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Copper Salts/TBAB-Catalyzed Chemo- and Regioselective β-C(sp^3)−H Acyloxylation of Aliphatic Amides

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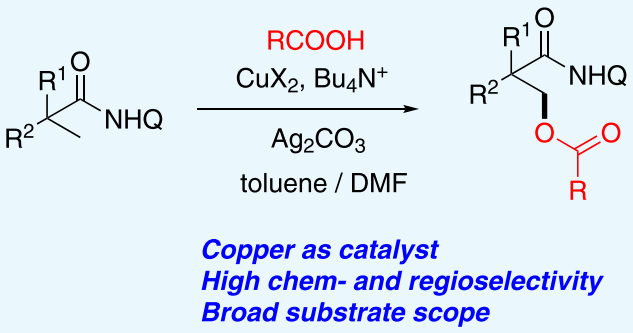
Supporting Information

ABSTRACT: An efficient Cu(II)-catalyzed and tetrabutylammonium bromide (TBAB)-promoted strategy for highly regioselective and chemoselective C(sp^3)−H acyloxylation of aliphatic amides is described. Acyloxylation occurs selectively at the β position with a broad substrate scope of carboxylic acids and aliphatic amides and good functional group compatibility. Notably, the competing reaction of intramolecular dehydrogenative amidation and intermolecular acyloxylation could be efficiently controlled by the amount of copper salt and the addition of TBAB. The intramolecular dehydrogenative amidation product was obtained in high yield when the amount of copper salts was increased. However, when TBAB was used as an additive, a preference for acyloxylation over intramolecular amidation was observed and the acyloxylated products were obtained in good yield. Preliminary studies were carried out to gain insights into the mechanism.



INTRODUCTION

Transition metal-catalyzed C(sp^2)−H functionalization via a directing group auxiliary has been extensively developed in the past decade.[1] In contrast to the direct functionalization of the C(sp^2)−H bond, direct functionalization of an unactivated C(sp^3)−H bond has been less researched because of the high bond dissociation energy of the C(sp^3)−H bond and lack of π electrons that can readily interact with transition metals.[2] Directing group-assisted transition metal-catalyzed C(sp^3)−H functionalization has emerged as a powerful method to overcome the tremendous challenges.[3] Recently, various precious metal-catalyzed C(sp^3)−H activations have been extensively explored with the assistance of a monodentate or bidentate directing group.[4] Although significant advances have been made with precious metal catalysts, the development of low-cost and environmentally benign first-row transition metals such as Fe, Co, Ni, and Cu is still in high demand.[5]

8-Aminoquinoline developed by Daugulis' group has been proven to be a powerful bidentate auxiliary in transition metal-catalyzed direct C−H bond activation,[3a,b,6] and it has been used in stereoselective as well as regioselective C−H functionalization reactions.[7] Palladium-catalyzed and nickel-catalyzed C(sp^3)−H functionalization by using an 8-aminoquinoline bidentate auxiliary has been applied extensively,[4c,5b,8,9] whereas the chelation-assisted examples involving copper catalysts are rare. Recently, Kanai, You, and Ge have demonstrated the copper-catalyzed intramolecular amidation of C(sp^3)−H bonds,[10] and the reaction provides a protocol for functionalization at β-C(sp^3)−H bonds in a highly regioselective manner. Ge also reported copper-promoted cross-dehydrogenative coupling of aliphatic amides and polyfluoroarenes by using an 8-aminoquinoline as the directing group.[11] Intermolecular amination of β-C(sp^3)−H bonds was reported by Qin[5f] and Yang[12] by using simple alkylamines as the amino source.

The development of C−O bond formation reactions has greatly accelerated in recent years following landmark reports on Pd-catalyzed C(sp^3)−H acetoxylation reactions by the Sanford[13] and Yu[14] laboratories using different organic oxidants.[15,16] In 2013, Roane and Daugulis reported the first copper-catalyzed 8-aminoquinoline-directed C−H to C−O transformation.[17] Recently, the copper-promoted direct acetoxylation and acyloxylation of β-C(sp^3)−H bonds with the assistance of an 8-aminoquinoline bidentate directing group have also been reported.[18] However, a large amount of oxidants, the limited substrate scope, and harsh reaction conditions have prevented the synthetic applications. Continuing our research efforts in the development of novel copper-catalyzed C−H acyloxylation,[19] herein we report a highly efficient method for copper-catalyzed and Bu_4N^+-promoted regioselective and chemoselective β-C(sp^3)−H acyloxylation of aliphatic amides with carboxylic acids including aromatic acids, cinnamic acids, heterocyclic carboxylic acids, and aliphatic acids (Scheme 1b).

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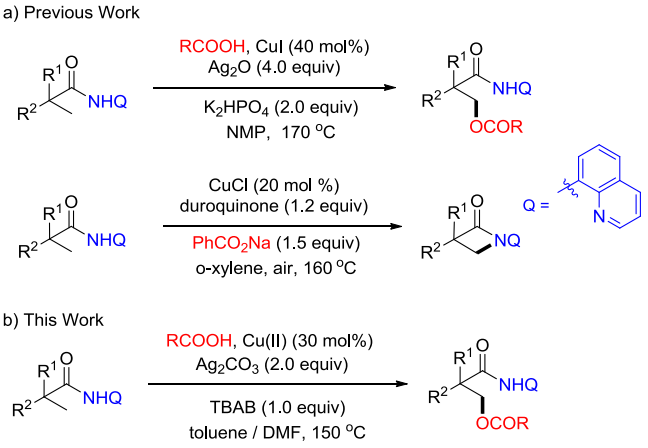
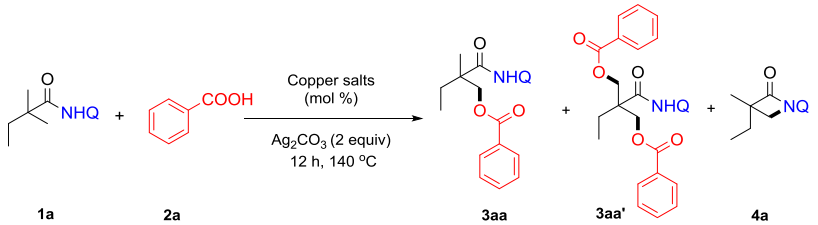
Scheme 1. (a,b) Copper-Catalyzed β-C(sp^3)−H Acyloxylation and Amidation of Aliphatic Amides



RESULTS AND DISCUSSION

On the basis of our previous direct acyloxylation of C(sp^2)−H bonds (Scheme 1), we began our study by conducting β-C(sp^3)−H acyloxylation of 2,2-dimethyl-*N*-(quinolin-8-yl)-butanamide substrate **1a** with benzoic acid in the presence of CuBr (30 mol %) and Ag_2CO_3 (2 equiv) in toluene/dimethylformamide (DMF) at 140 °C under air for 12 h. We were pleased to observe that acyloxylation of β-C(sp^3)−H bonds afforded a mixture of monoacyloxylated products **3aa** and diacyloxylated products **3aa′** in 1:1 ratio with a combined yield of 41% and the intramolecular amidated product **4a** in 18% yield, and the acyloxylation of γ-methyl group C−H bonds with benzoic acid was not observed. Interestingly, the yield of the intramolecular amidated product was increased with an increase in the amount of CuBr (Table 1, entries 1−3) and afforded **4a** in 80% yield in the absence of benzoic acid by using stoichiometric copper salts (entry 4). To our surprise, employing phase-transfer catalysts such as tetrabutylammonium bromide (TBAB) as an additive led to a dramatic improvement in the yield of the acyloxylated product **3a** and absolutely inhibited the intramolecular amidated reaction (entry 5). Encouraged by this result, a series of copper salts such as CuI, $CuBr_2$, $CuCl_2{\cdot}2H_2O$, $Cu(OAc)_2{\cdot}H_2O$, $Cu(OCOCF_3)_2$, and $CuSO_4{\cdot}5H_2O$ were then screened, which showed that the reaction could be catalyzed by either a copper(II) or copper(I) and $Cu(OCOCF_3)_2$ proved to be the best catalyst (entries 6−11). The absence of a copper catalyst or an oxidant fails to generate the desired products, which indicated that the copper catalyst and oxidant played indispensable roles in this reaction (entries 12 and 13). Various oxidants, such as AgOAc, $AgOCOCF_3$, and $K_2S_2O_8$,

Table 1. Optimization of Reaction Conditions[a]



			yield (%)[b]		
entry	catalyst (mol %)	additive (equiv)	**3aa**	**3aa′**	**4a**
1	CuBr (30)		22	19	18
2	CuBr (50)		13	25	38
3	CuBr (100)		trace	34	58
4[c]	CuBr (100)				80
5	CuBr (30)	TBAB	27	33	Trace
6	CuI (30)	TBAB	25	14	Trace
7	$CuBr_2$ (30)	TBAB	31	12	Trace
8	$CuCl_2{\cdot}2H_2O$ (30)	TBAB	28	35	Trace
9	$Cu(OAc)_2{\cdot}H_2O$ (30)	TBAB	23	27	Trace
10	$Cu(OCOCF_3)_2$ (30)	TBAB	28	40	Trace
11	$CuSO_4{\cdot}5H_2O$ (30)	TBAB	30	36	Trace
12		TBAB			
13[d]	$Cu(OCOCF_3)_2$ (30)	TBAB			
14[e]	$Cu(OCOCF_3)_2$ (30)	TBAB	24	trace	Trace
15[f]	$Cu(OCOCF_3)_2$ (30)	TBAB	17	trace	Trace
16[g]	$Cu(OCOCF_3)_2$ (30)	TBAB			
17	$Cu(OCOCF_3)_2$ (30)	TBAI	27	40	trace
18	$Cu(OCOCF_3)_2$ (30)	TBAC	26	43	trace
19[h]	$Cu(OCOCF_3)_2$ (30)	TBAB	31	21	trace
20[i]	$Cu(OCOCF_3)_2$ (30)	TBAB	26	46	trace
21[i,j]	$Cu(OCOCF_3)_2$ (30)	TBAB	31	40	trace

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Ag_2CO_3 (2 equiv), additive (1 equiv), solvent (2 mL): toluene/DMF (1:1), in air. [b]Isolated yield. [c]Without **2a**, 8 h. [d]Without Ag_2CO_3. [e]AgOAc (2 equiv). [f]$AgOCOCF_3$ (2 equiv). [g]$K_2S_2O_8$ (2 equiv). [h]130 °C. [i]150 °C. [j]Under Ar atmosphere.

