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# Chemoselective acylation of 2-amino-8-quinolinol in the generation of C2-amides or C8-esters†

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Two different ways to carry out the chemoselective acylation of 2-amino-8-quinolinol with unique features to generate C2-amides or C8-esters were developed. The coupling reaction with a variety of carboxylic acids using EDCI and DMAP provided C8-ester derivatives, whereas *N*-heteroaromatic acids were not introduced on the C8-hydroxy group, but rather on the C2-amino group under the same conditions. To obtain C2-amides selectively, the anionic nucleophile from 2-amino-8-quinolinol was treated with less reactive acyl imidazolides or esters.

## Introduction

Ester and amide functionalities are important structural components that serve as key motifs in a variety of bioactive natural products and pharmaceuticals. Amide and ester formation are fundamental reactions in chemical synthesis.<sup>1</sup> Typically, carbodiimides such as dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (EDCI) are applied as coupling reagents for esterification and amidation reactions. To increase the overall rate of the coupling reaction, DMAP (4-dimethylaminopyridine), 1-hydroxy-1*H*-benzotriazole (HOBT) and 1-hydroxy-7-azabenzotriazole (HOAt) are commonly used for carbodiimide-mediated reactions in either stoichiometric or catalytic fashions. Meanwhile, 1,1'-carbonyl diimidazole (CDI) is used because of the enhanced stability relative to that of acid halides and viability in large-scale syntheses.<sup>2</sup> In addition, numerous other methods have been developed for ester and amide bond formation.<sup>1c</sup>

Quinolines are valuable synthons and precursors in synthetic organic chemistry, as they comprise important heterocyclic pharmacophores with a broad spectrum of biological and medicinal activities. In particular, 8-hydroxyquinoline (8-HQ) is a well-known metal ion chelator and represents an excellent scaffold with a wide spectrum of pharmacological applications.<sup>3</sup> Similarly, 2-aminoquinoline (2-AQ)

exhibits various biological activities such as anthelmintic, antiprotozoal, anti-depressant, some effectiveness in the treatment of Alzheimer's disease.<sup>4</sup> Toward that end, we paid attention to unique 2-amino-8-quinolinol (**1**), which contains important structural components of 8-HQ and 2-AQ.<sup>5</sup> The synthesis of its derivatives may prove to be useful, owing to the utility of the parent compounds; however, the previous works for *O*- and *N*-acylation of **1** have hardly been reported to date.<sup>6</sup> We sought the synthesis of its derivatives, especially the esterification on C8 and the amidation on C2 (Fig. 1).

Recently, we reported an acyl derivative of 2-amino-8-quinolinol (**1**) called **SG-HQ2**. This compound is an anti-allergic inflammatory agent.<sup>7</sup> Unfortunately, NMR spectroscopic studies cast doubt on the originally proposed structure, which was regarded as the amide form. To prove that the ester form was obtained as the major product of the EDCI-mediated coupling reaction of 2-amino-8-quinolinol (**1**) and 3,4,5-tris(benzyloxy)benzoic acid, we reexamined the acylation and analyzed the structure of **SG-HQ1** via NMR spectroscopy and X-ray crystallography.<sup>8</sup> **SG-HQ2** from the catalytic hydrogenation of **SG-HG1** was determined to be the C8-ester instead of the amide as reported previously (Scheme 1).

## Results and discussion

Encouraged by the chemoselective *O*-acylation of 2-amino-8-quinolinol, our synthetic investigations regarding C2-amide derivatives began with initial studies of the 2 step synthesis

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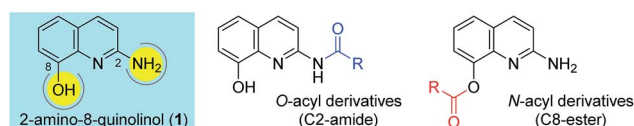
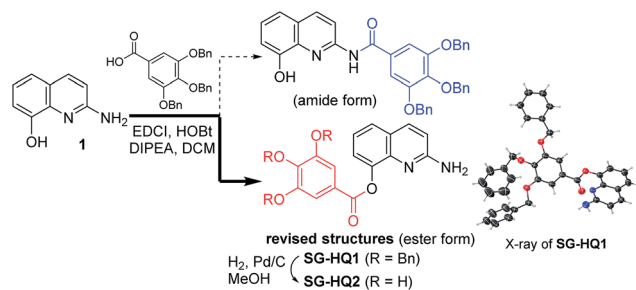


Fig. 1 2-Amino-8-quinolinol (**1**) and its acyl derivatives.

