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Unactivated C(sp^3)-H Hydroxylation through Palladium Catalysis with H_2O as the Oxygen Source

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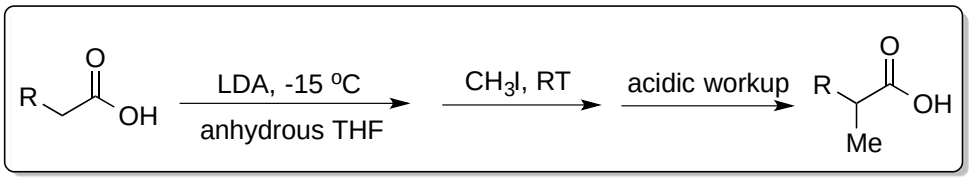
I. General Information

Unless otherwise noted, all reagents were commercially obtained from Aladdin, Alfa-Asea, Aldrich Chemical Co and Energy Chemical Co. All reagents were used as received. Solvents, such as MeOH, EtOH, *i*-PrOH, *t*-BuOH, MeCN, DMSO, DMF, DCE, Acetone, THF, Dioxane, MeCN, etc, were used directly without drying process. Acetone for the mechanistic study was dried according the standard procedure.

All the reactions were carried out under a nitrogen atmosphere except the optimization study involving oxygen. Silica gel plates (GF254) were used for TLC monitoring and silica gel (230-400 mesh) was used for flash column chromatography. All final compounds were characterized by ^{1}H NMR, ^{13}C NMR and Waters UPLC-mass spectroscopy. Copies of NMR spectra are included for all final compounds. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker models Avance DPX 400 (400 MHz) spectrometers. ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for $CHCl_3$ (7.26 ppm). All ^{13}C NMR spectra were reported in ppm and were obtained with ^{1}H decoupling. In reporting spectral data, the format (δ) chemical shift (multiplicity, *J* values in Hz, integration) was used with the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. MS analyses were carried out on Waters UPLC-Mass instrument

II. Preparation of α-methyl Aliphatic Carboxylic Acids

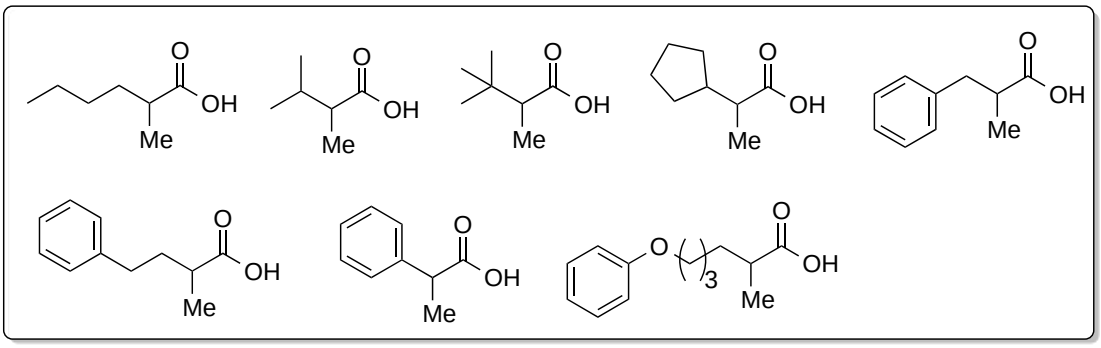
Scheme:



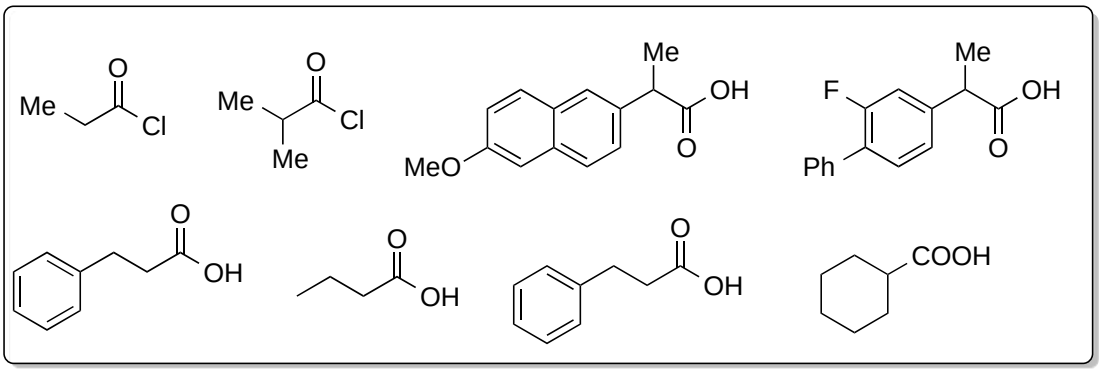
General procedure:

Based on a modified procedure, anhydrous THF and LDA (2.5equiv) were added to a round-bottom flask precooled to -15°C under argon atmosphere. The aliphatic acid (5.0mmol, 1.0equiv) was added slowly and the resulting mixture was allowed to stir for 1h. After the addition of CH_3I (2.2equiv), the mixture was warmed to ambient temperature for 4 hours. 10% HCl solution was added until pH=1 was reached. The aqueous layer was extracted with ethyl acetate for 3 times. The combined organic layer was dried over Na_2SO_4 and concentrated to get the crude product, which was used without further purification.

List of prepared acids:

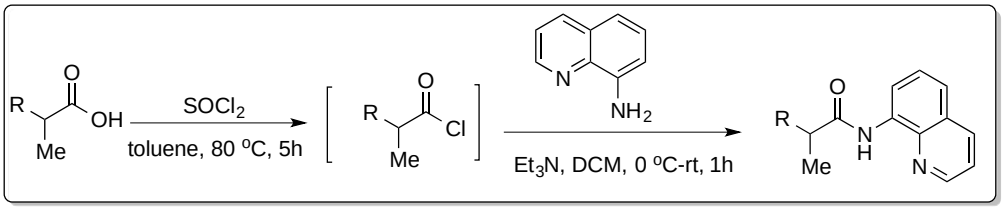


Commercially available acids or acyl chlorides:



III. Preparation of Amides

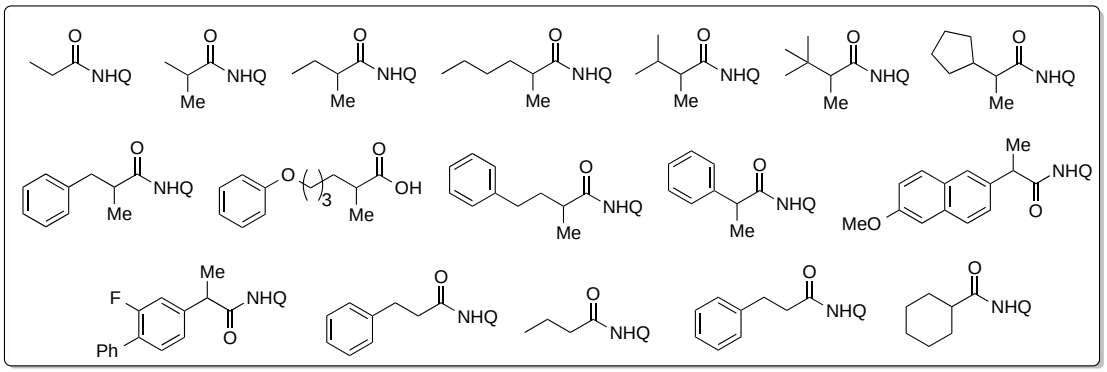
Scheme 1:



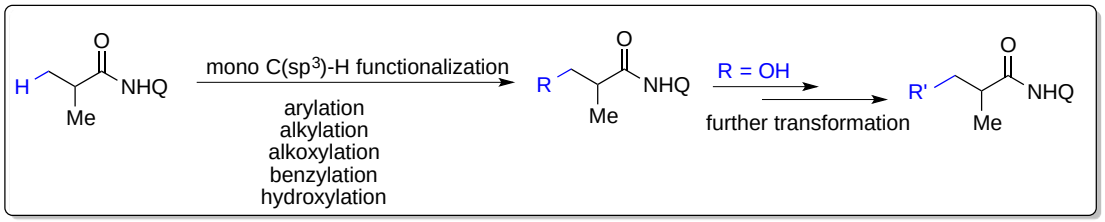
General procedure:

To a solution of the acid in toluene, 5equiv of $SOCl_2$ and 1-2 drops of DMF were added. The mixture was allowed to stir at 80°C for 5h. Then the mixture was concentrated to remove the solvent and excess $SOCl_2$ to afford the crude acyl chloride, which was subsequently dissolved in DCM followed by addition of 0.9equiv of 8-aminoquinoline and 1.0equiv of Et_3N in ice-water bath. The mixture was stirred for 1h (monitored by TLC). Then water was added to quench the reaction. The reaction mixture was extracted with DCM for 3 times. The combined organic layer was dried over Na_2SO_4. After filtration and concentration, the residue was purified by column chromatography to afford the pure compound, which was confirmed by NMR and LC-MS analysis.

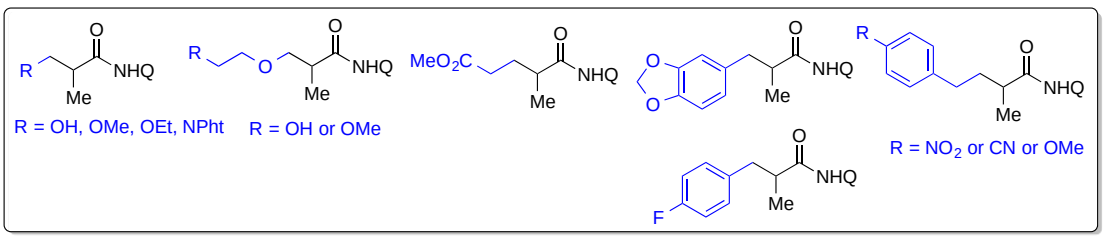
List of prepared amide:



Scheme 2: (refer to published papers in recent years) [1, 2, 3, 4]

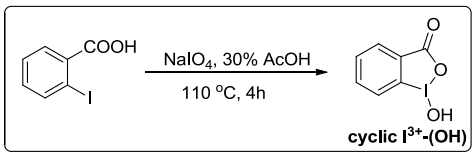


List of prepared amide:



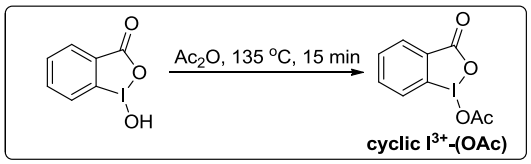
IV. Preparation of cyclic I^{3+} reagents

Synthesis of cyclic I^{3+}-(OH) oxidant: [5]



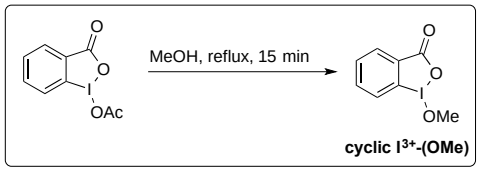
Following a slightly modified procedure from the literature, a 500 mL round-bottom flask was charged with 2-iodobenzoic acid (20.0 g, 80.64 mmol, 1.0 equiv), finely ground $NaIO_4$ (18.11 g. 84.67 mmol, 1.05 equiv), and 30% aqueous acetic acid (120 mL). The flask was affixed with a reflux condenser and was placed in an oil bath preheated to 110 ℃. The reaction mixture was allowed to stir at this temperature for four hours at which point the flask was removed from the oil bath and allowed to cool to room temperature. Ice water (100 mL) was added, and the suspension was allowed to stir for 5 min. The fine white needle-like crystals were isolated by Büchner filtration. The crystals were washed with ice water (2 x 100 mL) and dried in vacuo to afford S1 in greater than quantitative yield (contains impurities). To the obtained crude product was added 100 mL water to stir for 5min at room temperature and the mixture was filtrated again and dried to afford the more pure product, which was used directly in the following hydroxylation reactions without further purification.

Synthesis of cyclic I^{3+}-(OAc) oxidant: [6]



Following the reported procedure, in a 500 mL round-bottom flask containing the above obtained 1-hydroxy-1,2-benziodoxol-3-(1H)-one was suspended in 56 mL Ac_2O. The flask was affixed with a reflux condenser and placed in an oil bath pre-heated to 135 ℃. The reaction mixture was stirred for 15 min until most of the solid materials dissolved. (Note: heating the reaction for too long will result in decomposition of the product and stirring well and vigorously is necessary). The flask was removed from the oil bath and allowed to cool to room temperature, resulting in the formation of white crystals. The flask was then placed in a –20 ℃ freezer overnight to complete the crystallization. The liquids were decanted and the flask was covered with aluminum foil to protect the product from light.

Synthesis of cyclic I^{3+}-(OMe) oxidant: [7]



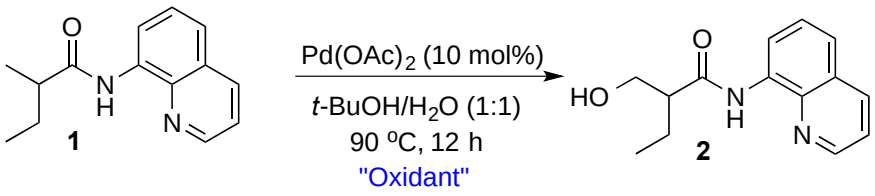
After heating the above obtained 1-acetoxy-1,2-benziodoxol-3-(1H)-one in MeOH to reflux for 15 min until a clear, colorless solution was obtained and cooling to ambient temperature followed by crystallization at -20°C, filtration, washing with a minimal amount of MeOH, and drying under vacuum, the desired product was obtained as white crystals.

V. Optimization Studies

Typical procedure:

To a 10 mL sealed tube, substrate (0.1-0.2mmol, 1.0equiv), $Pd(OAc)_2$ (0-0.2equiv) and oxidant (0-3.0equiv) were dissolved in 2mL of solvent/cosolvent under air. The reaction mixture was stirred for 1 minutes at room temperature for proper mixing of the reactants, and then additives was added or not. Then the sealed tube was tightly capped and moved into oil bath preheated to indicated temperature. After being stirred vigorously for 12h, the reaction was cooled to room temperature and filtered through celite and washed with DCM. Normal workup was conducted with DCM and saturated $NaHCO_3$ aq. To the combined organic layer, the same equivalent of internal standard (4-nitrobenzaldehyde) was added and mixed well. After dryness, filtration and evaporation, the crude mixture was characterized by ^1H NMR analysis.

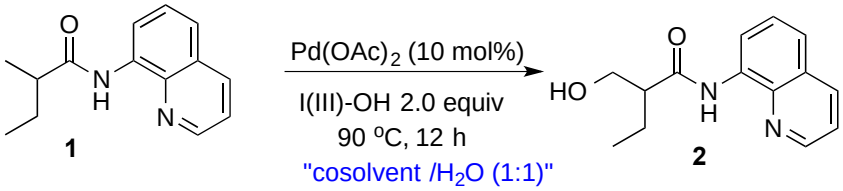
Table S1: Screening of oxidants [a]



Entry	Oxidants	Yield (%)[b]
1	DMP 2.0 equiv, *i*-PrOH/H_2O (1:1)	35
2	DMP 2.0 equiv, *t*-BuOH/H_2O (1:1)	0
3	I(III)-OH 2.0 equiv,	48
4	I(III)-OMe 2.0 equiv,	48
5	I(III)-OAc 2.0 equiv,	48
6	$PhI(OAc)_2$ 2.0 equiv,	0
7	$K_2S_2O_8$ 2.0 equiv,	0
8	benzoquinoe 2.0 equiv	0
9	selectfluor 2.0 equiv	0
10	$NaIO_4$ 2.0 equiv	0
11	$NaIO_3$ 2.0 equiv	0
12	$Cu(OAc)_2$ 2.0 equiv	0
13	oxone 2.0 equiv	0
14	PhI(OH)(OTs) 2.0 equiv	0
15	NFSI 2.0 equiv	0
16	$PhI(OTFA)_2$ 2.0 equiv,	0

a. 0.2 mmol **1** in 2.0 mL of mixed solvent;
b. ^1H NMR yield using 4-nitrobenzaldehyde as the internal standard.

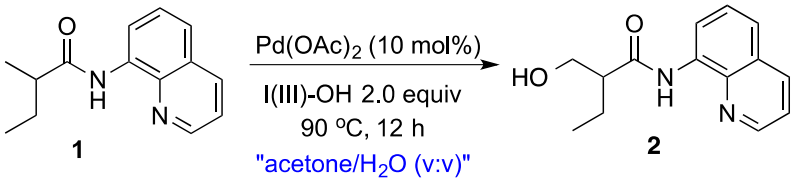
Table S2: Screening of solvents [a]



Entry	Cosolvent/H_2O (1:1)	Yield (%)[b]
1	*t*-BuOH/H_2O (1:1)	48
2	*t*-AmOH/H_2O (1:1)	22
3	THF/H_2O (1:1)	38
4	Dioxane/H_2O (1:1)	31
5	NMP/H_2O (1:1)	23
6	DMF/H_2O (1:1)	23
7	DMSO/H_2O (1:1)	33
8	MeCN/H_2O (1:1)	25
9	$MeNO_2$/H_2O (1:1)	39
10	toluene/H_2O (1:1)	0
11	acetone/H_2O (1:1)	55
12	AcOH/H_2O (1:1)	trace
13	EtOAc/H_2O (1:1)	trace

[a] 0.2 mmol **1** in 2.0 mL of mixed solvent;
[b] ^1H NMR yield using 4-nitrobenzaldehyde as the internal standard.

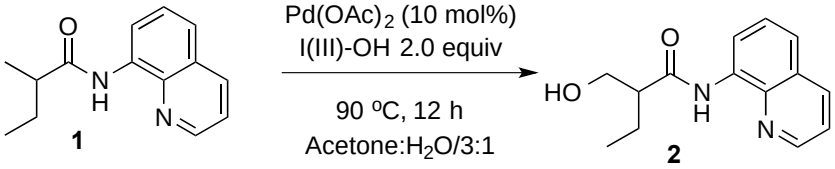
Table S3: Screening of solvent ratio [a]



Entry	Solvent ratio(v:v)	Yield (%)[b]
1	acetone (100%)	0
2	acetone/H_2O (100:1)	2
3	acetone/H_2O (25:1)	22
4	acetone/H_2O (10:1)	34
5	acetone/H_2O (8:1)	43
6	acetone/H_2O (4:1)	55
7	acetone/H_2O (3:1)	60
8	acetone/H_2O (2:1)	59
9	acetone/H_2O (1:1)	53
10	acetone/H_2O (1:2)	40
11	acetone/H_2O (1:3)	15
12	H_2O (100%)	12

[a] 0.2 mmol **1** in 2.0 mL of mixed solvent;
[b] Isolated yield.

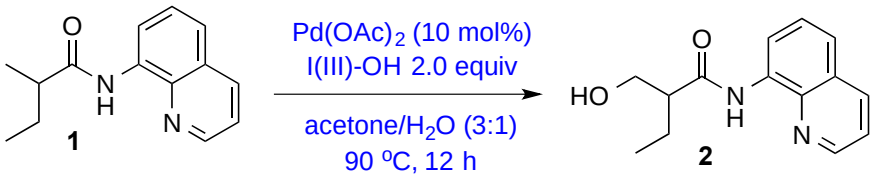
Table S4: Screening of additives [a]



Entry	Additives	Yield (%)[b]
1	AcOH 2.0 equiv	61
2	PivOH 2.0 equiv	54
3	TFA 2.0 equiv	0
4	$NaHCO_3$ 2.0 equiv	<5
5	NaOAc 2.0 equiv	<5
6	H_2O_2 2.0 equiv	52
7	TBAB 2.0 equiv	0
8	DMF 2.0 equiv	59
9	MeCN 2.0 equiv	60
10	Pyridine 2.0 equiv	<5
11	NaOH 2.0 equiv	0
12	none of additives	63

[a] 0.2 mmol **1** in 2.0 mL mixed solvent;
[b] ^{1}H NMR yield using 4-nitrobenzaldehyde as the internal standard.

