.9, 59.9, 37.5, 31.2, 29.8, 28.6$. HRMS (APCI) m/z calcd for $\text{C}_{24}\text{H}_{26}\text{N}_5\text{O}^+$ ($\text{M}+\text{H}$) $^+$ 400.2132, found 400.2128.



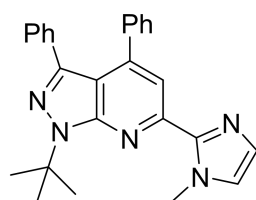
(S)-1-(tert-butyl)-6-(1-methyl-1H-imidazol-2-yl)-3-phenyl-4-(thiophen-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4l). Light yellow solid (38 mg, 91% yield). Mp: 163.4-165.8 °C. HPLC: 95% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 8.440 min, tr (minor) = 9.939 min. $[\alpha]_{\text{D}}^{20} = +25.5$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) $\delta = 7.69$ (d, $J = 7.3$ Hz, 2H), 7.35-7.28 (m, 2H), 7.26-7.20 (m, 1H), 7.12 (s, 1H), 7.04-7.00 (m, 1H), 6.95 (s, 1H), 6.82-6.77 (m, 1H), 6.73 (d, $J = 3.36$ Hz, 1H), 4.71 (d, $J = 8.12$ Hz, 1H), 4.13 (d, $J = 17.76$ Hz, 1H), 4.08 (s, 3H), 3.12-3.00 (m, 1H), 1.81 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) $\delta = 156.4, 147.1, 146.0, 144.2, 143.2, 133.9, 129.0, 128.5, 127.2, 126.9, 126.5, 126.2, 124.2, 124.0, 105.5, 59.9, 37.4, 35.2, 30.0, 29.8$. HRMS (APCI) m/z calcd for C₂₄H₂₆N₅S⁺ (M+H)⁺ 416.1903, found 416.1896.



(R,E)-1-(tert-butyl)-6-(1-methyl-1H-imidazol-2-yl)-3-phenyl-4-styryl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4m). Light yellow solid (41 mg, 94% yield). Mp: 71.2-73.7 °C. HPLC: 98% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 7.979 min, tr (minor) = 8.577 min. $[\alpha]_{\text{D}}^{20} = +33.5$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) $\delta = 7.72$ (d, $J = 7.56$ Hz, 2H), 7.30-7.23 (m, 2H), 7.20-7.00 (m, 7H), 6.89 (s, 1H), 6.17 (s, 2H), 4.00 (s, 3H), 3.93 (d, $J = 8.68$ Hz, 1H), 3.86 (d, $J = 16.92$ Hz, 1H), 2.85-2.75 (m, 1H), 1.72 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) $\delta = 156.8, 146.1, 144.3, 143.6, 137.1, 134.1, 130.5, 130.3, 128.9, 128.6, 128.4, 127.3, 127.2, 126.5, 126.4, 104.4, 59.9, 37.5, 32.1, 31.7, 29.9$. HRMS (APCI) m/z calcd for C₂₈H₃₀N₅⁺ (M+H)⁺ 436.2496, found 436.2488.



(R)-1-(tert-butyl)-6-(1-isopropyl-1H-imidazol-2-yl)-3,4-diphenyl-4,5-dihydro-1H-pyrazolo[3,4-b]pyridine (4n). Light yellow solid (38 mg, 88% yield). Mp: 92.3-93.7 °C. HPLC: 87% ee (Chiralpak IC column, 254 nm, hexane/isopropanol = 95:5, flow rate 1.0 mL/min, tr (major) = 6.686 min, tr (minor) = 7.607 min. $[\alpha]_D^{20} = +21.5$ (c = 0.2, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) $\delta = 7.61-7.48$ (m, 2H), 7.27-7.22 (m, 2H), 7.21-7.14 (m, 4H), 7.14-7.05 (m, 4H), 6.08-5.86 (m, 1H), 4.44 (d, $J = 6.9$ Hz, 1H), 3.95 (d, $J = 16.8$ Hz, 1H), 3.15 (dd, $J = 16.9, 9.1$ Hz, 1H), 1.82 (s, 9H), 1.50 (d, $J = 6.7$ Hz, 3H), 1.41 (d, $J = 6.7$ Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) $\delta = 157.1, 146.7, 143.7, 143.5, 142.8, 134.1, 129.5, 128.8, 128.5, 127.3, 127.1, 126.7, 126.6, 120.0, 105.1, 59.9, 48.7, 35.8, 34.4, 30.0, 24.0, 23.9$. HRMS (APCI) m/z calcd for C₂₈H₃₂N₅⁺ (M+H)⁺ 438.2652, found 438.2646.



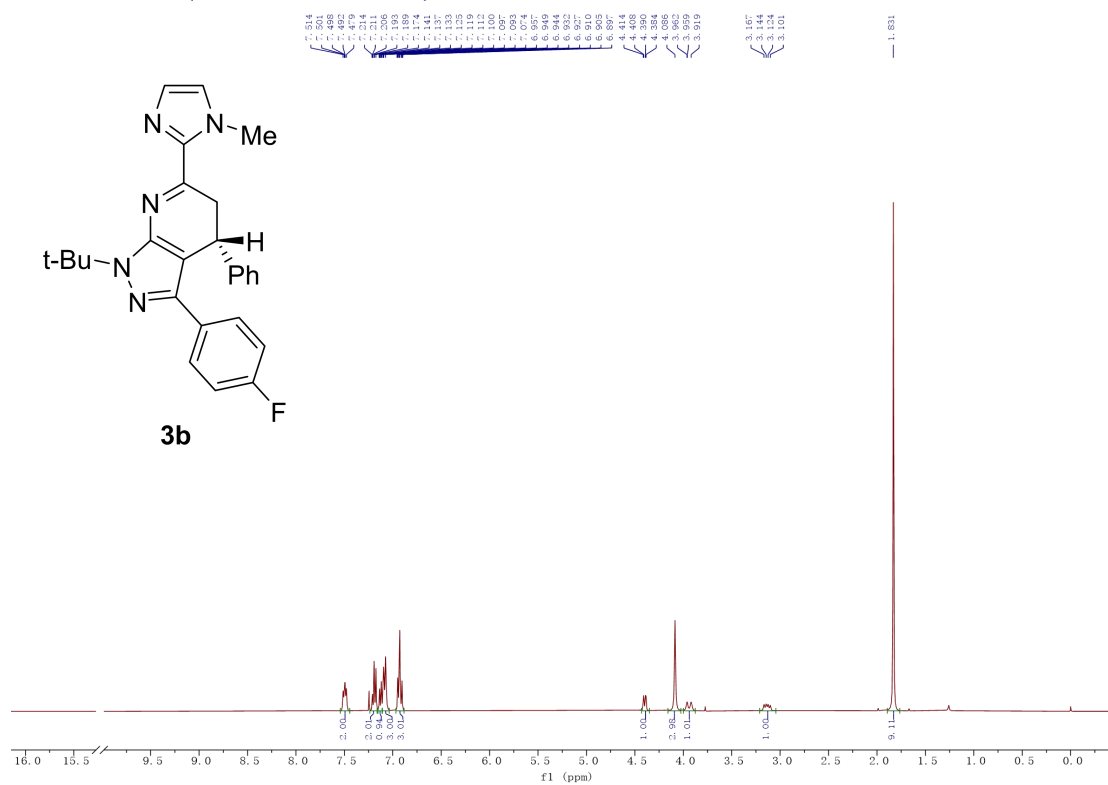
6a

1-(tert-butyl)-6-(1-methyl-1H-imidazol-2-yl)-3,4-diphenyl-1H-pyrazolo[3,4-b]pyridine (6a). Light yellow solid (24 mg, 60% yield). Mp: 124.5-126.6 °C. ¹H NMR (400 MHz, CDCl₃) $\delta = 8.12$ (s, 1H), 7.23 (d, $J = 6.8$ Hz, 3H), 7.19 (s, 1H), 7.17-7.11 (m, 5H), 7.09-7.04 (m, 3H), 4.29 (s, 3H), 1.95 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) $\delta = 150.8, 146.0, 145.3, 142.4, 137.4, 133.7, 129.4, 129.3, 128.4, 128.1, 127.7, 127.5, 127.2, 124.8, 116.8, 111.7, 60.0, 37.0, 29.3$. HRMS (APCI) m/z calcd for C₂₆H₂₆N₅⁺ (M+H)⁺ 408.2183, found 408.2176.

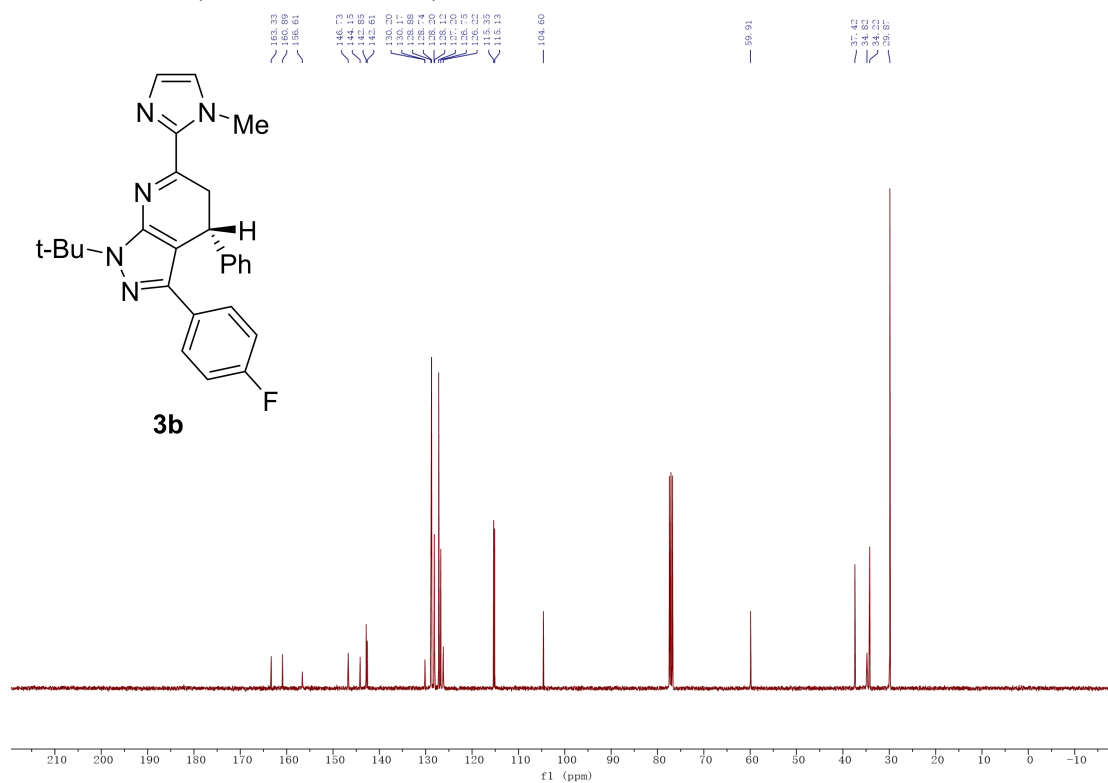
III References

- (1) C. Y. Wang, L. A. Chen, H. H. Huo, X. D. Shen, K. Harms, L. Gong, E. Meggers, *Chem. Sci.* **2015**, *6*, 1094-1100.
- (2) X. Gao, C. W. Li, Chen L, L. Xin, *Org. Lett.* **2023**, *25*, 7628-7632.
- (3) L. C. He, E.-A. M. A. Ahmed, H. X. Liu, X. G. Hu, H. P. Xiao, J. Li, J. Jiang, *J. Org. Chem.* **2021**, *86*, 4825-4834.

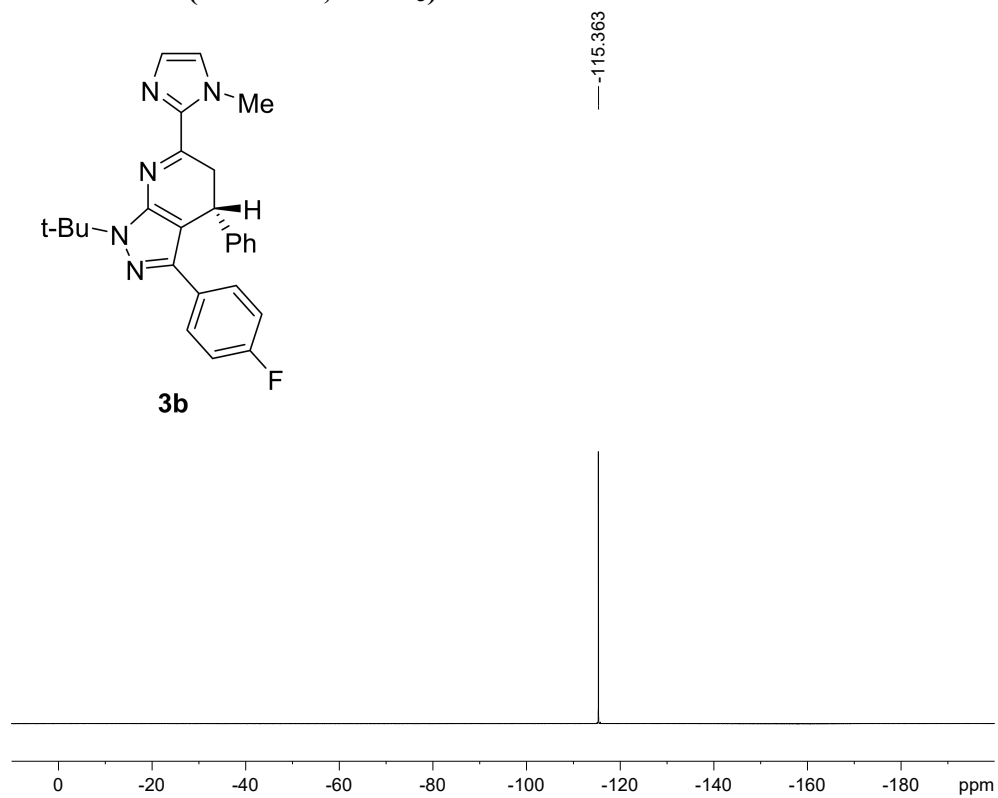
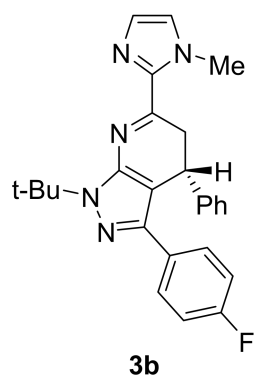
¹H NMR-3b (400 MHz, CDCl₃)



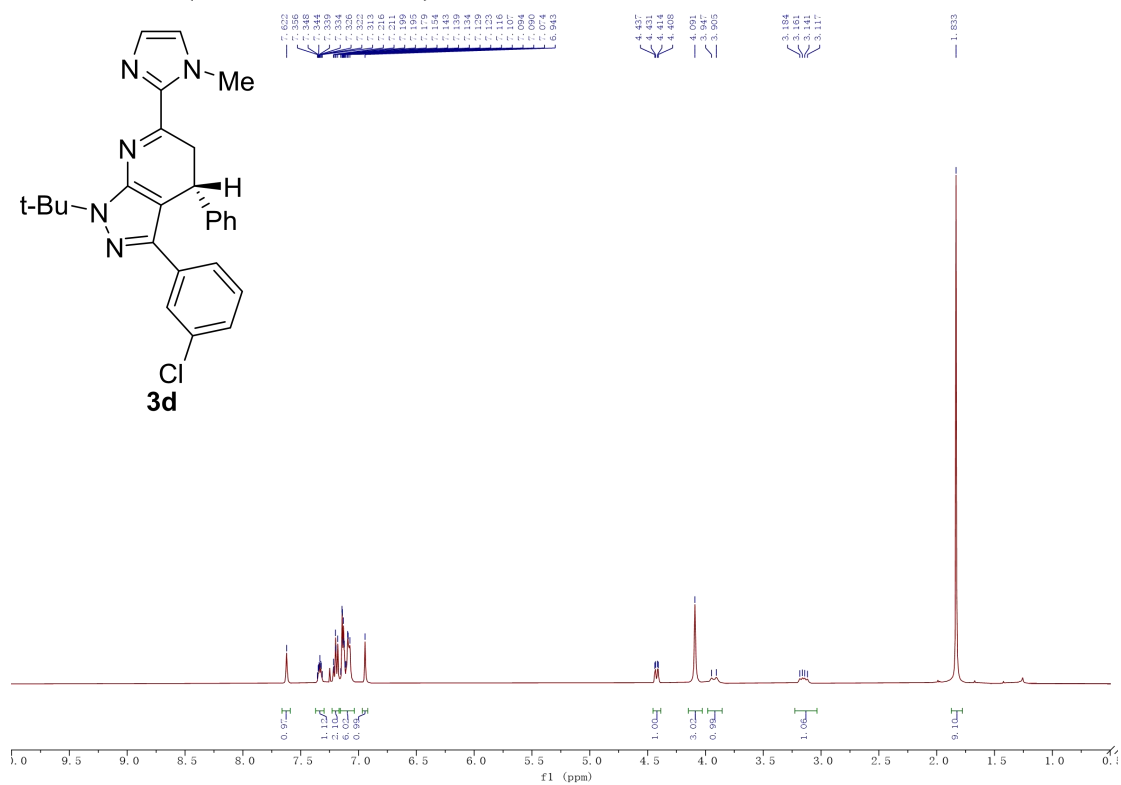
¹³C NMR-3b (100 MHz, CDCl₃)



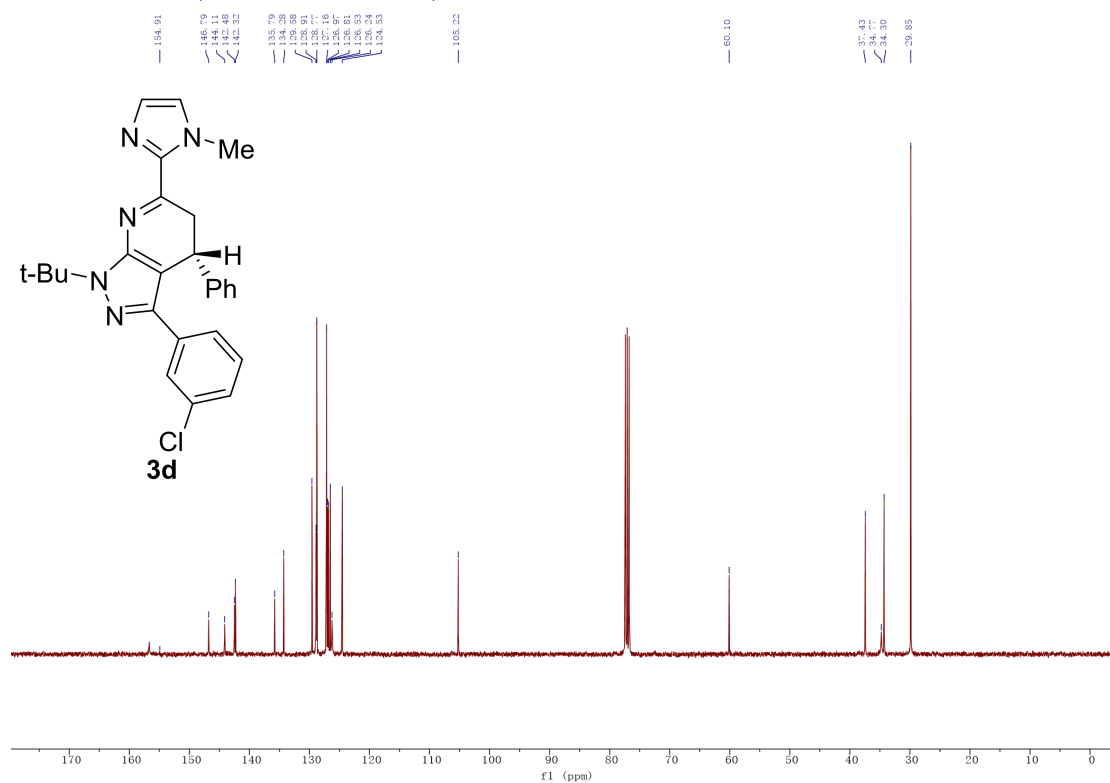
¹⁹F NMR-3b (376 MHz, CDCl₃)



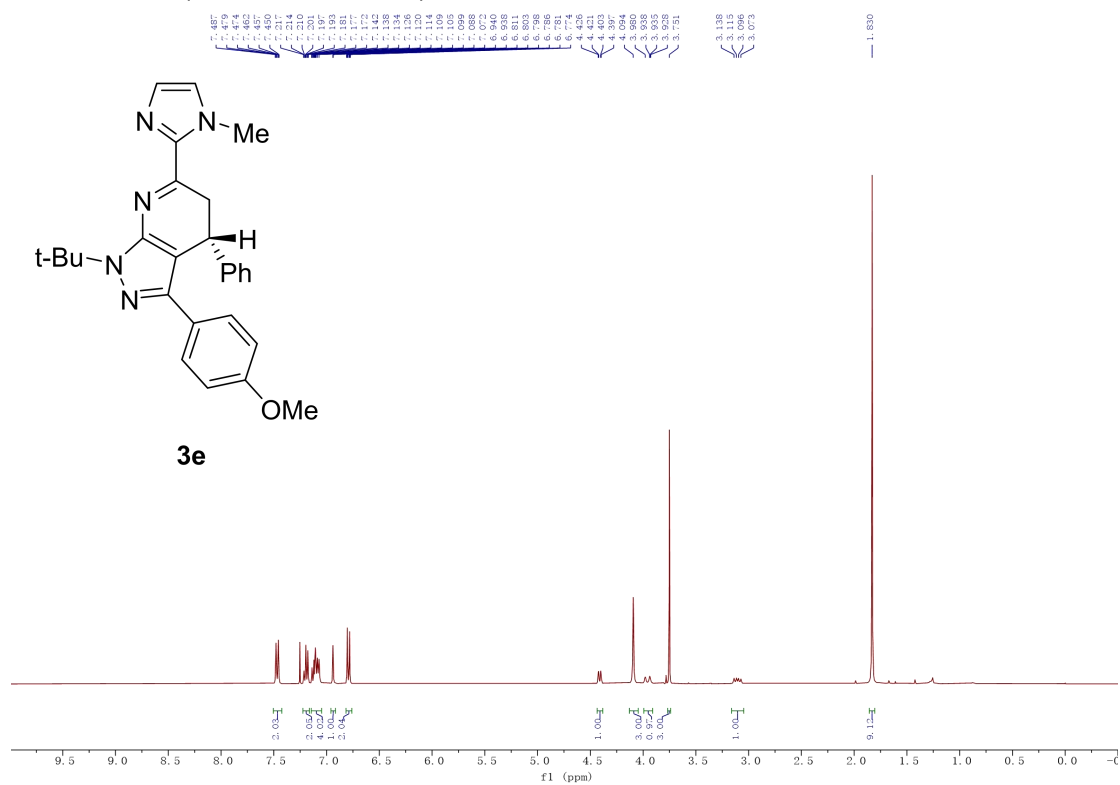
¹H NMR-3d (400 MHz, CDCl₃)



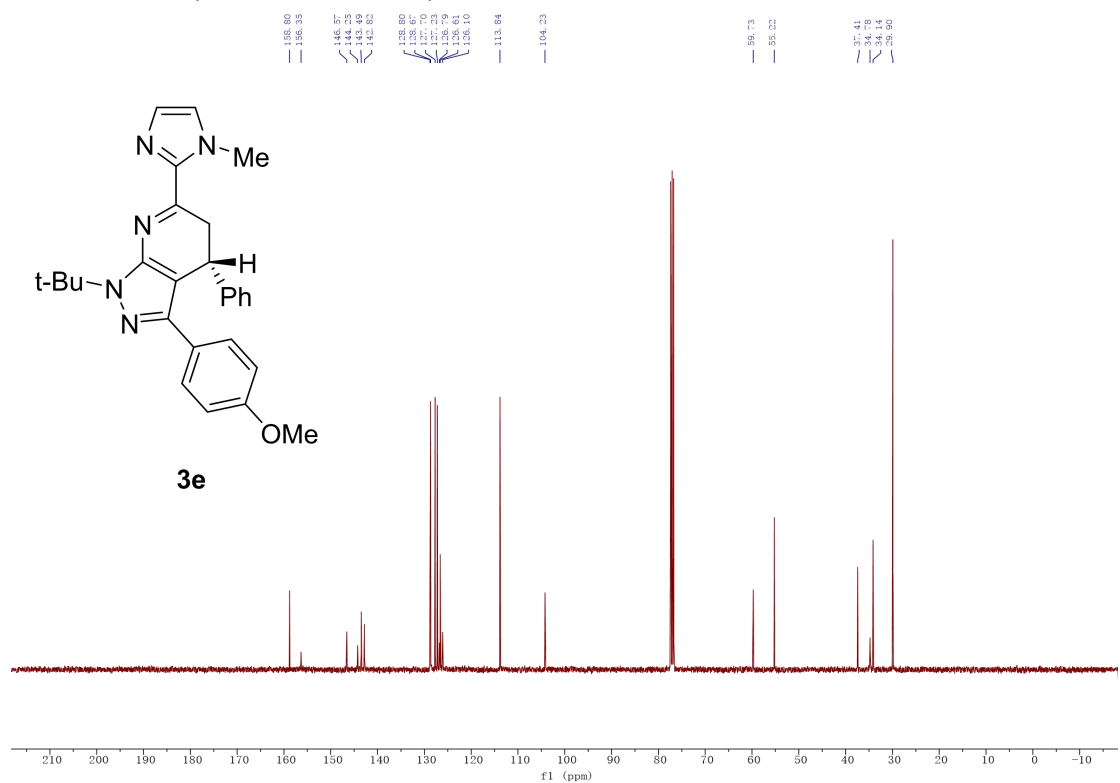
¹³C NMR-3d (100 MHz, CDCl₃)



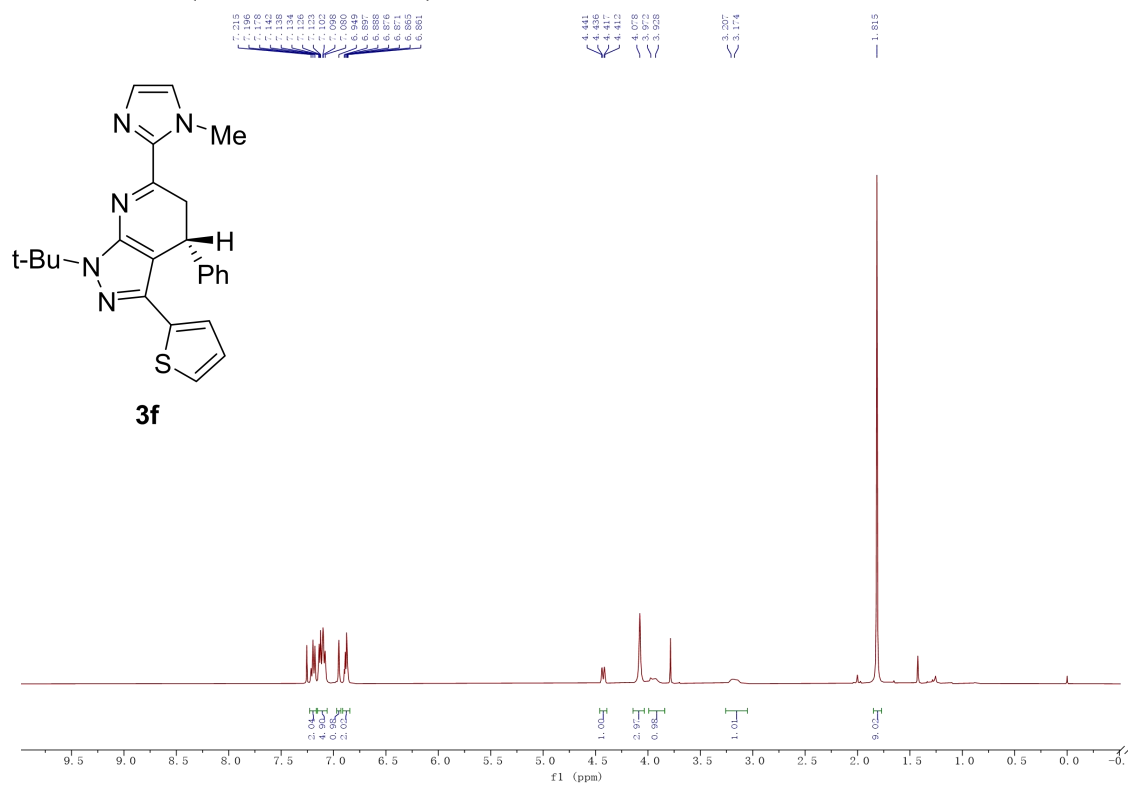
¹H NMR-3e (400 MHz, CDCl₃)



