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# Synthesis of Quinoline-4-carboxamides and Quinoline-4-carboxylates via a Modified Pfitzinger Reaction of *N*-Vinylisatins

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**Abstract:** A synthetic approach for the accelerated assembly of quinoline-4-carboxamide and quinoline-4-carboxylate nuclei is presented. The methodology is based on the rearrangement of *N*-vinylisatins promoted by different types of amines (or ethanol) in a Pfitzinger-type mechanism that in turn builds the quinoline ring system. The reaction took place only by heating the starting materials in ethanol, without any additive.

## Introduction

Quinolines (a benzo-fused pyridine system) are a class of heteroaromatic compounds present in a large family of alkaloids and lab-made scaffolds, with a wide range of important biological activities. For example, quinine **1** and quinidine **2** are two quinoline natural *Cinchona-alkaloids* which display antimalarial[1] and antiarrhythmic[2] properties, respectively. Besides, some derivatives of these latter 4-substituted alkaloids are used as asymmetric catalysts for a variety of applications[3] (Figure 1). Among the synthetic derivatives with important biological activities are several quinoline-4-carboxamide scaffolds. For example, talnetant **3** (SB-223,412) is a potent neurokinin 3 antagonist.[4] While cinchocaine **4** and DDD107498 **5** are used as a local anesthetic[5] and an antimalarial prodrug, respectively.[6] Accordingly, the development of practical synthetic methodologies for expedient preparation of quinoline derivatives is an active field of research.[7] This is especially important in drug development programs, where construction of molecular libraries in a few reaction steps from readily available starting materials is required.

The specific construction of quinoline 4-carboxamides **11** generally involves at least a two-step process: the synthesis of the corresponding quinoline-4-carboxylic acids followed by an amidation process with the assistance of a coupling agent such as DCC or EDC (Scheme 1a,b).[8] To this end, the condensation of isatin (**6**) and carbonyl compounds, under acid-basic conditions, is the choice methodology for the synthesis of quinoline-4-carboxylic acid derivatives **10** (Pfitzinger reaction, Scheme 1a).[9] The three-component reaction between aniline, an aldehyde, and pyruvic acid (Doebner synthesis) furnishes also quinoline-4-carboxylic acids; however, this process tends to suffer from low yields.[10]

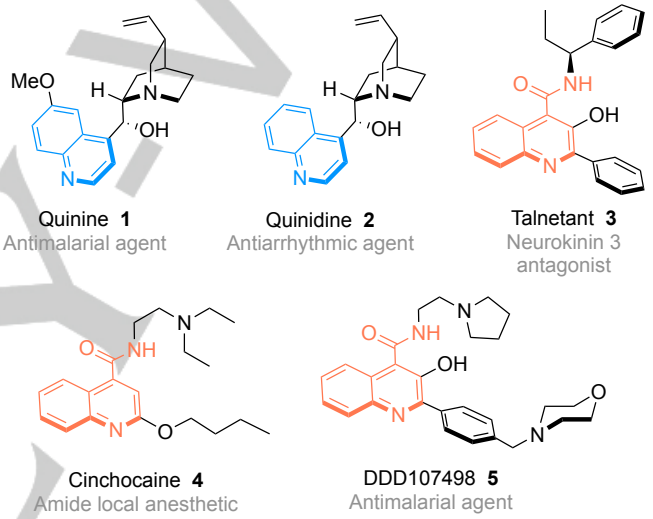
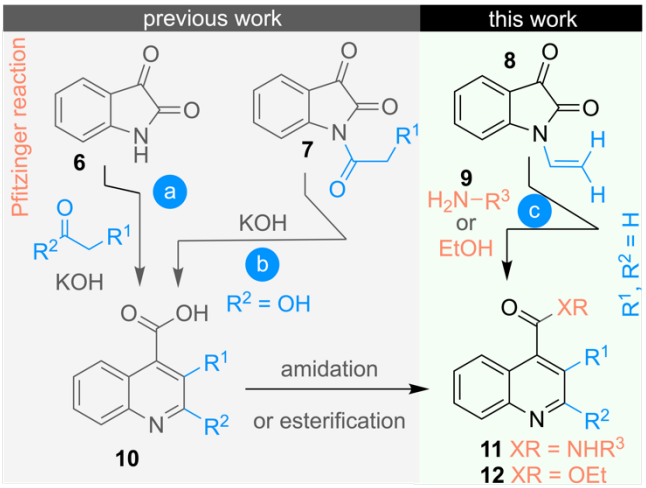



**Figure 1**. Natural products (*Shown in blue*) and synthetic quinolines (*Shown in red*) with a prominent bioactivity.

Along this line, several modifications of the classical Pfitzinger reaction have been reported for the direct construction of fused quinoline-4-carboxamides which are based on the substitution of the carbonyl compound with imidates,[11] vinylic amines,[12] heterocyclic ketene aminals,[13] enaminones,[14] and 1,1-enediamines.[15] In contrast, only one process has been published for the direct production of quinoline-4-carboxylates.[16] To our knowledge, since the Halberkann modification, which led to the formation of 2-hydroxyquinoline-4-carboxylic acids by using *N*-acylated isatins (Scheme 1b),[17] no further modifications of *N*-substituted isatins have been published for the construction of quinolines. Herein, we report the direct synthesis of quinoline-4-carboxamides **11** and quinoline-4-carboxylates **12** through a rearrangement of *N*-vinylisatins promoted by primary amines or ethanol under mild reaction conditions (Scheme 1, c). It is worth noting that the starting vinylisatin might be visualized as the enamide resulting from the condensation of isatin and acetaldehyde. Thus, the amine **9** would act as the Pfitzinger required

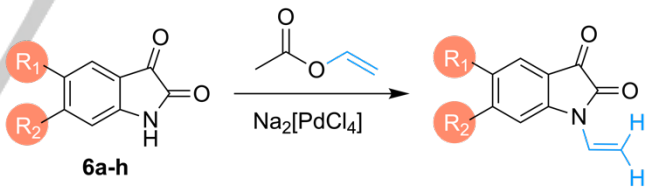
basic catalyst to the isatin opening process, with its concomitant condensation, to yield directly the quinoline-4-carboxamides. Under the classical conditions of a Pfitzinger reaction, the amine **9** would then condense with the acetaldehyde.




**Scheme 1**. Synthetic route to quinoline-4-carboxyl derivatives. a) The classical Pfitzinger reaction, b) Halberkann modification for 2-hydroxyquinoline-4-carboxylic acids[21] and our work.

## Results and Discussion

At the beginning of our research program, we conducted a small study to optimize the conditions. To this end, we chose the vinylisatin **8a** and benzylamine **9a** as model substrates. After a series of experiments, we discovered that by simply refluxing 1 equivalent of *N*-vinylisatin **8a** with 2 equivalents of benzylamine **9a** in ethanol for 5 hours, a satisfactory yield of 75% of compound **11a** was obtained. No marked improvement was observed when the reaction was carried out under microwave assistance, or when *p*-TsOH or camphorsulfonic acid (CSA) were used as additives. Also, yields were diminished with solvents such as toluene or acetonitrile. Therefore, we took this set of conditions with ethanol as optimal and proceeded to study the scope of this modified Pfitzinger reaction. First, the effect of the amine component was evaluated. Thus, *N*-vinylisatin **8a** was reacted with different types of amines (**9a-u**). We noted that the steric effect directly affected the performance of the reaction. For example, the desired rearrangement event leading to the formation of quinolines of type **11** proceeded in higher chemical yields only if primary amines with low steric hindrance were used, (*e.g.*, **11a** (75%), **11b** (72%), **11f** (72%), and **11i** (69%)). In contrast, amines with relatively more steric hindrance (*e.g.,* **9c** (cyclohexylamine) and **9d** (*sec*-butylamine)) afforded the corresponding quinoline-4-carboxamides **11c** and **11d** in modest yields of 29 and 22%, respectively (Table 1). Allyl (**11e**), propargyl (**11h**), and homopropargyl (**11j**) amines proved to be compatible with the reaction conditions and afforded the expected products, although in modest yields. Amines bearing a heteroaromatic system such as furan and thiophene afforded the quinoline **11l** and the **11m** (45 and 47%, respectively). *o*-Substituted-benzyl amines also produced the expected quinoline-4-carboxamides **11o**, **11p,** and **11q** in moderate yields. A limitation that we observed for the methodology was in the use of secondary amines. Diethyl amine, dicyclohexylamine, and piperidine (products **11r**, **11s,** and **11u**, respectively) failed to afford the expected quinoline and most of the starting *N*-vinylisatin **8a** was recovered after the process. Nonetheless, a very striking result was observed when the pyrrolidine was employed since the desired quinoline-4-carboxamide **11t** was obtained with an acceptable isolated yield of 66%. This result might be attributed to the greater conformational rigidity of pyrrolidine and this reagent may also participate in the quinoline cyclization pathway activating the carbonyl compound.[18] Suitable mono crystals of compounds **11h** (CCDC number: 1947249), **11l** (CCDC number: 1947244), and **11n** (CCDC number: 1947246), were obtained for study by X-ray diffraction, which confirmed their structures (Table 1). To further expand the scope of the methodology, we then turned our attention toward the study of the effect of substituents on the vinylisatin derivatives. Thus, the synthesis of a set of novel vinylisatins was necessary. This task was accomplished through a Pd-catalyzed transvinylation reaction of commercially available isatins with vinyl acetate.[19] Under these conditions, vinylisatins with isopropyl (**8b**), methyl (**8c**), and methoxy (**8h**) groups were obtained in 83%, 94%, and 91% yields, respectively. Furthermore, the transvinylation reaction provided *N*-vinylated isatins bearing fluoro (**8d**), bromo (**8e**), and chloro (**8g**) atoms in excellent isolated yields (83-93%). Unfortunately, the transvinylation of 5-nitroisatin (**8f**) did not proceed as a result of the poor solubility of the starting material (Scheme 2).




**8a** $R_1$= H, $R_2$ = H (95%)
**8b** $R_1$= i-Pr, $R_2$ = H (83%)
**8c** $R_1$= Me, $R_2$ = H (94%)
**8d** $R_1$= F, $R_2$ = H (94%)
**8e** $R_1$= Br, $R_2$ = H (75%)
**8f** $R_1$= $NO_2$, $R_2$ = H (0%)
**8g** $R_1$= H, $R_2$ = Cl (95%)
**8h** $R_1$= H, $R_2$ = OMe (91%)

**Scheme 2**. Pd-catalyzed transvinylation of isatins **6a-h**.

With vinylisatins **8a-h** in hand, we examined their involvement in the modified Pfitzinger reaction. Heptylamine, 3,4-dimethoxy phenethylamine, and pyrrolidine were selected for this purpose. Thus, quinoline-4-carboxamides that come from heptyl amine (**11aa**, **11ad**, **11ag**, **11aj**, **11m,** and **11ap**) were obtained in good to moderate yields (Table 2). Notably, vinylisatins bearing -F (**8d**), -Br (**8e**), and -Cl (**8g**) were applied in this reaction, affording the desired quinoline-4-carboxamides **11ag**, **11aj,** and **11ap**, although in modest 41%, 43%, and 50% yields, respectively.