Table S5: Control reaction [a]

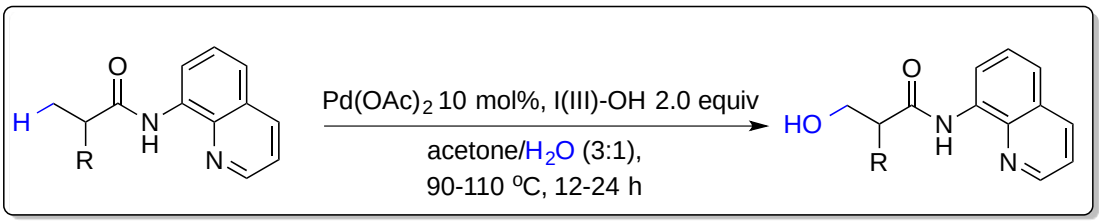


Entry	Conditions	Yield (%)[b]
1[c]	sole polar solvent	0
2	without $Pd(OAc)_2$	0
3	without cyclic I^{3+} reagents	0
4	cyclic I^{3+} 3.0 equiv	60
5	cyclic I^{3+} 1.0 equiv	50
6	80 °C	50
7	100 °C	70 (64)[d]
8	$Pd(MeCN)_2Cl_2$	35[d]
9	$Pd(acac)_2$	49[d]
10	$Pd(PPh_3)_2Cl_2$	37[d]
11	$Pd(dppf)Cl_2$ DCM	30[d]

[a] 0.2 mmol **1** in 2.0 mL mixed solvent;
[b] ^{1}H NMR yield using 4-nitrobenzaldehyde as the internal standard;
[c] DMSO, DMF, NMP, MeCN, *t*-BuOH or $MeNO_2$; [d] Isolated yield.

VI. General Procedure for C(sp^3)-H Hydroxylation Reactions

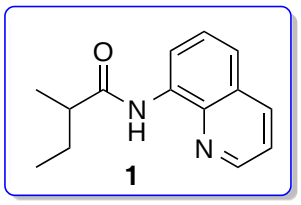
Scheme:



General procedure:

To a 10 mL sealed tube, substrate (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%), cyclic I(III)-OH (105.5 mg, 0.4 mmol, 2.0 equiv) were dissolved in 2 mL of mixed acetone/H_2O (3:1) under air. The reaction mixture was then tightly capped and stirred for 10 minutes at room temperature for proper mixing of the reactants, and then heated to 90-110 ℃ for 12-24h. The reaction mixture was then cooled to room temperature, diluted with DCM and filtered through a small pad of celite and washed with DCM. The filtrate was washed with saturated $NaHCO_3$ aq and extracted with DCM for 3 times. The combined organic layer was dried with Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography with petroleum ether/ethyl acetate or DCM/acetone to afford the final pure product.

Data characterization:



1

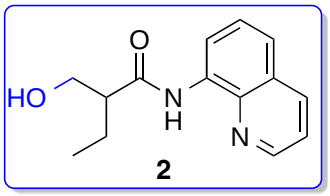
2-methyl-*N*-(quinolin-8-yl)butanamide (1)

General procedure for the synthesis of aliphatic amide was followed using 2-methylbutanoic acid (2.042 g, 20 mmol, 1.0 equiv), $SOCl_2$ (7.263 mL, 100 mmol, 5.0 equiv), 20.0 mL of toluene at 70 °C for 5h and then 8-aminoquinoline (2.60 g, 18.0 mmol, 0.9 equiv), TEA (3.07 mL, 22.0 mmol, 1.1 equiv) in 10.0 mL of DCM for 1h. Purification by column chromatography with petroleum ether: ethyl acetate/ 10:1-8:1 afforded the desired compound as a white solid (3.49 g, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.865 (s, 1H), 8.828-8.786 (m, 2H), 8.124 (d, *J* = 8.24 Hz, 1H), 7.537-7.407 (m, 3H), 2.571-2.487 (m, 1H), 1.922-1.814 (m, 1H), 1.658-1.554 (m, 1H), 1.321 (d, *J* = 6.76 Hz, 3H), 1.010 (t, *J* = 7.32 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 175.39, 148.20, 138.52, 136.40, 134.68, 127.99, 127.50, 121.62, 121.37, 116.46, 44.64, 27.58, 17.65, 12.03;

LC-MS (ESI$^+$): m / z calculated for $C_{14}H_{17}N_2O$ $(M+H)^+$: 229.13 found 229.11.



2

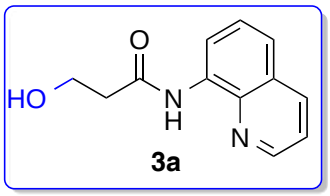
2-(hydroxymethyl)-*N*-(quinolin-8-yl)butanamide (2)

The general procedure was followed using substrate (45.6 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 100°C for 16h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (31 mg, 64% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.00 (s, 1H), 8.72-8.68 (m, 2H), 8.02 (dd, *J* = 8.20 Hz, *J* = 1.04 Hz, 1H), 7.42-7.32 (m, 3H), 3.96-3.91 (m, 1H), 3.87-3.83 (m, 1H), 3.63 (s, 1H), 2.67-2.61 (m, 1H), 1.86-1.75 (m, 1H), 1.70-1.59 (m, 1H), 0.99 (t, *J* = 7.44 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 174.06, 148.27, 138.38, 136.29, 134.23, 127.88, 127.17, 121.73, 121.53, 116.86, 63.47, 52.08, 22.31, 11.94;

LC-MS (ESI$^+$): m / z calculated for $C_{14}H_{17}N_2O_2$ $(M+H)^+$: 245.13 found 245.08.



3a

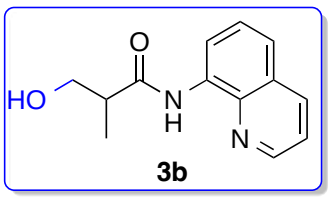
3-hydroxy-*N*-(quinolin-8-yl)propanamide (3a)

The general procedure was followed using substrate (40 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 110°C for 16h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (28 mg, 65% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.03 (s, 1H), 8.67-8.66 (m, 2H), 7.96 (dd, *J* = 8.24 Hz, *J* = 1.40 Hz, 1H), 7.38-7.31 (m, 2H), 7.27 (dd, *J* = 8.24 Hz, *J* = 4.24 Hz, 1H), 4.25 (s, 1H), 4.06 (t, *J* = 5.60 Hz, 2H), 2.79 (t, *J* = 5.64 Hz, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 170.86, 148.00, 137.99, 136.00, 133.97, 127.59, 126.85, 121.54, 121.29, 116.58, 58.52, 40.01;

LC-MS (ESI$^+$): m / z calculated for $C_{12}H_{13}N_2O_2$ $(M+H)^+$: 217.10 found 217.03.



3b

3-hydroxy-2-methyl-N-(quinolin-8-yl)propanamide (3b)

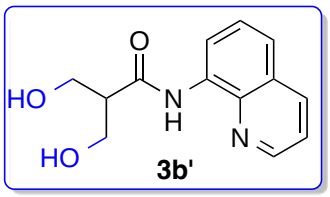
The general procedure was followed using substrate (514 mg, 2.4 mmol, 1.0 equiv), $Pd(OAc)_2$ (54 mg, 0.24 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (1.9 g, 7.2 mmol, 3.0 equiv) and 18 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 100-105°C for 18h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded

the desired compound **3b** as a white solid (177 mg, 32% yield) and DCM: acetone/ 4:1-2:1 afforded the desired compound **3b'** as a white solid (207 mg, 35% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.06 (s, 1H), 8.80 (d, *J* = 3.44Hz, 1H), 8.74 (d, *J* = 6.36 Hz, 1H), 8.14 (d, *J* = 8.16 Hz, 1H), 7.54-7.43 (m, 3H), 3.92-3.88 (m, 2H), 2.97 (s, 1H), 2.91-2.86 (m, 1H), 1.37 (d, *J* = 6.92Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 174.54, 148.43, 138.65, 136.50, 134.42, 128.09, 127.44, 121.90, 121.75, 116.96, 65.31, 44.12, 14.40;

LC-MS (ESI$^+$): m / z calculated for $C_{13}H_{15}N_2O_2$ $(M+H)^+$: 231.11 found 231.21.



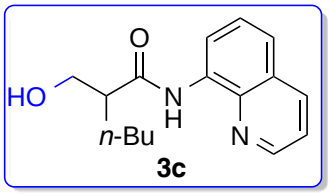
3-hydroxy-2-(hydroxymethyl)-*N*-(quinolin-8-yl)propanamide (3b')

The general procedure was followed using substrate (46 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 106 mg, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 105^{o}C for 11h. Purification by column chromatography with DCM: acetone/2:1 twice afforded the desired compound as a white solid (31 mg, 63% yield).

^{1}H-NMR (400 MHz, CD_3OD) δ (ppm) 8.86-8.85 (m, 1H), 8.70 (d, *J* = 7.56 Hz, 1H), 8.28 (d, *J* = 8.28 Hz, 1H), 7.61 (d, *J* = 8.16 Hz, 1H), 7.55-7.51 (m, 2H), 3.96-3.86 (m, 4H), 2.97-2.90 (m, 1H);

^{13}C-NMR (100 MHz, CD_3OD) δ (ppm) 174.02, 149.90, 140.08, 137.58, 135.75, 129.59, 127.99, 123.39, 122.98, 118.32, 61.61, 54.42;

LC-MS (ESI$^+$): m / z calculated for $C_{13}H_{15}N_2O_3$ $(M+H)^+$: 247.11 found 247.08.



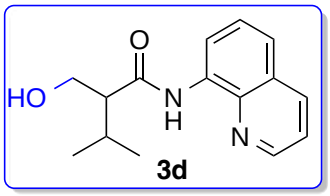
2-(hydroxymethyl)-*N*-(quinolin-8-yl)hexanamide (3c)

The general procedure was followed using substrate (51 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 110^{o}C for 16h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (33 mg, 61% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.01 (s, 1H), 8.80-8.79 (m, 1H), 8.75 (dd, *J* = 6.40 Hz, *J* = 2.48 Hz, 1H), 8.13 (d, *J* = 7.88 Hz, 1H), 7.52-7.47 (m, 2H), 7.43 (dd, *J* = 8.28 Hz, *J* = 4.24 Hz, 1H), 3.96-3.87 (m, 2H), 3.01 (s, 1H), 2.76-2.69 (m, 1H), 1.88-1.79 (m, 1H), 1.70-1.61 (m, 1H), 1.46-1.32 (m, 4H), 0.89 (t, *J* = 7.16 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 174.31, 148.43, 138.62, 136.47, 134.38, 128.08, 127.41, 121.89, 121.72, 116.99, 63.96, 50.43, 29.71, 29.05, 22.89, 14.00;

LC-MS (ESI$^+$): m / z calculated for $C_{16}H_{21}N_2O_2$ $(M+H)^+$: 273.16 found 273.04.



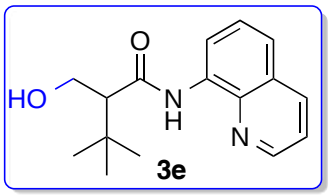
2-(hydroxymethyl)-3-methyl-*N*-(quinolin-8-yl)butanamide (3d)

The general procedure was followed using substrate (48 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 100°C for 18h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (29 mg, 57% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.98 (s, 1H), 8.77-8.73 (m, 2H), 8.09 (d, *J* = 8.20 Hz, 1H), 7.48-7.42 (m, 2H), 7.39 (dd, *J* = 8.24 Hz, *J* = 4.20 Hz, 1H), 4.04-4.00 (m, 1H), 3.94-3.91 (m, 1H), 3.25 (s, 1H), 2.45-2.40 (m, 1H), 2.24-2.15 (m, 1H), 1.04 (t, *J* = 5.44 Hz, 6H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 174.10, 148.36, 138.51, 136.37, 134.25, 127.99, 127.30, 121.81, 121.63, 116.90, 62.09, 57.34, 27.99, 21.18, 20.43;

LC-MS (ESI$^+$): m / z calculated for $C_{15}H_{19}N_2O_2$ $(M+H)^+$: 259.14 found 259.06.



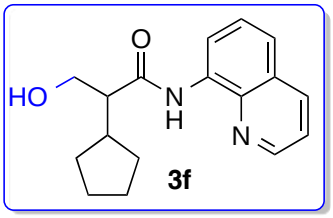
2-(hydroxymethyl)-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (3e)

The general procedure was followed using substrate (25.6 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (53 mg, 0.2 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 95°C for 36h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (15 mg, 56% yield).

^{1}H-NMR (400 MHz, $CDCl_3$)) δ (ppm) 9.91 (s, 1H), 8.80-8.76 (m, 2H), 8.13 (dd, *J* = 8.28 Hz, *J* = 1.60 Hz, 1H), 7.49-7.42 (m, 3H), 4.21 (t, *J* = 10.12 Hz, 1H), 3.92 (dd, *J* = 10.76 Hz, *J* = 3.44 Hz, 1H), 2.60 (dd, *J* = 9.32 Hz, *J* = 3.72 Hz, 1H), 2.50 (s, 1H), 1.12 (s, 9H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.08, 148.41, 138.57, 136.43, 134.35, 128.07, 127.41, 121.75, 121.70, 116.78, 61.75, 60.88, 32.89, 28.74;

LC-MS (ESI$^+$): m / z calculated for $C_{16}H_{21}N_2O_2$ $(M+H)^+$: 273.16 found 273.04.



2-cyclopentyl-3-hydroxy-*N*-(quinolin-8-yl)propanamide (3f)

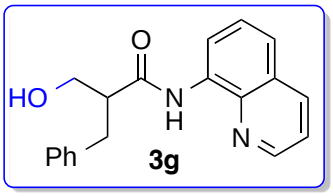
The general procedure was followed using substrate (53.7 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 100°C for

12h. Purification by column chromatography with petroleum ether: ethyl acetate/2:1-1.5:1 afforded the desired compound as a white solid (41 mg, 71% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.98 (s, 1H), 8.74-8.70 (m, 2H), 8.04 (dd, *J* = 8.26 Hz, *J* = 1.44 Hz, 1H), 7.43-7.34 (m, 3H), 3.99-3.90 (m, 2H), 3.56 (s, 1H), 2.51-2.46 (m, 1H), 2.24-2.17 (m, 1H), 1.88-1.76 (m, 2H), 1.63-1.44 (m, 4H), 1.37-1.29 (m, 1H), , 1.23-1.17 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 174.22, 148.28, 138.39, 136.29, 134.22, 127.88, 127.19, 121.69, 121.52, 116.84, 63.33, 56.35, 39.70, 31.35, 30.74, 24.82, 24.71;

LC-MS (ESI$^+$): m / z calculated for $C_{17}H_{21}N_2O_2$ $(M+H)^+$: 285.16 found 285.08.



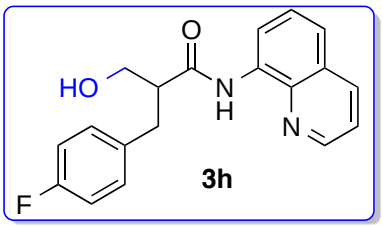
2-benzyl-3-hydroxy-*N*-(quinolin-8-yl)propanamide (3g)

The general procedure was followed using substrate (105 mg, 0.35 mmol, 1.0 equiv), $Pd(OAc)_2$ (8.0 mg, 0.036 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (185 mg, 0.70 mmol, 2.0 equiv) and 4.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 95 ^oC for 11h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (53 mg, 48% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.92 (s, 1H), 8.70-8.69 (m, 2H), 8.05 (d, *J* = 8.20 Hz, 1H), 7.46-7.41 (m, 2H), 7.35 (dd, *J* = 8.00 Hz, *J* = 4.08 Hz, 1H), 7.27-7.21 (m, 4H), 7.16-7.12 (m, 1H), 3.90 (d, *J* = 3.48 Hz, 2H), 3.38 (s, 1H), 3.16-3.12 (m, 1H), 3.02-2.95 (m, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.39, 148.28, 138.93, 138.42, 136.31, 134.17, 129.06, 128.63, 127.90, 127.24, 126.51, 121.91, 121.60, 116.97, 63.13, 51.92, 35.22;

LC-MS (ESI$^+$): m / z calculated for $C_{19}H_{19}N_2O_2$ $(M+H)^+$: 307.14 found 307.05.



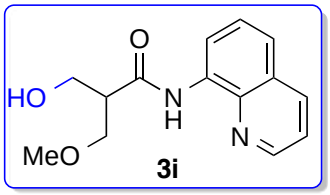
2-(4-fluorobenzyl)-3-hydroxy-N-(quinolin-8-yl)propanamide (3h)

The general procedure was followed using substrate (62 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90 ^oC for 15.5h. Purification by column chromatography with DCM: acetone/10:1 afforded the desired compound as a white solid (35 mg, 54% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.85 (s, 1H), 8.72-8.68 (m, 2H), 8.11 (d, *J* = 8.24 Hz, 1H), 7.50-7.47 (m, 2H), 7.42-7.39 (m, 1H), 7.24-7.21 (m, 2H), 6.94-6.89 (m, 2H), 3.94-3.87 (m, 2H), 3.17 (s, 1H), 3.13-3.09 (m, 1H), 3.00-2.96 (m, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.03, 162.80, 160.37, 148.20, 138.31, 136.27, 134.47, 134.44, 133.96, 130.46, 130.38, 127.84, 127.16, 121.91, 121.57, 116.86, 115.44, 115.23, 63.02, 51.89, 34.34;

LC-MS (ESI$^+$): m / z calculated for $C_{19}H_{18}FN_2O_2$ $(M+H)^+$: 325.14 found 325.03.



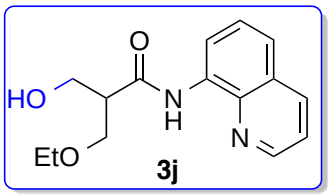
3-hydroxy-2-(methoxymethyl)-*N*-(quinolin-8-yl)propanamide (3i)

The general procedure was followed using substrate (24.4 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (3.3 mg, 0.015 mmol, 0.15 equiv), cyclic I(III)-OAc oxidant (75 mg, 0.24 mmol, 2.4 equiv) and 1.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90-95^{o}C for 12h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the pure compound as colorless oil (18.8 mg, 72% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.73 (s, 1H), 8.81 (d, *J* = 2.76 Hz, 1H), 8.76 (dd, *J* = 6.40 Hz, *J* = 2.12 Hz, 1H), 8.13 (d, *J* = 8.16 Hz, 1H), 7.54-7.50(m, 2H), 7.43 (dd, *J* = 8.16 Hz, *J* = 4.12 Hz, 1H), 4.08-4.04 (m, 1H), 3.99-3.95 (m, 1H), 3.85-3.78 (m, 2H), 3.50 (s, 3H), 3.21(s, 1H), 3.03-2.99 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 172.21, 148.47, 138.85, 136.34, 134.70, 128.09, 127.37, 121.94, 121.68, 117.09, 71.87, 62.07, 59.41, 49.42;

LC-MS (ESI$^+$): m / z calculated for $C_{14}H_{17}N_2O_3$ $(M+H)^+$: 261.12 found 261.06.



