

Supporting Information

Practical Synthesis of Chiral β -Aryl- α -Hydroxy Acids *via* Palladium-Catalyzed C(sp³)-H Arylation of Lactic Acid

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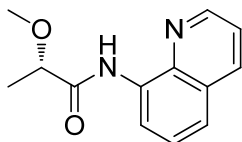
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General Information: Unless otherwise noted, all commercial materials were used without further purification. Anhydrous solvents obtained from Aladdin and Adamas were used directly without further purification, and solvents obtained from other commercial suppliers were used after purification as specified in *Purification of Laboratory Chemicals, 6th Ed.* Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker AVANCE 400MHz instrument. ^1H and ^{13}C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak ($\text{CHCl}_3 = 7.26$ (^1H NMR), $\text{DMSO} = 2.50$ (^1H NMR), $\text{CDCl}_3 = 77.16$ (^{13}C NMR)) unless otherwise noted. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. High-resolution mass spectra for new compounds were recorded at Mass Spectrometry Facilities, Zhejiang University. X-ray diffraction experiments were performed at X-Ray Facilities, Zhejiang University.

Experimental Procedures:

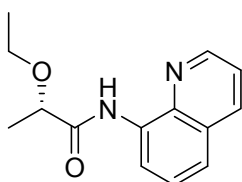
Preparation of Lactic Acid Substrates

(*S*)-2-Methoxy-*N*-(quinolin-8-yl)propanamide (**1a**)



To a stirred solution of (*S*)-2-methoxypropanoic acid ¹ (10.41 g, 100 mmol) in dry dichloromethane (300 mL), 4-methylmorpholine (NMM, 11.5 mL, 105 mmol) was added slowly at 0 °C. After the solution was stirred for five minutes, *iso*-butyl carbonochloridate (13.3 mL, 105 mmol) was added dropwise slowly at 0 °C. The mixture was then stirred at room temperature for 1.5 h. A solution of 8-aminoquinoline (8.65 g, 60 mmol) in dry dichloromethane (50 mL) was slowly added to the reaction at 0 °C. After the reaction was stirred at room temperature overnight, the resulting mixture was then washed by aqueous HCl (100 mL, 0.1 M), saturated Na₂CO₃ (100 mL), brine (100 mL), and dried over anhydrous MgSO₄. Evaporation of organic solvent and purification by silica gel column chromatography in 6:3:1 petroleum ether: dichloromethane: ethyl acetate, afforded the pure 8-aminoquinoline amide **1a** (13.12 g, 95%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 10.80 (s, 1H), 8.86 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.80 (dd, *J* = 6.4, 2.4 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.46 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.99 (q, *J* = 6.8 Hz, 1H), 3.58 (s, 3H), 1.55 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 170.89, 148.63, 138.92, 137.77, 136.20, 133.95, 129.51, 128.38, 128.03, 127.27, 126.60, 122.06, 121.69, 116.63, 84.55, 59.32, 39.58; HRMS (EI) *m/z*: 230.1058(M⁺), calc. for C₁₃H₁₄N₂O₂: 230.1055.

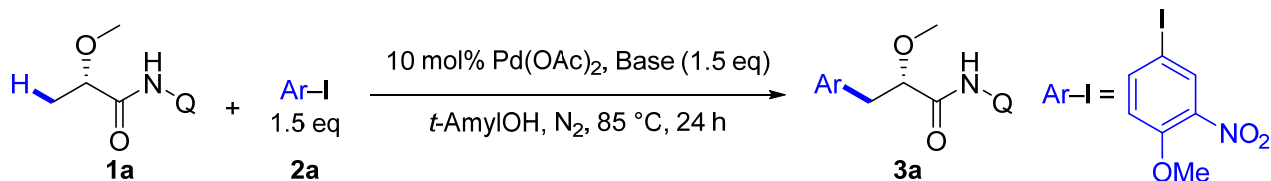
(*S*)-2-Ethyloxy-*N*-(quinolin-8-yl)propanamide (**1b**)



The preparation of **1b** followed the same procedure of **1a** except using (*S*)-2-ethoxypropanoic acid instead of (*S*)-2-methoxypropanoic acid. The compound **1b** was obtained as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 10.93 (s, 1H), 8.85 (dd, *J* = 4.0, 1.1 Hz, 1H), 8.79 (dd, *J* = 6.6, 1.9 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.71 – 7.50 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.06 (q, *J* = 6.8 Hz, 1H), 3.84 – 3.60 (m, 2H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.41 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 172.67, 148.64, 139.09, 136.29, 134.28, 128.14, 127.40, 121.93, 121.74, 116.59, 77.61, 66.28, 19.24, 15.54; HRMS (EI) *m/z*: 244.1214(M⁺), calc. for C₁₄H₁₆N₂O₂: 244.1212.

Optimization of Reaction Conditions Mono-arylation of **1a**

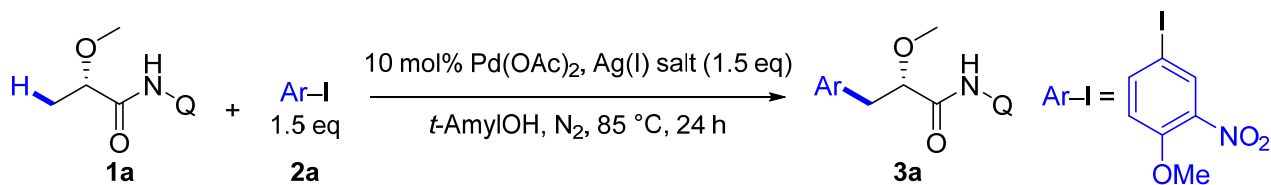
(1) Optimization of Base Additives (*t*-AmylOH used as solvent)



Entry	Base	Yield 3a
1	K ₂ CO ₃	17%
2	KOAc	trace
3	K ₃ PO ₄	26%
4	LiOAc	0
5	NaOAc	0
6	Na ₂ CO ₃	trace
7	CsOAc	trace
8	Cs ₂ CO ₃	18%

Reaction conditions: **1a** (0.20 mmol, 1.0 eq), **2a** (0.30 mmol, 1.5 eq), Pd(OAc)₂ (0.02 mmol, 10 mol%), base (0.30 mmol, 1.5 eq), *t*-AmylOH (2.0 ml), reaction for 24 hours at 85 °C and under N₂ atmosphere.

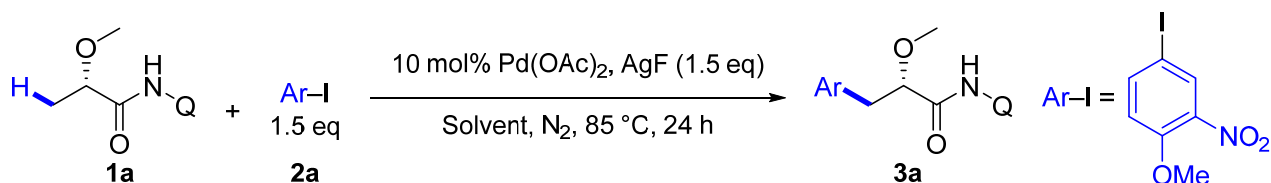
(2) Optimization of Silver(I) Salt Additives (*t*-AmylOH used as solvent)



Entry	Base	Yield 3a
1	AgOAc	16%
2	AgF	65%
3	AgTFA	0
4	Ag ₂ CO ₃	25%
5	Ag ₂ O	50%
6	Ag ₃ PO ₄	trace
7	AgOCN	trace
8	AgBF ₄	0
9	AgOPiv	trace

Reaction conditions: **1a** (0.20 mmol, 1.0 eq), **2a** (0.30 mmol, 1.5 eq), Pd(OAc)₂ (0.02 mmol, 10 mol%), silver salt (0.30 mmol, 1.5 eq), *t*-AmylOH (2.0 ml), reaction for 24 hours at 85 °C and under N₂ atmosphere.

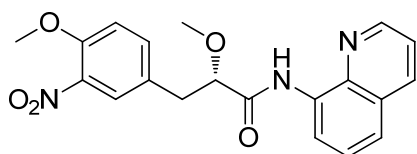
(3) Optimization of Solvent (AgF used as silver salt additive)



Entry	Solvent	Yield 3a
1	<i>t</i> -AmylOH	65%
2	DCE	51%
3	THF	30%
4	1,4-dioxane	18%
5	PhMe	14%
6	MeCN	0
7	DMF	60%
8	DMAc	54%
9	Acetone	52%
10	MeOH	64%
11 ^a	<i>t</i> -AmylOH	75%
12 ^{a, b}	<i>t</i> -AmylOH	64%
13 ^{a, c}	<i>t</i> -AmylOH	81% ^d
14 ^{a, c}	DMSO	trace
15 ^{a, c}	NMP	45%

Reaction conditions: **1a** (0.20 mmol, 1.0 eq), **2a** (0.30 mmol, 1.5 eq), Pd(OAc)_2 (0.02 mmol, 10 mol%), AgF (0.30 mmol, 1.5 eq), solvent (2.0 ml), reaction for 24 hours at 85°C and under N_2 atmosphere. ^a 3.0 equiv AgF was used; ^b 1.2 eq **2a** was used; ^c reaction for 12 hours; ^d isolated yield.

