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Discovery of intermolecular cascade annulation for dihydrobenzo[*b*][1,8]naphthyridine-ylidene-pyrrolidinetriones†

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Developing efficient procedures for the synthesis of combinations of pharmacophores continues to be a vital objective in synthetic science. Herein, we report an unprecedented family of dihydrobenzo[*b*][1,8]naphthyridine-ylidene-pyrrolidinetriones achieved by reacting *ortho*-halogenated quinolonechalcones with aminomaleimides under metal-free conditions. Among these compounds, several exhibit the potential to serve as fluorescent dyes for biological applications. Mechanistic investigations indicate that the reaction proceeds *via* a 1,4-Michael addition followed by an intermolecular cascade annulation, which involves aniline fragment transfer and S_NAr processes. As far as we know, studies regarding the synthesis of dihydrobenzo[*b*][1,8]naphthyridine-ylidene-pyrrolidinetriones are rare. This discovery offers great inspiration for a feasible approach toward the creation of more complex and useful molecules.

Introduction

Pyrrolidine-2.5-dione and dihydrobenzo[*b*][1,8]naphthyridine derivatives, as significant nitrogen-containing heterocyclic compounds, are widely found in pharmaceutical molecules.[1,2] For example, pyrrolidinetrione derivatives (**I**) have functioned as antifungal agents that effectively resist potato diseases.[3] Tivantinib (**II**) acts as a highly selective inhibitor of the c-Met tyrosine kinase.[4] The dihydrobenzo[*b*][1,8]naphthyridine compound RP60556A (**III**) shows activity in resisting multidrug-resistant Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), and demonstrates potential *in vivo* efficacy as an acetylcholine esterase inhibitor.[5] Compound **VI**, known as eucophylline, is part of the dihydrobenzo[*b*][1,8]naphthyridine series (Fig. 1).[6]

Developing efficient procedures for synthesizing combinations of pharmacophores remains a crucial objective in synthetic organic chemistry.[7] Consequently, our interest lies in investigating novel strategies or methodologies to synthesize dihydrobenzo[*b*][1,8]naphthyridines fused with pyrrolidine-diones, which could represent promising and innovative approaches in the field of drug discovery. According to the literature, various methodologies for preparing pyrrolidine-2.5-diones[8] and dihydrobenzo[*b*][1,8]-naphthyridine derivatives[9] from easily available materials have been well established. It is widely known that aminomaleimides can attack electrophiles at two positions: the carbon atom of the C=C group[10] and the N-group[11] substituted at the 3-position. As illustrated in Scheme 1b: (a) when reacting with a monoelectrophilic reagent, two or more distinct products may potentially form. (b) With an amphiphilic electrophilic reagent, one possible pathway involves reactions at the C-4 position and the N site substituted at the 3-position, leading to the formation of cyclized products.[12]

Similarly, *ortho*-halogenated quinolonechalcones can undergo nucleophilic attacks at three positions: the carbon atom of the C=O group, the β-carbon of the C=C bond, and the C2′-quinoline site.[13] These three active centers are all electron-deficient, making them susceptible to nucleophilic attack. As

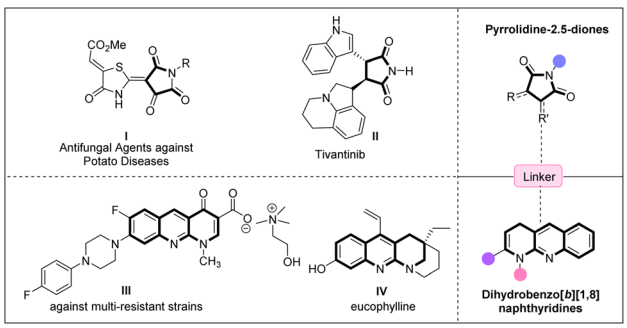

Fig. 1 The significance of pyrrolidine-2.5-diones and dihydrobenzo[*b*][1,8]naphthyridine derivatives.

