钯催化 1-萘酰胺的 8-烷基化反应及其在阿朴菲和马兜铃内酰胺类生物碱骨架合成中的应用

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摘要 报道了一种钯催化 1-萘酰胺的 8 位碳氢键烷基化反应. 在该反应中, 喹啉甲酰胺作为 *N,N*-双齿螯合基团, 各种取代的 α -溴乙酸烷基酯以及 α -溴代苯乙酮作为烷基化试剂, 高效、高区域选择性地合成了 8-烷基-1-萘胺衍生物. 最后, 将含酯基和酮基的烷基化产物分别通过相应的衍生化反应合成具有多种生物活性的阿朴菲和马兜铃内酰胺类生物碱结构单元.

关键词 钯催化; 烷基化; 1-萘酰胺; 阿朴菲类生物碱; 马兜铃内酰胺类生物碱

Palladium-Catalyzed C8 Alkylation of 1-Naphthylamides and Its Application to the Synthesis of the Core Structures of Aporphine and Aristolactam Alkaloids

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Abstract A practical methodology for the palladium-catalyzed regioselective alkylation of 8-C—H bonds in 1-naphthylamides containing a quinolinamide moiety as bidentate directing group with functionalized alkyl halides is reported. Various functionalized alkyl halides including α -bromo esters and ketones can be employed as coupling partners, providing exclusively 8-alkyl-1-naphthylamine derivatives. In particular, the alkylated products with these ester and carbonyl groups can readily be further converted into the core structures of aporphine and aristolactam alkaloids respectively.

Keywords palladium-catalyzed; alkylation; 1-naphthylamides; aporphine alkaloids; aristolactam alkaloids

1 Introduction

Direct and selective functionalization of C—H bonds has emerged as one of the most promising and powerful synthetic tools for the formation of C—C bonds.^[1] The application of this tactic to the rapid synthesis of bioactive molecules such as natural products and medicinal compounds has garnered significant attention of researchers due to the strategic advantages in terms of great efficiency and economy.^[2] In this context, our previous researches have focused on the quinolinamide or picolinamide-di-

rected regioselective C8 arylation and alkylation of 1-naphthylamides with aryl and alkyl iodides under the catalysis of Pd(OAc)₂ (Scheme 1, a)^[3] to offer exclusively 8-aryl-1-naphthylamine and 8-alkyl-1-naphthylamine derivatives. Subsequently, the picolinamide-directed palladium-catalyzed C8-H functionalization of 1-naphthylamines has been accomplished by the research groups,^[4] including alkylation,^[4a,11] arylation,^[4a] carbonylation,^[4b-4c] amination,^[4d] cyanation,^[4e-4f] chalcogenation^[4g] (Scheme 1, b). In view of the great regioselectivity, compatibility and efficiency of this methodology, we turned our attention

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Scheme 1 Pd(II)-catalyzed regioselective C8 functionalization of 1-naphthylamides

to the investigation of whether the method could also facilitate the C8 alkylation of 1-naphthylamides with functionalized alkyl halides in place of non-functionalized alkyl iodides as coupling partners. As an additional objective, we also wanted to explore the possibility of the direct alkylated products with the functional groups could serving as a versatile synthetic handle to synthesize the core structures of desired bioactive molecules via a series of transformations.

Aporphine and aristolactam alkaloids are two widespread and important families of aporphinoid alkaloids that exhibit a broad spectrum of biological activities,^[5] such as dopamine receptor agonist,^[6a] antitumoral,^[6b] antiviral,^[6c] antipoliavirus,^[6d] antiplatelet,^[7a] anti-inflammatory,^[7b] and antibacterial.^[7c] They share the characteristic 2,3,9,9a-tetrahydro-1*H*-benzo[*de*]quinoline and benzo[*cd*]indol-2(1*H*)-one motifs respectively, which all possess 1-naphthylamide skeleton with different functionalization on C8 position of 1-naphthylamide (Figure 1). In light of these observations and initial findings,^[3,8] our goal is to extend the compatibility of original methodology to diverse functionalized alkyl halides and develop the synthetic methods for preparing 2,3-dihydro-1*H*-benzo[*de*]quinoline and benzo[*cd*]indol-2(1*H*)-one respectively, which are high-value core structures of aporphine and aristolactam alkaloids.

Figure 1 Representative structures of aporphine and aristolactam alkaloids

To realize this goal, the exploration of suitable functionalized alkyl reagents is crucial for these transformations. α -halo esters and ketones are valuable and versatile synthetic agents in organic synthesis,^[9] even in C—H functionalization.^[8,10] We become interested in the use of α -halo esters and ketones because these ester and carbonyl groups in the alkylated product can be further transformed to access the target alkaloids. Recently, a similar work for

the palladium-catalyzed picolinamide directed C8-H alkoxy-carbonylmethylation of 1-naphthylamine derivatives with α -chloro alkyl esters has been reported by the Wu group. In this protocol, the 2.0 equiv. NaI as a chloro scavenger was necessary for the transformation at 130 °C for 20 h (Scheme 1, c).^[11] Herein we report on the palladium (II)-catalyzed quinolinamide-directed regioselective C-8 alkylation of 1-naphthylamides with a range of α -bromo esters and ketones without the use of NaI as an activator at a lower temperature. In particular, the alkylated products can be further converted into the core structures of aporphine and aristolactam alkaloids respectively (Scheme 1, d).

2 Results and discussion

We initiated our studies by employing ethyl 2-bromoacetate (**2a**) as a test functionalized alkyl reagent reacted with *N*-(naphthalen-1-yl)picolinamide (**1b**) under the original C8 alkylation conditions (Scheme 2).^[3b] To our delight, the desired alkylated product **3p** was generated in 32% yield. Prolonging the reaction time to 24 h moderately improved the yield of the product. Replacing **1b** with the analogue naphthylquinoline-2-carboxamide (**1a**) as the substrate provided a higher yield. No corresponding alkylated products **3q** and **3r** were observed when *N*-(naphthalen-1-yl)benzamide (**1c**) or *tert*-butyl naphthalen-1-yl-carbamate (**1d**) was used as the substrate in place of **1b**, showing that the coordination in a bidentate N,N fashion played a critical role on this transformation.

Scheme 2 Screening of 1-naphthylamides auxiliaries

This reaction was performed under slightly modified conditions to further improve the reactivity. It is noteworthy that the product **3a** could also be furnished in 61% yield by reducing the catalyst loading to 10 mol% and lowering the temperature to 90 °C simultaneously (Table 1, Entry 1). Replacing KOAc with PhCOOK as the additive gave a slight improvement (Table 1, Entry 2). Screen-

ing of the solvents demonstrated that 1,2-dichloroethane delivered the best yield (Table 1, Entries 2~7). Omission of additive resulted in a drastically decreased yield (Table 1, Entry 8). Variation in the type of additive was then screened (Table 1, Entries 9~14). Employing AgOAc additive as a halide scavenger greatly suppressed product **3a** formation (Table 1, Entry 9). The investigated inorganic base and organic acid additives all displayed lower efficiencies compared to PhCOOK additive in combination with 1,2-dichloroethane (Table 1, Entries 10~14). Other palladium catalysts such as PdCl₂, Pd(PPh₃)₄, Pd₂(dba)₃, and Pd(CH₃CN)₂Cl₂ were also effective in this transformation but gave slightly lower yields (Table 1, Entries 15~18). Thus, the optimal reaction was achieved with 2 equiv. of PhCOOK as the additive in 1,2-dichloroethane at 90 °C for 12 h (Table 1, Entry 7).

