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Synthesis of Medium-Ring-sized Benzolactams by Using Strong Electrophiles and Quantitative Evaluation of Ring-size Dependency of the Cyclization Reaction Rate

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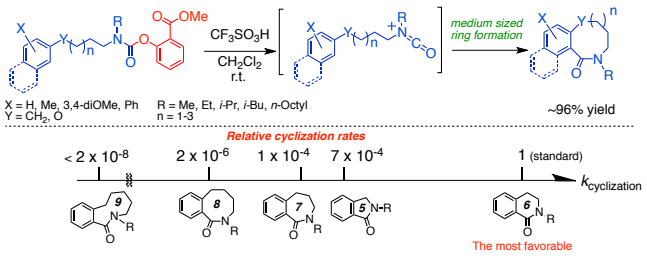


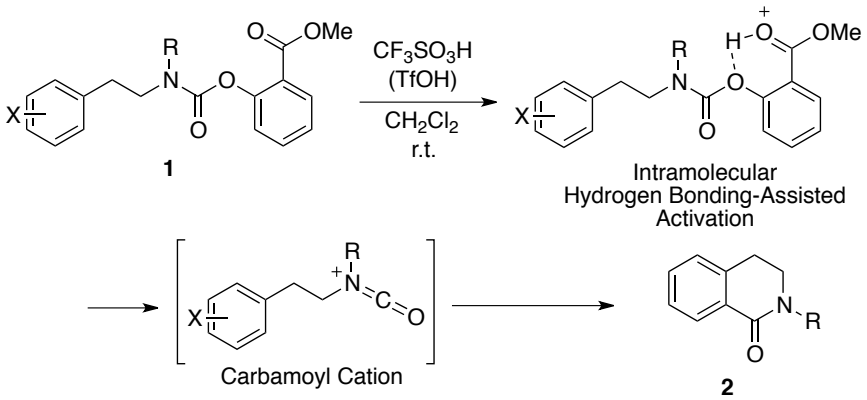
ABSTRACT: Benzolactams with medium-sized rings were synthesized via electrophilic aromatic substitution reaction of carbamoyl cations ($R_1R_2N^+$=C=O) in good to high yields without dilution. These reactions were utilized to quantitatively examine the extent of retardation of medium-sized ring formation, compared to 5- or 6-membered ring formation. The order of reaction rates of formation of cyclic benzolactams is 6- > 5- > 7- > 8- > 9-membered ring at 25 ºC. The present reaction provides a route to 8- and 9-membered benzolactams

Introduction

Benzolactam structures are important moieties of bioactive compounds,[1] and are frequently found in natural products and pharmaceuticals. Recently, medium-sized benzolactams have attracted attention as a new type of scaffold for bioactive compounds.[2] Benzolactams contain benzoyl functionalities, and ring closure reactions under various conditions have been employed for the synthesis of benzolactam derivatives containing 5-, 6- and 7-membered rings.[3] However, direct ring formation of benzolactams containing medium-sized rings has not been studied systematically,[4] and no synthetic method via intramolecular electrophilic aromatic substitution (IEAS) reaction has been reported. Instead, ring expansion reactions have frequently been used for the synthesis of benzolactams with 8- and 9-membered rings, even though the low regioselectivity of the rearrangement generally results in poor yields of the desired products.[5]

Indeed, medium-sized ring formation via intramolecular electrophilic aromatic substitution reactions is a

challenging area of chemistry. Intramolecular Friedel-Crafts acylation was reported as the first example, and the applicability of this reaction to formation of rings of various sizes was examined by Huisgen and his coworkers. [6] Their research revealed that medium- to large-sized benzoketones (8- to 19-membered rings) can be synthesized by means of IEAS reaction, but careful control of the substrate concentration is necessary. Very recently, Friedel-Crafts alkylation was also reported to give cyclic compounds with 8- and 9-membered rings,[7] although the yields were moderate to low. In spite of the long-standing history of IEAS reactions in organic synthesis, there have been few studies of medium-sized ring formation by means of IEAS reactions.



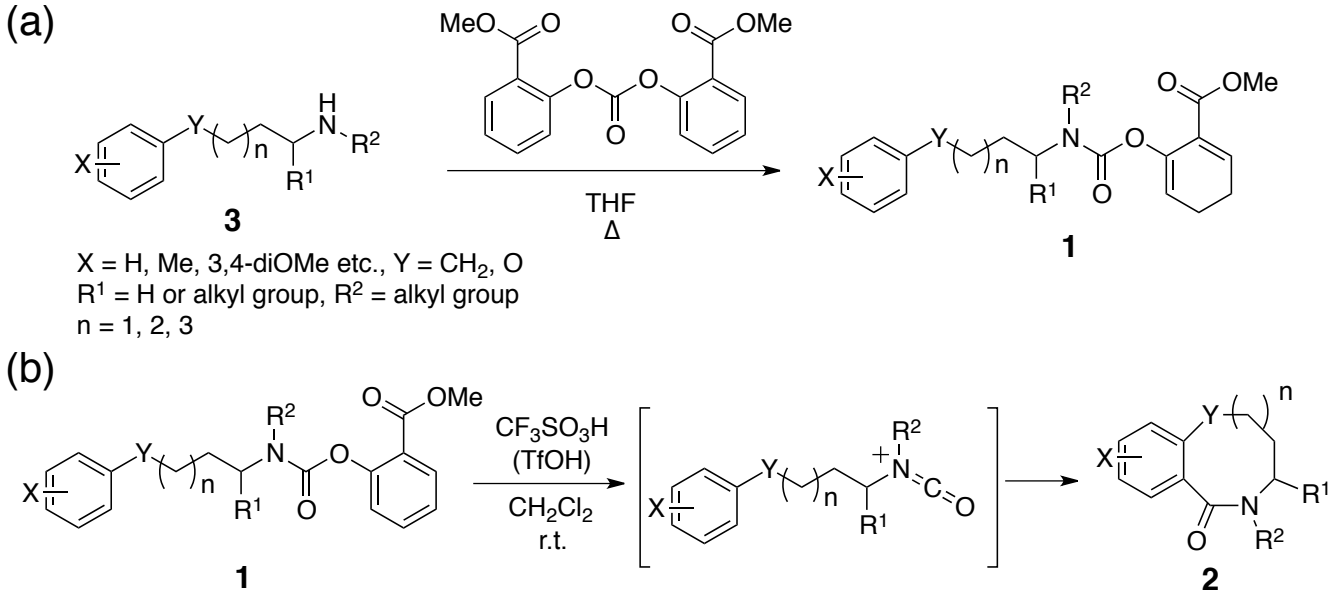
Scheme 1. Intramolecular hydrogen bonding-assisted activation of carbamate

Recently, we developed a system to activate carbamate compounds (**1**), which is applicable to highly efficient cyclization of phenethylcarbamates to afford 6-membered dihydroisoquinolone derivatives (**2**) in high yields. [8] We found that when *ortho*-methyl salicylate was used as a leaving group in carbamates, steady cleavage of the C-O bond occurred under mild conditions (at 20 °C in the presence of trifluoromethanesulfonic acid (CF_3SO_3H, TfOH)) to generate carbamoyl cations, and these systems offered considerable substrate generality (**Scheme 1**). Kinetic and computational studies indicated that the rate-determining step of this reaction is *not* the cyclization step but the C-O (*o*-methyl salicylate) bond cleavage step to generate carbamoyl cations. After generation of the carbamoyl cation, the reactive species immediately transforms to the cyclized product. We expected that this highly efficient reaction under mild conditions would be applicable to medium-sized ring formation. Further, we also expected that we could utilize the reaction rates as a quantitative scale to evaluate the ring-size dependency of the activation free energy of IEAS reaction.

Results and Discussion

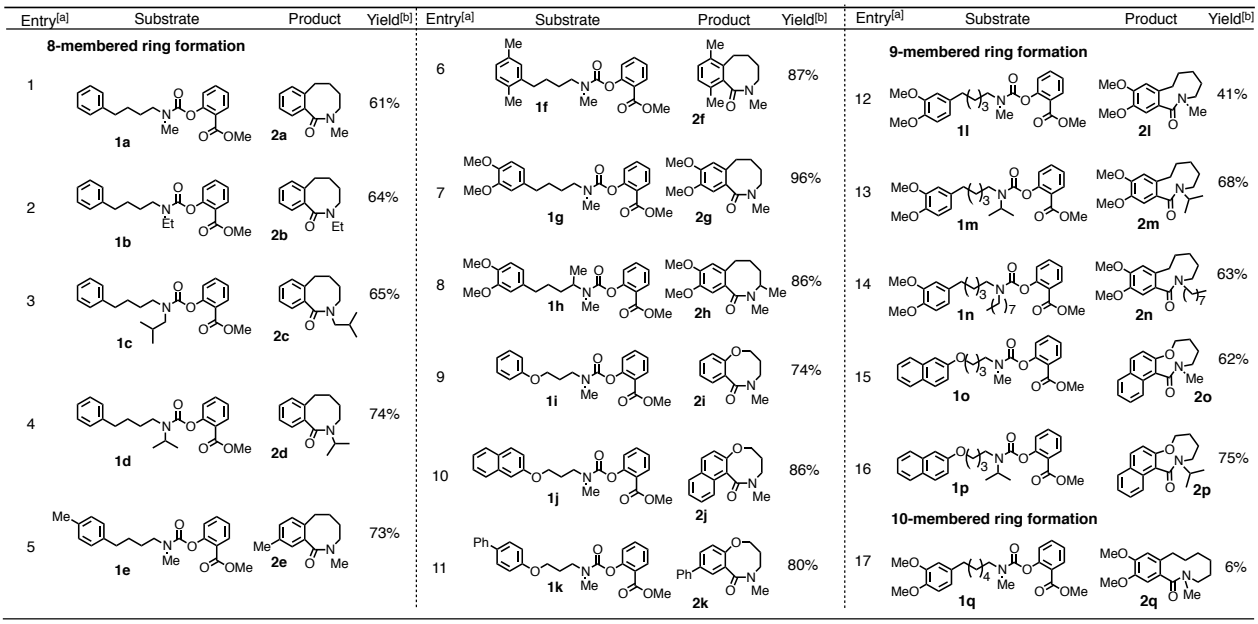
First, we examined the formation of benzolactams with 8-membered rings. The reaction conditions were screened and optimized (Supporting Information), and we found that carbamate

substrates bearing *ortho*-methyl salicylate as a leaving group gave 8-membered benzolactams in good yields under TfOH-activated conditions. By this method, various 8- and 9-membered benzolactams can be obtained from a simple amine compound (**Scheme 2 (a) (b)**).



Scheme 2. Formation of benzolactams with medium-sized rings from simple amine compounds (a and b)

Table 1. Substrate generality of medium-sized ring formation



[a] General procedure: Substrate (0.60 mmol) was dissolved in dichloromethane (3.0 mL) and TfOH (10 equiv.) was added at 0 ºC. The reaction mixture was stirred at 20-25 °C (r.t.) for 1-6 hrs. [b] Isolated yields.

The substrate generality of this reaction was investigated under these optimized conditions (Table 1). The reactions proceeded in good to high yields without dilution. Examples of 8-membered ring formation are shown in entries 1-11. For compounds with non-substituted aromatic rings, 8-membered ring products (**2a**-**2d**) were obtained in good to high yields (Entries 1-4). Interestingly, higher yields were obtained as the size of the alkyl group on the nitrogen atom became larger. Possible explanations for this include: (1) the Thorpe-Ingold effect, and (2) protection of the carbamoyl cation from the attack of triflate anion, which would result in formation of amine by-products (for evidence of counter anion attack, see Supporting Information). In the absence of an alkyl group on the nitrogen atom, the reaction afforded a complex mixture (data not shown).

Electron-donating groups were favorable for the cyclization (Entries 5-7). On the other hand, a methoxy group at the *para*-position with respect to the alkyl chain prevented the cyclization (data not shown), presumably because it is at the meta position with respect to the bond-forming carbon atom, leading to deactivation of the cyclization. A methyl group (**1h**) at the α-position of the nitrogen atom did not greatly affect the reaction (Entry 8). Substrates tethered by an oxygen-containing carbon chain (**1i**-**1k**) were also examined (Entries 9-11) and they afforded cyclized products in good yields.

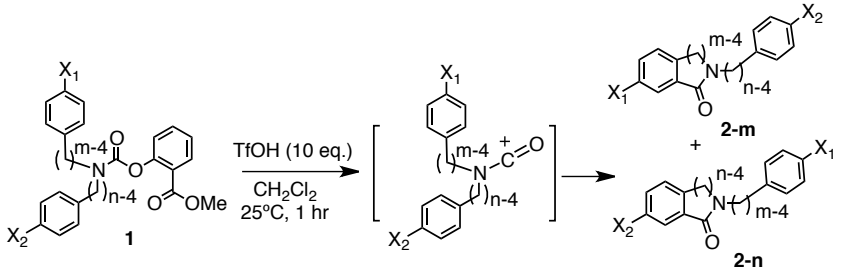
Nine-membered ring formation reactions were also investigated (Entries 12-16). Electron-rich aromatic rings were required for this ring size. Introduction of methoxy groups improved the reaction efficiency, affording the cyclized product in 41 % yield (Entry 12). As the steric bulkiness of the alkyl group on the nitrogen atom was increased, the reaction yield also increased (68 and 63 % in Entries 13, 14, respectively). This 9-membered ring formation reaction was also quite effective for naphthol derivative **1o** (Entry 15). When the size of the alkyl group on the nitrogen atom was increased (**1p**,

Entry 16), the reaction yield increased, reaching 75%. To examine the limitations of the reaction, the formation of a 10-membered ring was also investigated (Entry 17). Although the yield was low, the 10-membered ring product **2q** could be obtained.

Next, we quantitatively compared the reaction rates of formation of normal-size (5, 6 and 7 members) and medium-size rings (8 and 9 members).

In a previous study, it was found that the rate-determining step is not the cyclization reaction, but generation of the carbamoyl cation.[8] So, direct measurement of cyclization rates is impossible. However, relative cyclization rates can be obtained by means of competition experiments. We designed and prepared substrates **1r-x (Table 2)** that bear two aromatic rings connected to a nitrogen atom, tethered by two alkyl chains of different lengths; with these compounds, the relative ratios of the products of different ring sizes can be used to evaluate the relative reaction rates of the cyclizations. [9]

Table 2. Competition experiments to measure relative cyclization rates.



Entry[a]	Substrate	X_1	X_2	m	n	Product Ratio[b] **2-m** : **2-n**	Total Yield[c]
1	**1r**	H		6	6	86.5 : 13.5	90%
2	**1s**		Cl	6	6	98.5 : 1.5	72%
3	**1t**	Cl	H	6	5	77.4 : 22.6	83%
4	**1u**	H	H	5	7	86.7 : 13.3	84%
5	**1v**	H	Cl	7	5	97.6 : 2.4	81%
6	**1w**	Cl	H	5	8	59.4 : 40.6	55%
7	**1x**	H	H	6	5	100 : 0[d]	95%
8	**1y**	H	H	8	9	100 : 0[d]	53%

[a] General procedure: Substrate (0.40 mmol) was dissolved in dichloromethane (2.0 mL) and slowly dropped into a mixture of TfOH (10 equiv.) and dichloromethane (2.0 mL) at 25 ºC in an isothermal bath. The reaction mixture was stirred at 25 ºC for 1 hr under argon atmosphere. [b] ^{1}H NMR integration

ratio. Average values of two independent experiments. [c] Average values of the yield of the mixture of the two products in two independent experiments. [d] ^{1}H NMR integration ratio obtained from one experiment. The 9-membered-ring product **2x-n** was not detected.

To estimate the size effect on ring formation rates, a solution of substrate in dichloromethane was dropped into a mixture of TfOH and dichloromethane at 25 ºC and the product ratio was determined after 1 hr. All of the reactions were completed within one hour. The main reason of the loss of starting material mass, the total product yield did not reach 100%, is that the carbamoyl cation is not only trapped by tethered aromatic ring but also trapped by triflate anion to afford amine product (See supporting information). The intermolecular reaction was not observed based on the product analysis.

The attempt of quantitative comparison of the rate of 6- and 5-membered ring formation was difficult because 6-membered ring formation dominated (Entry 7). To make the product ratios measurable by means of ^{1}H-NMR, i.e., to avoid highly biased selectivity of cyclization reactions, the magnitude of the activation enthalpy was tuned by introduction of a deactivating 4-chloro group or 4-chlorophenyl group on the aromatic rings (see **Table 2**).

Introduction of a 4-chlorophenyl group decreased the cyclization rate by about one-sixth (**1r**, Entry 1). Introduction of a 4-chloro group decreased the reaction rate to greater extent (**1s**, Entry 2). The reaction rate of 6-membered ring formation (**2t-m**) for compounds with a 4-chloro-substituted benzene ring was about three times faster than 5-membered ring formation (**2t-n**) for compounds with a non-substituted benzene ring (Entry 3). In this context, 6-membered ring formation occurs more readily than 5-membered ring formation in the present reaction. This trend has also been observed in various Friedel-Crafts-type alkylation reactions. [10]

The reaction rate of 5-membered ring formation for compounds with a non-substituted benzene ring (**2u-m**) was six times faster than that of 7-membered ring formation for compounds with a non-substituted benzene ring (**2u-n**) (Entry 4). The reaction rate of 7-membered ring formation for compounds with a non-substituted benzene ring (**2v-m**) was forty times faster than that of 5-membered ring formation for compounds with a chloro-substituted benzene ring (**2v-n**) (Entry 5). The reaction rate of 5-membered ring formation of 4-chloro-substituted compounds (**2w-m**) was revealed to be 1.5 times faster than 8-membered ring formation of non-substituted compounds (**2w-n**) (Entry 6). Finally, 9-membered ring formation (**2y-n**) was not detected in compounds with the present combinations of the substituents (Entry 8). This result indicated that 9-membered ring formation is significantly slower than 8-membered ring formation.

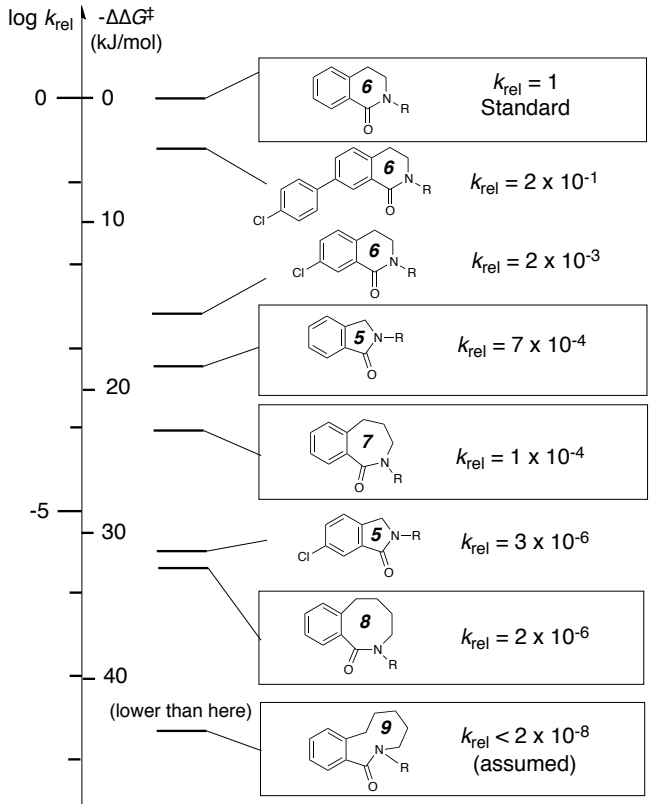


Figure 1. Relative reaction rates (errors: within ±3% for each competition experiment at maximum) and free energies of each ring formation and relative Gibbs free energy of activation (kJ/mol) at 25 ºC.

Based on these results (**Table 2**), we obtained relative reaction rates for formation of various-sized rings (**Figure 1**), and relative differences of Gibbs free energy of activation ($\Delta\Delta G_{298K}^{\ddagger}$) were calculated based on transition state theory.[11]

The results indicate that the rate of 5-membered ring formation is 7 x 10^{-4} times slower than 6-membered ring formation, and the 7-membered ring formation was 1 x 10^{-4} times slower than 6-membered ring formation. These results indicate that the Gibbs free energy of activation for the 5- and 7-membered ring formations are unfavorable by approximately 20 kJ/mol over the 6-membered ring formation. In addition, 8-membered ring formation was 2 x 10^{-6} times slower than 6-membered ring formation, that is, the former is energetically more unfavorable than 6-membered ring formation by approximately 30 kJ/mol. Because 9-membered ring formation is much slower than 8-membered ring formation, the relative Gibbs free energy of activation should be larger than approximately 40 kJ/mol at minimum in comparison with 6-membered ring formation (this value was derived from the product ratio of 100: 1 at 25 ºC, within the limits of experimental error). In order to overcome this energy barrier, activation of the aromatic ring is effective for formation of medium-sized benzolactams.

Conclusion

This work provides a facile method for the synthesis of medium-sized benzolactams, which are important substructures of bioactive compounds. Compounds containing non-substituted or activated benzene rings react with electrophile to afford 8- and 9-membered benzolactams in good to high yields. The method is also tolerant of atom replacement in the linker chain. These results are expected to be useful reference data for estimation of the difficulty of medium-sized ring formation in other IEAS reactions. However, the reaction mechanism of this cyclization is not as simple as that of usual IEAS reactions. Further mechanistic study to assess path bifurcation[12] is under way.

Experimental Section

I. General methods

Melting points were determined with a Yanaco micro melting point apparatus without correction. ^{1}H (400 MHz) – and ^{13}C (100 MHz) -NMR spectra were recorded on a Bruker Avance400. Chemical shifts were calibrated with tetramethylsilane as an internal standard or with the solvent peak, and are shown in ppm values, and coupling constants are shown in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, ddd = doublet of double doublet, dt = double triplet, dq = double quartet, h = heptet, m = multiplet, and brs = broad singlet. The NMR spectra are measured at 25 ºC if not mentioned. Electron spray ionization time-of-flight mass spectra (ESI-TOF MS) were recorded on a Bruker micrOTOF-05 to give high-resolution mass spectra (HRMS). HPLC separation was performed on HITACHI LaChrom Elite HPLC systems containing of following: pump, L-2130; detector, L-2400. All of the trifluoromethanesulfonic acid promoted cyclization reactions were performed using heat gun-dried or oven-dried glassware. Trifluoromethanesulfonic acid (TfOH) was dried with trifluoromethanesulfonic acid anhydride and purified with vacuum distillation prior to use. Other commercially available compounds and solvents were used as received. All microwave reactions were carried out in a single-mode microwave (Biotage Initiator^{TM} Eight Synthesizer programmed to heat constantly at the specified power). Reaction temperatures were determined using the built-in, on-line IR-sensor. The reaction temperature of the competition reactions was implemented in water bath; the temperature was kept at 25 ºC using HAAKE DC5 immersion circulator. Other heating reaction was conducted in oil bath.