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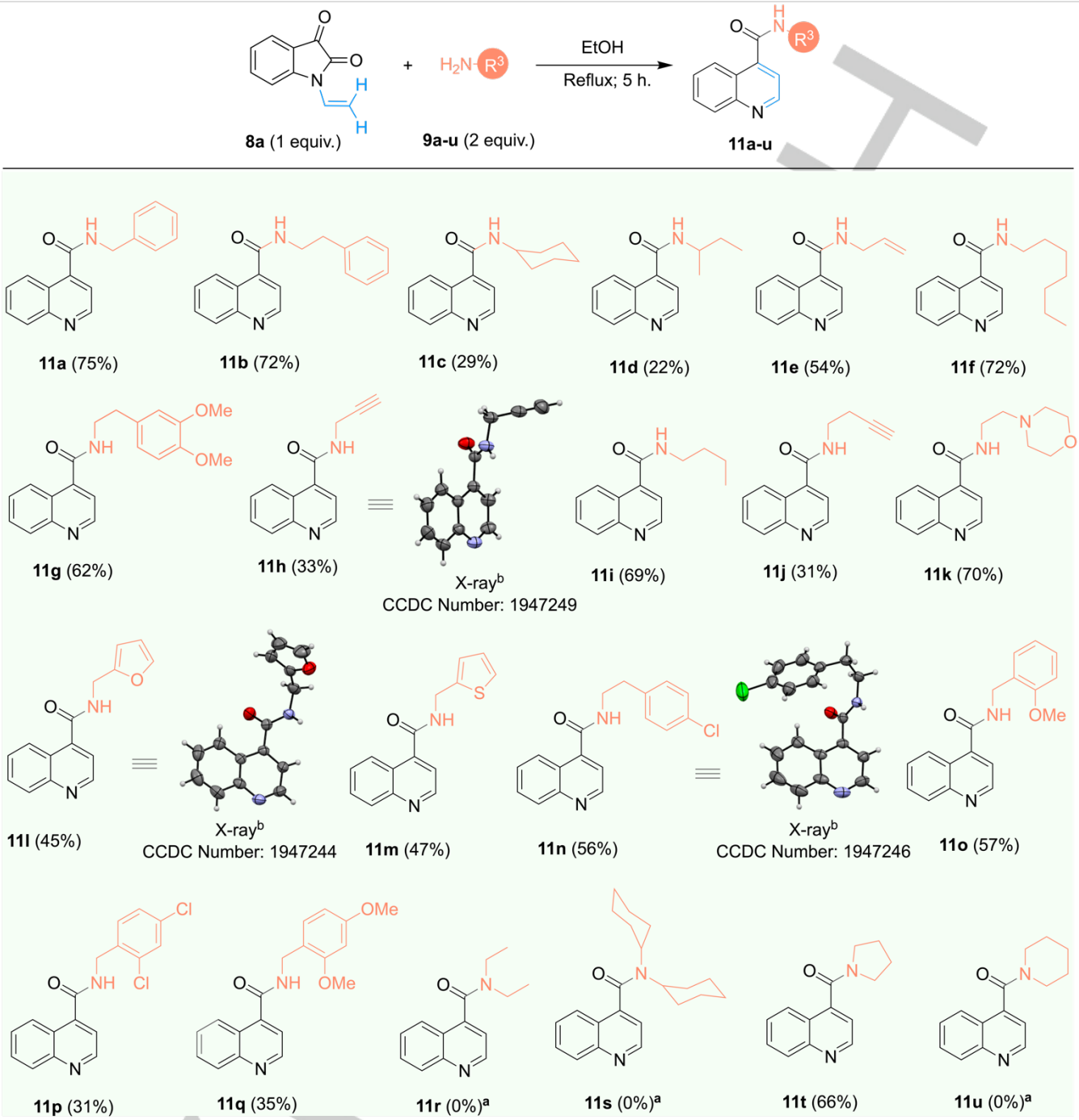
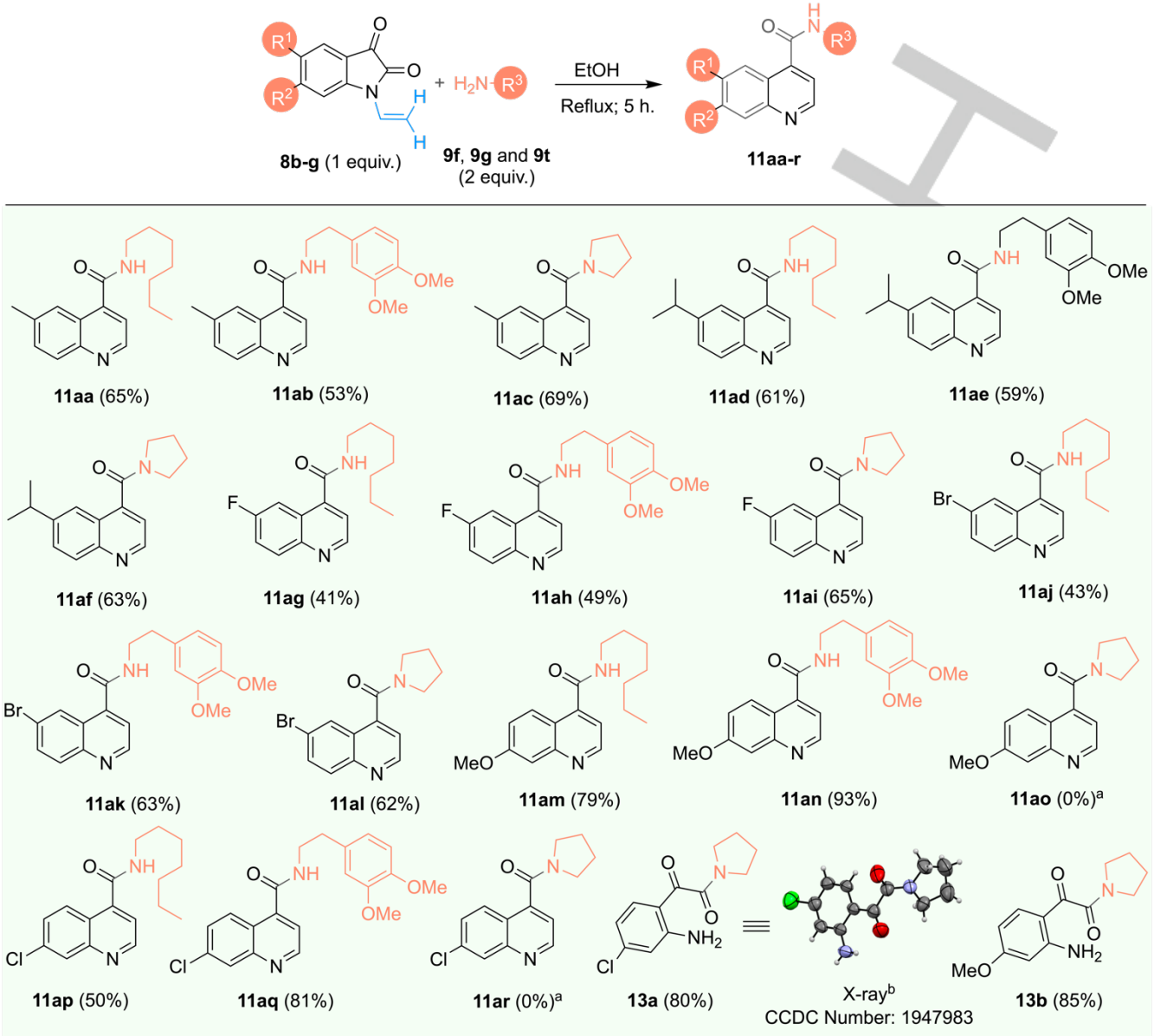
**Table 1**. Scope of the amino substrate.




[a] Only the isatin **8a** was recovered; [b] Thermal ellipsoids are drawn at 50% probability except for hydrogen. All reactions were carried out at 0.1[M] with respect to **8a.**

**Table 2**. Scope of the isatin substrate.




[a] A dicarbonyl compound was formed; [b] Thermal ellipsoids are drawn at 50% probability except for hydrogen All reactions were carried out at 0.1[M] with respect to compounds **8b-g.**

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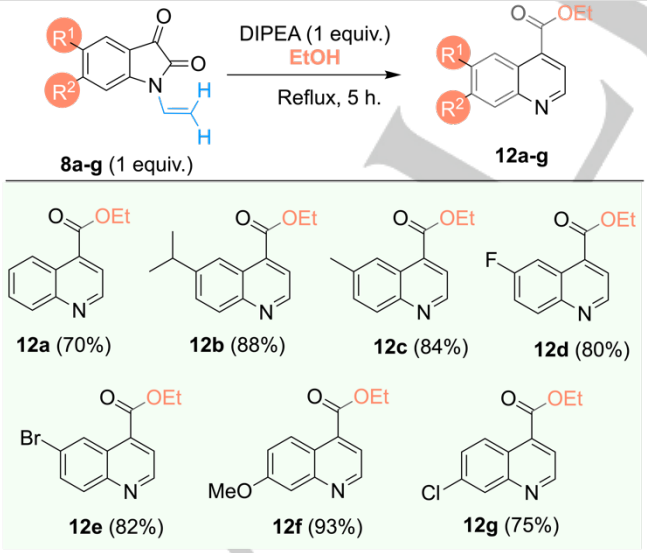
Otherwise, electron-donating groups binding directly on the isatin aromatic ring (*e.g.,* methyl **8c**, isopropyl **8b**, and methoxy **8h**) provided the desired compounds **11aa**, **11ad**, and **11am** in good yields. When dimethoxy phenethylamine was used, the corresponding quinoline-4-carboxamides **11ab**, **11ae**, **11ah**, **11ak**, **11an** and **11aq** were also obtained in good yields. Besides, the quinoline-4-carboxamides derived from isatins with electron-donating groups on the isatin aromatic rings, *e.g.,* methyl **8c**, isopropyl **8b**, and methoxy **8h,** provided the desired compounds **11ab**, **11ae**, and **11an** with isolated yields of 53%, 59%, and 93% respectively (Table 2). As expected, the desired quinoline-4-carboxamides **11ac**, **11af**, **11ai** and **11al** were obtained in good yields using pyrrolidine as the amine partner. However, we achieved an unexpected result when 6-substituted vinylisatins **8g** and **8h** were reacted with the same pyrrolidine. For an unknown reason, the outcome gave only the isatin ring-opening process by an enamine-imine isomerization type mechanism followed by imine hydrolysis to produce the corresponding dicarbonylamides **13a** and **13b** which were isolated in good yields. The structure of compound **13a** (CCDC number: 1947983), was corroborated by X-ray analysis (Table 2).

