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Note

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Copper-Catalyzed Chemoselective Cyclization Reaction of 2-Isocyanoacetophenone: Synthesis of 4-Hydroxyquinoline Compounds

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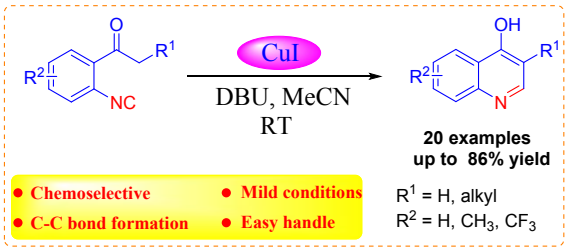
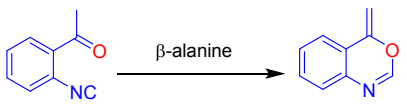


Abstract: A copper-catalyzed intramolecular cyclization reaction of 2-isocyanoacetophenone derivatives to afford 4-hydroxyquinolines chemoselectively is described. The transformation proceeds through enol tautomerism and subsequently C-C bond formation. Compared to previous methods, this study provides a new protocol for the construction of 4-hydroxyquinoline compounds from functionalized isocyanides under mild conditions.

Isocyanides are versatile building blocks and intermediates in chemical synthesis with wide applications for their unique structures and reactivities.[1a] Besides the well-known multicomponent Ugi[1b,2] and Passerini[3] reactions, isocyanides insertion and cyclization reaction are of the most powerful strategies for the preparation of nitrogen-containing heterocycles.[4,5] In view of their high reaction activities and variabilities, the application of isocyanides has drawn considerable attention. Notably, 2-isocyanoacetophenone derivatives was easily available starting materials for the

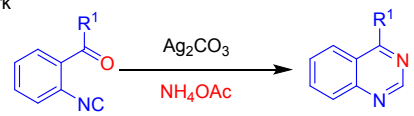
construction of various heterocyclic compounds in recent years.[6-13] In 2009, Konishi and co-workers reported a simple method for the synthesis of 4-alkylidene-4*H*-3,1-benzoxazine derivatives *via* acid-catalyzed cyclization of 2-isocyanophenyl ketones in the presence of vinyl ether.[6] Later, cyclization reaction of 2-isocyanoacetophenone derivatives with sulfur and Eschenmoser's salt were well developed for the preparation of corresponding nitrogen-containing heterocycles.[7] In addition, Würthwein[8] group reported the intramolecular cycloaddition of 2-isocyanoacetophenone for the synthesis of 4-methylene-4*H*-benzo[*d*][1,3]oxazine (Scheme 1, eq. 1). Recently, silver-catalyzed cyclization reaction of 2-isocyanoacetophenone derivatives with isocyanoacetamides has been developed for the facile and efficient synthesis of quinolones by Xu group.[9] As versatile building blocks, 2-isocyanoacetophenone derivatives have recently been employed in the assembly of indole/furan-fused heterocycles,[10] quinazolines[11] (Scheme 1, eq. 2) and indolin-3-ol derivatives.[12] Among these transformations, isocyanides attacked by nucleophile is indispensable. However, for the most parts, nucleophiles are heteroatom nucleophiles and carbon atom nucleophiles are not typical. It was seldom achieved when heteroatom and carbon atom nucleophile coexist simultaneously.[13] It's desirable to control the chemoselective cyclization of isocyanides. As continuation of our interests in isocyanides reactions,[14] herein, we reported a copper-catalyzed cyclization reaction of 2-isocyanoacetophenone for the synthesis of 4-hydroxyquinoline derivatives chemsoselectively under mild conditions.

a) Würthwein's wrok



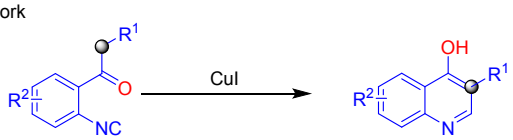
(1)

b) Xu's work



(2)

c) This work

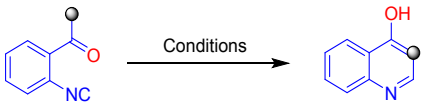


(3)