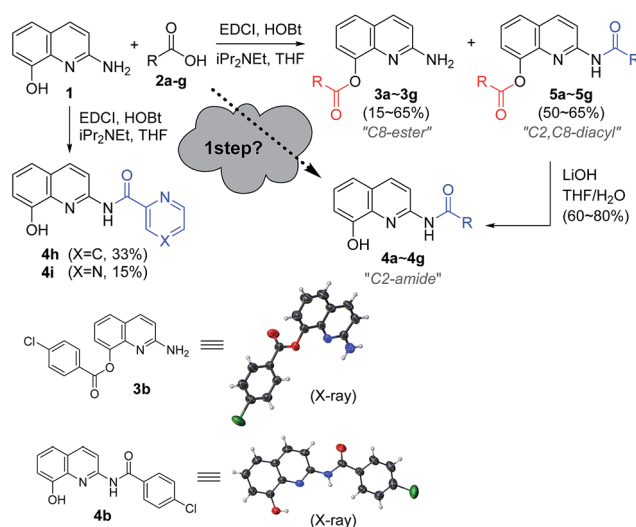




Scheme 1 Synthesis of SG-HQ1 and SG-HQ2 and their revised structures.<sup>8</sup>

comprised of the diacylation with excess of aromatic acid (up to 5 equiv.) and the hydrolysis of the ester moiety (Scheme 2). C2-amides of various aromatic acids were prepared, and the structures of **3b** and **4b** were confirmed by X-ray crystallography.<sup>8</sup> Interestingly, the acylation with heteroaromatic acids such as 2-picolinic acid and pyrazinecarboxylic acid afforded only the C2-amides (**4h** and **4i**), excluding C8-ester and diacyl compounds, albeit in low yield. Thus, the selective and efficient introduction of various carboxylic acids on 2-amino-8-quinolinol remains a challenge,<sup>9</sup> although some C2 and C8-acyl derivatives were prepared successfully. Inspired by the unique characteristics of 2-amino-8-quinolinol, herein we present the optimization of the chemoselective *O*- or *N*-acylation.

To investigate possible synthetic routes towards C2-amide and C8-ester derivatives of 2-amino-8-quinolinol, we first examined various acylation conditions with 4-methoxybenzoic acid (Table 1). THF was selected as the most favorable solvent in terms of solubility and purification. The use of carbodiimides provided the C8-ester **3a** preferentially as the major product.



Scheme 2 Initial synthesis of C8-ester and C2-amide derivatives of 2-amino-8-quinolinol. Aromatic acids including 4-methoxybenzoic (a), 4-chlorobenzoic (b), 4-(trifluoromethyl)benzoic (c), 4-*tert*-butylbenzoic (d), 3-methoxybenzoic (e), 3,4,5-tris(benzyloxy)benzoic (f), 2-furoic (g), picolinic (h), and pyrazinecarboxylic (i) acids.

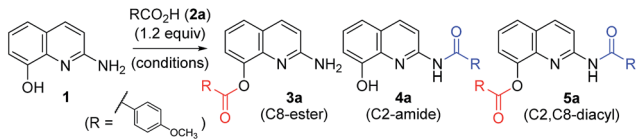
DMAP as an additive increased the chemical yield and ester selectivity (entry 1 and 7). However, when HOBT was employed, the formation of diacyl derivative **5a** increased with that of C8-ester (entry 3–5). Though the use of HOAt provided the C2-ester selectively, the isolated yield of **3a** was not satisfactory (entry 6). Uranium (HATU) and phosphonium (PyBop) salts did not exhibit significant effects (entry 8 and 9). The use of 4-methoxybenzoyl chloride with *i*Pr<sub>2</sub>NEt gave the C8-ester as the major product (entry 10). The yield decreased slightly when pyridine was used as a solvent (entry 11). Finally, we chose CDI for the amidation through the acyl imidazolide, leading to the formation of C2-amide **4a** although the C8-ester formed as the major product. Higher temperature increased the formation of C2-amide slightly (entry 12–14). C2-amide **4a** could be obtained in 75% yield with the ratio of 5 : 88 : 7, when the anionic nucleophile by the treatment of 2-amino-8-quinolinol with NaH reacted with the acyl imidazolide derived from 4-methoxybenzoic acid and CDI (entry 15).

The optimized acylation conditions were further investigated using a cheap and readily available ester instead of acyl imidazolide **6** with other strong bases (Table 2).<sup>10</sup> Methyl 4-methoxybenzoate **7** was used as an acyl donor. Even though the use of the methyl ester provided a lower yield than acyl imidazolide **6**, the acylation resulted in the selective formation of C2-amide. When NaH and *n*-BuLi were used to generate the anionic intermediate of 2-amino-8-quinolinol, the excellent selectivity was observed (entries 2 and 3). The use of *i*PrMgCl as a base resulted in a significant loss of reactivity and selectivity (entry 4). The formation of C2-amide **4a** was improved as the amount of *t*-BuOK was increased (entry 5–8). The anionic nucleophile of 2-amino-8-quinolinol could mostly be converted into C2-amide rather than C8-ester.