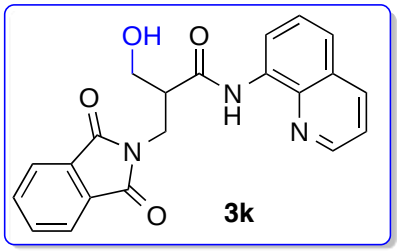
3-ethoxy-2-(hydroxymethyl)-*N*-(quinolin-8-yl)propanamide (3j)

The general procedure was followed using substrate (36 mg, 0.14 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.6 mg, 0.021 mmol, 0.15 equiv), cyclic I(III)-OAc oxidant (85 mg, 0.28 mmol, 2.0 equiv) and 1.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90^{o}C for 12h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a colorless oil (23 mg, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.83 (s, 1H), 8.80-8.77 (m, 2H), 8.13 (d, *J* = 7.76 Hz, 1H), 7.54-7.48 (m, 2H), 7.43 (dd, *J* = 8.24 Hz, *J* = 4.16 Hz, 1H), 4.08-4.04 (m, 1H), 3.98-3.94(m, 1H), 3.89-3.81 (m, 2H), 3.66 (q, *J* = 6.96 Hz, 2H), 3.25 (s, 1H), 3.03-2.97 (m, 1H), 1.36 (t, *J* = 7.00 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 172.52, 148.29, 138.92, 136.32, 134.88, 128.11, 127.38, 121.91, 121.66, 117.15, 69.78, 67.34, 62.20, 49.23, 15.12:

LC-MS (ESI$^+$): m / z calculated for $C_{15}H_{19}N_2O_3$ $(M+H)^+$: 275.14 found 275.09.



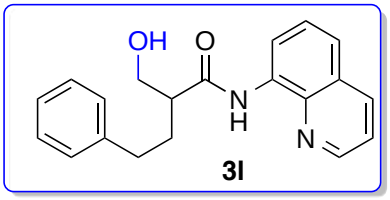
3-(1,3-dioxoisoindolin-2-yl)-2-(hydroxymethyl)-*N*-(quinolin-8-yl)propanamide (3k)

The general procedure was followed using substrate (90 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 0.10 equiv), cyclic I(III)-OAc oxidant (132 mg, 0.50 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 100°C for 17h. Purification by column chromatography with petroleum ether: ethyl acetate/1.5:1-1:1.5 afforded the desired compound as a white solid (66 mg, 70% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.20 (s, 1H), 8.69 (dd, *J* = 6.30 Hz, *J* = 2.42 Hz, 1H), 8.61 (d, *J* = 2.96 Hz, 1H), 8.09 (d, *J* = 8.16 Hz, 1H), 7.80 (dd, *J* = 5.28 Hz, *J* = 3.08 Hz, 2H), 7.67 (dd, *J* = 5.36 Hz, *J* = 3.04 Hz, 2H), 7.51-7.46 (m, 2H), 7.36 (dd, *J* = 8.24 Hz, *J* = 4.20 Hz, 1H), 4.27-4.22 (m, 1H), 4.14-4.03 (m, 2H), 3.96-3.92 (m, 1H), 3.36 (s, 1H), 3.21-3.15 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 170.68, 168.58, 148.34, 138.57, 136.33, 134.25, 134.22, 132.04, 127.97, 127.38, 123.57, 122.06, 121.62, 117.24, 61.37, 48.64, 36.93;

LC-MS (ESI$^+$): m / z calculated for $C_{21}H_{17}N_3O_4$ $(M+H)^+$: 375.38 found 376.05.



3l

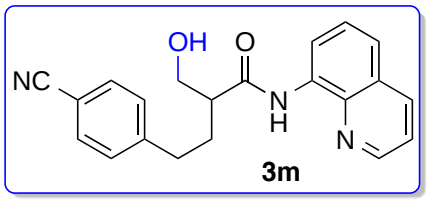
2-(hydroxymethyl)-4-phenyl-*N*-(quinolin-8-yl)butanamide (3l)

The general procedure was followed using substrate (62 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.6 mg, 0.03 mmol, 0.15 equiv), cyclic I(III)-OAc oxidant (124 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90°C for 10h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1.5:1 afforded the desired compound as slightly yellow oil (41 mg, 64% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.01 (s, 1H), 8.80 (dd, *J* = 4.20 Hz, *J* = 1.52 Hz, 1H), 8.76 (dd, *J* = 6.08 Hz, *J* = 2.88 Hz, 1H), 8.14 (dd, *J* = 8.26 Hz, *J* = 1.50 Hz, 1H), 7.53-7.48 (m, 2H), 7.44 (dd, *J* = 8.24 Hz, *J* = 4.20 Hz, 1H), 7.29-7.16 (m, 5H), 3.97-3.87 (m, 2H), 3.01 (s, 1H), 2.83-2.69 (m, 3H), 2.25-2.16 (m, 1H), 2.01-1.92 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.84, 148.43, 141.42, 138.61, 136.48, 134.29, 128.61, 128.60, 128.08, 127.41, 126.16, 122.02, 121.76, 117.08, 64.00, 49.62, 33.55, 30.82;

LC-MS (ESI$^+$): m / z calculated for $C_{20}H_{21}N_2O_2$ $(M+H)^+$: 321.16 found 321.03.



3m

4-(4-cyanophenyl)-2-(hydroxymethyl)-*N*-(quinolin-8-yl)butanamide (3m)

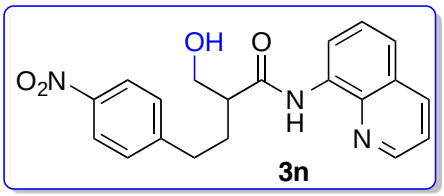
The general procedure was followed using substrate (65 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90°C for 12h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (20.4 mg, 30% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.99 (s, 1H), 8.79(dd, *J* = 4.24 Hz, *J* = 1.60 Hz, 1H),

8.71 (dd, *J* = 5.38 Hz, *J* = 3.58 Hz, 1H), 8.15 (dd, *J* = 8.26 Hz, *J* = 1.62 Hz, 1H), 7.51-7.43 (m, 5H), 7.29 (d, *J* = 8.20 Hz, 2H), 3.97-3.89 (m, 2H), 3.05 (s, 1H), 2.86-2.79 (m, 2H), 2.77-2.67 (m, 1H), 2.25-2.15 (m, 1H), 1.99-1.92 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.18, 148.45, 147.10, 138.49, 136.56, 134.09, 132.33, 129.37, 128.06, 127.35, 122.18, 121.81, 119.06, 117.06, 110.00, 77.36, 63.95, 49.74, 33.72, 30.16;

LC-MS (ESI$^+$): m / z calculated for $C_{21}H_{20}N_3O_2$ $(M+H)^+$: 346.16 found 346.03.



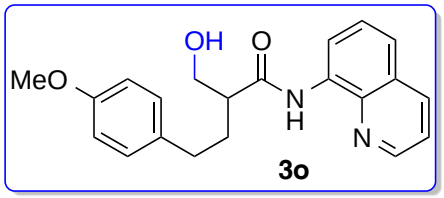
2-(hydroxymethyl)-4-(4-nitrophenyl)-*N*-(quinolin-8-yl)butanamide (3n)

The general procedure was followed using substrate (61 mg, 0.175 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.0 mg, 0.018 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (92 mg, 0.35 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 110^{o}C for 10h. Purification by column chromatography with petroleum ether: ethyl acetate/2:1-1:1 afforded the desired compound as a white solid (39 mg, 60% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.99 (s, 1H), 8.77(d, *J* = 3.20 Hz, 1H), 8.70 (dd, *J* = 5.06 Hz, *J* = 3.18 Hz, 1H), 8.14 (d, *J* = 8.08 Hz, 1H), 8.04 (d, *J* = 8.32 Hz, 2H), 7.48-7.43 (m, 3H), 7.33 (d, *J* = 8.32 Hz, 2H), 3.98-3.88 (m, 2H), 3.21 (s, 1H), 2.89-2.81 (m, 2H), 2.73 (m, 1H), 2.27-2.17 (m, 1H), 2.03-1.92 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.15, 149.27, 148.47, 146.50, 138.45, 136.57, 134.04, 129.37, 128.05, 127.31, 123.77, 122.20, 121.82, 117.05, 63.98, 49.78, 33.49, 30.15;

LC-MS (ESI$^+$): m / z calculated for $C_{20}H_{20}N_3O_4$ $(M+H)^+$: 366.15 found 366.01.



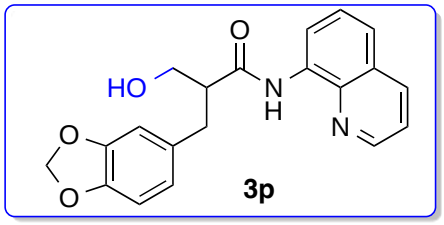
2-(hydroxymethyl)-4-(4-methoxyphenyl)-*N*-(quinolin-8-yl)butanamide (3o)

The general procedure was followed using substrate (67 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 100^{o}C for 16h. Purification by column chromatography with DCM: acetone/10:1 afforded the desired compound as a white solid (50 mg, 71% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.01 (s, 1H), 8.78 (d, *J* = 4.16 Hz, 1H), 8.75 (dd, *J* = 6.04 Hz, *J* = 2.72 Hz, 1H), 8.12 (d, *J* = 8.20 Hz, 1H), 7.51-7.46 (m, 2H), 7.42 (dd, *J* = 8.24 Hz, *J* = 4.16 Hz, 1H), 7.13 (d, *J* = 8.36 Hz, 2H), 6.80 (d, *J* = 8.40 Hz, 2H), 3.98-3.93 (m, 1H), 3.90-3.86 (m, 1H), 3.75 (s, 3H), 3.21 (s, 1H), 2.76-2.65 (m, 3H), 2.21-2.12 (m, 1H), 1.95-1.87 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.85, 157.95, 148.34, 138.49, 136.41, 134.25, 133.42, 129.46, 127.99, 127.32, 121.90, 121.69, 116.97, 113.93, 63.99, 55.29, 49.65, 32.60, 30.97;

LC-MS (ESI$^+$): m / z calculated for $C_{21}H_{23}N_2O_3$ $(M+H)^+$: 351.17 found 351.05.



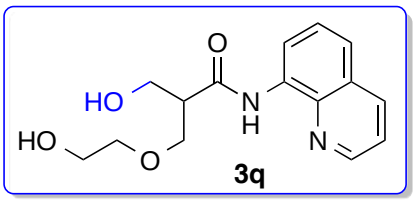
3-(benzo[*d*][1,3]dioxol-5-yl)-2-(hydroxymethyl)-*N*-(quinolin-8-yl)propanamide (3p)

The general procedure was followed using substrate (69 mg, 0.207 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.6 mg, 0.0207 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (109 mg, 0.414 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90^{o}C for 16.5h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (35 mg, 48% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.86 (s, 1H), 8.75-8.71 (m, 2H), 8.13 (dd, *J* = 8.24 Hz, *J* = 0.84 Hz, 1H), 7.53-7.48 (m, 2H), 7.42 (dd, *J* = 8.24 Hz, *J* = 4.20 Hz, 1H), 6.78 (s, 1H), 6.74 (d, *J* = 8.12 Hz, 1H), 6.68 (d, *J* = 7.88 Hz, 1H), 5.87 (s, 1H), 5.83 (d, *J* = 0.84 Hz, 1H), 3.95-3.86 (m, 2H), 3.11-3.05 (m, 1H), 2.97-2.90 (m, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.37, 148.32, 147.90, 146.30, 138.58, 136.41, 134.25, 132.66, 128.03, 127.40, 122.14, 121.99, 121.70, 117.03, 109.51, 108.49, 100.95, 63.18, 52.07, 35.15;

LC-MS (ESI$^+$): m / z calculated for $C_{20}H_{19}N_2O_4$ $(M+H)^+$: 351.13 found 351.00.



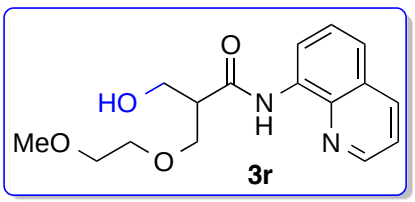
3-hydroxy-2-((2-hydroxyethoxy)methyl)-*N*-(quinolin-8-yl)propanamide (3q)

The general procedure was followed using substrate (55 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.6 mg, 0.03 mmol, 0.15 equiv), cyclic I(III)-OAc oxidant (124 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90^{o}C for 18h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (29 mg, 50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.60 (s, 1H), 8.83-8.79 (m, 2H), 8.14 (d, *J* = 8.24 Hz, 1H), 7.53-7.48 (m, 2H), 7.43 (dd, *J* = 8.24 Hz, *J* = 4.28 Hz, 1H), 4.05-3.82 (m, 7H), 3.77-3.67 (m, 2H), 3.39 (brs, 1H), 3.06-3.00 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 172.44, 148.92, 138.55, 137.03, 134.43, 128.35, 127.44, 122.25, 121.70, 117.79, 73.40, 69.98, 61.71, 61.65, 48.96;

LC-MS (ESI$^+$): m / z calculated for $C_{15}H_{19}N_2O_4$ $(M+H)^+$: 291.13 found 291.07.



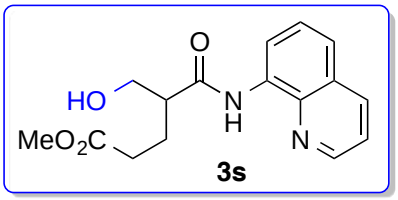
3-hydroxy-2-((2-methoxyethoxy)methyl)-*N*-(quinolin-8-yl)propanamide (3r)

The general procedure was followed using substrate (58 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 110°C for 10h. Purification by column chromatography with petroleum ether: ethyl acetate/2:1-1:2 afforded the desired compound as a white solid (38 mg, 62% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.65 (s, 1H), 8.79-8.75 (m, 2H), 8.12 (d, *J* = 8.08 Hz, 1H), 7.52-7.48 (m, 2H), 7.41 (dd, *J* = 8.00 Hz, *J* = 4.04 Hz, 1H), 4.07-4.05 (m, 1H), 3.96-3.90 (m, 3H), 3.74-3.61 (m, 4H), 3.37 (s, 4H), 3.05-3.02(m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 172.22, 148.26, 138.79, 136.31, 134.71, 128.05, 127.33, 121.88, 121.62, 117.09, 71.77, 70.96, 70.41, 61.88, 59.13, 49.43;

LC-MS (ESI$^+$): m / z calculated for $C_{16}H_{21}N_2O_4$ $(M+H)^+$: 305.15 found 305.5.



3s

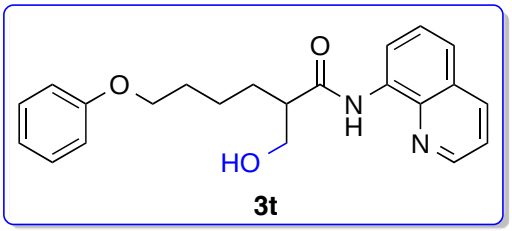
methyl 4-(hydroxymethyl)-5-oxo-5-(quinolin-8-ylamino)pentanoate (3s)

The general procedure was followed using substrate (58 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90°C for 12h. Purification by column chromatography with petroleum DCM: acetone/10:1 afforded the desired compound as slightly yellow oil (26 mg, 42% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.09 (s, 1H), 8.79 (dd, *J* = 4.12 Hz, *J* = 1.44 Hz, 1H), 8.73-8.71 (m, 1H), 8.12 (dd, *J* = 8.28 Hz, *J* = 1.40 Hz, 1H), 7.51-7.47 (m, 2H), 7.42 (dd, *J* = 8.26 Hz, *J* = 4.22 Hz, 1H), 3.92 (s, 2H), 3.67 (s, 3H), 3.08 (s, 1H), 2.85-2.79(m, 1H), 2.56-2.42(m, 2H), 2.21-2.12(m, 1H), 2.06-1.96 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.69, 173.27, 148.46, 138.60, 136.43, 134.28, 128.04, 127.32, 122.05, 121.73, 117.07, 63.51, 51.82, 49.16, 31.65, 24.21;

LC-MS (ESI$^+$): m / z calculated for $C_{16}H_{19}N_2O_4$ $(M+H)^+$: 303.13 found 303.05.



3t

2-(hydroxymethyl)-6-phenoxy-*N*-(quinolin-8-yl)hexanamide (3t)

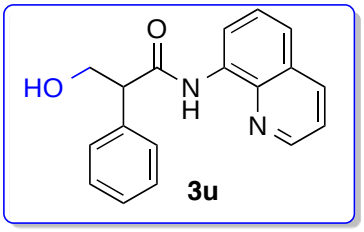
The general procedure was followed using substrate (70 mg, 0.20 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.10 equiv), cyclic I(III)-OH oxidant (106 mg, 0.40 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 110°C for 15h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a colorless oil (43 mg, 59% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.03 (s, 1H), 8.79-8.74 (m, 2H), 8.14 (dd, *J* = 8.26Hz, *J* = 1.50 Hz, 1H), 7.54-7.48 (m, 2H), 7.43 (dd, *J* = 8.26Hz, *J* = 4.22 Hz, 1H), 7.25-7.21 (m, 2H), 6.90 (t, *J* = 7.32 Hz, 1H), 6.84 (d, *J* = 7.88 Hz, 2H), 3.96-3.93 (m, 4H), 2.84 (s, 1H),

2.79-2.73 (m, 1H), 1.97-1.80 (m, 3H), 1.78-1.71 (m, 1H), 1.69-1.58 (m, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.97, 159.03, 148.39, 138.50, 136.40, 134.27, 129.44, 127.99, 127.30, 121.89, 121.65, 120.59, 116.98, 114.56, 67.52, 63.83, 50.44, 29.40, 28.97, 24.13;

LC-MS (ESI$^+$): m / z calculated for $C_{22}H_{25}N_2O_3$ $(M+H)^+$: 365.19 found 365.04.



3u

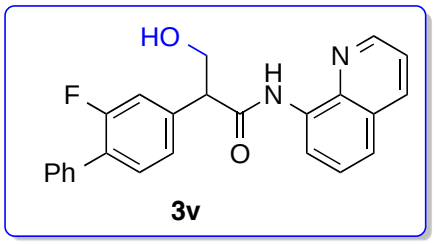
3-hydroxy-2-phenyl-*N*-(quinolin-8-yl)propanamide (3u)

The general procedure was followed using substrate (27.6 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (53 mg, 0.2 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90^{o}C for 6h. Purification by column chromatography with petroleum ether: ethyl acetate/2:1-1.1:1 afforded the desired compound as a white solid (13 mg, 45% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.93 (s, 1H), 8.76 (d, *J* = 7.00 Hz, 1H), 8.66 (d, *J* = 3.20 Hz, 1H), 8.10 (d, *J* = 8.16 Hz, 1H), 7.53-7.31 (m, 8H), 4.38-4.33 (m, 1H), 4.08-4.05 (m, 1H), 3.97-3.94 (m, 1H), 3.21 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 171.95, 148.40, 138.54, 136.57, 136.32, 134.27, 129.28, 128.63, 128.05, 128.00, 127.33, 122.02, 121.71, 116.70, 65.18, 56.25;

LC-MS (ESI$^+$): m / z calculated for $C_{18}H_{17}N_2O_2$ $(M+H)^+$: 293.13 found 293.20.