(*S*)-2-Methoxy-3-(4-methoxy-3-nitrophenyl)-*N*-(quinolin-8-yl)propanamide (**3a**)

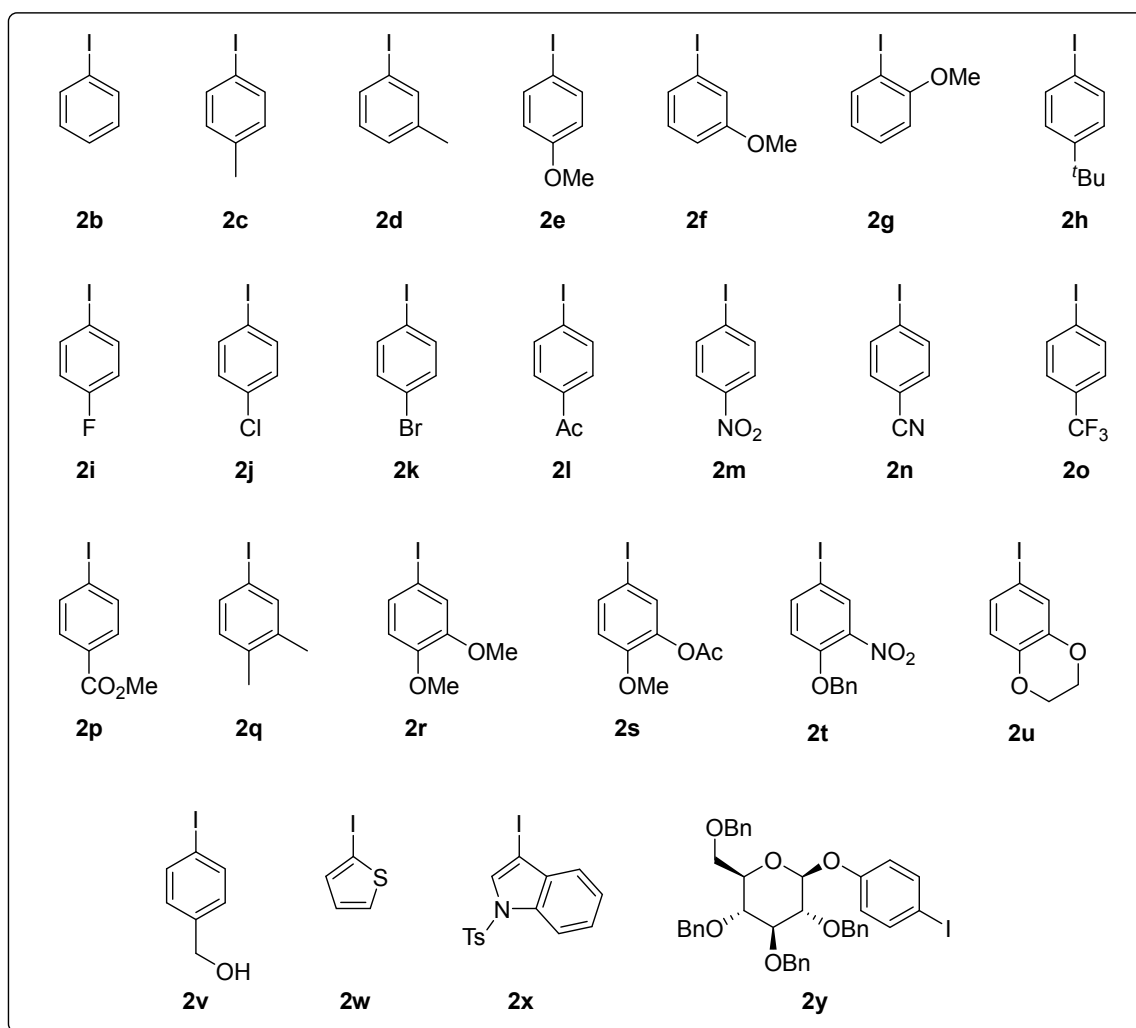


The title compound was prepared under the optimized condition. The crude product was purified by silica gel column chromatography in 4:1 petroleum ether:ethyl acetate, providing **3a** as a white solid (61.5 mg, 81%). ^1H NMR (400 MHz, CDCl_3) δ 10.65 (s, 1H), 8.79 (dd, $J = 4.4, 2.0$ Hz, 1H), 8.77 – 8.72 (m, 1H), 8.12 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.84 (d, $J = 2.4$ Hz, 1H), 7.54 – 7.49 (m, 2H), 7.45 – 7.41 (m, 2H), 6.90 (d, $J = 8.4$ Hz, 1H), 4.03 (dd, $J = 7.6, 3.6$ Hz, 1H), 3.82 (s, 3H), 3.53 (s, 3H), 3.24 (dd, $J = 14.4, 3.6$ Hz, 1H), 3.07 (dd, $J = 14.4, 7.6$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.06, 151.79, 148.70, 139.27, 138.81, 136.20, 135.41, 133.62, 129.78, 127.99, 127.16, 126.76, 122.24, 121.74, 116.66, 113.37, 83.69, 59.19, 56.47, 37.72. HRMS (EI) m/z : 381.1329 (M^+), calc. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_5$: 381.1325.

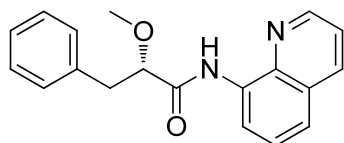
General Procedure (GP) for Mono-arylation of Lactic Acid Derivative

To a 30-mL resealable Schlenk flask was added **1a** (46.1 mg, 0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), aryl iodide (0.3 mmol), AgF (76.1 mg, 0.6 mmol), and *t*-AmylOH (2.0 mL). The Schlenk flask was charged with N₂. The mixture was stirred at 85 °C for 12 hours. After cooling to room temperature, the reaction was diluted with dichloromethane (5 mL), then filtered through a pad of Celite and washed by dichloromethane (20 mL). Evaporation of organic solvent and purification by column chromatography gave the corresponding product.

Scope of alkyl iodides:



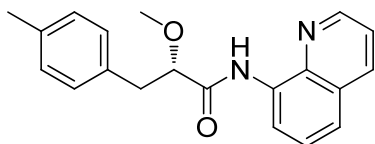
(*S*)-2-Methoxy-3-phenyl-*N*-(quinolin-8-yl)propanamide (**3b**)



The compound **3b** was prepared according to the **GP** and purified by column chromatography in toluene: ethyl acetate = 12:1. **3b** was obtained as a light yellow solid (45.5 mg, 74%). ¹H NMR (400

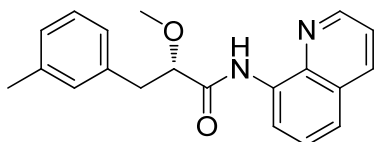
MHz, CDCl₃) δ 10.81 (s, 1H), 8.89 – 8.79 (m, 2H), 8.13 (dd, J = 8.3, 1.3 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.43 (dd, J = 8.3, 4.2 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.33 – 7.27 (m, 2H), 7.25 – 7.19 (m, 1H), 4.09 (dd, J = 8.7, 3.5 Hz, 1H), 3.49 (s, 2H), 3.33 (dd, J = 14.2, 3.4 Hz, 1H), 3.08 (dd, J = 14.2, 8.7 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 170.89, 148.63, 138.92, 137.77, 136.20, 133.95, 129.51, 128.38, 128.03, 127.27, 126.60, 122.06, 121.69, 116.63, 84.55, 59.32, 39.58; HRMS (EI) m/z : 306.1368 (M⁺); calc. for C₁₉H₁₈N₂O₂: 306.1368.

(S)-2-Methoxy-N-(quinolin-8-yl)-3-(p-tolyl)propanamide (3c)



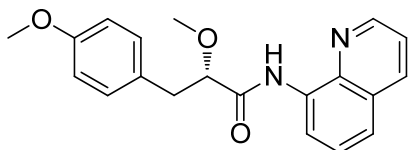
The compound **3c** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3c** was obtained as a colorless oil (45.8 mg, 72%). ¹H NMR (400 MHz, CDCl₃) δ 10.77 (s, 1H), 8.93 – 8.73 (m, 2H), 8.13 (dd, J = 8.2, 1.3 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.42 (dd, J = 8.2, 4.2 Hz, 1H), 7.22 (d, J = 7.8 Hz, 2H), 7.08 (d, J = 7.7 Hz, 2H), 4.04 (dd, J = 8.6, 3.5 Hz, 1H), 3.48 (s, 3H), 3.26 (dd, J = 14.2, 3.3 Hz, 1H), 3.03 (dd, J = 14.2, 8.6 Hz, 1H), 2.28 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.02, 148.63, 139.01, 136.21, 136.07, 134.68, 134.06, 129.39, 129.11, 128.08, 127.31, 122.03, 121.68, 116.71, 84.73, 59.29, 39.20, 21.13; HRMS (EI) m/z : 320.1523 (M⁺); calc. for C₂₀H₂₀N₂O₂: 320.1525.

