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Domino Reactions

# $FeCl_3$-Mediated Three-Component Cascade Reaction: An Effective Approach to the Construction of Highly Functionalized Pyrrolo[1,2-*c*]quinazolinones

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**Abstract:** An unexpected $FeCl_3$-mediated three-component cascade reaction has been used to construct structurally diverse pyrrolo[1,2-*c*]quinazolinone derivatives with potential biological activities. This method has advantages of mild conditions, simple work-up, as well as wide substrate scope, which makes it a powerful approach to the synthesis of diverse pyrrolo[1,2-*c*]quinazolinones. This cascade reaction involves 1,3-dipolar cycloaddition between azomethine ylides and allenoates, followed by intramolecular nucleophilic addition in the presence of $FeCl_3$. The obtained products could be easily transformed into derivatives with the pyrrolo[2,3-*c*]quinazoline alkaloid skeleton.

## Introduction

Pyrroloquinazoline and pyrroloquinazolinone are important structural skeletons in a diverse range of natural occurring alkaloids and pharmacologically active molecules. For example, (−)-martinellic acid and (+)-martinelline (Figure 1), which were isolated from an ethanolic extract of *Martinella iquitosensis* roots, have been shown to possess antagonist properties against bradykinin receptors,[1] and are used to cure conjunctivitis caused by infection from microorganisms in South America.[2] Pyrroloquinazoline or pyrroloquinazolinone derivatives possess versatile biological activities such as antitumor,[3] potent gastric ($H^+/K^+$)-ATPase inhibitor,[4] anti-inflammatory,[5] and antihypertensive activities.[6] The important medicinal properties and unique tricyclic skeleton of (−)-martinellic acid and (+)-martinelline have made the synthesis of pyrroloquinazoline or pyrroloquinazolinone architectures more attractive, and numerous synthetic methods, such as condensing quinazolines or quinazolinones with α-halopyruvates or α-haloketones,[7] intramolecular cyclization reaction,[8] 1,3-dipolar cycloaddition,[9] the Fischer indole synthesis,[10] transition-metal-mediated reactions,[11] aryl radical cyclization,[12] Diels–Alder reactions,[13] electrocyclization,[14] and others,[15] have been well-established. However, these methods usually require stepwise chemical processes or are limited by the availability of the starting materials. In addition, only the Fisher indole synthesis generates completely aromatized pyrroloquinolines and this requires high temperature (250 °C).

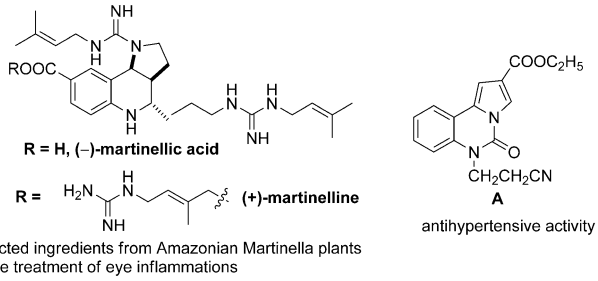


**Figure 1.** Pyrroloquinazoline or pyrroloquinazolinone structural motif in natural alkaloids and artificial bioactive molecules.

1,3-Dipolar cycloadditions of azomethine ylides to give electron-deficient olefins have been well explored and provide an effective method with which to access pyrrolidine-containing compounds (Scheme 1a).[16] In this context, most of the dipolarophiles used are electron-deficient alkenes,[17] imines,[18] and alkynes,[19] and there are only a few examples of 1,3-dipolar cycloadditions involving 2,3-butadienoates with azomethine ylides.[20] Very recently, Gong and co-workers reported the first 1,3-dipolar cycloaddition between 2,3-butadienoates and azomethine ylides, which was used to acess 3-methylenepyrrolidine derivatives with excellent enantioselectivity with a chiral bisphosphoric acid as the catalyst[20a] (Scheme 1b), and subse-

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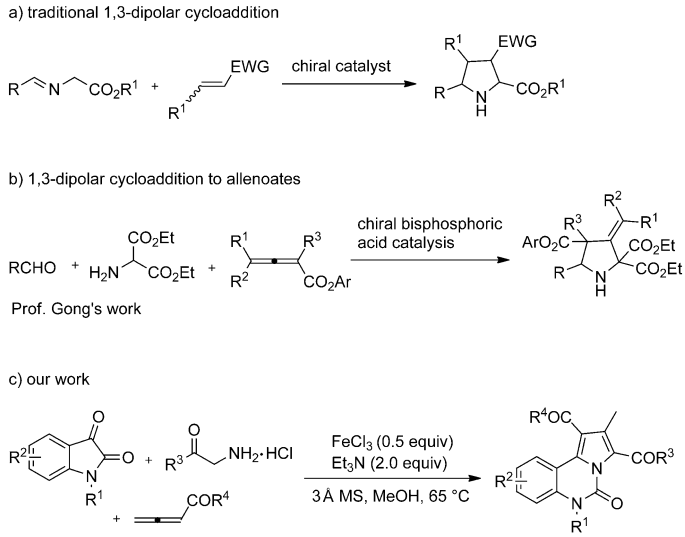


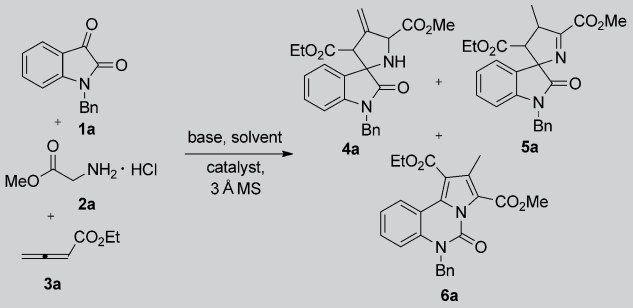

**Scheme 1.** 1,3-Dipolar cycloaddition reactions between azomethine ylides and dipolarophiles.

quently applied to the kinetic resolution of racemic 2,3-butadienoate.[20b] Due to their low price, nontoxicity, and environmentally friendly nature, iron(III) catalysts have received considerable attention from chemists during the last few years.[21] However, to the best of our knowledge, the use of an $FeCl_3$-mediated cascade reaction with azomethine ylides and 2,3-butadienoates to construct the pyrrolo[1,2-*c*]quinazolinone derivatives has not been studied. As part of our ongoing interest in developing concise, convenient, and environmentally benign methods for the synthesis of important biologically active nitrogen-containing heterocycles,[22] herein we report an unprecedented cascade process involving 2,3-butadienoates, isatins, and glycinate or α-amino ketone hydrogen chloride salts under mild conditions that provides a highly efficient synthetic route to structurally diverse pyrrolo[1,2-*c*]quinazolinones (Scheme 1 c).

## Results and Discussion

Initially, we investigated the reaction involving 1-benzyl isatin (**1a**), methyl glycinate hydrochloride (**2a**), and ethyl 2,3-butadienoate (**3a**) in the presence of $Et_3N$ (2.0 equiv) and 3 Å molecular sieve (100 mg) in MeOH (4.0 mL) at room temperature, and found that the expected [3+2] cycloaddition product **4a** (30%) and the endocyclic isomer **5a** (20%) could be isolated (Table 1, entry 1); the structure of **5a** was unambiguously established by X-ray crystallographic analysis.[23] When 0.5 equivalents $FeCl_3$ were added as the catalyst, the yield of **4a** increased to 58% and, unexpectedly, another product pyrrolo[1,2-*c*]quinazolinone **6a** was also isolated in 20% yield (Table 1, entry 2); the structure of **6a** was unambiguously determined by X-ray crystallographic analysis (Figure 2).[23] The results indicated that the yield of **6a** increased with increasing amount of $FeCl_3$ and with higher reaction temperature (Table 1, entries 3–5). On the other hand, increasing the amount of $Et_3N$ (3.0 equiv) did not improve the yield of **6a** significantly (Table 1, entry 6). We then investigated the effect of solvents