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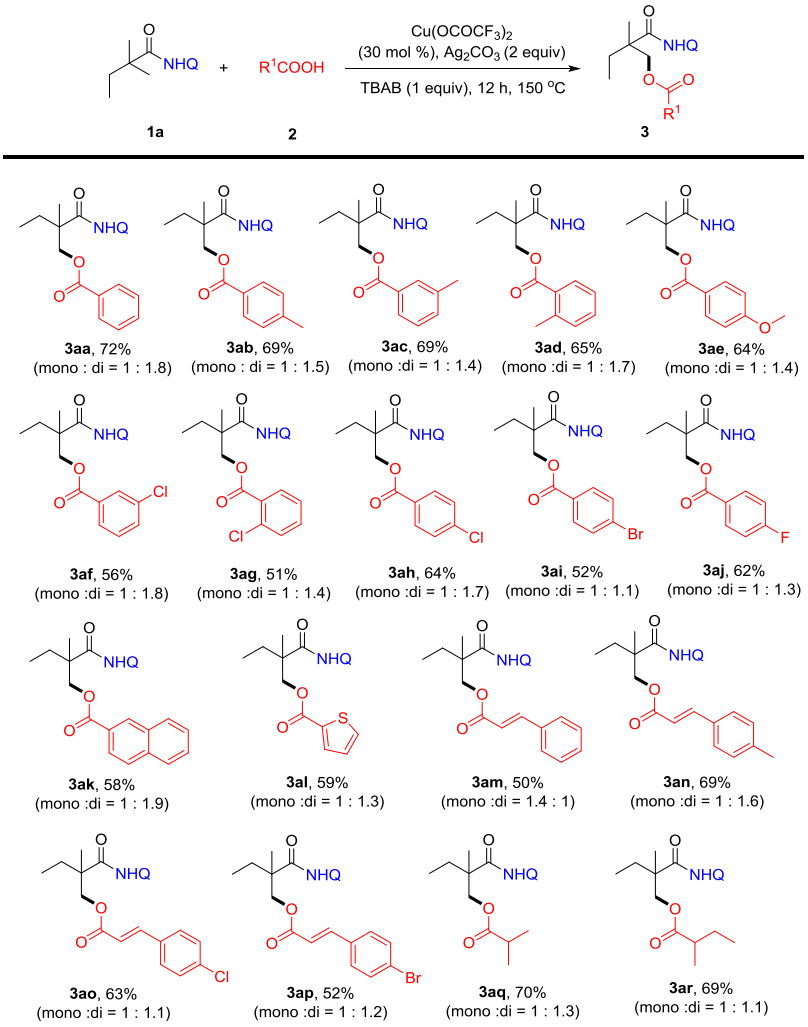
Table 2. Acyloxylation of Aliphatic Amides with Acids 2[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $Cu(OCOCF_3)_2$ (30 mol %), Ag_2CO_3 (2 equiv), TBAB (1 equiv), solvent (2 mL): toluene/DMF (1:1), in air.

were tested, and Ag_2CO_3 was determined to be especially effective (entries 14−16). A brief survey of reaction media showed that the reaction in toluene/DMF gave the best result, whereas toluene, DMF, and chlorobenzene only led to low yields (see the Supporting Information for more details). Instead of TBAB, the use of some other additives such as tetrabutylammonium iodide (TBAI) or tetrabutylammonium chloride (TBAC) had no obvious influence on the reaction efficiency (entries 17 and 18, see the Supporting Information for more details). When the reaction was performed at 130 and 150 °C, **3a** was isolated in 52 and 72% yield (entries 19 and 20). Further investigation showed that a similar yield could be obtained under Ar atmosphere (entry 21). Herein, we chose entry 20 as the optimized reaction conditions.

With an optimized catalytic system in hand, we investigated the scope of this acyloxylation reaction by using a series of acids. As shown in Table 2, substitution patterns and electronic properties of the phenyl ring of the benzoic acids and cinnamic acids had no obvious influence on the reaction efficiency (**3aa**−**3aj**, **3am**−**3ap**). A range of benzoic acids bearing electron-donating and electron-withdrawing groups at either the 2-, 3-, or 4-position of the aromatic ring underwent the desired reaction smoothly to give the corresponding products in moderate yield (**3ab**−**3ad**, **3af**−**3ah**). Notably, 2-naphthoic acid, thiophene-2-carboxylic acid, and aliphatic acids were also well tolerated and gave the desired product in moderate yield (**3ak**, **3al**, **3aq**, and **3ar**).

To further explore the generality of this protocol, we investigated the scope of aliphatic amides with benzoic acid. Although $Cu(OCOCF_3)_2$ exhibited considerable reactivity with $CuSO_4·5H_2O$ (Table 1), its applicability to other aliphatic amides was unsatisfactory. Therefore, we choose $CuSO_4·5H_2O$ as the catalyst to investigate the substrate scope (Table 3). A high selectivity of the *β*-methyl groups over *γ*- or *δ*-methyl was observed and methylene or benzene C−H bonds were not acyloxylated. Interestingly, the acyloxylation of aliphatic amide **1b** showed significant electronic effects. Benzoic acid with an electron-donating group exhibited excellent reactivity rather than an electron-withdrawing substituent on the para-position of the aryl ring (**3bb** and **3bc**). We were pleased to found that a wide variety of aliphatic amides bearing both linear (**3ba**−**3ja**) and cyclic chains (**3ka** and **3la**) were compatible with this protocol. However, the acyloxylation of 1-methyl-*N*-(quinolin-8-yl)cyclohexane-1-carboxamide **1o** was not observed because of the steric effect, and the spiro-*β*-lactam **4o** was obtained.

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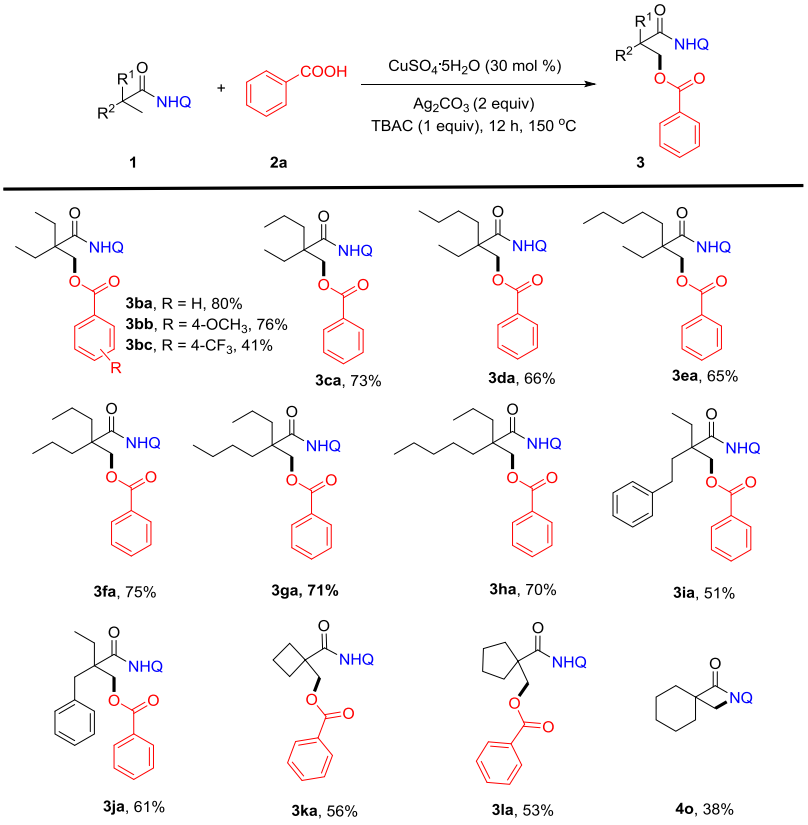
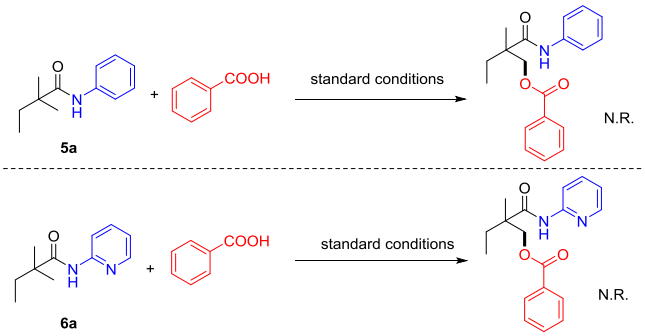
Table 3. Substrate Scope of Aliphatic Amides[a]



[a]**1** (0.1 mmol), **2a** (0.2 mmol), $CuSO_4·5H_2O$ (30 mol %), Ag_2CO_3 (2 equiv), TBAC (1 equiv), solvent (2 mL): toluene/DMF (1:1), 150 °C, in air.