Table 1 Optimization of the reaction conditions^a

Entry	Catalyst/mol%	Additive	Solvent	Yield ^b /%
1	Pd(OAc) ₂	KOAc	1,4-Dioxane	61
2	Pd(OAc) ₂	PhCOOK	1,4-Dioxane	68
3	Pd(OAc) ₂	PhCOOK	DMF	N.D.
4	Pd(OAc) ₂	PhCOOK	Xylene	82
5	Pd(OAc) ₂	PhCOOK	DMSO	N.D.
6	Pd(OAc) ₂	PhCOOK	<i>t</i> -BuOH	75
7	Pd(OAc)₂	PhCOOK	DCE	86
8	Pd(OAc) ₂	—	DCE	Trace
9	Pd(OAc) ₂	AgOAc	DCE	Trace
10	Pd(OAc) ₂	NaOAc	DCE	49
11	Pd(OAc) ₂	K ₂ CO ₃	DCE	45
12	Pd(OAc) ₂	CS ₂ CO ₃	DCE	Trace
13	Pd(OAc) ₂	HOAc	DCE	18
14	Pd(OAc) ₂	CF ₃ COOH	DCE	N.D.
15	PdCl ₂	PhCOOK	DCE	83
16	Pd(PPh ₃) ₄	PhCOOK	DCE	36
17	Pd ₂ (dba) ₃	PhCOOK	DCE	30
18	Pd(CH ₃ CN) ₂ Cl ₂	PhCOOK	DCE	80

^a Reaction conditions: **1a** (0.25 mmol, 75 mg), palladium catalyst (0.025 mmol), ethyl 2-bromoacetate (0.5 mmol, 84 mg), additive (0.5 mmol), solvent (2 mL), 90 °C, 12 h. ^b Isolated yields based on **1a**.

With the optimized reaction conditions in hand, the scope study of functionalized alkyl halides was carried out (Table 2). The naphthylquinoline-2-carboxamide (**1a**) could be alkylated by various alkyl 2-bromoacetates **2** such as ethyl 2-bromoacetate (**2a**), benzyl 2-bromoacetate (**2b**),

Table 2 Scope of the alkyl halides^a

Entry	RX	Product	Yield ^b /%
1		3a	86 (76 ^c)
2		3b	66
3		3c	72
4		3d	62
5 ^d		3d	61
6 ^e		3e	78
7 ^e		3e	80

^a Reaction conditions: **1a** (0.25 mmol, 75 mg), Pd(OAc)₂ (0.025 mmol, 6 mg), RX (0.5 mmol), PhCOOK (0.5 mmol, 80 mg), DCE (2 mL), 90 °C, 12 h.

^b Isolated yields based on **1a**. ^c Isolated yield on a 3.34 mmol scale for 24 h.

^d Reaction at 130 °C for 48 h. ^e Reaction for 24 h.

tert-butyl 2-bromoacetate (**2c**), and methyl 2-bromoacetate (**2d**) in moderate to good yields exclusively (Table 2, Entries 1~4), and no C2-alkylated product was detected in these reactions. It was worth mentioning that a gram scale reaction involving substrate **1a** was carried out and the corresponding C8-alkylated product **3a** was isolated in 76% yield (Table 2, Entry 1). Moreover, methyl 2-chloroacetate (**2e**) could be effectively employed to give the product **3d** in almost identical yield to **2d** by prolonging the reaction time to 48 h and raising the temperature to 130 °C simultaneously (Table 2, Entry 5). In addition, non-functionalized alkyl halides such as benzyl bromide (**2f**) and benzyl chloride (**2g**) could also be participated

well in the reaction to afford the desired products, albeit a longer reaction time of 24 h was required (Table 2, Entries 6 and 7).

With the alkyl 2-bromoacetates coupling partner scope established, we then probed the substrate scope of another functionalized alkyl bromides (Table 3). α -Bromoaryl ketones with both electron-withdrawing and electron-donating groups were compatible with the catalytic conditions in a lower temperature of 70 °C (Table 3, Entries 1~9). As for the substitution pattern, α -bromo aryl ketones bearing a *meta*- or *ortho*-methoxyl substituent **2k** and **2l** also worked well in the reaction to generate the desired products **3i** and **3j**, respectively (Table 3, Entries 4 and 5). To demonstrate the practicality of the alkylation protocol, a gram scale reaction also proceeded smoothly to give the corresponding C8-alkylated product **3f** in 74% yield. Besides the α -bromo aryl ketones, a α -bromo alkyl ketone, 1-bromopropan-2-one (**2q**), could also be effectively employed as the coupling partners in the reaction to provide the corresponding product **3o** in 56% yield in a lower temperature of 50 °C (Table 3, Entry 10).

With the goal of illustrating the utility of this methodology in the preparation of medicinal compounds, we chose the two target molecules 2,3-dihydro-1*H*-benzo[*de*]quinoline and benzo[*cd*]indol-2(1*H*)-one, which are high-value core structures of aporphine and aristolactam alkaloids. Compound **3a** was synthesized via C—H alkylation between naphthylquinoline-2-carboxamide (**1a**) and ethyl 2-bromoacetate (**2a**) with a yield of 86% followed by reduction of the ester in compound **3a** with LiAlH₄ in tetrahydrofuran (THF) giving alcohol **4a** in 65% yield (Scheme 3). Protection of the resulting alcohol **4a** with TsCl gave **5a** in 56% yield. Deprotection of naphthalen-1-amide and cyclization in one step using NaH in THF produced 2,3-dihydro-1*H*-benzo[*de*]quinoline (**6a**) in 72% yield. Finally, methylation of the cyclized substrate **6a** gave target molecule **7a** in 62% yield using CH₃I. Accordingly, compound **7a** was synthesized from **1a** in five steps in a total yield of 14%. It was worth mentioning that *N*-(phenanthren-10-yl)quinoline-2-carboxamide (**1a'**) was also compatible with the synthetic strategy to afford the desired aporphine alkaloid skeleton **7a'** in five steps in a total yield of 16% (Scheme 3).

Next, we sought to apply our methods to the late-stage diversification of drug molecules further. Compound **3f** was synthesized via C—H alkylation between naphthylquinoline-2-carboxamide (**1a**) and 2-bromo-1-phenylethanone (**2h**) with a yield of 82% (Scheme 4). To remove the amide protection group for further elaboration, the alkylated substrate **3f** was hydrolyzed by treatment with LiOH/H₂O₂.^[12] Surprisingly, the lactam **4f** was generated in 80% yield through a sequential benzylic oxidation/cyclization with oxidative C—C cleavage^[13] probably. Accordingly, the lactam **4f** was synthesized from **1a** in two steps in a total yield of 66%. In addition, the lactam **4f** could also be obtained in 60% yield when the alkylated substrate **3g** was employed in place of **3f**, indicating that

Table 3 Scope of the α -bromo ketones ^a

Entry	α -Bromo ketones	Product	Yield ^b /%	Entry	α -Bromo ketones	Product	Yield ^b /%
1		3f	82 (74 ^c)	6		3k	70
2		3g	79	7		3l	78
3		3h	64	8		3m	71
4		3i	55	9		3n	52
5		3j	76	10 ^d		3o	56

^a Reaction conditions: **1a** (0.25 mmol, 75 mg), $\text{Pd}(\text{OAc})_2$ (0.025 mmol, 6 mg), α -bromo ketones (0.5 mmol), PhCOOK (0.25 mmol, 40 mg), DCE (2 mL), 70 °C, 12 h. ^b Isolated yields based on **1a**. ^c Isolated yield on a 3.34 mmol scale. ^d Reaction at 50 °C.

Scheme 3 Synthesis of the core structures of aporphine alkaloids

removal of benzoyl group is a highly probable step for cyclization to proceed. Furthermore, *N*-(phenanthren-10-yl)quinoline-2-carboxamide (**1a'**) was also compatible with the synthetic method to give the desired aristolactam alka-

loids skeleton **4f'** in two steps in a total yield of 22.5% (Scheme 4).