Under typical Pfitzinger conditions, the protocol was unable to afford, in one step, the quinoline-4-carboxylate esters. Synthesis of these later scaffolds in an expedited manner is desirable because it might be regarded as a "masked" quinoline-4-carboxylic acid for successive transformations. We therefore undertook a preliminary extension of the methodology toward the direct generation of ethyl quinolin-4-carboxylate esters.

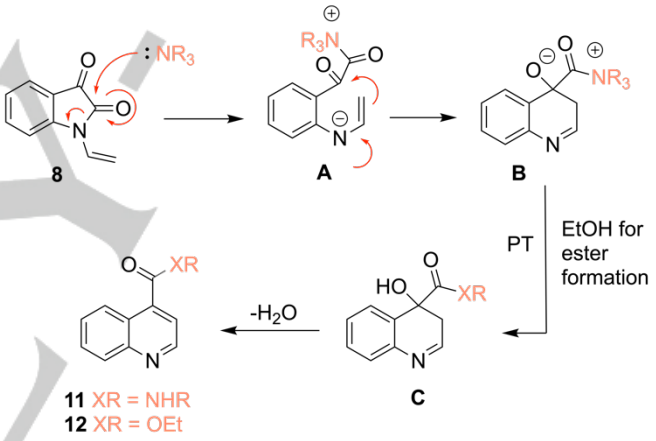
**Table 3**. Direct assembly of quinoline-4-carboxylates**.**




All reactions were carried out at 0.1[M] with respect to compounds **8a-h.**

To our delight, the quinoline-4-carboxylates **12a-g** were obtained in a *one-pot* fashion only by heating the *N*-vinylated compounds **8a-g** with DIPEA (*N*,*N*-diisopropylethylamine) in an ethanolic mixture for five hours. We observed the total consumption of the starting materials to yield, in a one-step procedure, the compounds **12a-g** in excellent yields (up to 93%). In this process, no by-products were observed in TLC. Moreover, all *N*-vinylisatins **8a-g** gave the corresponding carboxylate regardless of the decoration pattern on its aromatic ring (Table 3).

A plausible mechanism for the formation of the quinoline ring system is shown in Scheme 3. We suggest that the nucleophilic addition of the amines occurs directly at the amide carbon because the enamine functional group attached directly to the isatin nitrogen atom enhances its nucleophilicity.[20] Once nucleophilic addition has occurred, a zwitterionic intermediate (**A**) is formed after the ring-opening process. The enamine then reacts with the ketone in a 6-*exo*-trig cyclization to provide the dihydroquinoline intermediate. After a proton transfer event, subsequent dehydration produces the final quinolines of type **11** and **12** (Scheme 3).




**Scheme 3**. Plausible reaction mechanism to afford the quinoline ring system of type **11** and **12**.

## Conclusion

In summary, we report a new synthetic approach for the direct preparation of quinoline-4-carboxamides and 4-carboxylates via a modified Pfitzinger reaction via an *N*-vinylisatin rearrangement. This method provided the desired quinoline-4-carboxamides and quinoline-4-carboxylates in moderate to good yields (up to 93%). The reaction proceeds efficiently with primary amines with low steric hindrance. The scope of the reaction was demonstrated using primary amines with different steric hindrance effects and using *N*-vinylisatins with different substitution decoration patterns. We believe this methodology streamlines the quinoline Pfitzinger reaction utility and should be useful for accessing more complex scaffolds taking advantage of further C-H activation/functionalization methods (at C-2 and C-3) already available for this system.

## Experimental Section

General procedure for the *trans*-vinylation of isatins **6a-h**.

To a round bottom flask equipped with a magnetic stir bar, 10 mmol of the corresponding isatin **6a-h** was added with 25 mL of vinyl acetate. After that, 25 mg of sodium tetrachloropalladate ($Na_2[PdCl_4]$) were added to the strirring solution. Afterwards, the resulted solution was refluxed for 24 h under Ar-atmosphere. Finally, the volatiles were removed under reduced pressure, and the crude product was purified by flash chromatography on a silica gel ($SiO_2$) yielded the *N*-vinylated compounds **8a-h**.

*1-Vinylindoline-2,3-dione* ***(8a)***. Using the general procedure, this compound was obtained from commercial 1*H*-indole-2,3-dione (1.47 g, 10 mmol) as an orange solid (1.643 g, 9.5 mmol) in 95 % yield after purification by flash column chromatography, mp 107-109 °C. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.77 – 7.55 (m, 2H), 7.24 – 7.09 (m, 2H), 6.67 (dd, *J* = 16.1, 9.5 Hz, 1H), 5.88 (dd, *J* = 16.1, 0.9 Hz, 1H), 5.18 (dd, *J* = 9.5, 0.8 Hz, 1H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 168.3, 158.5, 152.1, 128.3, 124.9, 108.8, 105.8, 98.2, 56.2. IR (v=$_{max}$/cm$^{-1}$): 3448, 3103, 2925, 2855, 1738, 1609, 1470, 1365, 1303, 1197, 1105, 966, 866, 761, 471. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{10}H_8N_1O_2$ [M+H]$^+$ 174.0555, found 174.0555.

*5-Isopropyl-1-vinylindoline-2,3-dione* ***(8b)***. Using the general procedure, this compound was obtained from commercial 5-isopropyl-1*H*-indole-2,3-dione (1.9 g, 10 mmol) as a red solid (1.785 g, 8.27 mmol) in 83 % yield after purification by flash column chromatography), mp 81-83 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.55 – 7.52 (m, 1H), 7.49 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 6.68 (ddd, *J* = 16.1, 9.5, 0.8 Hz, 1H), 5.83 (d, *J* = 16.1 Hz, 1H), 5.12 (d, *J* = 9.5 Hz, 1H), 2.91 (hept, *J* = 6.9 Hz, 1H), 1.26 – 1.24 (m, 3H), 1.23 (d, *J* = 0.7 Hz, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 182.5, 157.4, 148.0, 145.8, 136.9, 125.3, 123.5, 118.1, 111.1, 105.2, 33.6, 23.8. IR (v=$_{max}$/cm$^{-1}$): 3454, 3092, 2958, 2927, 2871, 1730, 1618, 1595, 1488, 1459, 1361, 1308, 1209, 1129, 1104, 973, 880, 846, 476. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{13}H_{14}N_1O_2$ [M+H]$^+$ 216.1024, found 216.1024.

*5-Methyl-1-vinylindoline-2,3-dione* ***(8c)***. Using the general procedure, this compound was obtained from commercial 5-methyl-1*H*-indole-2,3-dione (1.61 g, 10 mmol) as an orange solid (1.777 g, 9.4 mmol) in 94 % yield after purification by flash column chromatography, mp 120-122 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.48 – 7.36 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.66 (ddd, *J* = 16.1, 9.6, 1.4 Hz, 1H), 5.82 (d, *J* = 16.1 Hz, 1H), 5.12 (d, *J* = 9.5 Hz, 1H), 2.34 (s, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 182.3, 157.3, 147.7, 139.0, 134.6, 126.0, 125.2, 117.9, 111.0, 105.2, 20.8. IR (v=$_{max}$/cm$^{-1}$): 3454, 3092, 2958, 2871, 1730, 1618, 1488, 1459, 1361, 1308, 1209, 1129, 1104, 973, 880, 846, 476. HRMS (DART, [M+H]$^+$) *m*/*z* for $C_{11}H_{10}N_1O_2$ [M+H]$^+$ 188.0711, found 188.0710.

*5-Fluoro-1-vinylindoline-2,3-dione* ***(8d)***. Using the general procedure, this compound was obtained from commercial 5-fluor-1*H*-indole-2,3-dione (1.65 g, 10 mmol) as a red solid (1.795 g, 9.4 mmol) in 94 % yield after purification by flash column chromatography, mp 120-122 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.35 (t, *J* = 7.8 Hz, 2H), 7.22 – 7.14 (m, 1H), 6.66 (dd, *J* = 16.1, 9.5 Hz, 1H), 5.93 – 5.80 (m, 1H), 5.19 (d, *J* = 9.5 Hz, 1H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 181.5, 161.0, 157.70 (d, *J* = 164.9 Hz), 146.03, 125.04 (d, *J* = 3.5 Hz), 124.8, 118.82 (d, *J* = 7.2 Hz), 112.8, 112.61 (d, *J* = 2.7 Hz), 112.5, 106.2. IR (v=$_{max}$/cm$^{-1}$): 3470, 3111, 3057, 2923, 1726, 1617, 1487, 1361, 1309, 1273, 1201, 1114, 891, 804, 640, 471. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{10}H_7F_1N_1O_2$ [M+H]$^+$ 192.0461, found 192.0463.

*5-Bromo-1-vinylindoline-2,3-dione* ***(8e)***. Using the general procedure, this compound was obtained from 5-bromo-1*H*-indole-2,3-dione prepared by bromination of 1*H*-indole-2,3-dione according to a literature procedure[21] (2.24 g, 10 mmol) as an orange solid (1.882 g, 7.5 mmol) in 75 % yield after purification by flash column chromatography, mp 144-145 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.79 – 7.70 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.71 – 6.57 (m, 1H), 5.91 – 5.81 (m, 1H), 5.27 – 5.16 (m, 1H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 182.3, 157.3, 147.7, 139.0, 134.6, 126.0, 125.2, 118.0, 111.0, 105.2, 20.8. IR (v=$_{max}$/cm$^{-1}$): 3455, 3090, 2924, 2854, 1737, 1633, 1603, 1468, 1350, 1302, 1186, 1104, 894, 830, 728, 466. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{10}H_7{}^{79}Br_1N_1O_2$ [M+H]$^+$ 251.9660, found 251.9663.

*6-Chloro-1-vinylindoline-2,3-dione* ***(8g)***. Using the general procedure, this compound was obtained from commercial 6-chloro-1*H*-indole-2,3-dione (1.81 g, 10 mmol) as an orange solid (1.966 g, 9.5 mmol) in 95 % yield after purification by flash column chromatography, mp 157-158°C. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.59 (d, *J* = 7.9 Hz, 1H), 7.22 – 7.08 (m, 2H), 6.60 (dd, *J* = 16.0, 9.5 Hz, 1H), 5.85 (d, *J* = 16.0 Hz, 1H), 5.21 (d, *J* = 9.4 Hz, 1H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 180.6, 157.0, 150.7, 145.1, 126.8, 124.9, 124.8, 116.1, 112.0, 106.9. IR (v=$_{max}$/cm$^{-1}$): 3454, 3107, 2926, 2854, 1734, 1603, 1431, 1366, 1273, 1079, 894, 792, 476. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{10}H_7Cl_1N_1O_2$ [M+H]$^+$ 208.0165, found 208.0157.