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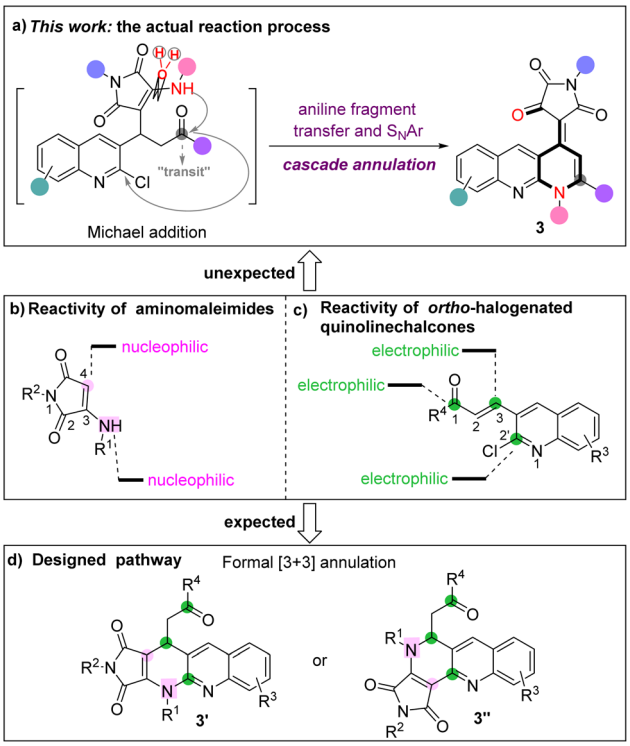


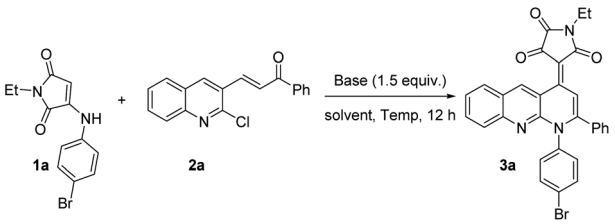
Scheme 1 Transformations of aminomaleimides and *ortho*-halogenated quinolinechalcones: (a) this work: the actual reaction process; (b) reactivity of aminomaleimides; (c) reactivity of *ortho*-halogenated quinolinechalcones; (d) designed pathway.

illustrated in Scheme 1c: (a) when reacting with a mono-nucleophilic reagent, three or more distinct products may potentially form.[14] (b) With an amphiphilic nucleophilic reagent, one possible pathway involves reactions at the C1 and C3 sites, leading to the formation of cyclized products.[15] Another pathway may involve reactions at the C2′ and C3 sites, also yielding cyclized products, or additional reaction pathways may exist.[16]

Building on our previous work,[17] we envision that the equilibrium of aminomaleimides indicates its potential as a suitable synthon in the proposed annulation. By using *ortho*-halogenated quinolonechalcones **1**, which contain a Michael acceptor and a chlorine or bromine leaving group at the *ortho*-position of the quinoline ring, the expected dihydrobenzo[*b*][1,8]naphthyridines fused with pyrrolidinediones 3′ or 3″ could be readily achieved (Scheme 1d). However, we did not obtain the anticipated products. Based on previous developments,[18] cascade annulation reactions have emerged as a useful strategy for preparing complex molecular structures, especially in metal-free reactions.[19] We discovered that the reaction unexpectedly proceeded *via* a 1,4-Michael addition followed by an intermolecular cascade annulation, resulting in the formation of dihydrobenzo[*b*][1,8]naphthyridines fused with pyrrolidinetrione, compound **3**, under metal-free conditions (Scheme 1a). Hopefully, this work has also been highlighted through gaining valuable insights into fluorescent dyes for potential biological applications.

