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Radical Addition/Insertion/Cyclization Cascade Reaction to Assemble Phenanthridines from *N*-Arylacrylamide Using Cyano as A Bridge under Photoredox Catalysis

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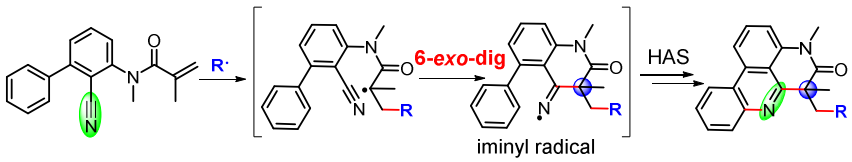


ABSTRACT: A radical addition/nitrile insertion/HAS cascade reaction to prepare 6-quaternary alkylated phenanthridines was developed. The addition of the active methylene radicals which generated from 2-bromoacetonitrile, ethyl 2-bromoacetate, 2-bromo-*N*,*N*-dimethylacetamide or 2-bromo-1-phenylethan-1-one to carbon-carbon double bonds of *N*-arylacrylamides followed by the cyano-participated sequential cyclization produced a serial of phenanthridines in moderate to good yields under photoredox catalysis.

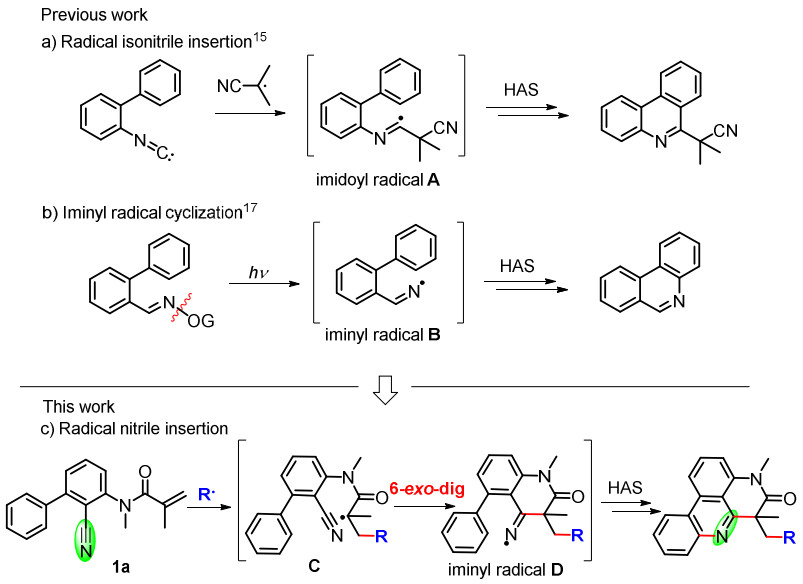
■ INTRODUCTION

Phenanthridine motifs are widespread in natural products[1] and demonstrate diverse biological activities such as anticancer and antitumor,[2] antimalarial,[3] antituberculosis[4] and cytotoxic activities.[5] They are also an important class of organic compounds in a wide range of materials applications.[6] As a consequence, many protocols have been developed for the construction of phenanthridines over the past decades. Among them, approaches based on cascade reaction are the most widely used because of their economy and efficiency. Many means, including aza-Wittig cyclizations,[7] [2+2+2] cycloaddition,[8] palladium-catalyzed cross-coupling cascade annulation

reactions,[9] acid-mediated modified Pictet−Spengler reactions,[10] annulation with arynes,[11] $In(OTf)_3$-catalyzed cascade reaction with alkynylbenzaldehydes and alkynylanilines,[12] nitrogenation of 2-acetylbiphenyls[13] and oxidative Robinson-type annulation[14] have been employed for this purpose.

Cascade radical reactions provided a new approach for the assembly of diversified substituted phenanthridines. In 1995, Nanni and co-workers firstly described a cascade reaction between 2-isocyanobiphenyl and 2-cyanopropyl radical stemmed from AIBN to access 6-substituted phenanthridines, in which the imidoyl radical **A** underwent a homolytic aromatic substitution (HAS) (Scheme 1a).[15] Since then the 2-isocyanobiphenyls appear to be the most versatile acceptors for various radicals initiated by oxidants or photocatalysts in the field of phenanthridines synthesis.[16] Oxime derivatives, in which the N−O bond could be broken under heating, photo or microwave radiation to form iminyl radicals, were also employed as alternative substrates to furnish phenanthridines (Scheme 1b).[17] As a versatile functional group, cyano is playing an important role in the construction of diverse heterocycles. Although the biaryl-2-carbonitriles could be readily obtained, so far only treating them with organometallic reagents *via* anionic cyclization could generate the phenanthridines.[18] Indeed, the direct intermolecular radical cyano insertion is not easy to occur, whereas the intramolecular cyano insertion is available and several excellent protocols to build nitrogen containing heterocycles *via* this strategy were developed.[19] In this work, we wish to report an active methylene radicals initiated cascade reaction. Through the intramolecular carbon−carbon double bond and cyano-participated radical addition and cyclization, the functionalized phenanthridines were synthesized under visible-light photocatalysis (Scheme 1c).

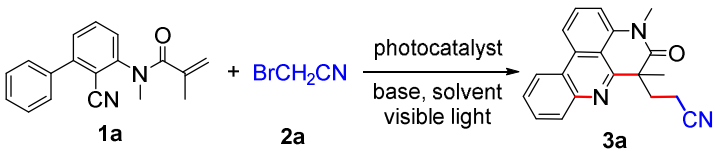
Scheme 1. Typical Radical Cyclization to Construct Phenanthridine and Our Strategy



■ RESULTS AND DISCUSSION

With this strategy in mind, we designed a polyfunctional compound *N*-(2-cyano-[1,1'-biphenyl]-3-yl)-*N*-methylmethacrylamide (**1a**) as the reactant and treated it with 2-bromoacetonitrile (**2a**) under photoredox catalysis (Table 1). Initially, the reaction was performed in the presence of 2 mol % *fac*-Ir(ppy)$_3$ in DMSO under argon atmosphere upon irradiation with 5 W blue LEDs at room temperature for 32 h. To our delight, a cyclization product 3-(4,6-dimethyl-5-oxo-5,6-dihydro-4*H*-pyrido[4,3,2-*gh*]phenanthridin-6-yl)propanenitrile (**3a**) was obtained in 25% yield (entry 1). Encouraged by this result, we then screened the reaction conditions. The reaction did not take place in the absence of the photocatalyst (entry 2) or in a dark environment (entry 3). When conducted in the open air, the reaction also could not perform successfully (entry 4). Further screening the additives revealed that the presence of base (2 equiv) such as $NaHCO_3$, NaOAc, Na_2CO_3, Na_2HPO_4, K_2HPO_4, DBU or DABCO could drastically improve the reaction yields, and Na_2CO_3 gave the highest yield of 74% (entries 5–11). With the optimized base, the solvent was then examined, and the mixed solvent (DMSO/CH_3CN = 1 : 1, 2 mL) turned out to be more effective and provided **3a** in 81% yield (entries 12–18). In addition, a series of photocatalysts were tested and *fac*-Ir(ppy)$_3$ gave the best result (entries 15, 19–22). Furthermore, upon irradiation of 23 W CFL light instead of blue LEDs, no improved yield was obtained (entry 23).

Table 1. Optimization of Reaction Conditions[a]



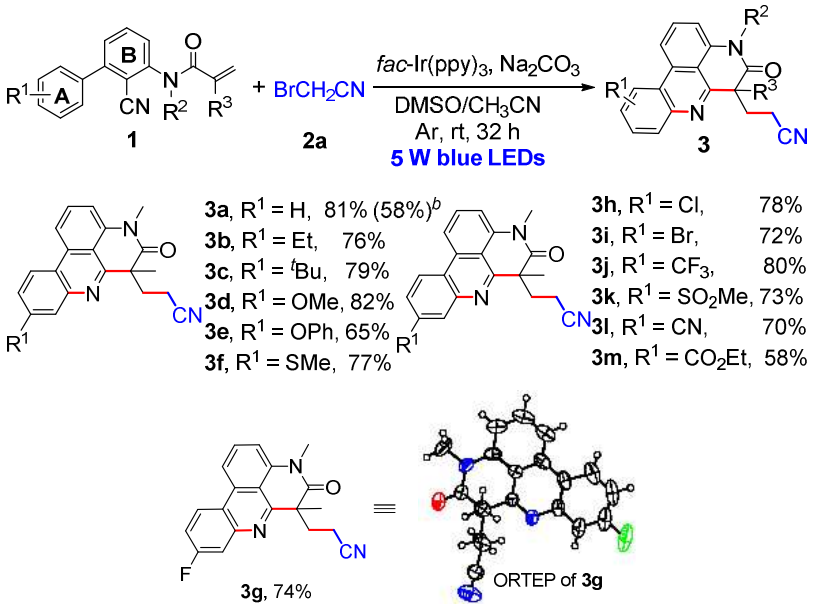
entry	photocatalyst	base	solvent	yield (%)
1	*fac*-Ir(ppy)$_3$	–	DMSO	25
2	–	–	DMSO	0
3[b]	*fac*-Ir(ppy)$_3$	–	DMSO	0
4[c]	*fac*-Ir(ppy)$_3$	–	DMSO	trace
5	*fac*-Ir(ppy)$_3$	$NaHCO_3$	DMSO	69
6	*fac*-Ir(ppy)$_3$	NaOAc	DMSO	63
7	*fac*-Ir(ppy)$_3$	Na_2CO_3	DMSO	74
8	*fac*-Ir(ppy)$_3$	Na_2HPO_4	DMSO	65
9	*fac*-Ir(ppy)$_3$	K_2HPO_4	DMSO	61
10	*fac*-Ir(ppy)$_3$	DBU	DMSO	50
11	*fac*-Ir(ppy)$_3$	DABCO	DMSO	53
12	*fac*-Ir(ppy)$_3$	Na_2CO_3	CH_3CN	72
13	*fac*-Ir(ppy)$_3$	Na_2CO_3	DMF	63
14	*fac*-Ir(ppy)$_3$	Na_2CO_3	EtOAc	68
15[d]	***fac*-Ir(ppy)$_3$**	**Na_2CO_3**	**DMSO/CH_3CN**	**81**
16[d]	*fac*-Ir(ppy)$_3$	Na_2CO_3	DMSO/DMF	75
17[d]	*fac*-Ir(ppy)$_3$	Na_2CO_3	DMSO/EtOAc	76
18[d]	*fac*-Ir(ppy)$_3$	Na_2CO_3	CH_3CN/DMF	73
19[d]	eosin Y	Na_2CO_3	DMSO/CH_3CN	45
20[d]	$Ru(bpy)_3Cl_2$	Na_2CO_3	DMSO/CH_3CN	30
21[d]	$Ru(bpy)_3(PF_6)_2$	Na_2CO_3	DMSO/CH_3CN	28
22[d]	$Ir(ppy)_2(dtbbpy)PF_6$	Na_2CO_3	DMSO/CH_3CN	25
23[d,e]	*fac*-Ir(ppy)$_3$	Na_2CO_3	DMSO/CH_3CN	72

