Supporting Information

Palladium-Catalyzed Sequential Monoarylation/Amidation of C(sp^3)–H Bonds: Stereoselective Synthesis of *α*-Amino-*β*-Lactams and *anti*-*α*,*β*-Diamino Acid

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General Information

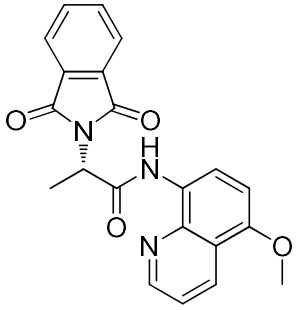
1,4-Dioxane were dried by sodium and freshly distilled. $Pd(OAc)_2$ was obtained from Stream® and $AgBF_4$ was obtained from TCI®. The other materials and solvents were purchased from Adamas-beta and other commercial suppliers and used without additional purification. Nuclear magnetic resonance (NMR) spectra were recorded with Bruker AVANCE 400 MHz. ^1H and ^{13}C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak as following: $CHCl_3$ = 7.26 (^1H NMR), DMSO = 2.50 (^1H NMR), $CDCl_3$ = 77.16 (^{13}C NMR), DMSO = 39.52 (^{13}C 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, ZhejiangUniversity.

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-amine[1] (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 $NaHCO_3$ (50 mL), brine (50 mL), and dried over anhydrous $MgSO_4$. Evaporation of organic solvent and purification by column chromatography afforded the desired amide.[2]

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

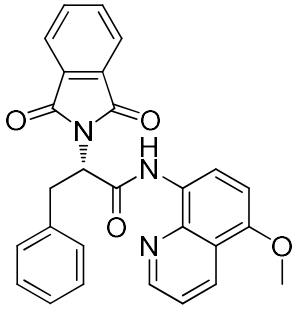


L-Alanine (8.91 g, 0.10 mol) and Na_2CO_3(10.60 g, 0.10 mol) were dissolved in water (100 mL) at room temperature and *N*-ethoxycarbonylphthalimide (21.91 g, 0.10 mol) was added to the solution in small portions. The reaction was stirred for 2 h, then the aqueous solution was slowly acidified with aqueous 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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{21}H_{17}N_3O_4$: 375.1219.

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

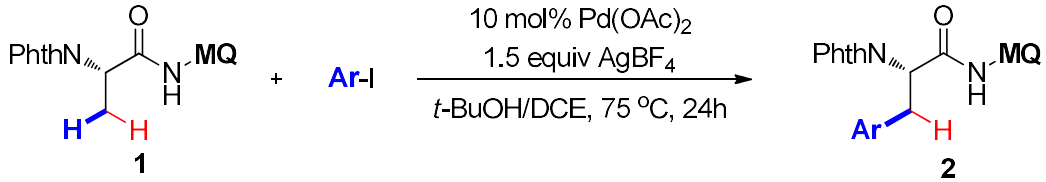


L-Phenylalanine (16.52 g, 0.10 mol) and Na_2CO_3 (10.60 g, 0.10 mol) were dissolved in water (100 mL) at room temperature and *N*-ethoxycarbonylphthalimide (21.91 g, 0.10 mol) was added to the solution in small portions. The reaction was stirred for 2 hours, then the aqueous solution was slowly acidified 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 Na_2SO_4. 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.

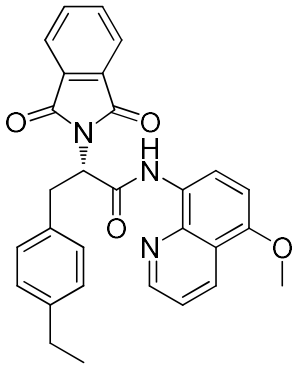
The compound **2a** was prepared according to **GP1**. Purified by silica gel column chromatography in petroleum ether : ethyl acetate = 4 : 1 gave **2a** as a white solid (7.13 g, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (brs, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.61 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.51 (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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{27}H_{21}N_3O_4$: 451.1532.

General Procedure (GP2) for Palladium-Catalyzed Methyl C(sp^3)–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), $AgBF_4$ (0.292 g, 1.5 mmol), *t*-BuOH (7 mL) and 1,2-dichloroethane (3 mL) were added. The tube was charged with N_2 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**.

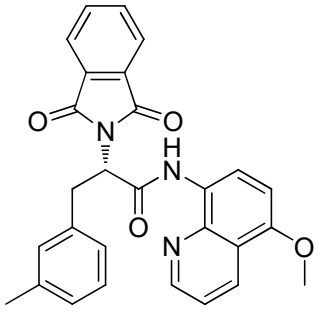
(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-3-(4-ethylphenyl)-*N*-(5-methoxyquinolin-8-yl)propanamide (2b)



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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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,

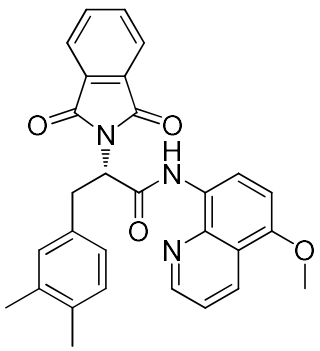
120.40, 116.98, 104.26, 56.39, 55.82, 34.49, 28.48, 15.52. HRMS (EI) *m/z*: 479.1844 (M^+); calc. for $C_{29}H_{25}N_3O_4$: 479.1845.

(S)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(5-methoxyquinolin-8-yl)-3-(m-tolyl)propana mide (2c)



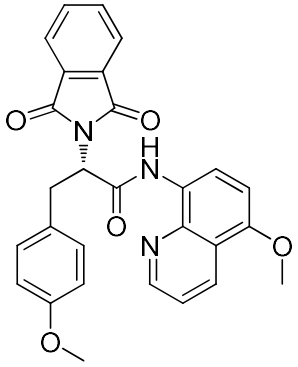
The title compound **2c** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 0.5 gave **2c** as a white solid (0.382 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (brs, 1H), 8.66 (d, *J* = 8.4 Hz, 1H), 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-dioxoisoindolin-2-yl)-*N*-(5-methoxyquinolin-8-yl)propanamide (2d)



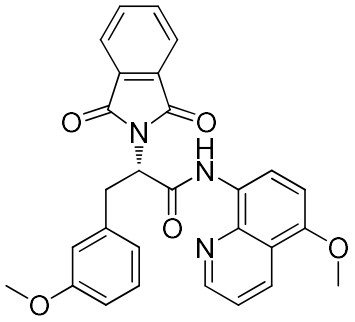
The title compound **2d** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 0.5 gave **2d** as a white solid (0.331 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (brs, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{29}H_{25}N_3O_4$: 479.1845.

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



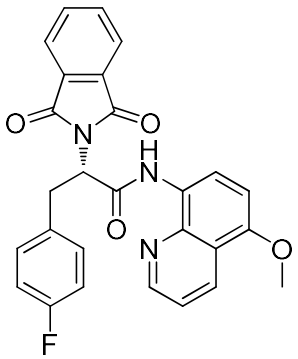
The title compound **2e** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : ethyl acetate : acetone = 6 : 1 : 1 gave **2e** as a light yellow solid (0.404 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (brs, 1H), 8.71 – 8.59 (m, 2H), 8.52 (d, *J* = 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{28}H_{23}N_3O_5$: 481.1638.

(*S*)-2-(1,3-Dioxoisoindolin-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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{28}H_{23}N_3O_5$: 481.1638.

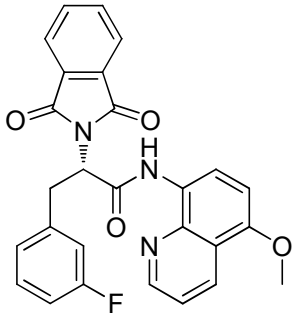
(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-3-(4-fluorophenyl)-*N*-(5-methoxyquinolin-8-yl)pr opanamide (2g)



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%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (brs,

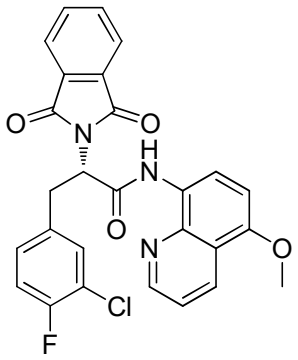
1H), 8.64 (d, *J* = 8.4 Hz, 1H), 8.60 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.50 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.89 – 7.76 (m, 2H), 7.74 – 7.63 (m, 2H), 7.35 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.26 – 7.21 (m, 2H), 6.90 (t, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.39 (dd, *J* = 9.2, 8.0 Hz, 1H), 3.95 (s, 3H), 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 $C_{27}H_{20}FN_3O_4$: 469.1438.

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



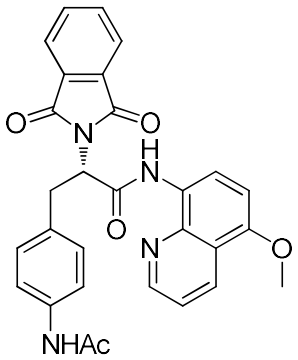
The title compound **2h** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 4 : 4 : 0.5 gave **2h** as a light yellow solid (0.399 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (brs, 1H), 8.63 (d, *J* = 8.4 Hz, 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 $C_{27}H_{20}FN_3O_4$: 469.1438.

(*S*)-3-(3-Chloro-4-fluorophenyl)-2-(1,3-dioxoisoindolin-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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{27}H_{19}ClFN_3O_4$: 503.1048.

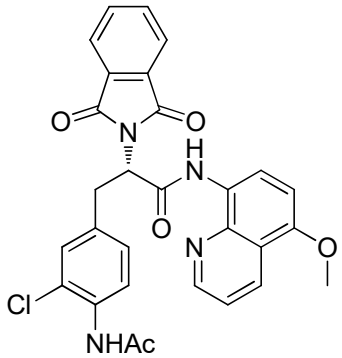
(*S*)-3-(4-Acetamidophenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(5-methoxyquinolin-8-yl)propanamide (2j)



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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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),

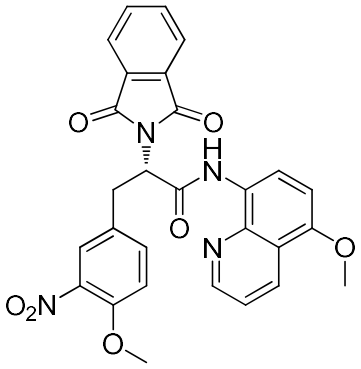
5.39 (dd, *J* = 9.6, 6.8 Hz, 1H), 3.95 (s, 3H), 3.81 – 3.69 (m, 2H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.50, 168.08, 166.05, 150.78, 148.88, 139.27, 137.05, 134.31, 132.50, 131.67, 131.26, 129.58, 127.29, 123.65, 120.84, 120.44, 120.00, 117.04, 104.24, 56.30, 55.85, 34.28, 24.60. HRMS (EI) *m/z*: 508.1760 (M^+); calc. for $C_{29}H_{24}N_4O_5$: 508.1747.

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



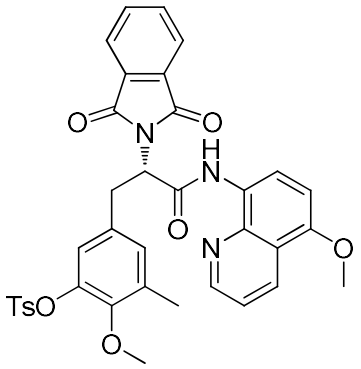
The title compound **2k** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : acetone = 1.7 : 1 gave **2k** as a white solid (0.369 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (brs, 1H), 8.68 – 8.56 (m, 2H), 8.51 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.22 (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 $C_{29}H_{23}ClN_4O_5$: 542.1357.

(*S*)-2-(1,3-Dioxoisoindolin-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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{28}H_{22}N_4O_7$: 526.1488.

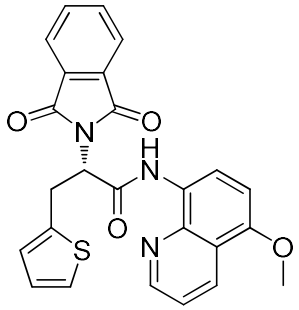
(*S*)-5-(2-(1,3-Dioxoisoindolin-2-yl)-3-((5-methoxyquinolin-8-yl)amino)-3-oxoprop yl)-2-methoxy-3-methylphenyl 4-methylbenzenesulfonate (2m)



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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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 –

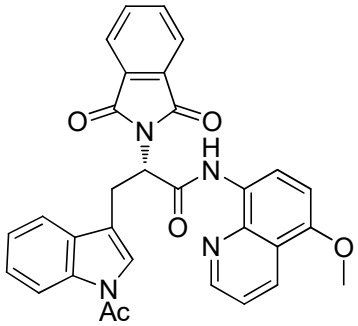
3.56 (m, 5H), 2.41 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.01, 165.73, 150.77, 149.89, 148.91, 145.38, 142.52, 139.22, 134.32, 133.46, 133.08, 132.47, 131.78, 131.26, 130.35, 129.71, 128.52, 127.28, 123.68, 121.87, 120.86, 120.43, 116.99, 104.23, 60.72, 56.09, 55.85, 34.15, 21.82, 16.06. HRMS (EI) *m/z*: 665.1855 (M^+); calc. for $C_{36}H_{31}N_3O_8S$: 665.1832.

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



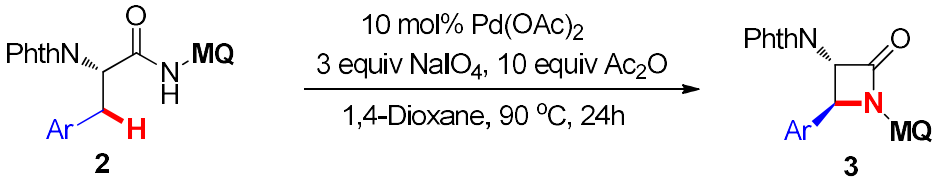
The title compound **2n** was prepared according to **GP2**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 5 : 3 : 0.6 gave **2n** as a light yellow solid (0.412 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (brs, 1H), 8.64 (d, *J* = 8.4 Hz, 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 $C_{25}H_{19}N_3O_4S$: 457.1096.

(*S*)-3-(1-Acetyl-1*H*-indol-3-yl)-2-(1,3-dioxoisoindolin-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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{31}H_{24}N_4O_5$: 532.1747.

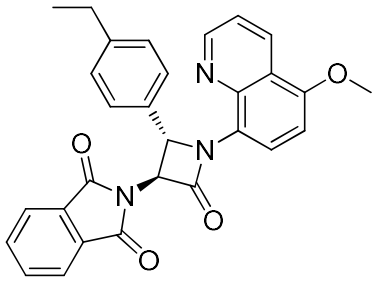
General Procedure (GP3) for Palladium-Catalyzed Methylene C(sp^3)–H Amidation



To a 50 mL Schlenk tube, **2** (0.5 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $NAIO_4$ (0.321 g, 1.5 mmol), Ac_2O (0.510 g, 5 mmol) and 1,4-dioxane (5 mL) were added. The tube was charged with N_2 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 $NaHCO_3$ (10 mL), dried over anhydrous $MgSO_4$.

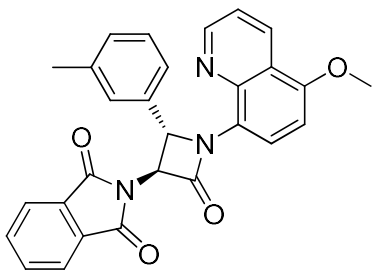
Evaporation of the organic solvent and purification by silica gel column chromatography gave the desired product **3**.

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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{29}H_{23}N_3O_4$: 477.1689.

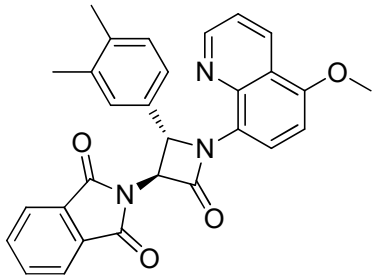
2-((3*S*,4*S*)-1-(5-Methoxyquinolin-8-yl)-2-oxo-4-(m-tolyl)azetidin-3-yl)isoindoline-1,3-dione (3c)



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%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd,

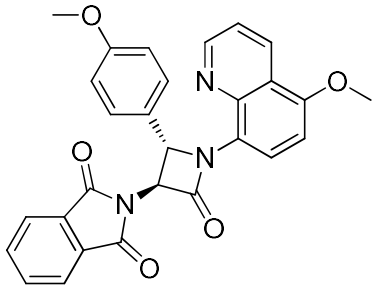
J = 4.0, 1.6 Hz, 1H), 8.44 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.90 – 7.84 (m, 2H), 7.76 – 7.70 (m, 2H), 7.29 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.01 – 6.96 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 5.42 (d, *J* = 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 $C_{28}H_{21}N_3O_4$: 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)



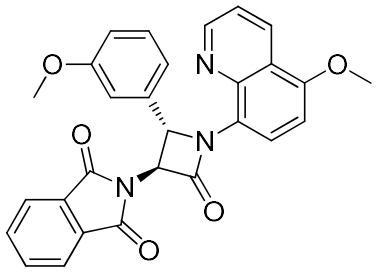
The title compound **3d** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 4 : 6 : 1 gave **3d** as a light yellow solid (0.203 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 4.0 Hz, *J* = 1.2 Hz, 1H), 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 $C_{29}H_{23}N_3O4$: 477.1689.

2-((2*S*,3*S*)-2-(4-Methoxyphenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)is oindoline-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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{28}H_{21}N_3O_5$: 479.1481.

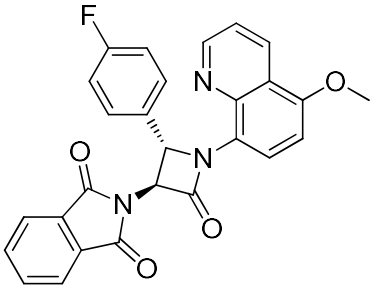
2-((2*S*,3*S*)-2-(3-Methoxyphenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3f)



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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.08, 163.30, 159.97, 153.32, 149.92, 142.69, 139.71, 134.52,

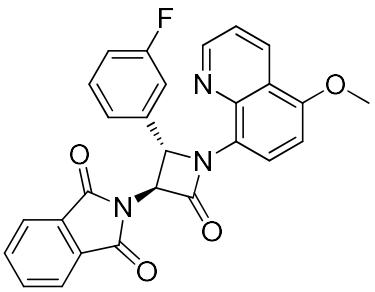
132.01, 130.59, 129.87, 125.62, 123.83, 123.39, 121.13, 120.70, 118.87, 114.02, 111.92, 104.01, 65.05, 62.94, 55.98, 55.26. HRMS (EI) *m/z*: 479.1487 (M^+); calc. for $C_{28}H_{21}N_3O_5$: 479.1481.

2-((2*S*,3*S*)-2-(4-Fluorophenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isoindoline-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%). ^{1}H 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.

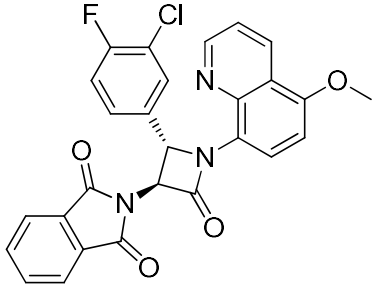
2-((2*S*,3*S*)-2-(3-Fluorophenyl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3h)



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

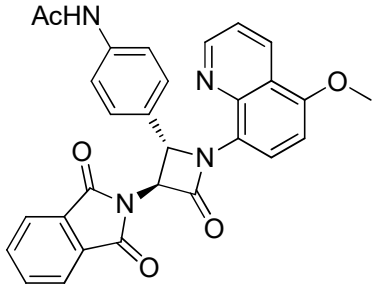
0.6 gave **3h** as a light yellow solid (0.079 g, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.46 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.92 – 7.84 (m, 2H), 7.79 – 7.71 (m, 2H), 7.30 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.15 – 7.09 (m, 1H), 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.35. HRMS (EI) *m/z*: 467.1282 (M^+); calc. for $C_{27}H_{18}FN_3O_4$: 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)



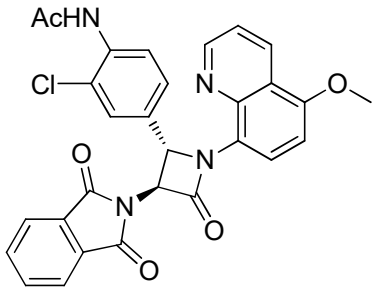
The title compound **3i** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : ethyl acetate = 2 : 1 gave **3i** as a light yellow solid (0.150 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.47 (dd, *J* = 8.4, 1.6 Hz, 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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. ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.64. HRMS (EI) *m/z*: 501.0891 (M^+); calc. for $C_{27}H_{17}ClFN_3O_4$: 501.0892.

***N*-(4-((2*S*,3*S*)-3-(1,3-Dioxoisoindolin-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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{29}H_{23}N_4O_5$: 507.1663.

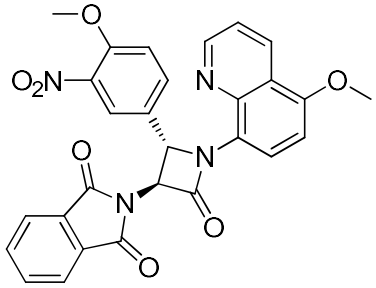
***N*-(2-Chloro-4-((2*S*,3*S*)-3-(1,3-dioxoisoindolin-2-yl)-1-(5-methoxyquinolin-8-yl)-4-oxoazetidin-2-yl)phenyl)acetamide (3k)**



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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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,

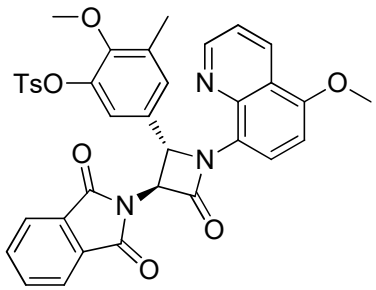
J = 2.8 Hz, 1H), 5.38 (d, *J* = 2.8 Hz, 1H), 3.96 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.29, 166.99, 162.99, 153.29, 149.84, 142.29, 134.77, 134.61, 134.58, 131.89, 130.64, 127.16, 126.11, 125.19, 123.86, 123.27, 122.84, 121.73, 121.07, 120.74, 104.03, 64.41, 62.94, 55.99, 24.85. HRMS (EI) *m/z*: 540.1207 (M^+); calc. for $C_{29}H_{21}ClN_4O_5$: 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)



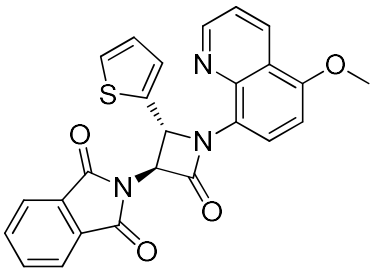
The title compound **3l** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 1.5 gave **3l** as a yellow solid (0.210 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.44 (dd, *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 $C_{28}H_{20}N_4O_7$: 524.1332.

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



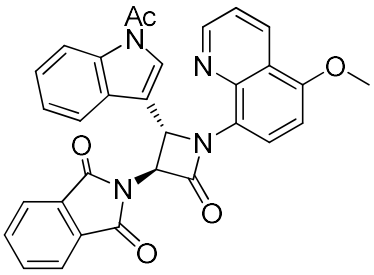
The title compound **3m** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : acetone = 1.8 : 1 gave **3m** as a yellow solid (0.279 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.47 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.07 (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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{36}H_{30}N_3O_8S$: 664.1748.

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



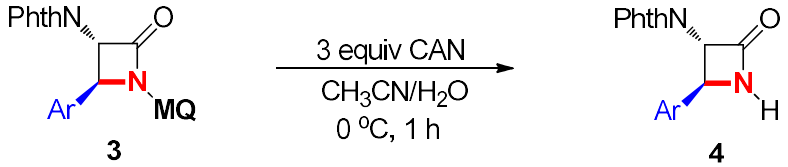
The title compound **3n** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 1 gave **3n** as a yellow solid (0.155 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.47 (dd, *J* = 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{25}H_{17}N_3O_4S$: 455.0940.

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



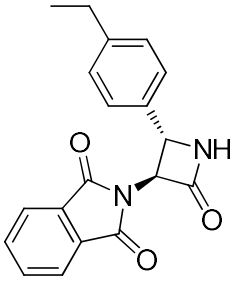
The title compound **3o** was prepared according to **GP3**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 1 : 6 : 1.2 gave **3o** as a yellow solid (0.111 g, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.46 (dd, *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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{31}H_{22}N_4O_5$: 530.1590.

General Procedure (GP4) for Removal of the Directing Group



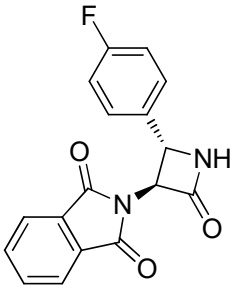
To an ice-water cooled solution of **3** (0.1 mmol) in acetonitrile (1.5 mL) and water (0.5 mL) was added ceric ammonium nitrate (3 equiv) in one portion. The reaction was kept in ice-water bath for 1 h. After completion, the reaction was diluted with ethyl acetate (25 mL), washed with saturated sodium thiosulfate (2 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4. 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)



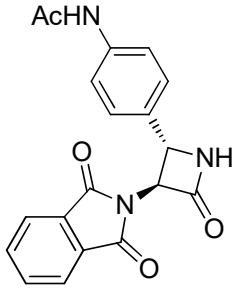
The title compound **4b** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 2 : 4 : 1 gave **4b** as a white solid (22.7 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 2H), 7.79 – 7.72 (m, 2H), 7.29 (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 $C_{19}H_{16}N_2O_3$: 320.1161.

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



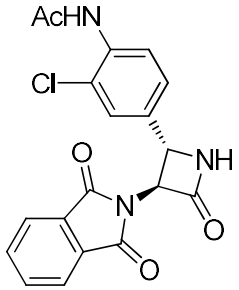
The title compound **4c** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : diethyl ether : ethyl acetate = 3 : 4 : 2 : 0.8 gave **4c** as a white solid (22.6 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.84 (m, 2H), 7.80 – 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 $C_{17}H_{11}FN_2O_3$: 310.0754.

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



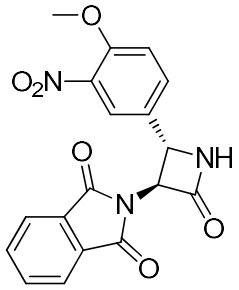
The title compound **4d** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 1 : 4 : 5 gave **4d** as a yellow solid (18.5 mg, 53%). ^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ 9.99 (brs, 1H), 8.93 (brs, 1H), 7.98 – 7.84 (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). ^{13}C 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 $C_{19}H_{15}N_3O_4$: 349.1063.

_N_-(2-Chloro-4-((2_S_,3_S_)-3-(1,3-dioxoisoindolin-2-yl)-4-oxoazetidin-2-yl)phenyl)acetamide (4e)



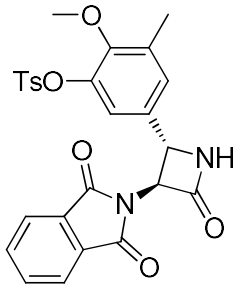
The title compound **4e** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 1 : 4 : 2.5 gave **4e** as a yellow solid (19.2 mg, 50%). ^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ 9.55 (brs, 1H), 8.97 (brs, 1H), 7.96 – 7.86 (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). ^{13}C 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 $C_{19}H_{14}ClN_3O_4$: 383.0673.

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



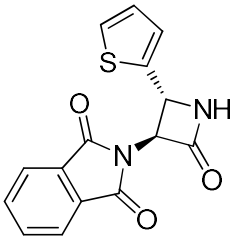
The title compound **4f** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 2.5 gave **4f** as a white solid (30.5 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.84 (m, 3H), 7.80 – 7.74 (m, 2H), 7.62 (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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{18}H_{13}N_3O_6$: 367.0804.

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



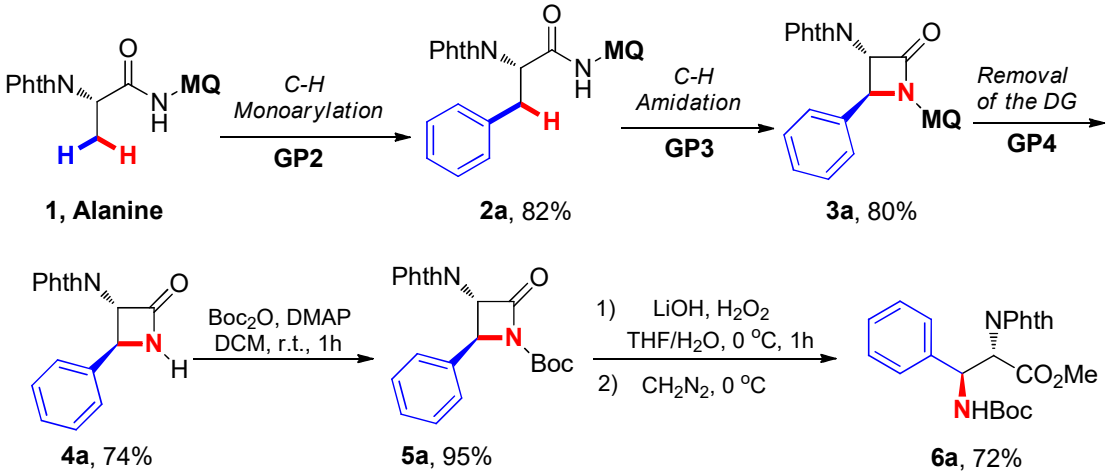
The title compound **4g** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 3 : 6 : 2 gave **4g** as a white solid (29.4 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.86 (m, 2H), 7.81 – 7.73 (m, 4H), 7.34 (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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{26}H_{22}N_2O_7S$: 506.1148.

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

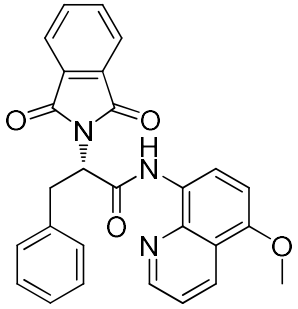


The title compound **4h** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 2 : 6 : 1 gave **4h** as a white solid (6.3 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.80 – 7.74 (m, 2H), 7.33 (dd, *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 $C_{15}H_{10}N_2O_3S$: 298.0412.

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

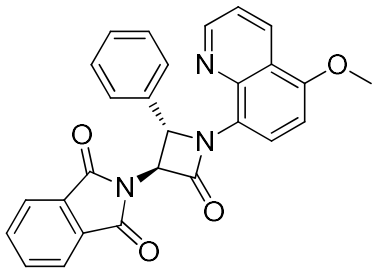


(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(5-methoxyquinolin-8-yl)-3-phenylpropanamide (2a)



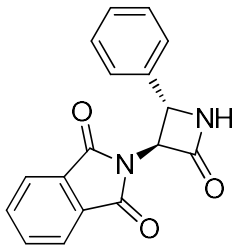
The compound **2a** was prepared according to **GP2**. Purified by silica gel column chromatography in petroleum ether : ethyl acetate = 4 : 1 gave **2a** as a white solid (0.370 g, 82 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (brs, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.61 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.51 (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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{27}H_{19}N_3O_4$: 449.1376.

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

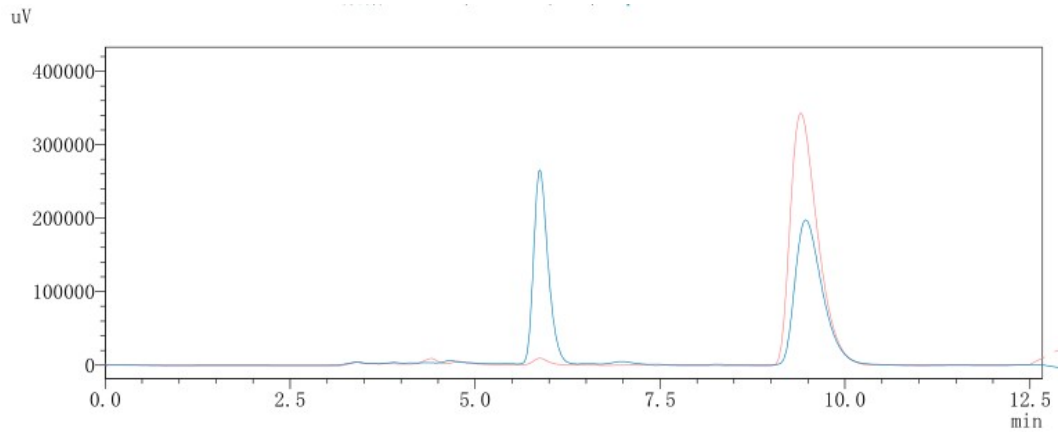


The title compound **4a** was prepared according to **GP4**. A purification by silica gel column chromatography in petroleum ether : dichloromethane : ethyl acetate = 2 : 4 : 1 gave **4a** as a white solid (21.6 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.79 – 7.73 (m, 2H), 7.42 – 7.32 (m, 5H), 6.67 (brs, 1H), 5.21 (d, *J* = 2.8 Hz, 1H), 5.14 (d, *J* = 2.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{17}H_{12}N_2O_3$: 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

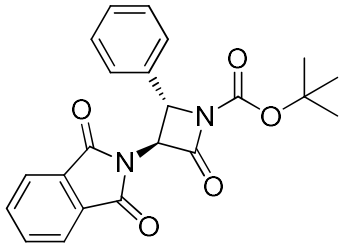
HPLC Conditions:

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



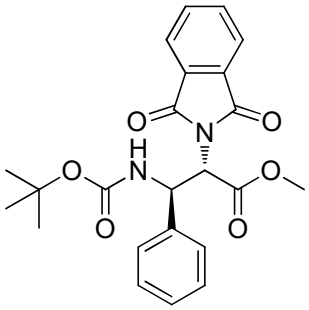
Retention Time	Area	Area%
5.874	120458	1.342
9.612	8856729	98.658
Totals	8977187	100

(3*S*,4*S*)-*tert*-Butyl-3-(1,3-dioxoisoindolin-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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{22}H_{20}N_2O_5Na$: 415.1264.

(2*S*,3*R*)-Methyl-3-((*tert*-butoxycarbonyl)amino)-2-(1,3-dioxoisoindolin-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 ºC then 30% H_2O_2 (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 ºC for 1 hour. The reaction was quenched at 0 ºC 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 H_2O) 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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{23}H_{24}N_2O_6Na$: 447.1527.

