

HETEROCYCLES, Vol. 91, No. 11, 2015, pp. 2180 - 2189. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 3rd September, 2015, Accepted, 2nd October, 2015, Published online, 9th October, 2015
DOI: 10.3987/COM-15-13314

A GENERAL SYNTHESIS OF NOVEL QUINOLINE-BASED ISOINDOLIN-1-ONE DERIVATIVES

Hong Zhang and Yang Li*

Institute of Superfine Chemicals, Bohai University, Jinzhou 121000, China
bhuzh@163.com

Abstract – A simple and general one-pot protocol for the synthesis of a series quinoline-based isoindolin-1-ones, namely 7-chloro-2-substituted-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-ones (**5a-p**) is described, involving a cascade Williamson-type condensation reaction of ethyl 6-chloro-2-(chloromethyl)-quinoline-3-carboxylate (**3**) with aromatic amines (**4a-i**), aliphatic amines (**4j-m**) and aliphatic diamines (**4n-p**) and subsequent intramolecular C-N bond cyclization of the resulting intermediates in refluxing EtOH–AcOH (v/v, 10:1) solvent system in a single synthetic operation.

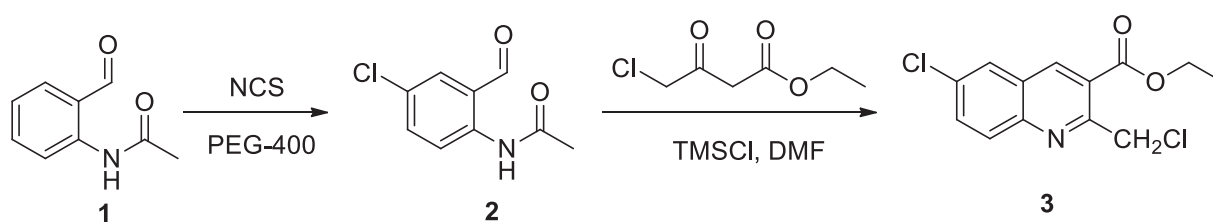
Isoindolin-1-ones constitute an exceptional class of structural motifs which have been found widely present in natural products like cichorine¹ and vitedoamine,² and also in pharmacologically important synthetic molecules such as indoprofen³ and lenalidomide.⁴ Consequently, attention has been increasingly paid to use of the isoindolin-1-one molecular template for further modification and functionalization of this class of compounds from both organic and medicinal chemists, aiming to find new applications from these compounds.⁵⁻⁷

On the other hand, it is well established that bioactive heterocyclic compounds when linked with quinoline moiety in fused or bonded forms usually results in new hybrids with potent pharmacological properties.⁸⁻¹⁰ Thus, in light of the combination principles for drug design,¹¹ it would be of synthetic importance to the construction of quinoline-based isoindolin-1-one derivatives, wherein the phenyl ring was replaced by quinoline moiety. Such compounds might be much more attractive and valuable for medicinal chemistry and drug discovery.

A literature survey revealed that there are several examples reported concerning the synthesis of quinoline-based isoindolin-1-one derivatives.¹²⁻¹⁶ However, all these reports are of individual and scattered syntheses, and no efforts have been made to develop a general synthetic approach. Herein, we wish to report a simple and general synthesis of a series of novel quinoline-based isoindolin-1-one,

namely N-substituted-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-ones through the one-pot reaction of ethyl 6-chloro-2-(chloromethyl)quinoline-3-carboxylate and various amines.

We recently reported on the reaction of 2-chloromethyl- or 2-bromomethylquinoline with phenols,^{17,18} salicylaldehydes,¹⁹ aromatic aldehydes,²⁰ and quinolin-8-ols²¹ for the synthesis of novel heterocycle-containing quinolines. Building on the evolving expertise and in our ongoing endeavor to create novel quinoline-based hybrids, our present work focused on an extension of this work to the reaction with various amines for the synthesis of novel quinoline-based isoindolin-1-one derivatives. Our synthesis commenced with the preparation of required substrate ethyl 6-chloro-2-(chloromethyl)quinoline-3-carboxylate (**3**) as shown in Scheme 1.

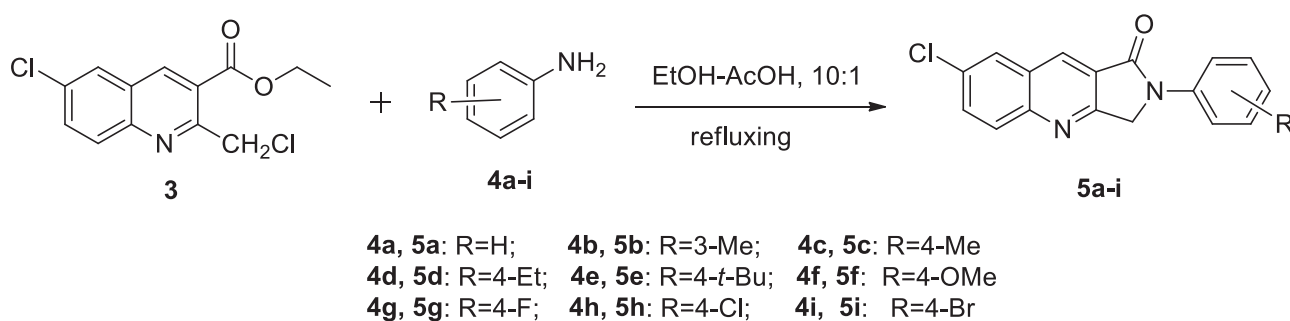


Scheme 1. Synthetic route for ethyl 2-(chloromethyl)quinoline-3-carboxylate (**3**)