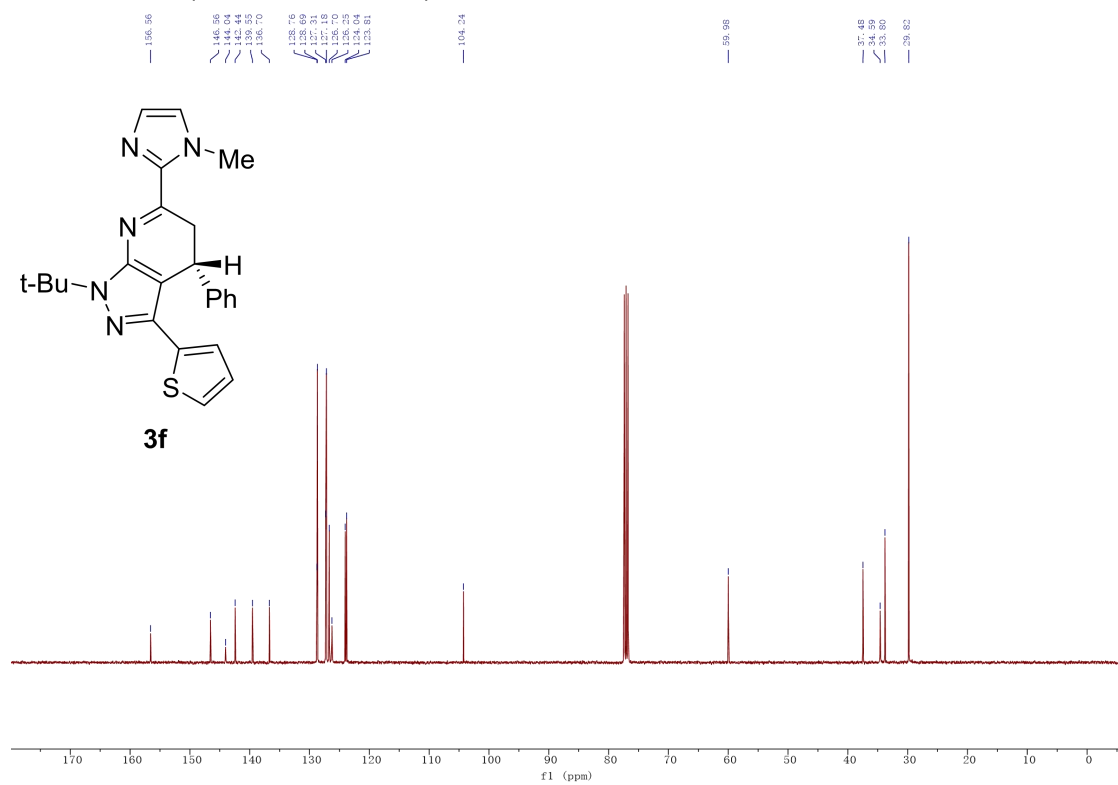
¹³C NMR-3e (100 MHz, CDCl₃)



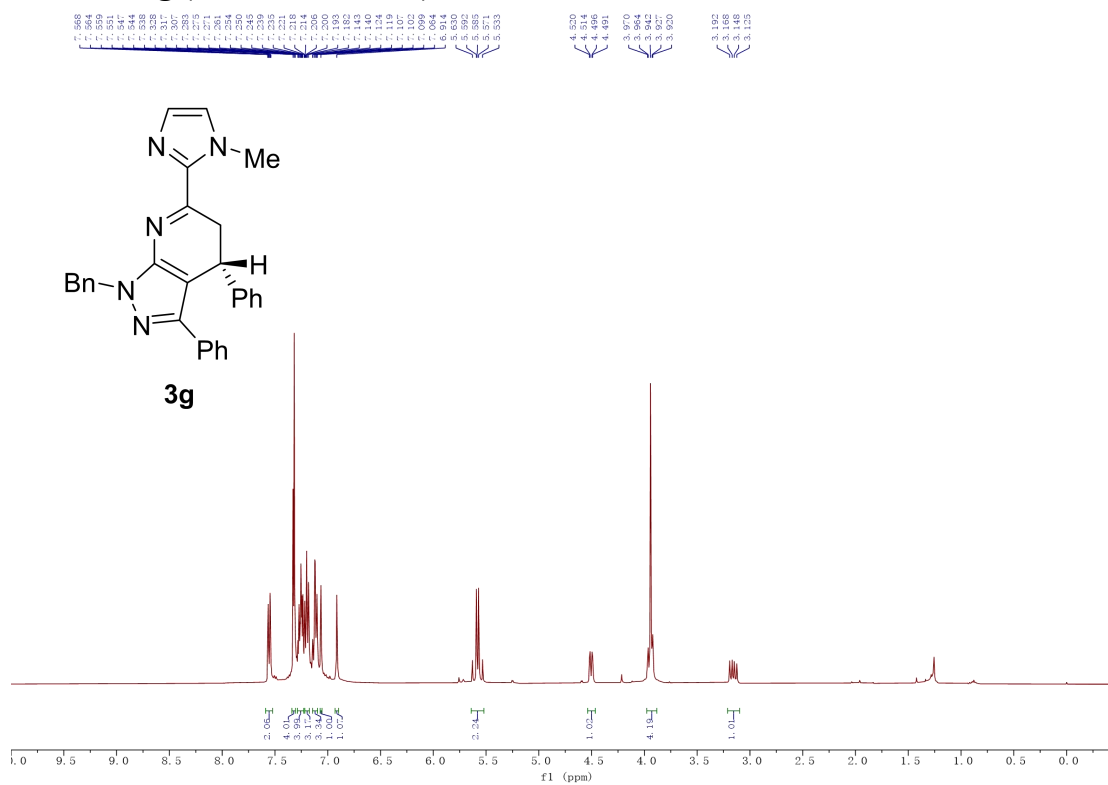
¹H NMR-3f (400 MHz, CDCl₃)



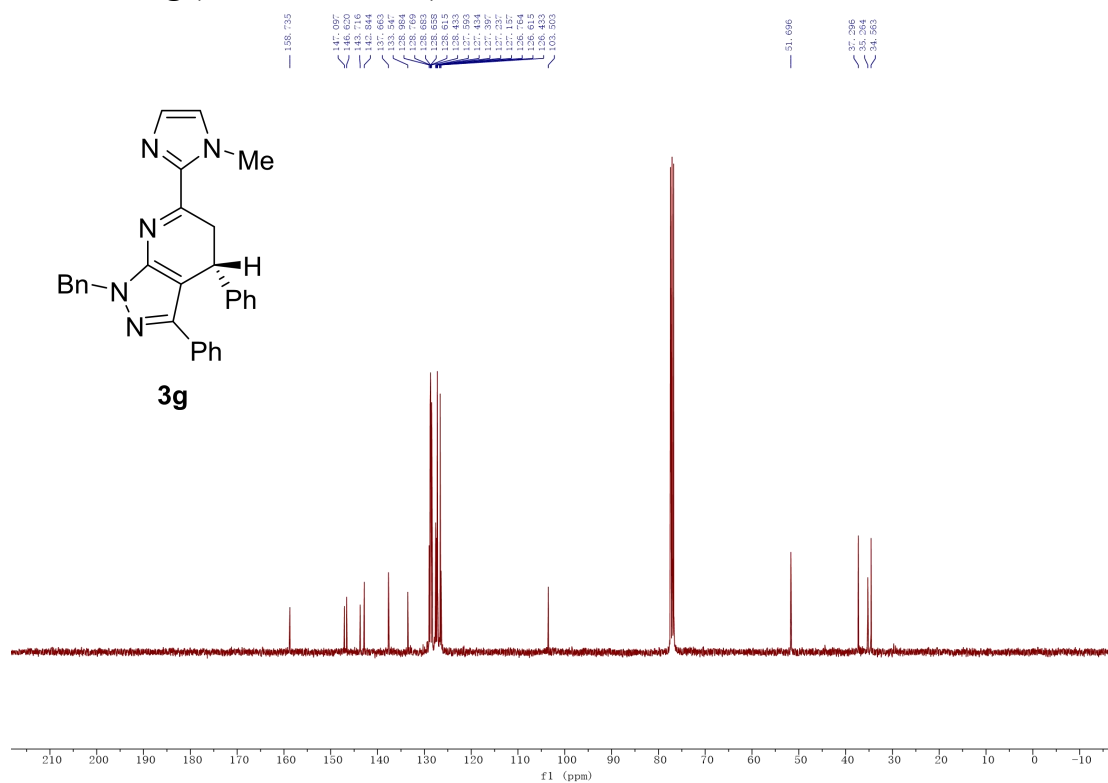
¹³C NMR-3f (100 MHz, CDCl₃)



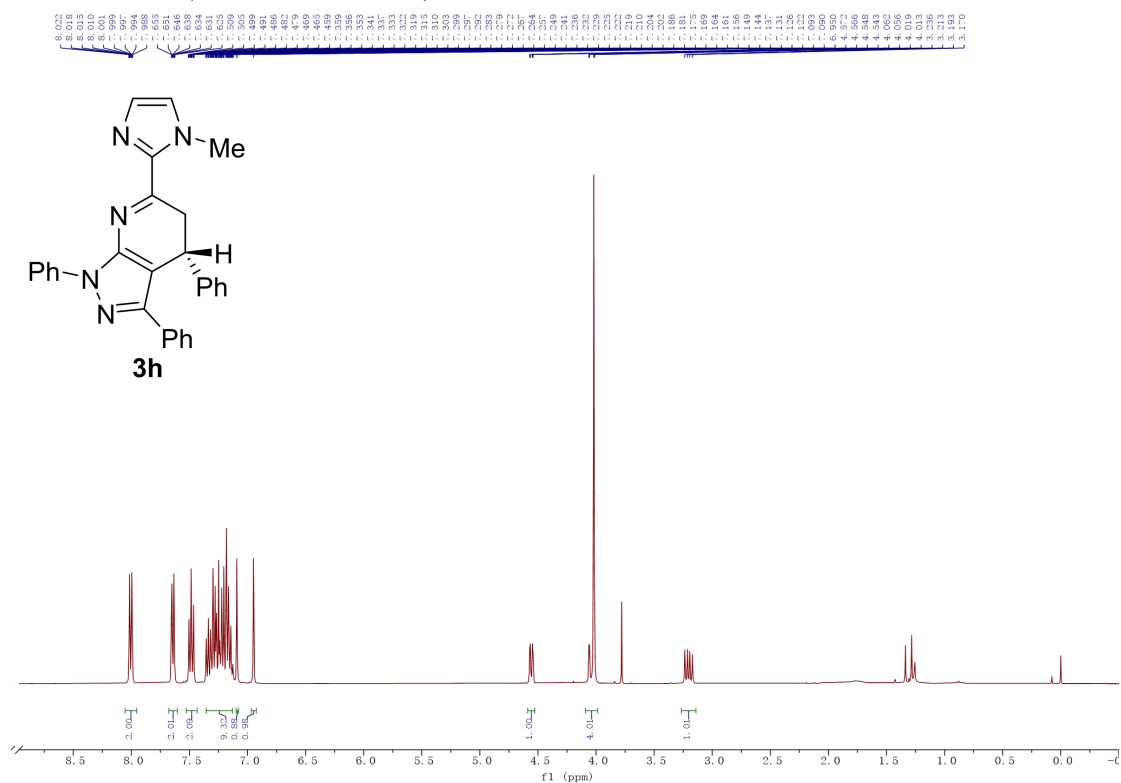
¹H NMR-3g (400 MHz, CDCl₃)



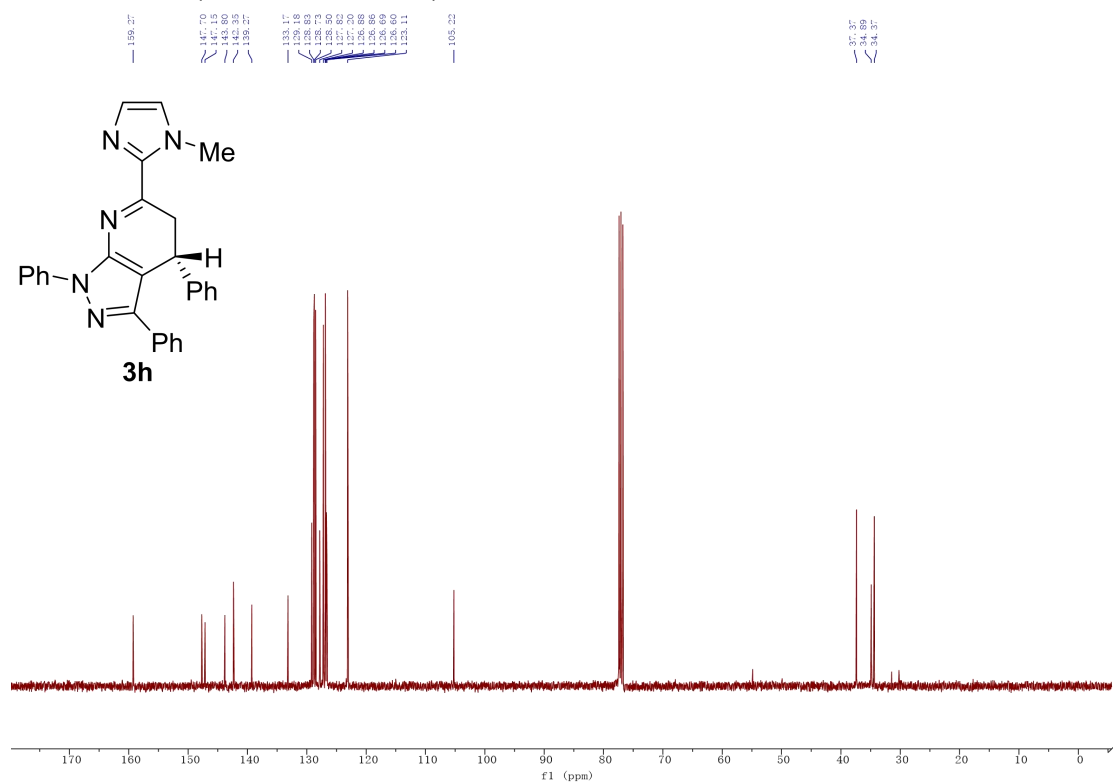
¹³C NMR-3g (100 MHz, CDCl₃)



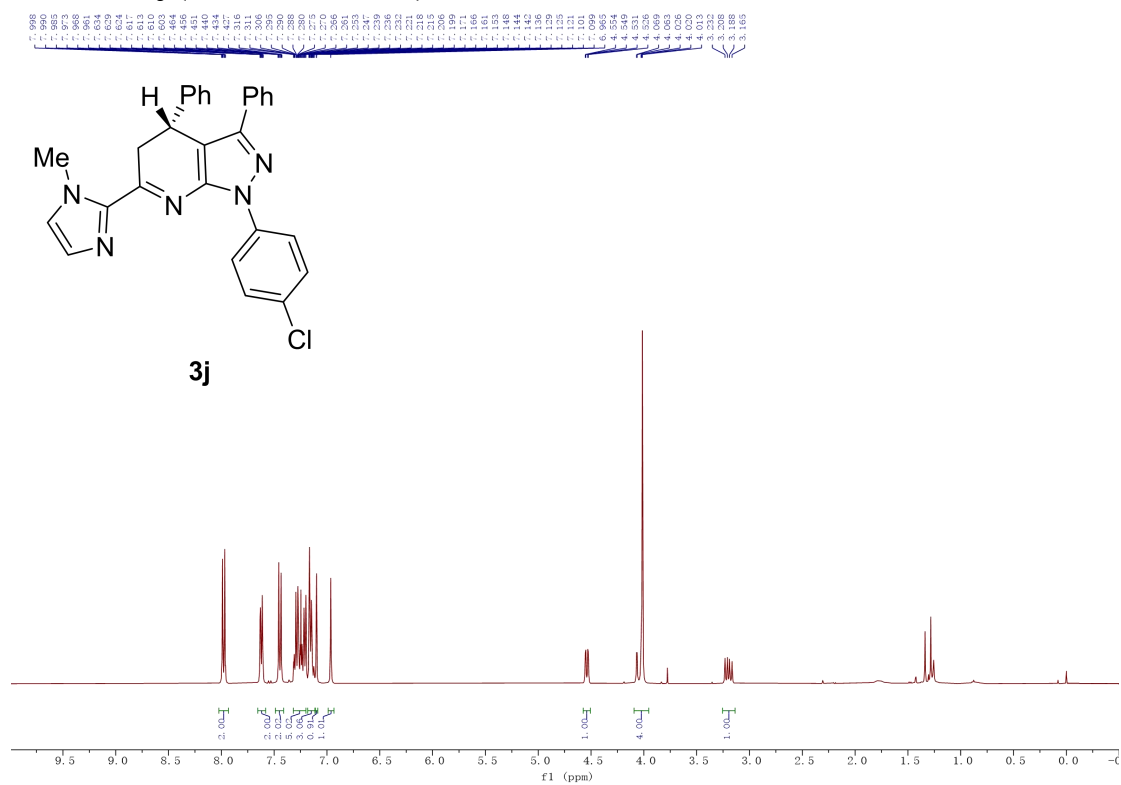
¹H NMR-3h (400 MHz, CDCl₃)



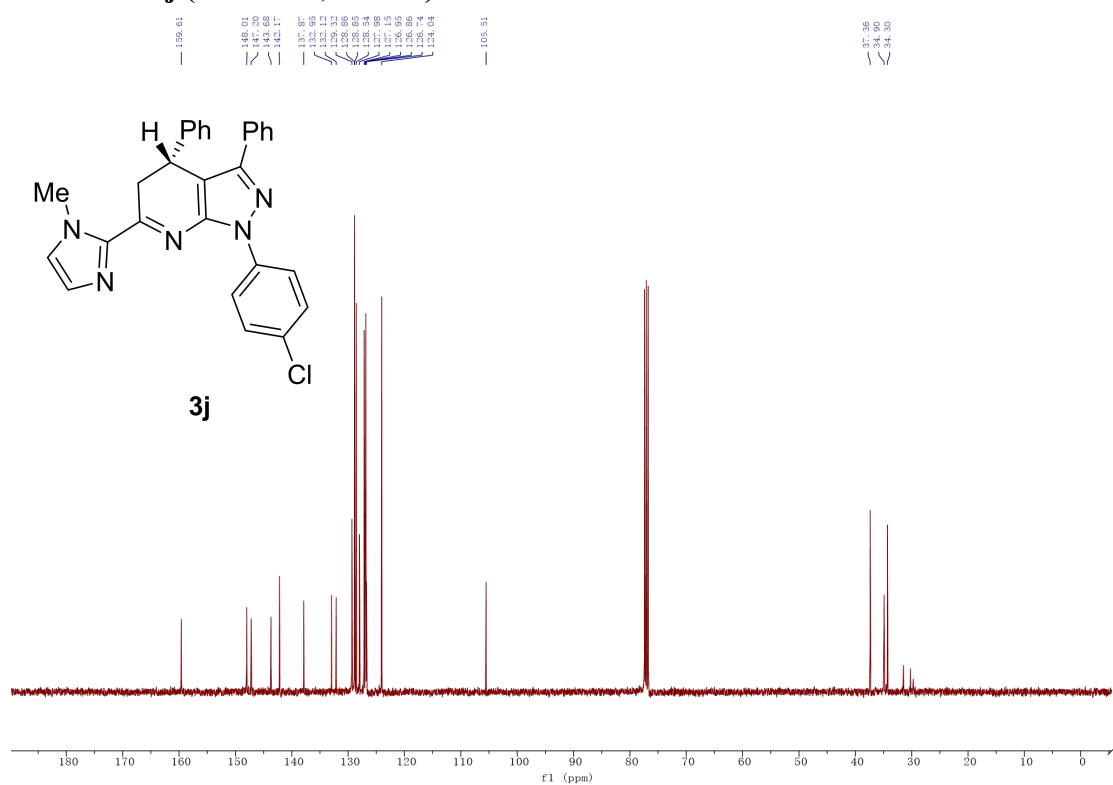
¹³C NMR-3h (100 MHz, CDCl₃)



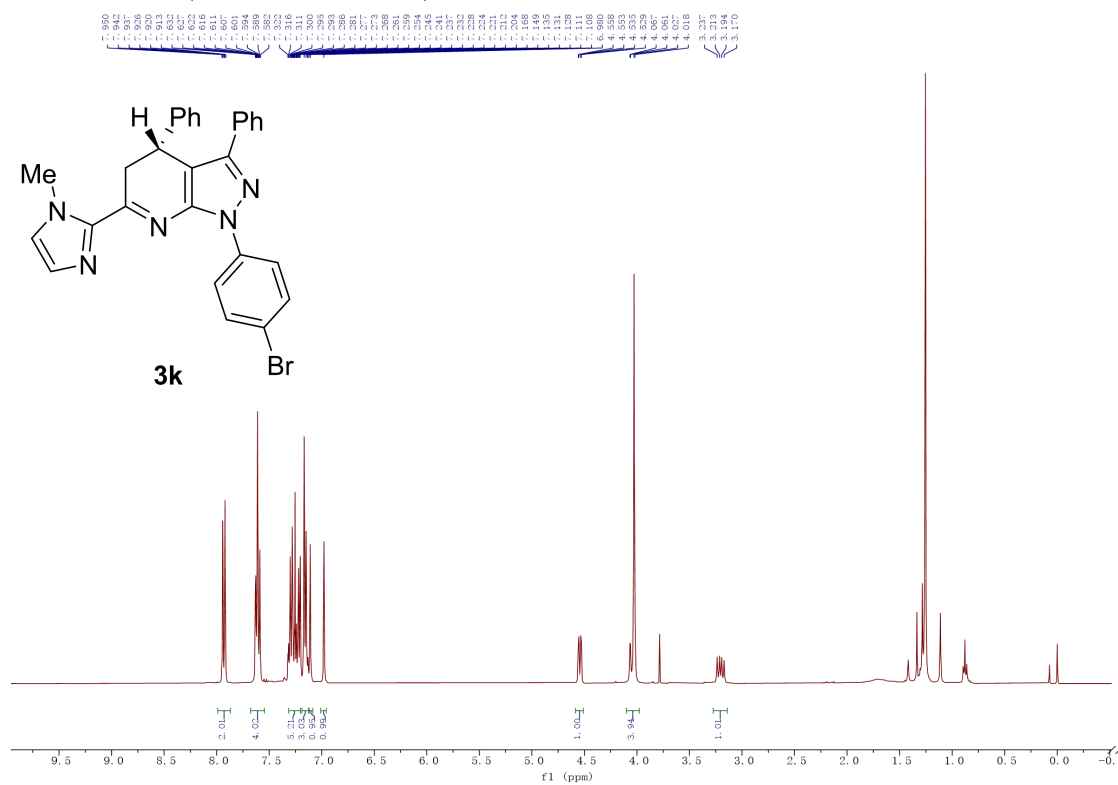
¹H NMR-3j (400 MHz, CDCl₃)



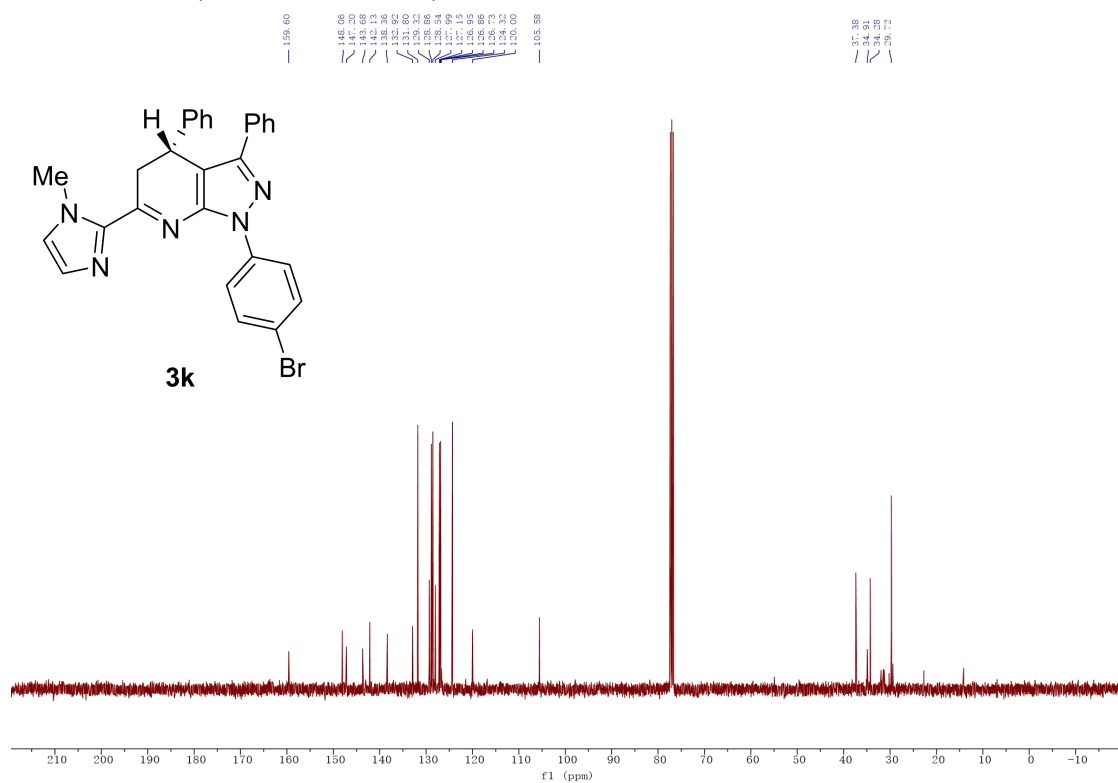
¹³C NMR-3j (100 MHz, CDCl₃)



