

Supporting Information

Palladium-Catalyzed Sequential Monoarylation/Amidation of C(sp³)–H Bonds: Stereoselective Synthesis of α -Amino- β -Lactams and *anti*- α,β -Diamino Acid

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General Information

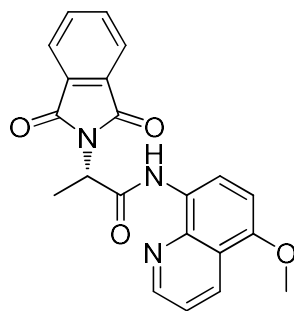
1,4-Dioxane were dried by sodium and freshly distilled. Pd(OAc)₂ was obtained from Stream[®] and AgBF₄ was obtained from TCI[®]. The other materials and solvents were purchased from Adamas-beta and other commercial suppliers and used without additional purification. Nuclear magnetic resonance (NMR) spectra were recorded with Bruker AVANCE 400 MHz. ¹H and ¹³C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak as following: CHCl₃ = 7.26 (¹H NMR), DMSO = 2.50 (¹H NMR), CDCl₃ = 77.16 (¹³C NMR), DMSO = 39.52 (¹³C NMR). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. High resolution mass spectra for new compounds were recorded at Mass Spectrometry Facilities, Zhejiang University.

Experimental Procedures

General Procedure (GP1) for Preparation of *N*-Phthaloyl-Amino Acid 5-Methoxyquinolin-8-amine Amide

To a stirred solution of the acid chloride (24 mmol) in dichloromethane (50 mL), 5-methoxyquinolin-8-amine¹ (3.484 g, 20 mmol) was added slowly at -15 °C. After the solution was stirred for five minutes, *N,N*-diisopropylethylamine (3.97 mL, 24 mmol) was added dropwise slowly at -15 °C. The resulting mixture was stirred at room temperature overnight and then the reaction was diluted with dichloromethane (50 mL), washed by aqueous HCl (50 mL, 1 M), saturated NaHCO₃ (50 mL), brine (50 mL), and dried over anhydrous MgSO₄. Evaporation of organic solvent and purification by column chromatography afforded the desired amide.²

(*S*)-2-(1,3-Dioxoisindolin-2-yl)-*N*-(5-methoxyquinolin-8-yl)propanamide (1)

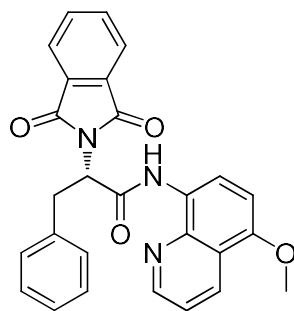


L-Alanine (8.91 g, 0.10 mol) and Na₂CO₃ (10.60 g, 0.10 mol) were dissolved in water (100 mL) at room temperature and *N*-ethoxycarbonylphthalimide (21.91 g, 0.10 mol) was added to the solution in small portions. The reaction was stirred for 2 h, then the aqueous solution was slowly acidified with aqueous HCl (6 M) until pH = 1 at 0 °C and white precipitate appeared slowly. Collecting and washing the precipitate with aqueous HCl (1M, 20 mL) and ethyl ether: petroleum ether = 1:5 (20 mL) gave (*S*)-2-phthalimidopropionic acid (17.97 g, 82%).

(*S*)-2-Phthalimidopropionic acid (5.26 g, 24 mmol), thionyl chloride (8.70 mL, 120 mmol), and 3 drops of dimethylformamide were heated in dichloromethane (50 mL) at 55 °C for 3 h. After the reaction, dichloromethane and excess of thionyl chloride were removed by vacuum. The acid chloride was dissolved in anhydrous dichloromethane (50 mL) and used for next reaction.²

The compound **1** was prepared according to **GP1**. Purified by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 5 : 0.5 gave **1** as a light yellow solid (5.86 g, 78%). ¹H NMR (400 MHz, CDCl₃) δ 10.07 (brs, 1H), 8.69 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 8.53 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.93 – 7.83 (m, 2H), 7.78 – 7.70 (m, 2H), 7.39 (dd, *J* = 8.4, 4.4 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 5.24 (q, *J* = 7.2 Hz, 1H), 3.96 (s, 3H), 1.96 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.99, 166.87, 150.68, 148.87, 139.32, 134.26, 132.15, 131.33, 127.46, 123.65, 120.83, 120.50, 116.90, 104.35, 55.88, 50.18, 15.54. HRMS (EI) *m/z*: 375.1220 (M⁺); calc. for C₂₁H₁₇N₃O₄: 375.1219.

(*S*)-2-(1,3-Dioxoisindolin-2-yl)-*N*-(5-methoxyquinolin-8-yl)-3-phenylpropanamide (2a)



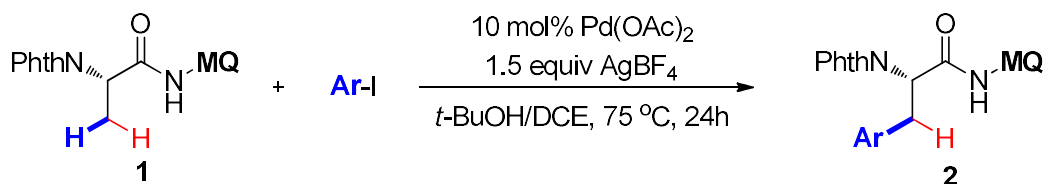
L-Phenylalanine (16.52 g, 0.10 mol) and Na₂CO₃ (10.60 g, 0.10 mol) were dissolved in water (100 mL) at room temperature and *N*-ethoxycarbonylphthalimide (21.91 g, 0.10 mol) was added to the solution in small portions. The reaction was stirred for 2 hours, then the aqueous solution was slowly acidified with aqueous HCl (6 M) until pH = 1 at 0 °C. The reaction mixture was extracted with dichloromethane (2 × 150 mL) and the combined organic phase was washed with brine (80 ml) and dried over anhydrous Na₂SO₄. Evaporation of organic solvent and purification by column chromatography in dichloromethane : methanol = 20 : 1 gave (*S*)-3-phenyl-2-phthalimidopropionic acid (24.50 g, 83 %).

(*S*)-3-Phenyl-2-phthalimidopropionic acid (7.09 g, 24 mmol), thionyl chloride (8.70 mL, 120 mmol), and 3 drops of dimethylformamide were heated in dichloromethane (50 mL) at 55 °C for 3 h. After the reaction, dichloromethane and excess of thionyl chloride were removed by vacuum. The acid chloride was dissolved in anhydrous dichloromethane (50 mL) and used for next reaction.

The compound **2a** was prepared according to **GP1**. Purified by silica gel column chromatography in petroleum ether : ethyl acetate = 4 : 1 gave **2a** as a white solid (7.13 g, 79 %). ¹H NMR (400 MHz, CDCl₃) δ 10.09 (brs, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.61 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.51 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.87 – 7.75 (m, 2H), 7.73 – 7.64 (m, 2H), 7.36 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.25 – 7.19 (m, 2H), 7.18 – 7.12 (m, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 5.44 (t, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 3.81 (d, *J* = 8.4 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 168.03, 166.05, 150.73, 148.82, 139.28, 136.93, 134.22, 131.74, 131.26, 129.11, 128.77, 127.38, 127.01, 123.60, 120.80, 120.45, 117.03, 104.29, 56.31, 55.85, 34.87. HRMS (EI) *m/z*: 451.1534 (M⁺); calc. for C₂₇H₂₁N₃O₄: 451.1532.

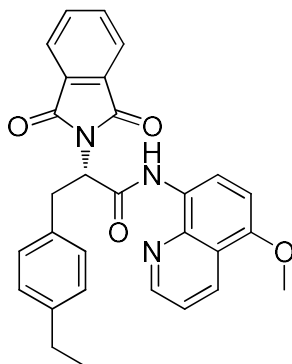
General Procedure (GP2) for Palladium-Catalyzed Methyl C(sp³)-H

Monoarylation of Alanine



To a 50 mL Schlenk tube, **1** (0.375 g, 1 mmol), aryl iodide (1.2 mmol), Pd(OAc)₂ (22.4 mg, 0.1 mmol), AgBF₄ (0.292 g, 1.5 mmol), *t*-BuOH (7 mL) and 1,2-dichloroethane (3 mL) were added. The tube was charged with N₂ and heated at 75 °C for 24 hours. After cooling to room temperature, the reaction mixture was diluted with dichloromethane and filtered through a pad of Celite and washed by dichloromethane. Evaporation of the organic solvent and purification by silica gel column chromatography gave the desired product **2**.

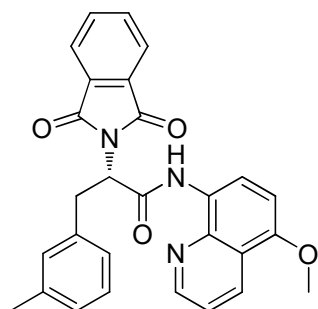
(*S*)-2-(1,3-Dioxoisindolin-2-yl)-3-(4-ethylphenyl)-*N*-(5-methoxyquinolin-8-yl)propanamide (**2b**)



The title compound **2b** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 5 : 3 : 0.5 gave **2b** as a white solid (0.388 g, 81%). ¹H NMR (400 MHz, CDCl₃) δ 10.09 (brs, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.61 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.50 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.86 – 7.75 (m, 2H), 7.72 – 7.63 (m, 2H), 7.35 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 1H), 5.43 (t, *J* = 8.4 Hz, 1H), 3.95 (s, 3H), 3.79 (d, *J* = 8.4 Hz, 2H), 2.54 (q, *J* = 7.6 Hz, 2H), 1.14 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.05, 166.14, 150.67, 148.77, 142.86, 139.25, 134.16, 134.00, 131.79, 131.22, 129.00, 128.22, 127.41, 123.55, 120.76,

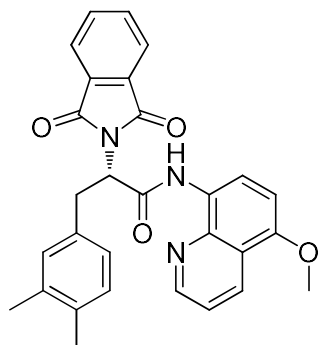
120.40, 116.98, 104.26, 56.39, 55.82, 34.49, 28.48, 15.52. HRMS (EI) m/z : 479.1844 (M^+); calc. for $C_{29}H_{25}N_3O_4$: 479.1845.

(S)-2-(1,3-Dioxoisindolin-2-yl)-N-(5-methoxyquinolin-8-yl)-3-(m-tolyl)propanamide (2c)



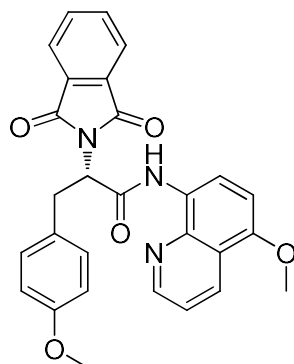
The title compound **2c** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 0.5 gave **2c** as a white solid (0.382 g, 82%). 1H NMR (400 MHz, $CDCl_3$) δ 10.07 (brs, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.62 (dd, J = 4.4, 1.6 Hz, 1H), 8.52 (dd, J = 8.4, 1.6 Hz, 1H), 7.87 – 7.79 (m, 2H), 7.74 – 7.65 (m, 2H), 7.37 (dd, J = 8.4, 4.4 Hz, 1H), 7.13 – 7.06 (m, 3H), 7.00 – 6.94 (m, 1H), 6.80 (d, J = 8.8 Hz, 1H), 5.42 (dd, J = 9.6, 7.2 Hz, 1H), 3.97 (s, 3H), 3.80 – 3.72 (m, 2H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.07, 166.13, 150.71, 148.81, 139.31, 138.37, 136.85, 134.21, 131.83, 131.26, 129.92, 128.66, 127.76, 127.44, 126.10, 123.60, 120.80, 120.45, 117.02, 104.30, 56.39, 55.86, 34.85, 21.39. HRMS (EI) m/z : 465.1686 (M^+); calc. for $C_{28}H_{23}N_3O_4$: 465.1689.

(S)-3-(3,4-Dimethylphenyl)-2-(1,3-dioxoisindolin-2-yl)-N-(5-methoxyquinolin-8-yl)propanamide (2d)



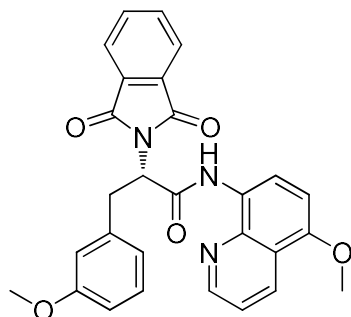
The title compound **2d** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 0.5 gave **2d** as a white solid (0.331 g, 69%). ¹H NMR (400 MHz, CDCl₃) δ 10.07 (brs, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.62 (dd, *J* = 4.4, 1.2 Hz 1H), 8.51 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.86 – 7.78 (m, 2H), 7.73 – 7.66 (m, 2H), 7.36 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.08 – 6.95 (m, 3H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.41 (dd, *J* = 8.8, 7.6 Hz, 1H), 3.96 (s, 3H), 3.81 – 3.72 (m, 2H), 2.15 (s, 3H), 2.12 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.11, 166.21, 150.67, 148.76, 139.28, 136.88, 135.11, 134.19, 134.15, 131.86, 131.23, 130.37, 129.99, 127.45, 126.37, 123.57, 120.77, 120.43, 117.00, 104.28, 56.49, 55.84, 34.48, 19.70, 19.43. HRMS (EI) *m/z*: 479.1844 (*M*⁺); calc. for C₂₉H₂₅N₃O₄: 479.1845.

(*S*)-2-(1,3-Dioxisoindolin-2-yl)-3-(4-methoxyphenyl)-*N*-(5-methoxyquinolin-8-yl)propanamide (2e)



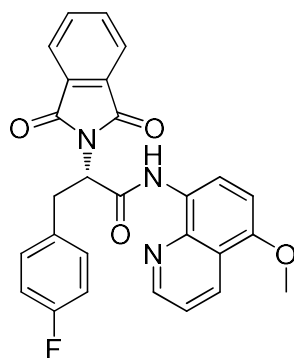
The title compound **2e** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : ethyl acetate : acetone = 6 : 1 : 1 gave **2e** as a light yellow solid (0.404 g, 84%). ¹H NMR (400 MHz, CDCl₃) δ 10.07 (brs, 1H), 8.71 – 8.59 (m, 2H), 8.52 (d, *J* = 8.0 Hz, 1H), 7.88 – 7.77 (m, 2H), 7.75 – 7.64 (m, 2H), 7.37 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 5.38 (t, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 3.75 (d, *J* = 8.4 Hz, 2H), 3.71 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.09, 166.14, 158.57, 150.70, 148.81, 139.28, 134.22, 131.78, 131.26, 130.13, 128.83, 127.42, 123.62, 120.81, 120.44, 117.02, 114.19, 104.29, 56.49, 55.86, 55.25, 34.07. HRMS (EI) *m/z*: 481.1638 (*M*⁺); calc. for C₂₈H₂₃N₃O₅: 481.1638.

(S)-2-(1,3-Dioxoisindolin-2-yl)-3-(3-methoxyphenyl)-N-(5-methoxyquinolin-8-yl)propanamide (2f)



The title compound **2f** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : ethyl acetate : acetone = 6 : 1 : 1 gave **2f** as a light yellow solid (0.385 g, 80%). ¹H NMR (400 MHz, CDCl₃) δ 10.07 (brs, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.62 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.51 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.87 – 7.79 (m, 2H), 7.73 – 7.66 (m, 2H), 7.36 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.85 – 6.78 (m, 2H), 6.70 (dd, *J* = 8.4, 1.6 Hz, 1H), 5.44 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.96 (s, 3H), 3.83 – 3.76 (m, 2H), 3.67 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.04, 166.03, 159.85, 150.72, 148.83, 139.28, 138.47, 134.25, 131.79, 131.26, 129.79, 127.39, 123.63, 121.42, 120.81, 120.44, 117.02, 114.25, 113.06, 104.28, 56.23, 55.86, 55.20, 34.94. HRMS (EI) *m/z*: 481.1639 (*M*⁺); calc. for C₂₈H₂₃N₃O₅: 481.1638.

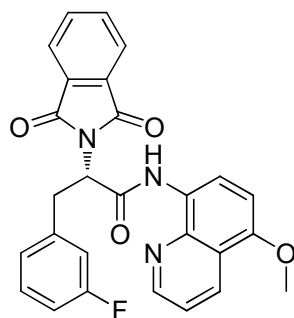
(S)-2-(1,3-Dioxoisindolin-2-yl)-3-(4-fluorophenyl)-N-(5-methoxyquinolin-8-yl)propanamide (2g)



The title compound **2g** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 5 : 3 : 0.6 gave **2g** as a white solid (0.376 g, 80%). ¹H NMR (400 MHz, CDCl₃) δ 10.05 (brs,

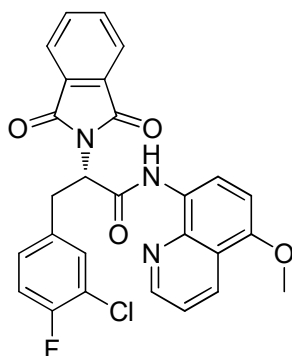
1H), 8.64 (d, $J = 8.4$ Hz, 1H), 8.60 (dd, $J = 4.0, 1.6$ Hz, 1H), 8.50 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.89 – 7.76 (m, 2H), 7.74 – 7.63 (m, 2H), 7.35 (dd, $J = 8.4, 4.4$ Hz, 1H), 7.26 – 7.21 (m, 2H), 6.90 (t, $J = 8.8$ Hz, 2H), 6.80 (d, $J = 8.4$ Hz, 1H), 5.39 (dd, $J = 9.2, 8.0$ Hz, 1H), 3.95 (s, 3H), 3.82 – 3.73 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.99, 165.81, 161.91 (d, $J = 246.0$ Hz), 150.75, 148.81, 139.23, 134.32, 132.64 (d, $J = 3.2$ Hz), 131.65, 131.27, 130.64 (d, $J = 8.1$ Hz), 127.29, 123.65, 120.81, 120.43, 117.02, 115.64 (d, $J = 21.4$ Hz), 104.26, 56.25, 55.84, 34.08. HRMS (EI) m/z : 469.1440 (M^+); calc. for $\text{C}_{27}\text{H}_{20}\text{FN}_3\text{O}_4$: 469.1438.

(S)-2-(1,3-Dioxoisindolin-2-yl)-3-(3-fluorophenyl)-N-(5-methoxyquinolin-8-yl)propanamide (2h)



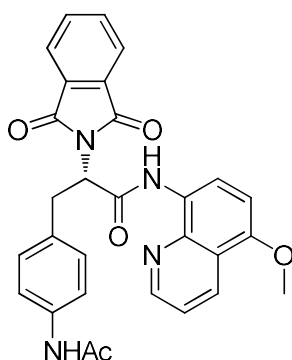
The title compound **2h** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 4 : 4 : 0.5 gave **2h** as a light yellow solid (0.399 g, 85%). ^1H NMR (400 MHz, CDCl_3) δ 10.05 (brs, 1H), 8.63 (d, $J = 8.4$ Hz, 1H), 8.60 (dd, $J = 4.0, 1.6$ Hz, 1H), 8.51 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.88 – 7.78 (m, 2H), 7.75 – 7.66 (m, 2H), 7.36 (dd, $J = 8.4, 4.0$ Hz, 1H), 7.23 – 7.15 (m, 1H), 7.11 – 7.05 (m, $J = 7.7$ Hz, 1H), 7.04 – 6.97 (m, $J = 9.7$ Hz, 1H), 6.85 (td, $J = 8.4, 2.0$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 5.41 (dd, $J = 9.2, 7.2$ Hz, 1H), 3.96 (s, 3H), 3.85 – 3.75 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.98, 165.69, 162.96 (d, $J = 247.2$ Hz), 150.78, 148.84, 139.55 (d, $J = 7.5$ Hz), 139.24, 134.35, 131.67, 131.29, 130.28 (d, $J = 8.4$ Hz), 127.26, 124.76 (d, $J = 2.8$ Hz), 123.70, 120.83, 120.44, 117.04, 116.15 (d, $J = 21.5$ Hz), 114.02 (d, $J = 21.1$ Hz), 104.26, 56.00, 55.85, 34.60. HRMS (EI) m/z : 469.1440 (M^+); calc. for $\text{C}_{27}\text{H}_{20}\text{FN}_3\text{O}_4$: 469.1438.

(S)-3-(3-Chloro-4-fluorophenyl)-2-(1,3-dioxoisindolin-2-yl)-N-(5-methoxyquinolin-8-yl)propanamide (2i)



The title compound **2i** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : ethyl acetate = 3 : 1 gave **2i** as a white solid (0.383 g, 76%). ¹H NMR (400 MHz, CDCl₃) δ 10.00 (brs, 1H), 8.67 – 8.56 (m, 2H), 8.51 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.93 – 7.78 (m, 2H), 7.76 – 7.64 (m, 2H), 7.40 – 7.29 (m, 2H), 7.20 – 7.10 (m, 1H), 6.99 (t, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.36 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.96 (s, 3H), 3.82 – 3.67 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 167.99, 165.48, 157.25 (d, *J* = 249.0 Hz), 150.83, 148.86, 139.22, 134.46, 134.13 (d, *J* = 4.0 Hz), 131.62, 131.31, 128.81 (d, *J* = 7.2 Hz), 127.18, 123.78, 121.15 (d, *J* = 17.8 Hz), 120.86, 120.46, 117.07, 116.88 (d, *J* = 21.0 Hz), 104.25, 55.97, 55.87, 33.97. HRMS (EI) *m/z*: 503.1053 (*M*⁺); calc. for C₂₇H₁₉ClFN₃O₄: 503.1048.

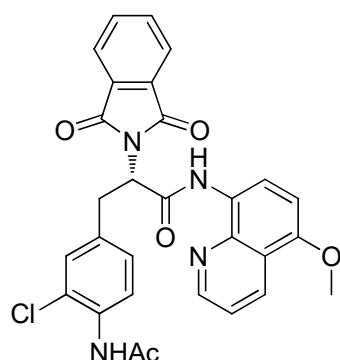
(S)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisindolin-2-yl)-N-(5-methoxyquinolin-8-yl)propanamide (2j)



The title compound **2j** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : acetone = 1.4 : 1 gave **2j** as a white solid (0.473 g, 93%). ¹H NMR (400 MHz, CDCl₃) δ 10.09 (brs, 1H), 8.68 – 8.55 (m, *J* = 8.6 Hz, 2H), 8.50 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.84 – 7.73 (m, 2H), 7.72 – 7.63 (m, 2H), 7.58 (brs, 1H), 7.43 – 7.29 (m, 3H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 1H),

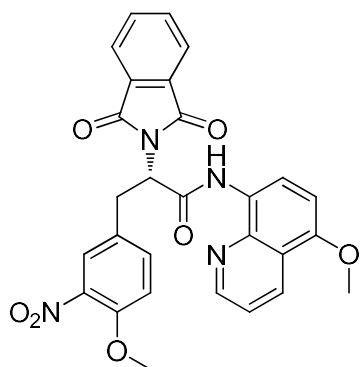
5.39 (dd, $J = 9.6, 6.8$ Hz, 1H), 3.95 (s, 3H), 3.81 – 3.69 (m, 2H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 168.50, 168.08, 166.05, 150.78, 148.88, 139.27, 137.05, 134.31, 132.50, 131.67, 131.26, 129.58, 127.29, 123.65, 120.84, 120.44, 120.00, 117.04, 104.24, 56.30, 55.85, 34.28, 24.60. HRMS (EI) m/z : 508.1760 (M^+); calc. for $\text{C}_{29}\text{H}_{24}\text{N}_4\text{O}_5$: 508.1747.

(S)-3-(4-Acetamido-3-chlorophenyl)-2-(1,3-dioxoisindolin-2-yl)-N-(5-methoxyquinolin-8-yl)propanamide (2k)



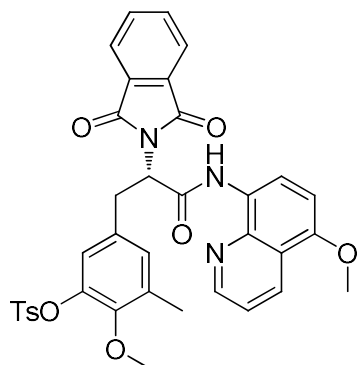
The title compound **2k** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : acetone = 1.7 : 1 gave **2k** as a white solid (0.369 g, 68%). ^1H NMR (400 MHz, CDCl_3) δ 10.03 (brs, 1H), 8.68 – 8.56 (m, 2H), 8.51 (dd, $J = 8.4, 1.6$ Hz, 1H), 8.22 (d, $J = 8.4$ Hz, 1H), 7.88 – 7.78 (m, 2H), 7.76 – 7.67 (m, 2H), 7.53 (brs, 1H), 7.40 – 7.30 (m, 2H), 7.17 (d, $J = 8.4$ Hz, 1H), 6.79 (d, $J = 8.4$ Hz, 1H), 5.36 (t, $J = 8.4$ Hz, 1H), 3.96 (s, 3H), 3.74 (d, $J = 8.4$ Hz, 2H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 168.21, 168.00, 165.64, 150.81, 148.87, 139.27, 134.38, 133.65, 133.57, 131.70, 131.30, 129.51, 128.44, 127.27, 123.76, 122.64, 121.66, 120.83, 120.47, 117.06, 104.28, 56.01, 55.87, 34.04, 24.92. HRMS (EI) m/z : 542.1351 (M^+); calc. for $\text{C}_{29}\text{H}_{23}\text{ClN}_4\text{O}_5$: 542.1357.

(S)-2-(1,3-Dioxoisindolin-2-yl)-3-(4-methoxy-3-nitrophenyl)-N-(5-methoxyquinolin-8-yl)propanamide (2l)



The title compound **2l** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 5 : 0.5 gave **2l** as a yellow solid (0.421 g, 80%). ¹H NMR (400 MHz, CDCl₃) δ 10.02 (brs, 1H), 8.65 – 8.56 (m, 2H), 8.51 (d, *J* = 8.4 Hz, 1H), 7.89 – 7.80 (m, 2H), 7.79 – 7.67 (m, 3H), 7.50 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.36 (dd, *J* = 8.4, 4.4 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 5.36 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 3.83 – 3.69 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 167.99, 165.39, 152.04, 150.87, 148.90, 139.48, 139.23, 134.90, 134.53, 131.58, 131.34, 129.47, 127.14, 126.30, 123.84, 120.88, 120.47, 117.09, 114.01, 104.25, 56.58, 55.91, 55.88, 33.63. HRMS (EI) *m/z*: 526.1492 (*M*⁺); calc. for C₂₈H₂₂N₄O₇: 526.1488.

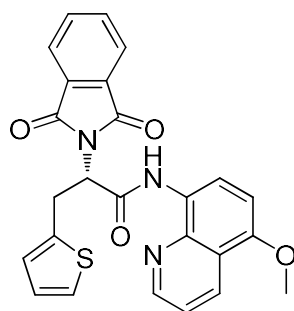
(S)-5-(2-(1,3-Dioxoisindolin-2-yl)-3-((5-methoxyquinolin-8-yl)amino)-3-oxopropyl)-2-methoxy-3-methylphenyl 4-methylbenzenesulfonate (2m)



The title compound **2m** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : acetone = 2.7 : 1 gave **2m** as a yellow solid (0.552 g, 83%). ¹H NMR (400 MHz, CDCl₃) δ 9.97 (brs, 1H), 8.66 – 8.56 (m, 2H), 8.51 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.88 – 7.82 (m, 2H), 7.75 – 7.68 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.37 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 1.6 Hz, 1H), 6.83 – 6.75 (m, 2H), 5.23 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.96 (s, 3H), 3.71 –

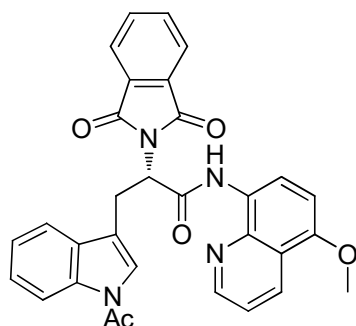
3.56 (m, 5H), 2.41 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 168.01, 165.73, 150.77, 149.89, 148.91, 145.38, 142.52, 139.22, 134.32, 133.46, 133.08, 132.47, 131.78, 131.26, 130.35, 129.71, 128.52, 127.28, 123.68, 121.87, 120.86, 120.43, 116.99, 104.23, 60.72, 56.09, 55.85, 34.15, 21.82, 16.06. HRMS (EI) m/z : 665.1855 (M^+); calc. for $\text{C}_{36}\text{H}_{31}\text{N}_3\text{O}_8\text{S}$: 665.1832.

(S)-2-(1,3-Dioxoisindolin-2-yl)-N-(5-methoxyquinolin-8-yl)-3-(thiophen-2-yl)propanamide (2n)



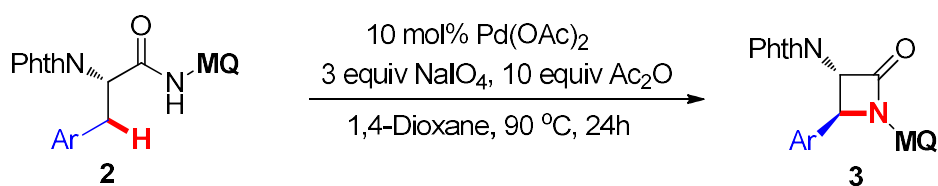
The title compound **2n** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 5 : 3 : 0.6 gave **2n** as a light yellow solid (0.412 g, 90%). ^1H NMR (400 MHz, CDCl_3) δ 10.07 (brs, 1H), 8.64 (d, J = 8.4 Hz, 1H), 8.60 (dd, J = 4.4, 1.6 Hz, 1H), 8.51 (dd, J = 8.4, 1.6 Hz, 1H), 7.90 – 7.82 (m, 2H), 7.76 – 7.69 (m, 2H), 7.36 (dd, J = 8.4, 4.4 Hz, 1H), 7.10 (dd, J = 5.2, 1.2 Hz, 1H), 6.93 – 6.89 (m, 1H), 6.85 (dd, J = 5.2, 3.6 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 5.39 (dd, J = 10.4, 5.6 Hz, 1H), 4.15 – 3.97 (m, 2H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.95, 165.53, 150.78, 148.85, 139.27, 139.09, 134.34, 131.81, 131.27, 127.29, 127.10, 126.63, 124.77, 123.72, 120.82, 120.44, 117.05, 104.27, 56.56, 55.86, 29.11. HRMS (EI) m/z : 457.1093 (M^+); calc. for $\text{C}_{25}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$: 457.1096.

(S)-3-(1-Acetyl-1H-indol-3-yl)-2-(1,3-dioxoisindolin-2-yl)-N-(5-methoxyquinolin-8-yl)propanamide (2o)



The title compound **2o** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 5 : 0.6 gave **2o** as a white solid (0.405 g, 76%). ¹H NMR (400 MHz, CDCl₃) δ 10.01 (brs, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 8.56 – 8.47 (m, 2H), 8.41 (d, *J* = 8.0 Hz, 1H), 7.89 – 7.79 (m, 2H), 7.76 – 7.69 (m, 2H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.42 – 7.27 (m, 4H), 6.79 (d, *J* = 8.8 Hz, 1H), 5.58 (dd, *J* = 8.8, 6.8 Hz, 1H), 4.03 – 3.97 (m, 1H), 3.96 (s, 3H), 3.83 (m, 1H), 2.45 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.56, 168.09, 165.73, 150.76, 148.78, 139.17, 136.09, 134.40, 131.81, 131.27, 130.00, 127.26, 125.69, 123.89, 123.87, 123.71, 120.82, 120.41, 118.91, 118.01, 117.04, 116.77, 104.25, 55.85, 54.27, 25.29, 23.99. HRMS (EI) *m/z*: 532.1752 (*M*⁺); calc. for C₃₁H₂₄N₄O₅: 532.1747.

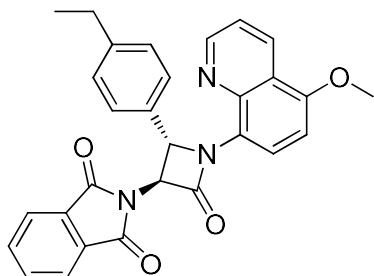
General Procedure (GP3) for Palladium-Catalyzed Methylene C(sp³)-H Amidation



To a 50 mL Schlenk tube, **2** (0.5 mmol), Pd(OAc)₂ (11.2 mg, 0.05 mmol), NaIO₄ (0.321 g, 1.5 mmol), Ac₂O (0.510 g, 5 mmol) and 1,4-dioxane (5 mL) were added. The tube was charged with N₂ and heated at 90 °C for 24 hours. After cooling to room temperature, the reaction mixture was diluted with dichloromethane and filtered through a pad of Celite and washed by dichloromethane (30 mL). The organic phase was washed with saturated aqueous NaHCO₃ (10 mL), dried over anhydrous MgSO₄.

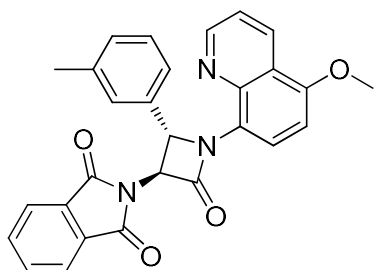
Evaporation of the organic solvent and purification by silica gel column chromatography gave the desired product **3**.

2-((2*S*,3*S*)-2-(4-Ethylphenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3b**)**



The title compound **3b** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 1 gave **3b** as a white solid (0.189 g, 79%). ¹H NMR (400 MHz, CDCl₃) δ 8.81 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.44 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.91 – 7.83 (m, 2H), 7.77 – 7.69 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.29 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.42 (d, *J* = 2.8 Hz, 1H), 5.42 (d, *J* = 2.8 Hz, 1H), 3.95 (s, 3H), 2.52 (q, *J* = 7.6 Hz, 2H), 1.13 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.09, 163.41, 153.22, 149.90, 144.41, 142.71, 135.15, 134.48, 132.01, 130.50, 128.29, 126.61, 125.59, 123.79, 123.42, 121.09, 120.66, 103.97, 64.97, 63.00, 55.96, 28.58, 15.36. HRMS (EI) *m/z*: 477.1691 (*M*⁺); calc. for C₂₉H₂₃N₃O₄: 477.1689.

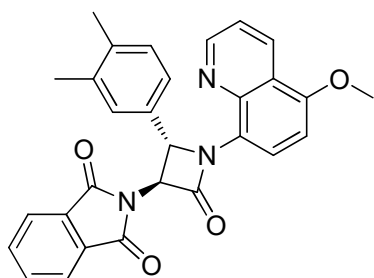
2-((3*S*,4*S*)-1-(5-Methoxyquinolin-8-yl)-2-oxo-4-(*m*-tolyl)azetidin-3-yl)isoindoline-1,3-dione (3c**)**



The title compound **3c** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 0.5 gave **3c** as a yellow solid (0.176 g, 76%). ¹H NMR (400 MHz, CDCl₃) δ 8.81 (dd,

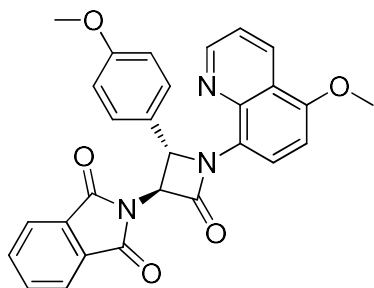
$J = 4.0, 1.6$ Hz, 1H), 8.44 (dd, $J = 8.4, 1.6$ Hz, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 7.90 – 7.84 (m, 2H), 7.76 – 7.70 (m, 2H), 7.29 (dd, $J = 8.4, 4.0$ Hz, 1H), 7.26 – 7.20 (m, 2H), 7.10 (t, $J = 7.2$ Hz, 1H), 7.01 – 6.96 (m, 1H), 6.82 (d, $J = 8.4$ Hz, 1H), 6.40 (d, $J = 2.0$ Hz, 1H), 5.42 (d, $J = 2.4$ Hz, 1H), 3.95 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.08, 163.39, 153.21, 149.84, 142.66, 138.42, 137.98, 134.48, 131.99, 130.51, 129.21, 128.64, 127.21, 125.62, 123.79, 123.72, 123.35, 121.09, 120.66, 103.97, 65.11, 63.01, 55.95, 21.49. HRMS (EI) m/z : 463.1537 (M^+); calc. for $\text{C}_{28}\text{H}_{21}\text{N}_3\text{O}_4$: 463.1532.