N-(4-Chloro-2-formylphenyl)acetamide (**2**) obtained from the chlorination of the corresponding N-(2-formylphenyl)acetamide (**1**) was subjected to the Friedländer annulation reaction with ethyl 4-chloro-3-oxobutanoate using chlorotrimethylsilane (TMSCl) as a promoter and water-acceptor agent in accordance with the method as described in the literature.²² After the usual workup then purification of crude product by column chromatography over silica gel, the required substrate **3** was obtained in 73% yield. In addition, our attempt to follow the route as described by Atar *et al.*²³ using lithium triflate as an expeditious catalyst under solvent free conditions could also obtain substrate **3** in a comparable yield of 71%.

Subsequently, our attention was transferred to its reaction with aromatic amines for building the desired quinoline-based isoindolin-1-one system as shown in Scheme 2. In fact, our initial investigation towards the reaction was conducted under the reaction conditions as described in the literature.¹⁴ Unfortunately, contrary to expectation, this purported approach was ineffective in our hands and the reaction did not proceed satisfactorily, giving poor yields of highly impure products. When the reaction was carried out using ethanol as solvent in accordance with the reaction conditions as described in the literature,¹⁶ the desired products could be obtained, but this was still plagued by low yields of 43-51%. We felt that the option of solvent was critical to this reaction. Accordingly, to further improve the yield of this synthetic approach, we examined this reaction by using some different organic solvents such as MeOH, THF, CHCl₃, DMF, and dioxane. However, these attempts were unfruitful, and no further improvements to the

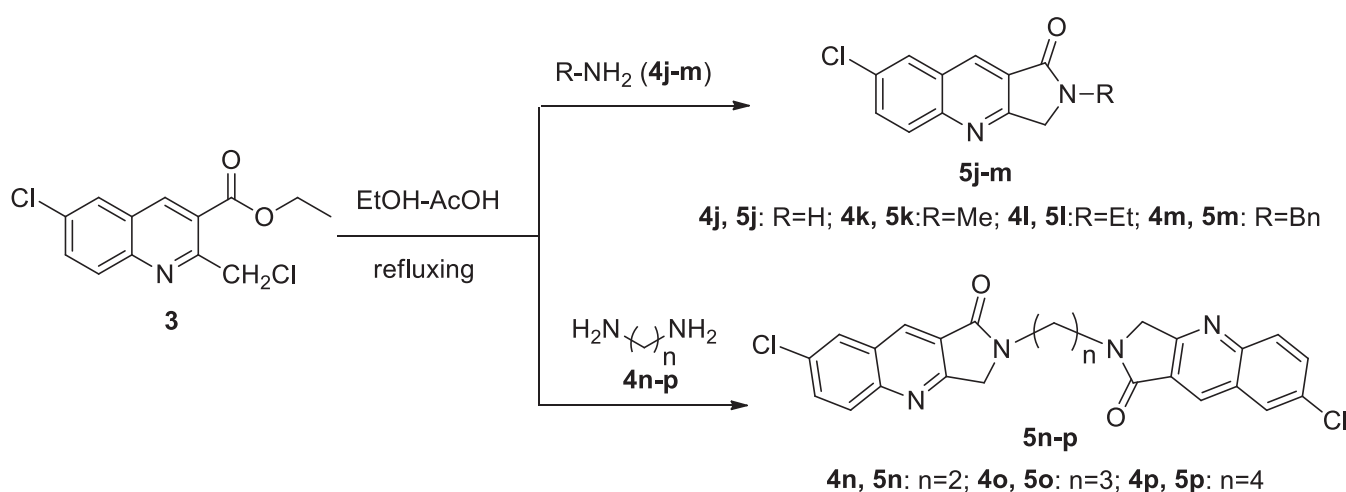
yield were observed. Further switching the solvent to H₂O or solvent-free condition, no product was detected by use of the method, the starting materials being recovered unchanged. After many attempts, we were delight to find that the use of EtOH–AcOH²⁴ solvent system afforded a significant amelioration in our synthesis, and after a simple optimal experiment, the best results were obtained with good yields ranging from 74% to 85% when the volume ratio of EtOH and AcOH was 10:1.



Scheme 2. Synthesis of N-aryl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-ones (**5a-i**)

In this series of reactions, the effect of substitution groups is not very strong; both the electron-donating (*e.g.*, Me, Et, OMe) and slightly electron-withdrawing groups (*e.g.*, Cl, Br) worked well, showing little distinction. However, it is noteworthy that as strong electron-withdrawing groups such as NO₂ and CN were present, the reaction scarcely proceeded and the desired product was detected in negligible amount that did not warrant isolation. A possible reason is that the presence of the strong electron-withdrawing group might render the aromatic amines highly electron-deficient and retard the reaction process.