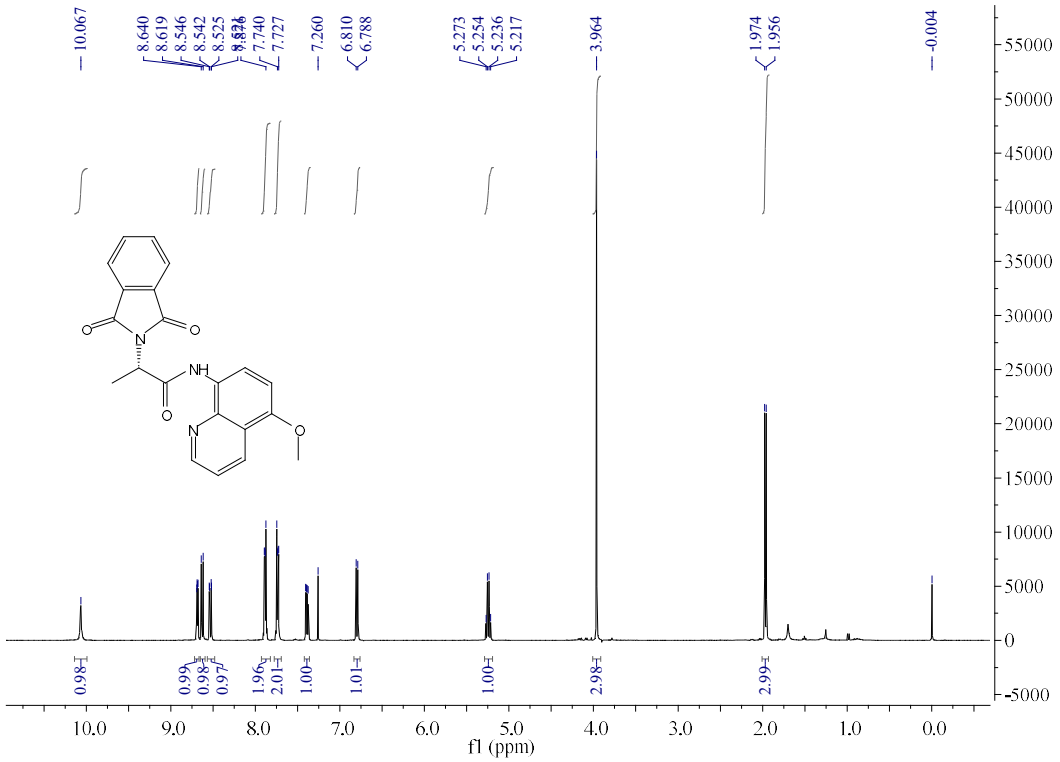
References

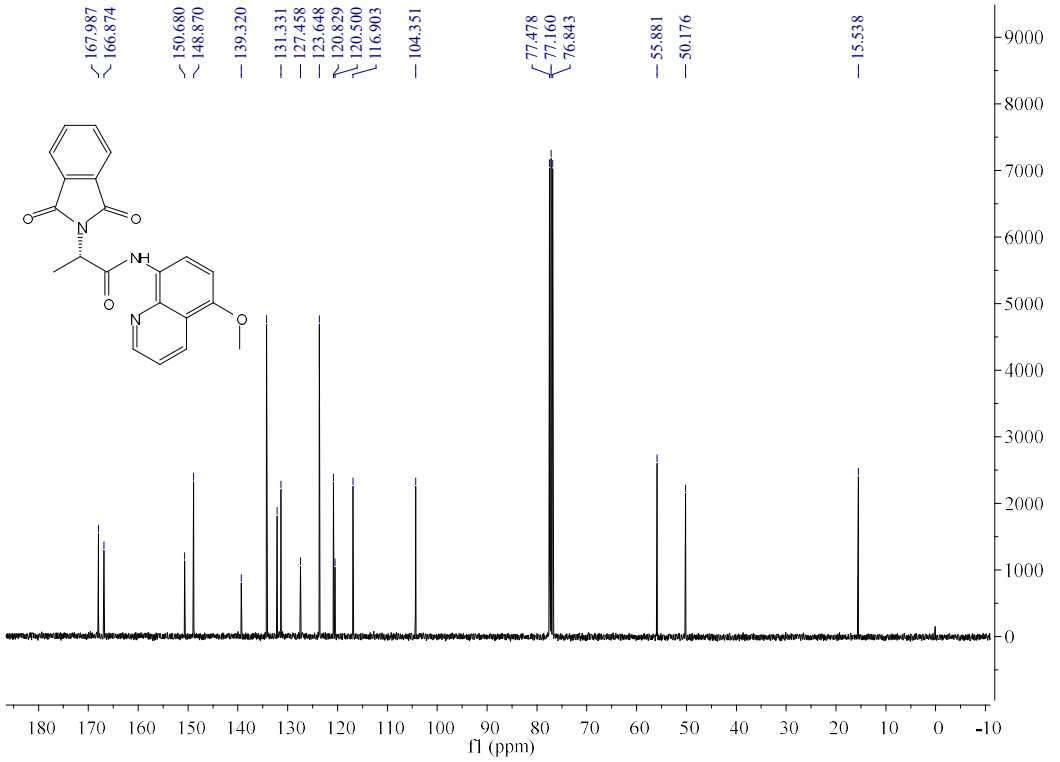
(1) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124.

(2) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906.

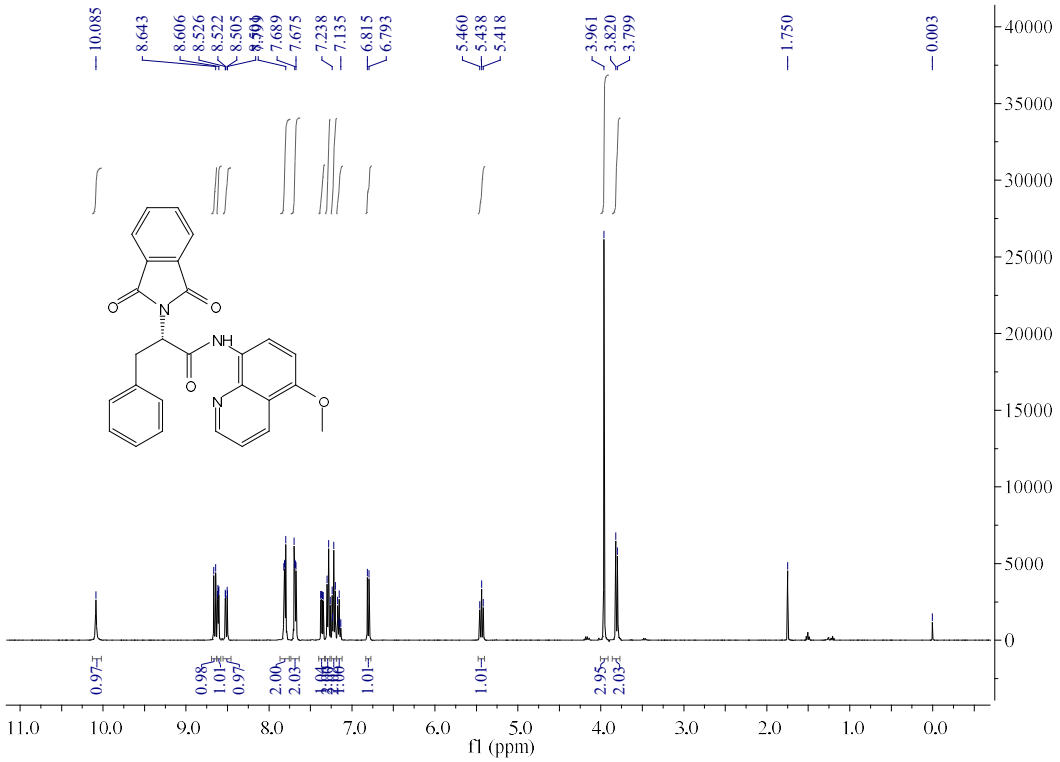
^{1}H and ^{13}C NMR Spectra

1





2a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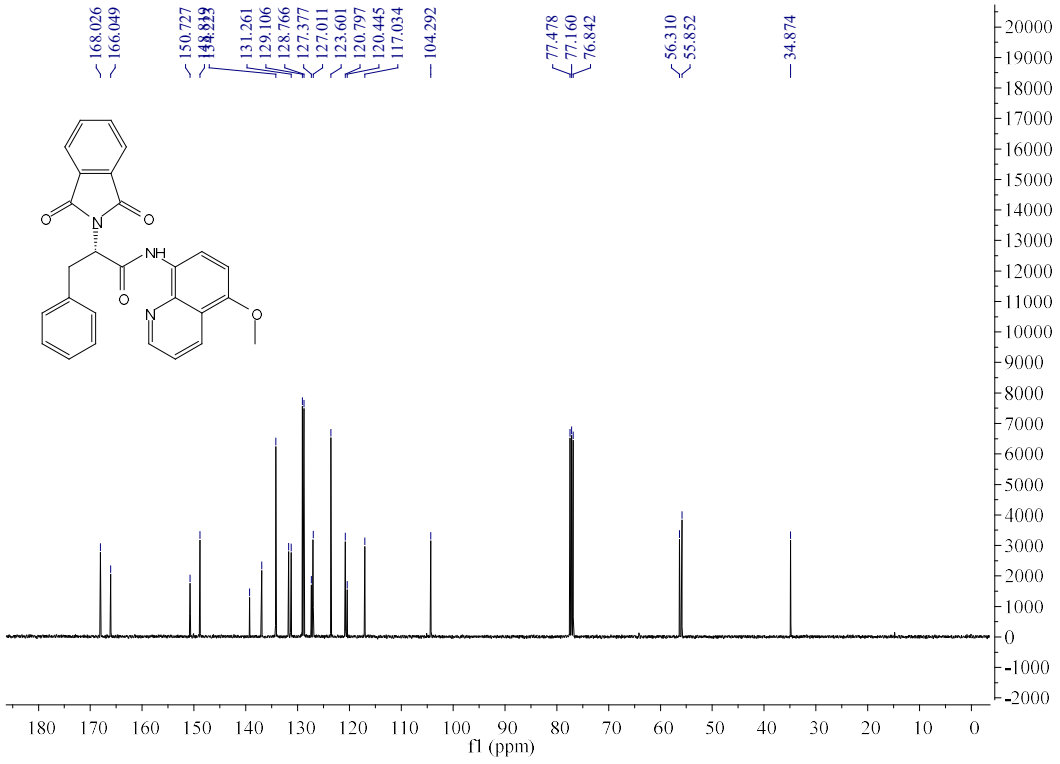
5.460
5.438
5.418
3.961
3.820
3.799
1.750
0.003
0.97
0.98
1.01
0.97
2.00
2.03
1.01
1.01
2.95
2.03
f1 (ppm)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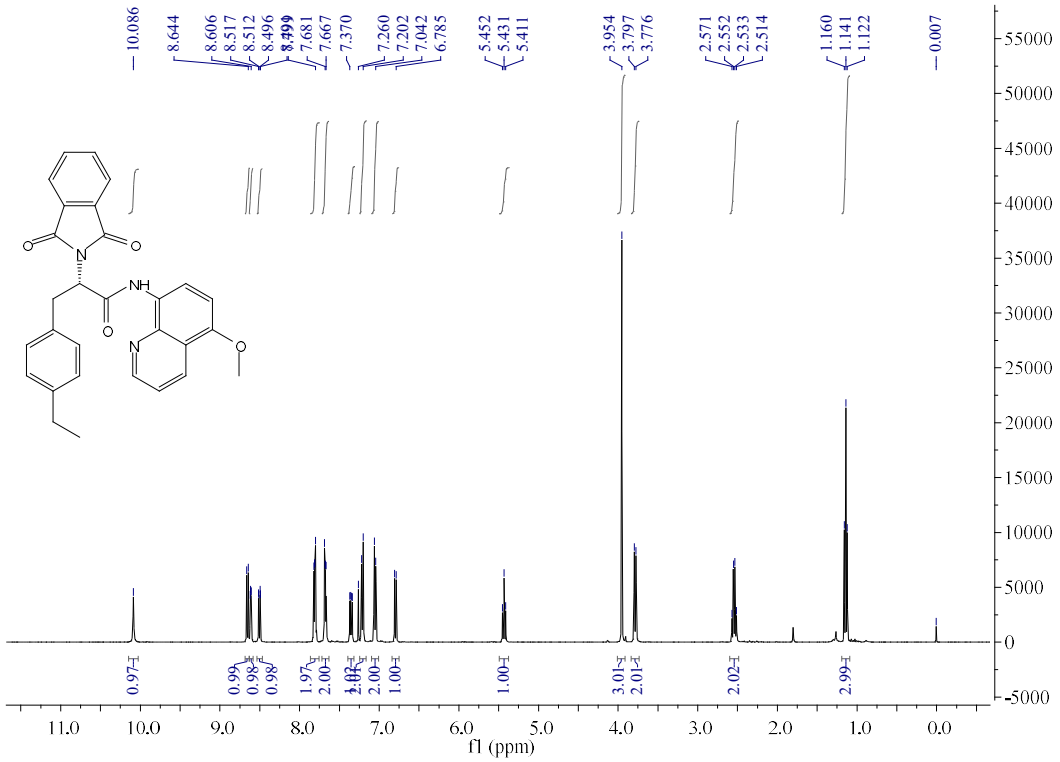
77.160
76.842
56.310
55.852
34.874
f1 (ppm)

2b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5.452
5.431
5.411
3.954
3.797
3.776
2.571
2.552
2.533
2.514
1.160
1.141
1.122
0.007
0.97
0.99
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0.98
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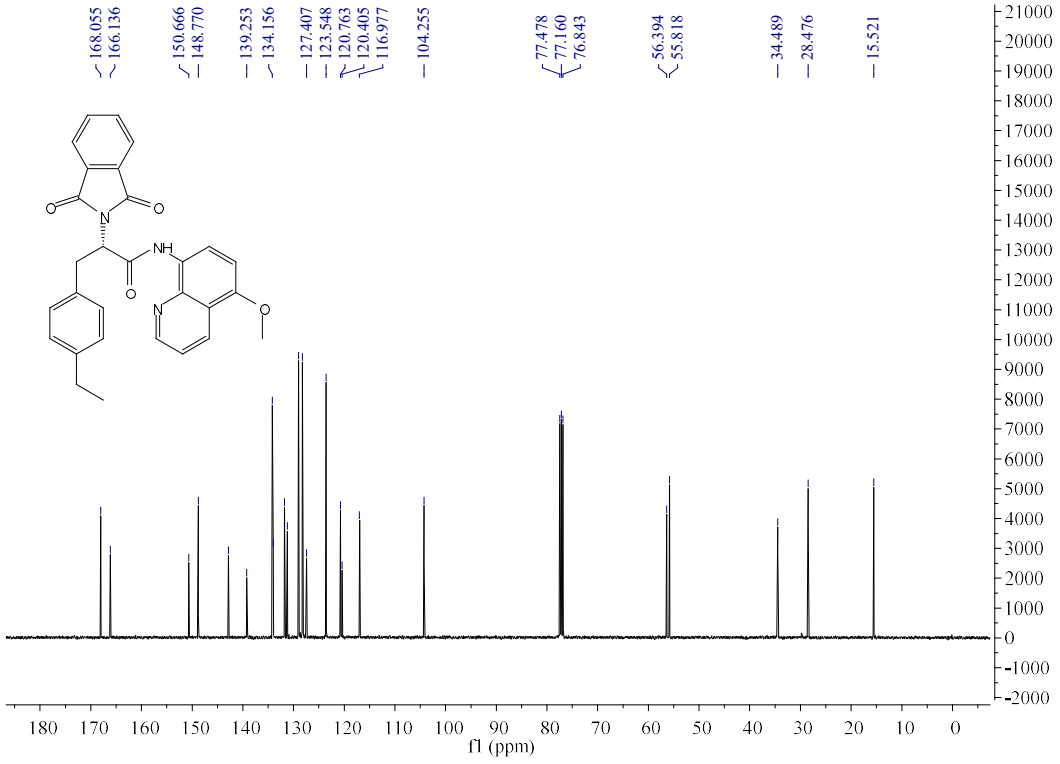
2.00
1.00
1.00
3.01
2.01
2.02
2.99
f1 (ppm)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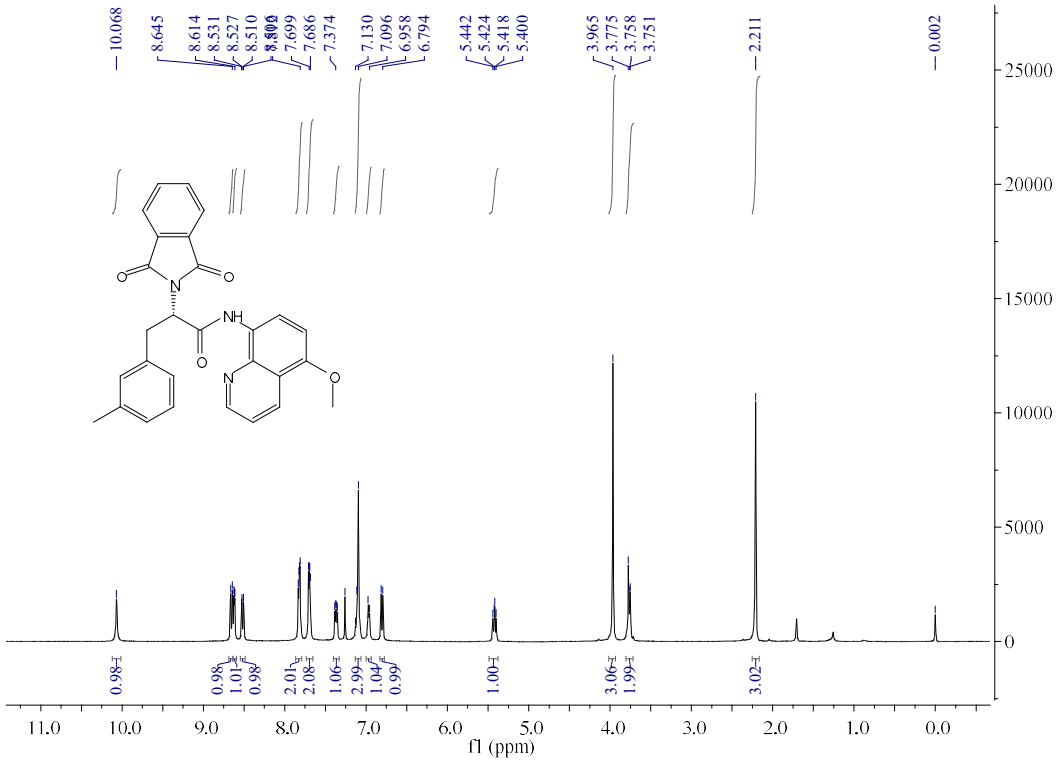
34.489
28.476
15.521
f1 (ppm)

2c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5.424
5.418
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3.965
3.775
3.758
3.751
2.211
0.002
0.98
0.98
1.01
0.98
2.01
2.08
1.06
2.99
1.04
0.99
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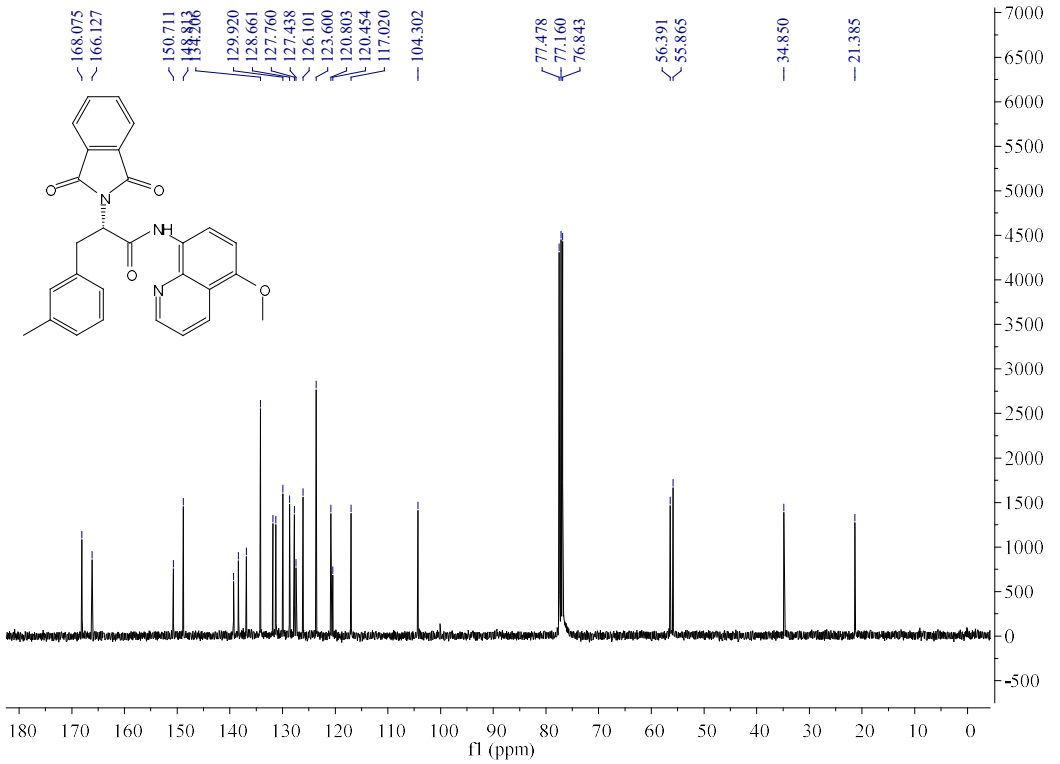
3.06
1.99
3.02
f1 (ppm)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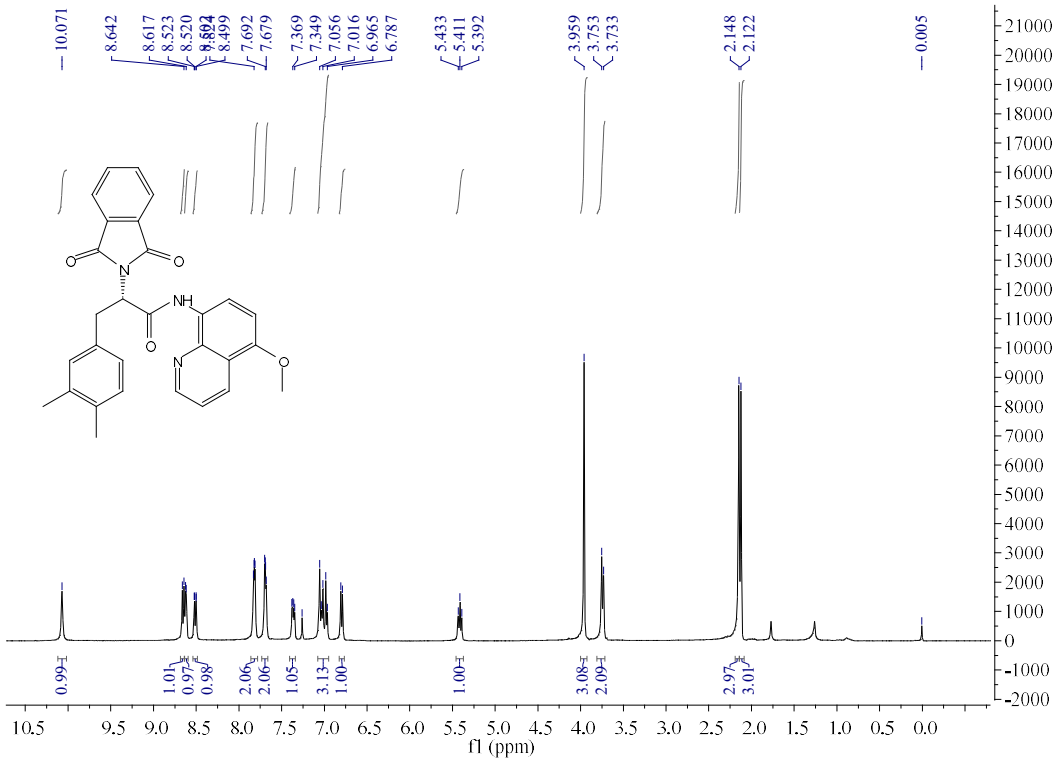
f1 (ppm)

2d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6.965
6.787
5.433
5.411
5.392
3.959
3.753
3.733
2.148
2.122
0.005
0.99
1.01
0.97
0.98
2.06
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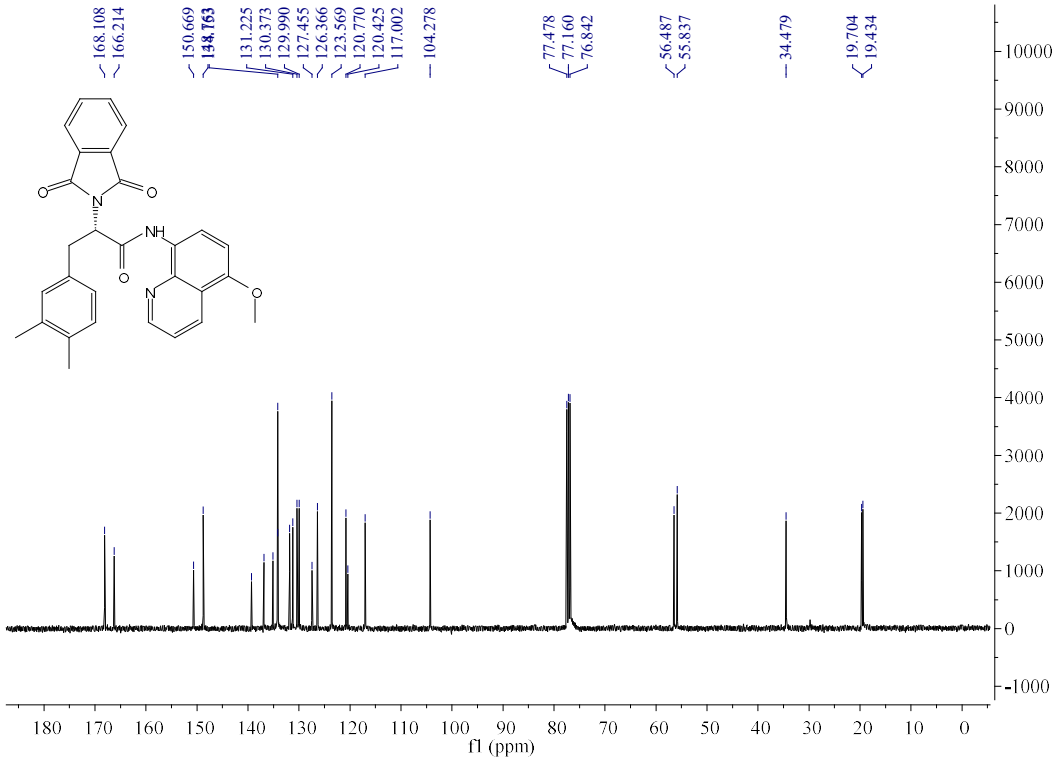
1.00
1.00
3.08
2.09
2.97
3.01
f1 (ppm)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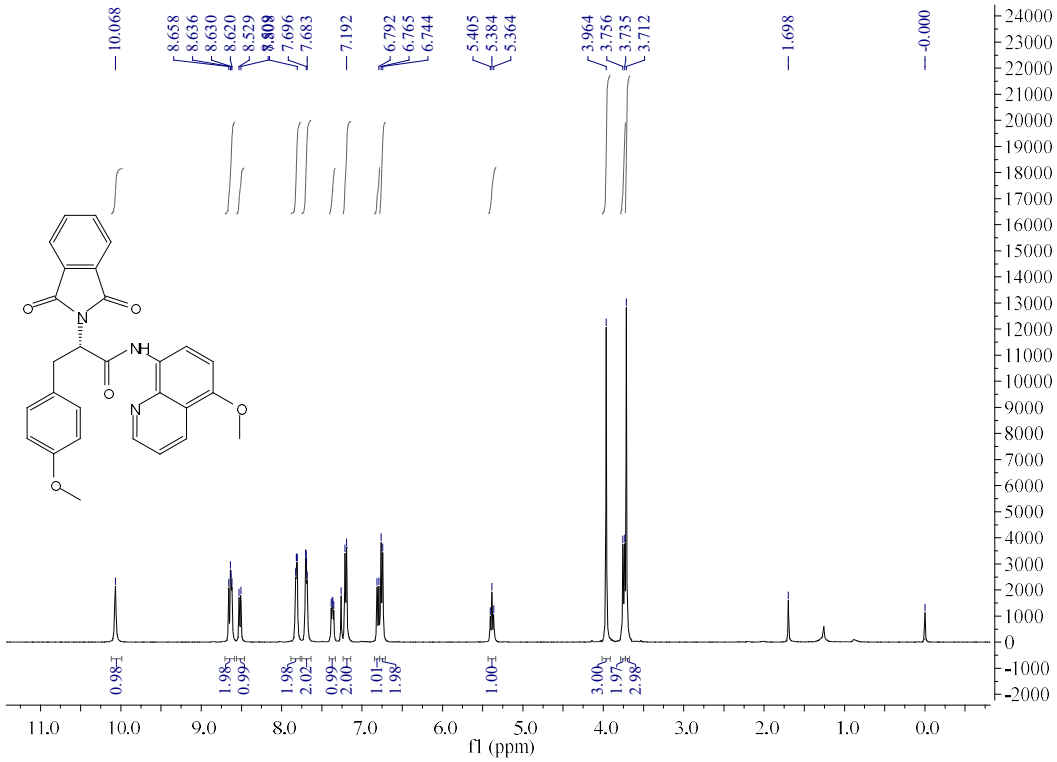
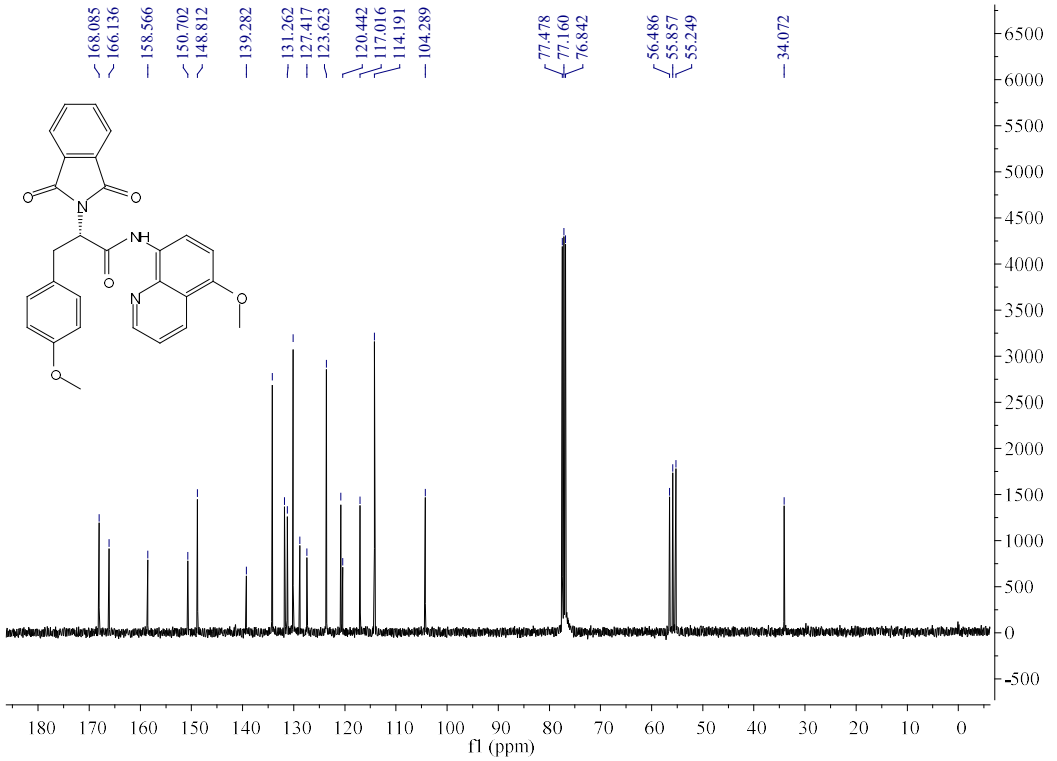
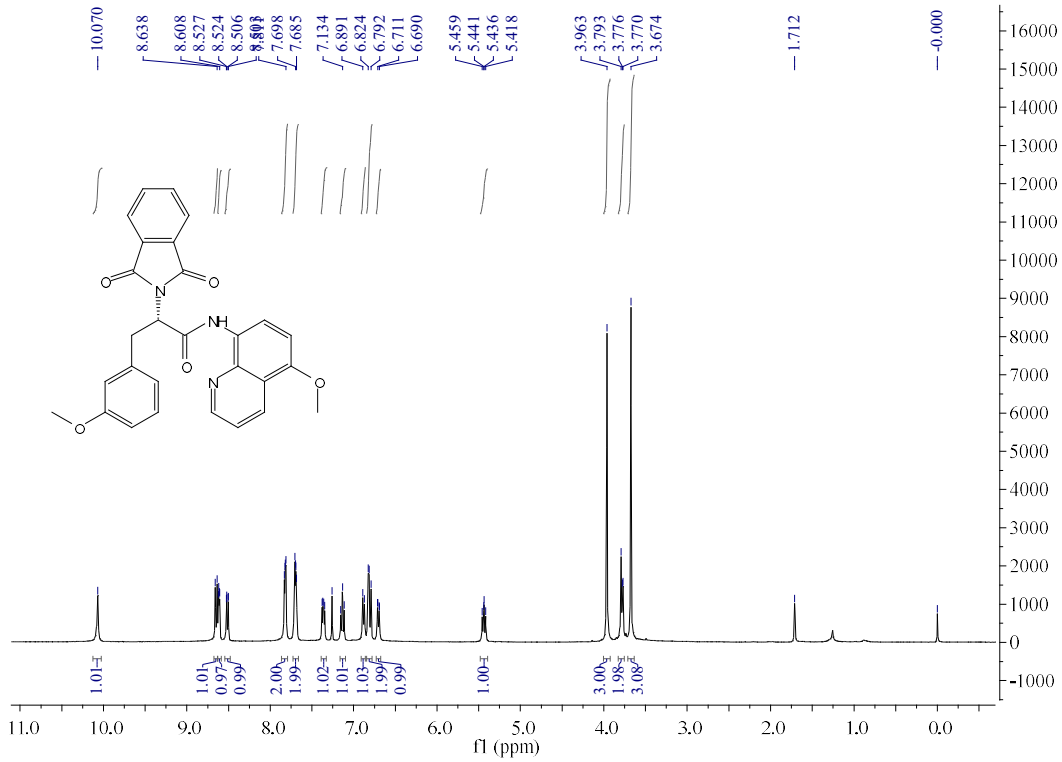
104.278
77.478
77.160
76.842
56.487
55.837
34.479
19.704
19.434
f1 (ppm)