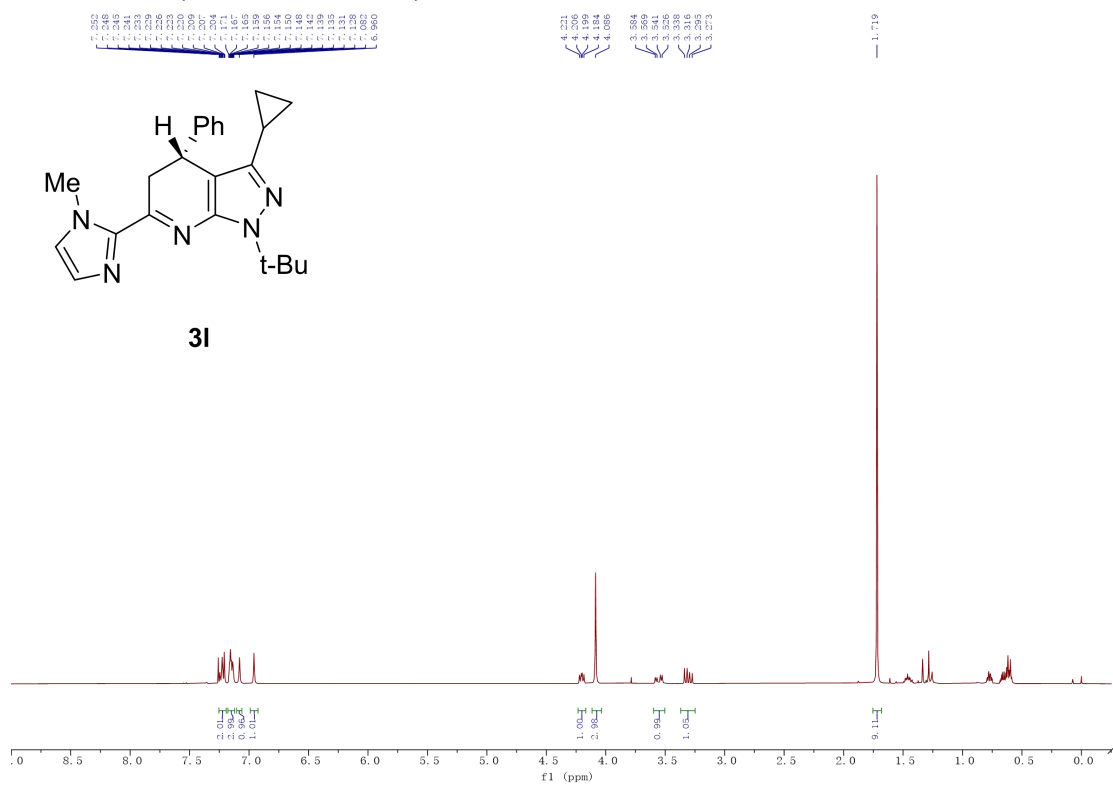
¹H NMR-3k (400 MHz, CDCl₃)



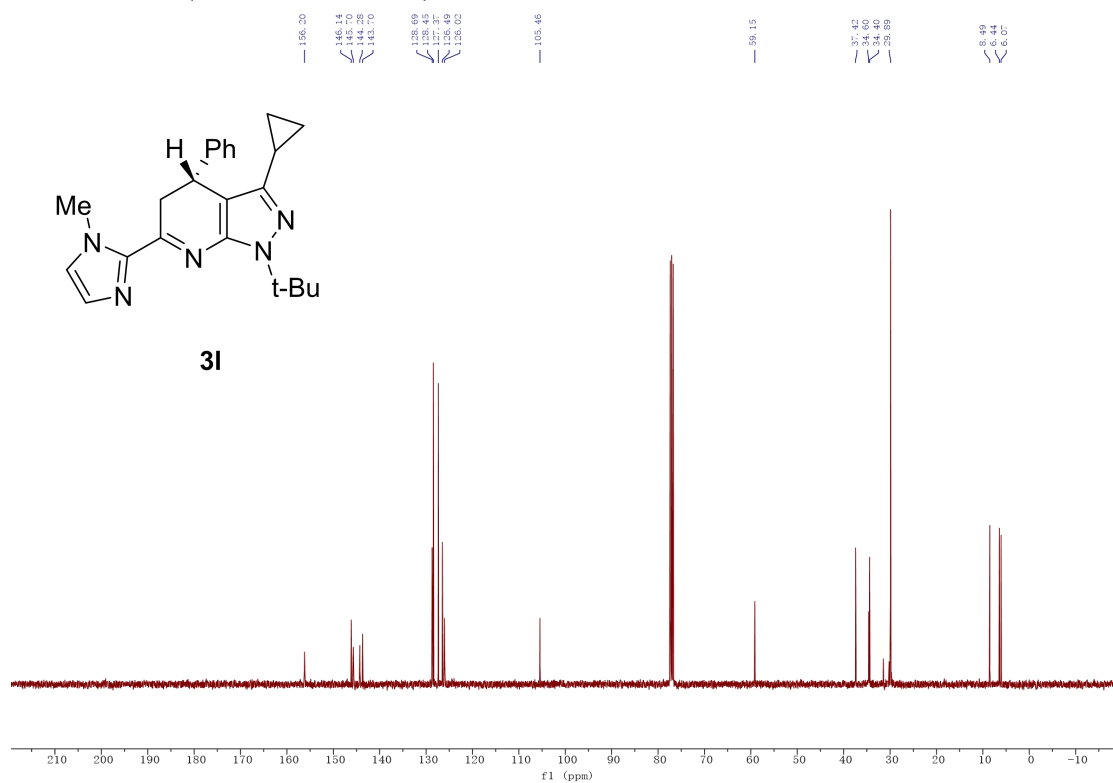
¹³C NMR-3k (100 MHz, CDCl₃)



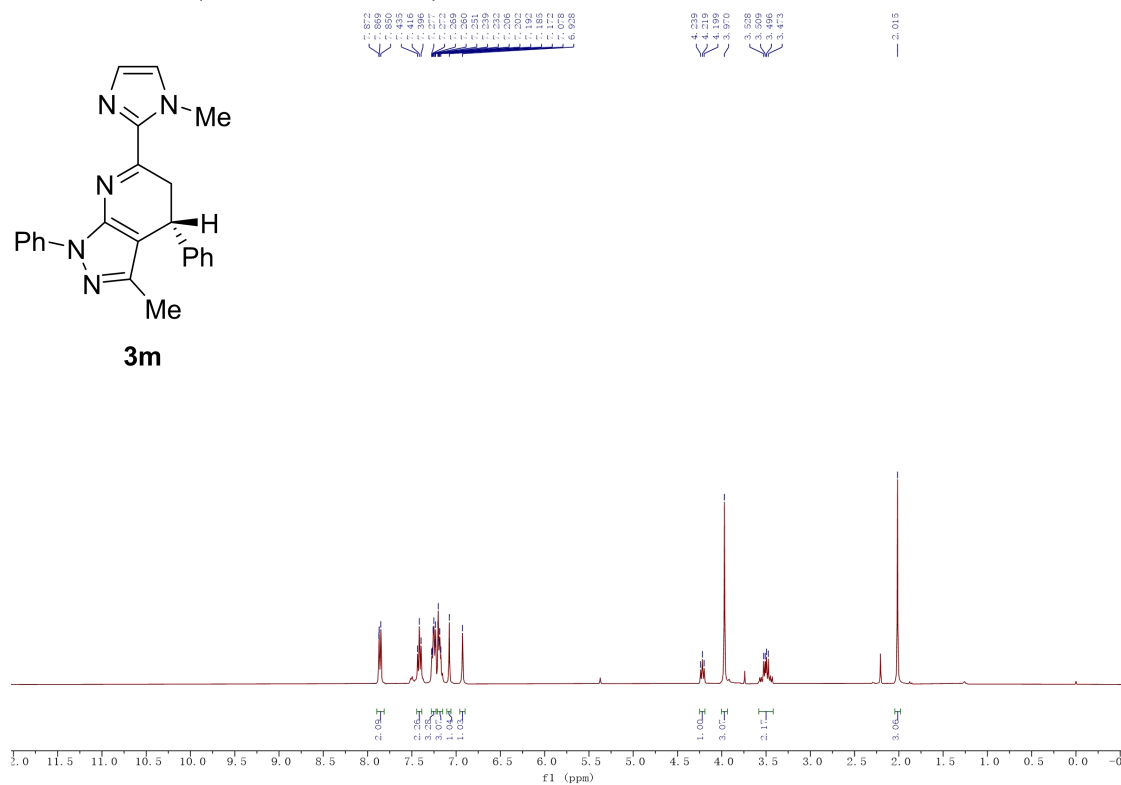
¹H NMR-31 (400 MHz, CDCl₃)



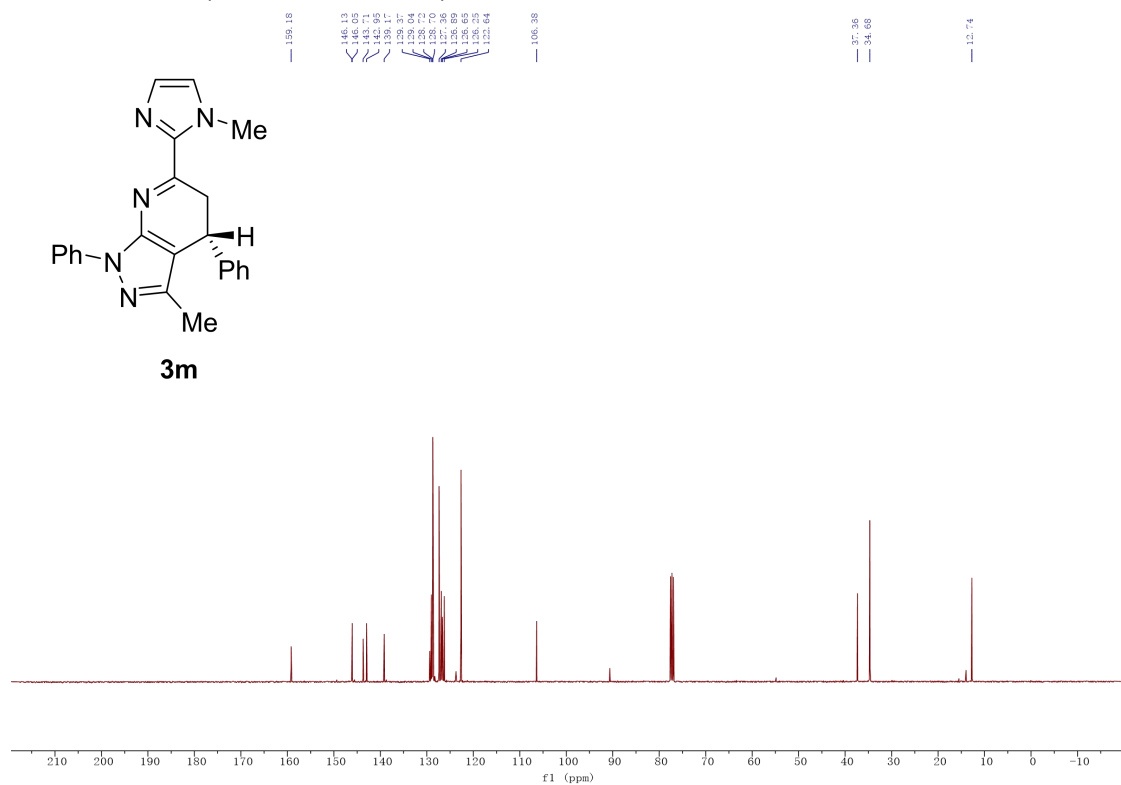
¹³C NMR-31 (100 MHz, CDCl₃)



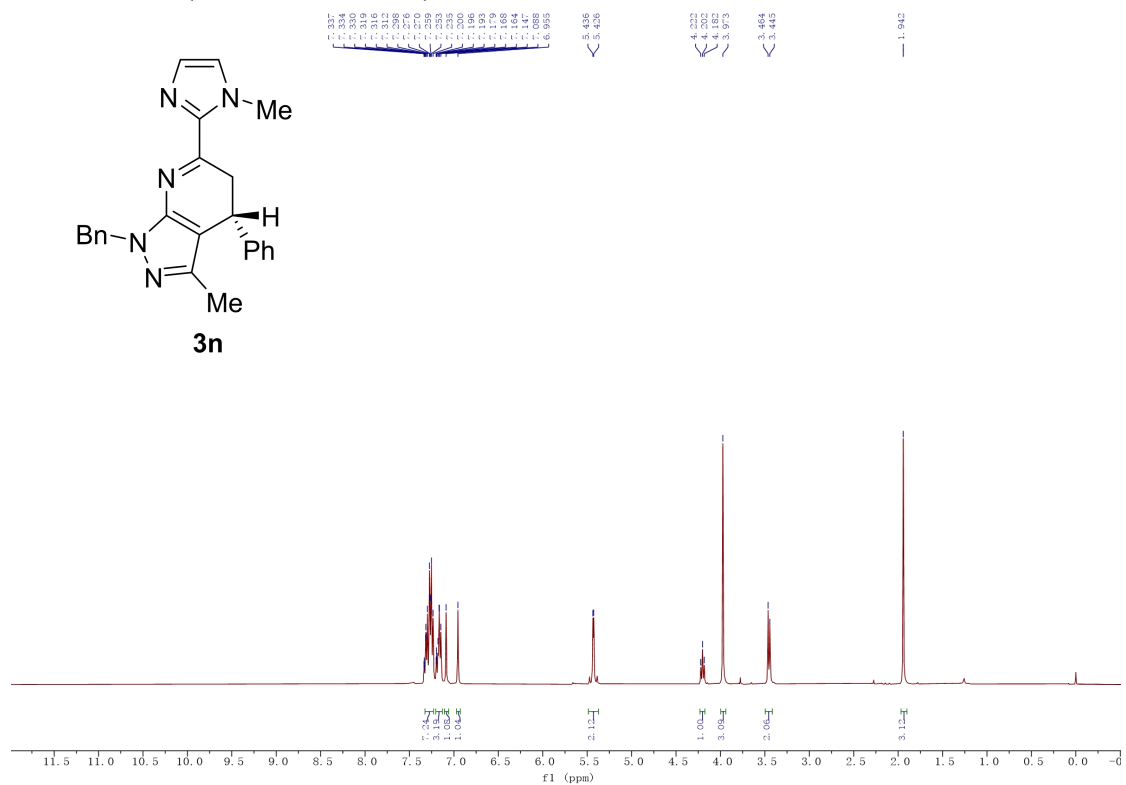
¹H NMR-3m (400 MHz, CDCl₃)



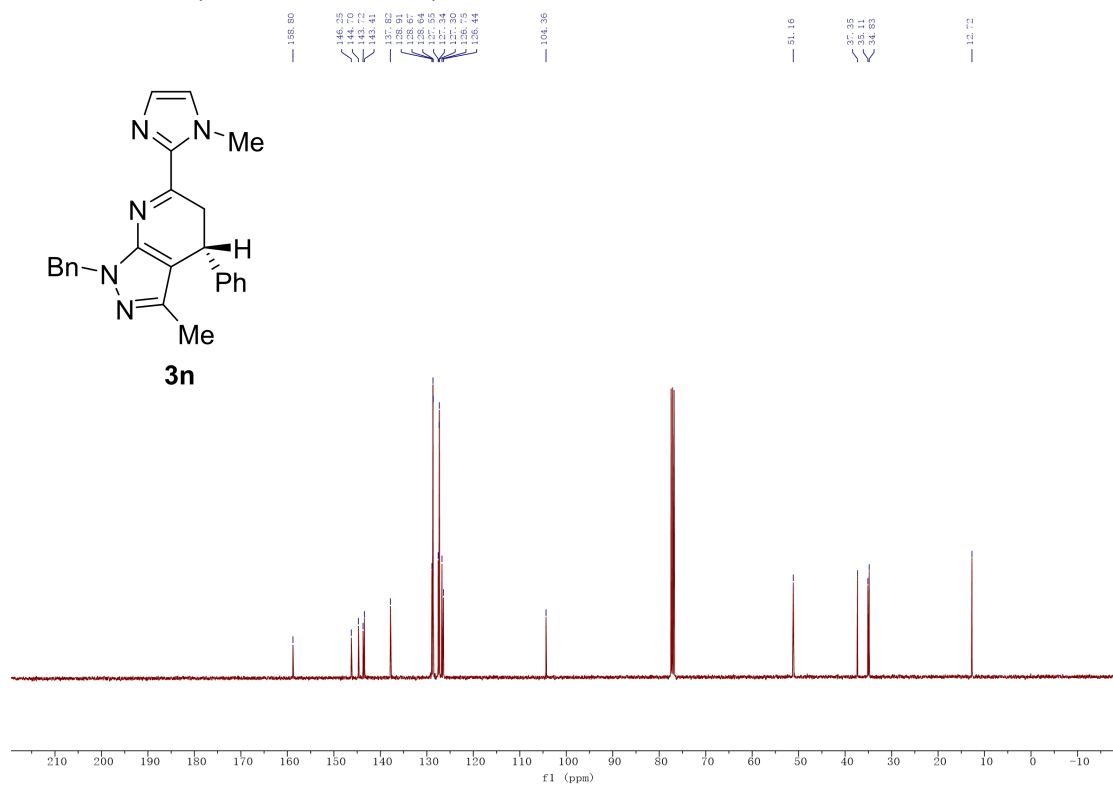
¹³C NMR-3m (100 MHz, CDCl₃)



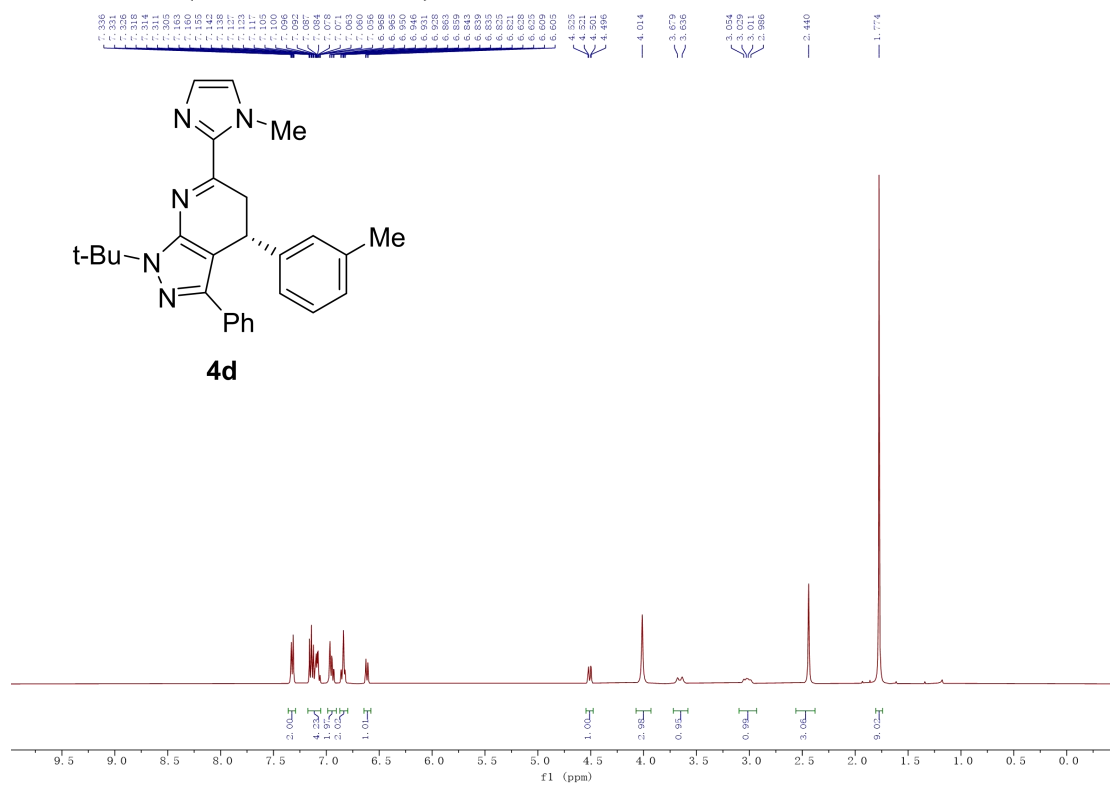
¹H NMR-3n (400 MHz, CDCl₃)



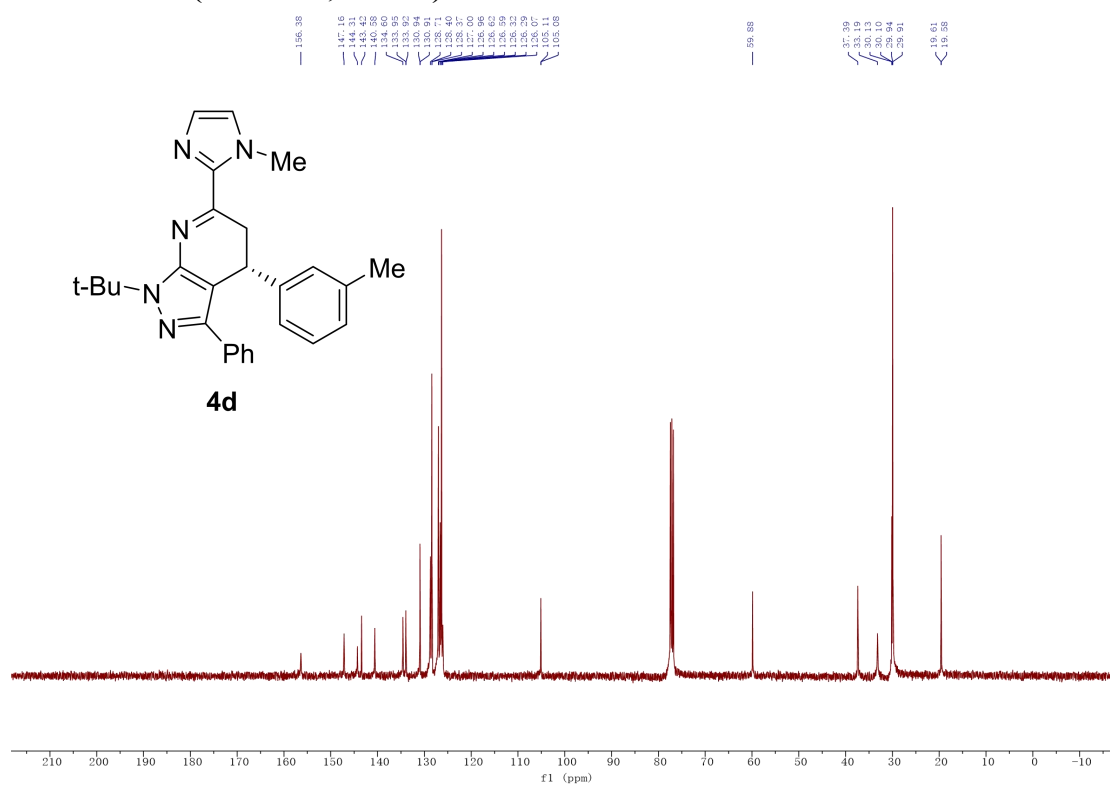
¹³C NMR-3n (100 MHz, CDCl₃)



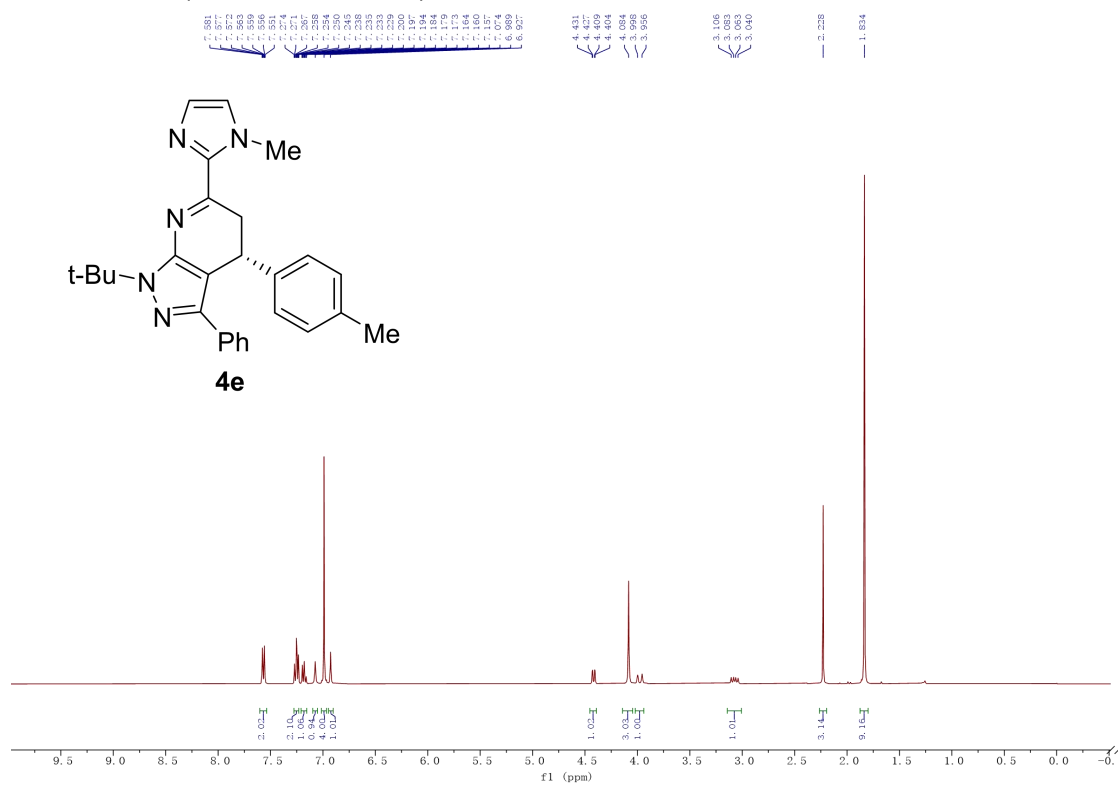
¹H NMR-4d (400 MHz, CDCl₃)



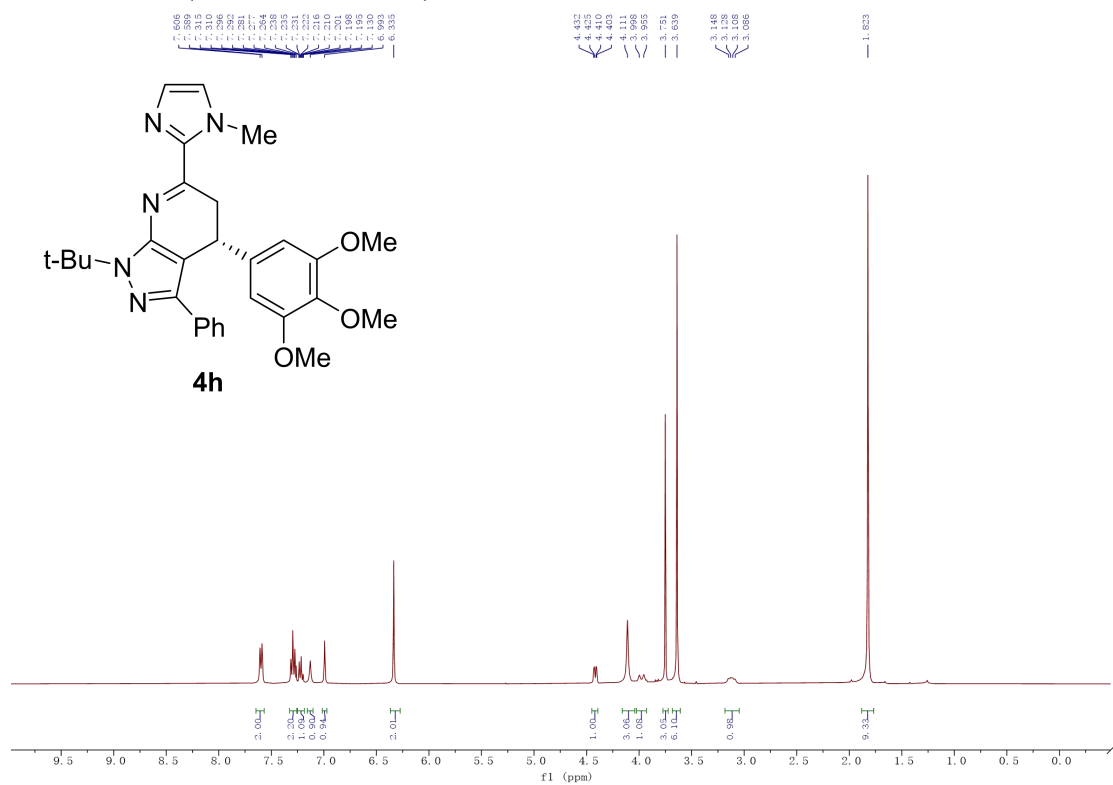
¹³C NMR-4d (100 MHz, CDCl₃)