3v

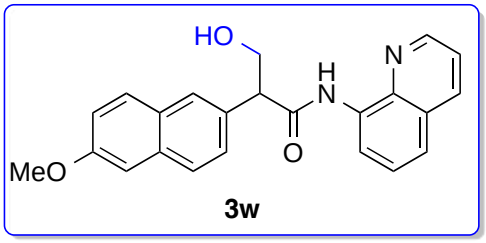
2-(2-fluoro-[1,1'-biphenyl]-4-yl)-3-hydroxy-*N*-(quinolin-8-yl)propanamide (3v)

The general procedure was followed using substrate (38 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (3.3 mg, 0.015 mmol, 0.15 equiv), cyclic I(III)-OAc oxidant (62 mg, 0.2 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90^{o}C for 14h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (23 mg, 59% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.07 (s, 1H), 8.76 (d, *J* = 6.80 Hz, 1H), 8.70 (d, *J* = 3.20 Hz, 1H), 8.08 (d, *J* = 8.12 Hz, 1H), 7.55-7.32 (m, 11H), 4.43-4.38 (m, 1H), 4.14-4.11 (m, 1H), 4.08-4.04 (m, 1H), 3.55 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 171.03, 161.15, 158.68, 148.43, 138.40, 137.91, 137.83, 136.37, 135.39, 134.05, 131.35, 131.31, 129.02, 129.00, 128.66, 128.56, 127.94, 127.86, 127.24, 124.60, 124.56, 122.16, 121.72, 116.83, 116.36,116.13, 64.88, 55.69;

LC-MS (ESI$^+$): m / z calculated for $C_{24}H_{20}FN_2O_2$ $(M+H)^+$: 387.15 found 387.02.



3w

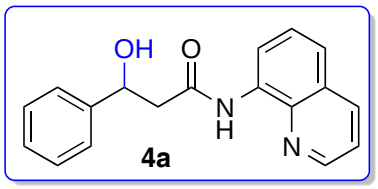
3-hydroxy-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (3w)

The general procedure was followed using substrate (36 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv), cyclic I(III)-OH oxidant (62 mg, 0.15 mmol, 1.5 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90°C for 18h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (19 mg, 51% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.02 (s, 1H), 8.77 (d, *J* = 7.52 Hz, 1H), 8.55 (dd, *J* = 4.20 Hz, *J* = 1.44 Hz, 1H), 8.01 (dd, *J* = 8.24 Hz, *J* = 1.32 Hz, 1H), 7.85 (s, 1H), 7.73 (dd, *J* = 8.40 Hz, *J* = 5.56 Hz, 2H), 7.52 (dd, *J* = 8.48 Hz, *J* = 1.40 Hz, 1H), 7.47 (t, *J* = 8.04 Hz, 1H), 7.41 (d, *J* = 8.16 Hz, 1H), 7.28 (dd, *J* = 8.24 Hz, *J* = 4.24 Hz, 1H), 7.15 (dd, *J* = 8.96 Hz, *J* = 2.44 Hz, 1H), 7.10 (d, *J* = 2.20 Hz, 1H), 4.46 (dd, *J* = 10.92 Hz, *J* = 8.76 Hz, 1H), 4.21 (dd, *J* = 8.48 Hz, *J* = 4.68 Hz, 1H), 4.03 (dd, *J* = 11.08 Hz, *J* = 8.68 Hz, 1H), 3.89 (s, 3H), 3.53 (brs, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 171.96, 157.89, 148.29, 138.37, 136.20, 134.19, 134.12, 131.64, 129.43, 129.13, 127.86, 127.78, 127.45, 127.18, 126.70, 121.93, 121.56, 119.27, 116.65, 105.66, 65.14, 56.18, 55.35;

LC-MS (ESI$^+$): m / z calculated for $C_{23}H_{21}N_2O_3$ $(M+H)^+$: 373.16 found 373.27.



4a

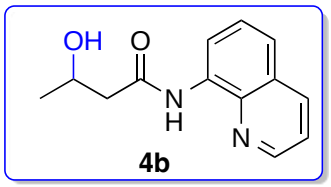
3-hydroxy-3-phenyl-*N*-(quinolin-8-yl)propanamide (4a)

The general procedure was followed using substrate (41.4 mg, 0.15 mmol, 1.0 equiv), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (79 mg, 0.3 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 100-105°C for 20h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (17 mg, 38% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.042 (s, 1H), 8.766-8.734 (m, 2H), 8.126 (dd, *J* = 8.28 Hz, *J* = 1.60 Hz, 1H), 7.532-7.482 (m, 2H), 7.456-7.401 (m, 3H), 7.351 (t, *J* = 7.40 Hz, 2H), 7.277 (t, *J* = 7.20 Hz, 1H), 5.308 (d, *J* = 9.12 Hz, 1H), 4.278 (s, 1H, OH), 3.013-2.878 (m, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 170.62, 148.38, 143.07, 138.43, 136.44, 134.19, 128.63, 128.01, 127.78, 127.36, 125.82, 122.01, 121.73, 116.99, 71.00, 46.44;

LC-MS (ESI$^+$): m / z calculated for $C_{18}H_{17}N_2O_2$ $(M+H)^+$: 293.13 found 293.24.



4b

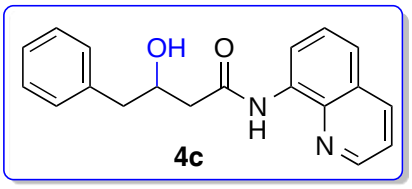
3-hydroxy-*N*-(quinolin-8-yl)butanamide (4b)

The general procedure was followed using substrate (42.9 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (106 mg, 0.4 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 100-105^{o}C for 20h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (7 mg, 15% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.970 (s, 1H), 8.679-8.625 (m, 2H), 7.986 (dd, *J* = 8.28 Hz, *J* = 1.48 Hz, 1H), 7.393-7.337 (m, 2H), 7.290 (dd, *J* = 8.28 Hz, *J* = 4.24 Hz, 1H), 4.379-4.302 (m, 1H), 4.237 (s, 1H), 2.666-2.578 (m, 2H), 1.258 (d, *J* = 6.28 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 170.92, 148.15, 138.18, 136.16, 134.05, 127.76, 127.03, 121.70, 121.46, 116.70, 64.80, 45.84, 22.84;

LC-MS (ESI$^+$): m / z calculated for $C_{13}H_{15}N_2O_2$ $(M+H)^+$: 231.11 found 231.17.



4c

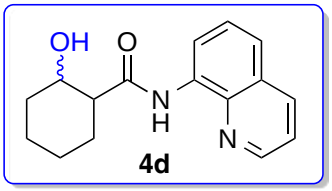
3-hydroxy-4-phenyl-*N*-(quinolin-8-yl)butanamide (4c)

The general procedure was followed using substrate (43.6 mg, 0.15 mmol, 1.0 equiv), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 0.1 equiv), cyclic I(III)-OH oxidant (79 mg, 0.3 mmol, 2.0 equiv) and 2.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 100-105^{o}C for 20h. Purification by column chromatography with petroleum ether: ethyl acetate/3:1-1:1 afforded the desired compound as a white solid (11 mg, 24% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.994 (s, 1H), 8.772-8.726 (m, 2H), 8.135 (dd, *J* = 8.24 Hz, *J* = 1.44 Hz, 1H), 7.537-7.484 (m, 2H), 7.425 (dd, *J* = 8.24 Hz, *J* = 4.24 Hz, 1H), 7.345-7.229 (m, 5H), 4.482-4.419 (m, 1H), 3.588 (s, 1H, OH), 2.973 (dd, *J* = 13.56 Hz, *J* = 7.12 Hz, 1H), 2.868 (dd, *J* = 13.56 Hz, *J* = 6.16 Hz, 1H), 2.774-2.688 (m, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 170.93, 148.34, 138.45, 137.92, 136.47, 134.26, 129.61, 128.69, 128.04, 127.39, 126.71, 121.95, 121.72, 116.98, 69.80, 43.40, 43.36;

LC-MS (ESI$^+$): m / z calculated for $C_{19}H_{19}N_2O_2$ $(M+H)^+$: 307.13 found 307.23.



4d

2-hydroxy-*N*-(quinolin-8-yl)cyclohexane-1-carboxamide (4d-cis)

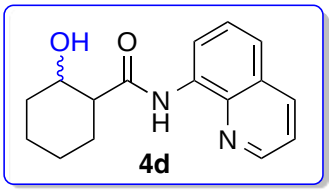
The general procedure was followed using substrate (76.3 mg, 0.3 mmol, 1.0 equiv), $Pd(OAc)_2$ (13.4 mg, 0.06 mmol, 0.2 equiv), cyclic I(III)-OH oxidant (158 mg, 0.6 mmol, 2.0 equiv) and 3.0 mL of acetone and H_2O (3:1). The reaction mixture was stirred at 90^{o}C for 13h.

Purification by column chromatography with petroleum ether: acetone/10:1-6:1-3:1-1:1 afforded the desired compound (cis+trans) as a white solid (72 mg, 44.5% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.071 (s, 1H), 8.799 (dd, *J* = 4.12 Hz, *J* = 1.40 Hz, 1H), 8.731 (dd, *J* = 6.28 Hz, *J* = 2.60 Hz, 1H), 8.141 (dd, *J* = 8.28 Hz, *J* = 1.40 Hz, 1H), 7.537-7.486 (m, 2H), 7.437 (dd, *J* = 8.24 Hz, *J* = 4.20 Hz, 1H), 4.348 (s, 1H), 4.143 (s, 1H), 2.612 (dt, *J* = 11.96 Hz, *J* = 2.32 Hz, 1H), 2.203-2.100 (m, 1H), 1.974-1.948 (m, 1H), 1.870-1.755 (m, 3H), 1.518-1.362 (m, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 175.26, 148.40, 138.62, 136.50, 134.28, 128.07, 127.41, 121.96, 121.76, 117.00, 66.90, 49.19, 32.08, 25.33, 24.90, 19.73;

LC-MS (ESI$^+$): m / z calculated for $C_{16}H_{19}N_2O_2$ $(M+H)^+$: 271.14 found 271.22.



4d

2-hydroxy-*N*-(quinolin-8-yl)cyclohexane-1-carboxamide (4d-trans)

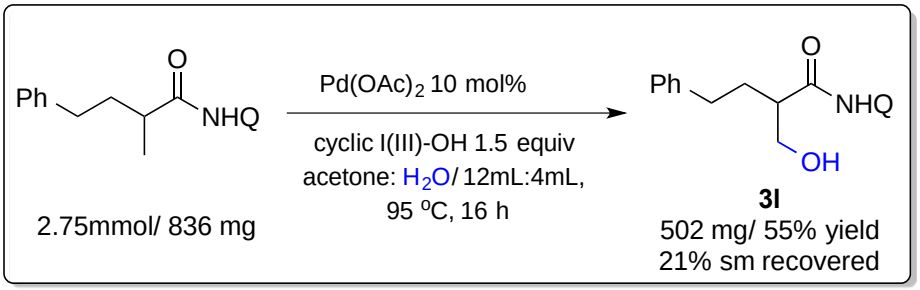
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.027 (s, 1H), 8.770 (dd, *J* = 4.20 Hz, *J* = 1.56 Hz, 1H), 8.694 (dd, *J* = 6.28 Hz, *J* = 2.64 Hz, 1H), 8.092 (dd, *J* = 8.28 Hz, *J* = 1.52 Hz, 1H), 7.466-7.387 (m, 3H), 3.995-3.934 (m, 1H), 3.597 (s, 1H, OH), 2.482 (dt, *J* = 11.04 Hz, *J* = 3.76 Hz, 1H), 2.146-2.085 (m, 2H), 1.811-1.789 (m, 2H), 1.675-1.579 (m, 1H), 1.453-1.247 (m, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.87, 148.34, 138.54, 136.43, 134.38, 128.00, 127.32, 121.76, 121.63, 116.91, 71.46, 54.11, 34.30, 28.84, 25.26, 24.54;

LC-MS (ESI$^+$): m / z calculated for $C_{16}H_{19}N_2O_2$ $(M+H)^+$: 271.14 found 271.22.

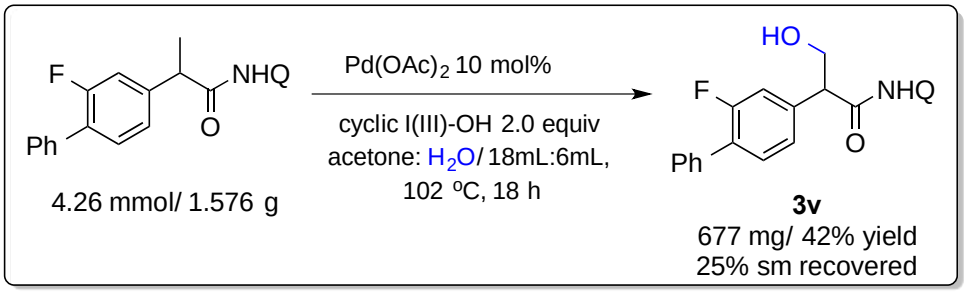
VII. General Procedure for Large-scale Reactions

Large-scale synthesis of compound 3l



In a 50mL sealed tube, substrate (2.75 mmol, 836 mg, 1.0 equiv), $Pd(OAc)_2$ (0.275 mmol, 61.0 mg, 0.1 equiv), cyclic I(III)-OH oxidant (4.125 mmol, 1.089 g, 1.5 equiv) were dissolved in 12 mL of acetone and 4 mL of H_2O. The sealed tube was tightly sealed and stirred at room temperature for 10 min for proper mixing of the reactants, and then heated to 95 ℃ for 16 h. The reaction mixture was then cooled to room temperature, diluted with DCM and filtered through a small pad of celite and washed with DCM. The filtrate was washed with saturated $NaHCO_3$ aq and extracted with DCM for 3 times. The combined organic layer was dried with Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography with petroleum ether/ethyl acetate to afford the desired product as a white solid (502 mg, 55% yield) and recover the starting material as a white solid (175 mg, 21% yield).

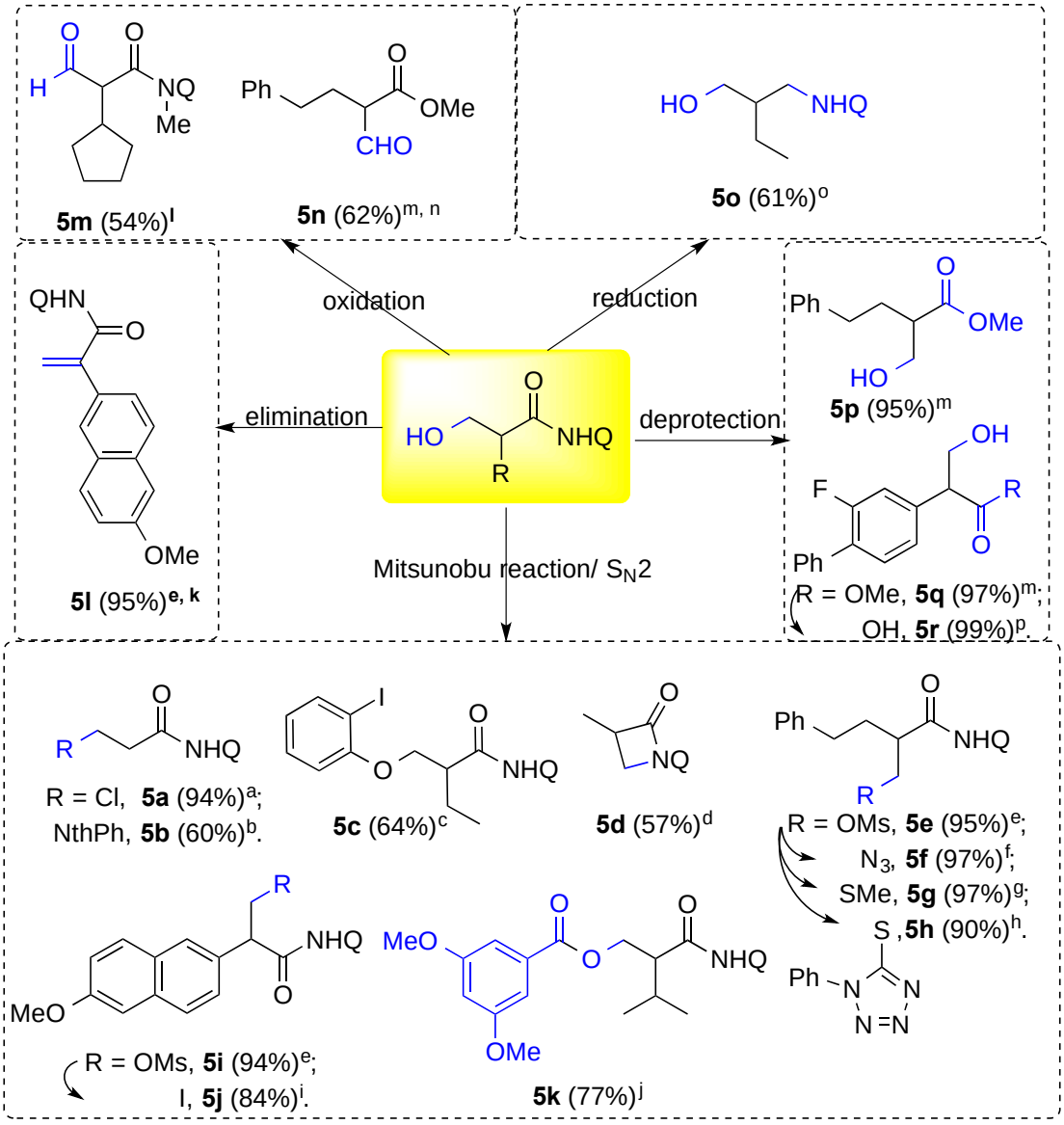
Gram-scale synthesis of compound 3v:



In a 50mL sealed tube, substrate (4.26 mmol, 1.576 g, 1.0 equiv), $Pd(OAc)_2$ (0.426 mmol, 95.6 mg, 0.1 equiv), cyclic I(III)-OH oxidant (8.52 mmol, 2.249 g, 2.0 equiv) were dissolved in 18 mL of acetone and 6 mL of H_2O. The sealed tube was tightly sealed and stirred at room temperature for 10 min for proper mixing of the reactants, and then heated to 100-105 ℃ for 18 h. The reaction mixture was then cooled to room temperature, diluted with DCM and filtered through a small pad of celite and washed with DCM. The filtrate was washed with saturated $NaHCO_3$ aq and extracted with DCM. The combined organic layer was dried with Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography with petroleum ether/ethyl acetate to afford the desired product as a white solid (677 mg, 41.2% yield) and recover the starting material as a white solid (396 mg, 25.1% yield).