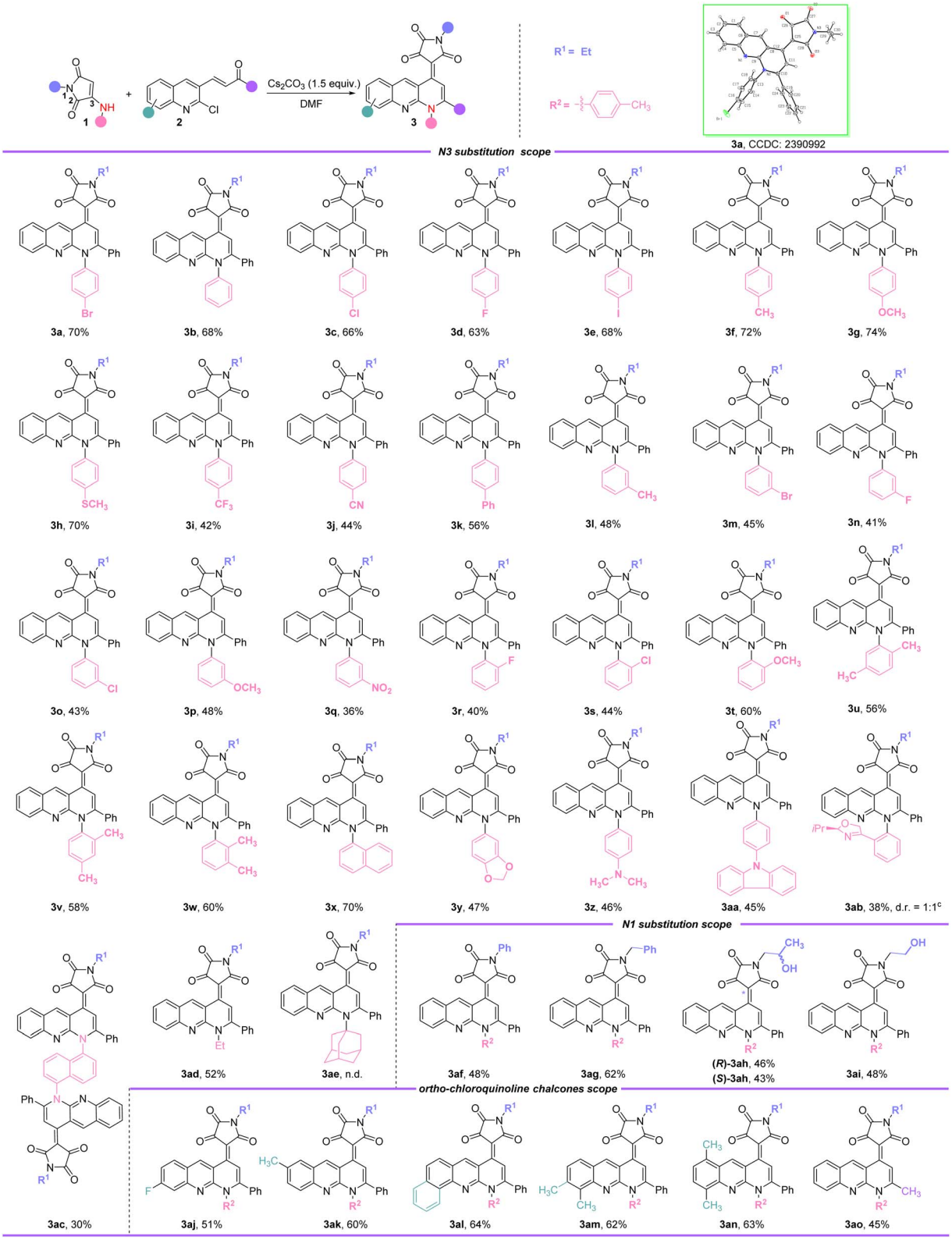
Initially, we investigated the reaction between 3-((4-bromophenyl)amino)-1-ethyl-1*H*-pyrrole-2,5-dione **1a** and (*E*)-1-phenyl-3-(phenylamino)prop-2-en-1-one (**2a**, 2.0 equiv.) in the presence of 1.5 equivalents of cesium carbonate (Cs_2CO_3) in ethanol at reflux for 12 hours (Table 1). To our delight, the unexpected product (*E*)-4-(1-(4-bromophenyl)-2-phenylbenzo-[*b*][1,8]naphthyridin-4(1*H*)-ylidene)-1-ethylpyrrolidine-2,3,5-trione **3a** was obtained in 26% yield (entry 1). Subsequently, various bases were screened (K_2CO_3, Na_2CO_3, Et_3N, DBU, and DABCO, entries 2–8), but none provided better results than Cs_2CO_3. The solvent effect was also investigated, and the results showed that *N*,*N*-dimethylformamide (DMF) proved to be the best choice, furnishing the desired product **3a** in 70% yield (entries 9–15). Next, the addition of oxidizing additives did not lead to the detection of **3a** (entries 16–19). When 'Br' was substituted for 'Cl' at C-2′ in substrate **2a**, product **3a** was also attained (entry 20). Additionally, decreasing the reaction temperature to 60 °C or replacing cesium carbonate with potassium carbonate failed to provide good yields (Table 1, entries 21 and 22). Consequently, the optimal reaction conditions were identified as using Cs_2CO_3 as the base and DMF as the solvent at 80 °C.

