



Microwave-assisted multi-step synthesis of novel pyrrolo-[3,2-c]quinoline derivatives

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ABSTRACT

A new approach for the synthesis of original substituted pyrrolo-[3,2-c]quinoline derivatives using microwave-assisted chemistry is described. The use of microwave activation in this synthesis resulted in high yielding and clean steps. The key step for introducing diversity is the amination or the Pd-catalyzed cross-coupling of an imidoyl chloride derivative, obtained in a straightforward manner and in good yield.

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1. Introduction

Microwave-assisted chemistry² has greatly expanded in recent years with the arrival of specifically adapted equipment for the synthesis. The microwave-assisted synthesis found its first applications in organic chemistry, where some reactions proved to be 100 times faster with the microwave heating than with traditional ones (oil bath, etc.). The involved reactions are very often cleaner. Many organic reactions have been explored and adapted under microwave activation.^{3,4} Examples of multi-step synthesis in which each step requiring heating performed under microwave are scarce in the literature. We report herein a new microwave-enhanced multi-step synthetic pathway for the preparation of pyrrolo-[3,2-c]quinoline derivatives.

The pyrrolo-[3,2-c]quinoline and its analogue pyrroloquinoxaline skeleton (Fig. 1) have been known for several years as one of the most widely used motifs in medicinal chemistry. Several derivatives of such heterocycles possess a wide spectrum of biological activities, including most notably antitumor⁵ and hypotensive⁶ properties, gastric (H⁺/K⁺)-ATPase inhibition,^{7–9} anti-inflammatory activities,¹⁰ and 5-HT₃ agonism^{11–13} (Fig. 1). The discovery of bradykinine receptor agonist in an extract from the tropical plant *Martinella iquitosensis*¹⁴ has renewed the interest of

researchers to plan new synthetic approaches^{8,10,15,16} for the preparation of these molecules.

The wide potential of such a structure core unit has prompted us to develop an alternative synthetic route for the synthesis of 4-amino-1-methyl-4-1H-pyrrolo-[3,2-c]quinoline and 4-aryl-1-methyl-4-1H-pyrrolo-[3,2-c]quinoline derivatives.

As a continuation of our ongoing studies in the development of novel routes for the synthesis of substituted pyrroles,^{17,18} an alternative and convenient pathway leading to new series of pyrrolo-[3,2-c]quinoline derivatives is presented. The key intermediate is an imidoyl chloride and the diversity was introduced efficiently using microwave-activated amination^{11–13,19–22} and Suzuki^{2,19,22–27} cross-coupling reaction. In recent years these methods have found a widespread application in several areas of organic synthesis because they lead to the C_{sp}²–N or C_{sp}²–C_{sp}² bond formation, which cannot be easily formed using classical transformations.

The proposed retrosynthetic approach of imidoyl chloride **8** is presented in Scheme 1.

Examination of Scheme 1 reveals that, 4-chloro-1-methyl-1H-pyrrolo-[3,2-c]quinoline can be obtained from the corresponding amide via a chlorination reaction, and 1-methyl-1H-pyrrolo-[3,2-c]quinolin-4(5H)-one in turn would arise from cyclization of 1-methyl-2-(2-aminophenyl)-1H-pyrrole-3-carboxylate. The latter precursor would be synthesized according to the procedure, which has been developed in our group,¹⁸ via an aza-Baylis–Hillman/ring-closing metathesis/aromatization sequence.^{28–30}

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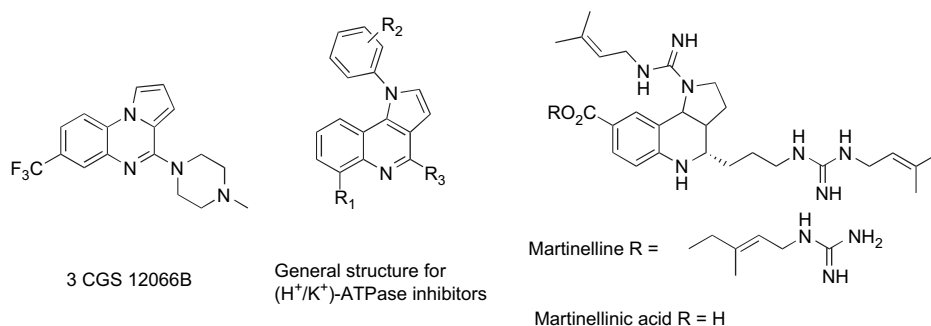
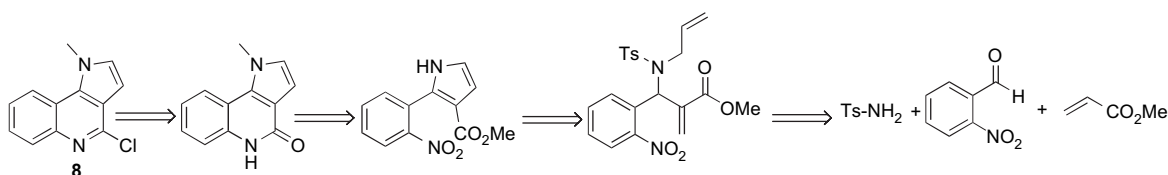


Figure 1. Examples of active pyrroloquinoline and quinoxaline derivatives.



