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A facile synthesis of novel pyrrolo[3,4-*b*]quinolin-1-one derivatives

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Abstract A simple and concise construction of a series of new quinoline-based isoindolin-l-ones, namely N-substituted-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-ones, wherein the benzene moiety of isoindolin-l-one is replaced by a quinoline ring has been achieved via a two-step procedure, involving the one-step synthesis of ethyl 2-chloromethyl-quinoline-3-carboxylate followed by its one-pot reaction with various amines in a refluxing EtOH–AcOH (v/v, 10:1) solvent system. These newly synthesized compounds could be good candidates for the development of lead compounds for use in medicinal chemistry.

Keywords Quinoline · Isoindolin-l-one · Hybrid · One-pot synthesis · Amine

Introduction

It is well established that when a number of bioactive heterocyclic compounds are linked with a quinoline moiety in fused or bonded forms the combination usually results in new hybrids with potent pharmacological properties, such as anti-ulcer [1], anti-tubercular [2], antimalarial [3], antimicrobial and anticancer activities [4]. For example, Guo et al. [5] recently found that rhodanine derivatives, upon bearing a quinoline moiety, are interesting scaffolds for the development of novel Gram-positive antibacterial agents. A recent review concerning the anticancer potential of bioactive heterocycle quinoline has been reported [6]. It is, therefore, not surprising that the design and synthesis of novel quinoline-containing heterocycle hybrids has attracted much attention and interest in these compounds continues unabated [7–9].

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On the other hand, isoindolin-1-one (or phthalimidine) is a key structural element present in many naturally occurring substances like cichorine (**1**, Fig. 1) [10], and vitedoamine A (**2**, Fig. 1) [11], and also in some pharmacologically important synthetic compounds such as indoprofen (**3**, Fig. 1) [12] and lenalidomide (**4**, Fig. 1) [13] (as shown in Fig. 1). Compounds of this family had earned the status of a privileged pharmacophore and exhibited a broad spectrum of biological activity, such as antimicrobial [14], anti-nociceptive [15], antipsychotic [16], and the inhibitory activities on tumor necrosis factor production and on histone deacetylase (HDAC) [17]. Moreover, this benzolactam system is also used as important synthons to access various drugs and natural products [18–20]. Therefore, numerous efforts have been invested in exploring new structures of isoindolin-l-one analogues [21, 22]. However, as far as we know, there are very seldom reports on the synthesis of quinoline-based isoindolin-l-ones wherein the benzene moiety of isoindolin-l-one is replaced by a quinoline ring. In this context, Isomae et al. [23] reported the synthesis of quinoline-based isoindolin-l-one T-82 (**5**, Fig. 1), which exhibited selective inhibitory activity against acetylcholinesterase. However, the report is of individual synthesis and no efforts have been made to develop a general synthetic approach.

On the basis of these observations, and in view of structural diversity playing a prominent role in medicinal and combinatorial chemistry for a faster and more efficient route towards new drug discovery [24], the synthesis of structurally novel quinoline-based isoindolin-l-one derivatives as possible drug-like candidates would be of synthetic importance. In the context of our ongoing studies concerning the synthesis of quinoline-based hybrid molecules [25–30], we would like to report herein a simple and efficient procedure for the synthesis of a series of novel N-substituted-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-ones (**6**, Fig. 1) through the one-pot reaction between ethyl 2-(chloromethyl)quinoline-3-carboxylate and amines.

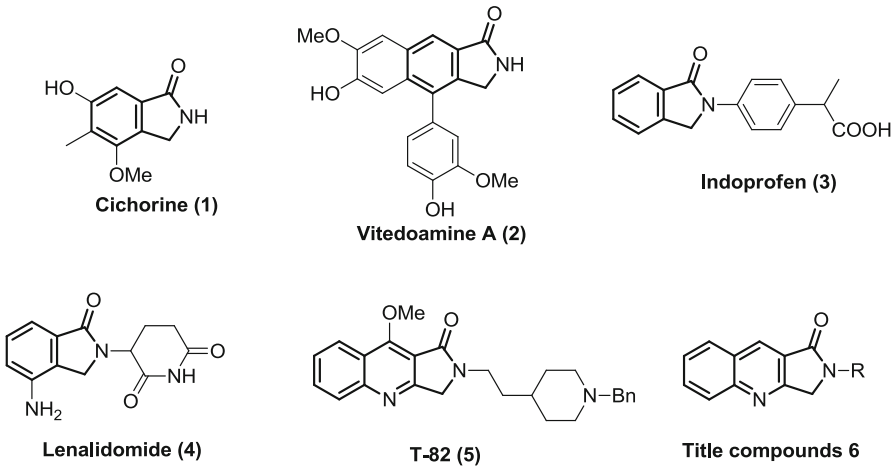
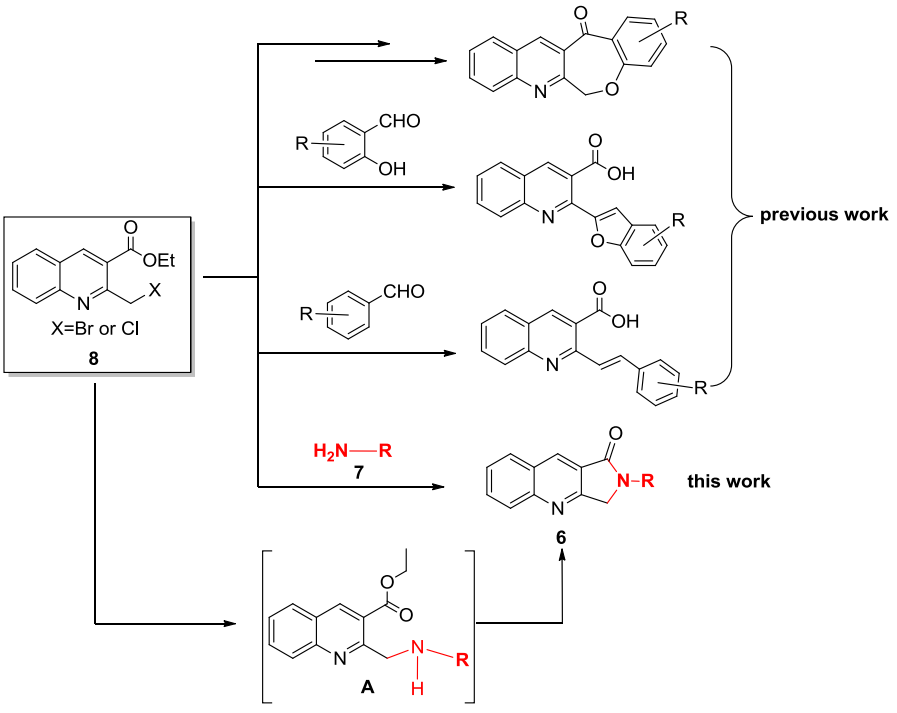