2-((2*S*,3*S*)-2-(3,4-Dimethylphenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3d)



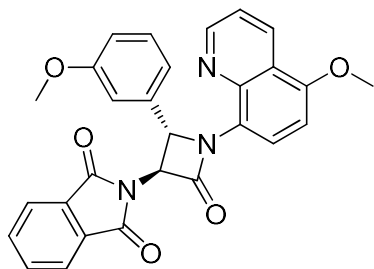
The title compound **3d** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 4 : 6 : 1 gave **3d** as a light yellow solid (0.203 g, 85%). ^1H NMR (400 MHz, CDCl_3) δ 8.83 (dd, $J = 4.0$ Hz, $J = 1.2$ Hz, 1H), 8.44 (dd, $J = 8.4, 1.2$ Hz, 1H), 8.05 (d, $J = 8.4$ Hz, 1H), 7.91 – 7.83 (m, 2H), 7.77 – 7.70 (m, 2H), 7.30 (dd, $J = 8.4, 4.0$ Hz, 1H), 7.20 (s, 1H), 7.15 (d, $J = 7.6$ Hz, 1H), 6.97 (d, $J = 7.6$ Hz, 1H), 6.82 (d, $J = 8.4$ Hz, 1H), 6.36 (d, $J = 2.4$ Hz, 1H), 5.41 (d, $J = 2.4$ Hz, 1H), 3.95 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.09, 163.48, 153.25, 149.90, 142.82, 136.97, 136.86, 135.30, 134.46, 132.04, 130.49, 129.97, 127.86, 125.64, 124.17, 123.78, 123.50, 121.13, 120.66, 103.97, 64.93, 63.06, 55.96, 19.90, 19.55. HRMS (EI) m/z : 477.1684 (M^+); calc. for $\text{C}_{29}\text{H}_{23}\text{N}_3\text{O}_4$: 477.1689.

2-((2*S*,3*S*)-2-(4-Methoxyphenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3e)



The title compound **3e** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 1 gave **3e** as a yellow solid (0.182 g, 76%). ¹H NMR (400 MHz, CDCl₃) δ 8.82 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.45 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.91 – 7.84 (m, 2H), 7.78 – 7.71 (m, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.30 (dd, *J* = 8.4, 4.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.38 (d, *J* = 2.4 Hz, 1H), 5.41 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H), 3.69 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.11, 163.39, 159.68, 153.26, 149.89, 142.67, 134.49, 132.04, 130.54, 129.87, 128.02, 125.53, 123.81, 123.45, 121.11, 120.67, 114.22, 103.99, 64.77, 62.98, 55.98, 55.29. HRMS (EI) *m/z*: 479.1487 (*M*⁺); calc. for C₂₈H₂₁N₃O₅: 479.1481.

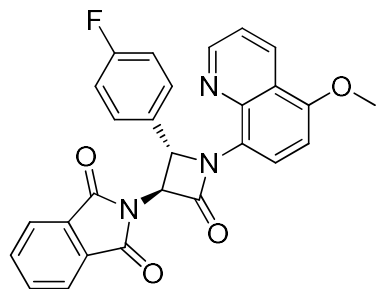
2-((2*S*,3*S*)-2-(3-Methoxyphenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isobenzindoline-1,3-dione (3f**)**



The title compound **3f** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 1 gave **3f** as a yellow solid (0.194 g, 81%). ¹H NMR (400 MHz, CDCl₃) δ 8.80 (dd, *J* = 4.0 Hz, *J* = 1.2 Hz, 1H), 8.45 (dd, *J* = 8.4 Hz, *J* = 1.2 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.91 – 7.82 (m, 2H), 7.78 – 7.68 (m, 2H), 7.30 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.17 – 7.10 (m, 1H), 7.02 – 6.95 (m, 2H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.75 – 6.67 (m, 1H), 6.39 (d, *J* = 2.0 Hz, 1H), 5.42 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H), 3.67 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.08, 163.30, 159.97, 153.32, 149.92, 142.69, 139.71, 134.52,

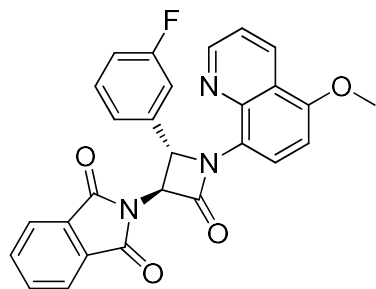
132.01, 130.59, 129.87, 125.62, 123.83, 123.39, 121.13, 120.70, 118.87, 114.02, 111.92, 104.01, 65.05, 62.94, 55.98, 55.26. HRMS (EI) m/z : 479.1487 (M^+); calc. for $C_{28}H_{21}N_3O_5$: 479.1481.

2-((2*S*,3*S*)-2-(4-Fluorophenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isoidoline-1,3-dione (3g)



The title compound **3g** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 1 gave **3g** as a yellow solid (0.180 g, 77%). 1H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, J = 4.4, 2.0 Hz, 1H), 8.45 (dd, J = 8.4, 2.0 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.77 – 7.70 (m, 2H), 7.44 – 7.35 (m, 2H), 7.29 (dd, J = 8.4, 4.4 Hz, 1H), 6.96 – 6.86 (m, 2H), 6.83 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 5.39 (d, J = 2.4 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.04, 163.08, 162.66 (d, J = 247.8 Hz), 153.22, 149.80, 142.34, 134.55, 133.90 (d, J = 3.1 Hz), 131.91, 130.60, 128.32 (d, J = 8.4 Hz), 125.33, 123.82, 123.21, 121.05, 120.69, 115.79 (d, J = 21.7 Hz), 103.98, 64.60, 63.00, 55.97. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.53. HRMS (EI) m/z : 467.1288 (M^+); calc. for $C_{27}H_{18}FN_3O_4$: 467.1281.

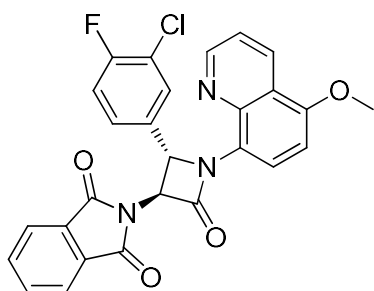
2-((2*S*,3*S*)-2-(3-Fluorophenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isoidoline-1,3-dione (3h)



The title compound **3h** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 :

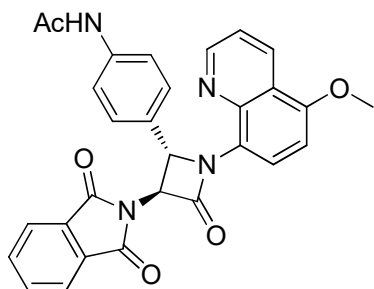
0.6 gave **3h** as a light yellow solid (0.079 g, 34%). ¹H NMR (400 MHz, CDCl₃) δ 8.75 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.46 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.92 – 7.84 (m, 2H), 7.79 – 7.71 (m, 2H), 7.30 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.15 – 7.09 (m, 1H), 6.91 – 6.81 (m, 2H), 6.46 (d, *J* = 2.4 Hz, 1H), 5.39 (d, *J* = 2.8 Hz, 1H), 3.98 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.02, 163.06 (d, *J* = 247.8 Hz), 162.99, 153.21, 149.80, 142.28, 141.05 (d, *J* = 7.2 Hz), 134.60, 131.96, 130.63, 130.49 (d, *J* = 8.3 Hz), 125.40, 123.90, 123.07, 122.03 (d, *J* = 2.8 Hz), 121.09, 120.73, 115.34 (d, *J* = 21.0 Hz), 113.51 (d, *J* = 22.2 Hz), 104.06, 64.82 (d, *J* = 1.7 Hz), 63.03, 56.01. ¹⁹F NMR (376 MHz, CDCl₃) δ -112.35. HRMS (EI) *m/z*: 467.1282 (M⁺); calc. for C₂₇H₁₈FN₃O₄: 467.1281.

2-((2*S*,3*S*)-2-(3-Chloro-4-fluorophenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3i**)**



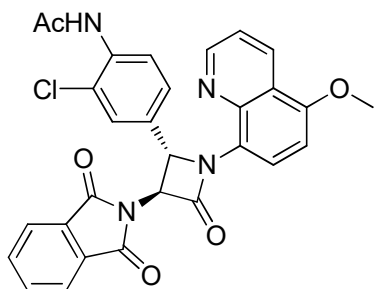
The title compound **3i** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : ethyl acetate = 2 : 1 gave **3i** as a light yellow solid (0.150 g, 60%). ¹H NMR (400 MHz, CDCl₃) δ 8.76 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.47 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.91 – 7.85 (m, 2H), 7.78 – 7.72 (m, 2H), 7.50 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.31 (dd, *J* = 8.4, 4.0 Hz, 2H), 6.99 (t, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 2.8 Hz, 1H), 5.37 (d, *J* = 2.8 Hz, 1H), 3.98 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 166.99, 162.85, 157.98 (d, *J* = 250.8 Hz), 153.31, 149.81, 142.19, 135.52 (d, *J* = 3.7 Hz), 134.64, 131.89, 130.73, 128.99, 126.31 (d, *J* = 7.5 Hz), 125.13, 123.91, 123.21, 121.50 (d, *J* = 18.1 Hz), 121.10, 120.79, 117.06 (d, *J* = 21.5 Hz), 104.07, 64.28, 63.04, 56.02. ¹⁹F NMR (376 MHz, CDCl₃) δ -115.64. HRMS (EI) *m/z*: 501.0891 (M⁺); calc. for C₂₇H₁₇ClFN₃O₄: 501.0892.

***N*-(4-((2*S*,3*S*)-3-(1,3-Dioxoisindolin-2-yl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-2-yl)phenyl)acetamide (3j)**



The title compound **3j** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : acetone = 1 : 1 gave **3j** as a light yellow solid (0.134 g, 53%). ¹H NMR (400 MHz, CDCl₃) δ 8.75 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.42 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.87 – 7.79 (m, 2H), 7.76 – 7.68 (m, 2H), 7.57 (brs, 1H), 7.31 (s, 4H), 7.25 (dd, *J* = 8.4 Hz, *J* = 4.0 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 5.38 (d, *J* = 2.8 Hz, 1H), 3.93 (s, 3H), 1.99 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.55, 167.08, 163.46, 153.37, 149.93, 142.52, 138.23, 134.56, 133.25, 131.88, 130.60, 127.29, 125.31, 123.83, 123.37, 121.07, 120.72, 119.96, 103.93, 64.75, 62.80, 55.98, 24.49. HRMS (ESI) *m/z*: 507.1646 (M+H⁺); calc. for C₂₉H₂₃N₄O₅: 507.1663.

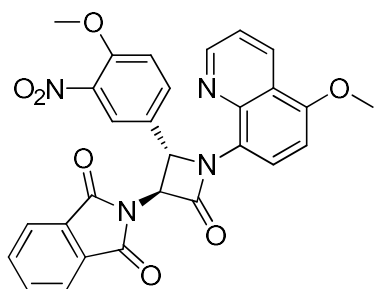
***N*-(2-Chloro-4-((2*S*,3*S*)-3-(1,3-dioxoisindolin-2-yl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-2-yl)phenyl)acetamide (3k)**



The title compound **3k** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : acetone = 1.4 : 1 gave **3k** as a yellow solid (0.157 g, 58%). ¹H NMR (400 MHz, CDCl₃) δ 8.76 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.44 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.77 – 7.70 (m, 2H), 7.52 (brs, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.32 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.29 (dd, *J* = 8.4, 4.0 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.36 (d,

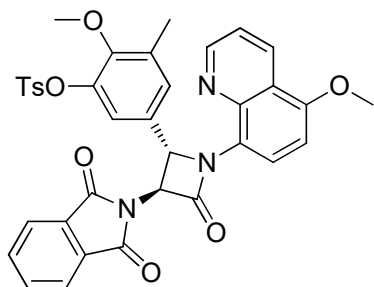
$J = 2.8$ Hz, 1H), 5.38 (d, $J = 2.8$ Hz, 1H), 3.96 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 168.29, 166.99, 162.99, 153.29, 149.84, 142.29, 134.77, 134.61, 134.58, 131.89, 130.64, 127.16, 126.11, 125.19, 123.86, 123.27, 122.84, 121.73, 121.07, 120.74, 104.03, 64.41, 62.94, 55.99, 24.85. HRMS (EI) m/z : 540.1207 (M^+); calc. for $\text{C}_{29}\text{H}_{21}\text{ClN}_4\text{O}_5$: 540.1200.

2-((2*S*,3*S*)-2-(4-Methoxy-3-nitrophenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3l**)**



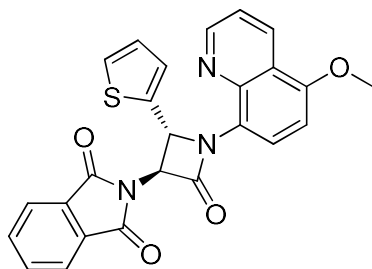
The title compound **3l** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 1.5 gave **3l** as a yellow solid (0.210 g, 80%). ^1H NMR (400 MHz, CDCl_3) δ 8.76 (dd, $J = 4.4, 1.6$ Hz, 1H), 8.44 (dd, $J = 8.4, 1.6$ Hz, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 8.00 (d, $J = 2.4$ Hz, 1H), 7.91 – 7.82 (m, 2H), 7.79 – 7.70 (m, 2H), 7.63 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.30 (dd, $J = 8.4, 4.4$ Hz, 1H), 6.93 (d, $J = 8.8$ Hz, 1H), 6.82 (d, $J = 8.4$ Hz, 1H), 6.42 (d, $J = 2.8$ Hz, 1H), 5.41 (d, $J = 2.8$ Hz, 1H), 3.96 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.97, 162.84, 153.33, 153.00, 149.86, 142.07, 139.44, 134.65, 132.14, 131.82, 130.72, 130.66, 124.97, 124.77, 123.89, 123.28, 121.04, 120.80, 114.12, 104.04, 64.05, 62.84, 56.62, 55.99. HRMS (EI) m/z : 524.1339 (M^+); calc. for $\text{C}_{28}\text{H}_{20}\text{N}_4\text{O}_7$: 524.1332.

5-((2*S*,3*S*)-3-(1,3-Dioxoisindolin-2-yl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-2-yl)-2-methoxy-3-methylphenyl 4-methylbenzenesulfonate (3m**)**



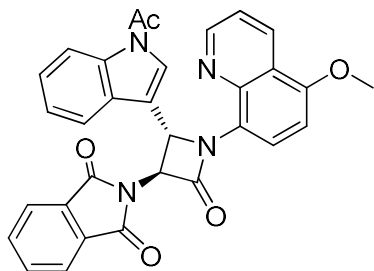
The title compound **3m** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : acetone = 1.8 : 1 gave **3m** as a yellow solid (0.279 g, 84%). ¹H NMR (400 MHz, CDCl₃) δ 8.80 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.47 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.92 – 7.85 (m, 2H), 7.79 – 7.73 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.32 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 1.6 Hz, 1H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 5.24 (d, *J* = 2.8 Hz, 1H), 3.98 (s, 3H), 3.63 (s, 3H), 2.37 (s, 3H), 2.07 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.01, 163.00, 153.21, 150.70, 149.94, 145.47, 142.55, 142.36, 134.60, 133.66, 133.58, 132.65, 131.93, 130.55, 129.65, 128.58, 127.28, 125.29, 123.86, 123.24, 121.03, 120.70, 119.66, 104.02, 64.36, 63.00, 60.71, 56.01, 21.77, 16.30. HRMS (ESI) *m/z*: 664.1722 (M+H⁺); calc. for C₃₆H₃₀N₃O₈S: 664.1748.

2-((3S,4R)-1-(5-Methoxyquinolin-8-yl)-2-oxo-4-(thiophen-2-yl)azetidin-3-yl)isoindoline-1,3-dione (3n)



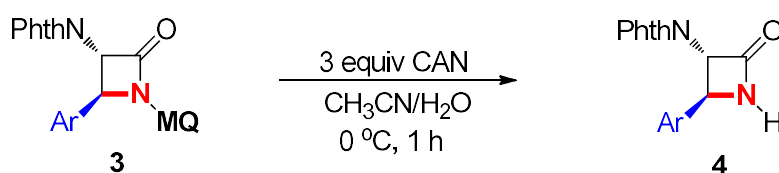
The title compound **3n** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 1 gave **3n** as a yellow solid (0.155 g, 68%). ¹H NMR (400 MHz, CDCl₃) δ 8.85 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.47 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.75 – 7.70 (m, 2H), 7.33 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.14 – 7.09 (m, 2H), 6.85 – 6.80 (m, 2H), 6.79 (d, *J* = 2.8 Hz, 1H), 5.61 (d, *J* = 2.8 Hz, 1H), 3.95 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 166.97, 162.86, 153.37, 149.99, 142.79, 140.78, 134.53, 131.89, 130.60, 127.00, 126.28, 125.79, 124.88, 123.87, 123.81, 121.05, 120.72, 103.94, 63.20, 61.01, 55.95. HRMS (EI) *m/z*: 455.0948 (M⁺); calc. for C₂₅H₁₇N₃O₄S: 455.0940.

2-((2*S*,3*S*)-2-(1-Acetyl-1*H*-indol-3-yl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3o**)**



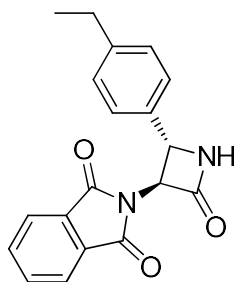
The title compound **3o** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 1 : 6 : 1.2 gave **3o** as a yellow solid (0.111 g, 42%). ¹H NMR (400 MHz, CDCl₃) δ 8.81 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.46 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.91 – 7.85 (m, 2H), 7.79 – 7.72 (m, 2H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.54 (s, 1H), 7.33 – 7.23 (m, 3H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 5.72 (d, *J* = 2.8 Hz, 1H), 3.94 (s, 3H), 2.45 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.36, 167.06, 163.20, 153.53, 149.97, 142.92, 136.19, 134.60, 131.93, 130.81, 128.35, 125.67, 125.57, 124.33, 124.04, 123.89, 123.75, 121.19, 120.78, 119.45, 119.32, 116.90, 104.06, 61.59, 59.13, 55.98, 23.96. HRMS (EI) *m/z*: 530.1592 (*M*⁺); calc. for C₃₁H₂₂N₄O₅: 530.1590.

General Procedure (GP4) for Removal of the Directing Group



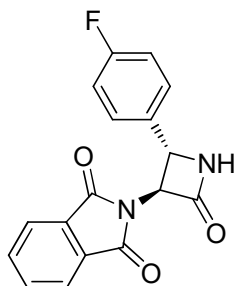
To an ice-water cooled solution of **3** (0.1 mmol) in acetonitrile (1.5 mL) and water (0.5 mL) was added ceric ammonium nitrate (3 equiv) in one portion. The reaction was kept in ice-water bath for 1 h. After completion, the reaction was diluted with ethyl acetate (25 mL), washed with saturated sodium thiosulfate (2 × 10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄. Evaporation of the organic solvent and purification by silica gel column chromatography gave the desired product **4**.

2-((2*S*,3*S*)-2-(4-Ethylphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (4b**)**



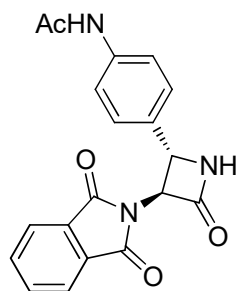
The title compound **4b** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 2 : 4 : 1 gave **4b** as a white solid (22.7 mg, 71%). ^1H NMR (400 MHz, CDCl_3) δ 7.93 – 7.83 (m, 2H), 7.79 – 7.72 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.55 (brs, 1H), 5.20 (d, J = 2.4 Hz, 1H), 5.11 (d, J = 2.8 Hz, 1H), 2.65 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.04, 165.43, 145.23, 134.91, 134.64, 131.83, 128.68, 126.02, 123.91, 63.48, 57.39, 28.71, 15.65. HRMS (EI) m/z : 320.1167 (M^+); calc. for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3$: 320.1161.

2-((2S,3S)-2-(4-Fluorophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (4c)



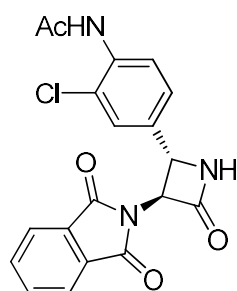
The title compound **4c** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : diethyl ether : ethyl acetate = 3 : 4 : 2 : 0.8 gave **4c** as a white solid (22.6 mg, 73%). ^1H NMR (400 MHz, CDCl_3) δ 7.92 – 7.84 (m, 2H), 7.80 – 7.73 (m, 2H), 7.40 – 7.33 (m, 2H), 7.12 – 7.04 (m, 2H), 6.63 (brs, 1H), 5.17 (d, J = 2.8 Hz, 1H), 5.13 (d, J = 2.8 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.02, 165.29, 163.07 (d, J = 248.8 Hz), 134.75, 133.55 (d, J = 3.1 Hz), 131.77, 127.80 (d, J = 8.4 Hz), 123.98, 116.24 (d, J = 21.9 Hz), 63.63, 56.92. ^{19}F NMR (376 MHz, CDCl_3) δ -112.55. HRMS (EI) m/z : 310.0750 (M^+); calc. for $\text{C}_{17}\text{H}_{11}\text{FN}_2\text{O}_3$: 310.0754.

N-(4-((2S,3S)-3-(1,3-Dioxoisindolin-2-yl)-4-oxoazetidin-2-yl)phenyl)acetamide (4d)



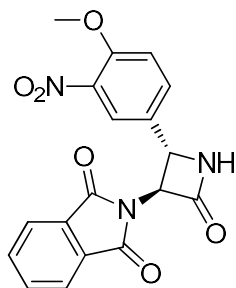
The title compound **4d** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 1 : 4 : 5 gave **4d** as a yellow solid (18.5 mg, 53%). ¹H NMR (400 MHz, *d*₆-DMSO) δ 9.99 (brs, 1H), 8.93 (brs, 1H), 7.98 – 7.84 (m, 4H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 4.96 (d, *J* = 2.4 Hz, 1H), 4.90 (d, *J* = 2.4 Hz, 1H), 2.04 (s, 3H). ¹³C NMR (101 MHz, *d*₆-DMSO) δ 168.33, 166.79, 164.65, 139.19, 134.87, 133.43, 131.36, 126.50, 123.47, 119.02, 62.71, 55.37, 23.99. HRMS (EI) *m/z*: 349.1068 (*M*⁺); calc. for C₁₉H₁₅N₃O₄: 349.1063.

***N*-(2-Chloro-4-((2*S*,3*S*)-3-(1,3-dioxoisindolin-2-yl)-4-oxoazetidin-2-yl)phenyl)acetamide (4e)**



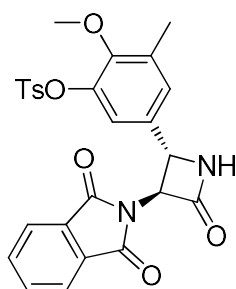
The title compound **4e** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 1 : 4 : 2.5 gave **4e** as a yellow solid (19.2 mg, 50%). ¹H NMR (400 MHz, *d*₆-DMSO) δ 9.55 (brs, 1H), 8.97 (brs, 1H), 7.96 – 7.86 (m, 4H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 1.6 Hz, 1H), 7.40 (dd, *J* = 8.4, 1.6 Hz, 1H), 5.01 (d, *J* = 2.4 Hz, 1H), 4.97 (d, *J* = 2.4 Hz, 1H), 2.10 (s, 3H). ¹³C NMR (101 MHz, *d*₆-DMSO) δ 168.68, 166.78, 164.50, 137.21, 134.83, 134.68, 131.45, 127.14, 126.40, 126.23, 124.86, 123.45, 62.54, 54.75, 23.32. HRMS (EI) *m/z*: 383.0678 (*M*⁺); calc. for C₁₉H₁₄ClN₃O₄: 383.0673.

2-((2*S*,3*S*)-2-(4-Methoxy-3-nitrophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (4f)



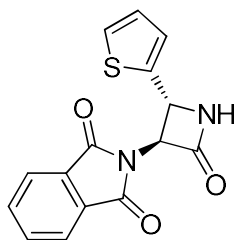
The title compound **4f** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 2.5 gave **4f** as a white solid (30.5 mg, 83%). ¹H NMR (400 MHz, CDCl₃) δ 7.92 – 7.84 (m, 3H), 7.80 – 7.74 (m, 2H), 7.62 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 6.74 (brs, 1H), 5.16 (d, *J* = 2.8 Hz, 1H), 5.14 (d, *J* = 2.4 Hz, 1H), 3.98 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 166.97, 165.06, 153.43, 139.77, 134.86, 131.72, 131.56, 130.26, 124.07, 123.74, 114.62, 63.70, 56.92, 56.24. HRMS (EI) *m/z*: 367.0811 (*M*⁺); calc. for C₁₈H₁₃N₃O₆: 367.0804.

5-((2*S*,3*S*)-3-(1,3-Dioxoisindolin-2-yl)-4-oxoazetidin-2-yl)-2-methoxy-3-methylphenyl 4-methylbenzenesulfonate (4g**)**



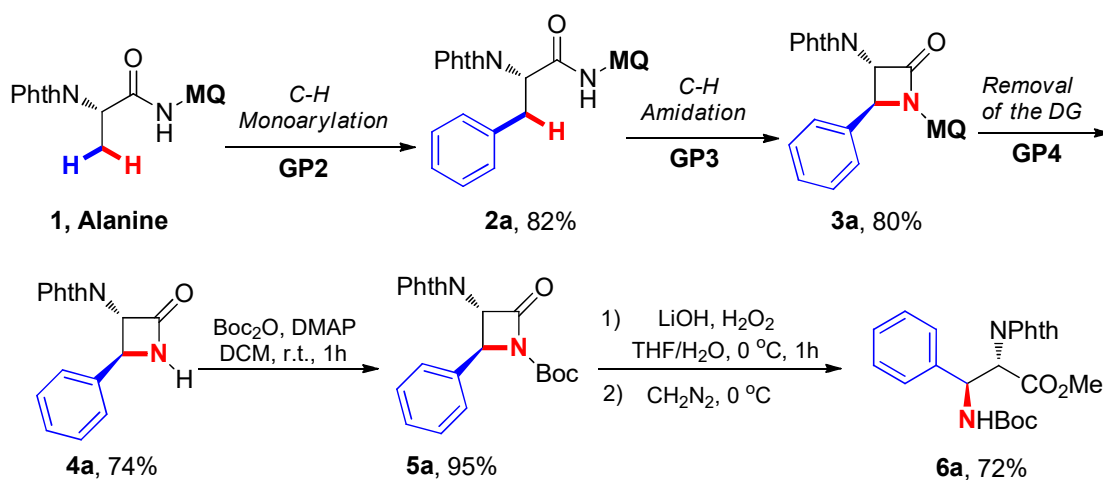
The title compound **4g** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 2 gave **4g** as a white solid (29.4 mg, 58%). ¹H NMR (400 MHz, CDCl₃) δ 7.92 – 7.86 (m, 2H), 7.81 – 7.73 (m, 4H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 1.2 Hz, 1H), 6.85 (d, *J* = 1.6 Hz, 1H), 6.44 (brs, 1H), 5.03 (d, *J* = 2.8 Hz, 1H), 4.99 (d, *J* = 2.4 Hz, 1H), 3.74 (s, 3H), 2.42 (s, 3H), 2.22 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 166.97, 165.05, 151.35, 145.76, 142.88, 134.77, 134.34, 133.17, 132.94, 131.77, 129.91, 128.65, 126.95, 123.99, 118.96, 63.60, 60.91, 56.55, 21.83, 16.36. HRMS (EI) *m/z*: 506.1146 (*M*⁺); calc. for C₂₆H₂₂N₂O₇S: 506.1148.

2-((3*S*,4*R*)-2-oxo-4-(thiophen-2-yl)azetidin-3-yl)isoindoline-1,3-dione (4h**)**

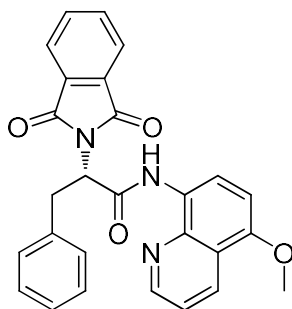


The title compound **4h** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 2 : 6 : 1 gave **4h** as a white solid (6.3 mg, 21%). ^1H NMR (400 MHz, CDCl_3) δ 7.92 – 7.85 (m, 2H), 7.80 – 7.74 (m, 2H), 7.33 (dd, J = 5.2, 1.2 Hz, 1H), 7.11 (dd, J = 3.6 Hz, J = 1.2 Hz, 1H), 7.00 (dd, J = 5.2, 3.6 Hz, 1H), 6.53 (brs, 1H), 5.40 (d, J = 2.4 Hz, 1H), 5.33 (d, J = 2.8 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.96, 164.86, 141.53, 134.74, 131.80, 127.54, 126.22, 125.90, 124.00, 64.22, 53.51. HRMS (EI) m/z : 298.0416 (M^+); calc. for $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_3\text{S}$: 298.0412.

Synthesis of Orthogonally Protected *trans*- α,β -Diamine

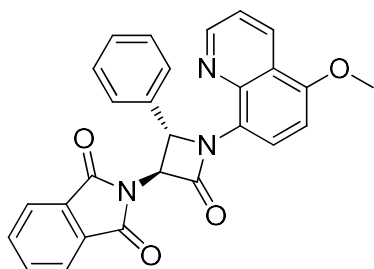


(*S*)-2-(1,3-Dioxoisindolin-2-yl)-*N*-(5-methoxyquinolin-8-yl)-3-phenylpropanamide (2a)



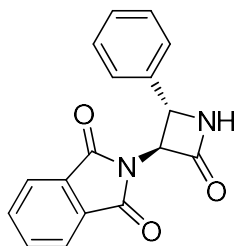
The compound **2a** was prepared according to **GP2**. Purified by silica gel column chromatography in petroleum ether : ethyl acetate = 4 : 1 gave **2a** as a white solid (0.370 g, 82 %). ¹H NMR (400 MHz, CDCl₃) δ 10.09 (brs, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.61 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.51 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.87 – 7.75 (m, 2H), 7.73 – 7.64 (m, 2H), 7.36 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.25 – 7.19 (m, 2H), 7.18 – 7.12 (m, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 5.44 (t, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 3.81 (d, *J* = 8.4 Hz, 2H).

2-((3*S*,4*S*)-1-(5-Methoxyquinolin-8-yl)-2-oxo-4-phenylazetidin-3-yl)isoindoline-1,3-dione (3a**)**



The title compound **3a** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : ethyl acetate = 2 : 1 gave **3a** as a white solid (0.180 g, 80%). ¹H NMR (400 MHz, CDCl₃) δ 8.78 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.44 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.91 – 7.83 (m, 2H), 7.78 – 7.70 (m, 2H), 7.46 – 7.37 (m, 2H), 7.29 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.25 – 7.14 (m, 3H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 2.8 Hz, 1H), 5.43 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.08, 163.30, 153.17, 149.83, 142.49, 138.09, 134.52, 131.96, 130.53, 128.80, 128.37, 126.55, 125.55, 123.82, 123.23, 121.06, 120.66, 103.97, 65.20, 62.97, 55.96. HRMS (EI) *m/z*: 449.1378 (*M*⁺); calc. for C₂₇H₁₉N₃O₄: 449.1376.

2-((3*S*,4*S*)-2-oxo-4-phenylazetidin-3-yl)isoindoline-1,3-dione (4a**)**

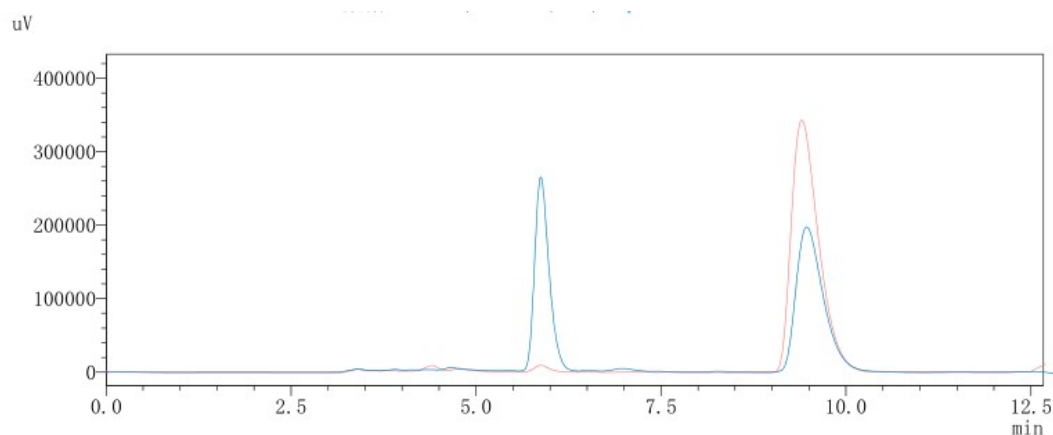


The title compound **4a** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 2 : 4 : 1 gave **4a** as a white solid (21.6 mg, 74%). ¹H NMR (400 MHz, CDCl₃) δ 7.91 – 7.84 (m, 2H), 7.79 – 7.73 (m, 2H), 7.42 – 7.32 (m, 5H), 6.67 (brs, 1H), 5.21 (d, *J* = 2.8 Hz, 1H), 5.14 (d, *J* = 2.8 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 167.03, 165.41, 137.72, 134.67, 131.79, 129.19, 128.94, 125.96, 123.93, 63.46, 57.52. HRMS (EI) *m/z*: 292.0850 (*M*⁺); calc. for C₁₇H₁₂N₂O₃: 292.0848. Enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H, *n*-hexane/2-propanol = 20/80, *v* = 0.8 mL·min⁻¹, λ = 254 nm, *t* (minor) = 5.874 min, *t* (major) = 9.612 min, 97% ee.

Chiral HPLC Data

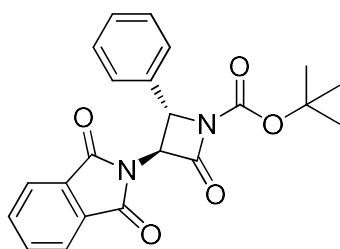
HPLC Conditions:

Chiral Stationary phase: Chiralpak[®] AD-H, *n*-hexane/isopropanol = 20:80, *v* = 0.8 ml/min, Signal: VWD1 A, Wavelength = 254 nm



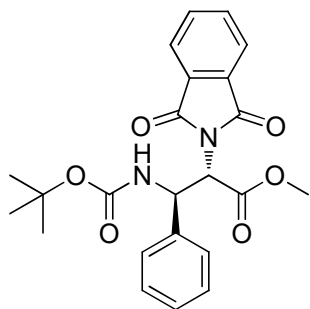
Retention Time	Area	Area%
5.874	120458	1.342
9.612	8856729	98.658
Totals	8977187	100

(3*S*,4*S*)-*tert*-Butyl-3-(1,3-dioxoisindolin-2-yl)-2-oxo-4-phenylazetidine-1-carboxylate (5a)



To a solution of compound **4a** (20.4 mg, 0.07 mmol, 1 equiv) in anhydrous dichloromethane (2 mL) was added 4-(dimethylamino)pyridine (11.8 mg, 0.105 mmol, 1.5 equiv) and Boc anhydride (61.1 mg, 0.28 mmol, 4 equiv). The mixture was stirred at room temperature for 1 hour then concentrated under reduced pressure. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 1 gave **5a** as a white solid (26.1 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ 7.92 – 7.84 (m, 2H), 7.81 – 7.73 (m, 2H), 7.44 – 7.32 (m, 5H), 5.28 (d, *J* = 3.2 Hz, 1H), 5.24 (d, *J* = 3.2 Hz, 1H), 1.40 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 166.64, 162.72, 147.32, 136.14, 134.83, 131.67, 129.14, 126.22, 124.03, 83.97, 61.77, 60.65, 27.93. HRMS (ESI) *m/z*: 415.1256 (M+Na⁺); calc. for C₂₂H₂₀N₂O₅Na: 415.1264.