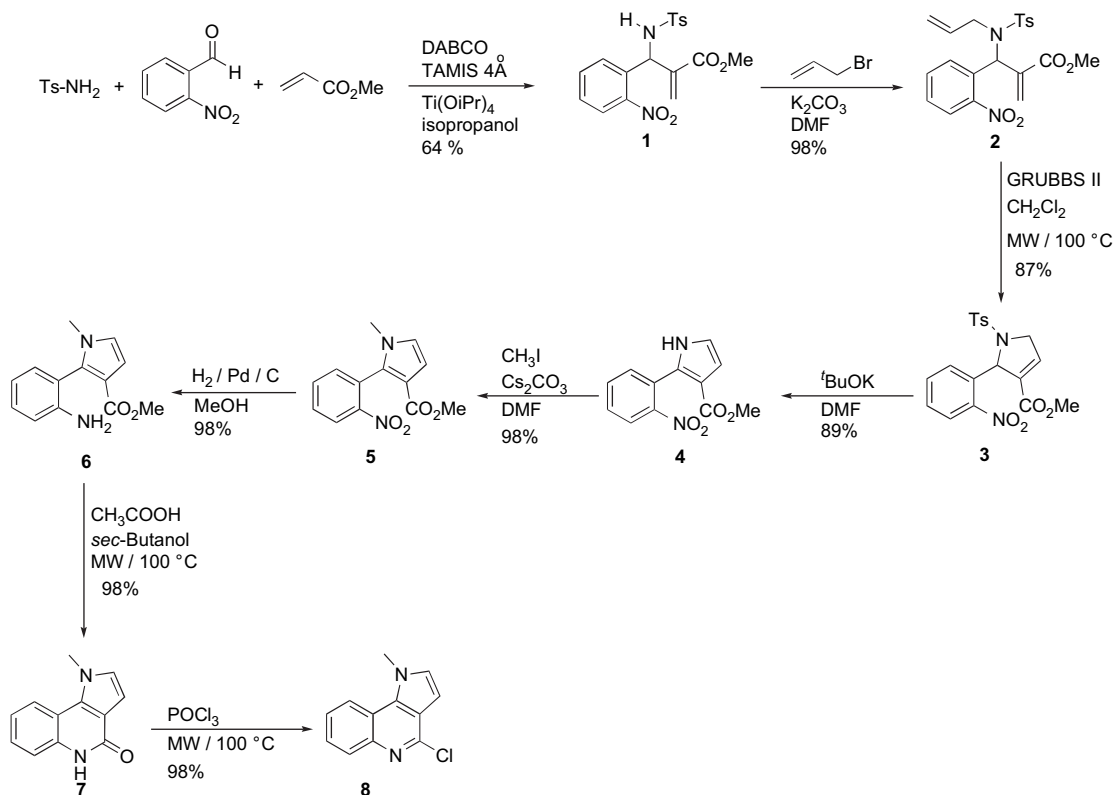
Scheme 1. Retrosynthesis of imidoyl chloride **8**.

2. Results and discussion

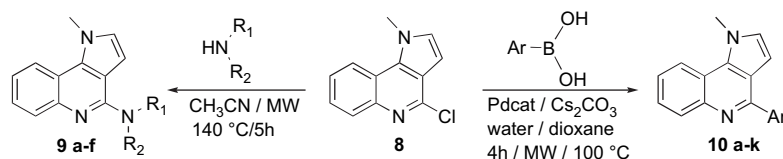
Scheme 2 describes the synthesis of the imidoyl chloride unit.⁸

The first step in this strategy was the synthesis of the unsaturated β -aminoester **1** through the 3-component one-pot aza-version of the Baylis–Hillman reaction.^{18,31–41} The reaction was performed using a nitrobenzaldehyde excess and methylacrylate, in the presence of DABCO, molecular sieves, titanium isopropoxide as a Lewis acid, and *i*-PrOH as solvent to yield 64% of **1** along with 30% of the corresponding β -hydroxyester. The β -aminoester **1** recovered

by crystallization in a mixture of dichloromethane, diethylether, and pentane was reacted with allyl bromide⁴² in the presence of K₂CO₃ in DMF to yield quantitatively the corresponding diene **2**. The reaction was performed either at room temperature within 12 h or heating under microwave irradiation at 100 °C within 10 min without affecting the yield. Diene **2** was used in the next step without further purification. Pyrroline **3** was formed using ring-closing metathesis⁴³ known to be an efficient method for the synthesis of heterocyclic structures from linear precursors. While cyclization of the diene **2** was complete within 12 h at room



Scheme 2. Procedure for the preparation of imidoyl chloride.⁸



Scheme 3. Amination and arylation of imidoyl chloride skeleton.

temperature using 10% second generation Grubbs' catalyst with 87% yield, it could be conveniently accelerated by microwave using only 4% of the catalyst. Under these conditions (microwaves, 100 °C, CH₂Cl₂) completion of the cyclization was reached within 2 h yielding 84% of **3**. An interesting point is that the cyclization of **2** was slower than in the case of other similar dienes without a nitro group.¹⁸ This result might be due to the coordinating effect^{44–46} between the nitro substituent and the ruthenium catalyst. The next step was cleavage of the tosyl group.^{17,47,48} Using *t*-BuOK in DMF at room temperature, 89% of substituted pyrrole **4** was obtained within 2 h via elimination–aromatization. The pyrrole **4** was reacted with methyl iodide⁴² in the presence of Cs₂CO₃ in DMF to yield the protected pyrrole **5** in quantitative yield. It should be noted that conversion was incomplete when K₂CO₃ was used instead of Cs₂CO₃. Reduction¹⁰ with Pd/C under H₂ atmosphere yielded the stable amine derivative **6** in excellent yield after simple filtration over Celite and evaporation of the solvent. Cyclization of the latter amine was first carried out using sodium hydride in THF. The conversion was complete but the cyclic product was difficult to recover since it was soluble only in DMSO. Finally a solution of **6** in *sec*-butanol in the presence of 1% acetic acid⁴⁹ was irradiated with microwaves for 4 h at 100 °C to afford the cyclic unit **7** in quantitative yield without further purifications. The key step in this strategy was the introduction of chlorine in the 4-position. This was achieved by transformation of the amide function into an imidoyl chloride using phosphorus oxychloride.¹¹ The reaction was carried out using classical conditions (refluxing **7** in phosphorus oxychloride for 7 h) or activation by microwave irradiation for only 15 min.

In contrast to what has been emphasized in the literature,^{9,50} the introduction of chlorine atom together with microwave-activated transformations allowed us to introduce successfully different substituent in the 4-position of the skeleton. These reactions are highlighted in Scheme 3.

Compound **8** was used for the preparation of substituted pyrroloquinolines. Reactions with amines and boronic acids were studied. The first tested reaction was the nucleophilic substitution of the chlorine atom by amines. Preliminary tests were carried out using different amines as nucleophiles and NaH as a base in THF but no product could be obtained under these conditions. Then the procedure described by Campiani¹¹ and co-workers was tried; a mixture of imidoyl chloride **8** and amine in ethylene glycol was heated using classical heating or activation by microwave irradiations. In both cases the reaction was incomplete. In sharp contrast, by using CH₃CN instead of ethylene glycol, completion of all the reactions was reached, even with less nucleophilic pyrrole. The reaction gave good to excellent yields with various amines. Results are summarized in Table 1. A lower yield was obtained in the case of morpholine (entry 4) due to the difficulty in separating the expected product **9d** from the starting amine.