Then, we investigated the effects of the directing group on the efficiency of the acyloxylation reaction (Scheme 2). No

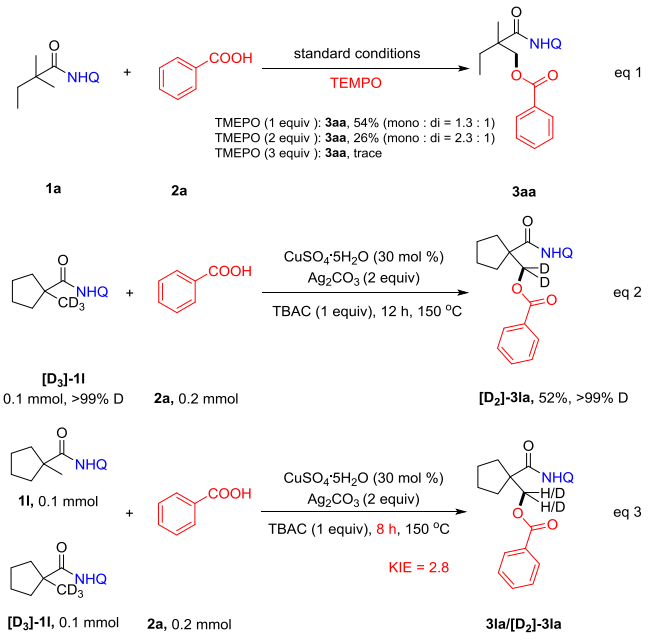
Scheme 2. Effects of the Directing Group



reaction occurred when amide **5a** or **6a** was used as the substrate, indicating that the presence of a bidentate directing group is crucial for the C−H bond activation and the formation of a five-membered ring intermediate is favorable in cyclometalation step.

To gain insights into the reaction pathway of copper-catalyzed acyloxylation, a series of additional experiments were carried out as shown in Scheme 3. The addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in the control experiment essentially suppressed the reaction, and only a trace amount of the desired product **3aa** was detected when the amount of TEMPO was increased to 3 equiv (Scheme 3, eq 1). These results suggested that the reaction probably involves a

Scheme 3. Radical and Deuterium-Labeling Experiments



radical pathway. The deuterium-labeling experiments were carried out to further explore the reaction mechanism. It was noticed that there was no apparent H/D exchange in this process and the result suggested the C−H bond metalation step to be not reversible in nature (Scheme 3, eq 2). A kinetic isotopic effect (KIE) experiment was also conducted and the

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KIE value was calculated to be 2.8, indicating that the C−H cleavage was probably involved in the rate-determining step of the reaction (Scheme 3, eq 3). However, the role of TBAB is still not clear; the exact reaction mechanism remains uncertain at present.

CONCLUSIONS

In conclusion, we have demonstrated the copper(II)/Bu_4N^+-catalyzed β-C(sp^3)−H acyloxylation of aliphatic amides. A high regioselectivity of the β-methyl groups over γ- or δ-methyl and methylene was observed. This method by using the catalytic amount of copper and Bu_4N^+ could effectively reduce the procedure of C(sp^3)−N bond formation. This protocol exhibits a wide substrate scope of carboxylic acids and aliphatic amides and good functional group compatibility, providing an operationally simple approach for the formation of C(sp^3)−O bond and C(sp^3)−N bond.

EXPERIMENTAL SECTION

General Information. All starting materials and reagents were commercially available and used directly without further purification. All aliphatic amides were prepared according to the literature procedures.[12,20] All known products gave satisfactory analytical data by NMR spectra, corresponding to the reported literature values. In addition, unknown compounds were confirmed by high-resolution mass spectra (HRMS). Melting points were determined using X-4 micro melting point apparatus and are uncorrected. NMR spectra were recorded at room temperature on a Bruker Avance-300, Bruker Avance-400, and Bruker Avance-500 at 300, 400, and 500 MHz with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ relative to TMS; the coupling constants J are given in hertz. HRMS were recorded on Agilent 6200 LC/MS TOF using electrospray ionization (ESI) in positive mode.

General Procedure for Copper-Catalyzed C(sp^3)−H Acyloxylation. To a 10 mL reaction tube were added amide **1a** (24.2 mg, 0.1 mmol), benzoic acid (24.4 mg, 0.2 mmol), $Cu(OCOCF_3)_2$ (8.7 mg, 30 mol %) or $CuSO_4{\cdot}5H_2O$ (7.5 mg, 30 mol %), Ag_2CO_3 (55.1 mg, 2 equiv), TBAB (32.2 mg, 1 equiv) or TBAC (27.8 mg, 1 equiv), and toluene/DMF (1 mL/1 mL) in air. The mixture was stirred at 150 °C for 12 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate, and quenched with saturated sodium chloride. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over Na_2SO_4. After concentration, the resulting residue was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate (20:1) as the eluent to afford the product.

Characterization Data of Products. *2-Methyl-2-(quinolin-8-ylcarbamoyl)butylbenzoate* ***3aa***.[13] Compound **3aa** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3aa** as a yellow liquid (9.4 mg, 26%). (R_f = 0.57, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.50 (s, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.08 (d, J = 7.5 Hz, 2H), 7.65−7.46 (m, 3H), 7.41 (dd, J = 8.1, 4.2 Hz, 1H), 7.37−7.27 (m, 2H), 4.65−4.54 (m, 1H), 4.53−4.43 (m, 1H), 2.16−1.95 (m, 1H), 1.92−1.74 (m, 1H), 1.53 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 166.3, 148.2, 138.7, 136.3, 134.5, 133.0, 129.9, 129.8, 128.3, 127.9, 127.4, 121.6, 116.6, 69.8, 47.7, 29.4, 19.5, 8.7. HRMS (ESI): calcd for $C_{22}H_{23}N_2O_3$ $[M + H]^+$, 363.1708; found, 363.1701.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diyldibenzoate ***3aa′***. Compound **3aa′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3aa′** as a white solid (22.2 mg, 46%). mp = 142.5−143.7 °C. (R_f = 0.42, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.69 (s, 1H), 8.82 (d, J = 6.3 Hz, 1H), 8.29 (d, J = 3.0 Hz, 1H), 8.19−7.99 (m, 5H), 7.67−7.46 (m, 4H), 7.45−7.28 (m, 5H), 4.82 (s, 4H), 2.14 (q, J = 7.2 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 166.2, 148.1, 138.6, 136.3, 134.3, 133.2, 129.8, 129.6, 128.4, 127.9, 127.4, 121.8, 121.6, 116.9, 65.6, 51.0, 25.3, 8.6. HRMS (ESI): calcd for $C_{29}H_{27}N_2O_5$ $[M + H]^+$, 483.1920; found, 483.1919.

3-Ethyl-3-methyl-1-(quinolin-8-yl)azetidin-2-one ***4a***.[11] Compound **4a** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **4a** as a yellow liquid (19.2 mg, 80%). (R_f = 0.61, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (d, J = 2.1 Hz, 1H), 8.49 (dd, J = 5.4, 3.0 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 7.59−7.43 (m, 2H), 7.38 (dd, J = 8.1, 3.9 Hz, 1H), 4.48−4.34 (m, 1H), 4.32−4.18 (m, 1H), 1.91−1.73 (m, 2H), 1.44 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 148.4, 135.9, 135.1, 129.0, 126.7, 122.7, 121.2, 119.4, 58.1, 55.8, 27.8, 19.2, 9.1. HRMS (ESI): calcd for $C_{15}H_{17}N_2O$ $[M + H]^+$, 241.1341; found, 241.1340.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl-4-methylbenzoate ***3ab***. Compound **3ab** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ab** as a yellow liquid (10.9 mg, 29%). (R_f = 0.50, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.50 (s, 1H), 8.83 (d, J = 5.4 Hz, 1H), 8.65−8.52 (m, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.61−7.47 (m, 2H), 7.45−7.34 (m, 1H), 7.12 (d, J = 7.8 Hz, 2H), 4.64−4.53 (m, 1H), 4.52−4.14 (m, 1H), 2.36 (s, 3H), 2.13−1.96 (m, 1H), 1.91−1.72 (m, 1H), 1.52 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 165.4, 147.1, 142.6, 137.6, 135.3, 133.5, 128.8, 128.0, 126.9, 126.4, 126.2, 120.5, 115.7, 68.6, 46.7, 28.4, 20.6, 18.5, 7.7. HRMS (ESI): calcd for $C_{23}H_{25}N_2O_3$ $[M + H]^+$, 377.1865; found, 377.1857.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(4-methylbenzoate) ***3ab′***. Compound **3ab′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ab′** as a white solid (20.4 mg, 40%). mp = 73.8−75.9 °C. (R_f = 0.38, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.67 (s, 1H), 8.82 (dd, J = 6.3, 1.5 Hz, 1H), 8.40−8.30 (m, 1H), 8.13 (d, J = 7.5 Hz, 1H), 7.96 (d, J = 7.8 Hz, 4H), 7.61−7.45 (m, 2H), 7.43−7.31 (m, 1H), 7.16 (d, J = 7.5 Hz, 4H), 4.80 (s, 4H), 2.38 (s, 6H), 2.12 (q, J = 7.2 Hz, 2H), 1.10 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 166.3, 148.1, 143.9, 138.6, 136.3, 134.3, 129.9, 129.1, 127.9, 127.4, 126.9, 121.8, 121.6, 116.9, 65.4, 51.1, 25.3, 21.7, 8.6. HRMS (ESI): calcd for $C_{31}H_{31}N_2O_5$ $[M + H]^+$, 511.2233; found, 511.2227.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl-3-methylbenzoate ***3ac***. Compound **3ac** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ac** as a yellow liquid (10.9 mg, 29%). (R_f = 0.37, petroleum ether/ethyl