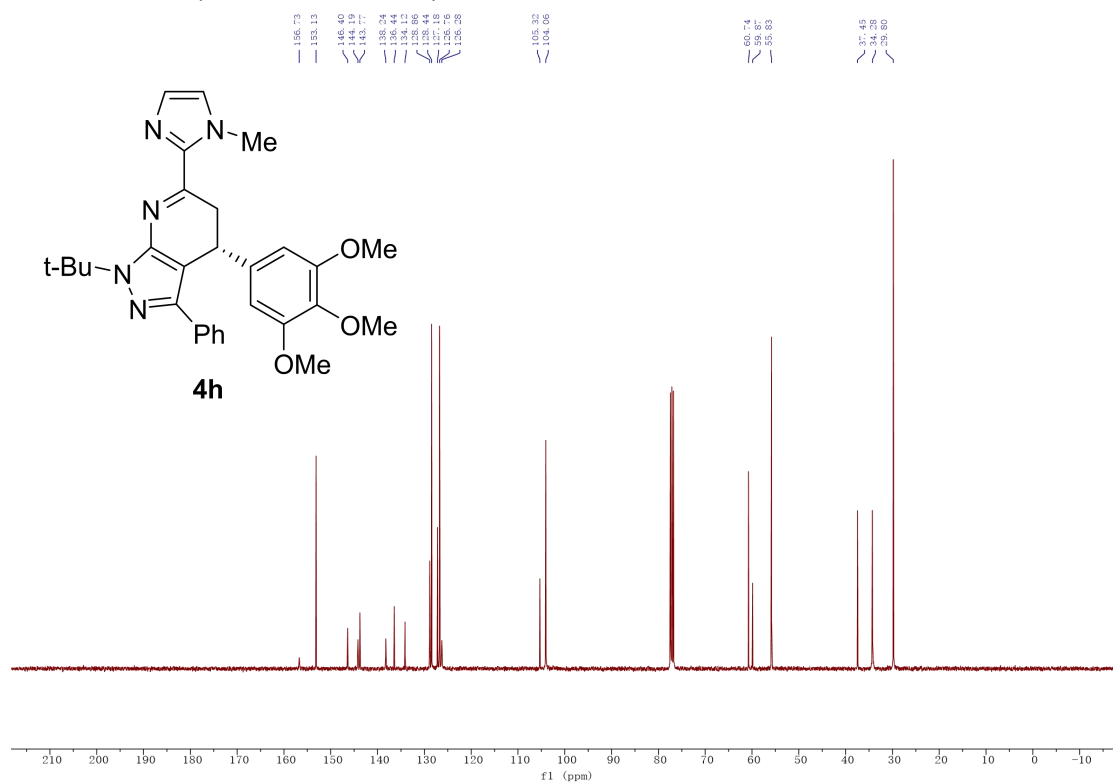
¹H NMR-4e (400 MHz, CDCl₃)



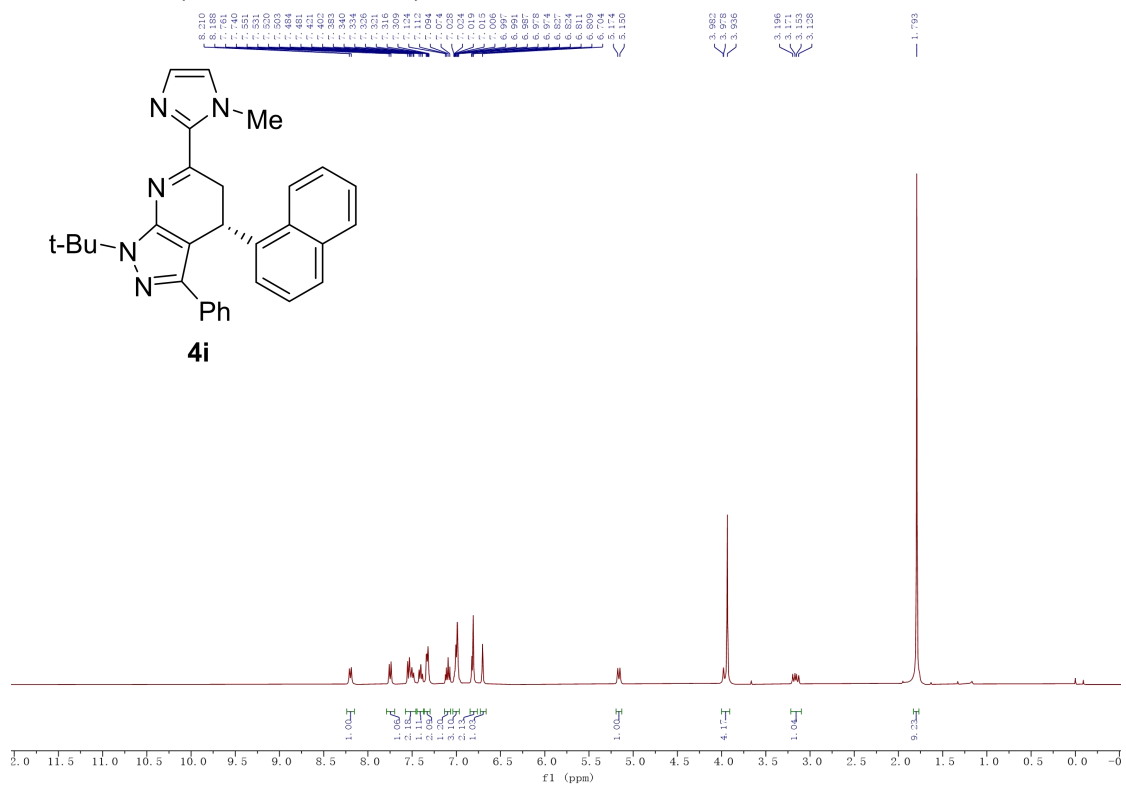
¹H NMR-4h (400 MHz, CDCl₃)



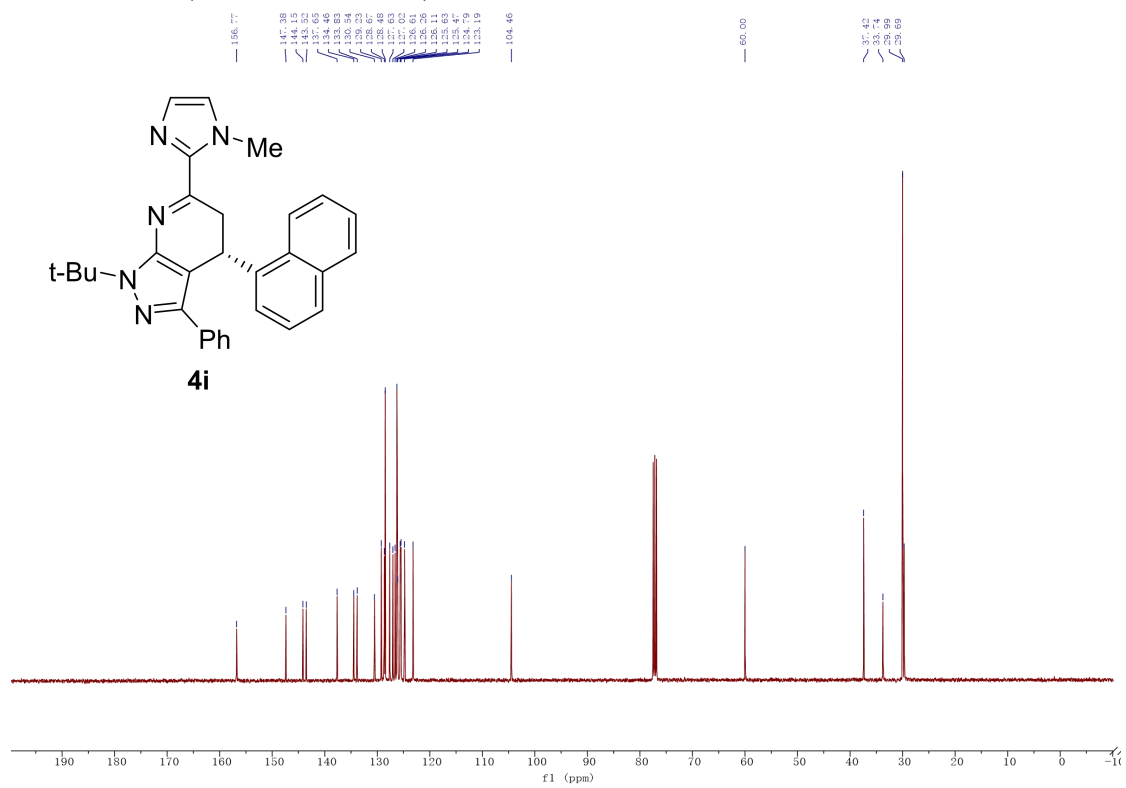
¹³C NMR-4h (100 MHz, CDCl₃)



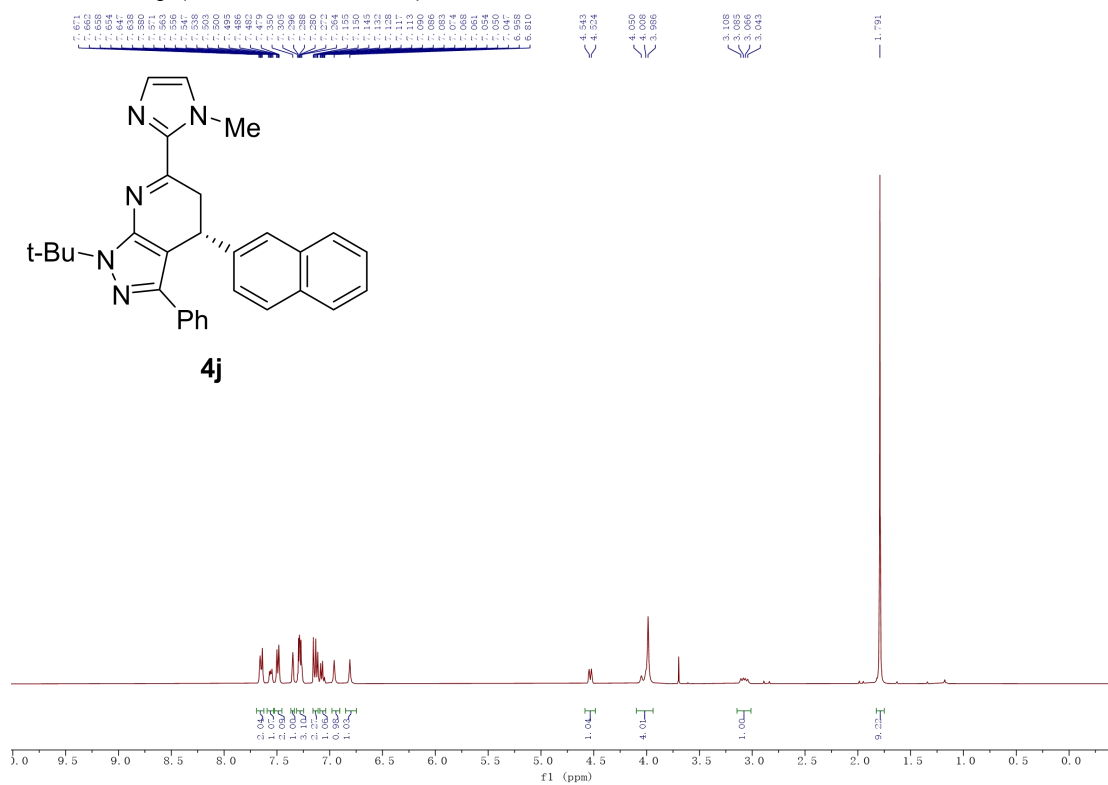
¹H NMR-4i (400 MHz, CDCl₃)



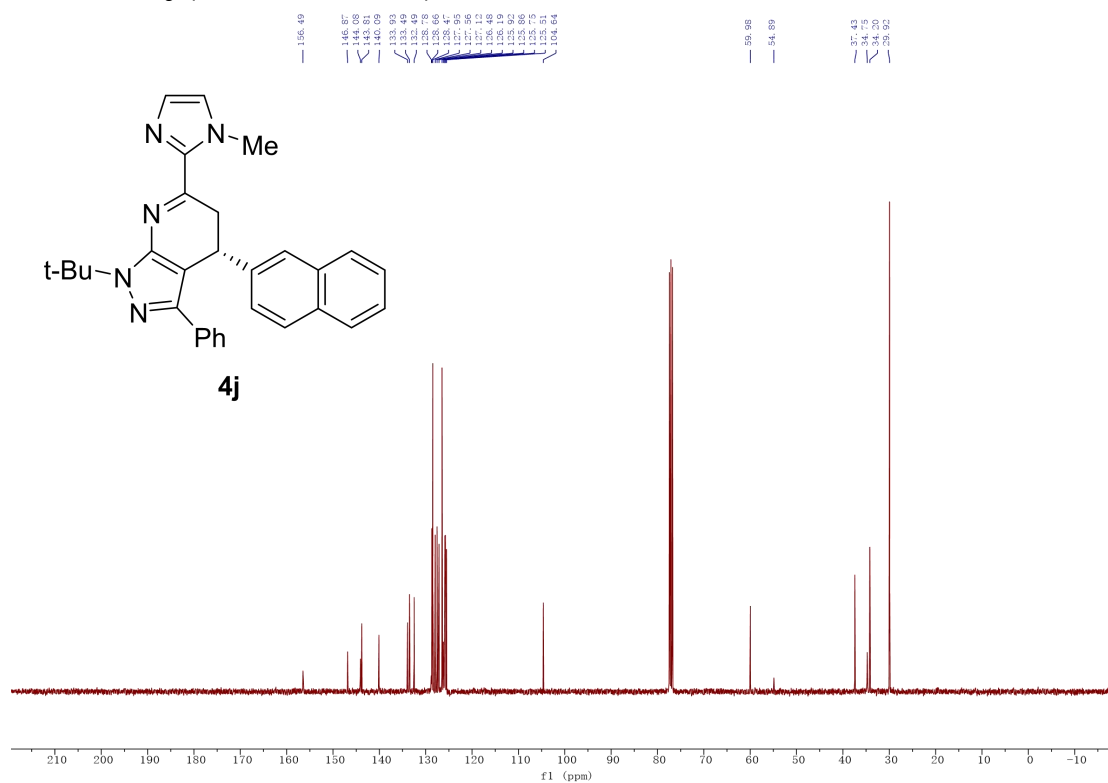
¹³C NMR-4i (100 MHz, CDCl₃)



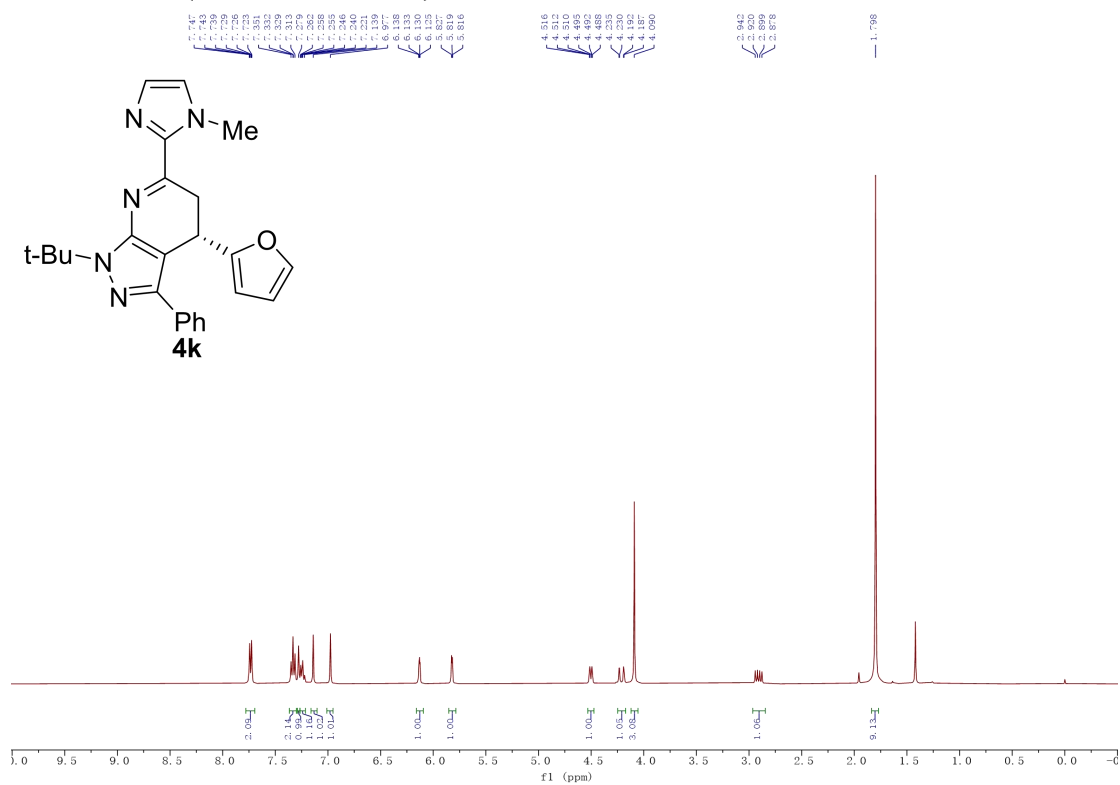
¹H NMR-4j (400 MHz, CDCl₃)



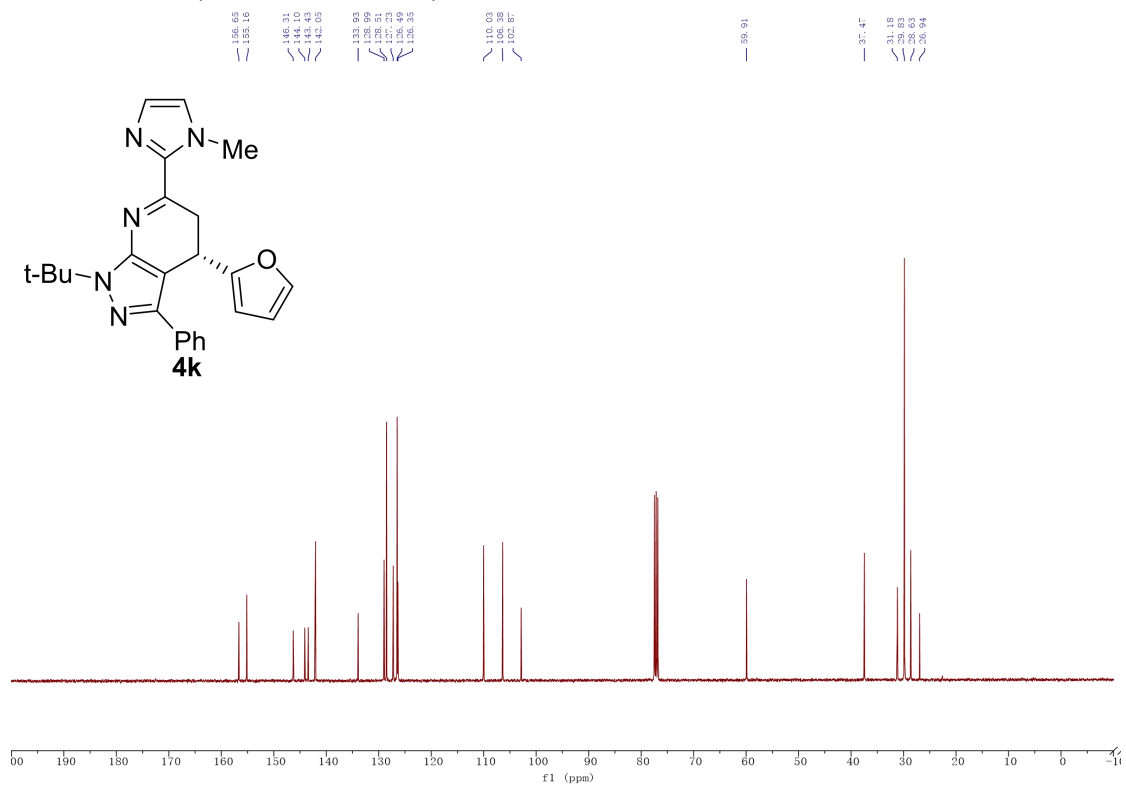
¹³C NMR-4j (100 MHz, CDCl₃)



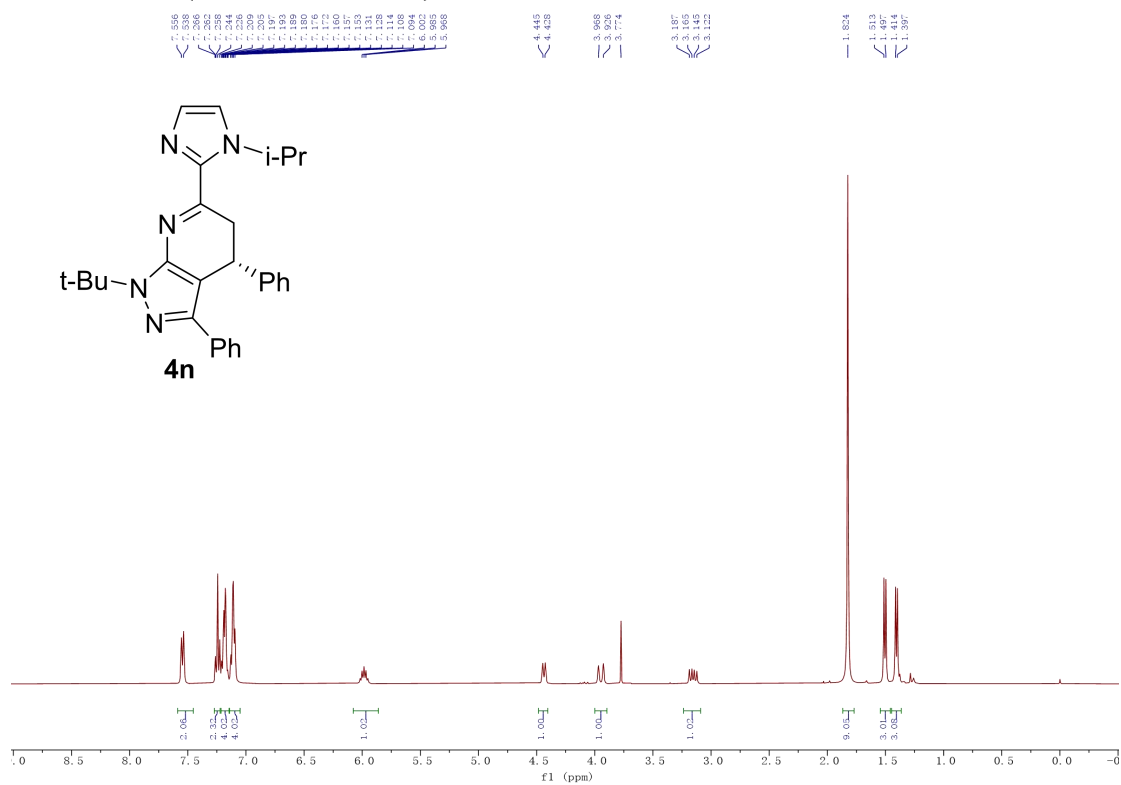
^1H NMR-4k (400 MHz, CDCl_3)



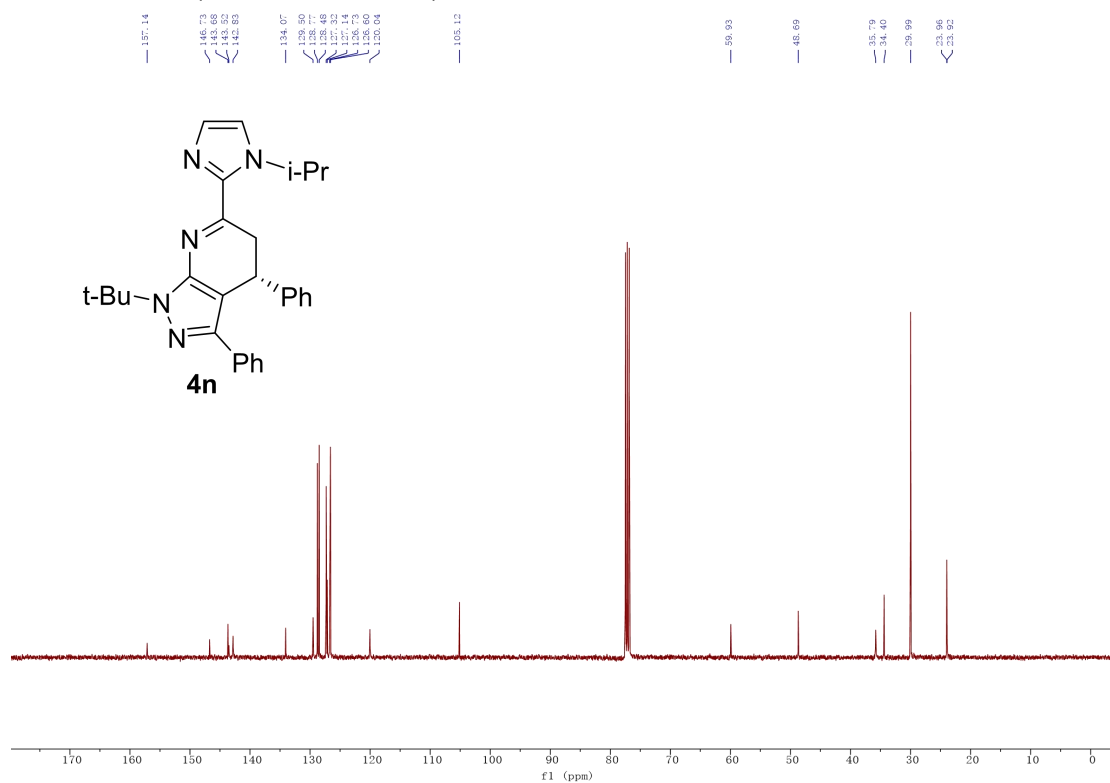
^{13}C NMR-4k (100 MHz, CDCl_3)



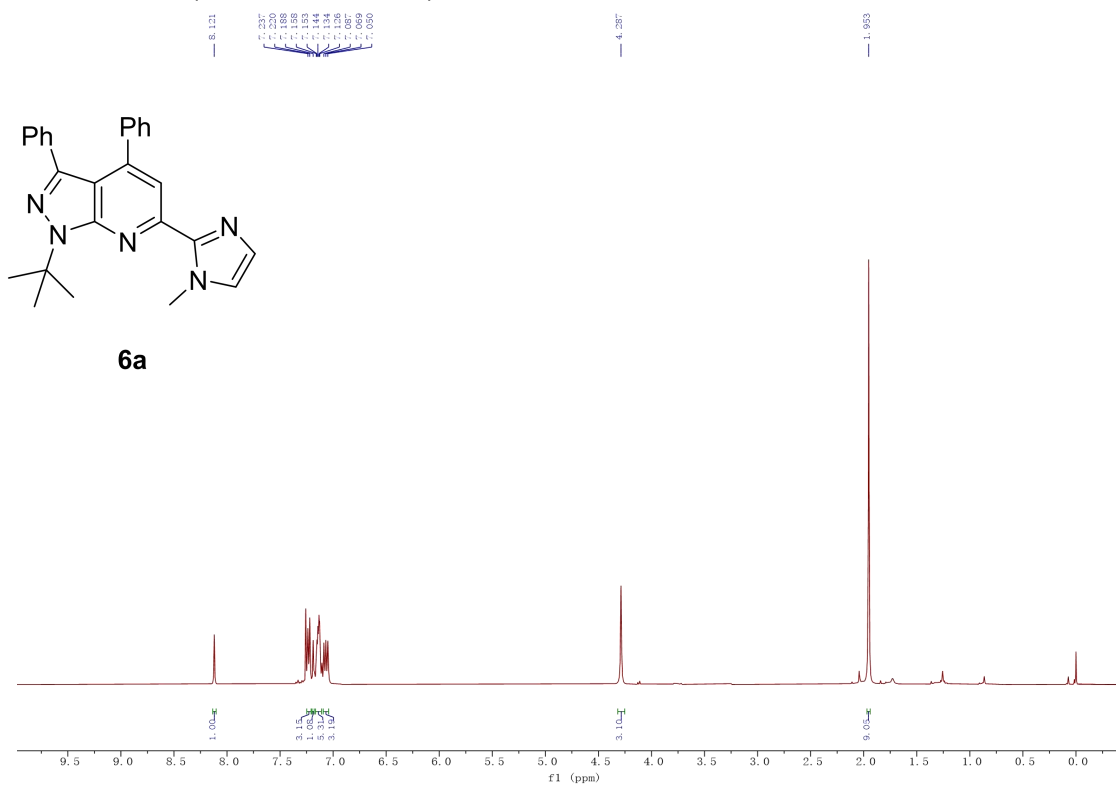
¹H NMR-4n (400 MHz, CDCl₃)