(2*S*,3*R*)-Methyl-3-((*tert*-butoxycarbonyl)amino)-2-(1,3-dioxoisindolin-2-yl)-3-phenylpropanoate (6a**)**



A solution of compound **5a** (23.5 mg, 0.06 mmol, 1 equiv) in THF and water (1 mL : 0.3 mL) was cooled to 0 °C then 30% H₂O₂ (60 μL, 0.528 mmol, 8.8 equiv) and lithium hydroxide monohydrate (2.7 mg, 0.066 mmol, 1.1 equiv) were added and stirred at 0 °C for 1 hour. The reaction was quenched at 0 °C with 1.5 M aqueous sodium thiosulfate (1.5 mL) and the solvent was concentrated under reduced pressure. The residue was washed with dichloromethane (10 mL), then the aqueous phase was

acidified to pH = 2 with 10% aqueous hydrochloric acid and extracted with ethyl acetate (2 × 15 mL). Evaporation of organic solvent gave the crude residue.

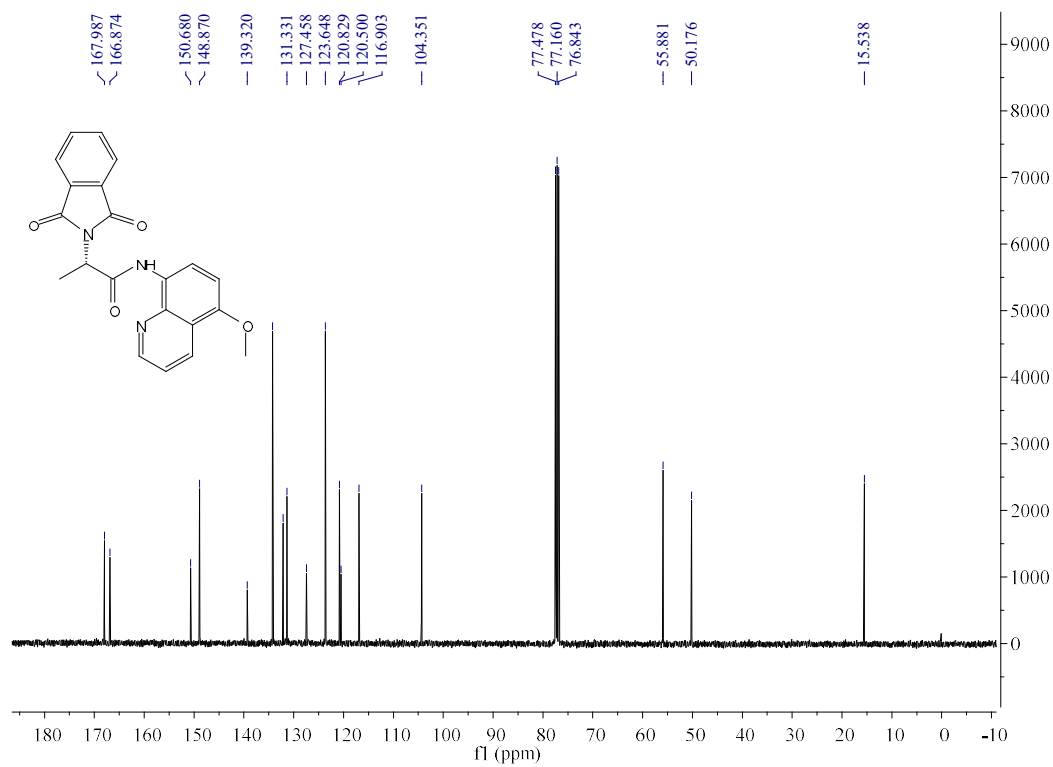
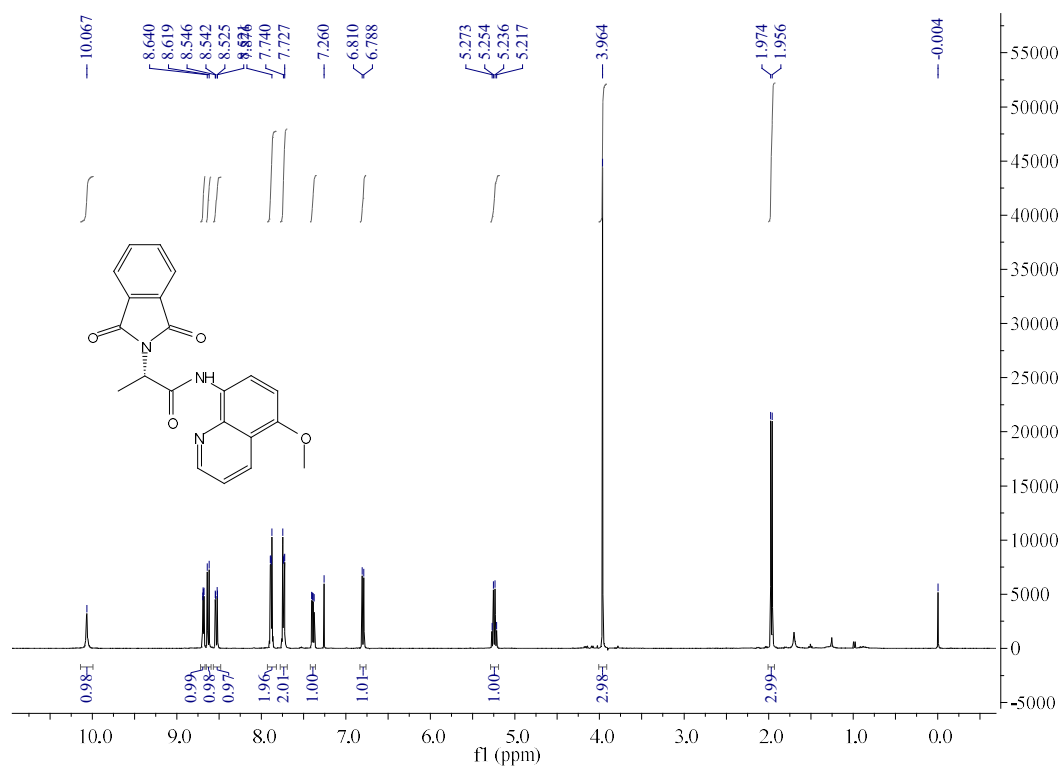
1-Methyl-1-nitrosourea was added in one portion to a stirring mixture of diethyl ether (20 mL) and aqueous KOH (2 g in 2 mL H₂O) in an ice bath. To the diethyl ether (5 mL) solution of the crude residue were added the light yellow upper layer until the latter solution also turned to the same color. Evaporation of organic solvent and purification by flash chromatography in petroleum ether : dichloromethane : ethyl acetate = 4 : 6 : 1 gave **6a** as a colorless oil (18.3 mg, 72%). ¹H NMR (400 MHz, CDCl₃) δ 7.88 – 7.79 (m, 2H), 7.76 – 7.68 (m, 2H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.26 – 7.19 (m, 1H), 5.96 (brs, 1H), 5.43 (dd, *J* = 9.6, 4.4 Hz, 1H), 5.18 (d, *J* = 4.4 Hz, 1H), 3.69 (s, 3H), 1.33 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 167.93, 167.20, 155.64, 138.44, 134.34, 131.70, 128.55, 127.71, 126.93, 123.71, 79.89, 55.91, 55.19, 52.81, 28.30. HRMS (ESI) *m/z*: 447.1524 (M+Na⁺); calc. for C₂₃H₂₄N₂O₆Na: 447.1527.

References

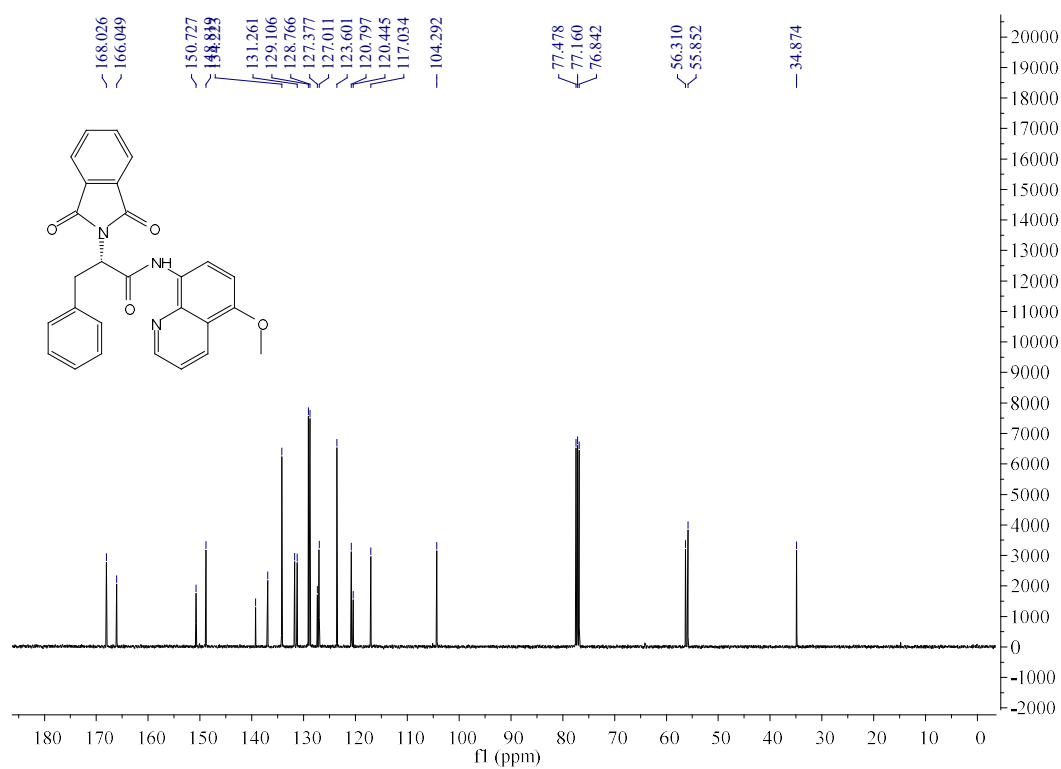
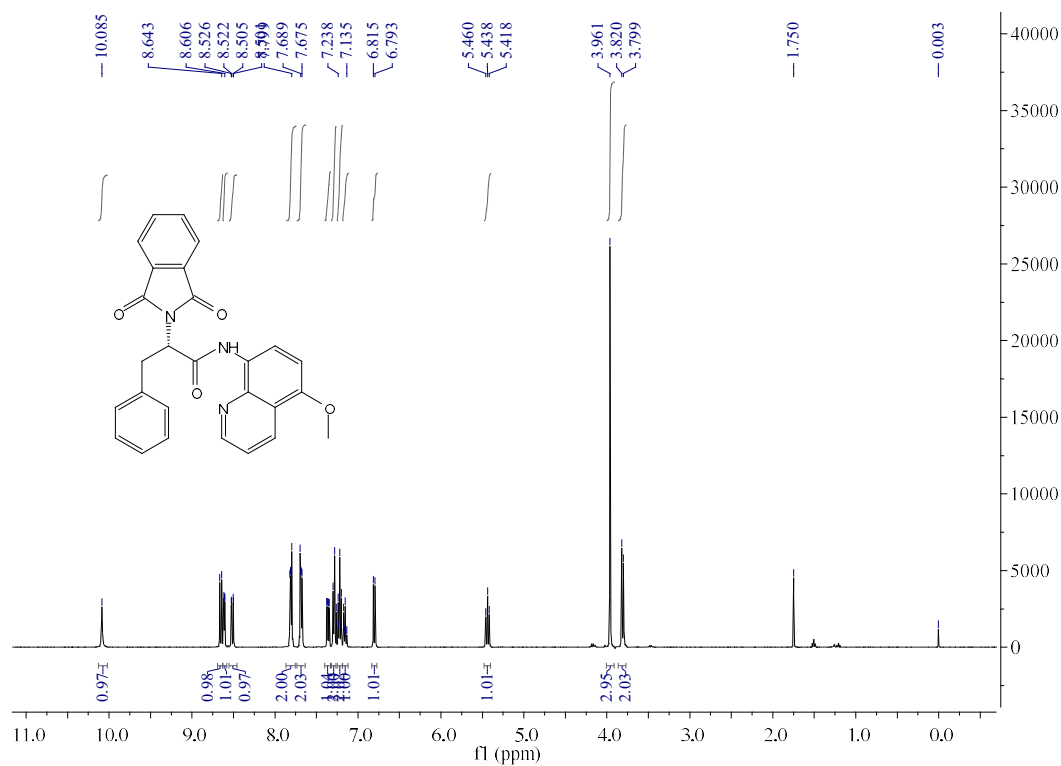
- (1) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, 52, 11124.
- (2) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, 4, 3906.

^1H and ^{13}C NMR Spectra

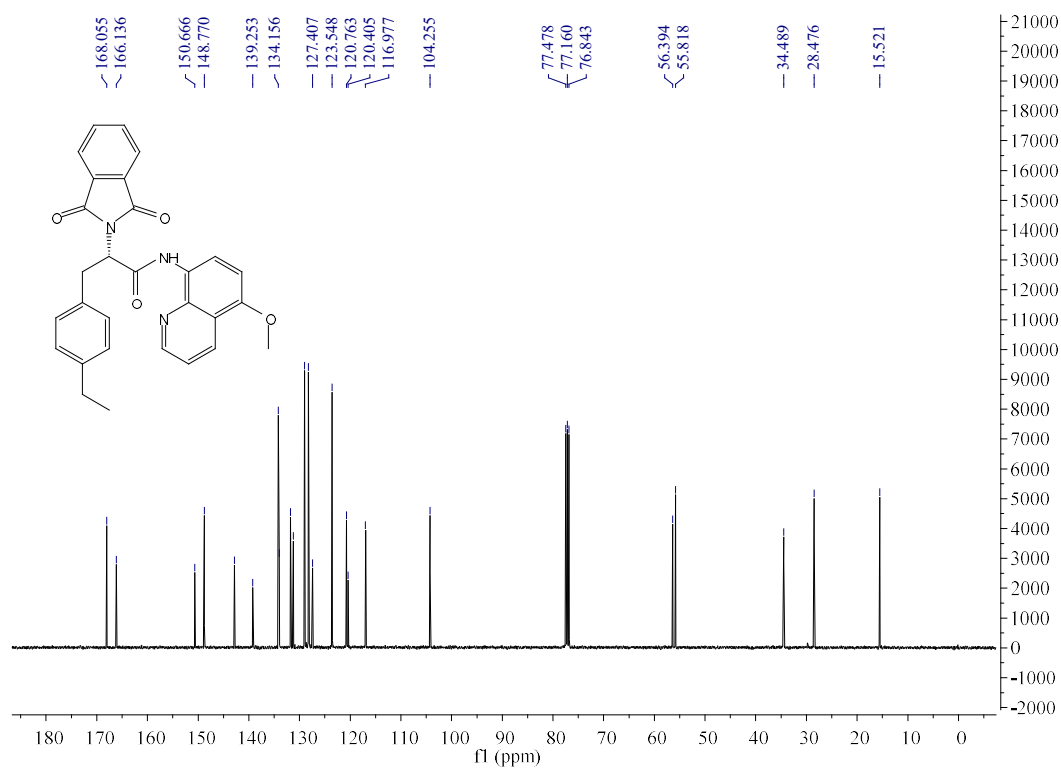
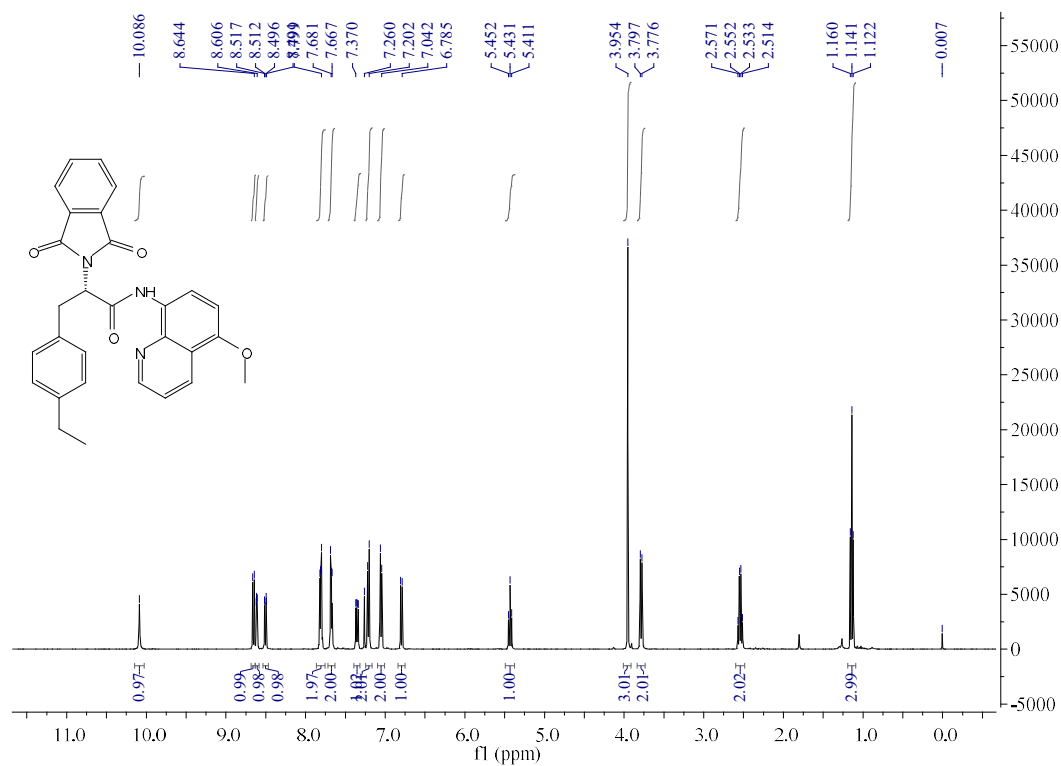
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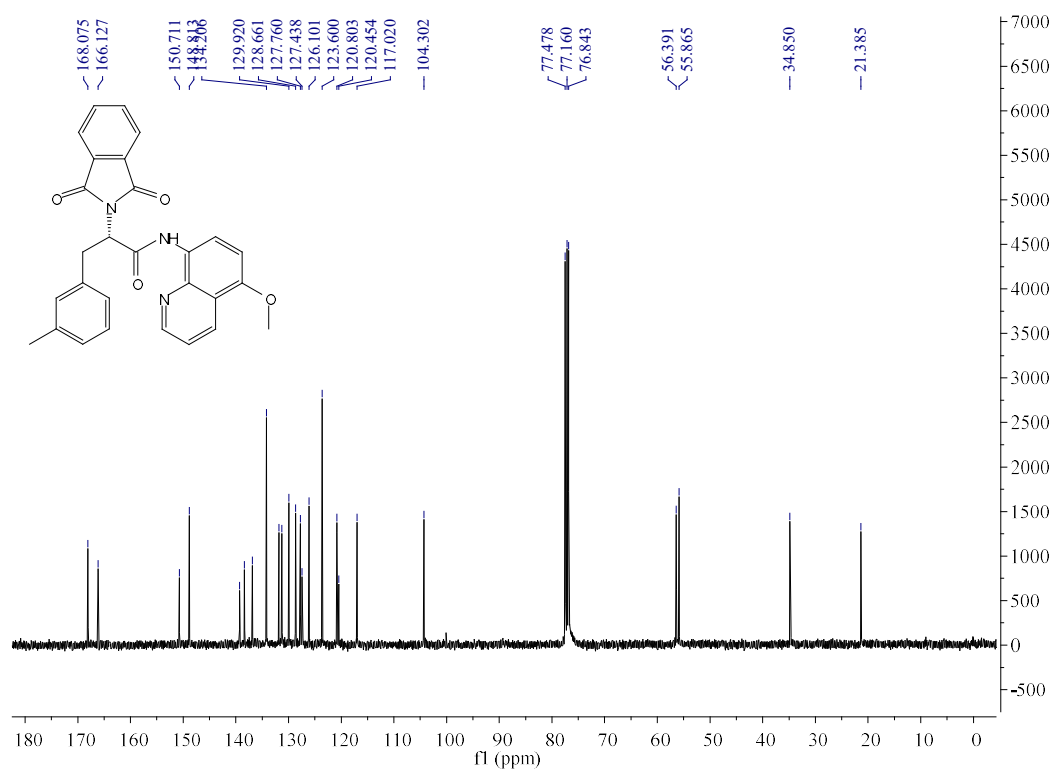
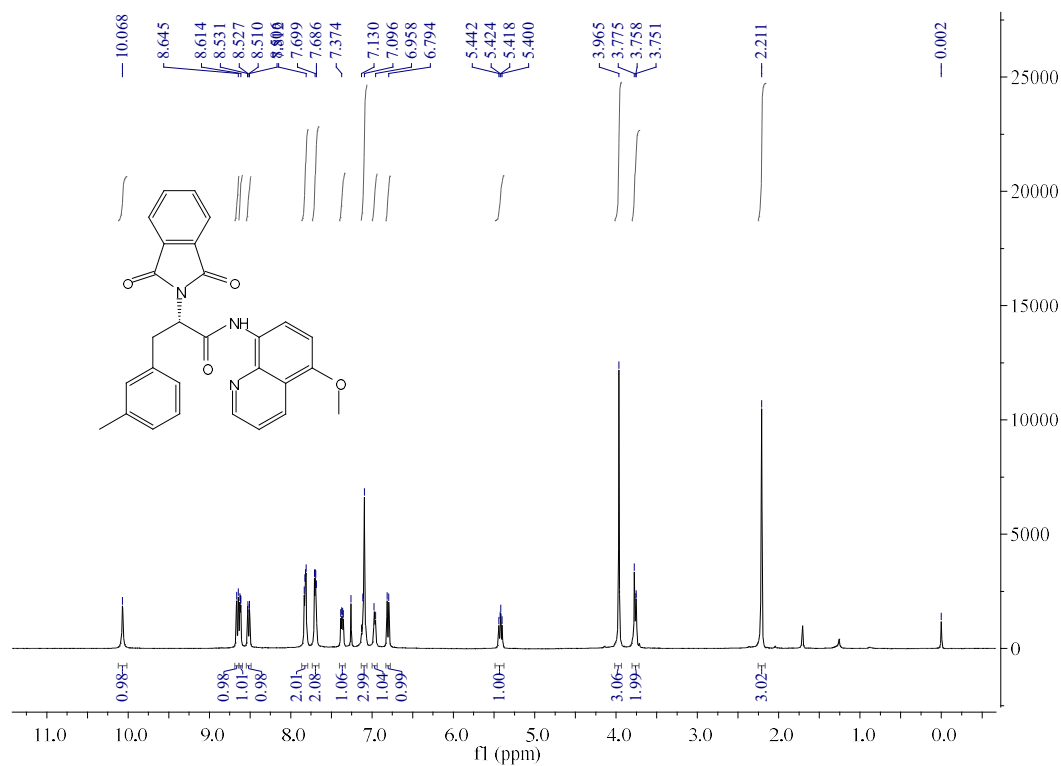
2a