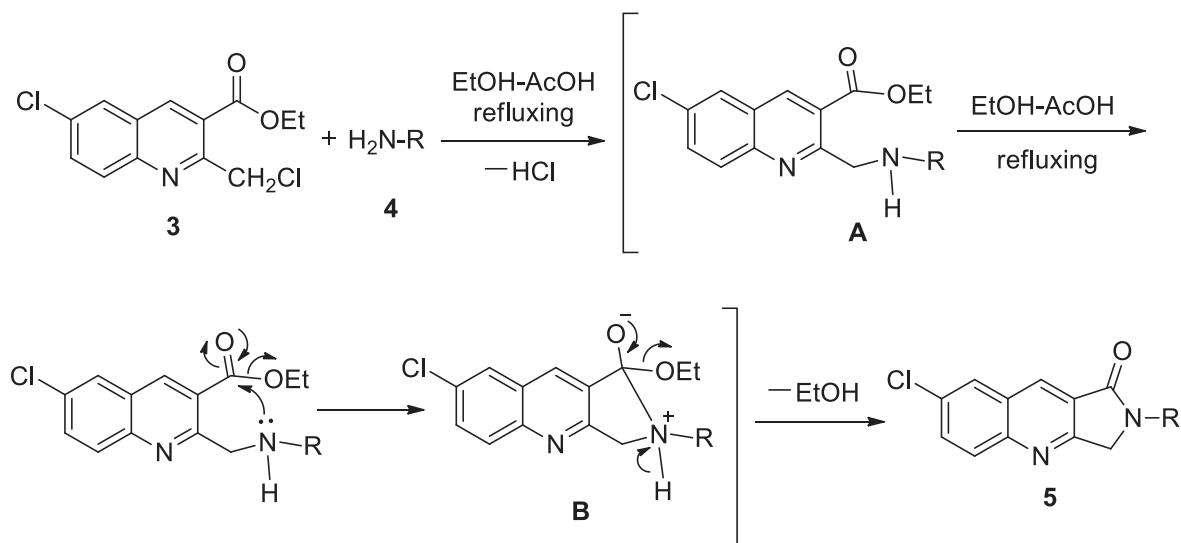
Due to the good yield obtained and to retain the simplicity of the procedure, no further changes in the reaction conditions were tested, and the above mentioned condition was chosen for the following work. In diversifying our work on new quinoline-based isoindolin-1-one derivatives, we decided to extend its scope



Scheme 3. Synthesis of N-alkyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-ones (**5j-p**)

to some aliphatic amines (**4j-m**) and aliphatic diamines (**4n-p**) as outlined in Scheme 3. Gratifyingly, these amines were equally amenable to the reaction process without any experimental difficulties, successfully furnishing the corresponding pyrrolo[3,4-*b*]quinolin-1-ones **5j-p** in comparable yields of 65-82%.

All the newly-synthesized quinoline-based isoindolin-1-ones **5a-p** have never been reported and their structures were easily confirmed by their spectroscopic and analytical data, which were in good agreement with the compounds expected (see Experimental section). On the basis of these experiments, a mechanistic proposal portraying the probable sequence of events for the formation of the title compounds is outlined in Scheme 4. The Williamson-type reaction of the two fragments involves in the first step the formation of intermediate **A**, 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**. The whole reactions occurred successively in one-pot effectively. It is worthy to mention that an example that is particularly relevant to the present discussion is described in the literature,²⁵ wherein 7-isopropyl-1-methylazulen-4-amine undergoes intramolecular ring annulation reactions with 3-position ester group to yield tricyclic δ -lactams with the elimination of methanol without the need for a catalyst.



Scheme 4. Possible mechanistic pathway for the formation of products **5**

In conclusion, we have provided an easy access to the general synthesis of structurally novel and biologically intriguing quinoline-based isoindolin-1-one derivatives in relatively environmentally benign EtOH–AcOH (v/v, 10:1) solvent system. These molecules we have synthesized should allow us, in the future, to investigate structure-activity relationships over various biotests. Moreover, all these molecules can be used for the synthesis of more complex quinoline-based compounds since chloro group on the quinoline ring can be further elaborated to a variety of other functional groups, for example, via

metal-catalyzed coupling reactions. Currently, the studies concerning their application in the synthesis of quinoline heterocycles are underway.

EXPERIMENTAL

The chemicals used in this work were obtained from Fluka and were used without purification. Melting points (uncorrected) were determined by using WRS-1B melting points apparatus. The IR spectra were obtained as KBr pellets in the range of 400-4000 cm^{-1} on a Shimadzu FTIR-8400S spectrophotometer (Shimadzu, Japan). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE NMR spectrometer. The reported chemical shifts (δ values) are given in parts per million downfield from tetramethylsilane (TMS) as the internal standard. Elemental analyses were performed for C, H, and N using an Elementar Vario EL-III element analyzer. The progress of reactions was monitored by thin-layer chromatography (TLC) on silica gel GF254 using EtOAc/petroleum ether (1:4) as eluent.

Procedure for preparation of ethyl 6-chloro-2-(chloromethyl)quinoline-3-carboxylate (**3**).

