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A Telescoping Synthesis of Chimeric Polyheterocycles through a Piperidine-Mediated Multicomponent Reaction

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A new piperidine-catalyzed Groebke–Bienaymé–Blackburn (GBB) multicomponent reaction of 2-aminobenzimidazoles, methyl 2-formylbenzoate, and isocyanides has been explored. A facile and straightforward postmodification leads to isoquinolinone-embedded imidazo[1,2-*a*]benzimidazoles. Insight into a plausible mechanism is discussed and supported by X-ray crystal structure analysis.

Introduction

Polyannulated heteroaromatic systems and their analogues are significant structural motifs that are found in many biologically important natural alkaloids and represent privileged scaffolds in medicinal chemistry.[1] Among them, molecules that have an isoquinolinone or a benzimidazole moiety (see Figure 1) display a wide range of pharmacological activities[2] including poly(ADP-ribose) polymerase-1 (PARP-1) inhibition,[3] topoisomerase I inhibition,[4] nitric oxide synthase (iNOS) inhibition,[5] pan class I phosphatidylinositol 3-kinase (PI3K) inhibition,[6] and prolyl-carboxypeptidase (PrCP) inhibition.[7] The integration of two privileged heterocyclic scaffolds into a new core skeleton to resemble drug-like compounds has a substantial intellectual appeal. It has become of pivotal importance to elaborate potent and selective modulators.[8] However, the biological profile investigation of isoquinolinone-embedded benzimidazole is rare, which might be because of the lack of general methods to access these compounds directly. The growing importance of these heterocycles in therapeutics as well as in the elaboration of green chemistry encouraged the development of environmentally benign methods to prepare these unique compounds.

Among the strategies utilized, multicomponent reactions (MCRs) are increasing in importance for their high efficiency for delivering molecular diversity in one pot.[9] Furthermore, MCRs have attracted wide attention, because complex molecules can be synthesized from inexpensive and easily available starting materials.[9] In addition, the implementation of several transformations in a single operation is highly compatible with the goals of sustainable and green chemistry.[10] An application of these domino processes is the Groebke–Bienaymé–Blackburn (GBB) MCR,[11] which is performed in a multicomponent fashion by the reaction of a heteroaromatic amidine, aldehyde, and isocyanide through an in situ imine formation and subsequent [4+1] cycloaddition. Various premeditated post-MCR strategies have achieved even higher levels of molecular complexity in few chemical manipulations.[12] Such a MCR/postmodification tandem design is of particular interest and could allow

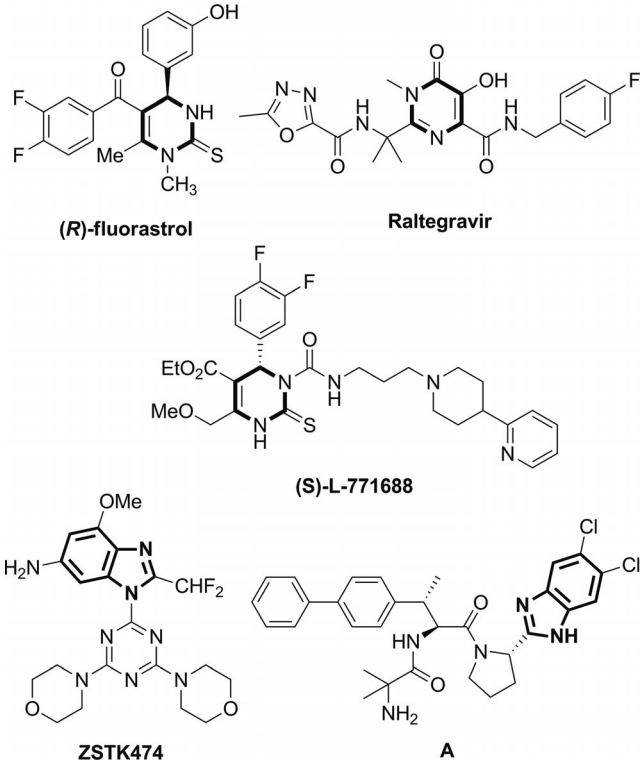

Figure 1. Various types of biologically active heterocycles that contain benzimidazole and dihydropyrimidine frameworks.

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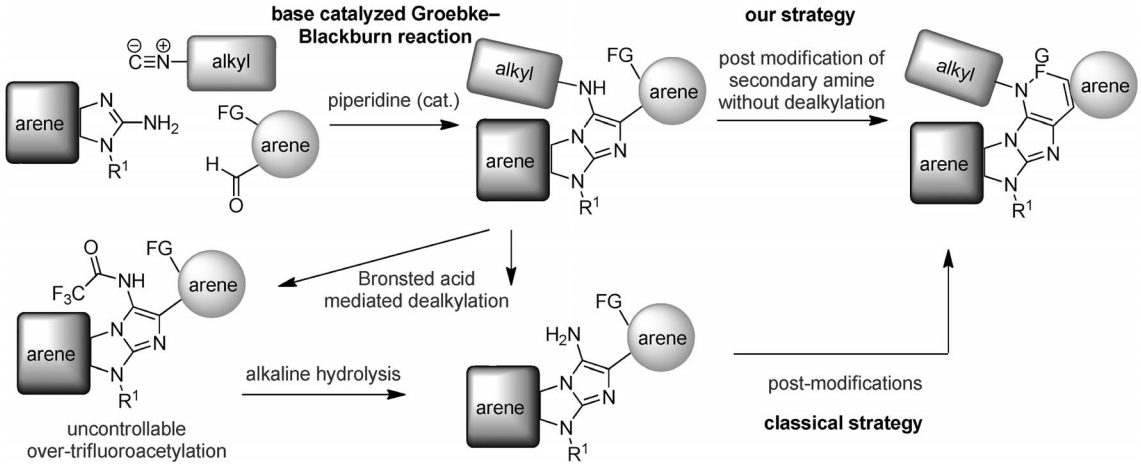


Scheme 1. Piperidine-catalyzed Groebke–Bienaymé–Blackburn reaction and subsequent postmodification.

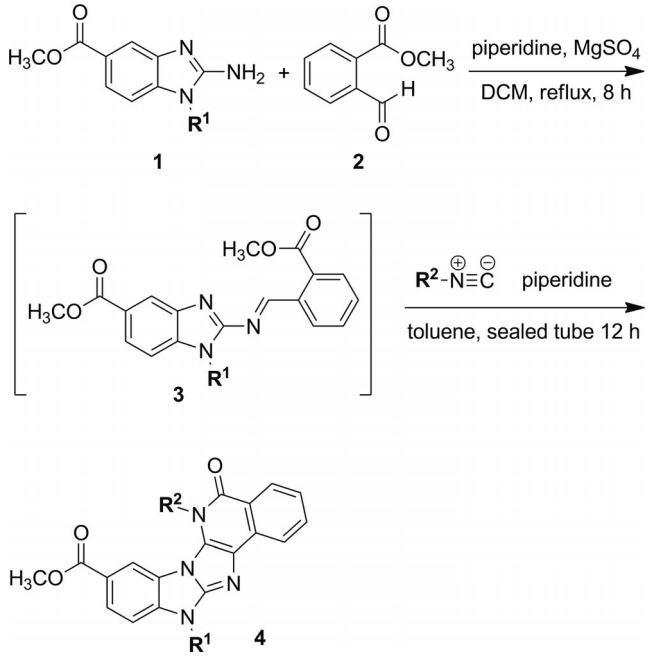
the product of an initial MCR to be the substrate for a subsequent reaction, and thus the complexity of resulting compounds could multiply.