Fig. 1 The structures of compounds **1–6**

Results and discussion

In recent years, a number of synthetic methods have been developed for the synthesis of isoindolin-1-one derivatives, such as the one-pot reaction of 2-formylbenzoic acid with amines and dimethyl phosphate followed by dephosphonylation reaction [31], palladium(0)-catalyzed carbonylation–amination [32], carbamoyl radical cyclization [33], the Parham-type cyclization of iodinated benzyldicarbamates [34], the condensation of anilines with *o*-phthalaldehydes [35], and inverse-electron demand Diels–Alder cycloadditions [36]. These synthetic methodologies described occur with medium to high yields, but they are not easily extended to the synthesis of quinoline-based isoindolin-l-ones due to the unavailability of the required starting materials.

Recently, ethyl 2-halomethyl-quinoline-3-carboxylates have been viewed as an ideal starting material for the flexible synthesis of a large range of quinoline derivatives because of the presence of an active halomethyl group [37, 38]. In this context, we have reported their reaction with various phenols or aromatic aldehydes in the synthesis of polycyclic systems structurally related to biologically active alkaloids (Scheme 1) [25, 27]. We have also developed their one-pot reaction with various salicylaldehydes for the synthesis of 2-benzofuran-containing quinoline-3-carboxylic acid derivatives [28]. Building on the evolving expertise, we envisioned

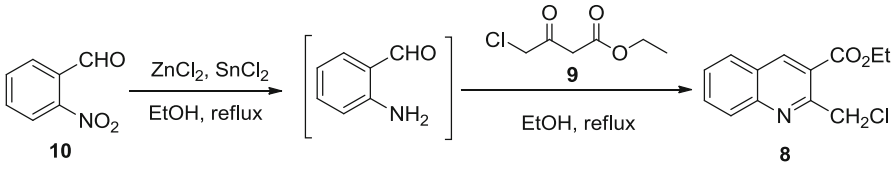


Scheme 1 One-pot synthesis of quinoline-based isoindolin-l-ones **6**

it might be possible to convert them into the desired quinoline-based isoindolin-l-one derivatives through a cascade Williamson-type condensation reaction with amines and subsequent intramolecular C–N bond cyclization of the resulting intermediates in a single synthetic operation, as shown in Scheme 1.

Therefore, the first stage in this strategy involved the preparation of ethyl 2-halomethyl-quinoline-3-carboxylate. Prior to the current investigation, we and other groups reported the preparation of 2-bromomethylquinoline via the radical bromination of the corresponding 2-methyquinolines with N-bromosuccinimide (NBS) [39, 40]. However, the reaction has suffered from both low yields and excess byproduct, because the desired mono-bromo product is always accompanied by the gem-dibromo byproduct, which has very close polarity to the mono-bromo product and cannot be easily separated by recrystallization or column chromatography. Recently, we also described an efficient synthesis of 2-(chloromethyl)benzoquinoline by the direct cyclization of 1-naphthylamine with ethyl 4-chloroacetoacetate by the treatment of a Vilsmeier reagent prepared from dimethylformamide and phosphorus oxychloride [41]. Unfortunately, our attempts to follow the route using aniline instead of naphthalen-1-amine were frustrated by poor yields of highly impure products. Additionally, we also tried the Friedländer reaction [42] of *o*-aminobenzaldehyde with ethyl 4-chloroacetoacetate employing microwave irradiation (MW) and a catalytic amount of hydrochloric acid, according to the method reported by Muscia et al. [43] Although the procedure is very easy and impressive, this purported approach was ineffective in our hands and the reaction did not proceed satisfactorily, giving poor yields of highly impure product.