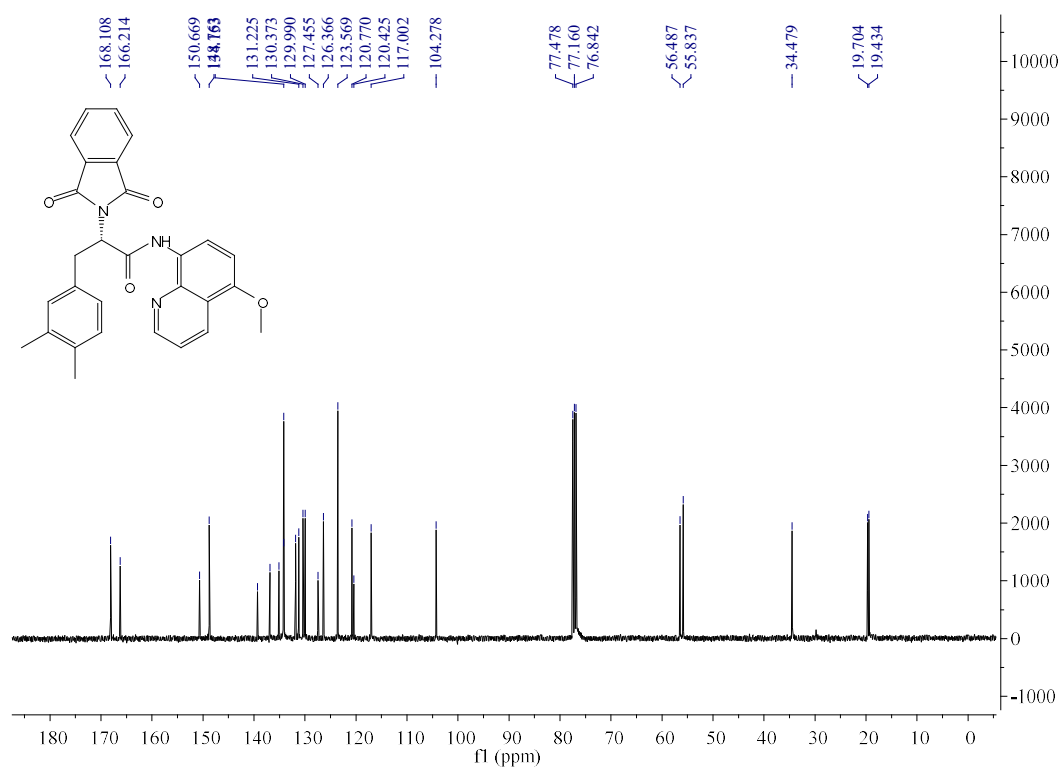
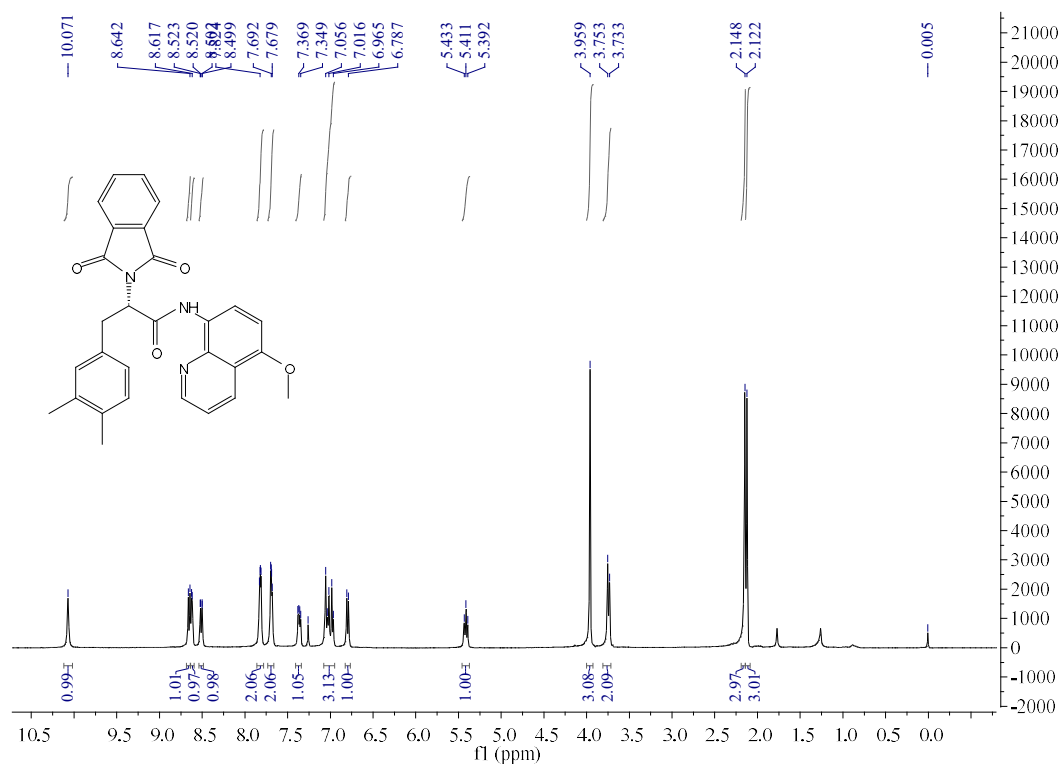
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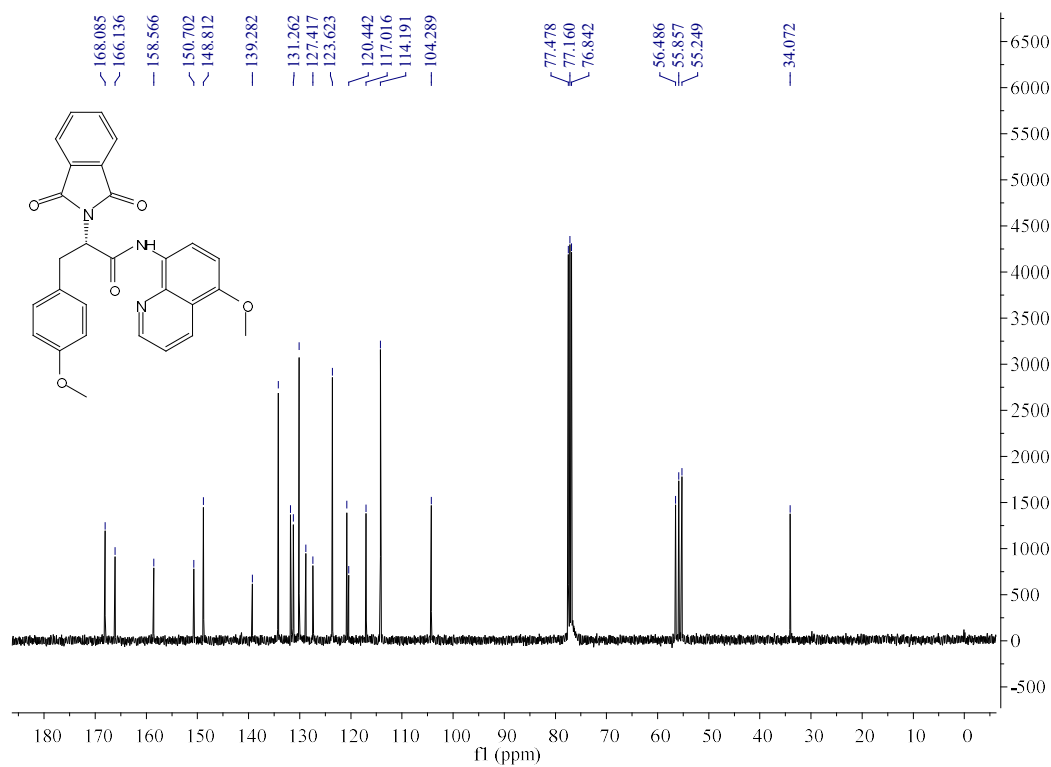
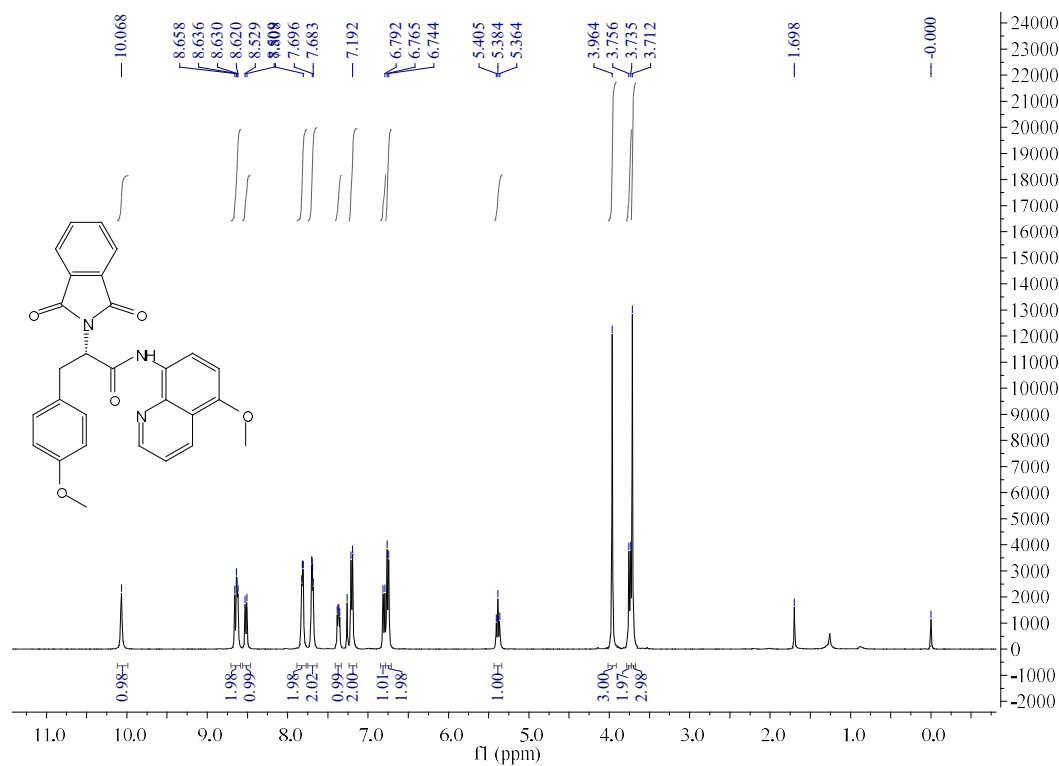
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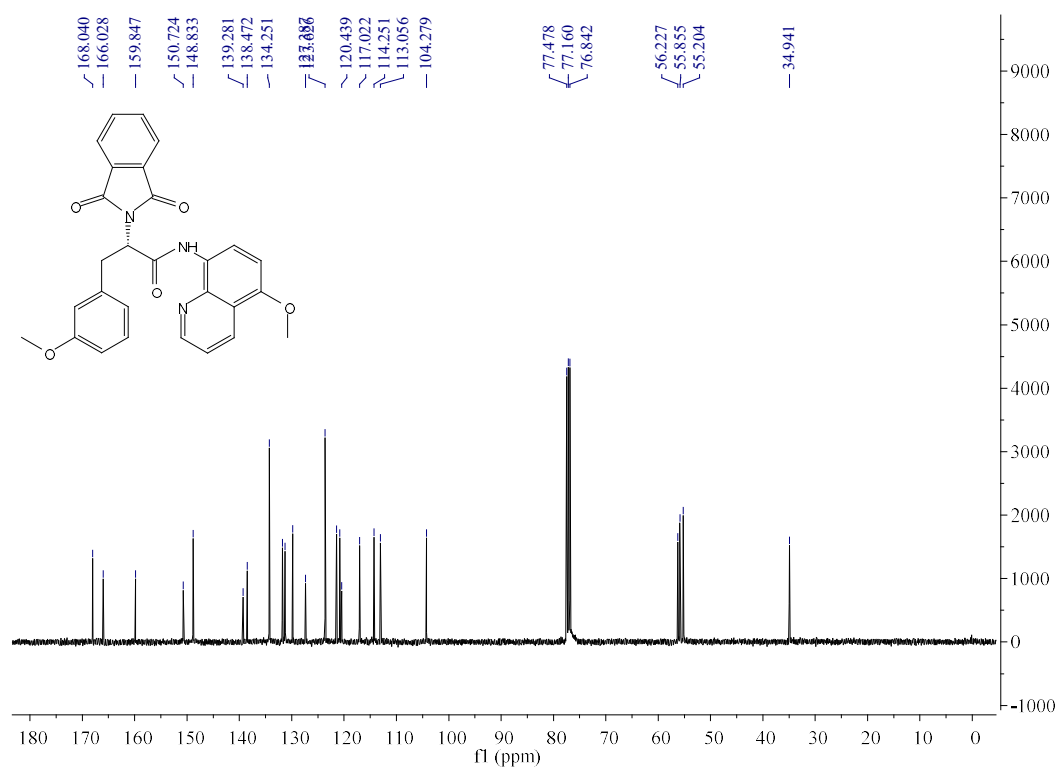
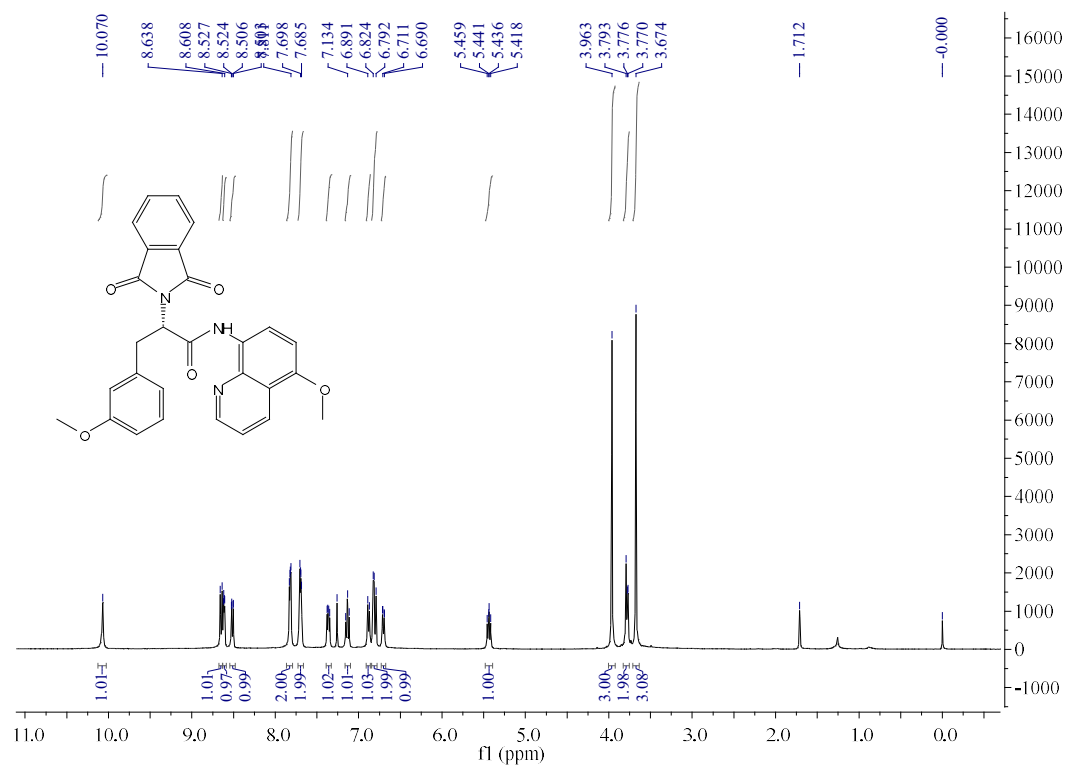
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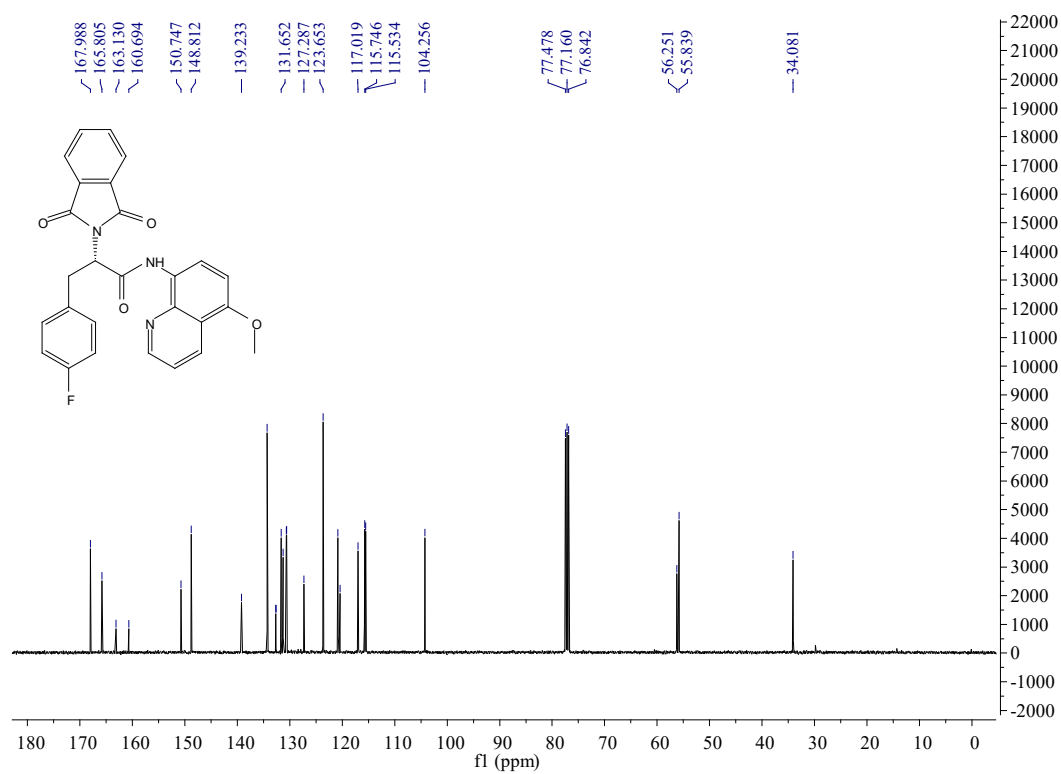
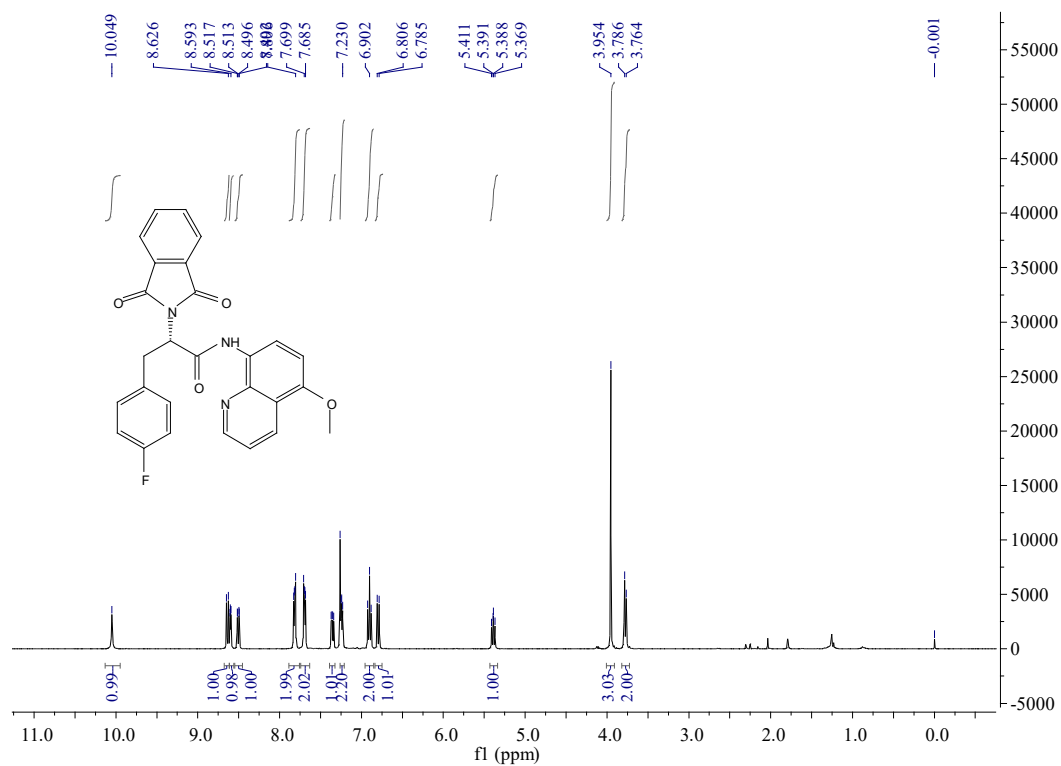
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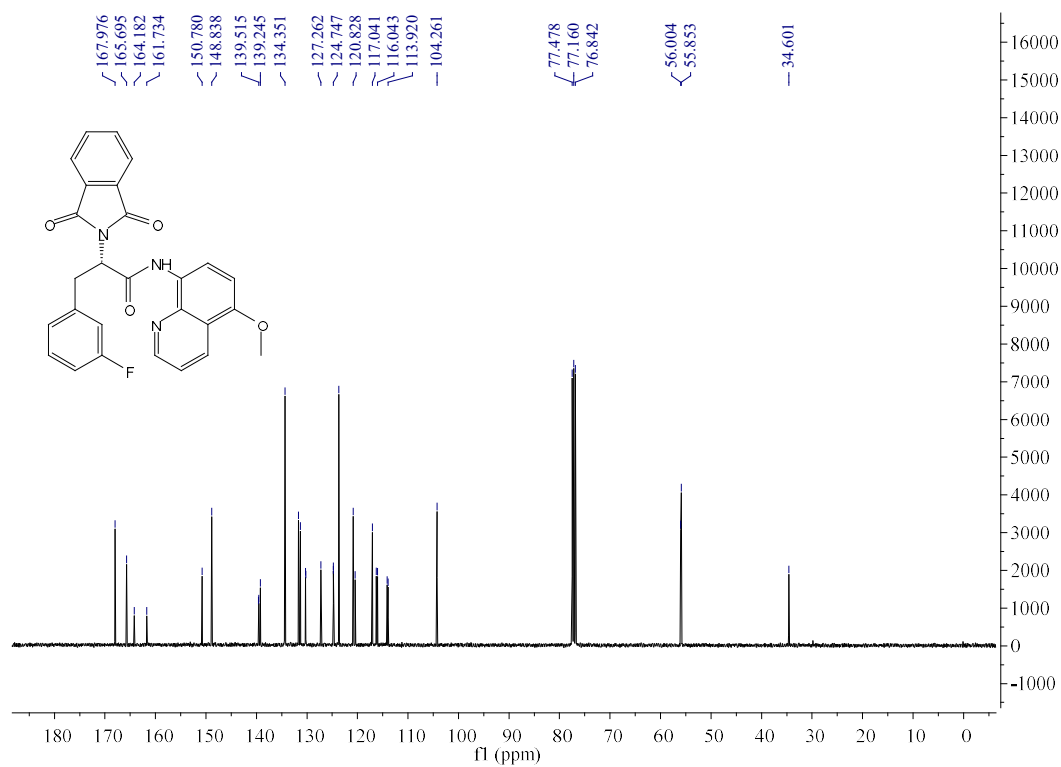
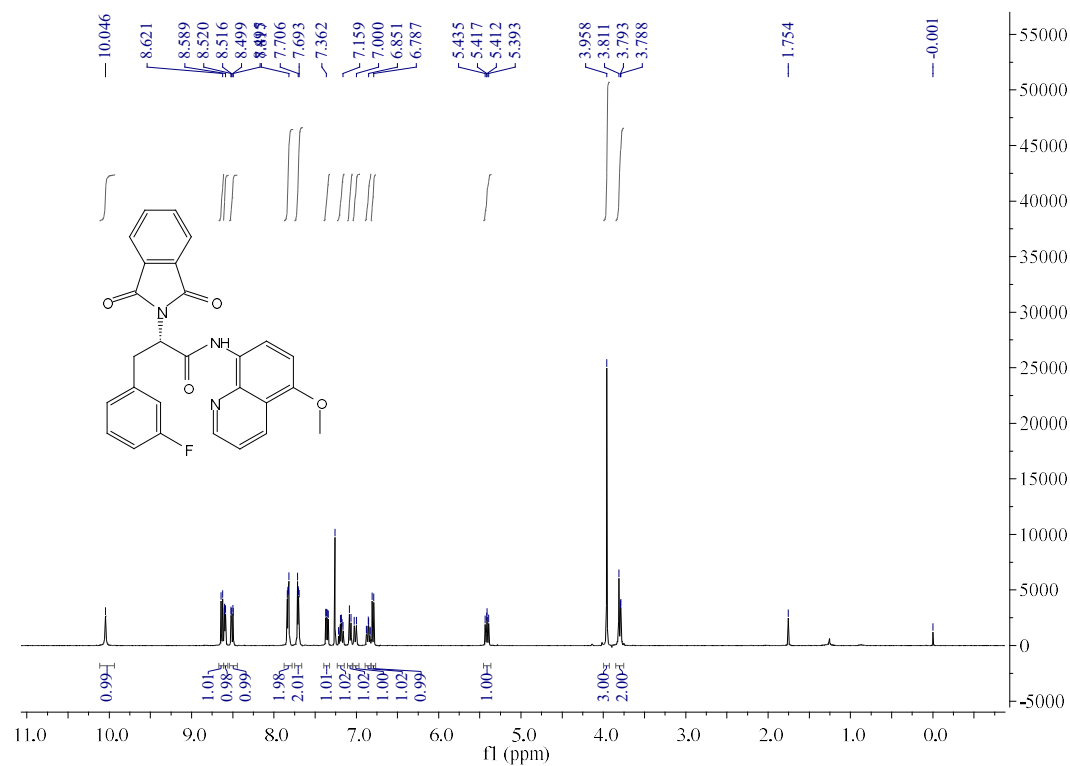
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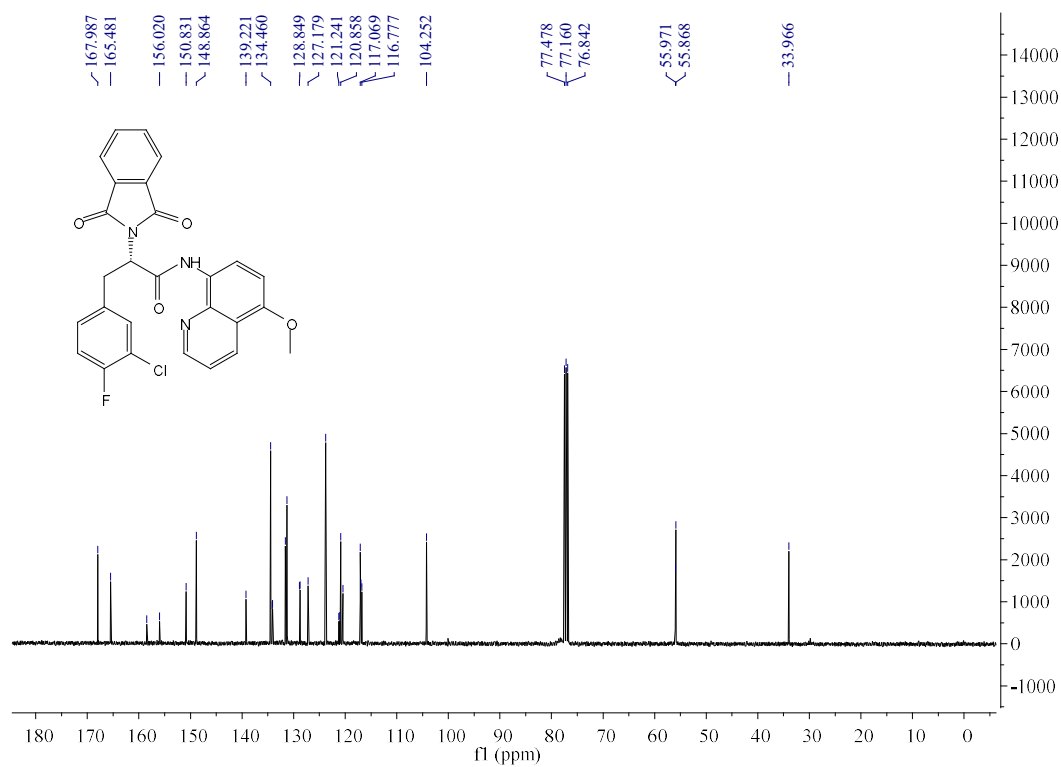
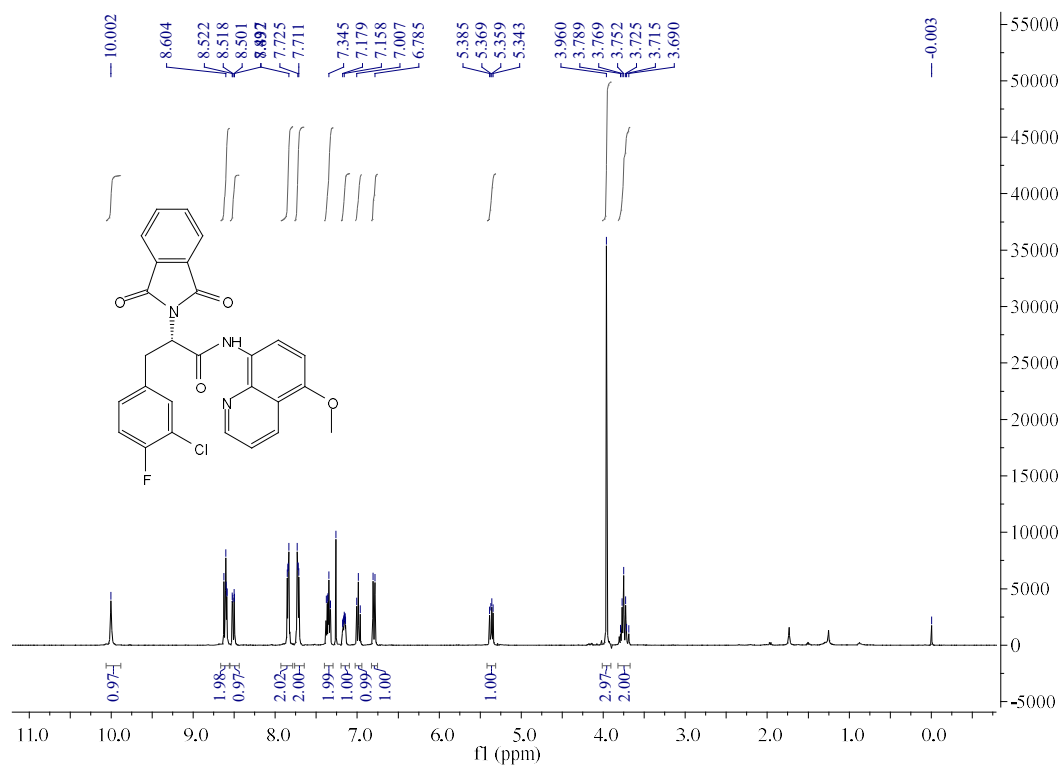
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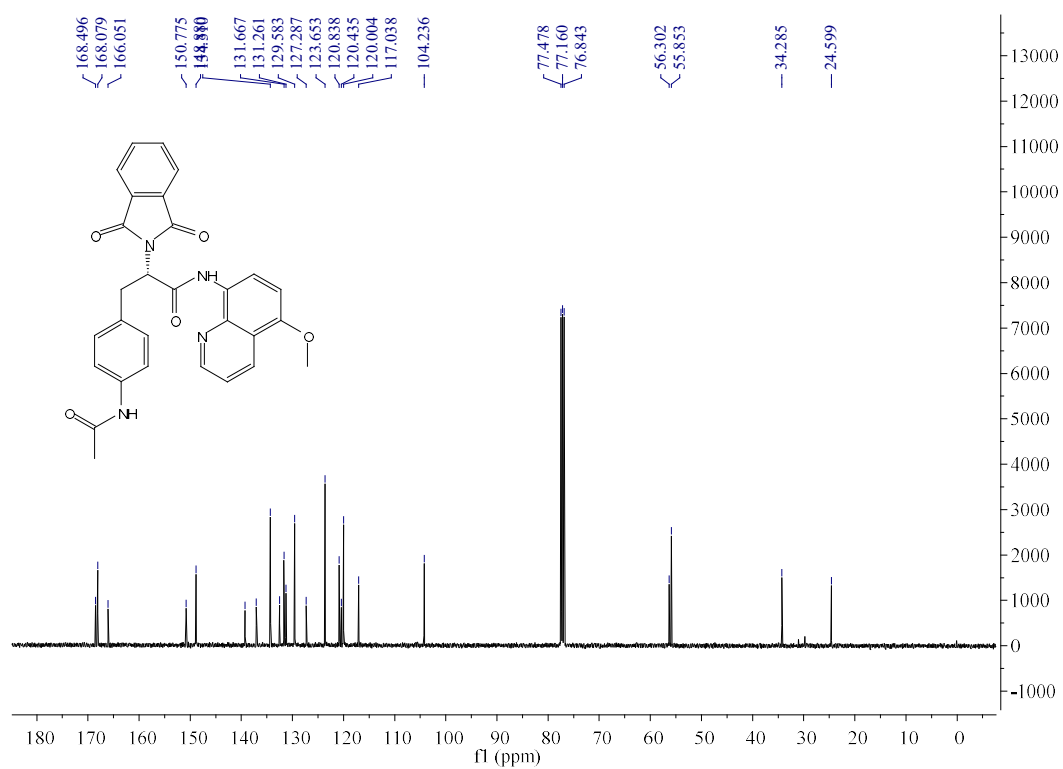
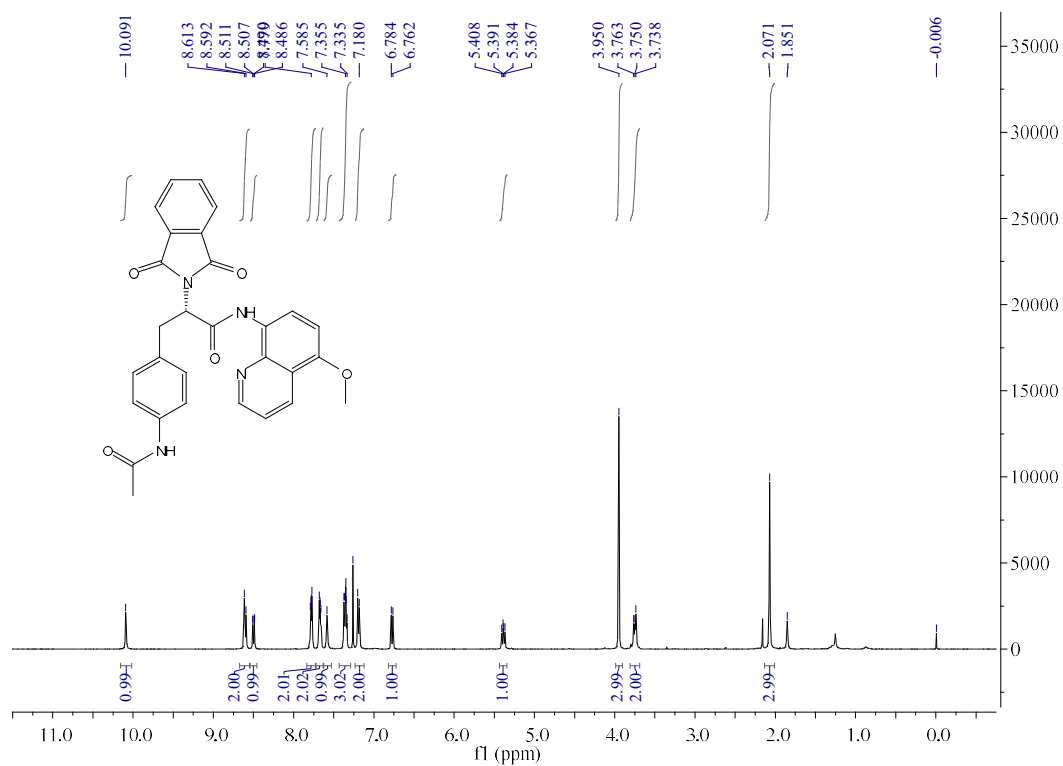
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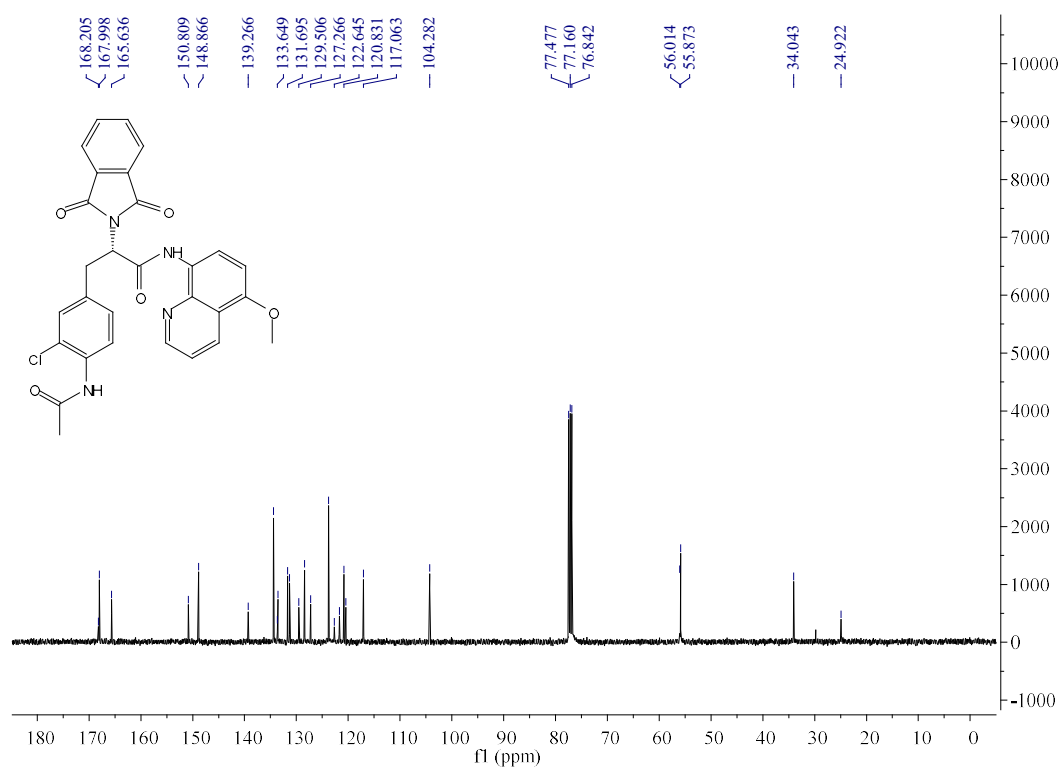
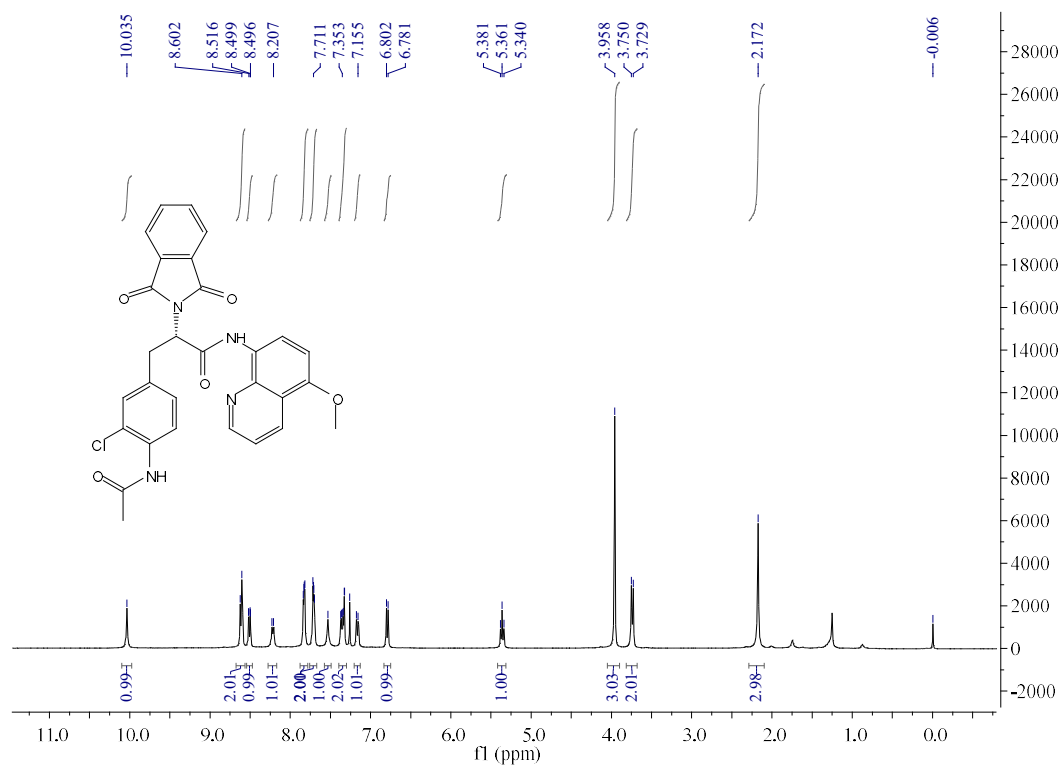
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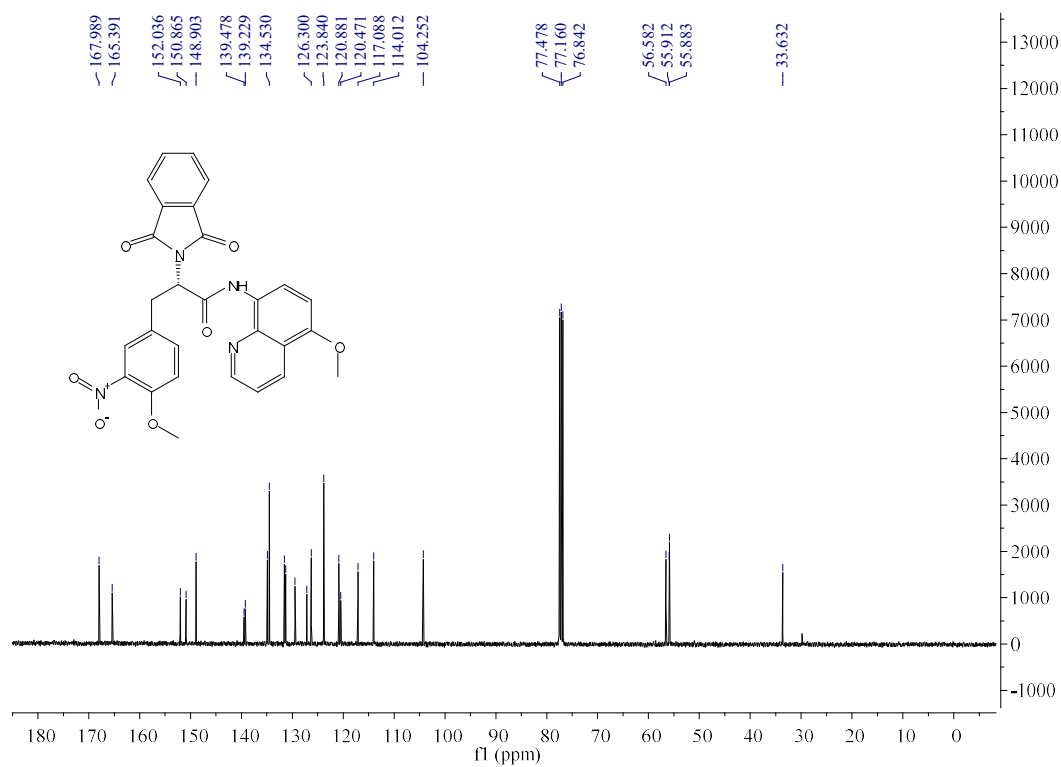
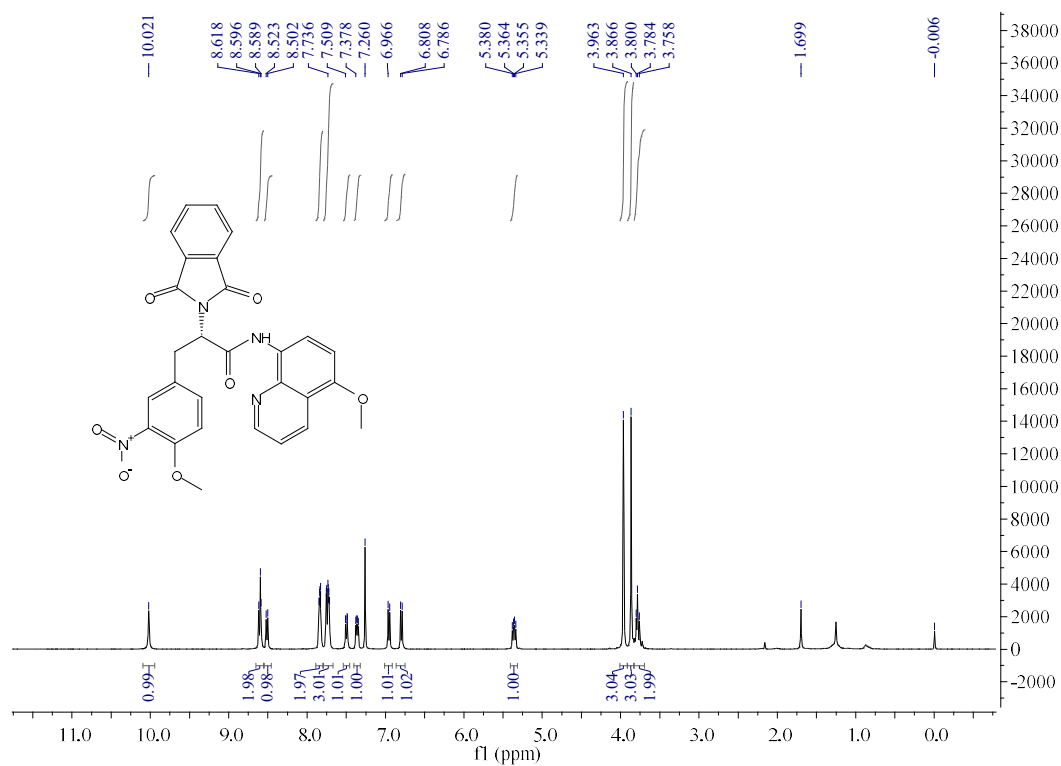


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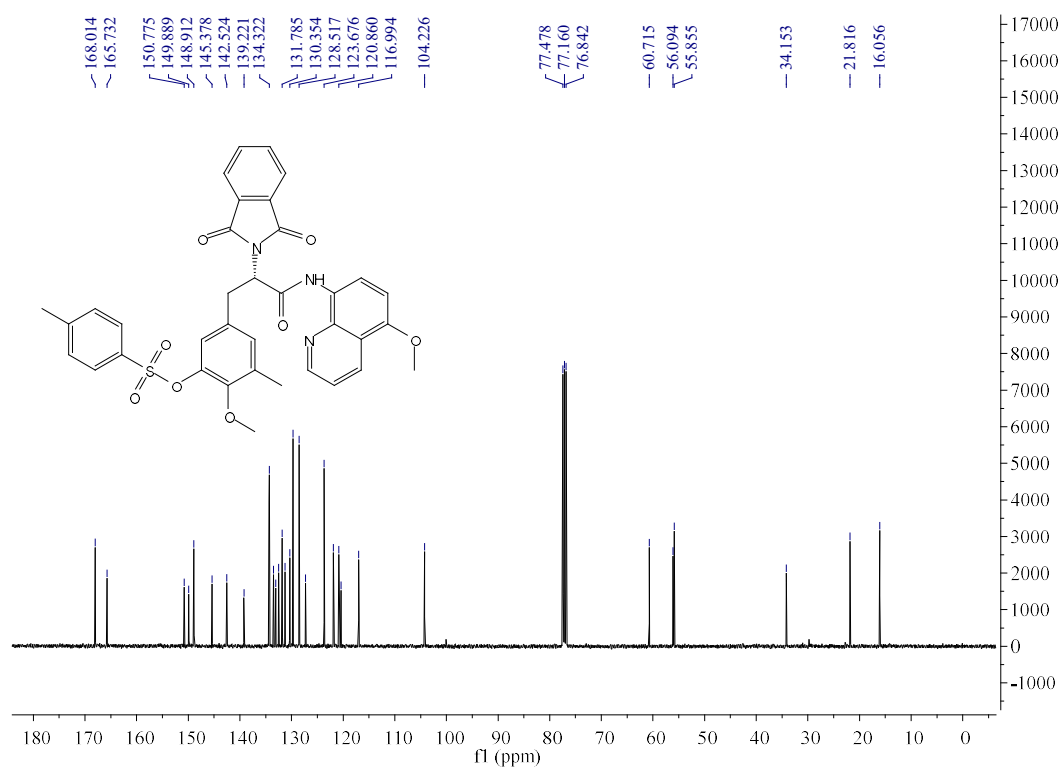
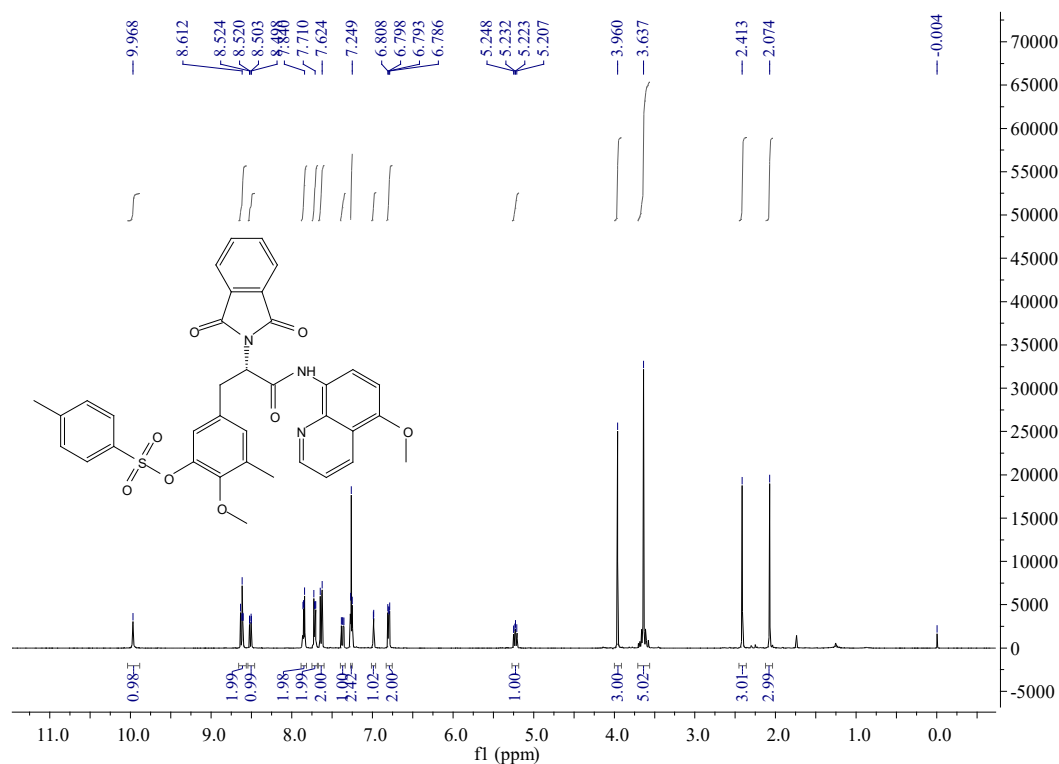