The chlorine atom could be substituted by cyclic secondary amines such as pyrrolidine, morpholine or piperazine. Benzylamine gave also good yield of the expected product. As a last example, pyrrole reacted with **8** to give a pyrrole-substituted pyrroloquinoline.

The second investigated reaction was the Suzuki coupling of the imidoyl chloride with a boronic acid. First, Pd(OAc)₂, PPh₃ in the presence of K₂CO₃ in a mixture of water/dioxane (1:1) was used as

Table 1
Amination^a products of imidoyl chloride **8**

Entry	Amine	Product	Yield (%)
1	Pyrrolidine	9a	95
2	Piperidine	9b	85
3	4-Methylpiperazine	9c	80
4	Morpholine	9d	63
5	Benzylamine	9e	73
6	Pyrrole	9f	87

^a CH₃CN, MW, 140 °C, 5 h.

a catalytic system.^{2,23} The reaction was heated from 80 to 180 °C and monitored by HPLC. After 2 h at 180 °C the boronic acid disappeared completely, although some of the imidoyl chloride remained. The reaction was complete by addition of one more equivalent of boronic acid. A column chromatography was necessary to obtain the pure final product. By using the PEPPSI⁵¹ precatalyst (Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation) instead of Pd(OAc)₂, and in the presence of Cs₂CO₃, the desired compounds were obtained by heating at 100 °C under microwaves. These products were obtained in pure form after usual work-up without further purification. PEPPSI is a Pd complex stabilized by NHC (*N*-Heterocyclic Carbene) and pyridine ligands. They are known to allow rapid and quantitative C–C bond formation in Suzuki cross-coupling reactions.⁵¹ These results suggest that bulky NHC ligands lead to fast reductive elimination, with no side reactions or catalyst decomposition similarly with bulky phosphines.^{52,53} This catalyst seemed well adapted to Pd-catalyzed microwave-enhanced reactions. Results are summarized in Table 2.

Various substituents can be borne by the boronic acid. The position of the substituent on the aromatic ring did not seem to influence the outcome of the reaction since the more hindered *o*-tolyl boronic acid (entry 2) or *o*-anisyl boronic acid (entry 5) gave essentially the same yield of product as in the case of *m*- or *p*-tolyl boronic acid (entries 3 and 4). Fluorinated quinolines could also be synthesized (entries 6 and 7). Finally this method provided access to a variety of polyaromatic compounds (entries 8–11).

Often, the introduction of specific substituents other than simple alkyl ones in the 4-position on the performed skeleton required laborious steps coupled with drastic experimental conditions.^{10,16} To our knowledge, this is the first time that introduction of various substituents was carried out without any problems.

Table 2
Arylation^a of imidoyl chloride

Entry	Aryl	Product	Yield (%)
1	Phenyl	10a	84
2	<i>o</i> -Tolyl	10b	70
3	<i>m</i> -Tolyl	10c	74
4	<i>p</i> -Tolyl	10d	73
5	2-Methoxyphenyl	10e	75
6	4-Fluorophenyl	10f	90
7	4-Trifluoromethoxyphenyl	10g	76
8	Naphthalen-1-yl	10h	84
9	Biphenyl	10i	80
10	Benzofuran-2-yl	10j	91
11	1,2,3,4-Tetrahydro-1,1,4,4-tetramethylnaphthalen-6-yl	10k	73

^a Water/dioxane (1:1), PEPPSI (0.02 equiv), Cs₂CO₃ (1.5 equiv), MW, 100 °C, 4 h.

3. Conclusion

A new approach to the synthesis of a series of 4-amino-1-methyl-4-*1H*-pyrrolo-[3,2-*c*]quinoline and 4-aryl-1-methyl-4-*1H*-pyrrolo-[3,2-*c*]quinoline derivatives is described. This approach is based on high yielding steps, which do not need cumbersome purifications. In contrast to previously described methods, this new pathway allowed convenient introduction onto the 4-position the title ring system of a variety of amines and aryl compounds. This is largely due the use of microwave activation during several steps of the synthesis.

4. Experimental section

4.1. Methyl 2-((2-nitrophenyl)(*p*-toluenesulfonylamino)-methyl)acrylate (1)

To a mixture of *p*-toluenesulfonamide (9 g, 52.6 mmol), DABCO (885 mg, 7.9 mmol), and molecular sieves (4 Å, 10.5 g, 200 mg/mmol of substrate) in 27 ml of 2-propanol were added 2-nitrobenzaldehyde (11.9 g, 78.8 mmol), methyl acrylate (7.44 g, 86.7 mmol), and titanium isopropoxide (0.3 g, 1.05 mmol). The reaction mixture was stirred at room temperature overnight and filtered over Celite. The Celite was rinsed three times with CH₂Cl₂. The solvent was evaporated and the residue was dissolved in AcOEt, neutralized with aqueous KHSO₄ (10%), and washed with saturated NaHCO₃ and brine. The organic layer was dried over MgSO₄, filtered, and evaporated. Hot crystallization in a 5:5:1 mixture of pentane, diethylether, and dichloromethane afforded 13 g (63%) of β-aminoester **1**.

Mp 109–111 °C; ¹H NMR (CDCl₃, Me₄Si) δ 2.41 (s, 3H), 3.58 (s, 3H), 5.69 (s, 1H), 5.98 (d, 1H, *J*=8.62 Hz), 6.11 (d, 1H, *J*=8.62 Hz), 6.23 (s, 1H), 7.23–7.29 (m, 2H), 7.38–7.41 (m, 1H), 7.52–7.57 (m, 1H), 7.70 (d, 3H, *J*=8.12 Hz), 7.84 (d, 1H, *J*=8.06 Hz); ¹³C NMR (CDCl₃, Me₄Si) δ 21.1, 52.1, 54.4, 124.5, 127.2, 128.8, 129.1, 129.6, 130.1, 133.1, 133.4, 137.1, 137.4, 143.6, 148.0, 165.4; ESIMS *m/z* 781.25 (2M+H)⁺, 391.1 (M+H)⁺, 220.00 (M–TsNH)⁺; HRMS calcd for C₁₈H₁₉O₆N₂S, 391.0964; found, 391.0978.

4.2. Methyl 2-((*N*-allyl-*N*-tosylamino)(2-nitrophenyl)-methyl)acrylate (2)

To a mixture of β-aminoester **1** (4 g, 10.2 mmol) and K₂CO₃ (14 g, 102 mmol) in 140 ml of DMF was added allylbromide (2.99 g, 108 mmol). The reaction mixture was stirred overnight at room temperature, then filtered and diluted with AcOEt. The organic layer was successively washed with water and brine, dried over MgSO₄, filtered, and evaporated, to yield 4.29 g (98%) of *N*-allyl-β-aminoester **2**.

