Supporting Information I

Pd(II)-Catalyzed Alkylation of Unactivated C(sp^3)–H Bonds : Efficient Synthesis of Optically Active Unnatural α-Amino Acids

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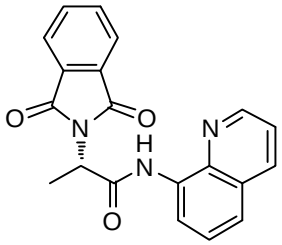
General Information: Unless otherwise noted all commercial materials were used without further purification. Solvents were used after purification directed by *Purification of Laboratory Chemicals, 6th Ed*. Nuclear magnetic resonance (NMR) spectra were recorded with Bruker AVANCE 400MHz. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak as following: $CHCl_3$ = 7.26 (^{1}H NMR), DMSO = 2.50 (^{1}H 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.X-ray diffractions were recorded at X-Ray Facilities, Zhejiang University.

Experimental Procedures:

General Procedure(GP-1) for Preparation of *N*-Phthaloyl-Amino Acid 8-Aminoquinoline Amides

To a stirred solution of the acid chloride (24 mmol) in dichloromethane (50 mL), 8-aminoquinoline (2.883 g, 20 mmol) was added slowly at 0 °C.After the solution was stirred for five minutes, triethylamine (3.97 mL, 24 mmol) was added dropwise slowly at 0 °C. The resulting mixture was stirredat room temperature for 5 h 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 overanhydrous $MgSO_4$.Evaporation of organic solvent and purification by column chromatography or recrystallization afforded pure 8-aminoquinoline amide.[1]

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-N-(quinolin-8-yl)propanamide(1a)



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 45 minutes, 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 (20 mL, 1M) and ethyl ether: petroleum ether = 1:5 (20 mL) gave (*S*)-2-phthalimidopropionic acid (19.10 g, 87%).

(*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 5 h. After the reaction, dichloromethane and excess of thionyl chloride were removed by vacuum. The acid chloride was dissolved in dichloromethane (50 mL) and used for next reaction.

The compound **1a** was prepared according to **GP-1**. The mixture was dissolved in ethyl acetate (5 mL), then petroleum ether (20 mL) was added slowly, and white solid appeared slowly. Collecting and washing the precipitate with ethyl ether: petroleum ether = 1:5 (10 mL) gave **1a** (5.36 g). Evaporation of the filtrate collected after filtration, followed by column chromatography in petroleum ether: ethyl acetate = 2:1 gave **1a** (0.64 g). The combined **1a** was obtained (6.00 g, 87%) as a white solid. This is a known compound.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.71 (dd, *J* = 5.4, 3.6 Hz, 1H), 8.67 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.89 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.53 – 7.47 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.26 (q, *J* = 7.3 Hz, 1H), 1.97 (d, *J* = 7.3

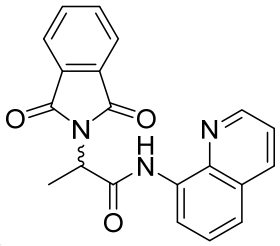
Hz, 3H); HPLC Chiralpack® AD-Hcolumn (*n*-hexane/isopropanol = 45:55, 0.70 mL/min) t_r = 17.410 min (major), >99% ee.

Chiral HPLC Data

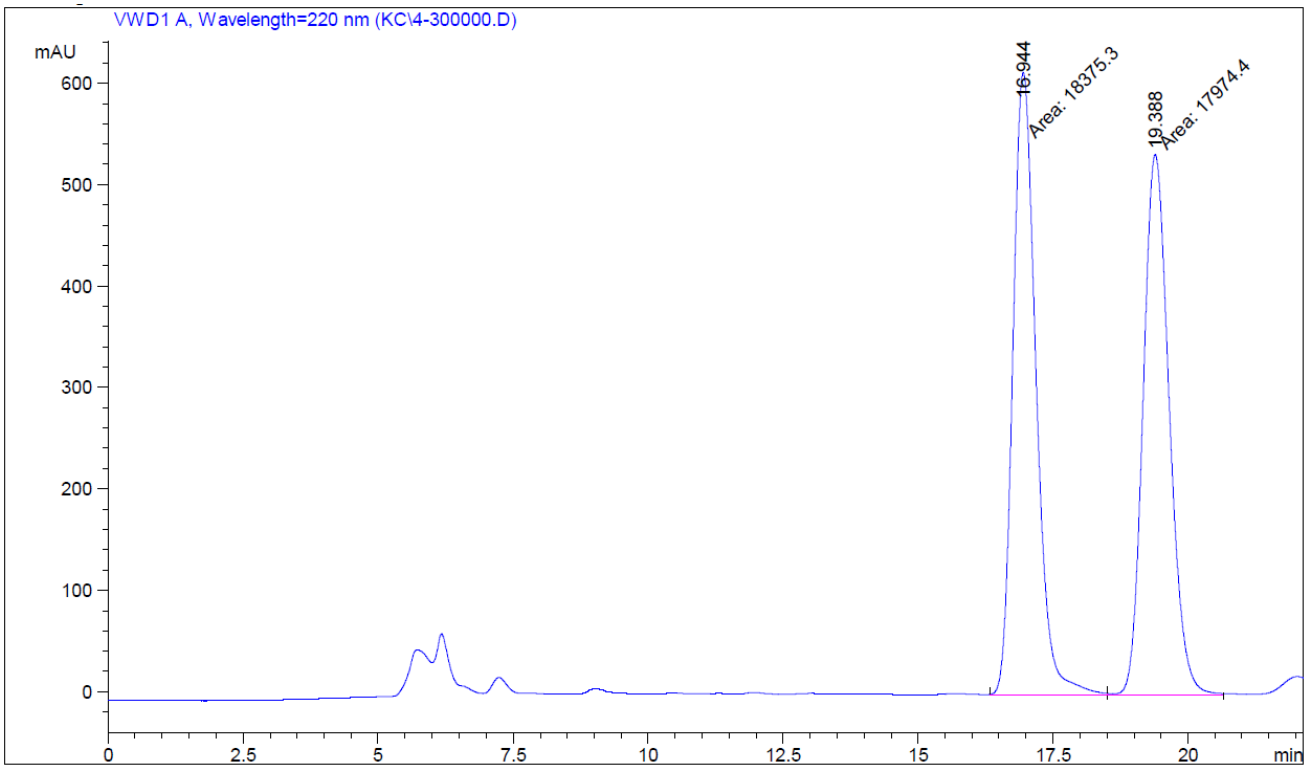
HPLC Conditions:

Chiral stationary phase: Chiralpack® AD-H, *n*-hexane/isopropanol = 45:55, 0.70 mL/min

Signal: VWD1 A, Wavelength = 220 nm

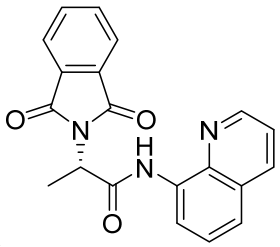


***DL*-1a**

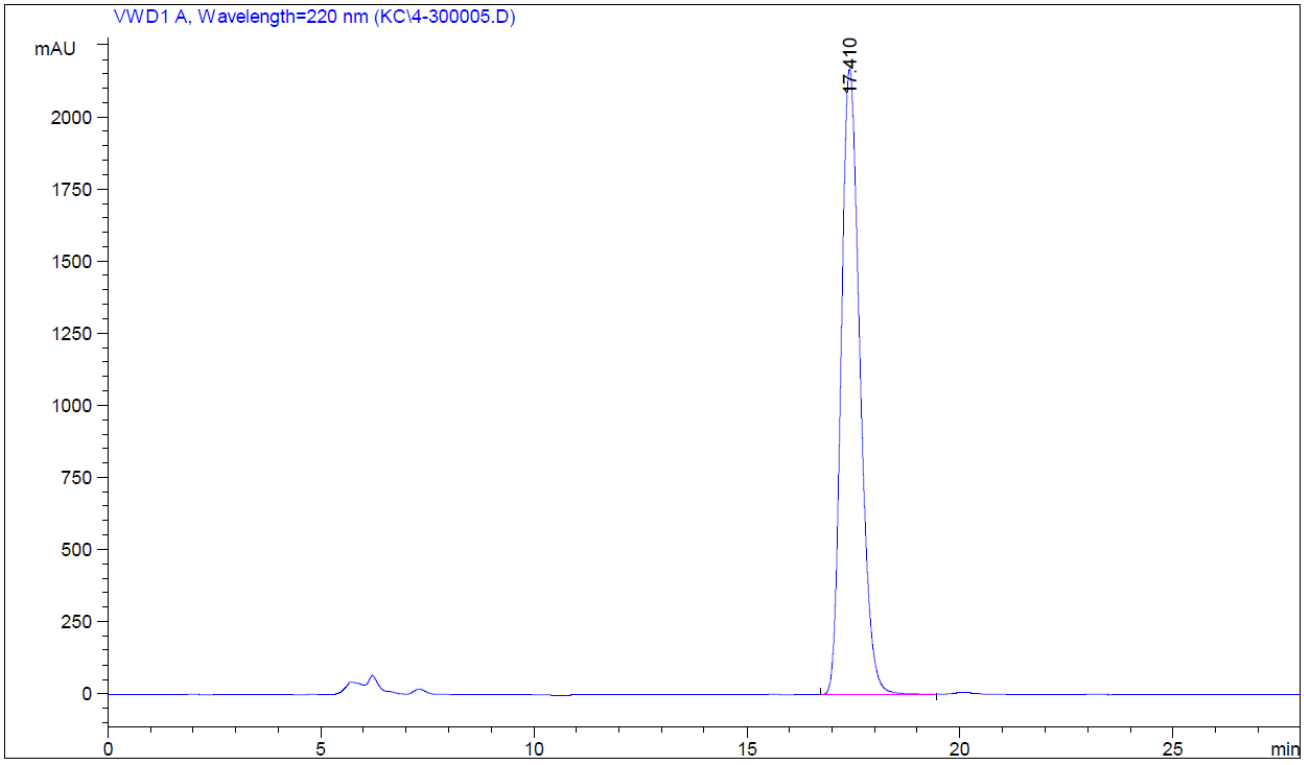


Area% report for *DL*-1a:

Retention Time (min)	Area (mAU*s)	Area %	Height (mAU)	Height %
16.944	1.83753e4	50.5516	615.89600	53.5397
19.388	1.79744e4	49.4484	534.45746	46.4603
Totals	3.63497e4	100.0000	1150.35345	100.0000



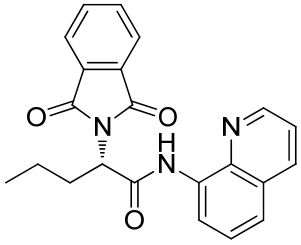
***L*-1a**



Area% report for *L*-1a:

Retention Time (min)	Area (mAU*s)	Area %	Height (mAU)	Height %
17.410	6.63528e4	100.0000	2165.16064	100.0000
Totals	6.63528e4	100.0000	2165.16064	100.0000

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (1b)

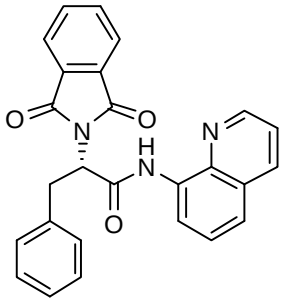


L-Norvaline (4.69 g, 40 mmol) and Na_2CO_3 (4.24 g, 40 mmol) were dissolved in water (100 mL) at room temperature and 8.76 g (40 mmol) of *N*-ethoxycarbonylphthalimide was added to the solution in small portions. The reaction was stirred for 1 hour, and then the aqueous solution was slowly acidified with aqueous HCl (6 M) until pH = 1 at 0 °C. Then the solution was extracted with dichloromethane (3×50 mL), and the organic phase was dried over anhydrous $MgSO_4$. Evaporation of organic solvent and purification by column chromatography in ether: ethyl acetate = 1:1gave (*S*)-2-phthalimidopentanoyl acid (9.48 g, 96%).

(*S*)-2-Phthalimidopentanoyl acid (5.93 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 8 h. After the reaction, dichloromethane and excess of thionyl chloride were removed by vacuum. The acid chloride was dissolved in dichloromethane (50 mL) and used for next reaction.

The compound **1b** was prepared according to **GP-1**. Purification by column chromatography in petroleum ether: ethyl acetate = 3:1 gave a white solid 6.68g (89%) of **1b**. This compound is known.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.93 – 8.49 (m, 2H), 8.13 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.90 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.56 – 7.45 (m, 2H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.15 (dd, *J* = 11.0, 5.2 Hz, 1H), 2.68 – 2.54 (m, 1H), 2.41 – 2.29 (m, 1H), 1.52 – 1.41 (m, 2H), 1.03 (t, *J* = 7.3 Hz, 3H).

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-3-phenyl-*N*-(quinolin-8-yl)propanamide (1c)

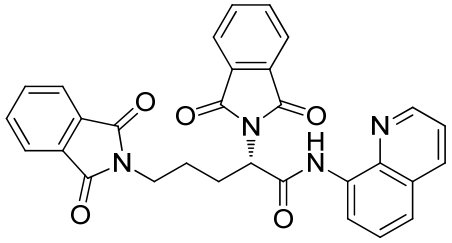


L-Phenylalanine (16.52 g, 0.10 mol) and Na_2CO_3 (10.60 g, 0.10 mol) were dissolved in water (100 mL) at room temperature and *N*-ethoxycarbonylphthalimide (21.91 g, 0.10 mol) was added to the solution in small portions. The reaction was stirred for 2 hours, then the aqueous solution was slowly acidified with aqueous HCl (6 M) until pH = 1 at 0 °C and white precipitate appeared slowly. Collecting and washing the precipitate with ethyl ether: petroleum ether = 1:2 (15 mL) gave (*S*)-3-phenyl-2-phthalimidopropionic acid (25.15 g, 85%).

(*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 5 h. After the reaction, dichloromethane and excess of thionyl chloride were removed by vacuum. The acid chloride was dissolved in dichloromethane (50 mL) and used for next reaction.

The compound **1c** was prepared according to **GP-1**. The mixture was dissolved in ethyl acetate (5 mL), then petroleum ether (20 mL) was added slowly, and white solid appeared slowly. Collecting and washing the precipitate with ethyl ether: petroleum ether = 1:5 (10 mL) gave **1c** (6.06 g). Evaporation of the filtrate collected after filtration, followed by column chromatography in petroleum ether: ethyl acetate = 5:2 gave 1.10 g of **1c**. The combined **1c** was obtained 7.16 g (85%) of a white solid. This compound is known.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.74 (dd, *J* = 6.4, 2.5 Hz, 1H), 8.61 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.54 – 7.48 (m, 2H), 7.39 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.19 – 7.14 (m, 1H), 5.45 (dd, *J* = 9.7, 6.9 Hz, 1H), 3.86 – 3.76 (m, 2H).

(*S*)-2,5-Bis(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (1d)



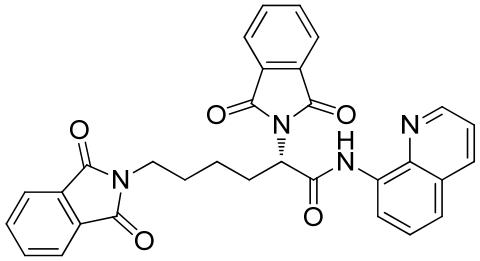
L-Ornithine hydrochloride (6.74 g, 40 mmol) and Na_2CO_3 (6.36 g, 60 mmol) were dissolved in water (100 mL) at room temperature and *N*-ethoxycarbonylphthalimide (17.52 g, 80 mmol) was added to the solution in small portions. The reaction was stirred for 2.5 hours, and then the aqueous solution was slowly acidified with aqueous HCl (6 M) until pH = 1 at 0 °C. Then the solution was extracted with dichloromethane (3×50 mL), and the organic phase was dried over anhydrous $MgSO_4$. The organic solvent was removed by evaporation. The mixture was dissolved in ethyl acetate (10 mL), then petroleum ether (30 mL) was added slowly, and white solid appeared slowly. Collecting and washing the precipitate with ethyl ether: petroleum ether = 1:5 (10 mL) gave (*S*)-2,5-diphthalimidopentanic acid (12.26 g, 78%).

(*S*)-2,5-Diphthalimidopentanic acid (9.41 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 8 h. After the reaction, dichloromethane and excess of thionyl chloride were removed by vacuum. The acid chloride was dissolved in dichloromethane (50 mL) and used for next reaction.