II. Synthesis of substrates

Synthesis of dimethyl 2,2'-(carbonylbis(oxy))dibenzoate

This compound was synthesized according to our previous literature.[8]

Synthesis of methyl 2-((methyl(4-phenylbutyl)carbamoyl)oxy)benzoate (1a)

To a solution of (4-bromobutyl)benzene (854 mg, 4.00 mmol) in methanol (2.0 mL), methylamine (40% solution in methanol) (5.0 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 6 hrs. The solvent was removed in vacuo and the crude residue was dissolved in dichloromethane. The solution was washed with aqueous sodium hydroxide (2M) (10 mL), dried over sodium sulfate and the solvent was evaporated under reduced pressure to give *N*-methyl-4-phenylbutan-1-amine (**3a**) as colorless oil (668 mg, 4.09 mmol, 102% crude yield). The amine was used without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.25 (m, 2H), 7.18-7.15 (m, 3H), 2.64-2.56 (m, 4H), 2.41 (s, 3H), 1.69-1.61 (m, 2H), 1.56-1.48 (m, 2H), 1.29 (brs, 1H).^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 142.4, 128.3, 128.2, 125.6, 52.0, 36.5, 35.8, 29.5, 29.1.ESI-HRMS: Calcd for $C_{11}H_{18}N^{+}$ $[M+H]^{+}$: 164.14338. Found: 164.14161.

A solution of **3a** (386 mg, 2.37 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (668 mmol) in tetrahydrofuran (5.0 mL) was stirred at room temperature for 13 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 5 ~ 1 : 4) to afford methyl 2-((methyl(4-phenylbutyl)carbamoyl)oxy)benzoate **1a** as colorless oil (590 mg, 1.80 mmol, 89% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.96 (dd, J = 7.6, 1.6 Hz, 1H, rotamer A and B), 7.53-7.49 (m, 1H, rotamer A and B), 7.28-7.08 (m, 7H, rotamer A and B), 3.81 (s, 1.3H, rotamer B), 3.79 (s, 1.7H, rotamer A), 3.48 (t, J = 6.8 Hz, 0.9H, rotamer B), 3.38 (t, J = 6.8 Hz, 1.1H, rotamer A), 3.09 (s, 1.7H, rotamer A), 2.98 (s, 1.3H, rotamer B), 2.70-2.64 (m, 2H, rotamer A and B), 1.73-1.66 (m, 4H, rotamer A and B).^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.2, 154.5, 154.3, 151.3, 151.1, 142.2, 142.0, 133.4, 131.4, 128.4, 128.3, 128.2, 125.74, 125.66, 125.2, 124.1, 124.0, 123.8, 123.7, 51.9, 49.12, 49.08, 35.5, 34.8, 34.4, 28.4, 28.3, 27.4, 26.9. ESI-HRMS: Calcd for $C_{20}H_{23}NNaO_4^+$ $[M+Na]^+$: 364.1519. Found: 364.1509.

Synthesis of methyl 2-((ethyl(4-phenylbutyl)carbamoyl)oxy)benzoate (1b)

To a stirred solution of 4-phenylbutan-1-amine (753 mg, 5.04 mmol) and triethylamine (1.0 mL) in dry dichloromethane (10 mL), acyl chloride (405 mg, 5.16 mmol) was added dropwise slowly at 0 ºC. The temperature was raised to 25 ºC and the mixture was stirred for 30 min. The reaction was quenched with 10 mL of ice water and the whole was extracted with dichloromethane (30 mL). The organic layer was washed with aqueous hydrogen chloride (1M, 5.0 mL), dried over sodium sulfate and the solvent was removed under reduced pressure to give crude oil which contains *N*-(4-phenylbutyl)acetamide (**3b**) (known compound) (1056 mg, 5.52 mmol, 109% crude yield). The crude product was used without further purification.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 5.82 (brs, 1H), 3.23 (q, J = 6.8 Hz, 2H), 2.62 (t, J = 7.6 Hz, 2H), 1.94 (s, 3H), 1.68-1.60 (m, 2H), 1.55-1.48 (m, 2H).^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 170.0, 142.0, 128.3, 128.2, 125.7, 39.4, 35.4, 29.1, 28.6, 23.2. ESI-HRMS: Calcd for $C_{12}H_{17}NNaO^+$ $[M+Na]^+$: 214.1202. Found: 214.1218.

A solution of the crude compound that contains **3b** (627 mg) and lithium aluminum hydride (307 mg, 8.09 mmol) in tetrahydrofuran (20 mL) was stirred at 60 ºC for 20 hrs. Then the reaction solution was cooled to 0 ºC and quenched with sodium sulfate decahydrate (10 g) and ethyl acetate (50 mL). Then the solution was filtered and the solvent was removed in vacuo to give crude oil, which contains *N*-ethyl-4-phenylbutylamine (**4b**) (known compound) (565 mg, 3.19 mmol, 97% crude yield). The amine was used directly in the next step without further purification.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.25 (m, 2H), 7.18-7.15 (m, 3H), 2.64-2.60 (m, 6H), 1.69-1.61 (m, 2H), 1.56-1.49 (m, 2H), 1.29 (brs, 1H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 142.4, 128.3, 128.2, 125.6, 49.7, 44.1, 35.8, 29.8, 29.2, 15.3. ESI-HRMS: Calcd for $C_{12}H_{20}N^+$ $[M+H]^+$: 178.1590. Found: 178.1601.

A solution of **4b** (407 mg, 2.30 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (660 mg, 2.00 mmol) in tetrahydrofuran (5.0 mL) was stirred at 50 ºC for 2 days. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 4) to afford methyl 2-((ethyl(4-phenylbutyl)carbamoyl)oxy)benzoate **1b** as colorless oil (596 mg, 1.68 mmol, 84% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed (approximately 1 : 1 ratio at 25 ºC), δ (ppm): 7.95 (d, J = 7.6 Hz, 1H), 7.52-7.48 (m, 1H), 7.23-7.22 (m, 3H), 7.19-7.10 (m, 4H), 3.80 (s, 1.5H), 3.78 (s, 1.5H), 3.49-3.42 (m, 2H), 3.38-3.33 (m, 2H), 2.67-2.63 (m, 2H), 1.76-1.66 (m, 4H), 1.26 (t, J = 6.8 Hz, 1.5H), 1.18 (t, J = 6.8 Hz, 1.5H). ^{13}C-NMR (100 MHz,

$CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.3, 154.2, 153.9, 151.04, 151.01, 142.2, 142.0, 133.3, 131.4, 128.32, 128.29, 128.22, 128.18, 125.7, 125.6, 125.2, 124.0, 51.9, 47.1, 46.9, 42.6, 42.2, 35.50, 35.48, 28.5, 28.4, 28.1, 27.6, 13.7, 13.0. ESI-HRMS: Calcd for $C_{21}H_{25}NNaO_4^+$ $[M+Na]^+$: 378.1676. Found: 378.1666. Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.03; H, 7.07; N, 4.07.

Synthesis of methyl 2-((isobutyl(4-phenylbutyl)carbamoyl)oxy)benzoate (1c)

To a stirred solution of 4-phenylbutan-1-amine (753 mg, 5.04 mmol) and triethylamine (1.0 mL) in dry dichloromethane (10 mL), isobutyryl chloride (541 mg, 5.08 mmol) was added dropwise slowly at 0 ºC. The temperature was raised to 25 ºC and the mixture was stirred for 30 min. The reaction was quenched with 10 mL of ice water and the whole was extracted with dichloromethane (30 mL). The organic layer was washed with aqueous hydrogen chloride (1M, 5.0 mL), dried over sodium sulfate and the solvent was removed under reduced pressure to give *N*-(4-phenylbutyl)isobutyramide (**3c**) as colorless oil (1091 mg, 4.98 mmol, 99% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.24 (m, 2H), 7.18-7.14 (m, 3H), 5.81 (brs, 1H), 3.23 (q, J = 6.8 Hz, 2H), 2.62 (t, J = 7.6 Hz, 2H), 2.32 (h, J = 7.2 Hz, 1H), 1.67-1.60 (m, 2H), 1.55-1.48 (m, 2H), 1.12 (d, J = 6.8 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 177.0, 142.2, 128.4, 128.3, 125.8, 39.2, 35.6, 35.5, 29.3, 28.7, 19.7. ESI-HRMS: Calcd for $C_{14}H_{21}NNaO^+$ $[M+Na]^+$: 242.1515. Found: 242.1527.

A solution of *N*-(4-phenylbutyl)isobutyramide (588 mg, 2.68 mmol) and lithium aluminum hydride (241 mg, 6.35 mmol) in tetrahydrofuran (15 mL) was stirred at 60 ºC for 7 hrs. Then the reaction solution was cooled to 0 ºC and quenched with sodium sulfate decahydrate (10 g) and ethyl acetate (50 mL). Then the solution was filtered and the solvent was removed in vacuo to give crude oil, which contains *N*-isobutyl-4-phenylbutan-1-amine (**4c**) (known compound) (532 mg). The amine was used directly in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29-7.25 (m, 2H), 7.19 -7.15 (m, 3H), 2.64-2.58 (m, 4H), 2.39 (d, J = 6.8 Hz, 2H), 1.73 (h, J = 6.8 Hz, 1H), 1.68-1.59 (m, 2H), 1.56-1.49 (m, 2H), 1.06 (brs, 1H), 0.89 (d, J = 6.4 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 142.5, 128.4, 128.2, 125.6, 58.2, 50.0, 35.9, 29.8, 29.2, 28.3, 20.7. ESI-HRMS: Calcd for $C_{14}H_{24}N^+$ $[M+H]^+$: 206.1903. Found: 206.1878.

A solution of **4c** (409 mg, 1.99 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (597 mg, 1.81 mmol) in tetrahydrofuran (5.0 mL) was stirred at 50 ºC for 42 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 3) to afford methyl 2-((isobutyl(4-phenylbutyl)carbamoyl)oxy)benzoate **1c** as colorless oil (547 mg, 1.43 mmol, 79% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed (approximately 1 : 1 ratio at 25 ºC), δ (ppm): 7.96-7.93 (m, 1H, rotamer A and B), 7.52-7.47 (m, 1H), 7.28-7.12 (m, 7H), 3.81 (s, 1.5H), 3.77 (s, 1.5H), 3.44 (t, J = 6.8 Hz, 1H), 3.34 (t, J = 6.8 Hz, 1H), 3.24 (d, J = 7.6 Hz, 1H), 3.12 (d, J = 7.6 Hz, 1H), 2.69-2.63 (m, 2H), 2.14-1.94 (m, 1H), 1.79-1.66 (m, 4H), 0.97 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.3, 154.5, 1510, 151.0, 142.2, 142.0, 133.3, 133.2, 131.4, 131.3, 128.32, 128.30, 128.22, 128.18, 125.7, 125.6, 125.2, 124.1, 124.03, 123.99, 123.9, 55.1, 54.6, 51.9, 48.0, 47.8, 35.6, 35.5, 28.6, 28.5, 27.8, 27.5, 27.11, 27.09, 20.1, 20.0. ESI-HRMS: Calcd for $C_{23}H_{29}NNaO_4^+$ $[M+Na]^+$: 406.1989. Found: 406.1983. Anal. Calcd. for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.04; H, 7.54; N, 3.73.

Synthesis of methyl 2-((isopropyl(4-phenylbutyl)carbamoyl)oxy)benzoate (1d)

To a solution of (4-bromobutyl)benzene (551 mg, 2.59 mmol) in tetrahydrofuran (2.0 mL), isopropylamine (4.0 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 24 hrs. The solvent was removed in vacuo and crude residue was dissolved in ethyl acetate. The solution was washed with aqueous sodium hydroxide (2M) (5 mL), washed with brine (10

mL), dried over sodium sulfate and the solvent was evaporated under reduced pressure to give *N*-isopropyl-4-phenylbutan-1-amine (**3d**) as colorless oil (489 mg, 2.56 mmol, 99% yield).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.25 (m, 2H), 7.18-7.15 (m, 3H), 2.76 (h, J = 6.4Hz, 1H), 2.64-2.58 (m, 4H), 1.69-1.62 (m, 2H), 1.56-1.48 (m, 2H), 1.04 (d, J = 6.0 Hz, 6H), 0.86 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 142.5, 128.4, 128.2, 125.6, 48.7, 47.4, 35.9, 30.2, 29.3, 23.0. ESI-HRMS: Calcd for $C_{13}H_{22}N^+$ $[M+H]^+$: 192.1747. Found: 192.1760.

A solution of **3d** (463 mg, 2.42 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (1016 mg, 3.07 mmol) in tetrahydrofuran (4.0 mL) was stirred at 50 ºC for 16 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 4) to afford methyl 2-((isopropyl(4-phenylbutyl)carbamoyl)oxy)benzoate **1d** (703 mg, 1.90 mmol, 79% yield (based on *N*-isopropyl-4-phenylbutan-1-amine)) as colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.95 (d, J = 7.6 Hz, 1H, rotamer A and B), 7.51 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H, rotamer A and B), 7.27-7.23 (m, 3H, rotamer A and B), 7.18-7.06 (m, 4H, rotamer A and B), 4.42-4.35 (m, 0.4H, rotamer B), 4.25-4.19 (m, 0.6H, rotamer A), 3.81 (s, 3H, rotamer A and B), 3.32 (t, J = 7.2 Hz, 1.2H, rotamer A), 3.24 (t, J = 6.8 Hz, 0.8H, rotamer B), 2.68-2.64 (m, 2H, rotamer A and B), 1.79-1.66 (m, 4H, rotamer A and B), 1.28 (d, J = 6.8 Hz, 2.4H, rotamer B), 1.21 (d, J = 6.8 Hz, 3.6H, rotamer A). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.5, 154.0, 151.1, 142.1, 133.4, 131.5, 128.33, 128.26, 125.7, 125.2, 124.2, 124.1, 124.0, 52.0, 48.7, 48.4, 43.5, 35.6, 35.5, 29.8, 29.3, 28.8, 21.1, 20.4. ESI-HRMS: Calcd for $C_{22}H_{27}NNaO_4^+$ $[M+Na]^+$: 392.1832. Found: 392.1829. Anal. Calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.59; H, 7.30; N, 3.82.

Synthesis of methyl 2-((methyl(4-(*p*-tolyl)butyl)carbamoyl)oxy)benzoate (1e)

A solution of 4-(*p*-tolyl)butanoic acid (532 mg, 2.99 mmol) in $SOCl_2$ (1.0 mL) was stirred at 60 ºC for 4 hours. Then the solvent was removed under reduced pressure to afford crude oil. The oil was dissolved in dry dichloromethane (4.0mL) and the solution was added dropwise to methylamine (40% solution in methanol) (2.5 mL) under stirring at 0 ºC. The temperature was raised to 25 ºC and the reaction mixture was stirred for 5 min. Then 10 mL of aqueous hydrogen chloride (1M) was added and the whole was extracted with dichloromethane (20 mL). The organic layer was washed with aqueous sodium carbonate (2M, 10 mL) and dried over sodium sulfate. The solvent was removed in vacuo to afford *N*-methyl-4-(p-tolyl)butanamide (**3e**) as white solid (562 mg, 2.94 mmol, 98% yield).
Mp. 60 - 61 ºC (colorless needles, recrystallized from $CHCl_3$/hexane)
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.09-7.04 (m, 4H), 5.63 (brs, 1H), 2.77 (d, J = 4.8 Hz, 3H), 2.60 (t, J = 7.6 Hz, 2H), 2.31 (s, 3H), 2.16 (t, J = 7.6 Hz, 2H), 1.98-1.90 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 173.4, 138.4, 135.3, 129.0, 128.3, 35.7, 34.7, 27.2, 26.2, 20.9. ESI-HRMS: Calcd for $C_{12}H_{17}NNaO^+$ $[M+Na]^+$: 214.1202. Found: 214.1198.

A solution of **3e** (483 mg, 2.53 mmol) and lithium aluminum hydride (195 mg, 5.14 mmol) in tetrahydrofuran (10 mL) was stirred at 65 ºC for 4 hrs. Then the reaction solution was cooled to 0 ºC and quenched with sodium sulfate decahydrate (10 g) and ethyl acetate (50 mL). Then the solution was filtered and the solvent was removed in vacuo to give crude oil which contains *N*-methyl-4-(p-tolyl)butan-1-amine (**4e**) (452 mg, 2.55 mmol, 101% crude yield). The amine was used directly in the next step without further purification.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.09-7.05 (m, 4H), 2.60-2.56 (m, 4H), 2.41 (s, 3H), 2.31 (s, 3H), 1.67-1.59 (m, 2H), 1.55-1.47 (m, 2H), 1.14 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 139.4, 135.0, 128.9, 128.2, 52.0, 36.5, 35.3, 29.6, 29.2, 20.9. ESI-HRMS: Calcd for $C_{12}H_{20}N^+$ $[M+H]^+$: 178.1590. Found: 178.1589.

A solution of **4e** (418 mg, 2.36 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (670 mg, 2.03 mmol) in tetrahydrofuran (5.0 mL) was stirred at 50 ºC for 2 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by

column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 3) to afford methyl 2-((methyl(4-(*p*-tolyl)butyl)carbamoyl)oxy)benzoate **1e** (670 mg, 1.89 mmol, 93% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))) as colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.96 (dd, J = 7.6, 1.6 Hz, 1H, rotamer A and B), 7.52-7.48 (m, 1H, rotamer A and B), 7.24 (dd, J = 7.6, 7.6 Hz, 1H, rotamer A and B), 7.15-7.07 (m, 5H, rotamer A and B), 3.80 (s, 1.4H, rotamer B), 3.79 (s, 1.6H, rotamer A), 3.47 (t, J = 6.8 Hz, 0.9H, rotamer B), 3.37 (t, J = 6.8 Hz, 1.1H, rotamer A), 3.08 (s, 1.6H, rotamer A), 2.97 (s, 1.4H, rotamer B), 2.65-2.60 (m, 2H, rotamer A and B), 2.30 (s, 3H, rotamer A and B), 1.71-1.64 (m, 4H, rotamer A and B).
^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.2, 154.4, 154.3, 151.2, 151.1, 139.1, 138.9, 135.1, 135.0, 133.4, 131.4, 128.89, 128.86, 128.2, 125.2, 124.1, 124.0, 123.8, 123.7, 51.9, 49.1, 35.0, 34.8, 34.4, 28.4, 28.3, 27.3, 26.9, 20.9. ESI-HRMS: Calcd for $C_{21}H_{25}NNaO_4^+$ $[M+Na]^+$: 378.1679. Found: 378.1657. Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.02; H, 7.09; N, 4.00.

Synthesis of methyl 2-(((4-(2,5-dimethylphenyl)butyl)(methyl)carbamoyl)oxy)benzoate (1f)
4-(2,5-dimethylphenyl)-4-oxobutanoic acid was synthesized according to the literature.[13]

A mixture of methyl 4-(2,5-dimethylphenyl)-4-oxobutanoic acid (1483 mg, 7.19 mmol) and tetraethylsilane (3316 mg, 28.5 mmol) was added trifluoroacetic acid (15 mL) at 0 ºC. The temperature was raised to room temperature and the reaction solution was stirred for 1 day. The reaction was quenched with aqueous sodium hydroxide (1M, 100 mL). The whole was washed with dichloromethane (50 mL). The water layer was acidified with aqueous hydrogen chloride (2M, 20 mL) and extracted with ethyl acetate (50 mL x 2). The organic layer was washed with brine (10 mL), dried over sodium sulfate and the solvent was removed under reduced pressure to give white powder which contains 4-(2,5-dimethylphenyl)butanoic acid (**3f**) (known compound) (1458 mg, 7.58 mmol, 105% crude yield).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 10.77 (brs, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.93 (s, 1H), 6.92 (d, J = 7.6 Hz, 1H), 2.64-2.60 (m, 2H), 2.42 (t, J = 7.6 Hz, 2H), 2.29 (s, 3H), 2.26 (s, 3H), 1.95-1.87 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 180.2, 139.2, 135.3, 132.7, 130.2, 129.7, 126.8, 33.7, 32.4, 25.1, 20.9, 18.7.

The crude mixture that contains **3f** (1279 mg) was dissolved in $SOCl_2$ (3 mL), and the solution was stirred at 70 ºC for 30 min. Then the solvent was removed under reduced pressure to afford crude oil. The oil was added methylamine (40% solution in methanol) (5.0 mL) under stirring at -78ºC. The temperature was raised to 25 ºC and the reaction mixture was stirred for 1 hour. Then 10 mL of aqueous hydrogen chloride (1M) was added and the whole was extracted with dichloromethane (50 mL). The organic layer was washed with aqueous sodium carbonate (2M, 10 mL) and dried over sodium sulfate. The solvent was removed in vacuo to afford crude oil. The crude oil was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 2) to afford 4-(2,5-dimethylphenyl)-*N*-methylbutanamide (**4f**) as white powder (941 mg, 4.58 mmol, 73% yield for 3 steps, the yield was calculated based on methyl 4-(2,5-dimethylphenyl)-4-oxobutanoic acid).
Mp. 77 - 78 ºC (colorless needles, recrystallized from $CHCl_3$/hexane)
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.01 (d, J = 7.6 Hz, 1H), 6.94-6.90 (m, 2H), 5.40 (brs, 1H), 2.80 (d, J = 4.8 Hz, 3H), 2.60 (t, J = 7.6 Hz, 2H), 2.28 (s, 3H), 2.26 (s, 3H), 2.22 (t, J = 7.6 Hz, 2H), 1.95-1.87 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 173.3, 139.5, 135.3, 132.8, 130.1, 129.7, 126.7, 36.1, 32.6, 26.3, 26.0, 20.9, 18.8. ESI-HRMS: Calcd for $C_{13}H_{19}NNaO^+$ $[M+Na]^+$: 228.1359. Found: 228.1370.