Based on the previous studies,^[3a,8,11,14] the plausible reaction mechanism was proposed as shown in Scheme 5.

Scheme 4 Synthesis of the core structures of aristolactam alkaloids

Scheme 5 Plausible catalytic cycle

First, intermediate **A** was formed by the coordination of substrate **1a** to Pd(II) species in the presence of base, which underwent reversible cyclometalation to give Pd(II) intermediate **B**, probably via a concerted metalation-deprotonation mechanism. The intermediate **C** underwent oxidative addition with α -bromo esters or α -bromo ketones to produce the Pd(IV) intermediate **C**, which was followed by a reductive elimination to result in the alkylation products **3** and regenerated the catalyst.

3 Conclusions

In summary, we have developed a practical methodology for the Pd-catalyzed quinoline-2-carboxamide directed C8 alkylation of 1-naphthylamides with functionalized alkyl halides. A broad range of α -bromo esters as well as α -bromo ketones are competent reagents in this transformation. In particular, the alkylated product with these ester and carbonyl groups can readily be further converted into the core structures of aporphine and aristolactam alkaloids respectively, providing a novel synthetic method for constructing the skeleton of these alkaloids.

4 Experimental section

4.1 General methods

Unless otherwise noted, the reactions were performed under air in oven-dried glassware. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker spectrometer (400, 500 or 600 MHz). Chemical shifts were reported in δ units relative to internal standard TMS (δ 0) for ¹H NMR (CDCl₃ or DMSO-*d*₆), ¹³C NMR (center peak is δ 77.00 in CDCl₃ or δ 39.90 in DMSO-*d*₆). High resolution mass spectra (HRMS) were performed on a microTOF-Q II mass spectrometry with ESI source or a LTQ-Orbitrap XL mass spectrometry with ESI or APCI source. Amide derivatives **1a** and **1b**^[3,15] and *N*-(phenanthren-10-yl)quinoline-2-carboxamide (**1a'**)^[16] were synthesized according to the literature procedure. *N*-(Naphthalen-1-yl)benzamide (**1c**)^[17] and *tert*-butyl naphthalen-1-ylcarbamate (**1d**)^[18] were prepared by known method. Palladium catalysts (>98% purity) were purchased from Alfa Aesar and other reagents (solvents, bases, α -halo esters/ketones *etc.*) were purchased from Energy Chemical (>95% purity) and used without further purification.

4.2 Preparation of amide compounds **1a** and **1b**^[3,15]

Picolinic acid or quinoline-2-carboxylic acid (20 mmol), naphthalen-1-amine (20 mmol, 2.86 g) and Et₃N (40 mmol, 5.6 mL) were dissolved in CH₂Cl₂ (40 mL) followed by addition of POCl₃ (3.76 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. Subsequently, the reaction was performed at room temperature for about 2 h until naphthalen-1-amine was consumed completely. At the conclusion of the reaction, the reaction mixture was allowed to cool to 0 °C, and ice-water was added slowly to quench the reaction. The organic layer was collected, and the aqueous phase was extracted with CH₂Cl₂ (20 mL $\times$ 3). The combined organic phase was washed with saturated NaHCO₃ (40 mL $\times$ 2) and dried over MgSO₄. The solvent was evaporated under reduced pressure and the residue was crystallized from CH₂Cl₂/petroleum ether to give the desired product.

N-(Naphthalen-1-yl)quinoline-2-carboxamide (**1a**):^[3] 4.29 g, 72% yield. Pink solid, m.p. 146~147 °C (lit.^[3] 146~147 °C); ¹H NMR (400 MHz, CDCl₃) δ : 10.95 (s, 1H), 8.43 (d, *J*=8.4 Hz, 2H), 8.36 (d, *J*=8.0 Hz, 1H), 8.25 (d, *J*=8.4 Hz, 1H), 8.16 (d, *J*=8.4 Hz, 1H), 7.91 (d, *J*=

8.0 Hz, 2H), 7.81 (t, $J=7.2$ Hz, 1H), 7.71 (d, $J=8.4$ Hz, 1H), 7.59 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 162.4, 149.9, 146.3, 138.0, 134.2, 132.5, 130.4, 129.9, 129.5, 128.9, 128.2, 127.9, 126.5, 126.3, 126.1, 126.0, 125.1, 120.5, 118.8, 118.7; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 299.1179, found 299.1182.

N-(Naphthalen-1-yl)picolinamide (**1b**):^[3] 2.98 g, 60% yield. pink solid, m.p. 128~129 °C (lit.^[3] 128~129 °C); ^1H NMR (400 MHz, CDCl_3) δ : 10.75 (s, 1H), 8.70 (d, $J=5.2$ Hz, 1H), 8.41 (d, $J=7.2$ Hz, 1H), 8.36 (d, $J=7.6$ Hz, 1H), 8.09 (d, $J=8.4$ Hz, 1H), 7.91 (m, 2 H), 7.70 (d, $J=8.4$ Hz, 1H), 7.55 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 162.3, 150.1, 148.2, 137.8, 134.1, 132.4, 128.8, 126.5, 126.4, 126.3, 126.0, 125.9, 125.0, 122.5, 120.5, 118.6; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 249.1022, found 249.1020.

4.3 Preparation of *N*-(phenanthren-9-yl)quinoline-2-carboxamide (**1a'**)

Step 1: To a solution of quinoline-2-carboxylic acid (3.46 g, 20 mmol, 1 equiv.) and $(\text{Boc})_2\text{O}$ (5.68 g, 26 mmol, 1.3 equiv.) in dioxane (100 mL), was added pyridine (2 mL). After stirring for 10 min, NH_4HCO_3 (2.06 g, 26 mmol, 1.3 equiv.) was added portionwise and then the mixture was stirred for 24 h at room temperature. After completion, the solvent was removed and the residue was dissolved by EtOAc (200 mL). The organic layers was washed with saturated NaHCO_3 (80 mL $\times$ 3) and water (80 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford quinoline-2-carboxamide,^[16a] 2.96 g, 86% yield. White solid, m.p. 126~128 °C (lit.^[16a] 118~120 °C); ^1H NMR (400 MHz, CDCl_3) δ : 8.31 (d, $J=8.4$ Hz, 1H), 8.25 (d, $J=8.4$ Hz, 1H), 8.18 (s, 1H), 8.08 (d, $J=8.4$ Hz, 1H), 7.82 (d, $J=8.4$ Hz, 1H), 7.72 (t, $J=7.6$ Hz, 1H), 7.58 (t, $J=7.6$ Hz, 1H), 6.92 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 167.5, 149.5, 146.6, 137.4, 130.1, 129.8, 129.3, 128.0, 127.7, 118.8.

Step 2: A mixture of quinoline-2-carboxamide (1.72 g, 10.0 mmol, 1.0 equiv.), phenanthren-9-ylboronic acid (4.44 g, 20.0 mmol, 2.0 equiv.), $\text{Cu}(\text{OAc})_2$ (1.99 g, 11 mmol, 1.1 equiv.) and pyridine (1.58 g, 20.0 mmol, 2.0 equiv.) in CH_2Cl_2 (40 mL) was stirred for 12 h at room temperature. The reaction mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel flash chromatography with dichloromethane/petroleum ether to afford the desired product in 30% yield.