The compound **1d** was prepared according to **GP-1**. The mixture was dissolved ethyl acetate (5 mL), then petroleum ether (20 mL) added slowly, and white solid appeared slowly. Collecting and washing the precipitate with ethyl ether: petroleum ether = 1:5 (10 mL) gave **1d** (6.85 g). Evaporation of the filtrate collected after filtration, followed by column chromatography in petroleum ether: ethyl acetate = 3:2 gave 2.53 g of **1d**. The combined **1d** was obtained 9.38 g (85%) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.72 – 8.63 (m, 1H), 8.59 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.88 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.80 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H),

7.68 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.50 – 7.44 (m, 2H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.26 (dd, *J* = 11.1, 5.0 Hz, 1H), 3.88 – 3.75 (m, 2H), 2.72 – 2.61 (m, 1H), 2.51 – 2.40 (m, 1H), 1.89 – 1.78 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.44, 168.12, 166.61, 148.39, 138.58, 136.33, 134.38, 134.03, 133.94, 132.18, 131.88, 127.91, 127.35, 123.77, 123.35, 122.02, 121.70, 116.81, 54.55, 37.12, 26.08, 25.85.HRMS (EI) *m/z*: 518.1590 (M^+); calc.for $C_{30}H_{22}N_4O_5$: 518.1590.

(*S*)-2,6-Bis(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide (1e)

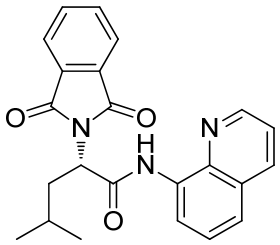


L-Lysine (5.85 g, 40 mmol) and Na_2CO_3 (4.24g, 40 mmol) were dissolved in water (100 mL) at room temperature and *N*-ethoxycarbonylphthalimide (17.52 g, 80 mmol) was added to the solution in small portions. The reaction was stirred for 3 hours, and then the aqueous solution was slowly aqueous acidified with HCl (6 M) until pH = 1 at 0 °C. Then the solution was extracted with dichloromethane (3×50 mL), and the organic phase was dried over anhydrous $MgSO_4$. Evaporation of organic solvent and purification by column chromatography in petroleum ether: ethyl acetate = 2:3 gave 12.04 g (74%) of (*S*)-2,6-diphthalimido-hexanoic acid.

(*S*)-2,6-Diphthalimidohexanoic acid (9.75 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 8 h. After the reaction, dichloromethane and excess of thionyl chloride were removed by vacuum. The acid chloride was dissolved in dichloromethane (50 mL) and used for next reaction.

The compound **1e** was prepared according to **GP-1**.Purification by column chromatography in petroleum ether: ethyl acetate = 3:2 gave 8.11 g (76%) of **1e**. This compound is known.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.75 – 8.43 (m, 2H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.87 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.67 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.52 – 7.43 (m, 2H), 7.39 (dd, *J* = 7.7, 4.1 Hz, 1H), 5.10 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.69 (t, *J* = 7.1 Hz, 2H), 2.69 – 2.54 (m, 1H), 2.52 – 2.39 (m, 1H), 1.93 – 1.82 (m, 1H), 1.80 – 1.72 (m, 1H), 1.58 – 1.41 (m, 2H).

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-4-methyl-*N*-(quinolin-8-yl)pentanamide (1f)

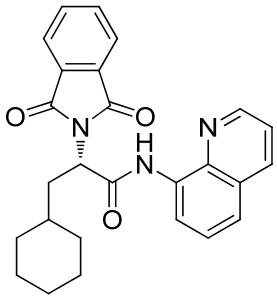


L-Leucine (5.25 g, 40 mmol) and Na_2CO_3 (4.24 g, 40 mmol) were dissolved in water (100 mL) at room temperature and *N*-ethoxycarbonylphthalimide (8.76 g, 40 mmol) was added to the solution in small portions. The reaction was stirred for 4 hour, and then the aqueous solution was slowly acidified with aqueous HCl (6 M) until pH = 1 at 0 °C. The solution was then extracted with dichloromethane (3×50 mL), and the organic phase was dried over anhydrous $MgSO_4$. Evaporation of organic solvent and purification by column chromatography in ether: ethyl acetate = 1:1 gave (*S*)-2-phthalimido-4-methyl-pentanoic acid (8.57 g, 82%).

(*S*)-2-Phthalimido-4-methyl-pentanoic acid (6.27 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 8 h. After the reaction, dichloromethane and excess of thionyl chloride were removed by vacuum. The acid chloride was dissolved in dichloromethane (50 mL) and used for next reaction.

The compound **1f** was prepared according to GP-1. Purification by column chromatography in petroleum ether: ethyl acetate = 3:1 gave a white solid 6.82g (88%) of **1f**. This compound is known.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.69 (dd, *J* = 5.3, 3.6 Hz, 1H), 8.66 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.87 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.49 – 7.42 (m, 2H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.23 (dd, *J* = 11.3, 4.9 Hz, 1H), 2.70 – 2.60 (m, 1H), 2.16 – 2.07 (m, 1H), 1.68 – 1.58 (m, 1H), 1.03 (dd, *J* = 10.6, 6.6 Hz, 6H).

(*S*)-3-Cyclohexyl-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)propanamide (1g)

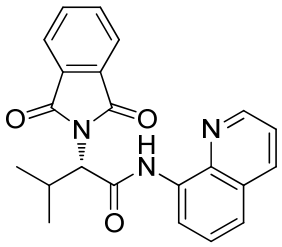


L-Cyclohexylalanine (6.85 g, 40 mmol) and Na_2CO_3 (4.24 g, 40 mmol) were dissolved in water (100 mL) at room temperature and *N*-ethoxycarbonylphthalimide (8.76 g, 40 mmol) was added to the solution in small portions. The reaction was stirred for 2 hours, and then the aqueous solution was slowly acidified with aqueous HCl (6 M) until pH = 1 at 0 °C. Then the solution was extracted with dichloromethane (3×50 mL), and the organic phase was dried over anhydrous $MgSO_4$. Evaporation of organic solvent and purification by column chromatography in ether: ethyl acetate = 1:1 gave (*S*)-3-cyclohexyl-2-phthalimidopropionic acid (10.30 g, 85%).

(*S*)-3-Cyclohexyl-2-phthalimidopropionic acid (7.23 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 8 h. After the reaction, dichloromethane and excess of thionyl chloride were removed by vacuum. The acid chloride was dissolved in dichloromethane (50 mL) and used for next reaction.

The compound **1g**was prepared according to GP-1. The mixture was dissolved ethyl acetate (5 mL), then petroleum ether (20 mL) was added slowly, and white solid appeared slowly. Collecting and washing the precipitate with ethyl ether: petroleum ether = 1:5 (10 mL) gave **1g** (5.44 g). Evaporation of the filtrate collected after filtration, followed by column chromatography in petroleum ether: ethyl acetate = 5:2 gave 1.83 g of **1g**. The combined **1g** was obtained 7.27 g (85%) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.77 – 8.59 (m, 2H), 8.10 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.51 – 7.43 (m, 2H), 7.39 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.25 (dd, *J* = 11.0, 5.1 Hz, 1H), 2.57 (ddd, *J* = 15.2, 11.1, 4.4 Hz, 1H), 2.20 (ddd, *J* = 14.2, 9.3, 5.2 Hz, 1H), 1.98 (d, *J* = 12.4 Hz, 1H), 1.80 – 1.66 (m, 3H), 1.63 (s, 1H), 1.37 – 1.28 (m, 1H), 1.23 – 0.98 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.29, 167.57, 148.45, 138.62, 136.38, 134.31, 134.08, 132.02, 127.96, 127.40, 123.72, 121.97, 121.73, 116.77, 53.06, 36.31, 34.99, 33.83, 32.18, 26.52, 26.29, 26.10.HRMS (EI) *m/z*: 427.1893 (M^+); calc.for $C_{26}H_{25}N_3O_3$: 427.1896.

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-3-methyl-*N*-(quinolin-8-yl)butanamide (1h)



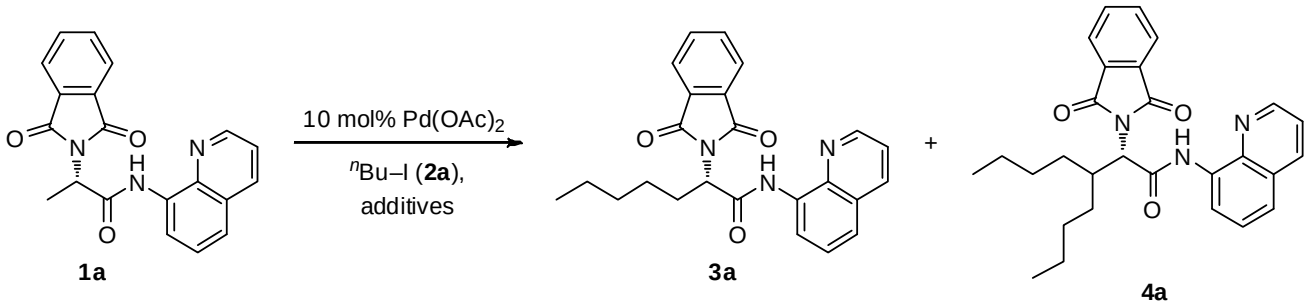
L-Valine (4.69 g, 40 mmol) and Na_2CO_3 (4.24 g, 40 mmol) were dissolved in water (100 mL) at room temperature and 8.76 g (40 mmol) of *N*-ethoxycarbonylphthalimide was added to the solution in small portions. The reaction was stirred for 5 hour, and then the aqueous solution was slowly acidified with aqueous HCl (6 M) until pH = 1 at 0 °C. Then the solution was extracted with dichloromethane (3×50 mL), and the organic phase was dried over anhydrous $MgSO_4$. Evaporation of organic solvent and purification by column chromatography in ether: ethyl acetate = 1:1 gave (*S*)-2-phthalimido3-methyl-butyric acid (8.88 g, 90%).

(*S*)-2-Phthalimidopentanoyl acid (5.93 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 8 h. After the reaction, dichloromethane and excess of thionyl chloride were removed by vacuum. The acid chloride was dissolved in dichloromethane (50 mL) and used for next reaction.

The compound **1h** was prepared according to **GP-1**. Purification by column chromatography in petroleum ether: ethyl acetate = 3:1 gave a white solid 6.05g (81%) of **1h**. This compound is known.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.84 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.79 – 8.72 (m, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.53 – 7.47 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.69 (d, *J* = 10.8 Hz, 1H), 3.30 – 3.16 (m, 1H), 1.23 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H).

Optimization of Reaction Conditions

Optimization of Reaction Conditions



Entry	Ag salts (eq)	Equiv of ^{n}Bu-I	Additive (eq)	Solvents	Temp. (^{o}C)	Time (h)	Results		
							3a	4a	RSM*
1	/	3.0	K_2CO_3 (1.5)	DCE	90	24	5	0	>60
2	/	3.0	K_3PO_4 (1.5)	DCE	90	24	<5	0	>60
3	/	3.0	KF (1.5)	DCE	90	24	<5	0	>60
4	/	3.0	KOPh (1.5)	DCE	90	24	0	0	~40
5	/	3.0	KNPhth (1.5)	DCE	90	24	<2	0	>60
6	/	3.0	Na_2CO_3 (1.5)	DCE	90	24	<10	0	>60
7	/	3.0	NaOAc (1.5)	DCE	90	24	<10	0	>60
8	/	3.0	$NaHCO_3$ (1.5)	DCE	90	24	<5	0	>60
9	/	3.0	LiOAc (1.5)	DCE	90	24	<5	0	>60
10	AgOAc (2.0)	2.0	/	DCE	100	24	18	3	>60
11	$AgBF_4$ (2.0)	2.0	/	DCE	100	24	0	0	>40
12	$AgSbF_6$ (2.0)	2.0	/	DCE	100	24	0	0	>50
13	AgOTf (2.0)	2.0	/	DCE	100	24	trace	trace	~20
14	AgTFA (2.0)	2.0	/	DCE	100	24	15	0	>70
15	$AgClO_4$ (2.0)	2.0	/	DCE	100	24	<5	0	~20
16	Ag_2CO_3 (2.0)	2.0	/	DCE	100	24	10	3	>70
17	Ag_2O(2.0)	2.0	/	DCE	100	24	12	3	>60
18	AgF (2.0)	2.0	/	DCE	100	24	<10	0	>60
19	Ag_2SO_4 (2.0)	2.0	/	DCE	100	24	<5	0	~40
20	AgOAc (2.5)	3.0	NaOAc (2.5eq)	DCE	60	24	15	3	>60
21	AgTFA (2.5)	3.0	NaOAc (2.5eq)	DCE	60	24	23	0	>60
22	AgTFA (2.5)	3.0	/	PhH	60	24	18	0	>60
23	AgTFA (2.5)	3.0	/	Acetone	60	24	0	0	>70
24	AgTFA (2.5)	3.0	/	THF	60	24	9	0	>70

25	AgTFA (2.5)	3.0	/	PhMe	60	24	13	0	>70
26	Ag_2CO_3 (1.25)	5.0	/	DCE/^{t}BuOH = 4:1	75	20	10	5	>70
27	Ag_2CO_3 (1.25)	5.0	NaCl (1.25)	DCE/^{t}BuOH = 4:1	75	20	10	5	>70
28	Ag_2CO_3 (1.25)	5.0	NaOAc (1.25)	DCE/^{t}BuOH = 4:1	75	20	11	5	>70
29	Ag_2CO_3 (1.25)	5.0	KOCN (1.25)	DCE/^{t}BuOH = 4:1	75	20	19	26	44
30	Ag_2CO_3 (1.25)	5.0	KCN (1.25)	DCE/^{t}BuOH = 4:1	75	20	11	3	>70
31	Ag_2CO_3 (1.25)	5.0	KF (1.25)	DCE/^{t}BuOH = 4:1	75	20	9	5	>70
32	Ag_2CO_3 (1.25)	5.0	$NaBF_4$ (1.25)	DCE/^{t}BuOH = 4:1	75	20	8	3	>70
33	Ag_2O (1.25)	5.0	KOCN (1.25)	DCE/^{t}BuOH = 4:1	75	20	21	7	51
34	AgF (1.25)	5.0	KOCN (1.25)	DCE/^{t}BuOH = 4:1	75	20	30	11	59
35	AgTFA (1.25)	5.0	KOCN (1.25)	DCE/^{t}BuOH = 4:1	75	20	29	0	66
36	AgOCN (1.25)	5.0	KOCN (1.25)	DCE/^{t}BuOH = 4:1	75	20	34	14	50
37	AgSCN (1.25)	5.0	KOCN (1.25)	DCE/^{t}BuOH = 4:1	75	20	0	0	>95
38	AgOCN (1.25)	5.0	KOCN (1.25) + LiCl(1.25)	DCE/^{t}BuOH = 4:1	75	20	50	0	48
39	Ag_2CO_3 (1.25)	5.0	KOCN (1.25) + LiCl(1.25)	DCE/^{t}BuOH = 4:1	75	20	33	18	47
40	Ag_2CO_3 (1.25)	5.0	PivOH (1.25)	DCE/^{t}BuOH = 4:1	75	20	28	5	57
41	Ag_2CO_3 (1.25)	5.0	Ph_3CCOOH (1.25)	DCE/^{t}BuOH = 4:1	75	20	49	5	40
42	Ag_2CO_3 (1.25)	5.0	MesCOOH (1.25)	DCE/^{t}BuOH = 4:1	75	20	34	6	44
43	Ag_2CO_3 (1.25)	5.0	TsOH (1.25)	DCE/^{t}BuOH = 4:1	75	20	0	0	>70
44	Ag_2CO_3 (1.25)	5.0	$Ph_2CHCOOH$ (1.25)	DCE/^{t}BuOH = 4:1	75	20	38	4	46
45	Ag_2CO_3 (1.25)	5.0	Bz-N-Leu-OH (1.25)	DCE/^{t}BuOH = 4:1	75	20	21	4	>50
46	Ag_2CO_3 (1.25)	5.0	Boc-N-gly-OH (1.25)	DCE/^{t}BuOH = 4:1	75	20	18	6	>60
47	Ag_2CO_3 (1.25)	5.0	Boc-N-Ile-OH (1.25)	DCE/^{t}BuOH = 4:1	75	20	16	7	>70
48	Ag_2CO_3 (1.25)	5.0	BINA-POOH (1.25)	DCE/^{t}BuOH = 4:1	75	20	78	1	15
49	Ag_2CO_3 (1.25)	5.0	$(BnO)_2POOH$ (1.25)	DCE/^{t}BuOH = 4:1	75	20	76	4	7
50	Ag_2CO_3 (1.25)	5.0	BINA-POOH (0.5)	DCE/^{t}BuOH = 4:1	75	20	58	2	27
51	Ag_2CO_3 (1.25)	5.0	$(BnO)_2POOH$ (0.5)	DCE/^{t}BuOH = 4:1	75	20	72	5	9
52	Ag_2O (1.25)	5.0	$(BnO)_2POOH$ (0.5)	DCE/^{t}BuOH = 4:1	75	20	28	4	50
53	AgOCN (1.25)	5.0	$(BnO)_2POOH$ (0.5)	DCE/^{t}BuOH = 4:1	75	20	49	0	48
54	AgF (1.25)	5.0	$(BnO)_2POOH$ (0.5)	DCE/^{t}BuOH = 4:1	75	20	33	0	64
55	$AgNO_3$ (1.25)	5.0	$(BnO)_2POOH$ (0.5)	DCE/^{t}BuOH = 4:1	75	20	0	0	>80
56	Ag_2SO_4 (1.25)	5.0	$(BnO)_2POOH$ (0.5)	DCE/^{t}BuOH = 4:1	75	20	12	0	>60
57	AgSCN (1.25)	5.0	$(BnO)_2POOH$ (0.5)	DCE/^{t}BuOH = 4:1	75	20	5	0	>80