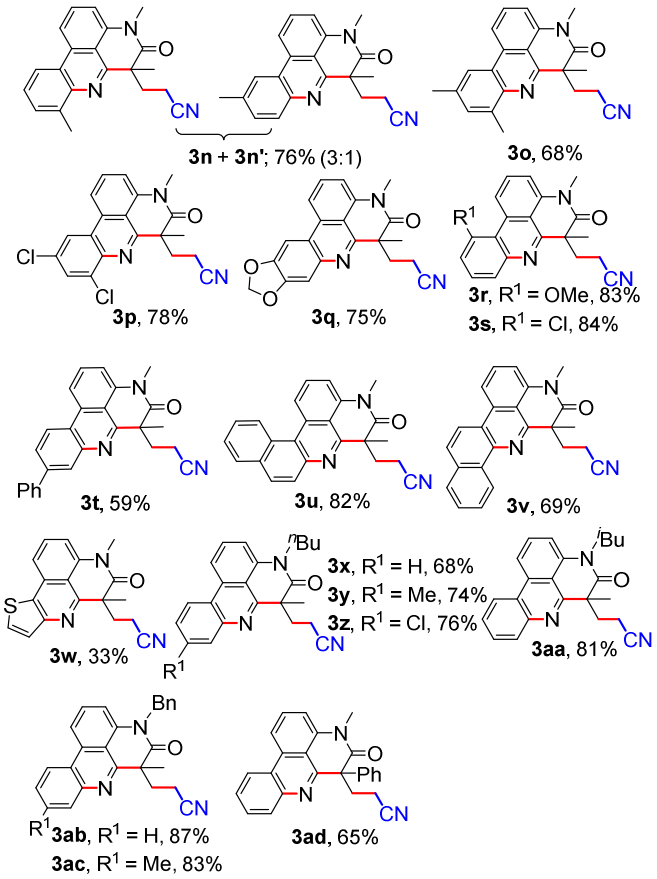
[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol), **2a** (0.6 mmol), base (0.4 mmol), photocatalyst (2 mol %) and solvent (2 mL) were carried out in a sealed tube under Ar atmosphere upon irradiation of 5 W blue LEDs for 32 h. [b]In the dark. [c]Under air. [d]Mixed solvent with a ratio of 1:1 (v/v) was used. [e]Using 23 W CFL.

With the optimized reaction conditions in hand, the substrate scope was investigated and the corresponding results were summarized in Scheme 2. The *N*-arylacrylamides **1** with a variety of substituents on the aromatic ring **A** were firstly employed as the reactants. The reactions of substrates **1** with either electron-donating or electron-withdrawing groups on the *para*-, *meta*- or *ortho*-position of the aromatic ring **A** performed well with 2-bromoacetonitrile and gave the desired phenanthridines (**3a**–**3s**) in 58–84% yields. The structure of product **3g** was determined by

an X-ray diffraction analysis (CCDC number: 1541486). For the *meta*-methyl substituted material **1n**, the cascade cyclization could take place at either 2- or 6-position and gave the two products **3n** and **3n'** (76%, 3:1). The reactions of the substrates with two substituents such as 3,5-dimethyl or 3,5-dichloro on the aromatic ring **A** also readily provided the corresponding products in good yields (**3o**, **3p**). It was found that the benzodioxole group had no obvious impact on the reactivity and afforded the expected site-selective product **3q** in 75% yield. From the substrates bearing biphenyl, α-naphthyl or β-naphthyl on the aromatic ring **B**, several novel pentacyclic phenanthridines were obtained (**3t**–**3v**). For the β-naphthyl substituted reactant **1v**, the cyclization selectively took place on the adjacent α-position to produce **3v** probably due to orienting effect. However, the thienyl substituted *N*-arylacrylamide **1w** gave the desired thieno[3,2-*c*]isoquinoline derivative **3w** in poor yield (33%) under our current conditions. Next, different substituent R^2 on nitrogen atom of **1** such as *n*-butyl, *i*-butyl and benzyl were evaluated and the corresponding products were obtained in good yields (**3x**–**3z**, **3aa**–**3ac**). Gratifyingly, when the substrate **1ad** bearing phenyl at the α-position of carbonyl, the space congested 6-quaternary alkylated phenanthridines **3ad** was isolated in 65% yield. In addition, if 2-chloroacetonitrile was used instead of 2-bromoacetonitrile, the product **3a** was obtained with a lower yield of 58%.

Scheme 2. Photo-Induced Cascade Synthesis of 3[a]

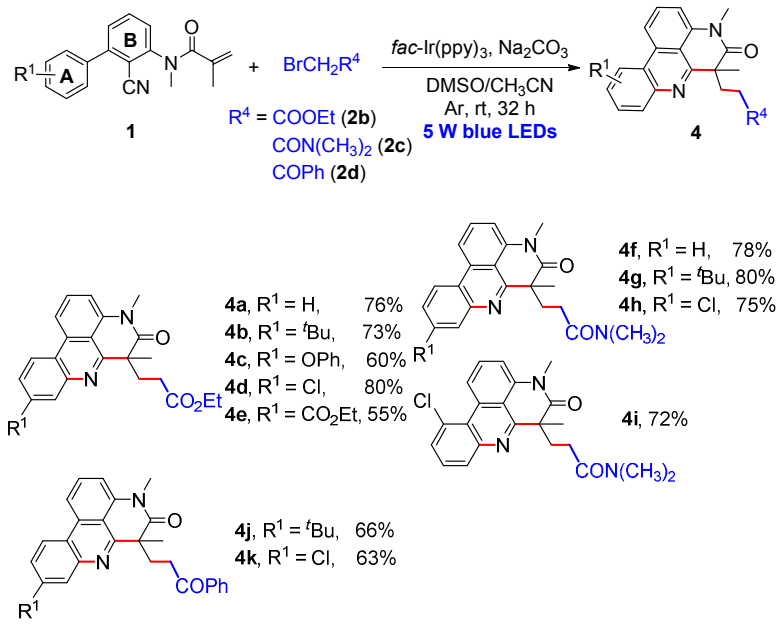




[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), Na_2CO_3 (0.4 mmol), *fac*-Ir(ppy)$_3$ (2 mol %), DMSO/MeCN (1:1, v/v, 2 mL), upon irradiation with 5 W blue LEDs under Ar atmosphere at room temperature for 32 h. [b]2-Chloroacetonitrile was used instead of **2a.**

Furthermore, some other active bromomethylene compounds ethyl 2-bromoacetate (**2b**), 2-bromo-*N*,*N*-dimethylacetamide (**2c**) and 2-bromo-1-phenylethan-1-one (**2d**) were employed to react with *N*-arylacrylamides under the standard conditions (Scheme 3). The *N*-arylacrylamides **1** bearing both electron-donating and electron-withdrawing groups on the *para*-position of aromatic ring **A** were proven to be suitable for this cascade process with ethyl 2-bromoacetate since they could provide the desired products **(4a–4e)** in moderate to high yields. 2-Bromo-*N*,*N*-dimethylacetamide, as well as 2-bromo-1-phenylethan-1-one were also suitable reaction partners for this similar transformation under the photoredox conditions (**4f–4k**).

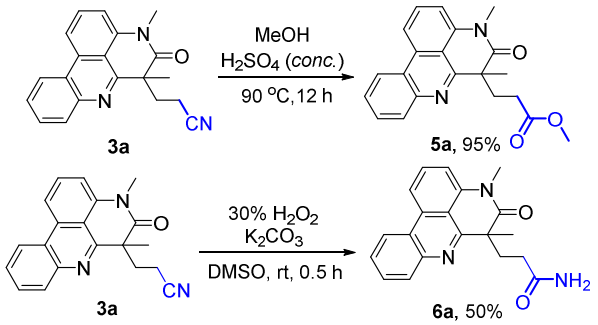
Scheme 3. Photo-Induced Cascade Synthesis of 4 [a]



[a]Reaction conditions: **1** (0.2 mmol), **2**(**b**-**d**) (0.6 mmol), Na_2CO_3 (0.4 mmol), *fac*-Ir(ppy)$_3$ (2 mol %), DMSO/MeCN (1:1, v/v, 2 mL), upon irradiation with 5 W blue LEDs under Ar atmosphere at room temperature for 32 h.