McNaughton and coworker reported a mild and efficient one-step synthesis of quinolines which employs $SnCl_2$ and $ZnCl_2$ to effect the reaction [44]. On this basis, we conjecture that this one-step reaction sequence might be extended to the synthesis of ethyl 2-(chloromethyl)quinoline-3-carboxylate by replacing ketones with ethyl 4-chloroacetoacetate. Accordingly, our attempt was made by refluxing *o*-nitrobenzaldehyde (**10**) and 1.1 equiv. of ethyl 4-chloroacetoacetate (**9**) in anhydrous ethanol, in the presence of 5 equiv of $SnCl_2$ and $ZnCl_2$ as well as 4 Å molecular sieves, as outlined in Scheme 2. To our delight, the use of ethyl 4-chloroacetoacetate (**9**) was amenable to the one-flask reaction conditions, and thin-layer chromatography (TLC) did not indicate the formation of any distinct byproduct. After the usual workup, the crude product was purified by column chromatography over silica gel, and the desired ethyl 2-(chloromethyl)quinoline-3-carboxylate (**8**) was obtained at a good yield of 83 %.



Scheme 2 One-step synthesis of ethyl 2-(chloromethyl)quinoline-3-carboxylate (**8**)

Having established the efficient one-pot synthesis of ethyl 2-(chloromethyl)quinoline-3-carboxylate, our attention was transferred to its reaction with aromatic amines for building the desired quinoline-based isoindolin-l-one system. At this stage, we first conducted the reaction of **8** and 1.0 equiv of aniline (**7a**) using refluxing ethanol (EtOH) as the solvent in accordance with the reaction conditions described in the literature [45]. As expected, the desired product *N*-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (**6a**) could be obtained, but this was plagued in our hands by a low yield of 53 %. To further improve the yield of this synthetic approach, various solvents were applied to promote this transformation and the results are summarized in Table 1.

As shown in Table 1, solvent choice is critical for this reaction. The usual organic solvents, such as EtOH, methanol (MeOH), acetonitrile (MeCN), tetrahydrofuran (THF), dimethylformamide (DMF), and dioxane proved to be ineffective, and low yields (37–53 %) of the desired product **6a** were obtained (Table 1, entries 1–6). By switching the solvent to H_2O or a solvent-free condition, no desired product was detected (Table 1, entries 7 and 8). Recently, You et al. [46] reported that by using an EtOH–acetic acid (AcOH) solvent system, the reaction of phthalaldehydic acid, primary amine, and 2-mercaptobenzimidazole or 2-hydroxybenzimidazole proceeded smoothly to give the targeted products in good yields. The report prompted us to further experiment using the solvent system. To our surprise, we found that the EtOH–AcOH solvent system also afforded a significant amelioration in our preparation of **6a**, and the best results were obtained when the volume ratio of EtOH and AcOH was 10:1 (Table 1, entry 11). The progress of the reaction was monitored by TLC, which exhibited a spot in the initial stages of the

Table 1 Synthesis of *N*-phenyl-pyrrolo[3,4-*b*]quinolin-1-one (**6a**) using various solvents

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	EtOH	Reflux	36	53
2	MeOH	Reflux	36	43
3	MeCN	Reflux	36	38
4	THF	Reflux	36	37
5	DMF	85	36	40
6	Dioxane	85	36	35
7	H_2O	Reflux	36	0
8	Solvent-free	r. t.	6	0
9	EtOH–AcOH (2:1, v/v)	Reflux	6	62
10	EtOH–AcOH (5:1, v/v)	Reflux	6	70
11	**EtOH–AcOH (10:1, v/v)**	**Reflux**	**6**	**83**
12	EtOH–AcOH (15:1, v/v)	Reflux	6	76
13	EtOH–AcOH (20:1, v/v)	Reflux	6	64

Reaction conditions: compound **8** (0.5 mmol), aniline (**7a**; 0.5 mmol), solvent (3 mL)

[a] Isolated yield

Table 2 Yields and physical properties of the compounds **6a–o**

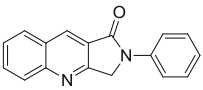
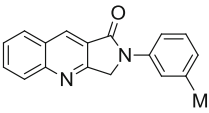
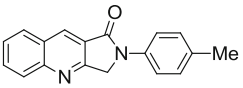
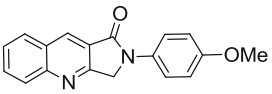
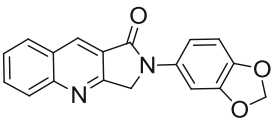
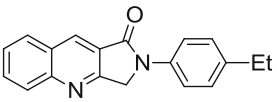
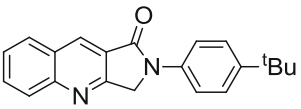
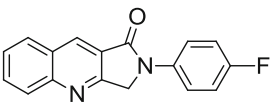
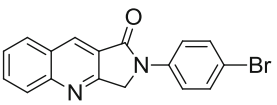
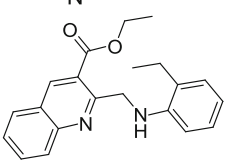
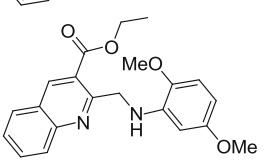
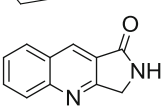
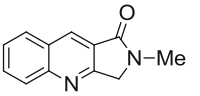
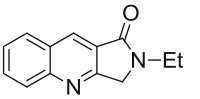
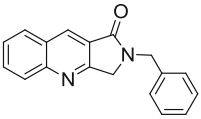
Entry	Product	**6a–o**	M.p./°C	Yield[a] (%)
1		**6a**	239–240[b]	84
2		**6b**	251–252	80
3		**6c**	262–263	87
4		**6d**	230–232	90
5		**6e**	254–255	83
6		**6f**	237–238	85
7		**6g**	267–268	82
8		**6h**	258–260	71
9		**6i**	278–279	74
10		**A1**	184–185	90
11		**A2**	201–202	88
12		**6l**	125–127	77