58	AgOAc (1.25)	5.0	$(BnO)_2POOH$ (0.5)	DCE/^{t}BuOH = 4:1	75	20	38	6	41
59	Ag_2CO_3 (1.25)	5.0	$(BnO)_2POOH$ (0.5) + LiCl (1.25)	DCE/^{t}BuOH = 4:1	75	20	53	5	29
60	Ag_2CO_3 (1.25)	5.0	$(BnO)_2POOH$ (0.5) + KOCN (1.25)	DCE/^{t}BuOH = 4:1	75	20	22	19	43
61	Ag_2CO_3 (1.25)	5.0	$(BnO)_2POOH$ (0.5) + KOCN (1.25) + LiCl (1.25)	DCE/^{t}BuOH = 4:1	75	20	54	0	31
62	Ag_2CO_3 (1.25)	5.0	$(BnO)_2POOH$ (0.5)	DCE/^{t}BuOH = 4:1	75	20	72	5	9
63	Ag_2CO_3 (1.0)	3.0	$(BnO)_2POOH$ (0.4)	DCE/^{t}BuOH = 4:1	75	2	70	5	10
64	Ag_2CO_3 (1.0)	3.0	$(BnO)_2POOH$ (0.4)	DCE/^{t}BuOH = 4:1	65	2	70	5	11
65	Ag_2CO_3 (1.0)	3.0	$(BnO)_2POOH$ (0.4)	DCE/^{t}BuOH = 4:1	55	2	69	5	11
66	Ag_2CO_3 (1.0)	3.0	$(BnO)_2POOH$ (0.4)	DCE/^{t}BuOH = 4:1	40	4	46	0	44
67	Ag_2CO_3 (1.0)	2.0	$(BnO)_2POOH$ (0.4)	DCE/^{t}BuOH = 4:1	50	2	64	0	28
68	Ag_2CO_3 (0.8)	2.0	$(BnO)_2POOH$ (0.3)	DCE/^{t}BuOH = 2:1	75	2	78	6	7
69	Ag_2CO_3 (0.8)	1.5	$(BnO)_2POOH$ (0.3)	DCE/^{t}BuOH = 3:2	75	2	80	3	4
70	Ag_2CO_3 (0.8)	1.5	$(BnO)_2POOH$ (0.3)	DCE/^{t}BuOH = 1:1	75	2	80	8	0
71	Ag_2CO_3 (0.8)	2.0	$(BnO)_2POOH$ (0.3)	DCE/^{t}BuOH = 2:1	50	2	81	0	8
72	Ag_2CO_3 (0.8)	1.5	$(BnO)_2POOH$ (0.3)	DCE/^{t}BuOH = 1:1	50	2	85	0	3

*RSM = Recovered Starting Material

General Procedure (GP-2) for Alkylation of Primary C(sp^3)–H Bonds

To a 30- mL resealable Schlenk flask was added *N*-phthaloyl-alanine 8-aminoquinoline amide (**1**) (0.2 mmol, overall concentration = 0.133 mol/L), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), alkyl iodide (**2**) or alkyl bromine (**2'**) (0.3-0.6 mmol), Ag_2CO_3 (0.16-0.25 mmol), $(BnO)_2POOH$ (0.06-0.08 mmol), DCE/*t*-BuOH (1.5 mL). The flask was then charged with N_2. The mixture was stirred at 50 to 75°C for 2 to 12 hours under N_2. After cooling to room temperature, the reaction was diluted with dichloromethane (5 mL) and then filtered through a pad of Celite and washed by dichloromethane (30 mL). Evaporation of organic solvent and purification by column chromatography gave the corresponding product.

The reaction conditions for alkyl iodide (**2**):

(**a**) **1** (0.2mmol, 1.0eq), **2** (1.5eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.8eq), $(BnO)_2POOH$ (0.3eq), DCE/^{t}BuOH = 1:1, 50°C, 2h;

(**b**) **1** (0.2mmol, 1.0eq), **2** (2.5eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (1.25eq), $(BnO)_2POOH$ (0.4eq), DCE/^{t}BuOH = 1:2, 60°C, 12h;

(**c**) **1** (0.2mmol, 1.0eq), **2** (1.5eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.8eq), $(BnO)_2POOH$ (0.3eq), DCE/^{t}BuOH = 1:1, 75°C, 2h;

(**d**) **1** (0.2mmol, 1.0eq), **2** (2.0eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (1.0eq), $(BnO)_2POOH$ (0.4eq), DCE/^{t}BuOH = 1:1, 65°C, 4h;

The reaction conditions for alkyl bromine (**2'**):

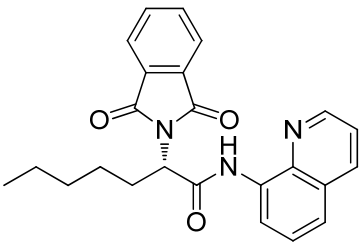
(**e**) **1** (0.2mmol, 1.0eq), **2'** (2.0eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (1.0eq), $(BnO)_2POOH$ (0.3eq), DCE/^{t}BuOH = 1:1, 75°C, 16h;

(**f**) **1** (0.2mmol, 1.0eq), **2'** (3.0eq), $Pd(OAc)_2$ (15 mol%), Ag_2CO_3 (1.5eq), $(BnO)_2POOH$ (0.5eq), DCE/^{t}BuOH = 1:1, 90°C, 24h;

(**g**) **1** (0.2mmol, 1.0eq), **2'** (1.5eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.8eq), $(BnO)_2POOH$ (0.3eq), DCE/^{t}BuOH = 1:1, 60°C, 4h;

(**h**) **1** (0.2mmol, 1.0eq), **2'** (1.5eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.8eq), $(BnO)_2POOH$ (0.3eq), DCE/^{t}BuOH = 1:1, 90°C, 14h.

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)heptanamide (3a)



The compound **3a** was prepared according to the **GP-2** under condition (**a**), (**f**) and purified by column chromatography in petroleum ether: dichloromethane: acetone = 6:3:1. **3a** was obtained as a white solid

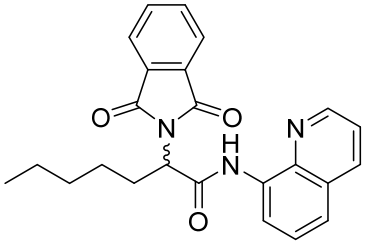
(68.4 mg, 85%) under condition (**a**); (47.8 mg, 60%) under condition (**f**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.78 – 8.64 (m, 2H), 8.13 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.90 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.54 – 7.46 (m, 2H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.13 (dd, *J* = 10.9, 5.3 Hz, 1H), 2.64 – 2.52 (m, 1H), 2.44 – 2.33 (m, 1H), 1.50 – 1.30 (m, 6H), 0.88 (t, *J* = 7.1 Hz, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 168.26, 167.23, 148.46, 138.65, 136.39, 134.33, 134.09, 131.98, 127.98, 127.42, 123.72, 122.00, 121.74, 116.82, 55.44, 31.34, 28.84, 26.49, 22.59, 14.10; HRMS (EI) *m/z*: 401.1740 (M^+); calc.for $C_{24}H_{23}N_3O_3$: 401.1739; HPLC Chiralpack® AS-H column followed by AD-H column (*n*-hexane/isopropanol = 60:40, 0.5 mL/min), t_r = 37.872 min (major), 42.050 min (minor), 99.1% ee (**condition a**), 98.9% ee (**condition f**).

Chiral HPLC Data

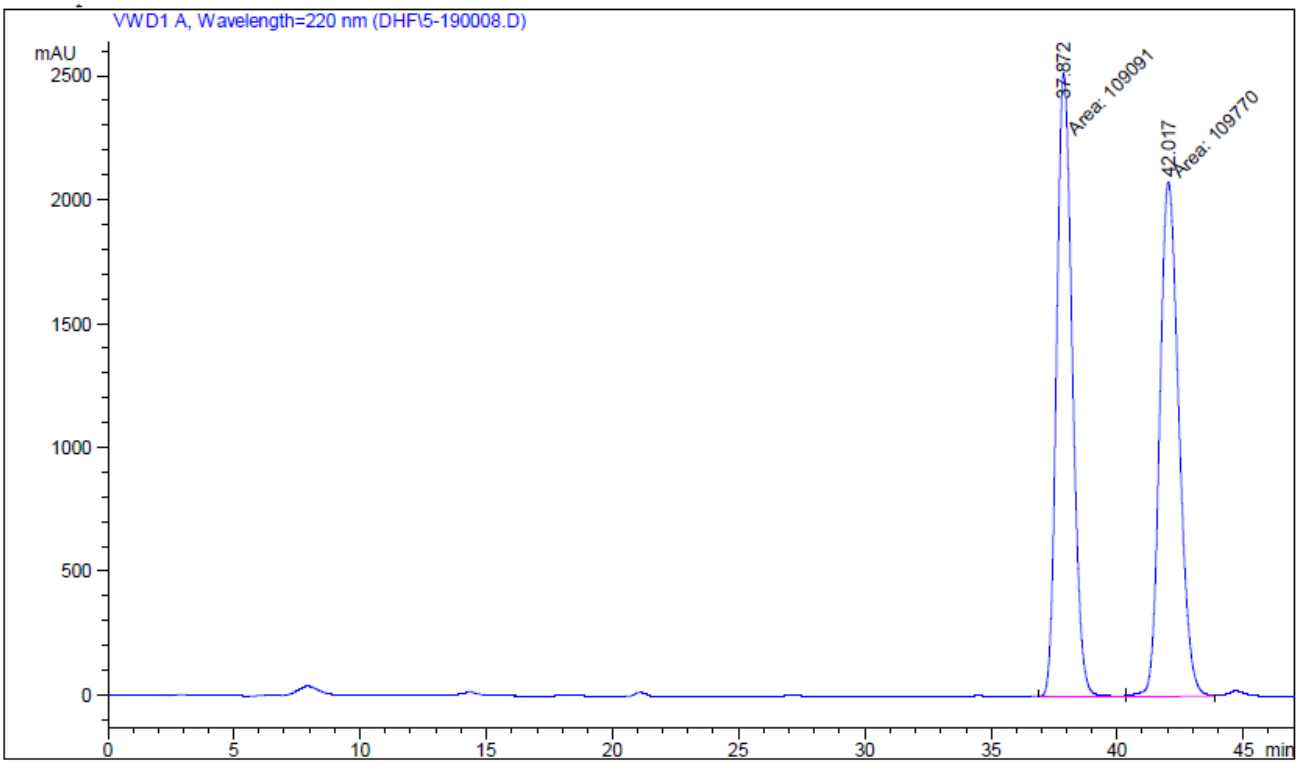
HPLC Conditions:

Chiral stationary phase: Chiralpack® AS-H followed by Chiralpack® AD-H, *n*-hexane/isopropanol = 60:40, 0.5 mL/min

Signal: VWD1A, Wavelength = 220 nm

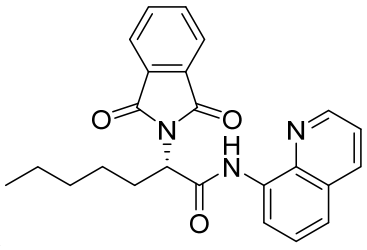


***DL*-3a**

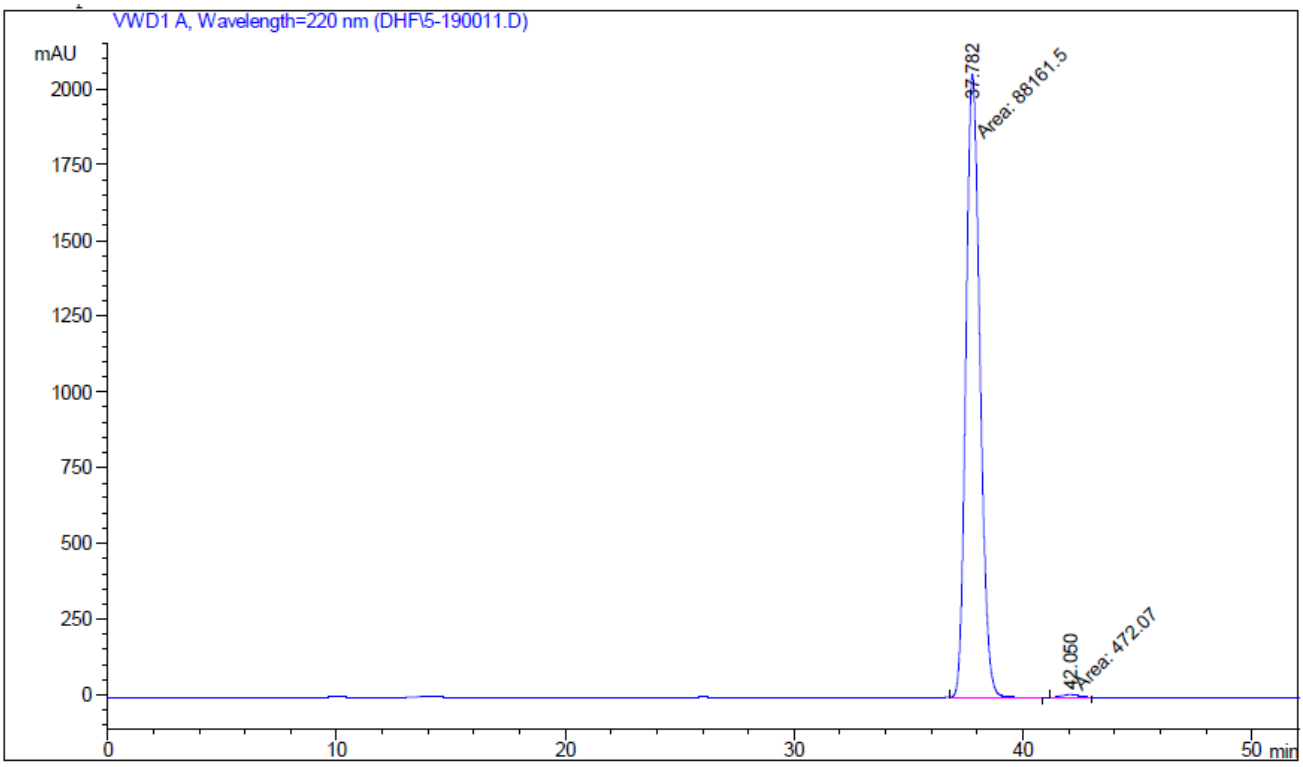


Area% report for *DL*-3a:

Retention Time (min)	Area (mAU*s)	Area %	Height (mAU)	Height %
37.872	1.09091e5	49.8449	2520.27319	54.7888
42.017	1.09770e5	50.1551	2079.70850	45.2112
Totals	2.18861e5	100.0000	4599.98169	100.00