**Table 1.** Optimization of the reaction conditions.[a]




| Entry | Solvent | Base | Catalyst | Time [h] | Yield [%][b] 4a | 5a | 6a |
|---|---|---|---|---|---|---|---|
| 1[c] | MeOH | $Et_3N$ | none | 36 | 30 | 20 | trace |
| 2[d] | MeOH | $Et_3N$ | $FeCl_3$ | 24 | 58 | trace | 20 |
| 3[e] | MeOH | $Et_3N$ | $FeCl_3$ | 24 | 20 | 18 | 40 |
| 4[f] | MeOH | $Et_3N$ | $FeCl_3$ | 24 | 0 | trace | 60 |
| **5** | **MeOH** | **$Et_3N$** | **$FeCl_3$** | **24** | **0** | **0** | **75** |
| 6[g] | MeOH | $Et_3N$ | $FeCl_3$ | 28 | 0 | 0 | 76 |
| 7 | DMF | $Et_3N$ | $FeCl_3$ | 24 | 0 | 12 | 38 |
| 8 | $CH_3CN$ | $Et_3N$ | $FeCl_3$ | 24 | 0 | 13 | 23 |
| 9 | THF | $Et_3N$ | $FeCl_3$ | 24 | 0 | 20 | 20 |
| 10[h] | $CH_2Cl_2$ | $Et_3N$ | $FeCl_3$ | 36 | 0 | 28 | 19 |
| 11 | toluene | $Et_3N$ | $FeCl_3$ | 24 | 0 | 16 | 40 |
| 12 | MeOH | $K_2CO_3$ | $FeCl_3$ | 24 | 0 | 9 | 45 |
| 13 | MeOH | pyridine | $FeCl_3$ | 24 | 0 | 15 | 45 |
| 14 | MeOH | DBU | $FeCl_3$ | 36 | 0 | 12 | 55 |
| 15 | MeOH | DMAP | $FeCl_3$ | 24 | 0 | 10 | 60 |
| 16 | MeOH | $Et_3N$ | $Cu(OAc)_2$ | 24 | 0 | trace | 57 |
| 17 | MeOH | $Et_3N$ | AgOAc | 24 | 0 | trace | 60 |
| 18 | MeOH | $Et_3N$ | $ZnCl_2$ | 24 | 0 | 25 | 30 |
| 19 | MeOH | $Et_3N$ | CuI | 24 | 0 | 14 | 35 |

[a] Reaction conditions (unless otherwise noted): **1a** (0.5 mmol), **2a** (0.75 mmol), **3a** (0.75 mmol), base (1.0 mmol), catalyst (0.25 mmol), 3 Å molecular sieve (100 mg), solvent (4.0 mL), stirred at 65 °C. Bn = benzyl. [b] Isolated yield based on **1a**. [c] Stirred at room temprature. [d] $FeCl_3$ (0.2 equiv), room temperature. [e] $FeCl_3$ (0.2 equiv), stirred at 40 °C. [f] $FeCl_3$ (0.2 equiv). [g] $Et_3N$ (3.0 equiv) was added. [h] Stirred at 40 °C.

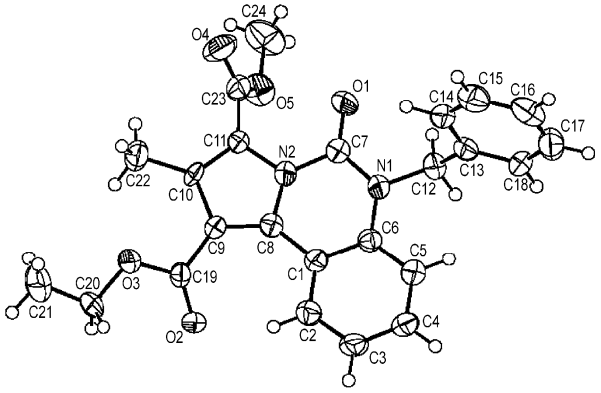
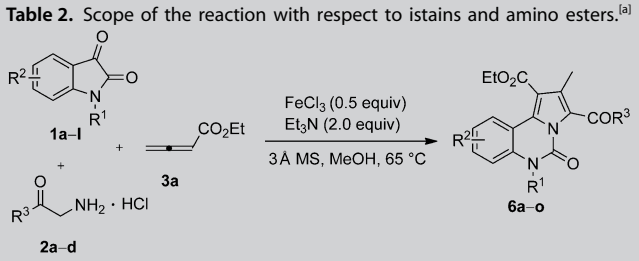



**Figure 2.** X-ray crystal structure of compound **6a**.

and bases on this cascade reaction in the presence of 50 mol% $FeCl_3$ (Table 1, entries 5 and 7–15) and found that methanol was the most effective solvent and $Et_3N$ was more suitable base. Encouraged by these interesting findings, a variety of Lewis acids were then examined (Table 1, entries 5 and 16–19); the results showed that, with the exception of $ZnCl_2$,

**Table 2.** Scope of the reaction with respect to istains and amino esters.[a]




| Entry | $R^1$ | $R^2$ | $R^3$ | Time [h] | Product | Yield [%][b] |
|---|---|---|---|---|---|---|
| 1 | Bn | H | OMe | 24 | **6a** | 75 |
| 2 | $CH_3$ | H | OMe | 24 | **6b** | 78 |
| 3 | Allyl | H | OMe | 24 | **6c** | 64 |
| 4 | propargyl | H | OMe | 24 | **6d** | 60 |
| 5 | H | H | OMe | 24 | **6e** | 58 |
| 6 | Boc | H | OMe | 48 | n.r. | n.r. |
| 7 | Bn | 5-F | OMe | 24 | **6f** | 79 |
| 8 | Bn | 5-Cl | OMe | 24 | **6g** | 69 |
| 9 | Bn | 5-Br | OMe | 24 | **6h** | 65 |
| 10 | Bn | 5-$CH_3$ | OMe | 24 | **6i** | 80 |
| 11 | Bn | 5-$OCH_3$ | OMe | 18 | **6j** | 78 |
| 12 | Bn | 6-Cl | OMe | 24 | **6k** | 65 |
| 13 | Bn | 7-F | OMe | 24 | **6l** | 72 |
| 14[c] | Bn | H | OEt | 24 | **6m** | 69 |
| 15[d] | Bn | H | O*i*Pr | 24 | **6n** | 61 |
| 16 | Bn | H | Ph | 24 | **6o** | 52 |

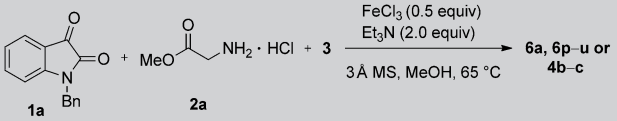
[a] Reaction conditions (unless indicated otherwise): **1** (0.5 mmol), **2** (0.75 mmol), **3a** (0.75 mmol), $Et_3N$ (3.0 equiv), $FeCl_3$ (0.5 equiv), 3 ÅMS (100 mg), MeOH (4 mL), 65 °C. Bn = benzyl. [b] Isolated yield based on **1**; n.r. = no reaction. [c] EtOH was used as solvent due to ester exchange of **2b**. [d] *i*PrOH was used as solvent.

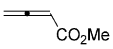
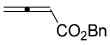
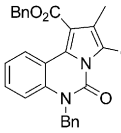
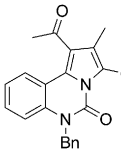
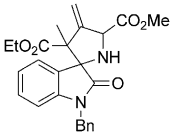
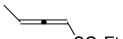
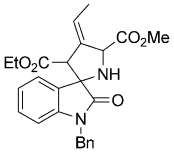
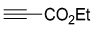
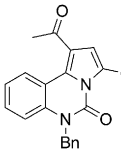
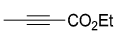
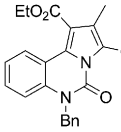
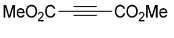
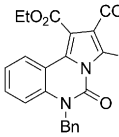
the addition of a Lewis acid was beneficial to the formation of pyrrolo[1,2-*c*]quinazolinone **6a** (Table 1, entry 18). The results also showed that $Cu(OAc)_2$ and AgOAc were effective catalysts, and that $FeCl_3$ was the most effective for the formation of pyrrolo[1,2-*c*]quinazolinone **6a**.