Table 2 continued

Entry	Product	**6a–o**	M.p./°C	Yield[a] (%)
13		**6m**	199–200	81
14		**6n**	151–152	76
15		**6o**	187–189	87

[a] Isolated yields

[b] Lit [45]. 240–241 °C

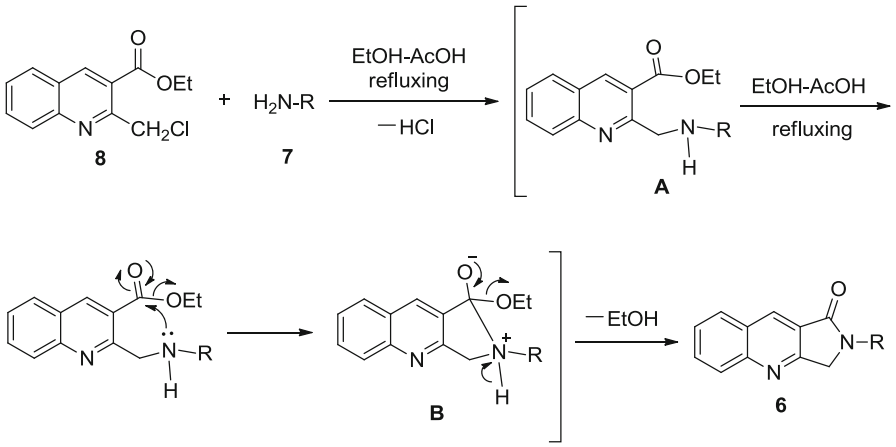
reaction, probably due to the formation of the intermediate ethyl 2-((phenylamino)methyl)quinoline-3-carboxylate, which gradually disappeared with the appearance of a new dark spot arising from the formation of the desired product **6a**. Due to the good yield obtained and in order to retain the simplicity of the procedure, no further optimization in reaction conditions was necessary and the above mentioned condition was chosen for the following work.

Thereafter, we extended the reaction to various substituted aromatic amines **7b–k** in a similar fashion. The results of this series of experiments are compiled in Table 2. Our results demonstrated that the reaction proceeded smoothly in good yields in the presence of a variety of functional groups, including methyl, ethyl, methoxy, *t*-butyl, and halogen atoms (Entries 1–9, Table 2), except in cases of entries 10 and 11, wherein the reaction of **8** with 2-ethylaniline (**7j**) and 2,5-dimethoxyaniline (**7k**) did not afford the desired cyclized products as determined by liquid chromatography–mass spectrometry (LC–MS), but only the intermediates **A1** and **A2**, respectively. This phenomenon might be due to the steric hindrance effect by the presence of an *ortho* substituent which makes the coplanar form of the lactam ring difficult to obtain during the intramolecular cyclization reaction. When R was an electron-withdrawing group in the *para*-position, such as in fluoride and bromide, the corresponding products were obtained in slightly lower yields of 71 and 74 %, respectively (entries 8 and 9, Table 2). While as *R* was strong electron-withdrawing groups, such as in NO_2 and CN, the reaction was found to be very complex and we could not separate and obtain any of the desired products in appreciable yields in these cases. Instead, intractable complex mixtures were observed on TLC.

Further, due to the simplicity of the one-pot synthesis, we decided to extend its scope to ammonia and some aliphatic amines such as methanamine, ethanamine, and benzylamine (entries 12–15, Table 1). Fortunately, all of these amine were equally amenable to the reaction process without any experimental difficulties, furnishing the corresponding pyrrolo[3,4-*b*]quinolin-1-ones **6l–o** in comparable yields.

The structures of all the newly-synthesized compounds were easily established based on spectral data elemental analyses, which were in good agreement with the compounds expected. As an example, the infrared (IR) spectrum of **6a** exhibited the disappearance of the ester carbonyl group at 1715 cm^{-1}, and the appearance of the lactam C=O stretching frequency at a decreased wave number of 1693 cm^{-1}, which were clear evidence for cyclization having occurred. Its proton nuclear magnetic resonance (^{1}H NMR) spectrum exhibited a singlet sharp line at 5.07 parts per million (ppm), readily recognizable as arising from methylene protons, supporting the signal of its carbon-13 (^{13}C) NMR spectrum at 48.3 ppm. Moreover, the presence of 10 aromatic protons in the range of the aromatic region of 7.19–8.77 ppm exactly matches its structure as well. Further, the structure assigned to **6a** was fully supported by its elemental analysis, which established its molecular formulae in accordance with the suggested molecular structure. The other synthesized compounds exhibited similar spectral characteristics, except the substituents, which exhibited characteristic signals with appropriate chemical shifts.