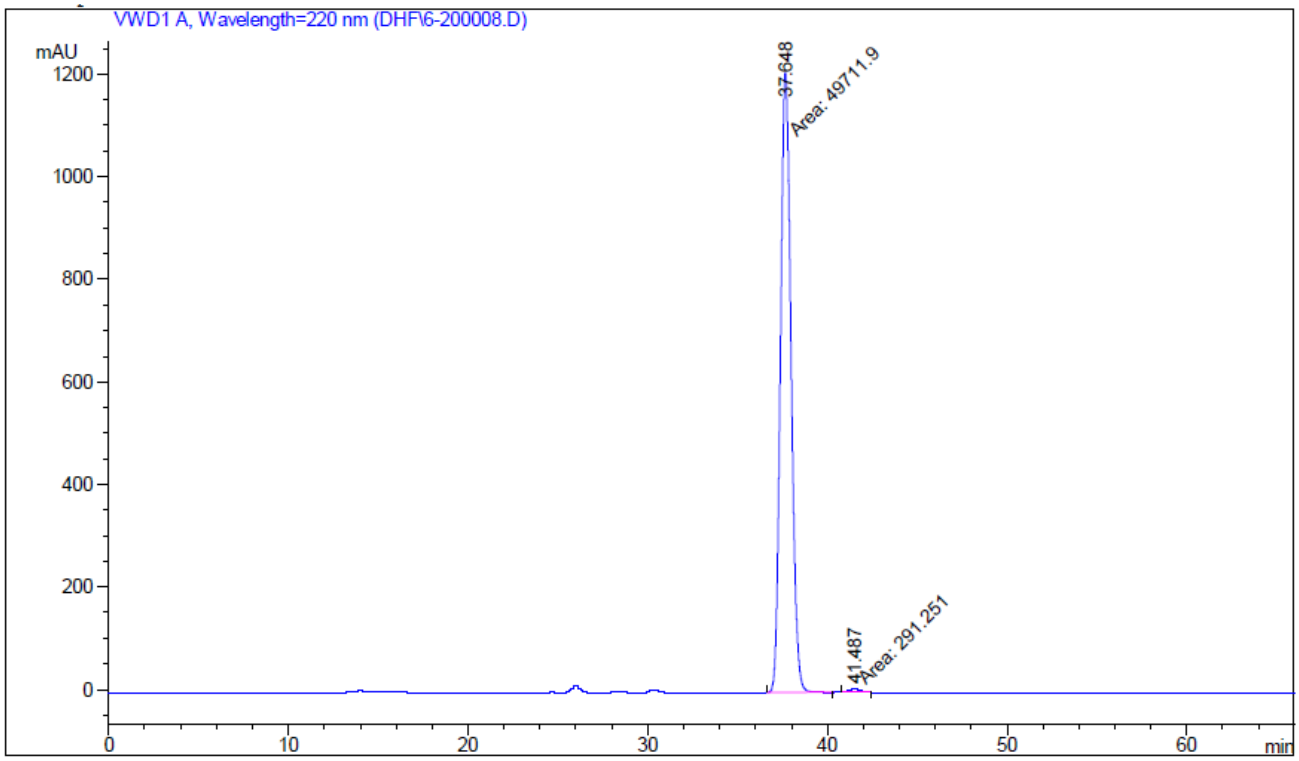


***L*-3a**



Area% report for *L*-3a obtained under condition (a):

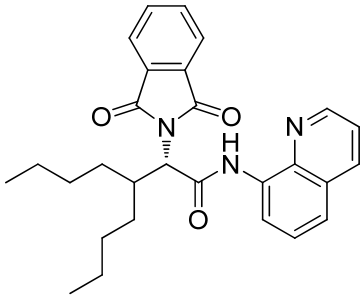
Retention Time (min)	Area (mAU*s)	Area %	Height (mAU)	Height %
37.782	8.81615e4	99.4676	2060.91479	99.5543
42.050	472.07037	0.5326	9.22753	0.4457
Totals	8.86336e4	100.0000	2070.14233	100.0000



Area% report for *L*-3aobtained under condition (f):

Retention Time (min)	Area (mAU*s)	Area %	Height (mAU)	Height %
37.648	4.97119e4	99.4175	1211.19080	99.4823
41.487	291.25140	0.5825	6.30312	0.5177
Totals	5.00031e4	100.0000	1217.49391	100.0000

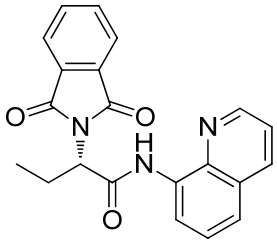
(*S*)-3-Butyl-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)heptanamide (4a)



The compound **4a** was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.85 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.78 – 8.72 (m, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.52 – 7.48 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 3.11 – 2.98 (m, 1H), 1.59 – 1.42 (m, 4H), 1.35 – 1.13 (m, 8H), 0.88 – 0.79 (m, 6H); ^{13}C NMR (101 MHz,

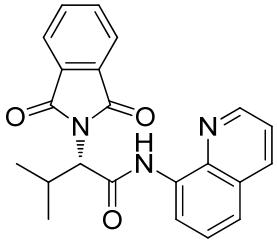
$CDCl_3$) δ 168.37, 167.26, 148.60, 138.87, 136.27, 134.45, 134.35, 131.76, 128.03, 127.36, 123.75, 122.05, 121.74, 117.15, 60.29, 36.15, 29.80, 29.15, 28.35, 27.49, 23.13, 23.06, 14.12, 14.08; HRMS (EI) *m/z*: 457.2370 (M^+); calc.for $C_{28}H_{31}N_3O_3$: 457.2365.

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)butanamide (3b)



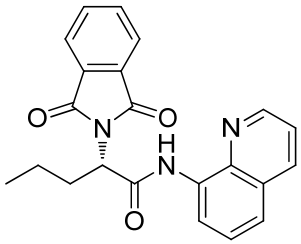
The compound **3b** was prepared according to the **GP-2** under condition (**a**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3b** was obtained as a white solid (39.7 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.71 (dd, *J* = 5.4, 3.6 Hz, 1H), 8.69 (dd, *J* = 4.1, 1.3 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.89 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.52 – 7.45 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.05 (dd, *J* = 10.9, 5.4 Hz, 1H), 2.66 – 2.53 (m, 1H), 2.53 – 2.41 (m, 1H), 1.07 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.26, 167.03, 148.43, 138.59, 136.37, 134.32, 134.02, 131.91, 127.94, 127.37, 123.68, 122.00, 121.72, 116.78, 56.87, 22.28, 11.29; HRMS (EI) *m/z*: 359.1267 (M^+); calc.for $C_{21}H_{17}N_3O_3$: 359.1270.

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-3-methyl-*N*-(quinolin-8-yl)butanamide (3b')



The compound **3b'** was obtained as a white solid (31.5 mg, 42%). This compound is the same as **1h**.

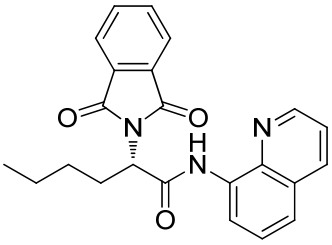
(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (3c)



The compound **3c** was prepared according to the **GP-2** under condition (**a**), (**f**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3c** was obtained as a white

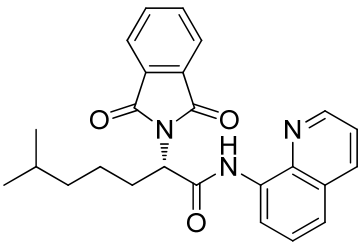
solid (59.2 mg, 79%) under condition (**a**); (40.8 mg, 55%) under condition (**f**). This compound is the same as **1b**.

(***S***)-**2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide** (**3d**)



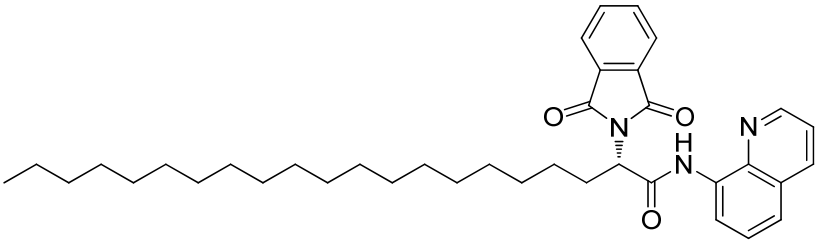
The compound **3d** was prepared according to the **GP-2** under condition (**a**), (**f**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3-d** was obtained as a white solid (65.3 mg, 84%) under condition (**a**); (41.9mg, 54%) under condition (**f**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.71 (dd, *J* = 5.6, 3.4 Hz, 1H), 8.69 – 8.64 (m, 1H), 8.13 – 8.07 (m, 1H), 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.51 – 7.45 (m, 2H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.12 (dd, *J* = 10.9, 5.3 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.45 – 2.35 (m, 1H), 1.54 – 1.32 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.20, 167.17, 148.40, 138.55, 136.33, 134.29, 134.00, 131.90, 127.91, 127.33, 123.65, 121.97, 121.69, 116.73, 55.34, 28.86, 28.53, 22.25, 13.99; HRMS (EI) *m/z*: 387.1576 (M^+);calc.for $C_{23}H_{21}N_3O_3$: 387.1583.

(***S***)-**2-(1,3-Dioxoisoindolin-2-yl)-6-methyl-N-(quinolin-8-yl)heptanamide** (**3e**)



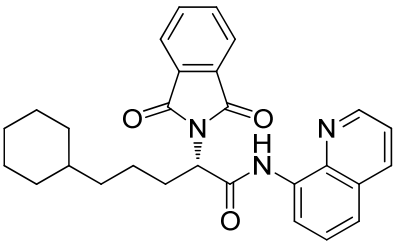
The compound **3e** was prepared according to the **GP-2** under condition (**a**), (**f**)and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3-e** was obtained as a white solid (71.0 mg, 85%) under condition (**a**); (35.4 mg, 43%) under condition (**f**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.71 (dd, *J* = 5.4, 3.6 Hz, 1H), 8.67 (dd, *J* = 4.2, 1.3 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.51 – 7.43 (m, 2H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.13 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.64 – 2.51 (m, 1H), 2.43 – 2.31 (m, 1H), 1.60 – 1.50 (m, 1H), 1.49 – 1.37 (m, 2H), 1.36 – 1.27 (m, 2H), 0.85 (dd, *J* = 6.6, 4.9 Hz, 6H);^{13}C NMR (101 MHz, $CDCl_3$) δ 168.20, 167.16, 148.39, 138.54, 136.33, 134.29, 134.00, 131.88, 127.90, 127.32, 123.64, 121.96, 121.69, 116.73, 55.36, 38.30, 29.05, 27.85, 24.58, 22.75, 22.44; HRMS (EI) *m/z*: 415.1903 (M^+); calc.for $C_{25}H_{25}N_3O_3$: 415.1896.

(***S***)-**2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)henicosanamide** (**3f**)



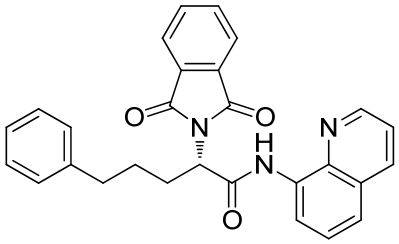
The compound **3f** was prepared according to the **GP-2** under condition (**a**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3f** was obtained as a white solid (103.4 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.71 (dd, *J* = 5.8, 3.1 Hz, 1H), 8.69 – 8.61 (m, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 7.87 (dd, *J* = 5.2, 2.2 Hz, 2H), 7.72 (dd, *J* = 5.3, 2.5 Hz, 2H), 7.47 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.37 (dd, *J* = 8.1, 4.2 Hz, 1H), 5.13 (dd, *J* = 10.8, 5.3 Hz, 1H), 2.66 – 2.52 (m, 1H), 2.47 – 2.32 (m, 1H), 1.48 – 1.37 (m, 4H), 1.28 – 1.21 (m, 28H), 0.87 (t, *J* = 6.7 Hz, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 168.16, 167.15, 148.35, 138.53, 136.29, 134.24, 134.01, 131.90, 127.89, 127.31, 123.61, 121.93, 121.65, 116.72, 55.36, 31.99, 29.77, 29.74, 29.72, 29.71, 29.66, 29.59, 29.48, 29.43, 29.11, 28.81, 26.76, 22.75, 14.19; HRMS (EI) *m/z*: 597.3950 (M +); calc.for $C_{38}H_{51}N_3O_3$: 597.3930.

(*S*)-5-Cyclohexyl-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)pentanamide (3g)



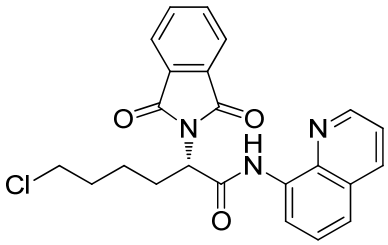
The compound **3g** was prepared according to the **GP-2** under condition (**a**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3g** was obtained as a colorless oil (69.3 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.70 (dd, *J* = 5.3, 3.7 Hz, 1H), 8.67 (dd, *J* = 3.9, 2.0 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.88 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.38 (dd, *J* = 8.2, 4.0 Hz, 1H), 5.13 (dd, *J* = 10.8, 5.3 Hz, 1H), 2.65 – 2.50 (m, 1H), 2.42 – 2.30 (m, 1H), 1.67 – 1.57 (m, 5H), 1.54 – 1.38 (m, 2H), 1.36 – 1.25 (m, 2H), 1.23 – 1.07 (m, 4H), 0.89 – 0.80 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.19, 167.17, 148.38, 138.53, 136.31, 134.27, 133.99, 131.88, 127.89, 127.30, 123.63, 121.95, 121.68, 116.72, 55.36, 37.47, 36.84, 33.47, 33.19, 29.10, 26.68, 26.40, 26.37, 24.05; HRMS (EI) *m/z*: 455.2204 (M^+); calc.for $C_{28}H_{29}N_3O_3$: 455.2209.

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-5-phenyl-*N*-(quinolin-8-yl)pentanamide (3h)



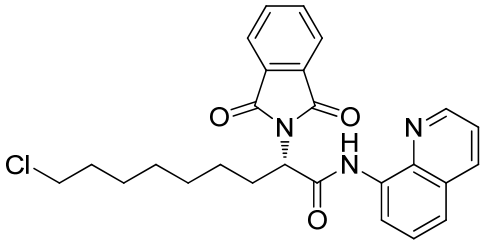
The compound **3h** was prepared according to the **GP-2** under condition (**b**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3h** was obtained as a white solid (63.2 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.72 (dd, *J* = 5.2, 3.5 Hz, 1H), 8.69 – 8.54 (m, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.89 (dd, *J* = 4.9, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.1, 3.1 Hz, 2H), 7.54 – 7.46 (m, 2H), 7.40 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.34 – 7.13 (m, 5H), 5.18 (dd, *J* = 10.9, 5.2 Hz, 1H), 2.84 – 2.71 (m, 2H), 2.70 – 2.60 (m, 1H), 2.53 – 2.40 (m, 1H), 1.84 – 1.75 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.17, 166.93, 148.39, 141.65, 138.54, 136.34, 134.33, 133.96, 131.86, 128.51, 128.49, 127.91, 127.34, 126.03, 123.69, 122.01, 121.71, 116.75, 55.08, 35.30, 28.57, 28.42; HRMS (EI) *m/z*: 449.1738 (M +); calc.for $C_{28}H_{23}N_3O_3$: 449.1739.

(*S*)-6-Chloro-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hexanamide (3i)



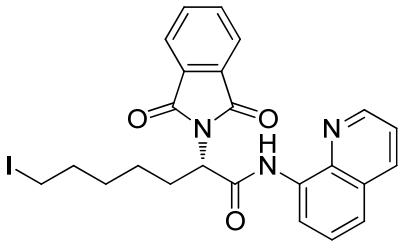
The compound **3i** was prepared according to the **GP-2** under condition (**d**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3i** was obtained as a colorless oil (55.4 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.69 (dd, *J* = 5.2, 3.8 Hz, 1H), 8.65 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.52 – 7.45 (m, 2H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.13 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.53 (t, *J* = 6.6 Hz, 2H), 2.68 – 2.54 (m, 1H), 2.48 – 2.37 (m, 1H), 2.00 – 1.80 (m, 2H), 1.68 – 1.49 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.15, 166.80, 148.43, 138.52, 136.36, 134.41, 133.88, 131.82, 127.91, 127.32, 123.73, 122.07, 121.73, 116.76, 55.03, 44.65, 31.96, 28.07, 24.06; HRMS (EI) *m/z*: 421.1191 (M^+); calc.for $C_{23}H_{20}ClN_3O_3$: 421.1193.