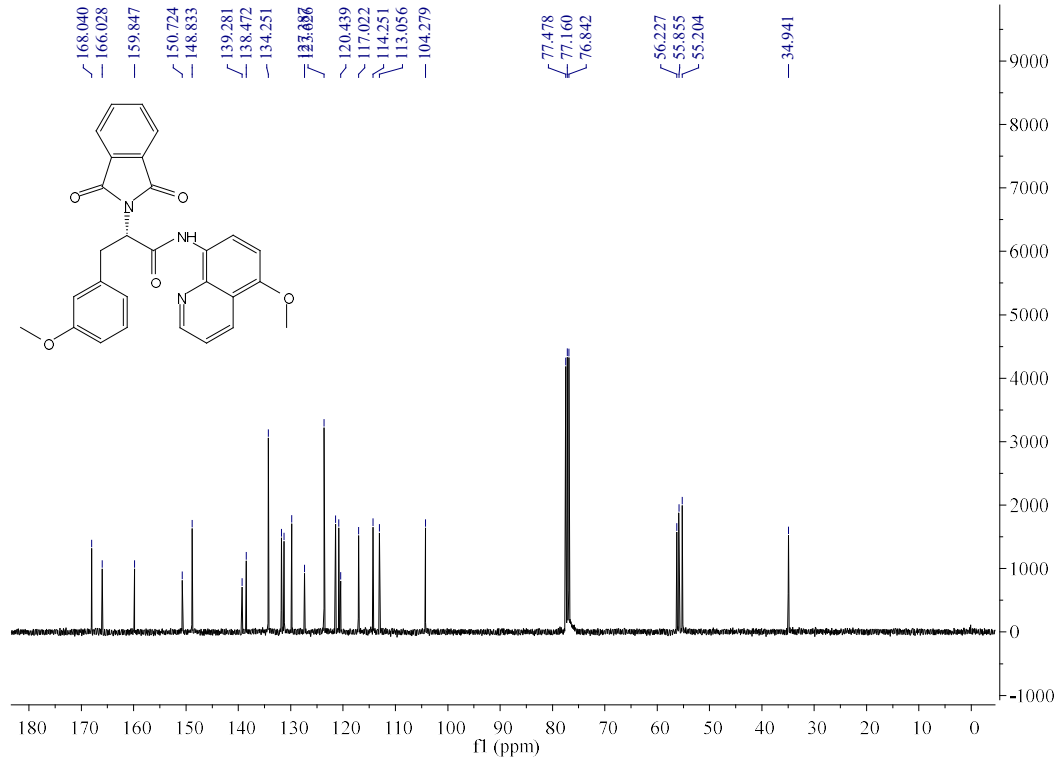
2e


10.068
8.658
8.636
8.630
8.620
8.529
7.696
7.683
7.192
6.792
6.765
6.744
5.405
5.384
5.364
3.964
3.756
3.735
3.712
1.698
-0.000
0.98
1.98
0.99
1.98
2.02
0.99
2.00
1.01
1.98
1.00
3.00
1.97
2.98
f1 (ppm)

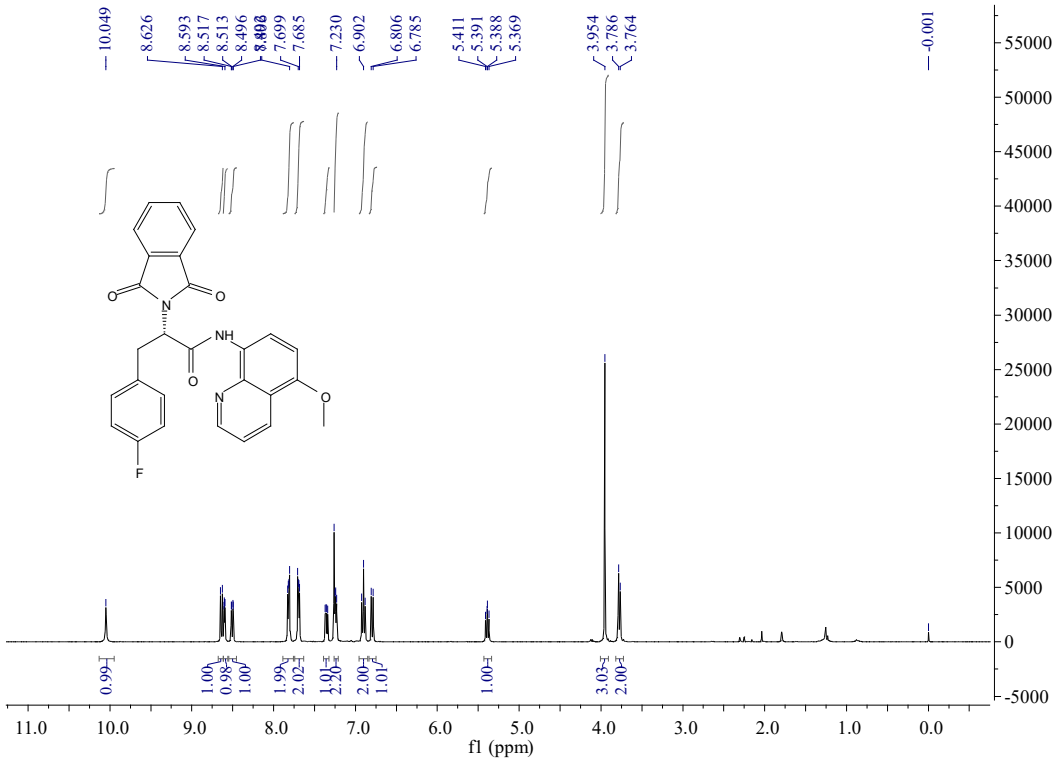

168.085
166.136
158.566
150.702
148.812
139.282
131.262
127.417
123.623
120.442
117.016
114.191
104.289
77.478
77.160
76.842
56.486
55.857
55.249
34.072
f1 (ppm)

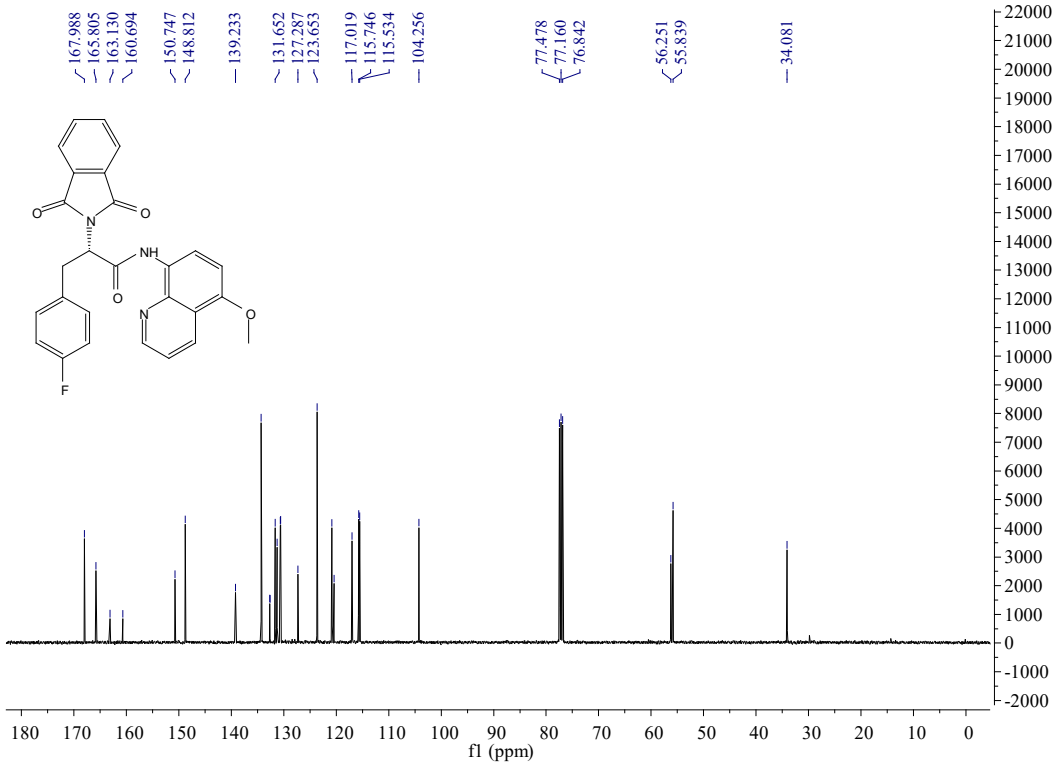
2f


10.070
8.638
8.608
8.527
8.524
8.506
7.698
7.685
7.134
6.891
6.824
6.792
6.711
6.690
5.459
5.441
5.436
5.418
3.963
3.793
3.776
3.770
3.674
1.712
-0.000
NH
f1 (ppm)

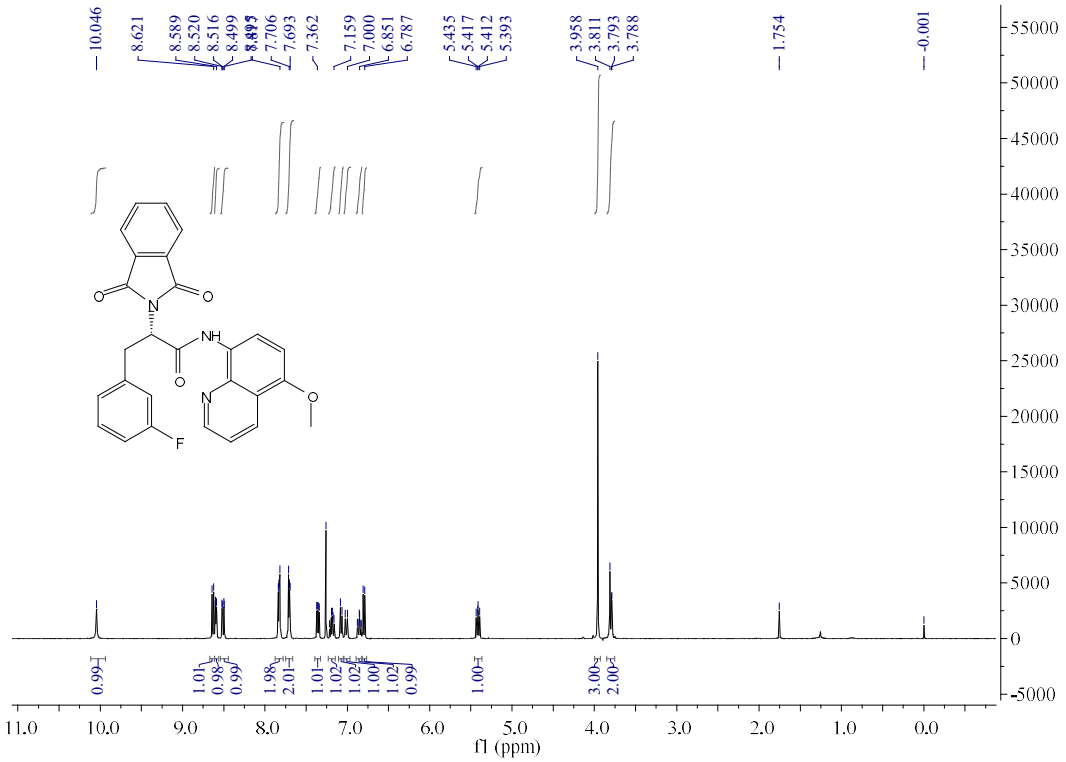

168.040
166.028
159.847
150.724
148.833
139.281
138.472
134.251
120.439
117.022
114.251
113.056
104.279
77.478
77.160
76.842
56.227
55.855
55.204
34.941
NH
f1 (ppm)

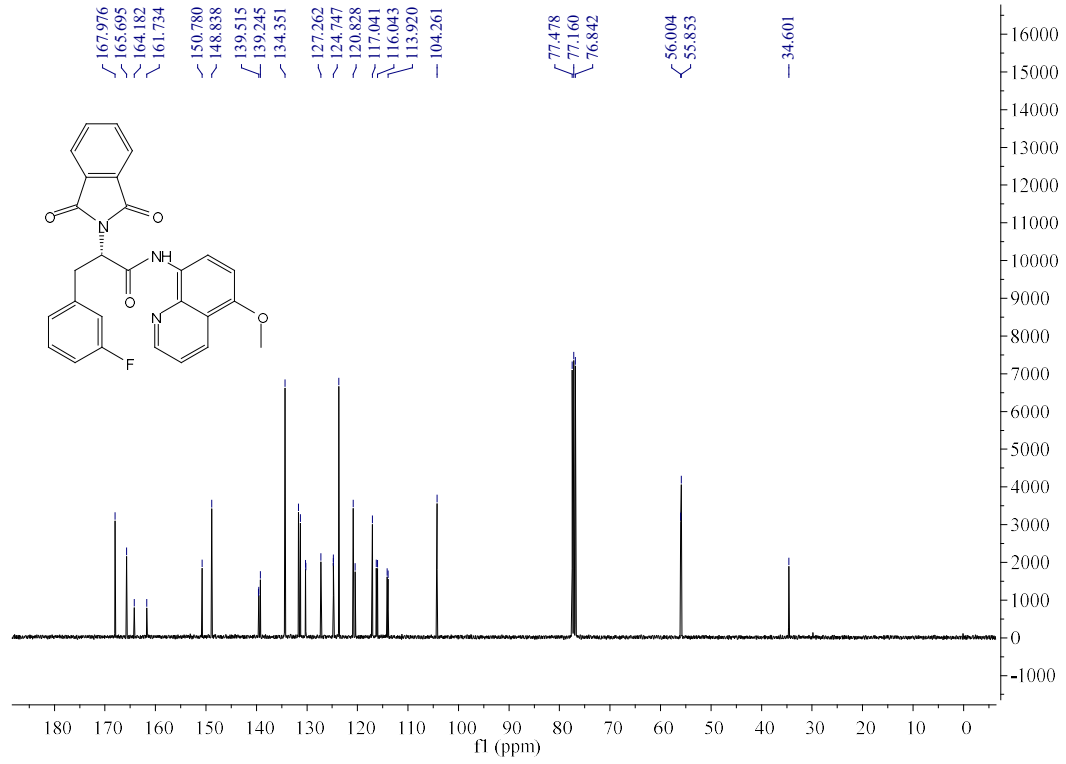
2g


10.049
8.626
8.593
8.517
8.513
8.496
7.699
7.685
7.230
6.902
6.806
6.785
5.411
5.391
5.388
5.369
3.954
3.786
3.764
-0.001
0.99
1.00
0.98
1.00
1.99
2.02
1.01
2.20
2.00
1.01
1.00
3.03
2.00
f1 (ppm)

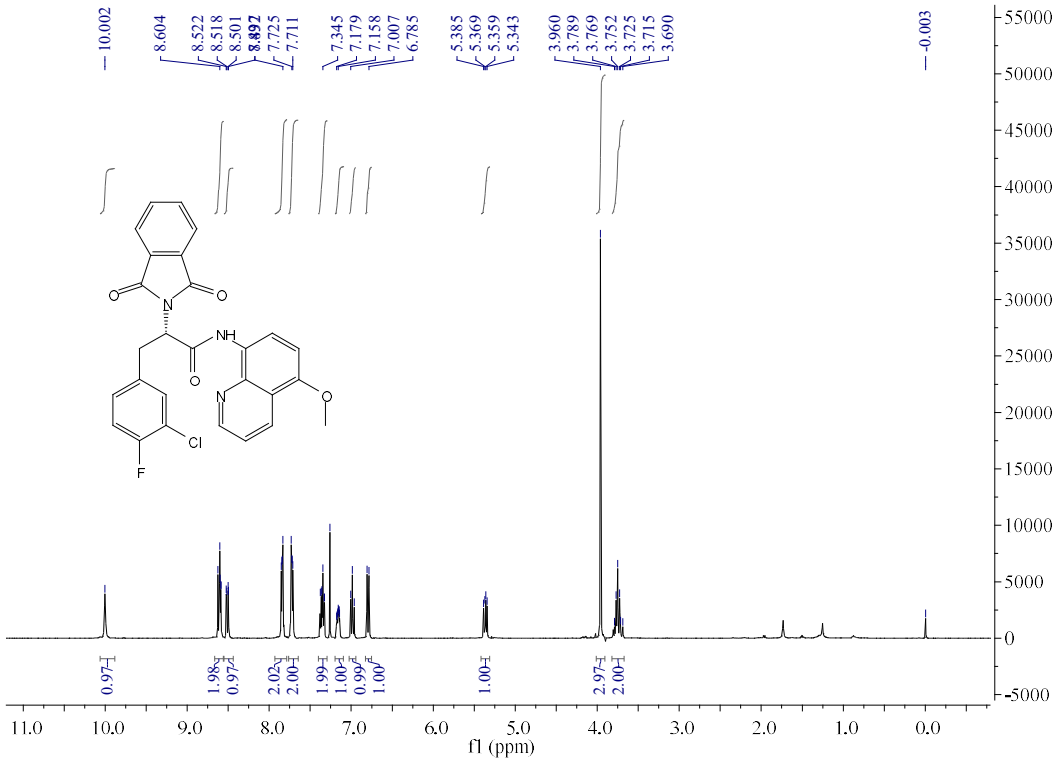

167.988
165.805
163.130
160.694
150.747
148.812
139.233
131.652
127.287
123.653
117.019
115.746
115.534
104.256
77.478
77.160
76.842
56.251
55.839
34.081
f1 (ppm)

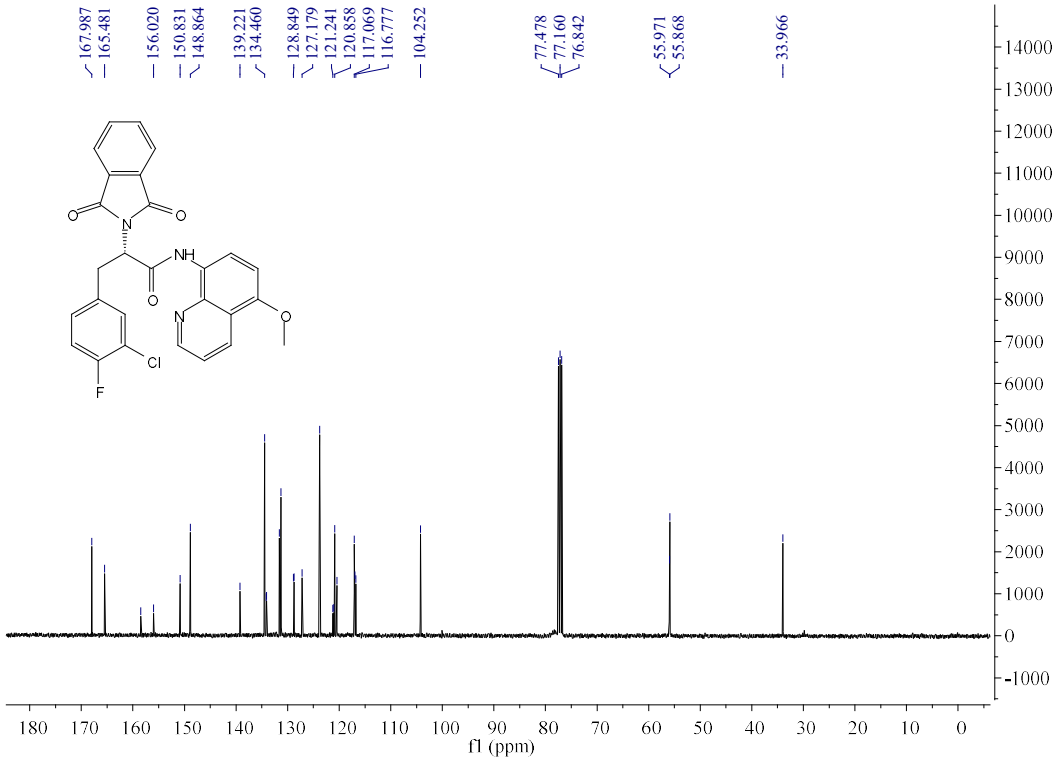
2h


10.046
8.621
8.589
8.520
8.516
8.499
7.706
7.693
7.362
7.159
7.000
6.851
6.787
5.435
5.417
5.412
5.393
3.958
3.811
3.793
3.788
1.754
-0.001
0.99
1.01
0.98
0.99
1.98
2.01
1.01
1.02
1.02
1.00
1.02
0.99
1.00
3.00
2.00
f1 (ppm)

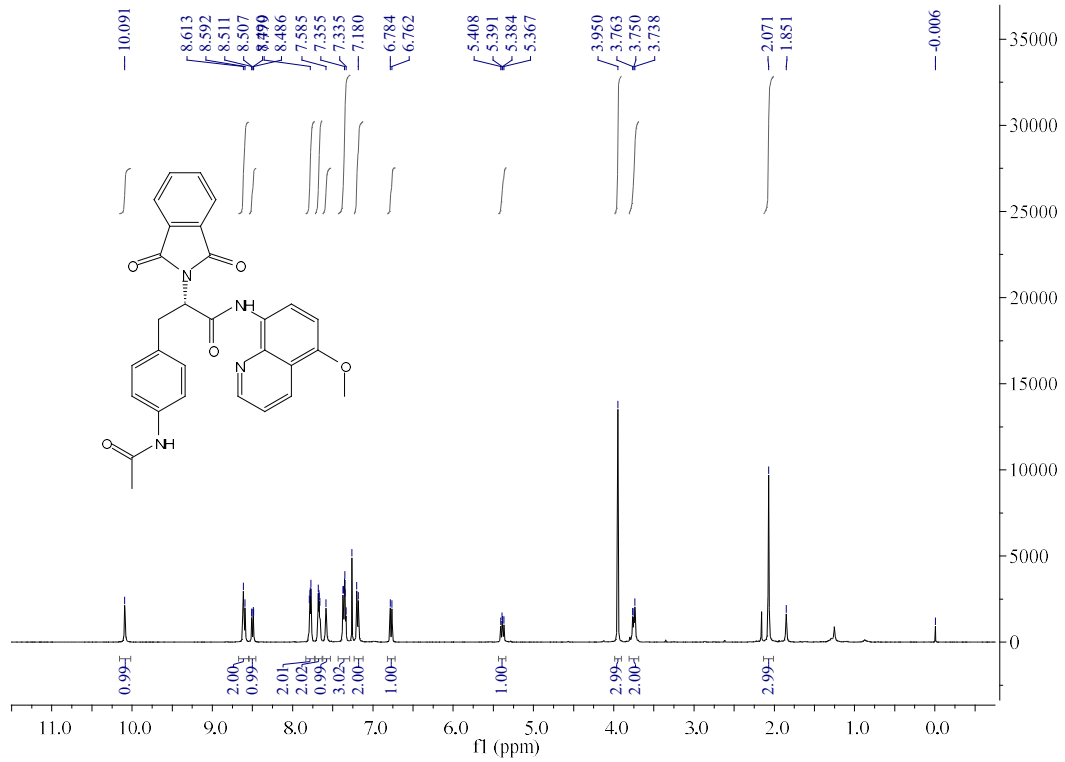

167.976
165.695
164.182
161.734
150.780
148.838
139.515
139.245
134.351
127.262
124.747
120.828
117.041
116.043
113.920
104.261
77.478
77.160
76.842
56.004
55.853
34.601
f1 (ppm)

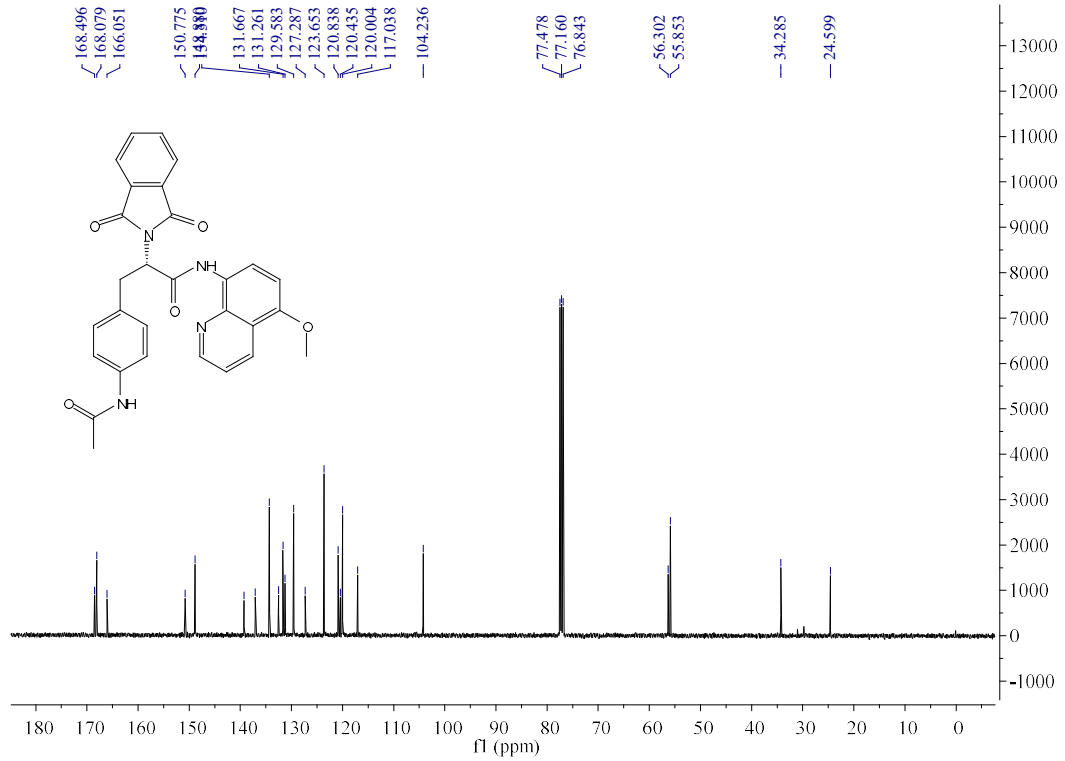
2i


10.002
8.604
8.522
8.518
8.501
7.725
7.711
7.345
7.179
7.158
7.007
6.785
5.385
5.369
5.359
5.343
3.960
3.789
3.769
3.752
3.725
3.715
3.690
-0.003
0.97
1.98
0.97
2.02
2.00
1.99
1.00
0.99
1.00
1.00
2.97
2.00
f1 (ppm)

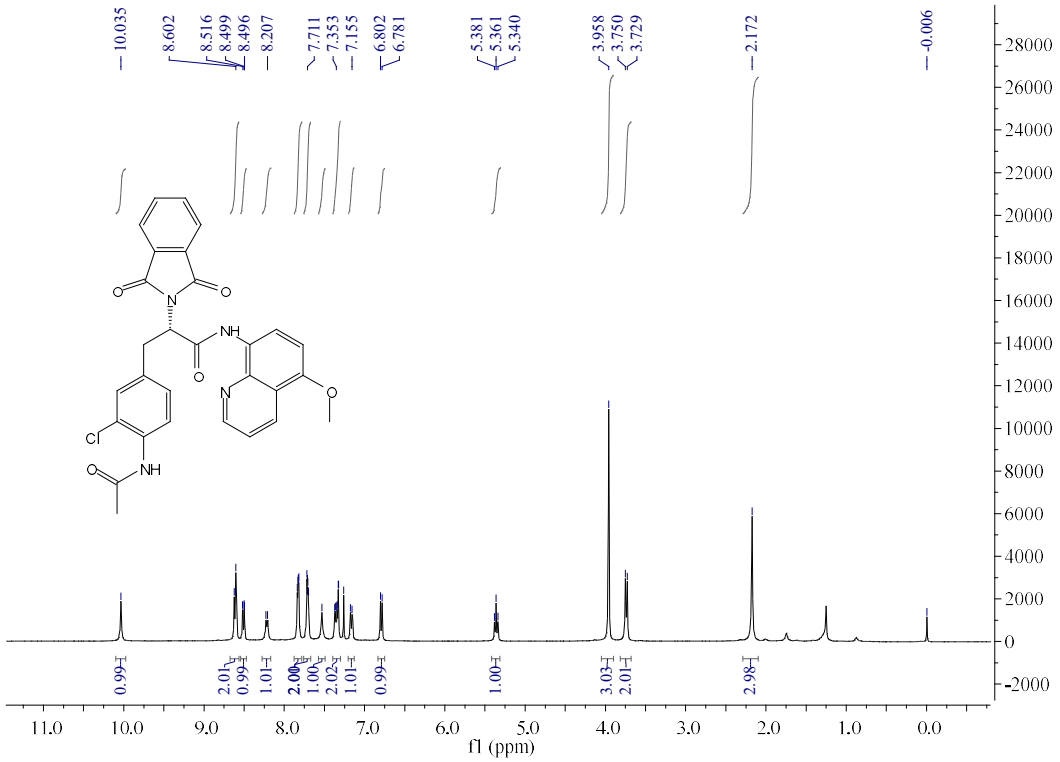

167.987
165.481
156.020
150.831
148.864
139.221
134.460
128.849
127.179
121.241
120.858
117.069
116.777
104.252
77.478
77.160
76.842
55.971
55.868
33.966
f1 (ppm)

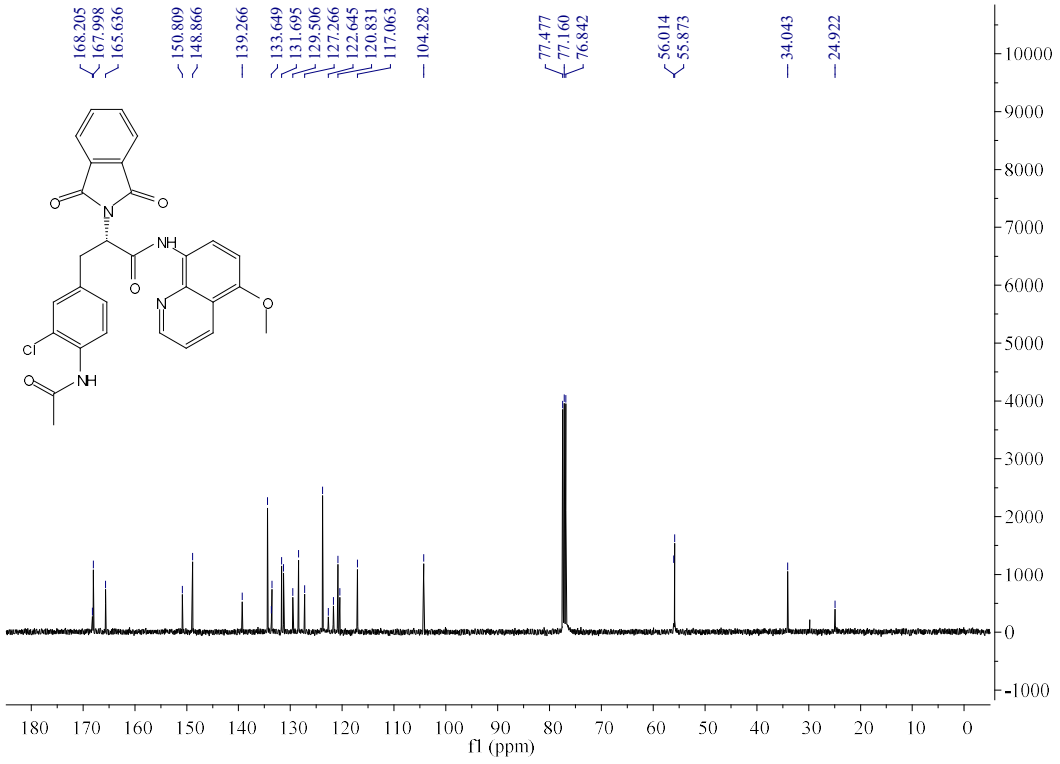
2j


10.091
8.613
8.592
8.511
8.507
8.490
8.486
7.585
7.355
7.335
7.180
6.784
6.762
5.408
5.391
5.384
5.367
3.950
3.763
3.750
3.738
2.071
1.851
-0.006
0.99
2.00
0.99
2.01
2.02
0.99
3.02
2.00
1.00
1.00
2.99
2.00
2.99
f1 (ppm)

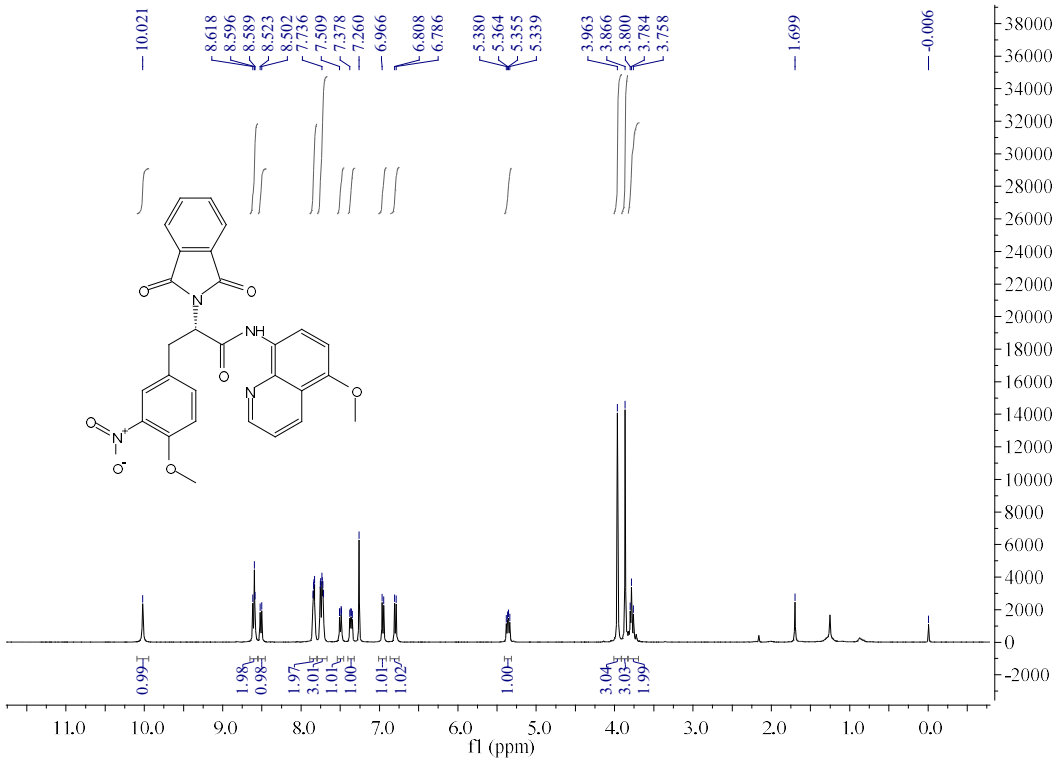

168.496
168.079
166.051
150.775
131.667
131.261
129.583
127.287
123.653
120.838
120.435
120.004
117.038
104.236
77.478
77.160
76.843
56.302
55.853
34.285
24.599
f1 (ppm)