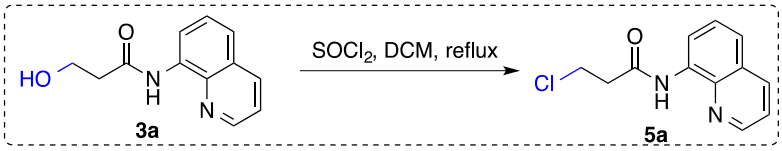
VIII. General Procedure for Product Transformation

General reaction scheme

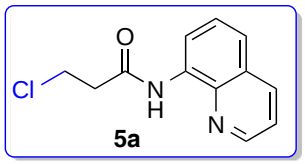


Conditions: a) $SOCl_2$, DCM, reflux, 12h; b) PPh_3, DIAD, Phthalimide, THF, 0°C-rt, 1h; c) MsCl, Et_3N, DCM, 0°C, 1h; 2-iodophenol, $Cu(OAc)_2$, K_2CO_3, , MeCN, 70°C, 2h; d) MsCl, Et_3N, DCM, 0°C, 1h; NaSMe, DMF, 50°C, 1.5h; e) MsCl, Et_3N, DCM, 0°C, 1h; f) NaN_3, $Cu(OAc)_2$, DMF, 70°C, 2h; g) NaSMe, MeOH/H_2O, rt, 2h; h) 1-phenyl-1H-tetrazole-5-thiol, K_2CO_3, DMF, 70°C, 2h; i) NaI, acetone, reflux, 48h; j) PPh_3, DIAD, 3,5-dimethoxybenzoic acid, THF, 0°C-rt, 1h; k) K_2CO_3, acetone, reflux, 48h; l) TBDBSCl, imidazole, THF, rt, 1h; *t*-BuOK, MeI, THF, rt, 2h; TBAF, THF, rt, 4h; DMP, DCM, rt, 1h; m) conc.H_2SO_4, MeOH, 105°C, 12h; n) DMP, rt, 1h; o) $LiAlH_4$, THF, 0 °C-rt, 6h; p) LiOH, MeOH/H_2O, rt, 1h;

Synthesis of compound 5a



In a 10 mL round-bottomed flask, substrate 3-hydroxy-*N*-(quinolin-8-yl)propanamide **(3a)** (86.4 mg, 0.4 mmol, 1.0 equiv) was dissolved in 3.0 mL of anhydrous DCM. After addition of $SOCl_2$ (290 μL, 4.0 mmol, 10.0 equiv) at room temperature, the reaction mixture was heated to reflux for 12 h. After cooling to room temperature, normal workup was conducted with DCM and saturated $NaHCO_3$ aq, brine. Purification by column chromatography with petroleum ether: ethyl acetate/ 20:1-8:1 afforded the desired compound as a white solid (88.2 mg, 94% yield).



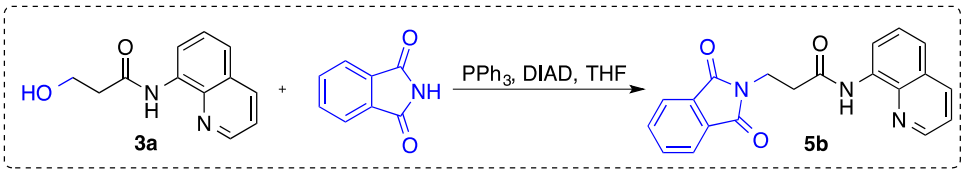
3-chloro-*N*-(quinolin-8-yl)propanamide (5a)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.876 (s, 1H), 8.757 (d, *J* = 5.20 Hz, 2H), 8.100 (d, *J* = 8.24 Hz, 1H), 7.513-7.454 (m, 2H), 7.418-7.386 (m, 1H), 3.943 (t, *J* = 6.56 Hz, 2H), 3.008 (t, *J* = 6.56 Hz, 2H);

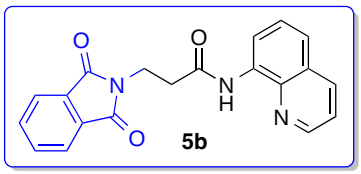
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 167.93, 148.25, 138.23, 136.36, 134.10, 127.89, 127.30, 121.88, 121.70, 116.66, 40.84, 39.82;

LC-MS (ESI^+): m / z calculated for $C_{12}H_{12}ClN_2O$ $(M+H)^+$: 235.06 found 235.05.

Synthesis of compound 5b



In a 10 mL round-bottomed flask, substrate 3-hydroxy-*N*-(quinolin-8-yl)propanamide **(3a)** (43.2 mg, 0.2 mmol, 1.0 equiv), PPh_3 (104.9 mg, 0.4 mmol, 2.0 equiv) and phthalimide (58.8 mg, 0.4 mmol, 2.0 equiv) were dissolved in 2.0 mL of anhydrous THF. The reaction was cooled to 0^{o}C, and DIAD (79.3 μL, 0.4 mmol, 2.0 equiv) was dropwised within 1min. The reaction was warmed to ambient temperature to stir for 1h. Normal workup was conducted with DCM and saturated $NaHCO_3$ aq, brine. Purification by column chromatography with petroleum ether: acetone/ 8:1-5:1 and DCM: ethyl acetate / 10:1 afforded the desired compound as a white solid (41.4 mg, 60% yield).



3-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)propanamide (5b)

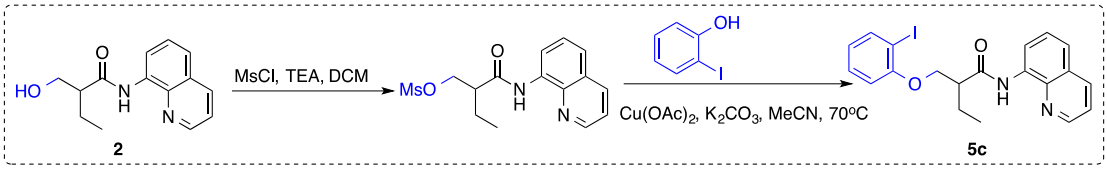
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.778 (s, 1H), 8.719-8.676 (m, 2H), 8.107 (dd, *J* =

8.28 Hz, *J* = 1.36 Hz, 1H), 7.824-7.803 (m, 2H), 7.685-7.663 (m, 2H), 7.506-7.449 (m, 2H), 7.394 (dd, *J* = 8.24 Hz, *J* = 4.24 Hz, 1H), 4.172 (t, *J* = 7.32 Hz, 2H), 3.006 (t, *J* = 7.32 Hz, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 168.38, 168.18, 148.18, 138.28, 136.38, 134.26, 134.03, 132.19, 127.93, 127.43, 123.37, 121.70, 121.66, 116.70, 36.11, 34.35;

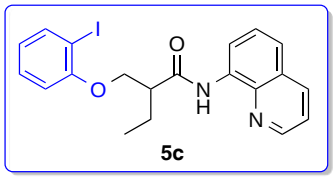
LC-MS (ESI$^+$): m / z calculated for $C_{20}H_{16}N_3O_3$ $(M+H)^+$: 346.12 found 346.03.

Synthesis of compound 5c



To the solution of **2** (245 mg, 1.0 mmol, 1.0 equiv) in 5.0 mL of anhydrous DCM was added TEA (279 µL, 2.0 mmol, 2.0 equiv) followed by MsCl (116 µL, 1.5 mmol, 1.5 equiv). After stirring at 0 °C for 1h, DCM was added to dilute the mixture and saturated $NaHCO_3$ (aq) was added to quench the reaction. After layers separation, the aqueous layer was extracted with DCM twice. The combined organic layer was washed with brine, dried over Na_2SO_4. After filtration and evaporation, purification by column chromatography with petroleum ether: ethyl acetate/ 3:1-2:1 afforded the desired compound as a white solid (320 mg, 99% yield).

The above-obtained compound (114 mg, 0.35 mmol, 1.0 equiv) was dissolved in 4.0 mL of acetonitrile. $Cu(OAc)_2$ (6.4 mg, 0.035 mmol, 1.0 equiv), K_2CO_3 (97 mg, 0.70 mmol, 2.0equiv), 2-iodophenol (154 mg, 0.7 mmol, 2.0 equiv) were added. The reaction mixture was stirred at 70 °C for 2h. After cooling to ambient temperature, solvent was evaporated and DCM was added to dilute the solution. Normal workup was conducted with DCM and brine. Purification by column chromatography with DCM: acetone/100:1-50:1 then second column with petroleum ether: acetone/ 20:1-15:1 afforded the desired compound as a white solid (100 mg, 64% yield).



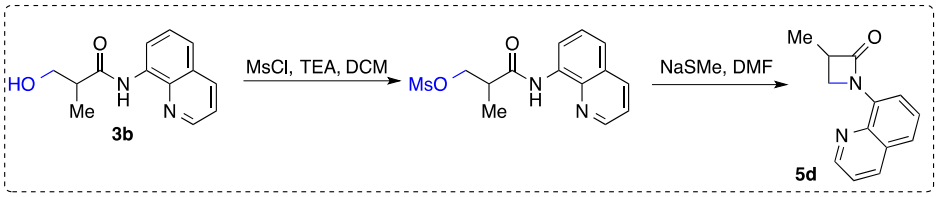
2-((2-iodophenoxy)methyl)-*N*-(quinolin-8-yl)butanamide (5c)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.028 (s, 1H), 8.865-8.847 (t, 1H), 8.770 (dd, *J* = 4.12 Hz, *J* = 1.40 Hz, 1H), 8.114 (dd, *J* = 8.24 Hz, *J* = 1.24 Hz, 1H), 7.701 (dd, *J* = 7.76 Hz, *J* = 1.20 Hz, 1H), 7.550-7.477 (m, 2H), 7.407 (dd, *J* = 8.24 Hz, *J* = 4.20 Hz, 1H), 7.265 (t, *J* = 7.76 Hz, 1H), 6.845 (d, *J* = 8.08 Hz, 1H), 6.676 (t, *J* = 7.20 Hz, 1H), 4.342 (t, *J* = 8.32 Hz, 1H), 4.207 (dd, *J* = 8.88 Hz, *J* = 5.32 Hz, 1H), 3.069-3.001 (m, 1H), 2.077-1.949 (m, 1H), 1.931-1,846 (m, 1H), 1.122 (t, *J* = 7.44 Hz, 3H);

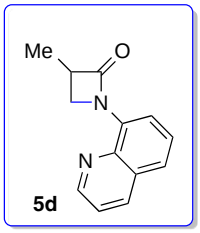
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 172.13, 157.22, 148.21, 139.41, 138.54, 136.26, 134.62, 129.49, 127.97, 127.40, 122.82, 121.69, 121.64, 116.74, 112.36, 86.78, 70.09, 50.44, 22.60, 11.91;

LC-MS (ESI$^+$): m / z calculated for $C_{20}H_{20}IN_2O_2$ $(M+H)^+$: 447.06 found 446.97.

Synthesis of compound 5d



To the solution of **3b** (44 mg, 0.19 mmol, 1.0 equiv) in 2.0 mL of anhydrous DCM was added TEA (53 µL, 0.38 mmol, 2.0 equiv) followed by MsCl (30 µL, 0.38 mmol, 2.0 equiv). After stirring at 0 ^{o}C for 1h, DCM was added to dilute the mixture and saturated $NaHCO_3$ (aq) was added to quench the reaction. After layers separation, the aqueous layer was extracted with DCM twice. The combined organic layer was washed with brine, dried over Na_2SO_4. After filtration and evaporation, DMF 2.0 mL and NaSMe (179 mg, 15%, 2.0 equiv) were added. The reaction mixture was stirred at 50 ^{o}C for 1h and cooled to room temperature. Normal workup was conducted with DCM and brine. Purification by column chromatography with petroleum ether: ethyl acetate/ 10:1-6:1 afforded the desired compound as a white solid (23 mg, 57% yield).



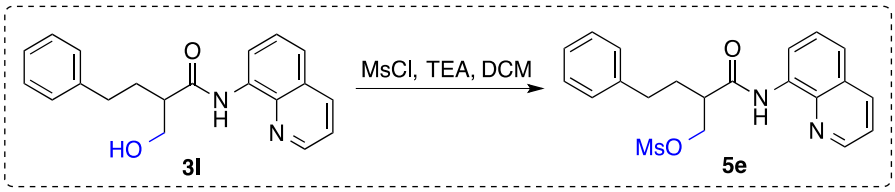
3-methyl-1-(naphthalen-1-yl)azetidin-2-one (5d)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 8.798 (dd, *J* = 8.12 Hz, *J* = 1.68 Hz, 1H), 8.458 (dd, *J* = 6.68 Hz, *J* = 2.32 Hz, 1H), 8.088 (dd, *J* = 8.36 Hz, *J* = 1.64 Hz, 1H), 7.516-7.456 (m, 2H), 7.367 (dd, *J* = 8.32 Hz, *J* = 4.12 Hz, 1H), 4.653 (dd, *J* = 7.28 Hz, *J* = 5.64 Hz, 1H), 4.148 (dd, *J* = 7.40 Hz, *J* = 2.84 Hz, 1H), 3.474-3.398 (m, 1H), 1.453 (d, *J* = 7.36 Hz, 3H);

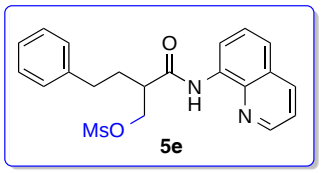
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 170.94, 148.60, 140.47, 136.01, 135.17, 129.05, 126.82, 122.96, 121.30, 119.52, 53.62, 45.76, 13.91;

LC-MS (ESI^{+}): m / z calculated for $C_{13}H_{13}N_2O$ $(M+H)^{+}$: 213.10 found 213.04.

Synthesis of compound 5e



To the solution of **3l** (235 mg, 0.734 mmol, 1.0 equiv) in 6.0 mL of anhydrous DCM was added TEA (204 µL, 1.47 mmol, 2.0 equiv) followed by MsCl (114 µL, 1.47 mmol, 2.0 equiv). After stirring at 0 ^{o}C for 1h, DCM was added to dilute the mixture and saturated $NaHCO_3$ (aq) was added to quench the reaction. After layers separation, the aqueous layer was extracted with DCM twice. The combined organic layer was washed with brine, dried over Na_2SO_4. After filtration and evaporation, purification by column chromatography with petroleum ether: ethyl acetate/ 3:1-2:1 afforded the desired compound as colorless oil (277 mg, 95% yield).



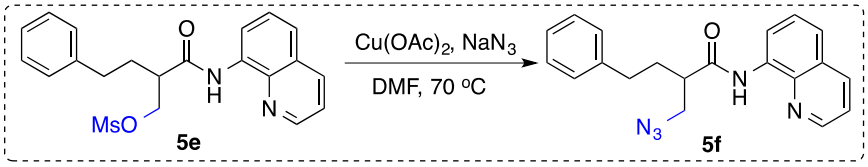
4-phenyl-2-(quinolin-8-ylcarbamoyl)butyl methanesulfonate (5e)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.050 (s, 1H), 8.853-8.833 (m, 2H), 8.162 (d, *J* = 8.24 Hz, 1H), 7.581-7.547 (m, 2H), 7.480-7.449 (m, 1H), 7.321-7.284 (m, 2H), 7.243-7.202 (m, 3H), 4.601 (t, *J* = 9.48 Hz, 1H), 4.412 (dd, *J* = 9.88 Hz, *J* = 4.76 Hz, 1H), 3.079-3.008 (m, 4H), 2.875-2.711 (m, 2H), 2.245-2.152 (m, 1H), 2.009-1.921 (m, 1H);

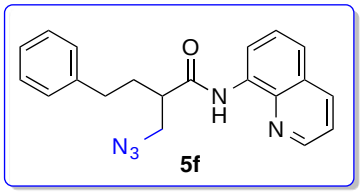
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 170.33, 148.33, 140.45, 138.24, 136.28, 133.90, 128.52, 128.38, 127.84, 127.13, 126.22, 122.07, 121.76, 116.62, 70.18, 47.25, 38.08, 32.91, 30.49;

LC-MS (ESI$^+$): m / z calculated for $C_{21}H_{23}N_2O_4S$ $(M+H)^+$: 399.14 found 399.01.

Synthesis of compound 5f



Compound **5e** (40 mg, 0.1 mmol, 1.0 equiv) was dissolved in 2.0 mL of DMF. $Cu(OAc)_2$ (18 mg, 0.1 mmol, 1.0 equiv) and NaN_3 (13 mg, 0.2 mmol, 2.0 equiv) were added. The reaction mixture was stirred at 70 °C for 2h. After cooling to ambient temperature, DCM was added to dilute the solution. Normal workup was conducted with DCM and brine. Purification by column chromatography with petroleum ether: ethyl acetate/ 30:1-15:1-10:1 afforded the desired compound as a white solid (33 mg, 97% yield).



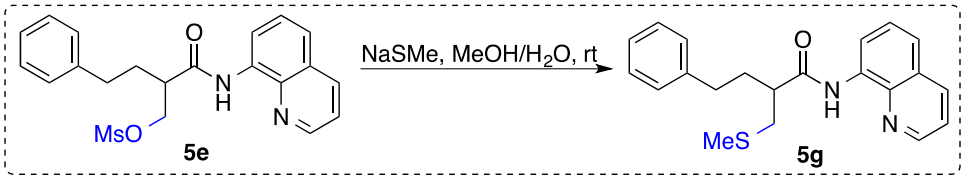
2-(azidomethyl)-4-phenyl-*N*-(quinolin-8-yl)butanamide (5f)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.003 (s, 1H), 8.849-8.828 (m, 2H), 8.179 (dd, *J* = 8.24 Hz, *J* = 1.16 Hz, 1H), 7.589-7.462 (m, 3H), 7.310-7.190 (m, 5H), 3.797 (dd, *J* = 12.08 Hz, *J* = 8.72 Hz, 1H), 3.517 (dd, *J* = 12.12 Hz, *J* = 5.36 Hz, 1H), 2.855-2.666 (m, 3H), 2.248-2.155 (m, 1H), 1.991-1.904 (m, 1H);

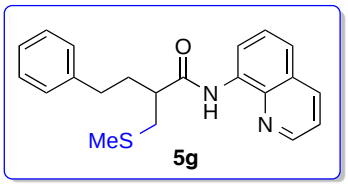
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 171.53, 148.43, 140.99, 138.57, 136.47, 134.25, 128.68, 128.60, 128.07, 127.49, 126.32, 122.04, 121.83, 116.94, 53.52, 48.04, 33.33, 32.08;

LC-MS (ESI$^+$): m / z calculated for $C_{20}H_{20}N_5O_2$ $(M+H)^+$: 346.17 found 346.08.

Synthesis of compound 5g



Compound **5e** (80 mg, 0.2 mmol, 1.0 equiv) was dissolved in 3.0 mL of MeOH and 1.0 mL of H_2O. NaSMe (187 mg, 15%, 0.4 mmol, 2.0 equiv) was added. The reaction mixture was stirred at room temperature for 2h. After evaporation to remove most of the solvent, the residue was diluted in DCM. Normal workup was conducted with DCM and brine. Purification by column chromatography with petroleum ether: ethyl acetate/ 30:1-15:1 afforded the desired compound as colorless oil (68 mg, 97% yield).



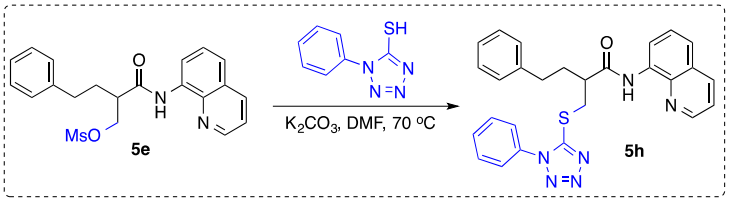
2-((methylthio)methyl)-4-phenyl-*N*-(quinolin-8-yl)butanamide (5g)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.999 (s, 1H), 8.879 (dd, *J* = 7.24 Hz, *J* = 1.92 Hz, 1H), 8.836 (dd, *J* = 4.20 Hz, *J* = 1.56 Hz, 1H), 8.157 (dd, *J* = 8.28 Hz, *J* = 1.48 Hz, 1H), 7.581-7.503 (m, 2H), 7.457 (dd, *J* = 8.28 Hz, *J* = 4.24 Hz, 1H), 7.306-7.183 (m, 5H), 3.042-2.980 (m, 1H), 2.874-2.665 (m, 4H), 2.286-2.193 (m, 1H), 2.126 (s, 3H), 2.096-2.028 (m, 1H);

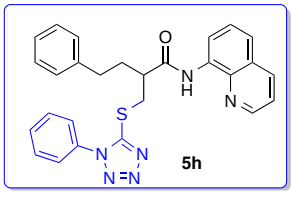
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 196.82, 172.76, 169.71, 161.45, 141.57, 140.43, 128.65, 128.63, 128.60, 128.42, 126.45, 126.04, 104.04, 57.62, 52.51, 51.58, 36.43, 33.06, 29.48, 27.95;

LC-MS (ESI$^+$): m / z calculated for $C_{21}H_{23}N_2OS$ $(M+H)^+$: 351.15 found 351.05.