N-(Phenanthren-9-yl)quinoline-2-carboxamide (**1a'**): 1.04 g, 30% yield. Yellow solid, m.p. 191~193 °C; ^1H NMR (500 MHz, CDCl_3) δ : 10.96 (s, 1H), 8.74 (m, 2H), 8.61 (m, 1H), 8.44 (d, $J=8.0$ Hz, 1H), 8.36 (d, $J=8.5$ Hz, 1H), 8.25 (d, $J=8.0$ Hz, 1H), 8.21 (d, $J=8.5$ Hz, 1H), 7.91 (m, 2H), 7.81 (t, $J=8.0$ Hz, 1H), 7.72 (m, 2H), 7.61 (m, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ : 162.6, 149.9, 146.3, 138.0, 132.1, 131.2, 130.4, 130.3, 129.9, 129.6, 128.8, 128.4, 128.2, 127.9, 127.1, 127.0, 126.8, 126.6, 126.1, 123.6, 122.4, 121.0, 118.8, 118.5; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{17}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 349.1335, found 349.1337.

4.4 Typical procedure for alkylation products **3a**~**3o**, **3a'**, **3f'**

A mixture of amide **1** (0.25 mmol, 1.0 equiv.), alkyl halide (0.5 mmol, 2.0 equiv.), $\text{Pd}(\text{OAc})_2$ (0.025 mmol, 10 mol%), PhCOOK (1.0 or 2.0 equiv.), and 1,2-dichloroethane (2.0 mL) was placed in a 35 mL pressure tube with PTFE cap under air. The tube was heated at 70, 90 or 130 °C for 12, 24 or 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (5 mL), filtered through celite, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with ethyl acetate/petroleum ether to afford the desired product.

4.5 Typical procedure for alkylation products **3a** and **3f** on a one-gram scale

A mixture of amide **1** (3.34 mmol, 1.0 equiv.), alkyl halide (6.68 mmol, 2.0 equiv.), $\text{Pd}(\text{OAc})_2$ (0.334 mmol, 10 mol%), PhCOOK (1.0 or 2.0 equiv.) and 1,2-dichloroethane (26.72 mL) was placed in a 100 mL round-bottom flask under air. The flask was refluxed for 12 or 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (25 mL), filtered through celite, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with ethyl acetate/petroleum ether to afford the desired product.

Ethyl 2-(8-quinoline-2-carboxamido)naphthalen-1-yl)-acetate (**3a**): 83 mg, 86% yield. White solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V:V=1:6$), m.p. 128~129 °C; ^1H NMR (400 MHz, CDCl_3) δ : 10.87 (s, 1H), 8.44 (d, $J=8.0$ Hz, 1H), 8.39 (d, $J=8.0$ Hz, 1H), 8.15 (d, $J=8.0$ Hz, 1H), 7.93 (d, $J=8.0$ Hz, 1H), 7.83 (m, 4H), 7.66 (t, $J=6.8$ Hz, 1H), 7.55 (t, $J=7.4$ Hz, 1H), 7.41 (t, $J=7.2$ Hz, 1H), 7.34 (d, $J=6.4$ Hz, 1H), 4.34 (s, 2H), 4.11 (q, $J=6.8$ Hz, 2H), 0.97 (t, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 172.8, 164.1, 150.2, 146.6, 137.7, 136.2, 132.5, 131.2, 130.3, 129.7, 129.5, 129.4, 129.2, 129.0, 128.6, 128.2, 127.9, 127.0, 125.5, 125.3, 119.3, 61.1, 42.0, 13.8. HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{21}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 385.1547, found 385.1549.

Benzyl 2-(8-(quinoline-2-carboxamide)naphthalen-1-yl)acetate (**3b**): 73 mg, 66% yield. Light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V:V=1:6$), m.p. 175~176 °C; ^1H NMR (400 MHz, CDCl_3) δ : 10.86 (s, 1H), 8.41 (d, $J=8.0$ Hz, 1H), 8.34 (d, $J=8.4$ Hz, 1H), 8.06 (d, $J=8.4$ Hz, 1H), 7.88 (m, 3H), 7.81 (d, $J=7.2$ Hz, 1H), 7.73 (t, $J=7.2$ Hz, 1H), 7.64 (t, $J=7.2$ Hz, 1H), 7.56 (t, $J=8.0$ Hz, 1H), 7.41 (t, $J=7.2$ Hz, 1H), 7.35 (d, $J=6.8$ Hz, 1H), 7.17 (m, 3H), 6.98 (d, $J=6.8$ Hz, 2H), 5.06 (s, 2H), 4.41 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 172.6, 164.1, 150.1, 146.6, 137.7, 136.2, 135.3, 132.4, 131.4, 130.3, 129.8, 129.6, 129.4, 129.1, 129.0, 128.7, 128.3, 128.1, 128.0, 127.8, 127.7, 127.1, 125.6, 125.3, 119.2, 66.8, 41.9. HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{23}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 447.1703, found 447.1690.

tert-Butyl 2-(8-(quinoline-2-carboxamide)naphthalen-1-yl)acetate (**3c**): 74 mg, 72% yield. Light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V:V=1:6$), m.p. 113~114 °C; ^1H NMR (400 MHz, CDCl_3) δ : 11.11 (s, 1H), 8.42 (d, $J=8.4$ Hz, 1H), 8.35 (d, $J=8.4$ Hz, 1H), 8.19 (d, $J=8.8$ Hz, 1H), 7.90 (t, $J=8.0$ Hz, 2H), 7.79 (m, 3H), 7.62 (t, $J=7.4$ Hz, 1H), 7.53 (t, $J=7.6$ Hz, 1H), 7.37 (m, 2H), 4.35 (s, 2H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 171.8, 164.0, 150.4, 146.6, 137.7, 136.2, 132.6, 131.0, 130.1, 130.0, 129.8, 129.4, 128.5, 128.4, 128.1, 127.8, 126.5, 125.5, 125.3, 119.4, 81.5, 43.3, 28.0. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 413.1860, found 413.1864.

Methyl 2-(8-(quinoline-2-carboxamido)naphthalen-1-yl)acetate (**3d**):^[11] 56 mg, 61% yield. White solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V:V=1:6$), m.p. 170~171 °C (lit.^[11] 162~163 °C); ^1H NMR (400 MHz, CDCl_3) δ : 10.81 (s, 1H), 8.43 (d, $J=8.0$ Hz, 1H), 8.37 (d, $J=8.4$ Hz, 1H), 8.14 (d, $J=8.4$ Hz, 1H), 7.91 (d, $J=7.6$ Hz, 1H), 7.81 (m, 4H), 7.64 (t, $J=7.2$ Hz, 1H), 7.55 (t, $J=7.2$ Hz, 1H), 7.40 (t, $J=7.2$ Hz, 1H), 7.33 (d, $J=6.4$ Hz, 1H), 4.35 (s, 2H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 173.1, 164.1, 150.2, 146.6, 137.7, 136.2, 132.4, 131.3, 130.3, 129.7, 129.6, 129.5, 129.1, 129.0, 128.7, 128.2, 127.9, 127.1, 125.6, 125.3, 119.3, 52.3, 41.8. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 371.1390, found 371.1392.

N-(8-Benzyl)naphthalen-1-yl)quinoline-2-carboxamide (**3e**): 77 mg, 80% yield. Light yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V:V=1:6$), m.p. 170~171 °C; ^1H NMR (400 MHz, CDCl_3) δ : 10.21 (s, 1H), 8.30 (s, 2H), 7.85 (m, 4H), 7.79 (d, $J=7.6$ Hz, 1H), 7.75 (t, $J=7.2$ Hz, 1H), 7.61 (t, $J=7.6$ Hz, 1H), 7.52 (t, $J=7.8$ Hz, 1H), 7.41 (t, $J=7.2$ Hz, 1H), 7.26 (d, $J=6.8$ Hz, 1H), 7.13 (t, $J=7.6$ Hz, 1H), 7.06 (t, $J=7.6$ Hz, 2H), 6.80 (d, $J=7.2$ Hz, 2H), 4.71 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.3, 149.8, 146.3, 141.2, 137.6, 136.2, 134.4, 132.6, 131.4, 130.1, 130.0, 129.4, 129.1, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8, 126.5, 126.0, 125.7, 125.5, 119.1, 42.2. HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{21}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 389.1648, found 389.1642.