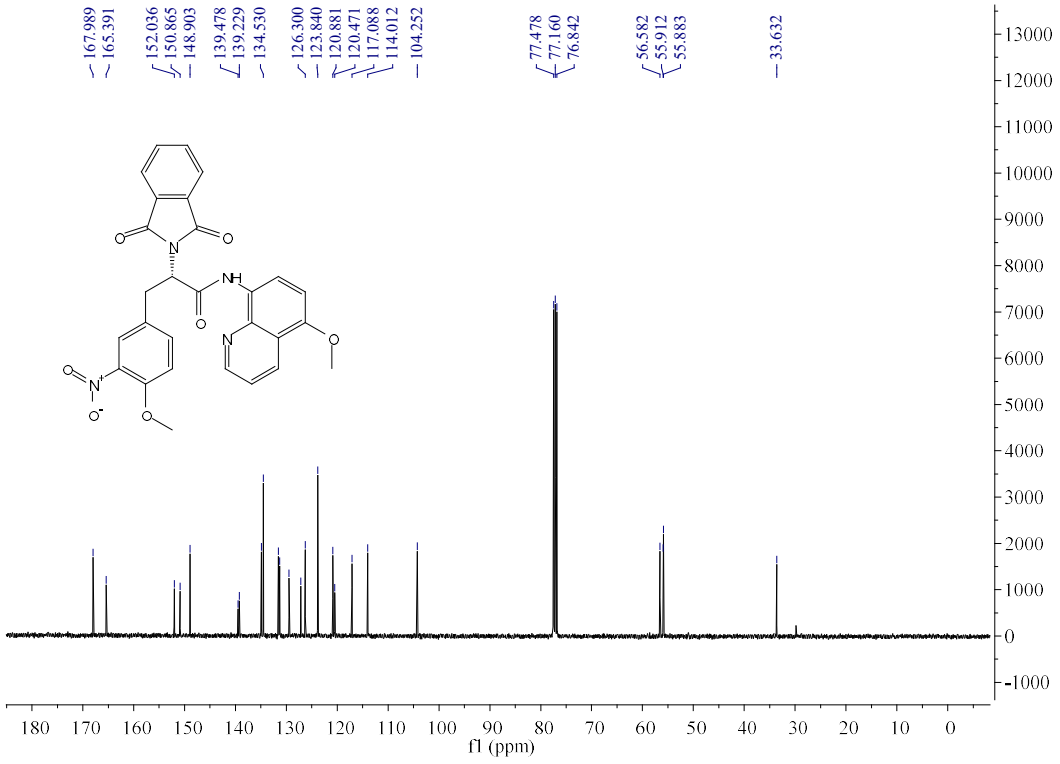
2k


10.035
8.602
8.516
8.499
8.496
8.207
7.711
7.353
7.155
6.802
6.781
5.381
5.361
5.340
3.958
3.750
3.729
2.172
-0.006
0.99
2.01
0.99
1.01
2.00
1.00
2.02
1.01
0.99
1.00
3.03
2.01
2.98
f1 (ppm)

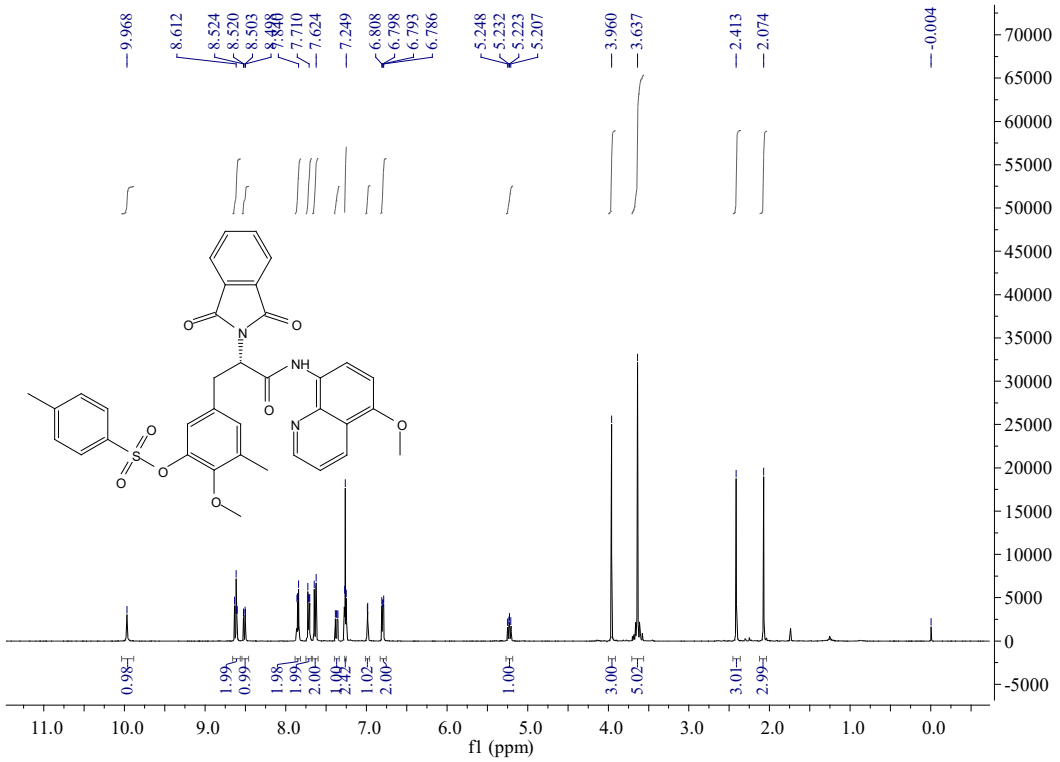

168.205
167.998
165.636
150.809
148.866
139.266
133.649
131.695
129.506
127.266
122.645
120.831
117.063
104.282
77.477
77.160
76.842
56.014
55.873
34.043
24.922
f1 (ppm)

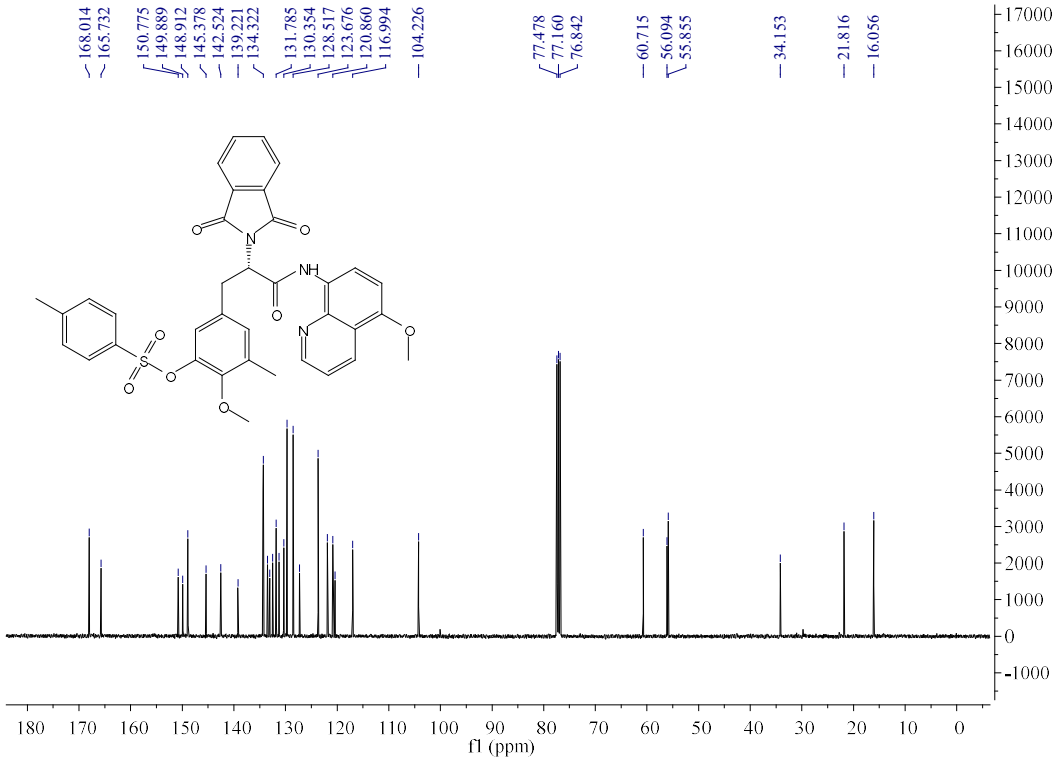
2l


10.021
8.618
8.596
8.589
8.523
8.502
7.736
7.509
7.378
7.260
6.966
6.808
6.786
5.380
5.364
5.355
5.339
3.963
3.866
3.800
3.784
3.758
1.699
-0.006
0.99
1.98
0.98
1.97
3.01
1.01
1.00
1.01
1.02
1.00
3.04
3.03
1.99
f1 (ppm)

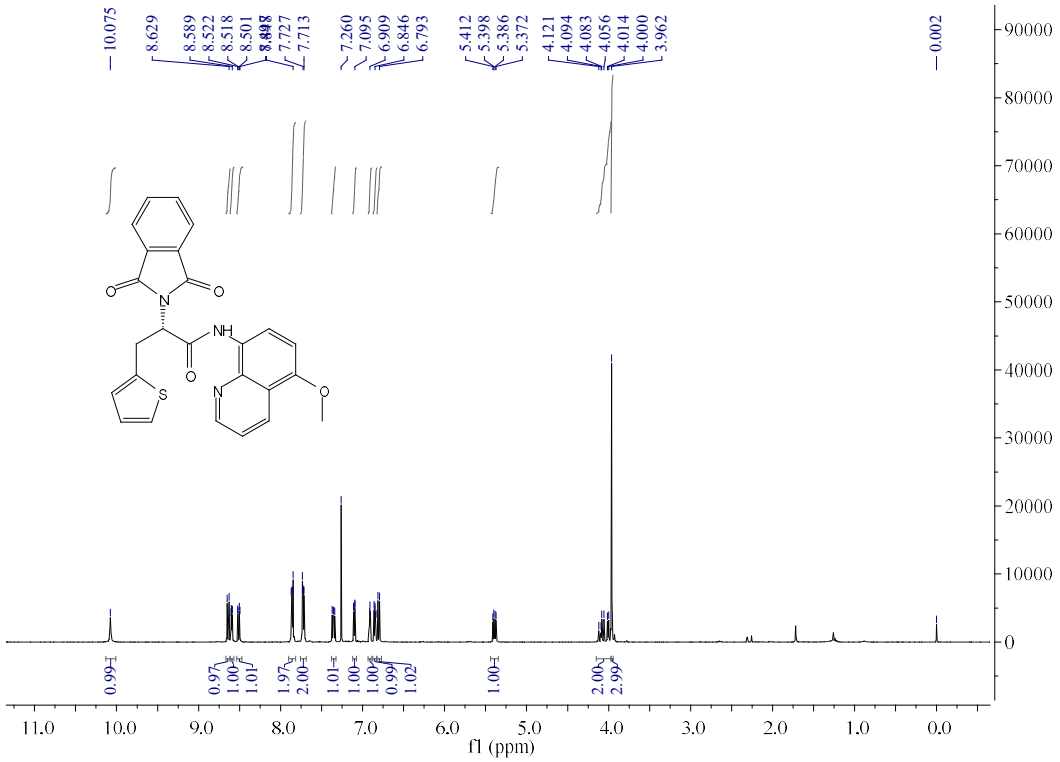

167.989
165.391
152.036
150.865
148.903
139.478
139.229
134.530
126.300
123.840
120.881
120.471
117.088
114.012
104.252
77.478
77.160
76.842
56.582
55.912
55.883
33.632
f1 (ppm)

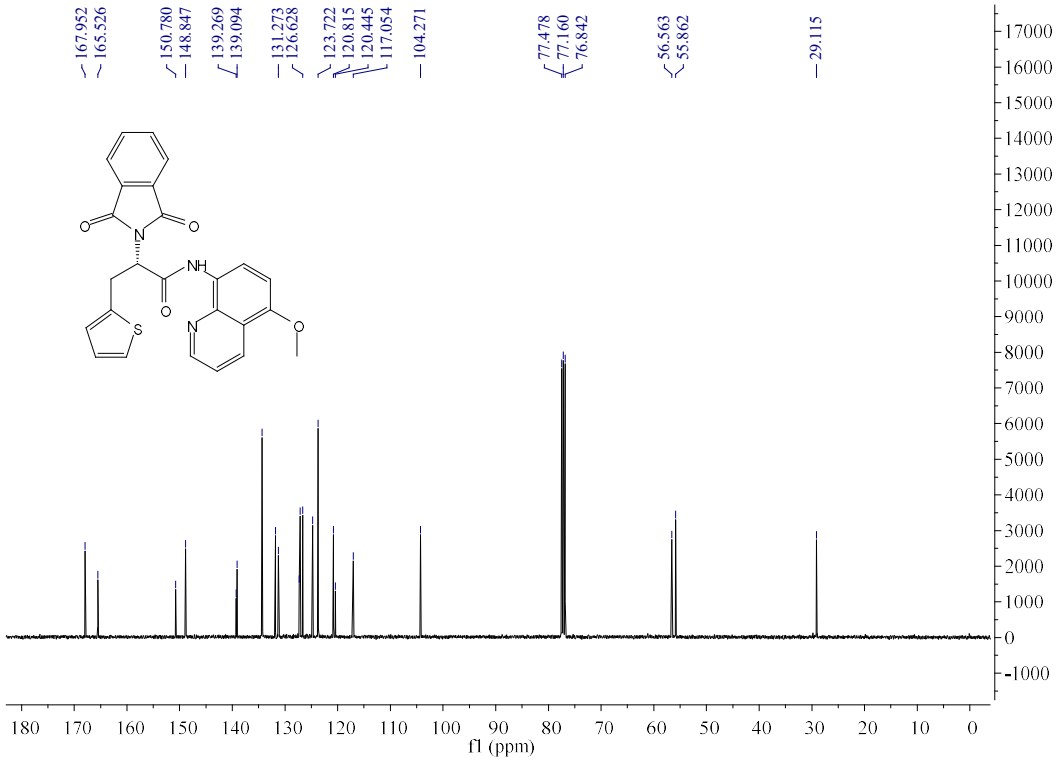
2m


9.968
8.612
8.524
8.520
8.503
7.710
7.624
7.249
6.808
6.798
6.793
6.786
5.248
5.232
5.223
5.207
3.960
3.637
2.413
2.074
-0.004
0.98
1.99
0.99
1.98
1.99
2.00
1.02
2.00
1.00
3.00
5.02
3.01
2.99
f1 (ppm)

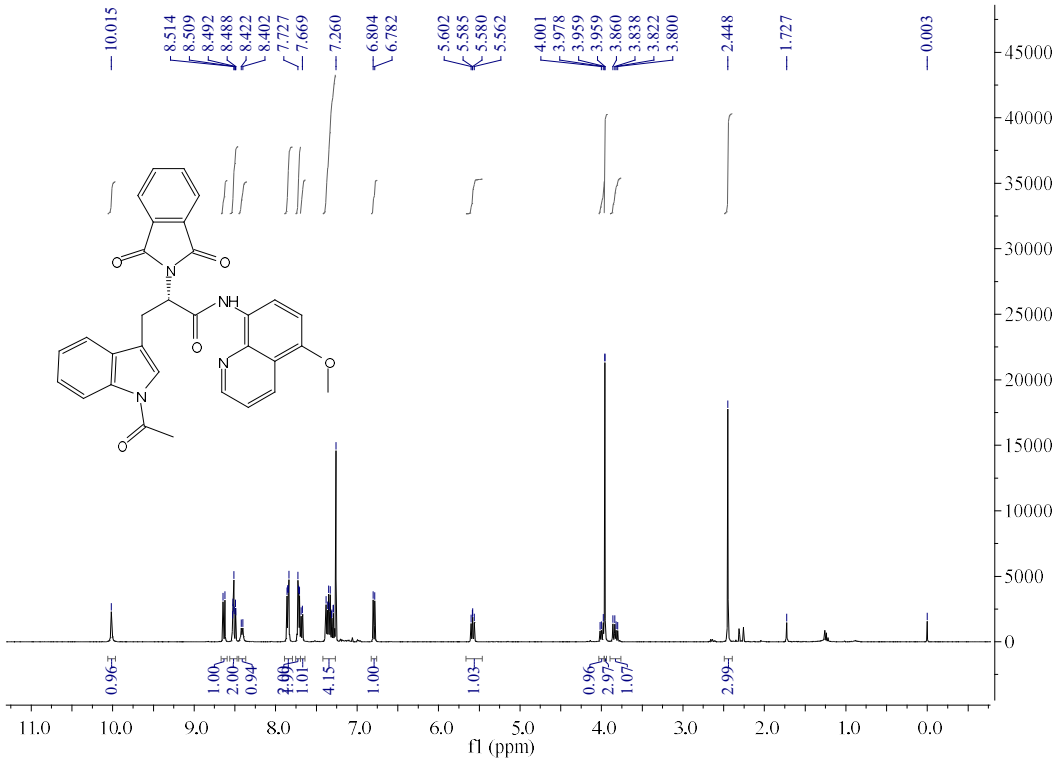

168.014
165.732
150.775
149.889
148.912
145.378
142.524
139.221
134.322
131.785
130.354
128.517
123.676
120.860
116.994
104.226
77.478
77.160
76.842
60.715
56.094
55.855
34.153
21.816
16.056
f1 (ppm)

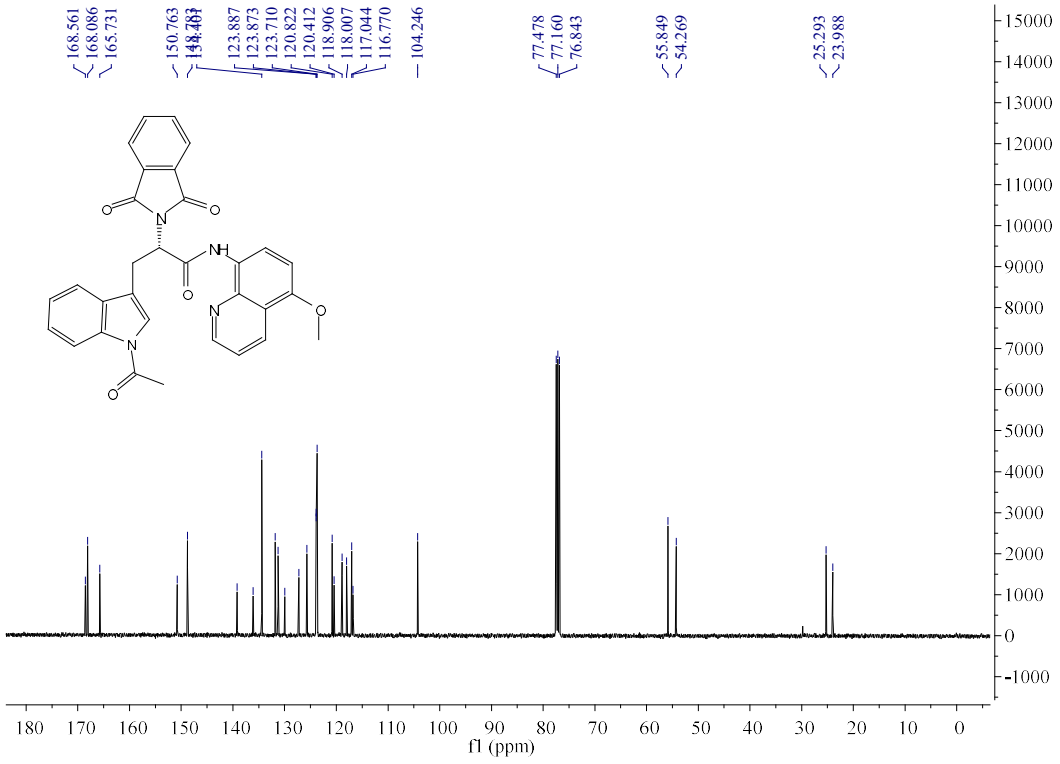
2n


10.075
8.629
8.589
8.522
8.518
8.501
7.727
7.713
7.260
7.095
6.909
6.846
6.793
5.412
5.398
5.386
5.372
4.121
4.094
4.083
4.056
4.014
4.000
3.962
0.002
0.99
0.97
1.00
1.01
1.97
2.00
1.01
1.00
1.00
0.99
1.02
1.00
2.00
2.99
f1 (ppm)

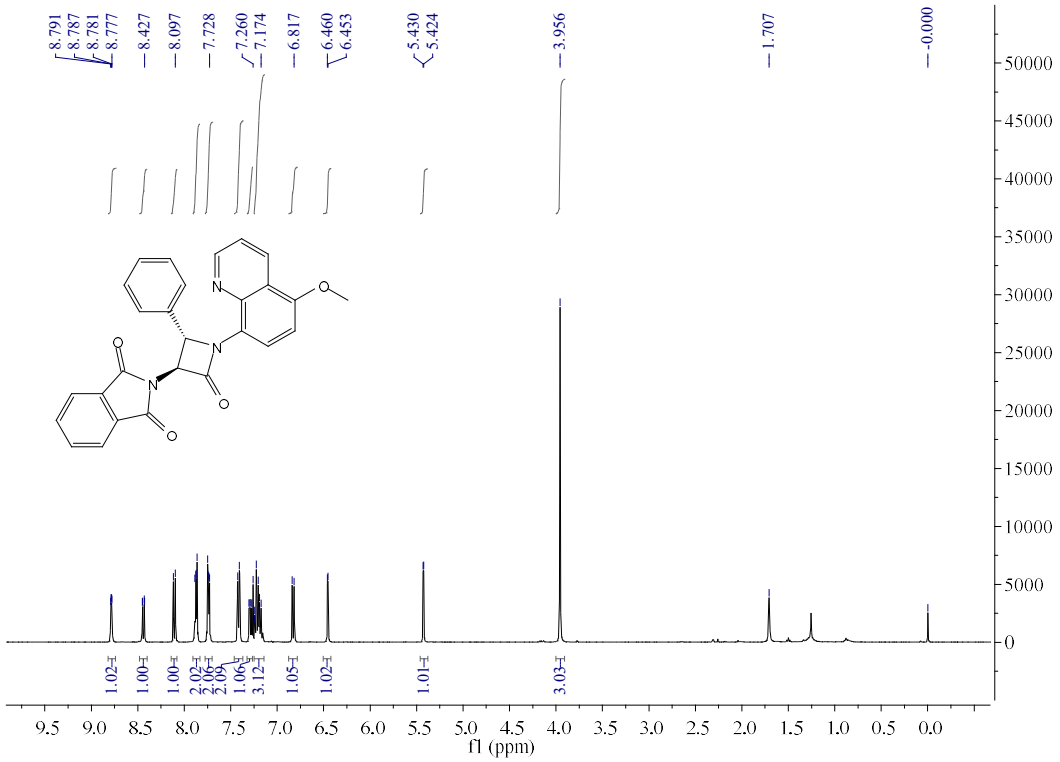

167.952
165.526
150.780
148.847
139.269
139.094
131.273
126.628
123.722
120.815
120.445
117.054
104.271
77.478
77.160
76.842
56.563
55.862
29.115
f1 (ppm)

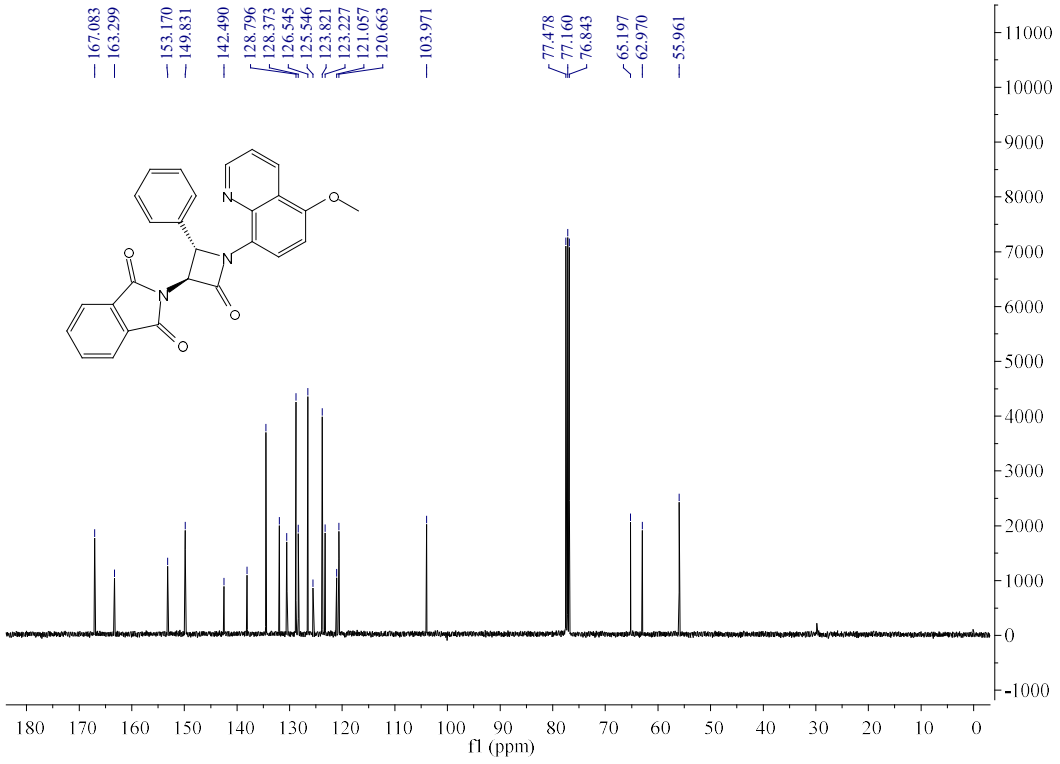
2o


10.015
8.514
8.509
8.492
8.488
8.422
8.402
7.727
7.669
7.260
6.804
6.782
5.602
5.585
5.580
5.562
4.001
3.978
3.959
3.959
3.860
3.838
3.822
3.800
2.448
1.727
0.003
0.96
1.00
2.00
0.94
4.15
1.00
1.03
0.96
2.97
1.07
2.99
f1 (ppm)

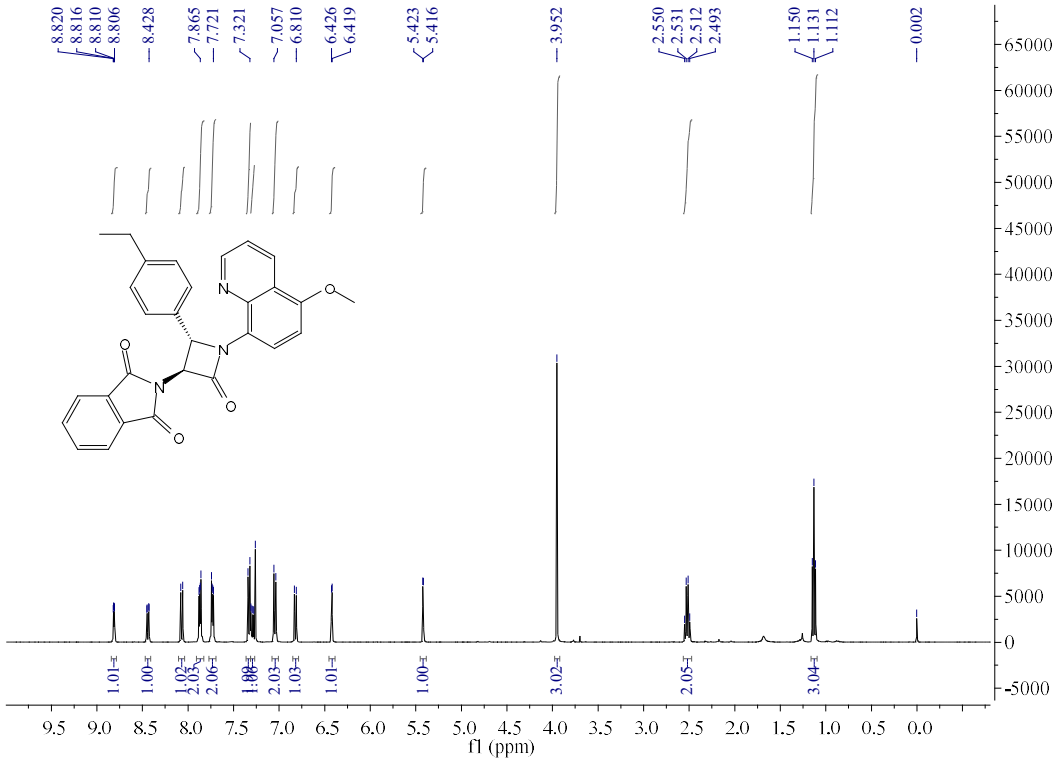

168.561
168.086
165.731
150.763
123.887
123.873
123.710
120.822
120.412
118.906
118.007
117.044
116.770
104.246
77.478
77.160
76.843
55.849
54.269
25.293
23.988
f1 (ppm)

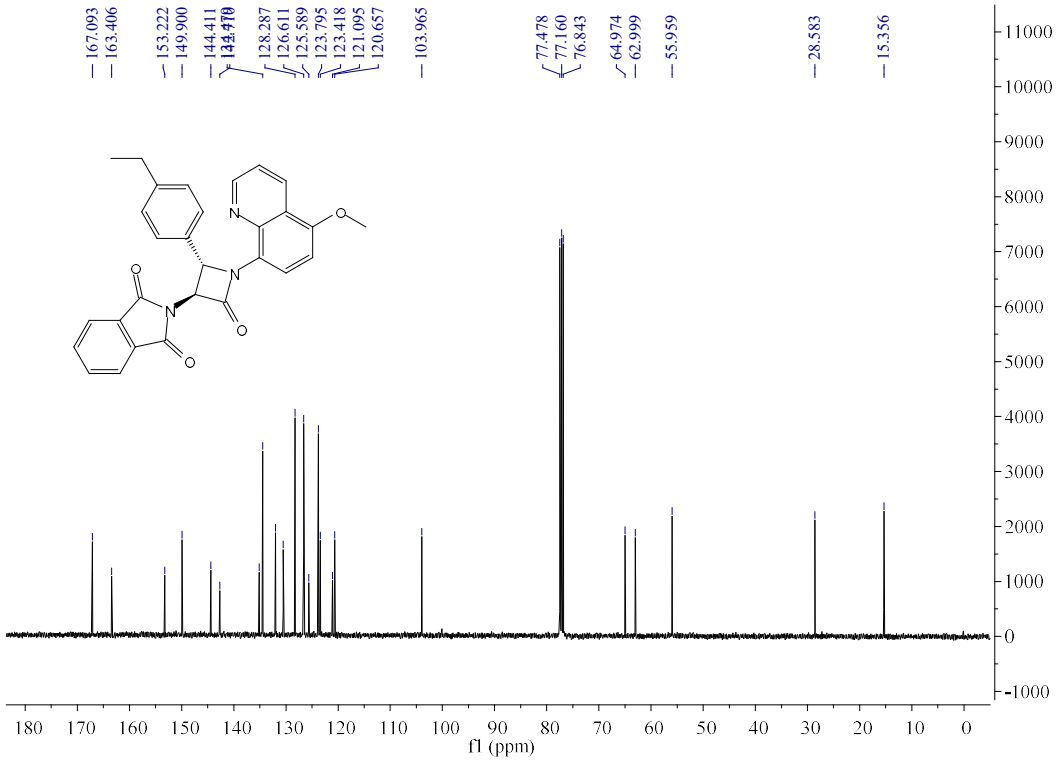
3a


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
-0.000
1.02
1.00
1.00
2.02
2.06
2.09
1.06
3.12
1.05
1.02
1.01
3.03
f1 (ppm)

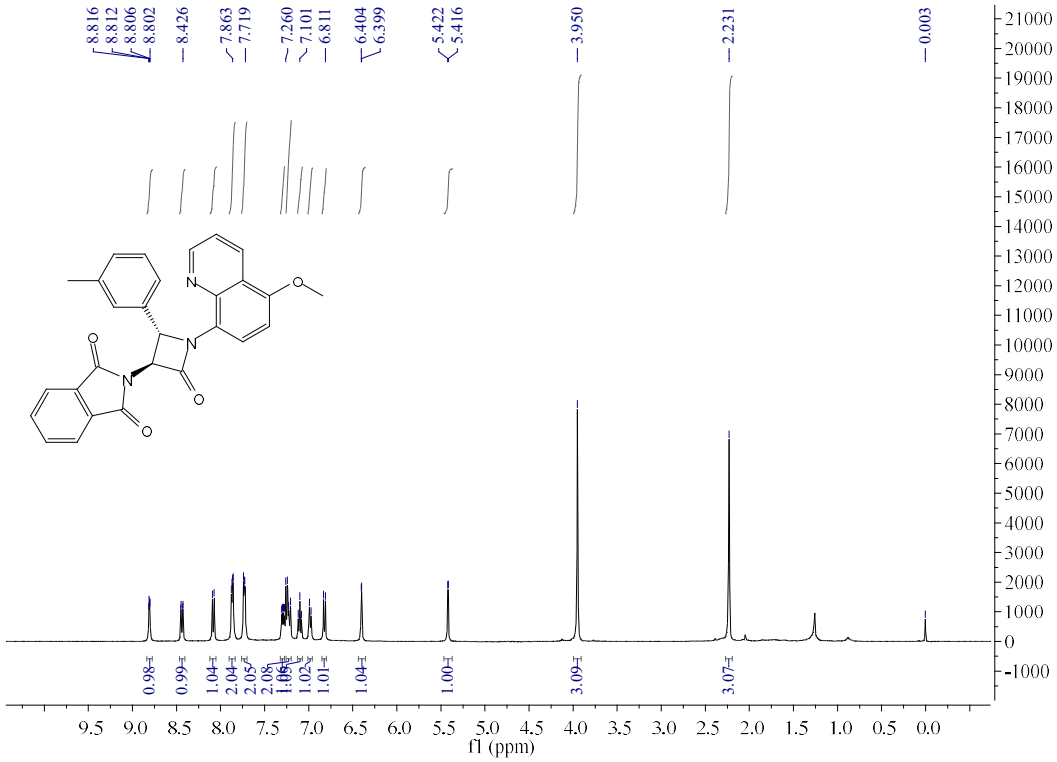

167.083
163.299
153.170
149.831
142.490
128.796
128.373
126.545
125.546
123.821
123.227
121.057
120.663
103.971
77.478
77.160
76.843
65.197
62.970
55.961
f1 (ppm)

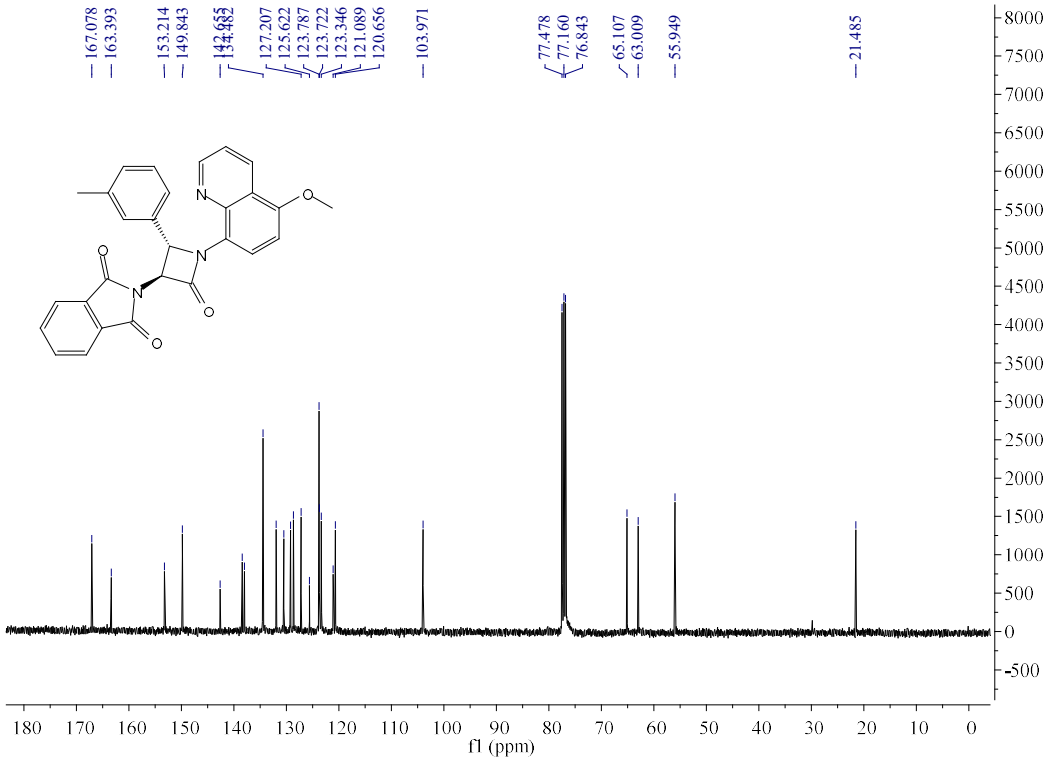
3b


8.820
8.816
8.810
8.806
8.428
7.865
7.721
7.321
7.057
6.810
6.426
6.419
5.423
5.416
3.952
2.550
2.531
2.512
2.493
1.150
1.131
1.112
0.002
f1 (ppm)