*6-Methoxy-1-vinylindoline-2,3-dione* ***(8h)***. Using the general procedure, this compound was obtained from commercial 6-methoxy-1*H*-indole-2,3-dione (1.77 g, 10 mmol) as an orange solid (1.85 g, 9.1 mmol) in 91 % yield after purification by flash column chromatography, mp 130-132 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, *J* = 8.1 Hz, 1H), 6.69 – 6.43 (m, 3H), 5.77 (d, *J* = 16.1 Hz, 1H), 5.09 (d, *J* = 9.5 Hz, 1H), 3.87 (s, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 179.5, 168.4, 158.6, 152.3, 128.4, 125.1, 111.6, 108.9, 105.9, 98.3, 56.4. IR (v=$_{max}$/cm$^{-1}$): 3422, 3089, 2942, 1720, 1604, 1450, 1372, 1228, 1100, 1013, 846, 484. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{11}H_{10}N_1O_3$ [M+H]$^+$ 204.0661, found 204.0660.

General procedure for the synthesis of the quinoline-4-carboxamides of type **11**.

To a round bottom flask equipped with a magnetic stirring bar and 5 mL of ethanol, The *N*-vinylated compound **8a** (1 equiv., 0.2887 mmol) was added. Successively, the corresponding amine (2 equiv., 0.5774 mmol) was added to the solution. The reaction mixture was heated at reflux temperature for five hours. After that, the crude of the reaction was directly purified by flash chromatography to afford the corresponding quinoline-4-carboxamides of type **11**.

*N-Benzylquinoline-4-carboxamide (**11a**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a brown solid (21.0 mg, 0.08263 mmol) in 29 % yield after purification by flash column chromatography, mp 124-126 °C $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.82 (d, *J* = 4.3 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.69 (m, 1H), 7.63 – 7.53 (m, 1H), 7.39 – 7.29 (m, 6H), 6.65 (s, 1H), 4.70 (d, *J* = 5.8 Hz, 2H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 167.3, 149.8, 148.7, 141.9, 137.7, 130.2, 129.9, 129.0, 128.0, 128.0, 127.9, 125.3, 124.5, 118.5, 44.3. IR (v=$_{max}$/cm$^{-1}$): 3271, 3062, 3031, 2920, 1635, 1578, 1537, 1453, 1319, 1288, 1151, 1030, 852, 766, 743, 695, 491, 454. HRMS (DART, [M+H]$^+$) *m*/*z* for $C_{17}H_{15}N_2O_1$ [M+H]$^+$ 263.11844, found 263.11807.

*N-Phenethylquinoline-4-carboxamide (**11b**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a pale brown solid (21.0 mg, 0.08263 mmol) in 29 % yield after purification by flash column chromatography, mp 123-125 °C. $^1$H NMR ($CDCl_3$, 400 MHz) δ: 8.77 (d, *J* = 4.3 Hz, 1H), 8.11 – 7.99 (m, 2H), 7.78 – 7.67 (m, 1H), 7.58 – 7.49 (m, 1H), 7.40 – 7.19 (m, 7H), 6.40 (s, 1H), 3.82 (q, *J* = 6.7 Hz, 2H), 3.01 (d, *J* = 13.7 Hz, 2H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 167.4, 149.8, 148.6, 142.2, 138.6, 130.1, 128.9, 128.9, 127.7, 126.9, 125.3, 124.4, 118.4, 41.2, 35.6. IR (v=$_{max}$/cm$^{-1}$): 3317, 3060, 3029, 2931, 1641, 1578, 1534, 1453, 1356, 1291, 1196, 1038, 871, 751, 697, 649, 496, 461. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{18}H_{17}N_2O_1$ [M+H]$^+$ 277.1341, found 277.1339.

*N-Cyclohexylquinoline-4-carboxamide (**11c**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a pale yellow solid (21.0 mg, 0.08263 mmol) in 29 % yield after purification by flash column chromatography, mp 165-167 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.79 (d, *J* = 4.1 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.71 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.56 (td, *J* = 7.6, 7.0, 1.0 Hz, 1H), 7.29 (d, *J* = 4.3 Hz, 1H), 6.22 (d, *J* = 7.8 Hz, 1H), 4.11 – 3.96 (m, 1H), 2.14 – 2.03 (m, 2H), 1.77 (dt, *J* = 13.3, 3.6 Hz, 2H), 1.66 (dt, *J* = 12.8, 3.6 Hz, 1H), 1.50 – 1.38 (m, 2H), 1.34 – 1.13 (m, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 166.6, 149.8, 148.6, 142.6, 130.0, 129.9, 127.7, 125.3, 124.5, 118.4, 49.2, 33.2, 29.8, 25.5, 25.0. IR (v=$_{max}$/cm$^{-1}$): 3290, 3072, 3042, 2934, 2852, 1635, 1579, 1538, 1452, 1327, 1291, 1150, 1093, 848, 755, 703, 650 HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{16}H_{19}N_2O_1$ [M+H]$^+$ 255.14974, found 255.15093.

*N-(sec-Butyl)quinoline-4-carboxamide (**11d**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a beige solid (14.2 mg, 0.0622 mmol) in 22 % yield after purification by flash column chromatography, mp 92-94 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.85 (d, *J* = 4.3 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.73 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.34 (d, *J* = 4.3 Hz, 1H), 6.01 (d, *J* = 7.6 Hz, 1H), 4.31 – 4.11 (m, 1H), 1.61 (p, *J* = 7.3 Hz, 2H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.02 (t, *J* = 7.4 Hz, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 166.8, 149.8, 148.6, 142.6, 130.0, 127.6, 125.2, 124.5, 118.2, 47.5, 29.7, 20.5, 10.5. IR (v=$_{max}$/cm$^{-1}$): 3276, 3073, 2968, 2928, 1637, 1579, 1535, 1456, 1299, 1156, 886, 757, 710, 654. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{14}H_{17}N_2O_1$ [M+H]$^+$ 229.1341, found 229.1348.

*N-Allylquinoline-4-carboxamide (**11e**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a beige solid (33.3 mg, 0.1569 mmol) in 54 % yield after purification by flash column chromatography, mp 92-94 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.78 (d, *J* = 4.3 Hz, 1H), 8.19 – 8.10 (m, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.32 (d, *J* = 4.3 Hz, 1H), 6.57 (s, 1H), 5.94 (ddt, *J* = 17.0, 10.3, 5.7 Hz, 1H), 5.35 – 5.15 (m, 2H), 4.11 (tt, *J* = 5.8, 1.5 Hz, 2H).$^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz) δ 167.3, 149.8, 148.6, 142.0, 133.6, 130.1, 129.8, 127.8, 125.3, 124.5, 118.4, 117.3, 42.5. IR (v=$_{max}$/cm$^{-1}$): 3275, 3070, 2922, 2853, 1643, 1579, 1536, 1415, 1303, 1259, 1147, 923, 757, 710, 650. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{13}H_{13}N_2O_1$ [M+H]$^+$ 213.1028, found 213.1024.

*N-Heptylquinoline-4-carboxamide (**11f**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a pale brown solid (56.4 mg, 0.2088 mmol) in 72 % yield after purification by flash column chromatography, mp 81-83 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.87 – 8.82 (m, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.79 – 7.71 (m, 1H), 7.63 – 7.55 (m, 1H), 7.34 (dd, *J* = 4.1, 2.5 Hz, 1H), 6.35 (s, 1H), 3.52 (q, *J* = 6.1 Hz, 2H), 1.66 (p, *J* = 7.2 Hz, 2H), 1.44 – 1.28 (m, 8H), 0.91 (t, *J* = 6.8 Hz, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 167.4, 149.9, 148.7, 142.5, 130.1, 129.9, 127.7, 125.4, 124.6, 118.4, 40.3, 31.9, 29.7, 29.1, 27.1, 22.7, 14.2. IR (v=$_{max}$/cm$^{-1}$): 3284, 3076, 2953, 2925, 2855, 1641, 1579, 1540, 1460, 1302, 1152, 872, 757, 714, 654. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{17}H_{23}N_2O_1$ [M+H]$^+$ 271.1810, found 271.1811.

*N-(3,4-Dimethoxyphenethyl)quinoline-4-carboxamide (**11g**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a pale brown solid (59.8 mg, 01.778 mmol) in 62 % yield after purification by flash column chromatography, mp 132-134 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.77 (d, *J* = 4.3 Hz, 1H), 8.05 (d, *J* = 9.6 Hz, 2H), 7.71 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 1H), 7.26 (d, *J* = 4.3 Hz, 1H), 6.84 – 6.77 (m, 2H), 6.76 (s, 1H), 6.40 (s, 1H), 3.85 (s, 3H),

3.81 (s, 5H), 2.94 (t, *J* = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 167.4, 149.8, 149.3, 148.6, 148.0, 142.2, 131.0, 130.1, 129.9, 127.7, 125.3, 124.4, 120.9, 118.4, 112.1, 111.6, 56.0, 55.9, 41.3, 35.2. IR ($v=_{max}/cm^{-1}$): 3306, 3069, 2928, 2934, 1634, 1583, 1543, 1513, 1461, 1302, 1263, 1232, 1149, 1028, 762, 700, 649. HRMS (DART+) *m*/*z* calcd for $C_{20}H_{21}N_2O_3$ $[M+H]^+$ 337.1552, found 337.1549.

*N-(Prop-2-yn-1-yl)quinoline-4-carboxamide (**11h**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a pale brown solid (20.0 mg, 0.09513 mmol) in 33 % yield after purification by flash column chromatography, mp 123-126 °C $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.78 (d, *J* = 4.3 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.91 (s, 1H), 7.65 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.50 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.35 (d, *J* = 4.3 Hz, 1H), 4.19 (dd, *J* = 5.4, 2.5 Hz, 2H), 2.24 (t, *J* = 2.5 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 167.1, 149.7, 148.4, 141.5, 129.9, 129.5, 127.5, 125.3, 124.5, 118.8, 79.4, 71.6, 29.4. IR ($v=_{max}/cm^{-1}$): 3469, 3193, 3004, 2920, 2854, 2829, 2120, 1659, 1554, 1505, 1289, 1052, 1027, 872, 764, 515. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{13}H_{11}N_2O_1$ $[M+H]^+$ 211.0871, found 211.0864.

*N-Butylquinoline-4-carboxamide (**11i**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a pale yellow solid (45.5 mg, 0.1993 mmol) in 69 % yield after purification by flash column chromatography, mp 104-106 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.73 (d, *J* = 4.3 Hz, 1H), 8.13 – 8.07 (m, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.24 (d, *J* = 4.3 Hz, 1H), 6.54 (s, 1H), 3.53 – 3.40 (m, 2H), 1.59 (p, *J* = 7.5 Hz, 2H), 1.40 (dq, *J* = 14.5, 7.3 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 167.4, 149.8, 148.5, 142.4, 130.0, 129.8, 127.6, 125.3, 124.5, 118.3, 39.9, 31.7, 20.2, 13.8. IR ($v=_{max}/cm^{-1}$): 3241, 3086, 2944, 2925, 2866, 1634, 1589, 1559, 1501, 1459, 1321, 1217, 1149, 850, 770, 720, 527. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{14}H_{17}N_2O_1$ $[M+H]^+$ 229.1341, found 229.1338.