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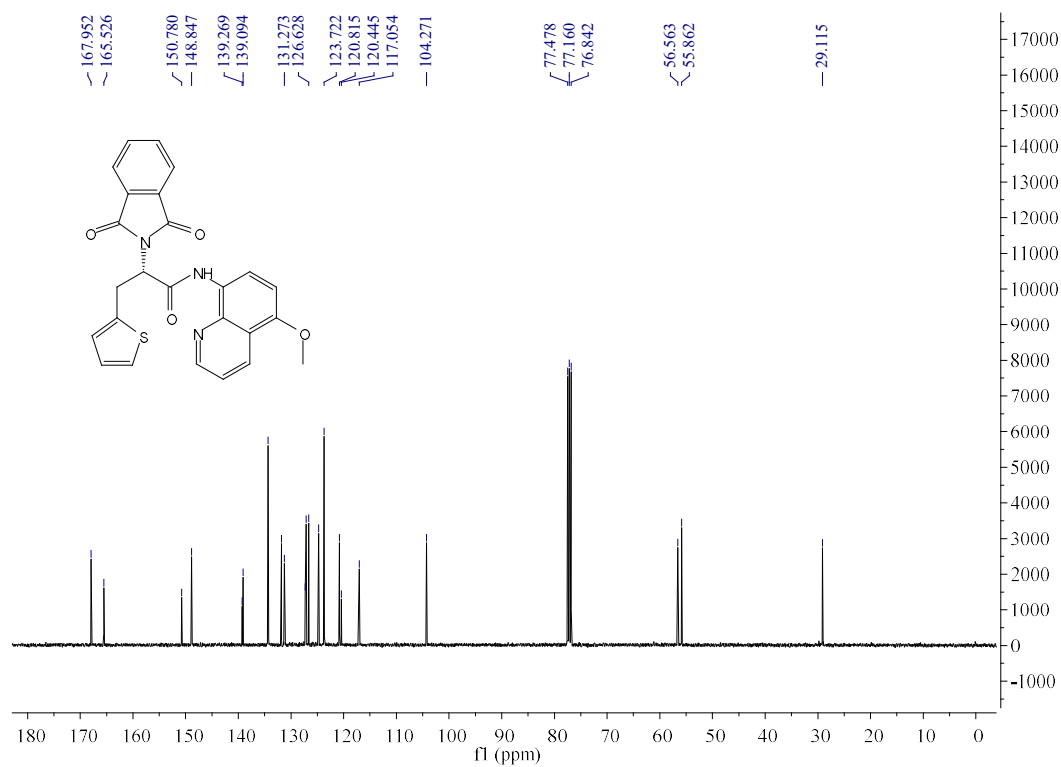
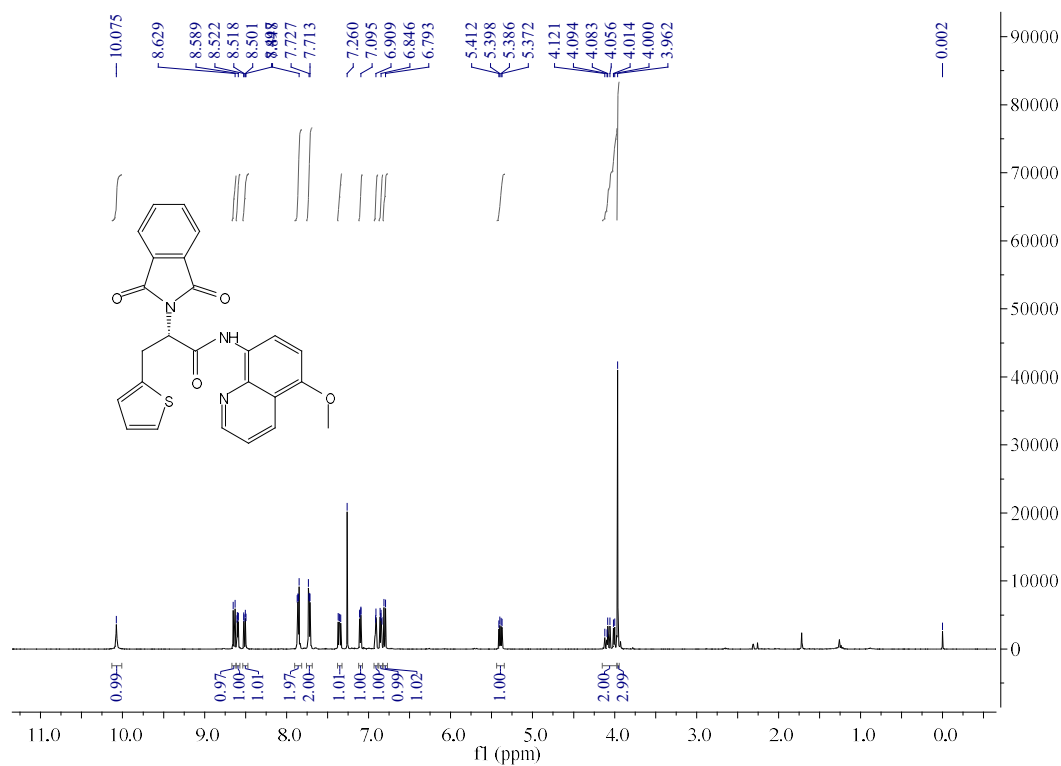




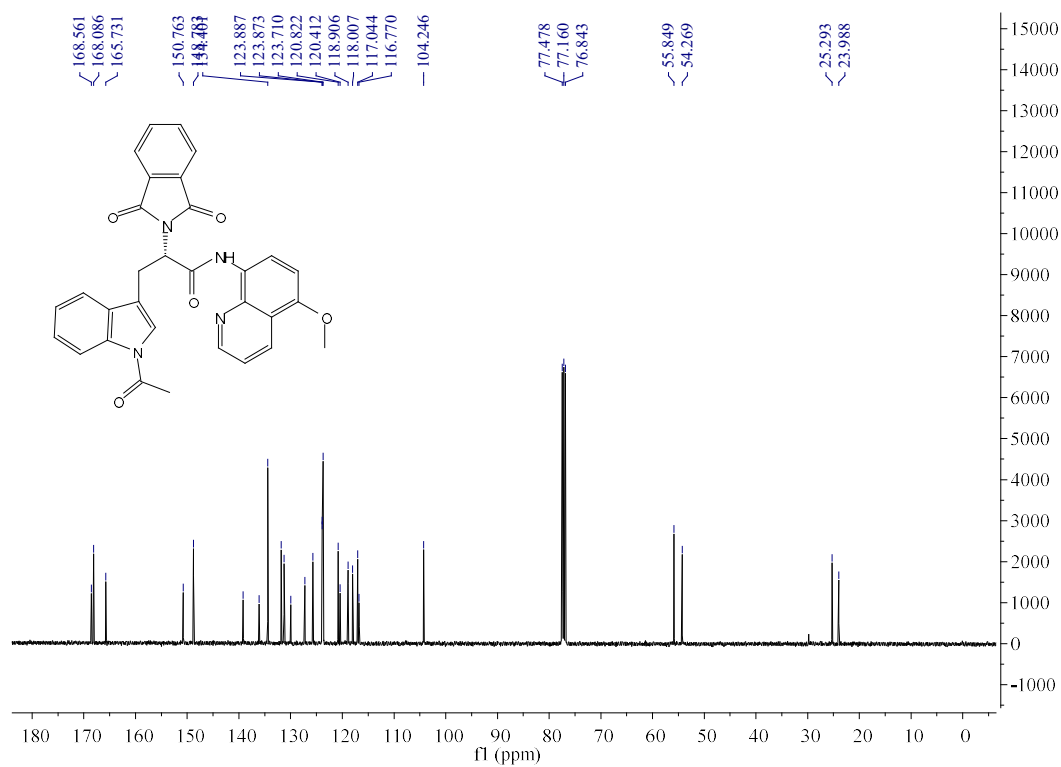
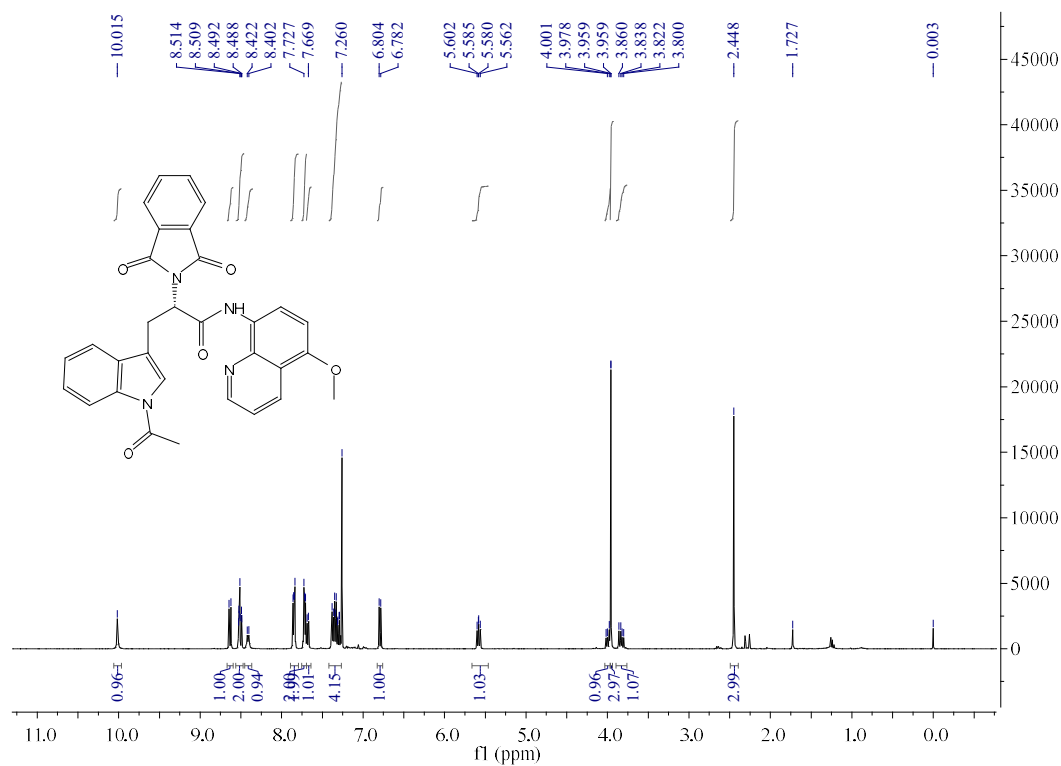
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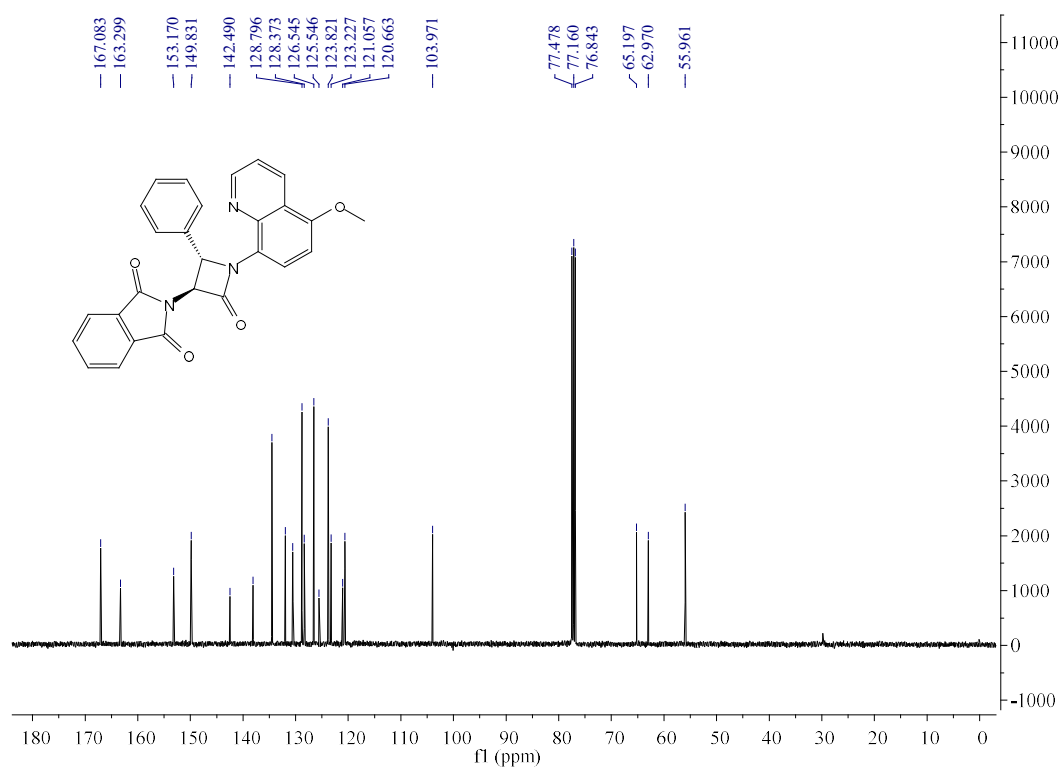
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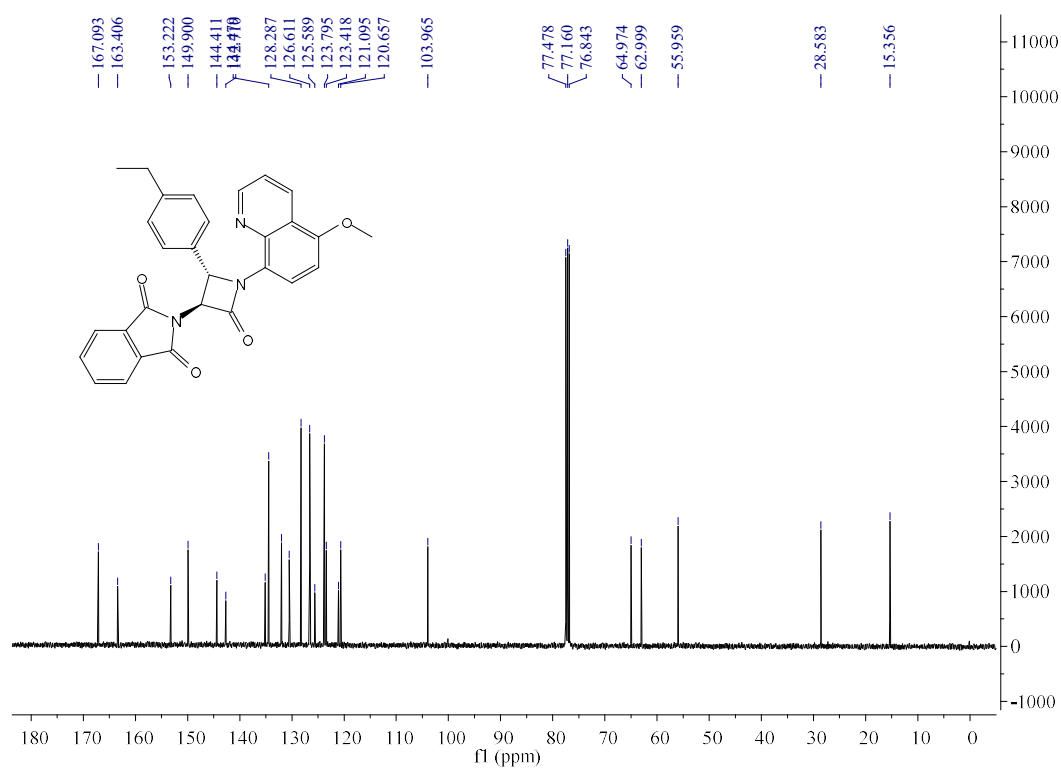
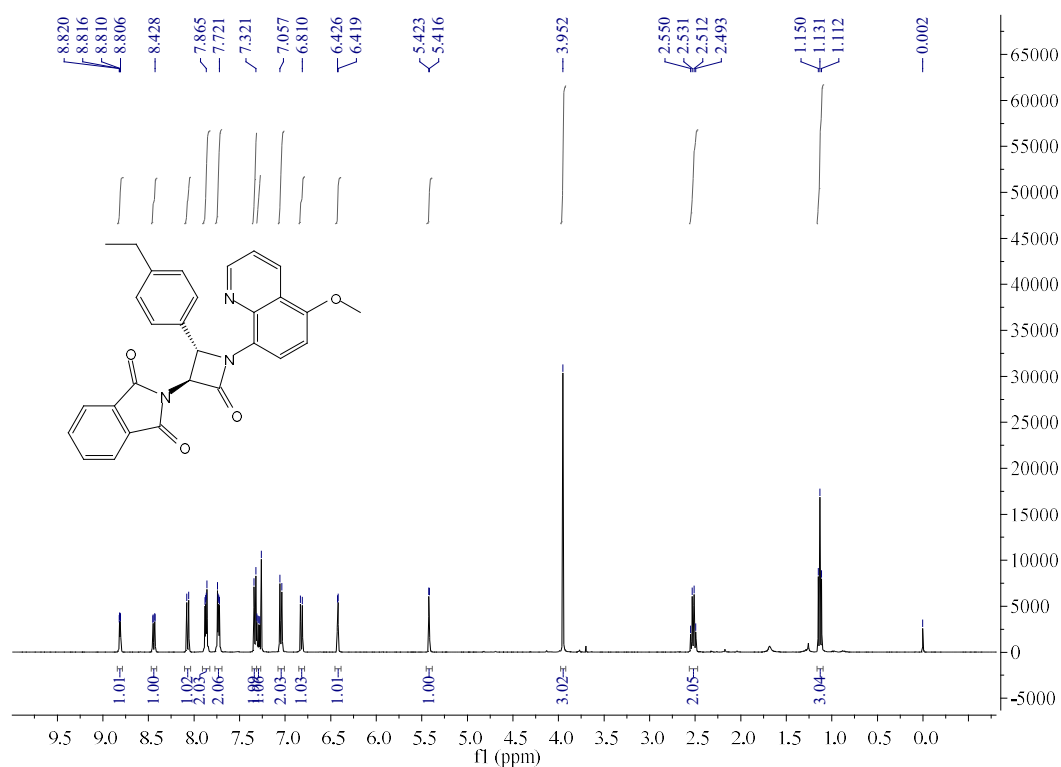
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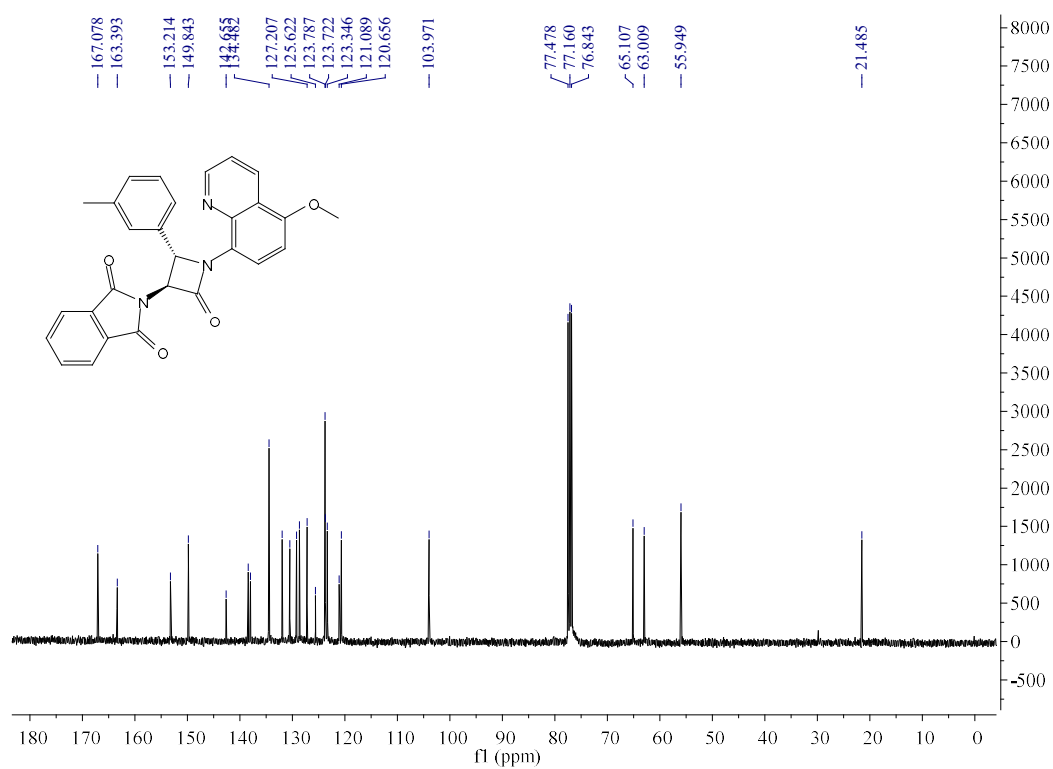
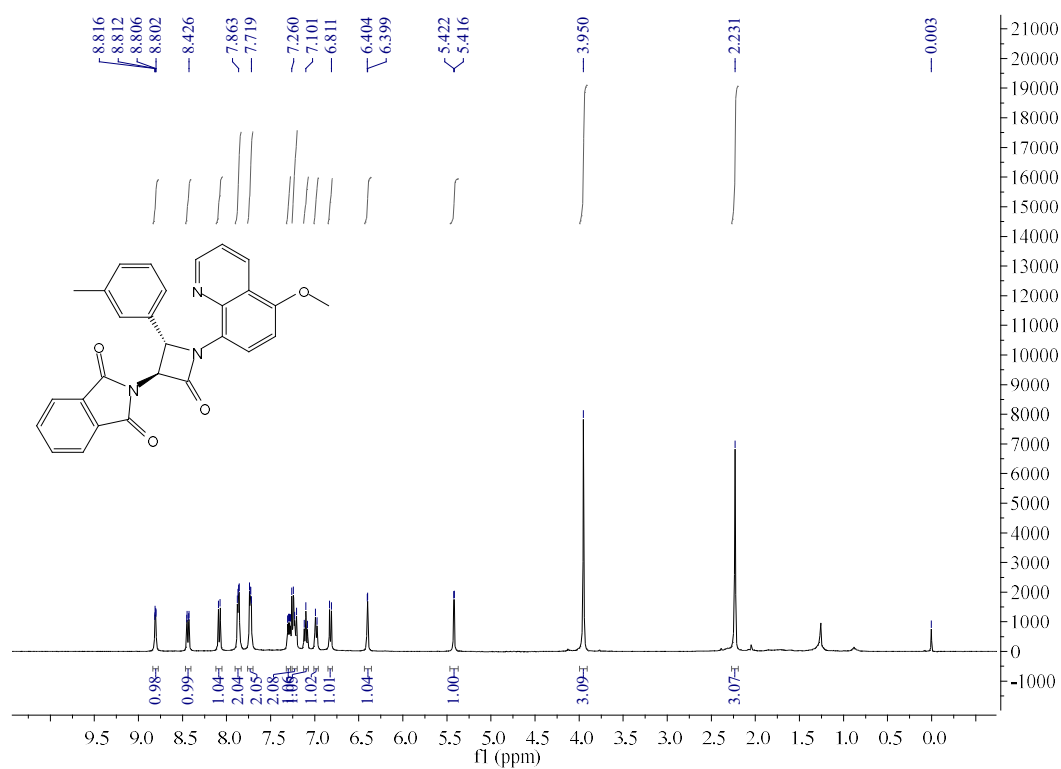
Chemical structure of compound 10 is shown. The ^1H NMR spectrum (CDCl₃) shows peaks at the following chemical shifts (ppm): 8.791, 8.787, 8.781, 8.777, 8.427, 8.097, 7.728, 7.260, 7.174, 6.817, 6.460, 6.453, 5.430, 5.424, 3.956, 1.707, and -0.000. The integration values are: 1.02, 1.00, 1.00, 2.02, 2.06, 1.06, 3.12, 1.05, 1.02, 1.01, and 3.03.