(S)-2-Methoxy-N-(quinolin-8-yl)-3-(m-tolyl)propanamide (3d)



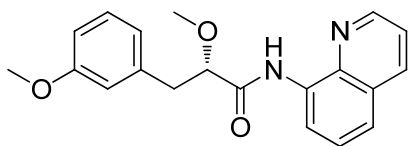
The compound **3d** was prepared according to the **GP** and purified by column chromatography in toluene: ethyl acetate = 20:1. **3d** was obtained as a colorless oil (46.3 mg, 72%). ¹H NMR (400 MHz, CDCl₃) δ 10.77 (s, 1H), 8.97 – 8.67 (m, 2H), 8.14 (dd, J = 8.2, 1.4 Hz, 1H), 7.63 – 7.48 (m, 2H), 7.43 (dd, J = 8.2, 4.2 Hz, 1H), 7.22 – 7.09 (m, 3H), 7.01 (d, J = 6.8 Hz, 1H), 4.06 (dd, J = 8.8, 3.4 Hz, 1H), 3.48 (s, 3H), 3.27 (dd, J = 14.2, 3.2 Hz, 1H), 3.01 (dd, J = 14.2, 8.8 Hz, 1H), 2.29 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.06, 148.66, 139.07, 137.95, 137.78, 136.24, 134.10, 130.35, 128.31, 128.12, 127.39, 127.35, 126.53, 122.05, 121.71, 116.74, 84.77, 59.37, 39.71, 21.46; HRMS (EI) m/z : 320.1520 (M⁺); calc. for C₂₀H₂₀N₂O₂: 320.1525.

(S)-2-Methoxy-3-(4-methoxyphenyl)-N-(quinolin-8-yl)propanamide (3e)



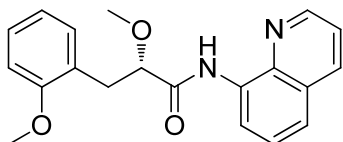
The compound **3e** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3e** was obtained as a colorless oil (36.8 mg, 55%). ¹H NMR (400 MHz, CDCl₃) δ 10.76 (s, 1H), 8.99 – 8.76 (m, 2H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 4.05 (dd, *J* = 8.1, 3.1 Hz, 1H), 3.77 (s, 3H), 3.51 (s, 3H), 3.26 (dd, *J* = 14.3, 3.1 Hz, 1H), 3.04 (dd, *J* = 14.3, 8.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 170.98, 158.36, 148.63, 138.95, 136.20, 133.99, 130.51, 129.73, 128.05, 127.28, 122.04, 121.68, 116.65, 113.78, 84.72, 59.28, 55.23, 38.65; HRMS (EI) *m/z*: 336.1479 (M⁺); calc. for C₂₀H₂₀N₂O₃: 336.1474.

(S)-2-Methoxy-3-(3-methoxyphenyl)-N-(quinolin-8-yl)propanamide (3f)



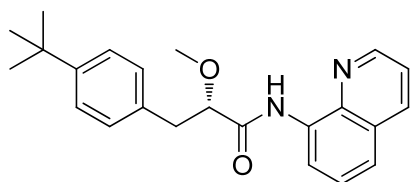
The compound **3f** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3f** was obtained as a white solid (54.0 mg, 80%). ¹H NMR (400 MHz, CDCl₃) δ 10.78 (s, 1H), 8.98 – 8.71 (m, 2H), 8.15 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.99 – 6.84 (m, 2H), 6.75 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.08 (dd, *J* = 8.6, 3.4 Hz, 1H), 3.76 (s, 3H), 3.50 (s, 3H), 3.29 (dd, *J* = 14.2, 3.2 Hz, 1H), 3.04 (dd, *J* = 14.2, 8.7 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ = 170.95, 159.70, 148.70, 139.42, 139.06, 136.27, 134.07, 129.37, 128.13, 127.35, 122.11, 121.99, 121.74, 116.74, 114.95, 112.41, 84.59, 59.40, 55.27, 39.73; HRMS (EI) *m/z*: 336.1476 (M⁺); calc. for C₂₀H₂₀N₂O₃: 336.1474.

(S)-2-Methoxy-3-(2-methoxyphenyl)-N-(quinolin-8-yl)propanamide (3g)



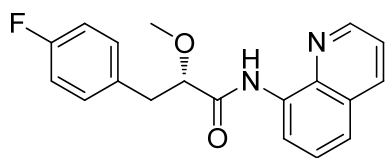
The compound **3g** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3g** was obtained as a colorless oil (27.7 mg, 41%). ¹H NMR (400 MHz, CDCl₃) δ 10.76 (s, 1H), 8.99 – 8.68 (m, 2H), 8.14 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.20 (td, *J* = 8.0, 1.4 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.19 (dd, *J* = 8.6, 4.3 Hz, 1H), 3.81 (s, 3H), 3.45 (s, 3H), 3.41 (dd, *J* = 14.0, 4.2 Hz, 1H), 3.02 (dd, *J* = 14.0, 8.6 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ = 171.43, 157.82, 148.61, 139.05, 136.25, 134.31, 131.48, 128.12, 128.00, 127.39, 126.08, 121.86, 121.69, 120.45, 116.69, 110.35, 83.15, 59.22, 55.45, 34.67; HRMS (EI) *m/z*: 336.1474 (M⁺); calc. for C₂₀H₂₀N₂O₃: 336.1474.

(S)-3-(4-(tert-Butyl)phenyl)-2-methoxy-N-(quinolin-8-yl)propanamide (3h)



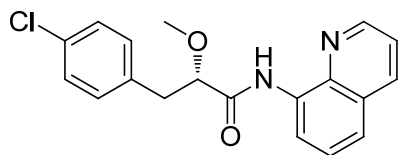
The compound **3h** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3h** was obtained as a colorless oil (50.5 mg, 70%). ¹H NMR (400 MHz, CDCl₃) δ 10.77 (s, 1H), 8.91 – 8.77 (m, 2H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.34 – 7.26 (m, 4H), 4.09 (dd, *J* = 8.6, 3.4 Hz, 1H), 3.51 (s, 3H), 3.29 (dd, *J* = 14.3, 3.4 Hz, 1H), 3.06 (dd, *J* = 14.3, 8.6 Hz, 1H), 1.28 (s, 9H); ¹³C NMR (100MHz, CDCl₃) δ 171.10, 149.33, 148.62, 138.95, 136.21, 134.69, 134.03, 129.14, 128.05, 127.30, 125.30, 122.02, 121.68, 116.63, 84.63, 59.29, 39.13, 34.44, 31.43; HRMS (EI) *m/z*: 362.1991 (*M*⁺); calc. for C₂₃H₂₆N₂O₂: 362.1994.

(S)-3-(4-Fluorophenyl)-2-methoxy-N-(quinolin-8-yl)propanamide (3i)



The compound **3i** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3i** was obtained as a white solid (51.1 mg, 79%). ¹H NMR (400 MHz, CDCl₃) δ 10.72 (s, 1H), 8.82 (dd, *J* = 4.0, 1.2 Hz, 1H), 8.79 (dd, *J* = 6.3, 2.5 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.32 – 7.23 (m, 2H), 6.95 (t, *J* = 8.7 Hz, 2H), 4.03 (dd, *J* = 8.2, 3.5 Hz, 1H), 3.50 (s, 3H), 3.26 (dd, *J* = 14.3, 3.4 Hz, 1H), 3.05 (dd, *J* = 14.3, 8.2 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 170.68, 161.90(d, *J*_{C-F} = 242.8 Hz), 148.71, 139.01, 136.28, 133.95, 133.32(d, *J*_{C-F} = 3.2 Hz), 131.08(d, *J*_{C-F} = 7.8 Hz), 128.12, 127.32, 122.17, 121.76, 116.73, 115.19(d, *J*_{C-F} = 21.0 Hz), 84.47, 59.32, 38.63; HRMS (EI) *m/z*: 324.1271 (*M*⁺); calc. for C₁₉H₁₇FN₂O₂: 324.1274.

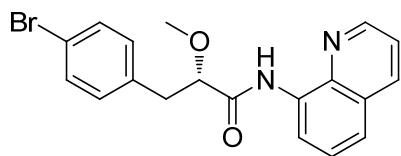
(S)-3-(4-Chlorophenyl)-2-methoxy-N-(quinolin-8-yl)propanamide (3j)



The compound **3j** was prepared according to the **GP** and purified by column chromatography in toluene: ethyl acetate = 12:1. **3j** was obtained as a yellow solid (56.1 mg, 83%). ¹H NMR (400 MHz, CDCl₃) δ 10.72 (s, 1H), 8.81 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.79 (dd, *J* = 6.6, 2.4 Hz, 1H), 8.13 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.24 (q, *J* = 8.4 Hz, 4H), 4.03 (dd, *J* = 8.2, 3.5 Hz, 1H), 3.49 (s, 3H), 3.25 (dd, *J* = 14.2, 3.4 Hz, 1H), 3.04 (dd, *J* = 14.2, 8.2 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 170.51, 148.70, 138.97, 136.25, 136.13, 133.89, 132.51, 130.98,

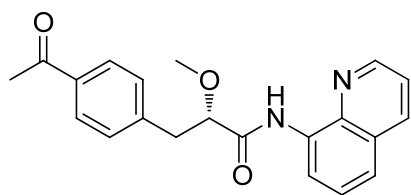
128.50, 128.09, 127.28, 122.18, 121.74, 116.72, 84.26, 59.31, 38.74; HRMS (EI) m/z : 340.0976 (M^+); calc. for $C_{19}H_{17}ClN_2O_2$: 340.0979.