Conventionally, the GBB reaction is usually catalyzed by a Lewis or Brønsted acid, such as *p*-toluenesulfonic acid,[13a] $ZrCl_4$,[12c] $Sc(OTf)_3$,[11b] perchloric acid,[11c] $MgCl_2$,[13b] and TMSCl.[13c] A careful literature survey revealed that the GBB MCR has never been explored under basic conditions. Furthermore, the diversity of products from GBB MCRs is extendable through various postmodifications at the primary amino group in their derivatives. However, this strategy is limited by the use of expensive convertible isonitriles and the redundant dealkylation step that is necessary for consequent functional group transformations. There is no report about a postmodification that does not involve dealkylation. The problem with a post-MCR protonolytic dealkylation from the isocyanide component in the GBB product, which is crucial for postmodification, is the uncontrollable overtrifluoroacetylation of primary amine that may occur during the dealkylation (see Scheme 1, classical strategy).[13a] In this content, we envisioned a facile Brønsted-base-catalyzed GBB reaction and subsequent intramolecular amide formation from the secondary amine without further dealkylation (see Scheme 1, Our strategy).

Results and Discussion

The envisioned tandem multicomponent reaction/postmodification sequence constitutes an efficient route for the assessment of biologically interesting chimeric heterocycles. The diversity in the target products is usually limited by the availability of the requisite isocyanides. The diversity can be extended further by using a convertible isocyanide, such as 1,1,3,4-tetramethylbutyl isocyanide[14] (Walborsky reagent) or *tert*-butyl isocyanide.[15] The removal of the *N*-alkyl group and subsequent derivatization at the primary amine site through a Pd-catalyzed arylation,[13c] acylation, carbamoylation,[15] and reductive alkylation[15] were demonstrated in the literature. A survey of the literature shows that the majority of the strategies for postmodification involve the dealkylation of the derived alkylamine to generate the reactive primary amine. We report herein the development of a new piperidine-catalyzed GBB MCR and postmodification of the resulting isocyanide-based secondary amine without the redundant dealkylation step.

Our initial investigation centered on developing optimized reaction conditions for the tandem GBB reaction and postmodification process. We initiated the screening of catalysts by investigating the reaction of 2-aminobenzimidazoles **1** and methyl 2-formylbenzoate (**2**), which was heated at reflux in the presence of various catalysts (see Scheme 2). A trace amount of the imine was formed when scandium triflate was used as the catalyst, as the reaction was heated to reflux in dichloromethane. Switching to trifluoroacetic acid in dichloromethane at reflux did not lead to any im-

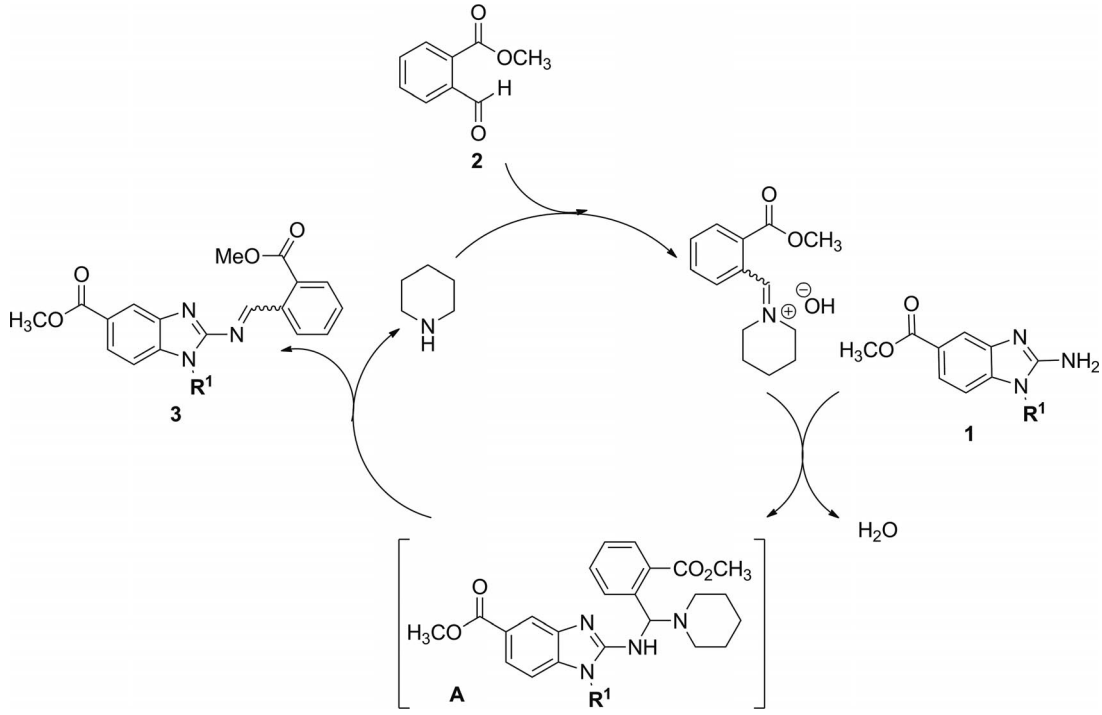


Scheme 2. Formation of the Groebke–Bienaymé–Blackburn primary adducts and intramolecular amide formation.

provement in the reaction outcome. The recent significant achievement of base-catalyzed imination[16] promoted us to explore the imination with piperidine. The imination did proceed smoothly to afford the desired imine **3** in excellent yield after 8 h at reflux in dichloromethane (DCM).

The putative mechanism for the piperidine-catalyzed imination of 2-aminobenzimidazoles **1** with methyl 2-formylbenzoate (**2**) is proposed in Scheme 3. Initially, the 2-formylbenzoate is activated by the addition of the base. Piperidine reacts with the 2-formylbenzoate to form the piperidinium hydroxide salt, which spontaneously reacts with 2-aminobenzimidazoles **1** to afford adduct **A** along with the elimination of water. Finally, the expulsion of the piperidine molecule from adduct **A** furnishes imine **3**.[17]

Next, we investigated a subsequent [4+1] cycloaddition. The Ugi-type multicomponent reaction is the annulation of



Scheme 3. Proposed mechanism for piperidine-catalyzed imination.