Scheme 1 The cyclization reaction of 2-isocyanoacetophenones

Initially, we investigated the reaction of 2-isocyanoacetophenone **1a** in 2 mL DMF at room temperature catalyzed by CuI in the presence of KOH. To our delight, the desired product quinolin-4-ol **2a** was formed in 32% yield (Table 1, entry 1). Encouraged by this promising result, we further tried the reactions by screening different copper catalysts. Nevertheless, other copper catalysts could not increase the yield of **2a** (Table 1, entries 2-6). Then, diverse bases have been applied to the reaction (Table 1, entries 7-12). When 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was served as the base, the yield of **2a** could be increased to 46%. A series of other solvents such as MeOH, dimethyl sulfoxide (DMSO), tetrahydrofuran (THF) and acetonitrile were also applied to the reactions and it was found that acetonitrile was the most suitable solvent for this reaction, affording **2a** in 57% yield (Table 1, entries 13-18). Thus, the optimized conditions is following, **2a** and DBU (1.2 equiv) catalyzed by CuI (10 mol%) in MeCN at room temperature for 6 h.

Table 1. Optimization of The Reaction Conditions[a]



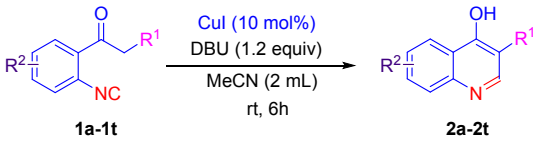
Entry	Cat (mol%).	Base (equiv)	Solvent	Yield[b] (%)
1	CuI (10)	KOH (1.2)	DMF	32
2	CuBr (10)	KOH (1.2)	DMF	28
3	CuCl (10)	KOH (1.2)	DMF	30
4	$Cu(OTf)_2$ (10)	KOH (1.2)	DMF	19
5	CuO (10)	KOH (1.2)	DMF	10
6	$Cu(OAc)_2$ (10)	KOH (1.2)	DMF	25
7	CuI (10)	CsOH (1.2)	DMF	28
8	CuI (10)	NaOH (1.2)	DMF	5
9	CuI (10)	LDA (1.2)	DMF	13
10	CuI (10)	DIPEA (1.2)	DMF	37
11	CuI (10)	DABCO (1.2)	DMF	35
12	CuI (10)	DBU (1.2)	DMF	46
13	CuI (10)	DBU (1.2)	DMSO	44
14	CuI (10)	DBU (1.2)	DMA	39
15	CuI (10)	DBU (1.2)	CH_3OH	21
16	CuI (10)	DBU (1.2)	DCM	48
17	CuI (10)	DBU (1.2)	THF	52
18	**CuI (10)**	**DBU (1.2)**	**MeCN**	**57**

[a]Reaction conditions: **1a** (0.5 mmol)，base (0.6 mmol)，copper reagent (10 mol%) , solvent (2 mL).

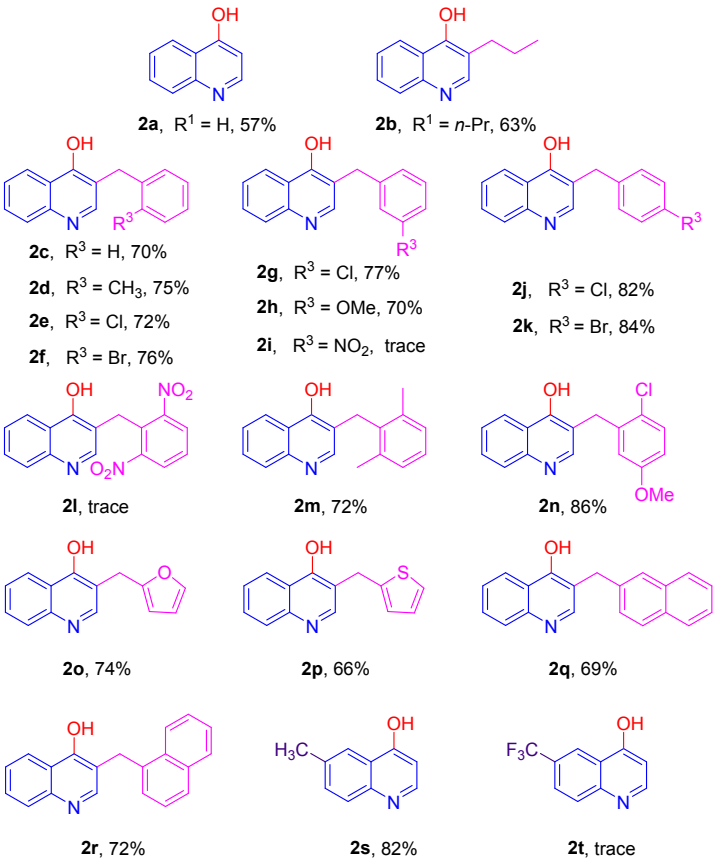
stirred at room temperature for 6 h under an air atmosphere. [b]Isolated yield.

