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ORIGINAL ARTICLE

Efficient one-pot synthesis of new 1-amino substituted pyrrolo[1,2-a]quinoline-4-carboxylate esters via copper-free Sonogashira coupling reactions

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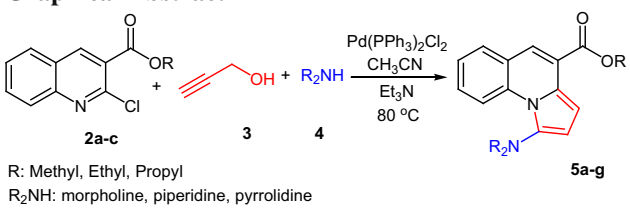
Abstract The reactions of several 2-chloroquinoline-3-carboxylate esters with propargyl alcohol and a secondary amine in the presence of palladium catalyst leads to the formation of new alkyl 1-amino substituted pyrrolo[1,2-a]quinoline-4-carboxylate derivatives. This one-pot process, carried out in the absence of any copper salt, provides an efficient method for the synthesis of functionalized pyrrolo[1,2-a]quinolines in good-to-high yields.

Graphical Abstract



Keywords Propargyl alcohol · Pyrrolo[1,2-a]quinoline · Palladium catalyst · Copper-free · Sonogashira coupling

Intoduction

Among all kinds of transition metal-catalyzed coupling reactions, the Sonogashira cross-coupling reaction [1] provides a powerful route to the C(sp)–C(sp^2) bond formation. It is a useful method for the synthesis of a variety of compounds including arylalkynes and conjugated enynes [2], heterocycles [3,4], several natural products, pharmaceuticals [5], and oligomers and polymers [6].

In general, the usual catalytic system for a Sonogashira coupling reaction is made up of palladium–phosphine complexes with copper(I) iodide in the presence of an excess or a stoichiometric amount of a base [7,8]. In the recent years, although a significant modification has been reported for the Sonogashira coupling procedure, efficient copper-free reactions have been developed to prevent the oxidative homocoupling reaction of acetylenes (Glaser-type reaction) [9,10]. The byproducts of the homocoupling reactions are usually difficult to separate from the desired products, and the copper acetylide formed in the reaction is a potentially explosive reagent [11]. Although copper-free Sonogashira coupling reactions have been widely investigated [12–14], few examples with aryl chlorides [15–17] and heteroaryl chlorides such as pyridyl chlorides [18] and 2-chloroquinolines [19] with terminal alkynes have been reported.

Quinolines are an important class of nitrogen-containing heterocyclic compounds, due to their wide occurrence in natural products [20] and their interesting biological properties [21]. Pyrrolo[1,2-a]quinolines, found extensively in nature in alkaloids such as gephyrotoxin [22,23], are natural alkaloids that have been the subject of many investigations. They also show a wide range of pharmaceutical activities, such as anti-inflammatory [24], anti-viral [25], analgesic [26], and antitumor [27] activities.

In view of their significant biological importances, many efforts have been dedicated to the development of new synthetic methodologies for the preparation of pyrrolo[1,2-a]quinolines [28–30]. Synthesis of these compounds based on the C–C bond formation synthetic strategies via tran-