With the optimized conditions in hand, we explored the substrate scope of the cascade reaction with regard to isatin derivatives **1**, glycine ester or α-amino ketone hydrochloride **2**, and ethyl 2,3-butadienoate **3a** (Table 2). Firstly, with **2a** and **3a** used as a representative partner, a variety of isatin derivatives **1** were investigated, as shown in Table 2; remarkably, the desired products **6** were obtained in moderate to excellent yields, irrespective of the nature of the protecting group at the N-1 position of the isatin derivatives **1** (Table 2, entries 1–4) or the electronic properties of the substituent on the aromatic ring of **1** (Table 2, entries 7–13). Moreover, when simple isatin was used, the reaction also occured and gave the corresponding product **6e** in modest yield (Table 2, entry 5). However, when a Boc-protected isatin was used, no pyrrolo[1,2-*c*]quinazolinone derivative was observed (Table 2, entry 6), which might be due to the difficultly of forming the corresponding azomethine ylide. Secondly, a variety of glycinate and α-amino ketone hydrochlorides **2a–d** also gave satisfactory results (Table 2, entries 14–16). Increasing the size of the ester group of the glycinate esters had a negative effect on the reaction (Table 2, entries 13–15).

To further evaluate the generality of this cascade annulation, a series of allenoates and allenone were also investigated (Table 3, entries 1–5). Firstly, methyl 2,3-butadienoate was also good candidate, giving **6p** in 83% yield (Table 3, entry 1), whereas the yield decreased slightly when benzyl 2,3-butadie-

**Table 3.** The cascade annulation of allenoates and alkynoates.[a]



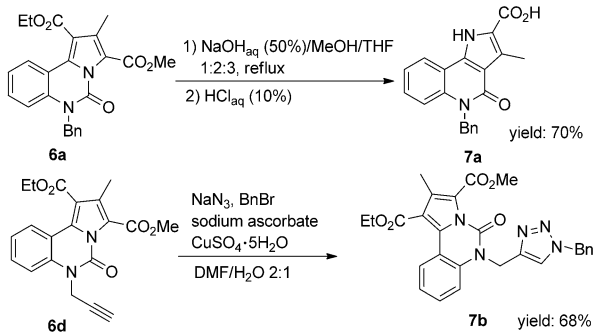

| Entry | **3** | | Time [h] | Product | | Yield [%][b] |
|---|---|---|---|---|---|---|
| 1 |  | **3b** | 22 |  | **6p** | 83 |
| 2 |  | **3c** | 12 |  | **6q** | 56 |
| 3 |  | **3d** | 18 |  | **6r** | 85 |
| 4 |  | **3e** | 24 |  | **4b** | 78 |
| 5 |  | **3f** | 24 |  | **4c** | 75 |
| 6 |  | **3g** | 18 |  | **6s** | 63 |
| 7 |  | **3h** | 24 |  | **6t** | 68 |
| 8 |  | **3i** | 24 |  | **6a** | 60 |
| 9 |  | **3j** | 22 |  | **6u** | 55 |

[a] Reaction conditions (unless indicated otherwise): **1a** (0.5 mmol), **2a** (0.75 mmol), **3** (0.75 mmol), $Et_3N$ (1.0 mmol), $FeCl_3$ (0.25 mmol), 3Å MS (100 mg), MeOH (4 mL), stirred at 65 °C. [b] Isolated yield based on **1a**.

noate was used (Table 3, entry 2). Interestingly, 3,4-pentadien-2-one was also a suitable substrate in this cascade process, with **6r** being isolated in 85% yield (Table 3, entry 3). However, when 2-methyl-2,3-butadienoate **3e** was used, only the [3+2] cycloadditon product **4b** was isolated (Table 3, entry 4), and when 4-methyl-2,3-butadienoate **3f** was used the [3+2] cycloadditon product **4c** was obtained in good yield with excellent stereoselectivity (Table 3, entry 5).

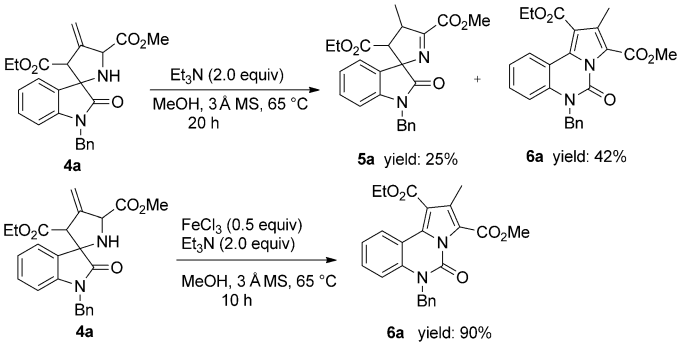
A variety of alkynoates and alkynone were also investigated. As shown in Table 3, all were effective candidates, giving the corresponding products **6a** and **6s–u** in moderate yields (Table 3, entries 6–9). It was found that increasing the steric bulk of the substituent on the alkynoates had a negative impact on these cascade reactions.

The obtained pyrrolo[1,2-*c*]quinazolinones **6**, could be used as useful building blocks in organic synthesis and were easily transformed into diverse potential biologically active heterocycles (Scheme 2). Firstly, pyrrolo[1,2-*c*]quinazolinone **6a** could




**Scheme 2.** Synthetic transformation of pyrrolo[1,2-*c*]quinazolinones.

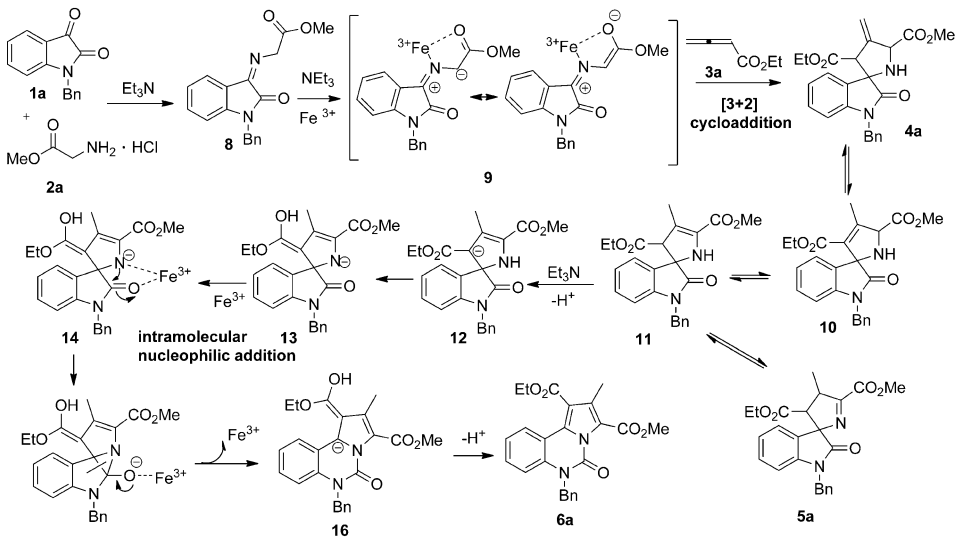
be readily transformed into pyrrolo[3,2-*c*]quinazoline derivative **7a** in one pot; this product not only exhibits important biological activities but also constitutes the core structural element of many natural alkaloids (Figure 1).[1,3–6,24] Moreover, the introduction of propargyl-protected isatin as a substrate not only effectively allowed the construction of pyrrolo[1,2-*c*]quinazolinone derivatives, but also increased the complexity of the products and the synthetic application. Transformations based on alkynes have been the subject of many intensive studies, with azide–alkyne Huisgen cycloaddition being an extremely powerful approach in combinatorial chemistry and drug discovery.[25] As expected, in the presence of sodium ascorbate and $CuSO_4$, **6d** could be conviently transformed into the desired triazole compound **7b** in 68% yield.