N-(4-Chloro-2-formylphenyl)acetamide (**2**) (3.96 g, 20 mmol) and ethyl 4-chloro-3-oxobutanoate (3.3 g, 20 mmol) were placed in a 50 mL reaction kettle and dissolved in DMF (20 mL). To the solution thus obtained, TMSCl (8.7 g, 80 mmol) was carefully added dropwise to the resulting mixture. The kettle was sealed and heated at 100 °C for 10 h. After cooling the kettle was opened and the mixture was poured into H_2O (1 L) and the mixture thus obtained was allowed to stand at rt in ultrasonic bath for 1 h. The resulting precipitate was filtered and purified by column chromatography on silica gel using hexane/EtOAc (10:1) as eluent, affording the pure product **3** in 73% yield. Mp 121-122 °C (Lit.²³ 122-123 °C). IR (KBr) ν/cm^{-1} : 3048, 2985, 1718 (C=O), 1613, 1560, 1479, 1442, 1289, 1243, 1078; ^1H NMR (400 MHz, CDCl_3) δ (ppm): 1.49 (t, $J=7.2$ Hz, 3H, OCH_2CH_3), 4.51 (q, $J=7.2$ Hz, 2H, OCH_2CH_3), 5.27 (s, 2H, Cl- CH_2 -Ar), 7.78 (d, $J=8.4$ Hz, 1H, Quino-H), 7.92 (s, 1H, Quino-H), 8.08 (d, $J=8.4$ Hz, 1H, Quino-H), 8.74 (s, 1H, Quino-H); ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 19.78, 51.91, 67.71, 129.69, 132.58, 132.86, 136.45, 138.56, 139.38, 145.48, 152.13, 161.51, 170.88; Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{Cl}_2\text{NO}_2$: C, 54.95; H, 3.90; N, 4.93. Found: C, 55.18; H, 4.15; N, 4.78.

General procedure for the synthesis of N-substituted-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-ones

(**5a-m**). A mixture of ethyl 6-chloro-2-(chloromethyl)quinoline-3-carboxylate (**3**) (0.284 g, 1.0 mmol) and the respective amine (**4**) (1.0 mmol) was refluxed in EtOH-AcOH (5 mL, v/v, 10:1). After the reaction has been completed as inferred through thin layer chromatographic 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 eluent, affording the pure products **5a-m**.

7-Chloro-2-phenyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5a). White solid; reaction time 8 h; yield 81%; mp 264-266 °C; IR (KBr) ν/cm^{-1} : 1685 (C=O), 1633, 1578, 1510, 1453, 1428, 1234, 1195, 1118, 834; ^1H NMR (CF_3COOD , 400 MHz) δ (ppm): 5.90 (s, 2H, $\text{CH}_2\text{N-Ph}$), 7.74-7.88 (m, 5H, Ben-H), 8.57 (d, $J=8.4$ Hz, 1H, Quino-H), 8.67 (d, $J=8.4$ Hz, 1H, Quino-H), 8.77 (s, 1H, Quino-H), 9.80 (s, 1H, Quino-H); ^{13}C NMR (CF_3COOD , 100 MHz) δ (ppm): 51.88, 122.02, 123.38, 127.45, 129.26, 129.74, 129.83, 129.97, 135.00, 137.48, 139.12, 139.45, 143.37, 156.90, 164.32. Anal. Calcd. for $\text{C}_{17}\text{H}_{11}\text{ClN}_2\text{O}$: C, 69.28; H, 3.76; N, 9.50. Found: C, 69.46; H, 3.94; N, 9.43.

7-Chloro-2-(*m*-tolyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5b). White solid; reaction time 8 h; yield 78%; mp 225-227 °C; IR (KBr) ν/cm^{-1} : 1683 (C=O), 1633, 1580, 1516, 1454, 1372, 1296, 1271, 1188, 1154, 956; ^1H NMR (CF_3COOD , 400 MHz) δ (ppm): 2.38 (s, 3H, Me), 5.58 (s, 2H, $\text{CH}_2\text{N-Ar}$), 7.27 (s, 1H, Ben-H), 7.34-7.38 (m, 3H, Ben-H), 8.26 (d, $J=8.4$ Hz, 1H, Quino-H), 8.37 (d, $J=8.4$ Hz, 1H, Quino-H), 8.46 (s, 1H, Quino-H), 9.48 (s, 1H, Quino-H); ^{13}C NMR (CF_3COOD , 100 MHz) δ (ppm): 19.20, 51.65, 120.09, 121.60, 123.64, 126.95, 126.99, 129.23, 129.33, 129.71, 134.31, 136.99, 138.61, 138.92, 140.72, 142.83, 156.50, 163.92; Anal. Calcd for $\text{C}_{18}\text{H}_{13}\text{ClN}_2\text{O}$: C, 70.02; H, 4.24; N, 9.07. Found: C, 69.73; H, 4.13; N, 9.01.

7-Chloro-2-(*p*-tolyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5c). White solid; reaction time 8 h; yield 82%; mp 227-228 °C; IR (KBr) ν/cm^{-1} : 1681 (C=O), 1636, 1577, 1503, 1453, 1418, 1354, 1281, 1236, 1129, 928; ^1H NMR (CF_3COOD , 400 MHz) δ (ppm): 2.34 (s, 3H, Me), 5.53 (s, 2H, $\text{CH}_2\text{N-Ar}$), 7.29 (d, $J=7.8$ Hz, 2H, Ben-H), 7.40 (d, $J=7.8$ Hz, 2H, Ben-H), 8.22 (d, $J=8.4$ Hz, 1H, Quino-H), 8.33 (d, $J=8.4$ Hz, 1H, Quino-H), 8.42 (s, 1H, Quino-H), 9.44 (s, 1H, Quino-H); ^{13}C NMR (CF_3COOD , 150 MHz) δ (ppm): 18.96, 51.68, 121.56, 123.03, 126.94, 19.21, 129.30, 130.04, 131.72, 136.91, 138.57, 138.88, 140.20, 142.72, 156.53, 163.93; Anal. Calcd. for $\text{C}_{18}\text{H}_{13}\text{ClN}_2\text{O}$: C, 70.02; H, 4.24; N, 9.07. Found: C, 70.23; H, 4.38; N, 8.92.