(S)-3-(4-Bromophenyl)-2-methoxy-N-(quinolin-8-yl)propanamide (3k)



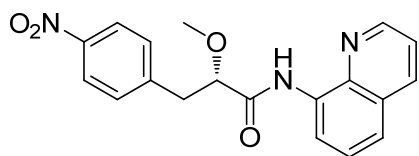
The compound **3k** was prepared according to the **GP** and purified by column chromatography in toluene: ethyl acetate = 20:1. **3k** was obtained as a light yellow oil (53.5 mg, 70%). 1H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.82 (dd, J = 4.1, 1.6 Hz, 1H), 8.79 (dd, J = 6.4, 2.5 Hz, 1H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.44 (dd, J = 8.2, 4.2 Hz, 1H), 7.38 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 4.03 (dd, J = 8.2, 3.6 Hz, 1H), 3.50 (s, 3H), 3.24 (dd, J = 14.2, 3.4 Hz, 1H), 3.03 (dd, J = 14.2, 8.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.48, 148.70, 138.98, 136.65, 136.24, 133.90, 131.45, 131.38, 128.09, 127.28, 122.18, 121.74, 120.64, 116.74, 84.19, 59.31, 38.81; HRMS (EI) m/z : 384.0477 (M^+); calc. for $C_{19}H_{17}BrN_2O_2$: 384.0473.

(S)-3-(4-Acetylphenyl)-2-methoxy-N-(quinolin-8-yl)propanamide (3l)



The compound **3l** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3l** was obtained as a white solid (48.3 mg, 69%). 1H NMR (400 MHz, $CDCl_3$) δ 10.73 (s, 1H), 8.85 – 8.74 (m, 2H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.58 – 7.50 (m, 2H), 7.46 – 7.38 (m, 3H), 4.09 (dd, J = 8.2, 3.6 Hz, 1H), 3.50 (s, 3H), 3.34 (dd, J = 14.1, 3.6 Hz, 1H), 3.14 (dd, J = 14.1, 8.2 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.96, 170.35, 148.68, 143.39, 138.92, 136.26, 135.68, 133.81, 129.83, 128.49, 128.05, 127.27, 122.22, 121.75, 116.70, 84.00, 59.34, 39.33, 26.65; HRMS (EI) m/z : 348.1477 (M^+); calc. for $C_{21}H_{20}N_2O_3$: 348.1474.

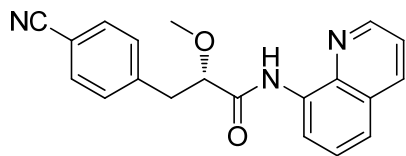
(S)-2-Methoxy-3-(4-nitrophenyl)-N-(quinolin-8-yl)propanamide (3m)



The compound **3m** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3m** was obtained as a light yellow solid (39.5 mg, 56%). 1H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.80 (d, J = 2.7 Hz, 1H), 8.78 – 8.65 (m, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.11 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 4.5 Hz, 2H), 7.51 – 7.39 (m, 3H), 4.11 (dd, J = 7.5,

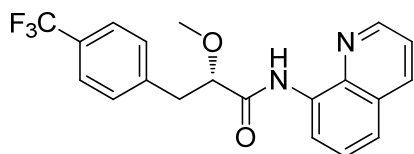
3.6 Hz, 1H), 3.54 (s, 3H), 3.38 (dd, $J = 14.0, 3.3$ Hz, 1H), 3.21 (dd, $J = 14.0, 7.7$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.92, 148.75, 147.03, 145.32, 138.95, 136.35, 133.67, 130.61, 128.12, 127.29, 123.58, 122.42, 121.85, 116.81, 83.63, 59.36, 39.01; HRMS (EI) m/z : 351.1220 (M^+); calc. for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_4$: 351.1219.

(S)-3-(4-Cyanophenyl)-2-methoxy-N-(quinolin-8-yl)propanamide (3n)



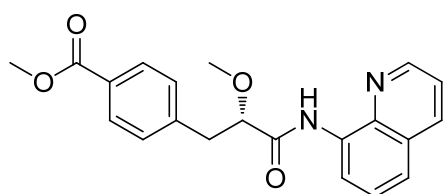
The compound **3n** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3n** was obtained as a colorless oil (14.0 mg, 21% under standard conditions; 32.4 mg, 49% under conditions of 2.0 equiv. Ag_2O and 2.0 mL DMF). ^1H NMR (400 MHz, CDCl_3) δ 10.67 (s, 1H), 8.82 (dd, $J = 4.0, 1.2$ Hz, 1H), 8.76 (t, $J = 4.4$ Hz, 1H), 8.16 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.55 – 7.53 (m, 4H), 7.48 – 7.42 (m, 3H), 4.08 (dd, $J = 8.0, 4.0$ Hz, 1H), 3.52 (s, 3H), 3.33 (dd, $J = 14.0, 3.6$ Hz, 1H), 3.16 (dd, $J = 14.0, 8.0$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.03, 148.77, 143.22, 138.98, 136.36, 133.74, 132.18, 130.54, 128.15, 127.32, 122.39, 121.87, 119.09, 116.80, 110.69, 83.74, 59.36, 39.35; HRMS (EI) m/z : 331.1319 (M^+); calc. for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_2$: 331.1321.

(S)-2-Methoxy-N-(quinolin-8-yl)-3-(4-(trifluoromethyl)phenyl)propanamide (3o)



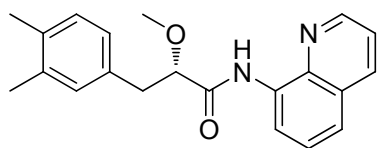
The compound **3o** was prepared according to the **GP** and purified by column chromatography in toluene: ethyl acetate = 12:1. **3o** was obtained as a white solid (48.3 mg, 65%). ^1H NMR (400 MHz, CDCl_3) δ 10.72 (s, 1H), 8.86 – 8.70 (m, 2H), 8.15 (dd, $J = 8.2, 1.0$ Hz, 1H), 7.59 – 7.48 (m, 4H), 7.47 – 7.40 (m, 3H), 4.08 (dd, $J = 8.1, 3.5$ Hz, 1H), 3.51 (s, 3H), 3.34 (dd, $J = 14.2, 3.3$ Hz, 1H), 3.14 (dd, $J = 14.1, 8.2$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.37, 148.74, 141.81, 138.98, 136.29, 133.85, 131.14, 129.99, 129.48, 129.16, 129.00 (q, $J_{\text{C-F}} = 32.1$ Hz), 128.12, 127.30, 125.30 (q, $J_{\text{C-F}} = 3.6$ Hz), 124.41 (q, $J_{\text{C-F}} = 270.2$ Hz), 122.28, 121.79, 116.76, 84.06, 59.36, 39.22; HRMS (EI) m/z : 374.1241 (M^+); calc. for $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_2$: 374.1242.

(S)-Methyl 4-(2-methoxy-3-oxo-3-(quinolin-8-ylamino)propyl)benzoate (3p)



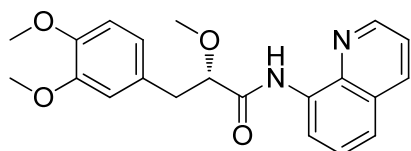
The compound **3p** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3p** was obtained as a white solid (48.2 mg, 66%). ¹H NMR (400 MHz, CDCl₃) δ 10.74 (s, 1H), 8.94 – 8.62 (m, 2H), 8.13 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.62 – 7.48 (m, 2H), 7.47 – 7.33 (m, 3H), 4.08 (dd, *J* = 8.3, 3.5 Hz, 1H), 3.87 (s, 3H), 3.49 (s, 3H), 3.34 (dd, *J* = 14.1, 3.3 Hz, 1H), 3.12 (dd, *J* = 14.1, 8.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 170.40, 167.14, 148.68, 143.18, 138.98, 136.24, 133.87, 129.70, 129.65, 128.63, 128.09, 127.27, 122.19, 121.71, 116.73, 84.11, 59.34, 52.05, 39.43; HRMS (EI) *m/z*: 364.1419 (M⁺); calc. for C₂₁H₂₀N₂O₄: 364.1423.