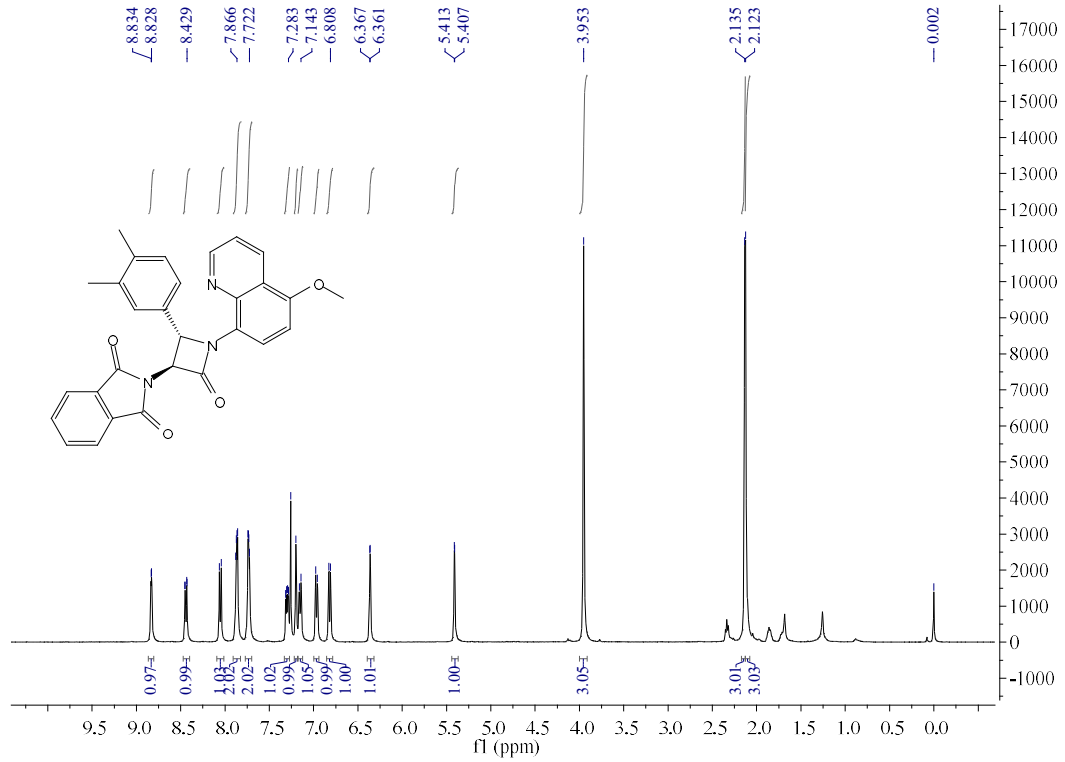

167.093
163.406
153.222
149.900
144.411
128.287
126.611
125.589
123.795
123.418
121.095
120.657
103.965
77.478
77.160
76.843
64.974
62.999
55.959
28.583
15.356
f1 (ppm)

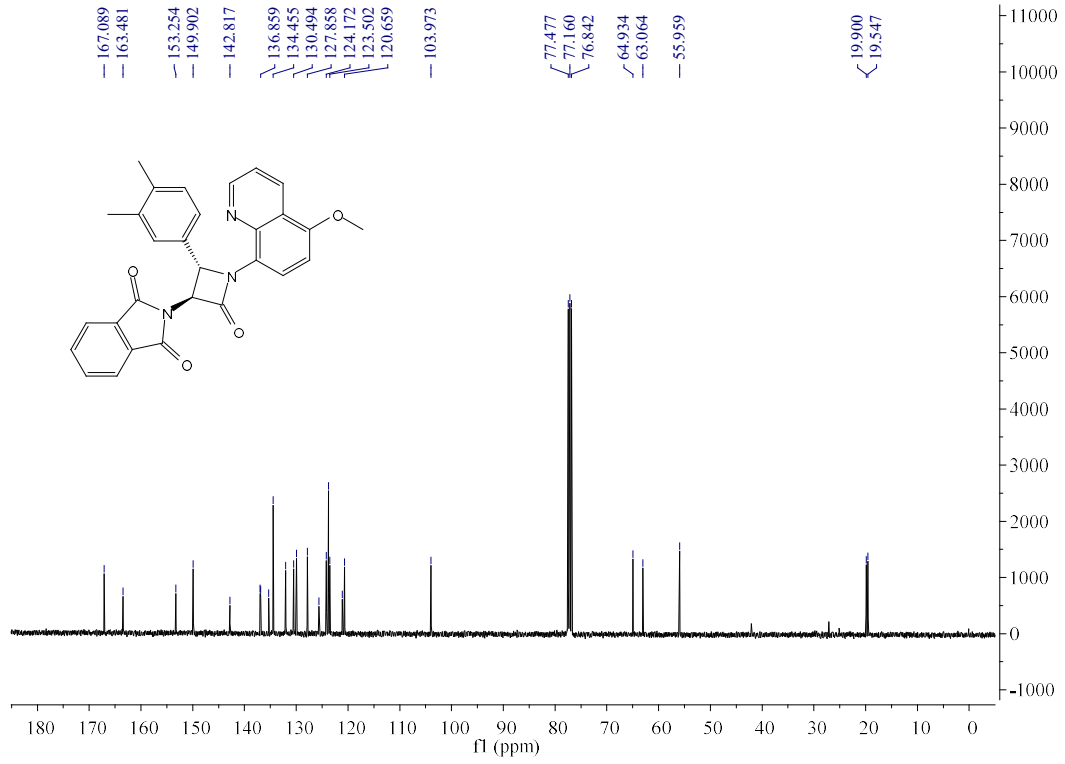
3c


8.816
8.812
8.806
8.802
8.426
7.863
7.719
7.260
7.101
6.811
6.404
6.399
5.422
5.416
3.950
2.231
0.003
0.98
0.99
1.04
2.04
2.05
2.08
1.06
1.02
1.01
1.04
1.00
3.09
3.07
f1 (ppm)

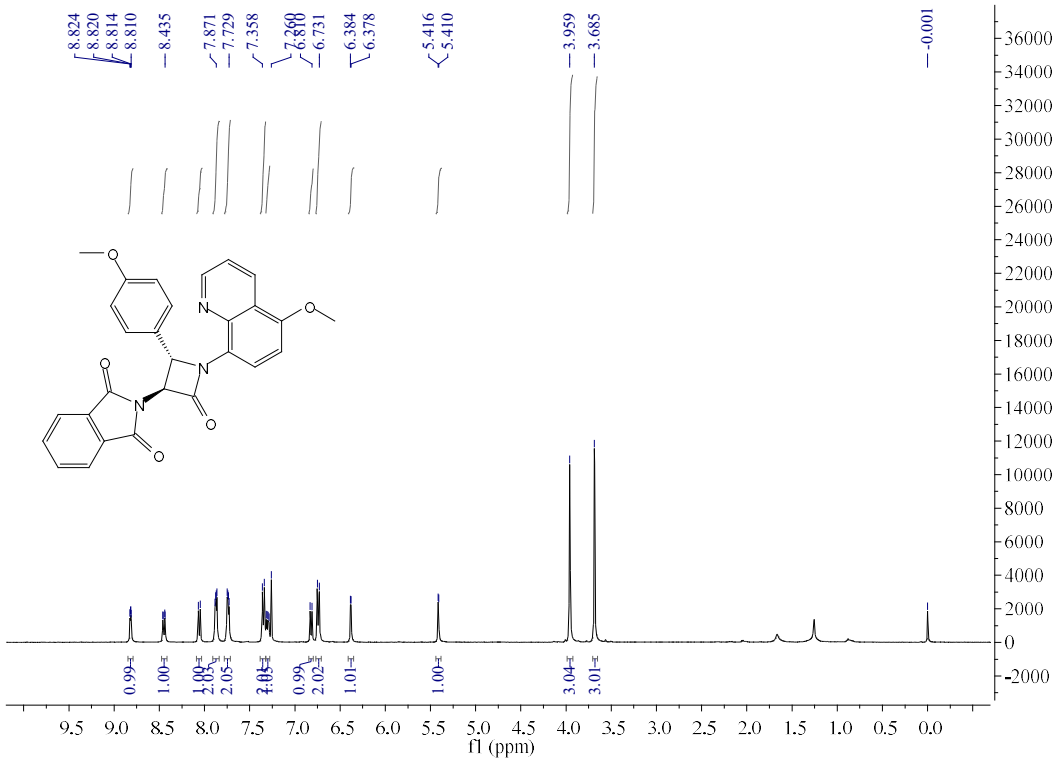

167.078
163.393
153.214
149.843
142.655
134.482
127.207
125.622
123.787
123.722
123.346
121.089
120.656
103.971
77.478
77.160
76.843
65.107
63.009
55.949
21.485
f1 (ppm)

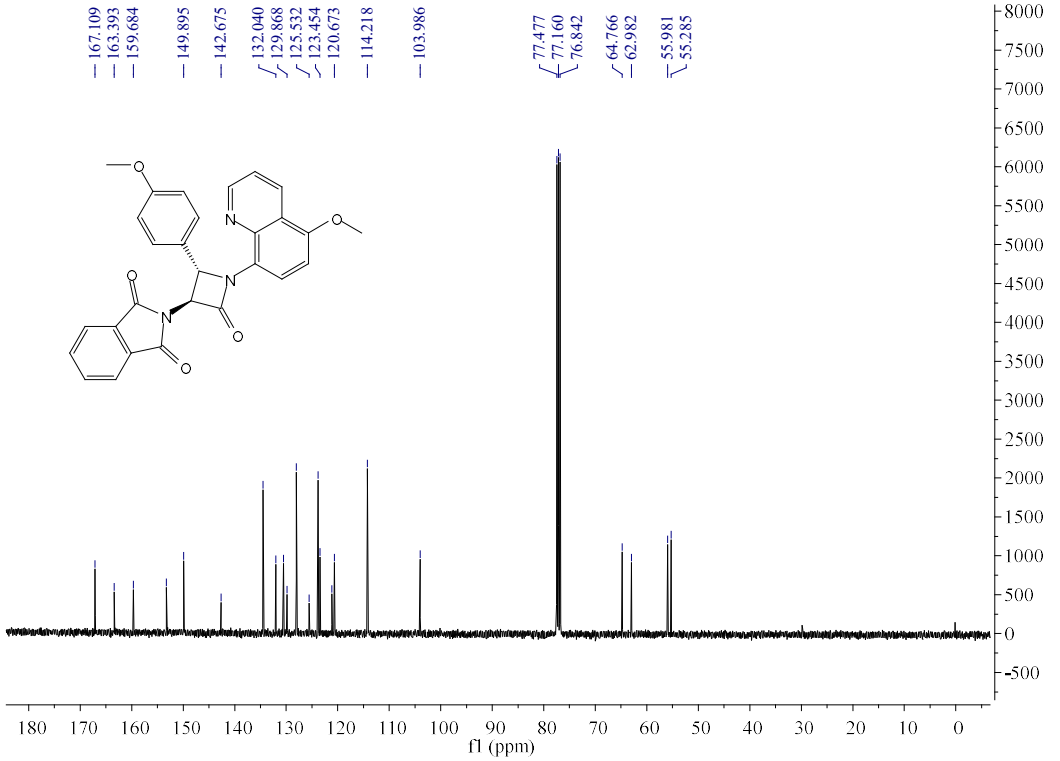
3d


8.834
8.828
8.429
7.866
7.722
7.283
7.143
6.808
6.367
6.361
5.413
5.407
3.953
2.135
2.123
0.002
0.97
0.99
1.03
2.02
2.02
1.02
0.99
1.05
0.99
1.00
1.01
1.00
3.05
3.01
3.03
f1 (ppm)

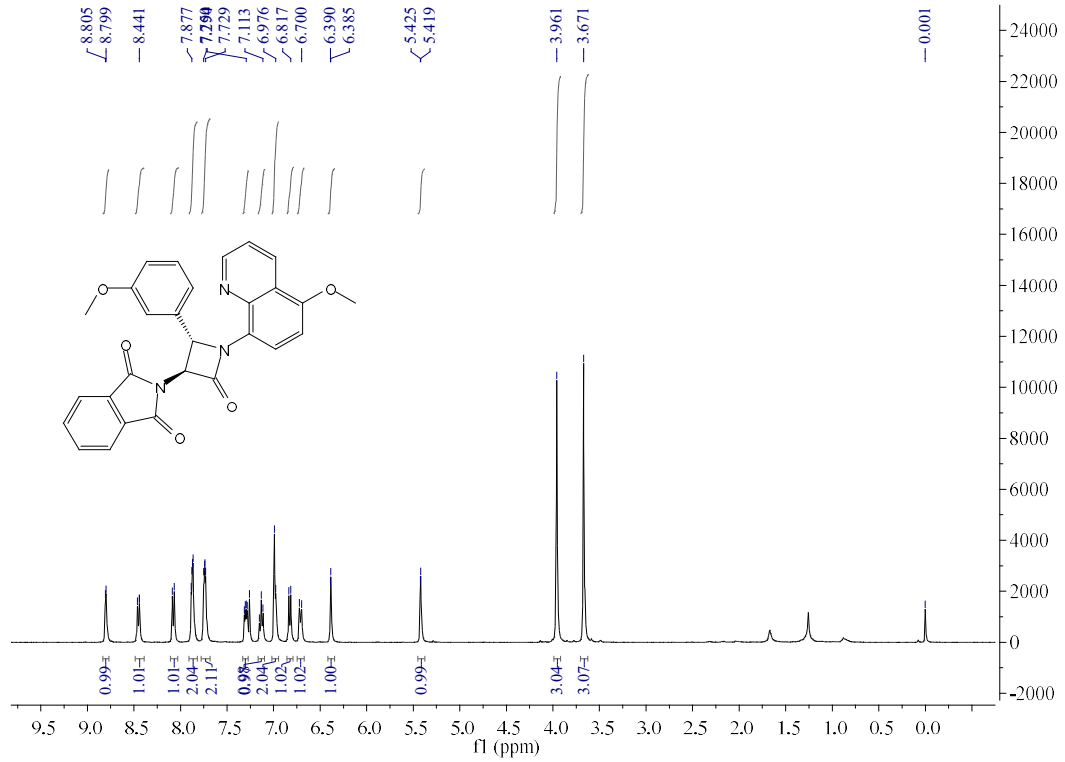

167.089
163.481
153.254
149.902
142.817
136.859
134.455
130.494
127.858
124.172
123.502
120.659
103.973
77.477
77.160
76.842
64.934
63.064
55.959
19.900
19.547
f1 (ppm)

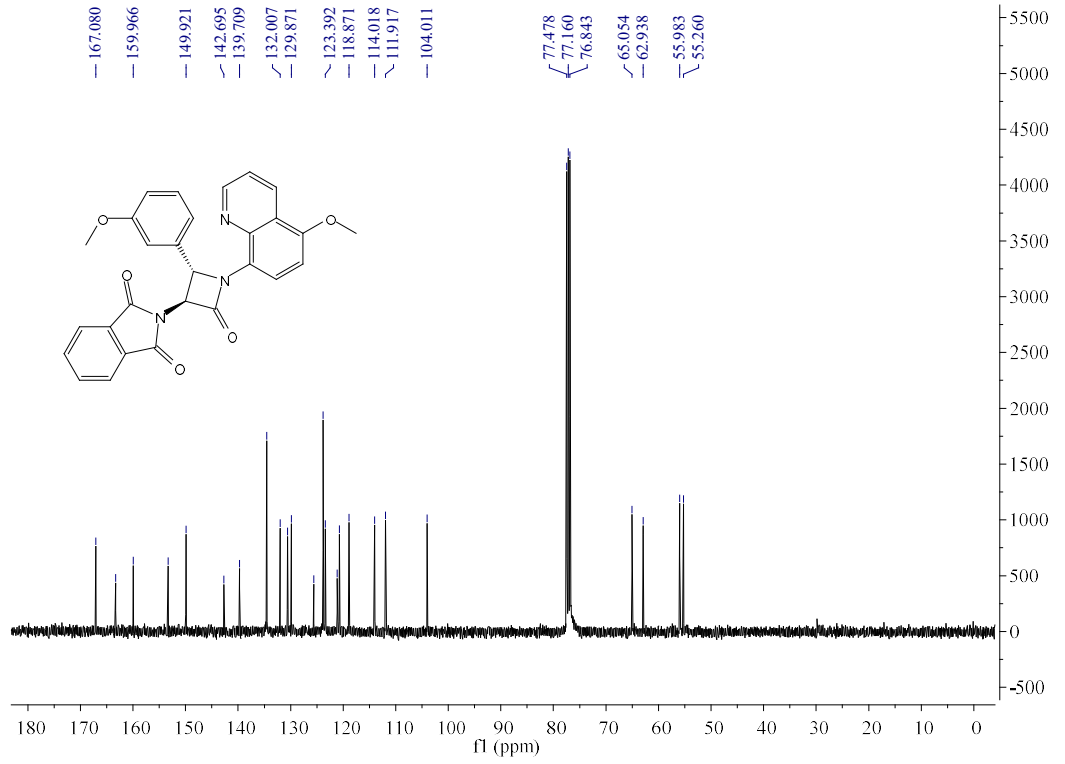
3e


8.824
8.820
8.814
8.810
8.435
7.871
7.729
7.358
7.260
6.731
6.384
6.378
5.416
5.410
3.959
3.685
-0.001
f1 (ppm)

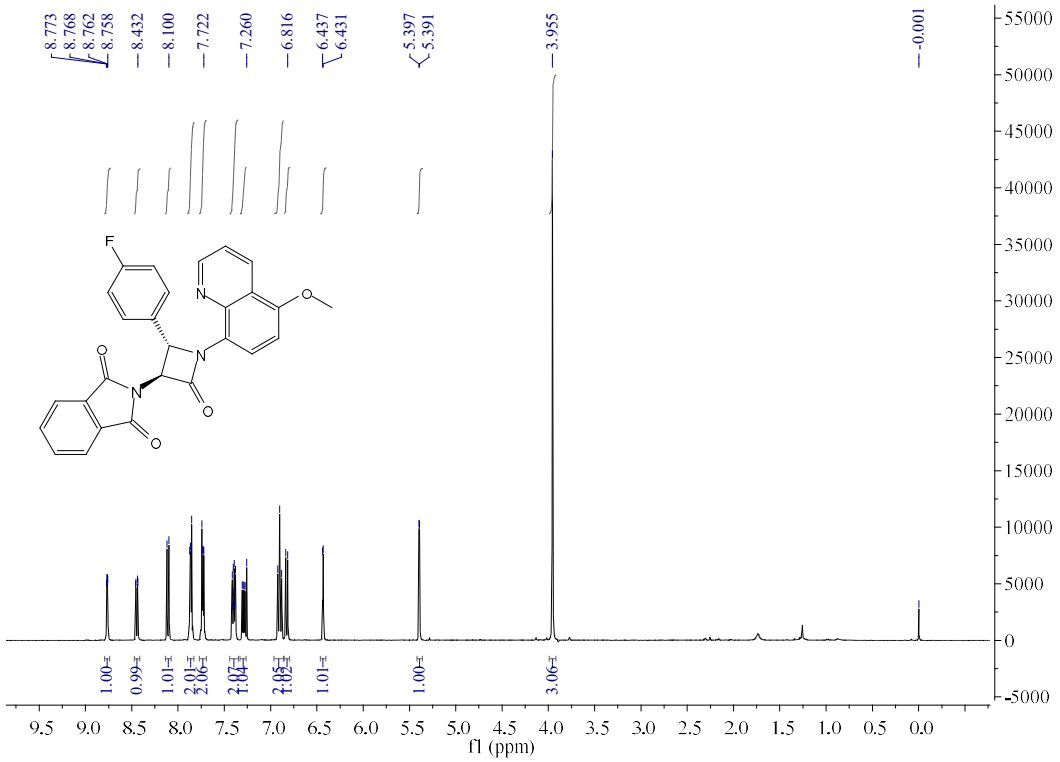

167.109
163.393
159.684
149.895
142.675
132.040
129.868
125.532
123.454
120.673
114.218
103.986
77.477
77.160
76.842
64.766
62.982
55.981
55.285
f1 (ppm)

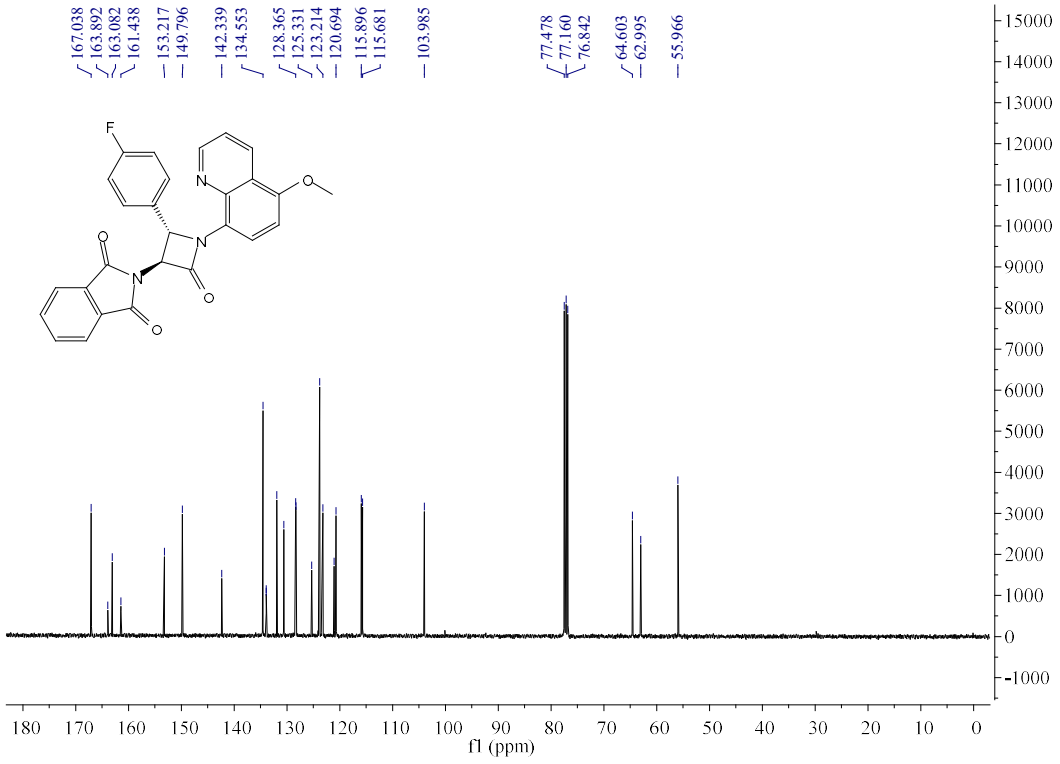
3f

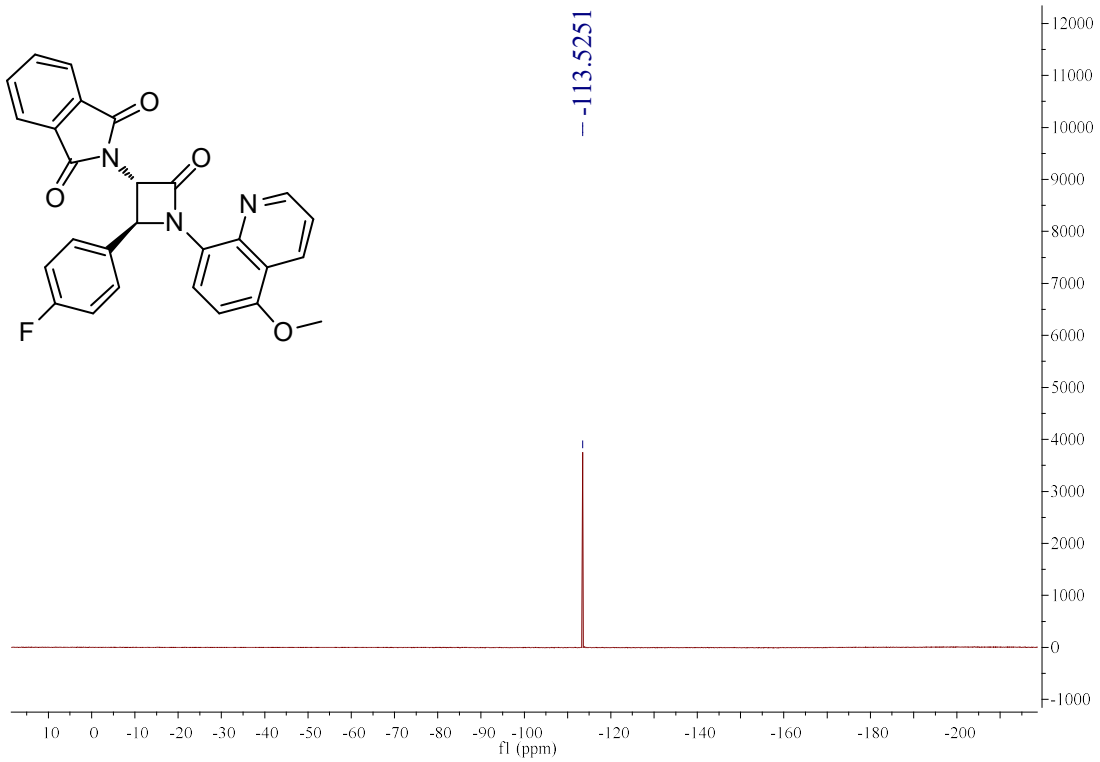

8.805
8.799
8.441
7.877
7.729
7.113
6.976
6.817
6.700
6.390
6.385
5.425
5.419
3.961
3.671
0.001
0.99
1.01
1.01
2.04
2.11
0.98
2.04
1.02
1.02
1.00
0.99
3.04
3.07
f1 (ppm)


167.080
159.966
149.921
142.695
139.709
132.007
129.871
123.392
118.871
114.018
111.917
104.011
77.478
77.160
76.843
65.054
62.938
55.983
55.260
f1 (ppm)

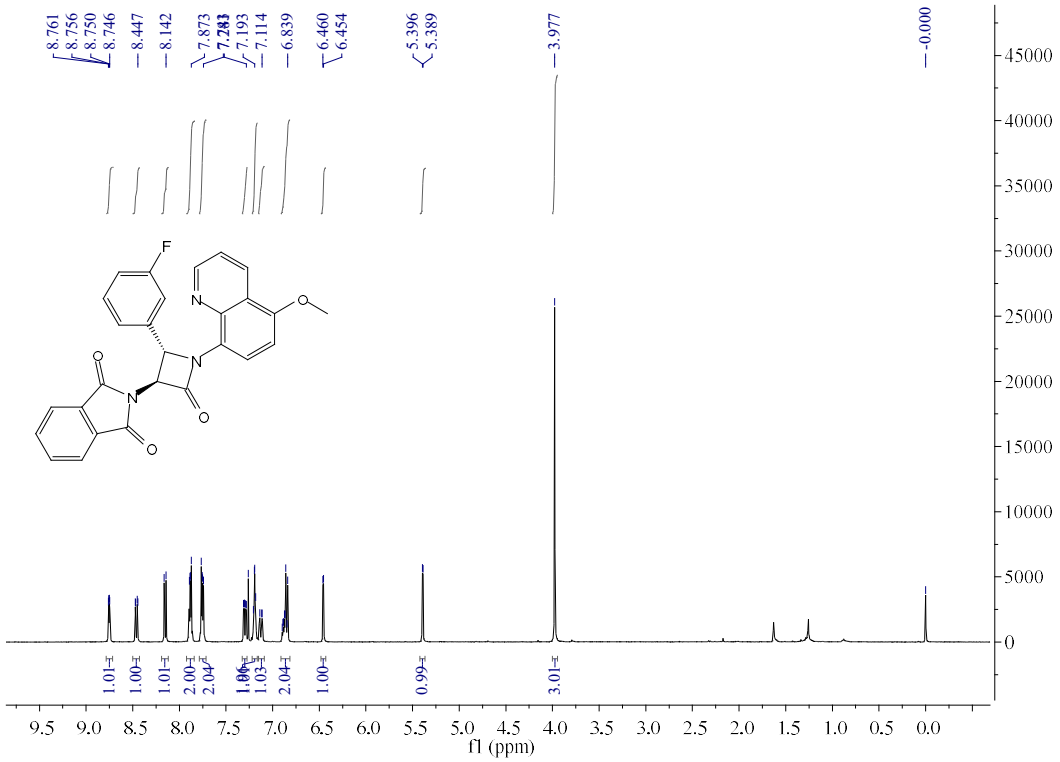
3g

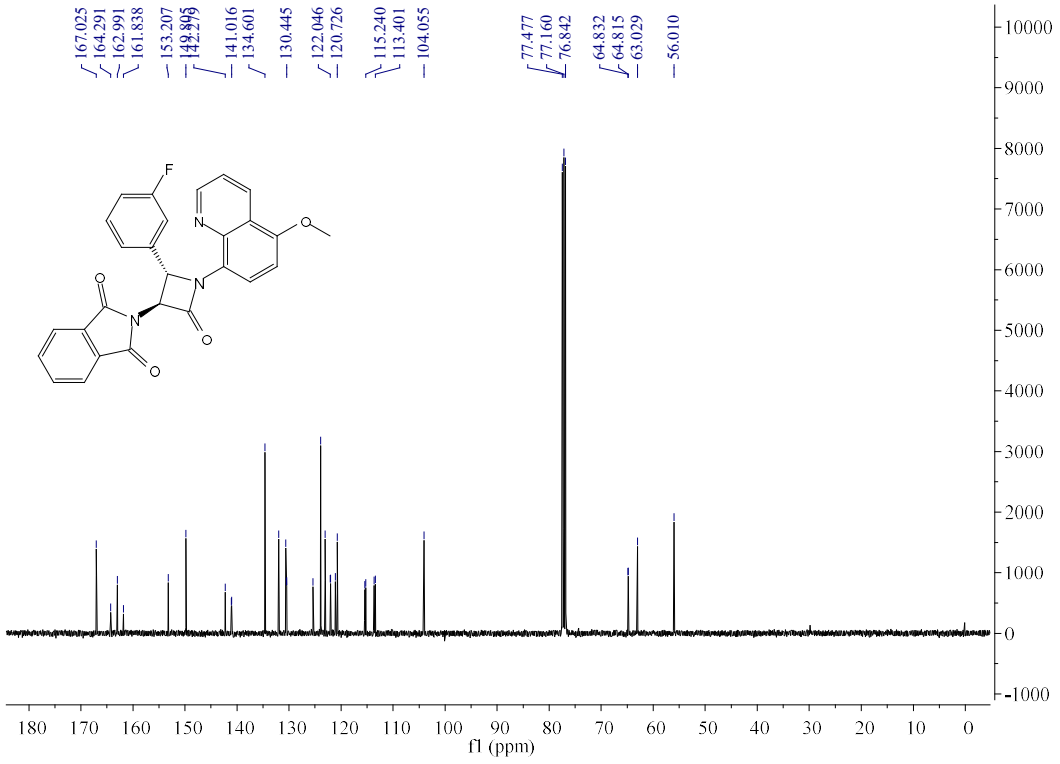

8.773
8.768
8.762
8.758
8.432
8.100
7.722
7.260
6.816
6.437
6.431
5.397
5.391
3.955
-0.001
F
N
O
N
O
N
O
O
1.00
0.99
1.01
2.01
2.06
1.01
1.00
3.06
f1 (ppm)

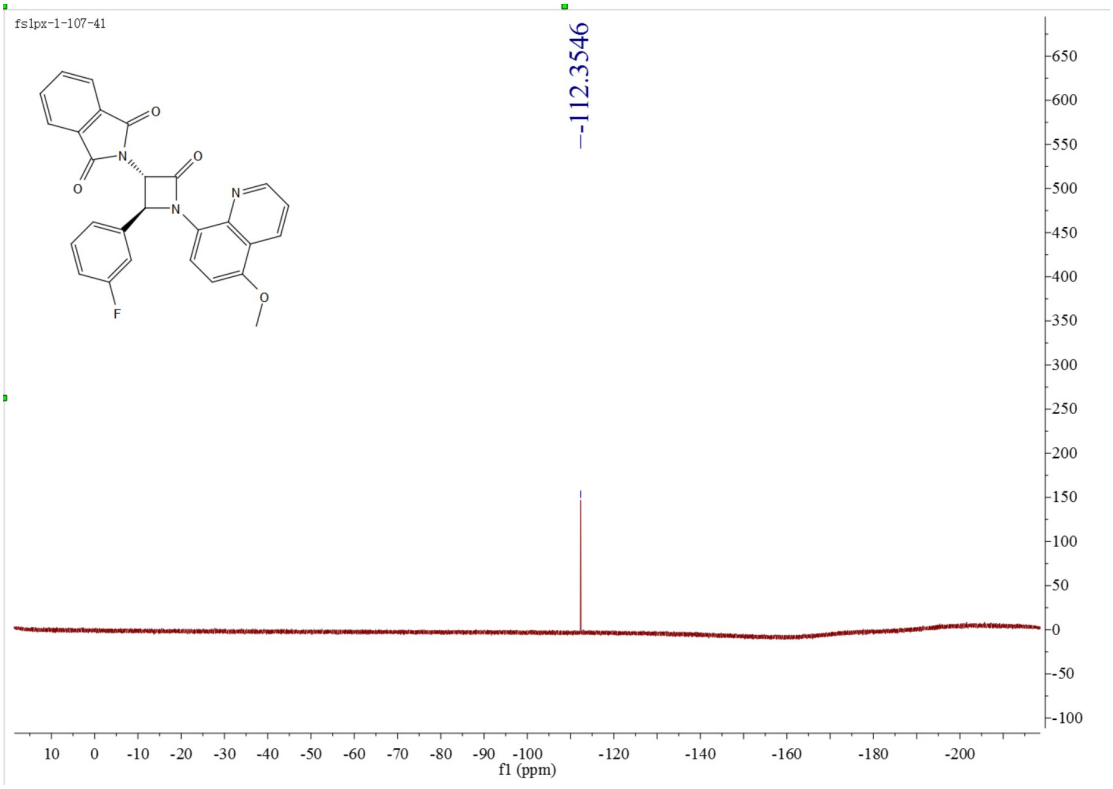

167.038
163.892
163.082
161.438
153.217
149.796
142.339
134.553
128.365
125.331
123.214
120.694
115.896
115.681
103.985
77.478
77.160
76.842
64.603
62.995
55.966
F
N
O
N
O
N
O
O
f1 (ppm)