Mp 83–85 °C; ¹H NMR (CDCl₃, Me₄Si) δ 2.33 (s, 3H), 3.46 (s, 3H), 4.01 (dd, 1H, *J*=6.57 Hz, *J'*=6.43 Hz), 8.03 (dd, 1H, *J*=6.57 Hz, *J'*=6.43 Hz), 4.88–4.89 (m, 1H), 4.90 (d, 1H, *J*=1.23 Hz), 5.40–5.49 (m, 2H), 6.36 (s, 1H), 6.37 (s, 1H), 7.15–7.18 (m, 2H), 7.36–7.41 (m, 1H), 7.54–7.59 (m, 3H), 7.69 (d, 1H, *J*=7.71 Hz), 7.85 (d, 1H, *J*=8.08 Hz); ¹³C NMR (CDCl₃, Me₄Si) δ 43.1, 50.8, 52.1, 58.5, 118.7, 125.3, 127.7, 128.7, 129.3, 129.6, 130.5, 131.5, 132.9, 133.2, 133.7, 134.4, 137.8, 138.3, 143.3, 148.0, 165.4; ESIMS *m/z* 883.4 (2M+Na)⁺, 453.2 (M+Na)⁺, 431.2 (M+H)⁺, 220.4 (M–TsNC₃H₅)⁺, 188.4 (M–TsNC₃H₅–OMe)⁺; HRMS calcd for C₂₁H₂₃N₂O₆S, 431.1277; found, 431.1272.

4.3. Methyl 2,5-dihydro-2-(2-nitrophenyl)-1-tosyl-1H-pyrrole-3-carboxylate (3)

Conditions A. Cl₂(PCy₃)-(IMes)Ru=CHPh (0.1 g, 0.32 mmol) was added to a solution of *N*-allyl-β-aminoester (1 g, 2.32 mmol) in

232 ml of CH₂Cl₂, and the mixture was stirred overnight at room temperature. Then 0.48 ml of DMSO (50 equiv/Ru) was added and the mixture was stirred for 24 h at room temperature. The solvent was evaporated under vacuum. Column chromatography over silica gel and Et₂O/cyclohexane (1:9 to 3:7) as developing solvent affords 0.81 g (87%) of the desired 2,5-dihydropyrrole **3**.

Conditions B. A solution of Cl₂(PCy₃)-(IMes)Ru=CHPh (6.4 μmol) in CH₂Cl₂ (3 ml) was added to a solution of *N*-allyl-β-aminoester (500 mg, 1.16 mmol) in CH₂Cl₂ (9 ml), and the mixture was irradiated by microwaves for 2 h at 150 °C. Then 165 μl of DMSO (50 equiv/Ru) was added and the mixture was stirred for an additional time of 24 h. The solvent was dried under vacuum. Column chromatography over silica gel and Et₂O/cyclohexane (1:9 to 3:7) as developing solvent affords 380 mg (82%) of the desired 2,5-dihydropyrrole **3**.

Mp 125–127 °C; ¹H NMR (CDCl₃, Me₄Si) δ 2.36 (s, 3H), 3.45 (s, 3H), 4.29 (td, 1H, *J*=2.68 Hz), 4.54 (ddd, 1H, *J*=6 Hz), 6.61–6.64 (m, 1H), 6.68 (t, 1H, *J*=2 Hz), 7.27 (d, 2H, *J*=8.27 Hz), 7.31–7.36 (m, 1H), 7.48–7.50 (t, 2H, *J*=4.23 Hz, *J'*=3.8 Hz), 7.74 (d, 2H, *J*=8.27 Hz), 7.83 (d, 1H, *J*=8.22 Hz); ¹³C NMR (CDCl₃, Me₄Si) δ 21.6, 52.1, 55.7, 62.3, 124.6, 127.8, 128.6, 129.7, 130.0, 133.1, 133.4, 135.1, 135.7, 136.6, 144.2, 148.7, 161.6; ESIMS *m/z* 827 (2M+Na)⁺, 425 (M+Na)⁺, 403.2 (M+H)⁺; HRMS calcd for C₁₉H₁₉N₂O₆S, 403.0964; found, 403.0970.

4.4. Methyl 2-(2-nitrophenyl)-1H-pyrrole-3-carboxylate (4)

To a stirred solution of 2,5-dihydropyrrole (2 g, 4.97 mmol) in 50 ml of DMF was added *t*-BuOK (2.78 g, 24.8 mmol). The mixture was stirred at room temperature for 2 h, then 350 ml of AcOEt was added and the mixture was neutralized with a 1% aqueous solution of KHSO₄ and washed with NaHCO₃ saturated water, and brine. The organic layer was dried over MgSO₄, filtered, and evaporated. Column chromatography over silica gel and Et₂O/cyclohexane (1:9 to 1:1) as developing solvent yields 1.09 g (89%) of **4**.

¹H NMR (CDCl₃, Me₄Si) δ 3.55 (s, 3H), 6.64 (t, 1H, *J*=2.8 Hz), 6.76 (t, 1H, *J*=2.8 Hz), 7.37 (d, 1H, *J*=1.5 Hz), 7.44–7.49 (m, 1H), 7.52–7.58 (m, 1H), 7.94 (d, 1H, *J*=1.5 Hz), 8.6 (s, 1H); ¹³C NMR (CDCl₃, Me₄Si) δ 51.0, 111.4, 113.4, 118.7, 124.4, 127.3, 129.5, 131.4, 132.4, 132.5, 149.5, 164.8; ESIMS *m/z* 215.1 (M–OCH₃)⁺, 247.2 (M+H)⁺, 264.2 (M+H₂O)⁺, 269.2 (M+Na)⁺; HRMS calcd for C₁₂H₁₁N₂O₄, 247.0719; found, 247.0738.

4.5. Methyl 1-methyl-2-(2-nitrophenyl)-1H-pyrrole-3-carboxylate (5)

To a mixture of **4** (1 g, 4.06 mmol) and Cs₂CO₃ (5.29 g, 16.25 mmol) in 250 ml of DMF was added methyl iodide (2.3 g, 16.25 mmol). The reaction mixture was stirred overnight at room temperature, the solvent was evaporated, and the residue was diluted with AcOEt. The organic layer was washed with water and brine, dried over MgSO₄, filtered, and evaporated, to yield 1 g (98%) of **5**.