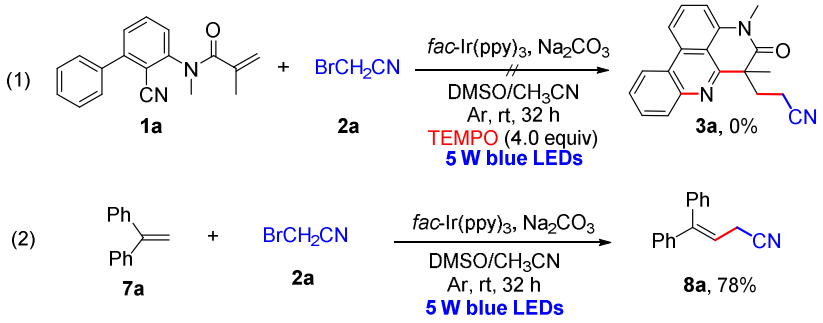
For further demonstrating the synthetic utility of this methodology, we tried to convert the cyano group of the cyclization product **3a** into some other functional groups. When the cyanomethylated product **3a** was treated with *conc*. H_2SO_4 in methanol at 90 ^oC for 12 h, hydrolyzation and esterification occurred to afford the product **5a** in excellent yield (95%). Furthermore, the compound **3a** could be easily hydrolyzed to generate 3-(4,6-dimethyl-5-oxo-5,6-dihydro-4*H*-pyrido[4,3,2-*gh*]phenanthridin-6-yl)propanamide (**6a**) in the presence of H_2O_2 (30% in water) and K_2CO_3 in 50% yield (Scheme 4).

Scheme 4. Transformation of Cyclization Product 3a



To gain insight into the mechanism of this cascade reaction, several control experiments were carried out as shown in Scheme 5. When the model reaction was performed in the presence of radical scavenge 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 4 equiv), no product **3a** was found (Scheme 5, eq. 1). Another radical scavenger 1,1-diphenylethylene (**7a**) could successfully trap the cyanomethyl radical under the standard reaction conditions to produce a coupling product 4,4-diphenylbut-3-enenitrile (**8a**) in 78% yield (Scheme 5, eq. 2). Based on these findings, we presumed that this cyclization reaction most likely proceeded *via* a radical pathway.

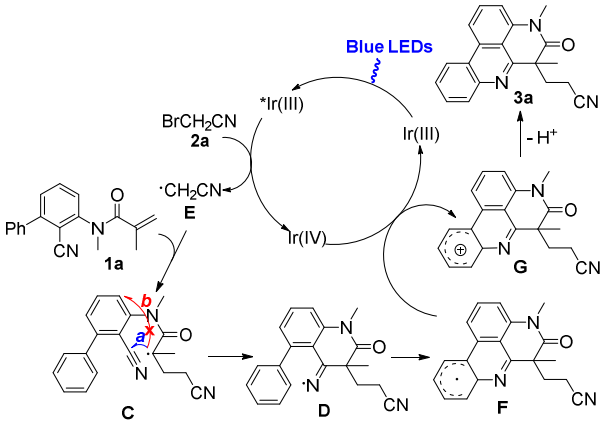
Scheme 5. Control Experiments



The proposed reaction mechanism for the photoredox conversion of *N*-arylacrylamide **1a** with 2-bromoacetonitrile (**2a**) into 6-quaternary alkylated phenanthridine **3a** is shown in Scheme 6. Initially, the photocatalyst [*fac*-Ir(III)(ppy)$_3$] was irradiated to the excited state [*fac*-Ir(III)(ppy)$_3$]*, which was oxidative quenched by **2a** with the generation of a [*fac*-Ir(IV)(ppy)$_3$]$^+$ complex and a cyanomethyl radical **E**.[20] Subsequently, addition of the cyanomethyl radical to the carbon-carbon double bond of **1a** led to alkyl radical **C**, followed by a regioselective addition to the cyano *via* 6-*exo*-dig to give iminyl radical **D** (*path a*),[19e] which then underwent intramolecular homolytic aromatic substitution to give the radical intermediate **F**. It should be pointed that under our reaction conditions, no radical addition to the *ortho*-carbon of the benzene ring occurred to result

in corresponding oxindole derivatives (*path b*). A single-electron oxidation of **F** by [*fac*-Ir(IV)(ppy)$_3$]$^+$ regenerated the photocatalyst and simultaneously produced the cation intermediate **G**. Finally, **G** underwent deprotonation to yield the desired product **3a**.

Scheme 6. Plausible Reaction Mechanism



■ CONCLUSIONS

In summary, we developed the radical addition/nitrile insertion/HAS cascade reaction to construct phenanthridines. The addition of the active methylene radicals from 2-bromoacetonitrile, ethyl 2-bromoacetate or 2-bromo-*N*,*N*-dimethylacetamide to carbon-carbon double bonds of *N*-arylacrylamides resulted in 6-quaternary alkylated phenanthridines in moderate to good yields under photoredox catalysis. The advantage of our method is that it proceeds with easily available material, broad substrate scope, low loading of catalyst, and generates highly complex polycyclic scaffold in one step. Most importantly, we anticipate that the *N*-arylacrylamides with *ortho*-cyano group as a bridge are good precursors and could therefore be applied to synthesize phenanthridine derivatives with diverse radicals based on this strategy.

■ EXPERIMENTAL SECTION

General Remarks. All reactions were run in a sealed tube with a Teflon lined cap under ambient Ar. Chemicals were commercially available from chemical suppliers and were used without purification. *N*-Arylacrylamides **1** were prepared according to the literature procedures.[21] The NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$ or DMSO-d_6

using TMS as an internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, dt = doublet of triplet, td = triplet of doublet, q = quartet, m = multiplet, ddd = doublet of doublet of doublet. Q-TOF was used for the HRMS measurement. Melting points are uncorrected.

General Procedure for Synthesis of Products 3 and 4. *N*-Arylacrylamide **1** (0.2 mmol), 2-bromoacetonitrile (72.0 mg, 42 μL, 0.6 mmol), *fac*-Ir(ppy)$_3$ (2 mol %, 2.6 mg), Na_2CO_3 (42.4 mg, 0.4 mmol) were added to the mixed solvents DMSO and acetonitrile (1:1, v/v, 2 mL). Then the reaction mixture was stirred under Ar atmosphere upon irradiation of 5 W blue LEDs for 32 h. After completion of the reaction, the resulting solution was extracted with EtOAc (15 × 3 mL), and the combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by silica gel chromatography using hexane/ethyl acetate (5:1) to afford the pure products **3**. The products **4** were synthesized according to the general produce of products **3** except ethyl 2-bromoacetate (100.2 mg, 67 μL, 0.6 mmol), 2-bromo-*N*,*N*-dimethylacetamide (99.6 mg, 0.6 mmol) or 2-bromo-1-phenylethan-1-one (118.8 mg, 0.6 mmol) was used.

3-(4,6-Dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3a**). Yellow solid (51.1 mg, 81% yield); mp 130–132 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.54 (dd, J = 8.2, 1.2 Hz, 1H), 8.30 (d, J = 8.2 Hz, 1H), 8.17 (dd, J = 8.2, 0.9 Hz, 1H), 7.86 (t, J = 8.1 Hz, 1H), 7.78 (t, J = 6.9 Hz, 1H), 7.68 (t, J = 8.3 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 3.61 (s, 3H), 3.02–2.75 (m, 2H), 2.30–2.26 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6, 157.4, 144.8, 138.4, 133.5, 132.2, 129.9, 129.4, 127.1, 122.8, 122.7, 119.4, 116.5, 112.0, 111.2, 50.8, 34.3, 30.4, 30.0, 13.7; HRMS (ESI) m/z: calcd for $C_{20}H_{18}N_3O$ $[M + H]^+$ 316.1444, found 316.1443.

3-(9-Ethyl-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3b**). Yellow solid (52.2 mg, 76% yield); mp 135–136 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.47 (d, J = 8.4 Hz, 1H), 8.28 (d, J = 8.3 Hz, 1H), 8.01 (s, 1H), 7.85 (t, J = 8.1 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 3.62 (s, 3H), 3.03–2.76 (m, 4H), 2.28 (t, J = 8.2 Hz, 2H), 1.71 (s, 3H), 1.43 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.7, 157.3, 146.0, 145.0, 138.3, 133.6, 132.1, 128.0, 127.9, 122.6, 120.7, 119.4, 116.4, 111.8, 110.7, 50.8, 34.3, 30.5,

30.0, 28.9, 15.4, 13.7; HRMS (ESI) m/z: calcd for $C_{22}H_{22}N_3O$ $[M + H]^+$ 344.1757, found 344.1757.

3-(9-(tert-Butyl)-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3c**). Yellow oil (58.6 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.50 (d, J = 8.7 Hz, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.16 (s, 1H), 7.85 (t, J = 8.1 Hz, 1H), 7.79 (dd, J = 8.7, 2.1 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 3.62 (s, 3H), 3.06–2.78 (m, 2H), 2.29 (t, J = 8.0 Hz, 2H), 1.72 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.7, 157.3, 152.9, 144.9, 138.3, 133.4, 132.1, 125.7, 125.6, 122.3, 120.5, 119.5, 116.4, 111.8, 110.7, 50.8, 35.1, 34.3, 31.3, 30.5, 30.0, 13.8; HRMS (ESI) m/z: calcd for $C_{24}H_{26}N_3O$ $[M + H]^+$, 372.2070 found 372.2073.

3-(9-Methoxy-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3d**). Yellow solid (56.6 mg, 82% yield); mp 126–127 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.42 (d, J = 9.1 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.82 (t, J = 8.1 Hz, 1H), 7.56 (s, 1H), 7.32 (dd, J = 9.0, 2.7 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 4.04 (s, 3H), 3.61 (s, 3H), 3.02–2.75 (m, 2H), 2.30–2.25 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6, 160.7, 157.8, 146.6, 138.4, 133.7, 132.2, 123.8, 119.5, 118.5, 116.9, 116.1, 111.2, 110.0, 109.3, 55.7, 50.8, 34.3, 30.5, 30.0, 13.7; HRMS (ESI) m/z: calcd for $C_{21}H_{20}N_3O_2$ $[M + H]^+$ 346.1550, found 346.1550.