*N-(But-3-yn-1-yl)quinoline-4-carboxamide (**11j**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a pale yellow solid (20.3 mg, 0.0905 mmol) in 31 % yield after purification by flash column chromatography, mp 104-106 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.84 (d, *J* = 4.3 Hz, 1H), 8.26 – 8.17 (m, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.73 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.38 (d, *J* = 4.3 Hz, 1H), 6.68 (s, 1H), 3.67 (q, *J* = 6.3 Hz, 2H), 2.59 (td, *J* = 6.3, 2.6 Hz, 2H), 2.05 (t, *J* = 2.6 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 167.5, 149.9, 148.6, 141.9, 130.2, 129.9, 127.8, 125.4, 124.4, 118.6, 81.3, 70.7, 38.6, 19.5. IR ($v=_{max}/cm^{-1}$): 3469, 3193, 3004, 2920, 2829, 1659, 1554, 1505, 1289, 1027, 872, 764, 515. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{13}H_{11}N_2O_1$ $[M+H]^+$ 211.0871, found 211.0864.

*N-(2-Morpholinoethyl)quinoline-4-carboxamide (**11k**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a beige solid (57.3 mg, 0.2008 mg) in 70 % yield after purification by flash column chromatography, mp 104-106 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.88 (d, *J* = 4.3 Hz, 1H), 8.28 – 8.20 (m, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.73 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.38 (d, *J* = 4.3 Hz, 1H), 6.75 (s, 1H), 3.69 – 3.64 (m, 4H), 3.61 (q, *J* = 5.5 Hz, 2H), 2.60 (t, *J* = 6.0 Hz, 2H), 2.52 – 2.45 (m, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 167.3, 149.9, 148.7, 142.2, 130.1, 130.0, 127.7, 125.4, 124.6, 118.6, 67.0, 57.0, 53.4, 36.3. IR ($v=_{max}/cm^{-1}$): 3279, 3067, 2930, 2959, 2816, 1660, 1548, 1527, 1448, 1278, 1119, 1027, 860, 771. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{16}H_{20}N_3O_2$ $[M+H]^+$ 286.1555, found 286.1554.

*N-(Furan-2-ylmethyl)quinoline-4-carboxamide (**11l**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a beige solid (32.5 mg, 0.1288 mmol) in 45 % yield after purification by flash column chromatography, mp 140-141 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.77 (d, *J* = 4.3 Hz, 1H), 8.20 – 8.11 (m, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.37 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.33 (d, *J* = 4.3 Hz, 1H), 6.91 (s, 1H), 6.39 – 6.25 (m, 2H), 4.68 (d, *J* = 5.6 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): 167.2, 150.7, 149.8, 148.6, 142.6, 141.7, 130.1, 129.8, 127.8, 125.3, 124.5, 118.6, 110.7, 108.1, 37.1. IR ($v=_{max}/cm^{-1}$): 3297, 3111, 3039, 2952, 1637, 1578, 1534, 1502, 1423, 1298, 1191, 1147, 1018, 749, 696, 592. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{15}H_{13}N_2O_2$ $[M+H]^+$ 253.0977, found 253.0982.

*N-(Thiophen-2-ylmethyl)quinoline-4-carboxamide (**11m**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a beige solid (36.5 mg, 0.1360 mmol) in 47 % yield after purification by flash column chromatography, mp 127-129 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.68 (d, *J* = 4.4 Hz, 1H), 8.12 (ddd, *J* = 8.5, 1.4, 0.7 Hz, 1H), 7.99 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.68 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.52 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.33 – 7.23 (m, 2H), 7.10 (s, 1H), 7.03 (ddt, *J* = 2.8, 1.4, 0.7 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.83 (dd, *J* = 5.8, 0.9 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 167.0, 149.6, 148.4, 141.5, 140.2, 130.0, 129.6, 127.7, 127.0, 126.4, 125.5, 125.2, 124.3, 118.4, 38.7. IR ($v=_{max}/cm^{-1}$): 3288, 3040, 2923, 1638, 1581, 1530, 1300, 1152, 1039, 703. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{15}H_{13}N_2O_1S_1$ $[M+H]^+$ 269.0749, found 269.0742.

*N-(4-Chlorobenzyl)quinoline-4-carboxamide (**11n**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a beige solid (50.0 mg, 0.1609 mmol) in 56 % yield after purification by flash column chromatography, mp 146-148 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.63 (d, *J* = 4.3 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.89 – 7.83 (m, 3H), 7.63 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 2H), 7.44 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 3H), 7.13 – 7.06 (m, 5H), 6.41 (t, *J* = 5.2 Hz, 3H), 3.68 (q, *J* = 6.9 Hz,

4H), 2.87 (t, *J* = 6.9 Hz, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 167.5, 149.7, 148.5, 142.0, 137.0, 132.7, 130.3, 130.1, 129.8, 129.0, 127.7, 125.2, 124.4, 118.3, 41.0, 35.0. IR ($v=_{max}/cm^{-1}$): 3215, 3061, 2929, 2864, 1632, 1580, 1486, 1439, 1315, 1246, 1086,1043, 811, 770, 636, 456. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{18}H_{16}ClN_2O_1$ $[M+H]^+$ 311.0951, found 311.094.

*N-(2-Methoxybenzyl)quinoline-4-carboxamide (**11o**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a beige solid (48.2 mg, 0.1649 mmol) in 57 % yield after purification by flash column chromatography. m. p. 104-106°C $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.76 (d, *J* = 4.3 Hz, 1H), 8.09 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.99 (d, *J* = 8.9 Hz, 1H), 7.63 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.46 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.31 (d, *J* = 1.6 Hz, 1H), 7.29 (s, 1H), 7.25 – 7.20 (m, 1H), 6.89 (td, *J* = 7.5, 1.0 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.67 (s, 1H), 4.63 (d, *J* = 5.8 Hz, 2H), 3.76 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 178.1, 150.8, 140.8, 134.3, 132.5, 129.6, 127.8, 127.5, 127.0, 126.4, 124.8, 123.4, 109.8, 108.8, 103.3, 61.4, 60.4, 47.5, 29.8, 21.1, 14.2. IR ($v=_{max}/cm^{-1}$): 3273, 3073, 2926, 2838, 1645, 1546, 1460, 1242, 1024, 868, 751, 705. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{18}H_{17}N_2O_2$ $[M+H]^+$ 293.1290, found 293.1295.

*N-(2,4-Dichlorobenzyl)quinoline-4-carboxamide (**11p**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a white solid (29.7 mg, 0.0897 mmol) in 31 % yield after purification by flash column chromatography, mp 175-177 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.76 (d, *J* = 4.3 Hz, 1H), 8.09 – 8.04 (m, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.66 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.35 (d, *J* = 2.2 Hz, 1H), 7.28 (d, *J* = 4.3 Hz, 1H), 7.19 (d, *J* = 1.8 Hz, 1H), 6.71 (t, *J* = 5.1 Hz, 1H), 4.65 (d, *J* = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 167.4, 148.7, 141.5, 134.7, 134.5, 133.8, 131.5, 130.2, 130.0, 129.7, 127.9, 127.7, 125.2, 124.5, 118.5, 41.8. IR ($v=_{max}/cm^{-1}$): 3296, 3057, 1634, 1583, 1531, 1456, 1288, 1098, 1056, 899, 791, 666. 451 HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{17}H_{13}Cl_2N_2O_1$ $[M+H]^+$ 331.0405, found 331.0417.

*N-(2,4-Dimethoxybenzyl)quinoline-4-carboxamide (**11q**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a beige solid (32.2 mg, 0.0999 mmol) in 35 % yield after purification by flash column chromatography, mp 119-121 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.84 (d, *J* = 4.3 Hz, 1H), 8.23 – 8.14 (m, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.37 (d, *J* = 4.3 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 6.63 (s, 1H), 6.46 (dq, *J* = 4.1, 2.4 Hz, 2H), 4.63 (d, *J* = 5.7 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 166.9, 161.0, 158.8, 149.9, 148.7, 142.4, 131.0, 130.0, 129.9, 127.6, 125.4, 124.6, 118.6, 118.2, 104.2, 98.8, 55.5, 39.9. IR ($v=_{max}/cm^{-1}$): 3295, 3074, 2924, 2837, 1641, 1616, 1584, 1539, 1461, 1428, 1295, 1262, 1209, 1126, 1034, 834, 755 634, 463. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{19}H_{19}N_2O_3$ $[M+H]^+$ 323.1396, found 323.1386.

*Pyrrolidin-1-yl(quinolin-4-yl)methanone (**11t**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50.0 mg, 0.2887 mmol) as a brown oil (43.2 mg, 0.1909 mmol) in 66 % yield after purification by flash column chromatography. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.95 (d, *J* = 4.3 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.91 – 7.81 (m, 1H), 7.80 – 7.69 (m, 1H), 7.66 – 7.52 (m, 1H), 7.34 (d, *J* = 4.3 Hz, 1H), 3.78 (t, *J* = 7.0 Hz, 2H), 3.11 (t, *J* = 6.7 Hz, 2H), 2.01 (p, *J* = 7.0 Hz, 2H), 1.85 (p, *J* = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 166.9, 166.7, 150.1, 148.5, 130.0, 127.6, 124.8, 123.8, 117.8, 48.4, 45.7, 26.0, 24.5. IR ($v=_{max}/cm^{-1}$): 3489, 3057, 2971, 2878, 1633, 1588, 1442, 1382, 1184, 855, 769, 638. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{14}H_{15}N_2O_1$ $[M+H]^+$ 227.1184, found 227.1189.

*N-Heptyl-6-methylquinoline-4-carboxamide (**11aa**).* Using the general procedure, this compound was obtained from 5-methyl-1-vinylindoline-2,3-dione (**8c**) (54.0 mg, 0.2887 mmol) as a beige solid (53.0 mg, 0.1864 mg) in 65 % yield after purification by flash column chromatography, mp 81-83 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.67 (d, *J* = 4.3 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.87 (s, 1H), 7.52 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.21 (d, *J* = 4.3 Hz, 1H), 6.46 (s, 1H), 3.55 – 3.41 (m, 2H), 2.50 (s, 3H), 1.63 (p, *J* = 7.7, 7.3 Hz, 2H), 1.45 – 1.23 (m, 8H), 0.95 – 0.83 (m, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 167.6, 148.8, 147.2, 141.7, 137.8, 132.3, 129.4, 124.5, 124.1, 118.3, 40.2, 31.9, 29.7, 29.1, 27.1, 22.7, 21.9, 14.2. IR ($v=_{max}/cm^{-1}$): 3291, 3063, 2957, 2925, 2854, 1638, 1577, 1540, 1463, 1307, 1150, 1041, 856, 825, 711, 622, 477. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{18}H_{25}N_2O_1$ $[M+H]^+$ 285.1967, found 285.1967.