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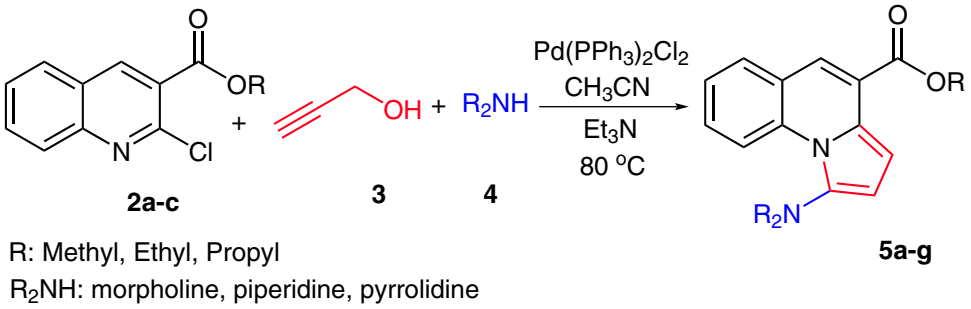
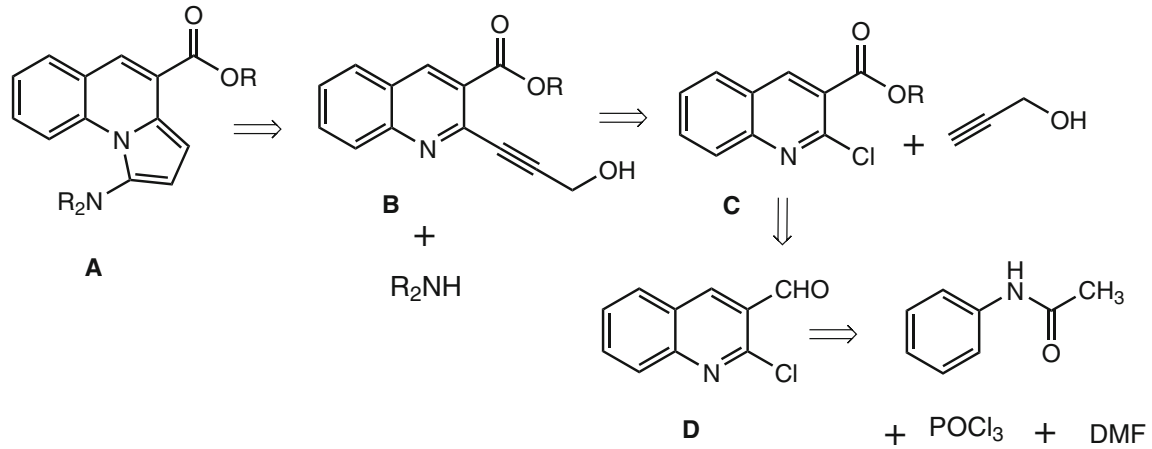
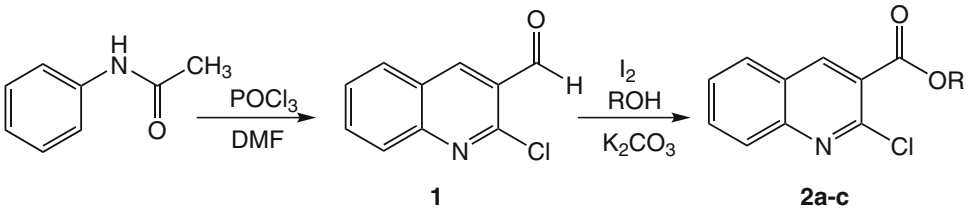


Scheme 1 Sonogashira coupling/cyclization reaction of alkyl 2-chloroquinoline-3-carboxylate with propargyl alcohol and a secondary amine. [a]Reaction conditions: 2a–c (1 mmol), 3 (1.25 mmol), secondary amine (3 mmol), Et_3N (3 mmol), $Pd(PPh_3)_2Cl_2$ (0.05 mmol), distilled CH_3CN (5 mL), 80 °C, 18 h, argon atmosphere



Scheme 2 Retrosynthetic analysis of 1-amino substituted pyrrolo[1,2-a]quinoline-4-carboxylate esters

Scheme 3 Synthesis of alkyl 2-chloroquinoline-3-carboxylates 2a–c from acetanilide in two steps



sition metal-catalyzed coupling reactions has been little explored. In continuation as part of our research [31–34] on the Pd-catalyzed reaction of acetylenes leading to heterocyclic compounds of biological significance, we decided to develop a modified Sonogashira coupling reaction/heteroannulation for the one-pot synthesis of new pyrrolo[1,2-a]quinoline esters. In this paper, a simple, direct, and convenient multicomponent approach to the synthesis of alkyl 1-aminopyrrolo[1,2-a]quinoline-4-carboxylate derivatives from readily available materials is presented (Scheme 1).

To introduce diversity to our pyrrolo[1,2-a]quinoline derivatives, our retrosynthetic strategy chose the use of alkyl 2-chloroquinoline-3-carboxylate esters, propargyl alcohol, and a secondary amine as starting materials (Scheme 2). The Sonogashira cross-coupling reaction is the key step in this synthesis.