3-(4,6-Dimethyl-5-oxo-9-phenoxy-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3e**). Yellow oil (52.9 mg, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.52 (d, J = 9.0 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H), 7.86 (t, J = 8.1 Hz, 1H), 7.59 (d, J = 2.5 Hz, 1H), 7.49–7.45(m, 3H), 7.28–7.20 (m, 4H), 3.62 (s, 3H), 2.96–2.72 (m, 2H), 2.28–2.23 (m, 2H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6, 158.9, 158.3, 156.1, 146.3, 138.4, 133.5, 132.4, 130.1, 124.4, 124.3, 120.1, 119.5, 119.4, 118.4, 116.3, 115.6, 111.5, 110.5, 50.8, 34.3, 30.4, 30.0, 13.7; HRMS (ESI) m/z: calcd for $C_{26}H_{22}N_3O_2$ $[M + H]^+$ 408.1707, found 408.1705.

3-(4,6-Dimethyl-9-(methylthio)-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3f**). Yellow solid (55.6 mg, 77% yield); mp 147–149 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.38 (d, J = 8.7 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 7.90 (s, 1H), 7.83 (t, J = 8.1 Hz, 1H), 7.53 (dd, J = 8.7, 2.1 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 3.61 (s, 3H), 3.02–2.75 (m, 2H), 2.69 (s, 3H), 2.29–2.25 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.5, 158.1, 145.4, 141.1, 138.4, 133.5, 132.3, 125.9, 124.3, 122.8, 119.9, 119.4, 116.3, 111.7, 110.7, 50.8, 34.2, 30.5, 30.0, 15.2, 13.8; HRMS (ESI) m/z: calcd for $C_{21}H_{20}N_3OS$ $[M + H]^+$ 362.1322, found 362.1319.

3-(9-Fluoro-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitril e (**3g**). Yellow solid (49.3 mg, 74% yield); mp 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.53 (dd, J = 9.1, 5.8 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 7.88 (t, J = 8.1 Hz, 1H), 7.80 (dd, J = 9.7, 2.7 Hz, 1H), 7.44 (ddd, J = 9.0, 8.2, 2.7 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 3.62 (s, 3H), 3.00–2.74 (m, 2H), 2.30–2.25 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.4, 163.0 (d, J = 247.9 Hz), 159.0, 146.1 (d, J = 12 Hz), 138.5, 133.3, 132.6, 124.7 (d, J = 9.6 Hz), 119.6 (d, J = 1.9 Hz), 119.3, 116.3 (d, J = 23.8 Hz), 116.3, 114.2 (d, J = 20.3 Hz), 111.7 (d, J = 1.1 Hz), 111.0, 50.8, 34.2, 30.4, 30.0, 13.7; HRMS (ESI) m/z: calcd for $C_{20}H_{17}FN_3O$ $[M + H]^+$ 334.1350, found 334.1347.

3-(9-Chloro-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitril e (**3h**). Yellow solid (54.5 mg, 78% yield); mp 160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.45 (d, J = 8.8 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.16 (d, J = 2.2 Hz, 1H), 7.89 (t, J = 8.1 Hz, 1H), 7.61 (dd, J = 8.8, 2.2 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 3.62 (s, 3H), 2.99–2.74 (m, 2H), 2.30–2.25 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.4, 159.0, 145.4, 138.6, 135.1, 133.1, 132.7, 129.0, 127.6, 124.1, 121.3, 119.2, 116.4, 112.0, 111.4, 50.9, 34.2, 30.5, 30.1, 13.7; HRMS (ESI) m/z: calcd for $C_{20}H_{17}ClN_3O$ $[M + H]^+$ 350.1055, found 350.1057.

3-(9-Bromo-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitril e (**3i**). Yellow solid (56.6 mg, 72% yield); mp 175–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.40 (d, J = 8.8 Hz, 1H), 8.35 (d, J = 2.0 Hz, 1H), 8.26 (d, J = 8.2 Hz, 1H), 7.89 (t, J = 8.1 Hz, 1H), 7.77 (dd, J = 8.8, 2.1 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 3.62 (s, 3H), 2.99–2.74 (m, 2H), 2.30–2.26 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.4, 158.9, 145.6, 138.6, 133.2, 132.7, 132.2, 130.3, 124.2, 123.3, 121.7, 119.2, 116.4, 112.0, 111.5, 50.9, 34.2, 30.5, 30.1, 13.7; HRMS (ESI) m/z: calcd for $C_{20}H_{17}BrN_3O$ $[M + H]^+$ 394.0550, found 394.0552.

3-(4,6-Dimethyl-5-oxo-9-(trifluoromethyl)-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)pr opanenitrile (**3j**). Yellow solid (61.3 mg, 80% yield); mp 176–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.67 (d, J = 8.6 Hz, 1H), 8.47 (s, 1H), 8.35 (d, J = 8.3 Hz, 1H), 7.96 (t, J = 8.1 Hz, 1H), 7.87 (dd, J = 8.6, 1.5 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 3.64 (s, 3H), 3.03–2.77 (m, 2H), 2.33–2.28 (m, 2H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 159.4, 144.1, 138.7, 132.9, 132.7, 131.4 (q, J = 32.7 Hz), 127.4 (q, J = 4.1 Hz), 125.2, 124.0 (q, J = 270.7 Hz), 123.9, 122.9 (q, J = 3.2 Hz), 119.1, 116.8, 112.6, 112.3, 50.9, 34.1, 30.6, 30.1, 13.7; HRMS (ESI) m/z:

calcd for $C_{21}H_{17}F_3N_3O$ $[M + H]^+$ 384.1318, found 384.1317.

3-(4,6-Dimethyl-9-(methylsulfonyl)-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3k**). Yellow solid (57.4 mg, 73% yield); mp 170–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.74–8.71 (m, 2H), 8.35 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.6 Hz, 1H), 7.97 (t, J = 8.1 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 3.63 (s, 3H), 3.21 (s, 3H), 3.00–2.74 (m, 2H), 2.36–2.23 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.2, 160.2, 144.1, 140.8, 138.8, 133.3, 132.4, 129.8, 126.6, 124.6, 123.9, 119.1, 117.0, 113.0, 112.8, 51.0, 44.6, 34.1, 30.6, 30.1, 13.7; HRMS (ESI) m/z: calcd for $C_{21}H_{20}N_3O_3S$ $[M + H]^+$ 394.1220, found 394.1219.

6-(2-Cyanoethyl)-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridine-9-carbonitrile (**3l**). Yellow solid (47.6 mg, 70% yield); mp 223–224 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.64 (d, J = 8.5 Hz, 1H), 8.52 (d, J = 1.6 Hz, 1H), 8.33 (d, J = 8.3 Hz, 1H), 7.98 (t, J = 8.1 Hz, 1H), 7.87 (dd, J = 8.5, 1.6 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 3.64 (s, 3H), 3.02–2.76 (m, 2H), 2.38–2.24 (m, 2H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.2, 160.1, 143.9, 138.8, 134.8, 133.2, 132.5, 128.4, 126.1, 124.1, 119.0, 118.4, 116.9, 112.8, 112.7, 112.7, 51.0, 34.1, 30.6, 30.1, 13.7; HRMS (ESI) m/z: calcd for $C_{21}H_{17}N_4O$ $[M + H]^+$ 341.1397, found 341.1401.

Ethyl 6-(2-cyanoethyl)-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridine-9-carboxylate (**3m**). Yellow solid (44.9 mg, 58% yield); mp 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.83 (d, J = 1.6 Hz, 1H), 8.57 (d, J = 8.6 Hz, 1H), 8.33 (d, J = 8.3 Hz, 1H), 8.27 (dd, J = 8.5, 1.6 Hz, 1H), 7.91 (t, J = 8.1 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 3.62 (s, 3H), 3.03–2.76 (m, 2H), 2.32–2.28 (m, 2H), 1.71 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.4, 166.2, 158.6, 144.2, 138.6, 132.9, 132.7, 131.7, 131.1, 127.0, 126.0, 123.0, 119.2, 117.0, 112.5, 112.2, 61.5, 50.9, 34.1, 30.5, 30.1, 14.4, 13.7; HRMS (ESI) m/z: calcd for $C_{23}H_{22}N_3O_3$ $[M + H]^+$ 388.1656, found 388.1657.

3-(4,6,8-Trimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3n**) *and 3-(4,6,10-trimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile* (**3n'**). White solid (50.0 mg, 76% yield); mp 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.42–8.35 (m, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.09 (s, 0.22H), 7.85 (t, J = 8.1 Hz, 1H), 7.67–7.56 (m, 1.72H), 7.25 (d, J = 7.9 Hz, 1H), 3.63 (s, 3H), 3.04–2.97 (m, 1H), 2.89 (s, 2.18H), 2.84–2.77 (m, 1H), 2.66 (s, 0.72H), 2.33–2.28 (m, 2H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm)

172.7, 172.7, 156.3, 155.8, 143.4, 143.2, 138.4, 138.3, 137.7, 137.1, 133.8, 133.2, 131.9, 131.9, 131.2, 130.0, 129.6, 126.8, 122.7, 122.6, 122.2, 120.5, 119.5, 116.8, 116.5, 111.8, 111.0, 110.9, 51.0, 50.7, 34.4, 34.3, 30.7, 30.3, 30.0, 30.0, 22.0, 18.3, 13.7, 13.7; HRMS (ESI) m/z: calcd for $C_{21}H_{20}N_3O$ $[M + H]^+$ 330.1601, found 330.1603.