Table 1 Optimization of reaction conditions[a,b]



Entry	Base	Additive	Solvent	Temp (°C)	Yield[b] (%)
1	Cs_2CO_3	—	EtOH	Reflux	26
2	K_2CO_3	—	EtOH	Reflux	15
3	Na_2CO_3	—	EtOH	Reflux	Trace
4	Et_3N	—	EtOH	Reflux	Trace
5	DBU	—	EtOH	Reflux	Trace
6	DABCO	—	EtOH	Reflux	Trace
7	Piperidine	—	EtOH	Reflux	n.d.
8	PPh_3	—	EtOH	Reflux	n.d.
9	Cs_2CO_3	—	MeOH	Reflux	12
10	Cs_2CO_3	—	EA	Reflux	10
11	Cs_2CO_3	—	Toluene	80	20
12	Cs_2CO_3	—	THF	Reflux	48
13	Cs_2CO_3	—	DMSO	80	44
14	**Cs_2CO_3**	**—**	**DMF**	**80**	**70**
15	Cs_2CO_3	—	CH_3CN	80	30
16	Cs_2CO_3	DDQ	DMF	80	n.d.
17	Cs_2CO_3	$K_2S_2O_8$	DMF	80	n.d.
18	Cs_2CO_3	BPO	DMF	80	Trace
19	Cs_2CO_3	IBX	DMF	80	Trace
20[c]	Cs_2CO_3	—	DMF	80	68
21	Cs_2CO_3	—	DMF	60	45
22	K_2CO_3	—	DMF	80	40

[a] Reaction conditions: **1a** (0.1 mmol) and **2a** (0.2 mmol) were reacted at reflux or 80 °C in the presence of base (0.15 mmol) in 2 mL of the solvent in air. [b] Isolated yields. n.d. = not detected. [c] 'Cl' at C-2′ of **2a** instead with 'Br'.

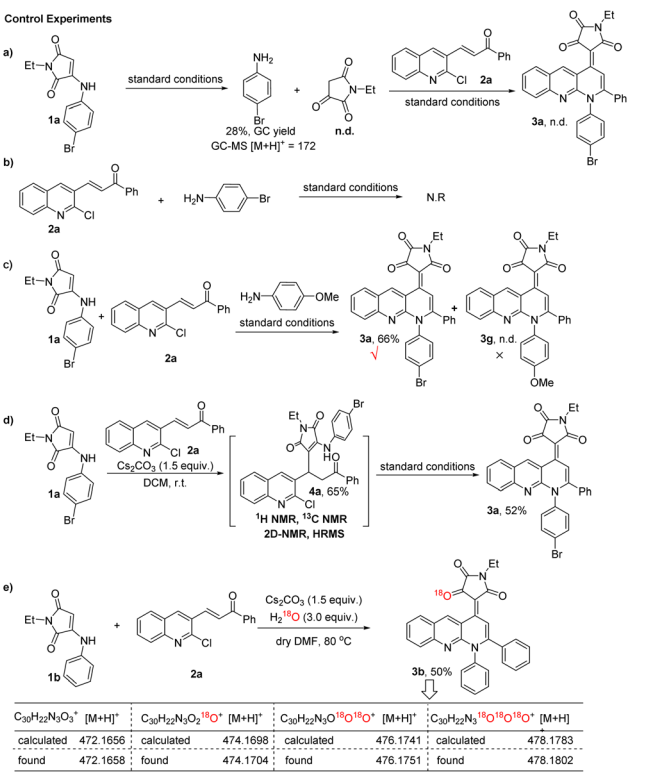


Scheme 2 Scope of the substrates.[a,b] [a] Reaction conditions: **1** (0.1 mmol) and **2** (0.2 mmol), and Cs_2CO_3 (0.15 mmol) in DMF (2.0 mL) at 80 °C for 12 h in air. [b] Yield was determined after the product was purified by silica-gel chromatography. [c] Determined by ^1H NMR analysis. [c] **1ac** (0.1 mmol) and **2a** (0.4 mmol).