The starting materials **2a–c** were prepared from commercially available acetanilide in several steps via a Vilsmeier-Haack reaction [35], followed by substituent oxidation/esterification in alcohol in the presence of iodine [36] (Scheme 3; Table 1).

Initially, we chose the reaction of methyl 2-chloroquinoline-3-carboxylate ester (**2a**) with propargyl alcohol (**3**) and morpholine as the model reaction to study the copper-free Sonogashira coupling and optimize the reaction conditions. In order to find the optimized conditions for the synthesis of methyl 1-morpholinopyrrolo[1,2-a]quinoline-4-

Table 1 Synthesis of alkyl 2-chloroquinoline-3-carboxylates **2a–c** from 2-chloroquinoline-3-carbaldehyde in the presence of iodine

Entry	R	Product	MP (°C)	Yield (%)
1	Methyl	**2a**	96	90
2	Ethyl	**2b**	106	80
3	Propyl	**2c**	112	80

Conditions: 2-chloroquinoline-3-carbaldehyde (1 mmol), I_2 (3 mmol), K_2CO_3 (3 mmol), alcohol (5 mL), room temperature

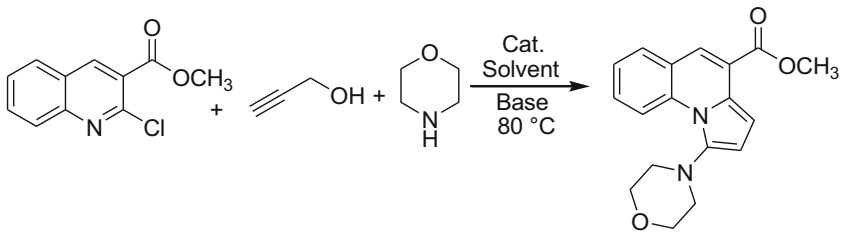
carboxylate (**5a**), the effects of various reaction parameters were studied (Table 2). We studied two catalytic systems: $Pd(PPh_3)_2Cl_2$and Pd/C, in different solvents and in the presence of several bases such as Et_3N, K_2CO_3, and DIPEA. We found that $Pd(PPh_3)_2Cl_2$ was the optimal catalyst based on product yields. Amongst the solvents tested, acetonitrile was found to be the most suitable one, and Et_3N was the optimal base to use.

After optimizing the reaction conditions, in order to explore the scope and generality of this protocol, we applied the reaction on three series of alkyl 2-chloroquinoline-3-carboxylate esters (**2a–c**) in the presence of propargyl alcohol (**3**) and a number of secondary amines (**4**), which afforded the corresponding products **5a–g** in good-to-high yields (Table 3).

The structural assignments of compounds **5a–g** were based on spectroscopic data and mass analysis. The ^{1}H NMR spectrum for methyl 1-morpholinopyrrolo[1,2-a]quinoline-4-carboxylate (**5a)** showed a doublet at δ 9.47, which is characteristic of an aromatic proton at position 9 of this heterocyclic system; it was deshielded by the diamagnetic pyrrole ring system. A singlet at δ 7.78 is characteristic of the proton at position 5, and the other three aromatic protons in the quinoline ring appeared at δ 7.32–7.75. The two doublets at δ 7.23 and δ 6.54 were assigned to the two protons at positions 2 and 3 in the fused pyrrole ring. In the aliphatic region, the 11 protons of the morpholine and methoxy substituents of this heterocyclic system appeared at δ 2.96–4.04.

Mechanistically, the key step of the process is the Sonogashira coupling reaction, catalyzed by a Pd(II) complex together with CuI as co-catalyst. Copper(I) iodide reacts with the terminal alkyne to yield a copper(I) acetylide which acts as an activated species in the transmetalation step [7]. In the copper-free Sonogashira coupling reaction, the initial oxidative addition is followed by alkyne coordination, and completed by subsequent deprotonation and reductive elimination [37].