A solution of **4f** (878 mg, 4.27 mmol) and lithium aluminum hydride (421 mg, 11.1 mmol) in tetrahydrofuran (20 mL) was stirred at 40 ºC for 10 hrs. Then the reaction solution was cooled to 0 ºC and quenched with sodium sulfate decahydrate (10 g) and ethyl acetate (50 mL). Then the solution was filtered and the solvent was removed in vacuo to give 4-(2,5-dimethylphenyl)-*N*-methylbutan-1-amine

(**5f**) as crude oil (777 mg, 4.06 mmol, 95%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.01 (d, J = 7.6 Hz, 1H), 6.94 (s, 1H), 6.89 (d, J = 7.6 Hz, 1H), 2.62-2.53 (m, 4H), 2.43 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H), 1.61-1.55 (m, 4H), 1.04 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 140.5, 135.1, 132.6, 130.0, 129.6, 126.4, 52.1, 36.6, 33.2, 30.0, 28.1, 20.9, 18.8. ESI-HRMS: Calcd for $C_{13}H_{22}N^+$ $[M+H]^+$: 192.1747. Found: 192.1737.

A solution of **5f** (763 mg, 3.99 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (1262 mg, 3.82 mmol) in dichloromethane (5.0 mL) was stirred at room temperature for 3 days. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 7) to afford methyl 2-(((4-(2,5-dimethylphenyl)butyl)(methyl)carbamoyl)oxy)benzoate **1f** as colorless oil (1086 mg, 2.94 mmol, 77% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.96 (dd, J = 8.0, 1.6 Hz, 1H, rotamer A and B), 7.52-7.49 (m, 1H, rotamer A and B), 7.26 (ddd, J = 7.6, 7.6, 0.4 Hz, 1H, rotamer A and B), 7.14 (d, J = 8.0 Hz, 0.6H, rotamer A), 7.10 (d, J = 8.0 Hz, 0.4H, rotamer A and B), 7.00 (d, J = 7.6 Hz, 1H, rotamer A and B), 6.95 (s, 1H, rotamer A and B), 6.90 (d, J = 7.6 Hz, 1H, rotamer A and B), 3.82 (s, 1.2H, rotamer B), 3.79 (s, 1.8H, rotamer A), 3.50 (t, 0.8H, J = 7.2 Hz, rotamer B), 3.39 (t, 1.2H, J = 7.2 Hz, rotamer A), 3.11 (s, 1.8H, rotamer A), 3.00 (s, 1.2H, rotamer B), 2.65-2.59 (m, 2H, rotamer A and B), 2.27 (s, 2.4H, rotamer B), 2.26 (s, 3.6H, rotamer A), 1.80-1.59 (m, 4H, rotamer A and B).
^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.2, 154.5, 151.3, 151.2, 140.2, 140.0, 135.1, 133.4, 132.5, 131.4, 130.03, 129.98, 129.63, 129.55, 126.54, 126.47, 125.2, 124.1, 124.0, 123.9, 123.8, 51.9, 49.2, 34.9, 34.4, 32.9, 27.8, 27.3, 27.2, 20.9, 18.8. ESI-HRMS: Calcd for $C_{22}H_{27}NNaO_4^+$ $[M+Na]^+$: 392.1832. Found: 392.1803. Anal. Calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.36; H, 7.16; N, 3.73.

Synthesis of methyl 2-(((4-(3,4-dimethoxyphenyl)butyl)(methyl)carbamoyl)oxy)benzoate (1g)

A suspension of succinic anhydride (3329 mg, 33.3 mmol), aluminum chloride (8556 mg, 64.0 mmol) in dry dichloromethane (40 mL) was stirred at 0 ºC. To the suspension, 1,2-dimethoxybenzene (3005 mg, 21.8 mmol) was added dropwise and the temperature was raised to room temperature (25 ºC). The mixture was stirred for 2 hours. The reaction was quenched with 100 mL of ice water. Then the whole was extracted with dichloromethane (100 mL x 2). The organic layer was washed with brine (100 mL), dried over sodium sulfate and the solvent was removed under reduced pressure to give crude mixture, which contains 4-(3,4-dimethoxyphenyl)-4-oxobutanoic acid (known compound) (3443 mg).

The crude mixture (3443 mg) and potassium carbonate (4201 mg) in acetone (20 mL) was added methyl iodide (2.0 mL). The reaction mixture was stirred at room temperature for 20 hours. To the reaction solution, acetone (20 mL), methyl iodide (2.0 mL), potassium carbonate (1567 mg) and dimethylformamide (10 mL) were added and the solution was stirred for 6 hours. The reaction was quenched with 30 mL of water and acetone was removed under reduced pressure. The whole was extracted with ethyl acetate : hexane = 1 : 1 (100 mL x 2). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure to give crude oil. The crude oil was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 4) to afford methyl 4-(3,4-dimethoxyphenyl)-4-oxobutanoate (**3g**) as white powder (known compound) (2574 mg, 10.2 mmol, 34% yield for 2 steps).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.63 (dd, J = 8.8, 2.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.71 (s, 3H), 3.29 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 6.8 Hz, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 196.5, 173.4, 153.3, 148.9, 129.7, 122.6, 110.0, 110.0, 56.0, 55.9, 51.7, 32.8, 28.1.

A mixture of **3g** (2311 mg, 9.16 mmol) and tetraethylsilane (4229 mg, 36.4 mmol) was added trifluoroacetic acid (20 mL) at 0 ºC. The temperature was raised to room temperature and the reaction solution was stirred for 2 days. The reaction was quenched with 50 mL of ice water and the whole was

extracted with dichloromethane (50 mL x 2). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure to give crude oil. The crude oil was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 8 ~ 1 : 2) to afford methyl 4-(3,4-dimethoxyphenyl)butanoate (**4g**) (known compound) as colorless oil (1890 mg, 7.93 mmol, 87% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.81-6.78 (m, 1H), 6.73-6.71 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.68 (s, 3H), 2.60 (t, J = 7.6 Hz, 2H), 2.35 (t, J = 7.6 Hz, 2H), 1.94 (p, J = 7.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 174.5, 148.8, 147.2, 134.0, 120.3, 111.8, 111.3, 55.9, 55.7, 51.6, 34.6, 33.3, 26.6.

To a solution of **4g** (1087 mg, 4.56 mmol) in methylamine (40% solution in methanol) (5.0 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 24 hrs. The solvent was removed in vacuo and crude residue was dissolved in dichloromethane (50 mL). The solution was washed with brine (10 mL), dried over sodium sulfate and the solvent was evaporated under reduced pressure to give 4-(3,4-dimethoxyphenyl)-*N*-methylbutanamide (**5g**) as colorless oil (1013 mg, 4.27 mmol, 94% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.79-6.77 (m, 1H), 6.71-6.69 (m, 2H), 5.65 (brs, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.79 (d, J = 5.2 Hz, 3H), 2.59 (t, J = 7.6 Hz, 2H), 2.17 (t, J = 7.6 Hz, 2H), 1.95 (p, J = 7.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 173.3, 148.8, 147.2, 134.1, 120.2, 111.7, 111.2, 55.8, 55.7, 35.7, 34.8, 27.2, 26.1. ESI-HRMS: Calcd for $C_{13}H_{19}NNaO_3^+$ $[M+Na]^+$: 260.1257. Found: 260.1278.

A solution of **5g** (953 mg, 4.01 mmol) and lithium aluminum hydride (382 mg, 10.1 mmol) in tetrahydrofuran (20 mL) was stirred at 50 ºC for 20 hrs. Then the reaction solution was cooled to 0 ºC and quenched with sodium sulfate decahydrate (10 g) and ethyl acetate (50 mL). Then the solution was filtered and the solvent was removed in vacuo to give crude oil, which contains 4-(3,4-dimethoxyphenyl)-*N*-methylbutan-1-amine (**6g**) (802 mg, 3.59 mmol, 90% crude yield). The amine was used directly in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.78 (d, J = 8.4 Hz, 1H), 6.73-6.70 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.61-2.56 (m, 4H), 2.42 (s, 3H), 1.68-1.48 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 148.8, 147.1, 135.2, 120.2, 111.8, 111.2, 55.9, 55.8, 52.1, 36.6, 35.5, 29.6, 29.4. ESI-HRMS: Calcd for $C_{13}H_{22}NO_2^+$ $[M+H]^+$: 224.1645. Found: 224.1635.

A solution of **6g** (778 mg, 3.49 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (997 mg, 3.02 mmol) in dichloromethane (5.0 mL) was stirred at room temperature for 22 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 2) to afford methyl 2-(((4-(3,4-dimethoxyphenyl)butyl)(methyl)carbamoyl)oxy)benzoate **1g** (831 mg, 2.07 mmol, 69% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.96 (dd, J = 7.6, 1.6 Hz, 1H, rotamer A and B), 7.51 (dd, J = 7.6, 7.6 Hz, 1H, rotamer A and B), 7.28-7.24 (m, 1H, rotamer A and B), 7.15 (d, J = 7.6 Hz, 0.6H, rotamer A), 7.09 (d, J = 7.6 Hz, 0.4H, rotamer B), 6.79-6.71 (m, 3H, rotamer A and B), 3.85 (s, 6H, rotamer A and B), 3.82 (s, 1.2H, rotamer B), 3.78 (s, 1.8H, rotamer A), 3.49 (t, J = 6.8Hz, 0.9H, rotamer B), 3.39 (t, J = 6.4 Hz, 1.1H, rotamer A), 3.10 (s, 1.7H, rotamer A), 2.99 (s, 1.3H, rotamer B), 2.64-2.59 (m, 2H, rotamer A and B), 1.71-1.66 (m, 4H, rotamer A and B). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.22, 154.5, 154.34, 151.29, 151.2, 148.8, 147.2, 147.1, 134.9, 134.7, 133.4, 131.4, 125.2, 124.1, 124.0, 123.9, 123.8, 120.2, 111.8, 111.7, 111.2, 55.9, 55.8, 51.9, 49.2, 49.1, 35.1, 35.0, 34.9, 34.4, 28.6, 28.4, 27.4, 26.8. ESI-HRMS: Calcd for $C_{22}H_{27}NNaO_6^+$ $[M+Na]^+$: 424.1731. Found: 424.1717. Anal. Calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.75; H, 6.95; N, 3.48.

Synthesis of methyl 2-(((5-(3,4-dimethoxyphenyl)pentan-2-yl)(methyl)carbamoyl)oxy)benzoate (1h)

1-bromo-2-(3,4-dimethoxyphenyl)ethane was synthesized according to the literature.[14]

To the solution of potassium tert-butoxide (1353 mg, 12 mmol) in dry tetrahydrofuran (20 mL), methyl acetoacetate (1513 mg, 13 mmol) was added under stirring at 0 ºC. The solution was stirred at 0 ºC for 30 min under argon atmosphere. To the stirring solution, 1-bromo-2-(3,4-dimethoxyphenyl)ethane (2463 mg, 10.0 mmol) in tetrahydrofuran (10 mL) was added slowly and refluxed for 21 hours. Then the reaction mixture was cooled to 0 ºC and 40 mL of water was added to quench the reaction. Then the whole was extracted with ethyl acetate (50 mL x 2) and the organic layer was washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford crude oil. The crude oil was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 4 ~ 1 : 3) to afford methyl 2-acetyl-4-(3,4-dimethoxyphenyl)butanoate (**3h**) as colorless oil (1347 mg, 4.80 mmol, 48% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.81 (dd, J = 8.4, 1.2 Hz, 1H), 6.73-6.71 (m 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H), 3.46 (t, J = 7.2 Hz, 1H), 2.65-2.52 (m, 2H), 2.22 (s, 3H), 2.19-2.14 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 202.8, 170.2, 148.9, 147.5, 133.1, 120.4, 111.8 , 111.3, 58.6, 55.9, 55.8, 52.4, 32.9, 29.8, 28.9. ESI-HRMS: Calcd for $C_{15}H_{20}NaO_5^+$ $[M+H]^+$: 303.1203. Found: 303.1176.

The solution of **3h** (652 mg, 2.33 mmol) and triethylbenzylammonium chloride (8.1 mg) in tetrahydrofuran (7 mL), aqueous sodium hydroxide (2M) (3 mL) was added at room temperature. The mixture was stirred at 50 ºC for 27 hours. And the reaction solution was acidified with 10 mL of aqueous hydrogen chloride (1M). The mixture was heated at 50 ºC for 1 hour and the reaction solution was basified with 10 mL of aqueous sodium carbonate (2M). Then the whole was extracted with dichloromethane (50 mL x 2) and the organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure to afford crude oil. The crude oil was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 4) to afford 5-(3,4-dimethoxyphenyl)pentan-2-one (**4h**) (known compound) (360.5 mg, 1.62 mmol, 70% yield for 2 steps).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.80-6.78 (m, 1H), 6.71-6.69 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 2.57 (t, J = 7.6 Hz, 2H), 2.43 (t, J = 7.6 Hz, 2H), 2.12 (s, 3H), 1.89 (p, J = 7.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 208.7, 148.9, 147.3, 134.2, 120.2, 111.7, 111.2, 55.9, 55.8, 42.8, 34.6, 29.9, 25.3.

To a mixture of sodium borohydride (208 mg, 5.49 mmol) and dichloromethane (10.0 mL), acetic acid (1.0 mL, 17.5 mmol) was added at 0 ºC. The mixture was stirred at room temperature for 30 min to form sodium triacetoxyborohydride. The solution was added **4h** (509 mg, 2.29 mmol), methylamine (40% solution in methanol) (1.5 mL) dichloromethane (8.0 mL) and stirred at room temperature for 24 hrs. To the reaction solution, ethyl acetate (20 mL) was added and the amine compounds are back-extracted in aqueous hydrogen chloride (1M) (20 mL). The water layer was basified with aqueous sodium hydroxide and extracted with ethyl acetate (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure to give crude oil. The crude oil was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 2) to afford 5-(3,4-dimethoxyphenyl)-*N*-methylpentan-2-amine (**5h**) as colorless oil (206 mg, 0.867 mmol, 38% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.78 (d, J = 8.4 Hz, 1H), 6.73-6.71 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.58-2.51 (m, 3H), 2.39 (s, 3H), 1.66-1.58 (m, 2H), 1.54-1.45 (m, 1H), 1.37-1.28 (m, 1H), 1.04 (brs, 1H), 1.03 (d, J = 6.0 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 148.8, 147.1, 135.2, 120.1, 111.8, 111.2, 55.9, 55.8, 54.8, 36.5, 35.7, 33.9, 28.0, 19.8. ESI-HRMS: Calcd for $C_{14}H_{24}NO_2^+$ $[M+H]^+$: 238.1802. Found: 238.1807.

A solution of **5h** (390 mg, 1.64 mmol) and dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (778 mg, 2.36 mmol) in dichloromethane (3.0 mL) was stirred at room temperature 31 hrs. Then five drops of ethylenediamine was added to decompose excess dimethyl 2,2'-(carbonylbis(oxy))dibenzoate). The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 3) to afford methyl 2-(((5-(3,4-dimethoxyphenyl)pentan-2-yl)(methyl)carbamoyl)oxy)benzoate **1h** (501 mg,

1.20 mmol, 73% yield (based on 5-(3,4-dimethoxyphenyl)-*N*-methylpentan-2-amine) as colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 2 : 1 ratio at 25 ºC), δ (ppm): 7.97-7.94 (m, 1H, rotamer A and B), 7.54-7.48 (m, 1H, rotamer A and B), 7.25 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, rotamer A and B), 7.15 (d, J = 8.0 Hz, 0.6H, rotamer A), 7.09 (d, J = 8.0 Hz, 0.4H, rotamer B), 6.77 (d, J = 8.8 Hz, 1H, rotamer A and B), 6.73-6.72 (m, 2H, rotamer A and B), 4.46-4.41 (m, 0.3H, rotamer B), 4.38-4.30 (m, 0.7H, rotamer A), 3.85 (s, 4H, rotamer A), 3.84 (s, 2H, rotamer B), 3.81 (s, 1H, rotamer B), 3.76 (s, 2H, rotamer A), 2.92 (s, 2H, rotamer A), 2.82 (s, 1H, rotamer B), 2.68-2.52 (m, 2H, rotamer A and B), 1.70-1.40 (m, 4H, rotamer A and B), 1.25 (d, J = 6.8 Hz, 1H, rotamer B), 1.18 (d, J = 6.8Hz, 2H, rotamer A). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.2, 154.6,154.4, 151.3, 151.0, 148.7, 147.14, 147.05, 134.9, 134.7, 133.34, 133.25, 131.4, 125.2, 124.2, 124.0, 123.9, 123.8, 120.2, 111.8, 111.7, 111.2, 55.9, 55.8, 51.9, 51.8, 51.4, 51.1, 35.1, 35.0, 33.4, 33.1, 28.2, 28.1, 27.7, 27.6, 18.4, 18.1. ESI-HRMS: Calcd for $C_{23}H_{29}NNaO_6^+$ $[M+Na]^+$: 438.1887. Found: 438.1894. Anal. Calcd. for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.60; H, 7.00; N, 3.38.

Synthesis of methyl 2-((methyl(3-phenoxypropyl)carbamoyl)oxy)benzoate (1i)

A mixture of phenol (529.0 mg, 5.62 mmol), 1,3-dibromopropane (3067 mg, 15.2 mmol), potassium carbonate (1988 mg) in acetone (5.0 mL) was stirred at room temperature for 28 hrs. Then the reaction solution was filtered and the solvent was removed in vacuo to give crude oil. The oil was chromatographed on silica gel (eluent: ethyl acetate : *n*-hexane = 1 : 10) to afford mixture of (3-bromopropoxy)benzene and 1,3-dibromopropane as colorless oil (2278 mg). The oil was dissolved in methylamine (40% solution in methanol) (100 mL) and stirred at room temperature for 24 hrs. The solvent was removed in vacuo and crude residue was dissolved in dichloromethane (20 mL). The organic phase was back-extracted with aqueous hydrogen chloride (1M) (20 mL). The water layer was basified with aqueous sodium hydroxide and extracted with ethyl acetate (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure to give crude oil, which contains *N*-methyl-3-phenoxypropan-1-amine (**3i**) (known compound) (665 mg, 4.02 mmol, 72% yield for two steps).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.20-7.25 (m, 2H), 6.95-6.89 (m, 3H), 4.03 (t, J = 6.4 Hz, 2H), 2.77 (t, J = 6.8 Hz, 2H), 2.45 (s, 3H), 2.00-1.94 (m, 2H), 1.86 (brs, 1H). ESI-HRMS: Calcd for $C_{10}H_{16}NO^+$ $[M+H]^+$: 166.12264. Found: 166.12157.

A solution of **3i** (506 mg, 3.06 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (792 mg, 2.40 mmol) in tetrahydrofuran (2.8 mL) was stirred at 50 ºC for 4 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 3) to afford methyl 2-((methyl(3-phenoxypropyl)carbamoyl)oxy)benzoate **1i** as colorless oil (679 mg, 1.98 mmol, 82% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 1 : 1 ratio at 25 ºC), δ (ppm): 7.97-7.95 (m, 1H), 7.52-7.45 (m, 1H), 7.28-7.22 (m, 3H), 7.12 (d, J = 8.0 Hz, 0.5H), 7.01 (d, J = 8.0 Hz, 0.5H), 6.95-6.90 (m, 3H), 4.09-4.04 (m, 2H), 3.83 (s, 1.5H), 3.81 (s, 1.5H), 3.69 (t, J = 7.2 Hz, 1H), 3.55 (t, J = 6.8 Hz, 1H), 3.15 (s, 1.6H), 3.03 (s, 1.4H), 2.21-2.08 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.1, 158.7, 154.5, 154.4, 151.3, 151.1, 133.42, 133.37, 131.4, 129.3, 125.3, 124.1, 123.9, 123.7, 123.6, 120.7, 120.6, 114.43, 114.40, 65.1, 64.9, 51.9, 46.7, 46.4, 35.2, 35.0, 27.8, 27.3. ESI-HRMS: Calcd for $C_{19}H_{21}NNaO_5^+$ $[M+Na]^+$: 366.1312. Found: 366.1294. Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.71; H, 6.32; N, 4.10.

Synthesis of methyl 2-((methyl(3-(naphthalen-2-yloxy)propyl)carbamoyl)oxy)benzoate (1j)

The mixture of naphthalen-2-ol (1074 mg, 7.45 mmol), 1,3-dibromopropane (4615 mg, 22.9 mmol), potassium carbonate (2073 mg) in acetone (20 mL) was stirred at room temperature for 3 days. Then the reaction was quenched with water (30 mL) and the whole was extracted with ethyl acetate (50

mL x 2). The organic layer was washed with brine and dried over sodium sulfate. Then the solvent was removed in vacuo to give crude oil. The oil was dissolved in methanol and filtered to remove 1,3-bis(naphthalen-2-yloxy)propane. Then the filtrate was evaporated under reduced pressure to afford mixture of 2-(3-bromopropoxy)naphthalene and 1,3-dibromopropane as colorless oil (2434 mg). The oil was dissolved in methylamine (40% solution in methanol) (10 mL) and stirred at room temperature for 24 hrs. The solvent was removed in vacuo and crude residue was dissolved in aqueous HCl (1M, 10 mL). The whole was extracted with dichloromethane (50 mL x 2). The organic phase was washed with aqueous sodium hydroxide (2M, 10 mL) and the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure to give crude oil. The oil was dissolved in *n*-hexane and filtered to remove impurities. Then the filtrate was evaporated under reduced pressure to afford crude oil pale yellow crude oil, which contains *N*-methyl-3-(naphthalen-2-yloxy)propan-1-amine (**3j**) (known compound) (1065 mg, 4.95 mmol, 66% crude yield).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76-7.70 (m, 3H), 7.44-7.40 (m, 1H), 7.34-7.30 (m, 1H), 7.16-7.12 (m, 2H), 4.16 (t, J = 6.4 Hz, 2H), 2.81 (t, J = 7.2 Hz, 2H), 2.48 (s, 3H), 2.07-1.99 (m, 2H), 1.28 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 156.9, 134.6, 129.3, 128.9, 127.6, 126.7, 126.3, 123.5, 118.9, 106.6, 66.3, 49.1, 36.6, 29.6. ESI-HRMS: Calcd for $C_{14}H_{18}NO^+$ $[M+H]^+$: 216.1383. Found: 216.1399.