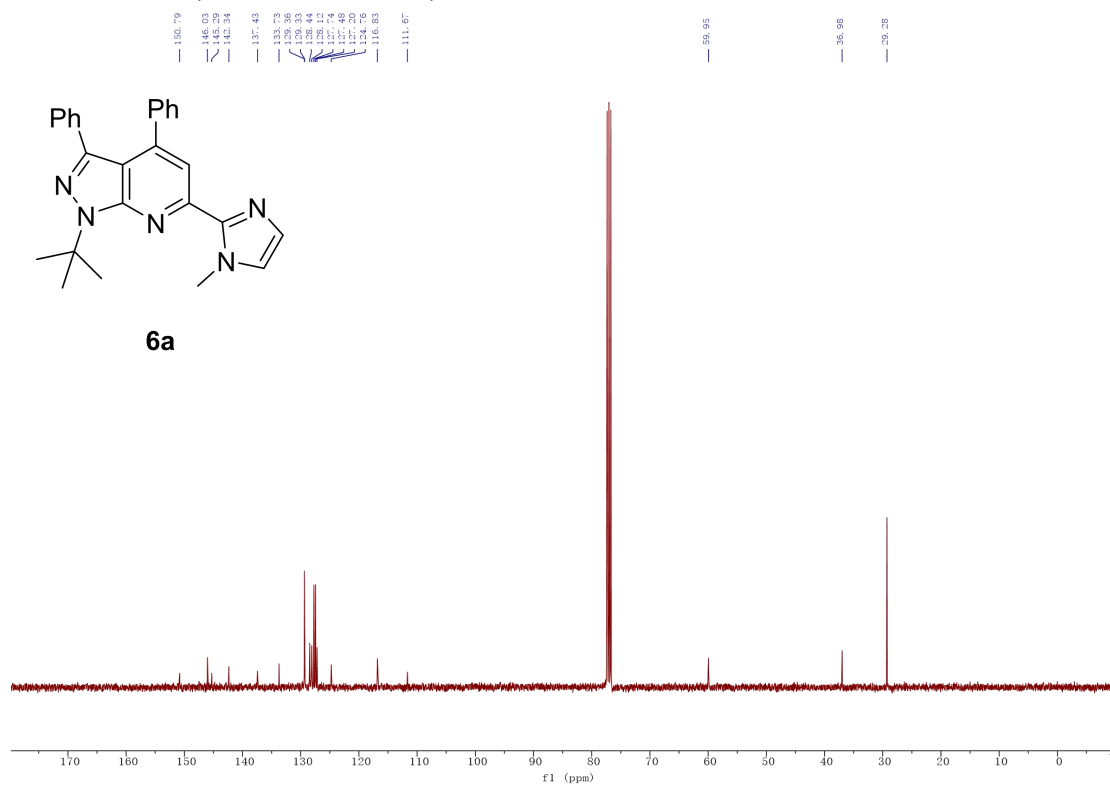
¹³C NMR-4n (100 MHz, CDCl₃)



¹H NMR-6a (400 MHz, CDCl₃)



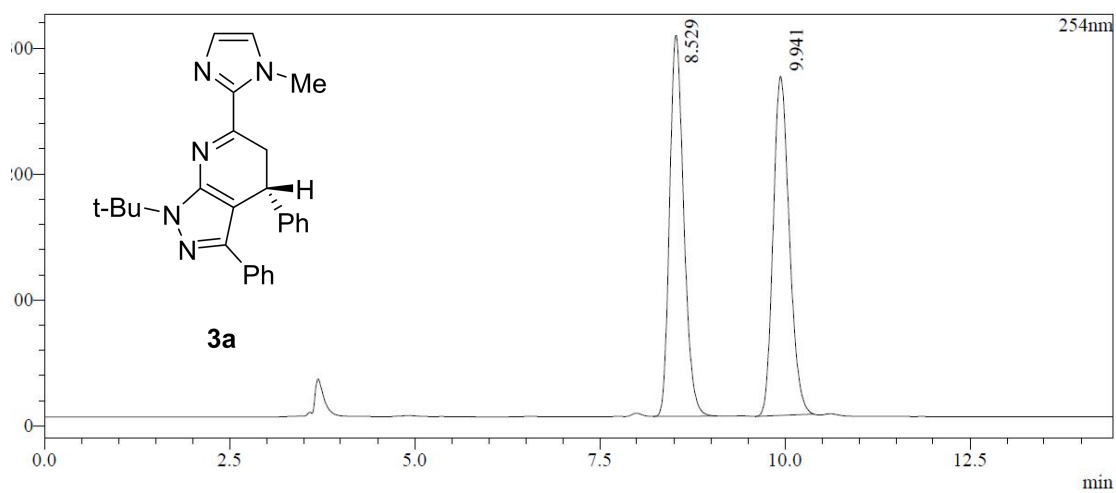
¹³C NMR-6a (100 MHz, CDCl₃)



V Chiral HPLC analysis trace

racemic-3a

Chromatogram

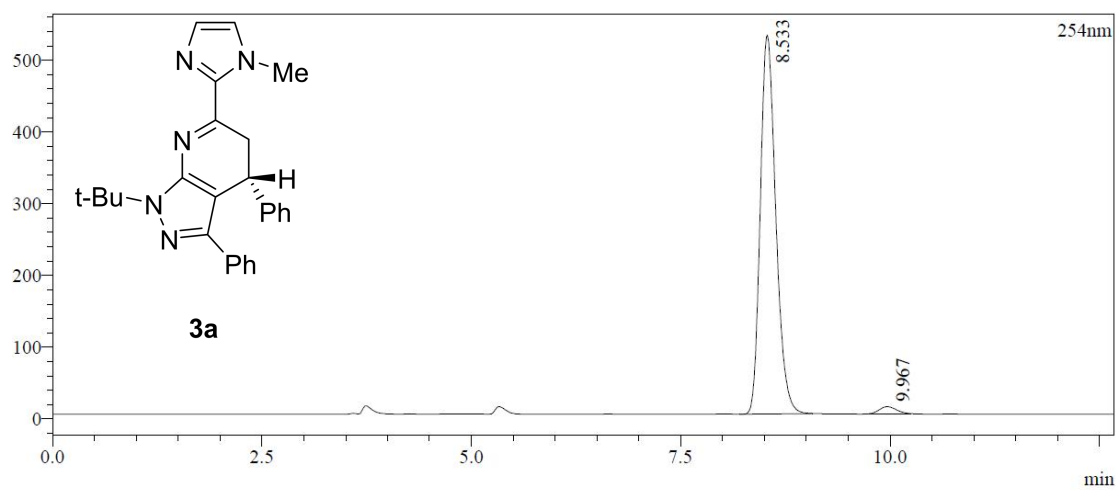


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.529	4034200	302291	49.605
2	9.941	4098496	269366	50.395
Total		8132696	571657	100.000

chiral-3a

Chromatogram

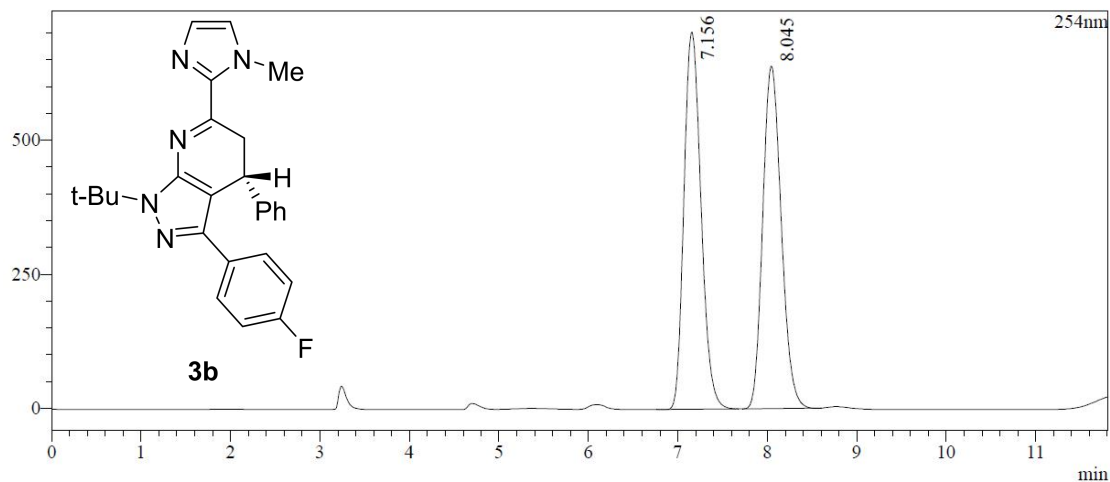


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.533	6799696	528033	98.048
2	9.967	135407	9825	1.952
Total		6935103	537858	100.000

racemic-3b

Chromatogram

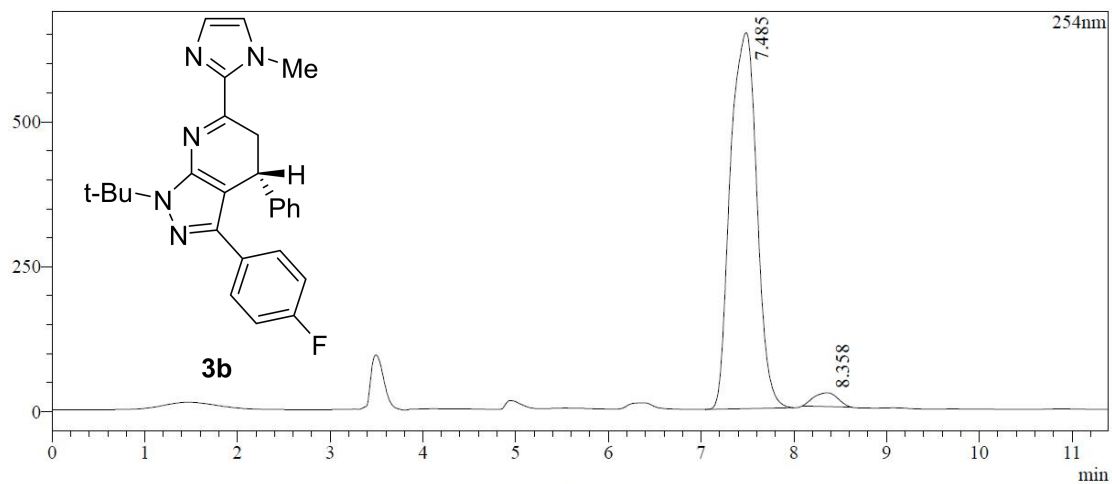


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.156	9330869	703589	50.383
2	8.045	9189128	638341	49.617
Total		18519996	1341930	100.000

chiral-3b

Chromatogram

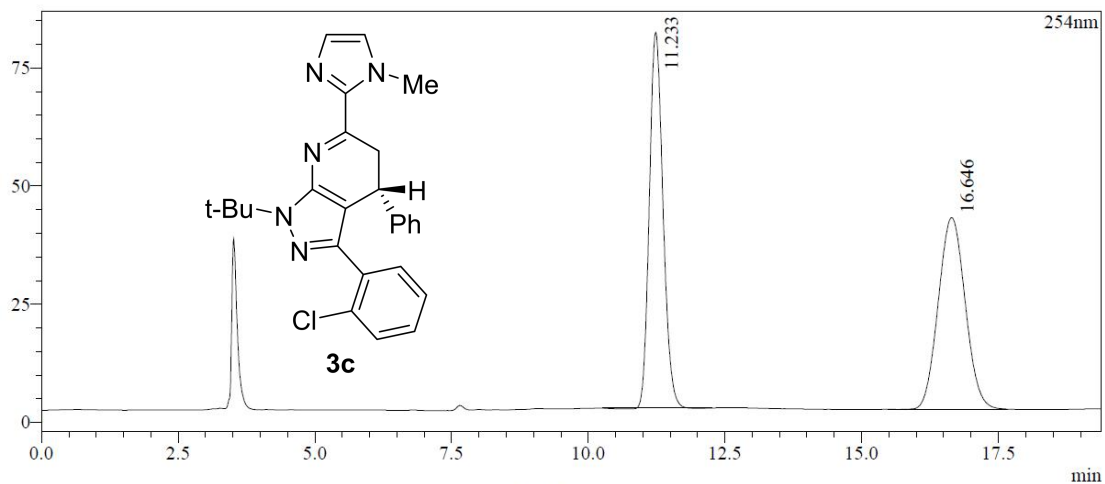


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.485	12865476	648230	96.766
2	8.358	430021	23862	3.234
Total		13295497	672092	100.000

racemic-3c

Chromatogram

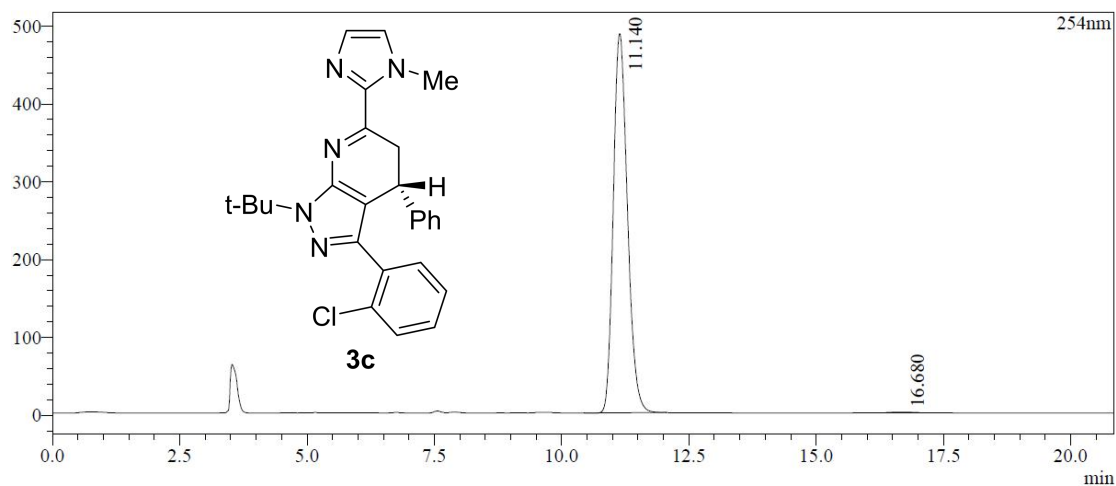


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.233	1378004	79489	49.812
2	16.646	1388405	40535	50.188
Total		2766409	120024	100.000

chiral-3c

Chromatogram

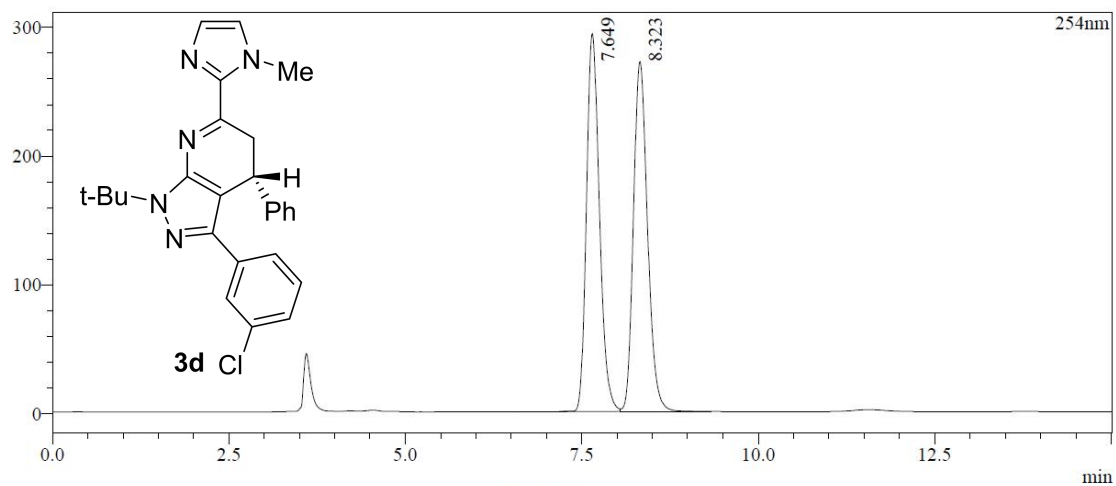


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	11.140	9423661	487562	99.710
2	16.680	27408	946	0.290
Total		9451069	488507	100.000

racemic-3d

Chromatogram

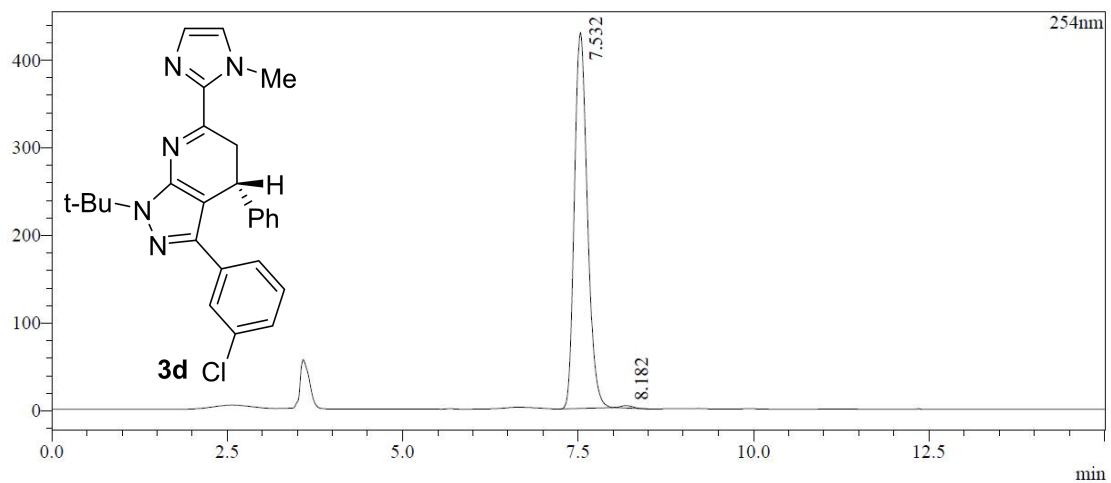


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.649	3761026	293599	49.890
2	8.323	3777538	271860	50.110
Total		7538564	565459	100.000

chiral-3d

Chromatogram

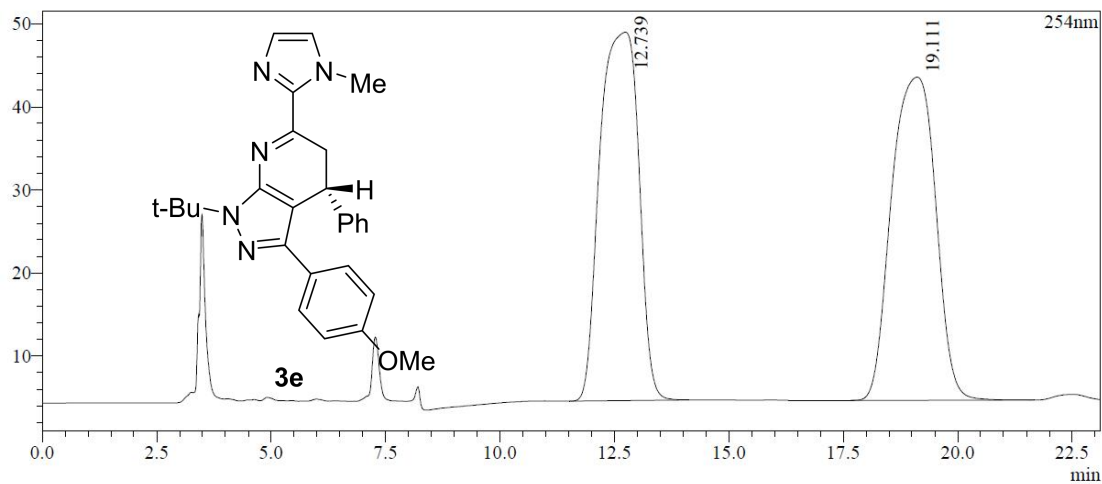


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.532	5539270	429069	99.410
2	8.182	32875	2877	0.590
Total		5572146	431946	100.000

racemic-3e

Chromatogram

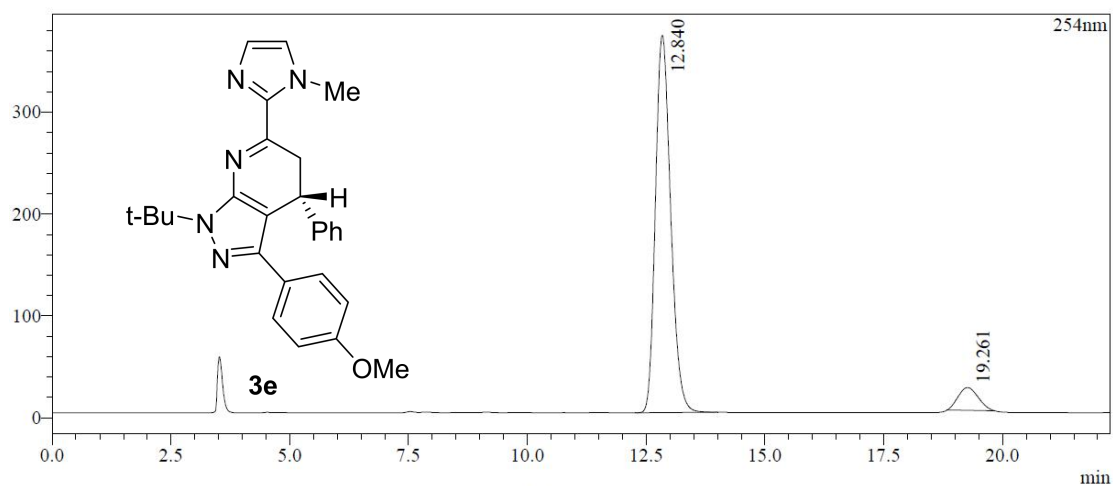


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	12.739	2619172	44325	50.032
2	19.111	2615861	38890	49.968
Total		5235033	83215	100.000

chiral-3e

Chromatogram

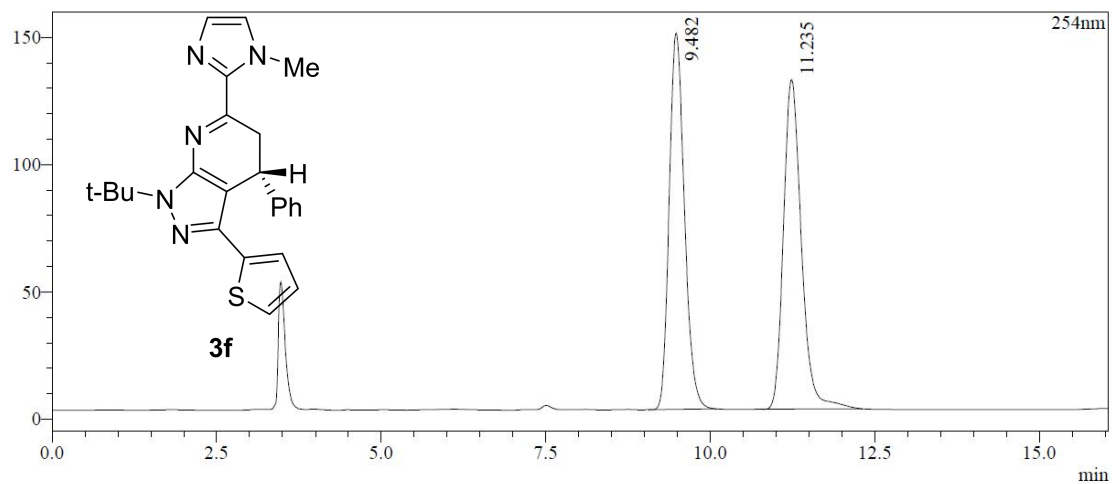


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	12.840	8288464	370675	92.556
2	19.261	666628	22507	7.444
Total		8955092	393182	100.000

racemic-3f

Chromatogram

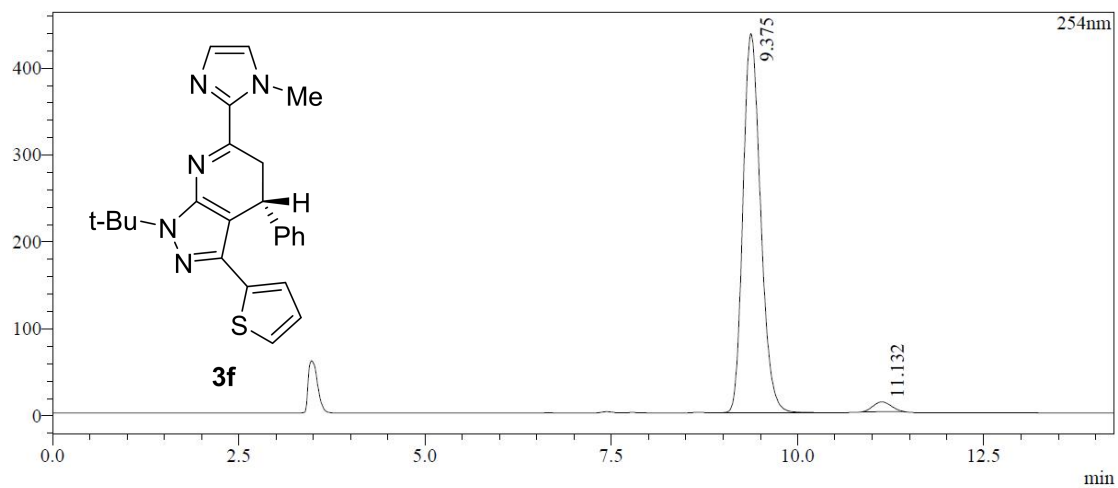


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.482	2378066	147840	49.245
2	11.235	2450995	129419	50.755
Total		4829061	277260	100.000

chiral-3f

Chromatogram

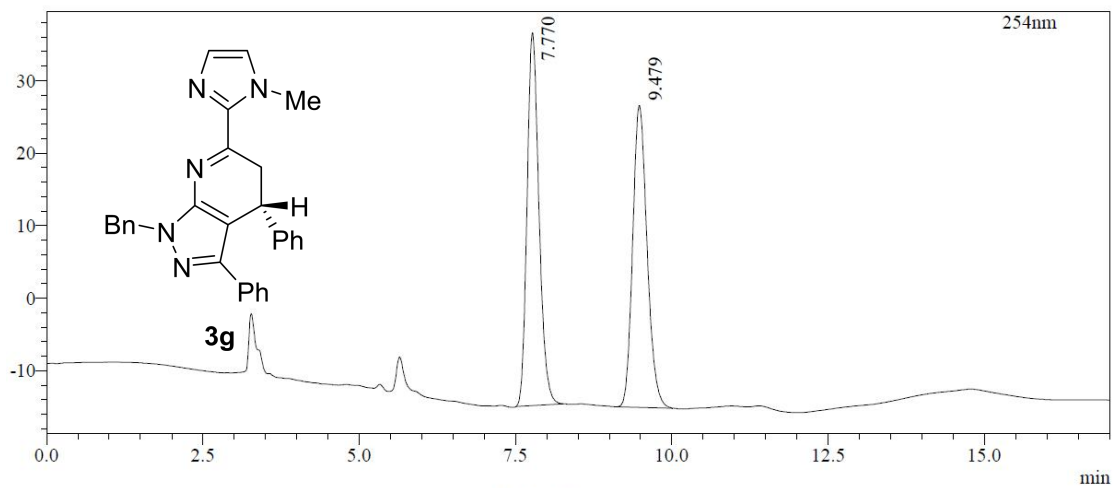


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.375	7165306	436175	97.380
2	11.132	192759	11385	2.620
Total		7358065	447560	100.000