With the optimization conditions in hand, we next explored the scope of the isocyanide substrates (Table 2). The reaction of 1-(2-isocyanophenyl)pentan-1-one **1b** afforded 3-propylquinolin-4-ol **2b** in 63% yield. 1-(2-Isocyanophenyl)-3-phenylpropan-1-one **1c** underwent smoothly to give 3-benzylquinolin-4-ol **2c** in 70% yield. 1-(2-isocyanophenyl)-3-ortho substituted arylpropan-1-ones reacted also well to furnish the corresponding 3-ortho substituted benzylquinolin-4-ols **2d-f** in 72% to 76% yields. The reactions of 3-(3-chlorophenyl)-1-(2-isocyanophenyl)propan-1-one **1g** and 1-(2-isocyanophenyl)-3-(3-methoxyphenyl)propan-1-one **1h** led to **2g** and **2h** in 77% and 70% yields, respectively. Unfortunately, 1-(2-isocyanophenyl)-3-(3-nitrophenyl)propan-1-one **2i** bearing NO_2 functional group failed to give the desired product. It should be noted that the reactions of 3-(4-chlorophenyl)-1-(2-isocyanophenyl)propan-1-one **1j** and 3-(4-bromophenyl)-1-(2-isocyanophenyl)propan-1-one **1k** frunished **2j** and **2k** in 82% and 84% yields, respectively. Similarly, no desired product was observed when di-NO_2 functionalized **1l** was applied to the reaction. To our delights, some 1-(2-isocyanophenyl)-3-disubstituted arylpropan-1-ones reacted well to give **2m** and **2n** in 72% and 86% yields, respectively. The isocyanides bearing heterocycle or naphthalenyl functionalized groups such as 3-(furan-2-yl)-1-(2-isocyanophenyl)propan-1-one **1o**, 1-(2-isocyanophenyl)-3-(thiophen-2-yl)propan-1-one **1p**, 3-(naphthalen-2-ylmethyl)quinolin-4-ol **1q** and 3-(naphthalen-1-ylmethyl)quinolin-4-ol **1r** could undergo smoothly to give **2o-2r** in 66% to 72% yields. The reaction of 1-(2-isocyano-5-methylphenyl)ethan-1-one **1a** under the standard conditions gave **2a** in 82% yield. In order to test the application of the reaction, we conducted the reaction of **1a** in 5 mmol scale and the desired product **2s** could be isolated in 78% yield. Unfortunately, 1-(2-isocyano-5-(trifluoromethyl)phenyl)ethan-1-one could not yield the desired 3-propylquinolin-4-ol for the strong electron-withdrawing effect.

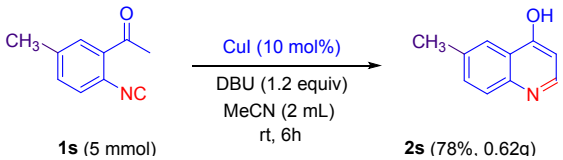
Table 2. Substrate scope of *2-Isocyanoacetophenone*[a]



1a-1t **2a-2t**



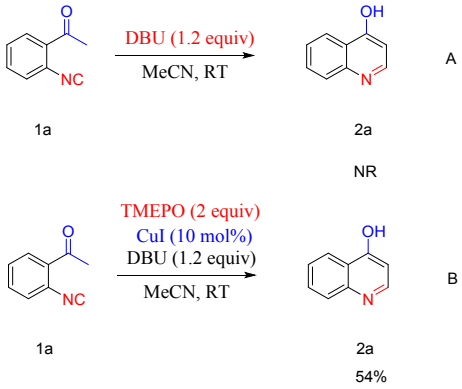
Gram-Scale synthesis:



1s (5 mmol) **2s** (78%, 0.62g)