**Scheme 3.** Control experiments.

To gain some insights into the unexpected cascade reaction, the following experiments were conducted (Scheme 3). Compound **4a** could be converted into the endocyclic isomer **5a** (25%) and **6a** (42%) in the presence of $Et_3N$ at 65 °C. However, when $FeCl_3$ (50 mol%) was added, **4a** was converted into **6a** in 90% yield. These results clearly indicated that $FeCl_3$ played a vital role in the transformation process from **4a** into **6a**.

Based on the above experimental results and on other control experiments, a plausible mechanism of $FeCl_3$-mediated three-component cascade reaction between azomethine ylides and allenoates has been proposed as depicted in Scheme 4. Firstly, the $Fe^{III}$-ion-stabilized azomethine ylide **9**, generated in situ from the substituted isatin **1a** and primary α-amino acid methyl ester **2a**, reacted with ethyl 2,3-butadienoate **3a** to furnish the 1,3-diplar cycloaddition product **4a**. Secondly, conversion of exocyclic **4a** into endocyclic **5a** can occur via intermediates **10** and **11** under reflux conditions. It is reasonable that **4a** could convert into **10** and **11** through keto–enol tautomerism and proton transfer under the basic conditions. Subsequently, **11** could transform into **14** after several rounds of proton transfer. Finally, product **6a** forms through intramolecular nitrogen anion nucleophilic attack of the carbonyl group, si-




**Scheme 4.** A plausible mechanism to account for the cascade annulation.

multaneously activated by $Fe^{3+}$ ion, followed by release of a proton.

## Conclusion

We have developed an unprecedented $FeCl_3$-triggered, three-component domino strategy to access highly functionalized pyrrolo[1,2-*c*]quinazolinones in moderate to excellent yields. Based on previous reports and on our own inverstigations, a plausible mechanism has been proposed. The obtained products were used as useful building blocks in the synthesis of a diverse range of potentially biologically active heterocycles. This method has advantages of mild conditions and simple work-up as well as wide substrate scope, which makes this approach powerful for the synthesis of diverse pyrrolo[1,2-*c*]quinazolinones. Further investigation on the pharmacological activities of these compounds is underway. The development of more sophisticated and powerful cascade reactions is ongoing in our laboratory and will be reported in due course.

## Experimental Section

### General information

Unless otherwise noted, all the reactions were conducted under a dry $N_2$ atmosphere. All solvents were treated according to general methods. Column chromatography purifications were performed using 200–300 mesh silica gel, and reactions were monitored by thin-layer chromatography (TLC). Melting points were determined with a WRS-1B digital melting-point apparatus, and the values are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded with a Varian Mercury PLUS 400 or a Varian Mercury PLUS 600 spectrometer in $CDCl_3$ or [$D_6$]DMSO. Chemical shifts ($\delta$) are reported in parts per million (ppm) relative to the singlet (0 ppm) for tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, and m = multiplet), integration, and coupling constant (Hz). $^{13}C$ NMR chemical shifts are reported in ppm from $CDCl_3$ (taken as 77.0 ppm). Mass spectra were measured with a Finnigan TRACEMS 2000 (EI-MS) spectrometer. X-ray diffraction analysis was carried out with a Bruker APEX-II CCD X-ray diffraction instrument. HRMS were recorded with an IonSpec FT-ICR mass spectrometer with ESI resource. Allenoates[26] and substituted isatins[27] were synthesized according to the reported methods. Other chemicals were purchased from commercial suppliers and used without further purification.

### General procedure for the synthesis of 4a or 5a

Under a nitrogen atmosphere, to a 10 mL flask equipped with a reflux condenser was added **1** (0.5 mmol), **2** (0.75 mmol), **3** (0.75 mmol), 3 Å molecular sieve (100 mg), $Et_3N$ (1.0 mmol), and MeOH (4.0 mL). This solution was stirred at room temperature for 36 hours until either the reaction reached completion or no further product was formed (reaction monitored by TLC). The reaction mixture was concentrated under reduced pressure, then the crude product was purified by flash chromatography on silica gel (silica: 200–300; petroleum ether/ethyl acetate 12:1 to 6:1) to afford the desired products **4a** (30%) and **5a** (20%) as white solids.

Compounds **4b** and **4c** were synthesized according to the procedure described for **6**, except that 2-methly-2,3-butadienoate (**3e**) or 4-methly-2,3-butadienoate (**3f**) was used.

**3′-Ethyl 5′-methyl 1-benzyl-4′-methylene-2-oxospiro[indoline-3,2′-pyrrolidine]-3′,5′-dicarboxylate (4a)**: Yield: 30%; white solid; m.p. 130–131 °C. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 7.23–7.34 (m, 6H), 7.17 (t, $J$ = 7.8 Hz, 1H), 7.00 (t, $J$ = 7.5 Hz, 1H), 6.70 (d, $J$ = 7.8 Hz, 1H), 5.77 (s, 1H), 5.57 (s, 1H), 4.99 (d, $J$ = 15.6 Hz, 1H), 4.83 (d, $J$ = 16.2 Hz, 1H), 4.68 (d, $J$ = 5.4 Hz, 1H), 4.15–4.19 (m, 1H), 4.06–4.10 (m, 1H), 3.87 (s, 3H), 3.69 (s, 1H), 1.18 ppm (t, $J$ = 6.9 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 174.5, 170.3, 168.9, 143.3, 141.8, 135.3, 131.1, 129.1, 128.6, 127.4, 127.1, 122.8, 122.6, 113.4, 109.2, 68.7, 63.0, 61.1, 58.2, 52.6, 43.7, 13.7 ppm; MS (EI, 70 eV): $m/z$ = 420 (1.5) $[M]^+$, 374 (3.1), 361 (51.2), 347 (6.3), 315 (17.5), 287 (11.0), 197 (12.3), 181 (3.3), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{24}H_{25}N_2O_5$: 421.1758 $[M+H]^+$; found: 421.1765.

**(*Z*)-3′-Ethyl 5′-methyl 1-benzyl-4′-ethylidene-2-oxospiro[indoline-3,2′-pyrrolidine]-3′,5′-dicarboxylate (4b)**: Yield: 75%; white solid; m.p. 163–164 °C. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 7.25–7.32 (m, 5H), 7.16 (t, $J$ = 7.2 Hz, 2H), 6.97 (t, $J$ = 7.2 Hz, 1H), 6.70 (d, $J$ = 8.4 Hz, 1H), 6.18 (q, $J$ = 6.0 Hz, 1H), 5.06 (d, $J$ = 15.6 Hz, 2H), 4.81 (d, $J$ = 15.6 Hz, 1H), 4.68 (s, 1H), 4.21–4.24 (m, 1H), 4.13–4.16 (m, 1H), 3.87 (s, 3H), 3.63 (s, 1H), 1.71 (d, $J$ = 6.0 Hz, 3H), 1.24 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.5, 170.4, 169.6, 140.9, 136.9, 135.0, 132.9, 128.9, 128.6, 127.5, 126.9, 124.1, 123.1, 122.1, 109.4, 69.8, 63.8, 61.2, 55.6, 52.6, 43.8, 15.7, 13.8 ppm; MS (EI, 70 eV): $m/z$ = 434 (3.0) $[M]^+$, 388 (4.8), 375 (90), 361 (5.4), 329 (23.9), 301 (30.1), 211 (17.3), 193 (6.3), 149 (4.4), 129 (2.9), 92 (9.9), 91 (100); HRMS (ESI): $m/z$ calcd. for $C_{25}H_{27}N_2O_5$: 435.1914 $[M+H]^+$; found: 435.1920.