N-(8-(2-oxo-2-Phenylethyl)naphthalen-1-yl)quinoline-2-carboxamide (**3f**): 85 mg, 82% yield. Brown solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V:V=1:4$), m.p. 146~147 °C; ^1H NMR (600 MHz, CDCl_3) δ : 10.31 (s, 1H), 8.25 (d, $J=7.8$ Hz, 1H), 8.18 (d, $J=9.0$ Hz, 1H), 7.88 (t, $J=8.4$ Hz, 2H), 7.77 (m, 3H), 7.71 (d, $J=7.2$ Hz, 1H), 7.54 (m, 4H), 7.42 (t, $J=7.2$ Hz, 1H), 7.26 (d, $J=6.6$ Hz, 1H), 7.07 (t, $J=7.2$ Hz, 1H), 6.97 (t, $J=7.8$ Hz, 2H), 4.93 (s, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ : 198.9, 164.2, 149.4, 146.1, 137.5, 136.5, 136.2, 132.5, 131.6, 130.1, 130.0, 129.9, 129.8, 129.3, 129.2, 129.1, 128.2, 128.1, 128.0, 127.9, 127.5, 127.3, 125.6, 125.5, 118.9, 46.4. HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{21}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 417.1598, found 417.1589.

N-(8-(2-oxo-2-(*p*-Tolyl)ethyl)naphthalen-1-yl)quinoline-

2-carboxamide (**3g**): 85 mg, 79% yield. Brown solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V:V=1:4$), m.p. 164~165 °C; ^1H NMR (500 MHz, CDCl_3) δ : 10.26 (s, 1H), 8.25 (d, $J=8.0$ Hz, 1H), 8.19 (d, $J=8.5$ Hz, 1H), 7.87 (t, $J=8.5$ Hz, 2H), 7.77 (d, $J=8.0$ Hz, 1H), 7.65 (d, $J=7.5$ Hz, 3H), 7.53 (m, 4H), 7.42 (t, $J=7.5$ Hz, 1H), 7.25 (d, $J=6.5$ Hz, 1H), 6.71 (d, $J=8.0$ Hz, 2H), 4.88 (s, 2H), 2.02 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 198.2, 164.2, 149.5, 146.1, 143.3, 137.2, 136.1, 134.0, 132.5, 131.5, 130.1, 130.0, 129.9, 129.5, 129.2, 129.0, 128.8, 128.1, 127.8, 127.3, 127.2, 125.4, 118.8, 46.1, 21.3; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{23}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 431.1754, found 431.1741.

N-(8-(2-(4-Methoxyphenyl)-2-oxoethyl)naphthalen-1-yl)quinoline-2-carboxamide (**3h**): 71 mg, 64% yield. Brown solid after purification by column chromatography (eluent, dichloromethane/petroleum ether, $V:V=1:3$), m.p. 120~121 °C; ^1H NMR (600 MHz, CDCl_3) δ : 10.31 (s, 1H), 8.26 (d, $J=8.4$ Hz, 1H), 8.20 (d, $J=8.4$ Hz, 1H), 7.87 (t, $J=8.4$ Hz, 2H), 7.79 (d, $J=7.2$ Hz, 1H), 7.74 (d, $J=9.0$ Hz, 2H), 7.68 (d, $J=7.8$ Hz, 1H), 7.56 (m, 4H), 7.42 (t, $J=7.2$ Hz, 1H), 7.26 (d, $J=6.6$ Hz, 1H), 6.40 (d, $J=8.4$ Hz, 2H), 4.86 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 197.3, 164.3, 163.1, 149.6, 146.2, 137.4, 136.2, 132.5, 131.6, 130.3, 130.2, 130.1, 129.7, 129.6, 129.3, 129.2, 129.1, 127.9, 127.4, 125.5, 119.0, 113.3, 55.3, 46.0; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{23}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 447.1703, found 447.1691.

N-(8-(2-(3-Methoxyphenyl)-2-oxoethyl)naphthalen-1-yl)quinoline-2-carboxamide (**3i**): 61 mg, 55% yield. Brown solid after purification by column chromatography (eluent, dichloromethane/petroleum ether, $V:V=1:3$), m.p. 148~149 °C; ^1H NMR (500 MHz, CDCl_3) δ : 10.25 (s, 1H), 8.25 (d, $J=8.5$ Hz, 1H), 8.19 (d, $J=8.5$ Hz, 1H), 7.88 (t, $J=7.0$ Hz, 2H), 7.77 (d, $J=7.5$ Hz, 1H), 7.68 (d, $J=7.5$ Hz, 1H), 7.56 (m, 4H), 7.42 (t, $J=7.5$ Hz, 1H), 7.31 (s, 2H), 7.25 (s, 1H), 6.80 (t, $J=8.0$ Hz, 1H), 6.55 (d, $J=7.5$ Hz, 1H), 4.90 (s, 2H), 3.61 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 198.3, 164.1, 159.3, 149.4, 146.0, 137.8, 137.3, 136.1, 132.4, 131.5, 130.0, 129.9, 129.8, 129.6, 129.2, 129.1, 129.0, 128.9, 127.8, 127.3, 127.2, 125.4, 125.3, 120.5, 118.7, 112.3, 55.1, 46.4; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{23}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 447.1703, found 447.1691.

N-(8-(2-(2-Methoxyphenyl)-2-oxoethyl)naphthalen-1-yl)quinoline-2-carboxamide (**3j**): 85 mg, 76% yield. Brown solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether/dichloromethane, $V:V:V=1:6:0.04$), m.p. 147~148 °C; ^1H NMR (500 MHz, CDCl_3) δ : 10.43 (s, 1H), 8.30 (d, $J=8.0$ Hz, 1H), 8.22 (d, $J=9.0$ Hz, 1H), 7.84 (m, 3H), 7.77 (d, $J=7.5$ Hz, 2H), 7.54 (t, $J=7.5$ Hz, 1H), 7.45 (m, 3H), 7.39 (t, $J=7.0$ Hz, 1H), 7.20 (d, $J=6.5$ Hz, 1H), 7.08 (t, $J=8.5$ Hz, 1H), 6.81 (t, $J=7.5$ Hz, 1H), 6.27 (d, $J=9.0$ Hz, 1H), 4.92 (s, 2H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ : 200.8, 163.6, 158.6, 149.7, 146.1, 137.1, 136.0, 133.5, 132.5, 131.0, 130.9, 129.9, 129.7, 129.6, 129.0, 128.9, 128.6, 127.8, 127.6, 127.2, 126.6, 125.4, 125.3, 120.4,

118.7, 110.8, 54.7, 52.1; HRMS (ESI) calcd for $C_{29}H_{23}N_2O_3$ $[M+H]^+$ 447.1703, found 447.1691.

N-(8-(2-(4-Bromophenyl)-2-oxoethyl)naphthalen-1-yl)quinoline-2-carboxamide (**3k**): 86 mg, 70% yield. Brown solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether/dichloromethane, $V:V:V=1:8:0.04$), m.p. 180~181 °C; 1H NMR (500 MHz, $CDCl_3$) δ : 10.10 (s, 1H), 8.21 (d, $J=8.5$ Hz, 1H), 8.19 (d, $J=8.5$ Hz, 1H), 7.88 (t, $J=7.0$ Hz, 2H), 7.82 (d, $J=7.5$ Hz, 1H), 7.59 (m, 7 H), 7.43 (t, $J=7.5$ Hz, 1H), 7.24 (d, $J=7.0$ Hz, 1H), 6.96 (d, $J=6.5$ Hz, 2H), 4.83 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 197.1, 164.1, 149.2, 146.0, 137.5, 136.1, 135.0, 132.2, 131.7, 131.2, 130.1, 130.0, 129.5, 129.4, 129.3, 129.2, 129.1, 128.2, 127.8, 127.7, 127.5, 125.5, 125.4, 118.7, 46.5; HRMS (ESI) calcd for $C_{28}H_{20}BrN_2O_2$ $[M+H]^+$ 495.0703, found 495.0708.