On the basis of these experiments, a proposed mechanism portraying the probable sequence of events for the formation of the title compounds is outlined in Scheme 3. The Williamson-type reaction of the two fragments involves the formation of intermediate **A** in the first step, which undergoes subsequent intramolecular nucleophilic cyclization with participation of the N atom and the ester C=O group to form a five-membered cyclic system **B**. After this cyclization, the elimination of an equiv. of EtOH led to the formation of pyrrolo[3,4-*b*]quinolin-1-one ring **6**. It is worth mentioning that an example particularly relevant to the present discussion is described in the literature [47], wherein 7-isopropyl-1-methylazulen-4-amine undergoes intromolecular ring annulation reactions with a 3-position ester group to yield tricyclic δ-lactams with the elimination of methanol without the need for a catalyst.



Scheme 3 Possible mechanistic pathway of formation of pyrrolo[3,4-*b*]quinolin-1-ones **6**

Conclusions

In conclusion, we have provided an easy access to the one-pot synthesis of structurally novel and biologically intriguing quinoline-based isoindolin-l-one derivatives in a relatively environmentally benign EtOH–AcOH (v/v, 10:1) solvent system. These newly synthesized compounds would likely possess significant biological activities and could be potentially applied for the development of biologically and pharmaceutically important drugs. Further investigation concerning the bioactive properties of the generated products as well as their application in the synthesis of more complex heterocycles are currently under investigation in our laboratory and will be reported in due course.

Experimental

All chemicals were analytical reagent (AR)-grade, commercially available and used without further purification. The melting points were determined by using a WRS-1B melting point apparatus and were uncorrected. The IR spectra were obtained using potassium bromide (KBr) pellets in the range of 400–4000 cm^{-1} on a Shimadzu Fourier transform (FT)-infrared spectrophotometer (FTIR-8400S, Shimadzu, Japan). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance NMR spectrometer using deuterated chloroform ($CDCl_3$) as the solvent. The reported chemical shifts (δ values) are given in ppm downfield from tetramethylsilane (TMS) as the internal standard. The mass spectra were determined using an MSD VL ESI1 spectrometer. The progress of reactions was monitored by TLC on silica gel GF254 using a hexane/ethyl acetate mixture (4:1, v/v) as the eluent.

Procedure for the preparation of ethyl 2-(chloromethyl)quinoline-3-carboxylate (8)

To a stirred solution of *o*-nitrobenzaldehyde (**10**; 1.51 g, 10.0 mmol) in 60 mL of anhydrous ethanol was added anhydrous $ZnCl_2$ (6.81 g, 50.0 mmol), $SnCl_2$ (9.48 g, 50.0 mmol) and approximately 1.6 g of 4 Å molecular sieves at room temperature. The resulting mixture was heated at refluxing temperature under an atmosphere of N_2 for 5 h. Ethyl 4-chloroacetoacetate (**9**; 1.82 g, 11.0 mmol) was then added dropwise to the mixture, and the reaction was continued for another 10 h. After completion, the reaction was cooled to room temperature and rendered basic (pH 8) with 10-% sodium bicarbonate (aq). EtOAc (3 × 100 ml) was added to the reaction mixture and organic phase was washed thoroughly with saturated NaCl (aq), separated and dried over anhydrous Na_2SO_4. The residue was subjected to column chromatography over silica gel eluting with hexane/ethyl acetate (12:1, v/v) to afford compound **8**. Yield 83 %, m.p. 117–118 °C. IR (KBr, ν, cm^{-1}): 3048, 2985, 1715 (C=O), 1617, 1562, 1492, 1429, 1389, 1273, 1257, 1133; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 1.48 (t, $J = 7.2$ Hz, 3H, $OCH_2\underline{CH_3}$), 4.50 (q, $J = 7.2$ Hz, 2H, $OC\underline{H_2}CH_3$), 5.28 (s, 2H, Cl-CH_2-Ar), 7.62 (t, $J = 7.8$ Hz, 1H, ArH), 7.83 (t,

$J = 8.4$ Hz, 1H, ArH), 7.91 (d, $J = 8.4$ Hz, 1H, ArH), 8.12 (d, $J = 8.4$ Hz, 1H, ArH), 8.82 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 14.2, 46.6, 61.9, 123.2, 126.7, 127.9, 128.5, 129.3, 132.1, 140.9, 148.3, 155.7, 165.7; EI-MS *m/z* (%): 250.3, 252.1 $[M+H]^+$. Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.74; H, 4.90; N, 5.75.

General procedure for synthesis of N-substituted-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-ones (6a–o)

A mixture of ethyl 2-(chloromethyl)quinoline-3-carboxylate (**8**; 0.25 g, 1.0 mmol) and the respective amine (**7**; 1.0 mmol) was refluxed in EtOH–AcOH (5 mL, v/v, 10:1). After the reaction was completed, as inferred through TLC studies (complete disappearance of the starting materials), the reaction was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by column chromatography using hexane/EtOAc (90:10) as the eluent, affording the pure products **6a–o**.

2-Phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6a)

White solid. IR (KBr, ν, cm^{-1}): 1693 (C=O), 1617, 1597, 1499, 1447, 1387, 1342, 1297, 1270, 1205; ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 5.07 (s, 2H, CH_2), 7.19–7.25 (m, 5H, ArH), 7.85 (t, $J = 7.6$ Hz, 1H, ArH), 8.03–8.06 (m, 2H, ArH), 8.38 (d, $J = 8.4$ Hz, 1H, ArH), 8.77 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 48.3, 107.7, 110.5, 113.4, 116.2, 118.3, 121.8, 124.1, 126.7, 127.4, 128.7, 129.7, 135.3, 155.2, 164.0. MS (ESI, *m/z*): 261.0 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.68; H, 4.91; N, 10.48.