Using the optimal reaction conditions, we began to evaluate the scope of various aminomaleimides **1** with (*E*)-1-phenyl-3-(phenylamino)prop-2-en-1-one **2a** (Scheme 2). It was observed that aminomaleimides bearing electron-rich at the N-3 position aryl groups reacted more favorably compared to those with electron-deficient substituents. Specifically, *N*-4-methoxyphenyl-substituted aminomaleimides yielded product **3g** in 74% yield, while the *N*-4-(trifluoromethyl)phenyl-substituted analogs provided product **3i** with a lower yield of 42%. The substituent position on the *N*-aryl group of acyclic enaminone significantly influences the reaction results. Both *meta*-substituted (**3l–3q**) and *ortho*-substituted (**3r–3t**) aminomaleimide substrates with *N*-aryl groups produced the target compounds, albeit with reduced yields. Aminomaleimides featuring disubstituted and trisubstituted aryl groups at the N-3 position also demonstrated effectiveness, generating products **3u–3w** in 56–60% yield. Moreover, substrates with 1-naphthyl and benzo[*d*][1,3]dioxol-5-yl substitutions at the N-3 position yielded the target compounds at 70% (**3x**) and 47% yield (**3y**), respectively. Notably, benzene rings substituted at the 4-position with a carbazole or *N*,*N*-dimethylphenyl group exhibited good compatibility, resulting in the respective products with 45% (**3z**) and 46% yield (**3aa**). It is noteworthy that aminomaleimides, which feature *ortho*-chiral oxazole-substituted groups at the benzene rings **1ab**, resulted in a 1 : 1 diastereoisomeric mixture of **3ab** with a yield of 38%. This outcome is likely attributed to their asymmetrical structure and the steric hindrance imposed by the *ortho*-substituted aminomaleimide. Such structural features lead to C–N axis chirality and the presence of racemic atropisomers in their configurations. Additionally, aminomaleimides derived from naphthalene-1,5-diamine (**1ac**) and the reaction with bis-molecular *ortho*-chloroquinolinechalcone **2a** yielded the desired product **3ac** with a 30% yield. Encouragingly, replacing the benzene ring with ethyl led to corresponding products in 52% yield (**3ad**), while adamantane substitution failed to produce the desired **3ae** product, possibly due to significant steric hindrance.

Additional functional group compatibility and substrate scope were examined by varying the substituents at the N-1 positions of aminomaleimides. Substrates carrying benzyl (**3af**), phenyl (**3ag**), (*R*) or (*S*)-2-hydroxypropyl (**3ah**), and hydroxyethyl (**3ai**) groups on nitrogen were well tolerated. Next, the effect of substituents on the quinoline ring of *ortho*-chloroquinolinechalcones **1** was investigated. Substituents including fluorine and methyl groups on the quinoline ring were compatible with aminomaleimide **2a**, facilitating the synthesis of the corresponding products in moderate yields (51% and 60%) (**3aj** and **3ak**). Furthermore, disubstituted aromatic rings and those containing a 1-naphthalene group on the quinoline moiety also produced cyclization products efficiently, with yields between 55% and 64% (**3al–3an**). Surprisingly, *ortho*-chloroquinolinechalcones **1a** with a methyl substitution on the phenyl group could still afford the desired products with a 45% yield (**3ao**). However, *ortho*-chloroquinolin-α,β-unsaturated esters (**2h** and **2i**) failed to produce the expected product, which may be attributed to the ester group being less reactive than the ketone. To broaden the chalcone varieties, 2-halopyridinechalcones **6a** and **6b** were subjected to testing. The identical target product **7a** was successfully obtained, with yields of 14% (for 2-Cl) and 23% (for 2-F), respectively (for more details see S38 and S39 in the ESI†). Additionally, the structure of compound **3** was confirmed by X-ray diffraction analysis of **3a** (CCDC 2390992†).[20]