Additive effect on reactivity and selectivity was evaluated in order to reveal the role of acyl imidazolide in C8-acylation. Some amines (such as pyridine, DMAP, and HOBT) and their HCl salts were treated in the reaction of **1** with the isolated acyl imidazolide **6** (Table 3). Without additives, C2-amide (**4a**) was obtained even though the reaction yield and ratio was slightly different with CDI-mediated acylation. However, the use of pyridine and DMAP at reflux provided C8-ester (**3a**) reversely. The use of their HCl salt (Pyr·HCl and DMAP·HCl) and HOBT provided selectively the C8-ester in good yield even at room temperature.

A variety of carboxylic acids were introduced on 2-amino-8-quinolinol under the optimized acylation conditions. Either condition A (EDCl, *i*Pr<sub>2</sub>NEt and catalytic DMAP) or condition B (PyBop and *i*Pr<sub>2</sub>NEt) was used for the synthesis of the C8-esters (Table 4). Various substituted-benzoic acids and furoic acid (*i.e.* **3a–3f**, **3j** and **3k**) were introduced on the C8 position in good yields, regardless of electron-withdrawing and donating groups. However, *N*-heteroaromatic acids were not incorporated on the phenol group in the C8 position; C2-amides (**4h–4i**, **4l–4m**) were isolated even in low yields instead. Interestingly, Boc-leucinyl C8-ester (**3n**) seems to be unstable during flash column chromatography like heteroaromatic acid, however Boc-valinyl C8-ester (**3o**) was obtained in moderate yield.

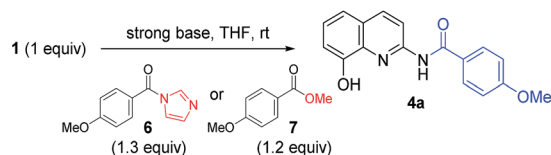


Table 1 Optimization of acylation conditions<sup>a</sup>


Entry	Activator (equiv.)	Base	Time (h)	% yield <sup>b</sup>		Ratio <sup>c</sup> (3a : 4a : 5a)
				3a	4a	
1	DCC (1.3), DMAP (0.5)		24	54	0	>99 : 0 : <1
2	EDCI (1.3)	iPr <sub>2</sub> NEt	24	21	0	>99 : 0 : <1
3	EDCI (1.3), HOBT (0.5)	iPr <sub>2</sub> NEt	24	60	0	67 : 1 : 32
4 <sup>d</sup>	EDCI (1.3), HOBT (0.5)	iPr <sub>2</sub> NEt	24	65	4	73 : 5 : 22
5	EDCI (1.3), HOBT (0.5)	Et <sub>3</sub> N	24	58	1	79 : 1 : 20
6	EDCI (1.3), HOAt (0.5)	iPr <sub>2</sub> NEt	24	35	0	93 : 0 : 7
7	<b>EDCI (1.3), DMAP (0.5)</b>	<b>iPr<sub>2</sub>NEt</b>	<b>3</b>	<b>92</b>	<b>0</b>	<b>99 : 0 : 1</b>
8	HATU (1.3)	iPr <sub>2</sub> NEt	24	65	0	83 : 0 : 17
9	PyBOP (1.3)	iPr <sub>2</sub> NEt	4	50	1	58 : 1 : 41
10 <sup>e</sup>		Et <sub>3</sub> N	4	82	1	86 : 1 : 13
11 <sup>e</sup>		Pyridine	24	65	0	81 : 0 : 19
12	CDI (1.3)		24	30	9	70 : 22 : 8
13 <sup>d</sup>	CDI (1.3)		24	40	14	56 : 19 : 24
14 <sup>d</sup>	CDI (1.0)		24	36	19	44 : 23 : 33
15 <sup>f</sup>	CDI (1.3)	<b>NaH</b>	<b>3</b>	<b>4</b>	<b>75</b>	<b>5 : 88 : 7</b>

<sup>a</sup> The reactions were carried out three times. <sup>b</sup> Isolated yield of **3a** and **4a** after column chromatography. <sup>c</sup> Ratio of **3a**, **4a** and **5a** determined by HPLC analysis. <sup>d</sup> At reflux. <sup>e</sup> 4-Methoxybenzoyl chloride was used. <sup>f</sup> Reaction conditions: a THF solution of CDI and 4-methoxybenzoic acid was added to 2-amino-8-quinolinol and NaH (2 equiv.) in THF.