Synthesis of compound 5h



Compound **5e** (114 mg, 0.286 mmol, 1.0 equiv) was dissolved in 3.0 mL of DMF. K_2CO_3 (79 mg, 0.572 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 70 °C for 2h. After cooling to room temperature, the residue was diluted in DCM. Normal workup was conducted with DCM and brine. Purification by column chromatography with petroleum ether: ethyl acetate/ 8:1-5:1 and petroleum ether: acetone/ 7:1-6:1 afforded the desired compound as a white solid (123 mg, 90% yield).



4-phenyl-2-(((1-phenyl-1*H*-tetrazol-5-yl)thio)methyl)-*N*-(quinolin-8-yl)butanamide (5h)

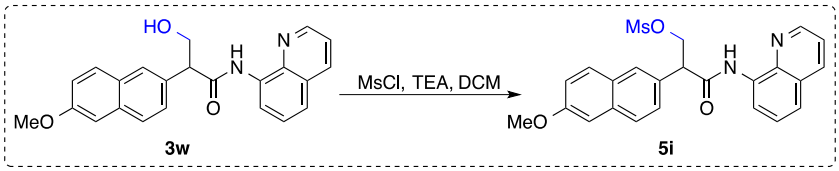
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.998 (s, 1H), 8.813-8.778 (m, 2H), 8.145 (dd, *J* = 8.24 Hz, *J* = 1.44 Hz, 1H), 7.558-7.510 (m, 2H), 7.453-7.387 (m, 6H), 7.290-7.226 (m, 4H), 7.181 (t, *J* = 6.88 Hz, 1H), 3.781-3.661 (m, 2H), 3.368-3.312 (m, 1H), 2.882-2.759 (m, 2H), 2.327-2.247 (m, 1H), 2.162-2.085 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 171.81, 154.33, 148.45, 141.00, 138.42, 136.33,

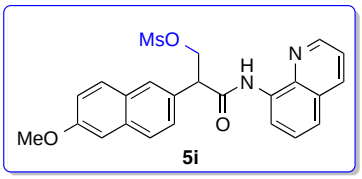
134.06, 133.52, 130.08, 129.73, 128.55, 128.49, 127.93, 127.31, 126.19, 123.74, 122.03, 121.79, 116.80, 47.75, 35.22, 34.48, 33.50;

LC-MS (ESI$^+$): m / z calculated for $C_{27}H_{25}N_6OS$ $(M+H)^+$: 481.18 found 481.00.

Synthesis of compound 5i



To the solution of **3w** (82 mg, 0.22 mmol, 1.0 equiv) in 2.0 mL of anhydrous DCM was added TEA (61 µL, 0.44 mmol, 2.0 equiv) followed by MsCl (31 µL, 0.39 mmol, 1.8 equiv). After stirring at 0 ^oC for 1h, DCM was added to dilute the mixture and saturated $NaHCO_3$ (aq) was added to quench the reaction. After layers separation, the aqueous layer was extracted with DCM twice. The combined organic layer was washed with brine, dried over Na_2SO_4. After filtration and evaporation, purification by column chromatography with petroleum ether: ethyl acetate/ 5:1-3:1 afforded the desired compound as colorless oil (93 mg, 94% yield).



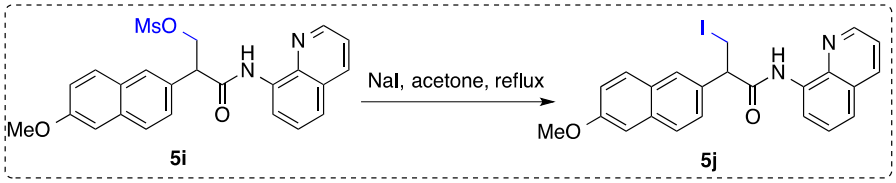
2-(6-methoxynaphthalen-2-yl)-3-oxo-3-(quinolin-8-ylamino)propyl methanesulfonate (5i)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.039 (s, 1H), 8.782 (d, *J* = 7.24 Hz, 1H), 8.646 (dd, *J* = 4.04 Hz, *J* = 1.20 Hz, 1H), 8.039 (d, *J* = 7.20 Hz, 1H), 7.894 (s, 1H), 7.739 (t, *J* = 7.88 Hz, 2H), 7.553 (dd, *J* = 8.48 Hz, *J* = 1.20 Hz, 1H), 7.512-7.435 (m, 2H), 7.330 (dd, *J* = 8.24 Hz, *J* = 4.24 Hz, 1H), 7.154 (dd, *J* = 9.00 Hz, *J* = 2.28 Hz, 1H), 7.089 (d, *J* = 1.84 Hz, 1H), 5.061 (t, *J* = 9.52 Hz, 1H), 4.600 (dd, *J* = 9.92 Hz, *J* = 5.24 Hz, 1H), 4.379 (dd, *J* = 8.96 Hz, *J* = 5.24 Hz, 1H), 3.877 (s, 3H), 3.028 (s, 3H);

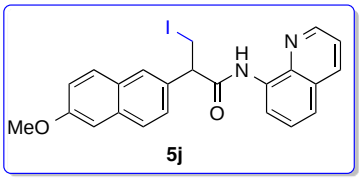
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 168.54, 158.13, 148.33, 138.23, 136.23, 134.37, 134.09, 129.51, 129.45, 129.00, 128.01, 127.84, 127.38, 127.14, 126.11, 122.07, 121.70, 119.52, 116.50, 105.64, 70.53, 55.33, 53.36, 37.29, 31.55;

LC-MS (ESI$^+$): m / z calculated for $C_{24}H_{23}N_2O_5S$ $(M+H)^+$: 451.13 found XXX.

Synthesis of compound 5j



Compound **5i** (45 mg, 0.1 mmol, 1.0 equiv) was dissolved in 4.0 mL of acetone and NaI (60 mg, 0.4 mmol, 4.0 equiv) was added. The reaction mixture was stirred at 70 ^oC to reflux for 48h. After cooling to ambient temperature and evaporation of acetone, normal workup was conducted with DCM and brine. Purification by column chromatography with petroleum ether: ethyl acetate/ 6:1-4:1 afforded the desired compound as a white solid (41 mg, 84 yield).



5j

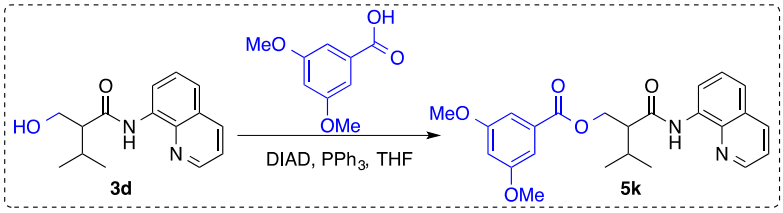
3-iodo-2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (5j)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.006 (s, 1H), 8.812 (dd, *J* = 7.48 Hz, *J* = 1.20 Hz, 1H), 8.680 (dd, *J* = 4.24 Hz, *J* = 1.56 Hz, 1H), 8.067 (dd, *J* = 8.28 Hz, *J* = 1.52 Hz, 1H), 7.888 (s, 1H), 7.766-7.737 (m, 2H), 7.568-7.441 (m, 3H), 7.358 (dd, *J* = 8.28 Hz, *J* = 4.28 Hz, 1H), 7.155 (dd, *J* = 9.00 Hz, *J* = 2.52 Hz, 1H), 4.305 (dd, *J* = 8.84 Hz, *J* = 6.24 Hz, 1H), 4.103 (dd, *J* = 9.76 Hz, *J* = 8.84 Hz, 1H), 3.555 (dd, *J* = 9.76 Hz, *J* = 6.20 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 169.51, 158.08, 148.30, 138.39, 136.32, 134.36, 134.24, 133.82, 129.57, 129.07, 127.92, 127.35, 126.80, 125.70, 121.93, 121.68, 119.45, 116.65, 105.75, 57.81, 55.42, 5.63;

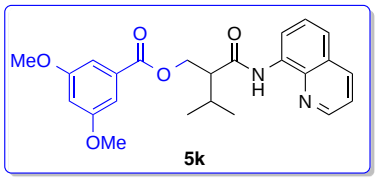
LC-MS (ESI$^+$): m / z calculated for $C_{23}H_{20}IN_2O_2$ $(M+H)^+$: 483.06 found 482.90.

Synthesis of compound 5k



3d 5k

In a 10 mL round-bottomed flask, substrate **3d** (76 mg, 0.293 mmol, 1.0 equiv), PPh_3 (154 mg, 0.587 mmol, 2.0 equiv) and 3,5-dimethoxybenzoic acid (107 mg, 0.587 mmol, 2.0 equiv) were dissolved in 3.0 mL of anhydrous THF. The reaction was cooled to 0^{o}C, and DIAD (117 µL, 0.587 mmol, 2.0 equiv) in 1.0 mL of THF was dropwised within 5min. The reaction was warmed to ambient temperature to stir for 1h. After evaporation of most of the solvent, normal workup was conducted with DCM, saturated $NaHCO_3$ aq and brine. Purification by column chromatography with petroleum ether: acetone/ 10:1-6:1-3:1 and DCM: ethyl acetate / 20:1 afforded the desired compound as a white solid (95 mg, 77% yield).



5k

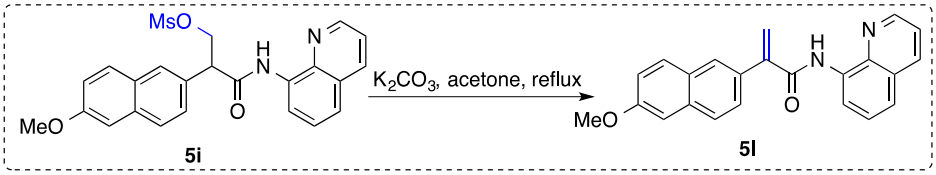
3-methyl-2-(quinolin-8-ylcarbamoyl)butyl 3,5-dimethoxybenzoate (5k)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.025 (s, 1H), 8.842 (dd, *J* = 7.12 Hz, *J* = 1.72 Hz, 1H), 8.691 (dd, *J* = 4.20 Hz, *J* = 1.56 Hz, 1H), 8.118 (dd, *J* = 8.28 Hz, *J* = 1.52 Hz, 1H), 7.513-7.466 (m, 2H), 7.402 (dd, *J* = 8.28 Hz, *J* = 4.24 Hz, 1H), 7.077 (d, *J* = 2.36 Hz, 2H), 6.493 (t, *J* = 2.36 Hz, 1H), 4.733 (dd, *J* = 10.80 Hz, *J* = 4.48 Hz, 1H), 4.557 (t, *J* = 10.22 Hz, 1H), 3.485 (s, 6H), 2.753-2.701 (m, 1H), 2.285-2.197 (m, 1H), 1.132 (t, *J* = 7.08 Hz, 6H);

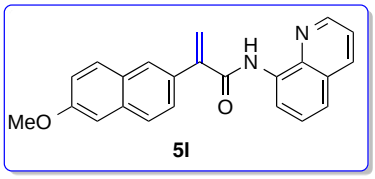
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 171.87, 166.14, 160.49, 148.35, 138.39, 136.31, 134.34, 131.85, 127.93, 127.43, 121.73, 121.66, 116.66, 107.08, 106.06, 65.16, 55.21, 28.71, 21.09, 20.49;

LC-MS (ESI$^+$): m / z calculated for $C_{24}H_{27}N_2O_5$ $(M+H)^+$: 423.19 found 423.09.

Synthesis of compound 5l



Compound **5i** (45 mg, 0.1 mmol, 1.0 equiv) was dissolved in 2.0 mL of acetone and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 70 ^oC to reflux for 48h. After cooling to ambient temperature and evaporation of acetone, normal workup was conducted with DCM and brine. Purification by column chromatography with petroleum ether: ethyl acetate/ 6:1-4:1 afforded the desired compound as a white solid (34 mg, 95% yield).



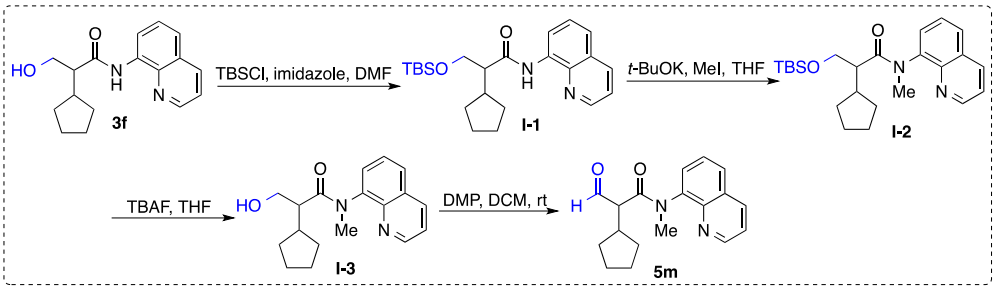
2-(6-methoxynaphthalen-2-yl)-*N*-(quinolin-8-yl)acrylamide (5l)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.352 (s, 1H), 8.935 (d, *J* = 7.52 Hz, 1H), 8.554 (dd, *J* = 4.16 Hz, *J* = 1.44 Hz, 1H), 8.113 (dd, *J* = 7.04 Hz, *J* = 1.20 Hz, 1H), 7.989 (s, 1H), 7.809-7.758 (m, 2H), 7.636-7.508 (m, 3H), 7.359 (dd, *J* = 8.24 Hz, *J* = 4.20 Hz, 1H), 7.198-7.175 (m, 2H), 6.338 (s, 1H), 5.929 (s, 1H), 3.950 (s, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 166.27, 158.32, 148.40, 146.05, 138.87, 136.29, 134.66, 131.90, 130.03, 128.92, 128.02, 127.63, 127.48, 127.33, 126.47, 122.00, 121.77, 121.66, 119.38, 116.87, 105.82, 55.46;

LC-MS (ESI$^+$): m / z calculated for $C_{23}H_{19}N_2O_2$ $(M+H)^+$: 355.14 found 355.05.

Synthesis of compound 5m



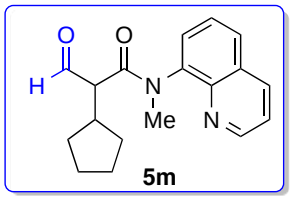
Compound **3f** (77 mg, 0.271 mmol, 1.0 equiv) was dissolved in 2.0 mL of DMF. TBSCl (62 mg, 0.407 mmol, 1.5 equiv) and imidazole (37 mg, 0.542 mmol, 2.0 equiv) were added. The reaction mixture was stirred at 0^{o}C-RT for 1h. Normal workup was conducted with DCM and brine. Purification by column chromatography with petroleum ether: ethyl acetate/ 100:1-50:1-20:1 afforded the intermediate (**I-1**) as colorless oil (85 mg, 79% yield).

The above-obtained **I-1** was dissolved in 2.0 mL of anhydrous THF. After cooling to 0^{o}C, t-BuOK (2.0 equiv) and MeI (2.0 equiv) were added. The reaction mixture was stirred at 0^{o}C-RT for 2h. After evaporation of the solvent, normal workup was conducted with DCM

and brine. Purification by column chromatography with petroleum ether: ethyl acetate/ 4:1-2.5:1 afforded the intermediate (**I-2**) as colorless oil (68 mg, 77% yield).

The above-obtained **I-2** was dissolved in 2.0 mL of anhydrous THF. TBAF (1M in THF, 2.0 equiv) was added. The reaction mixture was stirred at RT for 4h. After evaporation of the solvent, normal workup was conducted with DCM and brine. Purification by column chromatography with DCM: MeOH/ 20:1-10:1 afforded the intermediate (**I-3**) as a white solid (46 mg, 93% yield).

The above-obtained **I-3** was dissolved in 2.0 mL of DCM. DMP (3.0 equiv) was added. The reaction mixture was stirred at RT for 1h. After addition of saturated $Na_2S_2O_3$ aq to quench the reaction, normal workup was conducted with DCM, saturated $NaHCO_3$ aq and brine. Purification by column chromatography with petroleum ether: ethyl acetate/ 2:1-1.5:1 afforded the final compound as a white solid (44 mg, 96% yield).

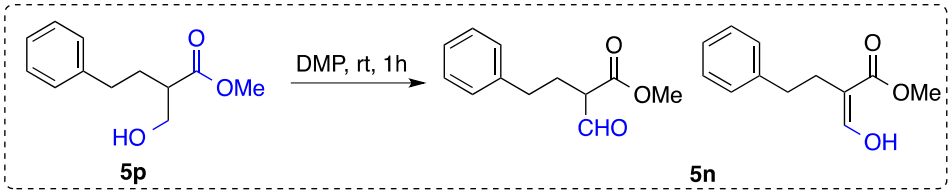


2-cyclopentyl-*N*-methyl-3-oxo-*N*-(quinolin-8-yl)propanamide (5m)

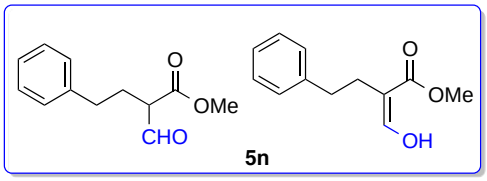
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.653 (d, *J* = 3.00 Hz, 0.7H), 9.546 (d, *J* = 3.52 Hz, 0.3H), 8.948 (d, *J* = 3.44 Hz, 0.3H), 8.831 (d, *J* = 3.92 Hz, 0.7H), 8.244-8.711 (m, 1H), 7.879-7.822 (m, 1H), 7.627-7.424 (m, 3H), 3.397 (s, 3H), 2.591-2.454 (m, 1H), 1.885-1.840 (m, 1H), 1.527-1.156 (m, 8H);

LC-MS (ESI^+): m / z calculated for $C_{18}H_{21}N_2O_2$ $(M+H)^+$: 297.16 found 297.06.

Synthesis of compound 5n



To the solution of **5p** (89 mg, 0.427 mmol, 1.0 equiv) in 3.0 mL of DCM, DMP (362 mg, 0.854 mmol, 2.0 equiv) was added. The reaction mixture was stirred at RT for 1h. After addition of saturated $Na_2S_2O_3$ aq to quench the reaction, normal workup was conducted with DCM, saturated $NaHCO_3$ aq and brine. Purification by column chromatography with petroleum ether: ethyl acetate/ 20:1-10:1 afforded the desired compound as colorless oil (54 mg, 62% yield).



methyl 2-formyl-4-phenylbutanoate/ methyl (*Z*)-2-(hydroxymethylene)-4-phenylbutanoate (5n)

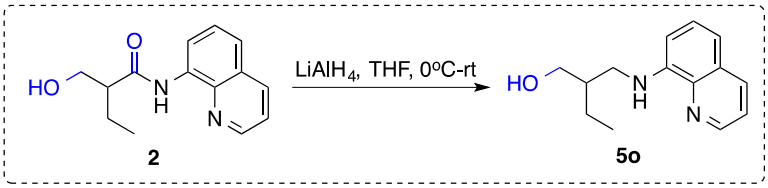
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 11.400 (d, *J* = 12.56 Hz, 0.51H), 9.714 (s, 0.32H), 7.330-7.154 (m, 5H), 6.910 (d, *J* = 12.56 Hz, 0.54H), 3.811-3.782 (d, 2.89H), 3.331 (t, *J* = 7.00 Hz, 0.37H), 2.750-2.670 (m, 2H), 2.385 (t, *J* = 7.70 Hz, 1.12H), 2.221 (dd, *J* = 14.92 Hz,

J = 7.52 Hz, 0.76H);

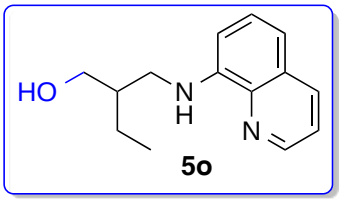
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 172.77, 148.28, 141.28, 138.50, 136.36, 134.33, 128.55, 128.51, 127.99, 127.43, 126.08, 121.77, 121.70, 116.73, 48.55, 37.24, 34.25, 33.51, 16.43;

LC-MS (ESI$^+$): m / z calculated for $C_{12}H_{15}O_3$ $(M+H)^+$: 207.10 found 207.09.