*N-(3,4-Dimethoxyphenethyl)-6-methylquinoline-4 carboxamide (**11ab**).* Using the general procedure, this compound was obtained from 5-methyl-1-vinylindoline-2,3-dione (**8c**) (54.0 mg, 0.2887 mmol) as a beige solid (53.5 mg, 01527 mmol) in 53 % yield after purification by flash column chromatography, mp 123-125 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.64 (d, *J* = 3.5 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.83 (s, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 4.2 Hz, 1H), 6.77 (s, 2H), 6.74 (s, 1H), 6.48 (s, 1H), 3.82 (s, 3H), 3.79 (s, 5H), 2.93 (t, *J* = 6.9 Hz, 2H), 2.48 (s, 3H) $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 167.7, 149.2, 148.7, 147.9, 147.2, 141.4, 137.8, 132.3, 131.0, 129.4, 124.4, 124.0, 120.8, 118.3, 111.9, 111.5, 56.0, 55.9, 41.2, 35.2, 21.9. IR ($v=_{max}/cm^{-1}$): 3322, 3063, 2963, 2933, 2876, 2836, 1637, 1578, 1537, 1462, 1443, 1330, 1261, 1236, 1156, 1025, 855, 805, 655, 633. HRMS (DART, $[M+H]^+$) *m/z* calcd for $C_{21}H_{23}N_2O_3$ $[M+H]^+$ 351.1709, found 351.1702.

*(6-Methylquinolin-4-yl)(pyrrolidin-1-yl)methanone (**11ac**).* Using the general procedure, this compound was obtained from 5-methyl-1-vinylindoline-2,3-dione (**8c**) (54.0 mg, 0.2887 mmol) as a brown oil (47.9 mg, 0.1993 mmol) in 69 % yield after purification by flash column chromatography. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, *J* = 4.3 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 9.1 Hz, 2H), 7.28 (d, *J* = 4.3 Hz, 1H), 3.79 (t, *J* = 7.1 Hz, 2H), 3.12 (t, *J* = 6.8 Hz, 2H), 2.52 (s, 3H), 2.01 (p, *J* = 6.9 Hz, 2H), 1.86 (p, *J* = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 167.0, 149.2, 147.3, 142.9, 137.8, 132.4, 129.8, 124.0,

123.6, 117.8, 48.5, 45.8, 26.1, 24.6, 21.9. IR ($v=_{max}$/cm$^{-1}$): 3485, 2971, 2877, 1636, 1585, 1423, 1360, 859, 824, 646, 436. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{15}H_{17}N_2O_1$ $[M+H]^+$ 241.1341, found 241.1344.

*N-heptyl-6-isopropylquinoline-4-carboxamide (**11ad**).* Using the general procedure, this compound was obtained from 5-isopropyl-1-vinylindoline-2,3-dione (**8b**) (62.1 mg, 0.2887 mmol) as a brown solid (55.2 mg, 01767 mg) in 61 % yield after purification by flash column chromatography, mp 62-64 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.73 (d, *J* = 4.3 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.96 (d, *J* = 1.9 Hz, 1H), 7.65 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.27 (d, *J* = 4.3 Hz, 1H), 6.45 (t, *J* = 4.8 Hz, 1H), 3.53 (q, *J* = 7.1 Hz, 2H), 3.17 – 3.03 (m, 1H), 1.67 (p, *J* = 7.2 Hz, 2H), 1.50 – 1.22 (m, 16H), 0.90 (t, *J* = 6.9 Hz, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 167.7, 148.9, 148.4, 147.6, 142.1, 129.8, 124.5, 121.5, 118.3, 40.2, 34.5, 31.9, 29.7, 29.1, 27.1, 23.9, 22.7, 14.2. IR ($v=_{max}$/cm$^{-1}$): 3420, 2959, 2927, 2856, 1644, 1582, 1545, 1462, 1034, 860. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{20}H_{29}N_2O_1$ $[M+H]^+$ 313.2280, found 313.2272.

*N-(3,4-Dimethoxyphenethyl)-6-isopropylquinoline-4-carboxamide (**11ae**).* Using the general procedure, this compound was obtained from 5-isopropyl-1-vinylindoline-2,3-dione (**8b**) (62.1 mg, 0.2887 mmol) as a brown solid (64.8 mg, 0.1712 mmol) in 59 % yield after purification by flash column chromatography, mp 103-104 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.70 (d, *J* = 4.2 Hz, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 1.6 Hz, 1H), 7.63 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.22 (dd, *J* = 4.3, 1.0 Hz, 1H), 6.78 (s, 2H), 6.75 (s, 1H), 6.37 (s, 1H), 3.83 (s, 3H), 3.80 (s, 5H), 3.06 (p, *J* = 6.9 Hz, 1H), 2.95 (t, *J* = 6.9 Hz, 2H), 1.31 (d, *J* = 6.9 Hz, 6H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 167.7, 149.2, 148.9, 148.5, 147.9, 147. 141.7, 131.0, 129.8, 129.7, 124.5, 121.6, 120.8, 118.4, 111.9, 111.5, 56.0, 55.9, 41.2, 35.2, 34.5, 23.9. IR ($v=_{max}$/cm$^{-1}$): 3290, 2959, 2931, 2868, 1647, 1585, 1514, 1461, 1262, 1236, 1148, 1028, 589. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{23}H_{27}N_2O_3$ $[M+H]^+$ 379.2022, found 379.2011.

*(6-Isopropylquinolin-4-yl)(pyrrolidin-1-yl)methanone (**11af**).* Using the general procedure, this compound was obtained from 5-isopropyl-1-vinylindoline-2,3-dione (**8b**) (62.1 mg, 0.2887 mmol) as a brown oil (49.1 mg, 0.1830 mmol) in 63 % yield after purification by flash column chromatography. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.88 (d, *J* = 4.2 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.69 – 7.62 (m, 1H), 7.61 – 7.55 (m, 1H), 7.30 (d, *J* = 4.2 Hz, 1H), 3.80 (t, *J* = 7.0 Hz, 2H), 3.11 (dt, *J* = 11.5, 7.1 Hz, 3H), 2.01 (p, *J* = 6.8 Hz, 2H), 1.87 (q, *J* = 6.7 Hz, 2H), 1.31 (d, *J* = 6.9 Hz, 6H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 167.0, 149.3, 148.5, 147.6, 143.2, 130.0, 129.7, 123.9, 121.0, 117.9, 48.5, 45.8, 34.4, 26.1, 24.6, 23.9. IR ($v=_{max}$/cm$^{-1}$): 3466, 2961, 2874, 1635, 1458, 1426, 1363, 860. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{17}H_{21}N_2O_1$ $[M+H]^+$ 269.1654, found 269.1656.

*6-Fluoro-N-heptylquinoline-4-carboxamide (**11ag**).* Using the general procedure, this compound was obtained from 5-fluor-1-vinylindoline-2,3-dione (**8d**) (55.2 mg, 0.2887 mmol) as a pale yellow solid (33.8 mg, 0.1172 mmol) in 41 % yield after purification by flash column chromatography, mp 69-70 ºC. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.78 (d, *J* = 4.3 Hz, 1H), 8.06 (dd, *J* = 9.3, 5.5 Hz, 1H), 7.82 (dd, *J* = 9.9, 2.8 Hz, 1H), 7.48 (ddd, *J* = 9.2, 8.0, 2.8 Hz, 1H), 7.33 (d, *J* = 4.3 Hz, 1H), 6.40 (s, 1H), 3.53 – 3.41 (m, 2H), 1.62 (p, *J* = 7.4 Hz, 2H), 1.40 – 1.26 (m, 8H), 0.92 – 0.83 (m, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 167.7, 148.01 (d, *J* = 81.3 Hz), 147.6, 142.1, 129.74 (d, *J* = 7.2 Hz), 124.5, 121.5, 118.3, 40.2, 34.5, 31.9, 29.7, 29.1, 27.1, 23.9, 22.7, 14.2. IR ($v=_{max}$/cm$^{-1}$): 3407, 2956, 2927, 2855, 1715, 1491, 1264, 1177, 816, 590, 431. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{17}H_{22}FN_2O_1$ $[M+H]^+$ 289.1716, found 289.1716.

*N-(3,4-Dimethoxyphenethyl)-6-fluoroquinoline-4-carboxamide (**11ah**).* Using the general procedure, this compound was obtained from 5-fluor-1-vinylindoline-2,3-dione (**8d**) (55.2 mg, 0.2887 mmol) as a brown solid (50.5 mg, 0.1425 mmol) in 49 % yield after purification by flash column chromatography, mp 115-116 ºC. $^1$H NMR ($CDCl_3$, 300 MHz): δ 8.75 (d, *J* = 4.3 Hz, 1H), 8.04 (dd, *J* = 9.3, 5.5 Hz, 1H), 7.77 (dd, *J* = 9.9, 2.8 Hz, 1H), 7.48 (ddd, *J* = 9.2, 8.1, 2.8 Hz, 1H), 7.28 (d, *J* = 4.3 Hz, 1H), 6.85 – 6.70 (m, 3H), 6.32 (t, *J* = 5.8 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.80 – 3.73 (m, 2H), 2.93 (t, *J* = 6.8 Hz, 2H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 167.0, 161.15 (d, *J* = 249.8 Hz), 149.3, 149.1, 148.0, 145.9, 141.5, 132.40 (d, *J* = 9.3 Hz), 130.9, 120.8, 120.51 (d, *J* = 26.0 Hz), 119.0, 111.78 (d, *J* = 30.3 Hz), 109.10 (d, *J* = 23.7 Hz), 56.0, 56.0, 41.3, 35.2. IR ($v=_{max}$/cm$^{-1}$): 3283, 2938, 1636, 1514, 1464, 1285, 1237, 1158, 1141, 1027, 858, 767, 720. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{20}H_{20}FN_2O_3$ $[M+H]^+$ 355.1458, found 355.1452.