Table 2 The amidation of 2-amino-8-quinolinol with acyl imidazole and ester under anionic conditions

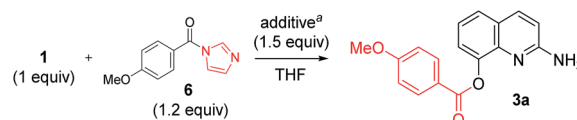


Entry	Acyl donor	Base (equiv.)	Time (h)	% yield <sup>a</sup>	Ratio <sup>b</sup>
1	<b>6</b>	NaH (2.0)	4	75	5 : 88 : 7
2	7	NaH (2.0)	24	25	2 : 98 : 0
3	7	<i>n</i> -BuLi (2.0)	4	56	0 : 99 : 1
4	7	iPrMgCl (2.0)	24	8	0 : 86 : 14
5	7	<i>t</i> -BuOK (1.0)	24	11	4 : 93 : 3
6	7	<i>t</i> -BuOK (2.0)	2	63	3 : 96 : 0
7	7	<i>t</i> -BuOK (2.5)	1	72	1 : 93 : 7
8	7	<i>t</i> -BuOK (3.0)	0.5	85	1 : 96 : 3

<sup>a</sup> Isolated yield of amide **3a**. <sup>b</sup> Ratio (**3a** : **4a** : **5a**) determined by HPLC analysis.

Next, we turned our attention to the amidation of 2-amino-8-quinolinol on the C2 position. The CDI-mediated amidation of some aromatic acids with electron-withdrawing substituents provided C2-amides as the major product in contrast to carbodiimide-mediated acylation (condition C, Table 5). Nevertheless, this general amidation was accompanied by the formation of the C8-ester species, which was difficult to

Table 3 The effect on additives in the reaction of 2-amino-8-quinolinol with acyl imidazole

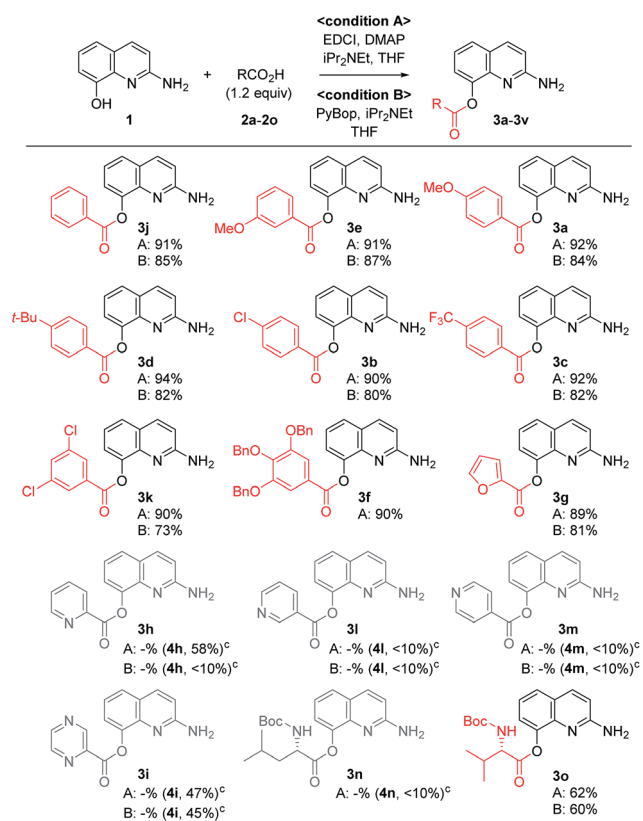


Entry	Additive (equiv.)	Temp (°C)	% yield <sup>b</sup>		Ratio <sup>c</sup> (3a : 4a : 5a)
			3a	4a	
1 <sup>d,e</sup>	—	65	9	15	15 : 25 : 60
2 <sup>d</sup>	Pyridine (1.5)	65	67	0	80 : 0 : 20
3 <sup>d</sup>	DMAP (1.5)	65	63	0	73 : 0 : 27
4	HOBT (1.5)	rt	56	0	80 : 0 : 20
5	Pyr·HCl (1.5)	rt	78	0	87 : 0 : 13
6	DMAP·HCl (1.5)	rt	75	0	87 : 0 : 13

<sup>a</sup> Reaction conditions: 2-amino-8-quinolinol (1 equiv.), acyl imidazole (1.2 equiv.), an additive (1.5 equiv.), THF (4 mL), at room temperature. <sup>b</sup> Isolated yield. <sup>c</sup> Ratio determined by HPLC analysis. <sup>d</sup> At reflux. <sup>e</sup> Added iPr<sub>2</sub>NEt (3 equiv.).

separate. With the optimized reaction conditions in hand, the substrate scope was examined (condition D, Table 5). 4-Methoxybenzoyl derivatives (**2a**) was obtained in 75% yield, whereas the isolated yields of other substituted benzoic acids and heteroaromatic acids were improved up to 99% (**4a** vs. **4b–4m**). Interestingly amides with *N*-protected amino acids (**4n** and