3-(4,6,8,10-Tetramethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3o**). Yellow solid (46.7 mg, 68% yield); mp 100–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.29 (d, J = 8.3 Hz, 1H), 8.19 (s, 1H), 7.81 (t, J = 8.1 Hz, 1H), 7.49 (s, 1H), 7.22 (d, J = 7.9 Hz, 1H), 3.61 (s, 3H), 3.03–2.96 (m, 1H), 2.85 (s, 3H), 2.83–2.76 (m, 1H), 2.60 (s, 3H), 2.33–2.27 (m, 2H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.8, 154.7, 141.8, 138.3, 137.3, 136.6, 133.5, 131.9, 131.6, 122.5, 120.0, 119.5, 116.8, 111.9, 110.7, 50.9, 34.5, 30.6, 30.0, 22.0, 18.2, 13.7; HRMS (ESI) m/z: calcd for $C_{22}H_{22}N_3O$ $[M + H]^+$ 344.1757, found 344.1758.

3-(8,10-Dichloro-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3p**). White solid (59.8 mg, 78% yield); mp 183–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.41 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.92 (t, J = 8.1 Hz, 1H), 7.84–7.83 (m, 1H), 7.34 (d, J = 7.9 Hz, 1H), 3.63 (s, 3H), 3.04–2.73 (m, 2H), 2.40–2.35 (m, 2H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.4, 158.6, 139.6, 138.8, 135.5, 133.0, 132.4, 132.3, 129.9, 125.0, 121.2, 119.2, 116.7, 112.3, 51.0, 34.2, 30.5, 30.1, 13.7; HRMS (ESI) m/z: calcd for $C_{20}H_{16}Cl_2N_3O$ $[M + H]^+$ 384.0665, found 384.0664.

3-(4,6-Dimethyl-5-oxo-5,6-dihydro-4H-[1,3]dioxolo[4,5-b]pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3q**). Yellow solid (53.9 mg, 75% yield); mp 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.06 (d, J = 8.4 Hz, 1H), 7.81 (s, 1H), 7.78 (t, J = 8.1 Hz, 1H), 7.49 (s, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.16 (d, J = 1.1 Hz, 2H), 3.60 (s, 3H), 2.97–2.72 (m, 2H), 2.31–2.17 (m, 2H), 1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.7, 154.9, 150.0, 148.3, 142.5, 138.2, 133.3, 131.6, 119.4, 118.8, 116.3, 111.5, 109.9, 107.3, 102.0, 99.6, 50.4, 34.5, 30.3, 30.0, 13.7; HRMS (ESI) m/z: calcd for $C_{21}H_{18}N_3O_3$ $[M + H]^+$ 360.1343, found 360.1342.

3-(11-Methoxy-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3r**). Yellow solid (57.3 mg, 83% yield); mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.31 (dd, J = 8.7, 0.5 Hz, 1H), 7.88–7.84 (m, 2H), 7.73 (t, J = 8.1 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.17 (s, 3H), 3.63 (s, 3H), 3.02–2.75 (m, 2H), 2.30 (t, J = 7.9 Hz, 2H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 158.3, 157.7, 146.5, 137.8, 133.5,

132.0, 129.0, 122.6, 122.4, 119.5, 113.8, 112.4, 111.0, 108.1, 56.0, 50.5, 34.1, 30.3, 30.1, 13.7; HRMS (ESI) m/z: calcd for $C_{21}H_{20}N_3O_2$ $[M + H]^+$ 346.1550, found 346.1551.

3-(11-Chloro-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3s**). Yellow solid (58.6 mg, 84% yield); mp 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.60 (dd, J = 8.7, 0.6 Hz, 1H), 8.11 (dd, J = 8.1, 1.4 Hz, 1H), 7.91–7.87 (m, 1H), 7.74 (dd, J = 7.7, 1.5 Hz, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 3.63 (s, 3H), 3.01–2.74 (m, 2H), 2.32–2.28 (m, 2H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.1, 158.1, 146.8, 138.1, 132.8, 131.6, 131.0, 130.8, 129.7, 128.6, 121.0, 120.7, 119.3, 112.8, 112.1, 50.5, 33.9, 30.3, 30.2, 13.7; HRMS (ESI) m/z: calcd for $C_{20}H_{17}ClN_3O$ $[M + H]^+$ 350.1055, found 350.1052.

3-(4,6-Dimethyl-5-oxo-9-phenyl-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3t**). White solid (46.2 mg, 59% yield); mp 213–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.61 (d, J = 8.6 Hz, 1H), 8.44 (s, 1H), 8.33 (d, J = 8.2 Hz, 1H), 7.96 (dd, J = 8.5, 2.0 Hz, 1H), 7.91–7.84 (m, 3H), 7.57–7.54 (m, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 3.64 (s, 3H), 3.07–2.79 (m, 2H), 2.31 (t, J = 8.0 Hz, 2H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6, 158.0, 145.1, 142.2, 140.0, 138.5, 133.4, 132.3, 129.0, 128.0, 127.7, 127.4, 126.3, 123.2, 121.9, 119.4, 116.6, 112.0, 111.1, 50.8, 34.2, 30.5, 30.0, 13.8; HRMS (ESI) m/z: calcd for $C_{26}H_{22}N_3O$ $[M + H]^+$ 392.1757, found 392.1759.

3-(4,6-Dimethyl-5-oxo-5,6-dihydro-4H-benzo[a]pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3u**). Orange solid (59.9 mg, 82% yield); mp 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.07 (d, J = 8.3 Hz, 1H), 8.81 (d, J = 8.5 Hz, 1H), 8.12–8.05 (m, 3H), 7.89 (t, J = 8.1 Hz, 1H), 7.75 (t, J = 7.3 Hz, 1H), 7.69 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 3.66 (s, 3H), 3.08–2.80 (m, 2H), 2.31 (t, J = 7.8 Hz, 2H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.5, 156.6, 144.8, 138.2, 133.5, 133.2, 131.8, 130.5, 129.7, 128.9, 128.0, 127.6, 126.9, 126.6, 121.3, 119.6, 119.4, 113.3, 110.4, 50.5, 34.3, 30.3, 30.2, 13.8; HRMS (ESI) m/z: calcd for $C_{24}H_{20}N_3O$ $[M + H]^+$ 366.1601, found 366.1603.

3-(4,6-Dimethyl-5-oxo-5,6-dihydro-4H-benzo[c]pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3v**). Yellow solid (50.4 mg, 69% yield); mp 171–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.43 (d, J = 8.2 Hz, 1H), 8.51 (d, J = 9.1 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 7.4 Hz, 1H), 7.90 (t, J = 8.1 Hz, 1H), 7.85–7.81 (m, 1H), 7.78–7.74 (m, 1H), 7.26 (d, J = 7.8 Hz, 1H), 3.66 (s, 3H), 3.18–2.87 (m, 2H), 2.32 (t, J = 7.9 Hz, 2H), 1.82 (s, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ (ppm) 172.7, 156.0, 142.0, 138.4, 133.7, 133.5, 132.0, 131.5, 128.0, 127.7, 127.2, 124.9, 120.1, 119.8, 119.4, 116.9, 112.7, 110.4, 51.0, 34.9, 30.8, 30.0, 13.8; HRMS (ESI) m/z: calcd for $C_{24}H_{20}N_3O$ $[M + H]^+$ 366.1601, found 366.1601.

3-(4,6-Dimethyl-5-oxo-5,6-dihydro-4H-benzo[de]thieno[3,2-b][1,6]naphthyridin-6-yl)propanenitrile (**3w**). Yellow solid (21.2 mg, 33% yield); mp 145–147 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83–7.69 (m, 4H), 7.16 (dd, J = 7.1, 1.5 Hz, 1H), 3.62 (s, 3H), 3.01–2.78 (m, 2H), 2.25–2.20 (m, 2H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6, 155.8, 139.9, 138.7, 132.6, 132.3, 128.3, 125.9, 119.2, 117.4, 111.2, 109.8, 50.5, 34.9, 30.9, 30.0, 13.8; HRMS (ESI) m/z: calcd for $C_{18}H_{16}N_3OS$ $[M + H]^+$ 322.1009, found 322.1007.

3-(4-Butyl-6-methyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3x**). Yellow oil (48.6 mg, 68% yield); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.52 (dd, J = 8.3, 0.9 Hz, 1H), 8.28 (d, J = 8.3 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.85 (t, J = 8.1 Hz, 1H), 7.79–7.74 (m, 1H), 7.68–7.64 (m, 1H), 7.26 (d, J = 8.0 Hz, 1H), 4.28–4.09 (m, 2H), 3.04–2.74 (m, 2H), 2.32–2.27 (m, 2H), 1.81–1.73 (m, 2H), 1.68 (s, 3H), 1.56–1.47 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 157.5, 144.7, 137.4, 133.7, 132.2, 129.8, 129.4, 127.1, 122.9, 122.6, 119.5, 116.4, 112.2, 111.2, 50.7, 42.5, 33.9, 30.5, 28.9, 20.3, 13.9, 13.7; HRMS (ESI) m/z: calcd for $C_{23}H_{24}N_3O$ $[M + H]^+$ 358.1914, found 358.1912.

3-(4-Butyl-6,9-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3y**). Yellow oil (54.9 mg, 74% yield); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.42 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H), 7.98 (s, 1H), 7.83 (t, J = 8.1 Hz, 1H), 7.51 (dd, J = 8.4, 1.6 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 4.28–4.10 (m, 2H), 3.04–2.75 (m, 2H), 2.62 (s, 3H), 2.32–2.27 (m, 2H), 1.81–1.73 (m, 2H), 1.68 (s, 3H), 1.54–1.49 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 157.4, 144.8, 139.7, 137.4, 133.8, 132.1, 129.3, 128.9, 122.4, 120.5, 119.5, 116.2, 112.0, 110.7, 50.7, 42.5, 33.9, 30.6, 28.9, 21.6, 20.3, 13.9, 13.7; HRMS (ESI) m/z: calcd for $C_{24}H_{26}N_3O$ $[M + H]^+$ 372.2070, found 372.2070.