-113.5251
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -120 -140 -160 -180 -200
f1 (ppm)
O
O
N
O
N
F
O

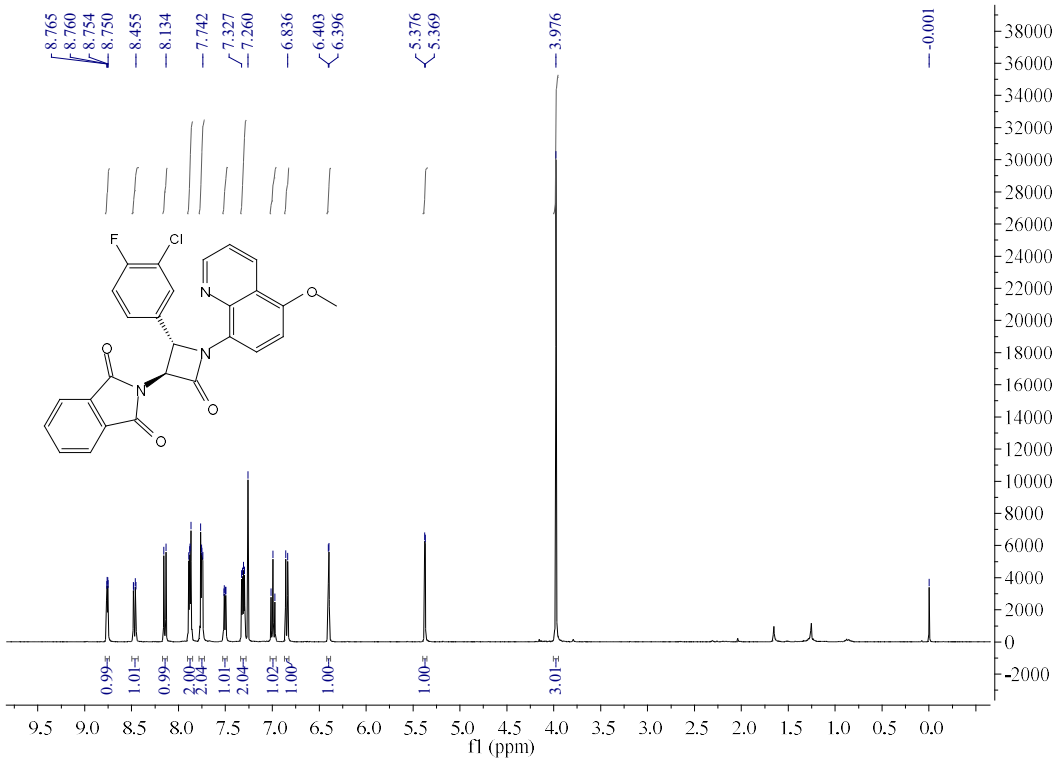
3h

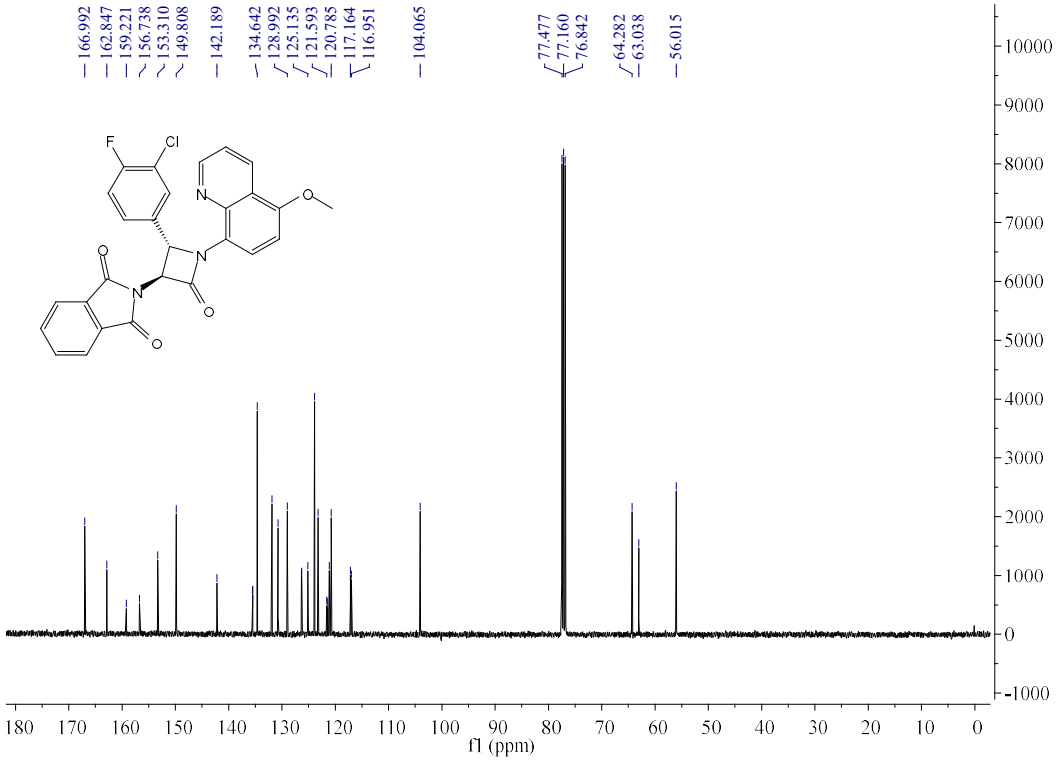

8.761
8.756
8.750
8.746
8.447
8.142
7.873
7.283
7.193
7.114
6.839
6.460
6.454
5.396
5.389
3.977
-0.000
F
N
O
O
N
O
N
O
O
1.01
1.00
1.01
2.00
2.04
1.06
1.03
2.04
1.00
0.99
3.01
f1 (ppm)

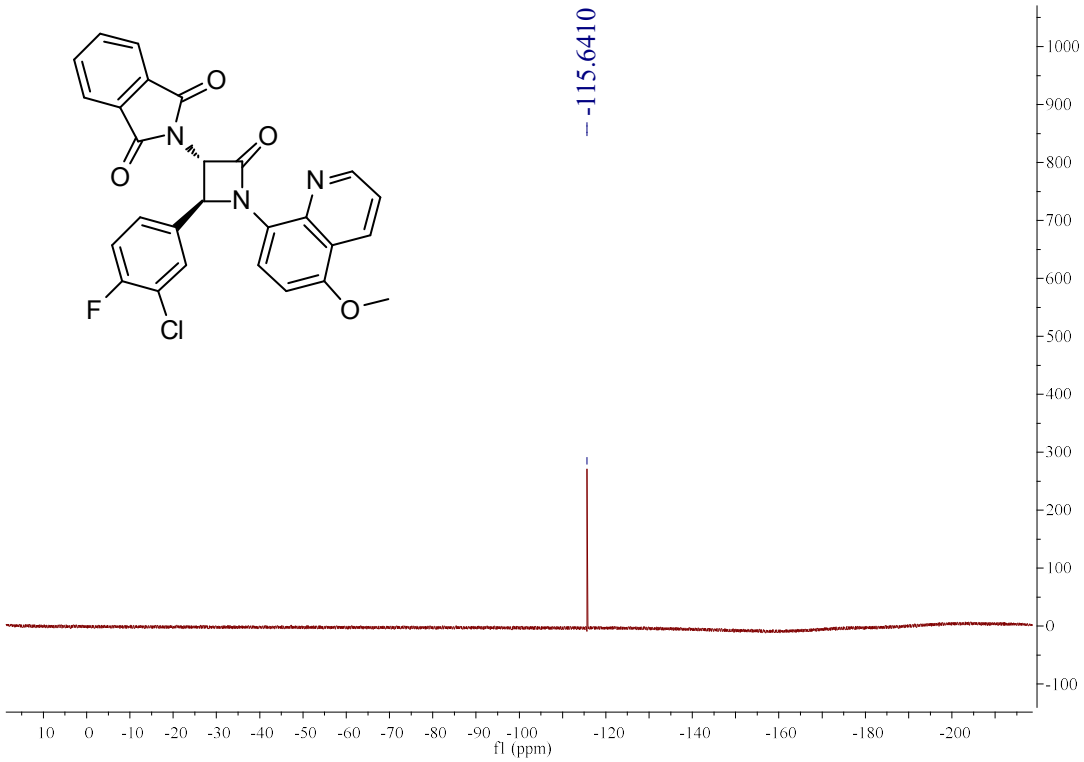

167.025
164.291
162.991
161.838
153.207
141.016
134.601
130.445
122.046
120.726
115.240
113.401
104.055
77.477
77.160
76.842
64.832
64.815
63.029
56.010
F
N
O
O
N
O
N
O
O
f1 (ppm)


fs1px-1-107-41
-112.3546
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-100
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -120 -140 -160 -180 -200
f1 (ppm)
O
N
O
O
N
N
F
O

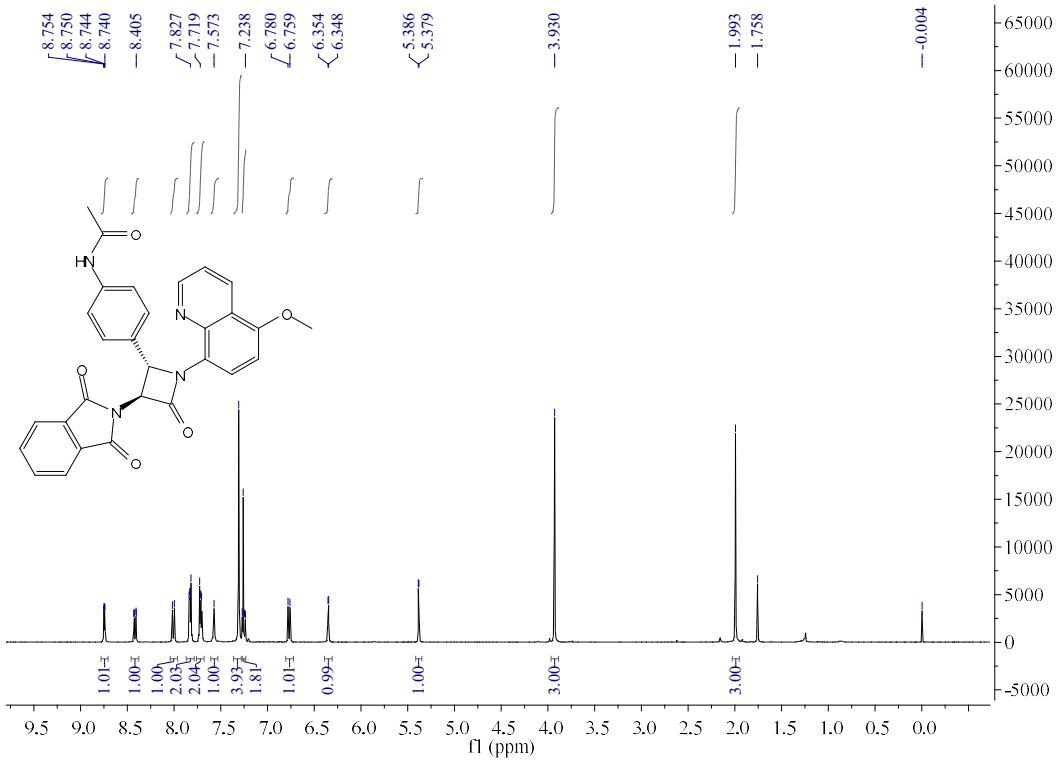
3i

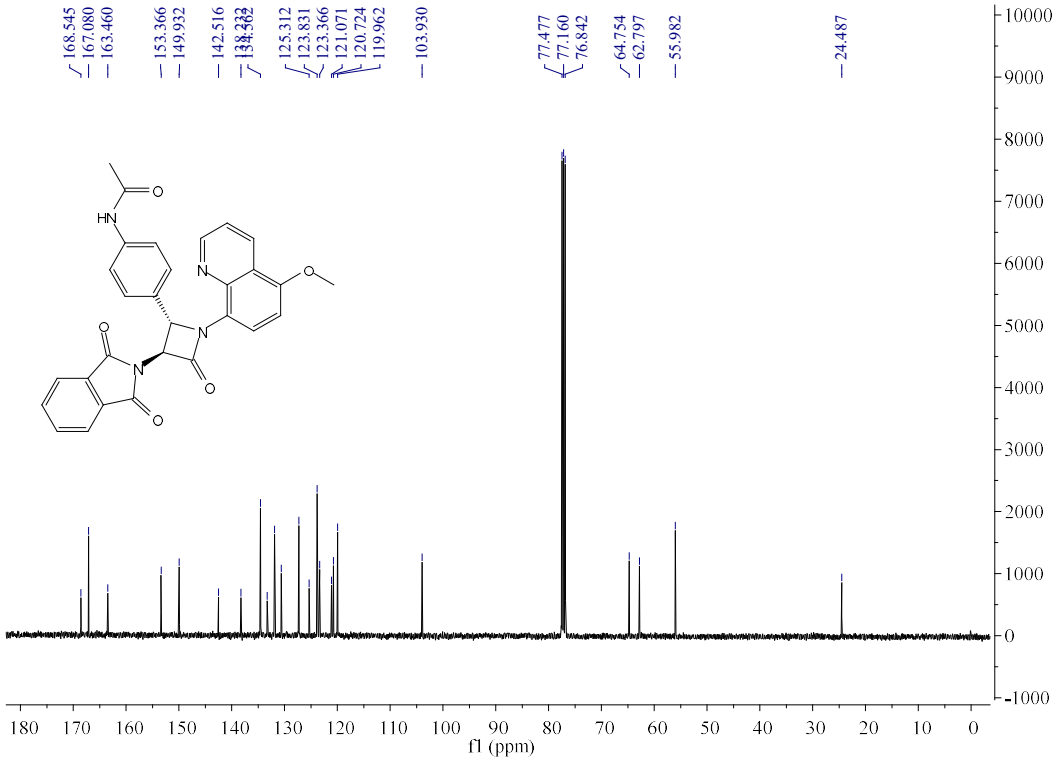

8.765
8.760
8.754
8.750
8.455
8.134
7.742
7.327
7.260
6.836
6.403
6.396
5.376
5.369
3.976
-0.001
F
Cl
N
O
O
N
O
O
0.99
1.01
0.99
2.00
2.04
1.01
2.04
1.02
1.00
1.00
1.00
3.01
f1 (ppm)


166.992
162.847
159.221
156.738
153.310
149.808
142.189
134.642
128.992
125.135
121.593
120.785
117.164
116.951
104.065
77.477
77.160
76.842
64.282
63.038
56.015
F
Cl
N
O
O
N
O
O
f1 (ppm)

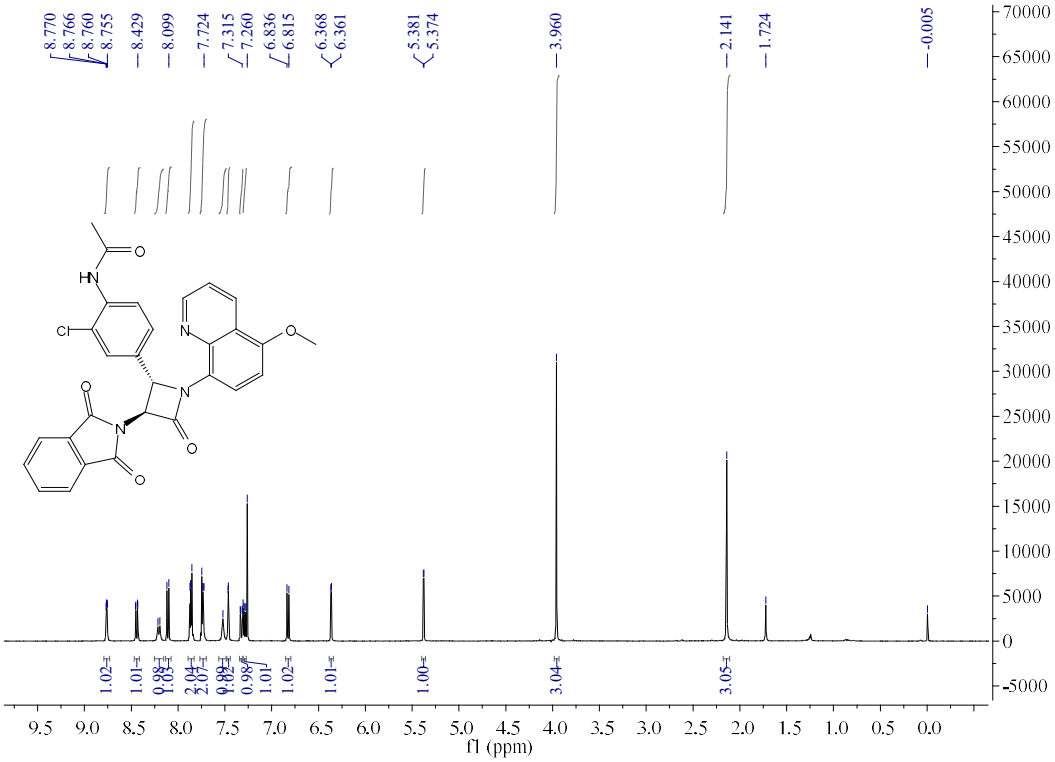

-115.6410
1000
900
800
700
600
500
400
300
200
100
0
-100
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)
O
O
N
O
N
F
Cl
O

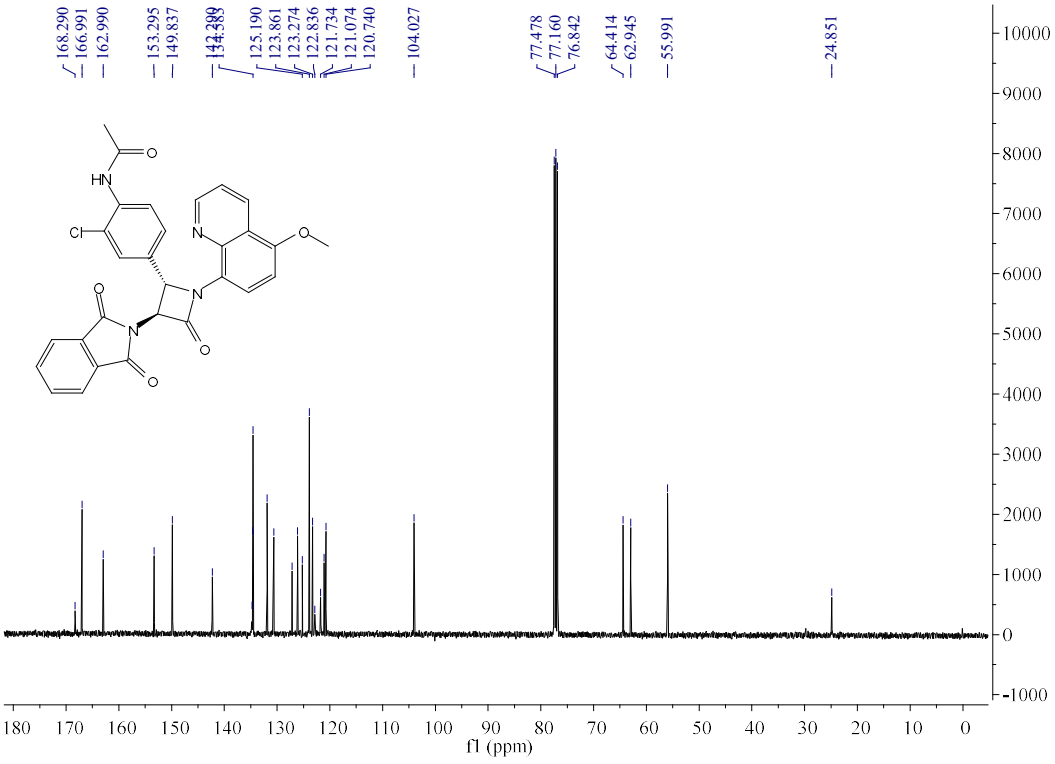
3j


8.754
8.750
8.744
8.740
8.405
7.827
7.719
7.573
7.238
6.780
6.759
6.354
6.348
5.386
5.379
3.930
1.993
1.758
-0.004
1.01
1.00
1.00
2.03
2.04
1.00
3.93
1.81
1.01
0.99
1.00
3.00
3.00
f1 (ppm)

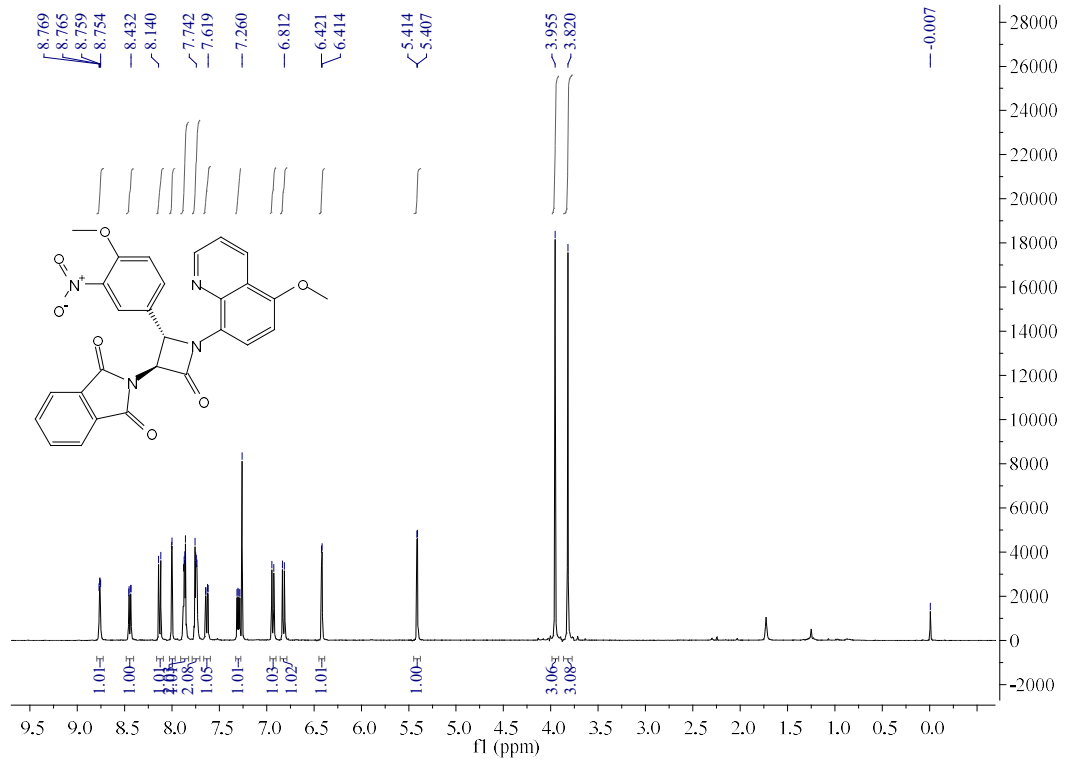

168.545
167.080
163.460
153.366
149.932
142.516
125.312
123.831
123.366
121.071
120.724
119.962
103.930
77.477
77.160
76.842
64.754
62.797
55.982
24.487
f1 (ppm)

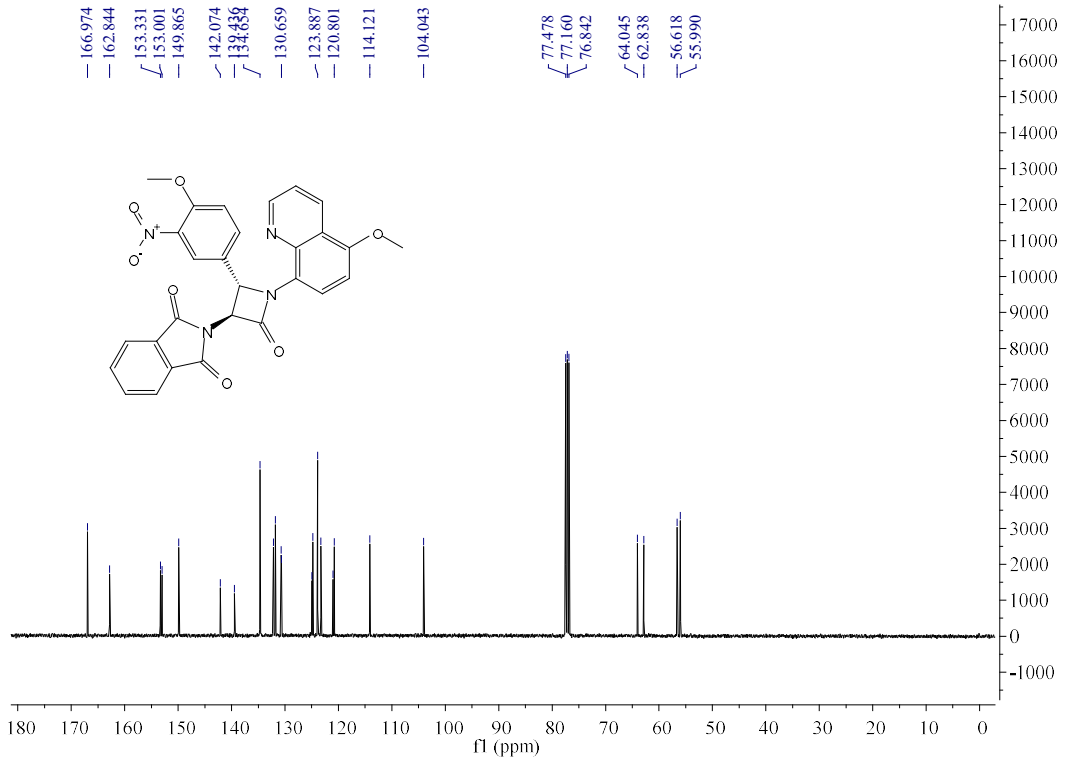
3k


8.770
8.766
8.760
8.755
8.429
8.099
7.724
7.315
7.260
6.836
6.815
6.368
6.361
5.381
5.374
3.960
2.141
1.724
-0.005
1.02
1.01
0.98
2.04
2.07
0.89
0.98
1.01
1.02
1.01
1.00
3.04
3.05
f1 (ppm)

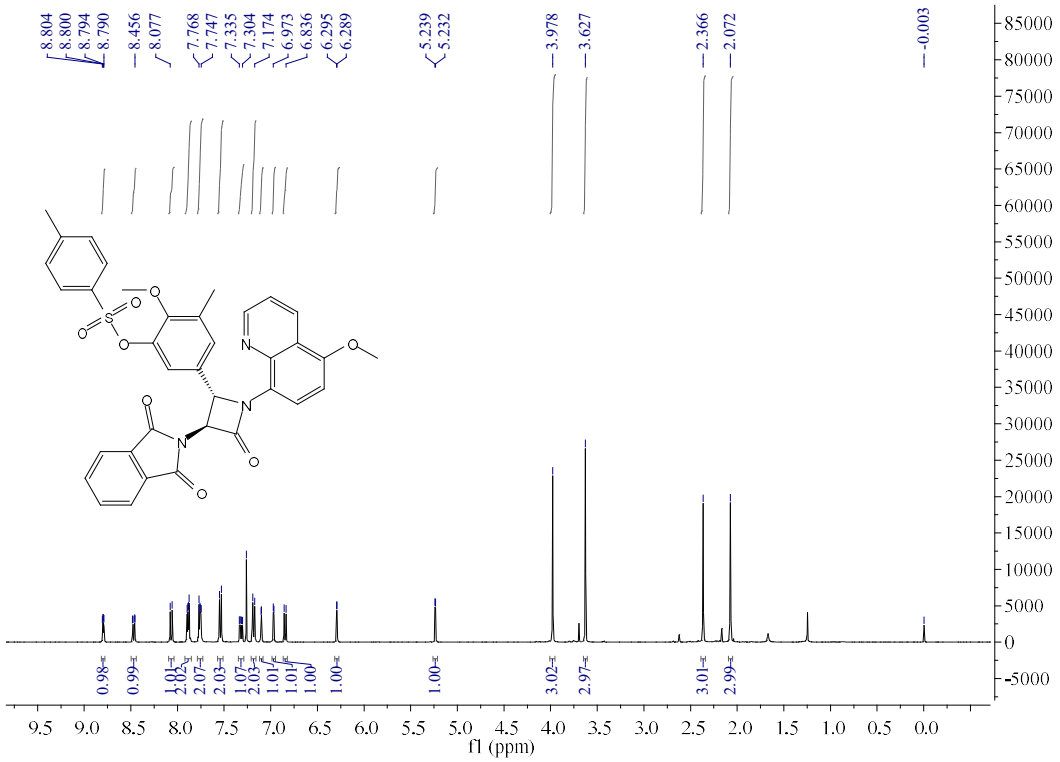

168.290
166.991
162.990
153.295
149.837
142.380
134.383
125.190
123.861
123.274
122.836
121.734
121.074
120.740
104.027
77.478
77.160
76.842
64.414
62.945
55.991
24.851
f1 (ppm)

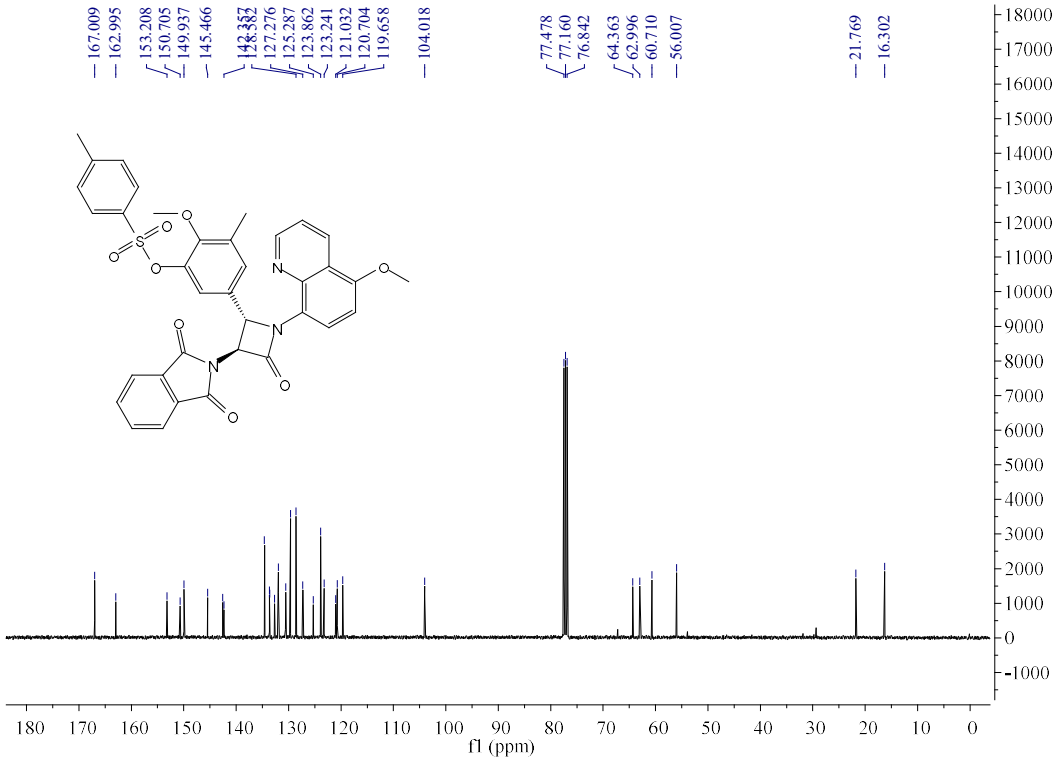
3l


8.769
8.765
8.759
8.754
8.432
8.140
7.742
7.619
7.260
6.812
6.421
6.414
5.414
5.407
3.955
3.820
-0.007
1.01
1.00
2.01
2.08
1.05
1.01
1.03
1.02
1.01
1.00
3.06
3.08
f1 (ppm)

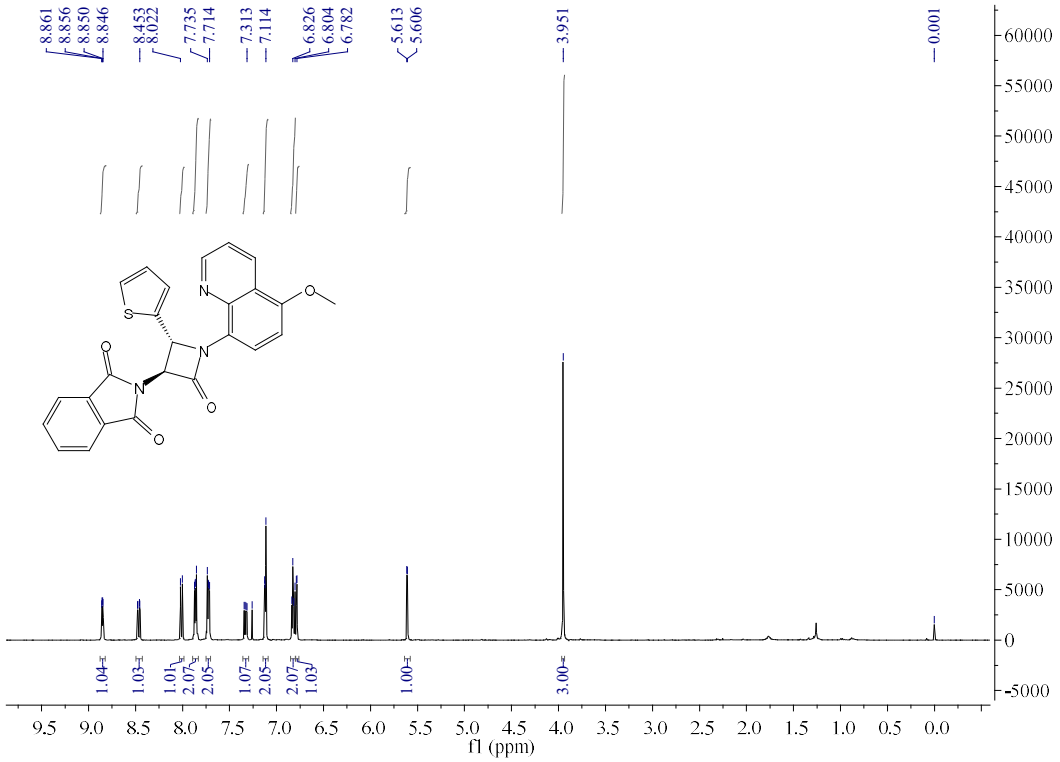

166.974
162.844
153.331
153.001
149.865
142.074
139.436
134.654
130.659
123.887
120.801
114.121
104.043
77.478
77.160
76.842
64.045
62.838
56.618
55.990
f1 (ppm)