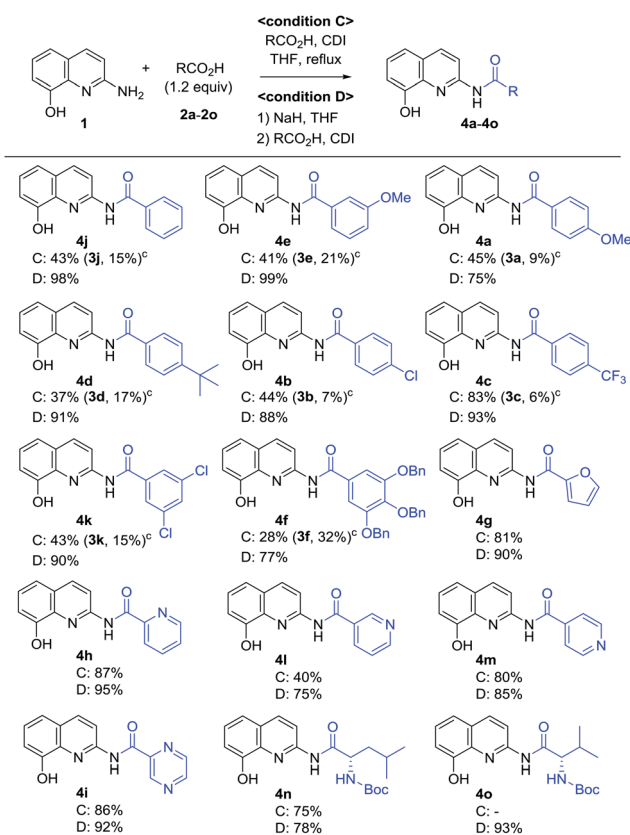
Table 4 Scope of C8-ester formation<sup>a,b</sup>

<sup>a</sup> Reaction conditions: 1 (0.2 mmol), carboxylic acid (0.4 mmol), EDCI (2.5 equiv.), DMAP (10 mol%), *i*Pr<sub>2</sub>NEt (3 equiv.), THF (1 mL).  
<sup>b</sup> Isolated yield by flash column chromatography. <sup>c</sup> Not obtained C8-ester; isolated yield of C2-amide in parenthesis.

4o) were easily prepared from the corresponding acyl imidazolides.

By using EDCI-mediated acylation, the bulky aliphatic acyl moieties such as piperidinylcarboxy, isovaleroyl, pivaloyl and 1-adamantylcarbonyl were introduced on the C8-hydroxy group successfully (3p–3s) as shown in Scheme 3. Similarly, sulfonyl chloride, benzyl chloroformate and Boc<sub>2</sub>O were used to prepare the sulfonate and carbonate derivatives (3t–3v) on the C8-position in good yield, respectively. Meanwhile, the C2-amides with bulky aliphatic amides bearing piperidinylcarboxy, isovaleroyl, pivaloyl and 1-adamantylcarbonyl (4p–4s), were easily prepared from the corresponding acyl imidazolides. Finally, a similar method was used to prepare two carbamates with Cbz and Boc on C2 position, in spite of the unsatisfactory result obtained with *p*-toluenesulfonamide (4t vs. 4u and 4v).

Additive effects besides imidazole are shown in Table 3 to shed light on the mechanism of the chemoselective synthesis of C8-ester and C2-amide derivatives. Thus, representative amines (such as pyridine, DMAP, and HOBt) and their HCl salts were treated with the imidazolide 6 to afford the C8-ester (Scheme 4). With reactive acyl donors, C8-ester was regarded as the kinetic product. On the contrary, two C8-esters (3a and 3k) were refluxed with imidazole to afford the corresponding amides (4a

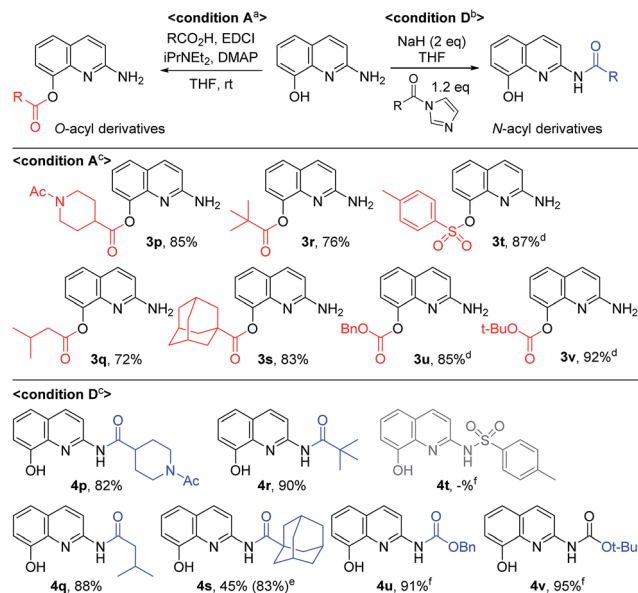
Table 5 Scope of C2-amide formation<sup>a,b</sup>

<sup>a</sup> Reaction conditions: a mixture of the carboxylic acid (1.2 equiv.) and CDI (1.3 equiv.) was added to a THF (4 mL) solution of 1 (0.20 mmol) and NaH (2 equiv.) at room temperature. <sup>b</sup> Isolated yield from flash column chromatography. <sup>c</sup> Isolated yield based on recovered starting material in parenthesis.