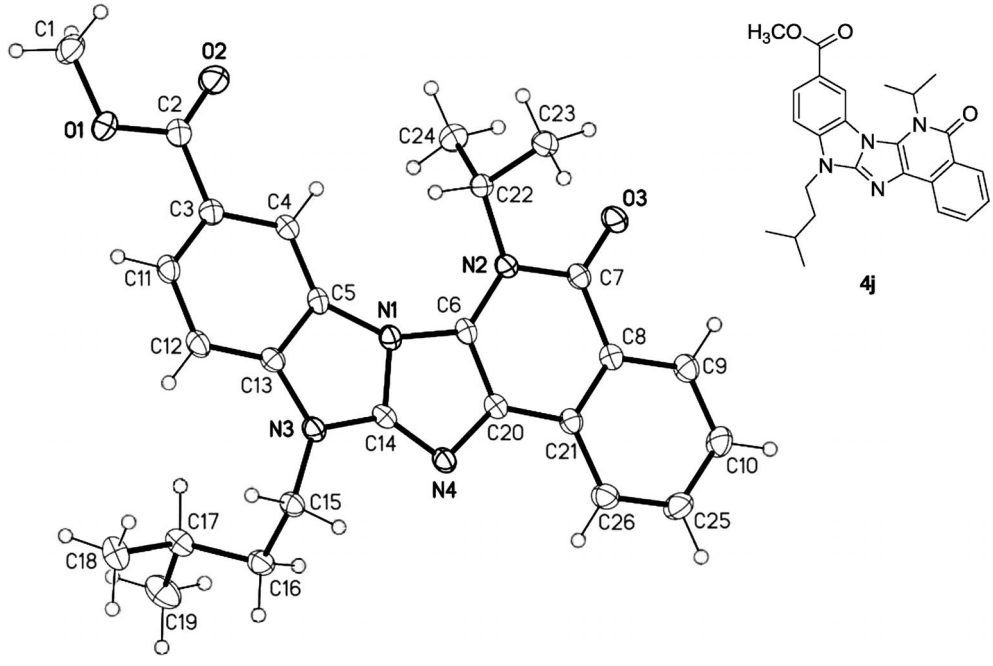
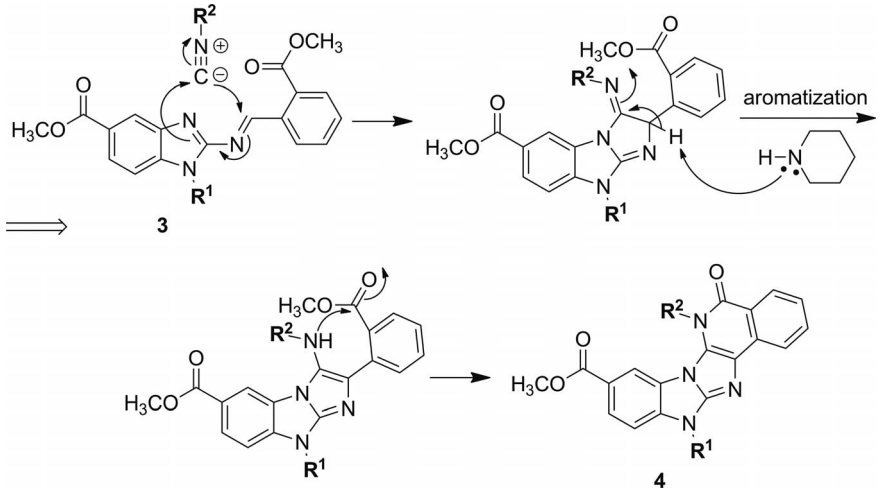


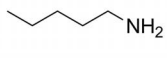
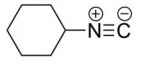
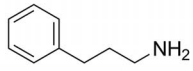
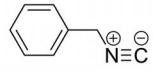
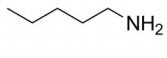
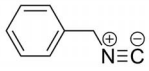
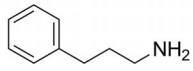
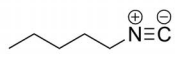
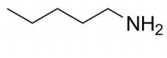
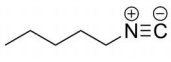
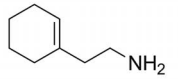
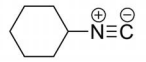
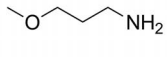
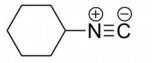
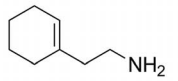
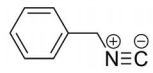
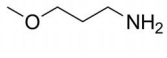
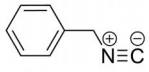
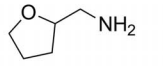
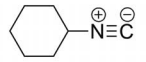
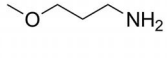
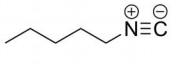
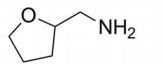
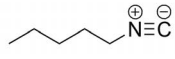
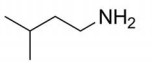
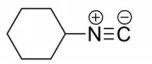
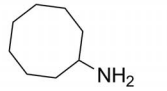
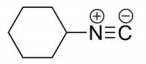
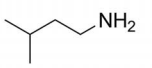
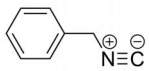
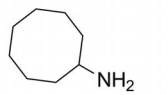
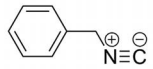
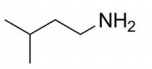
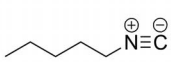
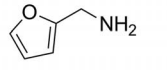
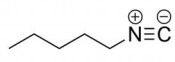
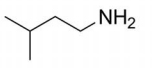
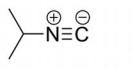
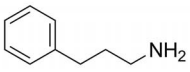
Figure 2. ORTEP diagram of **4j**.

formative Schiff bases and substituted isocyanides. This reaction did not perform under thermal conditions of heating at reflux in toluene. However, adding triethylamine and using a sealed tube afforded the target product in moderate yields. The treatment of a toluene solution of imine **3** with piperidine at 180 °C in sealed tube provided the pentacyclic ring product **4** in higher yields. It is known that without a dealkylation step the postmodification of Ugi-type MCR



Scheme 4. A plausible mechanism for the Groebke–Bienaymé–Blackburn reaction and postmodification.

Table 1. Scope of reaction substrates for tandem Groebke–Bienaymé–Blackburn reaction/postmodification.