Mp 125–127 °C; ¹H NMR (CDCl₃, Me₄Si) δ 3.35 (s, 3H), 3.49 (s, 3H), 6.56 (d, 1H, *J*=2.97 Hz), 6.63 (d, 1H, *J*=2.97 Hz), 7.31 (dd, 1H, *J*=1.6 Hz, *J'*=1.6 Hz), 7.50–7.64 (m, 1H), 7.74 (d, 1H, *J*=8.27 Hz), 8.03 (dd, 1H, *J*=1.3 Hz, *J'*=1.3 Hz); ¹³C NMR (CDCl₃, Me₄Si) δ 31.9, 50.8, 110.2, 113.5, 122.9, 124.3, 127.8, 129.8, 132.8, 133.0, 133.2, 149.9, 164.6; ESIMS *m/z* 283.2 (M+Na)⁺, 261.2 (M+H)⁺, 229.2 (M–OCH₃)⁺; HRMS calcd for C₁₃H₁₃N₂O₄, 261.0875; found, 261.0870.

4.6. Methyl 1-methyl-2-(2-aminophenyl)-1H-pyrrole-3-carboxylate (6)

To a solution of **5** (1 g, 3.84 mmol) in methanol (200 ml) was added 10% (0.35 g) of Pd(OH)₂/C. The mixture was stirred for 2 h at room temperature under H₂ atmosphere. The crude product was

filtered over Celite, washed with warmed methanol, and evaporated to afford 0.86 g (98%) of the title compound as a white solid.

Mp 113–115 °C; ^1H NMR (CDCl_3 , Me_4Si) δ 3.33 (s, 3H), 3.53 (s, 2H), 3.59 (s, 3H), 6.59–6.62 (m, 2H), 6.69–6.77 (m, 2H), 6.97 (dd, 1H, $J=J'=1.4$ Hz), 7.12–7.19 (m, 1H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 34.3, 50.9, 110.0, 113.6, 115.5, 117.4, 118.2, 122.5, 129.9, 131.4, 135.5, 145.8, 165.0; ESIMS m/z 461.1 ($2\text{M}+\text{H}$) $^+$, 253.1 ($\text{M}+\text{Na}$) $^+$, 231.1 ($\text{M}+\text{H}$) $^+$, 199.1 ($\text{M}-\text{OCH}_3$) $^+$; HRMS calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2$, 231.1045; found, 231.1040.

4.7. 1-Methyl-1H-pyrrolo-[3,2-c]quinolin-4(5H)-one (7)

To a solution of **6** (0.25 g, 1.08 mmol) in *sec*-butanol (10 ml), was added 100 μl of acetic acid. The mixture was irradiated with microwaves for 4 h at 100 °C. The solvent was evaporated under reduced pressure to yield 0.21 g (98%) of the product as a white solid.

Mp 285–289 °C; ^1H NMR (CD_3OD , Me_4Si) δ 4.95 (s, 3H), 7.42 (d, 1H, $J=2.9$ Hz), 7.99–8.04 (m, 2H), 7.50–8.25 (m, 2H), 8.96 (d, 1H, $J=8.08$ Hz), 12.08 (s, 1H); ^{13}C NMR (CD_3OD , Me_4Si) δ 40.2, 106.5, 116.2, 118.7, 119.0, 123.8, 124.1, 129.5, 131.7, 135.6, 139.1, 161.9; ESIMS m/z 419.1 ($2\text{M}+\text{Na}$) $^+$, 397.1 ($2\text{M}+\text{H}$) $^+$, 221.1 ($\text{M}+\text{Na}$) $^+$, 199.1 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}$, 199.0871; found, 199.0874.

4.8. 4-Chloro-1-methyl-1H-pyrrolo-[3,2-c]quinoline (8)

Thermal conditions. A mixture of quinolinone **7** (500 mg, 2.52 mmol) and freshly distilled POCl_3 (30 ml) was refluxed for 7 h. The cooled crude product was poured into ice-water and the precipitate was extracted with CH_2Cl_2 (3×40 ml). The combined extracts were dried over MgSO_4 and concentrated under reduced pressure. The product was recovered as a white solid. The precipitate in the aqueous phase was filtered and washed with water. The solid fractions were combined yielding 530 mg (98%) of imidoyl chloride **8**.

Microwave irradiation. A mixture of quinolinone **7** (500 mg, 2.52 mmol) and freshly distilled POCl_3 (10 ml) was irradiated by microwave for 15 min at 140 °C. Then the crude product was poured into ice-water and the precipitate was extracted with CH_2Cl_2 (3×40 ml). The combined extracts were dried over MgSO_4 and concentrated under reduced pressure. The product was recovered as a white solid. The precipitate in aqueous phase was filtered and washed with water. The solid fractions were combined to yield 530 mg (98%) of imidoyl chloride **8**.

Mp 83–85 °C; ^1H NMR (CDCl_3 , Me_4Si) δ 4.23 (s, 3H), 6.73 (d, 1H, $J=3.1$ Hz), 7.08 (d, 1H, $J=3.1$ Hz), 7.51–7.61 (m, 2H), 8.22 (d, 1H, $J=7.6$ Hz), 8.30 (dd, 1H, $J=1.74$ Hz, $J'=1.06$ Hz); ^{13}C NMR (DMSO , Me_4Si) δ 37.6, 101.2, 118.1, 119.7, 121.3, 126.3, 127.0, 128.5, 131.8, 134.6, 142.7, 144.0; ESIMS m/z 217.1 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{Cl}$, 217.0533; found, 217.0548.

4.9. General procedure for the synthesis of 4-amino-1-methyl-1H-pyrrolo-[3,2-c]quinolines 9a–f

To a solution of imidoyl chloride **8** (20 mg, 9.25×10^{-2} mmol) in acetonitrile (2 ml) was added 5 equiv of amine, then the mixture was irradiated under microwaves for 5 h at 140 °C. The mixture was diluted with diethylether (20 ml), washed with water (2×10 ml), dried over MgSO_4 , and concentrated under reduced pressure to obtain the title compounds **9a–e**, which were purified by silica gel chromatography.

4.9.1. 1-Methyl-4-(pyrrolidin-1'-yl)-1H-pyrrolo-[3,2-c]-quinoline (9a)

The crude product was purified by silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}=100:1$) to yield 22.09 mg (95%) of the title compound.