3-(4-Butyl-9-chloro-6-methyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3z**). Yellow oil (59.5 mg, 76% yield); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.43 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.88 (t, J = 8.1 Hz, 1H), 7.59 (dd, J = 8.8, 2.2 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 4.28–4.10 (m, 2H), 3.01–2.73 (m, 2H), 2.32–2.26 (m, 2H), 1.80–1.72 (m, 2H), 1.67 (s, 3H), 1.56–1.46 (m, 2H), 1.04 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ (ppm) 172.1, 159.0, 145.2, 137.6, 135.1, 133.4, 132.7, 128.9, 127.6, 124.1, 121.4, 119.3, 116.2, 112.2, 111.5, 50.8, 42.6, 33.8, 30.6, 28.8, 20.3, 13.9, 13.7; HRMS (ESI) m/z: calcd for $C_{23}H_{23}ClN_3O$ $[M + H]^+$ 392.1524, found 392.1525.

3-(4-Isobutyl-6-methyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3aa**). Yellow oil (57.9 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.56 (dd, J = 8.3, 1.0 Hz, 1H), 8.31 (d, J = 8.2 Hz, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.86 (t, J = 8.1 Hz, 1H), 7.80 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.70 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 4.25–4.20 (m, 1H), 3.99–3.94 (m, 1H), 3.10–2.76 (m, 2H), 2.34–2.25 (m, 3H), 1.69 (s, 3H), 1.05 (dd, J = 6.7, 2.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.8, 157.4, 144.5, 137.8, 133.8, 132.1, 129.8, 129.5, 127.2, 122.9, 122.6, 119.6, 116.4, 112.2, 111.7, 50.9, 49.1, 33.4, 31.0, 26.4, 20.3, 20.2, 13.7; HRMS (ESI) m/z: calcd for $C_{23}H_{24}N_3O$ $[M + H]^+$ 358.1914, found 358.1914.

3-(4-Benzyl-6-methyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3ab**). Yellow solid (68.1 mg, 87% yield); mp 133–135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.55 (dd, J = 8.2, 0.8 Hz, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.82 (t, J = 7.1 Hz, 1H), 7.76–7.69 (m, 2H), 7.40–7.36 (m, 2H), 7.33–7.28 (m, 3H), 7.19 (d, J = 7.9 Hz, 1H), 5.69 (d, J = 16.2 Hz, 1H), 5.23 (d, J = 16.2 Hz, 1H), 3.18–2.85 (m, 2H), 2.40 (t, J = 7.8 Hz, 2H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.9, 157.2, 137.6, 136.0, 133.7, 132.2, 129.8, 129.5, 129.0, 127.5, 127.3, 126.3, 122.9, 122.6, 119.4, 116.7, 112.3, 112.2, 51.0, 46.4, 33.7, 30.9, 13.8; HRMS (ESI) m/z: calcd for $C_{26}H_{22}N_3O$ $[M + H]^+$ 392.1757, found 392.1758.

3-(4-Benzyl-6,9-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3ac**). Yellow solid (67.3 mg, 83% yield); mp 129–131 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.43 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.02 (s, 1H), 7.71 (t, J = 8.1 Hz, 1H), 7.54 (dd, J = 8.4, 1.2 Hz, 1H), 7.40–7.31 (m, 5H), 7.14 (d, J = 7.9 Hz, 1H), 5.69 (d, J = 16.1 Hz, 1H), 5.22 (d, J = 16.1 Hz, 1H), 3.12–2.84 (m, 2H), 2.65 (s, 3H), 2.39 (t, J = 8.0 Hz, 2H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.0, 157.1, 144.8, 139.9, 137.5, 136.1, 133.7, 132.1, 129.3, 129.0, 127.5, 126.3, 122.4, 120.6, 119.5, 116.5, 111.9, 111.8, 51.0, 46.4, 33.7, 30.9, 21.7, 13.8; HRMS (ESI) m/z: calcd for $C_{27}H_{24}N_3O$ $[M + H]^+$ 406.1914, found 406.1913.

3-(4-Methyl-5-oxo-6-phenyl-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanenitrile (**3ad**). Yellow oil (49.0 mg, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.60 (d, J = 8.0 Hz, 1H), 8.34–8.32 (m, 2H), 7.88–7.83 (m, 2H), 7.76 (t, J = 7.2 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H),

7.18–7.16 (m, 3H), 7.08–7.05 (m, 2H), 3.64 (s, 3H), 3.53–3.46 (m, 1H), 3.30–3.23 (m, 1H), 2.59–2.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.4, 155.3, 144.3, 142.1, 138.4, 133.5, 132.4, 130.1, 129.6, 128.8, 127.7, 127.6, 126.3, 123.0, 122.7, 119.8, 116.6, 113.1, 111.4, 59.2, 32.9, 30.4, 14.4; HRMS (ESI) m/z: calcd for $C_{25}H_{20}N_3O$ $[M + H]^+$ 378.1601, found 378.1604.

Ethyl 3-(4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanoate (**4a**). Yellow solid (55.0 mg, 76% yield); mp 83–84 ^{o}C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.54 (d, J = 8.2 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 7.6 Hz, 1H), 7.84 (t, J = 8.1 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 3.96–3.90 (m, 2H), 3.61 (s, 3H), 2.83–2.60 (m, 2H), 2.28–2.05 (m, 2H), 1.82 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.5, 172.9, 158.8, 144.8, 138.7, 133.3, 131.9, 129.9, 129.2, 126.8, 122.7, 122.6, 116.2, 112.2, 110.9, 60.3, 50.7, 36.3, 30.5, 29.9, 28.5, 14.1; HRMS (ESI) m/z: calcd for $C_{22}H_{23}N_2O_3$ $[M + H]^+$ 363.1703, found 363.1704.

Ethyl 3-(9-(tert-butyl)-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl) propanoate (**4b**). Yellow oil (61.1 mg, 73% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.48 (d, J = 8.7 Hz, 1H), 8.27 (d, J = 8.3 Hz, 1H), 8.15 (s, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.76 (dd, J = 8.6, 1.8 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 3.95 (q, J = 7.1 Hz, 2H), 3.61 (s, 3H), 2.83–2.61 (m, 2H), 2.28–2.05 (m, 2H), 1.83 (s, 3H), 1.50 (s, 9H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.6, 172.9, 158.6, 152.6, 144.9, 138.7, 133.2, 131.8, 125.6, 125.2, 122.2, 120.4, 116.1, 112.0, 110.4, 60.3, 50.6, 36.4, 35.1, 31.3, 30.5, 29.8, 28.6, 14.1; HRMS (ESI) m/z: calcd for $C_{26}H_{31}N_2O_3$ $[M + H]^+$ 419.2329, found 419.2328.

Ethyl 3-(4,6-dimethyl-5-oxo-9-phenoxy-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl) propanoate (**4c**). Yellow oil (54.5 mg, 60% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.51 (d, J = 9.0 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H), 7.84 (t, J = 8.1 Hz, 1H), 7.63 (s, 1H), 7.47–7.42 (m, 3H), 7.24 (t, J = 7.4 Hz, 1H), 7.20–7.18 (m, 3H), 3.95 (q, J = 6.9 Hz, 2H), 3.60 (s, 3H), 2.79–2.57 (m, 2H), 2.25–2.02 (m, 2H), 1.79 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.5, 172.2, 159.9, 158.6, 156.3, 146.3, 138.9, 133.3, 132.1, 130.1, 124.2, 124.2, 119.9, 119.1, 118.4, 115.8, 115.8, 111.6, 110.2, 50.9, 37.2, 36.1, 35.3, 29.9, 29.7, 28.5; HRMS (ESI) m/z: calcd for $C_{28}H_{27}N_2O_4$ $[M + H]^+$ 455.1965, found 455.1966.

Ethyl 3-(9-chloro-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl) propanoate (**4d**). Yellow oil (63.4 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (d, J

= 8.8 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 1.5 Hz, 1H), 7.80 (t, *J* = 8.1 Hz, 1H), 7.50 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 3.90 (q, *J* = 7.1 Hz, 2H), 3.57 (s, 3H), 2.79–2.56(m, 2H), 2.27–2.03 (m, 2H), 1.77 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.2, 172.7, 160.3, 145.4, 138.8, 134.8, 132.8, 132.4, 128.9, 127.2, 123.9, 121.2, 116.0, 112.0, 111.1, 60.3, 50.7, 36.3, 30.4, 29.9, 28.3, 14.1; HRMS (ESI) m/z: calcd for $C_{22}H_{22}ClN_2O_3$ $[M + H]^+$ 397.1314, found 397.1313.

Ethyl 6-(3-ethoxy-3-oxopropyl)-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridine-9-carboxylate (**4e**). Yellow oil (47.8 mg, 55% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.86 (s, 1H), 8.59 (d, *J* = 8.6 Hz, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 8.29 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.91 (t, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 3.93 (q, *J* = 7.1 Hz, 2H), 3.62 (s, 3H), 2.86–2.60 (m, 2H), 2.29–2.06 (m, 2H), 1.82 (s, 3H), 1.50 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.3, 172.8, 166.4, 160.0, 144.3, 138.9, 132.7, 132.4, 131.8, 130.9, 126.7, 125.9, 122.8, 116.7, 112.7, 111.9, 61.4, 60.4, 50.8, 36.1, 30.4, 29.9, 28.5, 14.4, 14.1; HRMS (ESI) m/z: calcd for $C_{25}H_{27}N_2O_5$ $[M + H]^+$ 435.1915, found 435.1915.