A solution of the crude oil which contains **3j** (854 mg) and dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (1478 mg, 4.47 mmol) in tetrahydrofuran (5.0 mL) was stirred at room temperature for 2 days. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 2) to afford **1j** as colorless oil (1009 mg, 2.56 mmol, 43% yield for 3 steps (based on naphthalen-2-ol)).
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 1 : 1 ratio at 25 ºC), δ (ppm): 7.95 (dd, J = 7.6, 7.6 Hz, 1H), 7.75-7.69 (m, 3H), 7.51-7.46 (m, 0.5H), 7.43-7.39 (m, 1.5H), 7.31 (dd, J = 7.6, 7.6 Hz, 1H), 7.26-7.19 (m, 1H), 7.15-7.11 (m, 2.5H), 6.99 (d, J = 8.0 Hz, 0.5H), 4.21-4.15 (m, 2H), 3.82 (s, 1.5H), 3.79 (s, 1.5H), 3.72 (t, J = 6.8 Hz, 1H), 3.59 (t, J = 6.8 Hz, 1H), 3.16 (s, 1.5H), 3.04 (s, 1.5H), 2.27-2.14 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.1, 156.7, 154.6, 154.4, 151.3, 151.1, 134.50, 134.46, 133.45, 133.4, 131.4, 129.33, 129.28, 128.9, 127.5, 126.6, 126.2, 125.29, 125.26, 124.1, 123.9, 123.7, 123.6, 123.53, 123.48, 118.8, 106.7, 65.3, 65.1, 51.9, 46.7, 46.5, 35.3, 35.1, 27.8, 27.3. ESI-HRMS: Calcd for $C_{23}H_{23}NNaO_5^+$ $[M+Na]^+$: 416.1468. Found: 416.1453. Anal. Calcd. for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.21; H, 6.10; N, 3.62.

Synthesis of methyl 2-(((3-([1,1'-biphenyl]-4-yloxy)propyl)(methyl)carbamoyl)oxy)benzoate (1k)

The mixture of [1,1'-biphenyl]-4-ol (1015 mg, 5.96 mmol), 1,3-dibromopropane (3602 mg, 17.8 mmol), potassium carbonate (1718 mg) in acetone (20 mL) was stirred at room temperature for 3 days. Then the reaction was quenched with water (30 mL) and the whole was extracted with ethyl acetate (50 mL x 2). The organic layer was washed with brine and dried over sodium sulfate. Then the solvent was removed in vacuo to give crude mixture of 4-(3-bromopropoxy)-1,1'-biphenyl and 1,3-dibromopropane as colorless oil (2870 mg). The oil was dissolved in methylamine (40% solution in methanol) (10 mL) and stirred at room temperature for 21 hrs. The solvent was removed in vacuo and crude residue was dissolved in HCl aq (1M, 10 mL). The whole was extracted with dichloromethane (50 mL x 2). The organic phase was washed with aqueous sodium hydroxide (2M, 10 mL) and the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure to give pale yellow crude oil. The oil was dissolved in *n*-hexane and filtered to remove impurities. Then the filtrate was evaporated under reduced pressure to afford crude oil, which contains 3-([1,1'-biphenyl]-4-yloxy)-*N*-methylpropan-1-amine (**3k**) (1111 mg, 4.60 mmol, 77% crude yield for 2 steps).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.56-7.49 (m, 4H), 7.42-7.39 (m, 2H), 7.31-7.27 (m, 1H),

6.98-6.96 (m, 2H), 4.08 (t, J = 6.4 Hz, 2H), 2.78 (t, J = 6.8 Hz, 2H), 2.46 (s, 3H), 2.02-1.96 (m, 2H), 1.06 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 158.6, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.8, 66.4, 49.1, 36.6, 29.6. ESI-HRMS: Calcd for $C_{16}H_{20}NO^+$ $[M+H]^+$: 242.15394. Found: 242.15578.

A solution of the crude oil which contains **3k** (752 mg) and dimethyl 2,2'-(carbonylbis(oxy))dibenzoate (1106 mg, 3.35 mmol) in tetrahydrofuran (5.0 mL) was stirred at room temperature for 2 days. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 2) to afford methyl 2-((methyl(3-(naphthalen-2-yloxy)propyl)carbamoyl)oxy)benzoate **1k** as colorless oil (794 mg, 1.89 mmol, 47% yield for 3 steps (based on [1,1'-biphenyl]-4-ol)).
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 1 : 1 ratio at 25 ºC), δ (ppm): 7.96 (dd, J = 6.0, 6.0 Hz, 1H), 7.54-7.38 (m, 7H), 7.30-7.20 (m, 2H), 7.12 (d, J = 8.0 Hz, 0.5H), 7.01-6.96 (m, 2.5H), 4.13-4.08 (m, 2H), 3.83 (s, 1.5H), 3.81 (s, 1.5H), 3.70 (t, J = 6.8 Hz, 1H), 3.56 (t, J = 6.8 Hz, 1H), 3.16 (s, 1.5H), 3.04 (s, 1.5H), 2.23-2.10 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.1, 158.4, 154.5, 154.4, 151.3, 151.1, 140.7, 133.8, 133.7, 133.5, 133.4, 131.4, 128.6, 128.0, 126.6, 125.3, 124.1, 124.0, 123.7, 123.6, 114.8, 65.4, 65.2, 51.9, 46.7, 46.4, 35.2, 35.1, 27.8, 27.4. ESI-HRMS: Calcd for $C_{25}H_{25}NNaO_5^+$ $[M+Na]^+$: 442.1625. Found: 442.1632. Anal. Calcd. for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.69; H, 6.25; N, 3.36.

Synthesis of methyl 2-(((5-(3,4-dimethoxyphenyl)pentyl)(methyl)carbamoyl)oxy)benzoate (1l)

A suspension of glutaric anhydride (2279 mg, 19.9 mmol), aluminum chloride (5735 mg, 43.0 mmol) in dry dichloromethane (30 mL) was stirred at 0 ºC. To the suspension, 1,2-dimethoxybenzene (3005 mg, 21.8 mmol) was added dropwise and the temperature was raised to room temperature (25 ºC). The mixture was stirred for 2 hours. The reaction was quenched with 100 mL of ice water and 10 g of citric acid was added. Then the solution was basified with 200 mL of aqueous sodium hydroxide (2M) and the whole was washed with dichloromethane (50 mL x 2) to remove impurities. The water layer was acidified with aqueous hydrogen chloride (1M, 200 mL) and extracted with ethyl acetate (100 mL x 2). The organic layer was washed with brine (100 mL), dried over sodium sulfate and the solvent was removed under reduced pressure to give 5-(3,4-dimethoxyphenyl)-5-oxopentanoic acid (**3l**) as pale yellow solid (known compound) (3572 mg, 14.2 mmol, 71% yield).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 11.10 (brs, 1H), 7.59 (dd, J = 8.4, 2.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.04 (t, J = 7.2 Hz, 2H), 2.51 (t, J = 7.2 Hz, 2H), 2.08 (p, J = 7.2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 198.0, 179.1, 153.3, 149.1, 130.0, 122.7, 110.2, 110.0, 56.1, 56.0, 36.9, 33.1, 19.4.

A mixture of **3l** (3304 mg, 13.1 mmol) and potassium carbonate (2569 mg) in acetone (40 mL) was added methyl iodide (1.5 mL). The reaction mixture was stirred at room temperature for 14 hours. To the reaction solution, acetone (60 mL) and methyl iodide (2.0 mL) were added and the solution was stirred for 9 hours. The reaction was quenched with 50 mL of water and the whole was extracted with dichloromethane (50 mL x 2). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure to give methyl 5-(3,4-dimethoxyphenyl)-5-oxopentanoate **4l** as white powder (known compound) (2584 mg, 9.70 mmol, 74% yield).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.60 (dd, J = 8.4, 2.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.68 (s, 3H), 3.01 (t, J = 7.2 Hz, 2H), 2.45 (t, J = 7.2 Hz, 2H), 2.07 (p, J = 7.2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 198.0, 173.7, 153.2, 149.0, 130.1, 122.6, 110.1, 110.0, 56.0, 55.9, 51.4, 36.9, 33.1, 19.7.

A mixture of **4l** (2446 mg, 9.18 mmol) and tetraethylsilane (2985 mg, 25.7 mmol) was added trifluoroacetic acid (10 mL) at 0 ºC. The temperature was raised to room temperature and the reaction solution was stirred for 16 hours. The reaction was quenched with 50 mL of water and the whole was extracted with dichloromethane (50 mL x 2). The organic layer was dried over sodium sulfate and the

solvent was removed under reduced pressure to give crude oil. The crude oil was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 4) to afford methyl 5-(3,4-dimethoxyphenyl)pentanoate (**5l**) as colorless oil (known compound) (2303 mg, 9.13 mmol, 99% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.78 (d, J = 8.4 Hz, 1H), 6.72-6.70 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.66 (s, 3H), 2.58 (t, J = 7.2 Hz, 2H), 2.34 (t, J = 7.2 Hz, 2H), 1.71-1.60 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 174.3, 148.8, 147.1, 134.8, 120.2, 111.8, 111.3, 55.9, 55.8, 51.5, 35.1, 33.9, 31.0, 24.5. ESI-HRMS: Calcd for $C_{14}H_{20}NaO_4^+$ $[M+Na]^+$: 275.1254. Found: 275.1242.

The compound **5s** (1183 mg, 4.69 mmol) was dissolved in methylamine (40% solution in methanol) (5.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 17 hrs. The solvent was removed in vacuo and crude residue was dissolved in chloroform (100 mL). The solution was washed with water (20 mL), dried over sodium sulfate and the solvent was evaporated under reduced pressure to give 5-(3,4-dimethoxyphenyl)-*N*-methylpentanamide (**6l**) as colorless oil (1023 mg, 4.07 mmol, 87% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.79-6.77 (m, 1H), 6.71-6.69 (m, 2H), 5.62 (brs, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.78 (d, J = 4.8 Hz, 3H), 2.57 (t, J = 7.2 Hz, 2H), 2.18 (t, J = 7.2 Hz, 2H), 1.72-1.58 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 173.5, 148.7, 147.0, 134.8, 120.1, 111.7, 111.2, 55.9, 55.8, 36.4, 35.2, 31.2, 26.2, 25.3.

A solution of **6l** (679 mg, 2.70 mmol) and lithium aluminum hydride (289 mg, 7.48 mmol) in tetrahydrofuran (15 mL) was stirred at 50 ºC for 18 hrs. Then the reaction solution was cooled to 0 ºC and quenched with sodium sulfate decahydrate (10 g) and ethyl acetate (50 mL). Then the solution was filtered and the solvent was removed in vacuo to give crude oil, which contains 5-(3,4-dimethoxyphenyl)-*N*-methylpentan-1-amine (**7l**) (known compound) (425 mg, 1.79 mmol, 66% crude yield). The amine was used directly in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.78 (d, J = 8.8 Hz, 1H), 6.72-6.70 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.58-2.54 (m, 4H), 2.42 (s, 3H), 1.69-1.25 (m, 7H). ESI-HRMS: Calcd for $C_{12}H_{20}N^+$ $[M+H]^+$: 178.15903. Found: 178.15904.

A solution of the crude oil of **7l** (425 mg) and dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (661 mmol, 2.00 mmol) in dichloromethane (3.5 mL) was stirred at room temperature for 2 days. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 4 ~ 1 : 2) to afford methyl 2-(((5-(3,4-dimethoxyphenyl)pentyl)(methyl)carbamoyl)oxy)benzoate **1l** as colorless oil (393 mg, 0.946 mmol, 35% yield for two steps (based on 5-(3,4-dimethoxyphenyl)-*N*-methylpentanamide)).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed (approximately 1 : 1 ratio at 25 ºC), δ (ppm): 7.96 (dd, J = 8.0, 1.2 Hz, 1H), 7.52 (dd, J = 7.6, 7.6 Hz, 1H), 7.26 (t, J = 7.6, 7.6 Hz, 1H), 7.14 (d, J = 8.0 Hz, 0.5H), 7.11 (d, J = 8.0 Hz, 0.5H), 6.77 (d, J = 7.6 HZ, 1H), 6.70 (d, J = 7.6 Hz, 1H), 6.70 (s, 1H), 3.85 (s, 3H), 3.84 (s, 6H), 3.46 (t, J = 7.2 Hz, 1H), 3.35 (t, J = 7.2 Hz, 1H), 3.11 (s, 1.5H), 3.00 (s, 1.5H), 2.60-2.55 (m, 2H), 1.77-1.61 (m, 4H), 1.45-1.35 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.3, 154.5, 154.4, 151.3, 151.2, 148.8, 147.1, 135.2, 135.1, 133.4, 131.5, 125.3, 124.2, 124.0, 123.9, 123.8, 120.1, 111.8, 111.2, 55.9, 55.8, 52.0, 49.4, 49.3, 35.5, 34.9, 34.5, 31.4, 30.9, 27.7, 27.3, 26.3. ESI-HRMS: Calcd for $C_{23}H_{29}NNaO_6^+$ $[M+Na]^+$: 438.1887. Found: 438.1865. Anal. Calcd. for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.26; H, 6.98; N, 3.35.

Synthesis of methyl 2-(((5-(3,4-dimethoxyphenyl)pentyl)(isopropyl)carbamoyl)oxy)benzoate (1m)

To a solution of **5s** (1930 mg, 7.65 mmol) in methanol (10 mL), 5 mL of aqueous sodium hydroxide (2M) was added and stirred at room temperature for 2 days. Then the reaction solution was acidified by 20 mL of aqueous hydrogen chloride (1M) and the whole was extracted by dichloromethane (50 mL x 2). The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to afford 5-(3,4-dimethoxyphenyl)pentanoic acid (**3m**) (known compound) as white solids (1564 mg, 6.56 mmol, 86% yield).

A mixture of **3m** (847 mg, 3.55 mmol), $SOCl_2$ (0.5 mL) in toluene (4 mL) was stirred at 60 ºC for 1 hr. The reaction mixture was cooled to room temperature and the reaction solution was added dropwise into a solution of isopropylamine (2.0 mL) in dry dichloromethane (10 mL) under stirring at 0 ºC. The temperature was raised to 25 ºC and the reaction mixture was stirred for 10 min. Then 20 mL of water was added and the whole was extracted with dichloromethane (50 mL x 2). The organic phase was dried over sodium sulfate; the solvent was removed in vacuo to afford crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 1) to afford 5-(3,4-dimethoxyphenyl)-*N*-isopropylpentanamide (**4m**) as white solid (832 mg, 2.98 mmol, 84% yield).

Mp. 80 - 81 ºC (colorless needles, recrystallized from $CHCl_3$/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.78 (d, J = 8.4 Hz, 1H), 6.71-6.69 (m, 2H), 5.41 (brs, 1H), 4.11-4.03 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.57 (t, J = 6.8 Hz, 2H), 2.15 (t, J = 6.8 Hz, 2H), 1.65-1.62 (m, 4H), 1.12 (d, J = 6.4 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.9, 148.7, 147.0, 134.9, 120.1, 111.7, 111.2, 55.8, 55.7, 41.1, 36.7, 35.2, 31.2, 25.3, 22.7. ESI-HRMS: Calcd for $C_{16}H_{25}NNaO_3^+$ $[M+Na]^+$: 302.17266. Found: 302.17383.

A solution of **4m** (745 mg, 2.67 mmol) and lithium aluminum hydride (213 mg, 5.62 mmol) in tetrahydrofuran (10 mL) was stirred at 50 ºC for 18 hrs. Then the reaction solution was cooled to 0 ºC and quenched with large amount of sodium sulfate decahydrate and ethyl acetate. Then the solution was filtered and the solvent was removed in vacuo to give crude oil, which contains 5-(3,4-dimethoxyphenyl)-*N*-isopropylpentan-1-amine (**5m**) (661 mg, 2.49 mmol, 93% yield). The amine was used directly in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.78 (d, J = 8.4 Hz, 1H), 6.72-6.70 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.81-2.75 (m, 1H), 2.60-2.54 (m, 4H), 1.66-1.33 (m, 7H), 1.05 (d, J = 6.4 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 148.7, 147.0, 135.3, 120.0, 111.7, 111.1, 55.8, 55.7, 48.7, 47.4, 35.4, 31.5, 30.2, 27.0, 22.9. ESI-HRMS: Calcd for $C_{16}H_{28}NO_2^+$ $[M+H]^+$: 266.2115. Found: 266.2118.

A solution of the crude oil which contains **5m** (585 mg) and dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (935 mmol, 2.83 mmol) in tetrahydrofuran (5.0 mL) was stirred at 50 ºC for 13 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 2) to afford methyl 2-(((5-(3,4-dimethoxyphenyl)pentyl)(isopropyl)carbamoyl)oxy)benzoate **1m** as colorless oil (580 mg, 1.31 mmol, 55% yield for 2 steps (based on 5-(3,4-dimethoxyphenyl)-*N*-isopropylpentanamide))).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.98 (d, J = 8.0 Hz, 1H, rotamer A and B), 7.56-7.52 (m, 1H, rotamer A and B), 7.28 (dd, J = 7.6, 7.6 Hz, 1H, rotamer A and B), 7.16-7.14 (m, 1H, rotamer A and B), 6.81-6.71 (m, 3H, rotamer A and B), 4.47-4.36 (m, 0.4H, rotamer B), 4.36-4.23 (m, 0.6H, rotamer A), 3.88-3.86 (m, 9H, rotamer A and B), 3.31 (t, J = 8.0 Hz, 1.2H, rotamer A), 3.22 (t, J = 8.0 Hz, 0.8H, rotamer B), 2.61-2.56 (m, 2H, rotamer A and B), 1.81-1.62 (m, 4H, rotamer A and B), 1.44-1.35 (m, 2H, rotamer A and B), 1.32 (d, J = 6.4 Hz, 2.4H, rotamer B), 1.26 (d, J = 6.8 Hz, 3.6H, rotamer A). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.4, 154.0, 151.1, 151.0, 148.7, 147.0, 135.2, 135.1, 133.3, 133.2, 131.4, 125.1, 124.1, 124.0, 120.1, 111.7, 111.2, 55.9, 55.7, 52.0, 48.6, 48.3, 43.5, 35.4, 31.3, 30.1, 29.4, 26.7, 21.0, 20.4. ESI-HRMS: Calcd for $C_{25}H_{33}NNaO_6^+$ $[M+Na]^+$: 466.2200. Found: 466.2207.

Synthesis of methyl 2-(((5-(3,4-dimethoxyphenyl)pentyl)(octyl)carbamoyl)oxy)benzoate (1n)

A mixture of **4t** (649 mg, 2.72 mmol), $SOCl_2$ (0.4 mL) in toluene (3 mL) was stirred at 60 ºC for 3 hrs. The reaction mixture was cooled to room temperature and added dropwise to a solution of octan-1-amine (1275 mg, 9.85 mmol) in dry dichloromethane (10 mL) under stirring at 0 ºC. The temperature was raised to 25 ºC and the reaction mixture was stirred for 10 min. Then 20 mL of water was added and the whole was extracted with dichloromethane (50 mL x 2). The organic phase was dried over sodium sulfate; the solvent was removed in vacuo to afford crude oil. The crude product was

purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 2) to afford 5-(3,4-dimethoxyphenyl)-*N*-octylpentanamide (**3n**) as white solid (777 mg, 2.22 mmol, 82% yield).
Mp. 67 - 68 ºC (colorless cotton like crystals, recrystallized from $CHCl_3$/hexane)
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.78 (d, J = 8.8 Hz, 1H), 6.71-6.69 (m, 2H), 5.51 (brs, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.22 (dt, J = 6.8, 6.8 Hz, 2H), 2.57 (t, J = 7.2 Hz, 2H), 2.17 (t, J = 7.2 Hz, 2H), 1.70-1.60 (m, 4H), 1.49-1.45 (m, 2H), 1.27-1.26 (m, 10H), 0.88 (t, J = 6.4 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 172.7, 148.8, 147.1, 134.9, 120.1, 111.7, 111.2, 55.9, 55.8, 39.5, 36.6, 35.2, 31.7, 31.2, 29.6, 29.2, 29.1, 26.9, 25.4, 22.6, 14.0. ESI-HRMS: Calcd for $C_{21}H_{35}NNaO_3^+$ $[M+Na]^+$: 372.2509. Found: 372.2497.

A solution of **3n** (686 mg, 1.96 mmol) and lithium aluminum hydride (218 mg, 5.74 mmol) in tetrahydrofuran (8.0 mL) was stirred at 50 ºC for 15 hrs. Then the reaction solution was cooled to 0 ºC and quenched with large amount of sodium sulfate decahydrate and ethyl acetate. Then the solution was filtered and the solvent was removed in vacuo to give crude oil, which contains *N*-(5-(3,4-dimethoxyphenyl)pentyl)octan-1-amine (**4n**) (570 mg, 1.70 mmol, 87% crude yield). The amine was used directly in the next step without further purification.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.81 (d, J = 8.4 Hz, 1H), 6.74-6.72 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 2.63-2.56 (m, 6H), 1.70-1.60 (m, 2H), 1.58-1.47 (m, 4H), 1.42-1.26 (m, 13H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 148.8, 147.0, 135.4, 120.1, 111.8, 111.2, 55.9, 55.8, 50.2, 50.1, 35.5, 31.8, 31.6, 30.2, 30.1, 29.5, 29.2, 27.4, 27.0, 22.6, 14.1. ESI-HRMS: Calcd for $C_{21}H_{38}NO_2^+$ $[M+H]^+$: 336.2897. Found: 336.2897.

A solution of the crude oil which contains *N*-(5-(3,4-dimethoxyphenyl)pentyl)octan-1-amine (482 mg) and dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (808 mmol, 2.44 mmol) in tetrahydrofuran (4.0 mL) was stirred at 50 ºC for 19 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 2) to afford methyl 2-(((5-(3,4-dimethoxyphenyl)pentyl)(octyl)carbamoyl)oxy)benzoate **1n** as colorless oil (466 mg, 0.907 mmol, 55% yield for 2 steps (based on 5-(3,4-dimethoxyphenyl)-*N*-octylpentanamide)).
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed (approximately 1 : 1 ratio at 25 ºC), δ (ppm): 7.95 (dd, J = 7.6, 1.6 Hz, 1H), 7.51 (dd, J = 7.6, 7.6 Hz, 1H), 7.25 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 7.13 (d, J = 8.0 Hz, 0.5H), 7.11 (d, J = 7.6 Hz, 0.5H), 6.79-6.76 (m, 1H), 6.71-6.69 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.43-3.38 (m, 2H), 3.32-3.27 (m, 2H), 2.60-2.54 (m, 2H), 1.78-1.61 (m, 6H), 1.44-1.24 (m, 12H), 0.89-0.86 (t, J = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.4, 154.24, 154.20, 151.1, 148.8, 147.1, 147.0, 135.2, 135.1, 133.3, 131.4, 125.2, 124.1, 124.0, 120.1, 111.7, 111.2, 55.9, 55.7, 51.9, 48.0, 47.9, 47.7, 47.5, 35.4, 31.7, 31.4, 29.3, 29.2, 28.6, 28.4, 27.9, 27.8, 26.9, 26.8, 26.43, 26.41, 22.6, 14.0. ESI-HRMS: Calcd for $C_{30}H_{43}NNaO_6^+$ $[M+Na]^+$: 536.2983. Found: 536.2981. Anal. Calcd. for $C_{30}H_{43}NO_6$: C, 70.15; H, 8.44; N, 2.73. Found: C, 70.00; H, 8.41; N, 2.76.