To gain a deeper understanding of the reaction mechanism, we designed and conducted a series of control experiments. First, to investigate whether the cleavage and reformation of the aniline fragment during the reaction is an intramolecular process, we conducted the following experiments (Scheme 3): (a) compound **1a** was treated under standard conditions, and *p*-bromoaniline was successfully detected as a product. However, when an additional **2a** was added to this system, the expected formation of target product **3a** was not observed. (b) We attempted to react **2a** directly with *p*-bromoaniline under the same standard conditions, but the desired product, where the aniline substitutes for the chlorine atom, was not obtained. (c) We investigated whether a cross-reaction would occur between **1a** and **2a** in the presence of *p*-anisidine. Despite the introduction of *p*-anisidine, the final product remained **3a**, indicating that the expected cross-reaction did not take place. To further confirm this, we added aniline to the reaction mixture of **1g** and **2a**, and the experimental results showed that the only product formed was **3g** (for more details see S38 and S39 in the ESI†). These experiments collectively demonstrate that the reformation of the aniline fragment in this reaction occurs strictly

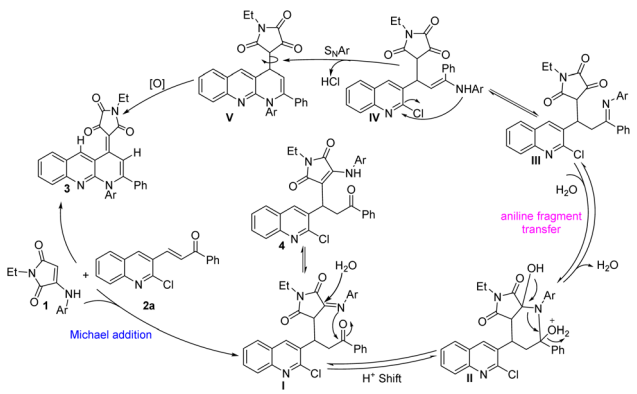


Scheme 3 Control experiments: (a) only compound **1a** treated under standard conditions; (b) compound **2a** directly react with *p*-bromoaniline under the standard conditions; (c) cross-over tested; (d) isolated intermediate; (e) $H_2{}^{18}O$ used.

through an intramolecular mechanism. Next, to further elucidate the specific pathway of the reaction, we conducted experiments using **1a** and **2a** in dichloromethane as the solvent, at room temperature, with Cs_2CO_3 (1.5 equiv.) as the base. From this setup, we successfully isolated intermediate **4a**. Detailed nuclear magnetic resonance (NMR) analysis, including ^{1}H-NMR, ^{13}C-NMR, and two-dimensional NMR spectra, along with high-resolution mass spectrometry (HRMS), confirmed that the reaction initially underwent a Michael addition step, forming intermediate **4a** (for more details see S40–S48 in the ESI†). Subsequently, submitting the obtained **4a** to the standard reaction conditions allowed us to achieve the final target product **3a** (Scheme 3d). This process further validated our understanding of the reaction pathway. The structures of the reactant and the product suggest that one molecule of water might be incorporated into the reaction system. Therefore, the role of water in the reaction was investigated. Interestingly, upon the addition of 3.0 equiv. of $H^{18}O$ to the unproductive anhydrous reaction system, the mixture of ^{18}O-labeled and the normal dihydrobenzo[*b*][1,8]naphthyridines fused with pyrrolidinetrione product **3b** was detected (Scheme 3e). This result demonstrated that a small amount of water participates in the reaction.

Considering that commercial solvent was used directly without drying, we hypothesized a plausible reaction mechanism as shown in Scheme 4. Initially, aminomaleimides **1** and *ortho*-chloroquinolinechalcones **2a** undergo Michael addition, leading to the formation of intermediate **I**, which can undergo tautomerism and transform into **4**. Subsequently, water attacks the imine structure of intermediate **I**, giving the resulting amine which undergoes a synergistic intramolecular addition-transfer-reaction with the carbonyl group of the chalcone, forming six-membered cyclic intermediate **II** by a series of imine/hemiaminal formations and a hydrolysis process occurs to form intermediate **III**, which further tautomerizes and transforms into intermediate **IV**. An intramolecular S_NAr substitution ultimately takes place, resulting in the formation of intermediate **V**, which then undergoes rotation and oxidation to yield the final product **3**.