3-(4,6-Dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)-N,N-dimethylpropanamide (**4f**). Yellow oil (56.3 mg, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.54 (d, *J* = 7.4 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.84 (t, *J* = 8.1 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.0 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 3.60 (s, 3H), 2.89–2.81 (m, 4H), 2.76 (s, 3H), 2.64–2.56 (m, 1H), 2.30–2.10 (m, 2H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.6, 172.2, 159.0, 144.8, 138.8, 133.3, 131.9, 129.8, 129.2, 126.7, 122.8, 122.6, 116.1, 112.2, 110.8, 50.9, 37.2, 35.9, 35.2, 29.9, 29.7, 28.7; HRMS (ESI) m/z: calcd for $C_{22}H_{24}N_3O_2$ $[M + H]^+$ 362.1863, found 362.1863.

3-(9-(tert-Butyl)-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)-N,N-dimethylpropanamide (**4g**). Yellow solid (66.8 mg, 80% yield); mp 184–185 ^{o}C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.46 (d, *J* = 8.7 Hz, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 8.12 (d, *J* = 0.9 Hz, 1H), 7.81 (t, *J* = 8.1 Hz, 1H), 7.74 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 3.60 (s, 3H), 2.90–2.83 (m, 4H), 2.78 (s, 3H), 2.65–2.57 (m, 1H), 2.30–2.07 (m, 2H), 1.77 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.7, 172.2, 158.8, 152.6, 145.0, 138.7, 133.2, 131.7, 125.7, 125.1, 122.2, 120.4, 116.1, 112.0, 110.4, 50.9, 37.2, 36.0, 35.3, 35.0, 31.3, 29.8, 29.7, 28.9;

HRMS (ESI) m/z: calcd for $C_{26}H_{32}N_3O_2$ $[M + H]^+$ 418.2489, found 418.2489.

3-(9-Chloro-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)-N,N-dimethylpropanamide (**4h**). Yellow oil (59.3 mg, 75% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.42 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.11 (d, J = 1.9 Hz, 1H), 7.84 (t, J = 8.1 Hz, 1H), 7.56 (dd, J = 8.8, 2.2 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 3.59 (s, 3H), 2.86 (s, 3H), 2.83–2.75 (m, 4H), 2.61–2.53 (m, 1H), 2.30–2.08 (m, 2H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.4, 172.1, 160.6, 145.4, 138.9, 134.8, 132.9, 132.4, 128.9, 127.2, 124.0, 121.3, 116.0, 112.1, 111.1, 51.0, 37.2, 35.9, 35.3, 29.9, 29.6, 28.5; HRMS (ESI) m/z: calcd for $C_{22}H_{23}ClN_3O_2$ $[M + H]^+$ 396.1473, found 396.1474.

3-(11-Chloro-4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)-N,N-dimethylpropanamide (**4i**). Yellow oil (56.9 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.53 (d, J = 8.7 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.83 (t, J = 8.4 Hz, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.59 (t, J = 7.9 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 3.59 (s, 3H), 2.87–2.80 (m, 4H), 2.75 (s, 3H), 2.59–2.52 (m, 1H), 2.28–2.08 (m, 2H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.1, 172.1, 159.7, 146.8, 138.5, 132.6, 131.4, 130.9, 130.4, 129.6, 128.4, 120.6, 113.0, 111.8, 50.6, 37.2, 35.7, 35.3, 30.1, 29.5, 28.5; HRMS (ESI) m/z: calcd for $C_{22}H_{23}ClN_3O_2$ $[M + H]^+$ 396.1473, found 396.1475.

9-(tert-Butyl)-4,6-dimethyl-6-(3-oxo-3-phenylpropyl)-4H-pyrido[4,3,2-gh]phenanthridin-5(6H)-one (**4j**). Yellow oil (59.4 mg, 66% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.49 (d, J = 8.7 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 1.6 Hz, 1H), 7.87–7.81 (m, 3H), 7.76 (dd, J = 8.7, 2.1 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.40–7.33 (m, 2H), 7.23 (d, J = 7.8 Hz, 1H), 3.63 (s, 3H), 3.03–2.73 (m, 4H), 1.82 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 199.6, 173.7, 158.8, 152.6, 145.0, 138.7, 136.7, 133.3, 132.8, 131.8, 128.3, 128.2, 125.7, 125.2, 122.2, 120.4, 116.1, 112.0, 110.4, 51.0, 35.5, 35.1, 31.3, 29.9, 29.1; HRMS (ESI) m/z: calcd for $C_{30}H_{31}N_2O_2$ $[M + H]^+$ 451.2380, found 451.2383.

9-Chloro-4,6-dimethyl-6-(3-oxo-3-phenylpropyl)-4H-pyrido[4,3,2-gh]phenanthridin-5(6H)-one (**4k**). White solid (53.9 mg, 63%); mp 140–142 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.43 (dd, J = 8.8, 1.5 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 1.1 Hz, 1H), 7.87 (t, J = 7.8 Hz, 1H), 7.79–7.77 (m, 2H), 7.60–7.56 (m, 1H), 7.50–7.46 (m, 1H), 7.37–7.33 (m, 2H), 7.27 (d, J = 8.0 Hz, 1H), 3.62 (s, 3H), 2.95–2.69 (m, 4H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm)

199.4, 173.4, 160.5, 145.4, 139.0, 136.6, 134.9, 133.0, 132.8, 132.4, 129.0, 128.4, 128.1, 127.3, 123.9, 121.3, 116.1, 112.1, 111.1, 51.1, 35.5, 34.8, 29.9, 28.6; HRMS (ESI) m/z: calcd for $C_{26}H_{22}N_2O_2$ $[M + H]^+$ 429.1364, found 429.1362.

The Hydrolyzation and Esterification of 3a.[22] To a stirred solution of **3a** (157.7 mg, 0.5 mmol) in MeOH (4 mL) in a sealed tube was added H_2O (4 drops), CH_3COOH (1 mL) and *conc*. H_2SO_4 (1.5 mL). The reaction mixture was heated at 90 ^oC for 24 h. After cooling to room temperature, the reaction mixture was slowly quenched with saturated aqueous $NaHCO_3$ to pH 8 and extracted with DCM (10 mL × 3). The combined organic phases were washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. The residue was purified by silica gel chromatography using hexane/ethyl acetate (5:1) to afford the pure product **5a**.

Methyl 3-(4,6-dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanoate (**5a**). Yellow oil (66.1 mg, 95% yield); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.53 (d, J = 8.1 Hz, 1H), 8.28 (d, J = 8.3 Hz, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.84 (t, J = 8.1 Hz, 1H), 7.76 (t, J = 7.5 Hz, 1H), 7.66 (t, J = 8.1 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 3.60 (s, 3H), 3.48 (s, 3H), 2.88–2.61 (m, 2H), 2.30–2.06 (m, 2H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.4, 173.3, 158.7, 144.7, 138.7, 133.3, 132.1, 129.8, 129.3, 126.8, 122.7, 122.6, 116.3, 112.1, 110.9, 51.5, 50.7, 36.1, 30.3, 29.9, 28.7; HRMS (ESI) m/z: calcd for $C_{21}H_{21}N_2O_3$ $[M + H]^+$ 349.1547, found 349.1546.

The Hydrolyzation and Amidation of 3a.[22] To a stirred solution of **3a** (157.7 mg, 0.5 mmol) in DMSO (2 mL) was added H_2O_2 (30% in water, 0.5 mL) and K_2CO_3 (69.1 mg, 0.5 mmol) at 0 ^oC. Then the reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (15 mL × 3). The combined organic phases were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography using hexane/ethyl acetate (5:1) to afford the pure product **6a**.

3-(4,6-Dimethyl-5-oxo-5,6-dihydro-4H-pyrido[4,3,2-gh]phenanthridin-6-yl)propanamide (**6a**). White solid (33.3 mg, 50% yield); mp 150–151 ^oC; ^1H NMR (400 MHz, DMSO–d_6) δ (ppm) 8.75 (d, J = 7.6 Hz, 1H), 8.48 (d, J = 8.3 Hz, 1H), 8.08 (dd, J = 8.2, 0.9 Hz, 1H), 7.94 (t, J = 8.1 Hz, 1H), 7.79 (t, J = 7.0 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.11 (s, 1H), 6.66 (s, 1H), 3.52 (s, 3H), 2.47–2.30 (m, 2H), 1.91–1.84 (m, 1H), 1.70 (s, 3H), 1.67–1.59 (m, 1H); ^{13}C NMR (100 MHz, DMSO–d_6) δ (ppm) 173.6, 173.0, 159.7, 144.7, 138.8, 133.1, 133.0, 129.8,

129.7, 127.3, 123.7, 122.9, 116.7, 112.2, 112.0, 50.5, 38.6, 31.1, 30.0, 28.1; HRMS (ESI) m/z: calcd for $C_{20}H_{20}N_3O_2$ $[M + H]^+$ 334.1550, found 334.1552.

4,4-Diphenylbut-3-enenitrile (**8a**).[23] Yellow solid (34.2 mg, 78% yield); mp 90–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.48–7.39 (m, 3H), 7.34–7.31 (m, 3H), 7.26–7.20 (m, 4H), 6.06 (t, J = 7.4 Hz, 1H), 3.18 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.5, 140.7, 138.0, 129.4, 128.8, 128.4, 128.2, 128.2, 127.5, 118.2, 115.5, 18.4.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^{1}H NMR and ^{13}C NMR spectra for all products, and the crystal structure of **3g** (PDF).

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Krane, B. D.; Fagbule, M. O.; Shamma, M. *J. Nat. Prod.* **1984**, *47*, 1. (b) Nakanishi, T.; Suzuki, M. *J. Nat. Prod.* **1998**, *61*, 1263.