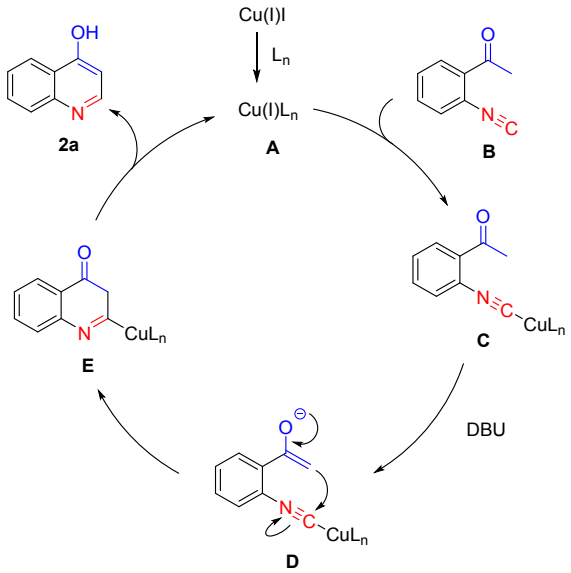
[a]Reaction conditions: **1a** (0.5 mmol)，DBU (0.6 mmol)，copper reagent (10 mol%) , MeCN (2 mL). stirred at room temperature for 6 h under an air atmosphere. [b]Isolated yield.

To understand the reaction mechanism, control experiments were performed (Scheme 2). When the reaction was carried out in the absence of CuI, no desired product was observed (Scheme 2, A). When the radical scavenger TEMPO was added to the reaction system, **2a** could also be obtained in the yield of 54% (Scheme 2, B). This result indicates that the reaction might not involve radical process.



Scheme 2. Control experiments

Based on the above results and related literature precedents,[15] we proposed a reasonable mechanism for the reaction (Scheme 3). The in situ generated Copper(I) **A** from CuI reacts with isocyanide **B**[15a] to give Complex **C**. De-protonation of **C** with the assistance of DBU leads to copper complex **D** *via* keto-enol tautomerism. Intramolecular cyclization of **D** affords **E**. Subsequently, the aromatization of **E** affords 4-hydroxyquinoline and releases the active copper complex **A**.



Scheme 3. Proposed Mechanism

In summary, we have developed a copper-catalyzed cyclization reaction of 2-isocyanoacetophenone derivatives for the construction of 4-hydroxyquinoline compounds. Moreover, the reaction explored the chemistry of copper-mediated carbon

atom nucleophile addition to isocyanides, which represents a valuable addition to isocyanide chemistry.

EXPERIMENTAL SECTION

1. General Information.

Unless otherwise noted, all commercially available compounds were used as provided without further purification. Solvents for chromatography were analytical grade and used without further purification. Analytical thin-layer chromatography (TLC) was performed on silica gel, visualized by irradiation with UV light. For column chromatography, 200-300 mesh silica gel was used. ^{1}H and $^{13}C\{^{1}H\}$ NMR were recorded on a BRUKER 400 MHz spectrometer in $(CD_3)_2SO$. Chemical shifts (δ) were reported referenced to an internal tetramethylsilane standard or the C_2D_6OS residual peak (δ 2.50) for ^{1}H NMR. Chemical shifts of $^{13}C\{^{1}H\}$ NMR are reported relative to $(CD_3)_2SO$ (δ 39.52). Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated s (singlet), bs (broad singlet), d (doublet), t (triplet), m (multiplet); coupling constants (J) are in Hertz (Hz). Melting points were measured on an Electrothermal digital melting point apparatus and were uncorrected. IR spectra were recorded on a BRUKER MODEL ALPHA spectrophotometer and are reported in terms of frequency of absorption (cm^{-1}). HRMS spectra were obtained by using BRUKER MICROTOF-Q III instrument with ESI source. The starting materials were isolated by SepaBean machine Flash Chromatography, which purchased from Santai Technologies Inc.

2.Synthesis of *2-isocyanoacetophenone*

***Method* A:** To a 100 mL round-bottom flask were added 2-aminoecetophenone (1.2 mL, 1.0 equiv, 10 mmol), benzaldehyde (1.1 mL, 1.1 equiv, 11 mmol), 10 % NaOH aqueous solution (40 mL), EtOH (10 mL). The reaction mixture was stirred for another 12-24h at room temperature. After the reaction was completed, mixture was solid recrystallized (EtOH) and reduced by H_2（balloon） and Pd/C (Palladium 10% on activated carbon, 100mg) in ethyl acetate to afford 1-(2-aminophenyl)-3-phenylpropan-1-one. Then according to the literature procedures[12] by the typical formylation and dehydration procedure to afford desired 2-isocyanoacetophenone.