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acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.51 (s, 1H), 8.83 (dd, J = 6.6, 1.2 Hz, 1H), 8.61−8.52 (m, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.82 (s, 1H), 7.60−7.46 (m, 2H), 7.45−7.36 (m, 1H), 7.35−7.27 (m, 1H), 7.24−7.15 (m, 1H), 4.62−4.52 (m, 1H), 4.51−4.42 (m, 1H), 2.21 (s, 3H), 2.13−1.97 (m, 1H), 1.90−1.75 (m, 1H), 1.53 (s, 3H), 1.04 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 166.5, 148.2, 138.8, 138.0, 136.3, 134.5, 133.8, 130.3, 129.9, 128.2, 127.9, 127.4, 126.9, 121.5, 116.5, 69.8, 47.8, 29.3, 21.1, 19.5, 8.7. HRMS (ESI): calcd for $C_{23}H_{25}N_2O_3$ $[M + H]^+$, 377.1865; found, 377.1858.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(3-methylbenzoate) ***3ac′***. Compound **3ac′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ac′** as a white solid (20.4 mg, 40%). mp = 73.6−74.4 °C. (R_f = 0.28, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.72 (s, 1H), 8.84 (d, J = 6.5 Hz, 1H), 8.34−8.26 (m, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 7.0 Hz, 2H), 7.84 (s, 2H), 7.60−7.49 (m, 2H), 7.41−7.30 (m, 3H), 7.29−7.21 (m, 2H), 4.81 (s, 4H), 2.27 (s, 6H), 2.14 (q, J = 7.0 Hz, 2H), 1.11 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 166.4, 148.2, 138.7, 138.1, 136.2, 134.4, 133.9, 130.3, 129.6, 128.3, 127.9, 127.4, 127.0, 121.8, 121.6, 116.9, 65.6, 51.1, 25.3, 21.1, 8.6. HRMS (ESI): calcd for $C_{31}H_{31}N_2O_5$ $[M + H]^+$, 511.2233; found, 511.2228.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl-2-methylbenzoate ***3ad***. Compound **3ad** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ad** as a white solid (9.0 mg, 24%). mp = 63.8−65.0 °C. (R_f = 0.50, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.48 (s, 1H), 8.82 (d, J = 5.4 Hz, 1H), 8.62−8.47 (m, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.61−7.46 (m, 2H), 7.45−7.28 (m, 2H), 7.23−7.13 (m, 1H), 7.13−7.01 (m, 1H), 4.66−4.52 (m, 1H), 4.52−4.39 (m, 1H), 2.55 (s, 3H), 2.16−1.95 (m, 1H), 1.91−1.73 (m, 1H), 1.54 (s, 3H), 1.04 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 167.3, 148.2, 140.4, 138.7, 136.2, 134.5, 132.0, 131.6, 130.9, 129.3, 127.9, 127.4, 125.6, 121.5, 116.5, 69.9, 47.7, 29.5, 21.9, 19.5, 8.7. HRMS (ESI): calcd for $C_{23}H_{25}N_2O_3$ $[M + H]^+$, 377.1865; found, 377.1868.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(2-methylbenzoate) ***3ad′***. Compound **3ad′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ad′** as a white solid (20.9 mg, 41%). mp = 123.1−125.4 °C. (R_f = 0.43, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.65 (s, 1H), 8.81 (d, J = 5.1 Hz, 1H), 8.27 (d, J = 2.7 Hz, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.61−7.45 (m, 2H), 7.44−7.29 (m, 3H), 7.25−7.17 (m, 2H), 7.17−7.06 (m, 2H), 4.78 (s, 4H), 2.57 (s, 6H), 2.12 (q, J = 7.2 Hz, 2H), 1.11 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 167.0, 148.1, 140.6, 136.2, 134.3, 132.2, 131.7, 130.9, 129.0, 127.9, 127.4, 125.7, 121.8, 121.6, 116.9, 65.4, 51.0, 25.4, 21.9, 8.5. HRMS (ESI): calcd for $C_{23}H_{25}N_2O_3$ $[M + H]^+$, 511.2233; found, 511.2230.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl-4-methoxybenzoate ***3ae***. Compound **3ae** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ae** as a yellow liquid (10.6 mg, 27%). (R_f = 0.40, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.50 (s, 1H), 8.83 (d, J = 6.6 Hz, 1H), 8.59 (d, J = 3.3 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 7.8 Hz, 2H), 7.59−7.46 (m, 2H), 7.41 (dd, J = 8.1, 4.2 Hz, 1H), 6.81 (d, J = 8.4 Hz, 2H), 4.60−4.50 (m, 1H), 4.50−4.42 (m, 1H), 3.81 (s, 3H), 2.13−1.96 (m, 1H), 1.90−1.72 (m, 1H), 1.51 (s, 3H), 1.03 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 165.5, 162.8, 147.6, 138.2, 135.7, 134.0, 131.8, 131.3, 127.4, 126.9, 121.8, 121.0, 116.1, 113.0, 69.0, 54.9, 47.2, 28.9, 19.0, 8.2. HRMS (ESI): calcd for $C_{23}H_{25}N_2O_3$ $[M + H]^+$, 393.1814; found, 393.1818.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(4-methoxybenzoate) ***3ae′***. Compound **3ae′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ae′** as a white solid (20.1 mg, 37%). mp = 126.5−128.1 °C. (R_f = 0.13, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.61 (s, 1H), 8.75 (dd, J = 6.6, 1.8 Hz, 1H), 8.35−8.23 (m, 1H), 8.05 (dd, J = 8.1, 1.2 Hz, 1H), 7.95 (d, J = 8.7 Hz, 4H), 7.57−7.38 (m, 2H), 7.29 (dd, J = 8.1, 4.2 Hz, 1H), 6.76 (d, J = 8.7 Hz, 4H), 4.70 (s, 4H), 3.75 (s, 6H), 2.03 (q, J = 7.2 Hz, 2H), 1.03 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 164.9, 162.5, 147.1, 137.6, 135.2, 133.3, 130.9, 126.9, 126.4, 121.1, 120.8, 120.6, 115.9, 112.6, 64.3, 54.4, 50.1, 24.3, 7.5. HRMS (ESI): calcd for $C_{31}H_{31}N_2O_7$ $[M + H]^+$, 543.2131; found, 543.2127.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl-3-chlorobenzoate ***3af***. Compound **3af** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3af** as a yellow liquid (7.9 mg, 20%). (R_f = 0.47, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.47 (s, 1H), 8.82 (d, J = 6.6 Hz, 1H), 8.67−8.59 (m, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.60−7.36 (m, 4H), 7.33−7.19 (m, 1H), 4.63−4.53 (m, 1H), 4.52−4.43 (m, 1H), 2.16−1.97 (m, 1H), 1.91−1.73 (m, 1H), 1.54 (s, 3H), 1.05 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 164.1, 147.3, 137.7, 135.3, 133.4, 133.3, 132.0, 130.6, 128.7, 128.6, 126.9, 126.4, 120.6, 120.6, 115.6, 69.2, 46.7, 28.3, 18.4, 7.6. HRMS (ESI): calcd for $C_{22}H_{22}N_2O_3Cl$ $[M + H]^+$, 397.1319; found, 397.1314.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(3-chlorobenzoate) ***3af′***. Compound **3af′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3af′** as a white solid (19.8 mg, 36%). mp = 66.5−67.7 °C. (R_f = 0.23, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.66 (s, 1H), 8.82 (dd, J = 6.0, 2.7 Hz, 1H), 8.42 (d, J = 3.0 Hz, 1H), 8.16 (d, J = 6.9 Hz, 1H), 8.00 (s, 2H), 7.94 (d, J = 7.8 Hz, 2H), 7.62−7.45 (m, 4H), 7.40 (dd, J = 8.1, 4.2 Hz, 1H), 7.34−7.27 (m, 2H), 4.82 (s, 4H), 2.12 (q, J = 7.2 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 163.9, 147.2, 135.5, 133.5, 133.1, 132.2, 130.3, 128.8, 128.7, 126.9, 126.4, 121.0, 120.6, 116.1, 64.9, 50.1, 24.3, 7.5. HRMS (ESI): calcd for $C_{29}H_{25}N_2O_5Cl_2$ $[M + H]^+$, 551.1140; found, 551.1140.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl-2-chlorobenzoate ***3ag***. Compound **3ag** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ag** as a yellow liquid (8.3 mg, 21%). (R_f = 0.25, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.43 (s, 1H), 8.81 (d, J = 6.9 Hz, 1H), 8.60 (d, J = 2.4 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.61−7.46 (m, 2H), 7.45−

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7.30 (m, 3H), 7.22−7.10 (m, 1H), 4.70−4.59 (m, 1H), 4.55−4.44 (m, 1H), 2.13−1.95 (m, 1H), 1.90−1.72 (m, 1H), 1.56 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 164.4, 147.1, 137.7, 135.3, 133.4, 132.9, 131.8, 131.6, 130.9, 130.0, 128.7, 126.9, 126.4, 125.5, 120.5, 115.5, 69.5, 46.7, 28.4, 18.4, 7.6. HRMS (ESI): calcd for $C_{22}H_{22}N_2O_3Cl$ $[M + H]^+$, 397.1319; found, 397.1314.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(2-chlorobenzoate) ***3ag′***. Compound **3ag′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ag′** as a white solid (16.5 mg, 30%). mp = 133.2−134.0 °C. (R_f = 0.17, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.56 (s, 1H), 8.79 (dd, J = 6.3, 1.8 Hz, 1H), 8.37 (d, J = 3.0 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.62−7.48 (m, 2H), 7.47−7.30 (m, 5H), 7.30−7.16 (m, 2H), 4.97−4.72 (m, 4H), 2.12 (q, J = 7.5 Hz, 2H), 1.11 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 164.3, 147.1, 135.2, 133.2, 132.9, 131.8, 130.9, 130.1, 128.5, 126.8, 126.3, 125.6, 120.8, 120.6, 115.8, 64.8, 49.9, 24.2, 7.4. HRMS (ESI): calcd for $C_{29}H_{25}N_2O_5Cl_2$ $[M + H]^+$, 551.1140; found, 551.1135.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl-4-chlorobenzoate ***3ah***. Compound **3ah** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ah** as a white solid (9.5 mg, 24%). mp = 65.6−67.1 °C. (R_f = 0.50, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.46 (s, 1H), 8.82 (d, J = 4.5 Hz, 1H), 8.62 (d, J = 2.7 Hz, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.99 (d, J = 8.1 Hz, 2H), 7.63−7.48 (m, 2H), 7.48−7.39 (m, 1H), 7.37−7.21 (m, 2H), 4.68−4.53 (m, 1H), 4.52−4.41 (m, 1H), 2.14−1.94 (m, 1H), 1.95−1.72 (m, 1H), 1.52 (s, 3H), 1.04 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 165.4, 148.2, 139.4, 138.7, 136.4, 134.4, 131.2, 128.6, 128.4, 128.0, 127.5, 121.6, 116.6, 70.1, 47.8, 29.3, 19.4, 8.7. HRMS (ESI): calcd for $C_{22}H_{22}N_2O_3Cl$ $[M + H]^+$, 397.1319; found, 397.1313.

Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(4-chlorobenzoate) ***3ah′***. Compound **3ah′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ah′** as a white solid (22.0 mg, 40%). mp = 91.2−92.3 °C. (R_f = 0.38, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.62 (s, 1H), 8.81 (dd, J = 6.0, 2.7 Hz, 1H), 8.40 (dd, J = 4.2, 1.2 Hz, 1H), 8.17 (dd, J = 8.4, 1.5 Hz, 1H), 7.99 (d, J = 8.7 Hz, 4H), 7.58−7.51 (m, 2H), 7.45−7.37 (m, 1H), 7.33 (d, J = 8.4 Hz, 4H), 4.80 (s, 4H), 2.10 (q, J = 7.5 Hz, 2H), 1.11 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 165.3, 148.2, 139.7, 138.6, 136.4, 134.2, 131.2, 128.8, 128.1, 128.0, 127.5, 122.0, 121.7, 117.0, 65.7, 51.2, 25.4, 8.5. HRMS (ESI): calcd for $C_{29}H_{25}N_2O_5Cl_2$ $[M + H]^+$, 551.1140; found, 551.1147.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl-4-bromobenzoate ***3ai***. Compound **3ai** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ai** as a yellow liquid (11.0 mg, 25%). (R_f = 0.54, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.44 (s, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.64 (d, J = 3.0 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.63−7.39 (m, 4H), 4.64−4.54 (m, 1H), 4.52−4.40 (m, 1H), 2.15−1.93 (m, 1H), 1.92−1.74 (m, 1H), 1.53 (s, 3H), 1.04 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 164.6, 147.0, 135.7, 133.3, 130.6, 130.3, 127.8, 127.1, 127.0, 126.5, 120.7, 120.6, 116.0, 109.0, 69.1, 46.8, 28.3, 18.4, 7.7. HRMS (ESI): calcd for $C_{22}H_{22}N_2O_3Br$ $[M + H]^+$, 441.0814; found, 441.0808.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(4-bromobenzoate) ***3ai′***. Compound **3ai′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ai′** as a white solid (17.2 mg, 27%). mp = 87.8−89.1 °C. (R_f = 0.28, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.64 (s, 1H), 8.82 (dd, J = 6.0, 2.0 Hz, 1H), 8.41 (d, J = 3.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.5 Hz, 4H), 7.61−7.53 (m, 2H), 7.50 (d, J = 8.5 Hz, 4H), 7.47−7.41 (m, 1H), 4.80 (s, 4H), 2.11 (q, J = 7.5 Hz, 2H), 1.11 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 165.4, 148.0, 138.3, 136.7, 134.0, 131.7, 131.3, 128.4, 127.9, 127.5, 122.1, 121.7, 117.2, 104.9, 65.6, 51.0, 25.2, 8.5. HRMS (ESI): calcd for $C_{29}H_{25}N_2O_5Br_2$ $[M + H]^+$, 639.0129; found, 639.0125.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl-4-fluorobenzoate ***3aj***. Compound **3aj** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3aj** as a white solid (10.3 mg, 27%). mp = 76.8−78.4 °C. (R_f = 0.36, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.47 (s, 1H), 8.83 (d, J = 6.6 Hz, 1H), 8.62 (d, J = 3.6 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.13−7.90 (m, 2H), 7.63−7.49 (m, 2H), 7.48−7.40 (m, 1H), 7.10−6.91 (m, 2H), 4.66−4.53 (m, 1H), 4.52−4.40 (m, 1H), 2.16−1.96 (m, 1H), 1.91−1.72 (m, 1H), 1.53 (s, 3H), 1.04 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 165.8 ($^1J_{C-F}$ = 252.8 Hz), 165.3, 148.1, 138.7, 136.4, 134.4, 132.4 ($^3J_{C-F}$ = 9.0 Hz), 128.0, 127.5, 126.2, 121.6, 116.7, 115.4 ($^2J_{C-F}$ = 21.8 Hz), 70.0, 47.7, 29.3, 19.4, 8.7. HRMS (ESI): calcd for $C_{22}H_{22}N_2O_3F$ $[M + H]^+$, 381.1614; found, 381.1610.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(4-fluorobenzoate) ***3aj′***. Compound **3aj′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3aj′** as a white solid (18.1 mg, 35%). mp = 136.7−138.1 °C. (R_f = 0.21, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.64 (s, 1H), 8.82 (d, J = 5.7 Hz, 1H), 8.38 (d, J = 3.0 Hz, 1H), 8.17 (d, J = 8.1 Hz, 1H), 8.14−7.94 (m, 4H), 7.63−7.50 (m, 2H), 7.46−7.37 (m, 1H), 7.32−6.95 (m, 4H), 4.80 (s, 4H), 2.12 (q, J = 7.2 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 165.9 ($^1J_{C-F}$ = 253.5 Hz), 165.2, 148.1, 138.6, 136.4, 134.2, 132.4 ($^3J_{C-F}$ = 9.0 Hz), 127.9, 127.4, 125.9 ($^4J_{C-F}$ = 3.0 Hz), 121.8 ($^2J_{C-F}$ = 21.8 Hz), 117.0, 115.6 ($^2J_{C-F}$ = 21.8 Hz), 65.6, 51.1, 25.3, 8.6. HRMS (ESI): calcd for $C_{29}H_{25}N_2O_5F_2$ $[M + H]^+$, 519.1731; found, 519.1729.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl-2-naphthoate ***3ak***. Compound **3ak** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ak** as a yellow liquid (8.2 mg, 20%). (R_f = 0.25, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.57 (s, 1H), 8.86 (d, J = 5.7 Hz, 1H), 8.57 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.14 (d, J = 7.5 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.87−7.72 (m, 2H), 7.68−7.48 (m, 4H), 7.47−7.40 (m, 1H), 7.40−7.30 (m, 1H), 4.71−4.61 (m, 1H), 4.60−4.50 (m, 1H), 2.19−1.99 (m, 1H), 1.95−1.75 (m, 1H), 1.58 (s, 3H), 1.07 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 165.4, 147.2, 137.7, 135.2, 134.4, 133.5, 131.3, 130.3, 128.2, 127.2, 127.0,