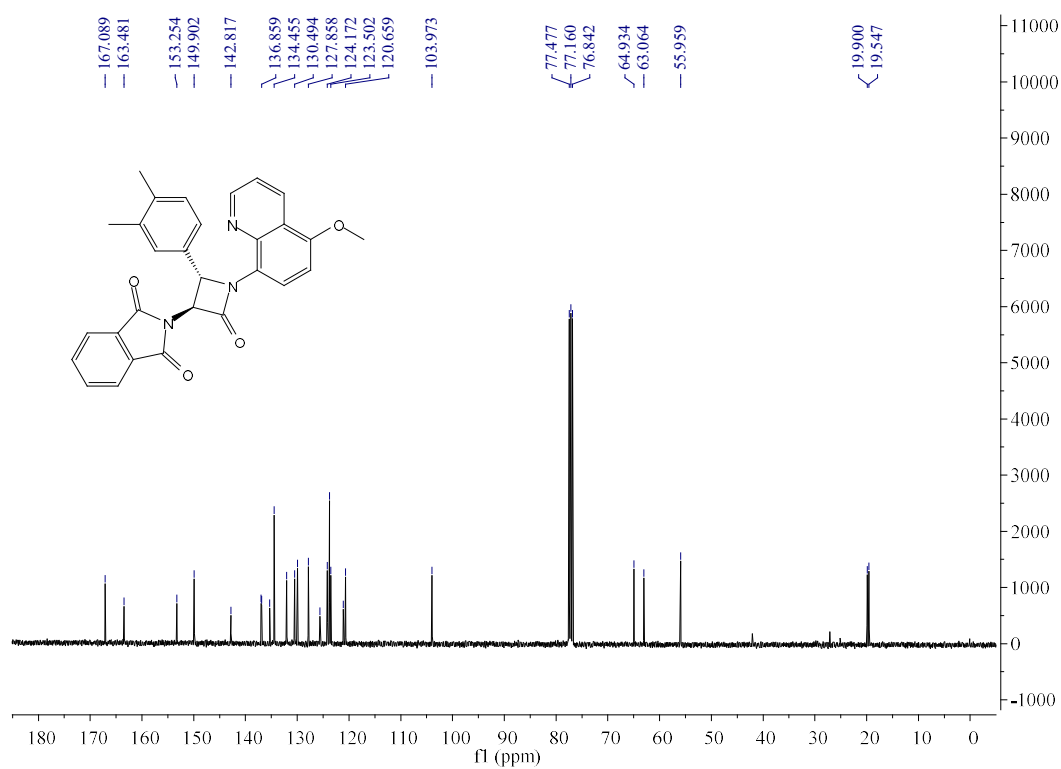
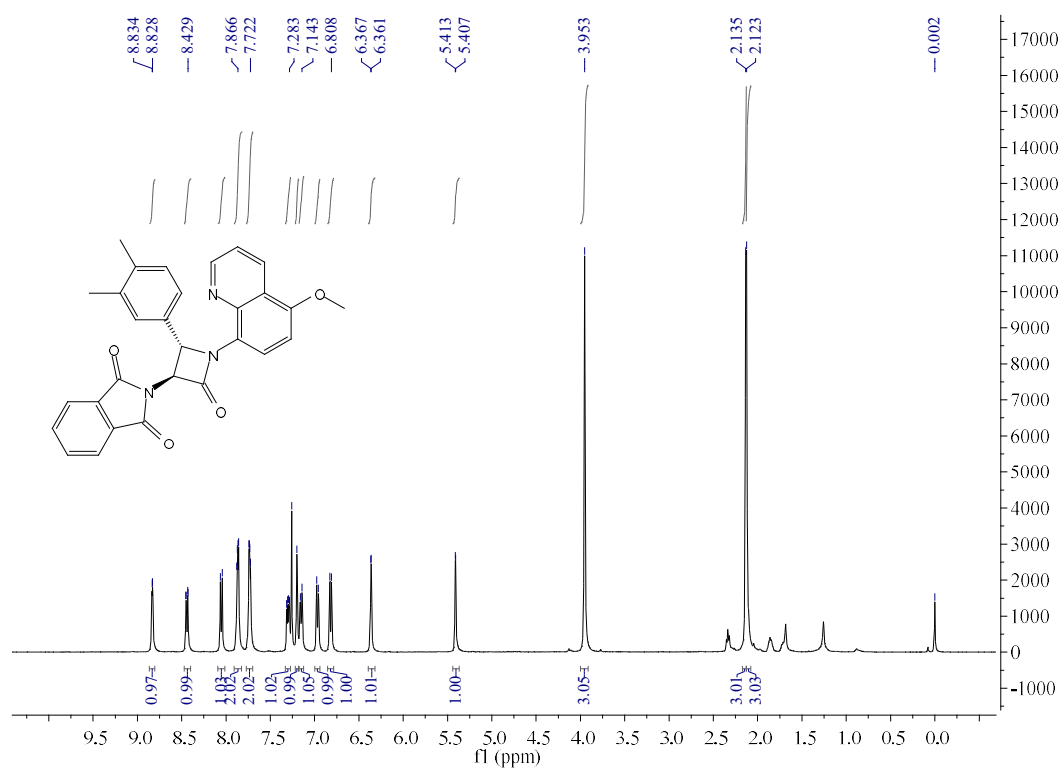
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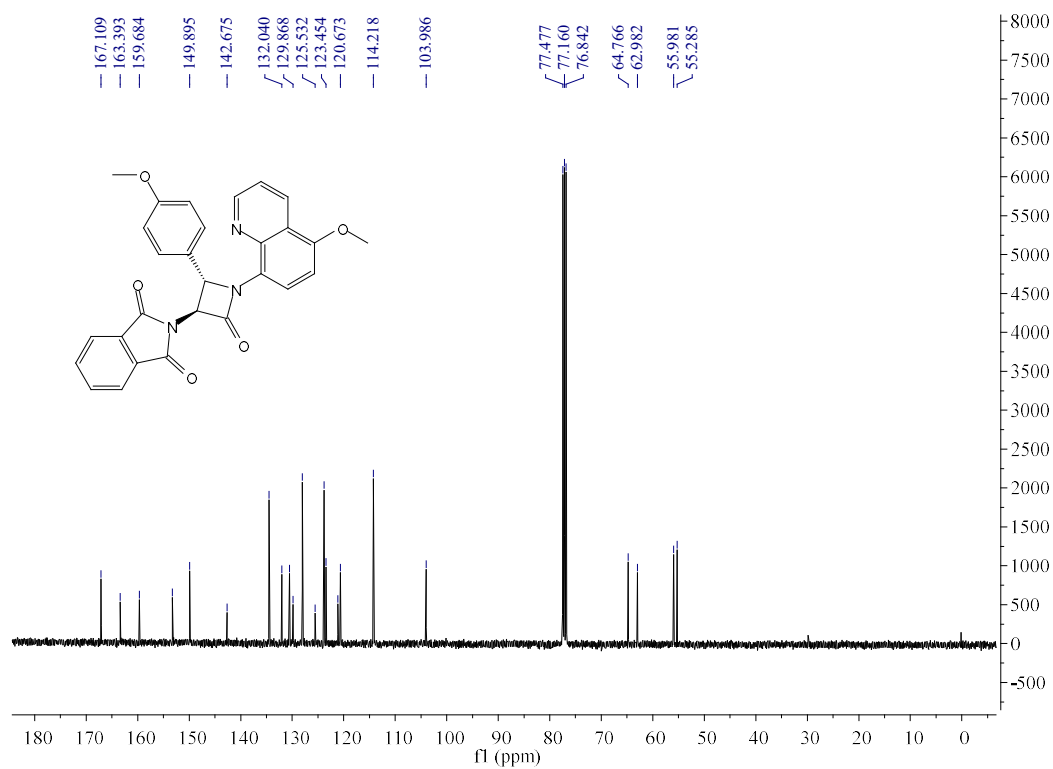
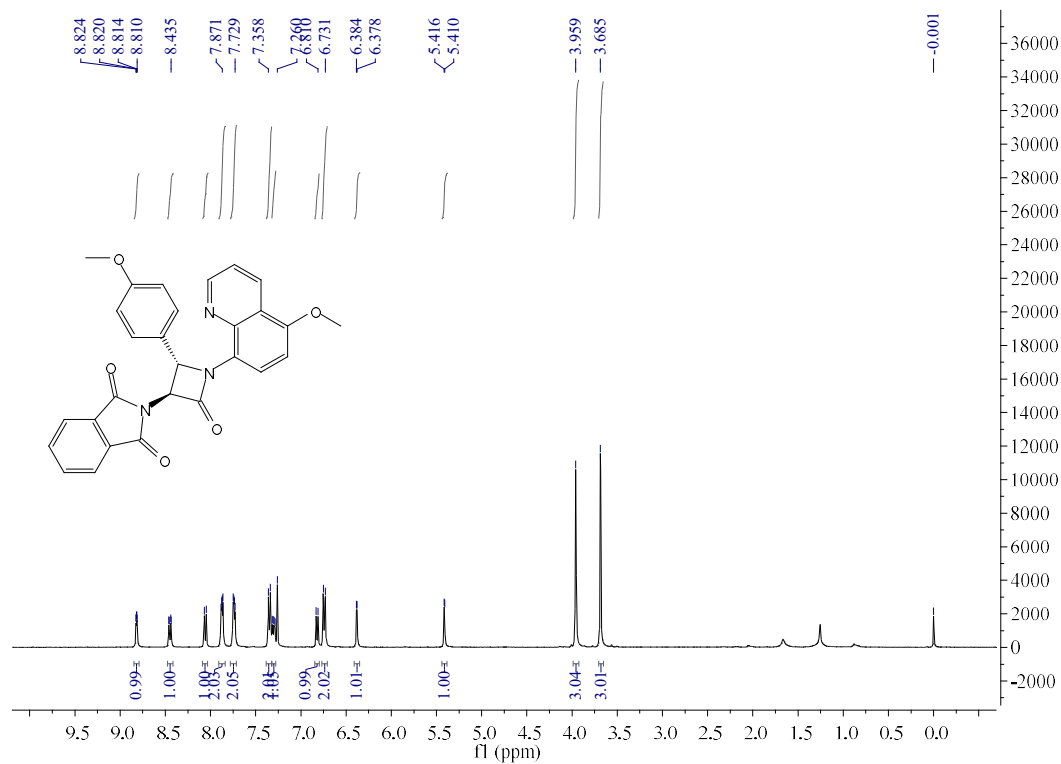
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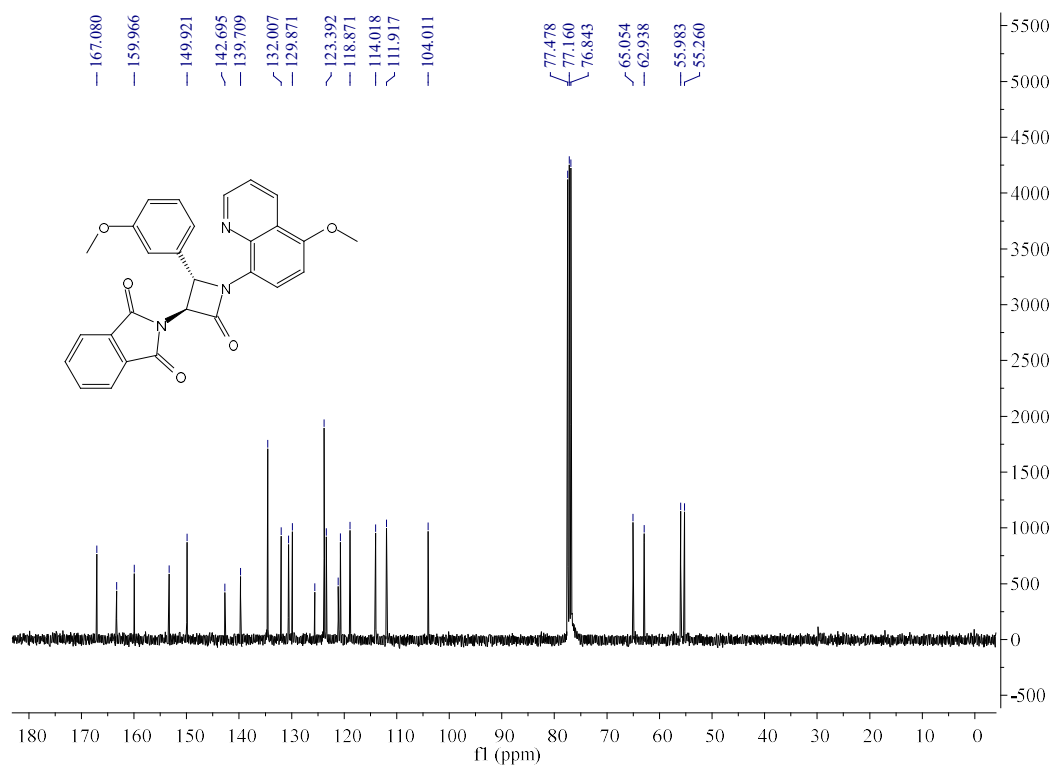
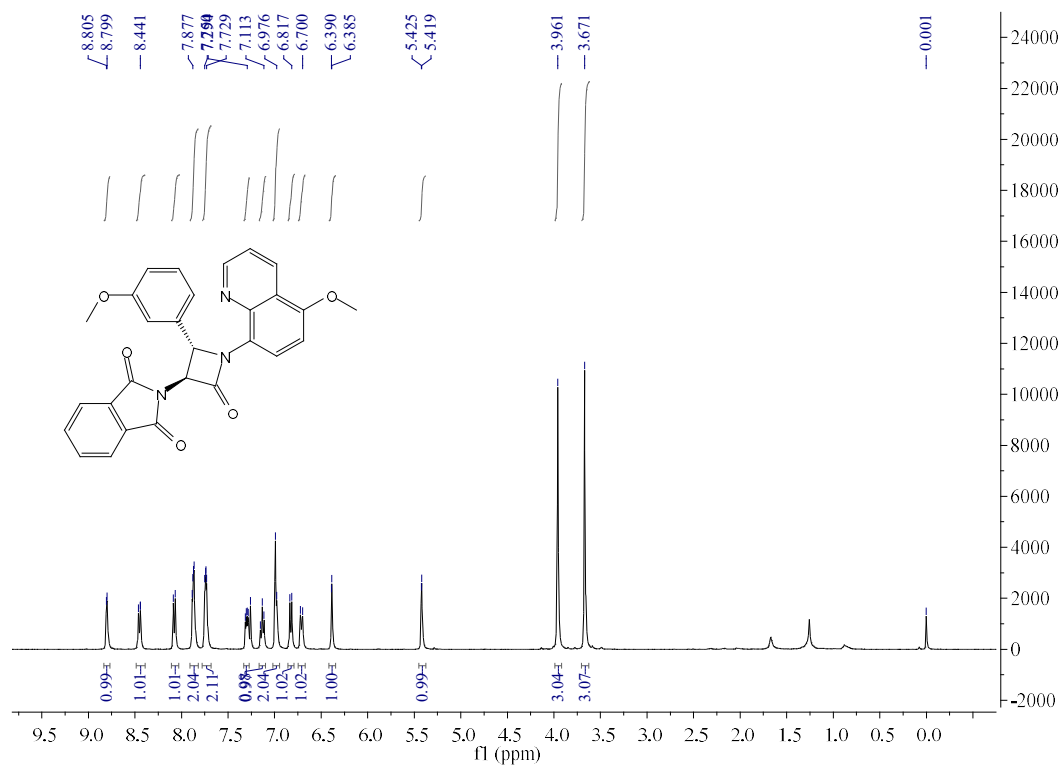
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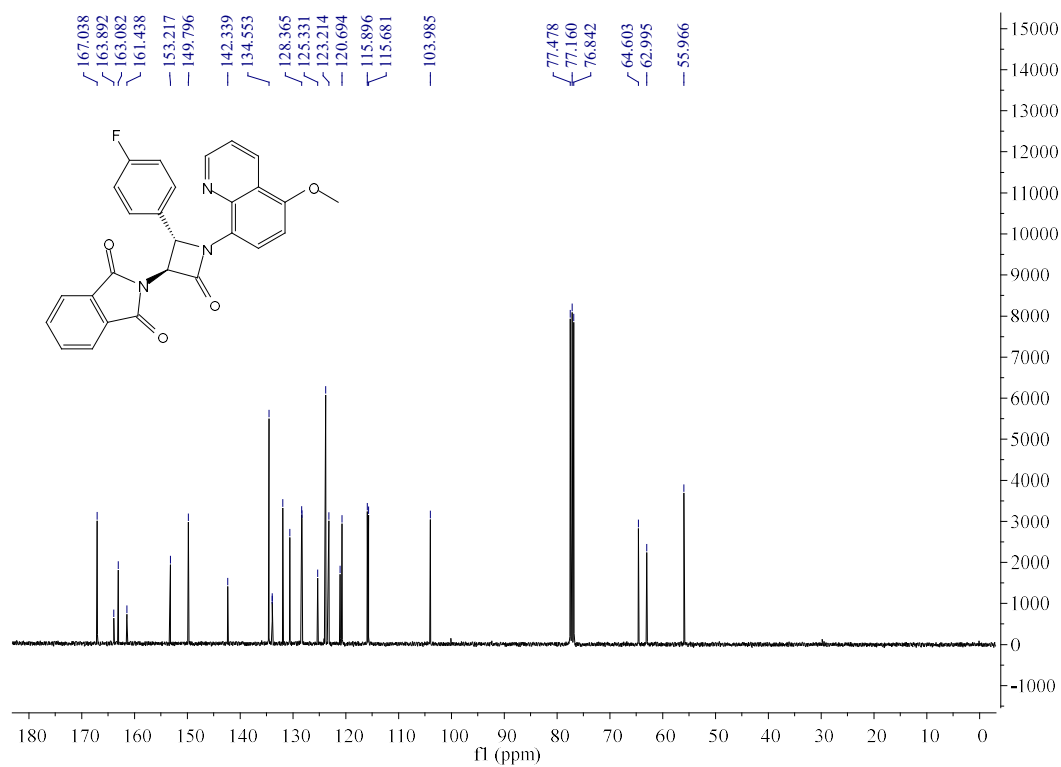
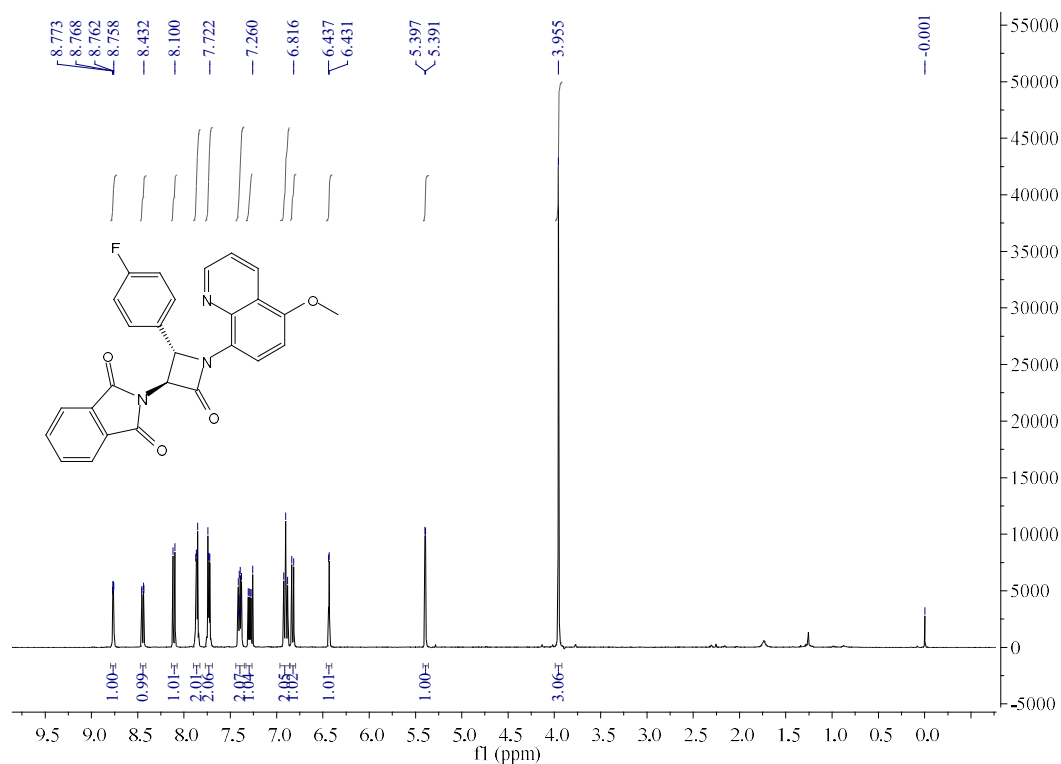
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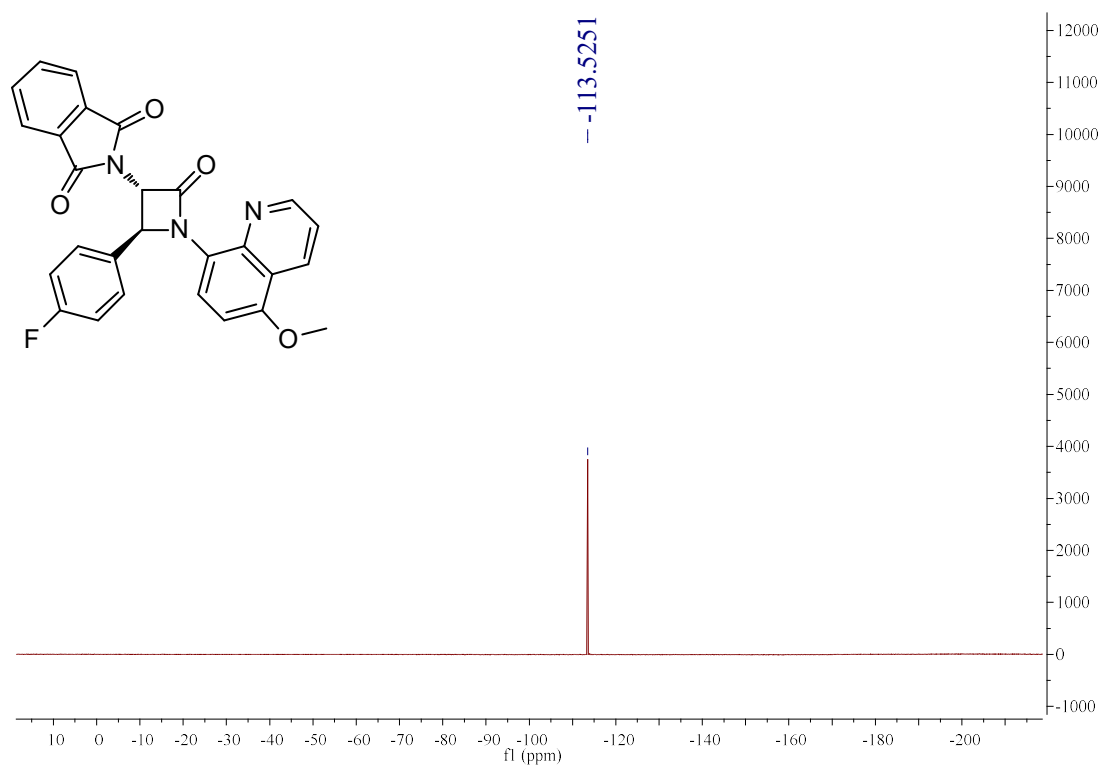


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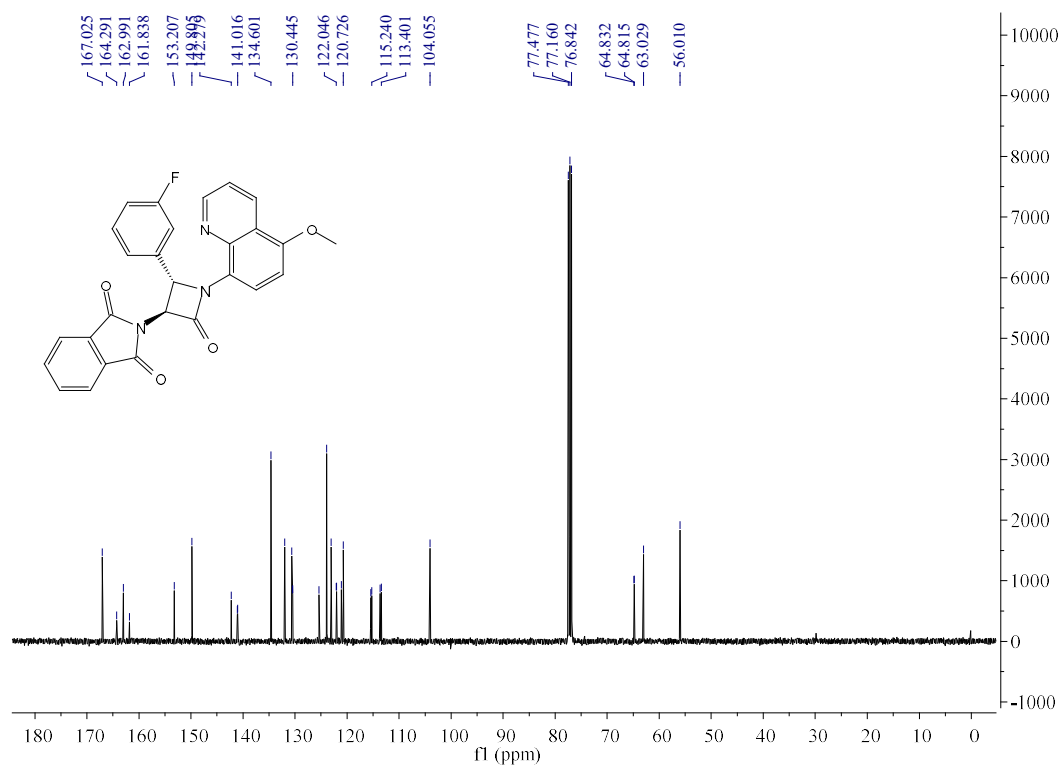
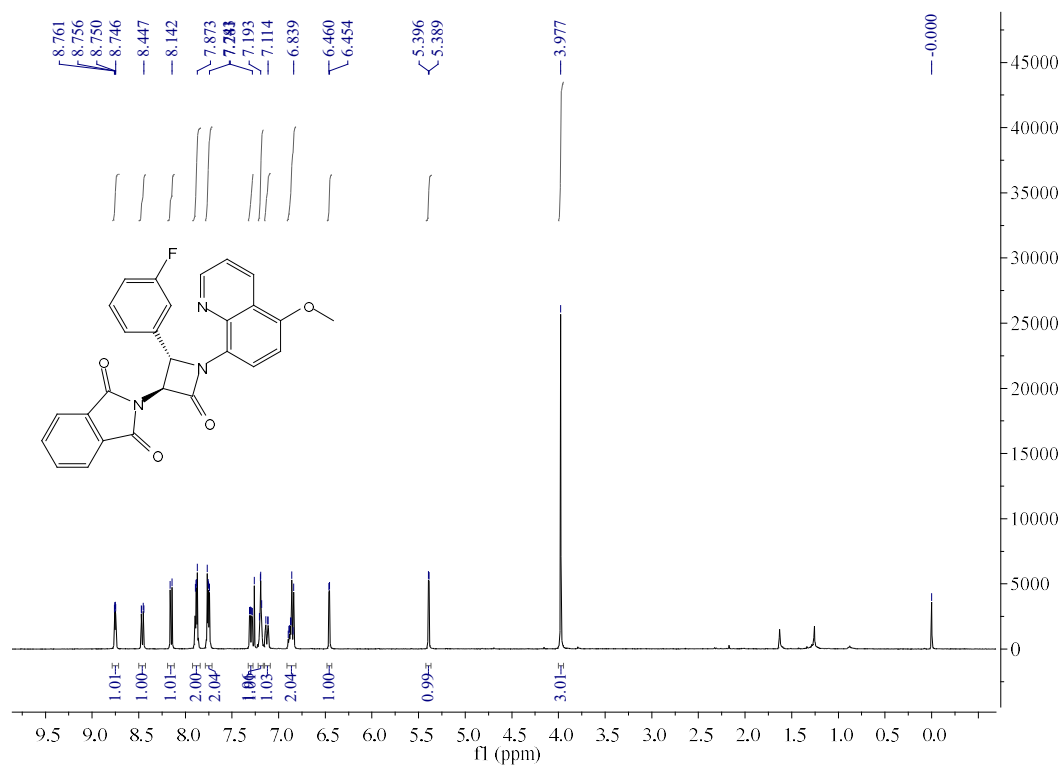


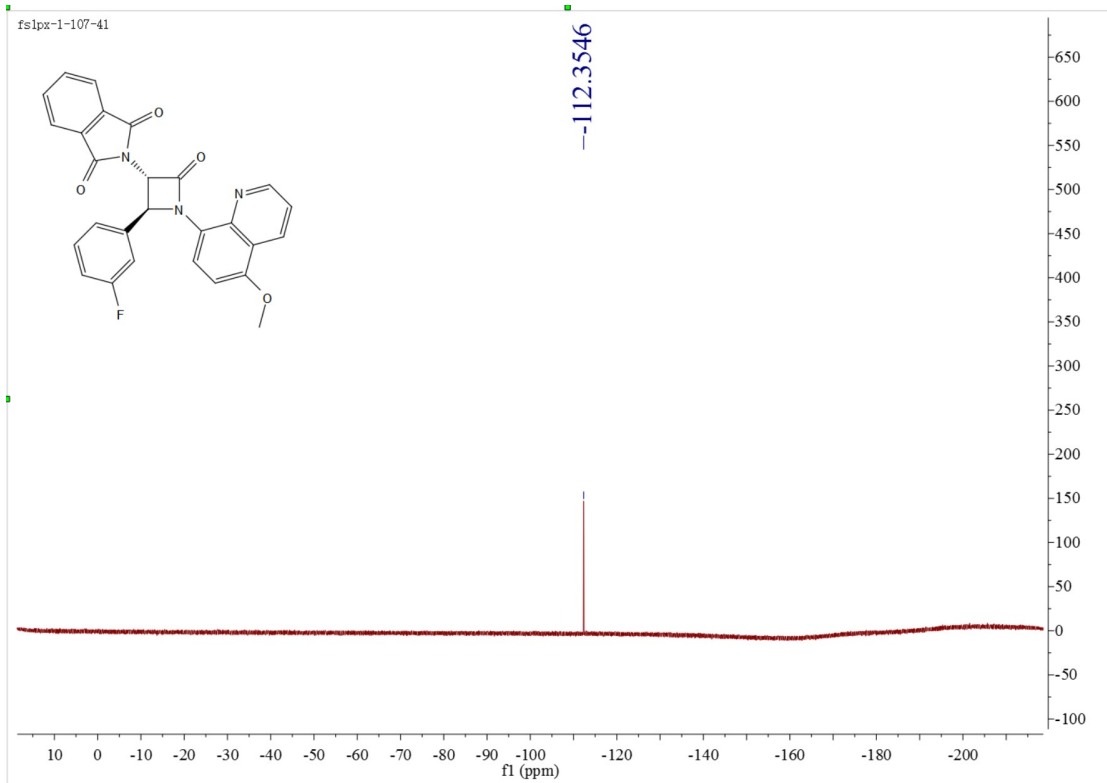
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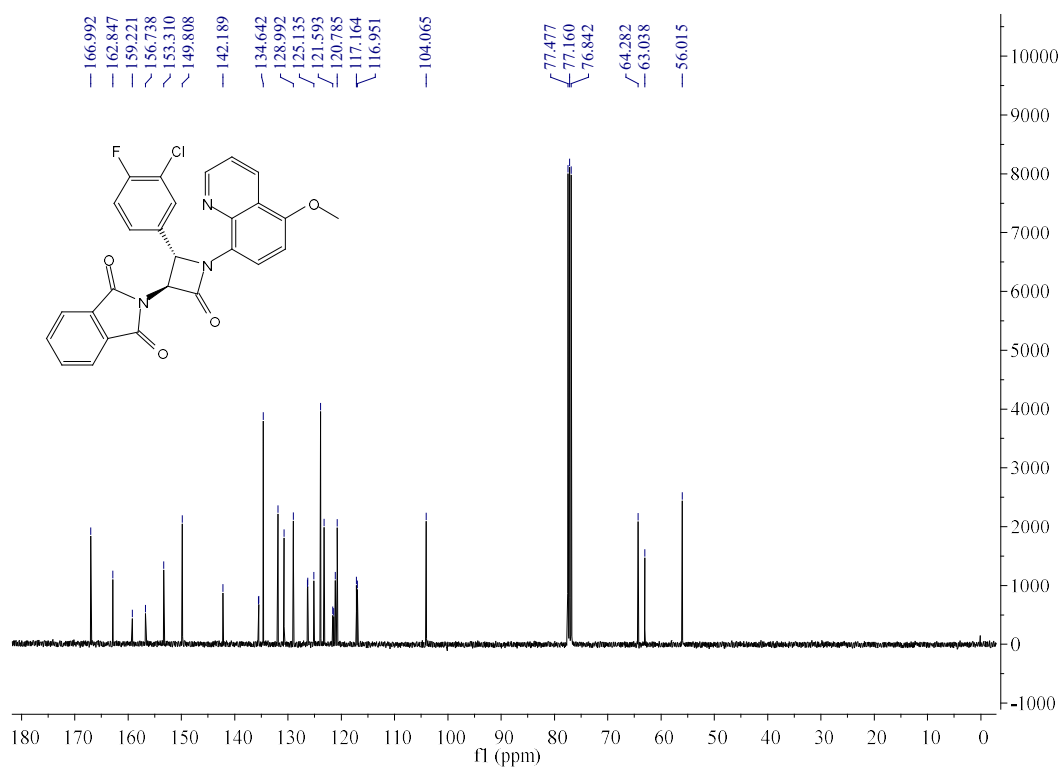
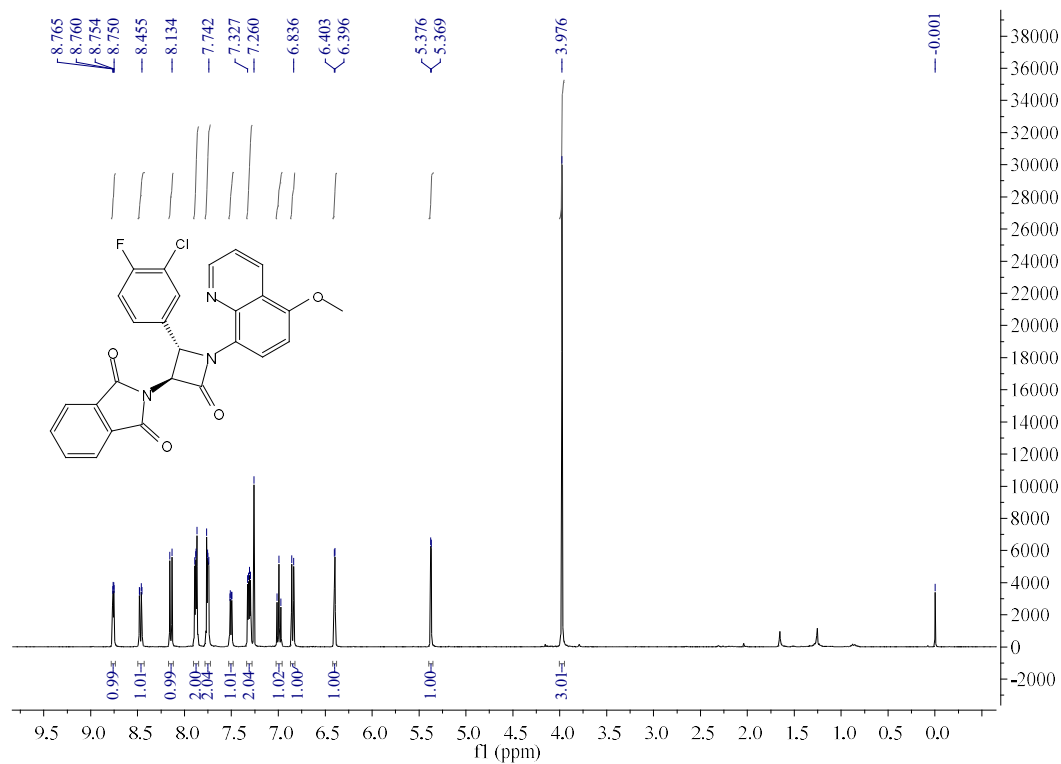


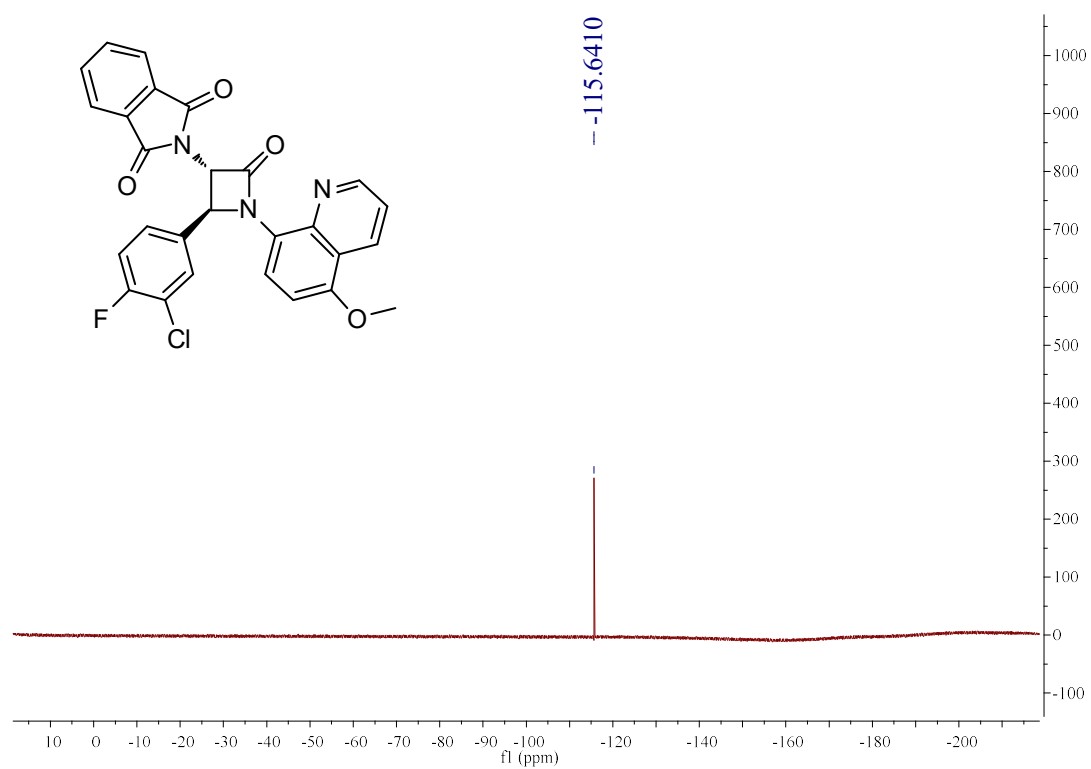
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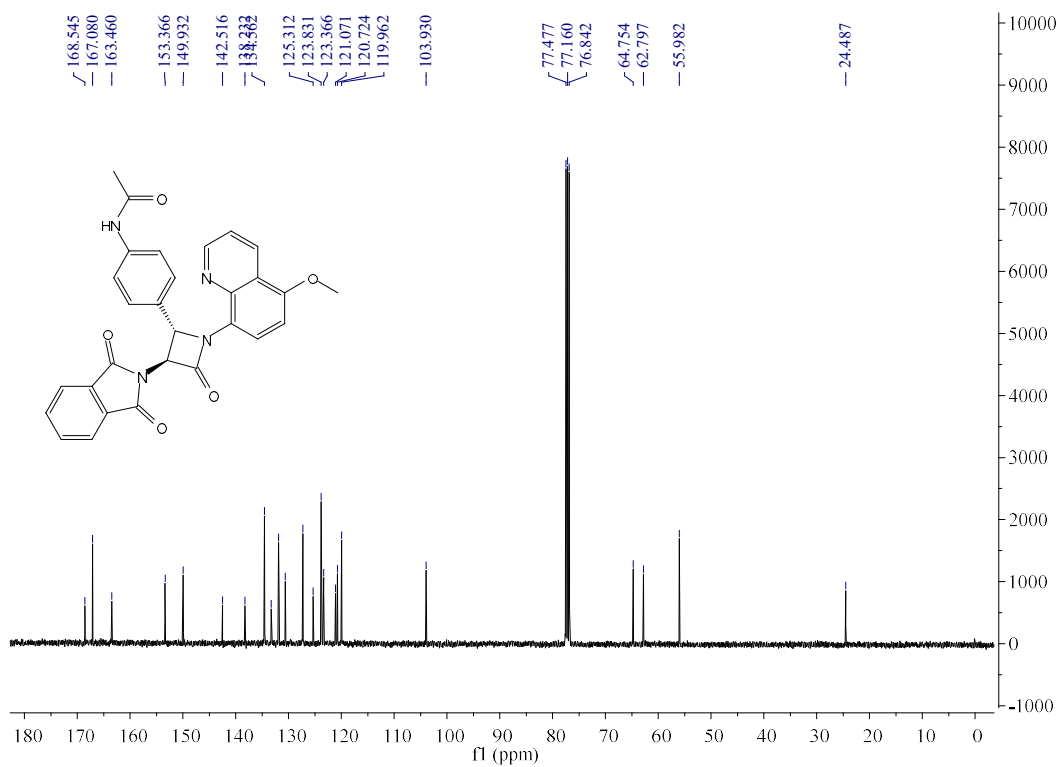
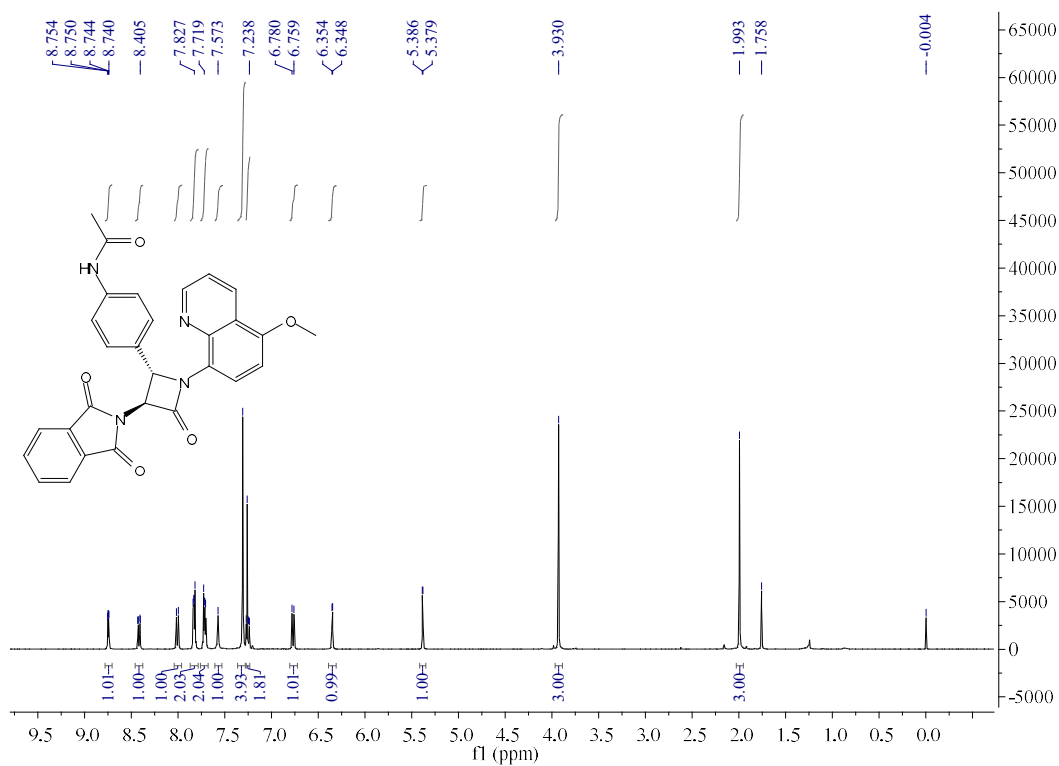