***Method* B:** To a 100 mL round-bottom flask were added 2-iodo-4-methylaniline (2.331 g, 1.0 equiv, 10 mmol), Trimethylsilylacetylene (1.7 mL, 1.2 equiv, 12 mmol), $PdCl_2(PPh_3)_2$ (0.140 g, 0.02 equiv, 0.2 mmol), CuI(0.076 g, 0.04 equiv, 0.4mmol), Et_3N (4 mL, 3 equiv, 30 mmol), THF (10 mL). The reaction mixture was stirred for 12h at room temperature under argon. After the reaction was completed, mixture was purified by flash chromatography on silica gel to afford the 2-(trimethylsilyl)ethynyl)aniline. Potassium carbonate (1.659 g, 1.2 equiv, 12 mmol) and 2-(trimethylsilyl)ethynyl)aniline (2.031 g, 1.0 equiv, 10mmol) were blended to stir for 12h at room temperature in MeOH (15 mL), then saturated salt solution was added and mixture was extracted by ethyl acetate for three times to afford 2-ethynylaniline. Concentrated hydrochloric acid (5 mL) and surfactant CTAB(hexadecyl trimethyl ammonium bromide, 5.5 g, 1.5 equiv, 15 mmol) were mixtured with 2-ethynylaniline to stir at 80℃ for 12h in distilled water to generate substituted 2-aminoecetophenone.Then according to the literature procedures[12] by the typical formylation and dehydration procedure to afford desired 2-isocyanoacetophenone

3.General procedure for the synthesis of compounds 2

To a stirring solution of 2-isocyanoacetophenone **1** (29 mg, 1.0 equiv, 0.2 mmol), copper iodide (3.8 mg, 0.1 equiv, 0.02 mmol), and DBU (36 μL, 1.2 equiv, 0.24 mmol). The mixture was pour into saturated salt solution and extracted three times with ethyl acetate. The pure products were obtained after purification by column chromatography on silica gel with petroleum ether/ethyl acetate (v:v = 1:1 − 3:1) as the eluent.

4-hydroxyquinoline (**2a**).White solid (89 mg, 57% yield); Mp (°C) 200.1 – 202.4; IR ν (cm^{-1}): 2775, 1501, 1472, 1200; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.11 (d, J = 9.2 Hz, 1H), 7.91 (d, J = 6.8 Hz, 1H), 7.64

– 7.61 (m, 2H), 7.55 – 7.28 (m, 1H), 6.06 (d, J = 7.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 177.4, 140.5, 139.9, 132.1, 126.3, 125.4, 123.5, 118.7, 109.2; HRMS (ESI$^+$) calcd for C_9H_7NO [M + H]$^+$: 145.0522, found 145.0519.

3-propylquinolin-4-ol **(2b)**. White solid (75 mg, 63% yield); Mp (°C) 205.5 – 208.1; IR ν (cm^{-1}): 2906, 1551, 1474, 1206; ^1H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 8.10 (d, J = 6.6 Hz, 1H), 7.80 (d, J = 5.7 Hz, 1H), 7.59 – 7.57 (m, 1H), 7.49 (d, J = 7.3 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 2.43 – 2.37 (m, 2H), 1.57 – 1.49 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ (100 MHz, DMSO-d_6) δ176.2, 139.6, 136.6, 131.0, 125.0, 124.5, 122.5, 120.6, 118.0, 29.5, 21.7, 13.8; HRMS (ESI$^+$) calcd for $C_{12}H_{13}NO$ [M + H]$^+$: 187.0992, found 187.0990.