^1H NMR (CD_3OD , Me_4Si) δ 2.01–2.06 (m, 4H), 3.79 (t, 4H, $J=6.4$ Hz), 4.06 (s, 3H), 6.84 (d, 1H, $J=3.2$ Hz), 7.12 (d, 1H, $J=3.2$ Hz), 7.27 (t, 1H, $J=7.3$ Hz), 7.41 (t, 1H, $J=7.3$ Hz), 7.60 (d, 1H, $J=8.3$ Hz), 8.15 (d, 1H, $J=8.3$ Hz); ^{13}C NMR (CD_3OD , Me_4Si) δ 26.4, 38.8, 51.2, 106.4, 111.7, 115.9, 121.8, 122.4, 124.5, 128.9, 131.1, 136.1, 150.6, 158.0; ESIMS m/z 252.0 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{N}_3$, 252.1501; found, 252.1500.

4.9.2. 1-Methyl-4-(piperidin-1'-yl)-1H-pyrrolo-[3,2-c]-quinoline (9b)

The crude product was purified by silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}=100:1$) to yield 20.9 mg (85%) of the title compound.

^1H NMR (CD_3OD , Me_4Si) δ 1.65–1.72 (m, 6H), 3.66 (t, 4H, $J=4.86$ Hz), 4.08 (s, 3H), 6.54 (d, 1H, $J=3.0$ Hz), 6.90 (d, 1H, $J=3.0$ Hz), 7.19–7.25 (m, 1H), 7.37–7.42 (m, 1H), 7.78–7.92 (m, 1H), 8.14 (d, 1H, $J=8.2$ Hz); ^{13}C NMR (CD_3OD , Me_4Si) δ 25.1, 26.2, 38.2, 49.7, 102.5, 113.9, 116.8, 119.9, 122.2, 126.2, 127.8, 131.1, 135.6, 150.6, 158.0; ESIMS m/z 266.3 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{17}\text{H}_{20}\text{N}_3$, 266.1657; found, 266.1642.

4.9.3. 1-Methyl-4-(4-methylpiperazin-1-yl)-1H-pyrrolo-[3,2-c]quinoline (9c)

The crude product was purified by silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}=100:1$) to yield 20.73 mg (80%) of the title compound.

^1H NMR (CD_3OD , Me_4Si) δ 2.31 (s, 3H), 2.58 (t, 4H, $J=4.9$ Hz), 3.76 (t, 4H, $J=4.9$ Hz), 4.12 (s, 3H), 6.54 (d, 1H, $J=3.1$ Hz), 6.89 (d, 1H, $J=3.1$ Hz), 7.18–7.26 (m, 1H), 7.37–7.43 (m, 1H), 7.83 (d, 1H, $J=8.2$ Hz), 8.14 (d, 1H, $J=8.2$ Hz); ^{13}C NMR (CD_3OD , Me_4Si) δ 38.2, 46.2, 48.2, 55.2, 102.2, 113.5, 116.9, 120.0, 122.4, 126.3, 127.9, 128.1, 135.7, 144.4, 154.9; ESIMS m/z 281.2 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{17}\text{H}_{21}\text{N}_4$, 281.1766; found, 281.1777.

4.9.4. 1-Methyl-4-morpholino-1H-pyrrolo-[3,2-c]quinoline (9d)

The crude product was purified by silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}=100:1$) to yield 15.56 mg (63%) of the title compound.

^1H NMR (CD_3OD , Me_4Si) δ 3.70 (t, 4H, $J=4.3$ Hz, $J'=4.9$ Hz), 3.86 (t, 4H, $J=4.3$ Hz, $J'=4.9$ Hz), 4.14 (s, 3H), 6.51 (d, 1H, $J=3.1$ Hz), 6.92 (d, 1H, $J=3.1$ Hz), 7.26 (t, 1H, $J=7.0$ Hz), 7.42 (t, 1H, $J=7$ Hz), 7.85 (d, 1H, $J=8.25$ Hz), 8.17 (d, 1H, $J=8.25$ Hz); ^{13}C NMR (CD_3OD , Me_4Si) δ 29.7, 38.2, 49.0, 67.1, 102.0, 113.5, 117.0, 120.0, 122.7, 126.4, 128.1, 135.3, 144.3, 154.9; ESIMS m/z 268.1 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}$, 268.1450; found, 268.1450.

4.9.5. N-Benzyl-1-methyl-1H-pyrrolo-[3,2-c]quinolin-4-amine (9e)

The crude product was purified by silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}=100:1$) to yield 19.38 mg (73%) of the title compound.

^1H NMR (CD_3OD , Me_4Si) δ 4.14 (s, 3H), 4.89 (d, 2H, $J=4.81$ Hz), 6.38 (d, 1H, $J=2.5$ Hz), 6.88 (d, 1H, $J=2.9$ Hz), 7.19–7.3 (m, 5H), 7.39–7.43 (m, 2H), 7.84 (d, 1H, $J=8.2$ Hz), 8.12 (d, 1H, $J=8.2$ Hz); ^{13}C NMR (CD_3OD , Me_4Si) δ 38.1, 42.7, 102.4, 118.3, 120.2, 124.2, 125.4, 126.3, 126.5, 128.2, 128.4, 128.9, 129.3, 129.7, 134.5, 139.0, 151.7; ESIMS m/z 288.0 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{19}\text{H}_{18}\text{N}_3$, 288.1501; found, 288.1496.

4.9.6. 1-Methyl-4-(1H-pyrrol-1'-yl)-1H-pyrrolo-[3,2-c]-quinoline (9f)

The crude product was purified by silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}=100:1$) to yield 19.88 mg (87%) of the title compound.

^1H NMR (CD_3OD , Me_4Si) δ 4.22 (s, 3H), 6.34–6.38 (m, 2H), 6.85 (d, 1H, $J=5.45$ Hz), 7.06 (d, 1H, $J=5.45$ Hz), 7.46 (t, 1H, $J=6.94$ Hz), 7.57 (t, 1H, $J=6.94$ Hz), 7.64 (d, 2H, $J=6.3$ Hz), 8.07 (d, 1H, $J=8.3$ Hz),

8.29 (d, 1H, $J=8.3$ Hz); ^{13}C NMR (CD_3OD , Me_4Si) δ 38.8, 102.1, 110.5, 114.1, 118.1, 120.7, 124.9, 126.8, 128.8, 129.7, 129.9, 130.9, 136.8, 143.6; ESIMS m/z 248.1 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{16}\text{H}_{14}\text{N}_3$, 248.1188; found, 248.1182.