7-Chloro-2-(4-ethylphenyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5d). White solid; reaction time 8 h; yield 77%; mp 208-209 °C; IR (KBr) ν/cm^{-1} : 1685 (C=O), 1632, 1577, 1514, 1454, 1417, 1373, 1295, 1268, 1195, 835; ^1H NMR (CF_3COOD , 400 MHz) δ (ppm): 1.21 (t, $J=7.6$ Hz, 3H, CH_3CH_2), 2.67 (q, $J=7.6$ Hz, 2H, CH_3CH_2), 5.55 (s, 2H, $\text{CH}_2\text{N-Ar}$), 7.34 (d, $J=8.0$ Hz, 2H, Ben-H), 7.44 (d, $J=8.4$ Hz, 2H, Ben-H), 8.24 (d, $J=8.4$ Hz, 1H, Quino-H), 8.34 (d, $J=8.4$ Hz, 1H, Quino-H), 8.43 (s, 1H, Quino-H), 9.45 (s, 1H, Quino-H); ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 13.37, 27.69, 65.49, 121.60, 123.15, 127.02, 128.95, 129.25, 129.34, 131.88, 136.94, 138.59, 138.90, 142.76, 146.57, 156.57, 163.97; Anal. Calcd for $\text{C}_{19}\text{H}_{15}\text{ClN}_2\text{O}$: C, 70.70; H, 4.68; N, 8.68. Found: C, 70.99; H, 4.48; N, 8.57.

2-(4-(*tert*-Butyl)phenyl)-7-chloro-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5e). White solid; reaction time 8 h; yield 76%; mp 197-198 °C; IR (KBr) ν/cm^{-1} : 1683 (C=O), 1632, 1578, 1505, 1480, 1425, 1396, 1275, 1239, 1110, 934; ^1H NMR (CF_3COOD , 400 MHz) δ (ppm): 1.33 (s, 9H, *t*-Bu), 5.58 (s,

2H, CH₂N-Ar), 7.48 (d, $J=7.6$ Hz, 2H, Ben-H), 7.59 (d, $J=8.0$ Hz, 2H, Ben-H), 8.26 (d, $J=8.4$ Hz, 1H, Quino-H), 8.37 (d, $J=8.4$ Hz, 1H, Quino-H), 8.46 (s, 1H, Quino-H), 9.48 (s, 1H, Quino-H); ¹³C NMR (CF₃COOD, 100 MHz) δ (ppm): 29.42, 34.03, 51.81, 121.64, 122.81, 126.67, 127.08, 129.29, 129.39, 131.61, 136.99, 138.67, 138.96, 142.79, 153.59, 156.69, 164.04; Anal. Calcd for C₂₁H₁₉ClN₂O: C, 71.89; H, 5.46; N, 7.98. Found: C, 72.12; H, 5.71; N, 7.83.

7-Chloro-2-(4-methoxyphenyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5f). Yellow solid; reaction time 8 h; yield 83%; mp 248-250 °C; IR (KBr) ν/cm^{-1} : 1686 (C=O), 1630, 1579, 1490, 1455, 1414, 1372, 1291, 1221, 999, 832; ¹H NMR (CF₃COOD, 400 MHz) δ (ppm): 3.99 (s, 3H, OMe), 5.57 (s, 2H, CH₂N-Ar), 7.16 (d, $J=7.6$ Hz, 2H, Ben-H), 7.58 (d, $J=7.6$ Hz, 2H, Ben-H), 8.27 (d, $J=8.4$ Hz, 1H, Quino-H), 8.37 (d, $J=8.4$ Hz, 1H, Quino-H), 8.47 (s, 1H, Quino-H), 9.48 (s, 1H, Quino-H); ¹³C NMR (CF₃COOD, 100 MHz) δ (ppm): 55.04, 55.16, 121.63, 125.06, 126.91, 129.29, 129.80, 130.36, 131.74, 137.01, 138.69, 138.99, 140.61, 142.81, 156.49, 164.00; Anal. Calcd for C₁₈H₁₃ClN₂O₂: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.26; H, 4.09; N, 8.33.

7-Chloro-2-(4-fluorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5g). White solid; reaction time 8 h; yield 74%; mp 261-263 °C; IR (KBr) ν/cm^{-1} : 1685 (C=O), 1621, 1581, 1508, 1481, 1402, 1380, 1336, 1286, 1240, 1116, 945, 874; ¹H NMR (CF₃COOD, 400 MHz) δ (ppm): 5.59 (s, 2H, CH₂N-Ar), 7.20 (d, $J=7.6$ Hz, 2H, Ben-H), 7.62 (d, $J=7.6$ Hz, 2H, Ben-H), 8.28 (d, $J=8.4$ Hz, 1H, Quino-H), 8.38 (d, $J=8.4$ Hz, 1H, Quino-H), 8.47 (s, 1H, Quino-H), 9.51 (s, 1H, Quino-H); ¹³C NMR (CF₃COOD, 100 MHz) δ (ppm): 51.53, 118.28, 121.62, 125.21, 126.76, 129.25, 129.35, 130.60, 130.62, 137.06, 138.67, 138.99, 143.02, 156.36, 163.84; Anal. Calcd for C₁₇H₁₀ClFN₂O: C, 65.29; H, 3.22; N, 8.96. Found: C, 65.46; H, 3.08; N, 9.19.