(S)-3-(3,4-Dimethylphenyl)-2-methoxy-N-(quinolin-8-yl)propanamide (3q)



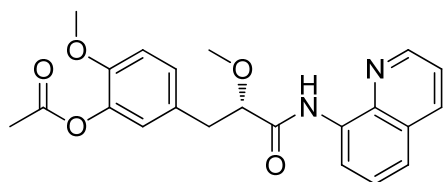
The compound **3q** was prepared according to the **GP** and purified by column chromatography in toluene: ethyl acetate = 20:1. **3q** was obtained as a colorless oil (50.5 mg, 76%). ¹H NMR (400 MHz, CDCl₃) δ 10.76 (s, 1H), 9.00 – 8.67 (m, 2H), 8.15 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.17 – 6.96 (m, 3H), 4.06 (dd, *J* = 8.7, 3.4 Hz, 1H), 3.49 (s, 3H), 3.24 (dd, *J* = 14.2, 3.3 Hz, 1H), 3.00 (dd, *J* = 14.2, 8.7 Hz, 1H), 2.20 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 171.20, 148.65, 139.08, 136.49, 136.25, 135.20, 134.74, 134.15, 130.86, 129.71, 128.13, 127.37, 126.85, 122.03, 121.71, 116.77, 84.88, 59.35, 39.34, 19.79, 19.44; HRMS (EI) *m/z*: 334.1685 (M⁺); calc. for C₂₁H₂₂N₂O₂: 334.1681.

(S)-3-(3,4-Dimethoxyphenyl)-2-methoxy-N-(quinolin-8-yl)propanamide (3r)



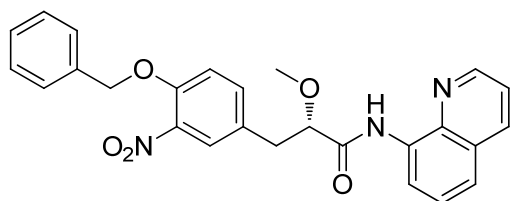
The compound **3r** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3r** was obtained as a colorless oil (52.2 mg, 71%). ¹H NMR (400 MHz, CDCl₃) δ 10.72 (s, 1H), 9.00 – 8.63 (m, 2H), 8.14 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.62 – 7.48 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 6.95 – 6.80 (m, 2H), 6.76 (d, *J* = 8.6 Hz, 1H), 4.04 (dd, *J* = 8.1, 3.5 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.51 (s, 3H), 3.24 (dd, *J* = 14.3, 3.4 Hz, 1H), 3.03 (dd, *J* = 14.3, 8.1 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 170.98, 148.81, 148.66, 147.81, 138.99, 136.25, 134.03, 130.22, 128.11, 127.29, 122.11, 121.74, 121.69, 116.66, 112.69, 111.14, 84.71, 59.32, 55.91, 55.88, 39.14; HRMS (EI) *m/z*: 366.1577 (M⁺); calc. for C₂₁H₂₂N₂O₄: 366.1580.

(S)-2-Methoxy-5-(2-methoxy-3-oxo-3-(quinolin-8-ylamino)propyl)phenyl acetate (3s)



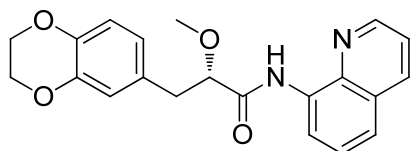
The compound **3s** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3s** was obtained as a colorless oil (54.1 mg, 69%). ^1H NMR (400 MHz, CDCl_3) δ 10.76 (s, 1H), 8.84 (dd, J = 4.0, 1.4 Hz, 1H), 8.80 (dd, J = 6.4, 2.3 Hz, 1H), 8.15 (dd, J = 8.2, 1.4 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.45 (dd, J = 8.2, 4.2 Hz, 1H), 7.16 (dd, J = 8.3, 1.4 Hz, 1H), 7.06 (s, 1H), 6.86 (d, J = 8.3 Hz, 1H), 4.00 (dd, J = 8.6, 3.1 Hz, 1H), 3.78 (s, 3H), 3.49 (s, 3H), 3.23 (dd, J = 14.3, 2.8 Hz, 1H), 2.98 (dd, J = 14.3, 8.7 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ = 170.84, 169.14, 149.94, 148.71, 139.60, 139.06, 136.26, 134.03, 130.50, 128.13, 127.82, 127.33, 124.09, 122.12, 121.74, 116.76, 112.37, 84.61, 59.45, 56.01, 38.69, 20.79; HRMS (EI) m/z : 394.1526 (M^+); calc. for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_5$: 394.1529.

(S)-3-(4-(Benzyloxy)-3-nitrophenyl)-2-methoxy-N-(quinolin-8-yl)propanamide (3t)



The compound **3t** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3t** was obtained as a colorless oil (57.5 mg, 63%). ^1H NMR (400 MHz, CDCl_3) δ 10.66 (s, 1H), 8.81 (dd, J = 4.0, 1.1 Hz, 1H), 8.76 (dd, J = 5.3, 3.6 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.87 (s, 1H), 7.58 – 7.49 (m, 2H), 7.46 – 7.28 (m, 7H), 6.95 (d, J = 8.5 Hz, 1H), 5.17 – 5.02 (m, 2H), 4.04 (dd, J = 7.3, 3.4 Hz, 1H), 3.54 (s, 3H), 3.25 (dd, J = 14.3, 3.3 Hz, 1H), 3.08 (dd, J = 14.3, 7.6 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.11, 150.82, 148.76, 140.02, 138.95, 136.24, 135.79, 135.21, 133.75, 130.34, 128.74, 128.24, 128.08, 127.26, 127.04, 126.78, 122.27, 121.78, 116.78, 115.15, 83.78, 71.31, 59.24, 37.90; HRMS (EI) m/z : 457.1639 (M^+); calc. for $\text{C}_{26}\text{H}_{23}\text{N}_3\text{O}_5$: 457.1638.

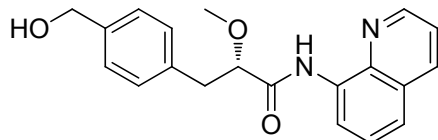
(S)-3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-2-methoxy-N-(quinolin-8-yl)propanamide (3u)



The compound **3u** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3u** was obtained as a colorless oil (46.8 mg, 64%). ^1H NMR (400 MHz, CDCl_3) δ 10.75 (s, 1H), 8.95 – 8.70 (m, 2H), 8.14 (dd, J = 8.2, 1.3 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.44 (dd, J = 8.2, 4.2 Hz, 1H), 6.86 (s, 1H), 6.83 – 6.67 (m, 2H), 4.20 (s, 4H), 4.02 (dd, J = 8.5, 3.4 Hz, 1H), 3.50 (s, 3H), 3.19 (dd, J = 14.3, 3.2 Hz, 1H), 2.96 (dd, J = 14.3, 8.5 Hz, 1H); ^{13}C

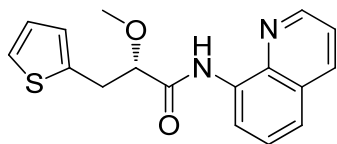
NMR (101 MHz, CDCl₃) δ 170.99, 148.66, 143.34, 142.35, 139.03, 136.25, 134.05, 131.02, 128.10, 127.34, 122.52, 122.05, 121.70, 118.24, 117.09, 116.75, 84.62, 64.43, 64.40, 59.32, 38.86; HRMS (EI) m/z : 364.1427 (M⁺); calc. for C₂₁H₂₀N₂O₄: 364.1423.

(S)-3-(4-(Hydroxymethyl)phenyl)-2-methoxy-N-(quinolin-8-yl)propanamide (3v)



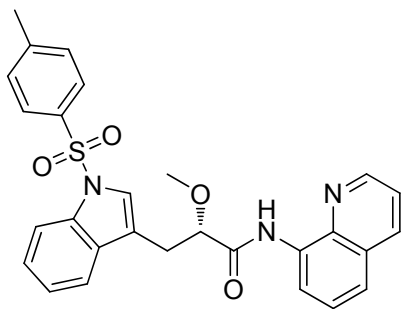
The compound **3v** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 2:1. **3v** was obtained as a light yellow solid (39.6 mg, 59%). ¹H NMR (400 MHz, CDCl₃) δ 10.75 (s, 1H), 8.96 – 8.63 (m, 2H), 8.15 (dd, J = 8.2, 1.0 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.44 (dd, J = 8.2, 4.2 Hz, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 4.63 (s, 2H), 4.05 (dd, J = 8.4, 3.5 Hz, 1H), 3.49 (s, 3H), 3.29 (dd, J = 14.2, 3.3 Hz, 1H), 3.07 (dd, J = 14.2, 8.5 Hz, 1H), 1.78 (brs, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 170.90, 148.69, 139.29, 139.04, 137.23, 136.29, 134.01, 129.79, 128.12, 127.36, 127.19, 122.14, 121.74, 116.78, 84.55, 65.29, 59.32, 39.24; HRMS (EI) m/z : 336.1475 (M⁺); calc. for C₂₀H₂₀N₂O₃: 336.1474.