Compound	R^1-NH_2	R^2-N≡C	Yield [%]	Compound	R^1-NH_2	R^2-N≡C	Yield [%]
4a			62	**4l**			95
4b			74	**4m**			87
4c			56	**4n**			54
4d			60	**4o**			76
4e			83	**4p**			40
4f			45	**4q**			34
4g			55	**4r**			68
4h			70	**4s**			79
4i			61	**4t**			50
4j			35				
4k			94				

products at the secondary amino group derived from hindered isonitriles is very difficult.[11b,18] In addition to extensive spectroscopic studies, the structure of fused pentacyclic heterocycle **4j** was unequivocally confirmed by single-crystal X-ray structure analysis. The ORTEP diagram of compound **4j** is depicted in Figure 2 (see Supporting Information for crystallographic data). The pentacyclic ring system is aligned in an "S" shape configuration, and the substituent derived from the isocyanide is retained. The present protocol for a one-pot MCR and postmodification is useful for the generation of further molecular diversity through various functionalizations at the secondary amino group of the product. A plausible mechanism for the observed results involves a nonconcerted [4+1] cycloaddition[19] between the Schiff base, which performs as both the electrophile and nucleophile, and the isocyanide, which behaves as a vinylidene carbenoid. A subsequent intramolecular amidation and prototropic shift furnishes the isoquinolinone-embedded imidazo[1,2-*a*]benzimidazole **4** (see Scheme 4). Previous syntheses of these fused polyheterocycles mostly involved multistep sequences,[20] expensive catalysts,[20c–20f,21] inert atmospheres,[20b,20c,20e,21a] anhydrous conditions, lengthy reaction times,[20c,20d] and laborious workups.[20b–20d]

Having achieved inspiring results for the model reaction of a base-catalyzed GBB reaction and in situ amidation, we explored its scope and limitations with various 2-aminobenzimidazoles and isocyanides. As can be seen in Table 1, a variety of 2-aminobenzimidazoles **1** that contain aliphatic, cyclic, and heterocyclic substituents (see Table 1, compounds **4a**–**4t**) successfully delivered the fused pentacyclic ring system in moderate to good yields through the Groebke–Bienaymé–Blackburn MCR and straightforward amide formation (see Scheme 4). A variety of isocyanides were also efficiently applied, though the ones that contain sterically hindered groups generated the product in low yield (see Table 1, Compound **4j**). This reaction was not limited to linear aliphatic isocyanides, and various cyclic, benzylic, and bulky variants were also tested. As a result, they underwent reaction with **3** to afford isoquinolinone-embedded imidazo[1,2-*a*]benzimidazoles **4** smoothly (see Table 1, compounds **4b**, **4j**, and **4k**). The products derived from our strategy retained the substituents from the isocyanides and avoided the complicated dealkylation for the postmodification process. The broad scope and versatility of this cascade process was demonstrated by the introduction of a variety of alkyl, aryl, and heteroaryl substituents at multiple sites in the isoquinolinone-embedded imidazo[1,2-*a*]benzimidazole compounds.

Conclusions

In summary, we have demonstrated a simple and efficient method for the regiospecific synthesis of isoquinolinone-embedded imidazo[1,2-*a*]benzimidazoles through a piperidine-catalyzed Groebke–Bienaymé–Blackburn MCR and postmodification of the resulting product at the secondary amine, which is derived from the isocyanide. This strategy has been achieved without the laborious dealkylation step. This approach to fused polyheterocycles offers a new piperidine-catalyzed isocyanide-based three-component reaction of 2-aminobenzimidazoles **1**, methyl 2-formylbenzoate (**2**), and isocyanides that leads to the construction of a nitrogen-containing polycyclic ring system. Furthermore, this approach provides a straightforward postmodification of the resulting GBB MCR adducts that avoids the redundant dealkylation step. Thus, from a practical point of view, the newly developed protocol is significant proof that the secondary amine derived from the employed isocyanide can be readily functionalized. Significantly, the tandem reaction occurred in a Brønsted-base-catalyzed fashion with high regioselectivity and atom economy. We are first to report the use of a piperidine-catalyzed GBB reaction and subsequent amidation of the resulting secondary amine to access isoquinolinone-embedded imidazo[1,2-*a*]benzimidazoles.

Experimental Section

General Procedures for the Synthesis of 4: Methyl 2-formylbenzoate (**2**, 2.70 mmol, 3.50 equiv.), magnesium sulfate (1.00 g), and piperidine (0.39 mmol, 0.50 equiv.) were added to a solution of 2-aminobenzimidazole **1** (0.20 g, 0.77 mmol) in dichloromethane. The reaction mixture was heated at reflux for 12 h. After completion of reaction, the magnesium sulfate was removed by filtration, and the solvent was removed under reduced pressure to afford the imine **3**. To a solution of the resulting imine **3** in toluene (10 mL) were added isocyanide (2.00 equiv., 15.40 mmol) and piperidine (1.50 equiv., 1.16 mmol), and the mixture was heated in a sealed tube for 12 h. When reaction was complete, methanol (50 mL) was added to precipitate the desired compound. After filtration, the crude product **4** was obtained and then purified by column chromatography (EA/hexane, 1:4) to afford the final compound in 34–95% yields.

Methyl 12-Cyclohexyl-13-oxo-6-pentyl-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, J = 1.2 Hz, 1 H), 8.45 (d, J = 7.8 Hz, 1 H), 8.21 (d, J = 7.8 Hz, 1 H), 8.17 (dd, J = 8.5, 1.2 Hz, 1 H), 7.73 (m, 1 H), 7.45 (m, 1 H), 7.36 (d, J = 8.5 Hz, 1 H), 4.62 (m, 1 H), 4.31 (t, J = 7.3 Hz, 2 H), 4.00 (s, 3 H), 3.23–3.05 (m, 2 H), 2.13–1.96 (m, 6 H), 1.88–1.69 (m, 4 H), 1.51–1.41 (m, 4 H), 0.94 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 162.2, 148.4, 139.6, 133.0, 132.8, 129.0, 126.8, 126.6, 125.7, 125.0, 124.8, 124.1, 122.2, 121.3, 114.5, 109.3, 63.2, 52.6, 43.8, 29.4, 29.3, 28.2, 26.4, 25.5, 22.7, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 2927, 2856, 1716, 1631, 1608 cm^{-1}. MS (EI): m/z = 484 [M]$^+$. HRMS: calcd. for $C_{29}H_{32}N_4O_3$ [M]$^+$ 484.2474; found 484.2482.

Methyl 12-Benzyl-13-oxo-6-pentyl-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, J = 8.0 Hz, 1 H), 8.26 (d, J = 8.0 Hz, 1 H), 8.14 (s, 1 H), 8.01 (dd, J = 8.5, 1.2 Hz, 1 H), 7.73 (dt, J = 7.6, 1.2 Hz, 1 H), 7.43 (dt, J = 7.6, 1.2 Hz, 1 H), 7.38–7.18 (m, 6 H), 6.01 (s, 2 H), 4.26 (t, J = 7.2 Hz, 2 H), 3.89 (s, 3 H), 2.02–1.90 (m, 2 H), 1.51–1.38 (m, 4 H), 0.93 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 161.0, 148.7, 139.3, 136.0, 133.3, 133.2, 129.7, 129.4, 127.9, 126.5, 126.2, 126.1, 125.9, 123.7, 123.5, 122.9, 122.3, 121.5, 114.8, 109.2, 52.4, 49.6, 43.9, 29.4, 28.2, 22.7, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 2925, 2858, 1714, 1633, 1241 cm^{-1}. MS (EI): m/z = 492 [M]$^+$. HRMS: calcd. for $C_{30}H_{28}N_4O_3$ [M]$^+$ 492.2161; found 492.2164.