Table 2 Optimization table for one-pot synthesis of methyl 1-morpholinopyrrolo[1,2-a]quinoline-4-carboxylate



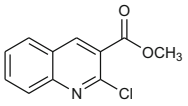
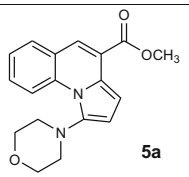
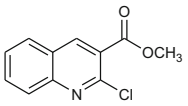
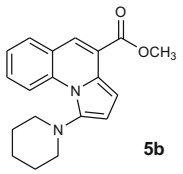
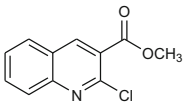
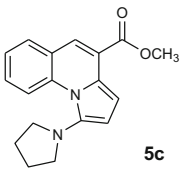
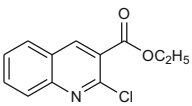
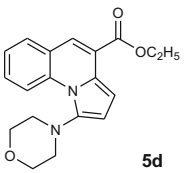
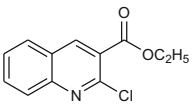
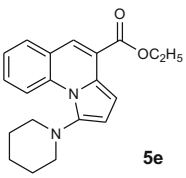
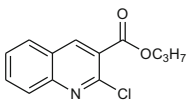
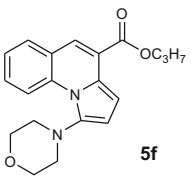
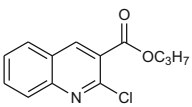
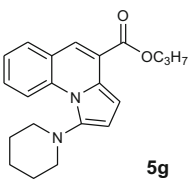
Entry	Solvent	Base	Catalyst	Yield
1	CH_3CN	K_2CO_3	$Pd(PPh_3)_2Cl_2$	35
2	CH_3CN	DIPEA	$Pd(PPh_3)_2Cl_2$	44
3	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	77
4	DMF	K_2CO_3	$Pd(PPh_3)_2Cl_2$	35
5	DMF	Na_2CO_3	$Pd(PPh_3)_2Cl_2$	30
6	DMF	Et_3N	$Pd(PPh_3)_2Cl_2$	60
7	CH_3CN	Et_3N	Pd/C	20
8	CH_3CN	DIPEA	Pd/C	17
9	DMF	K_2CO_3	Pd/C	Trace
10	H_2O	K_2CO_3	$Pd(PPh_3)_2Cl_2$	–
11	H_2O	Et_3N	$Pd(PPh_3)_2Cl_2$	25
12	CH_3CN	Et_3N	–	–
13	–	Et_3N	$Pd(PPh_3)_2Cl_2$	40[a]
14	CH_3CN	Et_3N	$Pd(PPh_3)_2Cl_2$	–[b]

Reaction conditions: **2a–e** (1 mmol)**, 3** (1.25 mmol), secondary amine (3 mmol), base (3 mmol), $Pd(PPh_3)_2Cl_2$ (0.05 mmol), CuI (1 mmol), solvent (5 mL), 80 °C, 18 h, argon atmosphere