(*S*)-9-Chloro-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)nonanamide (3j)



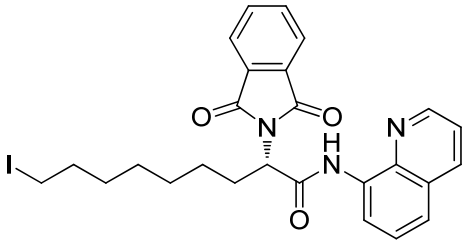
The compound **3j** was prepared according to the **GP-2** under condition (**a**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3j** was obtained as a colorless oil (78.2 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.70 (dd, *J* = 5.3, 3.7 Hz, 1H), 8.67 – 8.60 (m, 1H), 8.14 – 8.04 (m, 1H), 7.93 – 7.81 (m, 2H), 7.77 – 7.68 (m, 2H), 7.51 – 7.42 (m, 2H), 7.38 (dd, *J* = 4.2, 1.2 Hz, 1H), 5.12 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.48 (t, *J* = 6.7 Hz, 2H), 2.65 – 2.51 (m, 1H), 2.44 – 2.32 (m, 1H), 1.78 – 1.65 (m, 2H), 1.53 – 1.26 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.17, 167.07, 148.39, 138.49, 136.32, 134.31, 133.93, 131.82, 127.87, 127.28, 123.63, 121.98, 121.68, 116.70, 55.26, 45.11, 32.53, 28.86, 28.70, 28.64, 26.74, 26.57; HRMS (EI) *m/z*: 463.1668 (M^+); calc.for $C_{26}H_{26}ClN_3O_3$: 463.1663.

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-7-iodo-*N*-(quinolin-8-yl)heptanamide (3k)



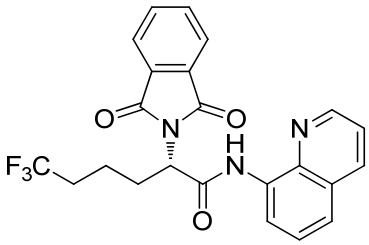
The compound **3k**was prepared according to the **GP-2** under condition (**d**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3k** was obtained as a colorless oil (39.0 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.74 – 8.65 (m, 2H), 8.13 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.90 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.52 – 7.47 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.12 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.16 (t, *J* = 7.0 Hz, 2H), 2.64 – 2.52 (m, 1H), 2.46 – 2.35 (m, 1H), 1.90 – 1.78 (m, 2H), 1.60 – 1.39 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.22, 166.96, 148.48, 138.60, 136.41, 134.41, 133.98, 131.91, 127.97, 127.40, 123.77, 122.07, 121.75, 116.83, 55.21, 33.30, 30.03, 28.65, 25.76, 6.75; HRMS (EI) *m/z*: 527.0714 (M^+); calc.for $C_{24}H_{22}IN_3O_3$: 527.0706.

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-9-iodo-*N*-(quinolin-8-yl)nonanamide (3l)



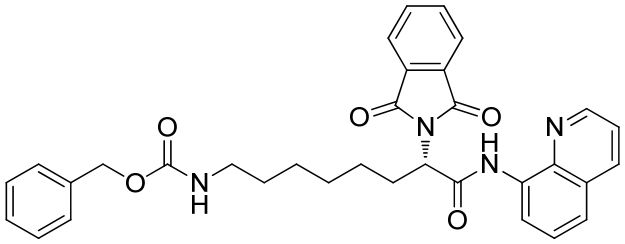
The compound **3l** was prepared according to the **GP-2** under condition (**a**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3l** was obtained as a colorless oil (48.6 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.70 (dd, *J* = 5.2, 3.8 Hz, 1H), 8.68 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.89 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.53 – 7.46 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.12 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.14 (t, *J* = 7.0 Hz, 2H), 2.65 – 2.52 (m, 1H), 2.45 – 2.33 (m, 1H), 1.82 – 1.74 (m, 2H), 1.50 – 1.29 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.20, 167.09, 148.43, 138.57, 136.36, 134.34, 134.00, 131.90, 127.93, 127.36, 123.70, 122.00, 121.71, 116.76, 55.30, 33.46, 30.38, 28.85, 28.74, 28.33, 26.61, 7.26; HRMS (EI) *m/z*: 555.1028 (M^+);calc.for $C_{26}H_{26}IN_3O_3$: 555.1019.

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-6,6,6-trifluoro-*N*-(quinolin-8-yl)hexanamide (3m)



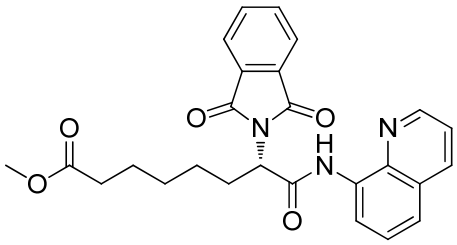
The compound **3m** was prepared according to the **GP-2** under condition (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3m** was obtained as a colorless oil (47.3 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.60 (dd, *J* = 4.9, 4.1 Hz, 1H), 8.54 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.03 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.45 – 7.38 (m, 2H), 7.31 (dd, *J* = 8.3, 4.3 Hz, 1H), 5.05 (dd, *J* = 10.6, 5.3 Hz, 1H), 2.62 – 2.48 (m, 1H), 2.47 – 2.35 (m, 1H), 2.27 – 2.02 (m, 2H), 1.68 – 1.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.11, 166.39, 148.47, 138.54, 136.41, 134.56, 133.81, 131.78, 131.06, 128.31, 127.95, 127.36, 125.57, 123.87, 122.18, 121.78, 116.83, 54.66, 33.76, 33.48, 33.19, 32.90, 27.87, 19.43, 19.40; HRMS (EI) *m/z*: 441.1304 (M^+);calc.for $C_{23}H_{18}F_3N_3O_3$: 441.1300.

(*S*)-Benzyl (7-(1,3-dioxoisoindolin-2-yl)-8-oxo-8-(quinolin-8-ylamino)octyl)carbamate (3n)



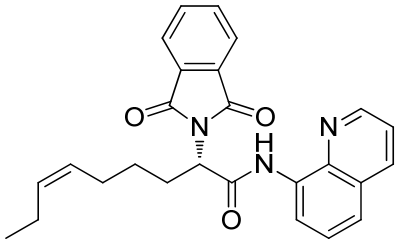
The compound **3n** was prepared according to the **GP-2** under condition (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 3:3:1. **3n** was obtained as a white solid (84.8 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.78 – 8.61 (m, 2H), 8.14 – 8.06 (m, 1H), 7.88 (dd, *J* = 4.6, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.0, 3.1 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.35 – 7.23 (m, 5H), 5.24 – 4.79 (m, 4H), 3.15 (dd, *J* = 12.9, 6.4 Hz, 2H), 2.65 – 2.48 (m, 1H), 2.44 – 2.28 (m, 1H), 1.51 – 1.23 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.15, 167.03, 156.45, 148.37, 138.46, 136.71, 136.29, 134.28, 133.89, 131.77, 128.47, 128.03, 128.01, 127.84, 127.25, 123.61, 121.97, 121.65, 116.68, 66.48, 55.17, 40.95, 29.79, 28.62, 26.54, 26.48; HRMS (EI) *m/z*: 564.2373 (M^+);calc.for $C_{33}H_{32}N_4O_5$: 564.2373.

(*S*)-Methyl7-(1,3-dioxoisoindolin-2-yl)-8-oxo-8-(quinolin-8-ylamino)octanoate (3o)



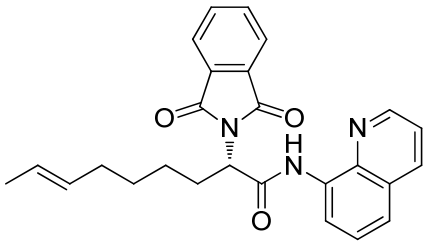
The compound **3o** was prepared according to the **GP-2** under condition (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 4:3:1. **3o** was obtained as a colorless oil (53.1 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.73 – 8.62 (m, 2H), 8.09 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.87 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.38 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.11 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.62 (s, 3H), 2.64 – 2.50 (m, 1H), 2.45 – 2.33 (m, 1H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.71 – 1.56 (m, 2H), 1.52 – 1.34 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.05, 168.15, 166.98, 148.40, 138.50, 136.32, 134.32, 133.93, 131.83, 127.88, 127.29, 123.66, 121.98, 121.68, 116.71, 55.16, 51.52, 33.93, 28.61, 28.58, 26.41, 24.76; HRMS (EI) *m/z*: 459.1802 (M^+);calc.for $C_{26}H_{25}N_3O_5$: 459.1794.

(*S*,*Z*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)non-6-enamide (3p)



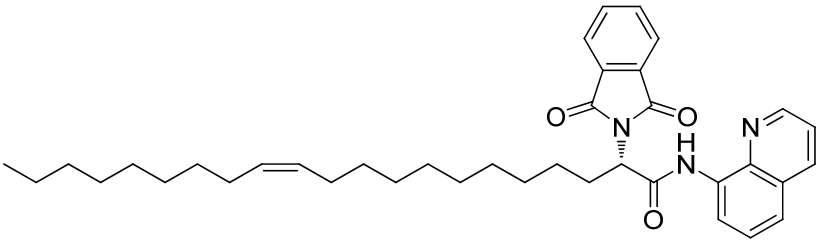
The compound **3p** was prepared according to the **GP-2** under condition (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3p** was obtained as a colorless oil (21.3 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.77 – 8.64 (m, 2H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.90 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.53 – 7.48 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.47 – 5.36 (m, 1H), 5.36 – 5.25 (m, 1H), 5.13 (dd, *J* = 11.0, 5.3 Hz, 1H), 2.67 – 2.52 (m, 1H), 2.47 – 2.35 (m, 1H), 2.25 – 2.10 (m, 2H), 2.10 – 2.00 (m, 2H), 1.57 – 1.42 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.25, 167.13, 148.45, 138.66, 136.41, 134.36, 134.08, 132.80, 131.98, 128.08, 127.99, 127.44, 123.74, 122.03, 121.75, 116.84, 55.24, 28.33, 26.77, 26.51, 20.71, 14.47; HRMS (EI) *m/z*: 427.1898 (M^+);calc.for $C_{26}H_{25}N_3O_3$: 427.1896.

(*S*,*E*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)non-7-enamide (3q)



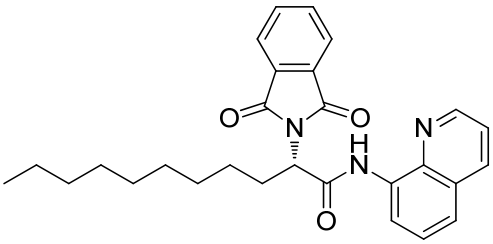
The compound **3q** was prepared according to the **GP-2** under condition (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3q** was obtained as a colorless oil (25.8 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.71 (dd, *J* = 5.4, 3.7 Hz, 1H), 8.69 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.90 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.53 – 7.46 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.48 – 5.25 (m, 2H), 5.12 (dd, *J* = 10.9, 5.3 Hz, 1H), 2.58 (tdd, *J* = 9.2, 7.0, 3.0 Hz, 1H), 2.39 (tdd, *J* = 14.0, 10.4, 3.9 Hz, 1H), 2.08 – 1.91 (m, 2H), 1.61 – 1.54 (m, 3H), 1.53 – 1.36 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.23, 167.18, 148.44, 138.62, 136.38, 134.32, 134.05, 131.95, 131.02, 127.96, 127.40, 125.30, 123.70, 122.00, 121.73, 116.80, 55.35, 32.31, 28.94, 28.65, 26.14, 17.96; HRMS (EI) *m/z*: 427.1893 (M^+);calc.for $C_{26}H_{25}N_3O_3$: 427.1896.

(*S*,*Z*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)henicos-12-enamide (3r)



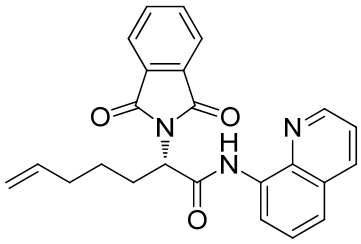
The compound **3r** was prepared according to the **GP-2** under condition (**d**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3r** was obtained as a white solid (79.6 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.71 (dd, *J* = 5.7, 3.3 Hz, 1H), 8.67 (dd, *J* = 4.1, 1.2 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.58 – 5.22 (m, 2H), 5.13 (dd, *J* = 10.9, 5.3 Hz, 1H), 2.68 – 2.49 (m, 1H), 2.47 – 2.32 (m, 1H), 2.09 – 1.87 (m, 4H), 1.50 – 1.37 (m, 4H), 1.33 – 1.22 (m, 22H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.12, 167.11, 148.32, 138.49, 136.26, 134.20, 133.96, 131.85, 129.90, 129.86, 127.85, 127.27, 123.57, 121.89, 121.61, 116.68, 55.31, 32.62, 31.91, 29.77, 29.71, 29.66, 29.61, 29.53, 29.51, 29.50, 29.43, 29.32, 29.29, 29.06, 28.76, 27.59, 27.22, 26.71, 22.69, 14.13; HRMS (EI) *m/z*: 595.3771 (M^+);calc.for $C_{38}H_{49}N_3O_3$: 595.3774.

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)undecanamide (3s)



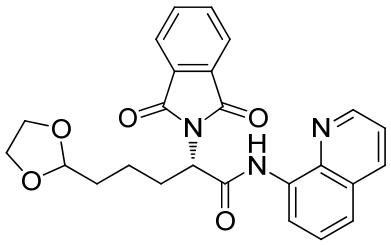
The compound **3s** was prepared according to the **GP-2** under condition (**f**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3-s** was obtained as a colorless oil (57.5 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.71 (dd, *J* = 5.5, 3.5 Hz, 1H), 8.67 (d, *J* = 4.0 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.3, 3.2 Hz, 2H), 7.53 – 7.44 (m, 2H), 7.39 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.13 (dd, *J* = 10.9, 5.3 Hz, 1H), 2.67 – 2.51 (m, 1H), 2.45 – 2.33 (m, 1H), 1.50 – 1.35 (m, 4H), 1.31 – 1.17 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.21, 167.19, 148.40, 138.56, 136.34, 134.28, 134.02, 131.91, 127.92, 127.34, 123.65, 121.96, 121.69, 116.75, 55.38, 31.90, 29.53, 29.48, 29.31, 29.11, 28.82, 26.76, 22.72, 14.18; HRMS (EI) *m/z*: 457.2356 (M^+);calc.for $C_{28}H_{31}N_3O_3$: 457.2365.

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)hept-6-enamide (3t)



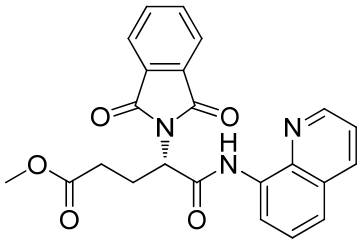
The compound **3t** was prepared according to the **GP-2** under condition (**f**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **3t** was obtained as a colorless oil (12.8 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.77 – 8.64 (m, 2H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.54 – 7.47 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.13 (dd, *J* = 10.9, 5.3 Hz, 1H), 5.06 (ddd, *J* = 17.1, 3.3, 1.6 Hz, 1H), 5.01 – 4.94 (m, 1H), 2.60 (tdd, *J* = 10.7, 10.2, 5.5 Hz, 1H), 2.48 – 2.37 (m, 1H), 2.28 – 2.10 (m, 2H), 1.61 – 1.46 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 168.25, 167.08, 148.47, 138.65, 137.98, 136.41, 134.38, 134.06, 131.97, 127.99, 127.44, 123.77, 122.04, 121.76, 116.84, 115.45, 55.21, 33.18, 28.29, 26.00; HRMS (EI) *m/z*: 399.1577 (M^+);calc.for $C_{24}H_{21}N_3O_3$: 399.1583.