Methyl 13-Oxo-6,12-dipentyl-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4c): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, J = 8.5 Hz, 1 H), 8.50 (s, 1 H), 8.26 (d, J = 8.0 Hz, 1 H), 8.18 (dd, J = 8.5, 1.1 Hz, 1 H), 7.76 (dt, J = 7.6, 1.3 Hz, 1 H), 7.48 (dt, J = 7.6, 1.1 Hz, 1 H), 7.38 (d, J = 8.5 Hz, 1 H), 4.77 (t, J = 7.9 Hz, 2 H), 4.33 (t, J = 7.3 Hz, 2 H), 4.01 (s, 3 H), 2.13–1.93 (m, 4 H), 1.81–1.69 (m, 2 H), 1.52–1.39 (m, 6 H), 0.97 (t, J = 7.3 Hz, 3 H), 0.94 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 161.0, 148.6, 139.5, 132.9, 132.9, 129.4, 126.7, 126.0, 125.8, 124.1, 123.6, 122.9, 122.4, 121.5, 114.3, 109.4, 52.7, 46.1, 43.9, 30.6, 29.4, 28.7, 28.2, 23.0, 22.7, 14.3, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 2954, 2927, 2862, 1711, 1626, 1242 cm^{-1}. MS (EI): m/z = 472 [M]$^+$. HRMS: calcd. for $C_{28}H_{32}N_4O_3$ [M]$^+$ 472.2474; found 472.2474.

Methyl 12-Cyclohexyl-6-(3-methoxypropyl)-13-oxo-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4d): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (s, 1 H), 8.38 (d, J = 8.1 Hz, 1 H), 8.12 (d, J = 7.6 Hz, 2 H), 7.65 (t, J = 7.2 Hz, 1 H), 7.45–7.34 (m, 2 H), 4.57 (m, 1 H), 4.38 (t, J = 6.5 Hz, 2 H), 3.97 (s, 3 H), 3.40 (t, J = 5.4 Hz, 2 H), 3.33 (s, 3 H), 3.19–3.02 (m, 2 H), 2.31–2.20 (m, 2 H), 2.13–1.98 (m, 4 H), 1.89–1.42 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 162.2, 148.2, 139.9, 132.9, 132.8, 129.0, 126.8, 126.6, 125.7, 125.0, 124.7, 124.1, 122.3, 121.3, 114.4, 109.4, 69.2, 63.2, 59.1, 52.7, 40.6, 29.4, 28.7, 26.4, 25.5 ppm. IR (neat): $\tilde{\nu}$ = 2954, 2868, 1724, 1631, 1608 cm^{-1}. MS (EI): m/z = 487 [M + H]$^+$. HRMS: calcd. for $C_{28}H_{30}N_4O_4$ [M + H]$^+$ 486.2267; found 487.2347.

Methyl 12-Benzyl-6-(3-methoxypropyl)-13-oxo-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, J = 8.0 Hz, 1 H), 8.29 (d, J = 8.0 Hz, 1 H), 8.17 (s, 1 H), 8.03 (d, J = 8.6 Hz, 1 H), 7.78 (t, J = 7.6 Hz, 1 H), 7.48 (t, J = 7.6 Hz, 1 H), 7.39–7.21 (m, 6 H), 5.95 (s, 2 H), 4.42 (t, J = 6.7 Hz, 2 H), 3.90 (s, 3 H), 3.43 (t, J = 5.5 Hz, 2 H), 3.34 (s, 3 H), 2.33–2.23 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 160.8, 148.4, 139.6, 136.0, 133.1, 129.5, 129.4, 129.4, 127.9, 126.5, 126.1, 126.1, 125.7, 123.5, 123.3, 122.7, 122.3, 121.4, 114.7, 109.3, 69.3, 59.1, 52.4, 49.5, 40.6, 28.7 ppm. IR (neat): $\tilde{\nu}$ = 2922, 2871, 1716, 1633, 1608, 1247 cm^{-1}. MS (EI): m/z = 494 [M]$^+$. HRMS: calcd. for $C_{29}H_{26}N_4O_4$ [M]$^+$ 494.1954; found 494.1958.

Methyl 6-(3-Methoxypropyl)-13-oxo-12-pentyl-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4f): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, J = 8.1 Hz, 1 H), 8.38 (s, 1 H), 8.16 (t, J = 8.1 Hz, 2 H), 7.67 (dt, J = 7.6, 1.1 Hz, 1 H), 7.42 (d, J = 8.6 Hz, 1 H), 7.38 (dt, J = 7.6, 1.1 Hz, 1 H), 4.69 (t, J = 8.1 Hz, 2 H), 4.41 (t, J = 6.7 Hz, 2 H), 3.99 (s, 3 H), 3.43 (t, J = 5.6 Hz, 2 H), 3.35 (s, 3 H), 2.33–2.22 (m, 2 H), 2.05–1.92 (m, 2 H), 1.78–1.66 (m, 2 H), 1.52–1.38 (m, 2 H), 0.95 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 160.6, 148.4, 139.8, 132.8, 132.8, 129.3, 126.7, 126.0, 125.7, 123.9, 123.4, 122.8, 122.4, 121.3, 114.2, 109.5, 109.5, 69.2, 59.1, 52.7, 46.1, 40.6, 30.6, 28.7, 23.0, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 2954, 2931, 2868, 1712, 1626, 1242 cm^{-1}. MS (EI): m/z = 474 [M]$^+$. HRMS: calcd. for $C_{27}H_{30}N_4O_4$ [M]$^+$ 474.2267; found 494.2268.

Methyl 12-Cyclohexyl-6-(3-methylbutyl)-13-oxo-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4g): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (s, 1 H), 8.42 (d, J = 8.1 Hz, 1 H), 8.22–8.12 (m, 2 H), 7.71 (dt, J = 7.1, 1.2 Hz, 1 H), 7.42 (dt, J = 7.6, 1.2 Hz, 1 H), 7.33 (d, J = 8.6 Hz, 1 H), 4.60 (m, 1 H), 4.31 (t, J = 7.3 Hz, 2 H), 3.99 (s, 3 H), 3.21–3.05 (m, 2 H), 2.15–2.00 (m, 4 H), 1.93–1.82 (m, 3 H), 1.66–1.46 (m, 4 H), 1.07 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 162.2, 148.4, 139.5, 133.0, 132.9, 129.0, 126.8, 126.6, 125.8, 125.0, 124.9, 124.1, 122.3, 121.4, 114.6, 109.2, 63.2, 52.7, 42.2, 37.1, 29.4, 26.4, 26.3, 25.5, 22.9 ppm. IR (neat): $\tilde{\nu}$ = 2929, 2864, 1716, 1633, 1610, 1242 cm^{-1}. MS (EI): m/z = 484 [M]$^+$. HRMS: calcd. for $C_{29}H_{32}N_4O_3$ [M]$^+$ 484.2474; found 494.2470.