Synthesis of compound 5o



To a solution of substrate **2** (73.3 mg, 0.30 mmol, 1.0 equiv) in 3.0 mL of anhydrous at 0 °C was added $LiAlH_4$ (34 mg, 0.9 mmol, 3.0 equiv) solution in 1.0 mL of THF. The reaction mixture was stirred at 0 °C for 1h, and then rt for 6h. MeOH was added slowly to quench the reaction and 1N HCl aq was added to stir for 5min. After evaporation of most of solvent, normal workup was conducted with DCM and H_2O (make pH~5-6). After dryness, filtration and evaporation, the crude mixture was purified by column chromatography with petroleum ether: ethyl acetate/ 4:1-3:1 to afford the desired compound as green-yellow oil (42 mg, 61% yield).



2-((quinolin-8-ylamino)methyl)butan-1-ol (5o)

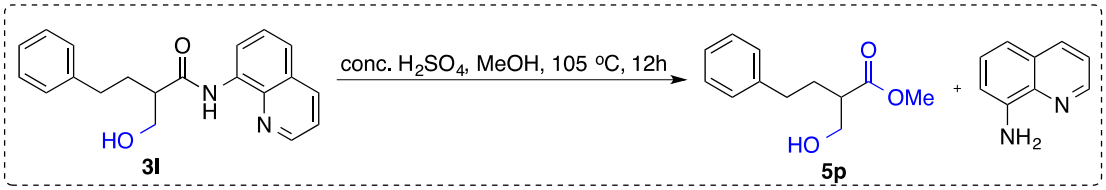
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 8.703 (d, *J* = 3.68 Hz, 1H), 8.049 (d, *J* = 8.20 Hz, 1H), 7.402-7.339 (m, 2H), 7.047 (d, *J* = 8.08 Hz, 1H), 6.736 (d, *J* = 7.56 Hz, 1H), 6.346 (s, 1H, NH), 3.829-3.806 (m, 1H), 3.757-3.716 (m, 1H), 3.374 (s, 2H), 1.974-1.916 (m, 2H), 1.556-1.485 (m, 2H), 1.022 (t, *J* = 7.40 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 147.02, 145.17, 138.43, 136.14, 128.79, 127.90, 121.49, 114.03, 105.00, 64.69, 45.49, 42.05, 22.37, 11.74;

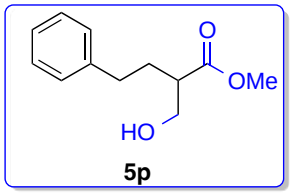
LC-MS (ESI$^+$): m / z calculated for $C_{14}H_{19}N_2O$ $(M+H)^+$: 231.15 found 231.06.

IX. General Procedure for Directing Group Removing

Synthesis of compound 5p [8]



To a stirred solution of compound **3l** (144 mg, 0.45 mmol, 1.0 equiv) in 5 mL of MeOH, concentrated sulfuric acid was added (~6.0 equiv). The resulting mixture was heated to 105 ^{o}C to stir for 12 h in sealed tube. After cooling to room temperature, the solvent was removed under vacuum, and Normal workup was conducted with DCM and saturated $NaHCO_3$ aq. After evaporation, the crude product was purified by column chromatography with petroleum ether: ethyl acetate/ 10:1-5:1-2:1 to recover 8-aminoquinoline as grew brown solid (60 mg, 93% yield) and afford the desired compound as colorless oil (89 mg, 95% yield).



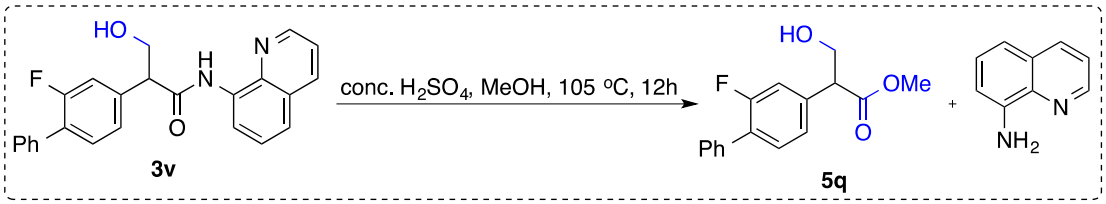
methyl 2-(hydroxymethyl)-4-phenylbutanoate (5p)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.306-7.268 (t, 2H), 7.210-7.176 (m, 3H), 3.793-3.711 (m, 5H), 2.674-2.596 (m, 4H), 2.047-1.954 (m, 1H), 1.889-1.799 (m, 1H);

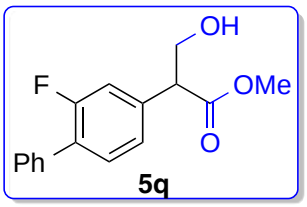
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 175.58, 141.24, 128.45, 128.43, 126.08, 63.08, 51.81, 47.09, 33.39, 30.10;

LC-MS (ESI^{+}): m / z calculated for $C_{12}H_{17}O_3$ $(M+H)^{+}$: 209.12 found 209.04.

Synthesis of compound 5q [8]



To a stirred solution of compound **3v** (436 mg, 1.128 mmol, 1.0 equiv) in 10 mL of MeOH, concentrated sulfuric acid was added (~6.0 equiv). The resulting mixture was heated to 105 ^{o}C to stir for 12 h in sealed tube. After cooling to room temperature, the solvent was removed under vacuum, and Normal workup was conducted with DCM and saturated $NaHCO_3$ aq. After evaporation, the crude product was purified by column chromatography with petroleum ether: ethyl acetate/ 10:1-5:1-2:1 to recover 8-aminoquinoline as grew brown solid (159 mg, 98% yield) and afford the desired compound as a white solid (300 mg, 97% yield).



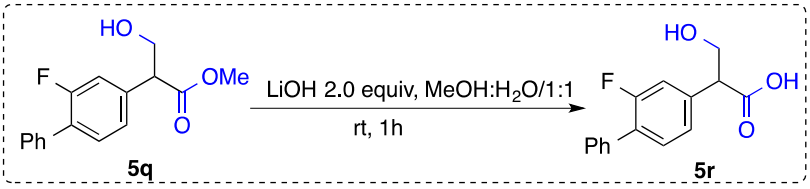
methyl 2-(2-fluoro-[1,1'-biphenyl]-4-yl)-3-hydroxypropanoate (5q)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.542 (d, *J* = 7.68 Hz, 2H), 7.466-7.358 (m, 4H), 7.164-7.135 (m, 2H), 4.200-4.127 (m, 1H), 3.928-3.903 (m, 2H), 3.754 (s, 3H), 2.839 (s, 1H);

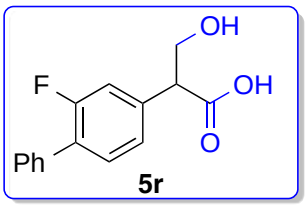
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 173.12, 159.75 (d, *J* = 247 Hz, C), 136.97 (d, *J* = 8 Hz, C), 135.30, 131.10 (d, *J* = 4 Hz, CH), 128.97 (d, *J* = 3 Hz, CH), 128.53 (d, *J* = 13 Hz, C), 128.52, 127.84, 124.33 (d, *J* = 3 Hz, CH), 116.01 (d, *J* = 24 Hz, CH), 64.32, 53.41, 52.41;

LC-MS (ESI$^+$): m / z calculated for $C_{16}H_{16}FO_3$ $(M+H)^+$: 275.11 found 275.14.

Synthesis of compound 5r



To a stirred solution of compound **5q** (120 mg, 0.437 mmol, 1.0 equiv) in 3.0 mL of MeOH and 3.0 mL of H_2O, LiOH (21.0 mg, 0.875 mmol, 2.0 equiv) was added. The resulting mixture was stirred at room temperature for 1h. Normal workup was conducted with EtOAc and diluted HCl aq. After evaporation, the crude product was purified by column chromatography with DCM: MeOH/ 50:1-20:1 to afford the desired compound as a white solid (113 mg, 99% yield).



2-(2-fluoro-[1,1'-biphenyl]-4-yl)-3-hydroxypropanoic acid (5r)

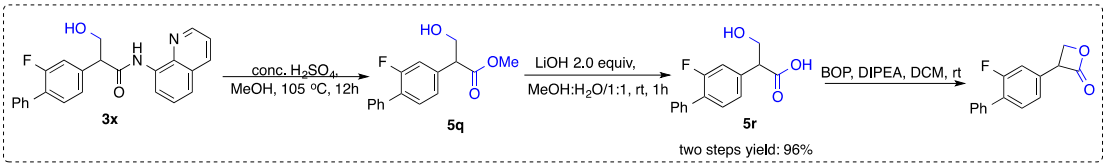
^{1}H-NMR (400 MHz, CD_3OD) δ (ppm) 7.501 (d, *J* = 7.40 Hz, 2H), 7.412 (t, *J* = 7.14 Hz, 3H), 7.337 (t, *J* = 7.20 Hz, 1H), 7.210 (t, *J* = 7.76 Hz, 2H), 4.106 (t, *J* = 11.56 Hz, 1H), 3.837-3.788 (m, 2H);

^{13}C-NMR (100 MHz, CD_3OD) δ (ppm) 175.50, 160.89 (d, *J* = 245 Hz, C), 139.65 (d, *J* = 7 Hz, C), 136.76, 131.89 (d, *J* = 3 Hz, CH), 129.94 (d, *J* = 3 Hz, CH), 129.47, 129.33 (d, *J* = 14 Hz, C), 128.75, 125.67 (d, *J* = 3 Hz, CH), 116.85 (d, *J* = 24 Hz, CH), 64.87, 55.22;

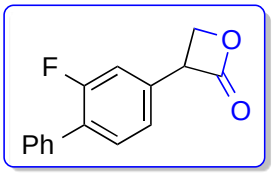
LC-MS (ESI$^-$): m / z calculated for $C_{15}H_{12}FO_3$ $(M-H)^-$: 259.08 found 259.01.

X. General Procedure for Synthetic Application

Synthesis of α-aryl-β-lactone [9]



To a solution of compound 5r (113 mg, 0.434 mmol, 1.0 equiv) in 3.0 mL of DCM, BOP (231 mg, 0.521 mmol, 1.2 equiv) and DIPEA (151 μL, 0.868 mmol, 2.0 equiv) were added. The resulting reaction mixture was stirred at room temperature for 2 h. DCM and saturated $NaHCO_3$ were added and normal workup was conducted. The combined organic layer was dried, filtration and evaporated to give the crude product, which was purified by column chromatography with petroleum ether: ethyl acetate/ 9:1-5:1 to afford the desired compound as a white solid (26 mg, 25% yield).



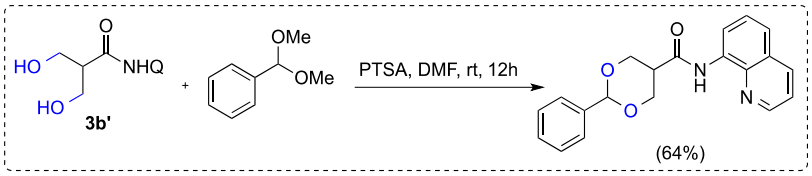
3-(2-fluoro-[1,1'-biphenyl]-4-yl)oxetan-2-one

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.527-7.375 (m, 6H), 7.180-7.115 (q, 2H), 4.982 (t, *J* = 5.62 Hz, 1H), 4.713 (t, *J* = 5.92 Hz, 1H), 4.409 (t, *J* = 4.84 Hz, 1H);

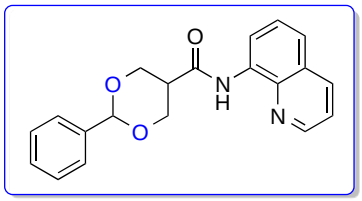
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 168.87, 160.02 (d, *J* = 248 Hz, C), 135.07, 133.70 (d, *J* = 8 Hz, C), 131.70 (d, *J* = 4 Hz, CH), 129.33 (d, *J* = 14 Hz, CH), 129.08, 129.06, 128.43 (d, *J* = 27 Hz, CH), 123.25 (d, *J* = 4 Hz, CH), 115.23 (d, *J* = 24 Hz, CH), 66.17, 56.43;

LC-MS (ESI⁻): m / z calculated for $C_{15}H_{12}FO_2$ $(M-H)^-$: 243.08 found 243.52.

Synthesis of 2-aryl-1,3-dioxane [10]



To a solution of compound 3b' (49 mg, 0.2 mmol, 1.0 equiv), and 4-methylbenzenesulfonic acid hydrate (38 mg, 0.2 mmol, 1.0 equiv) in dimethylformamide (2 mL) was added benzaldehyde dimethyl acetal (165 μL, 1.2 mmol, 6.0 equiv). The solution was stirred at room temperature overnight. Then the solution was poured into saturated $NaHCO_3$ aq and extracted with DCM. The combined organic layer was dried over Na_2SO_4. After filtration and evaporation, the crude product was purified by column chromatography with petroleum ether: ethyl acetate/25:1-10:1-7:1 to afford the desired compound as a white solid (42 mg, 64% yield)



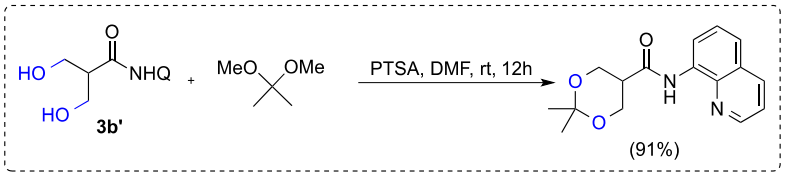
2-phenyl-*N*-(quinolin-8-yl)-1,3-dioxane-5-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.006 (s, 1H), 8.829 (d, *J* = 4.12 Hz, 1H), 8.739-8.717 (t, 1H), 8.168 (d, *J* = 8.24 Hz, 1H), 7.544-7.357 (m, 8H), 5.591 (s, 1H), 4.588 (dd, *J* = 11.52 Hz, *J* = 4.52 Hz, 2H), 4.309 (t, *J* = 11.20 Hz, 2H), 3.411-3.333 (m, 1H);

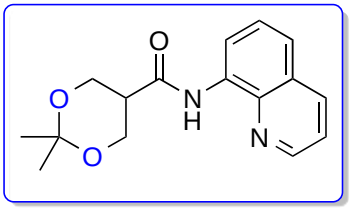
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 168.16, 148.49, 138.34, 138.01, 136.51, 133.95 129.18, 128.44, 127.99, 127.38, 126.20, 122.16, 121.89, 116.76, 101.55, 69.06, 43.81;

LC-MS (ESI$^-$): m / z calculated for $C_{20}H_{19}N_2O_3$ $(M-H)^-$: 335.14 found 335.02.

Synthesis of 2,2-dimethyl-1,3-dioxane



To a solution of compound 3b' (49 mg, 0.2 mmol, 1.0 equiv), and 4-methylbenzenesulfonic acid hydrate (38 mg, 0.2 mmol, 1.0 equiv) in dimethylformamide (2 mL) was added 2,2-dimethoxypropane (148 μL, 1.2 mmol, 6.0 equiv). The solution was stirred at room temperature overnight. Then the solution was poured into saturated $NaHCO_3$ aq and extracted with DCM. The combined organic layer was dried over Na_2SO_4. After filtration and evaporation, the crude product was purified by column chromatography with petroleum ether: ethyl acetate/15:1-7:1-5:1 to afford the desired compound as a white solid (52 mg, 91% yield).



2,2-dimethyl-*N*-(quinolin-8-yl)-1,3-dioxane-5-carboxamide

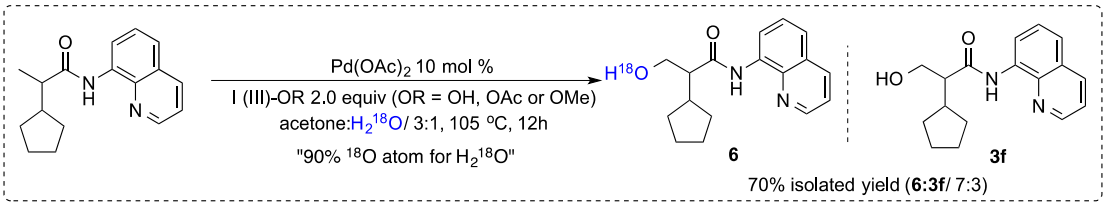
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 10.800 (s, 1H), 8.806-8.780 (m, 2H), 8.124 (d, *J* = 8.24 Hz, 1H), 7.541-7.479 (m, 2H), 7.420 (dd, *J* = 8.24 Hz, *J* = 4.16 Hz, 1H), 4.266-4.256 (m, 4H), 2.724-2.682 (m, 1H), 1.680 (s, 3H), 1.544 (s, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 171.12, 148.27, 138.84, 136.29, 134.94, 128.05, 127.37, 121.81, 121.63, 117.01, 98.92, 61.39, 43.40, 25.72, 21.88

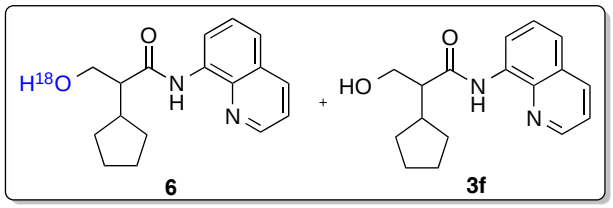
LC-MS (ESI$^-$): m / z calculated for $C_{16}H_{19}N_2O_3$ $(M-H)^-$: 287.14 found 287.07.

XI. General Procedure for Mechanism Study

1) Hydroxylation with $H_2{}^{18}O$ instead of $H_2{}^{16}O$:



To a 10 mL of flame-dried sealed tube, substrate (53.7 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%), cyclic I(III)-OH (106 mg, 0.4 mmol, 2.0 equiv) were dissolved in 0.75 mL of anhydrous acetone and 0.25 mL of $H_2{}^{18}O$ (containing 90% ^{18}O) under Ar. The reaction mixture was then tightly capped and stirred for 10 minutes at room temperature for proper mixing of the reactants, and then heated to 105 ℃ for 12 h. The reaction mixture was then cooled to room temperature, diluted with DCM and filtered through a small pad of celite and washed with DCM. The filtrate was washed with saturated $NaHCO_3$ aq and extracted with DCM for 3 times. The combined organic layer was dried with Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography with petroleum ether: ethyl acetate/ 2:1 to afford the desired compound (mixture of compound **6** and **3f**) as a white solid (40 mg, 70% yield). LC-MS showed the ratio of two compounds (**6**:**3f** = **7:3**). For the other two cyclic oxidants I(III)-OAc and I(III)-OMe, the total isolated yields and the ratio of **6** to **3f** were obtained similarly. These results helped to indicate that the hydroxyl group is originated from solvent water instead of oxidants.