3-benzylquionlin-4-ol **(2c)**. White solid (80 mg, 75% yield); Mp (°C) 204.2 – 206.2; IR ν (cm^{-1}): 2891, 1549, 1477, 1203; ^1H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.85 (s, 1H), 7.59 (d, J = 7.1 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.30 – 7.24 (m, 5H), 7.16 (d, J = 7.1 Hz, 1H), 3.77 (s, 2H); $^{13}C\{^1H\}$ (100 MHz, DMSO-d_6) δ 176.4, 141.9, 138.0, 131.7, 129.0, 128.6, 126.1, 125.6, 123.2, 118.6, 33.4; HRMS (ESI$^+$) calcd for $C_{16}H_{13}NO$ [M + H]$^+$: 235.0992, found 235.0995.

3-(2-methylbenzyl)quionlin-4-ol **(2d)**. White solid (85 mg, 75% yield); Mp (°C) 205.5 – 207.1; IR ν (cm^{-1}): 2909, 1553, 1501, 1205; ^1H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.52 – 7.49 (m, 2H), 7.31 – 7.28 (m, 1H), 7.16 – 7.07 (m, 4H), 3.75 (s, 2H), 2.27 (s, 3H); $^{13}C\{^1H\}$ (100 MHz, DMSO-d_6) δ 176.0, 139.6, 138.6, 137.1, 135.9, 131.3, 129.8, 129.1, 125.9, 125.7, 125.1, 124.4, 122.8, 119.4, 118.1, 30.2, 19.2; HRMS (ESI$^+$) calcd for $C_{17}H_{15}NO$ [M + H]$^+$: 249.1148, found 249.1150.

3-(2-chlorobenzyl)quionlin-4-ol **(2e)**. White solid (100 mg, 72% yield); Mp (°C) 199.7 – 201.2; IR ν (cm^{-1}): 2773, 1554, 1499, 1207; ^1H NMR (400 MHz, DMSO-d_6) δ11.73 (s, 1H), 8.12 (d, J = 6.6 Hz, 1H), 7.87 – 7.70 (m, 1H), 7.61 (d, J = 8.6, 7.7 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.37 – 7.02 (m, 5H), 3.82 (d, J = 38.2 Hz, 2H); $^{13}C\{^1H\}$ (100 MHz, DMSO-d_6) δ 176.4, 159.8, 140.2, 138.1, 131.8, 131.4, 128.3, 127.9, 125.5, 125.1, 124.5, 123.3, 118.9, 118.6, 115.5, 115.3, 26.6; HRMS (ESI$^+$) calcd for $C_{16}H_{12}ClNO$ [M + H]$^+$: 269.0602, found 269.0600.

3-(2-bromobenzyl)quionlin-4-ol **(2f)**. White solid (82 mg, 75% yield); Mp (°C) 180.0 – 181.4; IR ν (cm^{-1}): 2816, 1549, 1472, 1208; ^1H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.10 (d, J = 9.6 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.30 – 7.18 (m, 5H), 7.15 (d, J = 7.4 Hz, 1H), 3.81 (d, J = 34.8 Hz, 2H); $^{13}C\{^1H\}$ (100 MHz, DMSO-d_6) δ 141.8, 140.1, 137.9, 131.7, 129.0, 128.5, 126.1, 125.5, 125.2, 123.2, 120.8, 118.6, 40.5, 33.4; HRMS (ESI$^+$) calcd for $C_{16}H_{12}BrNO$ [M + H]$^+$: 313.0097, found 313.0100.

3-(3-chlorobenzyl)quionlin-4-ol **(2g)**. White solid (85 mg, 77% yield); Mp (°C) 185.0 – 186.9; IR ν (cm^{-1}): 2918, 1555, 1503, 1204; ^1H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.99 (s, 1H), 7.63 – 7.54 (m, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.36 (s, 1H), 7.31 – 7.23(m, 4H), 3.78 (s, 2H); $^{13}C\{^1H\}$ (100 MHz, DMSO-d_6) δ 176.4, 144.6, 140.2, 138.3, 133.1, 131.8, 130.3, 128.7, 127.7, 126.1, 125.5, 125.2, 123.3, 120.1, 118.6, 33.3; HRMS (ESI$^+$) calcd for $C_{16}H_{12}ClNO$ [M + H]$^+$: 269.0602, found 269.0605.