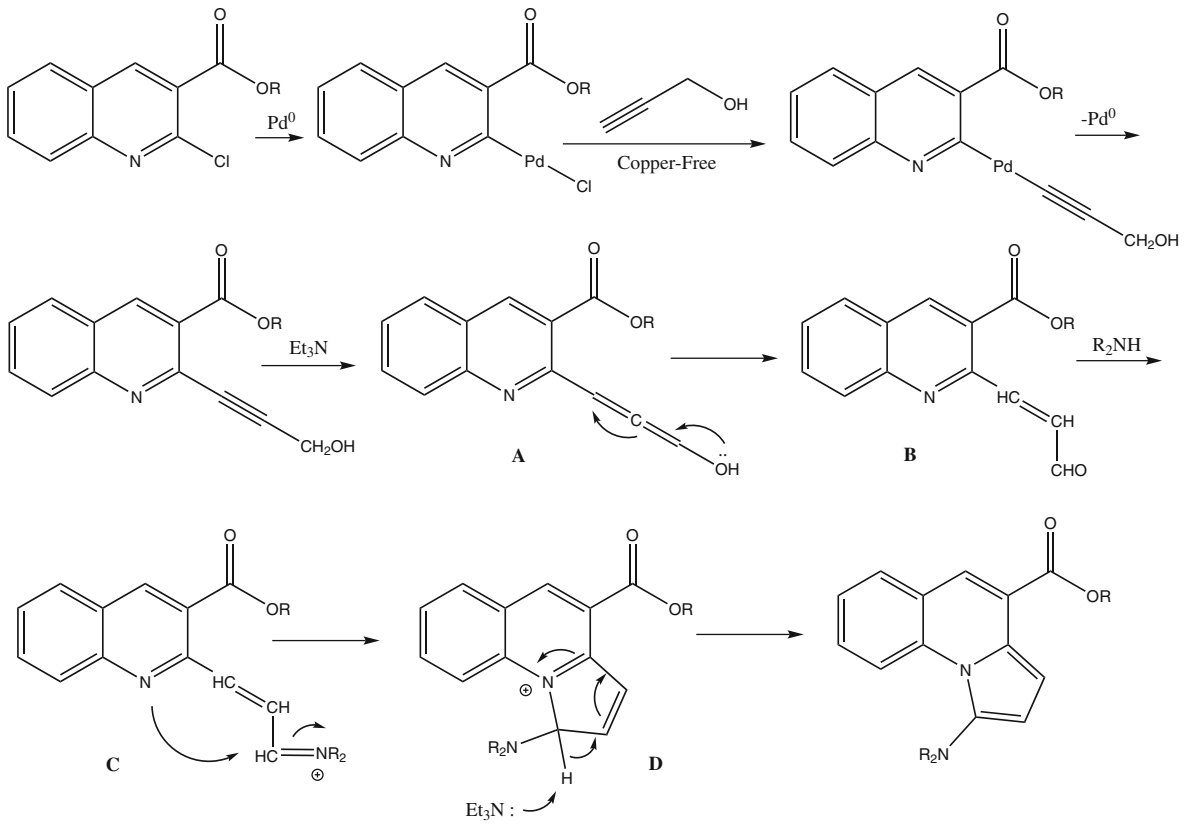
[a] Et_3N (6 mmol)

[b] At room temperature

Table 3 Synthesis of 1-amino substituted pyrrolo[1,2-a]quinoline-4-carboxylate esters

Entry	3-substituted 2-chloroquinoline **2**	Product	Mp (°C)	Yield (%)
1		 **5a**	101-102	77
2		 **5b**	77-80	75
3		 **5c**	85-87	70
4		 **5d**	88-90	81
5		 **5e**	79-81	78
6		 **5f**	92-94	75
7		 **5g**	89-91	80

Reaction conditions: **2** (1 mmol), **3** (1.25 mmol), secondary amine (3 mmol), Et_3N (3 mmol), $Pd(Ph_3P)_2Cl_2$ (0.05 mmol), CH_3CN (5 mL), 80 °C, 18 h, argon atmosphere



Scheme 4 Proposed mechanism for the formation of alkyl 1-amino substituted pyrrolo[1,2-a]quinoline-4-carboxylates

A plausible multistep mechanism for the copper-free Sonogashira coupling and heteroannulation reactions is proposed (Scheme 4). First, a copper-free Sonogashira coupling takes place by a Pd(0)-catalyzed reaction, followed by isomerization to the allene intermediate **A**, enone aldehyde **B**, and iminium ion **C**, cyclization to the fused ring system**D**, and finally, a base-induced aromatization to afford the product.

Conclusions

In summary, we have developed an efficient and successful copper-free palladium-catalyzed protocol for the synthesis of new 1-amino substituted pyrrolo[1,2-a]quinoline-4-carboxylate esters from alkyl 2-chloroquinoline-3-carboxylates and propargyl alcohol in the presence of secondary amines adopting a one-pot process.