(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-5-(1,3-dioxolan-2-yl)-*N*-(quinolin-8-yl)pentanamide (3u)



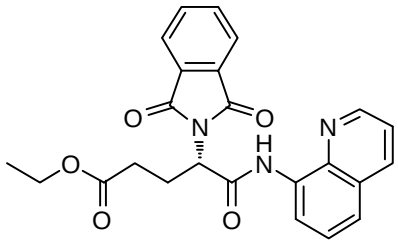
The compound **3u** was prepared according to the **GP-2** under condition (**f**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 3:3:1. **3u** was obtained as a white solid (48.0 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.69 (dd, *J* = 4.9, 4.1 Hz, 1H), 8.67 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.52 – 7.45 (m, 2H), 7.39 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.16 (dd, *J* = 11.1, 5.0 Hz, 1H), 4.87 (t, *J* = 4.6 Hz, 1H), 3.99 – 3.88 (m, 2H), 3.87 – 3.78 (m, 2H), 2.68 (ddt, *J* = 14.6, 11.2, 7.5 Hz, 1H), 2.53 – 2.37 (m, 1H), 1.88 – 1.72 (m, 2H), 1.64 – 1.50 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.21, 167.05, 148.39, 138.57, 136.36, 134.31, 134.02, 131.94, 127.93, 127.36, 123.69, 121.99, 121.71, 116.79, 104.27, 65.01, 64.91, 55.14, 32.99, 28.60, 21.17; HRMS (EI) *m/z*: 445.1636 (M^+);calc.for $C_{25}H_{23}N_3O_5$: 445.1638.

(*S*)-Methyl4-(1,3-dioxoisoindolin-2-yl)-5-oxo-5-(quinolin-8-ylamino)pentanoate (3v)



The compound **3v** was prepared according to the **GP-2** under condition (**e**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 3:3:1. **3v** was obtained as a white solid(65.8 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.81 – 8.55 (m, 2H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.91 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.77 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.53 – 7.47 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.21 (dd, *J* = 8.9, 6.8 Hz, 1H), 3.67 (s, 3H), 2.90 – 2.76 (m, 2H), 2.59 – 2.43 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.68, 167.97, 166.29, 148.37, 138.39, 136.25, 134.37, 133.77, 131.72, 131.71, 127.80, 127.18, 123.65, 122.03, 121.67, 116.67, 54.15, 51.86, 30.93, 24.14;HRMS (EI) *m/z*: 417.1318(M^+); calc.for $C_{23}H_{19}N_3O_5$: 417.1325.

(*S*)-Ethyl4-(1,3-dioxoisoindolin-2-yl)-5-oxo-5-(quinolin-8-ylamino)pentanoate (3w)



The compound **3w** was prepared according to the **GP-2** under condition (**e**), (**h**)and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 3:3:1. **3w** was obtained as a white solid (67.2 mg, 78%) under condition (**e**). Mono- and di-alkylated products were obtained as a mixture under condition (**h**) (71.2 mg, 83%, mono:di = 4.5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.81 – 8.55 (m, 2H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.91 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.77 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.53 – 7.47 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.21 (dd, *J* = 8.9, 6.8 Hz, 1H), 3.67 (s, 3H), 2.90 – 2.76 (m, 2H), 2.59 – 2.43 (m, 2H);^{13}C NMR (101 MHz, $CDCl_3$) δ 172.68, 167.97, 166.29, 148.37, 138.39, 136.25, 134.37, 133.77, 131.72, 131.71, 127.80, 127.18, 123.65, 122.03, 121.67, 116.67, 54.15, 51.86, 30.93, 24.14;HRMS (EI) *m/z*: 431.1483 (M^+); calc.for $C_{24}H_{21}N_3O_5$: 431.1481.

General Procedure (GP-3) for Alkylation of Secondary C(sp^3)–H Bonds

To a 30- mL resealable Schlenk flask was added 8-aminoquinoline amide (**1**) (0.2 mmol, overall concentration = 0.133 mol/L), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), α-bromoacetate estersor α-iodoacetate esters (**2'**) (0.3 mmol), Ag_2CO_3 (0.16 mmol), $(BnO)_2POOH$ (0.06 mmol), DCE/*t*-BuOH (1.5 mL). The flask was then charged with N_2. The mixture was stirred at 90°C for 9 to 12 hours under N_2. After cooling to room temperature, the reaction was diluted with dichloromethane (5 mL) and then filtered through a pad of Celite and washed by dichloromethane (30 mL). Evaporation of organic solvent and purification by column chromatography gave the corresponding products.

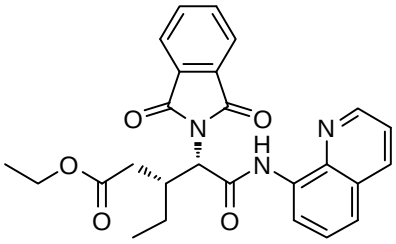
(**a**)**1** (0.2mmol, 1.0eq), α-bromoacetate esters (1.5eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.8eq), $(BnO)_2POOH$ (0.3eq), DCE/^{t}BuOH = 1:2, 90°C, 12h;

(**b**)**1** (0.2mmol, 1.0eq), methyl bromoacetate (1.5eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.8eq), $(BnO)_2POOH$ (0.3eq), DCE/^{t}BuOH = 1:2, 90°C, 9h;

(**c**)**1** (0.2mmol, 1.0eq), α-iodoacetate esters (1.5eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.8eq), $(BnO)_2POOH$ (0.3eq), DCE/^{t}BuOH = 1:2, 90°C, 9h;

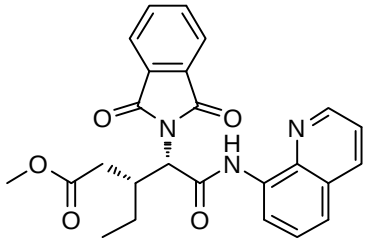
(**d**)**1** (0.2mmol, 1.0eq), α-iodoacetate esters (1.5eq), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.8eq), $(BnO)_2POOH$ (0.3eq), DCE/^{t}BuOH = 2:1, 90°C, 9h.

(3*R*,4*S*)-Ethyl4-(1,3-dioxoisoindolin-2-yl)-3-ethyl-5-oxo-5-(quinolin-8-ylamino)pentanoate (5a)



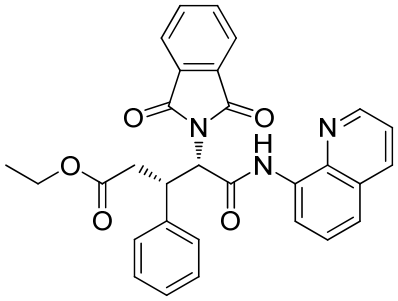
The compound **5a** was prepared according to the **GP-3** under condition (**a**) and (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 5:4:1. **5a** was obtained as colorless oil (75.5 mg, 84%) under condition (**a**); (50.5mg, 56%) under condition (**c**) with diastereoselectivity(d.r.) > 50:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.78 – 8.63 (m, 2H), 8.09 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.51 – 7.43 (m, 2H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.27 (d, *J* = 9.8 Hz, 1H), 4.13 (qd, *J* = 7.1, 1.3 Hz, 2H), 3.48 – 3.30 (m, 1H), 2.67 (qd, *J* = 16.2, 5.9 Hz, 2H), 1.67 (dqd, *J* = 15.0, 7.5, 3.8 Hz, 1H), 1.45 – 1.32 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.11, 168.15, 166.53, 148.48, 138.64, 136.21, 134.38, 134.13, 131.65, 127.90, 127.21, 123.71, 122.11, 121.69, 117.00, 60.64, 58.30, 35.37, 34.88, 23.25, 14.22, 10.51; HRMS (EI) *m/z*: 459.1796 (M^+); calc.for $C_{26}H_{25}N_3O_5$: 459.1794.

(3*R*,4*S*)-Methyl4-(1,3-dioxoisoindolin-2-yl)-3-ethyl-5-oxo-5-(quinolin-8-ylamino)pentanoate (5b)



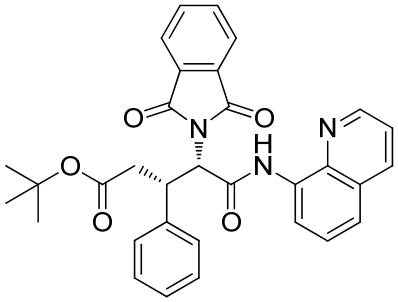
The compound **5b** was prepared according to the **GP-3** under condition (**b**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 5:4:1. **5b** was obtained as colorless oil (77.5 mg, 87%) under condition (**b**) with diastereoselectivity(d.r.) > 50:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.74 – 8.68 (m, 2H), 8.09 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.86 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.47 (d, *J* = 4.4 Hz, 2H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.23 (d, *J* = 9.7 Hz, 1H), 3.66 (s, 3H), 3.45 – 3.34 (m, 1H), 2.67 (qd, *J* = 16.3, 6.0 Hz, 2H), 1.68 (ddd, *J* = 14.2, 7.5, 3.8 Hz, 1H), 1.37 (dt, *J* = 14.4, 7.4 Hz, 1H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.60, 168.15, 166.49, 148.50, 138.64, 136.23, 134.41, 134.11, 131.65, 127.91, 127.23, 123.75, 122.14, 121.70, 117.03, 58.27, 51.77, 35.39, 34.71, 23.30, 10.46; HRMS (EI) *m/z*: 445.1647 (M^+); calc.for $C_{25}H_{23}N_3O_5$: 445.1638.

(3*S*,4*S*)-Ethyl4-(1,3-dioxoisoindolin-2-yl)-5-oxo-3-phenyl-5-(quinolin-8-ylamino)pentanoate (5c)



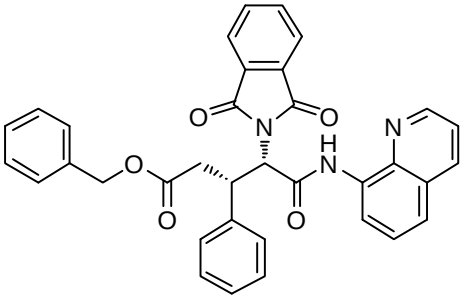
The compound **5c** was prepared according to the **GP-3**under condition (**a**), (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 5:4:1. **5c** was obtained as colorless oil (46.6 mg, 46%) under condition (**a**); (86.0mg, 85%) under condition (**c**) with diastereoselectivity(d.r.) > 50:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.82 – 8.71 (m, 2H), 8.12 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.60 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.55 – 7.49 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.14 (t, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 5.42 (d, *J* = 11.8 Hz, 1H), 4.76 (ddd, *J* = 11.6, 10.4, 4.1 Hz, 1H), 4.03 – 3.88 (m, 2H), 3.19 (dd, *J* = 15.5, 4.1 Hz, 1H), 2.88 (dd, *J* = 15.5, 10.3 Hz, 1H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.03, 167.65, 166.25, 148.66, 139.00, 138.73, 136.26, 134.21, 131.24, 128.49, 128.31, 127.96, 127.42, 127.26, 123.51, 122.34, 121.76, 117.23, 60.57, 59.24, 40.91, 39.50, 14.08; HRMS (EI) *m/z*: 507.1793 (M^+);calc.for $C_{30}H_{25}N_3O_5$: 507.1794.

(3*S*,4*S*)-*tert*-Butyl4-(1,3-dioxoisoindolin-2-yl)-5-oxo-3-phenyl-5-(quinolin-8-ylamino)pentanoate (5d)



The compound **5d** was prepared according to the **GP-3** under condition (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 5:4:1. **5d** was obtained as colorless oil(95.5 mg, 89%) under condition (**c**) with diastereoselectivity(d.r.) > 50:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.82 – 8.71 (m, 2H), 8.15 – 8.04 (m, 1H), 7.72 – 7.66 (m, 2H), 7.61 – 7.54 (m, 2H), 7.52 – 7.45 (m, 2H), 7.42 – 7.35 (m, 1H), 7.34 – 7.27 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 2H), 7.03 (dd, *J* = 7.1 Hz, 1H), 5.42 (dd, *J* = 11.7, 2.0 Hz, 1H), 4.70 (td, *J* = 11.0, 4.3 Hz, 1H), 3.14 (dd, *J* = 15.1, 4.4 Hz, 1H), 2.81 (dd, *J* = 15.0, 10.5 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.12, 167.60, 166.22, 148.54, 138.93, 138.64, 136.15, 134.14, 134.10, 131.16, 128.34, 128.28, 127.86, 127.26, 127.13, 123.37, 122.23, 121.66, 117.13, 80.67, 59.46, 41.05, 40.46, 27.80; HRMS (EI) *m/z*: 535.2114 (M^+); calc.for $C_{32}H_{29}N_3O_5$: 535.2107.

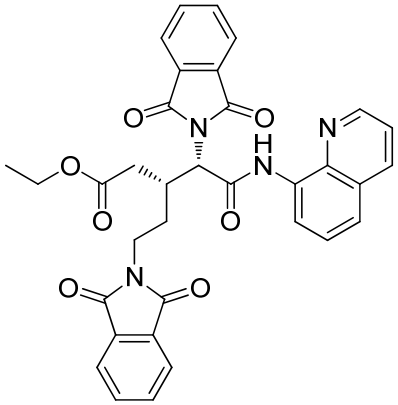
(3*S*,4*S*)-Benzyl4-(1,3-dioxoisoindolin-2-yl)-5-oxo-3-phenyl-5-(quinolin-8-ylamino)pentanoate (5e)



The compound **5e** was prepared according to the **GP-3** under condition (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 5:4:1. **5e** was obtained as colorless oil (113.9 mg, 91%) under condition (**c**) with diastereoselectivity(d.r.) > 50:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.77 (dd, *J* = 5.5, 3.4 Hz, 1H), 8.71 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.68 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.57 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.49 (d, *J* = 2.1 Hz, 1H), 7.48 (s, 1H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.28 – 7.21 (m, 5H), 7.14 – 7.08 (m, 4H), 7.03 (t, *J* = 7.3 Hz, 1H), 5.42 (d, *J* = 11.7 Hz, 1H), 4.94 (d, *J* = 2.4 Hz, 2H), 4.79 (td, *J* = 10.9, 4.1 Hz, 1H), 3.28 (dd, *J* = 15.5, 4.1 Hz, 1H), 2.96 (dd, *J* = 15.5, 10.3 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 170.88, 167.59, 166.17, 148.61, 138.86, 138.67, 136.21, 135.71, 134.18, 134.13, 131.18, 128.52, 128.44, 128.28,

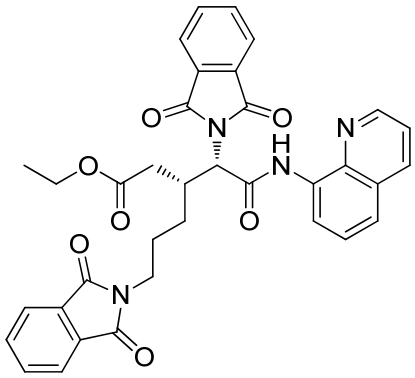
128.16, 128.06, 127.91, 127.42, 127.21, 123.46, 122.32, 121.72, 117.19, 66.35, 59.17, 40.91, 39.44; HRMS (EI) *m/z*: 569.1937 (M^+); calc.for $C_{35}H_{27}N_3O_5$: 569.1951; (ESI)*m/z*: 592.1826;calc.for $C_{35}H_{27}N_3O_5Na$: 592.1843.

(3*R*,4*S*)-Ethyl4-(1,3-dioxoisoindolin-2-yl)-3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-5-oxo-5-(quinolin-8-ylamino)pentanoate (5f)



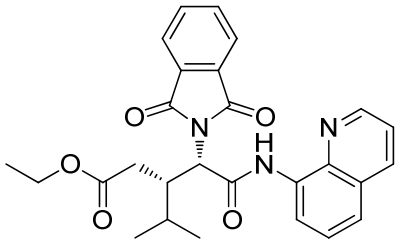
The compound **5f** was prepared according to the **GP-3** under condition (**a**), (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 2:2:1. **5f** was obtained as white solid (83.5 mg, 69%) under condition (**a**); (60.4mg, 50%) under condition (**c**) with diastereoselectivity(d.r.) > 50:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.75 – 8.57 (m, 2H), 8.07 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.81 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.64 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.36 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.38 (d, *J* = 9.7 Hz, 1H), 4.22 – 4.13 (m, 2H), 3.93 – 3.82 (m, 1H), 3.76 – 3.61 (m, 1H), 3.54 – 3.37 (m, 1H), 2.91 (dd, *J* = 16.6, 5.6 Hz, 1H), 2.79 (dd, *J* = 16.6, 5.3 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.82 – 1.70 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.87, 168.29, 168.11, 166.15, 148.43, 138.56, 136.18, 134.34, 133.95, 133.82, 132.20, 131.67, 127.85, 127.19, 123.68, 123.16, 122.14, 121.66, 117.02, 60.88, 57.92, 35.25, 34.66, 31.79, 28.97, 14.22;HRMS (ESI) *m/z*: 627.1829 (MNa^+); calc.for $C_{34}H_{28}N_4O_7Na$: 627.1850(calc.for $C_{34}H_{28}N_4O_7$: 604.1958).