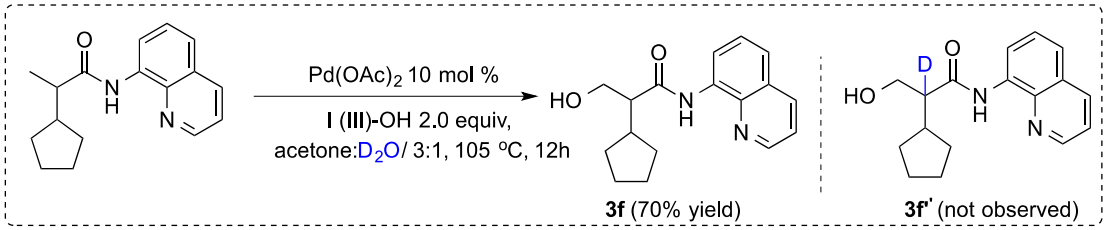


^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.977 (s, 1H), 8.781-8.732 (m, 2H), 8.112 (d, *J* = 8.20 Hz, 1H), 7.460-7.403 (m, 3H), 3.956 (s, 2H), 3.159 (s, 1H), 2.515-2.466 (m, 1H), 2.306-2.198 (m, 1H), 1.934-1.916 (m, 1H), 1.829-1.815 (m, 1H), 1.653-1.528 (m, 4H), 1.398-1.304 (m, 1H), 1.278-1.185 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 174.36, 148.41, 138.53, 136.43, 134.28, 128.01, 127.36, 121.85, 121.69, 116.92, 63.42, 56.22, 39.75, 31.52, 30.86, 24.88, 24.84;

LC-MS (ESI$^+$): m / z calculated for $C_{17}H_{21}N_2O^{18}O$ $(M+H)^+$: 287.16 found 287.07; m / z calculated for $C_{17}H_{21}N_2O_2$ $(M+H)^+$: 285.16 found 285.03.

2) Hydroxylation with D_2O instead of H_2O:



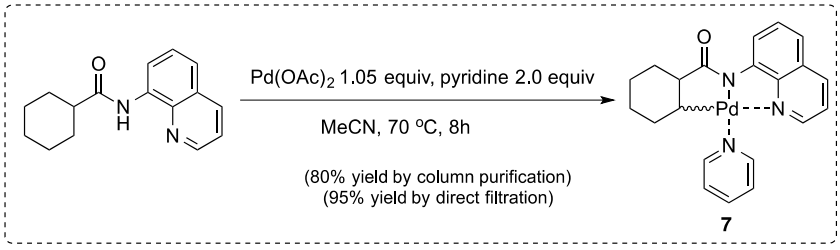
Following the procedure for the synthesis of compound **3f** and **6**, substrate (53.7 mg, 0.2 mmol, 1.0 equiv) was used in the hydroxylation reactions with D_2O instead of H_2O under otherwise the same conditions. Besides general workup following general procedure, another method was used, which involved direct purification by column chromatography after filtration and evaporation. ^{1}H NMR indicated the same results and none of **3f'** was observed, which helped to exclude the mechanistic pathway of elimination followed by Michael addition.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.978 (s, 1H), 8.793-8.738 (m, 2H), 8.123 (d, *J* = 8.28 Hz, 1H), 7.508-7.406 (m, 3H), 3.959 (s, 2H), 3.057 (s, 1H), 2.517-2.467 (m, 1H), 2.319-2.209 (m, 1H), 1.944-1.924 (m, 1H), 1.873-1.827 (m, 1H), 1.687-1.482 (m, 4H), 1.410-1.317 (m, 1H), 1.294-1.200 (m, 1H);

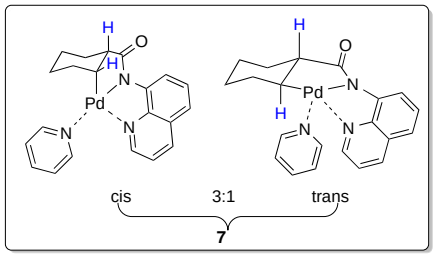
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 174.32, 148.41, 138.56, 136.43, 134.31, 128.03, 127.38, 121.85, 121.69, 116.93, 63.45, 56.22, 39.76, 31.52, 30.87, 24.90, 24.85;

LC-MS (ESI$^+$): m / z calculated for $C_{17}H_{21}N_2O^{18}O$ $(M+H)^+$: 287.16 found 287.07;

3) Preparation of Pd(II)-complex



To a flame-dried flask, substrate (50.9 mg, 0.2 mmol, 1.0 equiv) was dissolved in 2.0 mL of anhydrous acetonitrile. Then $Pd(OAc)_2$ (47.2 mg, 0.21 mmol, 1.05 equiv) and pyridine (32.3 μL, 0.4 mmol, 2.0 equiv) were added under Ar. The resulting mixture was stirred at 70 °C for 8h. After cooling to ambient temperature, the solvent was evaporated to give crude product, which was purified by column chromatography with DCM: acetone/ 10:1-3:1 to afford the desired compound **7** as a yellow solid (70 mg, 80% yield).

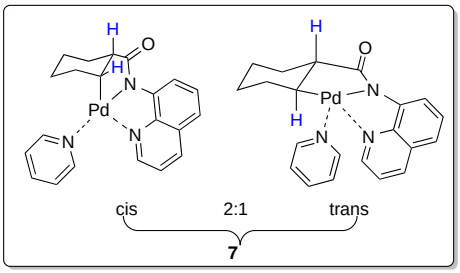


^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.068 (t, *J* = 9.46 Hz, 1H), 8.842 (d, *J* = 5.00 Hz, 2H), 7.988 (d, *J* = 8.28 Hz, 1H), 7.838-7.778 (m, 1H), 7.641 (d, *J* = 3.96 Hz, 0.75 H), 7.544 (d, *J* = 3.92 Hz, 0.25H), 7.432-7.366 (m, 3H), 7.121-7.060 (m, 2H), 2.847 (dd, *J* = 10.92 Hz, *J* = 5.56 Hz, 0.75H), 2.787 (dt, *J* = 10.92 Hz, *J* = 3.00 Hz, 0.25H), 2.575-2.541 (m, 0.75H), 2.441 (dt, *J* = 10.92 Hz, J = 3.24 Hz, 0.25H), 2.078-2.043 (m, 0.75H), 1.923-1.901 (m, 0.25H), 1.695-1.652 (m, 1H), 1.536-1.145 (m, 6H);

LC-MS (ESI$^+$): m / z calculated for $C_{18}H_{19}N_3OPd$ $(M\text{-pyridine}+MeCN+H)^+$: 399.06 found 399.93;

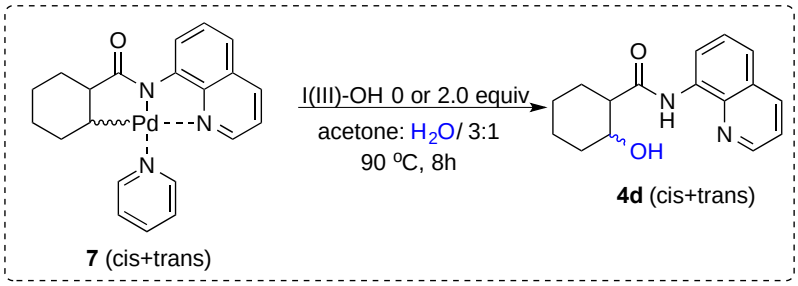
For filtration method, after cooling to ambient temperature, the reaction mixture was filtrated and washed the solid with little amount of acetonitrile to afford desired compound **9** as a

yellow solid (83 mg, 95% yield).



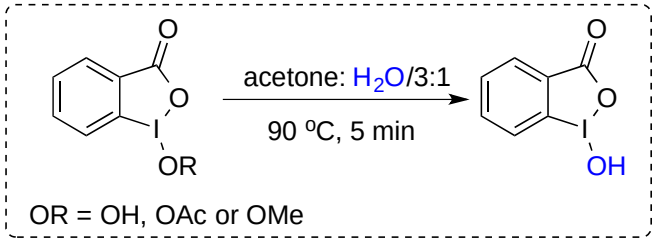
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.123 (t, *J* = 9.14 Hz, 1H), 8.946 (d, *J* = 4.84 Hz, 2H), 8.136 (d, *J* = 8.04 Hz, 1H), 7.919-7.865 (m, 1H), 7.769 (d, *J* = 3.68 Hz, 0.7 H), 7.688 (d, *J* = 3.60 Hz, 0.35H), 7.531-7.453 (m, 3H), 7.232-7.177 (m, 2H), 2.924 (dd, *J* = 10.76 Hz, *J* = 5.36 Hz, 0.68H), 2.850 (dt, *J* = 10.72 Hz, *J* = 3.24 Hz, 0.34H), 2.628-2.512 (m, 1H), 2.143-2.112 (m, 0.70H), 2.002-1.963 (m, 0.35H), 1.749-1.692 (m, 1H), 1.615-1.209 (m, 6H);

4) Hydroxylation reactions with or without oxidant from Pd(II)-complex



To a flame-dried sealed tube, Pd(II)-complex (74 mg, 0.169 mmol, 1.0 equiv) was dissolved in 2.0 mL of acetone/H_2O(3:1). Then oxidant (89 mg, 0.338 mmol, 2.0 equiv) was added or not under Ar. The resulting mixture was stirred at 90 °C for 8h. After cooling to ambient temperature, the reaction mixture was filtrated through celite and washed with DCM. Normal workup was conducted with DCM and saturated $NaHCO_3$. After dryness, filtration and evaporation, the crude mixture was purified by column chromatography with petroleum ether: ethyl acetate/ 3:1-1:1 to afford the desired compound **4d** (cis+trans) as a white solid (30 mg, 65% yield). If without oxidant, none of desired product was observed from TLC and LC-MS with all of the starting materials remained.

5) Exchange rate of cyclic I^{3+} oxidants with H_2O under similar reaction conditions



To a flame-dried sealed tube, three cyclic I^{3+} oxidants (0.1 mmol) were suspended in 1.0 mL of acetone/H_2O (3:1) separately. The resulting mixture was stirred at 90 °C for 5 min. Rapid dissolution and precipitation of white solid was observed. After cooling to ambient temperature, the solvent was evaporated to afford a white solid, which was characterized by ^{1}H NMR. Crude ^{1}H NMR indicated 100% conversion ratio.

XII. Computational Details

All DFT calculations were performed using B3LYP hybrid functional[11] with Gaussian 09 program package[12]. To address the scalar relativistic effect of Pd and iodine, the relativistic effective core potential (ECP) was utilized.[13,14] Geometries were fully optimized in gas phase using polarized double-ζ def2-SVP basis set[15] on all atoms, with Grimme's DFT-D3[16] empirical dispersion correction (with zero short range damping) included. Vibrational analyses were performed on all optimized geometries to ensure all positive frequencies for minima and one imaginary frequency for transition states. Larger polarized triple-ζ def2-TZVP basis set[15] was utilized in single point calculations to refine the calculated electronic energies of these optimized structures. Thermo correction to Gibbs free energy was calculated at the experimental temperature of 373.15 K. The solvent effect was taken into account in these single point calculations by SMD continuum solvation model,[17] employing acetone as the solvent. Reported energies (in kcal/mol) are the Gibbs free energies including thermal free energy correction, solvent effect correction, and DFT-D3 empirical dispersion correction.

XIII. Cartesian coordinates of DFT-optimized structures

A_{AE}

C	-3.91152200	3.54175200	-0.40513400
C	-3.85874700	2.14695200	-0.43227000
C	-2.75629800	1.50162700	0.23164200
C	-1.75050100	2.26854200	0.89718100
C	-1.84548000	3.68420500	0.89699400
C	-2.90756500	4.28767400	0.25432200
H	-4.73344900	4.04383800	-0.90781300
C	-0.70003400	1.54729300	1.52652300
H	-1.07968300	4.27440700	1.40547100
H	-2.98921300	5.37772800	0.24915900
C	-0.67496600	0.16898500	1.48030800
C	-1.71207000	-0.50760600	0.79612500
H	0.08534300	2.10309800	2.04620300
H	0.12314300	-0.40298400	1.95708300
H	-1.74529800	-1.59893000	0.72632600
N	-2.69449300	0.14038500	0.20760400
C	-6.40337300	0.51382800	-2.66094400
C	-6.27947300	-0.76721700	-1.85471700
H	-7.45200700	0.76256300	-2.89161700
H	-5.87930200	0.41299500	-3.62662000
H	-7.02603800	-0.85903500	-1.05618500
H	-6.20749300	-1.66942800	-2.46738000
N	-4.78899800	1.31907400	-1.06573600
C	-5.76554200	1.71026900	-1.96631800
O	-6.04835700	2.86839000	-2.21290200
Pd	-4.50213700	-0.61582900	-0.83772600
O	-5.47593200	-0.61250100	0.86269100
H	-5.85981100	0.27291400	0.96205700
C	-1.84264300	0.32554800	-6.26408400
C	-1.34371700	-0.68545800	-7.08871900
C	-1.52519300	-2.02451500	-6.73682500
C	-2.22138900	-2.35927000	-5.56763600
C	-2.73387800	-1.35603700	-4.72391600
C	-2.51859000	-0.01400300	-5.09446400
H	-1.70237800	1.37635800	-6.52831200
H	-0.80626200	-0.43968300	-8.00825100
H	-1.12241600	-2.81212700	-7.37596600
H	-2.90286000	0.76093400	-4.42985000
I	-2.36304700	-4.46175300	-5.17371000
C	-3.54003900	-1.61444000	-3.46374900
O	-3.45070600	-0.64541700	-2.60906500
O	-4.21290700	-2.63567700	-3.33835400
C	-5.75541200	-3.98092100	-0.99143600
H	-6.35776300	-3.19352800	-0.52375200
H	-5.92309000	-3.97460900	-2.08133600
H	-6.03902800	-4.96973400	-0.60329700
C	-3.32891200	-4.84326100	-1.01915100
H	-2.35351100	-4.61227300	-0.57189800
H	-3.70987100	-5.81354400	-0.67091700
H	-3.20091100	-4.89034900	-2.11711500
C	-4.29654300	-3.72315800	-0.78965700
O	-3.84663900	-2.61503700	-0.49587500

TS_{RE}

C	-3.47952500	2.99692300	-1.85243300
C	-3.72566000	1.79282100	-1.19094200
C	-2.61215100	1.15721800	-0.52015200
C	-1.30866600	1.75142800	-0.57139700
C	-1.11571700	2.97939900	-1.25574100
C	-2.19089600	3.57837100	-1.87495600
H	-4.30170700	3.49957100	-2.35205000
C	-0.24691000	1.05097300	0.06191100
H	-0.11862900	3.42539200	-1.28775000
H	-2.05787100	4.52248400	-2.40976400
C	-0.48869300	-0.15050500	0.69017200
C	-1.81218600	-0.65362700	0.68937300
H	0.76014900	1.47622300	0.02953900
H	0.31147900	-0.71582800	1.17194800
H	-2.04246700	-1.61415700	1.16282900
N	-2.81658600	-0.02424900	0.12007200
C	-7.42427100	0.91038300	-1.43587100
C	-7.23551900	-0.57004500	-1.41005300
H	-8.01744800	1.25462800	-0.57416500
H	-8.00313500	1.18168900	-2.33677200
H	-8.03389400	-1.17119400	-0.97490800
H	-6.87650300	-1.00076500	-2.35369500
N	-4.97515500	1.14542800	-1.16989000
C	-6.15211900	1.78363700	-1.47697600
O	-6.28499800	2.97405000	-1.71479600

Pd	-4.93643200	-0.87061600	-1.00863800
O	-6.37987100	-0.79179600	0.38214300
H	-6.31921200	0.11499000	0.72860200
C	-0.54655300	0.87729100	-4.74961100
C	0.30329300	0.03493000	-5.47012800
C	0.19542900	-1.35158800	-5.33092200
C	-0.74727800	-1.89573000	-4.45056900
C	-1.60662100	-1.06394400	-3.71050800
C	-1.49785700	0.32689400	-3.89289100
H	-0.47486500	1.96238300	-4.85371600
H	1.05105700	0.44913700	-6.15149400
H	0.84621400	-2.00890300	-5.91007700
H	-2.17553100	0.97240000	-3.33461700
I	-0.83259000	-4.03805700	-4.38966400
C	-2.59699500	-1.56099900	-2.67837500
O	-3.68276500	-0.85531600	-2.63315200
O	-2.33048200	-2.52823800	-1.96956300
C	-4.84079400	-3.82328600	-2.91524400
H	-5.08146100	-2.81118000	-3.25913600
H	-3.98904900	-4.21462000	-3.49007100
H	-5.70213100	-4.49368000	-3.08533100
C	-3.85338000	-5.07152800	-0.90462900
H	-3.96525700	-5.12502000	0.18574800
H	-4.20824800	-5.99267400	-1.39042000
H	-2.78583500	-4.94103900	-1.15322600
C	-4.52915300	-3.85016500	-1.44834500
O	-4.84216400	-2.94703700	-0.66890000

B_{AE}

C	-3.59814500	2.75198800	-2.25065300
C	-3.80813300	1.68607500	-1.38246300
C	-2.69013500	1.19931100	-0.61043000
C	-1.39700900	1.79462900	-0.78897100
C	-1.24000300	2.89749800	-1.66987800
C	-2.32850400	3.36347400	-2.37504800
H	-4.43404000	3.12892000	-2.83426500
C	-0.31236500	1.22803500	-0.06786300
H	-0.25250700	3.35131500	-1.78634000
H	-2.21636600	4.20677700	-3.06154700
C	-0.53111700	0.15681000	0.76897300
C	-1.85425500	-0.33458400	0.90011200
H	0.68927100	1.64776000	-0.19768400
H	0.28424400	-0.31142500	1.32435400
H	-2.05629300	-1.18155700	1.56658700
N	-2.88317400	0.16467000	0.25181900
C	-7.49639600	1.21692300	-0.58063600
C	-7.77449200	-0.27064900	-0.60724600
H	-7.53926500	1.57437500	0.46520400
H	-8.31644200	1.74044600	-1.09573000
H	-8.70404400	-0.50296700	-0.05880000
H	-7.88183500	-0.65959400	-1.62945400
N	-5.05965700	1.05700200	-1.21598200
C	-6.18884000	1.82885900	-1.12736100
O	-6.22449400	3.03982000	-1.31386900
Pd	-5.01915400	-0.97456600	-1.30350800
O	-6.69924900	-1.04225300	-0.02340100
H	-6.46089000	-0.67136800	0.84166300
C	-0.36252200	0.71821100	-4.78883400
C	0.60517000	-0.14835300	-5.30153400
C	0.56680700	-1.50726500	-4.97763700
C	-0.42610700	-1.99738400	-4.12045900
C	-1.40420500	-1.13800500	-3.58638200
C	-1.35936000	0.21880800	-3.95385200
H	-0.34592100	1.78218600	-5.03601900
H	1.39280900	0.22347000	-5.96217700
H	1.31254600	-2.18610700	-5.39468900
H	-2.12789400	0.87827800	-3.55431200
I	-0.37036900	-4.11402200	-3.77287700
C	-2.46826800	-1.56302900	-2.59545500
O	-3.55575000	-0.85517700	-2.69303400
O	-2.26875100	-2.47894000	-1.80621500
C	-4.55481600	-3.78552600	-3.42437800
H	-4.80719500	-2.76059800	-3.71831000
H	-3.57814400	-4.06960900	-3.84458800
H	-5.30476600	-4.48973000	-3.82577600
C	-3.94704800	-5.20545100	-1.37756100
H	-4.27192200	-5.36286600	-0.34113900
H	-4.16404300	-6.08137900	-2.00628500
H	-2.85524700	-5.03624300	-1.38836500
C	-4.53078900	-3.94299200	-1.93387700
O	-4.97422300	-3.09707900	-1.15588400

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