Experimental

Palladium(II) chloride, triphenylphosphine, and propargyl alcohol were purchased from Sigma-Aldrich chemical company, and used without further purification. Acetanilide, phosphorylchlorid, *N*,*N*-dimethylformamide, triethylamine, secondry amines, thin-layer chromatography plate, silica gel (particle size, 100–200 mesh), and all the solvents used for the reactions were purchased from Merck. NMR spectra were recorded on a Bruker 300 (300 MHz ^{1}H, 75 MHz ^{13}C) spectrometer. ^{1}H NMR signals were reported relative to Me_4Si (δ 0.0) or residual $CHCl_3$ (δ 7.26). ^{13}C NMR signals were reported relative to $CDCl_3$ (δ 77.16). Multiplicities were described using the following abbreviations: s = singlet, d = doublet, t = triplet, and m = multiplet. IR spectra were measured on a Shimadzu IR-435 grating spectrophotometer. Mass spectra were recorded on a 5975C spectrometer (manufactured in Agilent Technologies Company).

Synthesis of 2-chloroquinoline-3-carbaldehyde (1)

To a solution of acetanilide (5 mmol, 0.68 g) in dry DMF (15 mmol, 1.09 g) at 0–5 °C, under stirring, phosphoryl chloride (60 mmol, 9.20 g) was added dropwise, and the mixture was stirred at 80–90 °C for 16 h. The mixture was then poured onto crushed ice, stirred well, and the resulting solid was filtered, washed thoroughly with cold water, and dried. The products were purified by recrystallization from CH_3CN [35].

Synthesis of alkyl 2-chloroquinoline-3-carboxylates (2a–c)

A mixture of 2-chloroquinoline-3-carbaldehyde (0.5 mmol, 0.096 g), K_2CO_3 (3 mmol, 0.25 g), and iodine (2 mmol, 0.51 g) in alcohol (3 mL) was stirred at room temperature until the disappearance of the starting material (monitored by TLC). The reaction mixture was then quenched with saturated aq. $Na_2S_2O_3$ (5 mL) and water (5 mL). The resulting solid was filtered, washed with water (5 mL), and dried. The crude product was characterized and found to be pure enough to be used as is for further use [36]. The analytic data for **2b** and **2c** are given below.

Ethyl 2-chloroquinoline-3-carboxylate (2b)

Dark yellow solid; mp, 106 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.35 (t, J = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 4.42 (q, J = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 7.32–7.70 (m, 4H, 4CH of quinoline), 8.91 (s, 1H, CH of quinoline); IR (KBr): 2931, 1730 cm^{-1}; MS (EI): m/z [M]$^+$, 235.

Propyl 2-chloroquinoline-3-carboxylate (2c)

Brown solid; mp, 112 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07 (t, J = 7.3 Hz, 3H, $OCH_2CH_2C\underline{H}_3$), 1.68–1.80 (m, 2H, $OCH_2C\underline{H}_2CH_3$), 4.32 (t, J = 6.8 Hz, 2H, $OC\underline{H}_2CH_2CH_3$), 7.21–7.68 (m, 4H, 4CH of quinoline), 8.90 (s, 1H, CH of quinoline); IR (KBr): 2928, 1730 cm^{-1}; MS (EI): m/z[M]$^+$, 249.

General procedure for synthesis of 1-aminopyrrolo[1,2-a]quinoline-4-carboxylate esters (5a–g)

A mixture of 2-chloroquinoline-3-carboxylate (1 mmol), $Pd(PPh_3)_2Cl_2$ (0.05 mmol, 0.036 g), and Et_3N (3 mmol, 0.30 g) was stirred in CH_3CN (5 mL) at room temperature under an argon atmosphere. Propargyl alcohol (1.25 mmol, 0.07 g) was added, and the mixture was further stirred at 80 °C for 3 h. Then, a secondary amine was added, and the mixture was stirred at 80 °C for 12 h. The resulting solution was concentrated in vacuo, and the crude residue was subjected to column chromatography (silica gel) using $CHCl_3$ as eluent.