2-(*m*-Tolyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6b)

White solid, IR (KBr, ν, cm^{-1}): 1695 (C=O), 1621, 1574, 1518, 1491, 1444, 1375, 1342, 1291, 1207; ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 2.37 (s, 3H, Me), 4.98 (s, 2H, CH_2), 6.99 (d, $J = 7.6$ Hz, 1H, ArH), 7.29 (t, $J = 7.6$ Hz, 1H, ArH), 7.58–7.61 (m, 2H, ArH), 7.71 (s, 1H, ArH), 7.80 (t, $J = 8.4$ Hz, 1H, ArH), 7.97 (d, $J = 8.4$ Hz, 1H, ArH), 8.13 (d, $J = 8.4$ Hz, 1H, ArH), 8.64 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 19.7, 50.5, 115.0, 118.6, 122.6, 123.9, 125.0, 125.5, 126.9, 127.0, 127.6, 129.7, 131.1, 136.8, 137.1, 148.1, 157.2, 163.3; MS (ESI, *m/z*): 275.1 $[M+H]^+$. Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.99; H, 4.99; N, 10.33.

2-(*p*-Tolyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6c)

White solid. IR (KBr, ν, cm^{-1}): 1690 (C=O), 1635, 1580, 1508, 1454, 1418, 1393, 1372, 1298, 1270, 1191; ^{1}H NMR ($CDCl_3$, 600 MHz) (δ, ppm): 2.40 (s, 3H, Me), 5.05 (s, 2H, CH_2), 7.29 (d, $J = 8.4$ Hz, 2H, ArH), 7.66 (t, $J = 7.8$ Hz, 1H, ArH), 7.80 (d, $J = 8.4$ Hz, 2H, ArH), 7.89 (t, $J = 7.8$ Hz, 1H, ArH), 8.05 (d, $J = 7.8$ Hz, 1H, ArH), 8.20 (d, $J = 8.4$ Hz, 1H, ArH), 8.72 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$,

150 MHz) (δ, ppm): 20.9, 52.6, 120.0, 124.8, 127.1, 127.7, 129.1, 129.6, 129.8, 131.7, 133.1, 135.0, 136.5, 150.2, 159.4, 165.3; MS (ESI, *m/z*): 275.1 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 79.03; H, 4.96; N, 9.97.

2-(4-Methoxyphenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6d)

White solid. IR (KBr, ν, cm^{-1}): 1689 (C=O), 1619, 1511, 1437, 1373, 1340, 1250, 1205; ^1H NMR ($CDCl_3$, 600 MHz) (δ, ppm): 3.86 (s, 3H, OMe), 5.02 (s, 2H, CH_2), 7.02 (d, $J = 8.4$ Hz, 2H, ArH), 7.67 (t, $J = 7.8$ Hz, 1H, ArH), 7.81 (d, $J = 8.4$ Hz, 2H, ArH), 7.88 (t, $J = 7.8$ Hz, 1H, ArH), 8.03 (d, $J = 7.8$ Hz, 1H, ArH), 8.19 (d, $J = 8.4$ Hz, 1H, ArH), 8.70 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 150 MHz) (δ, ppm): 52.9, 55.5, 114.5, 121.8, 124.7, 127.0, 127.8, 129.2, 129.7, 131.6, 132.2, 133.0, 157.1, 159.4, 165.2; MS (ESI, *m/z*): 290.8 $[M+H]^+$; Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.31; H, 4.97; N, 9.78.

2-(Benzo[d][1, 3]dioxol-5-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6e)

White solid, IR (KBr, ν, cm^{-1}): 1683 (C=O), 1617, 1589, 1494, 1453, 1417, 1373, 1332, 1291, 1263, 1201; ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 5.04 (s, 2H, CH_2), 5.96 (s, 2H, OCH_2O), 6.83 (d, $J = 8.0$ Hz, 1H, ArH), 7.08 (d, $J = 8.4$ Hz, 1H, ArH), 7.56 (s, 1H, ArH), 7.66 (t, $J = 8.4$ Hz, 1H, ArH), 7.87 (t, $J = 8.0$ Hz, 1H, ArH), 8.03 (d, $J = 8.4$ Hz, 1H, ArH), 8.25 (d, $J = 8.4$ Hz, 1H, ArH), 8.73 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 52.5, 102.5, 105.7, 109.2, 117.2, 122.1, 126.9, 127.5, 129.1, 130.3, 133.5, 138.0, 142.4, 143.5, 148.6, 148.9, 157.1, 164.7; MS (ESI, *m/z*): 305.0 $[M+H]^+$. Anal. Calcd for $C_{18}H_{12}N_2O_3$: C, 71.05; H, 3.97; N, 9.21. Found: C, 71.17; H, 3.90; N, 9.03.