**3′-Ethyl 5′-methyl 1-benzyl-3′-methyl-4′-methylene-2-oxospiro[indoline-3,2′-pyrrolidine]-3′,5′-dicarboxylate (4c)**: Yield: 78%; white solid; m.p. 118–119 °C. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 7.25–7.34 (m, 5H), 7.16 (t, $J$ = 7.8 Hz, 1H), 7.08 (d, $J$ = 7.8 Hz, 1H), 6.98 (t, $J$ = 7.8 Hz, 1H), 6.72 (d, $J$ = 7.8 Hz, 1H), 5.74 (s, 1H), 5.29 (s, 1H), 5.08 (d, $J$ = 15.6 Hz, 1H), 4.78 (d, $J$ = 9.6 Hz, 1H), 4.74 (d, $J$ = 15.0 Hz, 1H), 4.18–4.25 (m, 2H), 3.88 (s, 3H), 1.27 (t, $J$ = 7.2 Hz, 3H), 1.02 ppm (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 173.7, 171.8, 169.8, 150.0, 141.7, 135.0, 129.3, 128.7, 128.3, 127.2, 126.7, 123.5, 122.4, 111.4, 109.1, 73.2, 64.1, 61.1, 58.5, 52.2, 43.5, 18.2, 13.4 ppm; HRMS (ESI): $m/z$ calcd for $C_{25}H_{27}N_2O_5$: 435.1914 $[M+H]^+$; found: 435.1918.

**3′-Ethyl 5′-methyl 1-benzyl-4′-methyl-2-oxo-3′,4′-dihydrospiro[indoline-3,2′-pyrrole]-3′,5′-dicarboxylate (5a)**: Yield: 20%; white solid; m.p. 161–162 °C. $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ = 7.38 (d, $J$ = 7.2 Hz, 2H), 7.32 (t, $J$ = 7.5 Hz, 2H), 7.28 (d, $J$ = 7.2 Hz, 1H), 7.16–7.18 (m, 1H), 6.93 (d, $J$ = 4.8 Hz, 2H), 6.71 (d, $J$ = 8.4 Hz, 1H), 5.26 (d, $J$ = 15.6 Hz, 1H), 4.67 (d, $J$ = 15.6 Hz, 1H), 4.11–4.16 (m, $J$ = 7.5 Hz, 1H), 3.89 (s, 3H), 3.75–3.79 (m, 1H), 3.61–3.65 (m, 1H), 3.58 (d, $J$ = 7.8 Hz, 1H), 1.55 (d, $J$ = 7.2 Hz, 3H), 0.46 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 174.8, 172.8, 169.2, 162.0, 142.9, 135.1, 130.0, 128.5, 127.6, 127.3, 125.9, 124.1, 122.8, 109.3, 81.3, 60.8, 56.9, 52.7, 46.8, 44.1, 17.1, 13.0 ppm; MS (EI, 70 eV): $m/z$ = 420 (25.7) $[M]^+$, 347 (13.9), 315 (24.6), 301 (3.9), 225 (16.1), 198 (5.8), 105 (3.9), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{24}H_{25}N_2O_5$: 412.1758 $[M+H]^+$; found: 421.1760.

### General procedure for the synthesis of pyrrolo[1,2-c]quinazolinones 6

Under a nitrogen atmosphere, to a 10 mL flask equipped with a reflux condenser was added isatin derivative **1** (0.5 mmol), α-amino acid ester or α-amino ketone hydrochloride **2** (0.75 mmol), 2,3-butadienoate **3** (0.75 mmol), $FeCl_3$ (0.25 mmol), 3 Å molecular

sieve (100 mg), $Et_3N$ (1.0 mmol), and MeOH (4.0 mL). The mixture was stirred at 65 °C for 12–24 h until **1** was completely consumed (reaction monitored by TLC). The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (petroleum ether/ethyl acetate 12:1 to 6:1) to give the corresponding product **6** as a white solid.

**1-Ethyl 3-methyl 6-benzyl-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6a)**: Yield: 75%; white solid; m.p. 172–173 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.81 (d, $J$ = 8.4 Hz, 1H), 7.36–7.30 (m, 3H), 7.26–7.22 (m, 4H), 7.18 (d, $J$ = 8.4 Hz, 1H), 5.50 (s, 2H), 4.46 (q, $J$ = 7.0 Hz, 2H), 3.97 (s, 3H), 2.39 (s, 3H), 1.44 ppm (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.1, 162.9, 145.4, 135.1, 134.2, 131.4, 129.5, 128.6, 128.4, 127.3, 126.3, 126.2, 123.0, 120.8, 114.9, 114.1, 112.8, 60.8, 52.4, 47.2, 14.0, 11.4 ppm; MS (EI, 70 eV): $m/z$ = 418 (16.8) $[M]^+$, 385 (8.8), 359 (1.9), 286 (3.2), 207 (3.2), 169 (2.8), 140 (3.5), 129 (5.4), 92 (7.9), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{24}H_{23}N_2O_5$: 419.1601 $[M+H]^+$; found: 419.1605.

**1-Ethyl 3-methyl 2,6-dimethyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]-quinazoline-1,3-dicarboxylate (6b)**: Yield: 78%; white solid; m.p. 142–143 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.82 (d, $J$ = 7.8 Hz, 1H), 7.50–7.48 (m, 1H), 7.29–7.24 (m, 2H), 4.45 (q, $J$ = 7.2 Hz, 2H), 3.98 (s, 3H), 3.70 (s, 3H), 2.36 (s, 3H), 1.43 ppm (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.2, 163.1, 144.9, 135.0, 131.3, 129.6, 128.2, 126.3, 123.0, 120.7, 114.0, 113.9, 112.6, 60.8, 52.5, 31.0, 14.1, 11.5 ppm; MS (EI, 70 eV): $m/z$ = 342 (100) $[M]^+$, 311 (23.7), 297 (28.3), 284 (26.7), 256 (7.1), 238 (46.7), 209 (14.4), 181 (5.6), 140 (6.1), 132 (13.7); HRMS (ESI): $m/z$ calcd for $C_{18}H_{19}N_2O_5$: 343.1288 $[M+H]^+$; found: 343.1290.

**1-Ethyl 3-methyl 6-allyl-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6c)**: Yield: 64%; white solid; m.p. 132–133 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.81 (s, $J$ = 8.4 Hz, 1H), 7.45 (t, $J$ = 7.5 Hz, 1H), 7.27–7.24 (m, 2H), 5.94 (dd, $J$ = 5.4, 5.4 Hz, 1H), 5.27 (d, $J$ = 10.8 Hz, 1H), 5.21 (d, $J$ = 17.4 Hz, 1H), 4.89 (s, 2H), 4.45 (q, $J$ = 7.0 Hz, 2H), 3.97 (s, 3H), 2.37 (s, 3H), 1.43 ppm (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.2, 163.0, 144.9, 134.3, 131.4, 130.8, 129.6, 128.4, 126.5, 123.1, 120.8, 117.7, 114.8, 114.2, 112.8, 60.9, 52.6, 46.1, 14.1, 11.5 ppm; MS (EI, 70 eV): $m/z$ = 368 (100) $[M]^+$, 354 (9.1), 337 (20.1), 323 (19.2), 307 (12.6), 264 (29.2), 223 (13.1), 207 (10.9), 195 (8.6), 179 (8.3), 167 (7.2), 140 (16.7); HRMS (ESI): $m/z$ calcd for $C_{20}H_{21}N_2O_5$: 369.1445 $[M+H]^+$; found: 369.1444.

**1-Ethyl 3-methyl 2-methyl-5-oxo-6-(prop-2-yn-1-yl)-5,6-dihydropyrrolo;[1,2-*c*]quinazoline-1,3-dicarboxylate (6d)**: Yield: 60%; white solid; m.p. 185–186 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.81 (d, $J$ = 8.4 Hz, 1H), 7.53 (t, $J$ = 7.8 Hz, 1H), 7.45 (d, $J$ = 8.4 Hz, 1H), 7.31 (t, $J$ = 7.8 Hz, 1H), 5.04 (s, 2H), 4.45 (q, $J$ = 7.0 Hz, 2H), 3.97 (s, 3H), 2.36 (s, 3H), 2.31 (s, 1H), 1.43 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.3, 163.0, 144.7, 133.6, 131.4, 129.9, 128.8, 126.7, 123.7, 121.0, 114.7, 114.4, 113.3, 73.6, 61.0, 52.7, 33.6, 29.6, 14.2, 11.6 ppm; MS (EI, 70 eV): $m/z$ = 366 (100) $[M]^+$, 335 (22.0), 321 (17.1), 308 (15.8), 262 (32.2), 223 (6.5), 195 (7.9), 179 (7.4), 167 (4.9), 140 (12.5); HRMS (ESI): $m/z$ calcd for $C_{20}H_{19}N_2O_5$: 367.1288 $[M+H]^+$; found: 367.1289.