Methyl 1-morpholinopyrrolo[1,2-a]quinoline-4-carboxylate (5a)

Light orange solid; mp, 101–102 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.96–3.05 (m, 2H, NCH_2), 3.16–3.20 (m, 2H, NCH_2), 3.92–4.04 (m, 7H, OCH_3, 2 OCH_2), 6.54 (d, J = 3.9 Hz, 1H, CH of pyrrole), 7.23 (d, J= 4.2 Hz, 1H, CH of pyrrole), 7.32–7.37 (m, 1H, CH of quinoline), 7.54–7.60 (m, 1H, CH of quinoline), 7.71–7.72 (m, 1H, CH of quinoline), 7.78 (s, 1H, CH of quinoline), 9.47 (d, J = 8.7 Hz, 1H, CH of quinoline); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.06, 52.01, 65.85, 101.39, 102.34, 115.99, 119.85, 122.52, 122.55, 123.44, 123.75, 128.68, 128.02, 135.32, 140.95, 164.93; IR (KBr): 2928, 1720, 1600 cm^{-1}; MS (EI): m/z[M]$^+$, 310.

Methyl 1-(piperidin-1-yl)pyrrolo[1,2-a]quinoline-4-carboxylate (5b)

Light orange solid; mp, 77–80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69–1.95 (m, 6H, 3 CH_2), 2.63–2.71 (m, 2H, NCH_2), 3.31–3.35 (m, 2H, NCH_2), 3.99 (s, 3H, OCH_3), 6.48 (d, J = 4.2 Hz, 1H, CH of pyrrole), 7.20 (d, J = 3.9 Hz, 1H, CH of pyrrole), 7.28–7.35 (m, 1H, CH of quinoline), 7.53–7.58 (m, 1H, CH of quinoline), 7.66–7.69 (m, 1H, CH of quinoline), 7.74 (s,1H, CH of quinoline), 9.47 (d, J = 8.7 Hz, 1H, CH of quinoline); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.07, 24.81, 51.00, 52.90, 100.82, 102.15, 116.36, 119.86, 122.29, 125.61, 123.05, 123.30, 127.81, 128.39, 135.57, 142.71, 165.11; IR (KBr): 2920, 1721 cm^{-1}; MS (EI): m/z[M]$^+$, 308.

Methyl 1-(pyrrolidin-1-yl)pyrrolo[1,2-a]quinoline-4-carboxylate (5c)

Yellow solid; mp, 85–87 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28–1.45 (m, 4H, 2CH_2), 2.70–2.86 (m, 2H, NCH_2), 3.20–3.38 (m, 2H, NCH_2), 3.99 (s, 3H, OCH_3), 6.53 (d, J = 3.9 Hz, 1H, CH of pyrrole), 7.20 (d, J = 3.9 Hz, 1H, CH of pyrrole), 7.31–7.34 (m, 1H, CH of quinoline), 7.54–7.57 (m, 1H, CH of quinoline), 7.64–7.69 (m, 1H, CH of quinoline), 7.74 (s, 1H, CH of quinoline), 9.22 (d, J = 8.7 Hz, 1H, CH of quinoline); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.50, 51.00, 52.08, 100.57, 102.17, 116.34, 119.80, 122.26, 122.69, 123.36, 127.71, 128.32, 129.86, 135.57, 140.23, 166.74; IR (KBr): 2920, 1728 cm^{-1}; MS (EI): m/z[M]$^+$, 294.

Ethyl 1-morpholinopyrrolo[1,2-a]quinoline-4-carboxylate (5d)

Orange solid; mp, 88–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (t,J = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 2.96–3.05 (m, 2H, NCH_2), 3.16–3.20 (m, 2H, NCH_2), 3.92–4.04 (m, 4H, $2OCH_2$), 4.77 (q, J = 7.0 Hz, 2H, $OC\underline{H}_2CH_3$), 6.54 (d, J = 4.2 Hz, 1H, CH of pyrrole), 7.23 (d, J = 4.2 Hz, 1H, CH of pyrrole), 7.32–7.38 (m, 1H, CH of quinoline), 7.54–7.60 (m, 1H, CH of quinoline), 7.70–7.75 (m, 1H, CH of quinoline), 7.78 (s, 1H, CH of quinoline), 9.48 (d, J = 8.7 Hz, CH of quinoline); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.39, 53.06, 61.09, 68.15, 102.38, 103.38, 117.03, 121.22, 123.55, 124.37, 128.82, 128.99, 129.70, 130.90, 136.33, 1414.97, 167.77; IR (KBr): 2940, 1733 cm^{-1}; MS (EI): m/z[M]$^+$, 324.