2-(4-Ethylphenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6f)

White solid. IR (KBr, ν, cm^{-1}): 1695 (C=O), 1617, 1516, 1437, 1374, 1340, 1301, 1272, 1205; ^1H NMR ($CDCl_3$, 600 MHz) (δ, ppm): 1.28 (t, $J = 7.8$ Hz, 3H, $C\underline{H}_3CH_2$), 2.70 (q, $J = 7.8$ Hz, 2H, $CH_3C\underline{H}_2$), 5.05 (s, 2H, CH_2), 7.31 (d, $J = 8.4$ Hz, 2H, ArH), 7.66 (t, $J = 7.8$ Hz, 1H, ArH), 7.82 (d, $J = 8.4$ Hz, 2H, ArH), 7.87 (t, $J = 7.8$ Hz, 1H, ArH), 8.04 (d, $J = 7.8$ Hz, 1H, ArH), 8.19 (d, $J = 8.4$ Hz, 1H, ArH), 8.71 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 150 MHz) (δ, ppm): 15.6, 28.4, 52.6, 120.1, 124.8, 127.1, 127.7, 128.7, 129.1, 129.6, 131.6, 133.1, 136.7, 141.3, 150.2, 159.4, 165.3; MS (ESI, *m/z*): 289.1 $[M+H]^+$. Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.35; H, 5.65; N, 9.86.

2-(4-(*tert*-Butyl)phenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6g)

White solid, IR (KBr, ν, cm^{-1}): 1692 (C=O), 1617, 1514, 1449, 1374, 1340, 1298, 1267, 1204; ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 1.33 (s, 9H, *t*-Bu), 5.02 (s, 2H, CH_2), 7.48 (d, $J = 7.2$ Hz, 2H, ArH), 7.62 (t, $J = 8.0$ Hz, 1H, ArH), 7.81 (d,

$J = 7.2$ Hz, 2H, ArH), 7.85 (t, $J = 8.0$ Hz, 1H, ArH), 8.00 (d, $J = 8.4$ Hz, 1H, ArH), 8.15 (d, $J = 8.4$ Hz, 1H, ArH), 8.68 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 29.2, 32.4, 50.4, 117.6, 122.6, 125.0, 125.5, 126.9, 127.5, 129.6, 131.1, 134.2, 146.1, 147.9, 157.2, 163.2; MS (ESI, *m/z*): 317.2 $[M+H]^+$. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.50; H, 6.54; N, 9.03.

2-(4-Fluorophenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6h)

Yellow solid, IR (KBr, ν, cm^{-1}): 1682 (C=O), 1613, 1510, 1436, 1378, 1343, 1291, 1264, 1220, 1176; ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 5.00 (s, 2H, CH_2), 7.11–7.14 (m, 2H, ArH), 7.61 (t, $J = 8.0$ Hz, 1H, ArH), 7.81–7.83 (m, 3H, ArH), 7.99 (d, $J = 8.4$ Hz, 1H, ArH), 8.15 (d, $J = 8.4$ Hz, 1H, ArH), 8.67 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 52.6, 110.0, 115.9, 116.2, 121.6, 121.7, 125.2, 125.6, 127.4, 128.8, 129.7, 132.1, 133.6, 158.8, 164.3; MS (ESI, *m/z*): 279.1 $[M+H]^+$. Anal. Calcd for $C_{17}H_{11}FN_2O$: C, 73.37; H, 3.98; N, 10.07. Found: C, 73.14; H, 4.12; N, 10.16.

2-(4-Bromophenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6i)

Yellow solid; IR (KBr, ν, cm^{-1}): 1691 (C=O), 1618, 1584, 1492, 1433, 1367, 1339, 1292, 1264, 1203; ^{1}H NMR ($CDCl_3$, 600 MHz) (δ, ppm): 4.96 (s, 2H, CH_2), 7.37 (d, $J = 8.4$ Hz, 2H, ArH), 7.60 (t, $J = 7.8$ Hz, 1H, ArH), 7.80–7.84 (m, 3H, ArH), 7.97 (d, $J = 7.8$ Hz, 1H, ArH), 8.12 (d, $J = 8.4$ Hz, 1H, ArH), 8.65 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 150 MHz) (δ, ppm): 52.4, 120.9, 124.3, 127.3, 127.7, 129.2, 129.3, 129.7, 130.3, 131.9, 133.4, 137.7, 150.4, 158.9, 165.5; MS (ESI, *m/z*): 339.0, 341.1 $[M+H]^+$. Anal. Calcd for $C_{17}H_{11}BrN_2O$: C, 60.20; H, 3.27; N, 8.26. Found: C, 60.06; H, 3.38; N, 8.39.

Ethyl 2-(((2-ethylphenyl)amino)methyl)quinoline-3-carboxylate (A1)

Yellow crystals, IR (KBr, ν, cm^{-1}): 3396 (NH), 1720 (C=O), 1596, 1510, 1452, 1375, 1315, 1257, 1209, 1137, 1056; ^{1}H NMR ($CDCl_3$, 600 MHz) (δ, ppm): 1.41 (t, $J = 7.2$ Hz, 3H, $CH_2C\underline{H}_3$), 1.51 (t, $J = 7.2$ Hz, 3H, $OCH_2C\underline{H}_3$), 2.77 (q, $J = 7.2$ Hz, 2H, $C\underline{H}_2CH_3$), 4.50 (q, $J = 7.2$ Hz, 2H, $OC\underline{H}_2CH_3$), 5.00 (s, 2H, CH_2), 6.73 (t, $J = 7.2$ Hz, 1H, ArH), 6.91 (d, $J = 7.2$ Hz, 1H, ArH), 7.13 (d, $J = 7.2$ Hz, 1H, ArH), 7.18 (td, $J = 7.8$, 1.2 Hz, 1H, ArH), 7.62 (d, $J = 7.2$ Hz, 1H, ArH), 7.86 (td, $J = 7.8$, 1.2 Hz, 1H, ArH), 7.93 (d, $J = 7.8$ Hz, 1H, ArH), 8.16 (d, $J = 8.4$ Hz, 1H, ArH), 8.87 (s, 1H, ArH), 9.63 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 150 MHz) (δ, ppm): 13.0, 14.4, 24.3, 48.8, 61.6, 122.4, 125.2, 126.1, 127.1, 127.2, 128.0, 128.6, 129.0, 132.0, 135.4, 137.9, 139.0, 139.6, 140.7, 147.9, 165.7; MS (ESI, *m/z*): 335.2 $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.21; H, 6.74; N, 8.47.