3-(3-methoxybenzyl)quionlin-4-ol **(2h)**. White solid (69 mg, 70% yield); Mp (°C) 210.0 – 211.8; IR ν (cm^{-1}): 2926, 1556, 1496, 1248; ^1H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.85 (s, 1H), 7.6 (t, J = 7.2 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.3 (t, J = 7.4 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 6.87 (d, J = 8.3 Hz, 2H), 6.72 (d, J = 6.9 Hz, 1H), 3.75 (s, 2H), 3.42 (s, 3H); $^{13}C\{^1H\}$ (100 MHz, DMSO-d_6) δ 176.4, 159.6, 143.4, 140.1, 138.0, 131.7, 129.55, 125.6, 125.1, 123.2, 121.3, 120.8, 118.6, 114.9, 111.3, 55.3, 33.4; HRMS (ESI$^+$) calcd for $C_{17}H_{15}NO_2$ [M + H]$^+$: 265.1097, found 265.1097.

3-(4-chlorobenzyl)quionlin-4-ol **(2j)**. White solid (110 mg, 82% yield); Mp (°C) 202.4 – 203.8; IR ν (cm^{-1}): 2786, 1548, 1474, 1204; ^1H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.85 (s, 1H), 7.63 – 7.50 (m, 2H), 7.30 – 7.11 (m, 5H), 3.72 (s, 2H); $^{13}C\{^1H\}$ (100 MHz, DMSO-d_6) δ176.4, 159.6, 143.4, 140.11, 138.0, 131.7, 129.6, 125.6, 125.2, 123.2, 121.3, 120.8, 118.6, 115.0, 111.3, 55.3, 33.4; HRMS (ESI$^+$) calcd for $C_{16}H_{12}ClNO$ [M + H]$^+$: 269.0602, found 269.0599.

3-(4-bromobenzyl)quionlin-4-ol **(2k)**. White solid (78 mg, 84% yield); Mp (°C) 192.4 – 194.1; IR ν (cm^{-1}): 2893, 1553, 1504, 1206; ^1H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.85 (s, 1H), 7.62

– 7.58 (m, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.21 (m, 5H), 3.78 (s, 2H); $^{13}C\{^{1}H\}$ (100 MHz, DMSO-d_6) δ176.4, 141.8, 140.1, 138.0, 131.7, 129.0, 128.6, 126.1, 125.6, 125.2, 123.2, 120.9, 118.6, 33.5; HRMS (ESI^+) calcd for $C_{16}H_{12}BrNO$ $[M + H]^+$: 313.0097, found 313.0095.

3-(2,6-dimethylbenzyl)quinolin-4-ol **(2m)**.White solid (80 mg, 72% yield); Mp (°C) 210.3 – 212.5; IR *v* (cm^{-1}): 2909, 1551, 1503, 1366; ^1H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 3H), 6.78 (s, 1H), 3.77 (s, 2H), 2.17 (s, 6H); $^{13}C\{^{1}H\}$ (100MHz, DMSO-d_6) δ 176.7, 139.9, 137.1, 136.5, 135.0, 131.8, 128.5, 126.6, 125.5, 124.5, 123.3, 118.6, 27.2, 20.0; HRMS (ESI^+) calcd for $C_{18}H_{17}NO$ $[M + H]^+$: 263.1305, found 263.1309.

3-(2-chloro-5-methoxybenzyl)quionlin-4-ol **(2n)**. White solid (105 mg, 86% yield); Mp (°C) 220.1 – 222.4; IR *v* (cm^{-1}): 2786, 1549, 1471, 1210; ^1H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.85 (s, 1H), 7.60 (t, *J* = 6.9 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 6.85 (s, 2H), 3.72 (d, *J* = 21.3 Hz, 5H); $^{13}C\{^{1}H\}$ (100 MHz, DMSO-d_6) δ 175.9, 159.1, 143.0, 139.6, 137.5, 131.2, 125.1, 124.7, 122.7, 120.8, 120.3, 118.1, 114.5, 110.8, 54.9, 33.0; HRMS (ESI^+) calcd for $C_{17}H_{14}ClNO_2$ $[M + H]^+$: 299.0708, found 299.0710.

3-(furan-2-ylmethyl)quionlin-4-ol **(2o)**. Flaxen solid (78 mg, 74% yield); Mp (°C) 175.3 – 176.9; IR *v* (cm^{-1}): 2897, 1498, 1250; ^1H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 8.10 (d, *J* = 6.6 Hz, 1H), 7.79 (d, *J* = 6.0 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.27 (m, 2H), 7.15 – 7.04 (m, 2H), 3.79 (s, 2H); $^{13}C\{^{1}H\}$ (100 MHz, DMSO) δ176.4, 162.2, 159.8, 140.2, 138.0, 131.8, 130.7, 130.6, 125.5, 125.2, 123.2, 120.8, 118.6, 115.2, 115.0, 32.7.; HRMS (ESI^+) calcd for $C_{14}H_{11}NO_2$ $[M + H]^+$; 225.0784, found 225.0782.