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126.9, 126.6, 126.4, 126.1, 125.5, 124.3, 120.5, 115.5, 69.0, 46.8, 28.3, 18.5, 7.7. HRMS (ESI): calcd for $C_{26}H_{25}N_2O_3$ $[M + H]^+$, 413.1865; found, 413.1860.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(2-naphthoate) ***3ak′***. Compound **3ak′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ak′** as a white solid (22.1 mg, 38%). mp = 153.6−155.3 °C. (R_f = 0.18, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.82 (s, 1H), 8.89 (d, J = 6.9 Hz, 1H), 8.60 (s, 2H), 8.22 (d, J = 3.0 Hz, 1H), 8.16−8.02 (m, 3H), 7.88−7.72 (m, 4H), 7.72−7.63 (m, 2H), 7.61−7.49 (m, 4H), 7.48−7.38 (m, 2H), 7.32−7.26 (m, 1H), 4.94 (s, 4H), 2.21 (q, J = 7.5 Hz, 2H), 1.18 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 166.4, 148.2, 138.6, 136.3, 135.6, 134.4, 132.3, 131.4, 129.3, 128.3, 128.2, 127.9, 127.7, 127.5, 126.9, 126.6, 125.3, 121.9, 121.6, 117.0, 66.0, 51.2, 25.5, 8.7. HRMS (ESI): calcd for $C_{37}H_{31}N_2O_5$ $[M + H]^+$, 583.2233; found, 583.2239.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butylthiophene-2-carboxylate ***3al***. Compound **3al** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3al** as a white solid (9.6 mg, 26%). mp = 54.1−55.9 °C. (R_f = 0.40, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.45 (s, 1H), 8.83 (dd, J = 6.9, 1.5 Hz, 1H), 8.65 (d, J = 3.0 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 3.0 Hz, 1H), 7.61−7.46 (m, 3H), 7.46−7.37 (m, 1H), 7.09−6.96 (m, 1H), 4.61−4.53 (m, 1H), 4.52−4.43 (m, 1H), 2.11−1.94 (m, 1H), 1.89−1.75 (m, 1H), 1.52 (s, 3H), 1.03 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 162.0, 148.2, 138.7, 136.3, 134.5, 133.7, 132.6, 127.9, 127.7, 127.4, 121.6, 116.6, 69.8, 47.8, 29.4, 19.5, 8.7. HRMS (ESI): calcd for $C_{20}H_{21}N_2O_3S$ $[M + H]^+$, 369.1273; found, 369.1271.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis-(thiophene-2-carboxylate) ***3al′***. Compound **3al′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3al′** as a white solid (16.3 mg, 33%). mp = 114.1−115.3 °C. (R_f = 0.12, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.63 (s, 1H), 8.80 (dd, J = 6.3, 2.1 Hz, 1H), 8.46 (d, J = 2.7 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 3.0 Hz, 2H), 7.70−7.45 (m, 4H), 7.44−7.32 (m, 1H), 7.15−6.98 (m, 2H), 4.78 (s, 4H), 2.08 (q, J = 7.5 Hz, 2H), 1.10 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 161.7, 148.1, 138.6, 136.3, 134.3, 133.9, 133.2, 132.9, 127.8, 127.4, 121.8, 121.6, 116.9, 65.3, 51.1, 25.2, 8.5. HRMS (ESI): calcd for $C_{25}H_{23}N_2O_5S_2$ $[M + H]^+$, 495.1048; found, 495.1040.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butylcinnamate ***3am***. Compound **3am** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3am** as a yellow liquid (11.3 mg, 29%). (R_f = 0.26, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.51 (s, 1H), 8.84 (d, J = 6.9 Hz, 1H), 8.74 (d, J = 4.2 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 15.9 Hz, 1H), 7.61−7.47 (m, 2H), 7.47−7.27 (m, 6H), 6.54 (d, J = 16.2 Hz, 1H), 4.57−4.44 (m, 1H), 4.43−4.28 (m, 1H), 2.09−1.90 (m, 1H), 1.85−1.67 (m, 1H), 1.48 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 165.7, 147.2, 144.2, 137.7, 135.3, 133.6, 133.3, 129.3, 127.8, 127.0, 126.5, 120.5, 116.8, 115.6, 68.3, 46.6, 28.4, 18.3, 7.6. HRMS (ESI): calcd for $C_{24}H_{25}N_2O_3$ $[M + H]^+$, 389.1865; found, 389.1859.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diyl-(2E,2′E)-bis(3-phenylacrylate) ***3am′***. Compound **3am′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3am′** as a yellow liquid (11.2 mg, 21%). (R_f = 0.28, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.73 (s, 1H), 8.85 (dd, J = 6.6, 1.5 Hz, 1H), 8.66 (d, J = 3.0 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 15.9 Hz, 2H), 7.61−7.49 (m, 2H), 7.48−7.27 (m, 11H), 6.55 (d, J = 16.2 Hz, 2H), 4.67 (s, 4H), 2.03 (q, J = 7.5 Hz, 2H), 1.08 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 165.5, 147.3, 144.5, 137.7, 135.4, 133.5, 133.2, 129.4, 127.9, 127.1, 127.0, 126.5, 120.8, 120.6, 116.6, 115.9, 64.2, 49.8, 24.3, 7.5. HRMS (ESI): calcd for $C_{33}H_{31}N_2O_5$ $[M + H]^+$, 535.2233; found, 535.2226.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl(E)-3-(p-tolyl)-acrylate ***3an***. Compound **3an** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3an** as a white solid (10.5 mg, 26%). mp = 62.9−63.5 °C. (R_f = 0.30, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.52 (s, 1H), 8.84 (dd, J = 7.2, 1.5 Hz, 1H), 8.74 (d, J = 2.7 Hz, 1H), 8.15 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 15.9 Hz, 1H), 7.59−7.46 (m, 2H), 7.44−7.36 (m, 1H), 7.34−7.23 (m, 2H), 7.18−7.08 (m, 2H), 6.50 (d, J = 15.9 Hz, 1H), 4.55−4.43 (m, 1H), 4.41−4.29 (m, 1H), 2.35 (s, 3H), 2.09−1.89 (m, 1H), 1.87−1.67 (m, 1H), 1.48 (s, 3H), 1.02 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 165.9, 147.2, 144.2, 139.7, 137.8, 135.3, 133.6, 130.6, 128.5, 127.0, 126.9, 126.4, 120.5, 120.5, 115.7, 115.5, 68.2, 46.6, 28.4, 20.4, 18.3, 7.6. HRMS (ESI): calcd for $C_{25}H_{27}N_2O_3$ $[M + H]^+$, 403.2021; found, 403.2020.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diyl-(2E,2′E)-bis(3-(p-tolyl)acrylate) ***3an′***. Compound **3an′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3an′** as a yellow liquid (24.2 mg, 43%). (R_f = 0.21, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.74 (s, 1H), 8.85 (dd, J = 6.6, 1.8 Hz, 1H), 8.66 (dd, J = 3.9, 1.2 Hz, 1H), 8.15 (dd, J = 8.1, 1.2 Hz, 1H), 7.71 (d, J = 16.2 Hz, 2H), 7.60−7.47 (m, 2H), 7.42−7.28 (m, 5H), 7.21−7.06 (m, 4H), 6.51 (d, J = 16.2 Hz, 2H), 4.66 (s, 4H), 2.36 (s, 6H), 2.03 (q, J = 7.5 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 166.8, 148.3, 145.5, 140.9, 138.8, 136.3, 134.6, 131.5, 129.6, 128.2, 128.0, 127.5, 121.7, 121.6, 116.9, 116.5, 65.2, 50.8, 25.3, 21.5, 8.5. HRMS (ESI): calcd for $C_{35}H_{35}N_2O_5$ $[M + H]^+$, 563.2546; found, 563.2553.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl(E)-3-(4-chlorophenyl)acrylate ***3ao***. Compound **3ao** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ao** as a yellow liquid (12.7 mg, 30%). (R_f = 0.32, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.48 (s, 1H), 8.84 (d, J = 6.9 Hz, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 16.2 Hz, 1H), 7.57−7.48 (m, 2H), 7.47−7.37 (m, 1H), 7.37−7.20 (m, 4H), 8.49 (d, J = 16.2 Hz, 1H), 4.63−4.45 (m, 1H), 4.42−4.25 (m, 1H), 2.14−1.90 (m, 1H), 1.85−1.72 (m, 1H), 1.48 (s, 3H), 1.02 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 166.4, 148.2, 143.7, 140.4, 138.8, 136.4, 134.5, 132.8, 129.2, 129.1, 128.0, 127.5, 121.6, 118.5, 116.6, 69.5, 47.7, 29.4, 19.3, 8.6.

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HRMS (ESI): calcd for $C_{24}H_{24}N_2O_3Cl$ $[M + H]^+$, 423.1475; found, 423.1470.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diyl-(2E,2′E)-bis(3-(4-chlorophenyl)acrylate) ***3ao′***. Compound **3ao′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ao′** as a white solid (19.9 mg, 33%). mp = 131.9−133.3 °C. (R_f = 0.16, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.68 (s, 1H), 8.84 (dd, J = 6.6, 2.1 Hz, 1H), 8.65 (d, J = 2.7 Hz, 1H), 8.17 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 15.9 Hz, 2H), 7.61−7.49 (m, 2H), 7.46−7.27 (m, 9H), 6.51 (d, J = 15.9 Hz, 2H), 4.66 (s, 4H), 2.02 (q, J = 7.5 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 166.3, 148.2, 144.1, 136.4, 136.4, 134.4, 132.7, 129.3, 129.2, 128.0, 127.5, 121.8, 121.6, 118.1, 116.9, 107.2, 65.2, 50.8, 25.3, 8.5. HRMS (ESI): calcd for $C_{33}H_{29}N_2O_5Cl_2$ $[M + H]^+$, 603.1453; found, 603.1455.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl(E)-3-(4-bromophenyl)acrylate ***3ap***. Compound **3ap** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ap** as a yellow liquid (11.2 mg, 24%). (R_f = 0.48, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.48 (s, 1H), 8.84 (d, J = 6.9 Hz, 1H), 8.74 (d, J = 2.7 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 15.9 Hz, 1H), 7.56−7.37 (m, 5H), 7.29−7.19 (m, 2H), 6.50 (d, J = 15.9 Hz, 1H), 4.57−4.44 (m, 1H), 4.42−4.31 (m, 1H), 2.08−1.90 (m, 1H), 1.86−1.69 (m, 1H), 1.48 (s, 3H), 1.02 (t, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 166.4, 148.2, 143.7, 136.4, 134.5, 133.2, 132.1, 131.4, 129.4, 128.0, 127.5, 124.6, 121.6, 118.6, 116.5, 110.0, 69.5, 47.6, 29.4, 19.3, 8.6. HRMS (ESI): calcd for $C_{24}H_{24}N_2O_3Br$ $[M + H]^+$, 467.0970; found, 467.0972.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diyl-(2E,2′E)-bis(3-(4-bromophenyl)acrylate) ***3ap′***. Compound **3ap′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ap′** as a white solid (19.3 mg, 28%). mp = 178.3−179.2 °C. (R_f = 0.18, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.69 (s, 1H), 8.85 (d, J = 6.5 Hz, 1H), 8.66 (d, J = 2.5 Hz, 1H), 8.20 (d, J = 7.5 Hz, 1H), 7.65 (d, J = 16.0 Hz, 2H), 7.61−7.54 (m, 2H), 7.48 (d, J = 8.5 Hz, 4H), 7.45−7.40 (m, 1H), 7.33−7.28 (m, 4H), 8.53 (d, J = 16.0 Hz, 2H), 4.73−4.60 (m, 4H), 2.03 (q, J = 7.5 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 166.2, 148.3, 144.1, 138.7, 136.5, 134.4, 133.1, 132.2, 129.5, 128.0, 127.5, 124.8, 121.9, 121.7, 118.3, 117.0, 65.3, 50.8, 25.3, 8.5. HRMS (ESI): calcd for $C_{33}H_{29}N_2O_5Br_2$ $[M + H]^+$, 691.0443; found, 691.0440.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butylisobutyrate ***3aq***. Compound **3aq** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3aq** as a yellow liquid (9.8 mg, 30%). (R_f = 0.46, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.40 (s, 1H), 9.02−8.67 (m, 2H), 8.17 (dd, J = 8.4, 1.2 Hz, 1H), 7.60−7.41 (m, 3H), 4.46−4.33 (m, 1H), 4.29−4.16 (m, 1H), 2.78−2.57 (m, 1H), 2.05−1.85 (m, 1H), 1.81−1.61 (m, 1H), 1.43 (s, 3H), 1.27−1.08 (m, 6H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.7, 172.6, 147.1, 137.7, 135.4, 133.5, 127.0, 126.4, 120.5, 120.5, 115.6, 67.9, 46.6, 33.0, 28.3, 18.3, 17.9, 7.6. HRMS (ESI): calcd for $C_{19}H_{25}N_2O_3$ $[M + H]^+$, 329.1865; found, 329.1863.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(2-methylpropanoate) ***3aq′***. Compound **3aq′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3aq′** as a yellow liquid (16.6 mg, 40%). (R_f = 0.41, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.48 (s, 1H), 8.91−8.73 (m, 2H), 8.18 (dd, J = 8.1, 1.2 Hz, 1H), 7.62−7.51 (m, 2H), 7.50−7.42 (m, 1H), 4.60−4.46 (m, 2H), 4.46−4.37 (m, 2H), 2.77−2.56 (m, 2H), 1.93 (q, J = 7.5 Hz, 2H), 1.30−1.13 (m, 12H), 1.01 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.5, 170.7, 148.1, 138.6, 136.4, 134.3, 128.0, 127.4, 121.8, 121.6, 116.9, 64.3, 50.9, 34.0, 25.0, 18.9, 8.3. HRMS (ESI): calcd for $C_{23}H_{31}N_2O_5$ $[M + H]^+$, 415.2233; found, 415.2230.