**1-Ethyl 3-methyl 2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6e)**: Yield: 58%; white solid; m.p. 205–206 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 10.63 (s, 1H), 8.77 (d, $J$ = 8.4 Hz, 1H), 7.42 (t, $J$ = 7.5 Hz, 1H), 7.24 (t, $J$ = 7.8 Hz, 1H), 7.17 (d, $J$ = 7.8 Hz, 1H), 4.46 (q, $J$ = 7.0 Hz, 2H), 3.98 (s, 3H), 2.39 (s, 3H), 1.44 ppm (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.2, 163.1, 146.0, 133.3, 132.7, 129.8, 129.1, 126.2, 123.6, 120.0, 115.5, 113.4, 113.2, 61.0, 52.6, 14.2, 11.7 ppm; MS (EI, 70 eV): $m/z$ = 328 (100) $[M]^+$, 314 (14.4), 297 (24.6), 283 (23.1), 270 (20.1), 224 (60.7), 207 (24.7), 195 (10.0), 168 (5.2), 140 (15.7), 103.5 (12.3); HRMS (ESI): $m/z$ calcd for $C_{17}H_{17}N_2O_5$: 329.1143 $[M+H]^+$; found: 329.1144.

**1-Ethyl 3-methyl 6-benzyl-9-fluoro-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6f)**: Yield: 79%; white solid; m.p. 172–173 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.72–8.70 (m, 1H), 7.32 (t, $J$ = 7.5 Hz, 2H), 7.26 (t, $J$ = 7.2 Hz, 1H), 7.22 (d, $J$ = 7.2 Hz, 2H), 7.14–7.04 (m, 2H), 5.48 (s, 2H), 4.47 (q, $J$ = 7.0 Hz, 2H), 3.97 (s, 3H), 2.39 (s, 3H), 1.45 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 164.9, 163.0, 159.3, 156.9, 145.3, 134.9, 130.7, 130.5, 128.8, 128.5, 127.6, 126.2, 121.5, 117.2, 116.9, 116.7, 116.6, 115.6, 115.5, 113.7, 113.0, 112.7, 61.0, 52.7, 47.7, 14.1, 11.6 ppm; MS (EI, 70 eV): $m/z$ = 436 (26.5) $[M]^+$, 422 (1.4), 404 (25.5), 391 (3.5), 377 (4.6), 303 (2.0), 225 (1.3), 92 (8.2), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{24}H_{22}FN_2O_5$: 437.1507 $[M+H]^+$; found: 437.1513.

**1-Ethyl 3-methyl 6-benzyl-9-chloro-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6g)**: Yield: 69%; white solid; m.p. 167–168 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.90 (s, 1H), 7.31 (t, $J$ = 7.5 Hz, 2H), 7.26–7.24 (m, 2H), 7.21 (d, $J$ = 7.8 Hz, 2H), 7.09 (d, $J$ = 8.4 Hz, 1H), 5.47 (s, 2H), 4.47 (q, $J$ = 7.0 Hz, 2H), 3.97 (s, 3H), 2.39 (s, 3H), 1.46 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 164.8, 162.9, 145.2, 134.8, 132.9, 130.0, 129.5, 128.8, 128.7, 127.6, 126.3, 126.1, 121.5, 116.4, 115.5, 113.6, 61.2, 52.7, 47.6, 14.1, 11.6 ppm; MS (EI, 70 eV): $m/z$ = 452 (23.3) $[M]^+$, 420 (19.9), 407 (3.2), 393 (4.2), 319 (1.6), 257 (1.7), 210 (1.4), 92 (7.8), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{24}H_{22}ClN_2O_5$: 453.1212 $[M+H]^+$; found: 453.1219.

**1-Ethyl 3-methyl 6-benzyl-9-bromo-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]-quinazoline-1,3-dicarboxylate (6h)**: Yield: 65%; white solid; m.p. 176–177 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 9.03 (d, $J$ = 7.8 Hz, 1H), 7.43–7.41 (m, 1H), 7.31 (t, $J$ = 7.5 Hz, 2H), 7.27–7.25 (m, 1H), 7.21 (d, $J$ = 7.2 Hz, 2H), 7.04 (d, $J$ = 9.0 Hz, 1H), 5.46 (s, 2H), 4.48 (q, $J$ = 7.2 Hz, 2H), 3.97 (s, 3H), 2.39 (s, 3H), 1.46 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 164.7, 162.9, 145.2, 134.7, 133.3, 132.3, 129.8, 129.0, 128.8, 127.6, 126.3, 121.5, 116.7, 116.3, 115.9, 113.6, 61.2, 52.7, 47.6, 14.1, 11.6 ppm; MS (EI, 70 eV): $m/z$ = 498 (12.4) $[M+2]^+$, 497 (2.8) $[M+1]^+$, 496 (11.8) $[M]^+$, 466 (11.5), 437 (2.6), 194 (1.2), 140 (1.0), 92 (6.8), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{24}H_{22}BrN_2O_5$: 497.0707 $[M+H]^+$; found: 497.0705.

**1-Ethyl 3-methyl 6-benzyl-2,9-dimethyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6i)**: Yield: 80%; white solid; m.p. 170–171 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.56 (s, 1H), 7.30 (t, $J$ = 7.5 Hz, 2H), 7.25 (t, $J$ = 7.2 Hz, 1H), 7.22 (d, $J$ = 7.8 Hz, 2H), 7.15 (d, $J$ = 8.4 Hz, 1H), 7.06 (d, $J$ = 9.0 Hz, 1H), 5.47 (s, 2H), 4.46 (q, $J$ = 7.2 Hz, 2H), 3.96 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H), 1.44 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.3, 163.1, 145.5, 135.3, 132.8, 132.3, 131.5, 130.8, 128.7, 128.6, 127.4, 126.4, 126.3, 120.9, 115.0, 114.1, 112.8, 60.9, 52.6, 47.3, 20.9, 14.2, 11.5 ppm; MS (EI, 70 eV): $m/z$ = 432 (51.2) $[M]^+$, 418 (5.5), 401 (12.7), 400 (41.0), 399 (29.4), 387 (4.8), 373 (7.1), 299 (3.4), 181 (3.5), 92.1 (6.0), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{25}H_{25}N_2O_5$: 433.1758 $[M+H]^+$; found: 433.1765.

**1-Ethyl 3-methyl 6-benzyl-9-methoxy-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6j)**: Yield: 78%; white solid; m.p. 165–166 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.56–8.544 (m, 1H), 7.30 (t, $J$ = 7.5 Hz, 2H), 7.26–7.21 (m, 3H), 7.09 (d, $J$ = 9.6 Hz, 1H), 6.94–6.92 (m, 1H), 5.47 (s, 2H), 4.45 (q, $J$ = 7.0 Hz, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 2.39 (s, 3H), 1.43 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.4, 163.3, 155.3, 145.4, 135.3, 131.6, 128.8, 128.4, 127.5, 126.3, 121.1, 117.6, 116.3, 115.2, 109.7, 61.0, 55.5, 52.7, 47.5, 14.2, 11.8 ppm; MS (EI, 70 eV): $m/z$ = 448 (79.2) $[M]^+$, 434 (5.2), 416 (31.2), 389 (11.4), 357 (36.2), 253 (9.5), 225 (7.2), 197 (4.0), 92 (10.9), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{25}H_{25}N_2O_6$: 449.1707 $[M+H]^+$; found: 449.1713.