Synthesis of methyl 2-((methyl(4-(naphthalen-2-yloxy)butyl)carbamoyl)oxy)benzoate (1o)

A mixture of 2-naphtol (1513 mg, 10.5 mmol), 1,4-dibromobutane (6747 mg, 31.2 mmol), potassium carbonate (2837 mg) in dry acetone (20 mL) was stirred at room temperature for 2 days. Then the reaction solution was filtered and the solvent was removed in vacuo to give crude oil. The oil was chromatographed on silica gel (eluent: ethyl acetate : *n*-hexane = 0 : 1 ~ 1 : 50) to afford 2-(4-bromobutoxy)naphthalene **3o** as white solids (known compound) (2144 mg, 7.68 mmol, 73% yield).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.77-7.70 (m, 3H), 7.45-7.41 (m, 1H), 7.34-7.30 (m, 1H), 7.14-7.12 (m, 2H), 4.11 (t, J = 6.0 Hz, 2H), 3.51 (t, J = 6.4 Hz, 2H), 2.15-2.08 (m, 2H), 2.03-1.97 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 156.8, 134.5, 129.4, 129.0, 127.6, 126.7, 126.4, 123.6, 118.9, 106.6, 66.8, 33.4, 29.5, 27.9.

To a solution of **3o** (744 mg, 2.67 mmol) in tetrahydrofuran (5.0 mL), methylamine (40%

solution in methanol) (5.0 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 16 hrs. The solvent was removed in vacuo and crude residue was dissolved in ethyl acetate. The solution was washed with aqueous sodium hydroxide (2M) (20 mL), washed with brine (10 mL), dried over sodium sulfate and the solvent was evaporated under reduced pressure to give *N*-methyl-4-(naphthalen-2-yloxy)butan-1-amine (**4o**) as colorless oil (614 mg, 2.68 mmol, 100% crude yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76-7.70 (m, 3H), 7.42 (dd, J = 7.2, 7.2 Hz, 1H), 7.33-7.30 (m, 1H), 7.15-7.12 (m, 2H), 4.09 (t, J = 6.4 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 2.46 (s, 3H), 1.92-1.86 (m, 2H), 1.74-1.67 (m, 2H), 1.40 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 157.0, 134.6, 129.3, 128.9, 127.6, 126.7, 126.3, 123.5, 119.0, 106.6, 67.7, 51.7, 36.5, 27.0, 26.5. ESI-HRMS: Calcd for $C_{15}H_{20}NO^+$ $[M+H]^+$: 230.1539. Found: 230.1540.

A solution of **4o** (516 mg, 2.25 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (1004 mg, 3.04 mmol) in tetrahydrofuran (10 mL) was stirred at 50 ºC for 20 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 5 ~ 1 : 1) to afford methyl 2-((methyl(4-(naphthalen-2-yloxy)butyl)carbamoyl)oxy)benzoate **1o** as colorless oil (732 mg, 1.80 mmol, 80% yield (based on *N*-methyl-4-(naphthalen-2-yloxy)butan-1-amine)).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.97-7.95 (m, 1H, rotamer A and B), 7.75-7.68 (m, 3H, rotamer A and B), 7.53-7.47 (m, 1H, rotamer A and B), 7.41 (dd, J = 7.6, 7.6 Hz, 1H, rotamer A and B), 7.31 (dd, J = 7.6, 7.6 Hz, 1H, rotamer A and B), 7.24 (dd, J = 7.6, 7.6 Hz, 1H, rotamer A and B), 7.16-7.12 (m, 3H, rotamer A and B), 4.11 (t, J = 6.0 Hz, 2H, rotamer A and B), 3.83 (s, 3H, rotamer A and B), 3.57 (brs, 0.8H, rotamer B), 3.46 (t, J = 6.8 Hz, 1.2H, rotamer A), 3.14 (s, 1.8H, rotamer A), 3.03 (s, 1.2H, rotamer B), 1.92-1.85 (m, 4H, rotamer A and B). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.2, 156.9, 154.6, 154.3, 151.3, 151.1, 134.5, 133.4, 131.4, 129.30, 129.25, 128.9, 127.5, 126.6, 126.2, 125.3, 124.1, 124.0, 123.8, 123.7, 123.5, 123.4, 118.8, 106.6, 67.4, 67.3, 52.0, 9.0, 48.9, 34.9, 34.4, 26.4, 26.2, 24.7, 24.1. ESI-HRMS: Calcd for $C_{24}H_{25}NNaO_5^+$ $[M+Na]^+$: 430.1625. Found: 430.1622. Anal. Calcd. for $C_{24}H_{25}NO_5$: C, 70.74; H, 6.18; N, 3.44. Found: C, 70.68; H, 6.42; N, 3.44.

Synthesis of methyl 2-((isopropyl(4-(naphthalen-2-yloxy)butyl)carbamoyl)oxy)benzoate (1p)

To a solution of **3v** (755 mg, 2.71 mmol) in tetrahydrofuran (5.0 mL), isopropylamine (5.0 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 15 hrs. The solvent was removed in vacuo and crude residue was dissolved in ethyl acetate (50 mL). The solution was washed with aqueous sodium hydroxide (2M) (20 mL), washed with brine (10 mL), dried over sodium sulfate and the solvent was evaporated under reduced pressure to give *N*-isopropyl-4-(naphthalen-2-yloxy)butan-1-amine (**3p**) as pale brown oil (684 mg, 2.66 mmol, 98% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75-7.69 (m, 3H), 7.44-7.39 (m, 1H), 7.33-7.29 (m, 1H), 7.14-7.12 (m, 2H), 4.08 (t, J = 6.4 Hz, 2H), 2.83-2.77 (m, 1H), 2.68 (t, J = 7.2 Hz, 2H), 1.92-1.85 (m, 2H), 1.72-1.65 (m, 2H), 1.06 (d, J = 6.4 Hz, 6H), 0.92 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 157.0, 134.6, 129.3, 128.9, 127.6, 126.6, 126.2, 123.4, 118.9, 106.5, 67.7, 48.7, 47.2, 27.2, 27.1, 23.0. ESI-HRMS: Calcd for $C_{17}H_{24}NO^+$ $[M+H]^+$: 258.1852. Found: 258.1860.

A solution of **3p** (659 mg, 2.56 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (992 mg, 3.00 mmol) in tetrahydrofuran (5.0 mL) was stirred at 50 ºC for 17 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 5 ~ 1 : 1) to afford methyl 2-((isopropyl(4-(naphthalen-2-yloxy)butyl)carbamoyl)oxy)benzoate **1p** as colorless oil (891 mg, 2.05 mmol, 80% yield (based on *N*-isopropyl-4-(naphthalen-2-yloxy)butan-1-amine)).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.95 (d, J = 8.0 Hz, 1H, rotamer A and B),

7.75-7.70 (m, 3H, rotamer A and B), 7.57-7.39 (m, 2H, rotamer A and B), 7.31 (t, *J* = 7.6 Hz, 1H, rotamer A and B), 7.26-7.21 (m, 1H, rotamer A and B), 7.14-7.12 (m, 3H, rotamer A and B), 4.42 (h, *J* = 6.8 Hz, 0.4H, rotamer B), 4.26 (h, *J* = 6.8 Hz, 0.6H, rotamer A), 4.13-4.10 (m, 2H, rotamer A and B), 3.82 (s, 3H, rotamer A and B), 3.41 (t, *J* = 6.8 Hz, 1.2H, rotamer A), 3.33 (t, *J* = 6.8 Hz, 0.8H, rotamer B), 1.98-1.88 (m, 4H, rotamer A and B), 1.32 (d, *J* = 6.8 Hz, 2.4H, rotamer B), 1.25 (d, *J* = 6.8 Hz, 3.6H, rotamer A). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.4, 156.8, 154.1, 154.0, 151.03, 150.95, 134.5, 133.3, 131.4, 129.3, 128.9, 127.6, 126.6, 126.2, 125.2, 124.2, 124.04, 123.96, 123.5, 118.9, 118.8, 106.6, 67.5, 52.0, 48.7, 48.4, 43.3, 27.0, 26.8, 26.7, 26.3, 21.1, 20.4. ESI-HRMS: Calcd for $C_{26}H_{29}NNaO_5^+$ $[M+Na]^+$: 458.1938. Found: 458.1922. Anal. Calcd. for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.58; H, 6.89; N, 3.31.

Synthesis of methyl 2-(((6-(3,4-dimethoxyphenyl)hexyl)(methyl)carbamoyl)oxy)benzoate (1q)

A stirring mixture of dimethyl adipate (5782 mg, 33.2 mmol) and 1,2-dimethoxybenzene (2134 mg, 15.4 mmol) was added TfOH (10 mL) at 0 ºC and the temperature was raised to room temperature (25 ºC). The mixture was stirred for 16 hours. The reaction was quenched with 100 mL of ice water and the whole was extracted with dichloromethane (50 mL x 2) The organic layer was washed with brine (10 mL x 2), dried over sodium sulfate and the solvent was removed under reduced pressure to give crude oil. The crude oil was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 5 ~ 1 : 3) to give methyl 6-(3,4-dimethoxyphenyl)-6-oxohexanoate (**3q**) as colorless oil (known compound) (2146 mg, 7.66 mmol, 50% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.59 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.67 (s, 3H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.38 (t, *J* = 7.2 Hz, 2H), 1.82-1.69 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 198.5, 173.9, 153.2, 149.1, 130.2, 122.6, 110.2, 110.0, 56.1, 56.0, 51.5, 37.6, 33.9, 24.7, 24.0.

A mixture of **3q** (1548 mg, 5.52 mmol) and tetraethylsilane (2019 mg, 17.4 mmol) was added trifluoroacetic acid (5 mL) at 0 ºC. The temperature was raised to room temperature and the reaction solution was stirred for 13 hours. The reaction was quenched with 50 mL of water and the whole was extracted with dichloromethane (50 mL x 2). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure to give crude oil. The crude mixture was dissolved in methylamine (40% solution in methanol) (40 mL) at room temperature. The reaction mixture was stirred at room temperature for 24 hrs. The solvent was removed in vacuo to give crude oil. The crude oil was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 1) to give 6-(3,4-dimethoxyphenyl)-*N*-methylhexanamide (**4q**) as white powder (1027 mg, 3.87 mmol, 70% yield for 2 steps).

Mp. 80 - 81 ºC (colorless needles, recrystallized from $CHCl_3$/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.80-6.77 (m, 1H), 6.71-6.69 (m, 2H), 5.45 (brs, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.79 (d, *J* = 4.8 Hz, 3H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.16 (t, *J* = 7.6 Hz, 2H), 1.70-1.58 (m, 4H), 1.39-1.32 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 173.6, 148.8, 147.1, 135.2, 120.1, 111.8, 111.2, 55.9, 55.8, 36.6, 35.3, 31.3, 28.8, 26.2, 25.5. ESI-HRMS: Calcd for $C_{15}H_{23}NNaO_3^+$ $[M+Na]^+$: 288.1570. Found: 288.1554.

The mixture of **4q** (1027 mg, 3.87 mmol) and 12 mL of borane-tetrahydrofuran complex (0.92M solution in tetrahydrofuran) was stirred under reflux for 10 hrs under argon atmosphere. Then the reaction solution was cooled to 0 ºC and quenched with aqueous hydrogen chloride (1M, 10 mL). Then the solution was heated at 50 ºC for 10 min and then cooled to 0 ºC. The solution was basified by aqueous sodium hydroxide (2M, 10 mL) and the whole was extracted with dichloromethane (50 mL x 2). The organic phase was dried over sodium sulfate and the solvent was removed in vacuo to give 6-(3,4-dimethoxyphenyl)-*N*-methylhexan-1-amine (**5q**) as colorless oil (959 mg, 3.82 mmol, 99% crude yield). The amine was used directly in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.78 (d, *J* = 8.4 Hz, 1H), 6.72-6.70 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.57-2.53 (m, 4H), 2.42 (s, 3H), 1.64 -1.33 (m, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 148.7, 147.0, 135.5, 120.1, 111.7, 111.2, 55.9, 55.8, 52.2, 36.6, 35.5, 31.6, 29.9, 29.2, 27.2. ESI-HRMS: Calcd

for $C_{15}H_{26}NO_2^+$ $[M+H]^+$: 252.1958. Found: 252.1953.

A solution of **5q** (959 mg, 3.82 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (1172 mg, 3.55 mmol) in tetrahydrofuran (5 mL) was stirred under reflux for 6 hrs. Then the solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 4 ~ 1 : 1) to afford **1q** as colorless oil (1294 mg, 3.01 mmol, 85% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.97 (dd, J = 7.6, 1.6 Hz, 1H, rotamer A and B), 7.54-7.49 (m, 1H, rotamer A and B), 7.27-7.24 (m, 1H, rotamer A and B), 7.15 (d, J = 7.6 Hz, 0.6H, rotamer A), 7.12 (d, J = 8.0 Hz, 0.4H, rotamer B), 6.79-6.77 (m, 1H, rotamer A and B), 6.71-6.70 (m, 2H, rotamer A and B), 3.86 (s, 3H, rotamer A and B), 3.85 (s, 3H, rotamer A and B), 3.83 (s, 3H, rotamer A and B), 3.45 (t, J = 7.6 Hz, 0.8H, rotamer B), 3.34 (t, J = 7.6 Hz, 1.2H, rotamer A), 3.11 (s, 1.8H, rotamer A), 3.02 (s, 1.2H, rotamer B), 2.56 (t, J = 6.8 Hz, 2H, rotamer A and B), 1.67-1.62 (m, 4H), 1.40-1.38 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.2, 154.41, 154.35, 151.3, 151.2, 148.7, 147.0, 135.4, 135.2, 133.4, 131.4, 125.2, 124.1, 124.0, 123.9, 123.7, 120.0, 111.7, 111.2, 55.9, 55.7, 51.9, 49.4, 49.3, 35.4, 34.8, 34.4, 31.53, 31.49, 28.9, 27.8, 27.3, 26.6, 26.4. ESI-HRMS: Calcd for $C_{24}H_{31}NNaO_6^+$ $[M+Na]^+$: 452.2044. Found: 452.2053. Anal. Calcd. for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.27; N, 3.26. Found: C, 66.94; H, 7.24; N, 3.30.

Synthesis of methyl 2-(((2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)(phenethyl)carbamoyl)oxy)benzoate (1r)

A solution of 2-phenylethan-1-amine (1886 mg, 15.6 mmol) in tetrahydrofuran (5 mL) was added 1-bromo-4-(2-bromoethyl)benzene (1325 mg, 5.02 mmol) and stirred at 25 ºC for 40 hrs. The reaction solution was cooled to room temperature and was added 40 mL of water. The whole was extracted with dichloromethane (30 mL x 2). The organic phase was dried over sodium sulfate and the solvent was evaporated under reduced pressure to give a crude oil. The crude product was roughly purified by column chromatography (eluent: acetone : *n*-hexane = 1 : 4) to afford *N*-(4-bromophenethyl)-2-phenylethanamine (**3r**) as pale yellow oil (853 mg, 2.80 mmol, 56% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39-7.35 (m, 2H), 7.29-7.25 (m, 2H), 7.22-7.18 (m, 1H), 7.16-7.14 (m, 2H), 7.03-7.00 (m, 2H), 2.90-2.84 (m, 4H), 2.77 (t, J = 7.2 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H), 0.96 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 139.9, 139.0, 131.5, 130.4, 128.6, 128.4, 126.1, 119.9, 51.0, 50.8, 36.3, 35.7. ESI-HRMS: Calcd for $C_{16}H_{19}BrN^+$ $[M+H]^+$: 304.0695. Found: 304.0705.

A solution of **3r** (821 mg, 2.70 mmol) and *N,N*-dimethylpyridin-4-amine (7.1 mg) in dry tetrahydrofuran (10 mL) was added triethylamine (2.0 mL) and di-tert-butyl dicarbonate 716 mg, 3.28 mmol) at 0 ºC. The reaction mixture was stirred at 25 ºC for 3.5 hours. Then the reaction solution was evaporated under reduced pressure and the residue was dissolved in 50 mL of dichloromethane. The solution was washed with aqueous hydrogen chlorode (0.1M, 50 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 12) to afford tert-butyl 4-bromophenethyl(phenethyl)carbamate (**4r**) as colorless oil (663 mg, 1.64 mmol, 61% yield).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 7.37 (d, J = 8.0 Hz, 2H), 7.27 (dd, J = 7.6, 7.6 Hz, 2H), 7.20-7.13 (m, 3H), 7.03-6.98 (m, 2H), 3.32-3.28 (m, 4H), 2.81-2.66 (m, 4H), 1.42 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 155.1, 139.1, 138.2, 131.4, 130.5, 128.7, 128.4, 126.2, 119.9, 79.3, 49.8, 49.4, 49.1, 35.2, 34.6, 33.9, 28.3. ESI-HRMS: Calcd for $C_{21}H_{26}BrNNaO_2^+$ $[M+Na]^+$: 426.1039. Found: 426.1025.

A mixture of **4r** (605 mg, 1.50 mmol), (4-chlorophenyl)boronic acid (310 mmol, 1.98 mmol), potassium carbonate (406 mg, 2.94 mmol), tetraethyl ammonium bromide (71 mg, 0.33 mmol) and palladium acetate (17 mg, 0.073 mmol, 4.9 mol%) was added to a 20-mL Biotage microwave bial with a

Teflon coated stirring bar. The reagents are dissolved in degassed ethanol (10.0 mL) and water (8.0 mL). The bial was sealed and heated at 120 ºC for 15 min. After cooling, the reaction solution was added 20 mL of water and extracted with 50 mL of ethyl acetate. The organic phase was washed with brine (20 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a crude oil. The crude product was roughly purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 10) to afford mixture of 4-bromophenethyl(phenethyl)carbamate (starting material) and tert-butyl (2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)(phenethyl)carbamate (569 mg). Because we could not separate these compounds, the Suzuki coupling reaction was conducted again. A mixture of the crude compound (569 mg), (4-chlorophenyl)boronic acid (151 mmol, 0.966 mmol), potassium carbonate (290 mg, 2.10 mmol), tetraethyl ammonium bromide (40 mg, 0.19 mmol) and palladium acetate (9.7 mg, 0.043 mmol) was added to a 20-mL Biotage microwave bial with a Teflon coated stirring bar. The reagents are dissolved in degassed ethanol (8.0 mL) and water (5.0 mL). The bial was sealed and heated at 120 ºC for 10 min. After cooling, the reaction solution was added 20 mL of water and extracted with 80 mL of ethyl acetate. The organic phase was washed with brine (20 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 10) to afford tert-butyl (2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)(phenethyl)carbamate (**5r**) as colorless oil (512 mg, 1.17 mmol, 78% yield).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 7.45-7.42 (m, 4H), 7.33 (d, J = 8.4 Hz, 2H), 7.27-7.24 (m, 3H), 7.19-7.13 (m, 4H), 3.39-3.32 (m, 4H), 2.82-2.75 (m, 4H), 1.43 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 155.1, 139.3, 139.2, 138.7, 137.7, 133.0, 129.3, 128.9, 128.7, 128.3, 128.0, 126.8, 126.1, 79.2, 49.7, 49.6, 49.3, 35.2, 34.8, 34.6, 34.2, 28.3. ESI-HRMS: Calcd for $C_{27}H_{30}ClNNaO_2^+$ $[M+Na]^+$: 458.1857. Found: 458.1853.

To a solution of **5r** (480 mg, 1.10 mmol) in dry dichloromethane (5.0 mL), trifluoroacetic acid (1.0 mL) was added at 0 ºC under stirring. The temperature was raised to room temperature (20 ºC) and the reaction solution was stirred for 21 hours. Then aqueous sodium carbonate (2M, 10 mL) was added to quench the reaction and the whole was extracted with dichloromethane (50 mL). The organic layer was dried over sodium sulfate and the solvent was removed under reduces pressure to afford 2-(4'-chloro-[1,1'-biphenyl]-4-yl)-*N*-phenethylethanamine (**6r**) as pale yellow solids (363 mg, 1.08 mmol, 98% yield).

Mp. 70 - 71 ºC (colorless plates, recrystallized from $CHCl_3$/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47-7.40 (m, 4H), 7.35 (d, J = 8.4 Hz, 2H), 7.26-7.14 (m, 7H), 2.92-2.85 (m, 4H), 2.81-2.74 (m, 4H), 1.12 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 139.9, 139.5, 139.3, 137.7, 133.0, 129.1, 128.8, 128.6, 128.3, 128.1, 126.9, 126.0, 50.94, 50.85, 36.3, 35.9. ESI-HRMS: Calcd for $C_{22}H_{23}ClN^+$ $[M+H]^+$: 336.1514. Found: 336.1524.

A solution of **6r** (337 mg, 1.00 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (330 mg, 1.00 mmol) in tetrahydrofuran (2.0 mL) was added to a 5-mL Biotage microwave bial with a Teflon coated stirring bar. The bial was sealed and heated at 100 ºC for 2 hrs. After cooling, the solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 8 ~ 1 : 4) to afford methyl 2-(((2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)(phenethyl)carbamoyl)oxy)benzoate **1r** as colorless oil (483 mg, 0.940 mmol, 94% yield).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed (approximately 1 : 1 ratio at 25 ºC), δ (ppm): 8.00-7.98 (m, 1H, rotamer A and B), 7.55-7.48 (m, 5H, rotamer A and B), 7.41-7.38 (m, 2H, rotamer A and B), 7.32-7.22 (m, 8H, rotamer A and B), 7.03 (d, J = 8.0 Hz, 0.6H, rotamer A), 6.97 (d, J = 8.4 Hz, 0.4H, rotamer B), 3.86 (s, 3H, rotamer A and B), 3.68-3.63 (m, 2H, rotamer A and B), 3.53-3.49 (m, 2H, rotamer A and B), 3.03-2.92 (m, 4H, rotamer A and B). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.0, 154.1, 154.0, 150.94, 150.91, 139.2, 139.1, 138.8, 138.4, 137.9, 137.8, 133.3, 133.1, 133.0, 131.3, 129.4, 129.3, 128.8, 128.73, 128.70, 128.40, 128.37, 128.0, 126.90, 126.86, 126.3, 126.2,

125.3, 123.92, 123.88, 123.7, 51.9, 50.3, 50.2, 49.9, 49.8, 35.0, 34.6, 34.2, 33.8. ESI-HRMS: Calcd for $C_{31}H_{28}ClNNaO_4^+$ $[M+Na]^+$: 536.1599. Found: 536.1594.