2-Methyl-2-(quinolin-8-ylcarbamoyl)butyl-2-methylbutanoate ***3ar***. Compound **3ar** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ar** as a yellow liquid (10.9 mg, 32%). (R_f = 0.42, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.39 (s, 1H), 8.93−8.69 (m, 2H), 8.17 (d, J = 8.4 Hz, 1H), 7.69−7.36 (m, 3H), 4.58−4.31 (m, 1H), 4.27−4.16 (m, 1H), 2.58−2.39 (m, 1H), 2.06−1.87 (m, 1H), 1.82−1.58 (m, 2H), 1.55−1.46 (m, 1H), 1.44 (s, 3H), 1.17−1.09 (m, 3H), 0.99 (t, J = 7.5 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.4, 172.5, 147.1, 137.7, 135.4, 133.5, 127.0, 126.4, 120.5, 120.5, 115.6, 67.9, 46.6, 40.0, 28.2, 25.6, 18.2, 15.4, 10.5, 7.6. HRMS (ESI): calcd for $C_{20}H_{27}N_2O_3$ $[M + H]^+$, 343.2021; found, 343.2029.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)propane-1,3-diylbis(2-methylbutanoate) ***3ar′***. Compound **3ar′** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ar′** as a yellow liquid (16.4 mg, 37%). (R_f = 0.38, petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.46 (s, 1H), 8.93−8.70 (m, 2H), 8.29−8.11 (m, 1H), 7.68−7.41 (m, 3H), 4.66−4.31 (m, 4H), 2.64−2.37 (m, 2H), 1.93 (q, J = 7.5 Hz, 2H), 1.78−1.60 (m, 2H), 1.57−1.40 (m, 2H), 1.25−1.12 (m, 6H), 1.00 (t, J = 7.5 Hz, 3H), 0.86 (t, J = 7.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 170.7, 148.1, 138.6, 136.5, 134.3, 127.5, 121.6, 117.0, 64.2, 50.9, 41.0, 26.6, 24.9, 16.5, 11.5, 8.3. HRMS (ESI): calcd for $C_{25}H_{35}N_2O_5$ $[M + H]^+$, 443.2545; found, 443.2547.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)butylbenzoate ***3ba***. Compound **3ba** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ba** as a yellow liquid (30.1 mg, 80%). (R_f = 0.60, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.52 (s, 1H), 8.99 (d, J = 7.5 Hz, 1H), 8.36 (dd, J = 2.5, 1.5 Hz, 1H), 8.10 (d, J = 7.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.41−7.32 (m, 1H), 7.30−7.26 (m, 1H), 7.25−7.21 (m, 1H), 7.17−7.11 (m, 2H), 7.04−6.99 (m, 1H), 4.64 (s, 2H), 1.89 (q, J = 7.5 Hz, 4H), 0.93 (t, J = 7.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 165.0, 146.9, 137.7, 133.7, 131.7, 129.1, 128.7, 127.2, 126.9, 126.7, 126.5, 126.4, 120.3, 115.6, 65.1, 49.9, 25.3, 7.3. HRMS (ESI): calcd for $C_{23}H_{25}N_2O_3$ $[M + H]^+$, 377.1865; found, 377.1869.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)butyl-4-methoxybenzoate ***3bb***. Compound **3bb** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3bb** as a white solid (30.9 mg, 76%). mp = 75.9−76.7 °C. (R_f = 0.51, petroleum

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ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.48 (s, 1H), 8.84 (d, J = 6.9 Hz, 1H), 8.58 (d, J = 2.7 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.7 Hz, 2H), 7.67−7.47 (m, 2H), 7.45−7.34 (m, 1H), 6.84 (d, J = 8.4 Hz, 2H), 4.60 (s, 2H), 3.83 (s, 3H), 1.97 (q, J = 7.5 Hz, 4H), 1.02 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 166.0, 163.4, 148.2, 138.8, 136.3, 136.2, 134.6, 131.8, 127.9, 127.4, 122.5, 121.5, 116.6, 113.5, 65.9, 55.4, 51.0, 26.2, 8.5. HRMS (ESI): calcd for $C_{24}H_{27}N_2O_4$ $[M + H]^+$, 407.1971; found, 407.1976.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)butyl-4-(trifluoromethyl)benzoatem ***3bc***. Compound **3bc** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3bc** as a white solid (18.2 mg, 41%). mp = 82.1−83.7 °C. (R_f = 0.58, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.42 (m, 1H), 8.82 (dd, J = 6.6, 2.1 Hz, 1H), 8.61 (dd, J = 4.5, 1.5 Hz, 1H), 8.24−8.08 (m, 3H), 7.61 (d, J = 8.4 Hz, 2H), 7.56−7.48 (m, 2H), 7.47−7.39 (m, 1H), 4.65 (s, 2H), 1.98 (q, J = 7.5 Hz, 4H), 1.03 (t, J = 7.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 165.1, 148.2, 138.7, 136.4, 136.5 (q, $^2J_{C-F}$ = 32.5 Hz), 136.4, 133.3, 130.2, 128.0, 127.5, 125.4 (q, $^3J_{C-F}$ = 3.6 Hz), 123.6 (q, $^1J_{C-F}$ = 271.0 Hz), 121.6, 116.7, 66.7, 51.1, 26.0, 8.5. HRMS (ESI): calcd for $C_{24}H_{24}N_2O_3F_3$ $[M + H]^+$, 445.1739; found, 445.1742.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)pentylbenzoate ***3ca***.[18b] Compound **3ca** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ca** as a yellow liquid (28.5 mg, 73%). (R_f = 0.63, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.49 (s, 1H), 8.88−8.77 (m, 1H), 8.59−8.48 (m, 1H), 8.16−8.03 (m, 3H), 7.57−7.41 (m, 3H), 4.64 (s, 2H), 2.05−1.95 (m, 2H), 1.92−1.82 (m, 2H), 1.51−1.38 (m, 2H), 1.03 (q, J = 4.5 Hz, 3H), 0.97 (q, J = 4.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 165.2, 147.1, 137.7, 135.2, 133.5, 131.9, 129.0, 128.7, 127.3, 126.9, 126.3, 120.5, 120.4, 115.5, 65.4, 49.7, 35.1, 25.7, 16.4, 13.7, 7.5. HRMS (ESI): calcd for $C_{24}H_{27}N_2O_3$ $[M + H]^+$, 391.2021; found, 391.2022.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)hexylbenzoate ***3da***. Compound **3da** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3da** as a yellow liquid (26.7 mg, 66%). (R_f = 0.62, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.50 (s, 1H), 8.84 (d, J = 7.2 Hz, 1H), 8.61−8.48 (m, 1H), 8.22−8.00 (m, 3H), 7.63−7.44 (m, 3H), 7.43−7.28 (m, 3H), 4.64 (s, 2H), 2.00 (q, J = 7.5 Hz, 2H), 1.94−1.82 (m, 2H), 1.53−1.29 (m, 4H), 1.04 (t, J = 7.2 Hz, 3H), 0.96−0.81 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 166.3, 148.2, 138.8, 136.3, 134.5, 133.0, 130.1, 129.8, 128.3, 127.9, 127.4, 121.5, 121.5, 116.6, 66.5, 50.7, 33.5, 26.8, 26.2, 23.3, 13.9, 8.6. HRMS (ESI): calcd for $C_{25}H_{29}N_2O_3$ $[M + H]^+$, 405.2178; found, 405.2183.