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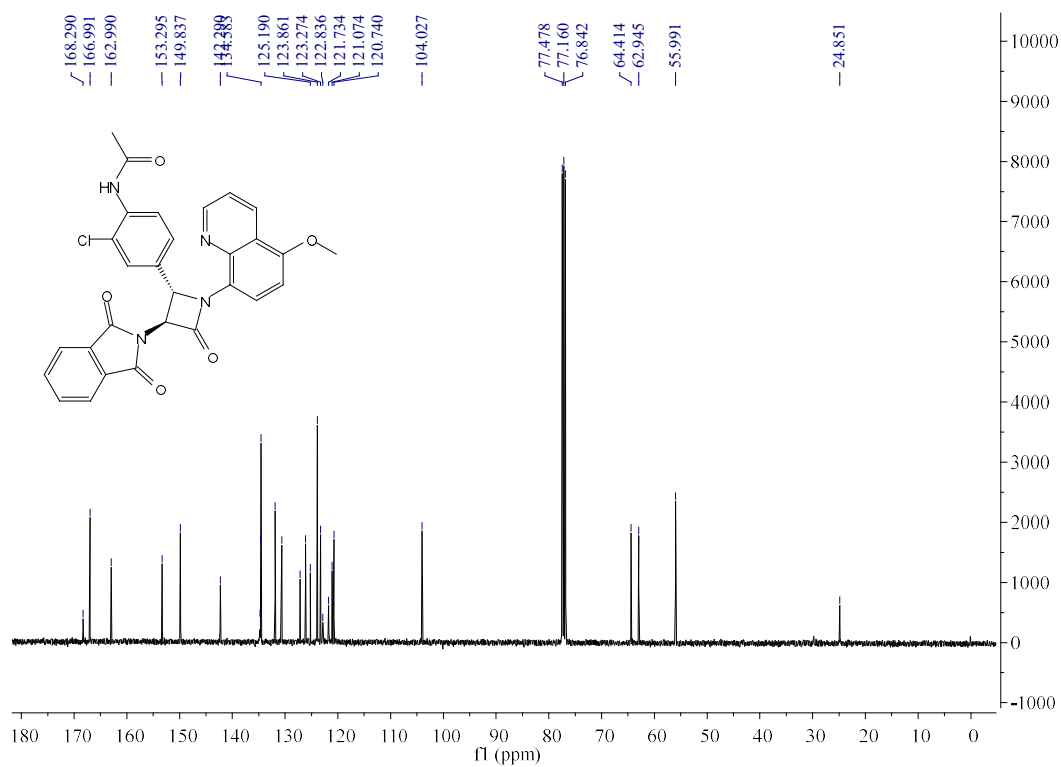
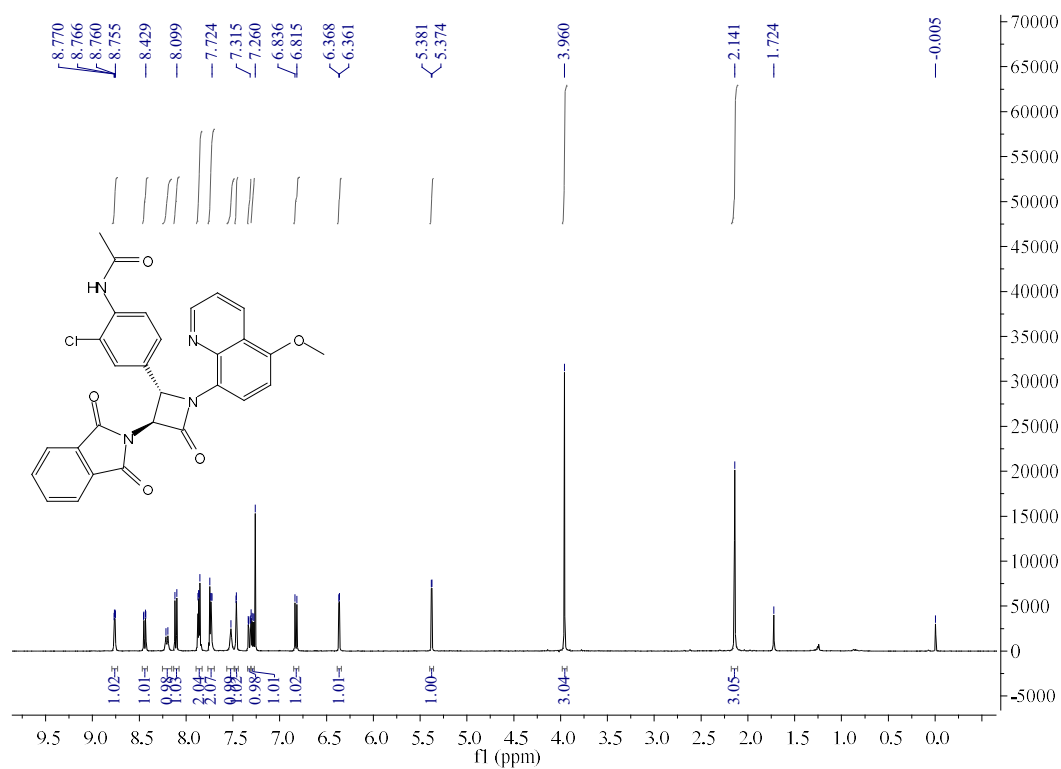




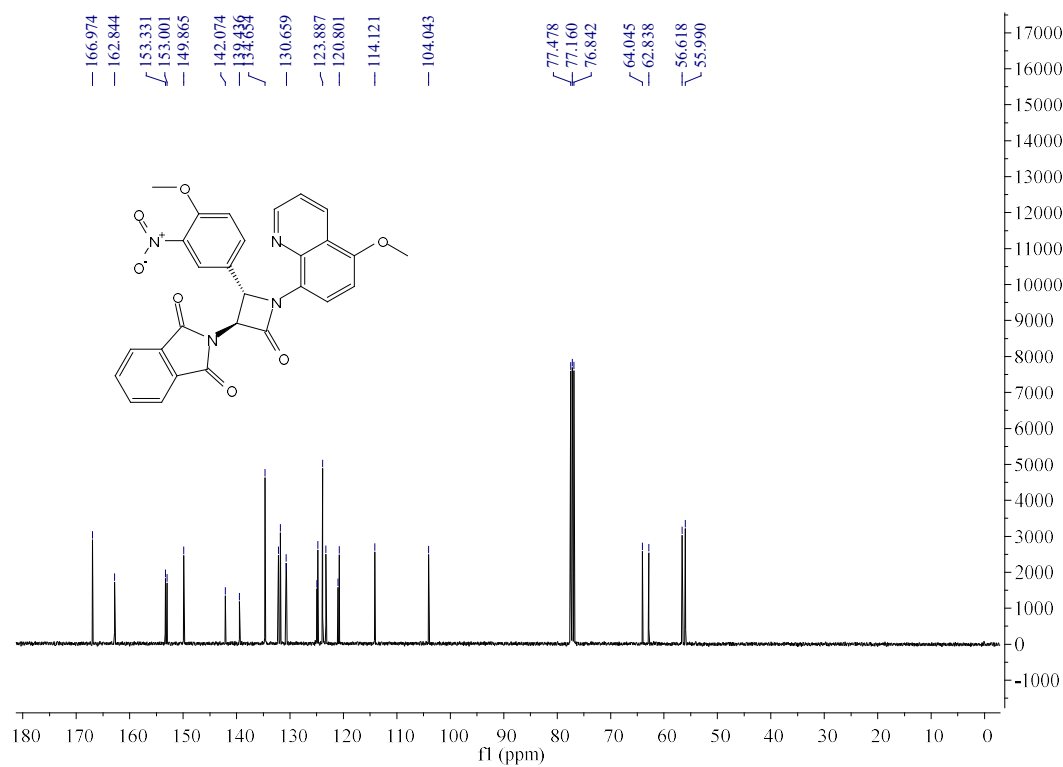
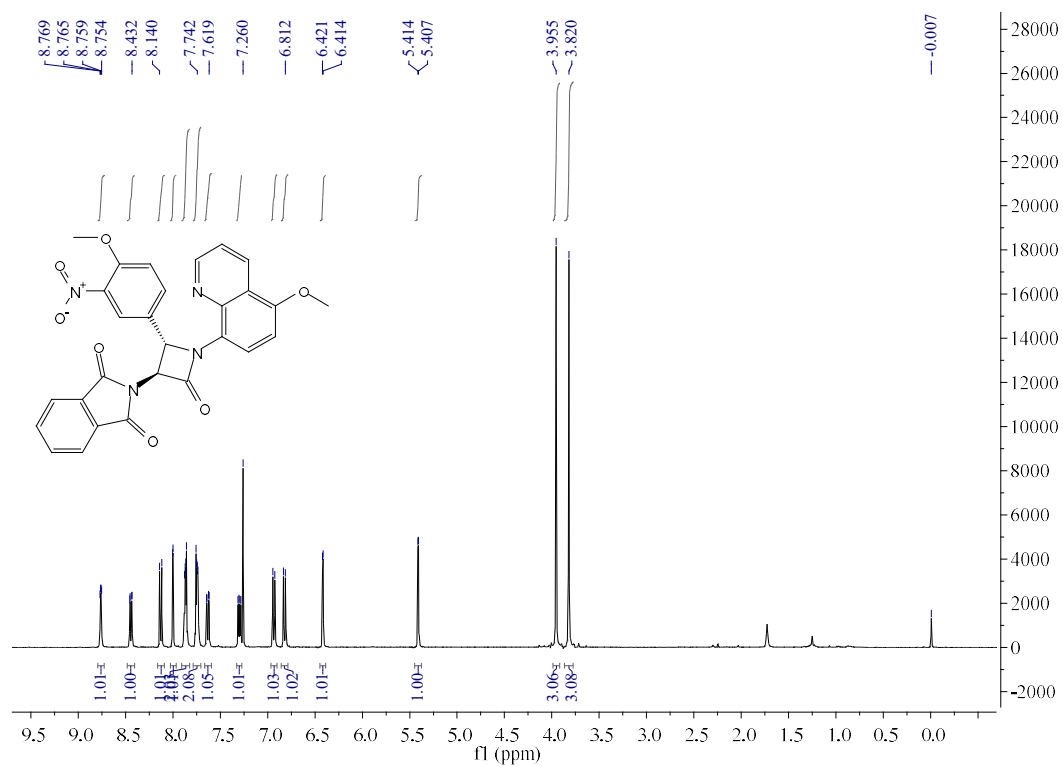
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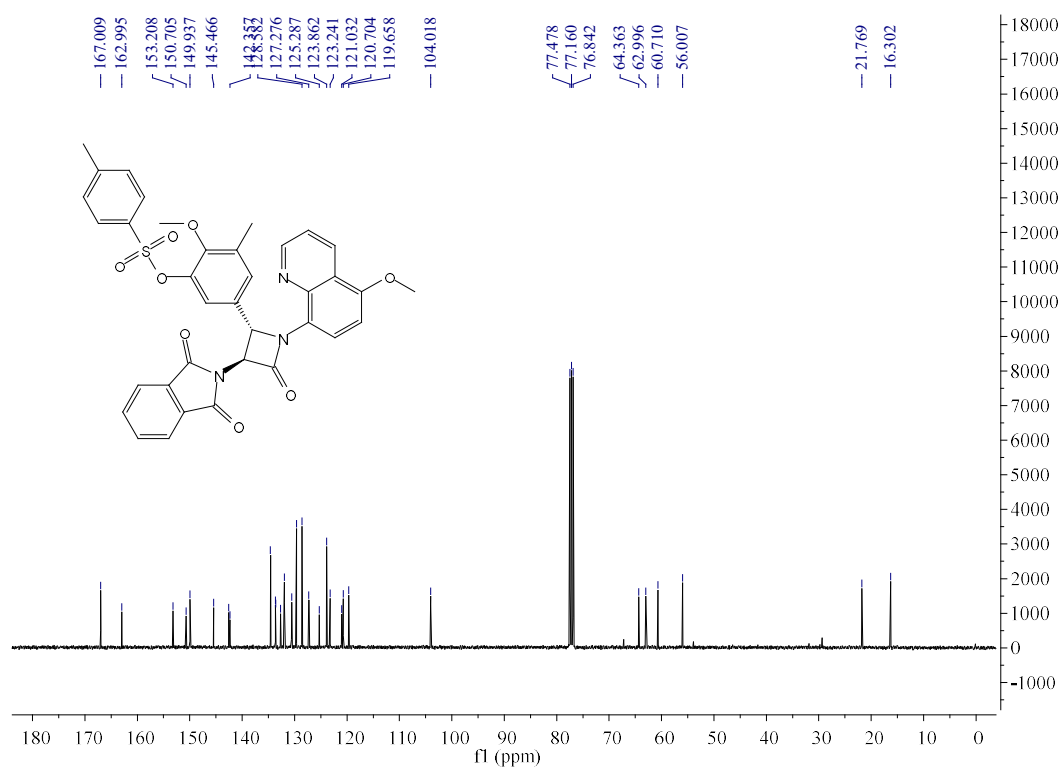
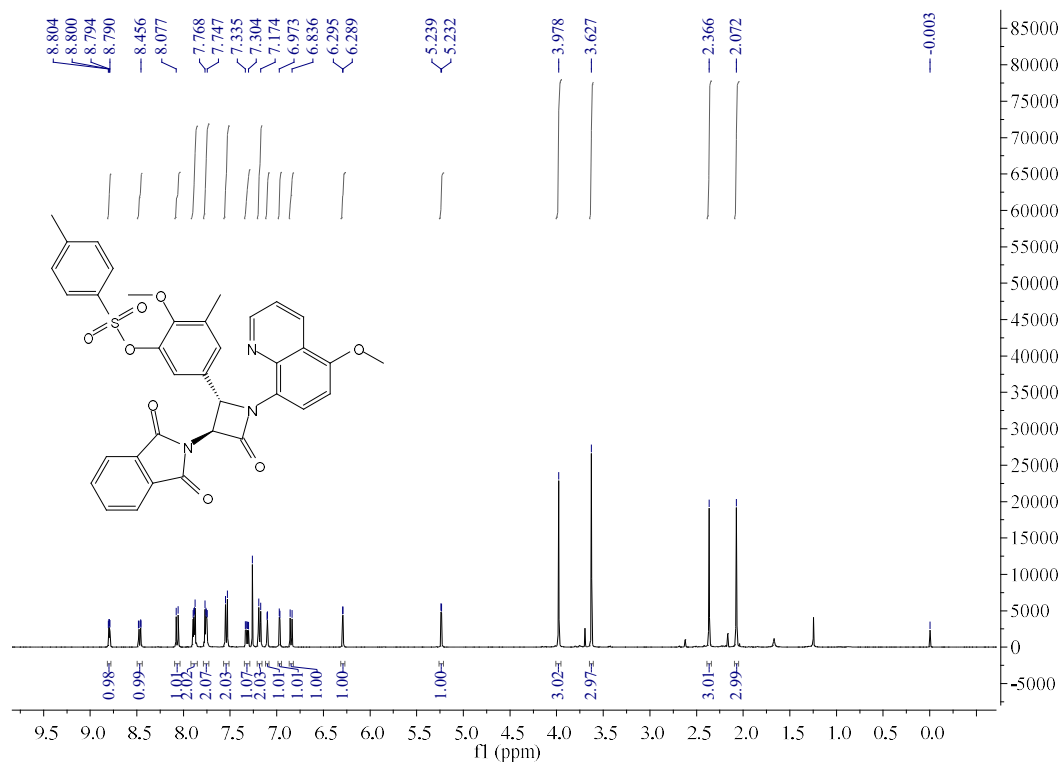
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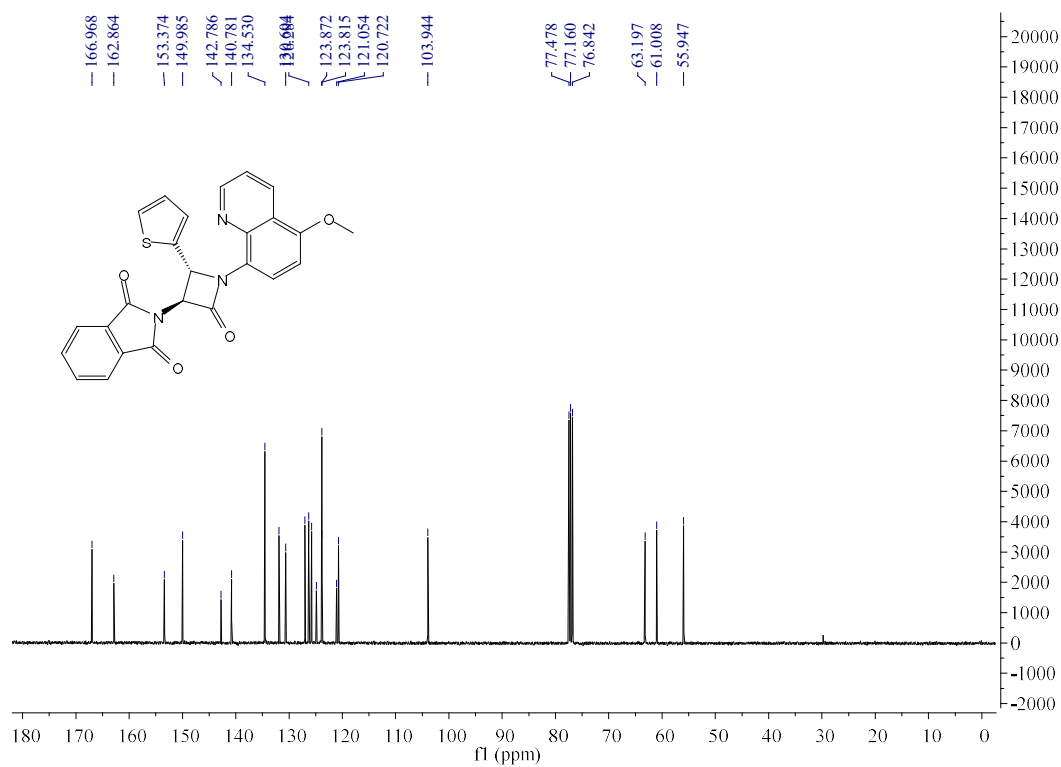
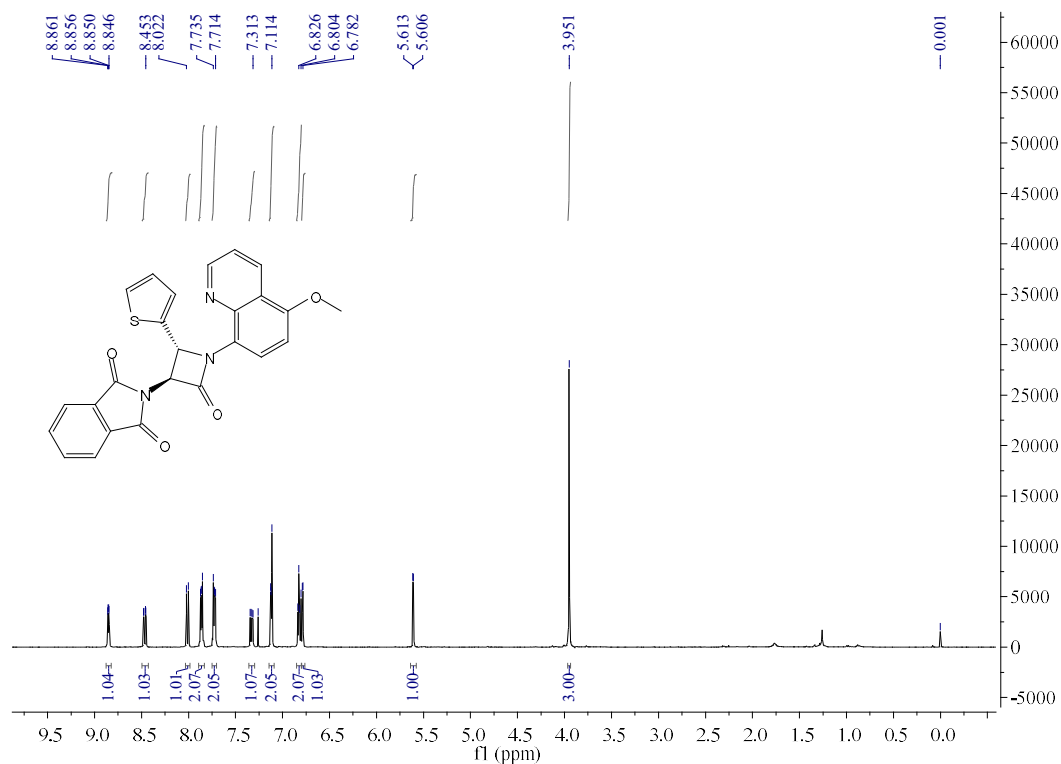
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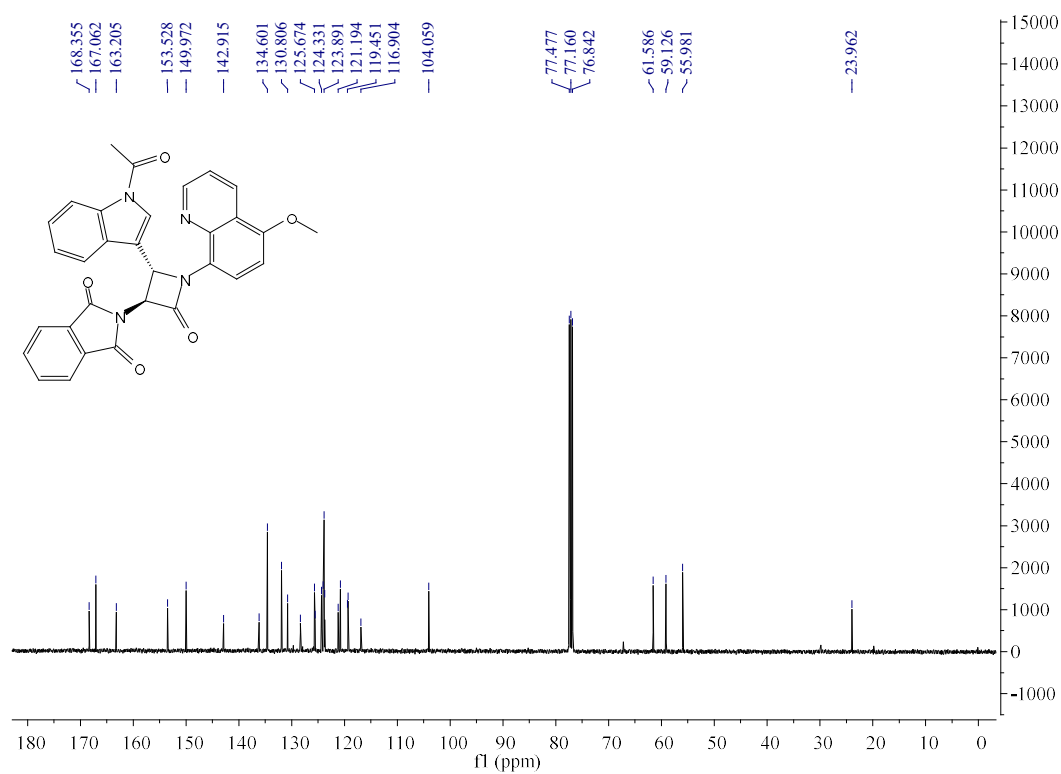
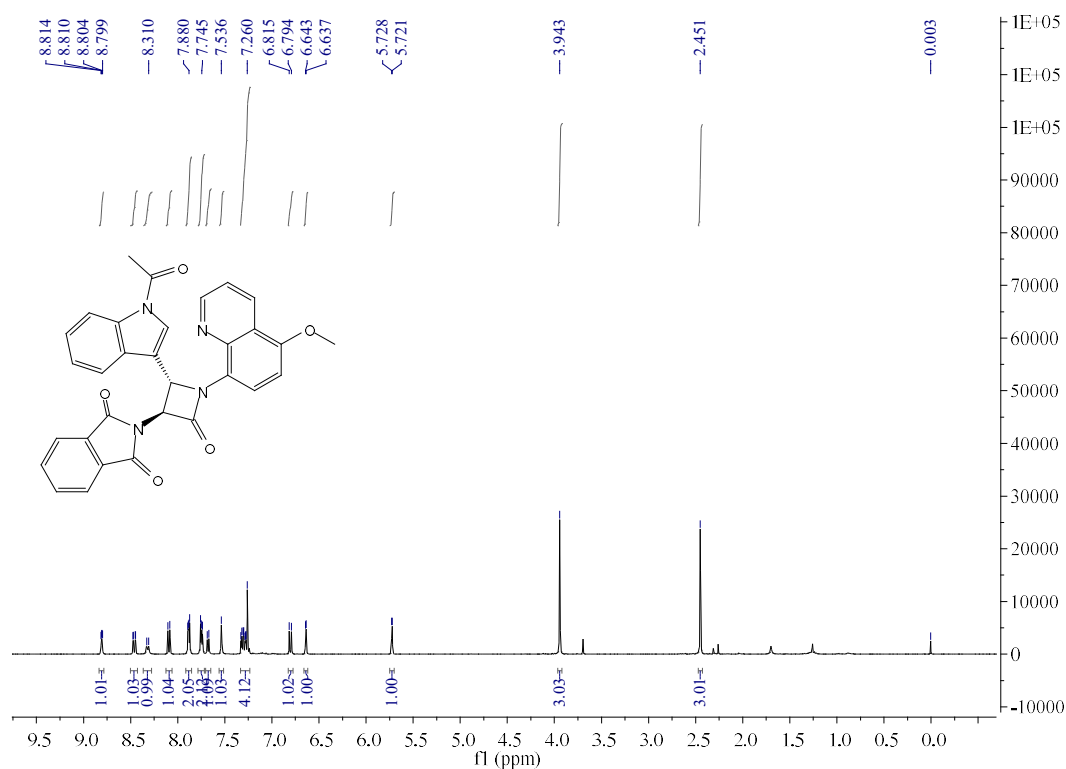
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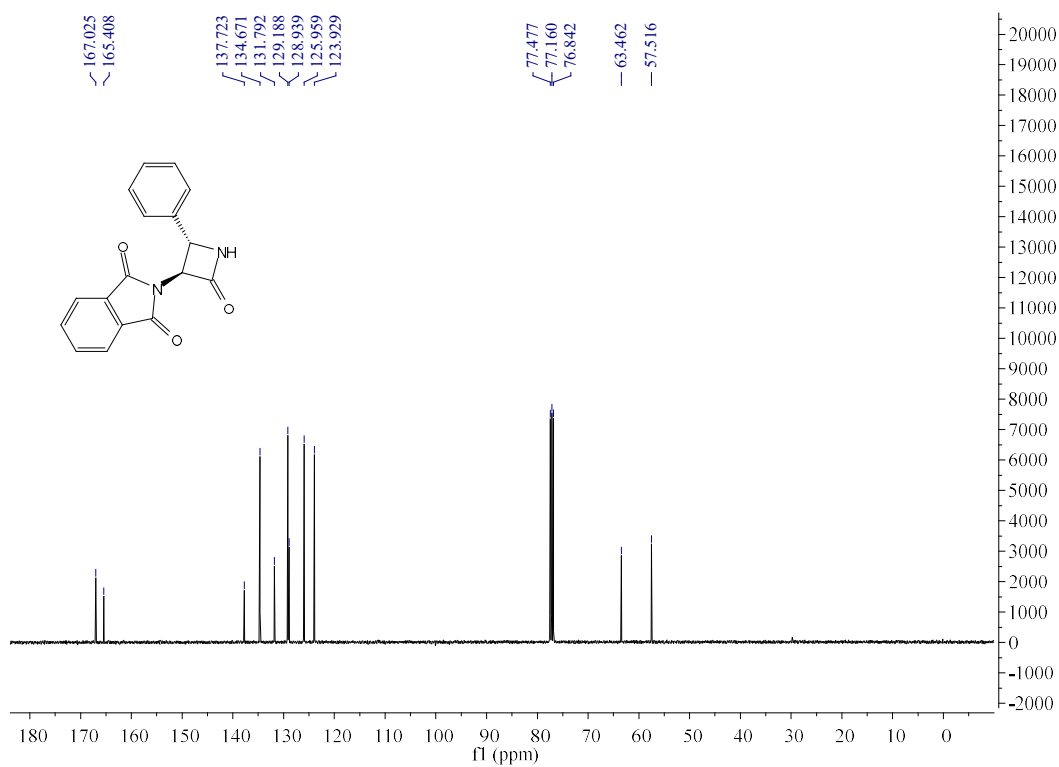
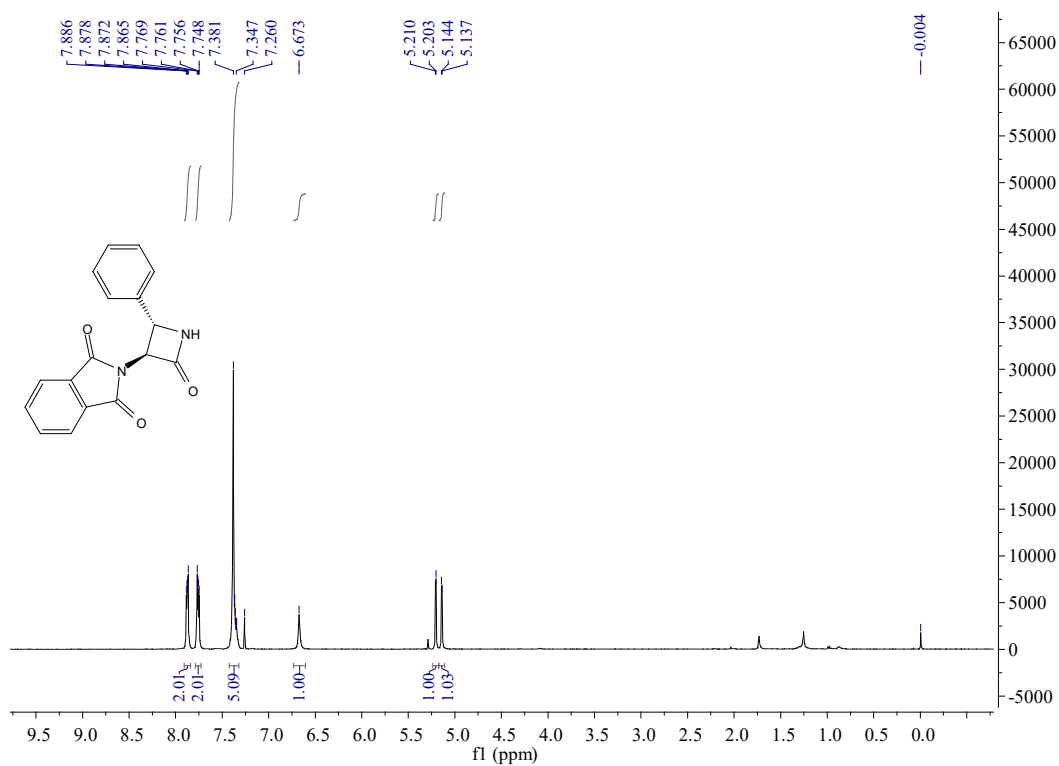
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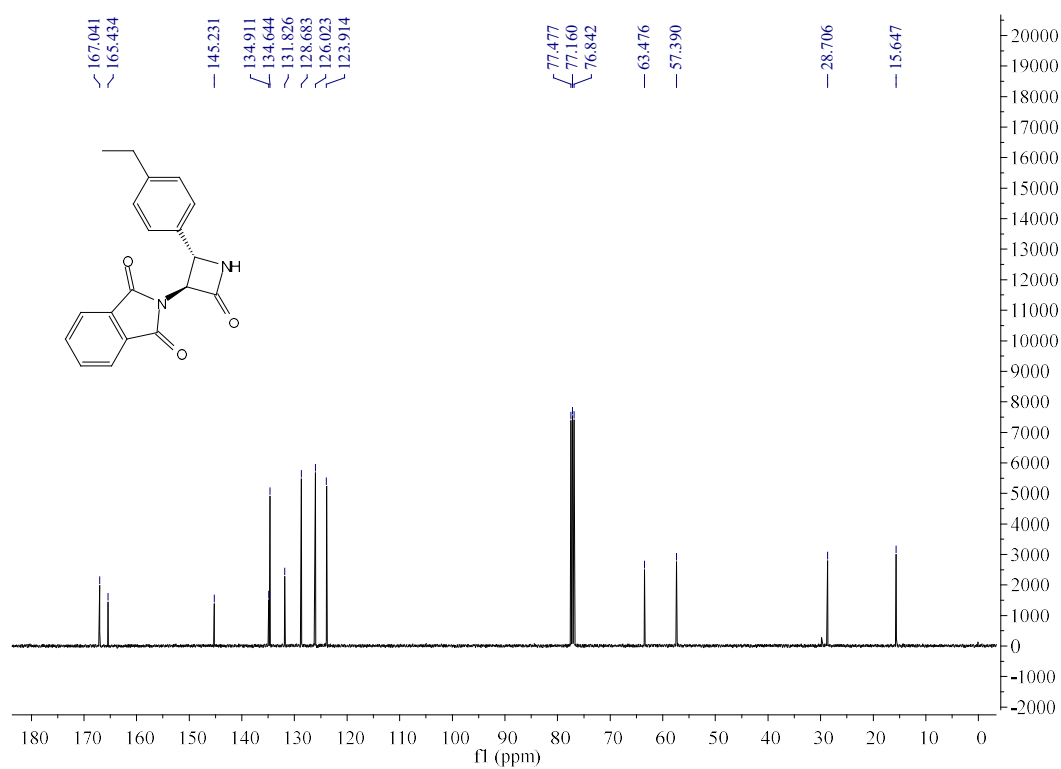
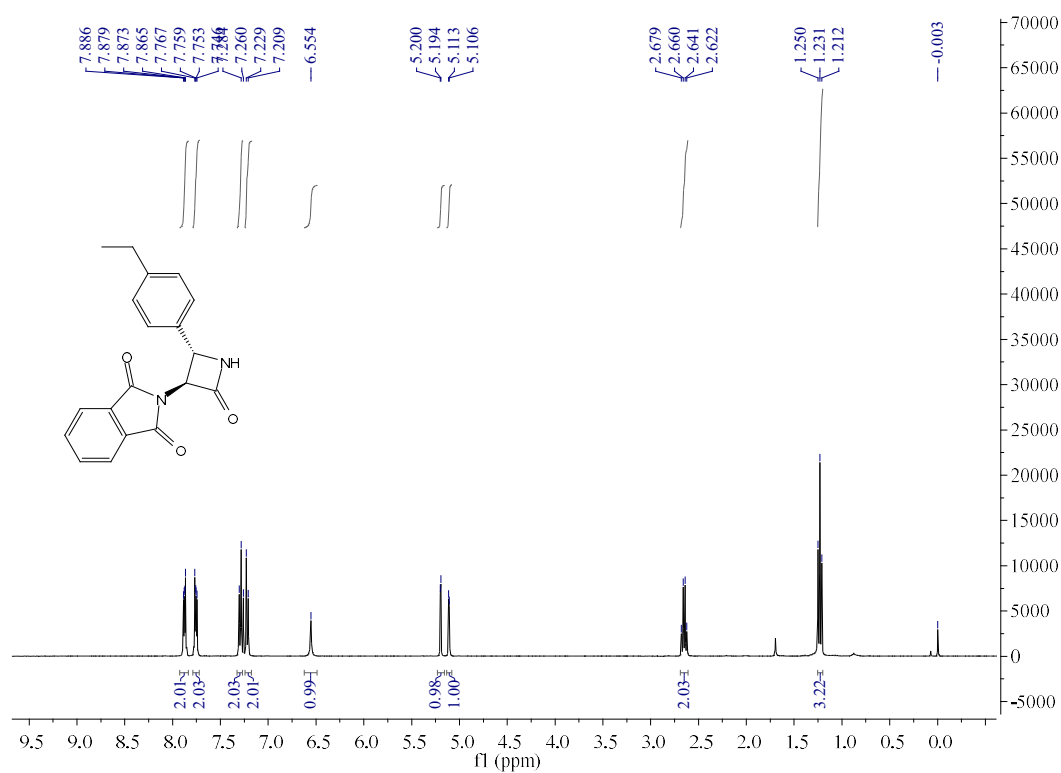
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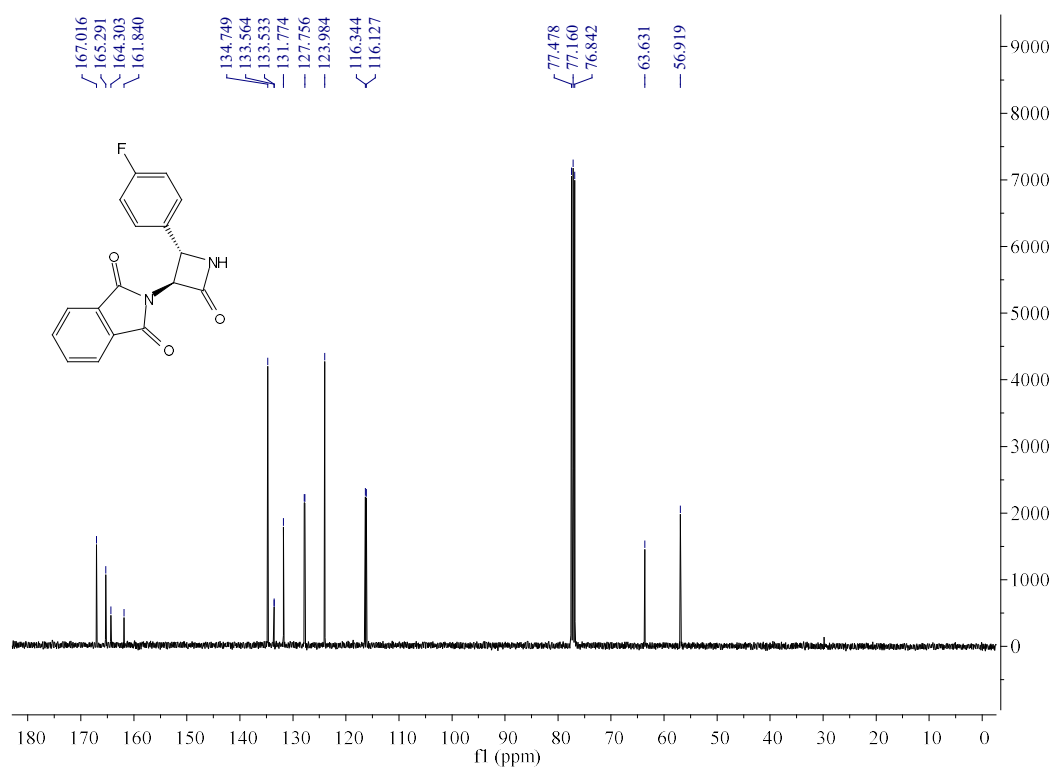
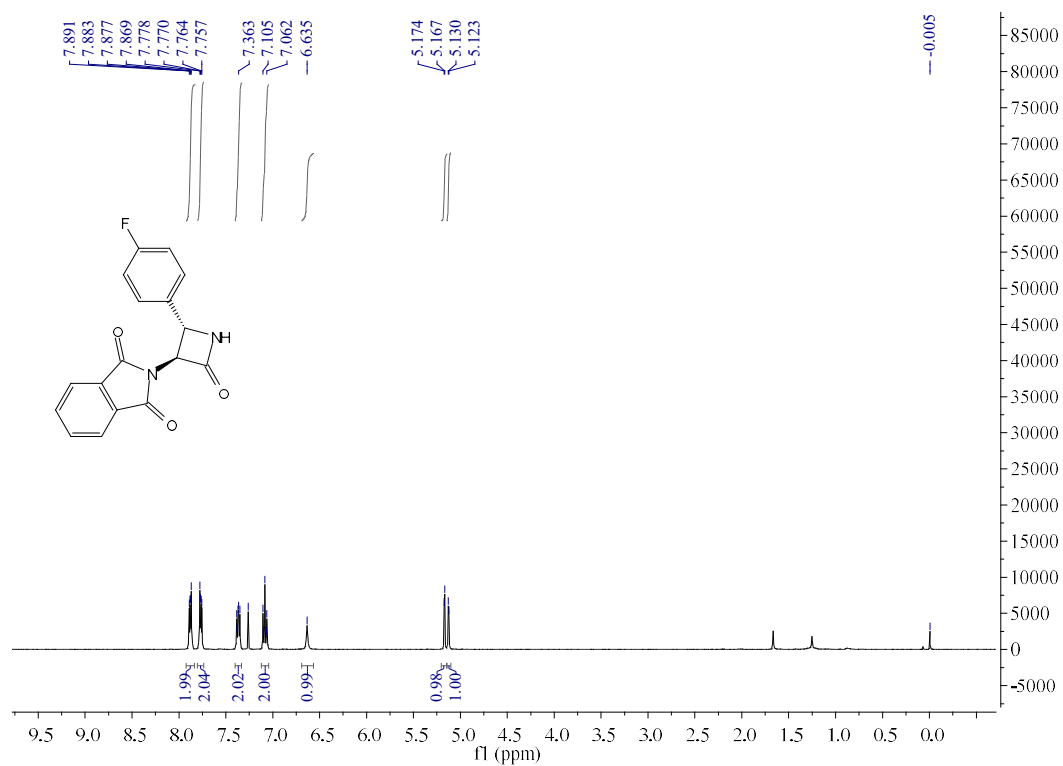
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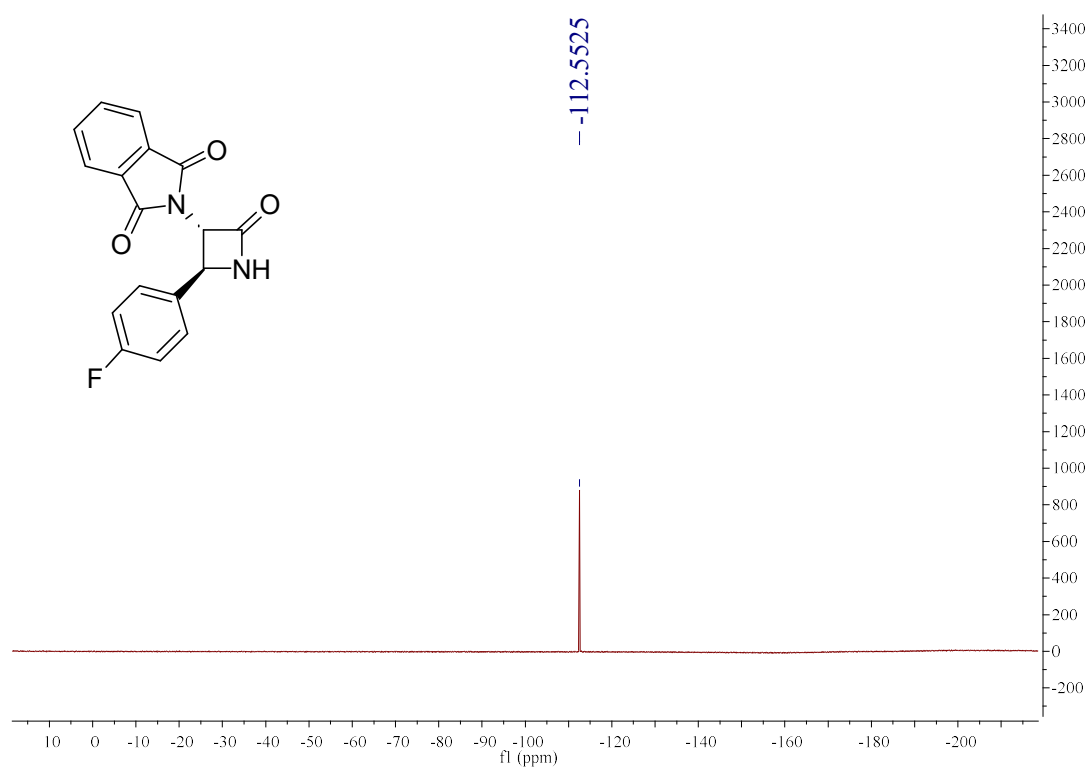