Methyl12-Benzyl-6-(3-methylbutyl)-13-oxo-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4h): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (d, J = 8.0 Hz, 1 H), 8.28 (d, J = 8.0 Hz, 1 H), 8.14 (d, J = 1.0 Hz, 1 H), 8.02 (dd, J = 8.5, 1.2 Hz, 1 H), 7.74 (dt, J = 7.6, 1.2 Hz, 1 H), 7.44 (dt, J = 7.6, 1.0 Hz, 1 H), 7.38–7.28 (m, 4 H), 7.29–7.20 (m, 2 H), 6.00 (s, 2 H), 4.29 (t, J = 7.3 Hz, 1 H), 3.89 (s, 3 H), 1.93–1.82 (m, 3 H), 1.73 (m, 1 H), 1.07 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 161.0, 148.6, 139.2, 133.3, 136.0, 133.2, 129.7, 129.4, 128.0, 126.6, 126.1, 126.1, 125.9, 123.6, 123.5, 122.9, 122.3, 121.6, 114.9, 109.1, 52.5, 49.6, 42.3, 37.0, 26.3, 22.9 ppm. IR (neat): $\tilde{\nu}$ = 2931, 2862, 1716, 1633, 1608, 1242 cm^{-1}. MS (EI): m/z = 493 [M + H]$^+$. HRMS: calcd. for $C_{30}H_{28}N_4O_3$ [M + H]$^+$ 492.2161; found 493.2237.

Methyl 6-(3-Methylbutyl)-13-oxo-12-pentyl-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4i): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39 (d, J = 8.1 Hz, 1 H), 8.34 (s, 1 H), 8.16 (d, J = 8.1 Hz, 1 H), 8.11 (d, J = 8.6 Hz, 1 H), 7.65 (dt, J = 7.5, 1.1 Hz, 1 H), 7.36 (dt, J = 8.1, 1.1 Hz, 1 H), 7.28 (d, J = 8.6 Hz, 1 H), 4.65 (t, J = 7.9 Hz, 2 H), 4.27 (t, J = 7.5 Hz, 2 H), 3.99 (s, 3 H), 2.23–1.90 (m, 2 H), 1.90–1.79 (m, 2 H),1.79–1.61 (m, 3 H), 1.53–1.37 (m, 2 H), 1.06 (d, J = 6.5 Hz, 6 H), 0.95 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 160.6, 148.5, 139.3, 132.8, 132.8, 129.3, 126.7, 125.9, 125.7, 124.0, 123.4, 122.8, 122.3, 121.4, 114.3,109.2, 52.7, 46.1, 42.2, 37.0, 30.6, 28.7, 26.3, 23.0, 22.9, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 2956, 2870, 1711, 1628, 1242 cm^{-1}. MS (EI): m/z = 472 [M]$^+$. HRMS: calcd. for $C_{28}H_{32}N_4O_3$ [M]$^+$ 472.2474; found 472.2476.

Methyl 6-(3-Methylbutyl)-13-oxo-12-(propan-2-yl)-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4j): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43 (s, 1 H), 8.42 (d, J = 7.9 Hz, 1 H), 8.16 (d, J = 7.9 Hz, 1 H), 8.12 (d, J = 7.9 Hz, 1 H), 7.68 (t, J = 7.2 Hz, 1 H), 7.40 (t, J = 7.2 Hz, 1 H), 7.31 (d, J = 8.5 Hz, 1 H), 5.04 (m, 1 H), 4.29 (t, J = 7.4 Hz, 2 H), 3.99 (s, 3 H), 2.01 (d, J = 6.7 Hz, 6 H), 1.90–1.82 (m, 2 H), 1.72 (m, 1 H), 1.06 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 161.9, 148.4, 139.5, 133.0, 132.8, 128.9, 126.7, 126.5, 125.7, 124.8, 123.9, 122.3, 121.4, 121.4, 114.5, 109.3, 55.1, 52.8, 42.2, 37.0, 26.3, 22.9, 20.8 ppm. IR (neat): $\tilde{\nu}$ = 2927, 2858, 1718, 1633, 1608, 1298, 1242 cm^{-1}. MS (EI): m/z = 445 [M + H]$^+$. HRMS: calcd. for $C_{26}H_{28}N_4O_3$ [M]$^+$ 444.2161; found 444.2157.

CCDC-850793 (for **4j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Methyl 12-Cyclohexyl-13-oxo-6-(3-phenylpropyl)-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4k): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43 (d, J = 7.9 Hz, 1 H), 8.42 (s, 1 H), 8.18 (d, J = 7.9 Hz, 1 H), 8.10 (dd, J = 8.5, 1.1 Hz, 1 H), 7.70 (dt, J = 8.1, 1.1 Hz, 1 H), 7.42 (dt, J = 7.6, 1.1 Hz, 1 H), 7.28–7.13 (m, 6 H), 4.55 (m, 1 H), 4.31 (t, J = 7.1 Hz, 2 H), 3.99 (s, 3 H), 3.23–3.06 (m, 2 H), 2.81 (t, J = 7.3 Hz, 2 H), 2.45–2.32 (m, 2 H), 2.19–1.99 (m, 4 H), 1.93–1.42 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 162.2, 148.3, 140.7, 139.4, 132.9, 129.0, 128.8, 128.7, 126.8, 126.6, 126.6, 126.6, 125.8, 125.0, 124.9, 124.1, 122.3, 121.3, 114.5, 109.3, 63.2, 52.7, 43.2, 33.3, 29.4, 29.3, 26.4, 25.5 ppm. IR (neat): $\tilde{\nu}$ = 2929, 2856, 1716, 1631, 1298,

1242 cm^{-1}. MS (EI): m/z = 532 $[M]^+$. HRMS: calcd. for $C_{33}H_{32}N_4O_3$ $[M]^+$ 532.2474; found 532.2477.