2-Ethyl-2-(quinolin-8-ylcarbamoyl)heptylbenzoate ***3ea***. Compound **3ea** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ea** as a yellow liquid (27.2 mg, 65%). (R_f = 0.65, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.48 (s, 1H), 8.82 (dd, J = 6.9, 1.5 Hz, 1H), 8.53 (dd, J = 4.2, 1.5 Hz, 1H), 8.14 (dd, J = 8.4, 1.5 Hz, 1H), 8.11−8.04 (m, 2H), 7.61−7.45 (m, 3H), 7.45−7.31 (m, 3H), 4.63 (s, 2H), 1.99 (q, J = 7.5 Hz, 2H), 1.94−1.82 (m, 2H), 1.55−1.21 (m, 6H), 1.03 (t, J = 7.5 Hz, 3H), 0.85 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 166.3, 148.2, 138.8, 136.3, 134.5, 133.0, 130.1, 129.8, 128.3, 127.9, 127.4, 121.5, 121.4, 116.6, 66.5, 50.7, 33.7, 32.4, 26.8, 23.7, 22.4, 14.0, 8.5. HRMS (ESI): calcd for $C_{26}H_{31}N_2O_3$ $[M + H]^+$, 419.2335; found, 419.2340.

2-Propyl-2-(quinolin-8-ylcarbamoyl)pentylbenzoate ***3fa***. Compound **3fa** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3fa** as a yellow liquid (30.3 mg, 75%). (R_f = 0.64, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.49 (s, 1H), 8.82 (dd, J = 7.2, 1.8 Hz, 1H), 8.52 (dd, J = 4.2, 1.5 Hz, 1H), 8.23−8.03 (m, 3H), 7.62−7.44 (m, 3H), 7.43−7.31 (m, 3H), 4.63 (s, 2H), 2.00−1.83 (m, 4H), 1.58−1.35 (m, 4H), 0.97 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 166.3, 148.2, 138.7, 136.2, 134.5, 133.0, 130.0, 129.8, 128.3, 127.9, 127.4, 121.5, 121.4, 116.6, 66.9, 50.6, 36.6, 17.4, 14.7. HRMS (ESI): calcd for $C_{25}H_{28}N_2O_3$ $[M + H]^+$, 405.2178; found, 405.2185.

2-Propyl-2-(quinolin-8-ylcarbamoyl)hexylbenzoate ***3ga***. Compound **3ga** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ga** as a yellow liquid (29.7 mg, 71%). (R_f = 0.65, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.49 (s, 1H), 8.81 (dd, J = 6.9, 1.8 Hz, 1H), 8.52 (dd, J = 4.2, 1.5 Hz, 1H), 8.14 (dd, J = 8.4, 1.5 Hz, 1H), 8.09 (d, J = 7.2 Hz, 2H), 7.59−7.45 (m, 3H), 7.43−7.32 (m, 3H), 4.62 (s, 2H), 1.98−1.81 (m, 4H), 1.52−1.33 (m, 6H), 0.97 (t, J = 7.5 Hz, 3H), 0.93−0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 165.3, 147.2, 137.8, 135.2, 133.5, 132.0, 129.1, 128.8, 127.3, 126.9, 126.4, 120.5, 120.4, 115.6, 65.9, 49.5, 35.7, 33.0, 25.2, 22.3, 16.4, 13.7, 12.9. HRMS (ESI): calcd for $C_{26}H_{31}N_2O_3$ $[M + H]^+$, 419.2335; found, 419.2341.

2-Propyl-2-(quinolin-8-ylcarbamoyl)heptylbenzoate ***3ha***. Compound **3ha** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ha** as a yellow liquid (30.2 mg, 70%). (R_f = 0.67, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.49 (s, 1H), 8.81 (dd, J = 7.2, 1.5 Hz, 1H), 8.52 (dd, J = 3.9, 0.9 Hz, 1H), 8.21−8.05 (m, 3H), 7.62−7.45 (m, 3H), 7.44−7.30 (m, 3H), 4.62 (s, 2H), 2.07−1.81 (m, 4H), 1.52−1.37 (m, 4H), 1.36−1.23 (m, 4H), 0.97 (t, J = 7.2 Hz, 3H), 0.91−0.77 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 166.3, 148.2, 138.8, 136.3, 134.5, 133.0, 130.1, 129.8, 128.3, 127.9, 127.4, 121.5, 121.4, 116.7, 66.9, 50.5, 36.7, 34.3, 32.4, 23.7, 22.4, 17.4, 14.7, 14.0. HRMS (ESI): calcd for $C_{27}H_{33}N_2O_3$ $[M + H]^+$, 433.2491; found, 433.2485.

2-Ethyl-4-phenyl-2-(quinolin-8-ylcarbamoyl)-butylbenzoate ***3ia***. Compound **3ia** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ia** as a yellow liquid (23.1 mg, 51%). (R_f = 0.57, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.55 (s, 1H), 8.84 (dd, J = 7.2, 1.8 Hz, 1H), 8.54 (dd, J = 4.2, 1.5 Hz, 1H), 8.28−8.04 (m, 3H), 7.63−7.48 (m, 3H), 7.45−7.34 (m, 3H), 7.32−7.10 (m, 5H), 4.73 (s, 2H), 2.94−2.65 (m, 2H), 2.34−2.16 (m, 2H), 2.07 (q, J = 7.2 Hz, 2H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 166.3, 148.2, 141.8, 138.7, 136.4, 134.4, 133.1, 129.9, 129.8, 128.4, 127.9, 127.4, 127.4, 125.9, 121.6, 116.8, 116.7, 66.2, 50.8, 36.3, 30.7,

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27.1, 8.6. HRMS (ESI): calcd for $C_{29}H_{29}N_2O_3$ $[M + H]^+$, 453.2178; found, 453.2184.

2-Benzyl-2-(quinolin-8-ylcarbamoyl)butylbenzoate ***3ja***. Compound **3ja** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ja** as a yellow liquid (26.7 mg, 61%). (R_f = 0.54, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.49 (s, 1H), 8.84 (d, J = 7.2 Hz, 1H), 8.42 (d, J = 2.7 Hz, 1H), 8.22−8.04 (m, 3H), 7.63−7.10 (m, 11H), 4.73−4.42 (m, 2H), 3.51−3.33 (m, 1H), 3.30−3.31 (m, 1H), 2.12−1.82 (m, 2H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 166.1, 148.1, 138.7, 136.4, 136.2, 134.3, 133.1, 130.2, 129.9, 129.8, 128.3, 127.9, 127.4, 126.7, 121.6, 116.6, 65.9, 51.9, 39.9, 27.0, 8.7. HRMS (ESI): calcd for $C_{28}H_{27}N_2O_3$ $[M + H]^+$, 439.2021; found, 439.2025.

(1-(Quinolin-8-ylcarbamoyl)cyclobutyl)methylbenzoate ***3ka***. Compound **3ka** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3ka** as a yellow liquid (20.2 mg, 56%). (R_f = 0.64, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.29 (s, 1H), 8.83 (dd, J = 7.2, 1.5 Hz, 1H), 8.58 (dd, J = 4.2, 1.5 Hz, 1H), 8.22−8.03 (m, 3H), 7.62−7.46 (m, 3H), 7.45−7.37 (m, 1H), 7.35−7.23 (m, 2H), 4.73 (s, 2H), 2.86−2.66 (m, 2H), 2.37−1.93 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 165.5, 147.1, 137.6, 135.3, 133.5, 132.0, 128.9, 128.8, 127.2, 126.9, 126.4, 120.5, 115.5, 115.4, 67.4, 47.6, 28.7, 26.4, 14.2. HRMS (ESI): calcd for $C_{22}H_{21}N_2O_3$ $[M + H]^+$, 361.1552; found, 361.1555.

(1-(Quinolin-8-ylcarbamoyl)cyclopentyl)methylbenzoate ***3la***. Compound **3la** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **3la** as a white solid (19.8 mg, 53%). mp = 71.9−72.3 °C. (R_f = 0.53, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.51 (s, 1H), 8.81 (dd, J = 7.2, 1.5 Hz, 1H), 8.50 (dd, J = 3.9, 1.5 Hz, 1H), 8.22−8.06 (m, 3H), 7.62−7.44 (m, 3H), 7.43−7.28 (m, 3H), 4.54 (s, 2H), 2.53−2.29 (m, 2H), 2.01−1.72 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 166.5, 148.1, 138.7, 136.3, 136.3, 134.8, 133.0, 129.9, 129.9, 128.2, 127.9, 127.4, 121.5, 116.5, 68.9, 55.3, 33.6, 25.1. HRMS (ESI): calcd for $C_{23}H_{23}N_2O_3$ $[M + H]^+$, 375.1708; found, 375.1712.

2-(Quinolin-8-yl)-2-azaspiro[3.5]nonan-1-one ***4o***.[11] Compound **4o** was prepared according to the general procedure. A purification by flash chromatography in petroleum ether/ethyl acetate = 20/1 gave **4o** as a yellow liquid (10.1 mg, 38%). (R_f = 0.63, petroleum ether/ethyl acetate = 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.86−8.77 (m, 1H), 8.54−8.44 (m, 1H), 8.10 (dd, J = 8.1, 1.5 Hz, 1H), 7.54−7.45 (m, 2H), 7.43−7.33 (m, 1H), 4.33 (s, 2H), 2.03−1.77 (m, 6H), 1.68−1.34 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 148.3, 140.3, 135.9, 135.3, 129.0, 126.8, 122.6, 121.1, 119.3, 59.3, 56.9, 31.2, 25.3, 23.4. HRMS (ESI): calcd for $C_{17}H_{19}N_2O$ $[M + H]^+$, 267.1497; found, 267.1494.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02430.

Preparation of starting materials, characterization data of some starting materials, deuteration experiments, KIE studies, and copies of ^{1}H and ^{13}C NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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