7-Chloro-2-(4-chlorophenyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5h). Yellow solid; reaction time 8 h; yield 78%; mp 265-267 °C; IR (KBr) ν/cm^{-1} : 1680 (C=O), 1618, 1515, 1450, 1407, 1384, 1338, 1235, 1159, 1074, 864; ¹H NMR (CF₃COOD, 400 MHz) δ (ppm): 5.58 (s, 2H, CH₂N-Ar), 7.46 (d, $J=8.4$ Hz, 2H, Ben-H), 7.59 (d, $J=8.4$ Hz, 2H, Ben-H), 8.25 (d, $J=8.4$ Hz, 1H, Quino-H), 8.37 (d, $J=8.4$ Hz, 1H, Quino-H), 8.45 (s, 1H, Quino-H), 9.48 (s, 1H, Quino-H); ¹³C NMR (CF₃COOD, 100 MHz) δ (ppm): 51.09, 121.68, 123.72, 126.85, 129.33, 129.42, 129.67, 133.36, 134.88, 137.13, 138.74, 139.08, 142.95, 156.29, 163.63; Anal. Calcd for C₁₇H₁₀Cl₂N₂O: C, 62.03; H, 3.06; N, 8.51. Found: C, 61.74; H, 2.84; N, 8.30.

2-(4-Bromophenyl)-7-chloro-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5i). White solid; reaction time 8 h; yield 85%; mp 242-243 °C; IR (KBr) ν/cm^{-1} : 1691 (C=O), 1621, 1511, 1446, 1374, 1340, 1294, 1263, 1204, 1118, 874; ¹H NMR (CF₃COOD, 400 MHz) δ (ppm): 5.58 (s, 2H, CH₂N-Ar), 7.53 (d, $J=8.4$ Hz, 2H, Ben-H), 7.63 (d, $J=7.6$ Hz, 2H, Ben-H), 8.26 (d, $J=8.4$ Hz, 1H, Quino-H), 8.37 (d, $J=8.4$ Hz, 1H, Quino-H), 8.44 (s, 1H, Quino-H), 9.49 (s, 1H, Quino-H); ¹³C NMR (CF₃COOD, 100 MHz) δ (ppm):

50.94, 121.66, 122.29, 123.75, 126.83, 129.30, 129.40, 132.72, 133.89, 137.11, 138.72, 139.06, 142.91, 156.24, 163.55; Anal. Calcd for C₁₇H₁₀BrClN₂O: C, 54.65; H, 2.70; N, 7.50. Found: C, 54.37; H, 2.81; N, 7.21.

7-Chloro-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5j). White solid; reaction time 8 h; yield 68%; mp 169-171 °C; IR (KBr) ν/cm^{-1} : 3259 (NH), 1706 (C=O), 1615, 1578, 1497, 1399, 1290, 1165, 847; ¹H NMR (CF₃COOD, 400 MHz) δ (ppm): 5.07 (s, 2H, CH₂N-H), 8.11 (d, $J=7.6$ Hz, 1H, Quino-H), 8.23 (d, $J=8.4$ Hz, 1H, Quino-H), 8.28 (s, 1H, Quino-H), 9.31 (s, 1H, Quino-H), 11.58 (br s, 1H, NH); ¹³C NMR (CF₃COOD, 100 MHz) δ (ppm): 45.65, 121.46, 126.01, 129.07, 129.25, 137.12, 138.61, 139.13, 143.32, 158.36, 167.54; Anal. Calcd for C₁₁H₇ClN₂O: C, 60.43; H, 3.23; N, 12.81. Found: C, 60.08; H, 3.48; N, 12.49.

7-Chloro-2-methyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5k). White solid; reaction time 8 h; yield 76%; mp 181-182 °C; IR (KBr) ν/cm^{-1} : 1692 (C=O), 1617, 1514, 1449, 1374, 1267, 1125, 831; ¹H NMR (CF₃COOD, 400 MHz) δ (ppm): 3.33 (s, 3H, N-Me), 4.61 (s, 2H, CH₂N-Ar), 7.79 (d, $J=8.4$ Hz, 1H, Quino-H), 7.99 (s, 1H, Quino-H), 8.11 (d, $J=8.4$ Hz, 1H, Quino-H), 8.53 (s, 1H, Quino-H); ¹³C NMR (CF₃COOD, 100 MHz) δ (ppm): 29.71, 53.58, 124.98, 128.01, 128.06, 130.47, 131.37, 132.23, 132.83, 147.86, 160.41, 166.02; Anal. Calcd for C₁₂H₉ClN₂O: C, 61.95; H, 3.90; N, 12.04. Found: C, 62.16; H, 3.97; N, 11.98.