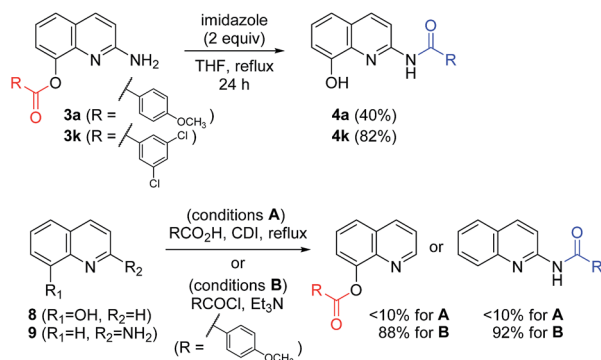
and 4k) in 40% and 82% yields, respectively. The observed conversion from the C8-ester to the C2-amide revealed that the C2-amide was the thermodynamically stable product. The conversion of 3k to 4k was superior to that of 3a, because of the electronic effect on substituents of benzene ring. This result is relevant to the lack of formation of C8-esters with *N*-hetero-aromatic carbonyls (3h–3n) under most of conditions, as shown in Scheme 3. In order to determine the origin of the unique reactivity of 2-amino-8-quinolinol, 8-hydroxyquinoline (8) and 2-aminoquinoline (9) reacted with 4-methoxybenzoic acid under various coupling conditions. The yields with EDCI, PyBop, HBTU, and CDI were not satisfactory, but the acylation was successful with using the reactive acid chloride in good yields (up to 92%). As the weak reactivity of 8 and 9, it is considered to have a beneficial effect between the 2-amino and 8-hydroxy moieties for the introduction of an acyl group to 1.

To investigate the acylation pattern of 1, we monitored the progress of C2-amide and C8-ester formation *via* CDI-mediated acylation by HPLC. Ester 3a formed faster than amide 4a (0–6 h). After 24 h, 4a was the major component, while starting material 1, 3a, and 5a were formed in similar amounts (almost 20%, Table 6).<sup>8</sup>





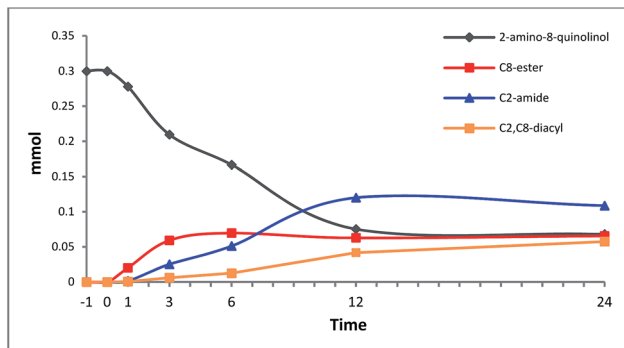
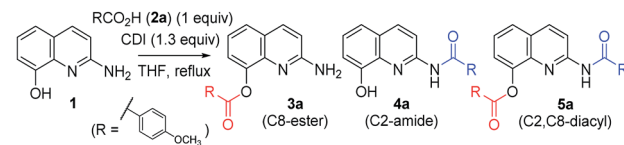
**Scheme 3** The introduction of aliphaticacyl, sulfonyl and alkoxycarbonyl groups. <sup>a</sup>Reaction conditions: **1** (0.2 mmol), carboxylic acid (0.4 mmol), EDCI (2.5 equiv.), DMAP (10 mol%),  $i\text{Pr}_2\text{NEt}$  (3 equiv.), THF (1 mL). <sup>b</sup>Reaction conditions: a mixture of the carboxylic acid (1.2 equiv.) and CDI (1.3 equiv.) was added to a THF (4 mL) solution of **1** (0.20 mmol) and NaH (2 equiv.). <sup>c</sup>Isolated yield by flash column chromatography. <sup>d</sup>*p*-toluenesulfonyl chloride, benzyl chloroformate and  $\text{Boc}_2\text{O}$  were used for **3t**, **3u**, and **3v** respectively. <sup>e</sup>Isolated yield based on recovered starting material in parenthesis. <sup>f</sup>*p*-Toluenesulfonyl chloride, benzyl chloroformate and  $\text{Boc}_2\text{O}$  were used with imidazole for **4t**, **4u**, and **4v** respectively, but **4t** was not isolated.