racemic-3g

Chromatogram

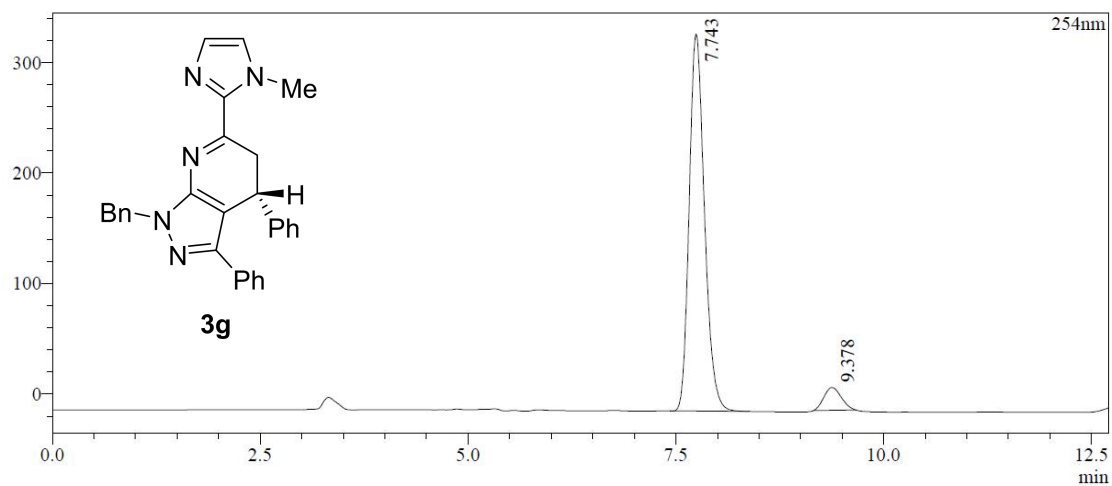


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.770	682035	51410	50.539
2	9.479	667495	41604	49.461
Total		1349530	93015	100.000

chiral-3g

Chromatogram

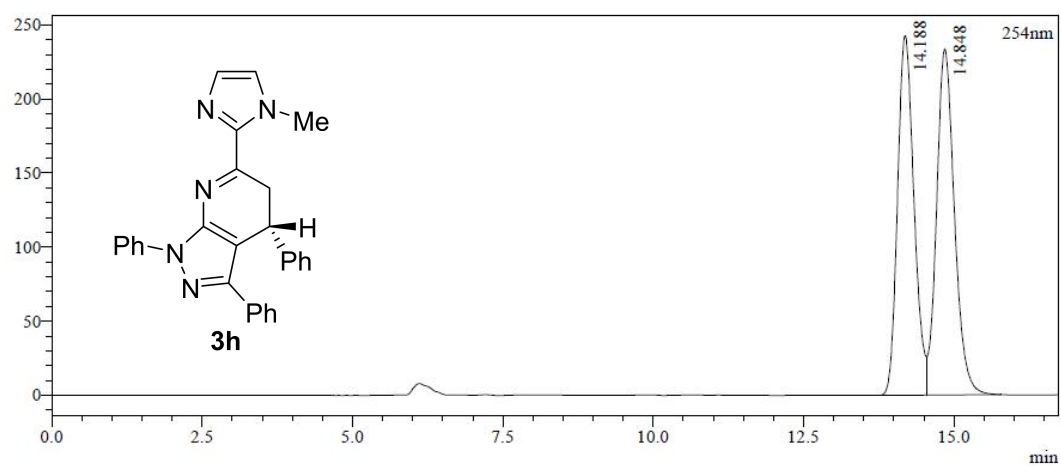


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.743	4364904	341253	93.578
2	9.378	299572	20594	6.422
Total		4664476	361847	100.000

racemic-3h

Chromatogram

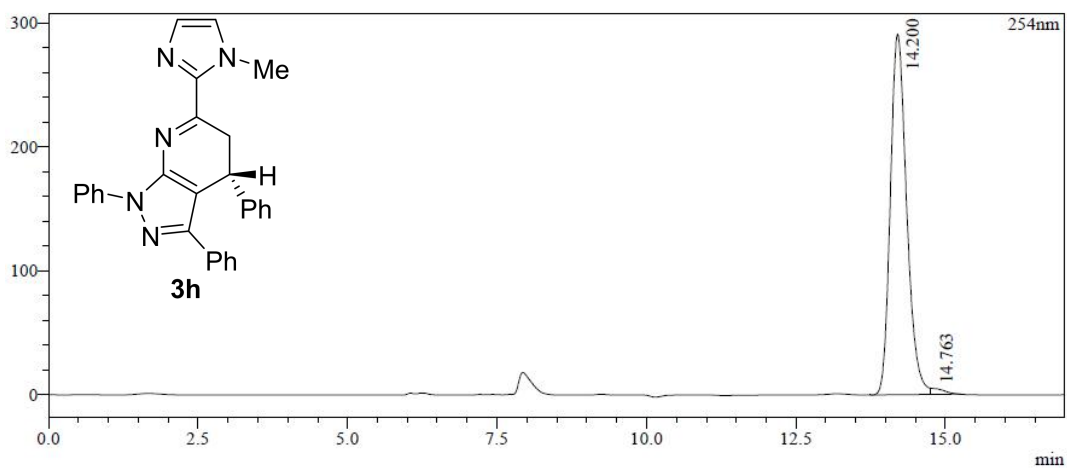


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.188	4613102	242707	48.767
2	14.848	4846341	233485	51.233
		9459443	476192	100.000

chiral-3h

Chromatogram

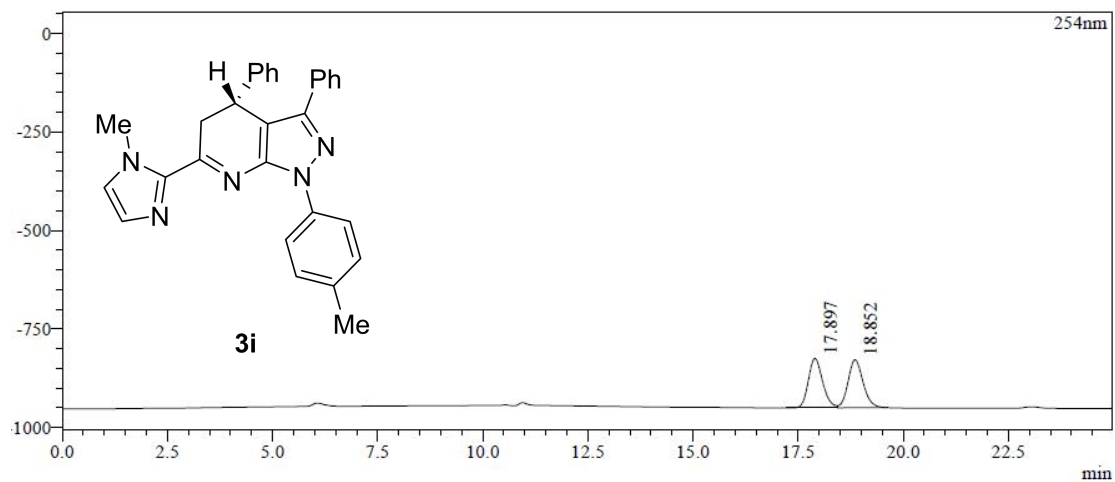


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.200	5521940	290967	98.665
2	14.763	74707	5004	1.335
		5596647	295972	100.000

racemic-3i

Chromatogram

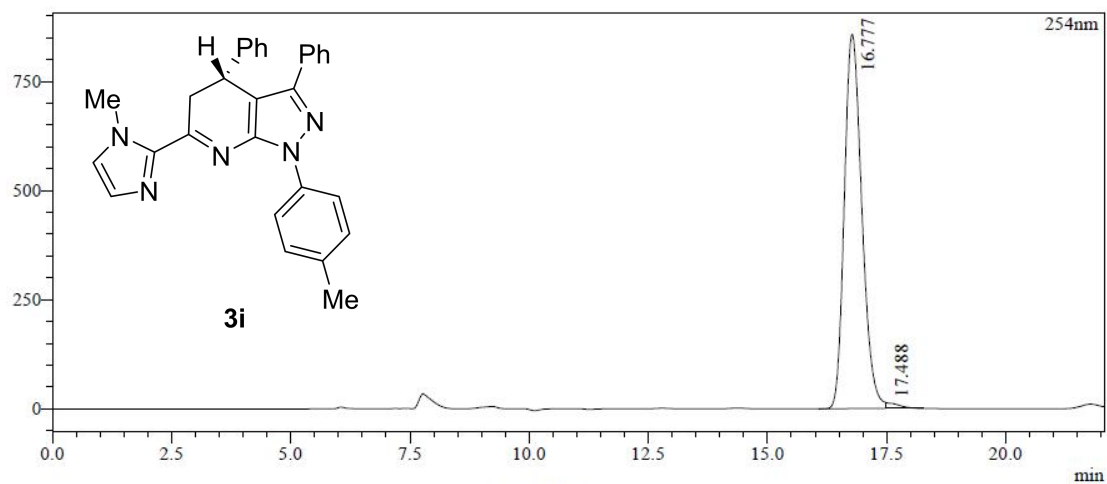


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	17.897	2930501	124833	49.438
2	18.852	2997076	121247	50.562
		5927577	246080	100.000

chiral-3i

Chromatogram

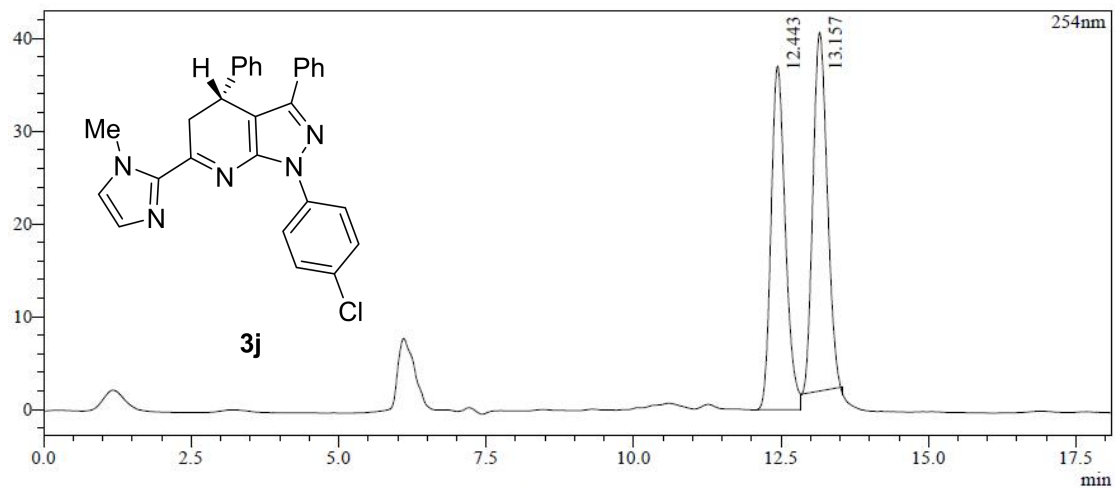


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	16.777	21902449	857021	98.839
2	17.488	257326	13984	1.161
		22159774	871004	100.000

racemic-3j

Chromatogram

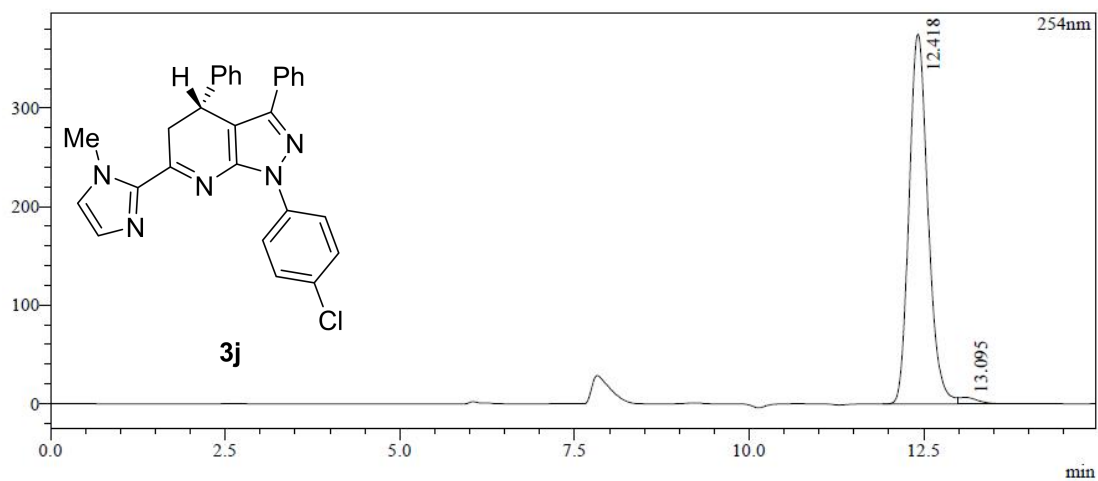


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	12.443	627162	37027	49.105
2	13.157	650020	38659	50.895
		1277182	75685	100.000

chiral-3j

Chromatogram

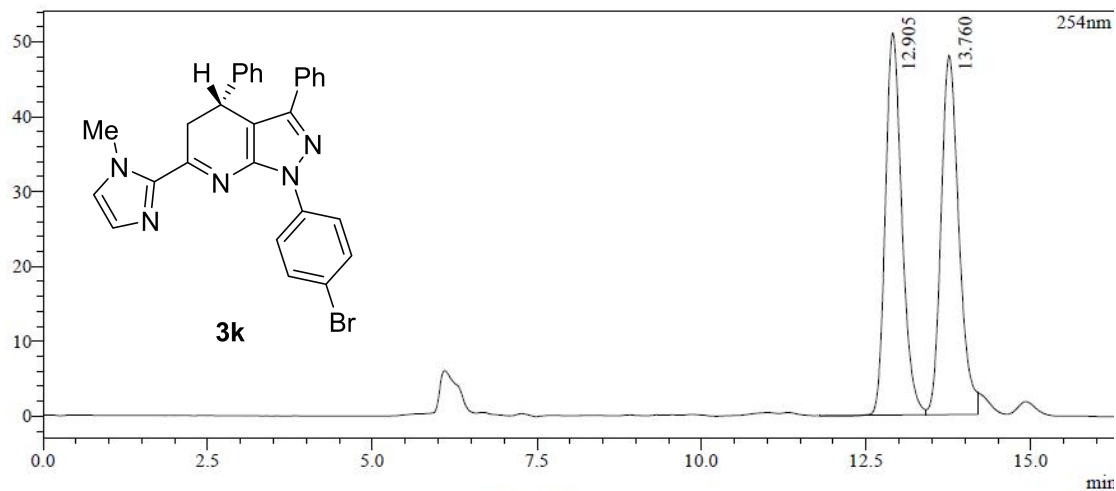


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	12.418	7069965	375266	98.398
2	13.095	115104	6356	1.602
		7185069	381622	100.000

racemic-3k

Chromatogram

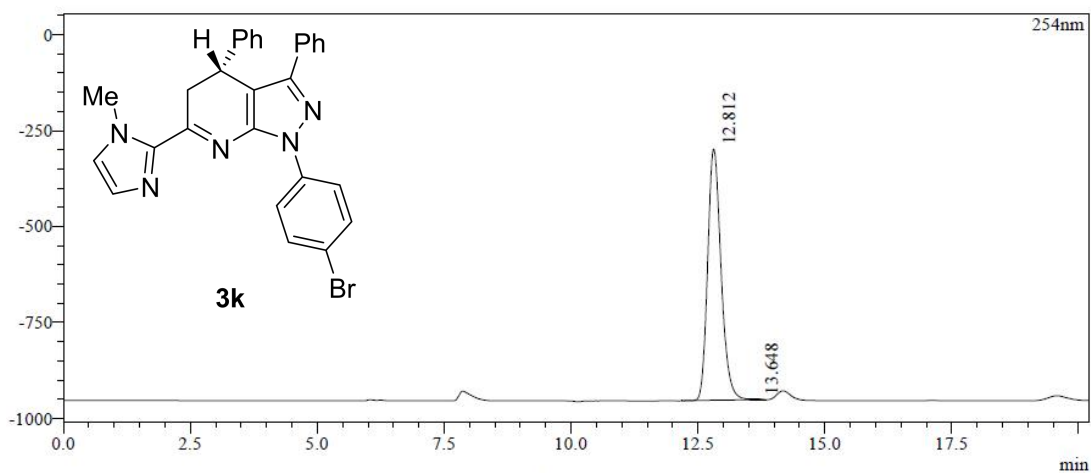


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	12.905	886822	51045	49.572
2	13.760	902121	47953	50.428
		1788943	98998	100.000

chiral-3k

Chromatogram

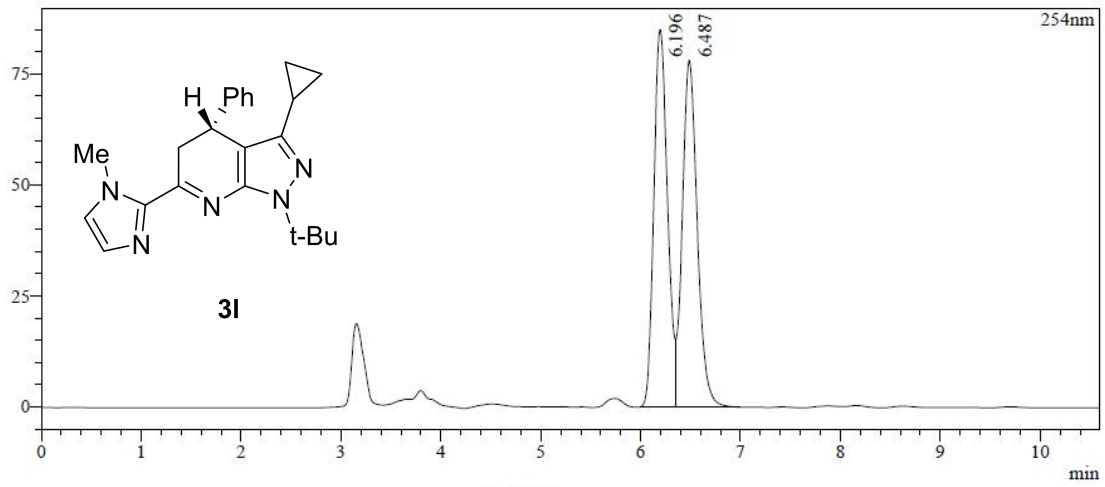


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	12.812	12018362	654354	99.736
2	13.648	31772	2355	0.264
		12050135	656708	100.000

racemic-3l

Chromatogram

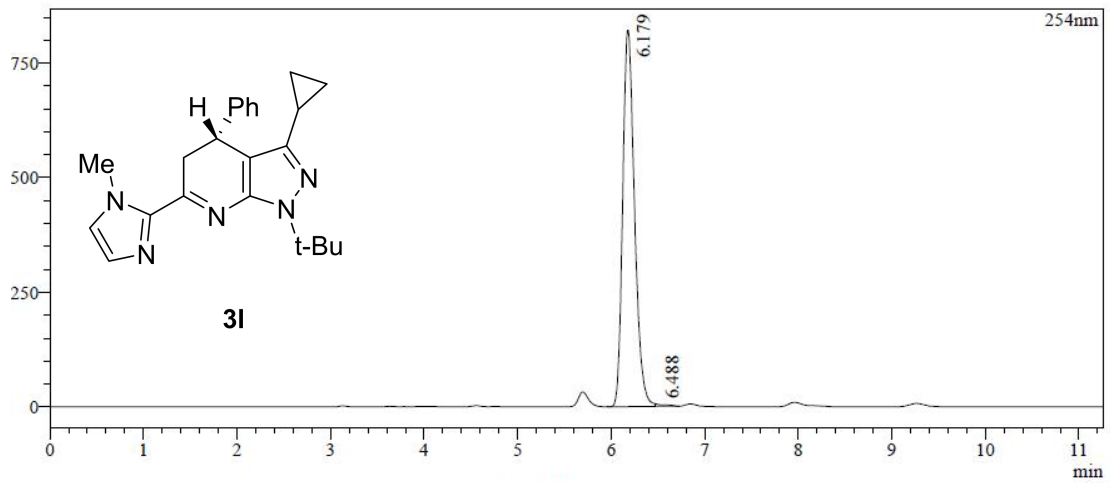


254nm

Peak#	Ret. Time	Area	Height	Area%
1	6.196	807894	84916	49.885
2	6.487	811630	78106	50.115
		1619524	163022	100.000

chiral-3l

Chromatogram

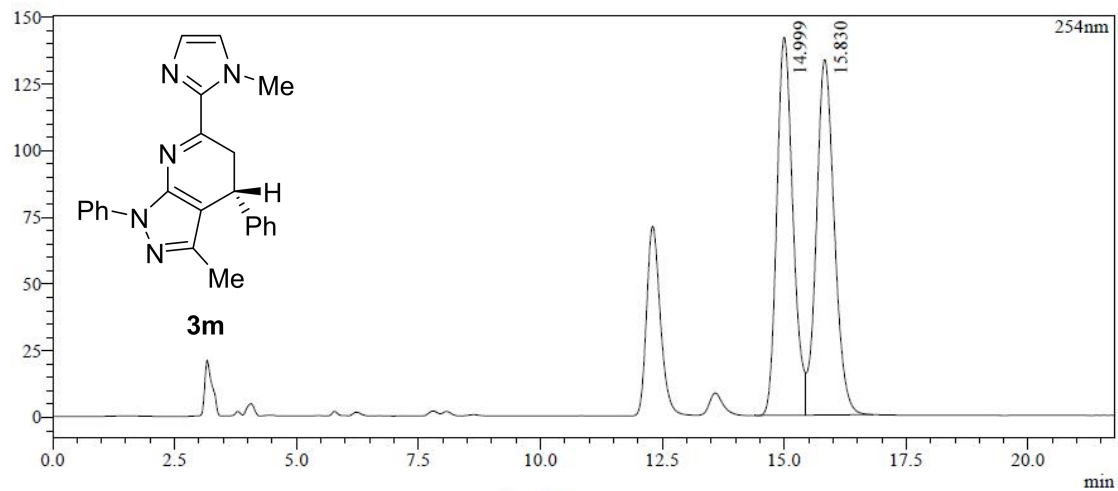


254nm

Peak#	Ret. Time	Area	Height	Area%
1	6.179	7210355	820607	99.502
2	6.488	36096	4917	0.498
		7246450	825524	100.000

racemic-3m

Chromatogram

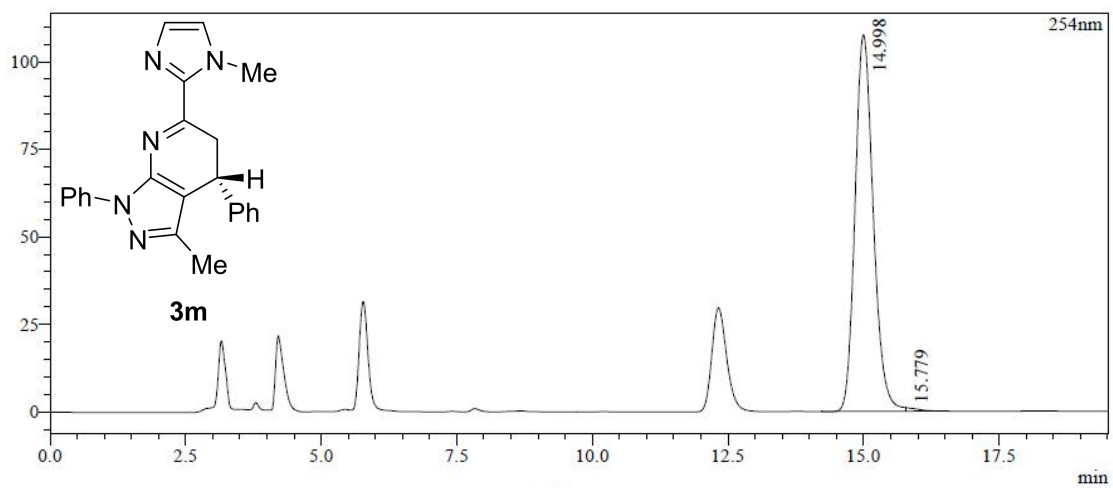


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.999	3266869	141801	48.922
2	15.830	3410774	133274	51.078
		6677642	275075	100.000

chiral-3m

Chromatogram

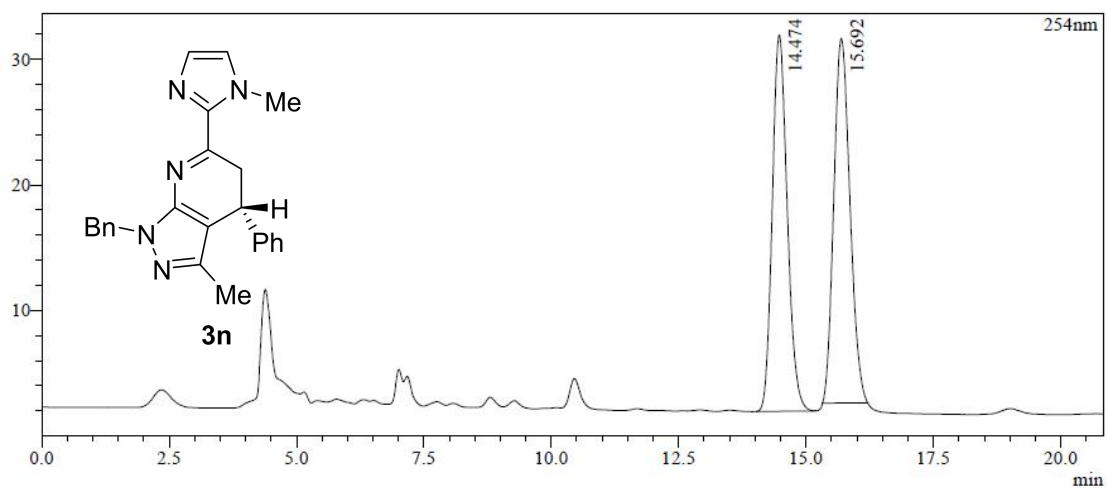


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.998	2514134	107641	99.418
2	15.779	14712	1035	0.582
		2528845	108676	100.000

racemic-3n

Chromatogram

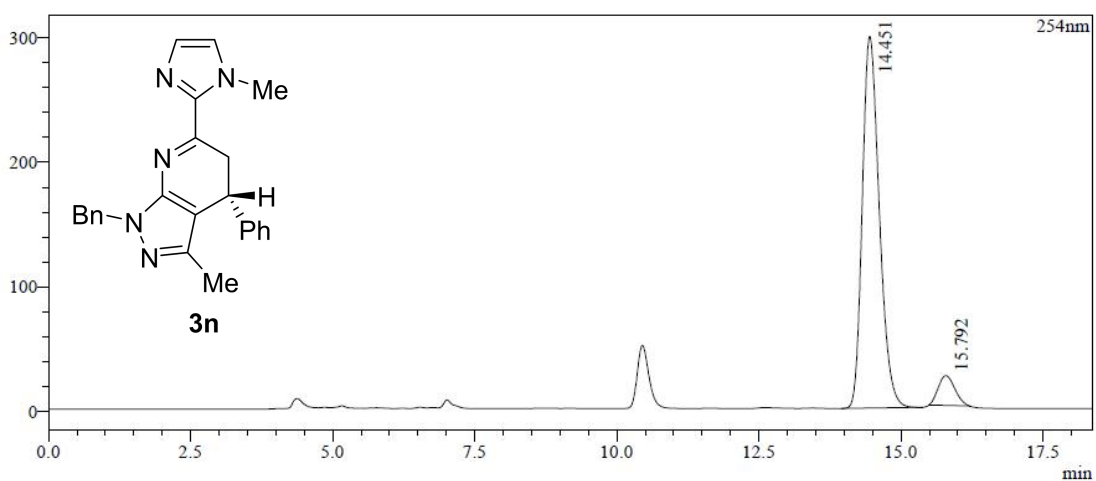


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.474	613409	29968	48.942
2	15.692	639932	29019	51.058
		1253341	58987	100.000