Synthesis of methyl 2-(((2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)(4-chlorophenethyl)carbamoyl)oxy)benzoate (1s)

A solution of 2-(4-chlorophenyl)ethan-1-amine (4500 mg, 28.9 mmol) in tetrahydrofuran (10 mL) was added 1-bromo-4-(2-bromoethyl)benzene (2552 mg, 9.67 mmol) and stirred at 50 ºC for 46 hrs. The reaction solution was cooled to room temperature and was added 40 mL of aqueous sodium hydroxide (0.5M, 40 mL). The whole was extracted with dichloromethane (30 mL x 2). The organic phase was dried over sodium sulfate and the solvent was evaporated under reduced pressure to give a crude oil. The crude product was roughly purified by column chromatography (eluent: acetone : *n*-hexane = 1 : 4 ~ 1 : 3) to afford *N*-(4-bromophenethyl)-2-(4-chlorophenyl)ethan-1-amine (**3s**) as pale yellow oil (2527 mg, 7.46 mmol, 77% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34-7.37 (m, 2H), 7.24-7.22 (m, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 2.86-2.83 (m, 4H), 2.74-2.69 (m, 4H), 0.91 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 138.9, 138.4, 131.9, 131.5, 130.4, 129.9, 128.5, 119.9, 50.8, 50.7, 35.7, 35.6. ESI-HRMS: Calcd for $C_{16}H_{18}BrClN^+$ $[M+H]^+$: 338.0306. Found: 338.0301.

The amine compound **3s** (2493 mg, 7.36 mmol) was dissolved in dry dichloromethane (10 mL) and the solution was added triethylamine (1.0 mL) and di-tert-butyl dicarbonate (1280 mg, 5.86 mmol) at 0 ºC. The reaction mixture was stirred at 25 ºC for 21 hours. The reaction was quenched with aqueous sodium carbonate (0.5M, 20 mL) and the whole was extracted with dichloromethane (30 mL x 2). The organic phase was dried over sodium sulfate and the solvent was evaporated under reduced pressure to give a crude oil. The crude product was roughly purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 8) to afford tert-butyl (4-bromophenethyl)(4-chlorophenethyl)carbamate (**4s**) (2242 mg, 5.11 mmol, 87%based on di-tert-butyl dicarbonate) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.09-7.00 (m, 4H), 3.32 (brs, 2H), 3.24 (brs, 2H), 2.76 (brs, 2H), 2.70 (brs, 2H), 1.42 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 155.1, 138.1, 137.6, 132.0, 131.4, 130.5, 130.1, 128.5, 120.0, 79.5, 49.5, 49.1, 34.6, 33.9, 28.3. ESI-HRMS: Calcd for $C_{21}H_{25}BrClNNaO_2^+$ $[M+Na]^+$: 460.0649. Found: 460.0648.

A mixture of **4s** (873 mg, 1.99 mmol), (4-chlorophenyl)boronic acid (790 mmol, 5.05 mmol), potassium carbonate (877 mg, 6.35 mmol), tetraethyl ammonium bromide (194 mg, 0.923 mmol) and palladium acetate (59 mg, 0.262 mmol, 13 mol%) was added to a 20-mL Biotage microwave bial with a Teflon coated stirring bar. The reagents are dissolved in degassed ethanol (8.0 mL) and water (8.0 mL). The bial was sealed and heated at 120 ºC for 15 min. After cooling, the reaction solution was extracted with 80 mL of ethyl acetate. The organic phase was washed with water (20 mL) and then brine (20 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 10 ~ 1 : 6) to afford tert-butyl (2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)(4-chlorophenethyl)carbamate **5s** as colorless oil (688 mg, 1.46 mmol, 73% yield).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 7.47-7.44 (m, 4H), 7.37-7.35 (m, 2H), 7.24-7.19 (m, 4H), 7.10 (brs, 1H), 7.05 (brs, 1H), 3.36 (brs, 2H), 3.31 (brs, 2H), 2.78 (brs, 4H), 1.42 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 155.1, 139.3, 138.6, 137.9, 137.7, 133.1, 132.0, 130.1, 129.3, 128.8, 128.5, 128.1, 126.9, 79.4, 49.5, 49.3, 34.8, 34.6, 34.2, 33.9, 28.3. ESI-HRMS: Calcd for $C_{27}H_{29}Cl_2NNaO_2^+$ $[M+Na]^+$: 492.1468. Found: 492.1479.

To a solution of **5s** (1347 mg, 2.86 mmol) in dry dichloromethane (5.0 mL), trifluoroacetic acid (2.0 mL) was added at 0 ºC under stirring. The temperature was raised to room temperature and the reaction solution was stirred for 4 hours. Then aqueous sodium carbonate (2M, 20 mL) was added to quench the reaction and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was removed under reduces pressure to afford 2-(4'-chloro-[1,1'-biphenyl]-4-yl)-*N*-(4-chlorophenethyl)ethanamine (**6s**) as colorless oil (998 mg, 2.69

mmol, 94% yield).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50-7.47 (m, 2H), 7.46-7.43 (m, 2H), 7.40-7.37 (m, 2H), 7.22-7.20 (m, 4H), 7.09-7.07 (m, 2H), 2.93-2.86 (m, 4H), 2.81 (t, J = 7.2 Hz, 2H), 2.75 (t, J = 7.2 Hz, 2H), 1.09 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 139.4, 139.3, 138.4, 137.9, 133.2, 131.9, 130.0, 129.2, 128.9, 128.5, 128.2, 127.0, 50.83, 50.77, 35.9, 35.6. ESI-HRMS: Calcd for $C_{22}H_{22}Cl_2N^+$ $[M+H]^+$: 370.1124. Found: 370.1130.

A solution of **6s** (813mg, 2.20 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (669 mg, 2.02mmol) in tetrahydrofuran (4.0 mL) was added to a 5-mL Biotage microwave bial with a Teflon coated stirring bar. The bial was sealed and heated at 100 ºC for 3 hrs. After cooling, the solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 8 ~ 1 : 6) to afford methyl 2-(((2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)(4-chlorophenethyl)carbamoyl)oxy)benzoate **1s** (999 mg, 1.82 mmol, 90% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).
Mp. 113 - 114 ºC (colorless needles, recrystallized from $CHCl_3$/*n*-hexane)
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed (approximately 1 : 1 ratio at 25 ºC), δ (ppm): 8.04-8.01 (m, 1H), 7.60-7.51 (m, 5H), 7.43 (dd, J = 8.4, 2.8 Hz, 2H), 7.36-7.28 (m, 5H), 7.23-7.19 (m, 2H), 7.05 (d, J = 8.0 Hz, 0.5H), 7.00 (d, J = 8.0 Hz, 0.5H), 3.90 (s, 3H), 3.70-3.64 (m, 2H), 3.56-3.50 (m, 2H), 3.07-2.93 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.1, 154.2, 151.0, 139.3, 138.4, 138.2, 138.1, 137.4, 133.51, 133.47, 133.3, 133.2, 132.3, 132.2, 131.4, 130.3, 130.2, 129.5, 129.4, 128.88, 128.85, 128.64, 128.60, 128.2, 127.1, 127.0, 125.5, 124.0, 123.8, 52.0, 50.4, 50.3, 50.0, 49.9, 34.7, 34.5, 34.0, 33.7. ESI-HRMS: Calcd for $C_{31}H_{27}Cl_2NNaO_4^+$ $[M+Na]^+$: 570.1209. Found: 570.1238.

Synthesis of methyl 2-((benzyl(4-chlorophenethyl)carbamoyl)oxy)benzoate (1t)

A solution of 2-(4-chlorophenyl)ethan-1-amine (771 mg, 4.95 mmol) in triethylamine (1.0 mL) was added benzyl bromide (347 mg, 2.15 mmol) and stirred at 25 ºC for 15 hrs. The reaction solution was cooled to room temperature and was added 40 mL of aqueous sodium hydroxide (0.5M, 40 mL). The whole was extracted with dichloromethane (30 mL x 2). The organic phase was dried over sodium sulfate and the solvent was evaporated under reduced pressure to give a crude oil. The crude product was roughly purified by column chromatography (eluent: acetone : *n*-hexane = 1 : 8) to afford *N*-benzyl-2-(4-chlorophenyl)ethan-1-amine (**3t**) as colorless oil (355 mg, 1.45 mmol, 67% yield).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.33-7.22 (m, 7H), 7.13-7.11 (m, 2H), 3.79 (s, 2H), 2.87 (t, J = 6.8 Hz, 2H), 2.78 (t, J = 6.8 Hz, 2H), 1.30 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 140.2, 138.5, 131.9, 130.0, 128.5, 128.4, 128.0, 126.9, 53.9, 50.3, 35.7. ESI-HRMS: Calcd for $C_{15}H_{17}ClN^+$ $[M+H]^+$: 246.1044. Found: 246.1034.

A solution of **3t** (931 mg, 3.79 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (854 mg, 2.59 mmol) in tetrahydrofuran (4.0 mL) was added to a 5-mL Biotage microwave bial with a Teflon coated stirring bar. The bial was sealed and heated at 100 ºC for 3 hrs. After cooling, the solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 8 ~ 1 : 4) to afford methyl 2-((benzyl(4-chlorophenethyl)carbamoyl)oxy)benzoate **1t** as colorless oil (1028 mg, 2.43 mmol, 94% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.99-7.97 (m, 1H, rotamer A and B), 7.55-7.50 (m, 1H, rotamer A and B), 7.36-7.23 (m, 8H, rotamer A and B), 7.14-7.10 (m, 2.4H, rotamer A and B), 7.04 (d, J = 7.6 Hz, 0.6H, rotamer A), 4.63 (s, 0.8H, rotamer B), 4.49 (s, 1.2H, rotamer A), 3.83 (s, 1.2H, rotamer B), 3.78 (s, 1.8H, rotamer A), 3.61 (t, J = 7.6 Hz, 1.2H, rotamer A), 3.49 (t, J = 7.6 Hz, 0.8H, rotamer B), 2.93 (t, J = 7.6 Hz, 1.2H, rotamer A), 2.87 (t, J = 7.6 Hz, 0.8H, rotamer B). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.1, 154.8, 154.2, 151.00, 150.95, 137.44, 137.40, 137.3, 137.2, 133.48, 133.45, 132.2, 132.1, 131.5, 130.22, 130.19,

128.59, 128.55, 128.1, 127.58, 127.55, 127.5, 125.5, 124.00, 123.97, 123.8, 52.0, 51.5, 51.2, 49.1, 48.3, 34.0, 33.3. ESI-HRMS: Calcd for $C_{24}H_{22}ClNNaO_4^+$ $[M+Na]^+$: 446.1130. Found: 446.1156.

Synthesis of methyl 2-((benzyl(3-phenylpropyl)carbamoyl)oxy)benzoate (1u)

A solution of benzoyl chloride (713 mg, 5.07 mmol) in 5 mL of dichloromethane was added dropwise to a solution of 3-phenylpropan-1-amine (663 mg, 4.90 mmol) and triethylamine (1.0 mL) in dry dichloromethane (5 mL) under stirring at -78ºC. The temperature was raised to 25 ºC and the reaction mixture was stirred for 30 min. Then 20 mL of water was added and the whole was extracted with dichloromethane (30 mL x 2). The organic phase was dried over sodium sulfate and the solvent was removed in vacuo to afford *N*-(3-phenylpropyl)benzamide (**3u**) as white powder (known compound) (1155 mg, 4.83 mmol, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.67-7.65 (m, 2H), 7.50-7.46 (m, 1H), 7.42-7.38 (m, 2H), 7.32-7.28 (m, 2H), 7.23-7.19 (m, 3H), 6.06 (brs, 1H), 3.51 (dt, J = 6.8, 6.8 Hz, 2H), 2.74 (t, J = 7.6 Hz, 2H), 2.02-1.94 (m, 2H). ESI-HRMS: Calcd for $C_{16}H_{17}NNaO^+$ $[M+Na]^+$: 262.1202. Found: 262.1202.

A solution of *N*-(3-phenylpropyl)benzamide (903 mg, 3.77 mmol) and lithium aluminum hydride (337 mg, 8.88 mmol) in tetrahydrofuran (14 mL) was stirred at 50 ºC for 12 hrs. Then the reaction solution was cooled to 0 ºC and quenched with large amount of sodium sulfate decahydrate and ethyl acetate. Then the solution was filtered and the solvent was removed in vacuo to give *N*-benzyl-3-phenylpropan-1-amine (**4u**) (known compound) (835 mg, 3.71 mmol, 98% crude yield) as colorless oil. The amine was used directly in the next step without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.31-7.14 (m, 10H), 3.76 (s, 2H), 2.67-2.63 (m, 4H), 1.86-1.79 (m, 2H), 1.38 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 142.1, 140.5, 128.30, 128.30, 128.2, 128.0, 126.8, 125.7, 53.9, 48.9, 33.6, 31.7. ESI-HRMS: Calcd for $C_{16}H_{20}N^+$ $[M+H]^+$: 226.1590. Found: 226.1577.

A solution of **4u** (818 mg, 3.63 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (997 mmol, 3.02 mmol) in tetrahydrofuran (4.0 mL) was added to a 5-mL Biotage microwave bial with a Teflon coated stirring bar. The bial was sealed and heated at 100 ºC for 3 hrs. After cooling, the solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 4) to afford methyl 2-((benzyl(3-phenylpropyl)carbamoyl)oxy)benzoate **1u** as colorless oil (1161 mg, 2.88 mmol, 95% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.99-7.96 (m, 1H, rotamer A and B), 7.56-7.50 (m, 1H, rotamer A and B), 7.35-7.26 (m, 8H, rotamer A and B), 7.19-7.12 (m, 4H, rotamer A and B), 4.71 (s, 0.8H, rotamer B), 4.55 (s, 1.2H, rotamer A), 3.81 (s, 1.2H, rotamer B), 3.77 (s, 1.8H, rotamer A), 3.45 (t, J = 7.6 Hz, 1.2H, rotamerA), 3.78 (t, J = 7.6 Hz, 0.8H, rotamer B), 2.64 (t, J = 7.6 Hz, 2H, rotamer A and B), 2.05-1.91 (m, 2H, rotamer A and B). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.3, 154.9, 154.3, 151.0, 141.6, 141.3, 137.5, 137.4, 133.4, 131.5, 131.4, 128.52, 128.46, 128.31, 128.28, 128.23, 128.19, 128.16, 127.5, 127.42, 127.37, 125.9, 125.8, 125.40, 125.36, 124.03, 123.97, 52.0, 50.9, 50.8, 47.0, 46.5, 33.0, 32.9, 29.5, 29.0. ESI-HRMS: Calcd for $C_{25}H_{25}NNaO_4^+$ $[M+Na]^+$: 426.1676. Found: 426.1654. Anal. Calcd. for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.22; H, 6.33; N, 3.45.

Synthesis of methyl 2-(((4-chlorobenzyl)(3-phenylpropyl)carbamoyl)oxy)benzoate (1v)

A solution of 3-phenylpropan-1-amine (1458mg, 10.8 mmol) in tetrahydrofuran (5 mL) was added 4-chlorobenzyl bromide (829 mg, 4.04 mmol) and stirred at 25 ºC for 45 hrs. The reaction solution was added 50 mL of dichloromethane and the whole was washed with aqueous hydrogen chloride (1M, 10 mL x 2) and then aqueous sodium hydroxide (2M, 10 mL). The organic phase was dried over sodium sulfate and the solvent was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: acetone : *n*-hexane = 1 : 4 ~ 1 : 3) to afford *N*-(4-chlorobenzyl)-3-phenylpropan-1-amine (**3v**) as colorless oil (729 mg, 2.81 mmol, 69%

yield).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29-7.24 (m, 6H), 7.22-7.15 (m, 3H), 3.73 (s, 2H), 2.67-2.62 (m, 4H), 1.82 (p, J = 7.2 Hz, 2H), 1.19 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 142.1, 139.0, 132.5, 129.4, 128.4, 128.34, 128.30, 125.8, 53.2, 48.8, 33.6, 31.7. ESI-HRMS: Calcd for $C_{16}H_{19}ClN^+$ $[M+H]^+$: 260.1201. Found: 260.1204.

A solution of **3v** (636 mg, 2.45 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (1015 mmol, 3.07 mmol) in tetrahydrofuran (4.0 mL) was stirred at 50 ºC for 22 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 4) to afford methyl 2-(((4-chlorobenzyl)(3-phenylpropyl)carbamoyl)oxy)benzoate **1v** as colorless oil (612 mg, 1.40 mmol, 57% yield (based on *N*-(4-chlorobenzyl)-3-phenylpropan-1-amine))).
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.98-7.95 (m, 1H, rotamer A and B), 7.53-7.47 (m, 1H), 7.32-7.23 (m, 7H), 7.20-7.09 (m, 4H), 4.64 (s, 0.8H, rotamer B), 4.48 (s, 1.2H, rotamer A), 3.80 (s, 1.2H, rotamer B), 3.77 (s, 1.8H, rotamer A), 3.42 (t, J = 7.2 Hz, 1.2H, rotamer A), 3.34 (t, J = 7.2 Hz, 0.8H, rotamer B), 2.63 (t, J = 7.6 Hz, 2H, rotamer A and B), 2.04-1.89 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.0, 154.9, 154.1, 151.0, 150.9, 141.4, 141.2, 136.0, 135.9, 133.4, 133.1, 131.4, 129.4, 128.9, 128.6, 128.5, 128.29, 128.26, 128.1, 125.9, 125.8, 125.4, 123.93. 124.86, 123.8, 51.9, 50.3, 50.2, 47.0, 46.5, 32.9, 32.8, 29.4, 28.9. ESI-HRMS: Calcd for $C_{25}H_{24}ClNNaO_4^+$ $[M+Na]^+$: 460.1286. Found: 460.1299. Anal. Calcd. for $C_{25}H_{24}ClNO_4$: C, 68.57; H, 5.52; N, 3.20. Found: C, 68.71; H, 5.72; N, 3.18.

Synthesis of methyl 2-(((4-chlorobenzyl)(4-phenylbutyl)carbamoyl)oxy)benzoate (1w)

A solution of 4-phenylbutan-1-amine (896 mg, 6.00 mmol) in tetrahydrofuran (5 mL) was added 4-chlorobenzyl bromide (621 mg, 3.02 mmol) and stirred at 25 ºC for 24 hrs. The reaction solution was added 50 mL of dichloromethane and the whole was washed with aqueous sodium hydroxide (2M, 10 mL). The organic phase was dried over sodium sulfate and the solvent was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: acetone : *n*-hexane = 1 : 4 ~ 1 : 2) to afford *N*-(4-chlorobenzyl)-4-phenylbutan-1-amine (**3w**) as colorless oil (559 mg, 2.04 mmol, 68% yield).
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29-7.22 (m, 6H), 7.19-7.15 (m, 3H), 3.73 (s, 2H), 2.63-2.59 (m, 4H), 1.69-1.62 (m, 2H), 1.57-1.50 (m, 2H), 1.15 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 142.4, 139.1, 132.5, 129.4, 128.4, 128.3, 125.7, 53.3, 49.2, 35.8, 29.7, 29.1. ESI-HRMS: Calcd for $C_{17}H_{21}ClN^+$ $[M+H]^+$: 274.1357. Found: 274.1357.

A solution of **3w** (526 mg, 1.92 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (661 mmol, 2.00 mmol) in tetrahydrofuran (6.0 mL) was added to a Biotage microwave bial with a Teflon coated stirring bar. The bial was sealed and heated at 80 ºC for 3 hrs. After cooling, the solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 4) to afford methyl 2-(((4-chlorobenzyl)(4-phenylbutyl)carbamoyl)oxy)benzoate **1w** as colorless oil (718 mg, 1.59 mmol, 83% yield (based on *N*-(4-chlorobenzyl)-4-phenylbutan-1-amine))).
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.98-7.95 (m, 1H, rotamer A and B), 7.52-7.47 (m, 1H, rotamer A and B), 7.33-7.20 (m, 7H, rotamer A and B), 7.18-7.08 (m, 4H, rotamer A and B), 4.63 (s, 0.8H, rotamer B), 4.48 (s, 1.2H, rotamer A), 3.76 (s, 3H, rotamer A and B), 3.42-3.33 (m, 2H, rotamer A and B), 2.64-2.60 (m, 2H, rotamer A and B), 1.70-1.63 (m, 4H, rotamer A and B). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.1, 154.9, 154.2, 151.1, 150.9, 142.1, 141.9, 136.0, 133.5, 133.2, 131.5, 131.4, 129.4, 128.9, 128.7, 128.6, 128.31, 128.25, 125.8, 125.7, 125.5, 125.4, 124.0, 123.90, 123.85, 51.9, 50.2, 50.0, 47.0, 46.8, 35.41, 35.36, 28.4, 28.3, 27.5, 26.9. ESI-HRMS: Calcd for $C_{26}H_{26}ClNNaO_4^+$ $[M+Na]^+$: 474.1443. Found: 474.1429.

methyl 2-((benzyl(phenethyl)carbamoyl)oxy)benzoate (1x)

A solution of *N*-benzyl-2-phenylethanamine (368 mg, 1.74 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (497 mg, 1.50 mmol) in tetrahydrofuran (5.0 mL) was stirred at 50 ºC for 43 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6) to afford methyl 2-((benzyl(phenethyl)carbamoyl)oxy)benzoate (538 mg, 1.38 mmol, 92% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately A : B = 6 : 4 ratio at 25 ºC), δ (ppm): 7.99 (dd, J = 8.0, 1.2 Hz, 1H, rotamer A and B), 7.52 (ddd, J = 8.0, 8.0, 1.2 Hz, 1H, rotamer A and B), 7.37-7.19 (m, total 11H, rotamer A and B), 7.14 (d, J = 8.4 Hz, 0.4H, rotamer B), 7.06 (dd, J = 8.0, 0.8 Hz, 0.6H, rotamer A), 4.64 (s, 0.8H, rotamer B), 4.49 (s, 1.2H, rotamer A), 3.82 (s, 1.2H, rotamer B), 3.78 (s, 1.8H, rotamer A), 3.64 (t, J = 7.6 Hz, 1.2H, rotamer A), 3.52 (t, J = 8.0 Hz, 0.8H, rotamer B), 2.97 (t, J = 7.6 Hz, 1.2 H, rotamer A), 2.92 (t, J = 8.0 Hz, 0.8H, rotamer B). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.3, 154.9, 154.3, 151.1, 151.0, 139.0, 137.44, 137.39, 133.5, 131.5, 128.90, 128.88, 128.63, 128.57, 128.54, 128.49, 128.2, 127.7, 127.6, 127.5, 126.4, 126.3, 125.5, 124.2, 124.1, 124.0, 52.1, 51.4, 51.1, 49.4, 48.5, 34.7, 34.0. ESI-HRMS: Calcd for $C_{24}H_{23}NNaO_4^+$ $[M+Na]^+$: 412.1519. Found: 412.1500.