4.10. General procedure for the synthesis of 4-aryl-1-methyl-1H-pyrrolo-[3,2-c]quinolines 10a–k

To a mixture of imidoylchloride (20 mg, 9.25×10^{-2} mmol), PEPSSI (1.25 mg, 1.85 μmol), Cs_2CO_3 (45 mg, 1.38×10^{-1} mmol), and boronic acid (9.25×10^{-2} mmol) were added water (1.5 ml) and dioxane (1.5 ml), then the mixture was irradiated under microwaves for 2 h at 100 °C. The mixture was diluted with CH_2Cl_2 (10 ml), washed with water (2×5 ml), dried over MgSO_4 , and concentrated under reduced pressure to obtain the title compounds.

4.10.1. 1-Methyl-4-phenyl-1H-pyrrolo-[3,2-c]quinoline (10a)

Following the general procedure, the title compound was obtained in 84% yield as a white solid (20 mg).

^1H NMR (CDCl_3 , Me_4Si) δ 4.25 (s, 3H), 6.78 (d, 1H, $J=3.1$ Hz), 7.23 (d, 1H, $J=3.1$ Hz), 7.40–7.61 (m, 5H), 7.97 (d, 2H, $J=2.89$ Hz), 8.24 (d, 1H, $J=2.89$ Hz), 8.34 (d, 1H, $J=2.89$ Hz); ^{13}C NMR (CDCl_3 , Me_4Si) δ 38.2, 102.4, 118.3, 120.2, 120.4, 125.3, 126.3, 128.5, 128.6, 129.1, 129.7, 130.7, 134.8, 140.3, 144.7, 154.7; ESIMS m/z 259.19 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{18}\text{H}_{15}\text{N}_2$, 259.1235; found, 259.12138.

4.10.2. 1-Methyl-4-o-tolyl-1H-pyrrolo-[3,2-c]quinoline (10b)

Following the general procedure, the title compound was obtained in 70% yield as a white solid (17.6 mg).

^1H NMR (CDCl_3 , Me_4Si) δ 2.21 (s, 3H), 4.26 (s, 3H), 6.34 (d, 1H, $J=3.0$ Hz), 7.00 (d, 1H, $J=3.0$ Hz), 7.48–7.60 (m, 6H), 8.22 (d, 1H, $J=8.3$ Hz), 8.38 (d, 1H, $J=8.3$ Hz); ^{13}C NMR (300 MHz, CDCl_3) δ 20.0, 38.0, 103.1, 118.4, 120.2, 121.7, 124.7, 125.5, 126.2, 128.2, 129.4, 129.6, 130.6, 130.6, 134.2, 136.4, 139.5, 144.5, 156.3; ESIMS m/z 273.1 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2$, 273.1392; found, 273.1387.

4.10.3. 1-Methyl-4-m-tolyl-1H-pyrrolo-[3,2-c]quinoline (10c)

Following the general procedure, the title compound was obtained in 74% yield as a white solid (18.7 mg).

^1H NMR (CDCl_3 , Me_4Si) δ 2.65 (s, 3H), 4.52 (s, 3H), 7.05 (d, 1H, $J=3.1$ Hz), 7.31 (d, 1H, $J=3.1$ Hz), 7.55 (d, 2H, $J=7.9$ Hz), 7.72–7.85 (m, 2H), 8.14 (d, 2H, $J=7.9$ Hz), 8.49 (d, 1H, $J=8.3$ Hz), 8.61 (d, 1H, $J=8.3$ Hz); ^{13}C NMR (CDCl_3 , Me_4Si) δ 21.4, 38.1, 103.2, 118.1, 120.2, 121.8, 125.0, 125.7, 126.2, 128.4, 129.2, 129.5, 130.6, 130.7, 134.3, 136.4, 139.5, 144.5, 156.3; ESIMS m/z 273.1 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2$, 273.1392; found, 273.1387.

4.10.4. 1-Methyl-4-p-tolyl-1H-pyrrolo-[3,2-c]quinoline (10d)

Following the general procedure, the title compound was obtained in 73% yield as a white solid (18.4 mg).

^1H NMR (CDCl_3 , Me_4Si) δ 2.48 (s, 3H), 4.31 (s, 3H), 6.87 (s, 1H), 7.12 (s, 1H), 7.38 (d, 2H, $J=9$ Hz), 7.57–7.65 (m, 2H), 7.98 (d, 2H, $J=6$ Hz), 8.33 (d, 1H, $J=6$ Hz), 8.43 (d, 1H, $J=6$ Hz); ^{13}C NMR (CDCl_3 , Me_4Si) δ 21.4, 38.1, 103.1, 118.3, 120.4, 125.2, 126.9, 127.7, 129.0, 129.2, 129.6, 130.6, 134.8, 137.5, 138.7, 144.7, 154.8; ESIMS m/z 273.0 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2$, 273.1392; found, 273.1391.

4.10.5. 4-(2'-Methoxyphenyl)-1-methyl-1H-pyrrolo-[3,2-c]-quinoline (10e)

Following the general procedure, the title compound was obtained in 75% yield as a white solid (20 mg).

^1H NMR (300 MHz, CDCl_3) δ 3.83 (s, 3H), 4.25 (s, 3H), 6.67 (d, 1H, $J=3.1$ Hz), 6.96–7.05 (m, 3H), 7.44–7.58 (m, 2H), 7.95 (d, 2H, $J=8.8$ Hz), 8.22 (d, 1H, $J=8.0$ Hz), 8.34 (d, 1H, $J=8.0$ Hz); ^{13}C NMR (CDCl_3 , Me_4Si) δ 38.1, 55.4, 103.1, 113.9, 114.5, 118.2, 120.1, 120.3,

125.1, 126.3, 128.2, 129.6, 130.4, 130.5, 133.0, 135.0, 144.7, 154.3, 160.2; ESIMS m/z 289.1 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}$, 289.1341; found, 289.1342.

4.10.6. 4-(4'-Fluorophenyl)-1-methyl-1H-pyrrolo-[3,2-c]-quinoline (10f)

Following the general procedure, the title compound was obtained in 90% yield as a white solid (23 mg).