chiral-3n

Chromatogram

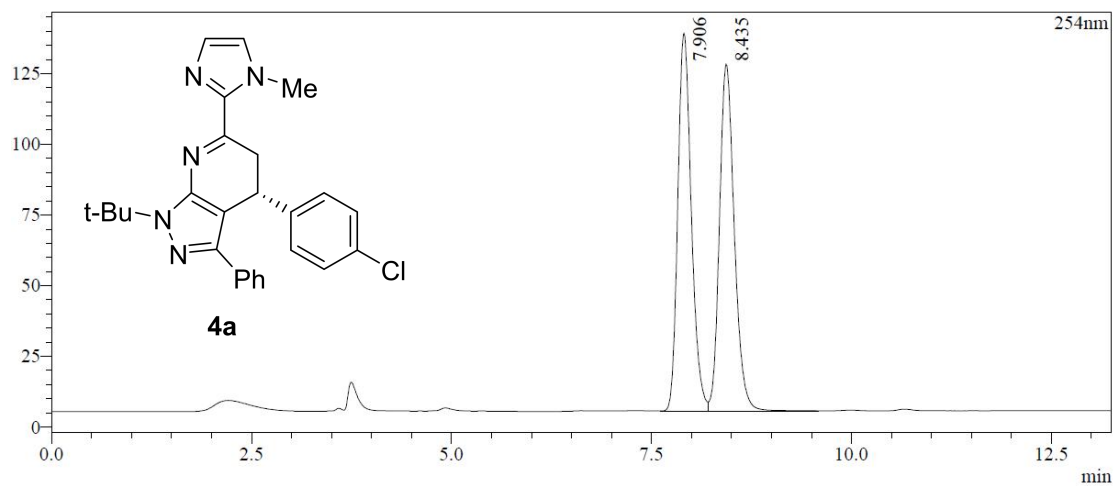


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	14.451	6200253	298373	92.711
2	15.792	487503	23950	7.289
		6687757	322323	100.000

racemic-4a

Chromatogram

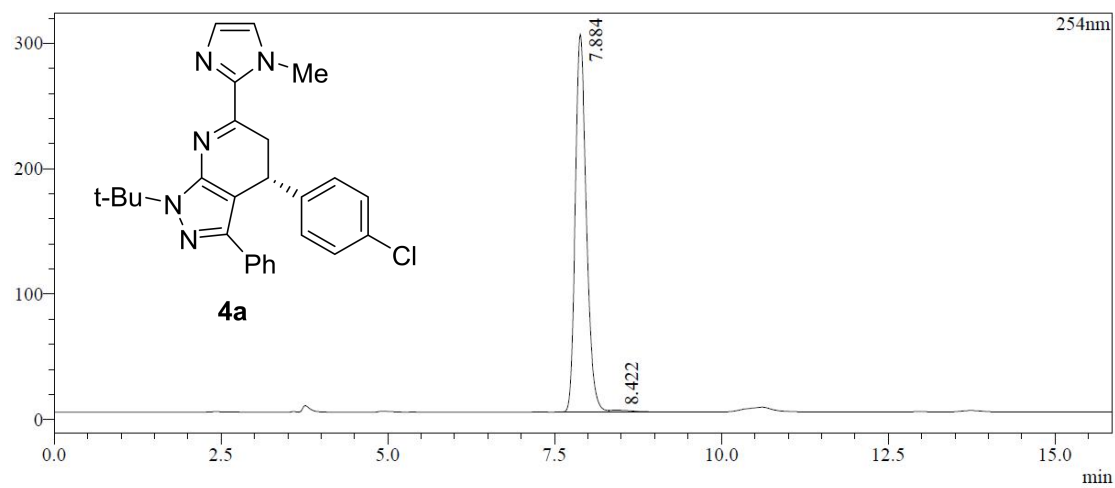


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.906	1572401	133604	49.822
2	8.435	1583627	122618	50.178
Total		3156028	256222	100.000

chiral-4a

Chromatogram

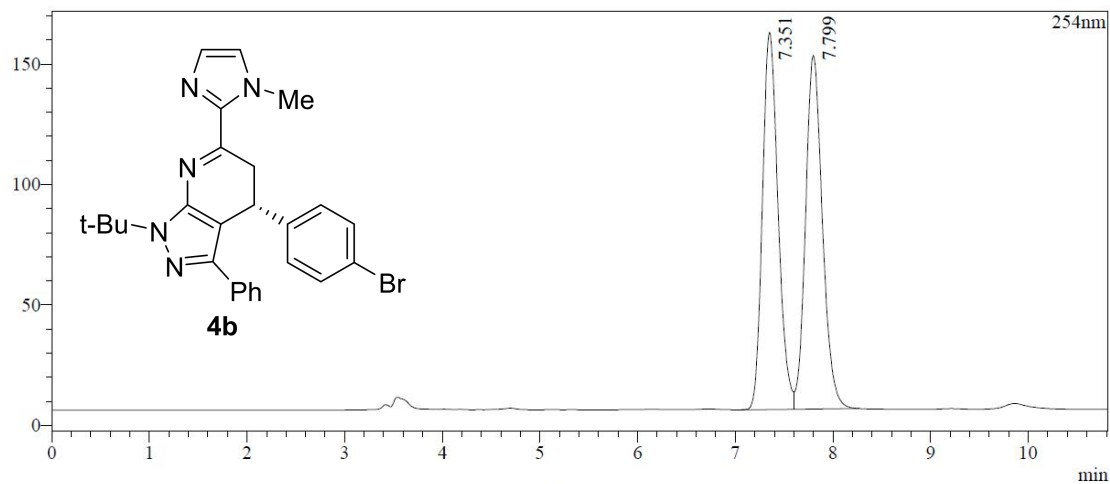


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.884	3466392	301177	99.172
2	8.422	28944	1433	0.828
Total		3495336	302610	100.000

racemic-4b

Chromatogram

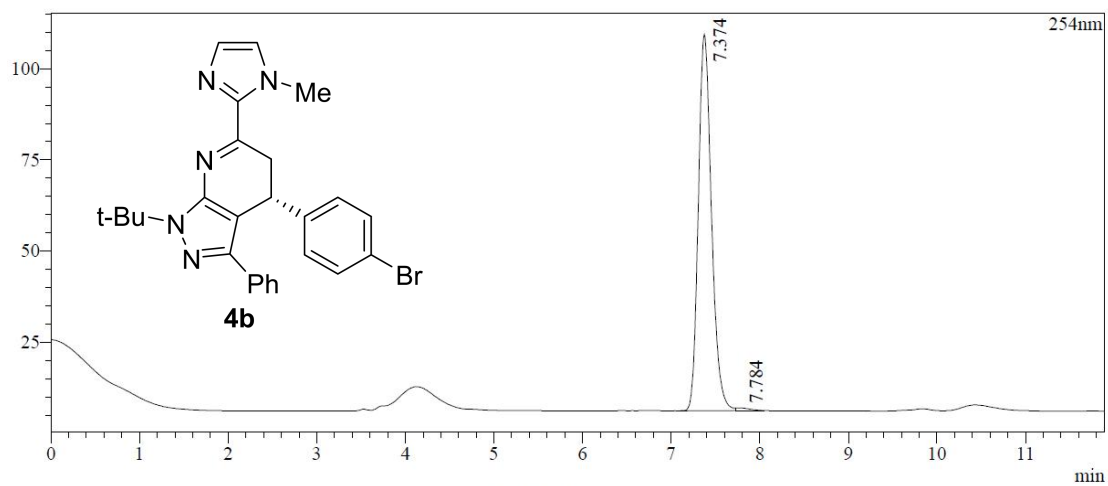


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.351	1741083	156490	49.644
2	7.799	1766028	146682	50.356
Total		3507110	303172	100.000

chiral-4b

Chromatogram

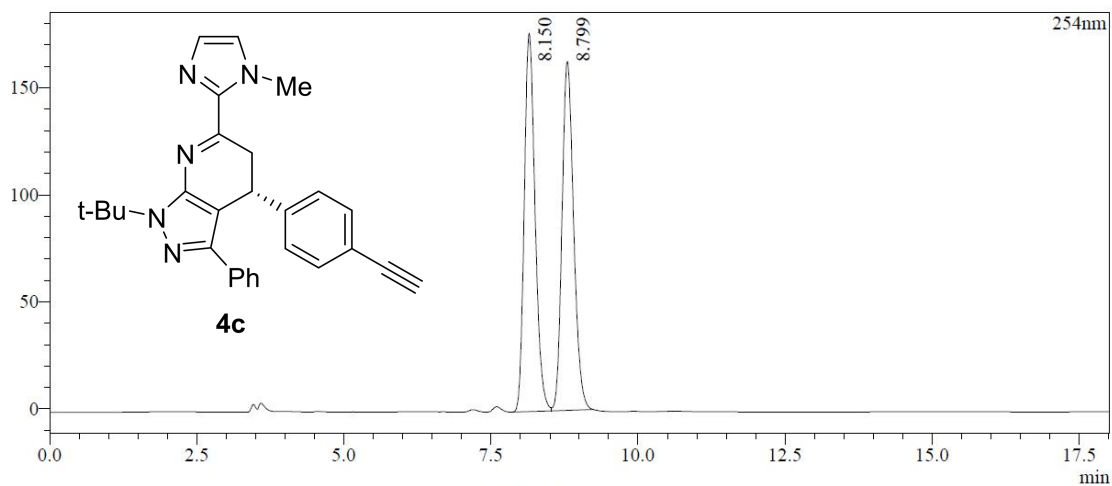


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.374	1068662	103215	99.328
2	7.784	7227	709	0.672
Total		1075889	103924	100.000

racemic-4c

Chromatogram

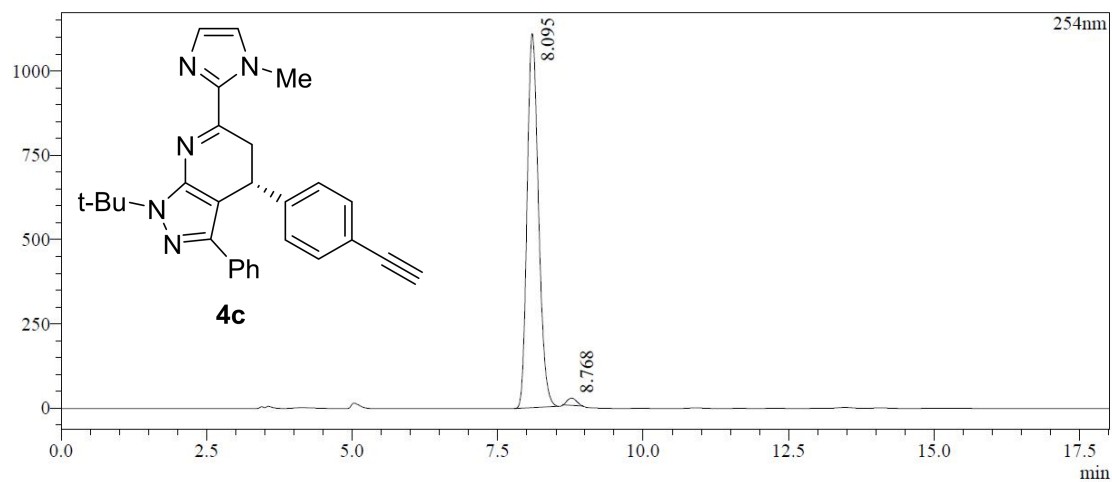


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.150	2262010	176620	50.203
2	8.799	2243673	162941	49.797
Total		4505683	339561	100.000

chiral-4c

Chromatogram

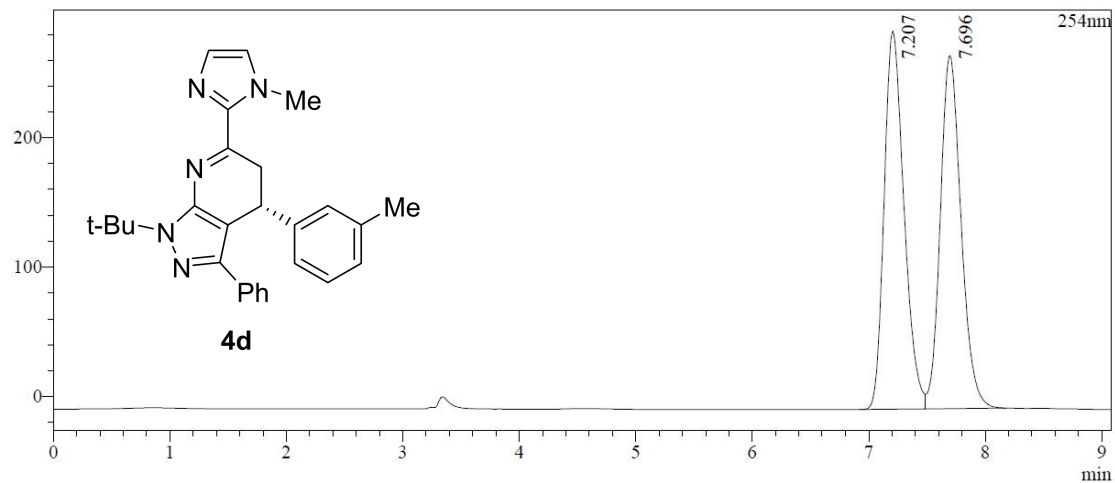


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.095	15120055	1109263	98.442
2	8.768	239235	21565	1.558
Total		15359290	1130828	100.000

racemic-4d

Chromatogram

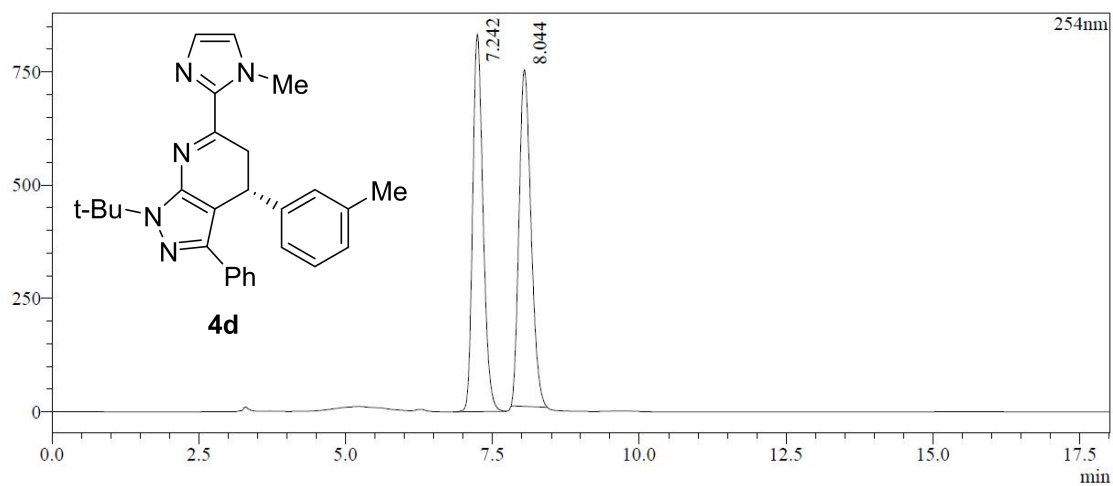


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.207	3466104	292344	50.560
2	7.696	3389256	272675	49.440
Total		6855360	565019	100.000

chiral-4d

Chromatogram

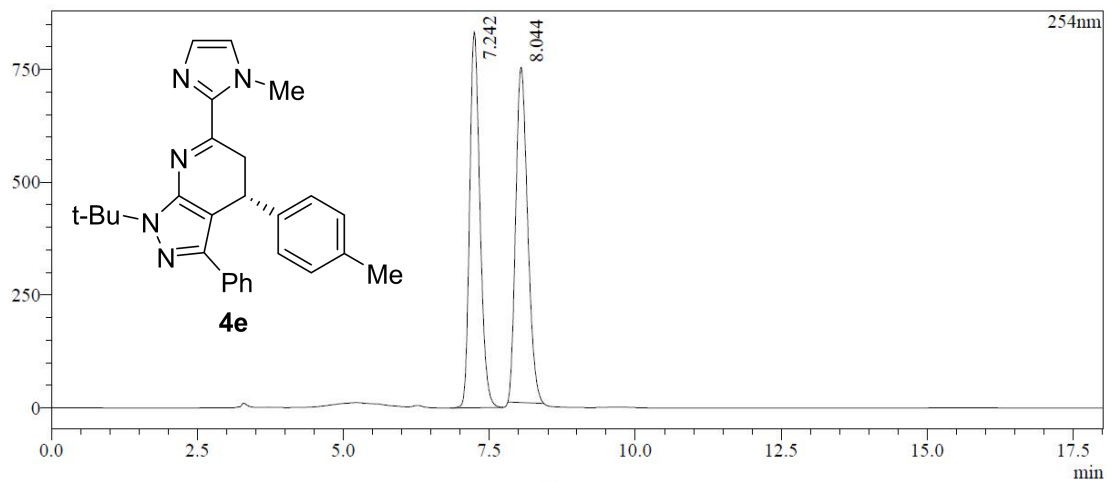


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.242	10242127	832767	49.266
2	8.044	10547434	742323	50.734
Total		20789560	1575089	100.000

racemic-4e

Chromatogram

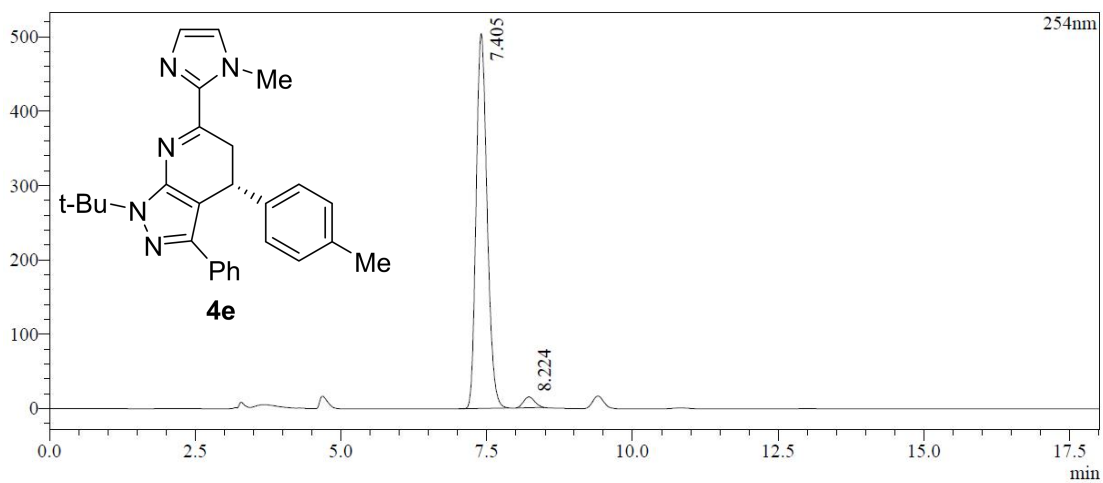


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.242	10242127	832767	49.266
2	8.044	10547434	742323	50.734
Total		20789560	1575089	100.000

chiral-4e

Chromatogram

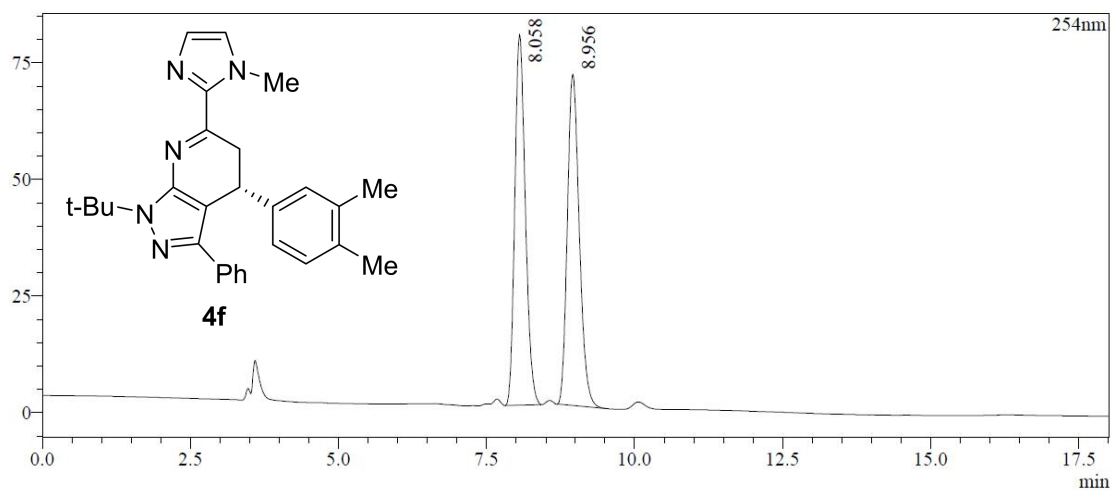


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.405	6594510	504106	97.170
2	8.224	192045	14495	2.830
Total		6786555	518600	100.000

racemic-4f

Chromatogram

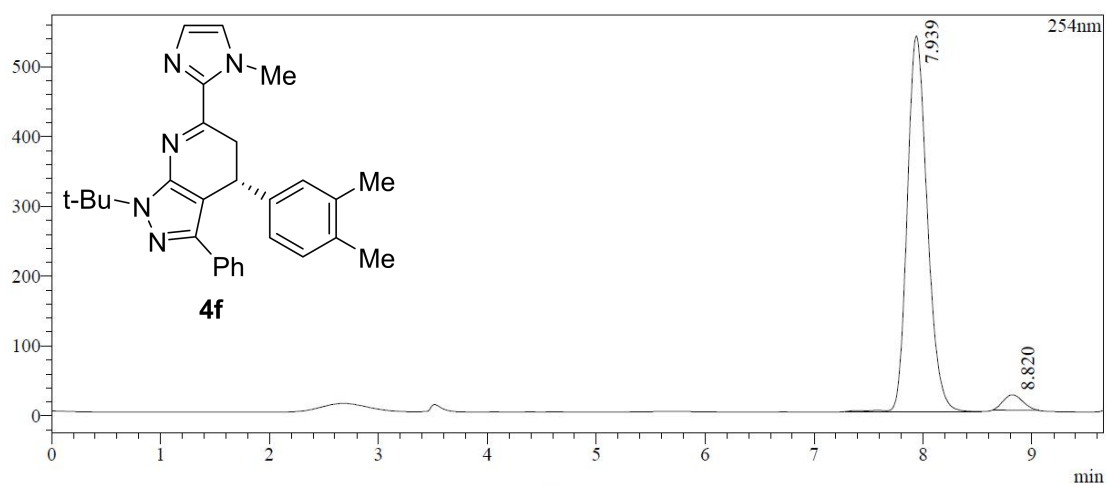


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.058	984102	79438	49.722
2	8.956	995096	71035	50.278
Total		1979198	150473	100.000

chiral-4f

Chromatogram

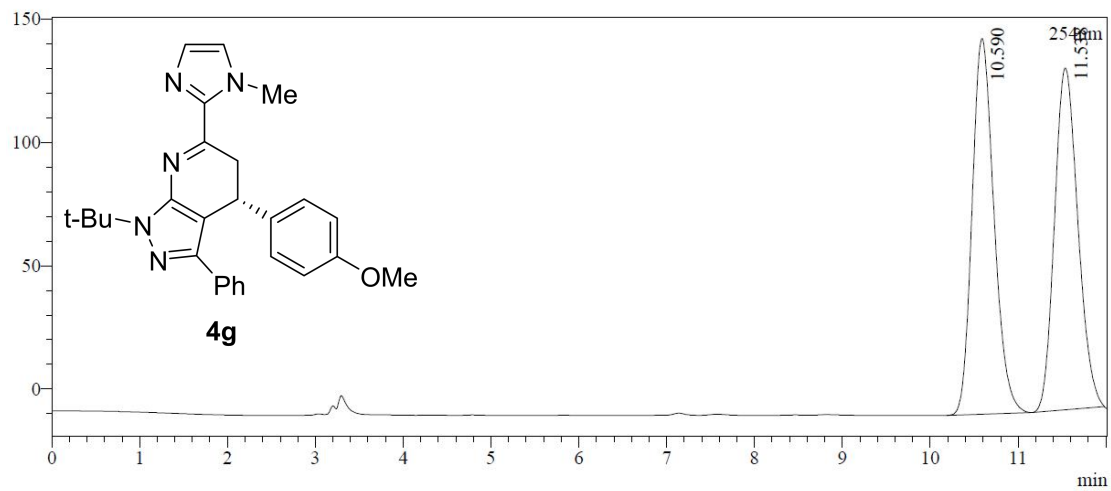


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.939	6879353	537982	96.195
2	8.820	272097	21942	3.805
Total		7151450	559924	100.000

racemic-4g

Chromatogram

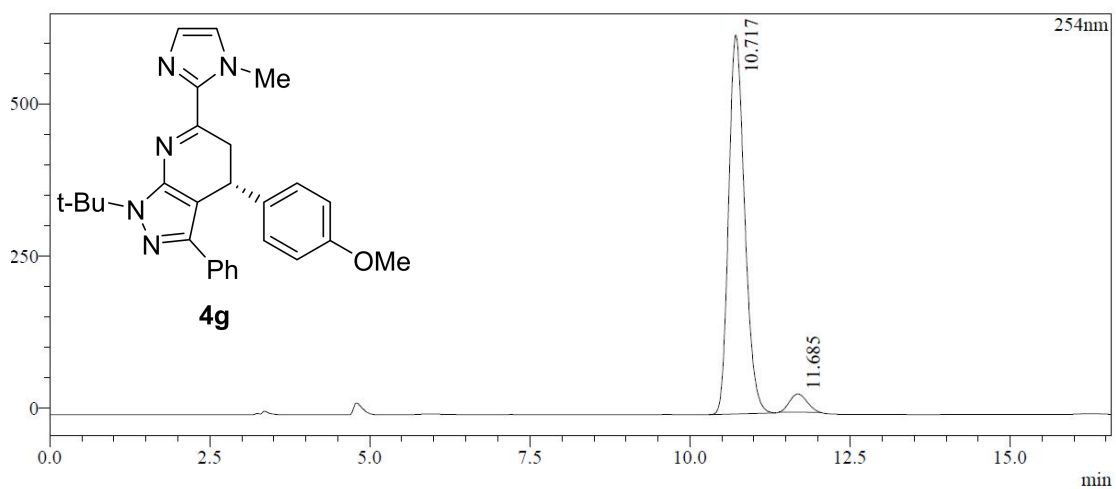


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.590	2630948	152303	50.649
2	11.538	2563513	138504	49.351
Total		5194462	290807	100.000

chiral-4g

Chromatogram

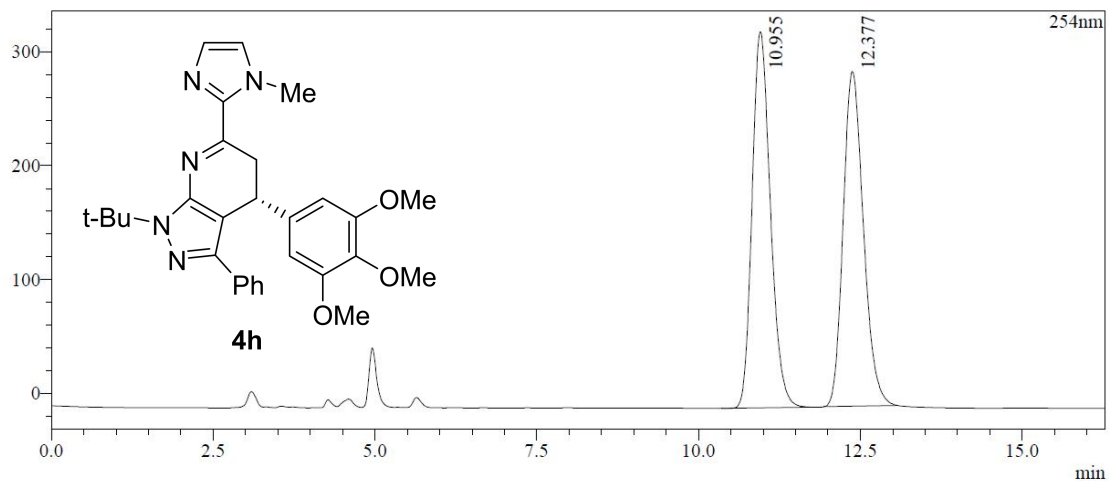


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.717	10833603	622991	95.062
2	11.685	562721	29968	4.938
Total		11396324	652958	100.000