(S)-2-Methoxy-N-(quinolin-8-yl)-3-(thiophen-2-yl)propanamide (3w)



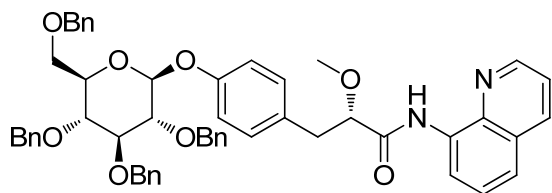
The compound **3w** was prepared according to the **GP** and purified by column chromatography in toluene: ethyl acetate = 20:1. **3w** was obtained as a light yellow oil (37.4 mg, 60%). ¹H NMR (400 MHz, CDCl₃) δ 10.82 (s, 1H), 8.84 (d, J = 3.9 Hz, 1H), 8.81 (dd, J = 6.2, 2.4 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.61 – 7.50 (m, 2H), 7.45 (dd, J = 8.2, 4.2 Hz, 1H), 7.15 (d, J = 5.0 Hz, 1H), 7.03 – 6.93 (m, 1H), 6.94 – 6.82 (m, 1H), 4.06 (dd, J = 8.2, 3.2 Hz, 1H), 3.60 (s, 3H), 3.53 (dd, J = 15.3, 3.0 Hz, 1H), 3.32 (dd, J = 15.2, 8.3 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 170.29, 148.73, 139.48, 139.05, 136.27, 133.98, 128.12, 127.34, 126.74, 126.41, 124.54, 122.19, 121.76, 116.79, 84.03, 59.34, 33.65; HRMS (EI) m/z : 312.0929 (M⁺); calc. for C₁₇H₁₆N₂O₂S: 312.0932.

(S)-2-Methoxy-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)propanamide (3x)



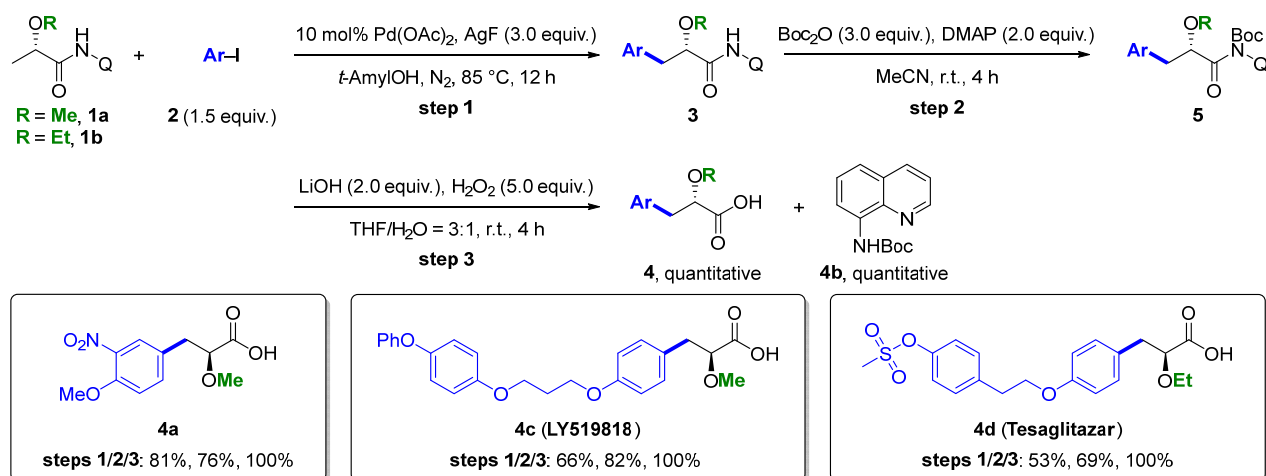
The compound **3x** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3x** was obtained as a colorless oil (58.6 mg, 59%). ¹H NMR (400 MHz, CDCl₃) δ 10.79 (s, 1H), 8.83 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.77 (dd, *J* = 4.9, 4.0 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.67 – 7.56 (m, 4H), 7.56 – 7.49 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.28 – 7.16 (m, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 4.13 (dd, *J* = 7.3, 3.7 Hz, 1H), 3.52 (s, 3H), 3.35 (dd, *J* = 15.2, 3.5 Hz, 1H), 3.20 (dd, *J* = 15.2, 7.3 Hz, 1H), 2.17 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ = 170.50, 148.80, 144.61, 138.99, 136.22, 135.36, 135.12, 133.94, 131.27, 129.69, 128.09, 127.31, 126.71, 124.79, 124.65, 123.19, 122.15, 121.79, 119.81, 118.46, 116.77, 113.67, 82.89, 59.15, 28.33, 21.49; HRMS (EI) *m/z*: 499.1570 (M⁺); calc. for C₂₈H₂₅N₃O₄S: 499.1566.

(S)-2-Methoxy-N-(quinolin-8-yl)-3-(4-(((2S,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)phenyl)propanamide (3y)

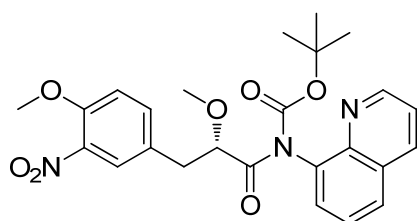


The compound **3y** was prepared according to the **GP** and purified by column chromatography in petroleum ether: ethyl acetate = 4:1. **3y** was obtained as a white solid (117.0 mg, 67%). ¹H NMR (400 MHz, CDCl₃) δ 10.78 (s, 1H), 8.84 – 8.81 (m, 2H), 8.14 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.43 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.20 – 7.18 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 5.02 (d, *J* = 10.8 Hz, 1H), 4.96 – 4.93 (m, 2H), 4.86 – 4.79 (m, 3H), 4.60 – 4.50 (m, 3H), 4.03 (dd, *J* = 8.8, 3.6 Hz, 1H), 3.78 (d, *J* = 10.4 Hz, 1H), 3.73 – 3.64 (m, 4H), 3.59 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.49 (s, 3H), 3.27 (dd, *J* = 14.0, 2.8 Hz, 1H), 3.03 (dd, *J* = 14.3, 8.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 170.94, 156.32, 148.69, 139.04, 138.65, 138.37, 138.26, 138.17, 136.26, 134.05, 132.05, 130.63, 128.53, 128.51, 128.49, 128.47, 128.33, 128.12, 128.07, 127.99, 127.92, 127.86, 127.76, 127.72, 127.34, 122.09, 121.74, 116.99, 116.91, 116.72, 102.01, 84.79, 84.71, 82.14, 77.85, 75.86, 75.23, 75.16, 75.11, 73.61, 68.98, 59.38, 38.84; HRMS (ESI) *m/z*: 867.3567 (MNa⁺); calc. for C₅₃H₅₂N₂O₈: 867.3616.

Synthetic Applications

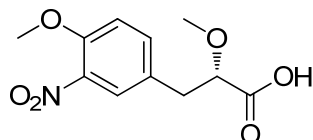


(*S*)-*tert*-Butyl(2-methoxy-3-(4-methoxy-3-nitrophenyl)propanoyl)(quinolin-8-yl)carbamate (**5a**)



To a solution of **3a** (152.6 mg, 0.4 mmol) in dry MeCN (4 mL) were added di-*tert*-butyl dicarbonate (Boc_2O , 261.9 mg, 1.2 mmol) and *N,N*-dimethylpyridin-4-amine (DMAP, 97.7 mg, 0.8 mmol). The mixture was stirred at room temperature for 4 hours. Then the reaction was diluted with dichloromethane (15 mL), washed by water (15 mL), brine (20 mL), and dried over anhydrous MgSO_4 . Evaporation of organic solvent and purification by column chromatography in petroleum ether: ethyl acetate = 2:1 gave the product **5a** as a white solid (146.3 mg, 76%). ^1H NMR (400 MHz, CDCl_3) δ 8.86 (dd, $J = 4.0, 1.5$ Hz, 1H), 8.17 (dd, $J = 8.3, 1.4$ Hz, 1H), 7.92 (d, $J = 1.7$ Hz, 1H), 7.83 (dd, $J = 8.1, 1.1$ Hz, 1H), 7.61 (dd, $J = 8.6, 1.9$ Hz, 1H), 7.56 (t, $J = 7.7$ Hz, 1H), 7.50 (dd, $J = 7.2, 1.0$ Hz, 1H), 7.42 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.02 (d, $J = 8.6$ Hz, 1H), 5.21 (dd, $J = 8.5, 2.6$ Hz, 1H), 3.94 (s, 3H), 3.46 (dd, $J = 13.4, 2.2$ Hz, 1H), 3.38 (s, 3H), 3.01 (dd, $J = 14.2, 8.6$ Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.11, 152.98, 151.73, 150.54, 144.15, 139.53, 136.41, 136.07, 135.84, 131.32, 129.05, 128.39, 126.74, 126.17, 121.72, 113.39, 83.26, 82.51, 58.27, 56.66, 38.21, 27.72.