N-(8-(2-(4-Chlorophenyl)-2-oxoethyl)naphthalen-1-yl)quinoline-2-carboxamide (**3l**): 88 mg, 78 % yield. Brown solid after purification by column chromatography (eluent, dichloromethane/petroleum ether, $V:V=1:3$), m.p. 181~182 °C; 1H NMR (500 MHz, $CDCl_3$) δ : 10.11 (s, 1H), 8.21 (s, 2H), 7.89 (t, $J=7.5$ Hz, 2H), 7.82 (t, $J=7.5$ Hz, 1H), 7.61 (m, 6H), 7.54 (t, $J=8.0$ Hz, 1H), 7.43 (t, $J=7.0$ Hz, 1H), 7.25 (d, $J=6.0$ Hz, 1H), 6.82 (d, $J=9.0$ Hz, 2H), 4.85 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 197.0, 164.1, 149.2, 146.0, 139.0, 137.4, 136.1, 134.7, 132.3, 131.6, 130.1, 129.9, 129.5, 129.4, 129.3, 129.2, 129.1, 128.2, 128.1, 127.6, 127.4, 125.5, 125.4, 118.7, 46.4; HRMS (ESI) calcd for $C_{28}H_{20}ClN_2O_2$ $[M+H]^+$ 451.1208, found 451.1184.

N-(8-(2-(4-Fluorophenyl)-2-oxoethyl)naphthalen-1-yl)quinoline-2-carboxamide (**3m**): 77 mg, 71% yield. Brown solid after purification by column chromatography (eluent, dichloromethane/petroleum ether, $V:V=1:3$), m.p. 185~186 °C; 1H NMR (500 MHz, $CDCl_3$) δ : 10.18 (s, 1H), 8.24 (d, $J=8.5$ Hz, 1H), 8.20 (d, $J=8.5$ Hz, 1H), 7.88 (t, $J=7.0$ Hz, 2H), 7.80 (d, $J=7.5$ Hz, 1H), 7.75 (t, $J=6.0$ Hz, 2H), 7.67 (d, $J=7.0$ Hz, 1H), 7.61 (m, 3H), 7.54 (t, $J=8.5$ Hz, 1H), 7.42 (d, $J=7.5$ Hz, 1H), 7.25 (d, $J=7.0$ Hz, 1H), 6.56 (t, $J=8.0$ Hz, 2H), 4.87 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 196.8, 165.2 (d, $J=253.0$ Hz), 164.0, 149.4, 146.0, 137.4, 136.1, 132.9 (d, $J=2.9$ Hz), 132.4, 131.5, 130.5, 130.4, 130.0, 129.8, 129.6, 129.5, 129.3, 129.1, 129.0, 128.1, 127.5, 127.3, 125.4 (d, $J=7.9$ Hz), 118.8, 115.0 (d, $J=21.5$ Hz), 46.3; HRMS (ESI) calcd for $C_{28}H_{20}FN_2O_2$ $[M+H]^+$ 435.1503, found 435.1504.

N-(8-(2-oxo-2-(4-(Trifluoromethyl)phenyl)ethyl)naphthalen-1-yl)quinoline-2-carboxamide (**3n**): 63 mg, 52% yield. Brown solid after purification by column chromatography (eluent, dichloromethane/petroleum ether, $V:V=1:3$), m.p. 178~179 °C; 1H NMR (500 MHz, $CDCl_3$) δ : 10.07 (s, 1H), 8.18 (d, $J=8.5$ Hz, 1H), 8.14 (d, $J=8.5$ Hz, 1H), 7.90 (dd, $J=8.0, 3.5$ Hz, 2H), 7.76 (m, 3H), 7.64 (d, $J=7.0$ Hz, 1H), 7.57 (m, 4H), 7.44 (t, $J=7.5$ Hz, 1H), 7.26 (d, $J=6.0$ Hz, 1H), 7.08 (d, $J=8.0$ Hz, 2H), 4.90 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 197.0, 164.0,

149.1, 145.8, 138.9, 137.5, 136.1, 133.5 (q, $J=32.8$ Hz), 132.2, 131.7, 130.1, 130.0, 129.5, 129.3, 129.2, 129.1, 129.0, 128.2, 128.1, 127.6, 127.5, 125.5, 125.4, 124.9 (q, $J=3.6$ Hz), 123.2 (q, $J=270.6$ Hz), 118.6, 46.9; HRMS (ESI) calcd for $C_{29}H_{20}F_3N_2O_2$ $[M+H]^+$ 485.1471, found 485.1439.

N-(8-(2-Oxopropyl)naphthalen-1-yl)quinoline-2-carboxamide (**3o**): 50 mg, 56% yield. Brown solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V:V=1:6$), m.p. 179~180 °C; 1H NMR (600 MHz, $CDCl_3$) δ : 10.52 (s, 1H), 8.44 (d, $J=7.8$ Hz, 1H), 8.39 (d, $J=8.4$ Hz, 1H), 8.19 (d, $J=8.4$ Hz, 1H), 7.94 (d, $J=8.4$ Hz, 1H), 7.85 (d, $J=8.4$ Hz, 2H), 7.81 (t, $J=7.2$ Hz, 1H), 7.75 (d, $J=7.2$ Hz, 1H), 7.67 (t, $J=7.2$ Hz, 1H), 7.54 (t, $J=7.8$ Hz, 1H), 7.41 (t, $J=7.8$ Hz, 1H), 7.23 (d, $J=7.8$ Hz, 1H), 4.41 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ : 208.0, 164.0, 150.0, 146.6, 137.9, 137.8, 136.2, 132.5, 131.3, 130.5, 129.9, 129.6, 129.5, 128.8, 128.4, 128.0, 127.2, 125.7, 125.5, 119.3, 51.2, 30.4; HRMS (ESI) calcd for $C_{23}H_{19}N_2O_2$ $[M+H]^+$ 355.1441, found 355.1444.

Ethyl 2-(10-(quinoline-2-carboxamido)phenanthren-1-yl)acetate (**3a'**): 78 mg, 72% yield. White solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V:V=1:4$), m.p. 134~138 °C; 1H NMR (500 MHz, $CDCl_3$) δ : 10.81 (s, 1H), 8.79 (d, $J=8.0$, 1H), 8.68 (d, $J=8.0$ Hz, 1H), 8.46 (d, $J=8.0$, 1H), 8.40 (d, $J=9.0$ Hz, 1H), 8.17 (d, $J=8.5$ Hz, 1H), 8.13 (s, 1H), 7.93 (d, $J=8.0$ Hz, 1H), 7.89 (d, $J=7.0$ Hz, 1H), 7.79 (t, $J=7.5$ Hz, 1H), 7.63 (m, 4H), 7.45 (d, $J=6.5$ Hz, 1H), 4.40 (s, 2H), 4.08 (q, $J=7.0$ Hz, 2H), 0.94 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 172.6, 164.0, 150.2, 146.5, 137.8, 133.1, 132.0, 131.4, 130.7, 130.3, 130.1, 130.0, 129.7, 129.5, 128.5, 128.3, 128.2, 127.9, 127.1, 127.0, 126.9, 126.2, 123.5, 123.0, 119.3, 61.1, 42.4, 13.8; HRMS (ESI) calcd for $C_{28}H_{23}N_2O_3$ $[M+H]^+$ 435.1703, found 435.1698.