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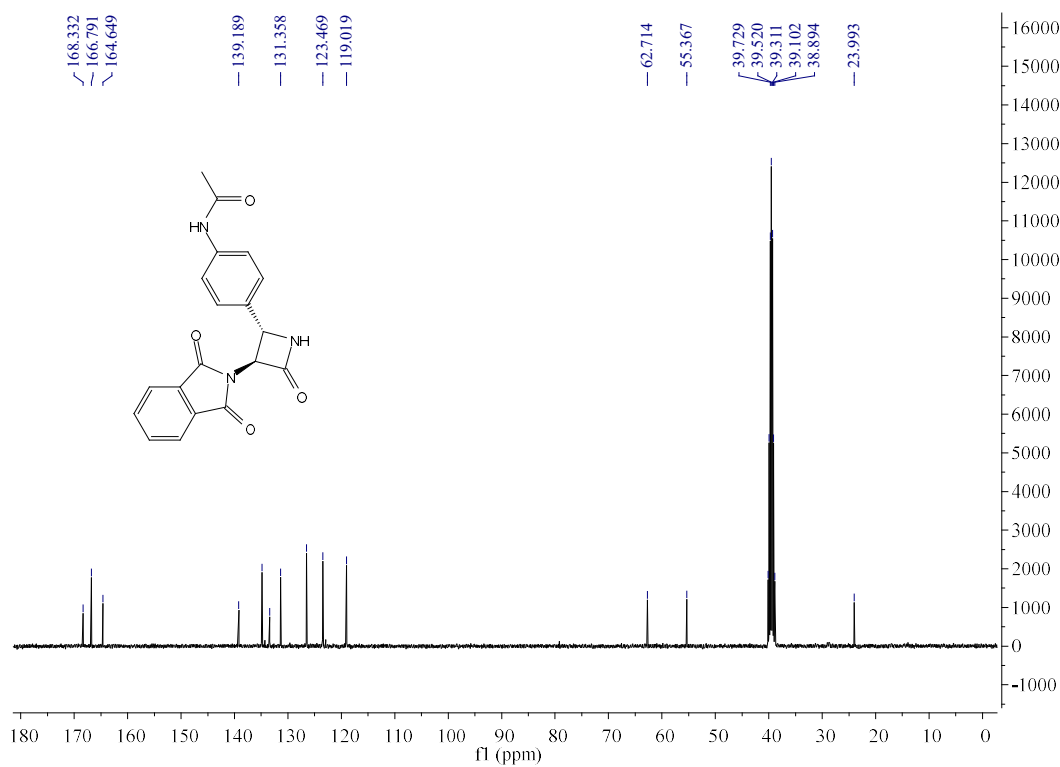
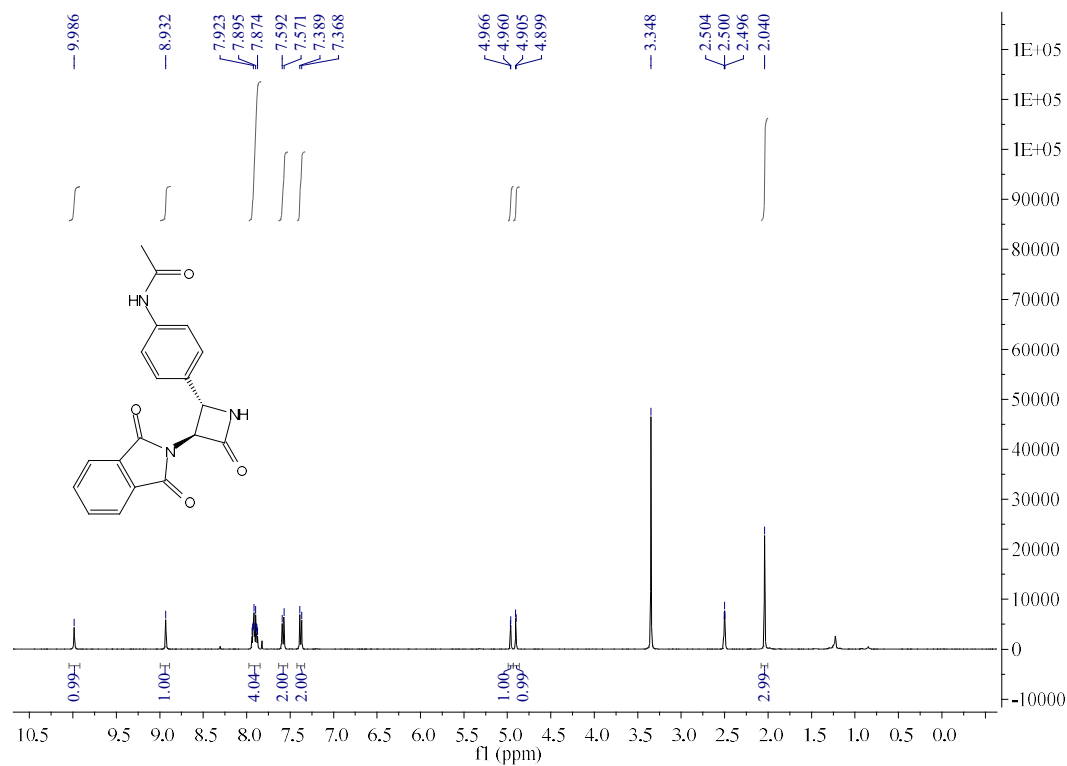


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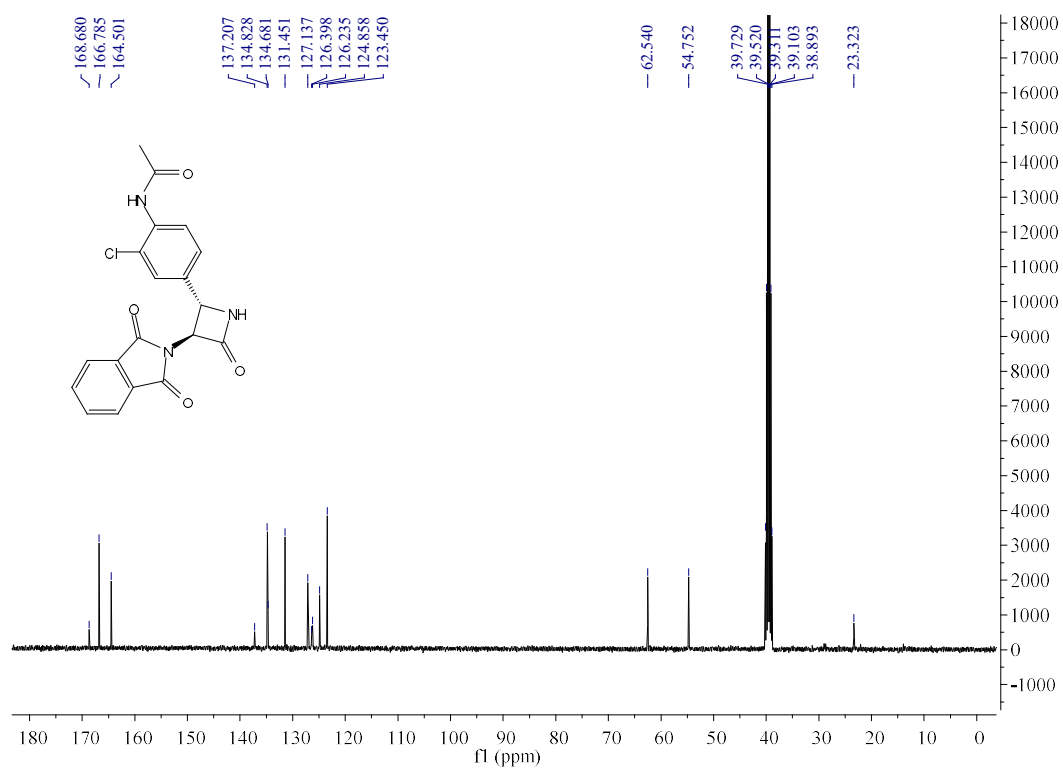
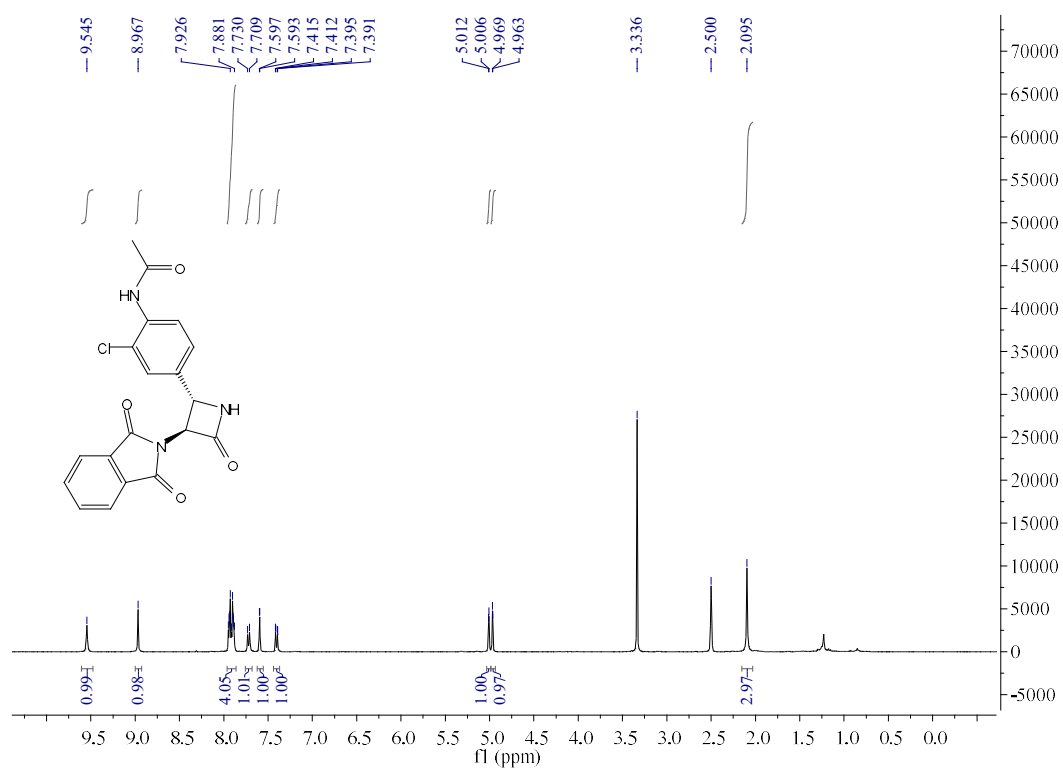




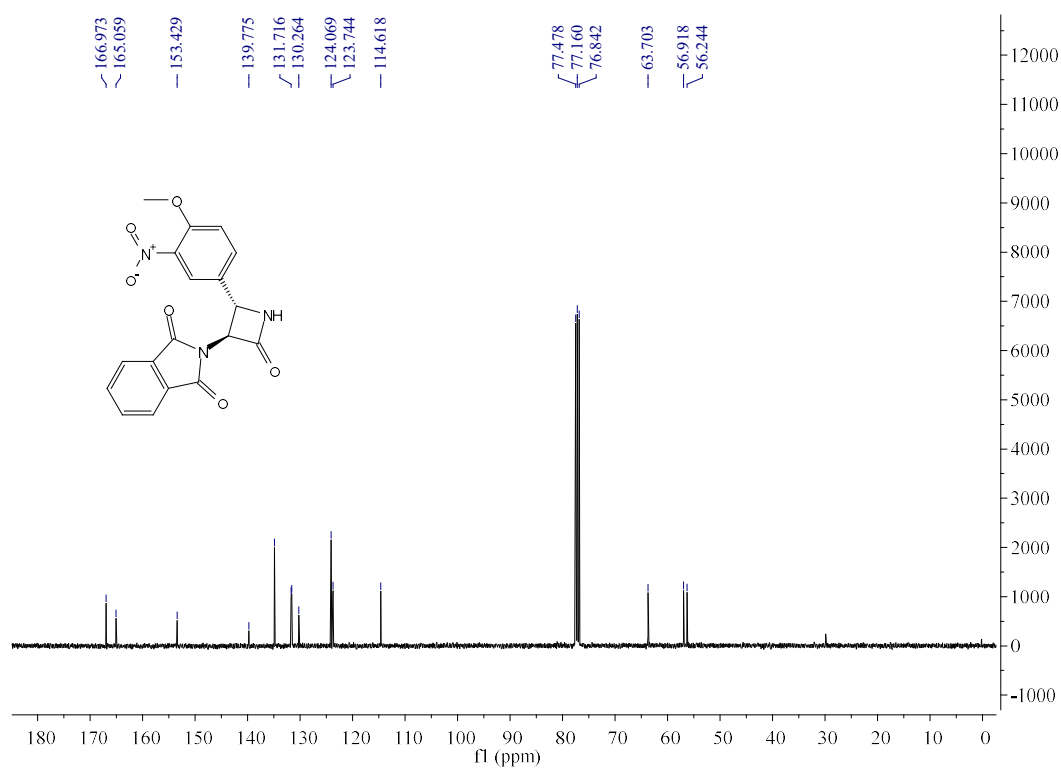
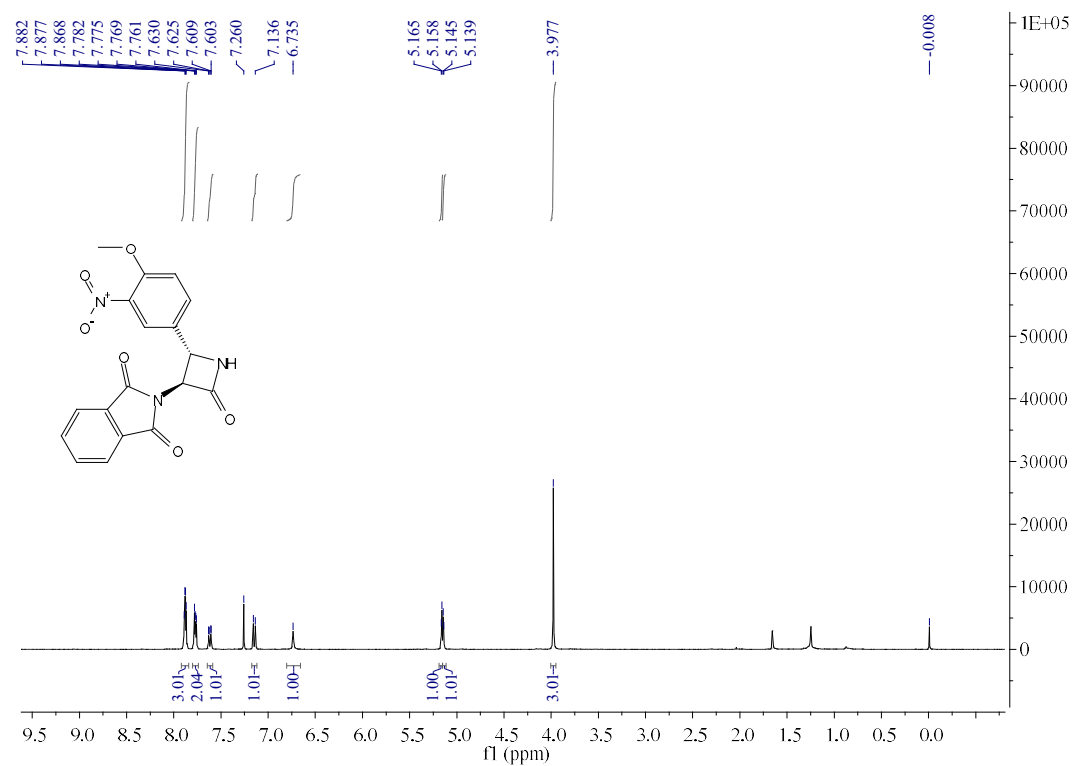
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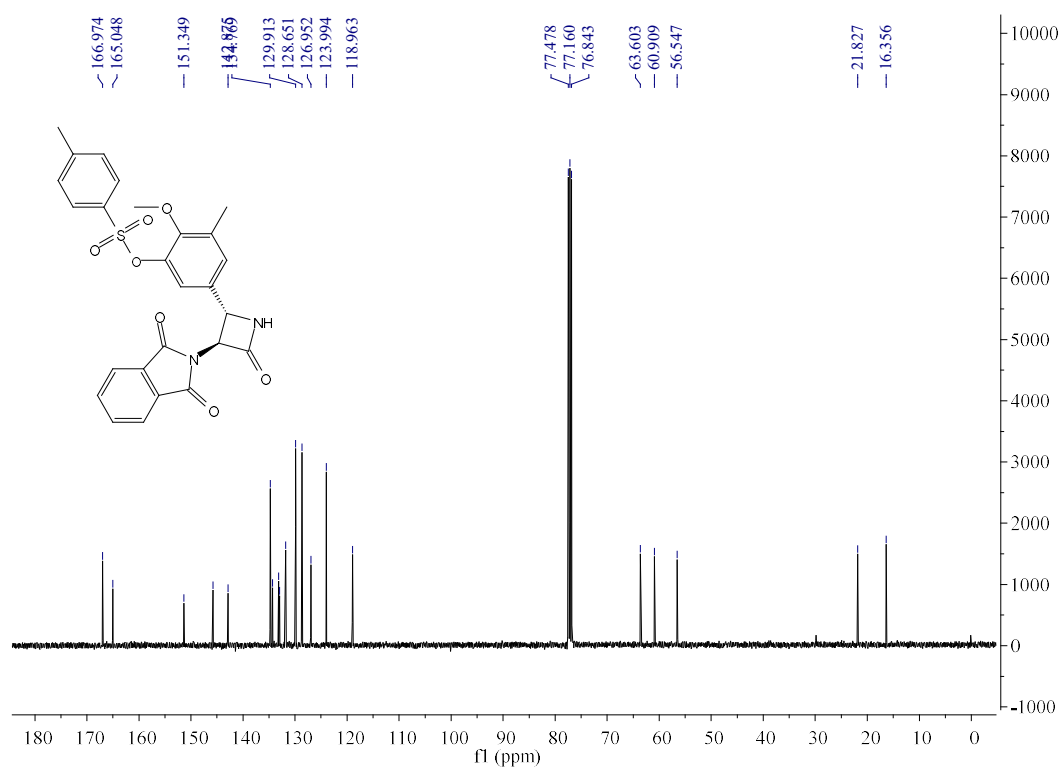
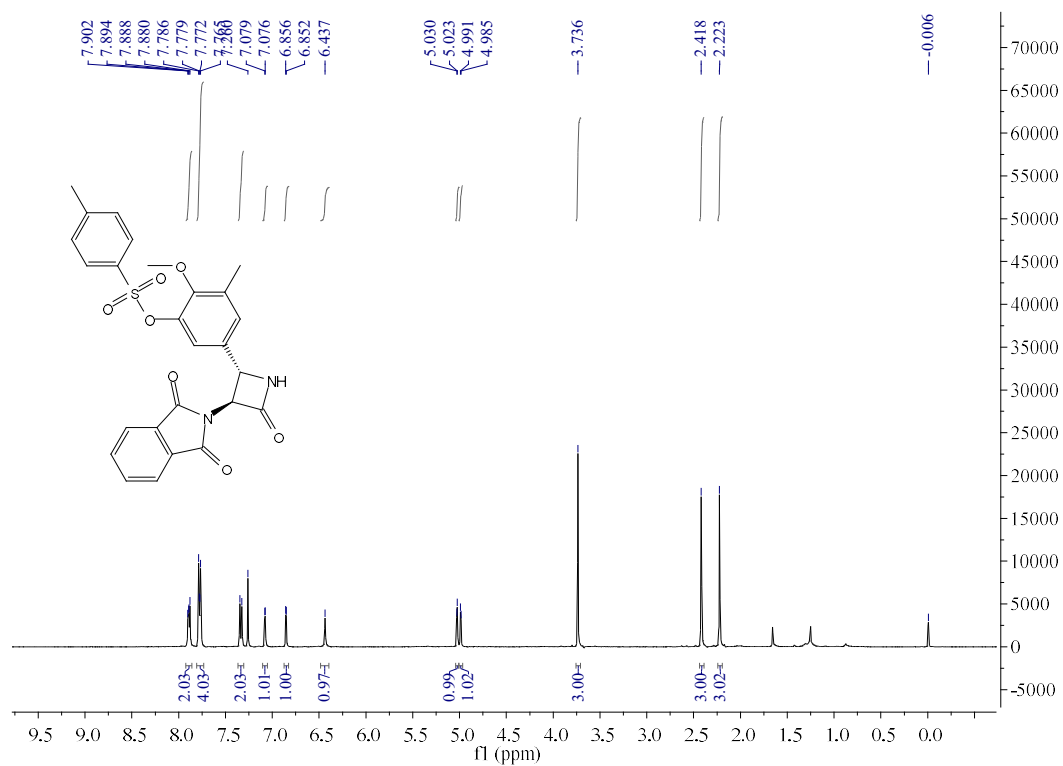
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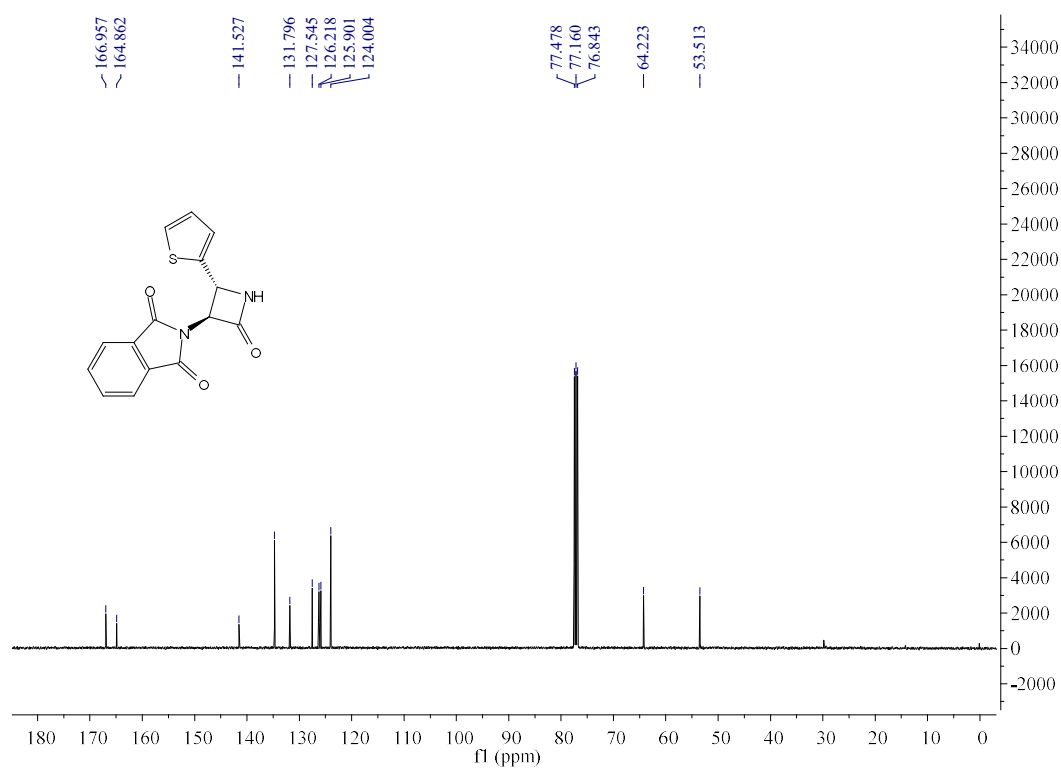
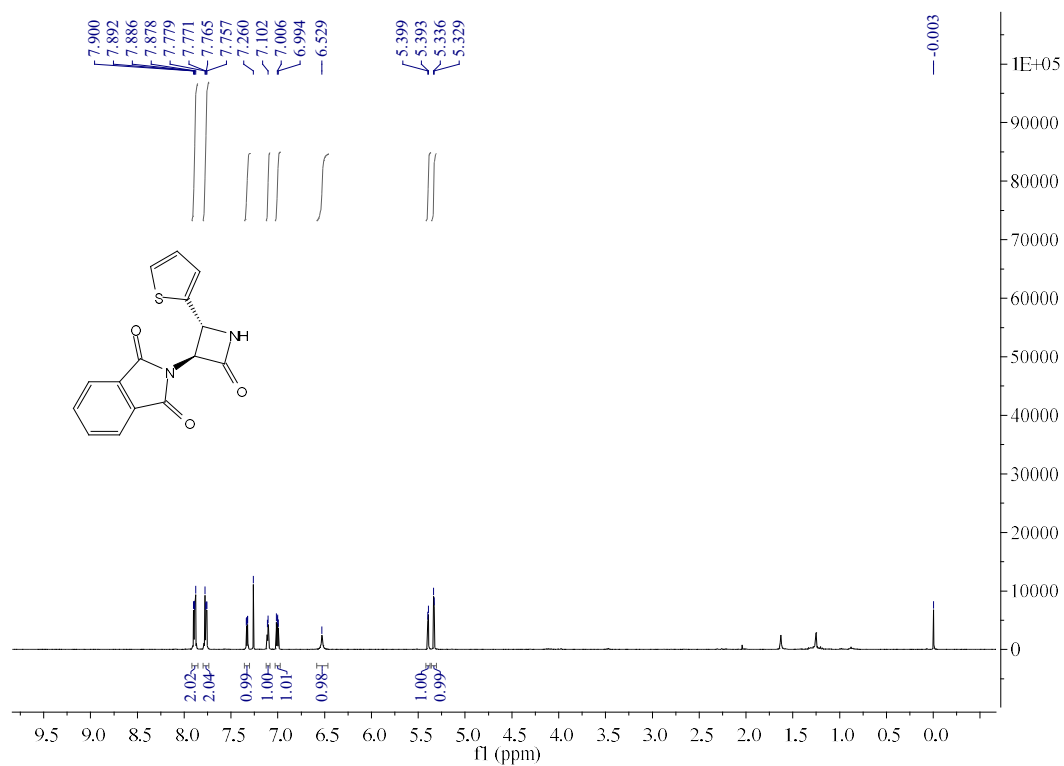
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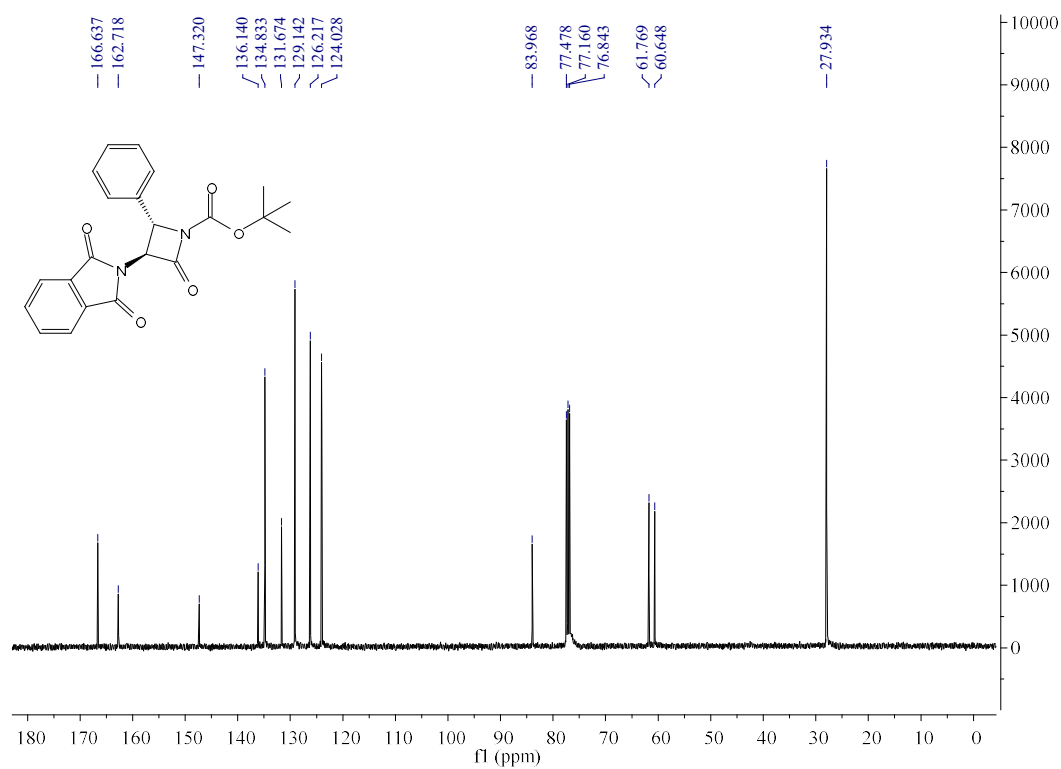
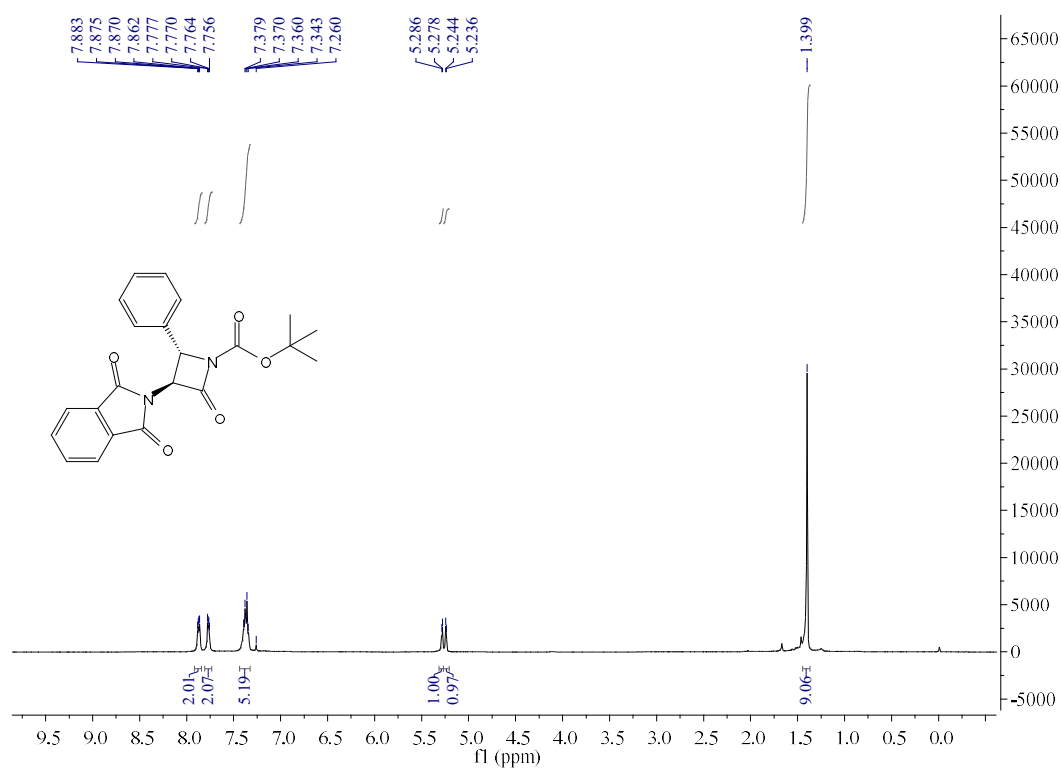
4g



4h



5a



6a