**1-Ethyl 3-methyl 6-benzyl-8-chloro-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6k)**: Yield: 65%; white solid; m.p. 195–197 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.87 (d, $J$ = 8.4 Hz, 1H), 7.34 (t, $J$ = 7.5 Hz, 2H), 7.29–7.18 (m, 5H), 5.45 (s, 2H), 4.44 (q, $J$ = 7.0 Hz, 2H), 3.97 (s, 3H), 2.39 (s, 3H), 1.43 ppm (t, $J$ = 7.2 Hz, 3H); C$^{13}$ NMR (100 MHz, $CDCl_3$): $\delta$ = 165.1, 162.9, 145.4, 135.5, 134.6, 131.0, 129.0, 128.1, 127.8, 126.4, 123.6, 121.3, 115.1, 113.3, 112.9, 61.1, 52.7, 47.6, 14.2, 11.7 ppm; MS (EI, 70 eV): $m/z$ = 455 (2.2) $[M+1]^+$, 452 (24.9) $[M]^+$, 452 (24.9), 420 (21.6), 393 (2.7), 257 (1.5), 207 (4.5), 196 (1.8), 92 (7.5), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{24}H_{22}ClN_2O_5$: 453.1212 $[M+H]^+$; found: 453.1214.

**1-Ethyl 3-methyl 6-benzyl-7-fluoro-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6l)**: Yield: 72%; white solid; m.p. 150–151 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.51 (d, $J$ = 8.4 Hz, 1H), 7.26 (t, $J$ = 7.2 Hz, 2H), 7.22 (d, $J$ = 6.6 Hz, 1H), 7.19 (d, $J$ = 7.8 Hz, 2H), 7.17–7.08 (m, 2H), 5.63 (s, 2H), 4.45 (q, $J$ = 7.0 Hz, 2H), 3.95 (s, 3H), 2.40 (s, 3H), 1.43 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.1, 162.5, 151.5, 149.0, 145.8, 136.4, 130.9, 129.8, 128.4, 127.2, 126.4, 124.3, 123.3, 122.3, 121.6, 117.6, 117.4, 113.8, 61.1, 52.5, 50.3, 50.1, 14.1, 11.5 ppm; MS (EI, 70 eV): $m/z$ = 436 (18.3) $[M]^+$, 404 (36.1), 377 (3.6), 303 (6.3), 92 (8.6), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{24}H_{22}FN_2O_5$: 437.1507 $[M+H]^+$; found: 437.1511.

**Diethyl 6-benzyl-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6m)**: Yield: 69%; white solid; m.p. 116–117 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.81 (d, $J$ = 7.8 Hz, 1H), 7.34 (t, $J$ = 7.8 Hz, 1H), 7.31 (t, $J$ = 7.5 Hz, 2H), 7.26–7.22 (m, 4H), 7.18 (d, $J$ = 8.4 Hz, 1H), 5.49 (s, 2H), 4.47–4.42 (m, 4H), 2.40 (s, 3H), 1.44 (t, $J$ = 7.2 Hz, 3H), 1.38 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.3, 162.5, 145.6, 135.3, 134.5, 131.5, 129.7, 128.8, 128.6, 127.5, 126.6, 126.4, 123.2, 121.4, 115.0, 114.4, 113.0, 61.7, 60.9, 47.5, 14.2, 14.1, 11.5 ppm; MS (EI, 70 eV): $m/z$ = 432 (26.5) $[M]^+$, 385 (16.5), 360 (14.5), 195 (2.0), 181 (2.0), 140 (2.8), 129 (3.2), 92 (11), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{25}H_{25}N_2O_5$: 433.1758 $[M+H]^+$; found: 433.1765.

**1-Ethyl 3-isopropyl 6-benzyl-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6n)**: Yield: 61%; white solid; m.p. 98–100 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.80 (d, $J$ = 8.4 Hz, 1H), 7.35–7.25 (m, 6H), 7.22 (t, $J$ = 7.5 Hz, 1H), 7.17 (d, $J$ = 8.4 Hz, 1H), 5.49 (s, 2H), 5.30–5.32 (m, 1H), 4.48 (q, $J$ = 7.0 Hz, 2H), 2.40 (s, 3H), 1.43 (t, $J$ = 7.2 Hz, 3H), 1.38 ppm (d, $J$ = 6.0 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.3, 161.9, 145.5, 135.3, 134.5, 131.4, 129.6, 128.7, 128.3, 127.4, 126.5, 126.4, 123.1, 121.7, 114.9, 114.4, 112.9, 69.4, 60.9, 47.4, 21.7, 14.2, 11.4 ppm; MS (EI, 70 eV): $m/z$ = 446 (20.3) $[M]^+$, 386 (20.0), 360 (19.8), 285 (3.5), 207 (2.2), 140 (2.6), 92 (9.6), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{26}H_{27}N_2O_5$: 447.1914 $[M+H]^+$; found: 447.1916.

**Ethyl 3-benzoyl-6-benzyl-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1-carboxylate (6o)**: Yield: 52%; white solid; m.p. 197–198 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.88 (d, $J$ = 7.2 Hz, 1H), 7.77 (d, $J$ = 7.2 Hz, 2H), 7.54 (t, $J$ = 7.2 Hz, 1H), 7.43 (t, $J$ = 7.5 Hz, 2H), 7.36 (t, $J$ = 7.8 Hz, 1H), 7.28–7.21 (m, 4H), 7.17 (d, $J$ = 8.4 Hz, 1H), 7.09 (d, $J$ = 7.2 Hz, 2H), 5.34 (s, 2H), 4.49 (q, $J$ = 7.0 Hz, 2H), 2.31 (s, 3H), 1.45 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 188.7, 165.6, 145.7, 139.0, 135.1, 134.4, 132.7, 130.9, 129.8, 128.7, 128.5, 128.2, 127.5, 126.5, 126.4, 123.4, 115.1, 114.5, 113.6, 61.0, 47.3, 14.2, 11.6 ppm; MS (EI, 70 eV): $m/z$ = 464 (43.8) $[M]^+$, 435 (2.2), 419 (4.1), 359 (5.5), 206 (3.2), 195 (2.3), 165 (2.9), 105 (26.1), 92 (8.6), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{29}H_{25}N_2O_4$: 465.1809 $[M+H]^+$; found: 465.1814.

**Dimethyl 6-benzyl-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6p)**: Yield: 83%; white solid; m.p. 199–200 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.80 (d, $J$ = 8.4 Hz, 1H), 7.35 (t, $J$ = 7.5 Hz, 1H), 7.31 (t, $J$ = 7.5 Hz, 2H), 7.25–7.23 (m, 4H), 7.18 (d, $J$ = 8.4 Hz, 1H), 5.49 (s, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 2.38 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.6, 162.9, 145.4, 135.1, 134.3, 131.6, 129.7, 128.7, 128.5, 127.4, 126.4, 126.3, 123.2, 120.9, 114.9, 114.1, 112.6, 52.5, 51.7, 47.3, 11.4 ppm; MS (EI, 70 eV): $m/z$ = 404 (35.7) $[M]^+$, 372 (27.4), 345 (2.8), 285 (3.0), 207 (1.7), 179 (2.0), 168 (2.6), 140 (1.9), 92 (9.1), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{23}H_{21}N_2O_5$: 405.1445 $[M+H]^+$; found: 405.1453.

**1-Benzyl 3-methyl 6-benzyl-2-methyl-5-oxo-5,6-dihydropyrrolo-[1,2-*c*]quinazoline-1,3-dicarboxylate (6q)**: Yield: 56%; white solid; m.p. 163–164 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.72 (d, $J$ = 8.4 Hz, 1H), 7.47 (d, $J$ = 7.8 Hz, 2H), 7.40 (t, $J$ = 7.2 Hz, 2H), 7.37 (d, $J$ = 7.2 Hz, 1H), 7.33–7.12 (m, 8H), 5.49 (s, 2H), 5.44 (s, 2H), 3.96 (s, 3H), 2.35 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.1, 163.0, 145.5, 135.3, 135.2, 134.4, 131.7, 129.8, 128.8, 128.7, 128.6, 128.3, 127.5, 126.6, 126.3, 123.2, 121.1, 115.0, 114.2, 112.6, 66.9, 52.6, 47.5, 11.6 ppm; MS (EI, 70 eV): $m/z$ = 480 (15.3) $[M]^+$, 448 (7.6), 389 (3.6), 346 (2.1), 314 (1.6), 140 (1.0), 129 (2.5), 92 (8.7), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{29}H_{25}N_2O_5$: 481.1758 $[M+H]^+$; found: 481.1767.