Among these dihydrobenzo[*b*][1,8]naphthyridine-ylidene-pyrrolidinetriones, we were surprised to find that **3d**, **3g**, **3k**, **3l**, **3n**, **3r**, **3v**, **3ag** and **3ak** showed significant photophysical properties. As part of a program for developing some multifunctional dyes in biological processes,[21–28] we evaluated their photophysical properties in six selected organic solvents with different properties (DMSO, EtOH, toluene, 1,4-dioxane, DCM, and PBS) *via* a multiwell analysis method. The results revealed that these compounds showed different spectral characteristics in different solvents, such as the fluorescence intensity and emission wavelength. As shown in Fig. 2, the monofluoro-substituted dihydrobenzo[*b*][1,8]naphthyridine-ylidene-pyrrolidinetriones (**3d**, **3n**, and **3r**) exhibited near-infrared photophysical properties in PBS (λ_{ex} = 420 nm, λ_{em} = ~744 nm), which provided their potential biological application. As expected, some of the dihydrobenzo[*b*][1,8]naphthyridine-ylidene-pyrrolidinetriones (**3d**, **3n**, **3r**, and **3ag**) were subjected as fluorescent dyes to live human glioma U251 cell imaging, which preliminarily indicated a positive aspect in biocompatibility and low-toxicity (for more details see S79–S84 in the ESI†). Further biological applications will be reported in due course.



Scheme 4 Proposed reaction mechanism.

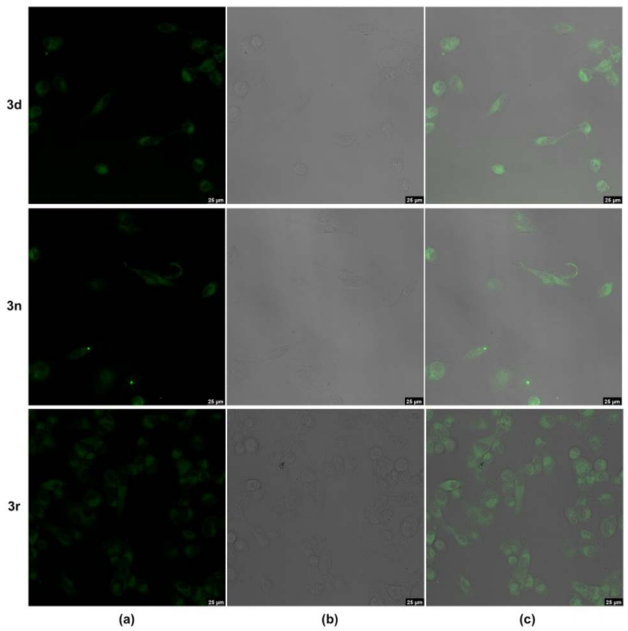


Fig. 2 Live human glioma U251 cell imaging after 4 h of incubation: (a) FITC channel: λ_{ex} = 488 nm; (b) bright field; (c) merged image.

Conclusions

In summary, we have disclosed a promising approach for developing a novel family of dihydrobenzo[*b*][1,8]naphthyridine-ylidene-pyrrolidinetriones through the fusion of aminomaleimides and quinoline chalcones. The reaction mechanism has been meticulously explored, and it proceeds *via* a key intermolecular cascade annulation pathway that involves aniline fragment transfer and S_NAr processes. Remarkably, our discovery indicates that such an annulation approach can be carried out under metal-free conditions, while also demonstrating excellent tolerance towards functional groups and featuring operational simplicity. Moreover, several of the

desired compounds have been validated as alternative fluorescent dyes by means of fluorescence spectrum analysis as well as live human glioma U251 cell imaging. These verifications have preliminarily showcased their potential for biological applications. This work offers valuable guidance for the construction of biologically active functional products, thus making significant contributions to the fields related to both chemical synthesis and biological functionality exploration.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

W. J. and Z. Z. discovered and developed the reactions. Z. Z. and H. L. performed a portion of the synthetic experiments. L. L, D. Y. and Z. C. participated in substrate scope surveys and discussions. L. F. and M. Y. performed the biological experiments. Z.-X. W., M. Y. and W. L. directed the project and wrote the original draft (including the ESI†).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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