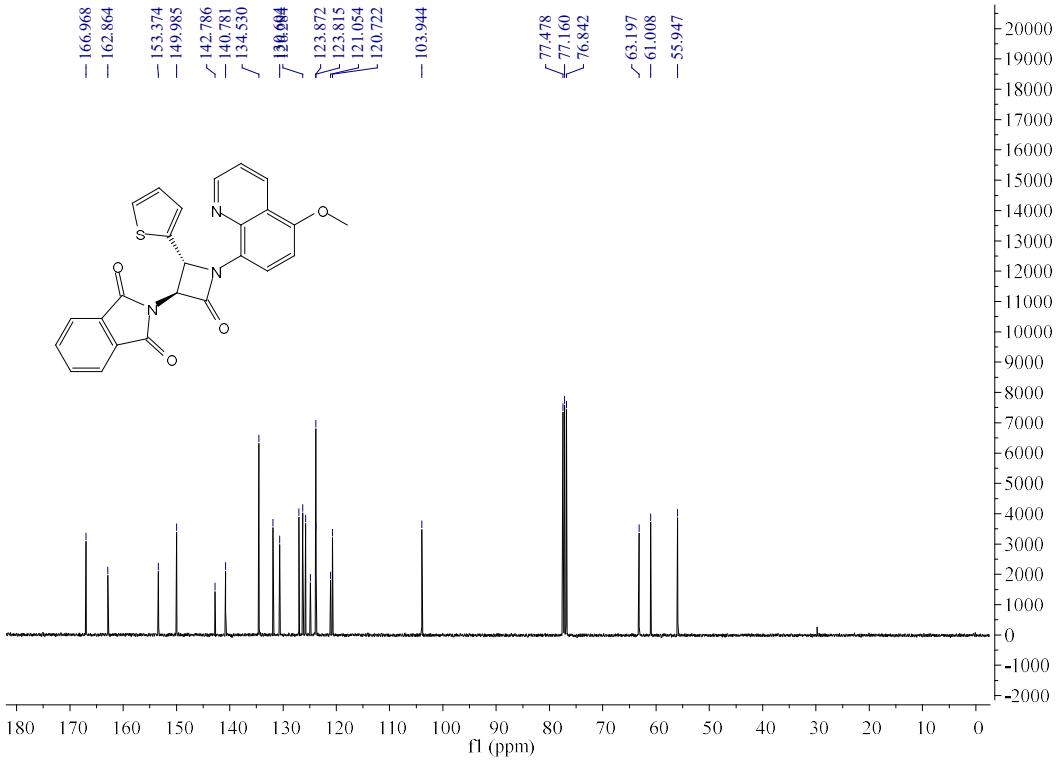
3m


8.804
8.800
8.794
8.790
8.456
8.077
7.768
7.747
7.335
7.304
7.174
6.973
6.836
6.295
6.289
5.239
5.232
3.978
3.627
2.366
2.072
-0.003
0.98
0.99
1.01
2.02
2.07
2.03
1.07
2.03
1.01
1.01
1.00
1.00
1.00
3.02
2.97
3.01
2.99
f1 (ppm)

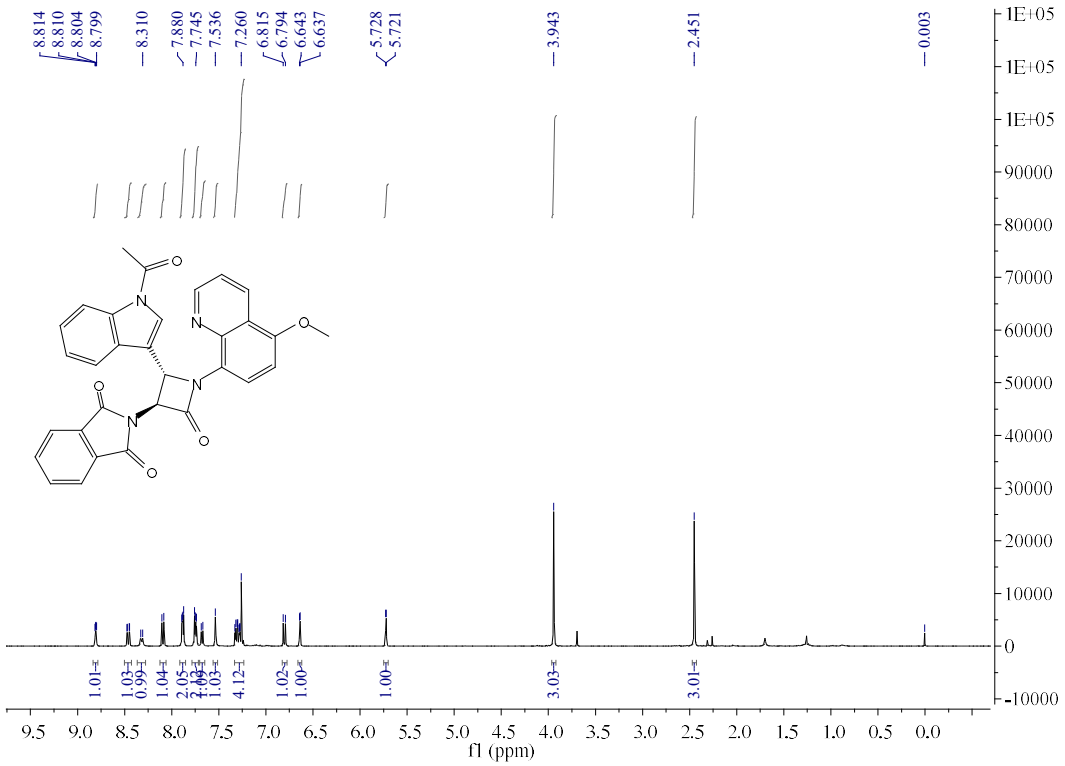

167.009
162.995
153.208
150.705
149.937
145.466
142.357
128.382
127.276
125.287
123.862
123.241
121.032
120.704
119.658
104.018
77.478
77.160
76.842
64.363
62.996
60.710
56.007
21.769
16.302
f1 (ppm)

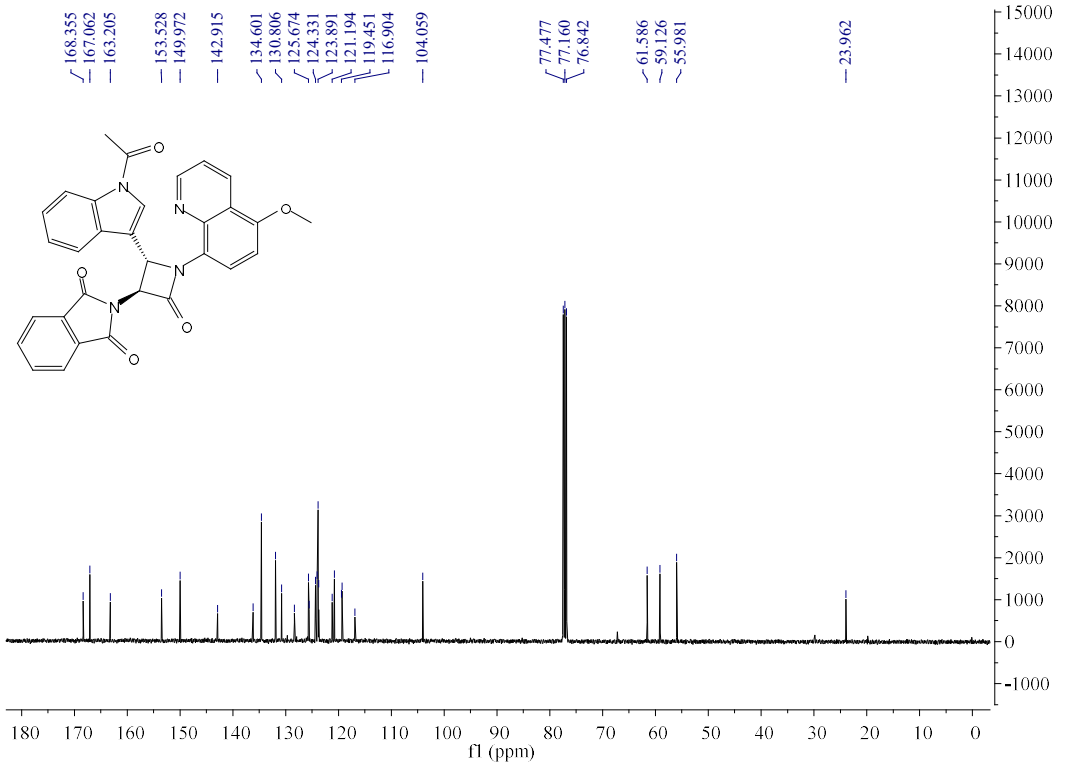
3n


8.861
8.856
8.850
8.846
8.453
8.022
7.735
7.714
7.313
7.114
6.826
6.804
6.782
5.613
5.606
3.951
0.001
1.04
1.03
1.01
2.07
2.05
1.07
2.05
2.07
1.03
1.00
3.00
f1 (ppm)

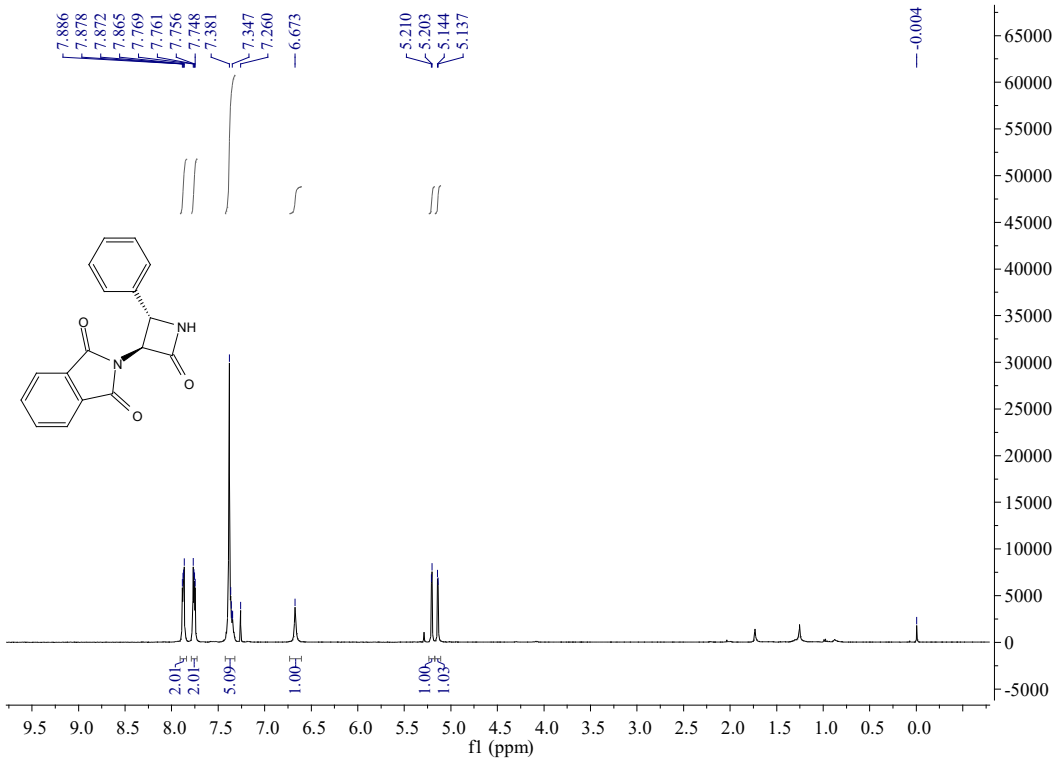

166.968
162.864
153.374
149.985
142.786
140.781
134.530
123.872
123.815
121.054
120.722
103.944
77.478
77.160
76.842
63.197
61.008
55.947
f1 (ppm)

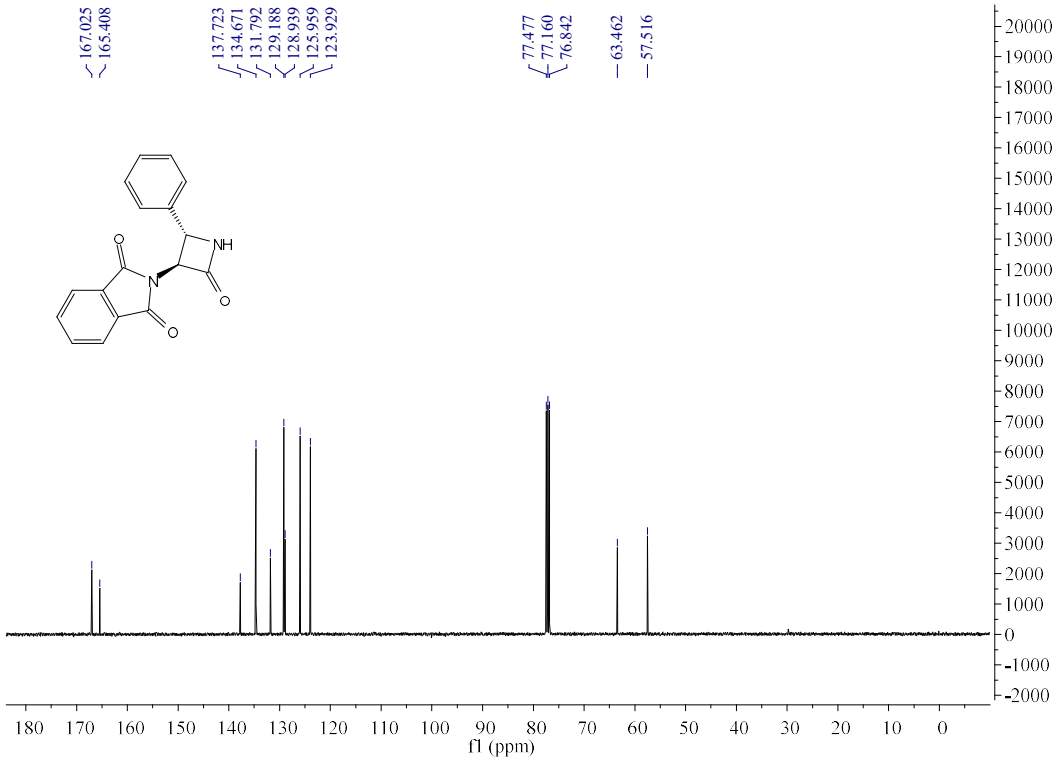
3o


8.814
8.810
8.804
8.799
8.310
7.880
7.745
7.536
7.260
6.815
6.794
6.643
6.637
5.728
5.721
3.943
2.451
0.003
1.01
1.03
0.99
1.04
2.05
2.04
1.03
4.12
1.02
1.00
1.00
3.03
3.01
f1 (ppm)

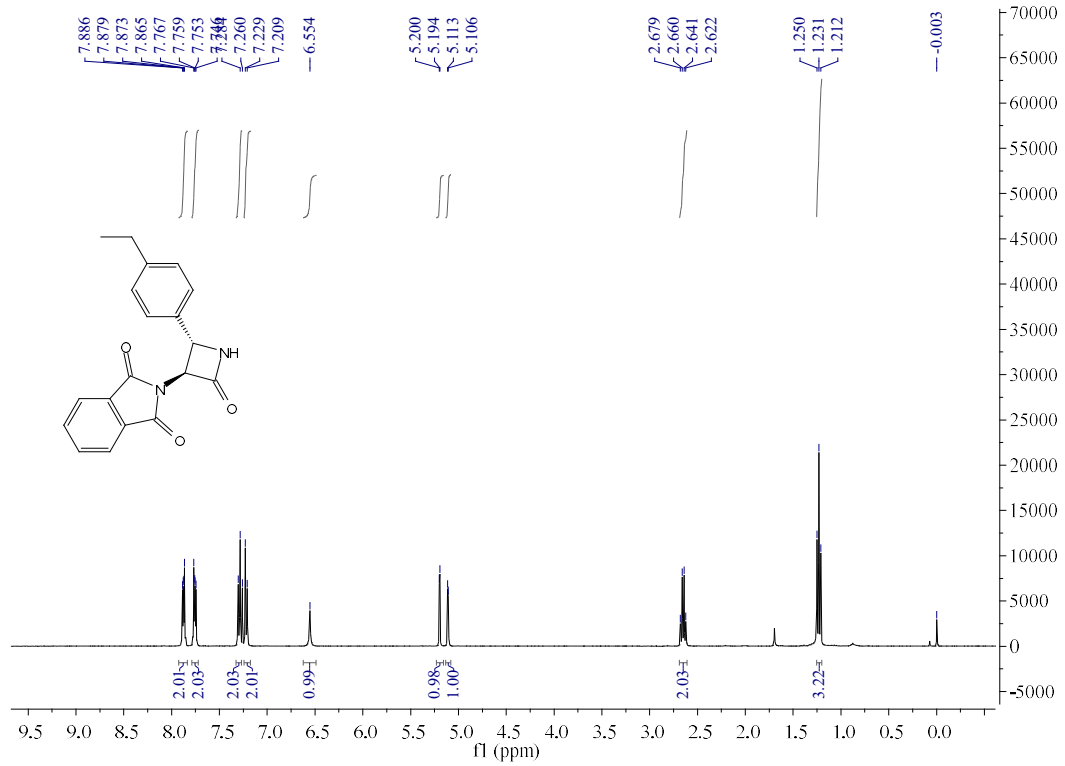

168.355
167.062
163.205
153.528
149.972
142.915
134.601
130.806
125.674
124.331
123.891
121.194
119.451
116.904
104.059
77.477
77.160
76.842
61.586
59.126
55.981
23.962
f1 (ppm)

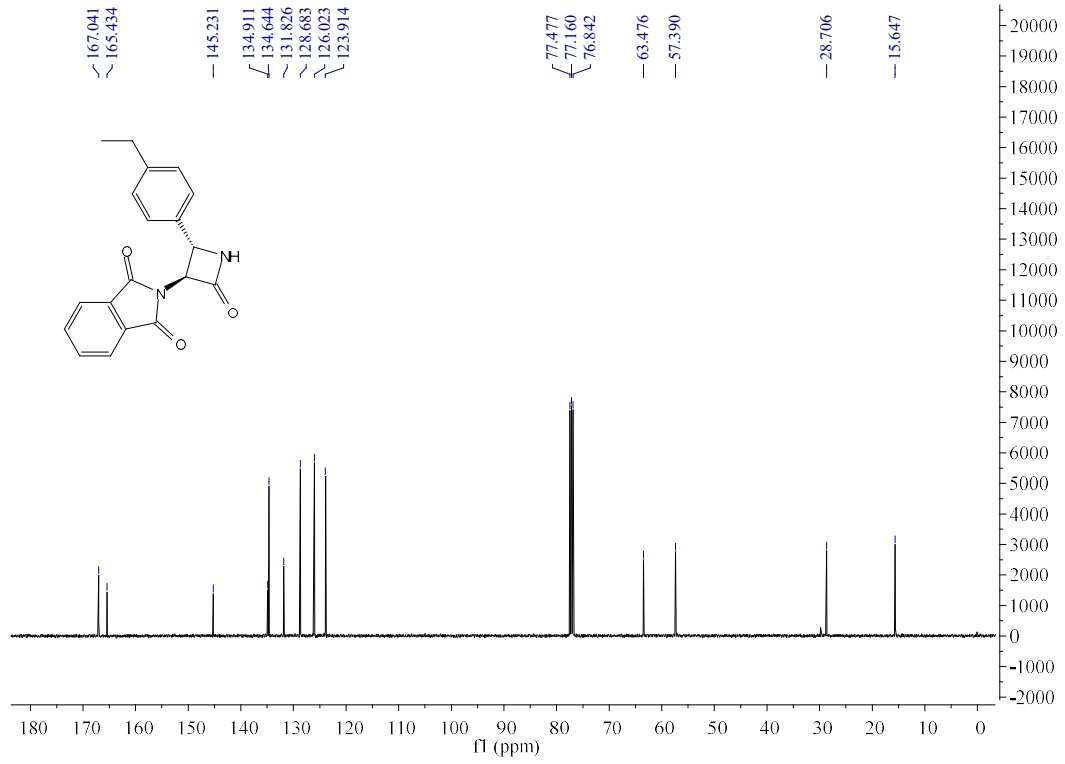
4a


7.886
7.878
7.872
7.865
7.769
7.761
7.756
7.748
7.381
7.347
7.260
6.673
5.210
5.203
5.144
5.137
-0.004
NH
O
N
O
O
2.01
2.01
5.09
1.00
1.00
1.03
f1 (ppm)

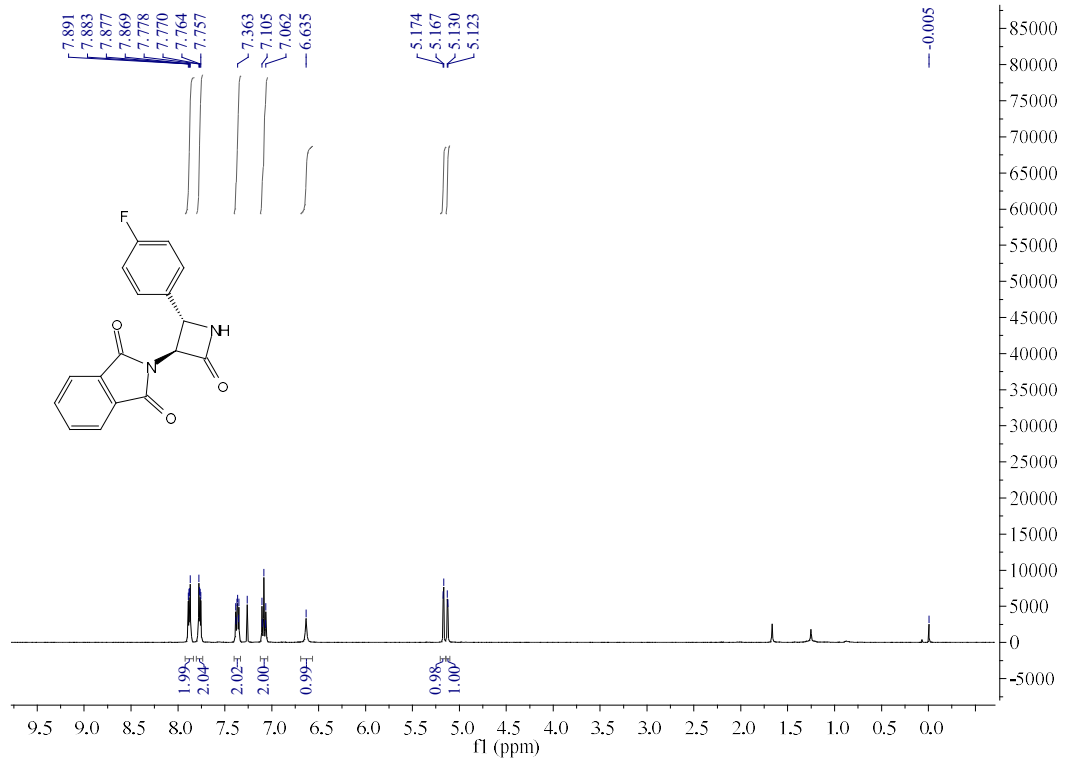

167.025
165.408
137.723
134.671
131.792
129.188
128.939
125.959
123.929
77.477
77.160
76.842
63.462
57.516
NH
O
N
O
O
f1 (ppm)

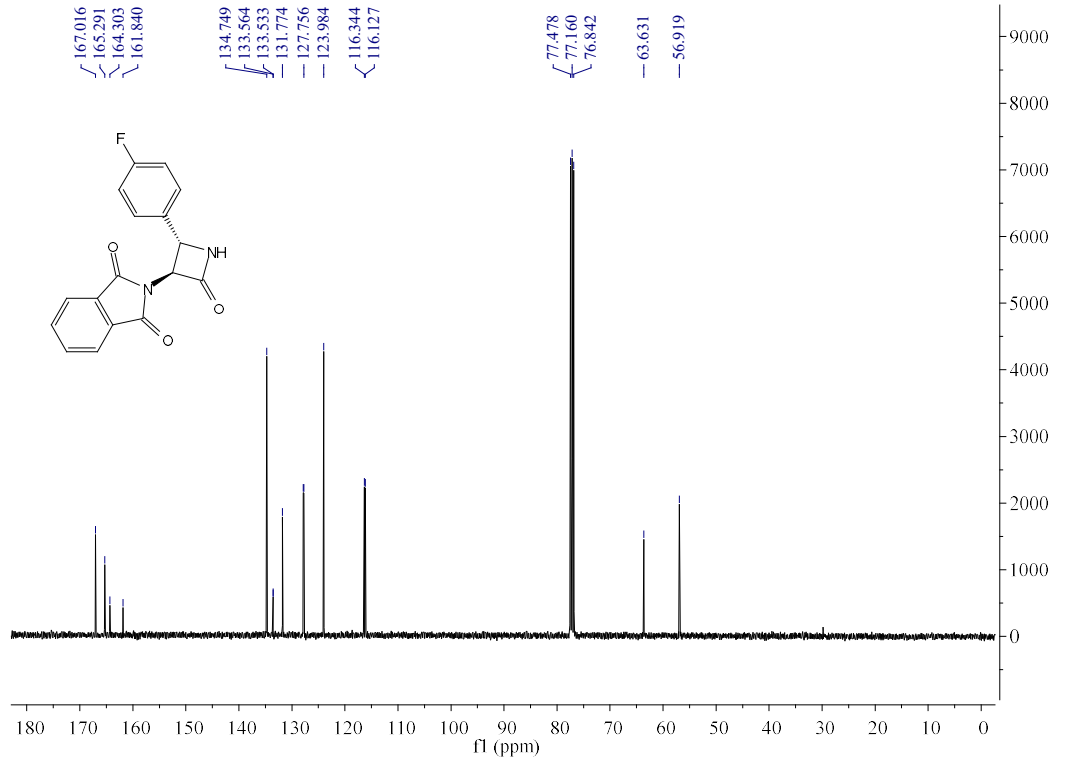
4b

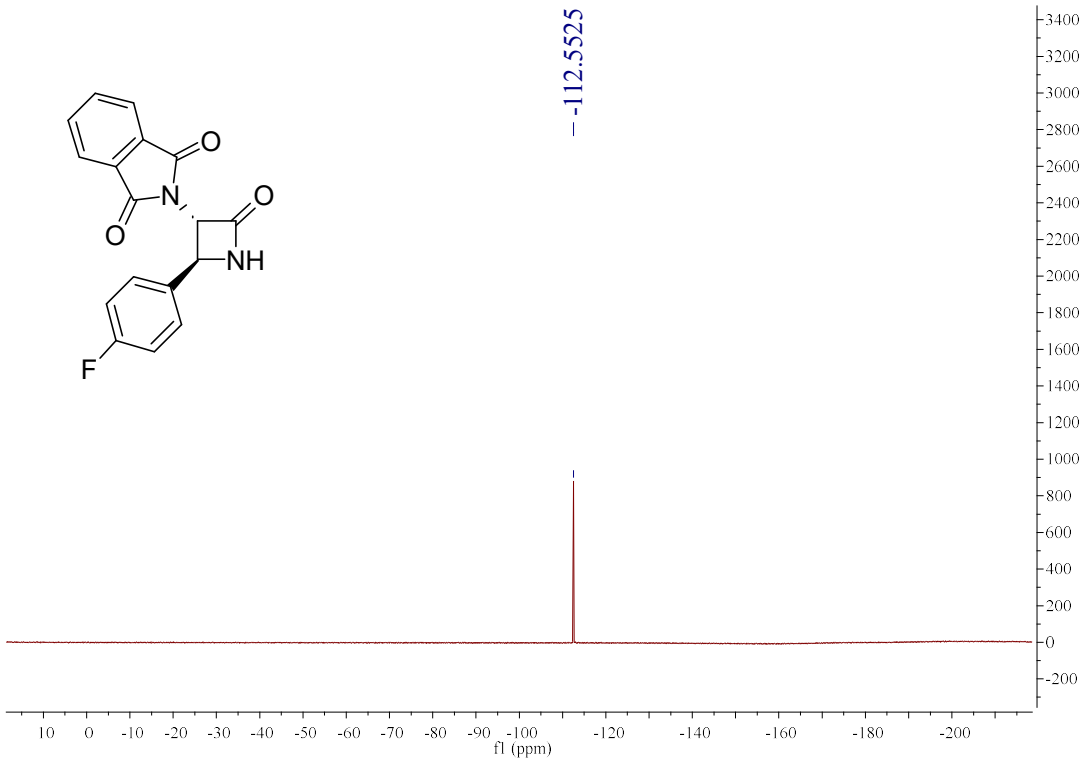

7.886
7.879
7.873
7.865
7.767
7.759
7.753
7.260
7.229
7.209
6.554
5.200
5.194
5.113
5.106
2.679
2.660
2.641
2.622
1.250
1.231
1.212
-0.003
2.01
2.03
2.03
2.01
0.99
0.98
1.00
2.03
3.22
f1 (ppm)


167.041
165.434
145.231
134.911
134.644
131.826
128.683
126.023
123.914
77.477
77.160
76.842
63.476
57.390
28.706
15.647
f1 (ppm)

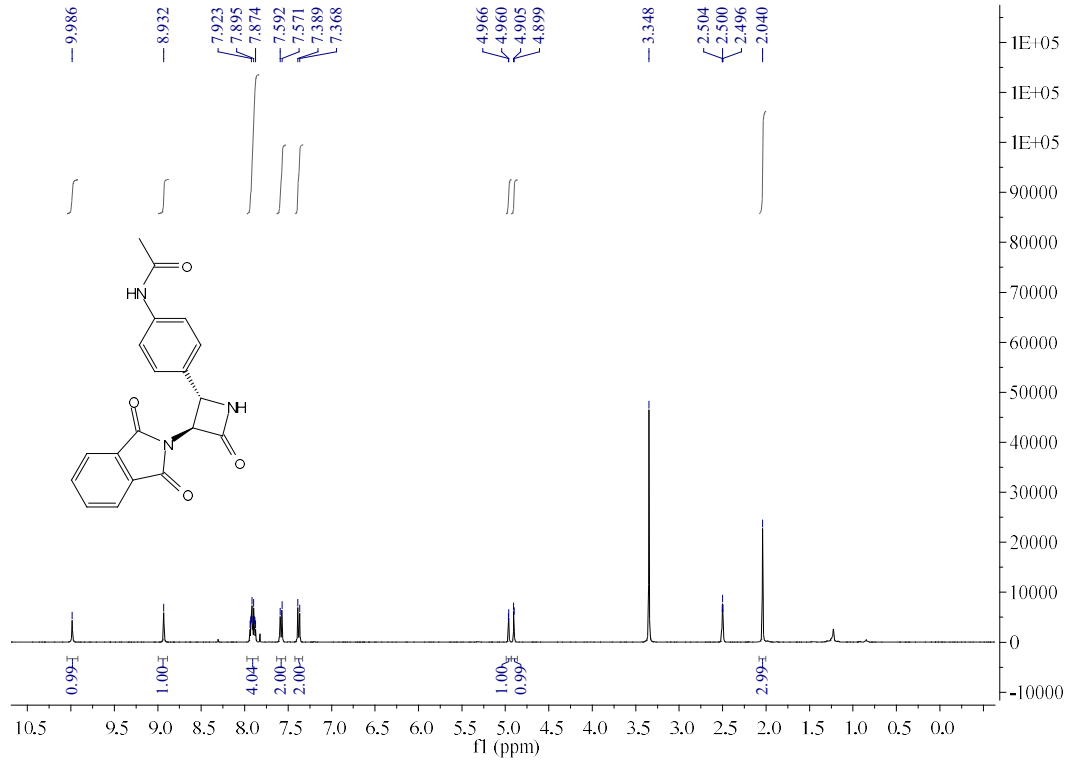
4c

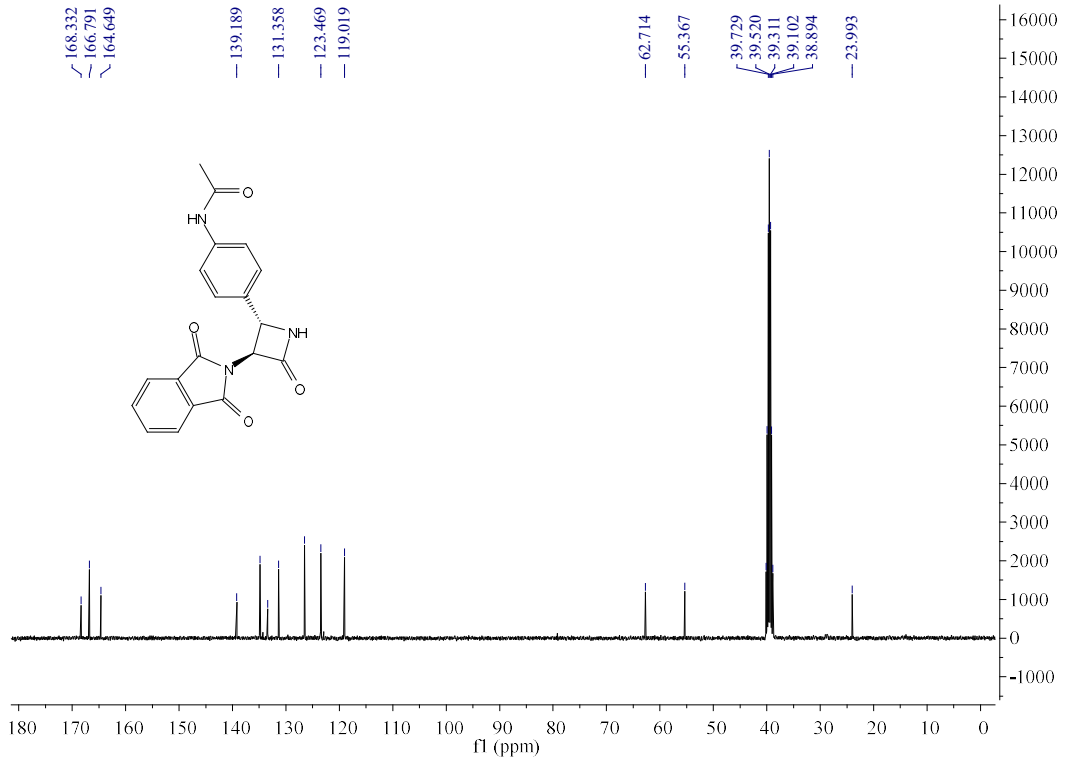

7.891
7.883
7.877
7.869
7.778
7.770
7.764
7.757
7.363
7.105
7.062
6.635
5.174
5.167
5.130
5.123
-0.005
F
NH
O
N
O
O
1.99
2.04
2.02
2.00
0.99
0.98
1.00
f1 (ppm)