Methyl 12-Benzyl-13-oxo-6-(3-phenylpropyl)-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4l): ^1H NMR (300 MHz, $CDCl_3$): δ = 8.48 (d, J = 8.1 Hz, 1 H), 8.28 (d, J = 8.1 Hz, 1 H), 8.11 (s, 1 H), 7.98 (d, J = 8.6 Hz, 1 H), 7.76 (dt, J = 7.6, 1.0 Hz, 1 H), 7.45 (t, J = 7.6 Hz, 1 H), 7.39–7.15 (m, 10 H), 7.10 (d, J = 8.6 Hz, 1 H), 5.99 (s, 2 H), 4.30 (t, J = 7.2 Hz, 2 H), 3.89 (s, 3 H), 2.81 (t, J = 7.4 Hz, 2 H), 2.44–2.32 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 161.0, 152.8, 148.8, 148.6, 140.7, 139.1, 136.0, 133.3, 129.7, 129.5, 128.9, 128.7, 128.0, 126.6, 126.5, 126.1, 126.0, 123.6, 123.5, 122.9, 122.4, 121.5, 114.8, 109.2, 52.5, 49.6, 43.3, 33.3, 29.5 ppm. IR (neat): $\tilde{\nu}$ = 2943, 2848, 1712, 1631, 1608, 1243 cm^{-1}. MS (EI): m/z = 540 $[M]^+$. HRMS: calcd. for $C_{34}H_{28}N_4O_3$ $[M]^+$ 540.2161; found 540.2162.

Methyl 13-Oxo-12-pentyl-6-(3-phenylpropyl)-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4m): ^1H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, J = 7.9 Hz, 1 H), 8.39 (s, 1 H), 8.22 (d, J = 7.9 Hz, 1 H), 8.12 (d, J = 8.6 Hz, 1 H), 7.73 (t, J = 7.6 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 1 H), 7.27–7.15 (m, 6 H), 4.71 (t, J = 8.0 Hz, 2 H), 4.33 (t, J = 7.1 Hz, 2 H), 4.00 (s, 3 H), 2.82 (t, J = 7.4 Hz, 2 H), 2.46–2.33 (m, 2 H), 2.08–1.93 (m, 2 H), 1.79–1.67 (m, 2 H), 1.55–1.39 (m, 2 H), 0.97 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 160.7, 148.6, 140.7, 139.3, 132.9, 132.9, 129.4, 128.8, 128.7, 126.7, 126.6, 126.0, 125.8, 124.1, 123.5, 123.0, 122.4, 121.5, 114.3, 109.4, 52.7, 46.1, 43.3, 33.3, 30.6, 29.4, 28.7, 23.0, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 2916, 2848, 1711, 1643, 1621, 1238 cm^{-1}. MS (EI): m/z = 520 $[M]^+$. HRMS: calcd. for $C_{32}H_{32}N_4O_3$ $[M]^+$ 520.2474; found 520.2471.

Methyl 6-[2-(Cyclohex-1-en-1-yl)ethyl]-12-cyclohexyl-13-oxo-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4n): ^1H NMR (300 MHz, $CDCl_3$): δ = 8.49 (s, 1 H), 8.44 (d, J = 7.8 Hz, 1 H), 8.20 (d, J = 7.8 Hz, 1 H), 8.15 (dd, J = 8.5, 1.2 Hz, 1 H), 7.72 (dt, J = 7.5, 1.0 Hz, 1 H), 7.44 (dt, J = 7.5, 1.0 Hz, 1 H), 7.34 (d, J = 8.5 Hz, 1 H), 5.37 (s, 1 H), 4.61 (m, 1 H), 4.38 (t, J = 7.1 Hz, 2 H), 4.00 (s, 3 H), 3.22–3.05 (m, 2 H), 2.58 (t, J = 7.1 Hz, 2 H), 2.16–2.00 (m, 6 H), 1.92–1.77 (m, 4 H), 1.76–1.67 (m, 2 H), 1.66–1.56 (m, 2 H), 1.55–1.42 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 162.3, 148.4, 139.7, 133.9, 133.1, 132.9, 129.0, 126.8, 126.5, 125.8, 125.0, 125.0, 124.9, 124.2, 122.3, 121.4, 114.5, 109.5, 63.2, 52.7, 42.6, 36.4, 29.4, 28.8, 26.4, 25.6, 15.5, 23.1, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 2927, 2858, 1718, 1633, 1608, 1298, 1242 cm^{-1}. MS (ESI): m/z = 523 $[M + H]^+$. HRMS: calcd. for $C_{32}H_{34}N_4O_3$ $[M]^+$ 522.2631; found 522.2627.

Methyl 12-Benzyl-6-[2-(cyclohex-1-en-1-yl)ethyl]-13-oxo-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4o): ^1H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, J = 7.8 Hz, 1 H), 8.32 (d, J = 7.8 Hz, 1 H), 8.19 (d, J = 1.2 Hz, 1 H), 8.03 (dd, J = 8.5, 1.2 Hz, 1 H), 7.81 (dt, J = 7.5, 1.1 Hz, 1 H), 7.50 (dt, J = 7.5, 1.1 Hz, 1 H), 7.38–7.18 (m, 6 H), 6.05 (s, 2 H), 5.31 (s, 1 H), 4.38 (t, J = 7.2 Hz, 2 H), 3.90 (s, 3 H), 2.58 (t, J = 6.9 Hz, 1 H), 2.14–2.05 (m, 2 H), 1.85–1.74 (m, 2 H), 1.63–1.54 (m, 3 H), 1.50–1.40 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 161.1, 148.7, 139.3, 136.1, 133.8, 133.4, 133.3, 129.7, 129.4, 128.0, 126.5, 126.1, 126.1, 125.9, 125.0, 123.7, 123.5, 123.0, 122.3, 121.6, 114.8, 109.4, 52.4, 49.5, 42.5, 36.3, 28.7, 25.6, 23.1, 22.4 ppm. IR (neat): $\tilde{\nu}$ = 2925, 2850, 1714, 1633, 1279, 1244 cm^{-1}. MS (EI): m/z = 530 $[M]^+$. HRMS: calcd. for $C_{33}H_{30}N_4O_3$ $[M]^+$ 530.2318; found 530.2321.

Methyl 12-Cyclohexyl-13-oxo-6-(tetrahydrofuran-2-ylmethyl)-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3] imidazo[4,5-*c*]isoquinoline-9-carboxylate (4p): ^1H NMR (300 MHz, $CDCl_3$): δ = 8.47 (s, 1 H), 8.44 (d, J = 7.8 Hz, 1 H), 8.18, (d, J = 7.8 Hz, 1 H), 8.15 (dd, J = 8.5, 1.2 Hz, 1 H), 7.72 (dt, J = 7.6, 1.2 Hz, 1 H), 7.57 (d, J = 8.5 Hz, 1 H), 7.44 (dt, J = 7.6, 1.2 Hz, 1 H), 4.67–4.42 (m, 2 H), 4.46 (dd, J = 14.6, 3.5 Hz, 1 H), 4.31 (dd, J = 14.6, 6.8 Hz, 1 H), 3.99 (s, 3 H), 3.95–3.84 (m, 1 H), 3.82–3.70 (m, 1 H), 3.25–3.00 (m, 2 H), 2.27–2.14 (m, 1 H), 2.14–2.01 (m, 4 H), 2.01–1.85 (m, 4 H), 1.79–1.62 (m, 2 H), 1.52 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 162.3, 148.7, 140.3, 133.0, 132.9, 129.1, 126.9, 126.7, 125.8, 125.0, 125.0, 124.1, 122.6, 121.4, 114.4, 110.8, 77.6, 68.9, 63.2, 52.7, 48.0, 29.5, 29.4, 26.4, 26.2, 25.5 ppm. IR (neat): $\tilde{\nu}$ = 2931, 2860, 1714, 1631, 1296, 1242 cm^{-1}. MS (EI): m/z = 498 $[M]^+$. HRMS: calcd. for $C_{29}H_{30}N_4O_4$ $[M]^+$ 498.2267; found 498.2270.