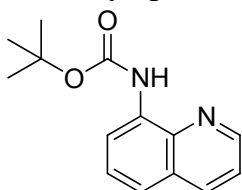
(*S*)-2-Methoxy-3-(4-methoxy-3-nitrophenyl)propanoic acid (**4a**)



To a solution of **5a** (48.1 mg, 0.1 mmol) in THF/ H_2O (3:1, 0.5 mL) were added LiOH (4.8 mg, 0.2 mmol) and H_2O_2 (30%, 50 μL , 0.5 mmol). The mixture was stirred at room temperature for 4 hours. Then the reaction was acidified by HCl (0.5 M, 12 mL), diluted with ethyl acetate (15 mL), washed by water (15 mL), brine (20 mL), and dried over anhydrous MgSO_4 . Evaporation of organic solvent and

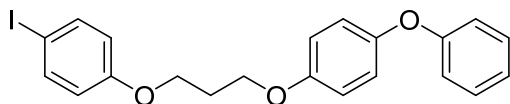
purification by column chromatography in petroleum ether: ethyl acetate = 1:1 gave the product **4a** as a light yellow oil (25.5 mg, 100%) with **4b** (24.1 mg, 100%) isolated. ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, J = 1.7 Hz, 1H), 7.44 (dd, J = 8.5, 1.8 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 3.99 (dd, J = 7.4, 4.2 Hz, 1H), 3.94 (s, 3H), 3.42 (s, 3H), 3.12 (dd, J = 14.3, 4.0 Hz, 1H), 3.01 (dd, J = 14.4, 7.5 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.99, 152.13, 139.48, 135.54, 129.03, 126.57, 113.72, 80.63, 58.85, 56.68, 37.28; HRMS (EI) m/z : 255.0745 (M^+); calc. for $\text{C}_{11}\text{H}_{13}\text{NO}_6$: 255.0743.

tert-Butyl quinolin-8-ylcarbamate (4b)



^1H NMR (400 MHz, CDCl_3) δ 9.02 (s, 1H), 8.79 (dd, J = 4.1, 1.5 Hz, 1H), 8.42 (d, J = 7.4 Hz, 1H), 8.13 (dd, J = 8.2, 1.4 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.46 – 7.35 (m, 2H), 1.58 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 153.05, 148.09, 138.41, 136.37, 135.35, 128.21, 127.49, 121.63, 120.28, 114.59, 80.54, 28.55; HRMS (EI) m/z : 244.1210 (M^+); calc. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$: 244.1212.

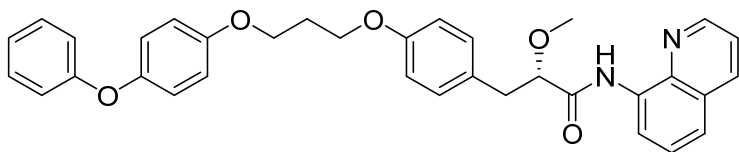
1-Iodo-4-(3-(4-phenoxyphenoxy)propoxy)benzene (2z)



To a solution of 4-phenoxyphenol (1.86 g, 10 mmol) and 1,3-dibromopropane (10.09 g, 50 mmol) in anhydrous DMF (50 mL) was slowly added cesium carbonate (4.24 g, 13 mmol). The resulting suspension was heated at 65 °C overnight. After being allowed to cool to the room temperature, the reaction mixture was diluted with water (50 mL). Then the aqueous layer was extracted with Et_2O (3×50 mL). The organic layer was washed by brine (2×40 mL), and dried over anhydrous MgSO_4 . Evaporation of organic solvent and purification by column chromatography in petroleum ether: ethyl acetate = 50:1 gave the product 1-(3-bromopropoxy)-4-phenoxybenzene as a yellow liquid.

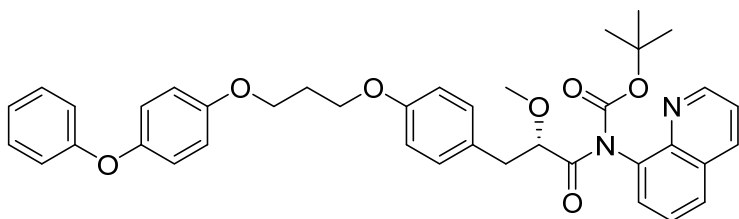
To a solution of 4-iodophenol (1.32 g, 6 mmol) and 1-(3-bromopropoxy)-4-phenoxybenzene (2.03 g, 6.6 mmol) in anhydrous DMF (30 mL) was slowly added cesium carbonate (2.35 g, 7.2 mmol). The resulting suspension was heated at 65 °C overnight. After being allowed to cool to the room temperature, the reaction mixture was diluted with water (30 mL). Then the aqueous layer was extracted with Et_2O (3×40 mL). The organic layer was washed by brine (2×20 mL), and dried over anhydrous MgSO_4 . Evaporation of organic solvent and purification by column chromatography in petroleum ether: ethyl acetate = 50:1 gave the product **2z** as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.56 (d, J = 8.5 Hz, 2H), 7.31 (t, J = 7.7 Hz, 2H), 7.05 (t, J = 7.0 Hz, 2H), 7.00 – 6.93 (m, 4H), 6.90 (d, J = 8.9 Hz, 2H), 6.71 (d, J = 8.5 Hz, 2H), 4.14 (t, J = 6.0 Hz, 4H), 2.31 – 2.21 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 158.88, 158.58, 155.22, 150.39, 138.35, 129.74, 122.59, 120.94, 117.75, 117.06, 115.65, 82.90, 77.48, 77.16, 76.84, 64.87, 64.67, 29.38; HRMS (EI) m/z : 446.0381 (M^+); calc. for $\text{C}_{21}\text{H}_{19}\text{IO}_3$: 446.0379.

(S)-2-Methoxy-3-(4-(3-(4-phenoxyphenoxy)propoxy)phenyl)-N-(quinolin-8-yl)propanamide (3z)



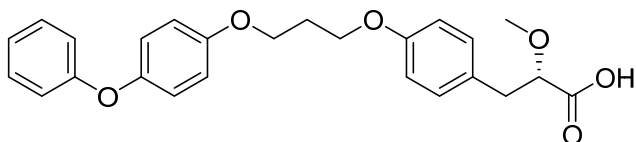
The compound **3z** was prepared according to the **GP** (using **1a** and **2z** as substrates) and purified by column chromatography in petroleum ether: ethyl acetate = 2:1. **3z** was obtained as a light yellow oil (72.5 mg, 66%). ¹H NMR (400 MHz, CDCl₃) δ 10.74 (s, 1H), 8.91 – 8.71 (m, 2H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.63 – 7.49 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 9.8 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 7.01 – 6.91 (m, 4H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.12 (dd, *J* = 11.0, 5.6 Hz, 4H), 4.02 (dd, *J* = 8.3, 3.5 Hz, 1H), 3.49 (s, 3H), 3.24 (dd, *J* = 14.3, 3.3 Hz, 1H), 3.02 (dd, *J* = 14.3, 8.4 Hz, 1H), 2.23 (dt, *J* = 11.8, 5.8 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 170.97, 158.59, 157.68, 155.28, 150.26, 148.62, 138.98, 136.21, 134.03, 130.55, 129.87, 129.69, 128.07, 127.30, 122.51, 122.03, 121.67, 120.90, 117.68, 116.68, 115.62, 114.44, 84.73, 65.03, 64.40, 59.26, 38.65, 29.45; HRMS (EI) *m/z*: 548.2310 (*M*⁺); calc. for C₃₄H₃₂N₂O₅: 548.2311.

(S)-tert-Butyl-(2-methoxy-3-(4-(3-(4-phenoxyphenoxy)propoxy)phenyl)propanoyl)(quinolin-8-yl)carbamate (5b)



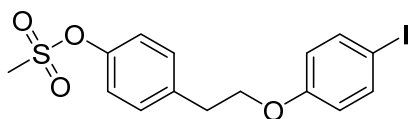
To a solution of **3z** (53.5 mg, 0.1 mmol) in dry MeCN (1 mL) were added di-*tert*-butyl dicarbonate (Boc₂O, 65.5 mg, 0.3 mmol) and *N,N*-dimethylpyridin-4-amine (DMAP, 24.4 mg, 0.2 mmol). The mixture was stirred at room temperature for 8 hours. Then the reaction was diluted with dichloromethane (10 mL), washed by water (10 mL), brine (10 mL), and dried over anhydrous MgSO₄. Evaporation of organic solvent and purification by column chromatography in petroleum ether: ethyl acetate = 2:1 gave the product **5b** as light yellow oil (53.2 mg, 82%). ¹H NMR (400 MHz, CDCl₃) δ 8.86 (s, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.39 (dd, *J* = 7.9, 4.0 Hz, 1H), 7.36 – 7.22 (m, 4H), 7.14 – 6.72 (m, 9H), 5.25 (d, *J* = 7.2 Hz, 1H), 4.15 (dd, *J* = 11.7, 5.7 Hz, 4H), 3.57 – 3.16 (m, 4H), 2.96 (dd, *J* = 13.9, 9.0 Hz, 1H), 2.40 – 2.12 (m, 2H), 1.22 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 175.86, 158.63, 157.60, 155.33, 152.90, 150.44, 150.23, 144.22, 136.63, 136.00, 130.85, 130.73, 129.70, 128.98, 128.21, 126.14, 122.51, 121.63, 120.94, 117.68, 115.64, 114.35, 82.90, 65.08, 64.44, 58.30, 38.80, 29.51, 27.70.