(*R*)-Ethyl6-(1,3-dioxoisoindolin-2-yl)-3-((*S*)-1-(1,3-dioxoisoindolin-2-yl)-2-oxo-2-(quinolin-8-ylamino)ethyl)hexanoate (5g)



The compound **5g** was prepared according to the **GP-3** under condition (**a**), (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 2:2:1. **5g** was obtained as white solid (96.4 mg, 78%) under condition (**a**); (70.2mg, 58%) under condition (**c**) with diastereoselectivity(d.r.) > 50:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.68 (dd, *J* = 4.2, 1.3 Hz, 1H), 8.66 (dd, *J* = 5.3, 4.0 Hz, 1H), 8.06 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.79 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 – 7.65 (m, 4H), 7.62 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.48 – 7.40 (m, 2H), 7.35 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.25 (d, *J* = 9.4 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.69 – 3.53 (m, 2H), 3.49 – 3.37 (m, 1H), 2.66 (qd, *J* = 16.3, 5.8 Hz, 2H), 1.87 – 1.72 (m, 2H), 1.72 – 1.61 (m, 1H), 1.50 – 1.37 (m, 1H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.83, 168.15, 168.02, 166.14, 148.46, 138.52, 136.15, 134.32, 133.94, 133.80, 131.97, 131.51, 127.81, 127.12, 123.67, 123.08, 122.09, 121.65, 116.92, 60.68, 58.03, 37.81, 35.11, 33.90, 27.70, 25.33, 14.13; HRMS (ESI) *m/z*: 641.1998 (MNa^+); calc.for $C_{35}H_{30}N_4O_7Na$: 641.2007 (calc.for $C_{35}H_{30}N_4O_7$: 618.2114).

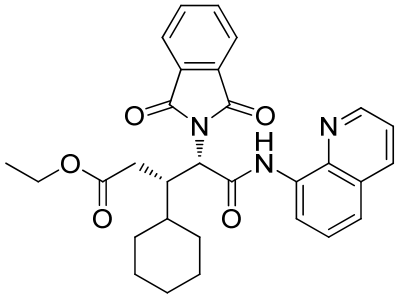
(3*S*,4*S*)-Eethyl4-(1,3-dioxoisoindolin-2-yl)-3-isopropyl-5-oxo-5-(quinolin-8-ylamino)pentanoate (5h)



The compound **5h** was prepared according to the **GP-3** under condition (**a**), (**c**), (**d**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 5:4:1. **5h** was obtained as colorless oil (41.2 mg, 44%) under condition (**a**); (50.8mg, 54%) under condition (**c**); (72.7mg, 77%) under condition (**c**) with diastereoselectivity(d.r.) > 50:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.80 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.72 (dd, *J* = 5.1, 3.9 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.19 (d, *J* = 10.9 Hz, 1H), 3.95 (qq, *J* = 10.8, 7.1 Hz, 2H), 3.63 – 3.41 (m, 1H),

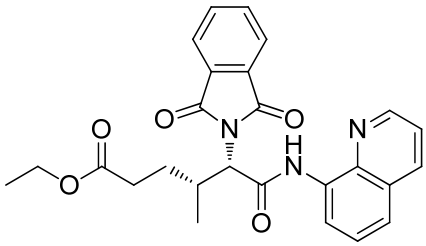
2.58 (dd, *J* = 5.6, 1.0 Hz, 2H), 1.92 – 1.78 (m, 1H), 1.10 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.81, 168.13, 166.86, 148.55, 138.74, 136.18, 134.43, 134.36, 131.69, 127.92, 127.22, 123.80, 122.11, 121.70, 117.10, 60.67, 58.55, 38.70, 32.33, 28.25, 20.95, 16.66, 14.02; HRMS (EI) *m/z*: 473.1939 (M^+);calc.for $C_{27}H_{27}N_3O_5$: 473.1951.

(3*S*,4*S*)-Ethyl3-cyclohexyl-4-(1,3-dioxoisoindolin-2-yl)-5-oxo-5-(quinolin-8-ylamino)pentanoate (5i)



The compound **5i** was prepared according to the **GP-3** under condition (**a**), (**c**), (**d**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 5:4:1. **5i** was obtained as colorless oil (45.1 mg, 44%) under condition (**a**); (54.4 mg, 54%) under condition (**c**); (74.7mg, 74%) under condition (**c**) with diastereoselectivity(d.r.) > 50:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.71 (dd, *J* = 8.9, 4.6 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.49 – 7.44 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.26 (d, *J* = 10.0 Hz, 1H), 4.04 – 3.90 (m, 2H), 3.49 – 3.35 (m, 1H), 2.64 (d, *J* = 5.7 Hz, 2H), 1.79 – 1.44 (m, 6H), 1.28 – 1.18 (m, 2H), 1.11 (t, *J* = 7.1 Hz, 3H), 1.09 – 0.93 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.91, 168.16, 166.86, 148.51, 138.74, 136.20, 134.42, 134.33, 131.70, 127.94, 127.26, 123.81, 122.09, 121.70, 117.08, 60.63, 57.78, 39.45, 39.03, 33.43, 31.32, 27.83, 26.87, 26.68, 26.46, 14.06; HRMS (EI) *m/z*: 513.2261 (M^+);calc.for $C_{30}H_{31}N_3O_5$: 513.2264.

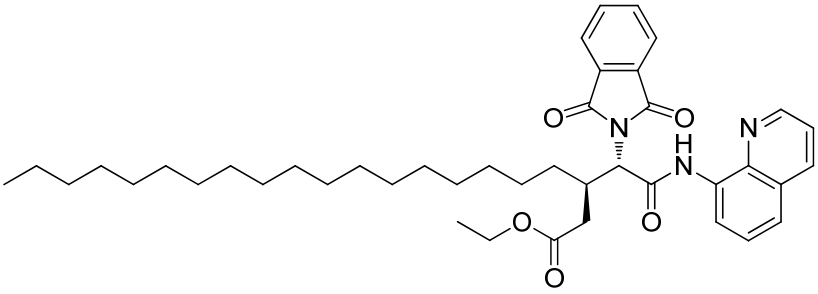
(4*R*,5*S*)-Ethyl5-(1,3-dioxoisoindolin-2-yl)-4-methyl-6-oxo-6-(quinolin-8-ylamino)hexanoate (5j)



The compound **5j** was prepared according to the **GP-3** under condition (**c**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 5:4:1. **5j** was obtained as colorless oil (37.4 mg, 41%) under condition (**c**) with diastereoselectivity(d.r.) = 17:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.78 (dd, *J* = 4.2, 1.2 Hz, 1H), 8.75 – 8.71 (m, 1H), 8.11 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.87 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.50 – 7.48 (m, 2H), 7.41 (dd, *J* = 8.3, 4.3 Hz, 1H), 4.83 (d, *J* = 10.2 Hz, 1H), 4.09 – 4.03 (m, 2H), 3.08 (dtd, *J* = 13.5, 6.7,

3.6 Hz, 1H), 2.57 – 2.41 (m, 2H), 2.13 – 2.03 (m, 1H), 1.72 – 1.60 (m, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.29, 168.16, 166.43, 148.58, 138.74, 136.28, 134.45, 134.22, 131.64, 127.97, 127.31, 123.81, 123.74, 122.15, 121.73, 117.12, 61.11, 60.49, 32.05, 31.93, 29.37, 16.08, 14.24; HRMS (EI) *m/z*: 459.1798 (M^+);calc.for $C_{26}H_{25}N_3O_5$: 459.1794.

(*R*)-Ethyl3-((*S*)-1-(1,3-dioxoisoindolin-2-yl)-2-oxo-2-(quinolin-8-ylamino)ethyl)henicosanoate (7a)

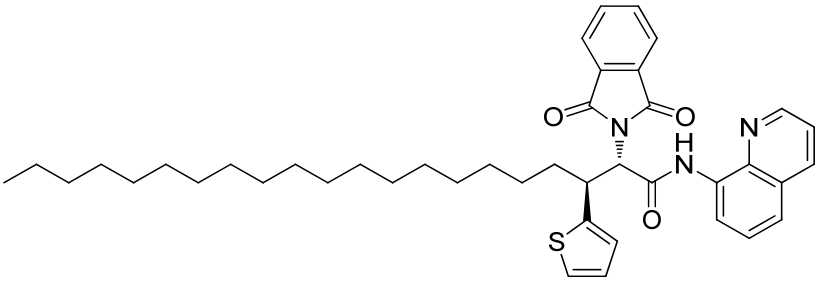


The compound **7a** was prepared according to the **GP-3** under condition (**a**) and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 7:2:1. **5i** was obtained as white solid (113.5 mg, 83%) under condition (**a**) with diastereoselectivity(d.r.) > 50:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.75 – 8.71 (m, 2H), 8.10 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.47 (d, *J* = 4.2 Hz, 2H), 7.39 (ddd, *J* = 8.3, 4.2, 0.9 Hz, 1H), 5.30 (d, *J* = 9.5 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.47 – 3.37 (m, 1H), 2.67 (qd, *J* = 16.2, 5.8 Hz, 2H), 1.63 – 1.53 (m, 1H), 1.29 – 1.13 (m, 36H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.18, 168.17, 166.54, 148.45, 138.67, 136.22, 134.35, 134.17, 131.72, 127.92, 127.26, 123.72, 122.09, 121.68, 117.03, 60.64, 58.51, 35.39, 34.34, 31.99, 30.57, 29.77, 29.73, 29.71, 29.68, 29.57, 29.52, 29.43, 26.26, 22.76, 14.25, 14.19; HRMS (ESI) *m/z*: 706.4048 (MNa^+); calc.for $C_{42}H_{57}N_3O_5Na$: 706.4190 (calc.for $C_{42}H_{57}N_3O_5$: 683.4298).

General Procedure (GP-4) for Arylation of Secondary C(Sp^3)-H

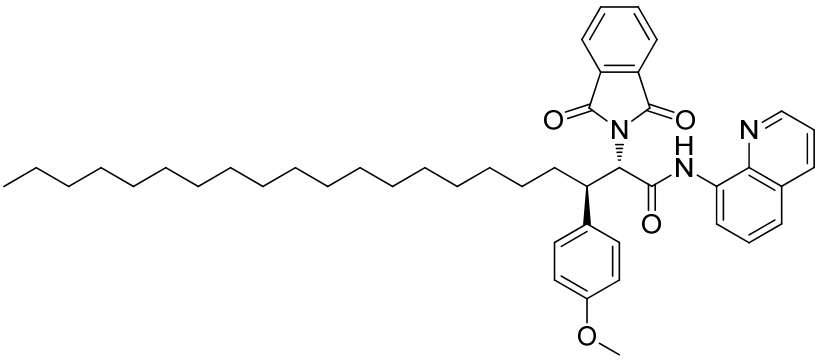
To a 30-mL resealable Schlenk flask was added **3f** (0.2 mmol, overall concentration = 0.133 mol/L), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), aryl iodo (0.3 mmol), AgOAc (0.30 mmol), *t*-BuOH (1.5 mL). The flask was then charged with N_2. The mixture was stirred at 90°C for 4 hours under N_2. After cooling to room temperature, the reaction was diluted with dichloromethane (5 mL) and then filtered through a pad of Celite and washed by dichloromethane (30 mL). Evaporation of organic solvent and purification by column chromatography gave the corresponding products.

(2*S*,3*S*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-3-(thiophen-2-yl)henicosanamide (7b)



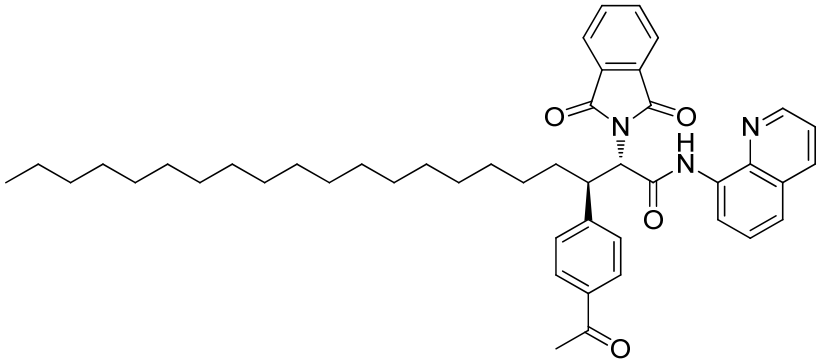
The compound **7b** was prepared according to the **GP-4** and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 7:2:1. **7b** was obtained as a colorless oil (109.2 mg, 80%) with diastereoselectivity (d.r.) = 5:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.72 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.61 (dd, *J* = 6.5, 2.6 Hz, 1H), 8.05 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.90 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.75 – 7.71 (m, 2H), 7.42 – 7.35 (m, 3H), 7.17 (d, *J* = 5.1 Hz, 1H), 7.12 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.88 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.26 (d, *J* = 11.2 Hz, 1H), 4.59 (td, *J* = 11.1, 3.2 Hz, 1H), 1.77 – 1.53 (m, 2H), 1.35 – 1.10 (m, 32H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.26, 165.93, 148.15, 144.04, 138.56, 136.06, 134.15, 131.82, 127.79, 127.21, 127.07, 126.80, 124.62, 123.80, 121.91, 121.58, 116.90, 61.93, 39.88, 34.58, 32.01, 29.79, 29.75, 29.57, 29.45, 29.34, 26.64, 22.78, 14.22; HRMS (ESI) *m/z*: 702.3589 (MNa^+); calc.for $C_{42}H_{53}N_3O_3S$ Na: 702.3700 (calc.for $C_{42}H_{53}N_3O_3S$: 679.3808).

(2*S*,3*R*)-2-(1,3-Dioxoisoindolin-2-yl)-3-(4-methoxyphenyl)-*N*-(quinolin-8-yl)henicosanamide (7c)



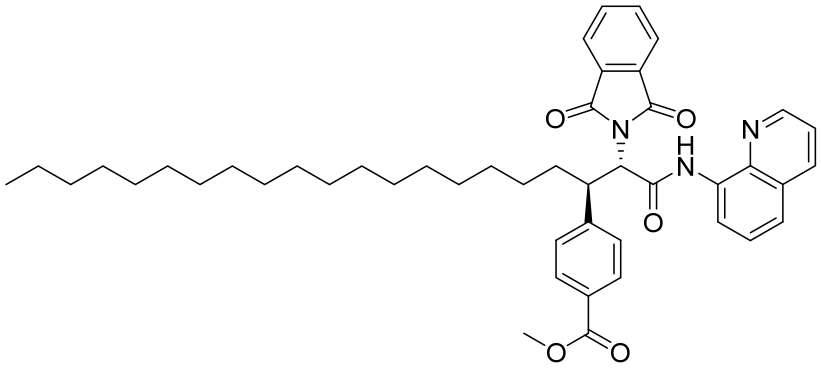
The compound **7c** was prepared according to the **GP-4** and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 7:2:1. **7c** was obtained as white solid (111.1 mg, 79%) with diastereoselectivity(d.r.) > 20:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.68 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.57 (dd, *J* = 6.7, 2.3 Hz, 1H), 8.07 – 8.01 (m, 1H), 7.91 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.41 – 7.34 (m, 5H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.29 (d, *J* = 11.7 Hz, 1H), 4.14 (td, *J* = 11.0, 4.5 Hz, 1H), 3.68 (s, 3H), 1.66 – 1.56 (m, 2H), 1.31 – 1.05 (m, 32H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.48, 166.30, 158.84, 148.01, 138.53, 136.01, 134.30, 134.21, 132.49, 131.90, 129.69, 127.77, 127.20, 123.75, 121.79, 121.52, 116.85, 114.56, 61.51, 55.13, 43.45, 33.43, 32.01, 29.79, 29.76, 29.71, 29.67, 29.59, 29.53, 29.48, 29.45, 26.70, 22.78, 14.22; HRMS (ESI) *m/z*: 726.3998 (MNa^+); calc.for $C_{45}H_{57}N_3O_4Na$: 726.4241 (calc.for $C_{45}H_{57}N_3O_4$: 703.4349).