167.016
165.291
164.303
161.840
134.749
133.564
133.533
131.774
127.756
123.984
116.344
116.127
77.478
77.160
76.842
63.631
56.919
F
NH
O
N
O
O
f1 (ppm)

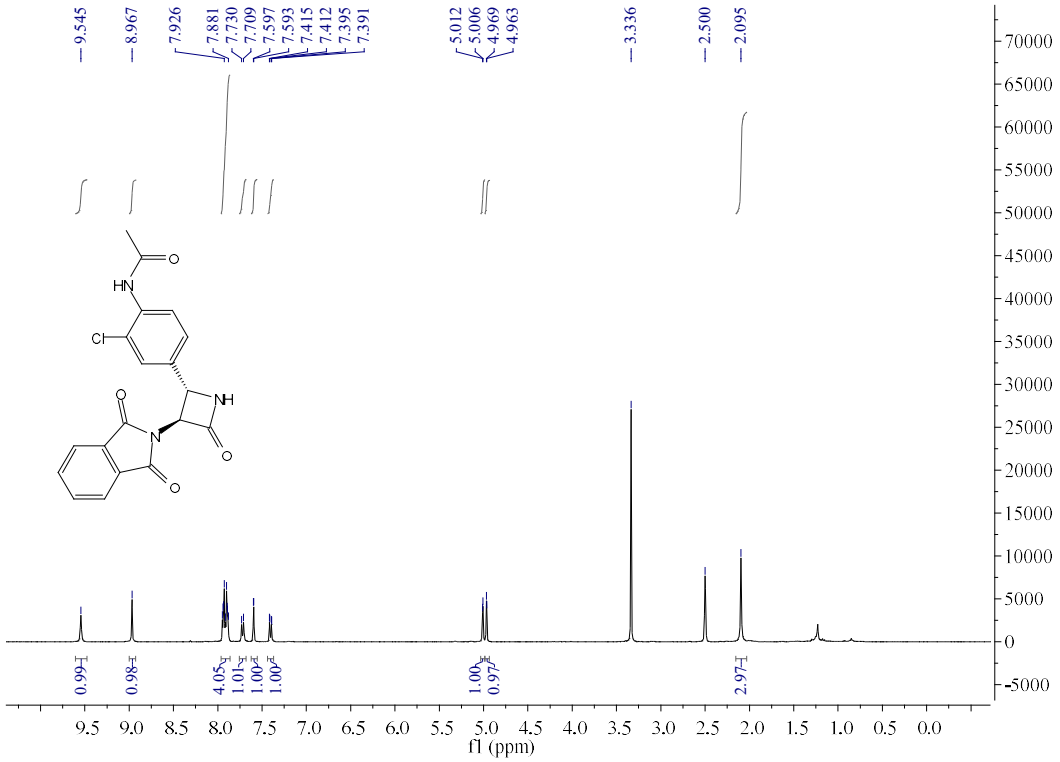

-112.5525
O
N
O
O
NH
F
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -120 -140 -160 -180 -200
f1 (ppm)

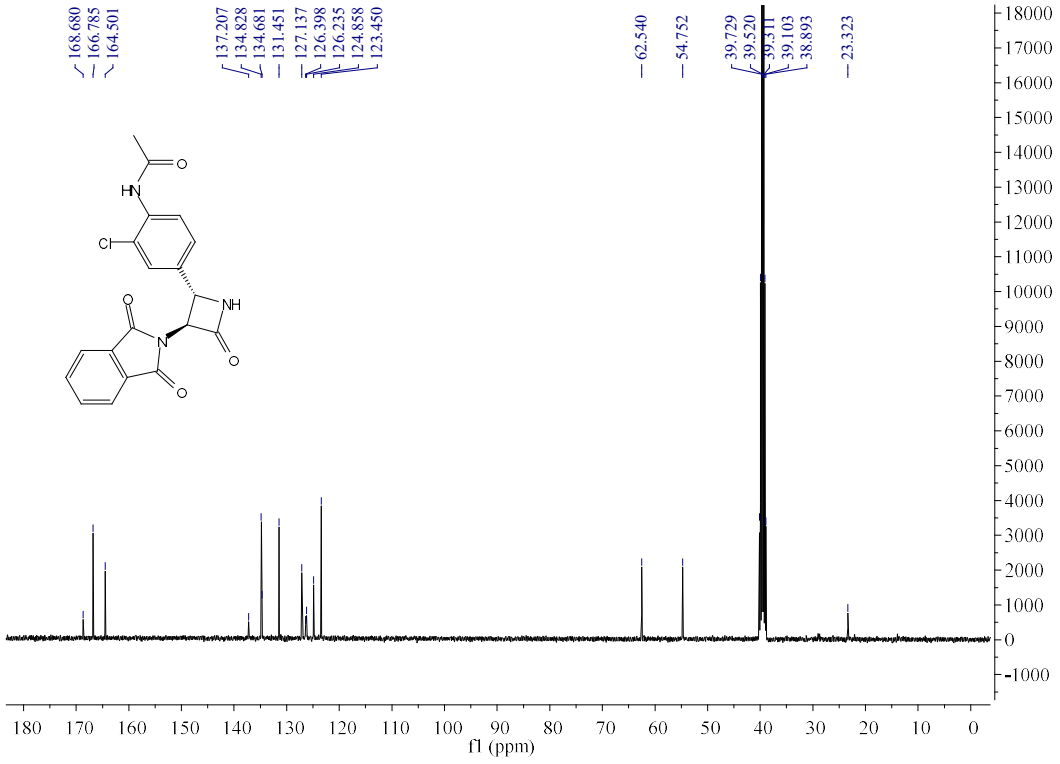
4d


9.986
8.932
7.923
7.895
7.874
7.592
7.571
7.389
7.368
4.966
4.960
4.905
4.899
3.348
2.504
2.500
2.496
2.040
HN
O
NH
N
0.99
1.00
4.04
2.00
2.00
1.00
0.99
2.99
f1 (ppm)

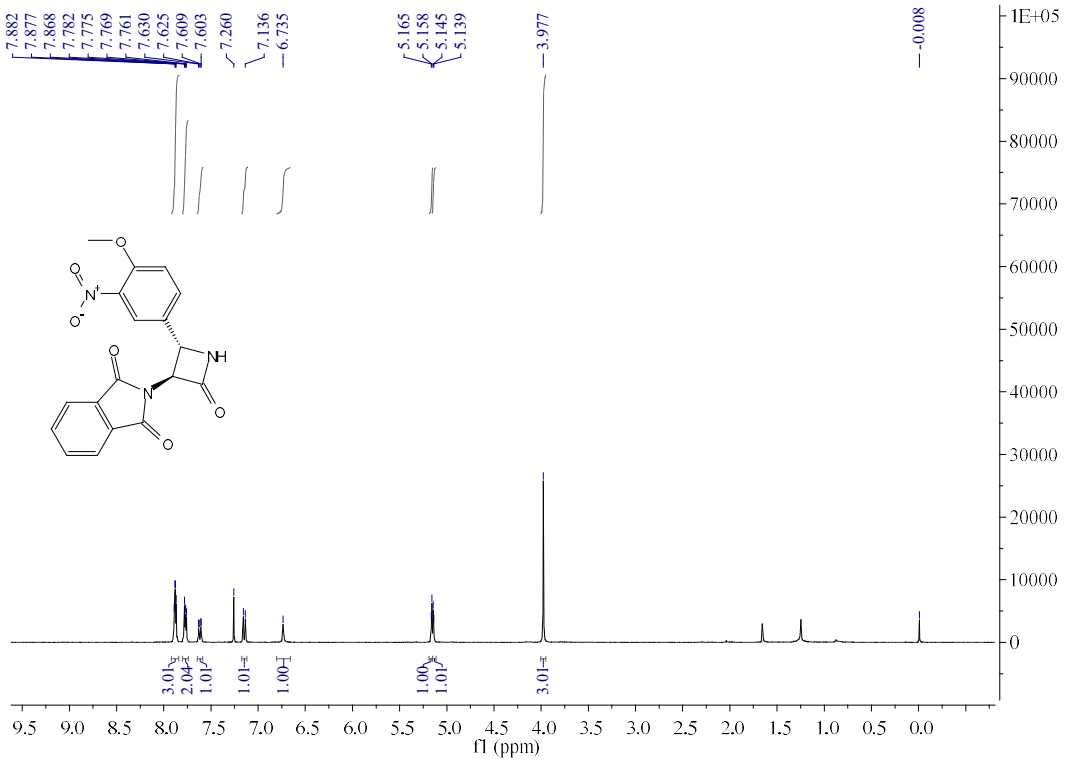

168.332
166.791
164.649
139.189
131.358
123.469
119.019
62.714
55.367
39.729
39.520
39.311
39.102
38.894
23.993
HN
O
NH
N
f1 (ppm)

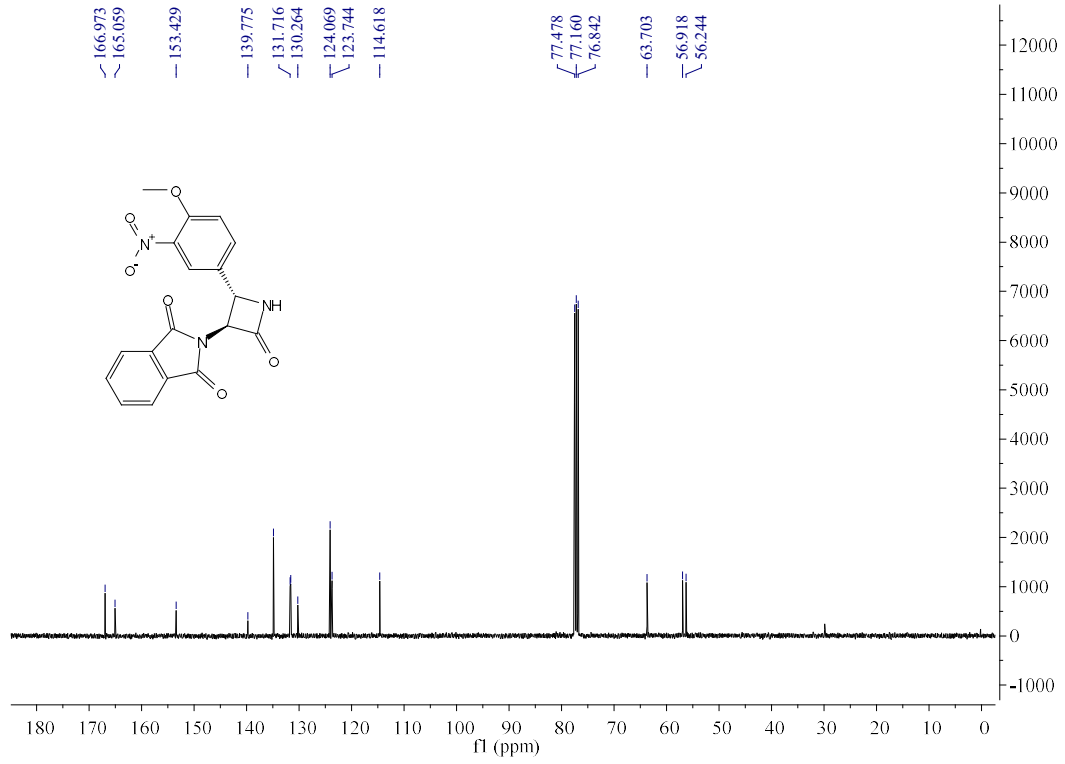
4e


9.545
8.967
7.926
7.881
7.730
7.709
7.597
7.593
7.415
7.412
7.395
7.391
5.012
5.006
4.969
4.963
3.336
2.500
2.095
HN
Cl
NH
O
N
0.99
0.98
4.05
1.01
1.00
1.00
1.00
0.97
2.97
f1 (ppm)

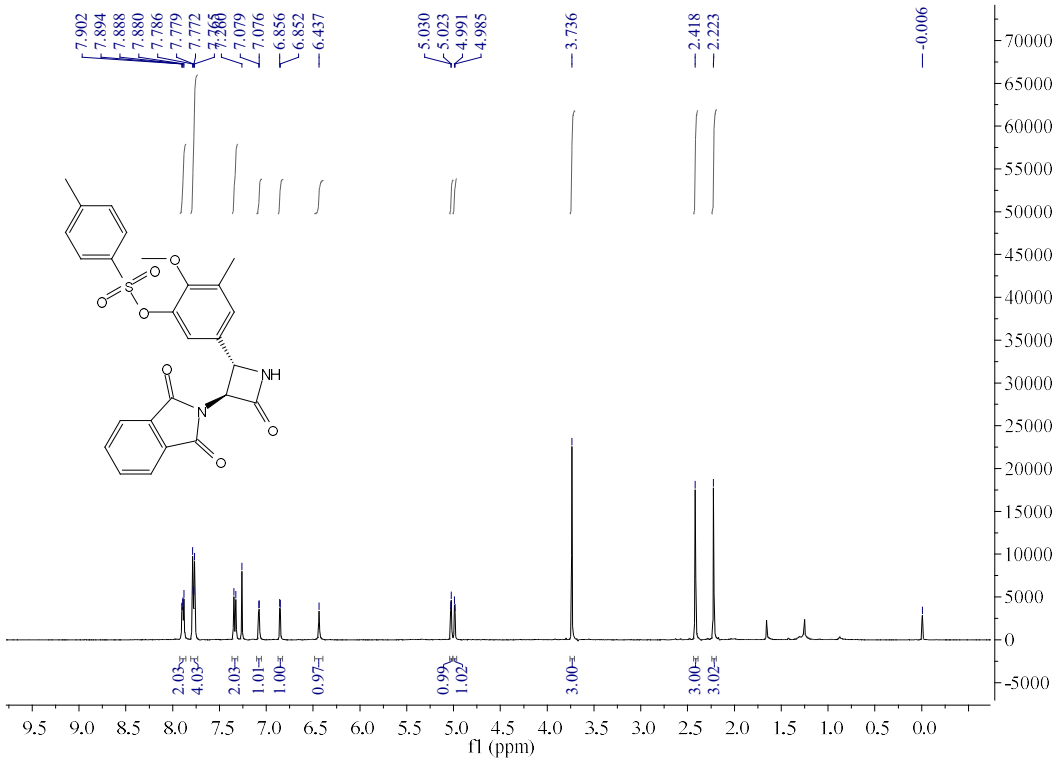

168.680
166.785
164.501
137.207
134.828
134.681
131.451
127.137
126.398
126.235
124.858
123.450
62.540
54.752
39.729
39.520
39.311
39.103
38.893
23.323
HN
Cl
NH
O
N
f1 (ppm)

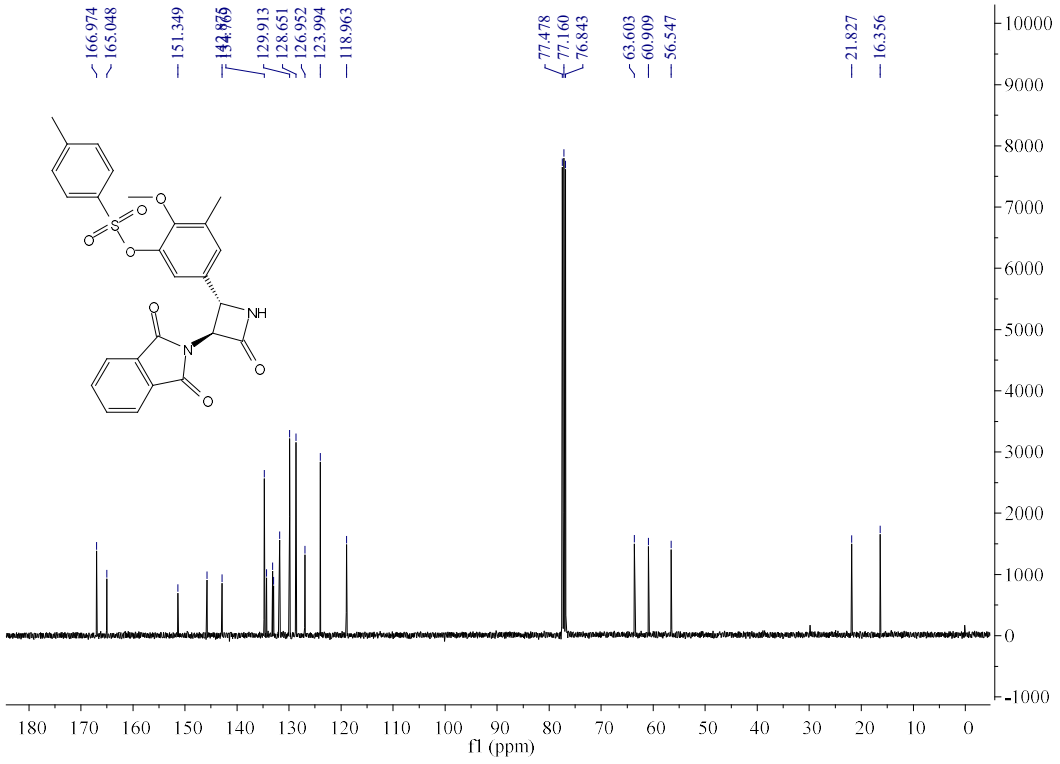
4f


7.882
7.877
7.868
7.782
7.775
7.769
7.761
7.630
7.625
7.609
7.603
7.260
7.136
6.735
5.165
5.158
5.145
5.139
3.977
-0.008
NH
3.01
2.04
1.01
1.01
1.00
1.00
1.01
3.01
f1 (ppm)

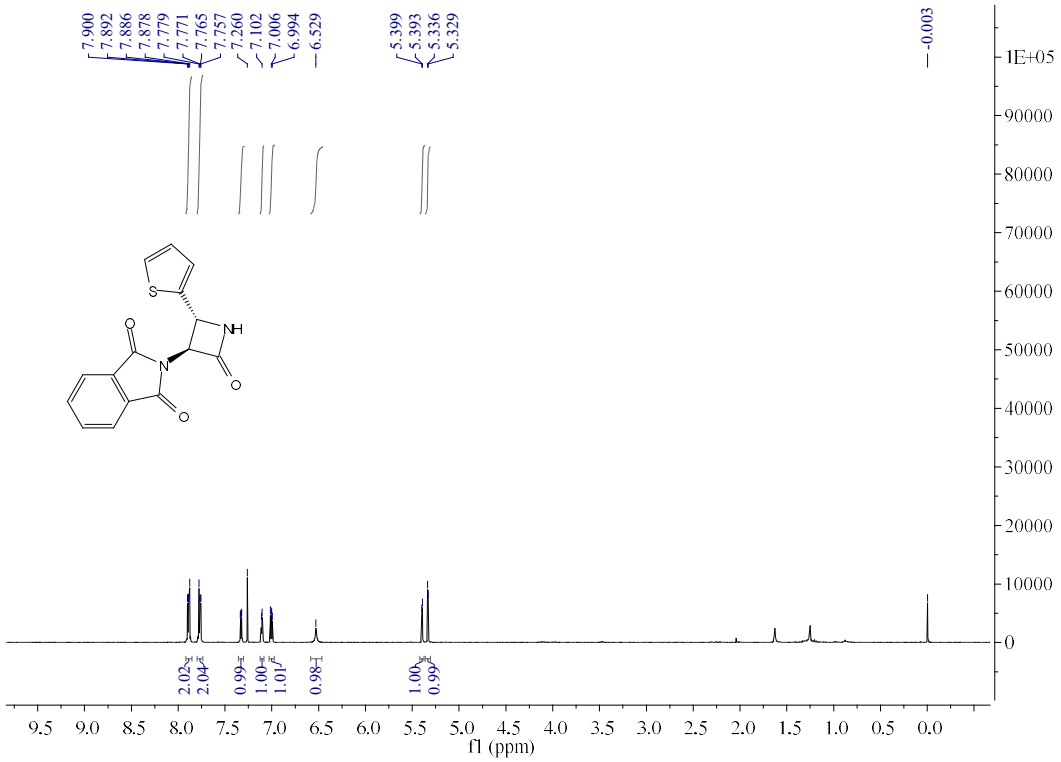

166.973
165.059
153.429
139.775
131.716
130.264
124.069
123.744
114.618
77.478
77.160
76.842
63.703
56.918
56.244
NH
f1 (ppm)

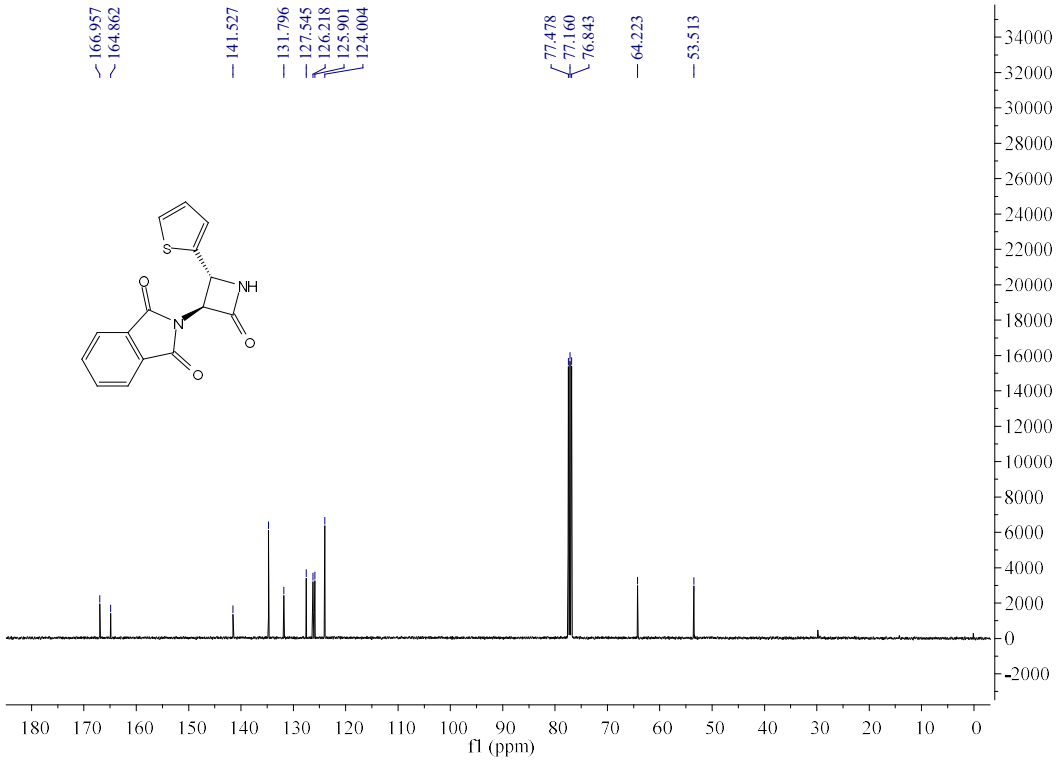
4g


7.902
7.894
7.888
7.880
7.786
7.779
7.772
7.265
7.260
7.079
7.076
6.856
6.852
6.437
5.030
5.023
4.991
4.985
3.736
2.418
2.223
-0.006
2.03
4.03
2.03
1.01
1.00
0.97
0.99
1.02
3.00
3.00
3.02
f1 (ppm)

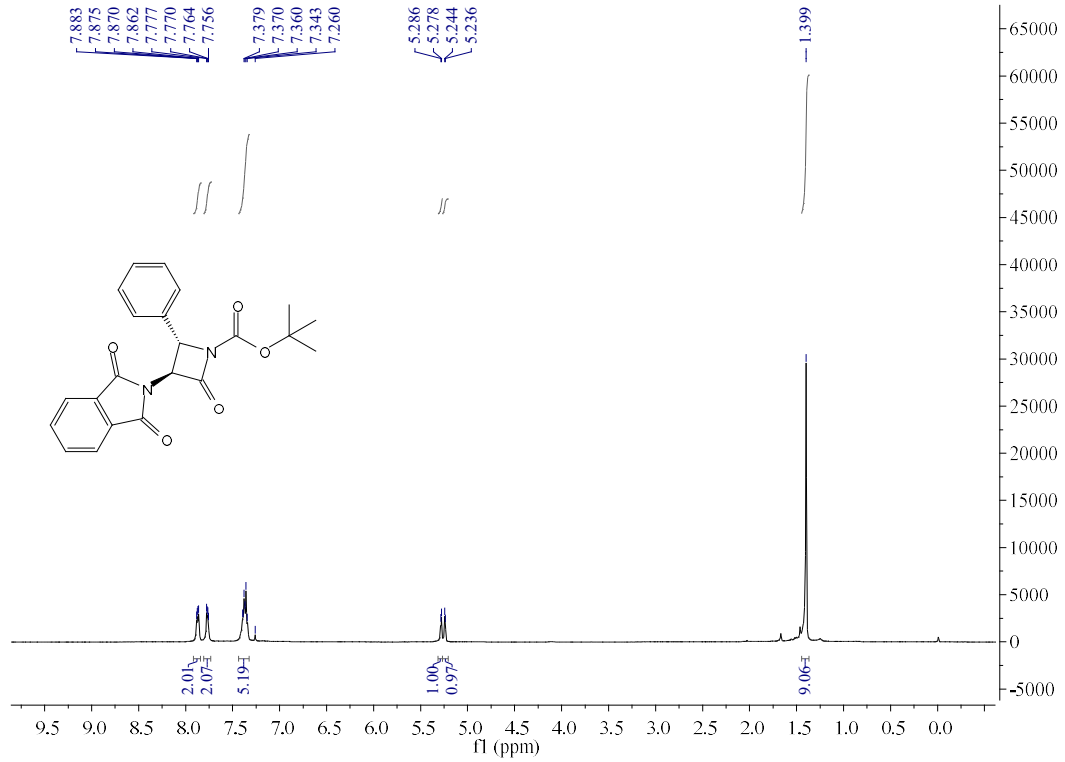

166.974
165.048
151.349
129.913
128.651
126.952
123.994
118.963
77.478
77.160
76.843
63.603
60.909
56.547
21.827
16.356
f1 (ppm)

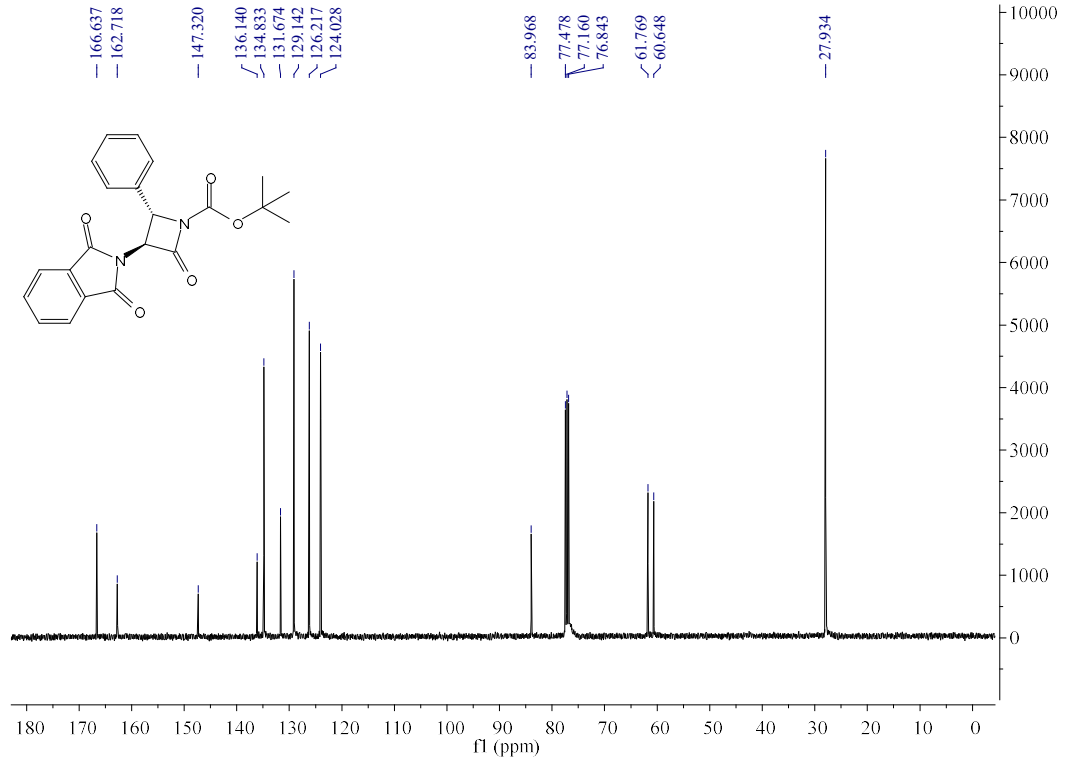
4h


7.900
7.892
7.886
7.878
7.779
7.771
7.765
7.757
7.260
7.102
7.006
6.994
6.529
5.399
5.393
5.336
5.329
-0.003
2.02
2.04
0.99
1.00
1.01
0.98
1.00
0.99
f1 (ppm)

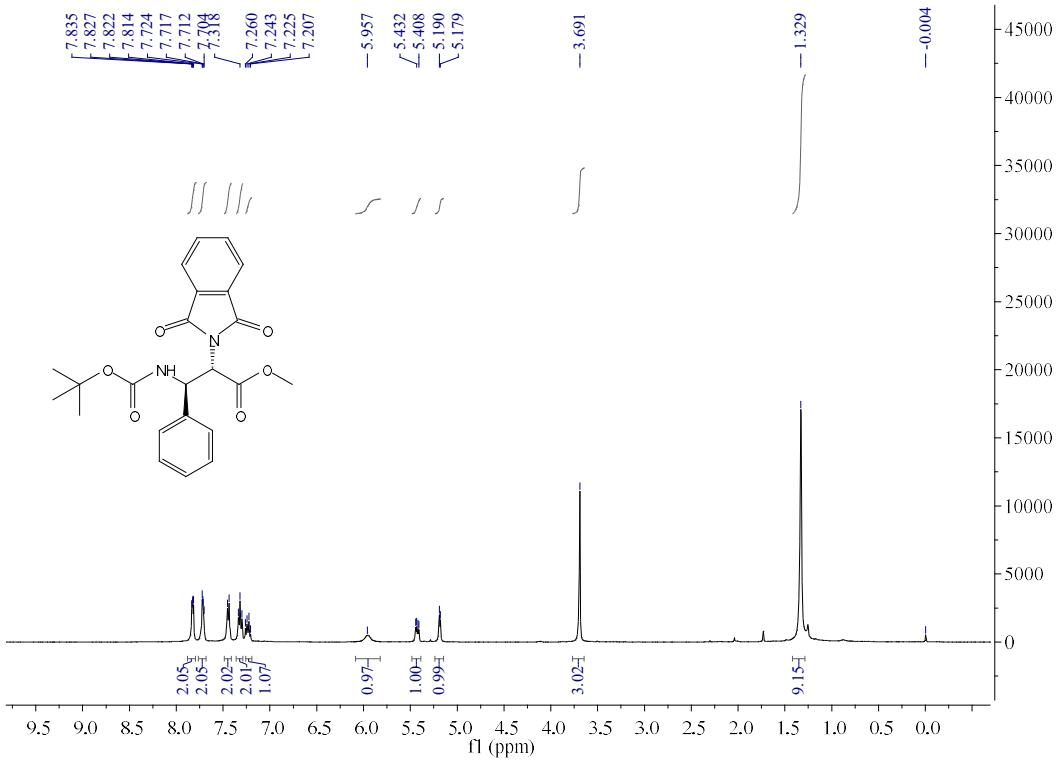

166.957
164.862
141.527
131.796
127.545
126.218
125.901
124.004
77.478
77.160
76.843
64.223
53.513
f1 (ppm)

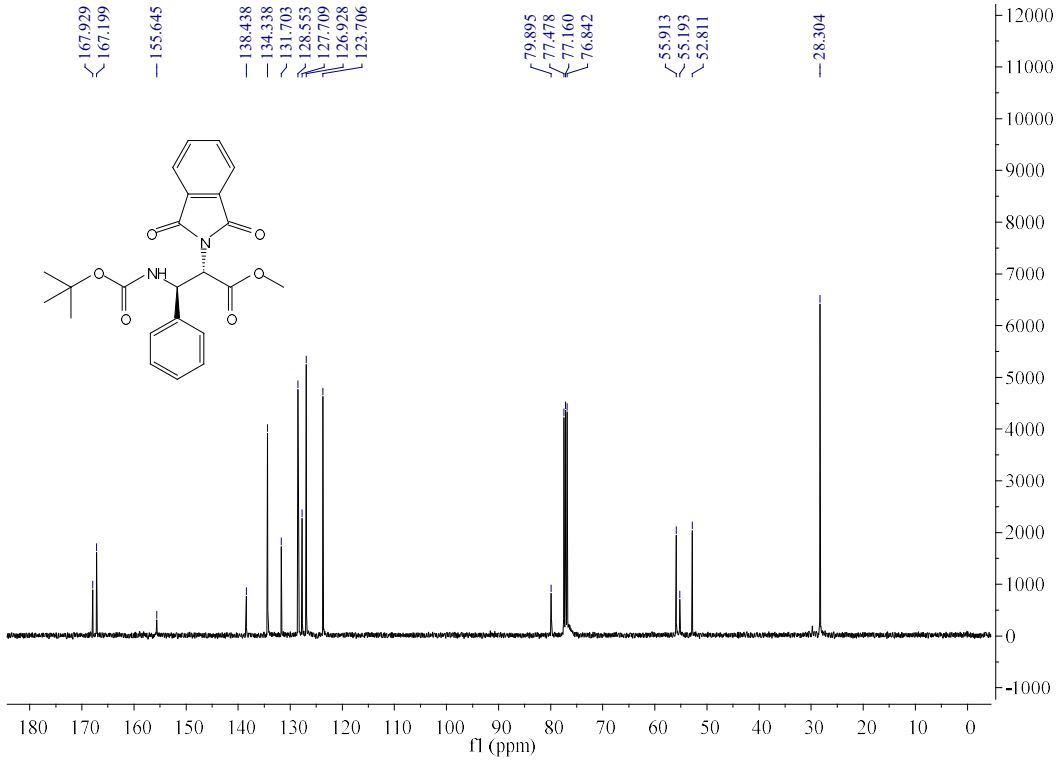
5a


7.883
7.875
7.870
7.862
7.777
7.770
7.764
7.756
7.379
7.370
7.360
7.343
7.260
5.286
5.278
5.244
5.236
1.399
2.01
2.07
5.19
1.00
0.97
9.06
f1 (ppm)


166.637
162.718
147.320
136.140
134.833
131.674
129.142
126.217
124.028
83.968
77.478
77.160
76.843
61.769
60.648
27.934
f1 (ppm)

6a


7.835
7.827
7.822
7.814
7.724
7.717
7.712
7.704
7.318
7.260
7.243
7.225
7.207
5.957
5.432
5.408
5.190
5.179
3.691
1.329
-0.004
2.05
2.05
2.02
2.01
1.07
0.97
1.00
0.99
3.02
9.15
f1 (ppm)


167.929
167.199
155.645
138.438
134.338
131.703
128.553
127.709
126.928
123.706
79.895
77.478
77.160
76.842
55.913
55.193
52.811
28.304
f1 (ppm)