*(6-Fluoroquinolin-4-yl)(pyrrolidin-1-yl)methanone (**11ai**).* Using the general procedure, this compound was obtained from 5-fluor-1-vinylindoline-2,3-dione (**8d**) (55.2 mg, 0.2887 mmol) as a dark oil (45.7 mg, 0.1871 mmol) in 65 % yield after purification by flash column chromatography. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.90 (d, *J* = 4.3 Hz, 1H), 8.13 (dd, *J* = 9.2, 5.4 Hz, 1H), 7.60 – 7.41 (m, 2H), 7.35 (d, *J* = 4.3 Hz, 1H), 3.77 (t, *J* = 7.1 Hz, 2H), 3.13 (t, *J* = 6.8 Hz, 2H), 2.01 (p, *J* = 6.7 Hz, 2H), 1.87 (p, *J* = 6.8 Hz, 2H) $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 166.3, 161.19 (d, *J* = 249.6 Hz), 149.4, 145.9, 143.1, 132.72 (d, *J* = 9.3 Hz), 124.80 (d, *J* = 10.1 Hz), 120.49 (d, *J* = 25.9 Hz), 118.6, 108.50 (d, *J* = 22.9 Hz), 48.6, 45.9, 26.1, 24.6. IR ($v=_{max}$/cm$^{-1}$): 3439, 2961, 2929, 2876, 1724, 1635, 1511, 1468, 1434, 1276, 1223, 865, 715, 747. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{14}H_{14}FN_2O_1$ $[M+H]^+$ 245.1090, found 245.1095.

*6-Bromo-N-heptylquinoline-4-carboxamide (**11aj**).* Using the general procedure, this compound was obtained from 5-bromo-1-vinylindoline-2,3-dione (**8e**) (72.8 mg, 0.2887 mmol) as a white solid (43.5 mg, 01239 mmol) in 43 % yield after purification by flash column chromatography, mp 87-89 ºC. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.82 (d, *J* = 4.3 Hz, 1H), 8.34 (d, *J* = 2.1 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.78 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.33 (d, *J* = 4.3 Hz, 1H), 6.42 (t, *J* = 5.2 Hz, 1H), 3.59 – 3.43 (m, 2H), 1.65 (p, *J* = 7.3 Hz, 2H), 1.43 – 1.23 (m, 8H), 0.97 – 0.82 (m, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 166.7, 150.1, 147.1, 141.2, 133.5, 131.3, 127.6, 125.5, 122.0, 118.9, 40.2, 31.7,

29.5, 28.9, 27.0, 22.6, 14.1. IR (v=$_{max}$/cm$^{-1}$): 3272, 3065, 2955, 2926, 2855, 1641, 1546, 1440, 1307, 863, 849, 661, 504. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{17}H_{22}BrN_2O_1$ [M+H]$^+$ 349.0915, found 349.0907.

*6-Bromo-N-(3,4-dimethoxyphenethyl)quinoline-4-carboxamide (**11ak**).* Using the general procedure, this compound was obtained from 5-bromo-1-vinylindoline-2,3-dione (**8e**) (72.8 mg, 0.2887 mmol) as a white solid (76.1 mg, 0.1832 mmol) in 63 % yield after purification by flash column chromatography, mp 161-163 ºC. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.70 (d, *J* = 4.3 Hz, 1H), 8.30 (d, *J* = 2.1 Hz, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.73 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.22 (d, *J* = 4.3 Hz, 1H), 6.83 – 6.75 (m, 2H), 6.72 (s, 1H), 6.55 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.75 (q, *J* = 6.7 Hz, 2H), 2.92 (t, *J* = 6.9 Hz, 2H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 166.8, 150.0, 149.2, 147.9, 147.1, 141.0, 133.6, 131.4, 130.9, 127.6, 125.5, 122.1, 120.8, 119.0, 111.9, 111.5, 55.9, 41.3, 35.1. IR (v=$_{max}$/cm$^{-1}$): 3405, 3320, 2926, 2855, 1721, 1639, 1516, 1266, 1141, 1026, 864, 535, 501. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{20}H_{20}BrN_2O_3$ [M+H]$^+$ 415.0657, found 415.0655.

*(6-Bromoquinolin-4-yl)(pyrrolidin-1-yl)methanone (**11al**).* Using the general procedure, this compound was obtained from 5-bromo-1-vinylindoline-2,3-dione (**8e**) (72.8 mg, 0.2887 mmol) as a brown solid (54.3 mg, 0.1779 mmol) in 62 % yield after purification by flash column chromatography, mp 114-115 ºC. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.94 (d, *J* = 4.3 Hz, 1H), 8.04 – 7.99 (m, 1H), 7.80 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.34 (d, *J* = 4.3 Hz, 1H), 3.77 (t, *J* = 7.1 Hz, 2H), 3.13 (t, *J* = 6.8 Hz, 2H), 2.02 (p, *J* = 6.7 Hz, 2H), 1.89 (q, *J* = 6.5 Hz, 2H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 166.1, 150.5, 147.3, 142.6, 133.7, 131.8, 127.2, 125.2, 122.0, 118.7, 48.7, 45.9, 26.1, 24.6. IR (v=$_{max}$/cm$^{-1}$): 3432, 2969, 2926, 2877, 1720, 1634, 1452, 1424, 1346, 864, 848, 642, 606. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{14}H_{14}BrN_2O_1$ [M+H]$^+$ 305.0289, found 305.0289.

*N-Heptyl-7-methoxyquinoline-4-carboxamide (**11am**).* Using the general procedure, this compound was obtained from 6-methoxy-1-vinylindoline-2,3-dione (**8h**) (58.7 mg, 0.2887 mmol) as a white solid (68.2 mg, 0.2270) in 79 % yield after purification by flash column chromatography, mp 99-100 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.67 (d, *J* = 4.4 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.32 (d, *J* = 2.6 Hz, 1H), 7.15 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.12 (d, *J* = 4.4 Hz, 1H), 6.52 (s, 1H), 3.91 (s, 3H), 3.43 (q, *J* = 7.1 Hz, 2H), 1.58 (q, *J* = 7.3 Hz, 2H), 1.40 – 1.21 (m, 8H), 0.90 – 0.84 (m, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 167.5, 160.9, 150.5, 150.0, 142.1, 126.4, 120.7, 119.6, 116.3, 107.6, 55.6, 40.2, 31.8, 29.6, 29.0, 27.0, 22.7, 14.2. IR (v=$_{max}$/cm$^{-1}$): 3287, 3072, 2925, 2854, 1638, 1580, 1546, 1432, 1311, 1243, 1142, 1032, 945, 873. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{18}H_{25}N_2O_2$ [M+H]$^+$ 301.1916, found 301.1925.

*N-(3,4-Dimethoxyphenethyl)-7-methoxyquinoline-4-carboxamide (**11an**).* Using the general procedure, this compound was obtained from 6-methoxy-1-vinylindoline-2,3-dione (**8h**) (58.7 mg, 0.2887 mmol) as a pale white solid (97.9 mg, 0.2672 mmol) in 93 % yield after purification by flash column chromatography, mp 125-127 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.68 (d, *J* = 4.3 Hz, 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 7.34 (d, *J* = 2.6 Hz, 1H), 7.16 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.12 (d, *J* = 4.4 Hz, 1H), 6.81 – 6.72 (m, 3H), 6.50 (t, *J* = 5.9 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.76 (td, *J* = 6.9, 5.8 Hz, 2H), 2.91 (t, *J* = 6.9 Hz, 2H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 167.5, 160.9, 150.5, 150.0, 149.1, 147.9, 141.9, 131.0, 126.4, 120.7, 119.6, 116.2, 111.9, 111.4, 107.6, 56.0, 55.9, 55.6, 41.2, 35.2. IR (v=$_{max}$/cm$^{-1}$): 3368, 2927, 2854, 1645, 1621, 1514, 1432, 1298, 1262, 1236, 1141, 1027, 832. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{21}H_{23}N_2O_4$ [M+H]$^+$ 367.1658, found 367.1652.

*7-Chloro-N-heptylquinoline-4-carboxamide (**11ap**).* Using the general procedure, this compound was obtained from 6-chloro-1-vinylindoline-2,3-dione (**8g**) (59.5 mg, 0.2887 mmol) as a white solid (44.0 mg, 0.1443 mmol) in 50 % yield after purification by flash column chromatography (EtOAc–hexanes), mp 98-99 ºC. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.69 (d, *J* = 4.3 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.94 (d, *J* = 2.1 Hz, 1H), 7.39 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.19 (d, *J* = 4.3 Hz, 1H), 6.48 (t, *J* = 5.2 Hz, 1H), 3.44 – 3.33 (m, 2H), 1.55 (p, *J* = 7.4 Hz, 2H), 1.26 (tdd, *J* = 18.8, 14.3, 9.4 Hz, 8H), 0.90 – 0.77 (m, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 100 MHz): δ 166.9, 150.8, 148.9, 142.3, 136.1, 128.7, 126.8, 122.9, 118.4, 40.3, 31.8, 29.6, 29.0, 27.0, 22.7, 14.2. IR (v=$_{max}$/cm$^{-1}$): 3289, 3069, 2956, 2926, 2855, 1724, 1637, 1547, 1295, 1188, 1150, 1087, 885, 829, 717, 630. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{17}H_{22}ClN_2O_1$ [M+H]$^+$ 305.1421, found 305.1431.

*7-Chloro-N-(3,4-dimethoxyphenethyl)quinoline-4-carboxamide (**11aq**).* Using the general procedure, this compound was obtained from 6-chloro-1-vinylindoline-2,3-dione (**8g**) (59.5 mg, 0.2887 mmol) as a white solid (86.8 mg, 0.2341 mmol) in 81 % yield after purification by flash column chromatography, mp 150-151 ºC. $^1$H NMR ($CDCl_3$, 300 MHz): δ 8.68 (d, *J* = 4.3 Hz, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 7.42 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.18 (d, *J* = 4.3 Hz, 1H), 6.79 – 6.68 (m, 3H), 6.56 (t, *J* = 5.5 Hz, 1H), 3.82 (s, 3H), 3.80 – 3.69 (m, 5H), 2.90 (t, *J* = 6.8 Hz, 2H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 166.9, 150.8, 149.2, 148.9, 147.9, 142.1, 136.0, 130.9, 128.6, 126.8, 122.8, 120.8, 118.4, 111.9, 111.5, 56.0, 55.9, 41.2, 35.1. IR (v=$_{max}$/cm$^{-1}$): 3295, 3074, 2934, 2839, 1636, 1515, 1463, 1417, 1263, 1236, 1152, 1020, 895, 820, 709, 630, 467. HRMS (DART, [M+H]$^+$) *m*/*z* calcd for $C_{20}H_{20}ClN_2O_3$ [M+H]$^+$ 371.1162, found 371.1165.

General procedure for the synthesis of the quinoline-4-carboxylates of type **12**.