7-Chloro-2-ethyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5l). White solid; reaction time 8 h; yield 82%; mp 177-179 °C; IR (KBr) ν/cm^{-1} : 1689 (C=O), 1619, 1511, 1437, 1373, 1340, 1205, 1182, 1123, 1047, 880; ¹H NMR (CF₃COOD, 400 MHz) δ (ppm): 1.35 (t, $J=7.2$ Hz, 3H, CH₂CH₃), 3.84 (q, $J=7.2$ Hz, 2H, CH₂CH₃), 5.14 (s, 2H, CH₂N-Ar), 8.19 (d, $J=8.4$ Hz, 1H, Quino-H), 8.28 (d, $J=8.4$ Hz, 1H, Quino-H), 8.39 (s, 1H, Quino-H), 9.36 (s, 1H, Quino-H); ¹³C NMR (CF₃COOD, 100 MHz) δ (ppm): 10.81, 38.39, 48.41, 121.47, 126.94, 126.97, 129.17, 136.66, 138.47, 138.66, 142.29, 156.79, 164.30; Anal. Calcd for C₁₃H₁₁ClN₂O: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.51; H, 4.61; N, 11.28.

2-Benzyl-7-chloro-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (5m). White solid; reaction time 8 h; yield 74%; mp 198-200 °C; IR (KBr) ν/cm^{-1} : 1702 (C=O), 1618, 1584, 1492, 1433, 1367, 1339, 1291, 1264, 1203, 1167, 1075, 839; ¹H NMR (CF₃COOD, 400 MHz) δ (ppm): 4.98 (s, 2H, NCH₂Ph), 5.02 (s, 2H, CH₂N-Bn), 7.30-7.36 (m, 5H, Ben-H), 8.22 (d, $J=8.4$ Hz, 1H, Quino-H), 8.30 (d, $J=8.4$ Hz, 1H, Quino-H), 8.43 (s, 1H, Quino-H), 9.45 (s, 1H, Quino-H); ¹³C NMR (CF₃COOD, 100 MHz) δ (ppm): 47.19, 48.54, 121.47, 126.78, 127.69, 128.65, 128.85, 129.18, 132.41, 132.70, 136.71, 138.48, 138.69, 142.53, 156.93, 164.26; Anal. Calcd for C₁₈H₁₃ClN₂O: C, 70.02; H, 4.24; N, 9.07. Found: C, 69.82; H, 4.18; N, 9.20.

General procedure for the synthesis of bis(7-chloro-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one) (5n-p). A mixture of ethyl 6-chloro-2-(chloromethyl)quinoline-3-carboxylate (**3**) (0.568 g, 2.0 mmol) and

the corresponding diamines (**4n-p**) (1.0 mmol) was refluxed in EtOH–AcOH (8 mL, v/v, 10:1). After the reaction has been completed as inferred through thin layer chromatographic 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 eluent, affording the pure products **5n-p**.

2,2'-(Ethane-1,2-diyl)bis(7-chloro-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one) (5n). White solid; reaction time 10 h; yield 67%; mp >300 °C; IR (KBr) ν/cm^{-1} : 1682 (C=O), 1613, 1510, 1436, 1378, 1343, 1264, 1220, 1176, 1124, 862; ^1H NMR (CF_3COOD , 400 MHz) δ (ppm): 3.76 (d, $J=7.2$ Hz, 4H, $2\times\text{CH}_2$), 5.35 (s, 4H, $2\times\text{CH}_2\text{N}$), 8.26 (d, $J=8.4$ Hz, 2H, Quino-H), 8.42 (d, $J=8.4$ Hz, 2H, Quino-H), 8.66 (s, 2H, Quino-H), 9.42 (s, 2H, Quino-H); ^{13}C NMR (CF_3COOD , 100 MHz) δ (ppm): 40.32, 41.96, 121.98, 126.33, 127.06, 130.11, 133.54, 138.03, 142.67, 143.32, 157.33, 167.36; Anal. Calcd for $\text{C}_{24}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_2$: C, 62.22; H, 3.48; N, 12.09. Found: C, 61.88; H, 3.18; N, 11.72.

2,2'-(Propane-1,3-diyl)bis(7-chloro-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one) (5o). White solid; reaction time 10 h; yield 64%; mp >300 °C; IR (KBr) ν/cm^{-1} : 1681 (C=O), 1619, 1515, 1450, 1407, 1384, 1338, 1234, 1159, 1074, 864; ^1H NMR (CF_3COOD , 400 MHz) δ (ppm): 3.35–3.38 (m, 2H, CH_2), 3.96 (t, $J=7.2$ Hz, 4H, $2\times\text{CH}_2$), 5.28 (s, 4H, $2\times\text{CH}_2\text{N}$), 8.22 (d, $J=8.4$ Hz, 2H, Quino-H), 8.29 (d, $J=8.4$ Hz, 2H, Quino-H), 8.40 (s, 2H, Quino-H), 9.36 (s, 2H, Quino-H); ^{13}C NMR (CF_3COOD , 100 MHz) δ (ppm): 25.10, 40.31, 54.05, 121.50, 126.55, 129.23, 129.27, 136.80, 138.61, 138.87, 142.50, 156.96, 164.96; Anal. Calcd for $\text{C}_{25}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_2$: C, 62.90; H, 3.80; N, 11.74. Found: C, 62.68; H, 3.73; N, 12.06.