(2) (a) Cushman, M.; Mohan, P.; Smith, E. C. R. *J. Med. Chem.* **1984**, *27*, 544. (b) Fang, S.-D.; Wang, L.-K.; Hecht, S. M. *J. Org. Chem.* **1993**, *58*, 5025. (c) Nakanishi, T.; Suzuki, M.;

Saimoto, A.; Kabasawa, T. *J. Nat. Prod.* **1999**, *62*, 864. (d) Li, D.-J.; Zhao, B.-P.; Sim, S.-P.; Li, T.-K.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 521. (e) Kock, I.; Heber, D.; Weide, M.; Wolschendorf, U.; Clement, B. *J. Med. Chem.* **2005**, *48*, 2772. (f) Tsukamoto, H.; Kondo, S.; Mukudai, Y.; Nagumo, T.; Yasuda, A.; Kurihara, Y.; Kamatani, T.; Shintani, S. *Anticancer Res*. **2011**, *31*, 2841. (g) Wang, D.; Chu, P.-C.; Yang, C.-N.; Yan, R.; Chuang, Y.-C.; Kulp, S. K.; Chen, C.-S. *J. Med. Chem.* **2012**, *55*, 3827. (h) Johnstone, T. C.; Lippard, S. J. *J. Am. Chem. Soc*. **2014**, *136*, 2126.

(3) Rivaud, M.; Mendoza, A.; Sauvain, M.; Valentin, A.; Jullian, V. *Bioorg. Med. Chem.* **2012**, *20*, 4856.

(4) Ishikawa, T. *Med. Res. Rev*. **2001**, *21*, 61.

(5) (a) Nakanishi, T.; Suzuki, M. *Org. Lett*. **1999**, *1*, 985. (b) Nakanishi, T.; Masuda, A.; Suwa, M.; Akiyama, Y.; Hoshino-Abe, N.; Suzuki, M. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2321.

(6) (a) Zhang, J.; Lakowicz, J. R. *J. Phys. Chem. B* **2005**, *109,* 8701. (b) Stevens, N.; O'Connor, N.; Vishwasrao, H.; Samaroo, D.; Kandel, E. R.; Akins, D. L.; Drain, C. M.; Turro, N. J. *J. Am. Chem. Soc*. **2008**, *130*, 7182. (c) Chen, Y.-L.; Li, F.-H.; Bo, Z.-S. *Macromolecules* **2010**, *43*, 1349.

(7) Marsden, S. P.; McGonagle, A. E.; McKeever-Abbas, B. *Org. Lett*. **2008**, *10*, 2589.

(8) (a) Hsieh, J.-C.; Cheng, C.-H. *Chem. Commun*. **2008**, *44*, 2992. (b) Li, Y.-J.; Zhu, J.-T.; Zhang, L.-S.; Wu, Y.-M.; Gong, Y.-F. *Chem. Eur. J*. **2013**, *19*, 8294.

(9) (a) Lamba, J. J. S.; Tour, J. M. *J. Am. Chem. Soc*. **1994**, *116*, 11723. (b) Gug, F.; Blondel, M.; Desban, N.; Bouaziz, S.; Vierfond, J.-M.; Galons, H. *Tetrahedron Lett*. **2005**, *46*, 3725. (c) Shabashov, D.; Daugulis, O. *J. Org. Chem*. **2007**, *72*, 7720. (d) Candito, D. A.; Lautens, M. *Angew. Chem., Int. Ed*. **2009**, *48*, 6713. (e) Maestri, G.; Larraufie, M.-H.; Derat, E.; Ollivier, C.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Org. Lett*. **2010**, *12*, 5692. (f) Blanchot, M.; Candito, D. A.; Larnaud, F.; Lautens, M. *Org. Lett*. **2011**, *13*, 1486. (g) Liu, Y.-Y.; Song, R.-J.; Wu, C.-Y.; Gong, L.-B.; Hu, M.; Wang, Z.-Q.; Xie, Y.-X.; Li, J.-H. *Adv. Synth. Catal*. **2012**, *354*, 347. (h) Wang, W.-Y.; Feng, X.; Hu, B.-L.; Deng, C.-L.; Zhang, X.-G. *J. Org. Chem*. **2013**, *78*, 6025. (i) Ghosh, M.; Ahmed, A.; Singha, R.; Ray, J. K. *Tetrahedron Lett*. **2015**, *56*, 353.

(10) (a) Mehta, B. K.; Yanagisawa, K.; Shiro, M.; Kotsuki, H. *Org. Lett*. **2003**, *5*, 1605. (b) Youn, S. W.; Bihn, J. H. *Tetrahedron Lett*. **2009**, *50*, 4598. (c) Zheng, Y.-H.; Lu, H.-Y.; Li, M.; Chen, C.-F. *Eur. J. Org. Chem*. **2013**, 3059.

(11) (a) Pawlas, J.; Begtrup, M. *Org. Lett*. **2002**, *4*, 2687. (b) Shou, W.-G.; Yang, Y.-Y.; Wang, Y.-G. *J. Org. Chem*. **2006**, *71*, 9241. (c) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed*. **2009**, *48*, 572.

(12) Yanada, R.; Hashimoto, K.; Tokizane, R.; Miwa, Y.; Minami, H.; Yanada, K.; Ishikura, M.; Takemoto, Y. *J. Org. Chem*. **2008**, *73*, 5135.

(13) Tang, C.-H.; Yuan, Y.-Z.; Jiao, N. *Org. Lett*. **2015**, *17*, 2206.

(14) Hu, Z.-Y.; Dong, J.-H.; Men, Y.; Li, Y.-F.; Xu, X.-X. *Chem. Commun*. **2017**, *53*, 1739.

(15) Nanni, D.; Pareschi, P.; Rizzoli, C.; Sgarabotto, P.; Tundo, A. *Tetrahedron*, **1995**, *51*, 9045.

(16) For selected papers and reviews, see: (a) Tobisu, M.; Koh, K.; Furukawa, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11363. (b) Wang, Q.-L.; Dong, X.-C.; Xiao, T.-B.; Zhou, L. *Org. Lett*. **2013**, 15, 4846. (c) Jiang, H.; Cheng, Y.-Z.; Wang, R.-Z.; Zheng, M.-M.; Zhang, Y.; Yu, S.-Y. *Angew. Chem., Int. Ed*. **2013**, *52*, 13289. (d) Zhang, B.; Daniliuc, C. G.; Studer, A. *Org. Lett*. **2014**, *16*, 250. (e) Zhang, B.; Studer, A. *Chem. Soc. Rev*. **2015**, *44*, 3505. (f) Wang, Y.-X.; Wang, J.-H.; Li, G.-X.; He, G.; Chen, G. *Org. Lett*. **2017**, *19*, 1442.

(17) (a) Forrester, A. R.; Gill, M.; Sadd, J. S.; Thomson, R. H. *J. Chem. Soc.*, *Perkin Trans. 1* **1979**, 612. (b) Alonso, R.; Campos, P. J.; García, B.; Rodríguez, M. A. *Org. Lett*. **2006**, *8*, 3521. (c) Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *Chem. Commun*. **2007**, *43*, 4041. (d) Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Org. Chem*. **2008**, *73*, 5558. (e) McBurney, R. T.; Slawin, A. M. Z.; Smart, L. A.; Yu, Y.; Walton, J. C. *Chem. Commun.* **2011**, *47*, 7974. (f) McBurney, R. T.; Walton, J. C. *J. Am. Chem. Soc*. **2013**, *135*, 7349. (g) Jiang, H.; An, X.-D.; Tong, K.; Zheng, T.-Y.; Zhang, Y.; Yu, S.-Y. *Angew. Chem., Int. Ed*. **2015**, *54*, 4055.

(18) (a) Lysén, M.; Kristensen, J. L.; Vedsø, P.; Begtrup, M. *Org. Lett*. **2002**, *4*, 257. (b) Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett*. **2010**, *12*, 3682. (c) Chen, Y.-F.; Hsieh, J.-C. *Org.*

Lett. **2014**, *16*, 4642. (d) Chen, W.-L.; Chen, C.-Y.; Chen, Y.-F.; Hsieh, J.-C. *Org. Lett*. **2015**, *17*, 1613.

(19) (a) Snider, B. B.; Buckman, B. O. *J. Org. Chem*. **1992**, *57*, 322. (b) Servais, A.; Azzouz, M.; Lopes, D.; Courillon, C.; Malacria, M. *Angew. Chem., Int. Ed*. **2007**, *46*, 576. (c) Streuff, J.; Feurer, M.; Bichovski, P.; Frey, G.; Gellrich, U. *Angew. Chem., Int. Ed*. **2012**, *51*, 8661. (d) Zhao, W.; Montgomery, J. *Angew. Chem., Int. Ed*. **2015**, *54*, 12683. (e) Li, Y.-M.; Wang, S.-S.; Yu, F-C.; Shen, Y.-H.; Chang, K.-J. *Org. Biomol. Chem*. **2015**, *13*, 5376. (f) Han, Y.-Y.; Jiang, H.; Wang, R.-Z.; Yu, S.-Y. *J. Org. Chem*. **2016**, *81*, 7276.

(20) (a) Yi, H.; Zhang, X.; Qin, C.; Liao, Z.; Liu, J.; Lei, A. *Adv. Synth. Catal.* **2014**, *356*, 2873. (b) Welin, E. R.; Warkentin, A. A.; Conrad, J. C.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 9668.

(21) Li, X.; Fang, X.; Zhuang, S.; Liu, P.; Sun, P. *Org. Lett*. **2017**, *19*, 3580.

(22) Yu, Y.; Zhuang, S.; Liu, P.; Sun, P. *J. Org. Chem*. **2016**, *81*, 11489.

(23) Liu, Q.; Yi, H.; Liu, J.; Yang, Y.; Zhang, X.; Zeng, Z.; Lei, A. *Chem. Eur. J*. **2013**, *19*, 5120.