Ethyl 2-(((2,5-dimethoxyphenyl)amino)methyl)quinoline-3-carboxylate (A2)

Yellow solid, IR (KBr, ν, cm^{-1}): 3445 (NH), ^{1}H NMR ($CDCl_3$, 600 MHz) (δ, ppm): 1.32 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 3.63 (s, 3H, OMe), 3.70 (s, 3H, OMe), 4.33 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.57 (s, 2H, CH_2), 6.86 (s, 1H, ArH), 7.05 (d, J = 7.2 Hz, 1H, ArH), 7.17 (d, J = 7.2 Hz, 1H, ArH), 7.66 (td, J = 8.4, 1.8 Hz, 1H, ArH), 7.85 (td, J = 8.4, 1.8 Hz, 1H, ArH), 7.94 (d, J = 8.4 Hz, 1H, ArH), 8.13 (d, J = 7.8 Hz, 1H, ArH), 8.85 (s, 1H, ArH), 9.61 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 150 MHz) (δ, ppm): 14.2, 48.6, 55.9, 56.0, 61.7, 121.3, 124.6, 125.2, 126.6, 127.8, 128.1, 128.6, 129.3, 131.9, 132.1, 133.4, 139.6, 140.3, 148.1, 149.8, 165.8; MS (ESI, *m/z*): 367.2 $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 69.06; H, 6.23; N, 7.50.

2,3-Dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6l)

White solid, IR (KBr, ν, cm^{-1}): 3459 (NH), 1702 (C=O), 1621, 1514, 1472, 1437, 1346, 1241; ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 4.49 (s, 2H, CH_2), 7.70 (t, J = 7.6 Hz, 1H, ArH), 7.91 (t, J = 8.0 Hz, 1H, ArH), 8.12 (d, J = 8.4 Hz, 1H, ArH), 8.22 (d, J = 8.4 Hz, 1H, ArH), 8.77 (s, 1H, ArH), 8.98 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 47.1, 124.4, 127.0, 127.4, 128.9, 130.2, 131.7, 132.5, 149.6, 163.5, 168.2; MS (ESI, *m/z*): 185.2 $[M+H]^+$. Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N,15.21. Found: C, 72.05; H, 4.30; N, 15.40.

2-Methyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6m)

White solid, IR (KBr, ν, cm^{-1}): 1685 (C=O), 1621, 1508, 1449, 1402, 1381, 1336, 1286, 1240; ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 3.23 (s, 3H, N-Me), 4.51 (s, 2H, CH_2), 7.57 (t, J = 8.4 Hz, 1H, ArH), 7.76 (t, J = 8.4 Hz, 1H, ArH), 7.92 (d, J = 8.4 Hz, 1H, ArH), 8.06 (d, J = 8.8 Hz, 1H, ArH), 8.52 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 29.6, 53.6, 124.1, 126.9, 127.4, 128.9, 129.6, 131.4, 132.3, 149.5, 160.2, 166.5; MS (ESI, *m/z*): 199.1 $[M+H]^+$. Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.83; H, 5.20; N, 13.95.

2-Ethyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6n)

White solid, IR (KBr, ν, cm^{-1}): 2937, 2934, 1675 (C=O), 1621, 1581, 1511, 1463, 1406, 1379, 1320, 1239; ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 1.30 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 3.73 (q, J = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 4.53 (s, 2H, CH_2), 7.57 (d, J = 8.4 Hz, 1H, ArH), 7.78 (t, J = 8.0 Hz, 1H, ArH), 7.94 (t, J = 8.4 Hz, 1H, ArH), 8.09 (t, J = 8.4 Hz, 1H, ArH), 8.54 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 11.3, 35.1, 48.8, 107.9, 122.3, 124.8, 126.8, 127.4, 129.2, 130.2, 147.5, 158.3, 163.9; MS (ESI, *m/z*): 213.3 $[M+H]^+$. Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.41; H, 5.60; N, 13.34.

2-Benzyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (6o)

White solid, IR (KBr, ν, cm^{-1}): 1681 (C=O), 1619, 1515, 1450, 1407, 1384, 1338, 1234; ^{1}H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 4.40 (s, 2H, CH_2), 4.82 (s, 2H, NCH_2Ph), 7.22–7.28 (m, 5H, ArH), 7.54 (t, $J = 8.0$ Hz, 1H, ArH), 7.75 (t, $J = 8.4$ Hz, 1H, ArH), 7.93 (d, $J = 8.4$ Hz, 1H, ArH), 8.04 (d, $J = 8.8$ Hz, 1H, ArH), 8.58 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ, ppm): 46.5, 51.0, 120.7, 124.0, 127.0, 127.4, 127.9, 128.2, 128.9, 129.4, 131.1, 131.8, 132.0, 132.1, 132.8, 136.2, 149.6, 160.3; MS (ESI, *m/z*): 275.2 $[M+H]^+$. Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 79.24; H, 5.19; N, 10.45.

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