Synthesis of methyl 2-(((4-phenylbutyl)(5-phenylpentyl)carbamoyl)oxy)benzoate (1y)

A mixture of 5-phenylpentanoic acid (904 mg, 5.07 mmol) in $SOCl_2$ (3.0 mL) was stirred at 60 ºC for 4 hrs. Then the solvent was removed under reduced pressure to afford crude oil. The oil was dissolved in 5 mL of dichloromethane and added dropwise to a solution of 4-phenylbutan-1-amine (1037 mg, 6.95 mmol) and triethylamine (1.0 mL) in dry dichloromethane (5 mL) under stirring at -78ºC. The temperature was raised to 25 ºC and the reaction mixture was stirred for 30 min. Then 10 mL of aqueous sodium hydroxide (2M) was added and the whole was extracted with dichloromethane (30 mL x 2). The organic phase was washed with aqueous hydrogen chloride (1M, 10 mL) and dried over sodium sulfate. The solvent was removed in vacuo to afford 5-phenyl-*N*-(4-phenylbutyl)pentanamide (**3x**) as colorless oil (1473 mg, 4.76 mmol, 94%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.24 (m, 4H), 7.19-7.14 (m, 6H), 5.41 (brs, 1H), 3.23 (dt, J = 6.8, 6.8 Hz, 2H), 2.61 (t, J = 7.6 Hz, 4H), 2.14 (t, J = 7.2 Hz, 2H), 1.70-1.59 (m, 6H), 1.57-1.46 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 172.7, 142.2, 142.0, 128.4 (duplicated), 128.29, 128.27, 125.8, 125.7, 39.2, 36.6, 35.6, 35.4, 31.0, 29.2, 28.6, 25.4. ESI-HRMS: Calcd for $C_{21}H_{27}NNaO^+$ $[M+Na]^+$: 332.1985. Found: 332.1985.

A solution of **3x** (1413 mg, 4.57 mmol) and lithium aluminum hydride (472 mg, 12.4 mmol) in tetrahydrofuran (20 mL) was stirred for 8 hrs under reflux. Then the reaction solution was cooled to 0 ºC and quenched with large amount of sodium sulfate decahydrate and ethyl acetate. Then the solution was filtered and the solvent was removed in vacuo to give 5-phenyl-*N*-(4-phenylbutyl)pentan-1-amine (**4x**) as colorless oil (1240 mg, 4.20 mmol, 92% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.25 (m, 4H), 7.18-7.15 (m, 6H), 2.64-2.55 (m, 8H), 1.68-1.57 (m, 4H), 1.55-1.46 (m, 4H), 1.39-1.31 (m, 2H), 0.99 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 142.7, 142.5, 128.38, 128.37, 128.24, 128.22, 125.65, 125.59, 50.03, 49.97, 35.87, 35.85, 31.4, 30.1, 29.9, 29.3, 27.0. ESI-HRMS: Calcd for $C_{21}H_{30}N^+$ $[M+H]^+$: 296.2373. Found: 296.2374.

A solution of **4x** (1028 mg, 3.48 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (998 mg, 3.02 mmol) in tetrahydrofuran (4.0 mL) was stirred at 60 ºC for 4 hrs. The solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 3) to afford methyl 2-(((4-phenylbutyl)(5-phenylpentyl)carbamoyl)oxy)benzoate **1x** as colorless oil (1249 mg, 2.64 mmol, 87% yield (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed (approximately 1 : 1 ratio at 24ºC), δ (ppm): 7.94 (d, J = 7.6 Hz, 1H), 7.48-7.44 (m, 1H), 7.25-7.14 (m,

11H), 7.10-7.05 (m, 1H), 3.77 (s, 1.5H), 3.74 (s, 1.5H), 3.42-3.24 (m, 4H), 2.67-2.57 (m, 4H), 1.73-1.58 (m, 8H), 1.40-1.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.1, 154.1, 154.0, 151.0, 142.3, 142.2, 142.1, 141.9, 133.2, 131.3, 128.23, 128.19, 128.12, 128.08, 128.06, 125.6, 125.52, 125.45, 125.1, 123.9, 123.8, 51.8, 47.8, 47.4, 47.3, 35.7, 35.40, 35.35, 31.0, 28.4, 28.3, 28.2, 27.9, 27.6, 27.3, 26.3, 26.2. ESI-HRMS: Calcd for $C_{30}H_{35}NNaO_4^+$ $[M+Na]^+$: 496.2458. Found: 496.2478.

III. Substrate generality of the cyclization reaction

Synthesis of 2-methyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one (2a)

To a solution of methyl 2-(((4-phenylbutyl)carbamoyl)oxy)benzoate (**1a**) (240.9 mg, 0.736 mmol) in dry dichloromethane (3.68 ml, 0.2 M), trifluoromethanesulfonic acid (0.66 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 20 ºC under argon atmosphere for 2 hrs. Then the mixture was quenched with 10 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 1) to afford 2-methyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one (**2a**) (85.2 mg, 0.450 mmol, 61% yield) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 (dd, J = 7.6, 1.6 Hz, 1H), 7.34 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 7.24 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.15 (dd, J = 7.6, 0.4 Hz, 1H), 3.36-3.30 (m, 1H), 3.14 (s, 3H), 3.10-3.04 (m, 1H), 2.80 (dd, J = 13.6, 8.0 Hz, 1H), 2.65 (m, 1H), 2.13-2.04 (m, 1H), 1.81-1.66 (m, 2H), 1.56-1.44 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.0, 140.2, 135.5, 130.1, 129.2, 127.2, 126.4, 49.8, 33.2, 32.4, 27.7, 25.7. ESI-HRMS: Calcd for $C_{12}H_{15}NNaO^+$ $[M+Na]^+$: 212.1046. Found: 212.1059. Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.93; H, 8.08; N, 7.41.

Synthesis of 2-ethyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one (2b)

To a solution of methyl 2-((ethyl(4-phenylbutyl)carbamoyl)oxy)benzoate (**1b**) (235.8 mg, 0.663 mmol) in dry dichloromethane (3.3 ml, 0.2 M), trifluoromethanesulfonic acid (0.59 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 20 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 2) to afford 2-ethyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one (**2b**) (86.2 mg, 0.424 mmol, 64% yield) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 (dd, J = 7.6, 1.2 Hz, 1H), 7.33 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.24 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 4.03-3.94 (m, 1H), 3.21-3.13 (m, 3H), 2.81-2.76 (m, 1H), 2.72-2.66 (m, 1H), 2.13-2.06 (m, 1H), 1.75-1.68 (m, 2H), 1.54-1.43 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 170.5, 140.1, 135.7, 130.0, 129.1, 127.3, 126.3, 46.7, 40.4, 32.2, 27.7, 26.4, 12.6. ESI-HRMS: Calcd for $C_{13}H_{17}NNaO^+$ $[M+Na]^+$: 226.1202. Found: 226.1200. Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.43; H, 8.39; N, 6.94.

Synthesis of 2-isobutyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one (2c)

To a solution of methyl 2-((isobutyl(4-phenylbutyl)carbamoyl)oxy)benzoate (**1c**) (230.6 mg, 0.601 mmol) in dry dichloromethane (3.0 ml, 0.2 M), trifluoromethanesulfonic acid (0.53 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 20 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 30 mL of ice water and the whole was extracted with dichloromethane (20 mL x 3). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 2) to afford 2-isobutyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one (**2c**) (89.8 mg, 0.388 mmol, 65% yield) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36-7.30 (m, 2H), 7.23 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 7.14 (d, J

= 7.6 Hz, 1H), 3.92 (ddd, *J* = 13.2, 8.4, 1.2 Hz, 1H), 3.25-3.11 (m, 2H), 2.84 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.78 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.69-2.62 (m, 1H), 2.19-2.04 (m, 2H), 1.79-1.64 (m, 2H), 1.53-1.41 (m, 1H), 0.98 (t, *J* = 6.4 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.3, 139.6, 136.1, 129.7, 128.9, 127.0, 126.3, 52.0, 47.1, 32.4, 27.6, 26.5, 26.3, 20.2, 20.0. ESI-HRMS: Calcd for $C_{15}H_{21}NNaO^+$ $[M+Na]^+$: 254.1515. Found: 254.1523.

Synthesis of 2-isopropyl-3,4,5,6-tetrahydrobenzo[c]azocin-1(2H)-one (2d)

To a solution of methyl 2-((isopropyl(4-phenylbutyl)carbamoyl)oxy)benzoate (**1d**) (286.1 mg, 0.774 mmol) in dry dichloromethane (3.9 ml, 0.2 M), trifluoromethanesulfonic acid (0.69 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 22ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 6 ~ 1 : 2) to afford 2-isopropyl-3,4,5,6-tetrahydrobenzo[c]azocin-1(2H)-one (**2d**) (125.3 mg, 0.577 mmol, 74% yield) as white solid.

Mp. 79 - 80 ºC (colorless cubes, recrystallized from $CHCl_3$/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.32 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.23 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 4.74-4.64 (m, 1H), 3.27-3.21 (m, 1H), 3.13-3.06 (m, 1H), 2.82-2.73 (m, 2H), 2.12-2.05 (m, 1H), 1.78-1.71 (m, 2H), 1.50-1.42 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.30 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.2, 139.9, 136.5, 129.9, 129.1, 127.6, 126.3, 47.3, 43.8, 32.4, 28.6, 27.6, 21.1, 19.9. ESI-HRMS: Calcd for $C_{14}H_{19}NNaO^+$ $[M+Na]^+$: 240.1359. Found: 240.1360. Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.27; H, 8.77; N, 6.39.

Synthesis of 2,9-dimethyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one (2e)

To a solution of methyl 2-((methyl(4-(*p*-tolyl)butyl)carbamoyl)oxy)benzoate (**1e**) (324.5 mg, 0.913 mmol) in dry dichloromethane (4.6 ml, 0.2 M), trifluoromethanesulfonic acid (0.81 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 25 ºC under argon atmosphere for 1.5 hr. Then the mixture was quenched with 30 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 2) to afford 2,9-dimethyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one (**2e**) (134.7 mg, 0.663 mmol, 73% yield) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.20 (s, 1H), 7.13 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 3.37-3.30 (m, 1H), 3.12 (s, 3H), 3.08-3.03 (m, 1H), 2.75 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.62-2.56 (m, 1H), 2.32 (s, 3H), 2.10-2.03 (m, 1H), 1.80-1.64 (m, 2H), 1.52-1.44 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.1, 137.1, 135.8, 135.2, 130.7, 129.0, 127.5, 49.7, 33.0, 31.8, 27.7, 25.7, 20.7. ESI-HRMS: Calcd for $C_{13}H_{17}NNaO^+$ $[M+Na]^+$: 226.1202. Found: 226.1212.

Synthesis of 2,7,10-trimethyl-3,4,5,6-tetrahydrobenzo[c]azocin-1(2H)-one (2f)

To a solution of methyl 2-(((4-(2,5-dimethylphenyl)butyl)(methyl)carbamoyl)oxy)benzoate (**1f**) (266.1 mg, 0.720 mmol) in dry dichloromethane (3.6 ml, 0.2 M), trifluoromethanesulfonic acid (0.64 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 30 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 1) to afford 2,7,10-trimethyl-3,4,5,6-tetrahydrobenzo[c]azocin-1(2H)-one (**2f**) (135.4 mg, 0.623 mmol, 87% yield) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.06 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 3.38 (dd, *J* = 14.8, 11.6 Hz, 1H), 3.16 (s, 3H), 3.05 (dd, *J* = 14.8, 5.6 Hz, 1H), 2.90 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.41 (dd, *J* = 14.0, 12.4 Hz, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 2.06-1.99 (m, 1H), 1.83-1.72 (m, 1H), 1.67-1.60

(m, 1H), 1.44-1.33 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.1, 138.0, 135.3, 132.3, 132.2, 130.8, 128.0, 49.5, 32.6, 27.9, 25.7, 25.4, 19.3, 19.1. ESI-HRMS: Calcd for $C_{14}H_{19}NNaO^+$ $[M+Na]^+$: 240.1359. Found: 240.1364. Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.22; H, 8.79; N, 6.50.

Synthesis of 8,9-dimethoxy-2-methyl-3,4,5,6-tetrahydrobenzo[c]azocin-1(2H)-one (2g)

To a solution of methyl 2-(((4-(3,4-dimethoxyphenyl)butyl)(methyl)carbamoyl)oxy)benzoate (**1g**) (222.8 mg, 0.555 mmol) in dry dichloromethane (2.8 ml, 0.2 M), trifluoromethanesulfonic acid (0.49 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 24ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 5 ~ 1 : 2) to afford 8,9-dimethoxy-2-methyl-3,4,5,6-tetrahydrobenzo[c]azocin-1(2H)-one (**2g**) (133.3 mg, 0.535 mmol, 96% yield) as colorless solid.

Mp. 119 - 120 ºC (Colorless cubes, recrystallized from CH_2Cl_2/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.93 (s, 1H), 6.63 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.42-3.35 (m, 1H), 3.12 (s, 3H), 3.10-3.05 (m, 1H), 2.72 (dd, J = 13.6, 8.0 Hz, 1H), 2.62 (dd, J = 8.0, 8.0 Hz, 1H), 2.08-2.02 (m, 1H), 1.77-1.66 (m, 2H), 1.55-1.44 (m, 1H).

^{1}H-NMR (400 MHz, DMSO-d_6, 120 ºC) δ (ppm): 6.85 (s, 1H), 6.78 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.19 (brs, 2H), 3.02 (s, 3H), 2.75 (brs, 2H), 1.71 (brs, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 170.7, 150.1, 147.2, 133.0, 127.2, 111.7, 110.1, 55.7 (2 x OMe), 49.8, 33.1, 31.9, 27.3, 25.6. ESI-HRMS: Calcd for $C_{14}H_{19}NNaO_3^+$ $[M+Na]^+$: 272.1257. Found: 272.1260. Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.23; H, 7.68; N, 5.63.

Synthesis of 8,9-dimethoxy-2,3-dimethyl-3,4,5,6-tetrahydrobenzo[c]azocin-1(2H)-one (2h)

To a solution of methyl 2-(((5-(3,4-dimethoxyphenyl)pentan-2-yl)(methyl)carbamoyl)oxy)benzoate (**1h**) (242.2 mg, 0.583 mmol) in dry dichloromethane (2.9 ml, 0.2 M), trifluoromethanesulfonic acid (0.52 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 20 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 30 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 1) to afford 8,9-dimethoxy-2,3-dimethyl-3,4,5,6-tetrahydrobenzo[c]azocin-1(2H)-one (**2h**) (132.6 mg, 0.504 mmol, 86% yield) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.87 (s, 1H), 6.54 (s, 1H), 3.811 (s, 3H), 3.805 (s, 3H), 3.75-3.69 (m, 1H), 2.90 (s, 3H), 2.65-2.54 (m, 2H), 1.96-1.88 (m, 1H), 1.70-1.60 (m, 1H), 1.54-1.43 (m, 1H), 1.41-1.36 (m, 1H), 1.05 (d, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.0, 150.0, 147.4, 133.0, 127.6, 111.8, 110.3, 55.8 (2 x OMe), 52.3, 32.0, 31.9, 27.1, 26.3, 21.1. ESI-HRMS: Calcd for $C_{15}H_{21}NNaO_3^+$ $[M+Na]^+$: 286.1414. Found: 286.1394. Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.23; H, 8.05; N, 5.26.

Synthesis of 5-methyl-4,5-dihydro-2H-benzo[b][1,5]oxazocin-6(3H)-one (2i)

To a solution of methyl 2-((methyl(3-phenoxypropyl)carbamoyl)oxy)benzoate (**1i**) (259.5 mg, 0.756 mmol) in dry dichloromethane (3.8 ml, 0.2 M), trifluoromethanesulfonic acid (0.67 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 29ºC under argon atmosphere for 1.5 hr. Then the mixture was quenched with 30 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 2) to afford 5-methyl-4,5-dihydro-2H-benzo[b][1,5]oxazocin-6(3H)-one (**2i**) (107.6 mg, 0.563 mmol, 74% yield) as white solid.

Mp. 110 - 111 ºC (colorless needles, recrystallized from hexane)
^{1}H-NMR (400 MHz, $CDCl_3$, 27ºC) δ (ppm): 7.50 (dd, J = 8.0, 1.6 Hz, 1H), 7.33-7.29 (m, 1H), 7.04-7.00 (m, 1H), 6.91 (dd, J = 8.0 0.8 Hz, 1H), 4.20 (brs, 2H), 3.64 (brs, 1H), 3.25 (brs, 1H), 3.11 (s, 3H), 1.94 (brs, 2H).
^{1}H-NMR (400 MHz, $CDCl_3$, 50 ºC) δ (ppm): 7.50 (dd, J = 8.0, 1.6 Hz, 1H), 7.31-7.26 (m, 1H), 7.02-6.98 (m, 1H), 6.90 (dd, J = 8.4 0.4 Hz, 1H), 4.19 (t, J = 5.2 Hz, 2H), 3.43 (brs, 2H), 3.09 (s, 3H), 1.96-1.90 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$, 50 ºC) δ (ppm): 169.9, 157.3, 131.5, 131.4, 124.0, 122.0, 119.9, 66.8, 47.1, 33.8, 27.6. ESI-HRMS: Calcd for $C_{11}H_{13}NNaO_2^+$ $[M+Na]^+$: 214.0839. Found: 214.0831. Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.00; H, 6.86; N, 7.42.

Synthesis of 2-methyl-2,3,4,5-tetrahydro-1H-naphtho[2,1-b][1,5]oxazocin-1-one (2j)

To a solution of methyl 2-((methyl(3-(naphthalen-2-yloxy)propyl)carbamoyl)oxy)benzoate (**1j**) (313.5 mg, 0.797 mmol) in dry dichloromethane (4.0 ml, 0.2 M), trifluoromethanesulfonic acid (0.71 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 20 ºC under argon atmosphere for 6 hrs. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 3). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 6 ~ 1 : 1) to afford 2-methyl-2,3,4,5-tetrahydro-1H-naphtho[2,1-b][1,5]oxazocin-1-one (**2j**) (164.8 mg, 0.683 mmol, 86% yield) as white solid.
Mp. 151 - 152 ºC (colorless plates, recrystallized from $CHCl_3$/hexane)
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.97 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.48 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.40 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 4.53 (ddd, J = 12.8, 4.8, 4.8 Hz, 1H), 4.03 (ddd, J = 12.8, 8.4, 4.0 Hz, 1H), 3.72 (ddd, J = 15.2, 12.4, 2.0 Hz, 1H), 3.24 (s, 3H), 3.21 (ddd, J = 15.2, 3.6, 3.6 Hz, 1H), 2.25-2.15 (m, 1H), 1.81-1.74 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$, 50 ºC) δ (ppm): 168.7, 154.5, 131.6, 131.5, 130.3, 127.8, 127.2, 125.5, 124.8, 121.0, 120.3, 68.8, 48.0, 33.5, 28.0. ESI-HRMS: Calcd for $C_{15}H_{15}NNaO_2^+$ $[M+Na]^+$: 264.0995. Found: 264.0994. Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.65; H, 6.45; N, 5.81.

Synthesis of 5-methyl-8-phenyl-4,5-dihydro-2H-benzo[b][1,5]oxazocin-6(3H)-one (2k)

To a solution of methyl 2-(((3-([1,1'-biphenyl]-4-yloxy)propyl)(methyl)carbamoyl)oxy)benzoate (**1k**) (271.5 mg, 0.647 mmol) in dry dichloromethane (3.2 ml, 0.2 M), trifluoromethanesulfonic acid (0.58 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 22ºC under argon atmosphere for 3 hrs. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 6 ~ acetone: hexane = 1 : 4) to afford 5-methyl-8-phenyl-4,5-dihydro-2H-benzo[b][1,5]oxazocin-6(3H)-one (**2k**) (137.6 mg, 0.515 mmol, 80% yield) as white amorphous.
Mp. 137 - 138 ºC (colorless cubes, recrystallized from $CHCl_3$/hexane)
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (d, J = 2.4 Hz, 1H), 7.57-7.52 (m, 3H), 7.41-7.37 (m, 2H), 7.31-7.27 (m, 1H), 6.97 (d, J = 8.4 Hz, 1H), 4.22 (brs, 2H), 3.69 (brs, 1H), 3.27 (brs, 1H), 3.12 (s, 3H), 1.95 (brs, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 169.9, 156.5, 139.7, 134.9, 130.0, 129.9, 128.6, 127.0, 126.6, 123.6, 120.2, 66.6, 47.0, 33.8, 27.4. ESI-HRMS: Calcd for $C_{17}H_{17}NNaO_2^+$ $[M+Na]^+$: 290.1152. Found: 290.1156. Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.33; H, 6.57; N, 5.20.

Synthesis of 9,10-dimethoxy-2-methyl-2,3,4,5,6,7-hexahydro-1H-benzo[c]azonin-1-one (2l)

To a solution of methyl 2-(((5-(3,4-dimethoxyphenyl)pentyl)(methyl)carbamoyl)oxy)benzoate (**1l**) (192.7 mg, 0.464 mmol) in dry dichloromethane (2.32 ml, 0.2 M), trifluoromethanesulfonic acid (0.41 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 20 ºC under argon atmosphere for 1 hr.