N-(8-(2-oxo-2-phenylethyl)phenanthren-9-yl)quinoline-2-carboxamide (**3f'**): 87 mg, 75% yield. yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V:V=1:4$), m.p. 176~177 °C; 1H NMR (500 MHz, $CDCl_3$) δ : 10.28 (s, 1H), 8.77 (d, $J=8.5$ Hz, 1H), 8.68 (d, $J=8.5$ Hz, 1H), 8.22 (d, $J=8.5$ Hz, 1H), 8.13 (d, $J=8.5$ Hz, 1H), 8.03 (s, 1H), 7.85 (d, $J=7.5$ Hz, 1H), 7.72 (m, 3H), 7.58 (m, 6H), 7.35 (d, $J=7.5$ Hz, 1H), 7.03 (t, $J=7.5$ Hz, 1H), 6.91 (t, $J=7.5$, 2H), 4.96 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ : 198.4, 164.0, 149.3, 146.0, 137.4, 136.4, 133.0, 132.4, 132.2, 131.4, 130.7, 130.6, 130.2, 129.8, 129.7, 129.2, 129.1, 128.3, 128.0, 127.9, 127.8, 127.4, 127.2, 127.0, 126.9, 126.2, 123.2, 123.0, 118.7, 46.8; HRMS (ESI) calcd for $C_{32}H_{23}N_2O_2$ $[M+H]^+$ 467.1754, found 467.1746.

4.6 Preparation of *N*-(8-(2-hydroxyethyl)naphthalen-1-yl)quinoline-2-carboxamide (**4a**) and *N*-(8-(2-hydroxyethyl)phenanthren-9-yl)quinoline-2-carboxamide (**4a'**)

To a stirred solution of product **3a** or **3a'** (1.2 mmol) in

10 mL of anhydrous THF was added LiAlH₄ (228 mg, 6.0 mmol) at 0 °C in small portions over a period of 5 min. Subsequently, the reaction was performed at 0 °C for about 1 h until the starting materials were consumed completely. Then, the reaction was quenched by adding ice-water (5 mL) slowly, and then 20% NaOH (0.5 mL) was added to the reaction solution. The solution was extracted with EtOAc (10 mL×3). The combined organic layer was washed with water (10 mL) and dried over Na₂SO₄. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography using ethyl acetate/petroleum ether as eluent to give the desired product **4a** or **4a'**.

N-(8-(2-Hydroxyethyl)naphthalen-1-yl)quinoline-2-carboxamide (**4a**): 267 mg, 65% yield. Light green solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, *V*: *V*=1:4), m.p. 141~143 °C; ¹H NMR (600 MHz, CD₃Cl) δ: 11.17 (s, 1H), 8.48 (d, *J*=9.0 Hz, 1H), 8.39 (d, *J*=8.4 Hz, 1H), 8.21 (d, *J*=8.4 Hz, 1H), 8.02 (d, *J*=7.8 Hz, 1H), 7.93 (d, *J*=7.8 Hz, 1H), 7.81 (t, *J*=7.2 Hz, 1H), 7.78 (m, 2H), 7.67 (t, *J*=7.2 Hz, 1H), 7.52 (t, *J*=7.8 Hz, 1H), 7.42 (t, *J*=7.8 Hz, 1H), 7.36 (d, *J*=6.6 Hz, 1H), 4.20 (t, *J*=6.0 Hz, 2H), 3.60 (t, *J*=6.0 Hz, 2H), 3.34 (s, 1H); ¹³C NMR (150 MHz, CD₃Cl) δ: 162.1, 150.1, 146.0, 137.6, 135.6, 134.1, 132.1, 130.2, 130.1, 129.0, 128.8, 128.1, 128.0, 127.8, 127.5, 127.4, 125.0, 124.8, 124.7, 119.3, 64.6, 38.2; HRMS (APCI) calcd for C₂₂H₁₉N₂O₂ [M+H]⁺ 343.1441, found 343.1432.

N-(8-(2-Hydroxyethyl)phenanthren-9-yl)quinoline-2-carboxamide (**4a'**): 376 mg, 80% yield. White solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, *V*: *V*=1:4), m.p. 150~153 °C; ¹H NMR (500 MHz, CD₃Cl) δ: 11.08 (s, 1H), 8.65 (d, *J*=8.5 Hz, 1H), 8.58 (d, *J*=8.0 Hz, 1H), 8.44 (d, *J*=8.5 Hz, 1H), 8.32 (d, *J*=8.5 Hz, 1H), 8.28 (s, 1H), 8.16 (d, *J*=8.5 Hz, 1H), 7.87 (d, *J*=8.5 Hz, 1H), 7.84 (d, *J*=8.5 Hz, 1H), 7.76 (t, *J*=7.5 Hz, 1H), 7.58 (m, 4H), 7.43 (d, *J*=7.0 Hz, 1H), 4.19 (t, *J*=6.0 Hz, 2H), 3.68 (s, 1H), 3.59 (t, *J*=6.0 Hz, 2H); ¹³C NMR (125 MHz, CD₃Cl) δ: 162.5, 150.6, 146.4, 138.1, 135.3, 132.8, 131.4, 131.3, 130.6, 129.6, 129.4, 129.1, 128.3, 128.2, 127.9, 127.8, 126.9, 126.5, 126.3, 124.9, 122.9, 122.4, 119.8, 64.9, 38.8; HRMS (ESI) calcd for C₂₆H₂₁N₂O₂ [M+H]⁺ 393.1598, found 393.1591.

4.7 Preparation of 2,3-dihydro-1*H*-benzo[*de*]quinoline (**6a**) and 5,6-dihydro-4*H*-dibenzo[*de,g*]quinoline (**6a'**)

Step 1: **4a** or **4a'** (0.8 mmol), DMAP (0.16 mmol, 20 mg), and Et₃N (6.4 mmol, 646 mg) were dissolved in CH₂Cl₂ (5 mL) followed by addition of TsCl (4.0 mmol, 763 mg) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 3.0~4.0 h until **4a** or **4a'** was consumed completely. Subsequently, the reaction was quenched by adding water. The organic layer was collected, and the aqueous phase was extracted with CH₂Cl₂ (10 mL×3). The combined organic phase was dried over

MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (eluent, ethyl acetate/petroleum ether, *V*: *V*=1:8 for **5a** or dichloromethane/petroleum ether, *V*: *V*=1:1 for **5a'**) to give the desired product **5a** (223 mg, 56%) as a yellow oil or **5a'** (197 mg, 45%) as a white solid.

Step 2: To a stirred solution of **5a** or **5a'** (0.4 mmol) in 5 mL of anhydrous THF at 0 °C was added NaH (48 mg, 2.0 mmol) slowly. The reaction mixture was performed at 50 °C for 12 h. Then, the reaction was quenched by adding water slowly. The solution was extracted with EtOAc (10 mL×3). The combined organic layer was dried over MgSO₄. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography using ethyl acetate/petroleum ether as eluent to give the desired product **6a** or **6a'**.

2,3-Dihydro-1*H*-benzo[*de*]quinoline (**6a**): 49 mg, 72% yield. Colorless oil after purification by column chromatography (eluent, ethyl acetate/petroleum ether, *V*: *V*=1:5); ¹H NMR (600 MHz, CD₃Cl) δ: 7.67 (d, *J*=8.4 Hz, 1H), 7.40 (t, *J*=7.8 Hz, 1H), 7.31 (t, *J*=7.8 Hz, 1H), 7.26 (d, *J*=8.4 Hz, 1H), 7.14 (d, *J*=6.6 Hz, 1H), 6.63 (d, *J*=7.8 Hz, 1H), 4.13 (s, 1H), 3.53 (t, *J*=6.0 Hz, 2H), 3.26 (t, *J*=6.0 Hz, 2H); ¹³C NMR (150 MHz, CD₃Cl) δ: 144.3, 134.6, 133.1, 126.7, 126.0, 125.8, 122.1, 121.7, 117.3, 106.9, 41.8, 30.7; HRMS (ESI) calcd for C₁₂H₁₂N [M+H]⁺ 170.0964, found 170.0962.