**Methyl 1-acetyl-6-benzyl-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-3-carboxylate (6r)**: Yield: 85%; white solid; m.p. 200–201 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.11 (d, $J$ = 7.8 Hz, 1H), 7.34 (t, $J$ = 7.2 Hz, 1H), 7.31 (d, $J$ = 7.8 Hz, 2H), 7.25–7.18 (m, 5H), 5.50 (s, 2H), 3.98 (s, 3H), 2.63 (s, 3H), 2.36 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 199.7, 162.8, 145.6, 135.2, 134.4, 129.6, 128.8, 127.5, 126.6, 126.3, 125.3, 123.4, 122.7, 121.0, 115.3, 114.2, 52.6, 47.4, 32.2, 11.0 ppm; MS (EI, 70 eV): $m/z$ = 388 (30.4) $[M]^+$, 356 (16.3), 329 (2.5), 265 (3.0), 207 (1.2), 128 (1.8), 92 (8.4), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{23}H_{21}N_2O_4$: 389.1496 $[M+H]^+$; found: 389.1496.

**1-Ethyl 3-methyl 6-benzyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (6s)**: Yield: 63%; white solid; m.p. 166–168 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 9.54 (d, $J$ = 7.8 Hz, 1H), 7.53 (s, 1H), 7.41 (t, $J$ = 7.5 Hz, 1H), 7.33–7.22 (m, 6H), 7.23 (d, $J$ = 8.4 Hz, 1H), 5.53 (s, 2H), 4.40 (q, $J$ = 7.2 Hz, 2H), 3.96 (s, 3H), 1.42 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 63.7, 161.8, 145.7, 135.1, 134.8, 130.5, 128.9, 128.1, 127.6, 126.4, 123.5, 122.9, 122.4, 114.9, 114.6, 112.3, 60.9, 52.7, 47.7, 14.3 ppm; MS (EI, 70 eV): $m/z$ = 404 (16.7) $[M]^+$, 390 (5.9), 372 (16.0), 358 (5.5), 271 (5.3), 165 (1.4), 92 (8.1), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{23}H_{21}N_2O_5$: 405.1445 $[M+H]^+$; found: 405.1448.

**Methyl 1-acetyl-6-benzyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-3-carboxylate (6t)**: Yield: 68%; white solid; m.p. 156–157 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 9.50 (d, $J$ = 7.8 Hz, 1H), 7.46 (s, 1H), 7.43 (t, $J$ = 7.8 Hz, 1H), 7.33–7.25 (m, 6H), 7.23 (d, $J$ = 8.4 Hz, 1H), 5.53 (s, 2H), 3.97 (s, 3H), 2.66 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 194.0, 161.7, 145.6, 135.0, 134.8, 133.8, 131.0, 128.9, 127.9, 127.6, 126.4, 123.5, 123.0, 122.2, 120.5, 114.8, 114.7, 52.8, 47.8, 30.4 ppm; MS (EI, 70 eV): $m/z$ = 374 (30.4) $[M]^+$, 342 (30.2), 351 (3.0), 271 (4.6), 171 (1.8), 129 (2.2), 92 (8.7), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{22}H_{19}N_2O_4$: 375.1339 $[M+H]^+$; found: 375.1345.

**Trimethyl 6-benzyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,2,3-tricarboxylate (6u)**: Yield: 55%; white solid; m.p. 233–234 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.06 (d, $J$ = 8.4 Hz, 1H), 7.35 (t, $J$ = 7.8 Hz, 1H), 7.32 (d, $J$ = 7.8 Hz, 2H), 7.28–7.23 (m, 4H), 7.19 (d, $J$ = 8.4 Hz, 1H), 5.49 (s, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.89 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.8, 162.2, 162.1, 145.4, 134.7, 133.9, 129.9, 128.9, 127.7, 126.9, 126.3, 125.6, 124.3, 124.2, 118.5, 115.7, 113.8, 111.9, 53.4, 52.9, 52.4, 47.6 ppm, MS (EI, 70 eV): $m/z$ = 448 (17.9) $[M]^+$, 416 (12.2), 329 (1.8), 297 (5.2), 208 (1.9), 121 (2.0), 92 (7.9), 91 (100); HRMS (ESI): $m/z$ calcd for $C_{24}H_{21}N_2O_7$: 449.1343 $[M+H]^+$; found: 449.1345.

### Synthesis of 5-benzyl-3-methyl-4-oxo-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylic acid (7a)

A solution of **6a** (0.209 g, 0.5 mmol) in THF/MeOH/50% aqueous NaOH (3:2:1, 12 mL) was stirred and heated to reflux for 12 h. The reaction was acidified with 10% aq. HCl and extracted with EtOAc. The combined organic layer was dried over $Na_2SO_4$ and the filtrate was concentrated under reduced pressure to give the product **7a**. Yield: 70%; white solid; m.p. 242–243 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 13.0 (s, 1H), 12.6 (s, 1H), 8.53 (d, $J$ = 7.6 Hz, 1H), 7.38 (t, $J$ = 7.2 Hz, 1H), 7.36–7.18 (m, 7H), 5.55 (s, 2H), 2.7 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 163.0, 160.0, 137.7, 137.5, 135.4, 128.9, 128.7, 126.9, 126.6, 126.5, 123.4, 123.2, 121.9, 115.9, 113.8, 113.2, 40.2, 11.4 ppm; MS (EI, 70 eV): $m/z$ = 332 (90.4) $[M]^+$, 313 (17.4), 288 (14.5), 241 (36.1), 223 (58.1), 197 (17.4), 180 (12.8), 91 (100.0); HRMS (ESI): $m/z$ calcd for $C_{27}H_{26}N_5O_5$: 333.1234 $[M+H]^+$; found: 333.1231.

### Synthesis of 1-ethyl 3-methyl 6-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-2-methyl-5-oxo-5,6-dihydropyrrolo[1,2-*c*]quinazoline-1,3-dicarboxylate (7b)

To a 10 mL flask was added **6d** (0.6 mmol), $NaN_3$ (0.6 mmol), BnBr (0.5 mmol), sodium ascorbate (0.02 mmol), $CuSO_4{\cdot}5H_2O$ (0.04 mmol), and 8.0 mL (DMF/$H_2O$ = 3:1), and the reaction mixture was stirred at 30–40 °C for several hours. Water (25 mL) was added to the mixture and the crude product was extracted with $CH_2Cl_2$ (3×20 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (silica: 200–300; petroleum ether/ethyl acetate) to afford **7b**. Yield: 68%; white solid; m.p. 202–203 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 8.72 (d, $J$ = 8.4 Hz, 1H), 7.82 (d, $J$ = 8.4 Hz, 1H), 7.53 (s, 1H), 7.49 (t, $J$ = 8.1 Hz, 1H), 7.34–7.25 (m, 4H), 7.23 (d, $J$ = 7.2 Hz, 2H), 5.50 (s, 2H), 5.45 (s, 2H), 4.43 (q, $J$ = 7.0 Hz, 2H), 3.93 (s, 3H), 2.36 (s, 3H), 1.42 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 165.2, 162.9, 145.3, 143.0, 134.2, 134.1, 131.8, 130.1, 129.1, 129.0, 128.7, 128.1, 126.4, 123.4, 123.3, 120.6, 115.3, 114.1, 113.0, 61.0, 54.1, 52.5, 39.8, 14.2, 11.5 ppm; MS (EI, 70 eV): $m/z$ = 499 (60.2) $[M]^+$, 328 (52.9), 296 (37.7), 282 (11.3), 207 (12.8), 143 (10.4), 114 (17.7), 91 (100.0); HRMS (ESI): $m/z$ calcd for $C_{27}H_{26}N_5O_5$: 500.1928 $[M+H]^+$; found: 500.1933.

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