^1H NMR (CDCl_3 , Me_4Si) δ 4.26 (s, 3H), 6.73 (d, 1H, $J=3.1$ Hz), 7.05 (d, 1H, $J=3.1$ Hz), 7.12–7.19 (m, 2H), 7.47–7.60 (m, 2H), 7.93–7.99 (m, 2H), 8.2 (d, 1H, $J=7.7$ Hz), 8.39 (d, 1H, $J=7.7$ Hz); ^{13}C NMR (acetone, Me_4Si) δ 38.3, 102.3, 115.8, 116.1, 120.7, 121.7, 126.2, 127.0, 131.2, 131.5, 131.87, 131.97, 135.7, 137.8, 145.4, 153.3, 162.45, 165.7; ESIMS m/z 277.1 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{F}$, 277.1141; found, 277.1136.

4.10.7. 1-Methyl-4-(4'-(trifluoromethoxy)phenyl)-1H-pyrrolo-[3,2-c]quinoline (10g)

Following the general procedure, the title compound was obtained in 76% yield as a white solid (24.05 mg).

^1H NMR (CDCl_3 , Me_4Si) δ 4.24 (s, 3H), 6.73 (d, 1H, $J=3.1$ Hz), 7.06 (d, 1H, $J=3.1$ Hz), 7.28–7.33 (m, 2H), 7.48–7.60 (m, 2H), 7.98–8.03 (m, 2H), 8.22 (d, 1H, $J=7.8$ Hz), 8.36 (d, 1H, $J=7.8$ Hz); ^{13}C NMR (CDCl_3 , Me_4Si) δ 38.2, 102.7, 118.3, 120.17, 120.2, 121.0, 122.2, 125.6, 126.5, 129.93, 130.6, 130.7, 135.0, 139.0, 144.6, 149.7, 153.2; ESIMS m/z 342.9 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{OF}_3$, 343.1058; found, 343.1082.

4.10.8. 1-Methyl-4-(naphthalen-1'-yl)-1H-pyrrolo-[3,2-c]-quinoline (10h)

Following the general procedure, the title compound was obtained in 84% yield as a white solid (23.9 mg).

^1H NMR (CDCl_3 , Me_4Si) δ 4.27 (s, 3H), 6.27 (d, 1H, $J=3$ Hz), 6.97 (d, 1H, $J=3$ Hz), 7.33–7.68 (m, 5H), 7.69 (d, 1H, $J=6.8$ Hz), 7.81 (m, 3H), 8.27 (d, 1H, $J=8.2$ Hz), 8.43 (d, 1H, $J=8.2$ Hz); ^{13}C NMR (CDCl_3 , Me_4Si) δ 38.1, 103.3, 118.5, 120.3, 122.5, 125.3, 125.6, 126.0, 126.4, 127.9, 128.1, 129.6, 130.8, 131.8, 132.8, 133.5, 134.0, 134.4, 137.5, 138.4, 144.6, 155.2; ESIMS m/z 309.1 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{22}\text{H}_{17}\text{N}_2$, 309.1392; found, 309.1387.

4.10.9. 4-Biphenyl-1-methyl-1H-pyrrolo-[3,2-c]quinoline (10i)

Following the general procedure, the title compound was obtained in 80% yield as a white solid (20 mg).

^1H NMR (CDCl_3 , Me_4Si) δ 4.25 (s, 3H), 6.83 (d, 1H, $J=3.1$ Hz), 7.23 (d, 1H, $J=3.1$ Hz), 7.28–7.66 (m, 7H), 7.71 (d, 2H, $J=8.4$ Hz), 8.07 (d, 2H, $J=8.4$ Hz), 8.24 (d, 1H, $J=8.3$ Hz), 8.37 (d, 1H, $J=8.3$ Hz); ^{13}C NMR (CDCl_3 , Me_4Si) δ 38.2, 103.1, 118.3, 120.2, 120.4, 125.4, 126.4, 127.1, 127.2, 127.3, 127.4, 127.6, 127.8, 128.82, 128.89, 129.6, 129.7, 130.7, 134.9, 139.3, 140.9, 141.6, 144.8, 154.3; ESIMS m/z 335.1 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{24}\text{H}_{19}\text{N}_2$, 335.54; found, 335.1548.

4.10.10. 4-(Benzofuran-2'-yl)-1-methyl-1H-pyrrolo-[3,2-c]-quinoline (10j)

Following the general procedure, the title compound was obtained in 91% yield as a white solid (25 mg).

^1H NMR (CDCl_3 , Me_4Si) δ 4.22 (s, 3H), 7.09 (t, 1H, $J=3.0$ Hz), 7.18–7.33 (m, 3H), 7.45–7.66 (m, 5H), 8.24 (d, 1H, $J=8.1$ Hz), 8.32 (d, 1H, $J=8.1$ Hz); ^{13}C NMR (CDCl_3 , Me_4Si) δ 38.2, 103.2, 107.3, 111.8, 118.6, 119.1, 120.2, 121.7, 123.1, 125.2, 125.7, 126.5, 128.6, 130.2, 130.7, 135.3, 144.09, 144.5, 155.5, 156.1; ESIMS m/z 299.0 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}$, 299.1184; found, 299.1197.

4.10.11. 1-Methyl-4-(1',2',3',4'-tetrahydro-1',1',4',4'-tetramethyl-naphthalen-6-yl)-1H-pyrrolo-[3,2-c]quinoline (10k)

Following the general procedure, the title compound was obtained in 73% yield as a white solid (24.7 mg).

^1H NMR (CDCl_3 , Me_4Si) δ 1.21–1.31 (m, 12H), 1.54–1.68 (m, 4H), 4.26 (s, 3H), 6.77 (d, 1H, $J=3$ Hz), 7.04 (d, 1H, $J=3$ Hz), 7.40–7.56 (m, 3H), 7.73 (d, 1H, $J=9.0$ Hz), 7.88 (s, 1H), 8.23 (d, 1H, $J=3.0$ Hz), 8.34 (d, 1H, $J=3.0$ Hz); ^{13}C NMR (CDCl_3 , Me_4Si) δ 31.8, 31.9, 34.3, 34.4, 35.1, 35.2, 38.1, 103.3, 112.7, 118.3, 120.1, 124.5, 125.1, 126.2, 127.0, 127.51, 129.5, 130.7, 134.8, 137.4, 138.9, 144.6, 144.8, 145.0, 145.6, 155.2; ESIMS m/z 369.0 ($\text{M}+\text{H}$) $^+$; HRMS calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2$, 369.2331; found, 369.2333.

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