(S)-2-Methoxy-3-(4-(3-(4-phenoxyphenoxy)propoxy)phenyl)propanoic acid (4c)



To a solution of **5b** (45.1 mg, 0.07 mmol) in THF/H₂O (3:1, 0.5 mL) were added LiOH (3.4 mg, 0.14 mmol) and H₂O₂ (30%, 35 μ L, 0.35 mmol). The mixture was stirred at room temperature for 4 hours. Then the reaction was acidified by HCl (0.5 M, 10 mL), diluted with ethyl acetate (10 mL), washed by water (10 mL), brine (10 mL), and dried over anhydrous MgSO₄. Evaporation of organic solvent and purification by column chromatography in petroleum ether: ethyl acetate = 1:1 gave the product **4c** as a light yellow oil (30.5 mg, 100%) with **4b** (17.0 mg, 100%) isolated. ¹H NMR (400 MHz, CDCl₃) δ 7.30 (t, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 7.04 (t, *J* = 7.3 Hz, 1H), 7.00 – 6.91 (m, 4H), 6.91 – 6.81 (m, 4H), 4.14 (t, *J* = 5.1 Hz, 4H), 3.98 (dd, *J* = 6.9, 4.1 Hz, 1H), 3.40 (s, 3H), 3.09 (dd, *J* = 14.2, 3.8 Hz, 1H), 2.97 (dd, *J* = 14.2, 7.6 Hz, 1H), 2.30 – 2.20 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 176.02, 158.62, 157.96, 155.30, 150.30, 130.57, 129.73, 128.75, 122.56, 120.95, 117.72, 115.65, 114.56, 81.56, 65.03, 64.47, 58.76, 37.83, 29.50; HRMS (ESI) *m/z*: 421.4 ([M-H]⁻); calc. for C₂₅H₂₅O₆: 421.2.

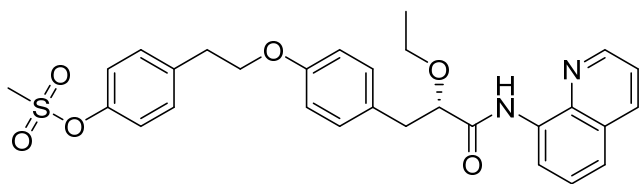
4-(2-(4-Iodophenoxy)ethyl)phenyl methanesulfonate (**2aa**)



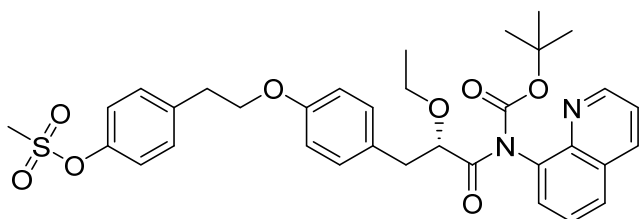
A mixture of 4-hydroxyphenethyl alcohol (2.76 g, 20 mmol) and triethylamine (8.8 mL, 63 mmol) in anhydrous dichloromethane (40 mL) was stirred at 0 °C. Then methane sulfonic chloride (4.0 mL, 50 mmol) was slowly added to the solution. After stirring for 30 minutes, the reaction was diluted with ethyl acetate (20 mL), washed by aqueous NH₄Cl (40 mL), brine (20 mL), and dried over anhydrous MgSO₄. After evaporation of organic solvent, the crude product was directly used for the next step without any purification.

The crude product 4-(2-((methylsulfonyl)oxy)ethyl)phenyl methanesulfonate (20 mmol) was dissolved in acetonitrile (30 mL). The resulting solution was then slowly added to a mixture of 4-iodophenol (11.0 g, 50 mmol) and potassium carbonate (8.29g, 60.0 mmol) in acetonitrile (50 mL). The reaction was heated at a refluxing temperature for 3.0 h. After being allowed to cool to room temperature, the reaction mixture was filtered through a pad of Celite. After the evaporation of the solvent, the mixture was diluted with dichloromethane (50 mL), washed by water (40 mL), brine (20 mL), and dried over anhydrous MgSO₄. Evaporation of the solvent and purification by column chromatography in petroleum ether: ethyl acetate = 3:1 gave the product **2aa** as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 4.13 (t, *J* = 6.8 Hz, 1H), 3.13 (s, 2H), 3.09 (t, *J* = 6.8 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 158.65, 148.05, 138.40, 137.80, 130.67, 122.18, 117.08, 83.09, 68.45, 37.48, 35.15; HRMS (EI) *m/z*: 417.9738 (M⁺); calc. for C₁₅H₁₅IO₄S: 417.9736.

(S)-4-(2-(4-(2-Ethoxy-3-oxo-3-(quinolin-8-ylamino)propyl)phenoxy)ethyl)phenyl methanesulfonate (3aa)

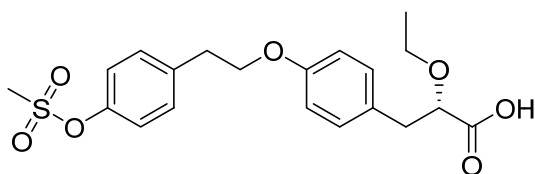


The compound **3aa** was prepared according to the **GP** (using **1b** and **2aa** as substrates) and purified by column chromatography in petroleum ether: ethyl acetate = 2:1. **3aa** was obtained as a light yellow oil (56.5 mg, 53%). ¹H NMR (400 MHz, CDCl₃) δ 10.92 (s, 1H), 8.91 – 8.70 (m, 2H), 8.13 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.59 – 7.48 (m, 2H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.24 (m, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.12 (t, *J* = 6.7 Hz, 2H), 4.05 (dd, *J* = 8.9, 3.1 Hz, 1H), 3.64 (tt, *J* = 14.0, 7.0 Hz, 1H), 3.49 (dq, *J* = 14.1, 7.0 Hz, 1H), 3.23 (dd, *J* = 14.2, 3.0 Hz, 1H), 3.12 (s, 3H), 3.06 (t, *J* = 6.7 Hz, 2H), 2.97 (dd, *J* = 14.2, 9.0 Hz, 1H), 1.29 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.47, 157.40, 148.61, 147.96, 139.02, 138.13, 136.24, 134.15, 130.66, 130.64, 130.49, 128.10, 127.34, 122.04, 121.99, 121.72, 116.56, 114.42, 82.93, 68.25, 67.38, 39.04, 37.38, 35.24, 15.37; HRMS (EI) *m/z*: 534.1829 (M⁺); calc. for C₂₉H₃₀N₂O₆S: 534.1825. **(S)-4-(2-(4-(3-((tert-Butoxycarbonyl)(quinolin-8-yl)amino)-2-ethoxy-3-oxopropyl)phenoxy)ethyl)phenyl methanesulfonate (5c)**



To a solution of **3aa** (53.5 mg, 0.1 mmol) in dry MeCN (1 mL) were added di-*tert*-butyl dicarbonate (Boc₂O, 65.5 mg, 0.3 mmol) and *N,N*-dimethylpyridin-4-amine (DMAP, 24.4 mg, 0.2 mmol). The mixture was stirred at room temperature for 8 hours. Then the reaction was diluted with dichloromethane (10 mL), washed by water (10 mL), brine (10 mL), and dried over anhydrous MgSO₄. Evaporation of organic solvent and purification by column chromatography in petroleum ether: ethyl acetate = 2:1 gave the product **5c** as light yellow oil (44.0 mg, 69%). ¹H NMR (400 MHz, CDCl₃) δ 8.86 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.46 – 7.37 (m, 2H), 7.36 – 7.31 (m, 3H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.34 – 5.21 (m, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.66 (dq, *J* = 14.0, 7.0 Hz, 1H), 3.44 – 3.30 (m, 2H), 3.24 – 2.99 (m, 5H), 2.96 (dd, *J* = 14.0, 9.1 Hz, 1H), 1.22 (s, 9H), 1.11 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 176.34, 157.33, 152.99, 150.45, 148.02, 144.30, 138.26, 136.78, 136.01, 130.85, 130.73, 129.00, 128.19, 126.17, 122.08, 121.64, 114.33, 100.13, 82.86, 81.35, 68.34, 66.13, 38.90, 37.40, 35.34, 27.75, 15.34.

(S)-2-Ethoxy-3-(4-(4-((methylsulfonyl)oxy)phenethoxy)phenyl)propanoic acid (4d)



To a solution of **5c** (38.1 mg, 0.06 mmol) in THF/H₂O (3:1, 0.5 mL) were added LiOH (2.9 mg, 0.12 mmol) and H₂O₂ (30%, 30 μ L, 0.3 mmol). The mixture was stirred at room temperature for 4 hours. Then the reaction was acidified by HCl (0.5 M, 8 mL), diluted with ethyl acetate (10 mL), washed by water (10 mL), brine (10 mL), and dried over anhydrous MgSO₄. Evaporation of organic solvent and purification by column chromatography in petroleum ether: ethyl acetate = 1:1 gave the product **4d** as a light yellow oil (25.7 mg, 100%) with **4b** (14.8 mg, 100%) isolated. ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 4.14 (t, *J* = 6.7 Hz, 2H), 4.04 (dd, *J* = 7.3, 4.2 Hz, 1H), 3.60 (dt, *J* = 14.0, 7.0 Hz, 1H), 3.49 – 3.37 (m, 1H), 3.13 (s, 3H), 3.11 – 3.02 (m, 3H), 2.94 (dd, *J* = 14.1, 7.7 Hz, 1H), 1.17 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.13, 157.71, 147.98, 138.10, 130.70, 130.68, 128.98, 122.10, 114.54, 79.89, 68.30, 66.97, 37.87, 37.42, 35.28, 15.18; HRMS (ESI) *m/z*: 407.5 ([M-H]⁻); calc. for C₂₀H₂₃O₇S⁻: 407.2.

References

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