2,2'-(Butane-1,4-diyl)bis(7-chloro-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one) (5p). White solid; reaction time 10 h; yield 69%; mp >300 °C; IR (KBr) ν/cm^{-1} : 1675 (C=O), 1621, 1581, 1511, 1463, 1407, 1380, 1321, 1185, 1061, 874; ^1H NMR (CF_3COOD , 400 MHz) δ (ppm): 1.96–1.99 (m, 4H, $2\times\text{CH}_2$), 3.94 (t, $J=7.2$ Hz, 4H, $2\times\text{CH}_2$), 5.24 (s, 4H, $2\times\text{CH}_2\text{N}$), 8.25 (d, $J=8.4$ Hz, 2H, Quino-H), 8.33 (d, $J=8.4$ Hz, 2H, Quino-H), 8.42 (s, 2H, Quino-H), 9.37 (s, 2H, Quino-H); ^{13}C NMR (CF_3COOD , 100 MHz) δ (ppm): 24.37, 42.84, 49.14, 121.51, 126.70, 129.23, 136.78, 138.61, 138.83, 142.37, 156.88, 156.91, 164.83; Anal. Calcd for $\text{C}_{26}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_2$: C, 63.55; H, 4.10; N, 11.40. Found: C, 63.84; H, 3.90; N, 11.29.

ACKNOWLEDGEMENTS

The authors would like to thank the Scientific Research Foundation of the National Natural Science Foundation of China (Grant No. 21402011) for financial support.

REFERENCES

1. A. Stierle, J. Hershenhorn, and G. Strobel, *Phytochemistry*, 1993, **32**, 1145.
2. M. Ono, Y. Nishida, C. Masuoko, J.-C. Li, M. Okawa, T. Ikeda, and T. Nohara, *J. Nat. Prod.*, 2004,

67, 2073.

3. V. Ventafridda, G. Martino, V. Mandelli, and A. Emanuelli, *Clin. Pharmacol. Ther.*, 1975, **17**, 284.
4. J. B. Bartlett, K. Dredge, and A. G. Dalgleish, *Nat. Rev. Cancer*, 2004, **4**, 314.
5. C. S. Cho and W. X. Ren, *Tetrahedron Lett.*, 2009, **50**, 2097.
6. D. M. Shacklady-McAtee, S. Dasgupta, and M. P. Watson, *Org. Lett.*, 2011, **13**, 3490.
7. E. Mertz, S. Mattei, and S. C. Zimmerman, *Bioorg. Med. Chem.*, 2004, **12**, 1517.
8. M. Guo, C.-J. Zheng, M.-X. Song, Y. Wu, L.-P. Sun, Y.-J. Li, Y. Liu, and H.-R. Piao, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 4358.
9. C. B. Sangani, J. A. Makawana, X. Zhang, S. B. Teraiya, L. Lin, and H.-L. Zhu, *Eur. J. Med. Chem.*, 2014, **76**, 549.
10. M. I. Abdullah, A. Mahmood, M. Madni, S. Masood, and M. Kashif, *Bioorg. Chem.*, 2014, **54**, 31.
11. R. E. Dolle and K. H. Nelson Jr., *J. Comb. Chem.*, 1999, **1**, 235.
12. M. Anzini, S. Vomero, A. Garofalo, A. Cappelli, and A. Cagnotto, *Il Farmaco*, 1989, **44**, 555.
13. K. Isomae, S. Morimoto, H. Hasegawa, K. Morita, and J. Kamei, *Eur. J. Pharmacol.*, 2003, **465**, 97.
14. D. S. Bose, M. Idrees, N. M. Jakka, and J. V. Rao, *J. Comb. Chem.*, 2010, **12**, 100.
15. A. S. S. H. Elgazwy, *Appl. Organometal. Chem.*, 2009, **23**, 32.
16. A. Cappelli, G. Giuliani, S. Valenti, M. Anzini, S. Vomero, G. Giorgi, C. Sogliano, E. Maciocco, G. Biggio, and A. Concas, *Bioorg. Med. Chem.*, 2008, **16**, 3428.
17. Y. Li, C. Zhang, M. Sun, and W. Gao, *J. Heterocycl. Chem.*, 2009, **46**, 1190.
18. Y. Li, G. H. Lin, and W. T. Gao, *Poly. Arom. Compd.*, 2012, **32**, 469.
19. W. Gao, C. Zhang, and Y. Li, *J. Braz. Chem. Soc.*, 2010, **21**, 806.
20. W. Gao, X. Xing, Y. Li, and S. Lan, *Tetrahedron*, 2014, **70**, 2180.
21. Y. Li and W. T. Gao, *Heterocycl. Commun.*, 2013, **19**, 405.
22. S. V. Ryabukhin, D. M. Volochnyuk, A. S. Plaskon, V. S. Naumchik, and A. A. Tolmachev, *Synthesis*, 2007, 1214.
23. A. B. Atar, S. D. Dindulkar, and Y. T. Jeong, *Monatsh. Chem.*, 2013, **144**, 695.
24. H. You, F. Chen, M. Lei, and L. Hu, *Tetrahedron Lett.*, 2013, **54**, 2972.
25. A. Kiriazis, I. B. Aumüller, and J. Yli-Kauhaluoma, *Tetrahedron Lett.*, 2011, **52**, 1151.