To a round bottom flask equipped with a magnetic stirring bar and 5 mL of ethanol, The *N*-vinylated compound **8a-h** (1 equiv., 0.2887 mmol) was added to the flask. Sequentially, *N,N*-Diisopropylethylamine (1 equiv. 0.2887) was added. Then, the reaction crude was heated at reflux for five hours. Finally, the crude of the reaction was directly purified by flash chromatography to afford the corresponding quinoline-4-carboxylates **12.**

*Ethyl quinoline-4-carboxylate (**12a**).* Using the general procedure, this compound was obtained from 1-vinylindoline-2,3-dione (**8a**) (50 mg, 0.2887 mmol) as a yellow oil (40.5 mg, 0.2013 mmol) in 70 % yield after purification by flash column chromatography. $^1$H NMR ($CDCl_3$, 300 MHz): δ 9.03 (d, *J* = 3.4 Hz, 1H), 8.77 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 4.3 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.71 – 7.62 (m, 1H), 4.52 (q, *J* = 7.1 Hz, 2H), 1.64 – 1.31 (m, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 166.3, 149.9, 149.2, 135.4, 130.2, 129.8, 128.2, 125.7, 122.2, 62.0, 14.4. IR ($\nu_{max}$/cm$^{-1}$): 3429, 2982, 2933, 1723, 1584, 1507, 1275, 1250, 1191, 1147, 1072, 1034, 858, 775, 654. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{12}H_{12}N_1O_2$ $[M+H]^+$ 202.0868, found 202.0869.

*Ethyl 6-isopropylquinoline-4-carboxylate (**12b**).* Using the general procedure, this compound was obtained from 5-isopropyl-1-vinylindoline-2,3-dione (**8b**) (62.14 mg, 0.2887 mmol) as a brown oil (61 mg, 0.2540 mmol) in 88 % yield after purification by flash column chromatography. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, *J* = 4.4 Hz, 1H), 8.19 (d, *J* = 1.9 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 4.4 Hz, 1H), 7.27 (dd, *J* = 8.7, 2.0 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.74 (hept, *J* = 6.9 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 6H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 166.5, 149.0, 148.3, 134.8, 130.0, 129.6, 125.3, 122.2, 121.9, 61.8, 34.7, 23.9, 14.4. IR ($\nu_{max}$/cm$^{-1}$): 3431, 3068, 2962, 2930, 1724, 1580, 1503, 1275, 1254, 1167, 1031, 870, 661. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{15}H_{18}NO_2$ $[M+H]^+$ 244.1337, found 244.1334.

*Ethyl 6-methylquinoline-4-carboxylate (**12c**).* Using the general procedure, this compound was obtained from 5-methyl-1-vinylindoline-2,3-dione (**8c**) (54.0 mg, 0.2887 mmol) as a brown oil (52.13 mg, 0.2425 mmol) in 84 % yield after purification by flash column chromatography. $^1$H NMR ($CDCl_3$, 300 MHz): δ 8.92 (d, *J* = 4.4 Hz, 1H), 8.52 (s, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 4.4 Hz, 1H), 7.58 (dd, *J* = 8.6, 1.6 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 2.56 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 166.5, 148.9, 147.9, 138.4, 134.5, 132.1, 129.8, 125.3, 124.5, 122.1, 61.8, 22.2, 14.4. IR ($\nu_{max}$/cm$^{-1}$): 3430, 2981, 2926, 1723, 1505, 1273, 1252, 1148, 1033, 868, 824, 663. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{13}H_{14}NO_2$ $[M+H]^+$ 216.1024, found 216.1029.

*Ethyl 6-fluoroquinoline-4-carboxylate (**12d**).* Using the general procedure, this compound was obtained from 5-fluor-1-vinylindoline-2,3-dione (**8d**) (55.15 mg, 0.2887 mmol) as a dark oil (50 mg, 0.2309 mg) in 80 % yield after purification by flash column chromatography. $^1$H NMR ($CDCl_3$, 300 MHz): δ 8.96 (d, *J* = 4.3 Hz, 1H), 8.51 (dd, *J* = 10.8, 2.8 Hz, 1H), 8.14 (dd, *J* = 9.2, 5.7 Hz, 1H), 7.95 (d, *J* = 4.4 Hz, 1H), 7.52 (ddd, *J* = 9.3, 7.9, 2.8 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 165.9, 161.68 (d, *J* = 249.5 Hz), 149.1, 146.6, 132.64 (d, *J* = 9.5 Hz), 123.2, 120.21 (d, *J* = 26.1 Hz), 109.73 (d, *J* = 24.9 Hz), 62.1, 29.8, 14.4. IR ($\nu_{max}$/cm$^{-1}$): 3109, 2983, 2932, 1723, 1623, 1511, 1465, 1269, 1209, 1142, 1030, 874, 784, 724, 663, 500. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{12}H_{11}FNO_2$ $[M+H]^+$ 220.0774, found 220.0779.

*Ethyl 6-bromoquinoline-4-carboxylate (**12e**).* Using the general procedure, this compound was obtained from 5-bromo-1-vinylindoline-2,3-dione (**8e**) (72.4 mg, 0.2887 mmol) as a dark oil (66 mg, 0.2336 mg) in 82 % yield after purification by flash column chromatography. $^1$H NMR ($CDCl_3$, 300 MHz): δ 9.03 (d, *J* = 2.1 Hz, 1H), 9.00 (d, *J* = 4.4 Hz, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.93 (d, *J* = 4.4 Hz, 1H), 7.82 (dd, *J* = 9.0, 2.2 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 165.7, 150.2, 147.9, 134.1, 133.4, 131.7, 128.2, 126.3, 123.1, 123.0, 62.2, 14.4. IR ($\nu_{max}$/cm$^{-1}$): 3113, 2973, 2931, 1722, 1492, 1271, 1245, 1175, 1059, 1033, 830, 748, 758. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{12}H_{11}{}^{79}BrN_1O_2$ $[M+H]^+$ 279.9973, found 279.9970.

*Ethyl 7-methoxyquinoline-4-carboxylate (**12f**).* Using the general procedure, this compound was obtained from 6-methoxy-1-vinylindoline-2,3-dione (**8h**) (58 mg, 0.2887 mmol) as a yellow oil (62 mg, 0.2684) in 93 % yield after purification by flash column chromatography. $^1$H NMR ($CDCl_3$, 300 MHz): δ 8.92 (d, *J* = 4.5 Hz, 1H), 8.67 (d, *J* = 9.4 Hz, 1H), 7.75 (d, *J* = 4.5 Hz, 1H), 7.47 (d, *J* = 2.6 Hz, 1H), 7.30 (dd, *J* = 9.4, 2.7 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 166.4, 160.7, 151.2, 150.2, 135.1, 126.8, 121.4, 120.5, 120.0, 107.9, 61.9, 55.6, 14.4. IR ($\nu_{max}$/cm$^{-1}$): 2967, 2932, 2884, 1724, 1623, 1511, 1434, 1316, 1267, 1189, 1135, 1023, 861, 824, 660. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{13}H_{14}NO_3$ $[M+H]^+$ 232.0976, found 232.0976.

*Ethyl 7-chloroquinoline-4-carboxylate (**12g**).* Using the general procedure, this compound was obtained from 6-chloro-1-vinylindoline-2,3-dione (**8g**) (59.8 mg, 0.2887 mmol) as a dark oil (50.8 mg, 0.2165 mmol) in 75 % yield after purification by flash column chromatography. $^1$H NMR ($CDCl_3$, 400 MHz): δ 9.00 (d, *J* = 4.4 Hz, 1H), 8.75 (d, *J* = 9.2 Hz, 1H), 8.14 (d, *J* = 2.2 Hz, 1H), 7.89 (d, *J* = 4.4 Hz, 1H), 7.57 (dd, *J* = 9.2, 2.2 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 165.8, 151.0, 149.7, 135.8, 135.1, 129.2, 129.0, 127.2, 123.7, 122.4, 62.1, 14.4. IR ($\nu_{max}$/cm$^{-1}$): 3429, 3041, 2982, 2929, 2856, 1724, 1604, 1583, 1496, 1265, 1184, 1144, 1079, 1028, 889, 830, 754, 634. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{12}H_{11}ClN_1O_2$ $[M+H]^+$ 236.0478, found 236.0482.

*1-(2-Amino-4-chlorophenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (**13a**).* Using the general procedure, this compound was obtained from 6-chloro-1-vinylindoline-2,3-dione (**8g**) (59.8 mg, 0.2887 mmol) as a yellow solid (58.2 mg, 0.2309 mmol) in 80 % yield after purification by flash column chromatography. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.37 (d, *J* = 8.6 Hz, 1H), 6.62 (d, *J* = 1.9 Hz, 1H), 6.52 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.42 (s, 2H), 3.56 (t, *J* = 6.8 Hz, 2H), 3.31 (t, *J* = 6.4 Hz, 2H), 1.97 – 1.77 (m, 4H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 193.2, 165.1, 152.6, 142.1, 134.7, 116.9, 116.4, 112.5, 46.7, 45.1, 25.9, 24.1. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{12}H_{14}Cl_1N_2O_2$ $[M+H]^+$ 253.0770, found 253.0770.

*1-(2-Amino-4-methoxyphenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (**13b**)*. Using the general procedure, this compound was obtained from 6-methoxy-1-vinylindoline-2,3-dione (**8h**) (58 mg, 0.2887 mmol) as a yellow solid (60 mg, 0.2454) in 85 % yield after purification by flash column chromatography. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.34 (d, *J* = 9.0 Hz, 1H), 6.43 (s, 2H), 6.15 (d, *J* = 11.3 Hz, 1H), 6.02 (s, 1H), 3.73 (s, 3H), 3.55 (t, *J* = 6.7 Hz, 2H), 3.32 (t, *J* = 6.4 Hz, 2H), 1.91 – 1.80 (m, 4H). $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz): δ 192.2, 165.9, 165.7, 154.5, 135.4, 108.6, 105.8, 98.7, 55.4, 46.7, 45.0, 25.9, 24.1. HRMS (DART, $[M+H]^+$) *m*/*z* calcd for $C_{13}H_{17}N_2O_3$ $[M+H]^+$ 249.1277, found 249.1280.

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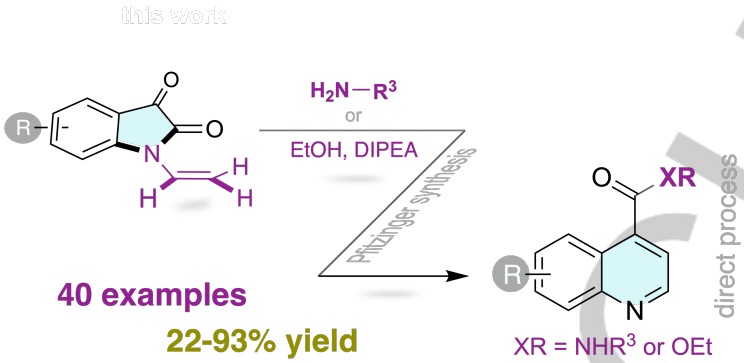
FULL PAPER

# Synthesis of Quinoline-4-carboxamides and Quinoline-4-carboxylates via a Modified Pfitzinger Reaction of *N*-Vinylisatins.




Quinoline-4-carboxamides and 4-carboxylates are a class of heteroaromatic compounds present in a large family of laboratory-made molecules, with a wide range of important biological activities. We describe a synthetic approach to its accelerated assembly using a rearrangement of *N*-vinylisatins promoted by different types of amines (or ethanol) in a Pfitzinger-like mechanism that in turn builds the quinoline ring system.