**Scheme 4** Mechanistic investigation.

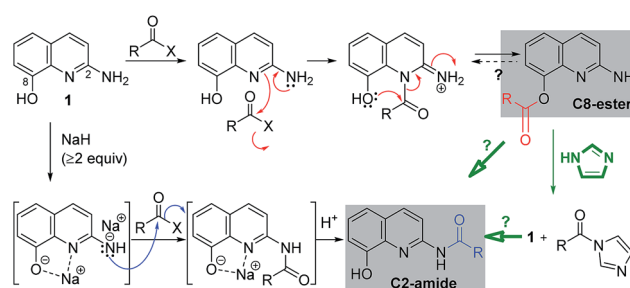
Based on the above mechanistic investigation, a proposed reaction pathway is outlined in Scheme 5. Notably, Joussef *et al.* reported the chemoselectivity *O*-sulfonylation at C8.<sup>11</sup> For the C8-ester formation, the nitrogen nucleophile at N1 induced from the lone pair of the amino at C2 attacks acyl donors such as acid chlorides preferentially; this step is followed by an intra- or intermolecular acyl transfer to the neighboring hydroxy at C8.<sup>12</sup> Meanwhile, the formation of C2-amides involves the anions of **1**, generated by strong bases such as NaH. We speculated that a sodium ion which interacts with the anion at C8 might coordinate to the nitrogen atom at N1, whereas the

**Table 6** The representative time-course data (HPLC) for the formation of C8-ester and C2-amide under CDI-mediated condition<sup>a</sup>



Time (h)	<b>1</b> (mmol)	<b>3a</b> (mmol)	<b>4a</b> (mmol)	<b>5a</b> (mmol)
0	0.3000	0	0	0
1	0.2780	0.0201	0.0014	0.0005
3	0.2096	0.0593	0.0252	0.0060
6	0.1666	0.0697	0.0512	0.0125
12	0.0753	0.0628	0.1201	0.0418
24	0.0681	0.0656	0.1087	0.0576

<sup>a</sup> Reaction conditions: a THF (4 mL) solution of 2-amino-8-quinolinol (1 equiv.), *p*-methoxybenzoic acid (1 equiv.), and CDI (1.3 equiv.) was stirred at reflux.



**Scheme 5** Proposed reaction pathways.

second anion at C2 might attack acyl donors such as acyl imidazolides and esters. As with the unstable C8-ester (*i.e.* **3k**) could be converted into the C2-amide by imidazole, the reactivity of the amino at C2 with acyl imidazolides under neutral conditions remains to be elucidated.

## Conclusions

In conclusion, we developed chemoselective acylation of 2-amino-8-quinolinol on amino group at C2 and hydroxy group at C8. The coupling reaction with a variety of carboxylic acids using EDCI and DMAP provided C8-ester derivatives in excellent



yield. When the dianion of 2-amino-8-quinolinol reacts with less reactive acylimidazoles and esters, the corresponding C2-amides and carbamate derivatives could be prepared as the major product. Biological evaluations of the C2-amide and C8-ester derivatives of 2-amino-8-quinolinol are underway in our laboratory and will be reported in due course.

## Experimental

All the starting materials, solvents and reagents were obtained from commercial suppliers and were used without further purification. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker 600 MHz spectrometer as solutions in deuterated  $\text{CDCl}_3$ , methanol- $d_4$  or  $\text{DMSO}-d_6$ .  $^1\text{H}$  NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet and/or multiple resonances), number of protons, and coupling constant ( $J$ ) in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 (FAB and EI) and an Agilent 6530 Q-TOF LC/MS/MS system (ESI). For conversion measurements, the samples prepared for the HPLC were analyzed at 256 nm using an Agilent 1260 HPLC system equipped with a 6 mm  $\times$  50 mm Sunfire 5 $\mu$  C18 column, in which the mobile phase was a gradient from water to acetonitrile for 30 min.

### General procedure of condition A (Table 4) for *O*-acylation at C8

To a solution of 2-amino-8-quinolinol (30 mg, 0.19 mmol) and a carboxylic acid (1.2 equiv.) in anhydrous tetrahydrofuran (4 mL) were added EDCI (1.3 equiv.), DMAP (0.5 equiv.) and *N,N*-diisopropylethylamine (3.0 equiv.) under  $\text{N}_2$  atmosphere with an ice bath. After stirring for 3 h at ambient temperature, the mixture was diluted with dichloromethane, washed by sat.  $\text{NH}_4\text{Cl}$ , sat.  $\text{NaHCO}_3$ , and brine, dried by  $\text{MgSO}_4$ , filtered, and concentrated. The residue was purified by silica gel column chromatography to afford the desired product.

### General procedure of condition B (Table 4) for *O*-acylation at C8

To a solution of 2-amino-8-quinolinol (30 mg, 0.19 mmol) and a carboxylic acid (1.2 equiv.) in anhydrous tetrahydrofuran were added PyBop (1.3 equiv.) and *N,N*-diisopropylethylamine (3.0 equiv.) under  $\text{N}_2$  atmosphere with an ice bath and stirring for 4 h at ambient temperature. The reaction mixture was diluted with dichloromethane, washed by  $\text{NH}_4\text{Cl}$ , saturated  $\text{NaHCO}_3$ , and brine, dried by  $\text{MgSO}_4$ , filtered, and concentrated. The residue was purified by flash column chromatography to the desired product.