(2*S*,3*R*)-3-(4-Acetylphenyl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)henicosanamide (7d)



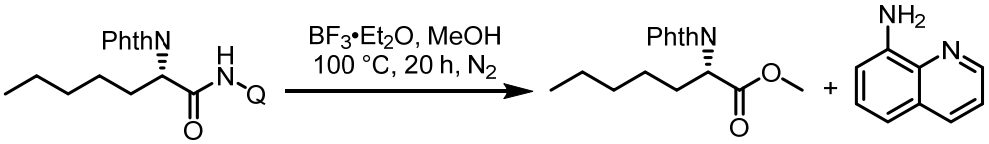
The compound **7d** was prepared according to the **GP-4** and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 6:3:1. **7d** was obtained as a white solid (110.2 mg, 77%) with diastereoselectivity(d.r.) > 20:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.64 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.51 (dd, *J* = 7.2, 1.7 Hz, 1H), 8.05 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.93 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.34 (m, 3H), 5.32 (d, *J* = 11.6 Hz, 1H), 4.34 – 4.26 (m, 1H), 2.47 (s, 3H), 1.71 – 1.62 (m, 2H), 1.29 – 1.07 (m, 32H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.73, 168.28, 165.71, 148.14, 146.57, 138.39, 136.22, 136.11, 134.46, 133.87, 131.73, 129.15, 128.96, 127.75, 127.16, 123.85, 121.98, 121.61, 116.83, 61.02, 44.19, 32.90, 31.99, 29.76, 29.74, 29.72, 29.67, 29.62, 29.53, 29.42, 26.68, 26.56, 22.76, 14.20; HRMS (ESI) *m/z*: 738.4235 (MNa^+); calc.for $C_{46}H_{57}N_3O_4Na$: 738.4241 (calc.for $C_{46}H_{57}N_3O_4$: 715.4349).

Methyl4-((2*S*,3*R*)-2-(1,3-dioxoisoindolin-2-yl)-1-oxo-1-(quinolin-8-ylamino)henicosan-3-yl)benzoate (7e)



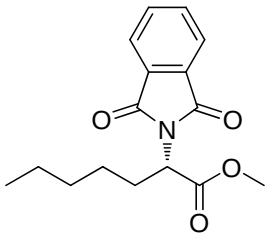
The compound **7e** was prepared according to the **GP-4** and purified by column chromatography in petroleumether: dichloromethane: ethyl acetate = 7:3:1. **7e** was obtained as a white solid (113.3 mg, 77%) with diastereoselectivity(d.r.) > 20:1 estimated by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.65 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.51 (dd, *J* = 7.2, 1.7 Hz, 1H), 8.05 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.93 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.34 (m, 3H), 5.33 (d, *J* = 11.6 Hz, 1H), 4.33 – 4.24 (m, 1H), 3.85 (s, 3H), 1.71 – 1.61 (m, *J* = 14.4, 6.4 Hz, 2H), 1.25 – 1.08 (m, 32H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.29, 166.91, 165.69, 148.12, 146.30, 138.41, 136.08, 134.43, 133.89, 131.76, 130.39, 129.23, 128.79, 127.75, 127.14, 123.83, 121.96, 121.55, 116.83, 61.00, 52.04, 44.23, 33.01, 31.99, 29.76, 29.73, 29.72, 29.66, 29.61, 29.51, 29.43, 29.39, 26.65, 22.76, 14.20; HRMS (ESI) *m/z*: 754.4198 (MNa^+);calc.for $C_{46}H_{57}N_3O_5Na$: 754.4190 (calc.for $C_{46}H_{57}N_3O_5$: 731.4298).

Cleavage of the 8-Aminoquinoline Group



3a **8**, 96% (97.5% ee) 87%

(*S*)-Methyl 2-(1,3-dioxoisoindolin-2-yl)heptanoate (8)



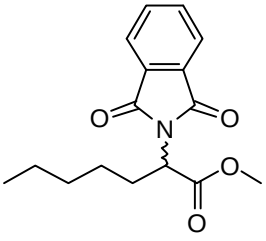
To a 30-mL resealable Schlenk flask was added 8-aminoquinoline amide (**3a**) (60.2 mg, 0.15 mmol, overall concentration = 0.1 mol/L), dry methanol (1.5 mL), $BF_3 \cdot Et_2O$ (114μL, 0.9 mmol). The flask was then charged with N_2. The mixture was stirred at 100°C for 20 hours under N_2. After cooling to room temperature, the reaction was diluted with dichloromethane (5 mL) and then quenched by Et_3N (0.21 mL, 1.50 mmol). Evaporation of organic solvent and purification by column chromatography in petroleum ether: ethyl acetate = 4:1 gave the corresponding products **8** (41.8mg, 96%) as a colorless oil and 8-aminoquinoline (18.8mg, 87%). The compound **8** is known.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 5.5, 3.1 Hz, 2H), 7.74 (dd, J = 5.5, 3.1 Hz, 2H), 4.84 (dd, J = 10.5, 5.3 Hz, 1H), 3.72 (s, 3H), 2.32 – 2.15 (m, 2H), 1.37 – 1.22 (m, 6H), 0.84 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.12, 167.85, 134.29, 131.99, 123.67, 52.79, 52.35, 31.19, 28.76, 26.10, 22.50, 14.05.HPLC Chiralpack® OJ-H column followed by OJ-H column (*n*-hexane/isopropanol = 92:8, 0.40mL/min) t_r = 34.301 min (major), t_r = 36.187 (minor), 97.5% ee.

Chiral HPLC Data

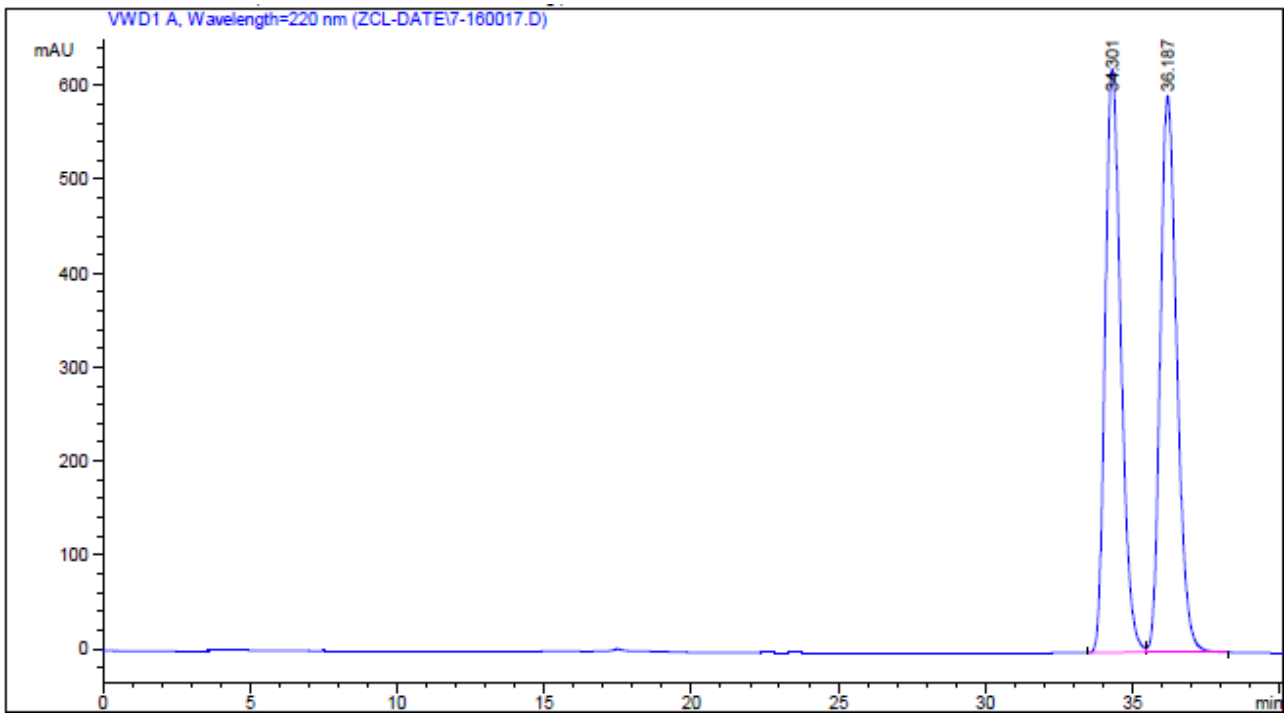
<u>HPLC Conditions</u>:

Chiral stationary phase: Chiralpack® OJ-H column followed by OJ-H column, *n*-hexane/isopropanol = 92:8, 0.40mL/min

Signal: VWD1 A, Wavelength = 220 nm

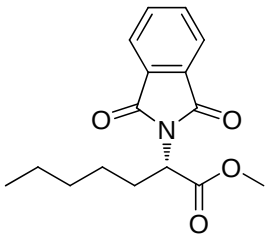


***DL*-8**

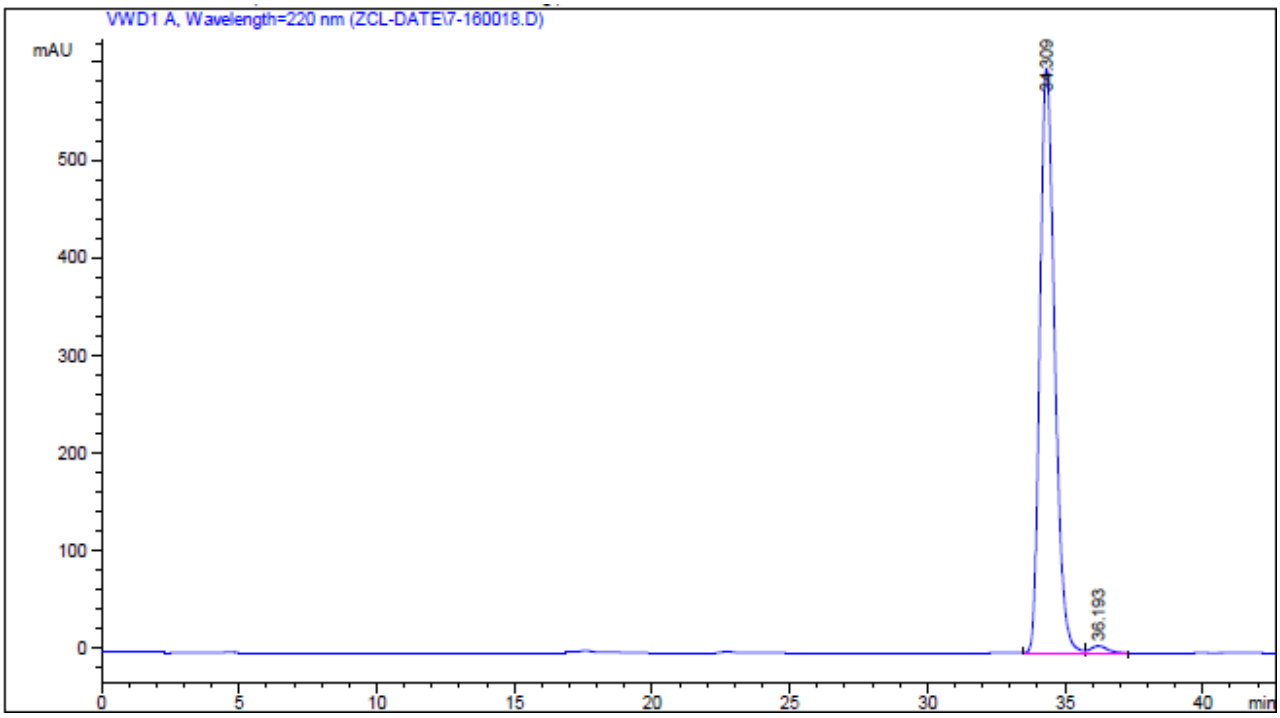


Area% report for *DL*-8:

Retention Time (min)	Area (mAU*s)	Area %	Height (mAU)	Height %
34.301	2.31798e4	49.9240	622.19818	51.1983
36.187	2.32504e4	50.0760	593.07214	48.8017
Totals	4.64302e4	100.0000	1215.27032	100.0000



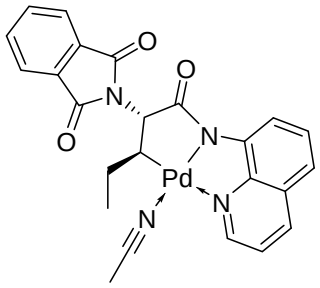
***L*-8**



Area% report for *L*-8:

Retention Time (min)	Area (mAU*s)	Area %	Height (mAU)	Height %
34.309	2.22416e4	98.7216	598.46210	98.8347
36.193	288.02582	1.2784	7.05596	1.1653
Totals	2.25296e4	100.0000	605.51806	100.0000

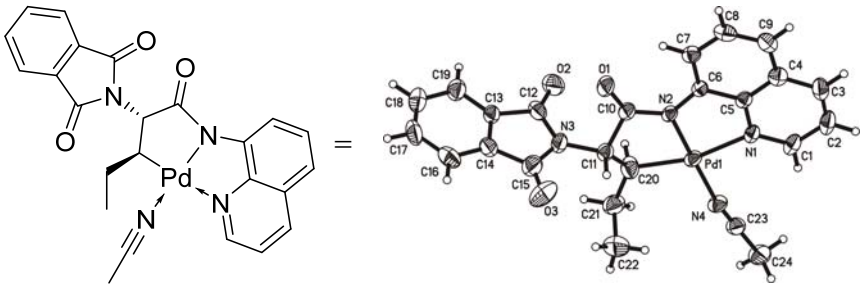
Synthesis of Palladacycle Compound



(**6**)

$Pd(OAc)_2$ (224.5 mg, 1.0 mmol) and **1b** (373.4 mg, 1.0 mmol) were added to CH_3CN/DCE (4 mL + 2 mL). The reaction was stirred at 50°C for 5h, and then the solvent was removed in vacuum. To the crude product, dichloromethane (3 mL) was added, followed by petroleum ether (10 mL), and then the purified product was collected by vacuum filtration, washed with petroleum ether: dichloromethane = 10:1, and dried under vacuum to afford **6** mixed with an unknown complex **6'** as a yellow powder (510.0 mg in total, estimated ratio of **6** to **6'** as 5.9:1 and estimated yield 80% of **6** based on crude ^{1}H NMR).Pure complex **6** was obtained from satuated solution in dimethyl sulfoxide.^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (d, *J* = 4.2 Hz, 1H), 8.81 (dd, *J* = 5.4, 3.5 Hz, 1H), 8.59 (d, *J* = 8.2 Hz, 1H), 7.96 – 7.83 (m, 4H), 7.72 (dd, *J* = 8.2, 4.9 Hz, 1H), 7.60 – 7.50 (m, 2H), 4.90 (d, *J* = 7.6 Hz, 1H), 2.79 (t, *J* = 6.3 Hz, 1H), 2.08 (s, 3H), 1.67 – 1.54 (m, 1H), 1.28 – 1.05 (m, 4H).

X-ray crystal data of 6:



Bond precision	C-C = 0.0094 Å	
Wavelength	0.71073	
Cell	a = 9.1886(7)	alpha = 81.563(6)
	b = 10.6165(7)	beta = 81.840(6)
	c = 11.5601(9)	gamma = 72.521(7)
Temperature	293 K	

	Calculated	Reported
Volume	1058.25(14)	1058.25(13)
Space group	P -1	P -1

Hall group	-P 1	-P 1
Moiety formula	C24 H20 N4 O3 Pd	C24 H20 N4 O3 Pd
Sum formula	C24 H20 N4 O3 Pd	C24 H20 N4 O3 Pd
Mr	518.84	518.84
Dx,g cm^{-3}	1.628	1.628
Z	2	2
Mu (mm^{-1})	0.912	0.912
F000	524.0	524.0
F000’	522.19	
h,k,lmax	11,12,13	11,12,13
Nref	3876	3867
Tmin,Tmax	0.754,0.811	0.759,0.818
Tmin’	0.739	

Correction method = MULTI-SCAN

Data completeness = 0.998 Theta(max) = 25.350

R(reflections) = 0.0513(3180) wR2(reflections) = 0.1085(3867)

S = 1.104 Npar = 295

References

1. Tran, L.D.; Daugulis, O. *Angew.Chem.Int.Ed.*, **2012**, *51*, 5188.
2. Reddy, B.V.S.; Reddy, L.R.; Corey, E.J. *Org.Lett.*, **2006** (8): 3391-3394.
3. Huang, T. S.; Keh, C. C. K.; Li, C. J. *Chem.Commun.*, **2002**, 2440-2441.