3-(thiophen-2-ylmethyl)quionlin-4-ol **(2p)**. White solid (99 mg, 66% yield); Mp (°C) 168.4 – 171.1; IR *v* (cm^{-1}): 2891, 1477, 1203; ^1H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.143 – 8.11 (m, 1H), 7.92 (s, 1H), 7.65 – 7.60 (m, 1H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.31 – 7.23 (m, 2H), 6.90 (d, *J* = 3.7 Hz, 2H), 3.96 (s, 2H); $^{13}C\{^{1}H\}$ (100 MHz, DMSO) δ 175.6, 144.2, 139.7, 137.5, 131.4, 126.6, 125.1, 124.8, 123.7, 122.9, 119.9, 118.2, 27.2; HRMS (ESI^+) calcd for $C_{14}H_1NOS$ $[M + H]^+$: 242.0634, found 242.0631

3-(naphthalene-2-ylmethyl)quinolin-4-ol **(2q)**. White solid (89 mg, 69% yield); Mp (°C) 190.3 – 195.1; IR *v* (cm^{-1}): 2898, 1553, 1494, 1202; ^1H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.94 (s, 1H), 7.78 (d, *J* = 5.9 Hz, 4H), 7.60 – 7.27 (m, 6H), 3.99 (s, 2H); $^{13}C\{^{1}H\}$ (100 MHz, DMSO-d_6) δ 176.6, 140.2, 139.5, 138.3, 133.6, 131.9, 128.0, 126.8, 126.3, 125.6, 125.3, 123.3, 120.8, 118.7, 33.7; HRMS (ESI^+) calcd for $C_{20}H_{15}NO$ $[M + H]^+$: 285.1148, found 285.1149.

3-(naphthalene-1-ylmethyl)quinolin-4-ol **(2r).** Flaxen solid (75 mg, 72% yield); Mp (°C) 195.6 – 197.0; IR *v* (cm^{-1}): 2912, 1520, 1471, 1196; ^1H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 8.21 (d, *J* = 7.4 Hz, 1H), 8.12 – 7.91 (m, 1H), 7.90 – 7.78 (m, 1H), 7.62 (d, *J* = 6.1 Hz, 1H), 7.53 (t, *J* = 7.0 Hz, 1H), 7.49 – 7.32 (m, 8H), 4.27 (s, 2H); $^{13}C\{^{1}H\}$ (100 MHz, DMSO-d_6) δ 176.2, 140.0, 138.0, 137.3, 133.9, 132.0, 131.8, 128.9, 127.1, 126.5, 126.1, 125.7, 125.0, 124.6, 123.4, 120.1, 118.6, 30.0; HRMS (ESI^+) calcd for $C_{20}H_{15}NO$ $[M + H]^+$: 285.1148, found 285.1140.

6-methylquinolin-4-ol **(2s)**. Flaxen solid (110 mg, 83% yield); Mp (°C) 189.4 – 191.2; IR *v* (cm^{-1}): 2768, 1511, 1499, 1216; ^1H NMR (400 MHz, DMSO-d_6) δ11.71 (s, 1H), 7.90 – 7.83 (m, 2H), 7.45 (s, 2H), 6.00 (d, *J* = 7.3 Hz, 1H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ (100 MHz, DMSO-d_6) δ 177.2, 139.4, 138.6, 133.4, 132.8, 126.2, 124.6, 118.6, 108.8, 21.2; HRMS (ESI^+) calcd for $C_{10}H_9NO$ $[M + H]^+$: 159.0679, found 159.0676.

ASSOCIATED CONTENT

Supporting Information Available.

This material is available free of charge *via* the Internet at http://pubs.acs.org.

The synthetic route of substrates and the copies of ^1H and ^{13}C spectra of products

The syntheses and characterization of compounds **2h, 2k, 2m, and 2q** were repeated and checked by Jing-Hao Li in our group.

Notes

The authors declare no competing financial interest.

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