Methyl 13-Oxo-12-pentyl-6-(tetrahydrofuran-2-ylmethyl)-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3] imidazo[4,5-*c*]isoquinoline-9-carboxylate (4q): ^1H NMR (300 MHz, $CDCl_3$): δ = 8.41 (d, J = 8.0 Hz, 1 H), 8.36 (s, 1 H), 8.16 (d, J = 8.0 Hz, 1 H), 8.11 (dd, J = 8.6, 1.0 Hz, 1 H), 7.66 (dt, J = 7.6, 1.0 Hz, 1 H), 7.56 (d, J = 8.6 Hz, 1 H), 7.37 (dt, J = 7.6, 1.0 Hz, 1 H), 4.78–4.60 (m, 2 H), 4.54 (m, 1 H), 4.43 (dd, J = 14.7, 3.5 Hz, 1 H), 4.28 (dd, J = 14.7, 6.9 Hz, 1 H), 3.98 (s, 3 H), 3.88 (m, 1 H), 3.75 (m, 1 H), 2.08–1.81 (m, 6 H), 1.78–1.65 (m, 2 H), 1.52–1.37 (m, 2 H), 0.94 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 160.6, 148.8, 140.1, 132.9, 132.8, 129.3, 126.7, 126.1, 125.7, 124.1, 123.4, 122.9, 122.6, 121.4, 114.1, 110.8, 68.8, 52.6, 48.1, 46.1, 31.3, 30.5, 29.5, 28.6, 26.2, 23.0, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 2954, 2933, 2868, 1716, 1631, 1608, 1286, 1244 cm^{-1}. MS (EI): m/z = 487 $[M + H]^+$. HRMS: calcd. for $C_{28}H_{30}N_4O_4$ $[M + H]^+$ 486.2267; found 487.2347.

Methyl 12-Cyclohexyl-6-cyclooctyl-13-oxo-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*] isoquinoline-9-carboxylate (4r): ^1H NMR (300 MHz, $CDCl_3$): δ = 8.48 (s, 1 H), 8.44 (d, J = 7.6 Hz, 1 H), 8.24 (d, J = 7.6 Hz, 1 H), 8.13 (dd, J = 8.6, 1.2 Hz, 1 H), 7.74 (dt, J = 7.6, 1.2 Hz, 1 H), 7.48–7.40 (m, 2 H), 4.80 (m, 1 H), 4.60 (m, 1 H), 4.00 (s, 3 H), 3.22–3.04 (m, 2 H), 2.68–2.53 (m, 2 H), 2.17–1.42 (m, 20 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 162.4, 148.0, 138.6, 133.1, 132.9, 129.0, 126.6, 126.3, 125.8, 125.1, 125.0, 124.2, 121.9, 121.6, 114.5, 110.3, 63.2, 57.1, 52.7, 32.1, 29.4, 26.8, 26.4, 26.3, 25.6, 25.5 ppm. IR (neat): $\tilde{\nu}$ = 2924, 2856, 1716, 1625, 1298, 1242 cm^{-1}. MS (EI): m/z = 524 $[M + H]^+$. HRMS: calcd. for $C_{32}H_{36}N_4O_3$ $[M]^+$ 524.2787; found 524.2789.

Methyl 12-Benzyl-6-cyclooctyl-13-oxo-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*] isoquinoline-9-carboxylate (4s): ^1H NMR (300 MHz, $CDCl_3$): δ = 8.50 (d, J = 8.0 Hz, 1 H), 8.35 (d, J = 8.0 Hz, 1 H), 8.16 (s, 1 H), 7.99 (d, J = 8.6 Hz, 1 H), 7.78 (t, J = 7.9 Hz, 1 H), 7.46 (t, J = 7.9 Hz, 1 H), 7.42–7.3 (m, 6 H), 6.00 (s, 2 H), 4.79 (m, 1 H), 3.87 (s, 3 H), 2.69–2.52 (m, 2 H), 2.18–1.65 (m, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 161.1, 148.2, 138.3, 136.1, 133.5, 133.2, 129.7, 129.4, 127.9, 126.2, 126.1, 126.0, 125.9, 123.8, 123.6, 122.9, 121.9, 121.8, 114.8, 110.2, 57.1, 52.4, 49.6, 32.1, 26.8, 26.4, 25.5 ppm. IR (neat): $\tilde{\nu}$ = 2924, 2856, 1718, 1628, 1604, 1274, 1246 cm^{-1}. MS (ESI): m/z = 533 $[M + H]^+$. HRMS: calcd. for $C_{33}H_{32}N_4O_3$ $[M + H]^+$ 532.2474; found 533.2527.

Methyl 6-(Furan-2-ylmethyl)-13-oxo-12-pentyl-12,13-dihydro-6*H*-benzimidazo[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (4t): ^1H NMR (300 MHz, $CDCl_3$): δ = 8.44 (d, J = 8.0 Hz, 1 H), 8.40 (s, 1 H), 8.21 (d, J = 8.0 Hz, 1 H), 8.14 (dd, J = 8.5, 1.2 Hz, 1 H), 7.69 (dt, J = 7.6, 1.2 Hz, 1 H), 7.48 (d, J = 8.5 Hz, 1 H), 7.44–7.35 (m, 2 H), 6.56 (d, J = 3.2 Hz, 1 H), 6.36 (dd, J = 3.2, 1.9 Hz, 1 H), 5.47 (s, 2 H), 4.70 (t, J = 8.1 Hz, 2 H), 4.00 (s, 3 H), 2.05–1.92 (m, 2 H), 1.78–1.65 (m, 2 H), 1.52–1.38 (m, 2 H), 0.95 (t, J = 7.2 Hz,

3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 160.7, 148.4, 148.2, 143.5, 139.1, 132.9, 132.9, 129.4, 126.8, 126.2, 125.8, 124.3, 123.5, 123.0, 123.0, 121.5, 114.3, 111.1, 110.1, 110.1, 52.7, 46.1, 40.2, 30.6, 28.7, 23.0, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 2947, 2860, 1709, 1631, 1281, 1242 cm^{-1}. MS (EI): *m/z* = 482 $[M]^+$. HRMS: calcd. for $C_{28}H_{26}N_4O_4$ $[M]^+$ 482.1954; found 482.1951.

Supporting Information (see footnote on the first page of this article): The ^1H and ^{13}C NMR, IR, and HRMS for compounds **4**.

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