### General procedure of condition C (Table 5) for *N*-acylation at C2

To a solution of a carboxylic acid (1.2 equiv.) in anhydrous tetrahydrofuran was added 1,1'-carbodiimidazole (1.3 equiv.).

After stirring for 1 h under  $\text{N}_2$  atmosphere, 2-amino-8-quinolinol (30 mg, 0.19 mmol) was added to the reaction mixture. After stirring for 24 h at reflux, the mixture was diluted with tetrahydrofuran, washed by  $\text{NH}_4\text{Cl}$ , saturated  $\text{NaHCO}_3$ , and brine, dried by  $\text{MgSO}_4$ , filtered, and concentrated. The residue was purified by flash column chromatography to the desired product.

### General procedure of condition D (Table 5) for *N*-acylation at C2

To a solution of carboxylic acid (1.2 equiv.) in anhydrous tetrahydrofuran (4 mL), 1,1'-carbonyldiimidazole (1.3 equiv.) was added under  $\text{N}_2$  atmosphere at ambient temperature. After stirred for 1 h. The mixture was diluted with dichloromethane, extracted by brine and dichloromethane, dried by  $\text{MgSO}_4$ , filtered, and concentrated to obtain the acyl imidazolide intermediate. To a solution of 2-amino-8-quinolinol (30 mg, 0.19 mmol) and  $\text{NaH}$  (2.0 equiv.) in anhydrous tetrahydrofuran (4 mL) was added the acyl imidazolide intermediate under  $\text{N}_2$  atmosphere with an ice bath. After stirring for 2 h at ambient temperature, the reaction was quenched with sat.  $\text{NH}_4\text{Cl}$ , washed by dichloromethane and dried by  $\text{MgSO}_4$ , filtered, and concentrated. The residue was purified by silica gel column chromatography to afford the desired product.

**2-Aminoquinolin-8-yl 4-methoxybenzoate (3a).** General procedure A, white solid, yield: 92%, and purification by column chromatography (ethyl acetate/*n*-hexane = 1 : 3,  $R_f$  = 0.1).  $^1\text{H}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (dd, 2H,  $J$  = 9.0 Hz), 7.86 (d, 1H,  $J$  = 9.0 Hz), 7.53 (dd, 1H,  $J$  = 8.4 and 1.2 Hz), 7.39 (dd, 1H,  $J$  = 7.8 and 1.2 Hz), 7.26 (t, 1H,  $J$  = 7.8 Hz), 6.99 (dd, 2H,  $J$  = 9.0 and 1.8 Hz), 6.66 (d, 1H,  $J$  = 9.0 Hz), 4.85 (bs, 2H), 3.89 (s, 3H);  $^{13}\text{C}$ -NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  165.3, 163.7, 157.0, 145.3, 140.7, 137.9, 132.5, 125.4, 125.0, 122.2, 122.1, 121.9, 113.7, 112.3, 55.5; HRMS (EI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3$ : 294.1004; found: 294.1006.

***N*-(8-Hydroxyquinolin-2-yl)-4-methoxybenzamide (4a).** General procedure D, white solid, yield: 75%, and purification by column chromatography (dichloromethane/methanol = 20 : 1,  $R_f$  = 0.25).  $^1\text{H}$ -NMR (600 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.68 (s, 1H), 9.29 (bs, 1H), 8.34 (d, 1H,  $J$  = 9.0 Hz), 8.28 (d, 1H,  $J$  = 9.0 Hz), 8.10 (d, 2H,  $J$  = 8.4 Hz), 7.38 (d, 1H,  $J$  = 7.8 Hz), 7.35 (t, 1H,  $J$  = 7.8 Hz), 7.10 (t 3H,  $J$  = 7.5 Hz), 3.86 (s, 3H);  $^{13}\text{C}$ -NMR (150 MHz,  $\text{DMSO}-d_6$ )  $\delta$  165.9, 162.8, 152.4, 150.7, 138.4, 137.2, 130.5, 127.0, 126.3, 126.2, 118.2, 116.4, 114.1, 111.9, 55.9; HRMS (EI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3$ : 294.1004; found: 294.1003.

## Conflicts of interest

There are no conflicts to declare.

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- The  $pK_a$  values of 2-amino-8-quinolinol (1) and its conjugate acid are 10.5 and 6.7, respectively, calculated using the ACD/Percepta 14 (ACD/Labs, Toronto, Canada). The chemical shift perturbation of the ring proton of N1 position of 1 depending on pHs was monitored by NMR. The result also showed three plateaus exist around the calculated  $pK_a$  values, which supported that the  $pK_a$  values should be correct. For details, see ESI.†