racemic-4h

Chromatogram

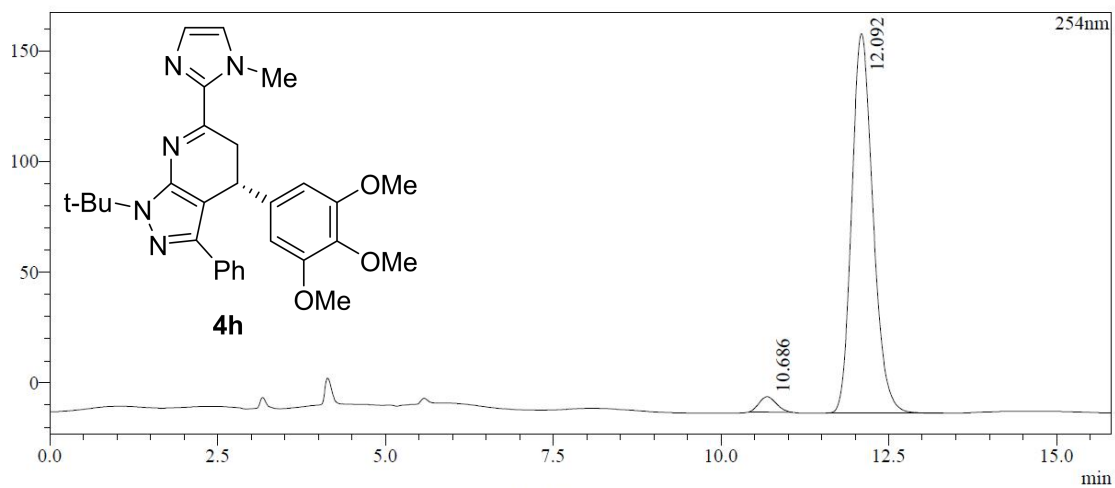


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.955	6495378	330081	50.414
2	12.377	6388813	293801	49.586
Total		12884191	623883	100.000

chiral-4h

Chromatogram

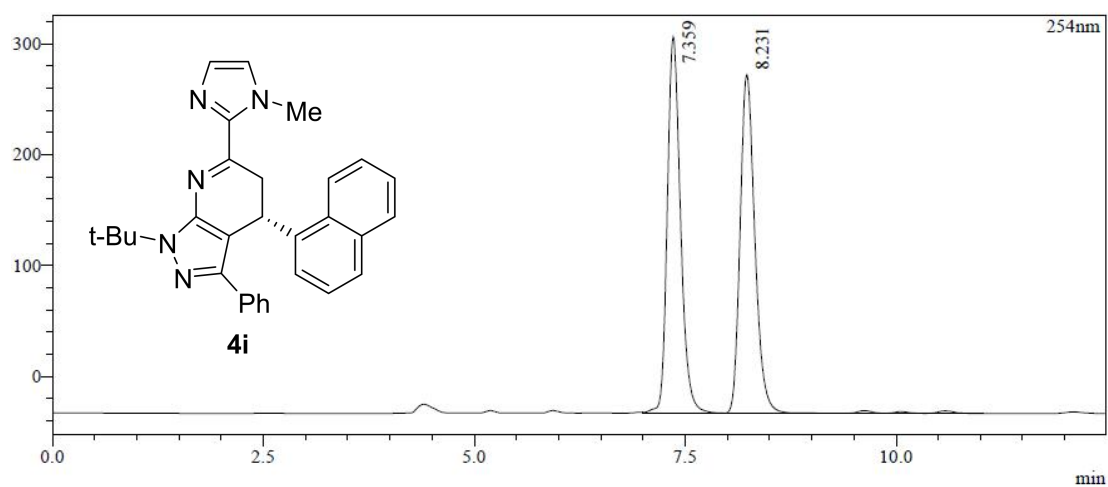


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	10.686	124458	6947	3.190
2	12.092	3777250	171474	96.810
Total		3901708	178421	100.000

racemic-4i

Chromatogram

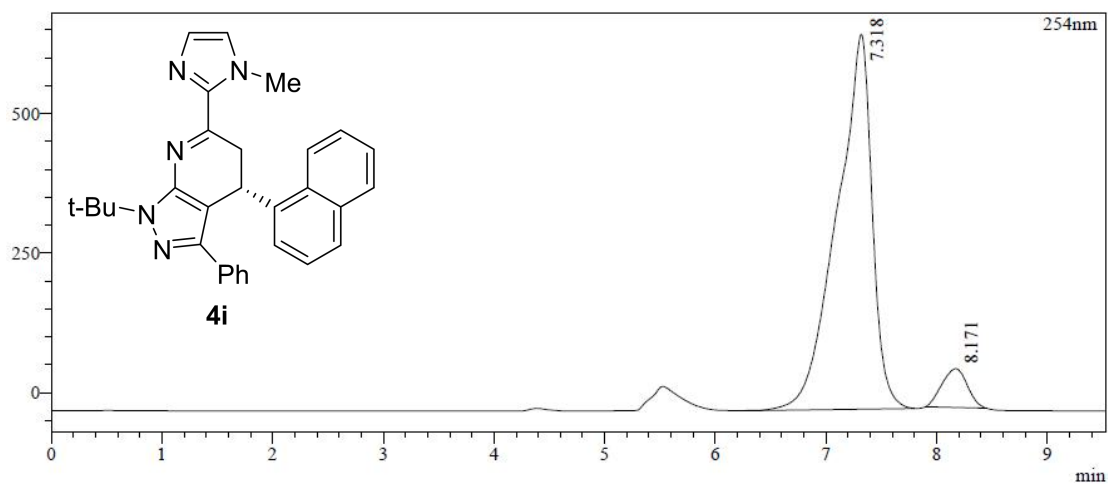


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.359	3733693	339687	49.375
2	8.231	3828197	305375	50.625
		7561890	645062	100.000

chiral-4i

Chromatogram

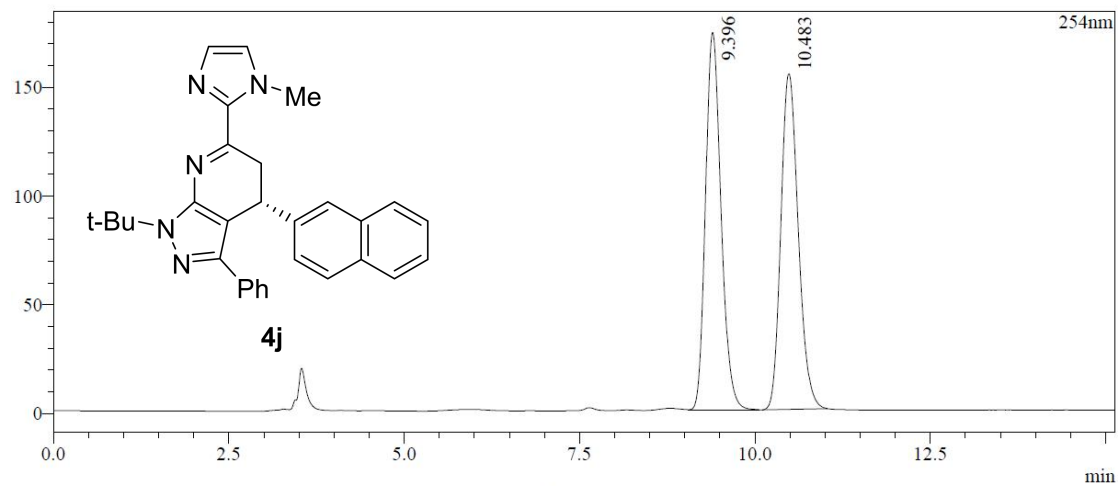


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.318	14881558	671215	93.073
2	8.171	1107503	69239	6.927
		15989061	740454	100.000

racemic-4j

Chromatogram

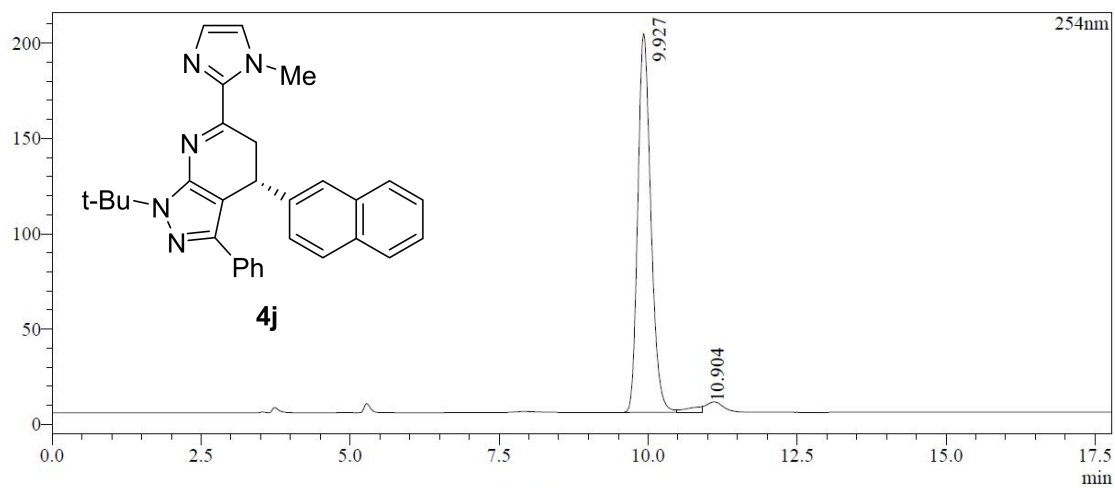


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.396	2672998	173439	50.175
2	10.483	2654318	154304	49.825
Total		5327316	327743	100.000

chiral-4j

Chromatogram

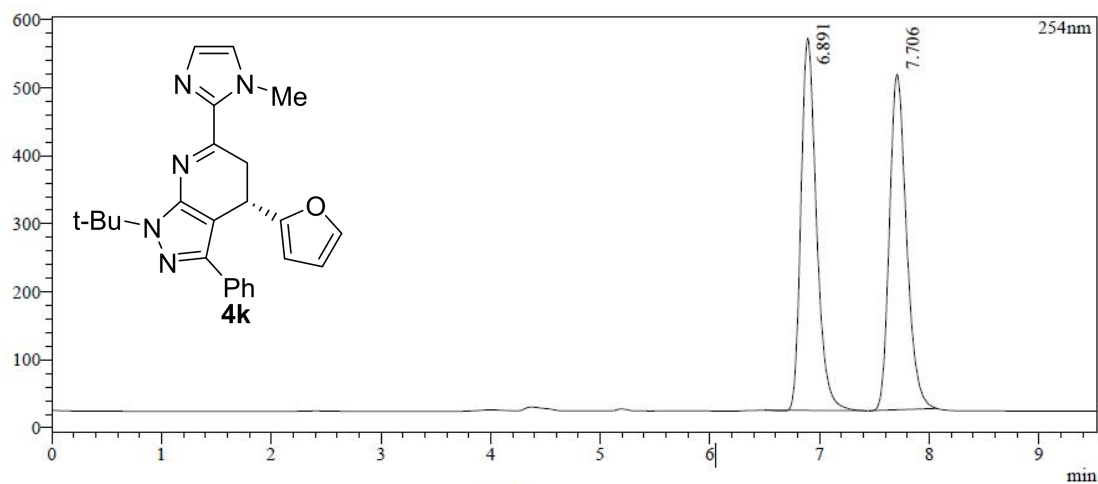


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	9.927	3030602	198664	98.269
2	10.904	53374	2964	1.731
Total		3083976	201629	100.000

racemic-4k

Chromatogram

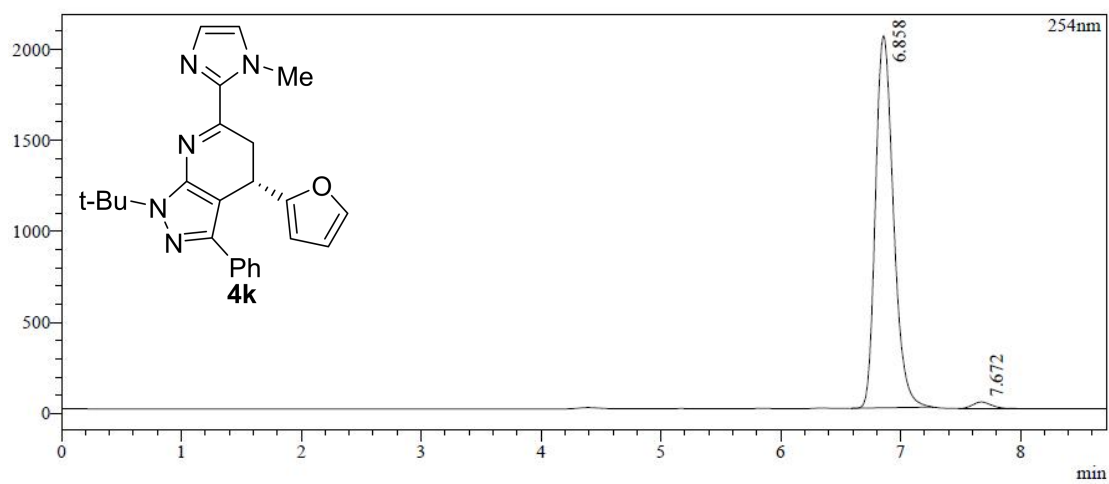


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.891	5377044	547707	50.223
2	7.706	5329331	493375	49.777
		10706376	1041082	100.000

chiral-4k

Chromatogram

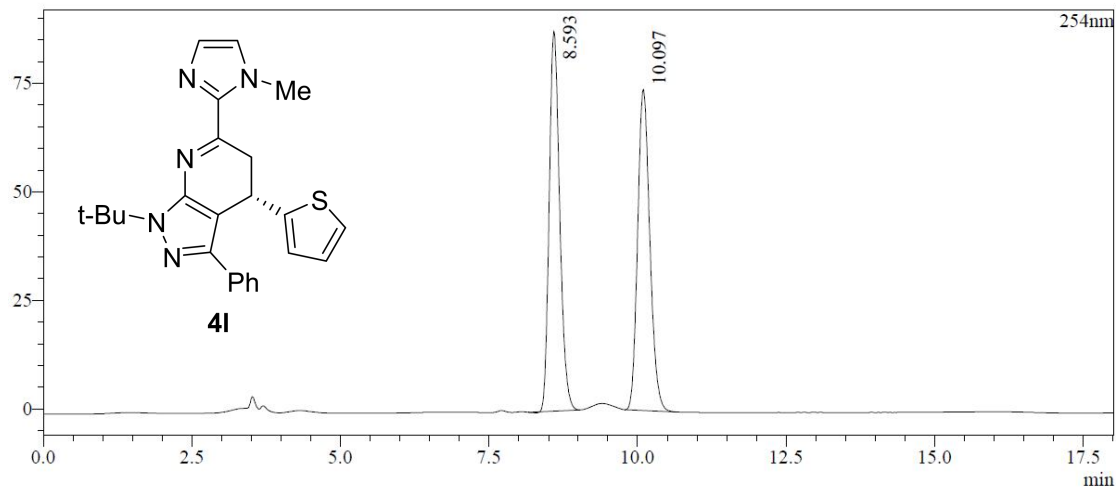


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.858	21283660	2042974	98.226
2	7.672	384459	35700	1.774
		21668119	2078674	100.000

racemic-4I

Chromatogram

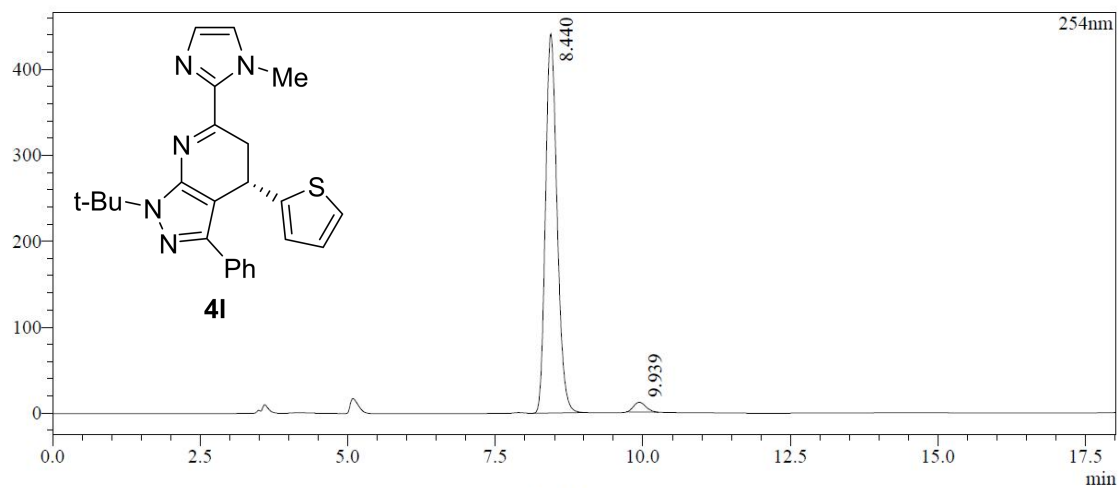


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.593	1075489	87469	50.443
2	10.097	1056607	73891	49.557
Total		2132095	161360	100.000

chiral-4I

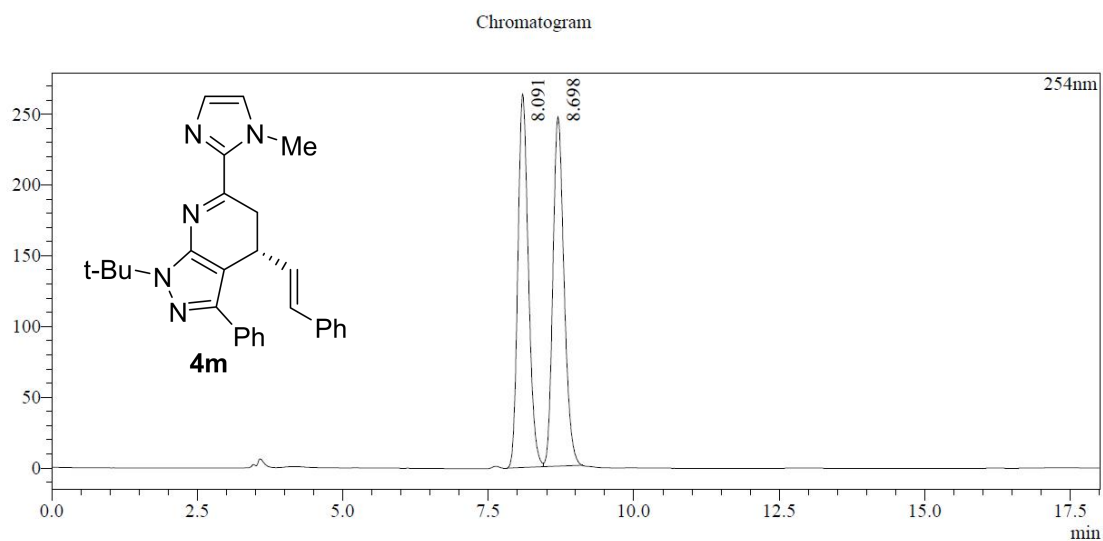
Chromatogram



Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.440	6021802	441631	97.420
2	9.939	159462	11187	2.580
Total		6181264	452819	100.000

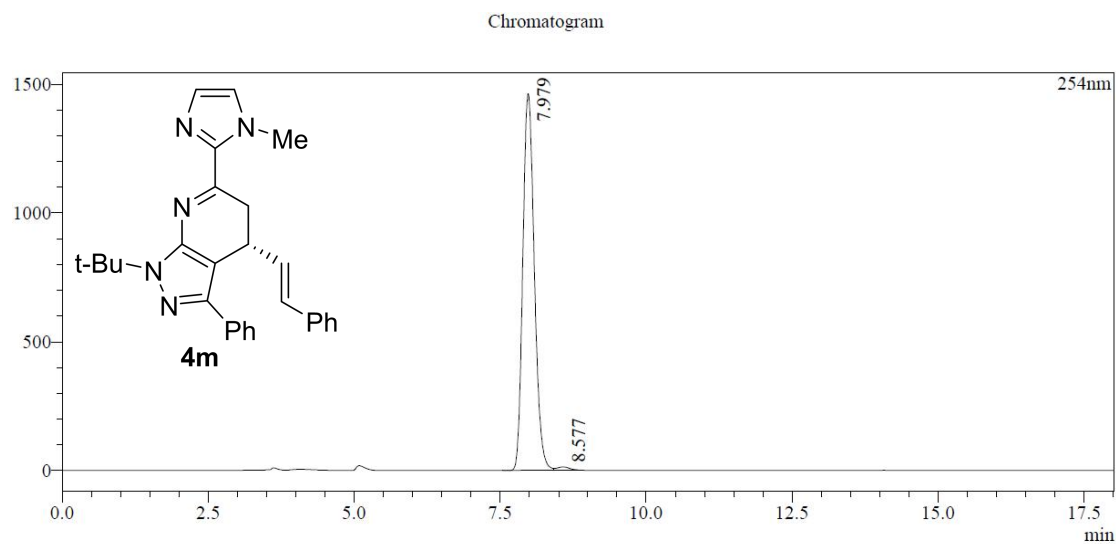
racemic-4m



Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	8.091	3319399	263957	50.095
2	8.698	3306765	246888	49.905
Total		6626164	510845	100.000

chiral-4m

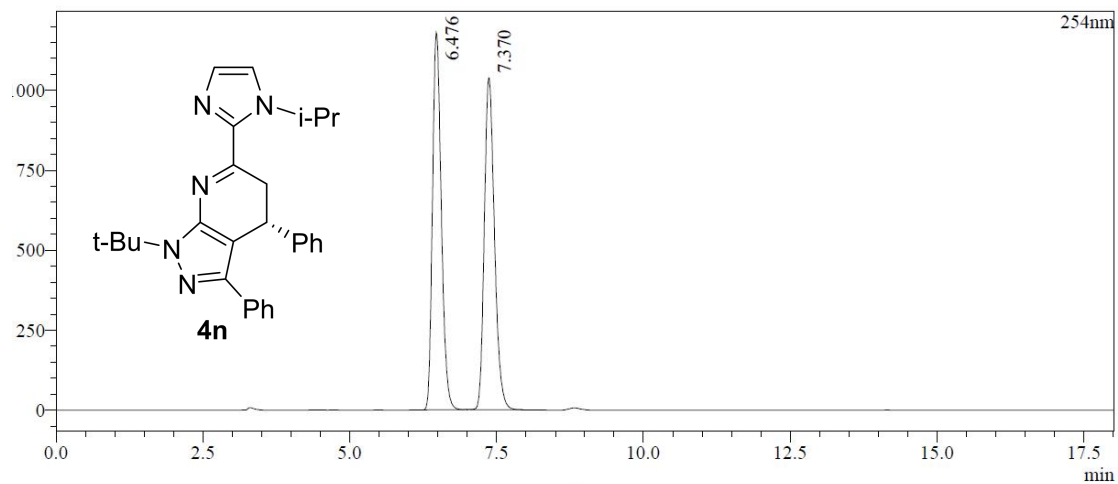


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	7.979	20005846	1462492	99.060
2	8.577	189838	13027	0.940
Total		20195685	1475519	100.000

racemic-4n

Chromatogram

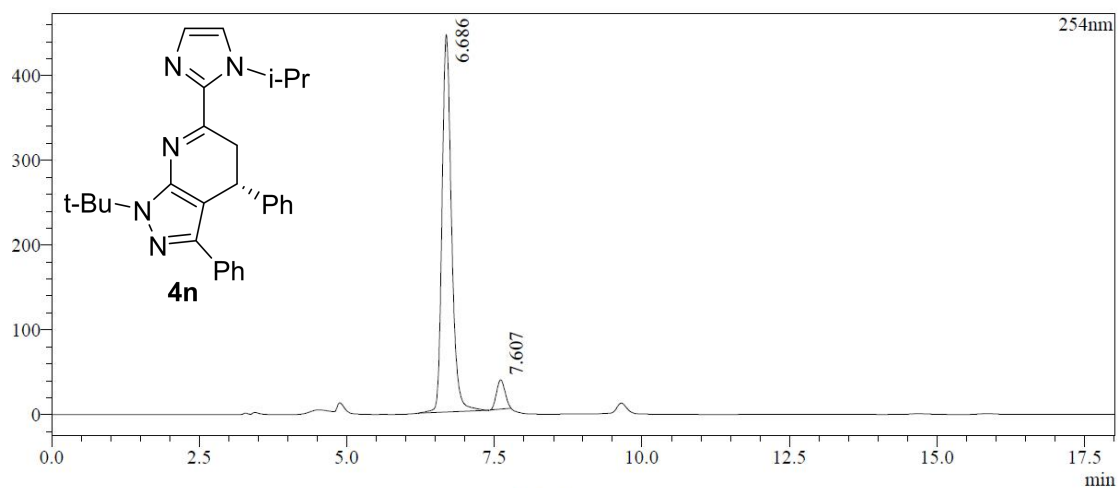


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.476	12340734	1180480	49.688
2	7.370	12495913	1038086	50.312
Total		24836647	2218566	100.000

chiral-4n

Chromatogram

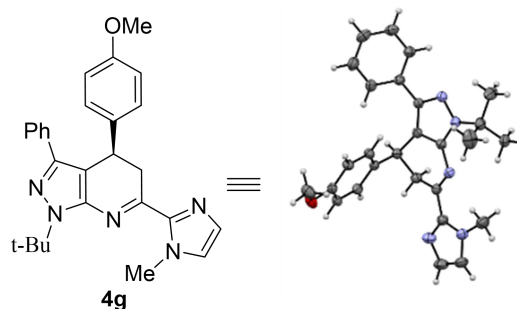


Peak Table

Peak#	Ret. Time	Area	Height	Area%
1	6.686	4983551	445047	93.511
2	7.607	345833	34440	6.489
Total		5329384	479488	100.000

VI. Single Crystal X-Ray Diffraction of 4g

Crystal data and structure refinement for **4g**. The method for crystal growth: mixture of Petroleum ether and ethyl acetate, at room temperature. X-ray derived ORTEP of **4g** with thermal ellipsoids shown at the 35% probability level.



CCDC: 2321389

Identification code	4g
Empirical formula	C ₂₇ H ₂₉ N ₅ O
Formula weight	439.55
Temperature	173.0 K
Wavelength	1.54178 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.4283(2) Å α = 106.2550(10)° b = 10.7638(2) Å β = 113.6160(10)° c = 12.6122(2) Å γ = 100.9400(10)°
Volume	1169.63(4) Å ³
Z	2
Density (calculated)	1.248 Mg/m ³
Absorption coefficient	0.618 mm ⁻¹
F(000)	468
Crystal size	0.25 x 0.21 x 0.19 mm ³
Theta range for data collection	4.165 to 72.061°
Index ranges	-12 ≤ h ≤ 12, -13 ≤ k ≤ 13, -15 ≤ l ≤ 15
Reflections collected	28682
Independent reflections	4573 [R(int) = 0.0505]
Completeness to theta = 67.679°	99.3 %
Absorption correction	Semi-empirical from equivalents

Max. and min. transmission	0.7536 and 0.6970
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	4573 / 0 / 303
Goodness-of-fit on F2	1.040
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0408, wR2 = 0.0984
R indices (all data)	R1 = 0.0486, wR2 = 0.1037
Extinction coefficient	n/a
Largest diff. peak and hole	0.190 and -0.192 e.Å ⁻³