Ethyl 1-(piperidin-1-yl)pyrrolo[1,2-a]quinoline-4-carboxylate (5e)

Orange solid; mp, 79–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.37 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.65–1.80 (m, 6H, $3CH_2$), 2.51–2.60 (m, 2H, NCH_2), 3.20–3.23 (m, 2H, NCH_2), 4.35 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 6.37 (d, J = 4.2 Hz, 1H, CH of pyrrole), 7.10 (d, J = 4.5 Hz, 1H, CH of pyrrole), 7.18–7.23 (m, 1H, CH of quinoline), 7.41–7.47 (m, 1H, CH of quinoline), 7.55–7.61 (m, 1H, CH of quinoline), 7.63 (s, 1H, CH of quinoline), 9.36 (d, J = 8.7 Hz, 1H, CH of quinoline); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.15, 25.85, 29.68, 53.94, 61.02, 101.80, 103.17, 117.39, 121.22, 123.31, 167.79, 124.43, 128.77, 129.41, 130.90, 136.58, 143.73, 167.79; IR (KBr): 2931, 1730 cm^{-1}; MS (EI): m/z[M]$^+$, 322.

Propyl 1-morpholinopyrrolo[1,2-a]quinoline-4-carboxylate (5f)

Orange solid; mp, 92–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.11 (t, J = 7.5 Hz, 3H, $OCH_2CH_2C\underline{H}_3$), 1.85–1.92 (m, 2H, $OCH_2C\underline{H}_2CH_3$), 2.96–3.05 (m, 2H, NCH_2), 3.16–3.20 (m, 2H, NCH_2), 3.92–4.03 (m, 4H, $2OCH_2$), 4.38 (t, J = 6.6 Hz, 2H, $OC\underline{H}_2CH_2CH_3$), 6.54 (d, J = 4.2 Hz, 1H, CH of pyrrole), 7.23 (d,J= 4.2 Hz, 1H, CH of pyrrole), 7.32-7.39 (m, 1H, CH of quinoline), 7.54–7.60 (m, 1H, CH of quinoline), 7.70–7.75 (m, 1H, CH of quinoline), 7.78 (s, 1H, CH of quinoline), 9.48 (d, J = 8.7 Hz, 1H, CH of quinoline); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.64, 21.12, 52.02, 65.70, 65.86, 101.35, 102.33, 115.99, 120.23, 122.50, 122.62, 123.33, 123.88, 128.67, 129.85, 135.30, 140.93, 164.63; IR (KBr): 2920, 1720 cm^{-1}; MS (EI): m/z[M]$^+$, 338.

Propyl 1-(piperidin-1-yl)pyrrolo[1,2-a]quinoline-4-carboxylate (5g)

Orange solid; mp, 89–91 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (t, J = 7.5 Hz, 3H, $OCH_2CH_2C\underline{H}_3$), 1.47–1.94 (m, 8H, $4CH_2$), 2.62–2.71 (m, 2H, NCH_2), 3.31–3.46 (m, 2H, NCH_2), 3.36 (t, J = 6.6 Hz, 2H, $OC\underline{H}_2CH_2CH_3$), 6.47 (d, J = 3.9 Hz, 1H, CH), 7.20 (d, J = 4.2 Hz, 1H, CH), 7.29–7.34 (m, 1H, CH of quinoline), 7.55–7.58 (m, 1H, CH of quinoline), 7.67–7.71 (m, 1H, CH of quinoline), 7.78 (s, 1H, CH of quinoline), 9.47 (d, J = 8.7 Hz, 1H, CH of quinoline); ^{13}C NMR (75 MHz, $CDCl_3$): 10.69, 22.17, 25.68, 29.72, 53.49, 66.67, 68.17, 101.82, 103.19, 117.39, 121.27, 123.31, 123.61, 123.99, 124.45, 128.61, 129.41, 136.58, 143.72, 165.85;; IR (KBr): 2925, 1720 cm^{-1}; MS (EI): m/z[M]$^+$, 336.

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