5,6-Dihydro-4*H*-dibenzo[*de,g*]quinoline (**6a'**):^[19] 75 mg, 86% yield. White solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, *V*: *V*=1:20), m.p. 127~128 °C (lit.^[19] 132~133 °C); ¹H NMR (500 MHz, CD₃Cl) δ: 8.42 (d, *J*=8.0 Hz, 2H), 7.52 (d, *J*=7.5 Hz, 1H), 7.47 (t, *J*=7.5 Hz, 1H), 7.38 (d, *J*=8.0 Hz, 1H), 7.28 (d, *J*=7.5 Hz, 1H), 7.23 (d, *J*=6.0 Hz, 1H), 6.70 (s, 1H), 4.10 (s, 1H), 3.42 (t, *J*=6.0 Hz, 2H), 3.18 (t, *J*=6.0 Hz, 2H); ¹³C NMR (125 MHz, CD₃Cl) δ: 141.4, 133.5, 133.4, 131.2, 126.9, 126.5, 126.0, 125.6, 124.8, 122.8, 122.7, 121.0, 104.1, 41.5, 30.7; HRMS (ESI) calcd for C₁₆H₁₄N [M+H]⁺ 220.1121, found 220.1117.

4.8 Preparation of 1-methyl-2,3-dihydro-1*H*-benzo[*de*]quinoline (**7a**) and 6-methyl-5,6-dihydro-4*H*-dibenzo[*de,g*]quinoline (**7a'**)

To a stirred solution of **6a** or **6a'** (0.25 mmol) in 2 mL of DMF was added KOH (14 mg, 0.25 mmol). After stirring 10 min, iodomethane (178 mg, 1.25 mmol) was added dropwise. The reaction mixture was performed at room temperature for 2~3 h. After completion, the reaction was diluted with water. The solution was extracted with EtOAc (5 mL×3). The organic layers were washed with water (10 mL), dried over anhydrous Na₂SO₄. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography using ethyl acetate/petroleum ether as eluent to give the desired product **7a** or **7a'**.

1-Methyl-2,3-dihydro-1*H*-benzo[*de*]quinoline (**7a**). 28 mg, 62% yield. Colorless oil after purification by column chromatography (eluent, ethyl acetate/petroleum ether,

$V: V=1:20$); ^1H NMR (600 MHz, CD_3Cl) δ : 7.64 (d, $J=8.4$ Hz, 1H), 7.37 (t, $J=7.8$ Hz, 2H), 7.24 (t, $J=8.4$ Hz, 1H), 7.12 (d, $J=7.2$ Hz, 1H), 6.61 (s, 1H), 3.41 (t, $J=6.0$ Hz, 2H), 3.28 (t, $J=6.0$ Hz, 2H), 3.04 (s, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ : 145.9, 134.4, 132.8, 126.8, 125.8, 125.7, 122.4, 122.2, 117.1, 104.6, 50.9, 40.3, 30.7; HRMS (APCI) calcd for $\text{C}_{13}\text{H}_{14}\text{N}$ $[\text{M}+\text{H}]^+$ 184.1121, found 184.1115.

6-Methyl-5,6-dihydro-4*H*-dibenzo[*de,g*]quinoline (7a'): ^{19}F 42 mg, 72% yield. Yellow oil after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V: V=1:40$); ^1H NMR (500 MHz, CD_3Cl) δ : 8.43 (d, $J=8.5$ Hz, 2H), 7.62 (d, $J=8.0$ Hz, 1H), 7.47 (t, $J=7.5$ Hz, 1H), 7.39 (t, $J=7.5$ Hz, 1H), 7.29 (t, $J=7.5$ Hz, 1H), 7.23 (d, $J=7.0$ Hz, 1H), 6.67 (s, 1H), 3.33 (t, $J=6.0$ Hz, 2H), 3.23 (t, $J=6.0$ Hz, 2H), 3.03 (s, 3H); ^{13}C NMR (125 MHz, CD_3Cl) δ : 143.5, 133.8, 133.2, 131.0, 126.9, 126.7, 126.2, 125.2, 124.8, 123.4, 122.8, 122.6, 121.0, 102.3, 50.6, 40.4, 30.7; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{N}$ $[\text{M}+\text{H}]^+$ 234.1277, found 234.1271.

4.9 Preparation of benzo[*cd*]indol-2(1*H*)-one (4f) and dibenzo[*cd,f*]indol-4(5*H*)-one (4f')

To a stirred solution of 3f, 3g or 3f' (0.15 mmol) in 1.6 mL of THF at 0 °C was added H_2O (0.4 mL). The mixture was allowed to cool to 0 °C, $\text{LiOH}\cdot\text{H}_2\text{O}$ (48 mg, 1.15 mmol) and H_2O_2 (37%, 0.12 mL, 1.50 mmol) were added and the resulting mixture was stirred at room temperature for 24 h. After completion, the reaction was diluted with water. The solution was extracted with EtOAc (5 mL $\times$ 3). The organic layers were washed with water (5 mL), dried over anhydrous Na_2SO_4 . The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography using ethyl acetate/petroleum ether as eluent to give the desired product 4f or 4f'.

Benzo[*cd*]indol-2(1*H*)-one (4f): 20 mg, 80% yield. Yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V: V=1:5$), m.p. 176~177 °C (lit.^[4c] 173~176 °C); ^1H NMR (500 MHz, CDCl_3) δ : 8.75 (s, 1H), 8.11 (d, $J=7.0$ Hz, 1H), 8.06 (d, $J=8.0$ Hz, 1H), 7.74 (t, $J=7.5$ Hz, 1H), 7.56 (d, $J=8.5$ Hz, 1H), 7.46 (t, $J=7.5$ Hz, 1H), 7.01 (d, $J=7.0$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ : 170.1, 137.1, 131.2, 129.5, 128.7, 128.6, 126.7, 126.4, 124.4, 120.3, 106.5; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_8\text{NO}$ $[\text{M}+\text{H}]^+$ 170.0600, found 170.0597.

Dibenzo[*cd,f*]indol-4(5*H*)-one (4f').^[20] 10 mg, 30% yield. Yellow solid after purification by column chromatography (eluent, ethyl acetate/petroleum ether, $V: V=1:10$), m.p. 227~229 °C (lit.^[20] 227~228 °C); ^1H NMR (500 MHz, $\text{C}_2\text{D}_6\text{SO}$) δ : 11.00 (s, 1H), 8.89 (d, $J=8.0$ Hz, 1H), 8.72 (d, $J=7.5$ Hz, 1H), 8.07 (d, $J=7.5$ Hz, 1H), 8.01 (d, $J=7.5$ Hz, 1H), 7.94 (t, $J=7.5$ Hz, 1H), 7.61 (m, 2H), 7.29 (s, 1H); ^{13}C NMR (125 MHz, $\text{C}_2\text{D}_6\text{SO}$) δ : 168.9, 135.6, 134.2, 129.3, 128.9, 127.7, 127.6, 126.9, 126.8, 126.6, 126.5, 125.2, 123.4, 123.3, 105.4; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{10}\text{NO}$ $[\text{M}+\text{H}]^+$ 220.0757, found

220.0753.

Supporting Information ^1H NMR and ^{13}C NMR spectra for all products. The Supporting Information is available free of charge via the Internet at <http://sioc-journal.cn/>.

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