Then the mixture was quenched with 30 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 1) to afford 9,10-dimethoxy-2-methyl-2,3,4,5,6,7-hexahydro-1H-benzo[c]azonin-1-one (**2l**) (50.7 mg, 0.193 mmol, 41% yield) as colorless solid.

Mp. 158 - 159ºC (Colorless needles, recrystallized from $CHCl_3$/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.74 (s, 1H), 6.63 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.22-3.15 (m, 1H), 3.09-3.04 (m, 1H), 3.05 (s, 3H), 2.83-2.77 (m, 1H), 2.46-2.40 (m, 1H), 2.04-1.96 (m, 1H), 1.75-1.68 (m, 1H), 1.55-1.41 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.9, 149.5, 147.6, 131.4, 129.1, 112.0, 108.8, 55.9 (2 x OMe), 51.2, 33.3, 31.7, 29.1, 27.4, 26.6. ESI-HRMS: Calcd for $C_{15}H_{21}NNaO_3^+$ $[M+Na]^+$: 286.1414. Found: 286.1396. Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.12; H, 8.04; N, 5.34.

Synthesis of 2-isopropyl-9,10-dimethoxy-2,3,4,5,6,7-hexahydro-1H-benzo[c]azonin-1-one (2m)

To a solution of methyl 2-(((5-(3,4-dimethoxyphenyl)pentyl)(isopropyl)carbamoyl)oxy)benzoate (**1m**) (225 mg, 0.507 mmol) in dry dichloromethane (2.53 ml, 0.2 M), trifluoromethanesulfonic acid (0.45 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 22ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 6 ~ acetone : hexane = 1 : 2) to afford 2-isopropyl-9,10-dimethoxy-2,3,4,5,6,7-hexahydro-1H-benzo[c]azonin-1-one (**2m**) (101 mg, 0.345 mmol, 68% yield) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.69 (s, 1H), 6.64 (s, 1H), 4.65 (h, J = 6.8 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.34-3.28 (m, 1H), 2.89 (dd, J = 14.8, 8.0 Hz, 1H), 2.74 (ddd, J = 14.4, 4.8, 4.8 Hz, 1H), 2.64 (ddd, J = 14.4, 11.2, 5.6 Hz, 1H), 1.85-1.74 (m, 2H), 1.72-1.64 (m, 2H), 1.48-1.40 (m, 1H), 1.33 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 6.4 Hz, 3H), 1.18-1.08 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 172.0, 149.5, 147.6, 130.5, 130.4, 111.1, 109.0, 55.9 (2 x OMe), 47.3, 46.6, 30.6, 30.0, 29.3, 27.5, 21.0, 19.7. ESI-HRMS: Calcd for $C_{17}H_{25}NNaO_3^+$ $[M+Na]^+$: 314.1727. Found: 314.1737.

Synthesis of 9,10-dimethoxy-2-octyl-2,3,4,5,6,7-hexahydro-1H-benzo[c]azonin-1-one (2n)

To a solution of methyl 2-(((5-(3,4-dimethoxyphenyl)pentyl)(octyl)carbamoyl)oxy)benzoate (**1n**) (357 mg, 0.694 mmol) in dry dichloromethane (3.5 ml, 0.2 M), trifluoromethanesulfonic acid (0.62 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 20 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 5 ~ 1 : 1) to afford 9,10-dimethoxy-2-octyl-2,3,4,5,6,7-hexahydro-1H-benzo[c]azonin-1-one (**2n**) (159 mg, 0.440 mmol, 63% yield) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.71 (s, 1H), 6.63 (s, 1H), 3.94-3.84 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.23-3.16 (m, 1H), 3.08-2.96 (m, 2H), 2.82-2.75 (m, 1H), 2.50-2.45 (m, 1H), 2.00-1.92 (m, 1H), 1.68-1.26 (m, 17H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.7, 149.4, 147.6, 131.1, 129.7, 111.8, 108.8, 56.0, 55.9, 48.9, 44.1, 32.7, 31.8, 29.4, 29.30, 29.25, 27.5, 27.2, 27.0, 26.9, 22.6, 14.1. ESI-HRMS: Calcd for $C_{22}H_{35}NNaO_3^+$ $[M+Na]^+$: 384.2509. Found: 384.2496.

Synthesis of 2-methyl-3,4,5,6-tetrahydronaphtho[2,1-b][1,5]oxazonin-1(2H)-one (2o)

To a solution of methyl 2-((methyl(4-(naphthalen-2-yloxy)butyl)carbamoyl)oxy)benzoate (**1o**) (400 mg, 0.982 mmol) in dry dichloromethane (4.9 ml, 0.2 M), trifluoromethanesulfonic acid (0.87 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 19ºC under argon atmosphere for 5 hrs. Then the

mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: acetone : hexane = 1 : 8 ~ 1 : 2) to afford 2-methyl-3,4,5,6-tetrahydronaphtho[2,1-b][1,5]oxazonin-1(2H)-one (**2o**) (160 mg, 0.628 mmol, 64% yield) as white powder.

Mp. 175 - 177 ºC (colorless needles, recrystallized from acetone/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.86-7.80 (m, 3H), 7.51-7.47 (m, 1H), 7.44-7.40 (m, 1H), 7.25 (d, J = 7.6 Hz, 1H), 4.38 (ddd, J = 12.0, 9.6, 2.4 Hz, 1H), 4.22 (ddd, J = 12.0, 5.2, 2.8 Hz, 1H), 3.22 (s, 3H), 3.19-3.15 (m, 2H), 1.93-1.82 (m, 2H), 1.76-1.67 (m, 1H), 1.62-1.53 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 168.3, 152.2, 131.0, 130.8, 130.4, 128.0, 127.3, 125.0, 124.9, 124.5, 118.7, 73.0, 50.8, 32.0, 29.0, 25.6. ESI-HRMS: Calcd for $C_{16}H_{17}NNaO_2^+$ $[M+Na]^+$: 278.1152. Found: 278.1173. Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.67; H, 6.84; N, 5.49.

Synthesis of 2-isopropyl-3,4,5,6-tetrahydronaphtho[2,1-b][1,5]oxazonin-1(2H)-one (2p)

To a solution of methyl 2-((isopropyl(4-(naphthalen-2-yloxy)butyl)carbamoyl)oxy)benzoate (**1p**) (309 mg, 0.708 mmol) in dry dichloromethane (3.5 ml, 0.2 M), trifluoromethanesulfonic acid (0.63 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 20 ºC under argon atmosphere for 7 hrs. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate : hexane = 1 : 5 ~ 1 : 2) to afford 2-isopropyl-3,4,5,6-tetrahydronaphtho[2,1-b][1,5]oxazonin-1(2H)-one (**2p**) (151 mg, 0.533 mmol, 75% yield) as white powder.

Mp. 106 - 107 ºC (colorless plates, recrystallized from $CHCl_3$/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (d, J = 9.2 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.47 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 7.41 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 4.88 (h, J = 6.8 Hz, 1H), 4.41 (ddd, J = 12.0, 3.6, 3.6 Hz, 1H), 4.24 (ddd, J = 7.2, 7.2, 2.4 Hz, 1H), 3.35-3.29 (m, 1H), 2.92-2.85 (m, 1H), 1.83-1.66 (m, 3H), 1.65-1.55 (m, 1H), 1.42 (d, J = 6.8 Hz, 3H), 1.39 (d, J = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 168.5, 151.2, 131.1, 130.4 (two carbons are duplicated), 128.0, 127.2, 125.6, 124.9, 124.6, 118.6, 72.9, 46.4, 45.7, 29.5, 29.0, 21.1, 20.2. ESI-HRMS: Calcd for $C_{18}H_{21}NNaO_2^+$ $[M+Na]^+$: 306.1465. Found: 306.1480. Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.26; H, 7.68; N, 4.92.

Synthesis of 10,11-dimethoxy-2-methyl-3,4,5,6,7,8-hexahydrobenzo[c]azecin-1(2H)-one (2q)

To a solution of methyl 2-(((6-(3,4-dimethoxyphenyl)hexyl)(methyl)carbamoyl)oxy)benzoate (**1q**) (337 mg, 0.785 mmol) in dichloromethane (3.9 ml, 0.2 M), trifluoromethanesulfonic acid (0.70 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 20 ºC under argon atmosphere for 3 hrs. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate : hexane = 1 : 5 ~ 1 : 1) to afford 10,11-dimethoxy-2-methyl-3,4,5,6,7,8-hexahydrobenzo[c]azecin-1(2H)-one (**2q**) (13 mg, 0.048 mmol, 6% yield) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 6.70 (s, 1H), 6.60 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.68-3.61 (m, 1H), 3.03-2.98 (m, 1H), 3.01 (s, 3H), 2.77 (ddd, J = 10.0, 4.8, 4.8 Hz, 1H), 2.68-2.63 (m, 1H), 1.87-1.78 (m, 1H), 1.74-1.54 (m, 3H), 1.46-1.24 (m, 2H), 1.17-1.04 (m, 1H), 0.65-0.54 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 172.4, 149.6, 147.2, 130.9, 130.4, 111.8, 108.5, 56.0, 55.9, 47.5, 31.3, 28.2, 27.9, 25.2, 21.0, 18.1. ESI-HRMS: Calcd for $C_{16}H_{23}NNaO_3^+$ $[M+Na]^+$: 300.1570. Found: 300.1559.

IV. Competition experiments

All of the competition experiments (Table 2, Entry 1-6) are conducted twice to check reproducibility except for reaction of **1x** and **1y** (Entry 7 and 8) that afforded 100:0 product ratios. The

yield and product ratio values are averaged values.

Competition reaction (Table 2, Entry 1)

Product ratio analysis at 25 ºC (The 1st trial)

To a solution of trifluoromethanesulfonic acid (0.34 mL, 10 eq.) in dry dichloromethane (1.9 mL), solution of methyl 2-(((2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)(phenethyl)carbamoyl)oxy)benzoate (**1r**) (199 mg, 0.386 mmol) in dry dichloromethane (1.9 mL) was slowly added dropwise at 25 ºC for 10 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 8 ~ 1 : 1) to afford inseparable mixture of 2-(2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (**2r-m**) and 7-(4-chlorophenyl)-2-phenethyl-3,4-dihydroisoquinolin-1(2*H*)-one (**2r-n**) as colorless oil (the ratio was approximately 6.26 : 1) (127 mg, 0.351 mmol, total 91% yield). The separation of the mixture was achieved *via* HPLC (PEGASIL Silica SP100, 20 x 250 mm) eluting with AcOEt / hexane = 1 : 1 as eluent at a flow rate of 3.0 mL / min using a loading of 10 mg / injection. The UV absorption was measured at 260 nm.

Product ratio analysis at 25 ºC (The 2nd trial)

To a solution of trifluoromethanesulfonic acid (0.17 mL, 10 eq.) in ichloromethane (1.0 mL), solution of **1r** (101 mg, 0.386 mmol) in dry dichloromethane (1.0 mL) was slowly added dropwise at 25 ºC for 7 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 8 ~ 1 : 2) to afford inseparable mixture of **2r-m** and **2r-n** as colorless oil (the ratio was approximately 6.51 : 1) (63.3 mg, 0.175 mmol, total 89% yield).

2-(2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)-3,4-dihydroisoquinolin-1(2H)-one (2r-m)

Mp. 159 - 161 ºC (colorless cubes, recrystallized from $CHCl_3$/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.09 (dd, J = 7.6, 1.2 Hz, 1H), 7.52-7.49 (m, 4H), 7.43-7.37 (m, 3H), 7.36-7.33 (m, 3H), 7.14 (d, J = 7.6 Hz, 1H), 3.82 (t, J = 7.2 Hz, 2H), 3.44 (t, J = 6.8 Hz, 2H), 3.01 (t, J = 7.2 Hz, 2H), 2.88 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 164.3, 139.3, 138.7, 138.0, 133.2, 131.5, 129.5, 129.4, 128.8, 128.8, 128.1, 128.1, 127.0, 127.0, 126.8, 49.8, 47.0, 33.9, 28.0.

HPLC (chiral column: PEGASIL Silica SP100, 20 x 250 mm; solvent: ethyl acetate/hexane = 1/1; flow rate: 3.0 mL/min; detection: at 300 nm): t_R = 22.1 min. ESI-HRMS: Calcd for $C_{23}H_{20}ClNNaO^+$ $[M+Na]^+$: 384.1126. Found: 384.1126.

7-(4-chlorophenyl)-2-phenethyl-3,4-dihydroisoquinolin-1(2H)-one (2r-n)

Colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.29 (d, J = 2.0 Hz, 1H), 7.60 (dd, J = 8.0, 2.0 Hz, 1H), 7.58-7.54 (m, 2H), 7.43-7.40 (m, 2H), 7.28-7.26 (m, 3H), 7.24-7.19 (m, 3H), 3.80 (t, J = 7.2 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.89 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 164.1, 138.8, 138.6, 137.6, 137.2, 133.6, 132.2, 130.2, 129.90, 129.85, 129.0, 128.6, 128.2, 127.5, 126.4, 49.8, 47.1, 33.6, 27.7.

HPLC (chiral column: PEGASIL Silica SP100, 20 x 250 mm; solvent: ethyl acetate/hexane = 1/1; flow rate: 3.0 mL/min; detection: at 300 nm): t_R = 20.9 min. ESI-HRMS: Calcd for $C_{23}H_{20}ClNNaO^+$ $[M+Na]^+$: 384.1126. Found: 384.1114.

Competition reaction (Table 2, Entry 2)

Product ratio analysis at 25 ºC (The 1st trial)

To a solution of trifluoromethanesulfonic acid (0.066 mL, 10 eq.) in dry dichloromethane (0.37 mL), solution of methyl 2-(((2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)(4-chlorophenethyl)carbamoyl)oxy)benzoate (**1s**) (40.7 mg, 0.0742 mmol) in dry dichloromethane (0.37 mL) was slowly added dropwise at 25 ºC for 7 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 8 ~ 1 : 2) to afford inseparable mixture of 2-(4-chlorophenethyl)-7-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one (**2s-m**) and 7-chloro-2-(2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)-3,4-dihydroisoquinolin-1(2H)-one (**2s-n**) as colorless oil (the ratio was approximately 66.6 : 1) (20.6 mg, 0.0520 mmol, total 70% yield). The separation of the mixture was tried *via* HPLC (PEGASIL Silica SP100, 20 x 250 mm) eluting with AcOEt / hexane = 1 : 1 as eluent at a flow rate of 3.0 mL / min using a loading of 10 mg / injection. The UV absorption was measured at 260 nm.

Product ratio analysis at 25 ºC (The 2nd trial)

To a solution of trifluoromethanesulfonic acid (0.077 mL, 10 eq.) in dry dichloromethane (0.38 mL), solution of **1s** (42.2 mg, 0.0769 mmol) in dry dichloromethane (0.38 mL) was slowly added dropwise at 25 ºC for 7 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 8 ~ 1 : 2) to afford inseparable mixture of **2s-m** and **2s-n** as colorless oil (the ratio was approximately 66.8 : 1) (22.1 mg, 0.0558 mmol, total 73% yield).

2-(4-chlorophenethyl)-7-(4-chlorophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (2s-m)

Mp. 131 - 133 ºC (colorless cubes, recrystallized from $CHCl_3$/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.29 (d, J = 2.0 Hz, 1H), 7.60 (dd, J = 8.0, 2.0 Hz, 1H), 7.58-7.54 (m, 2H), 7.43-7.40 (m, 2H), 7.28-7.26 (m, 2H), 7.24-7.19 (m, 3H), 3.80 (t, J = 7.2 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.89 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 164.1, 138.8, 138.6, 137.6, 137.2, 133.6, 132.2, 130.2, 129.90, 129.85, 129.0, 128.6, 128.2, 127.5, 126.4, 49.8, 47.1, 33.6, 27.7.

HPLC (chiral column: PEGASIL Silica SP100, 20 x 250 mm; solvent: ethyl acetate/hexane = 1/1; flow rate: 5.0 mL/min; detection: at 300 nm): t_R = 21.4 min. ESI-HRMS: Calcd for $C_{23}H_{19}Cl_2NNaO^+$ $[M+Na]^+$: 418.0736. Found: 418.0759.

The synthesis of authentic compound 7-chloro-2-(2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)-3,4-dihydroisoquinolin-1(2H)-one (2s-n)

Since the yield of **2s-n** was very low, it was difficult to obtain enough amount of **2s-n** for ^{13}C-NMR measurement. To confirm the structure of **2s-n** and obtain ^{13}C NMR spectrum, an authentic sample was synthesized. The ^{1}H NMR spectrum of the cyclized product **2s-n** was identical to the authentic compound.

The starting material 7-chloro-3,4-dihydroisoquinolin-1(2H)-one was synthesized according to our previous literature. [8]

To the solution of 7-chloro-3,4-dihydroisoquinolin-1(2H)-one (102 mg, 0.562 mmol) in dry tetrahydrofuran (2.0 mL), in a 5-mL Biotage microwave bial with a Teflon coated stirring bar was added potassium t-butoxide (73 mg, 0.65 mmol) at 25 ºC and stirred for 10 min at 25 ºC under argon atmosphere. To the reaction solution, 1-bromo-4-(2-bromoethyl)benzene (199 mg, 0.755 mmol) in tetrahydrofural (1.0 mL) was added and the bial was sealed and heated at 100 ºC for 7 hrs. After cooling, the solvent of the reaction mixture was quenched with 5 mL of aqueous HCl (1M) and the whole was

extracted with ethyl acetate (50 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 10 ~ 1 : 1) to afford 2-(4-bromophenethyl)-7-chloro-3,4-dihydroisoquinolin-1(2H)-one (**7s-n**) as white powder (42 mg, 0.11 mmol, 20% yield).
Mp. 123 - 125 ºC (colorless cubes, recrystallized from $CHCl_3$/hexane)
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.04 (d, J = 2.4 Hz, 1H), 7.42-7.40 (m, 2H), 7.37-7.35 (m, 1H), 7.14-7.08 (m, 3H), 3.75 (t, J = 7.2 Hz, 2H), 3.37 (t, J = 6.8 Hz, 2H), 2.92 (t, J = 7.2 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 163.2, 138.0, 136.2, 133.1, 131.6, 131.5, 130.9, 130.6, 128.3, 128.1, 120.3, 49.7, 47.0, 33.6, 27.5. ESI-HRMS: Calcd for $C_{17}H_{15}BrClNNaO^+$ $[M+Na]^+$: 385.9918. Found: 385.9897.

A mixture of 2-(4-bromophenethyl)-7-chloro-3,4-dihydroisoquinolin-1(2H)-one (34 mg, 0.094 mmol), (4-chlorophenyl)boronic acid (44 mmol, 0.28 mmol), potassium carbonate (54 mg, 0.392 mmol), tetraethyl ammonium bromide (19 mg, 0.090 mmol) and palladium acetate (7.0 mg, 0.031 mmol, 33 mol%) was added to a 5-mL Biotage microwave bial with a Teflon coated stirring bar. The reagents are dissolved in degassed ethanol (2.0 mL) and water (1.0 mL). The bial was sealed and heated at 120 ºC for 15 min. After cooling, the reaction solution was added 20 mL of water and extracted with 50 mL of ethyl acetate for two times. The organic phase was washed with brine (20 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give a crude oil. The crude product was roughly purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 10 ~ 1 : 2) to afford mixture of the product **2s-n** and several byproducts (34.6 mg). The separation of the mixture was achieved *via* HPLC (PEGASIL Silica SP100, 20 x 250 mm) eluting with AcOEt / hexane = 1 : 1 as eluent at a flow rate of 5.0 mL / min using a loading of 10 mg / injection. The UV absorption was measured at 280 nm. After separation, 12.7 mg of the product **2s-n** was obtained (0.033 mmol, 35% yield).

7-chloro-2-(2-(4'-chloro-[1,1'-biphenyl]-4-yl)ethyl)-3,4-dihydroisoquinolin-1(2H)-one (2s-n)
Mp. 188 - 190 ºC (colorless cubes, recrystallized from $CHCl_3$/hexane)
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07 (d, J = 2.4 Hz, 1H), 7.51-7.49 (m, 4H), 7.41-7.38 (m, 2H), 7.36 (dd, J = 8.0, 2.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.0 Hz, 1H), 3.82 (t, J = 7.6 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 2.83 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 163.2, 139.2, 138.5, 138.1, 136.2, 133.3, 133.1, 131.5, 131.0, 129.4, 128.9, 128.3, 128.18, 128.16, 127.1, 49.9, 47.0, 33.8, 27.5.
HPLC (chiral column: PEGASIL Silica SP100, 20 x 250 mm; solvent: ethyl acetate/hexane = 1/1; flow rate: 5.0 mL/min; detection: at 300 nm): t_R = 18.99 min. ESI-HRMS: Calcd for $C_{23}H_{19}Cl_2NNaO^+$ $[M+Na]^+$: 418.0736. Found: 418.0732.

Competition reaction (Table 2, Entry 3)
Product ratio analysis at 25 ºC (The 1st trial)
To a solution of trifluoromethanesulfonic acid (0.50 mL, 10 eq.) in dry dichloromethane (2.8 mL), solution of methyl 2-((benzyl(4-chlorophenethyl)carbamoyl)oxy)benzoate (**1t**) (239 mg, 0.563 mmol) in dry dichloromethane (2.8 mL) was slowly added dropwise at 25 ºC for 10 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (20 mL x 3). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture (the ratio of the products **2t-m** : **2t-n** was approximately 3.35 : 1). The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 6 ~ 1 : 2) to afford 2-(4-chlorophenethyl)isoindolin-1-one (**2t-n**) (28.1 mg, 0.103 mmol, 18% yield) as colorless powder and 2-benzyl-7-chloro-3,4-dihydroisoquinolin-1(2H)-one (**2t-m**) (91.6 mg, 0.337 mmol, 60% yield) as colorless oil.

Product ratio analysis at 25 ºC (The 2nd trial)

To a solution of trifluoromethanesulfonic acid (0.15 mL, 10 eq.) in dry dichloromethane (0.85 mL), solution of **1t** (72.1 mg, 0.170 mmol) in dry dichloromethane (0.85 mL) was slowly added dropwise at 25 ºC for 7 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (20 mL x 3). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 8 ~ 1 : 2) to afford mixture of **2t-m** and **2t-n** (the ratio was approximately 3.52 : 1) (40.1 mg, 0.148 mmol, total 87% yield) as colorless oil.

2-benzyl-7-chloro-3,4-dihydroisoquinolin-1(2H)-one (2t-m)

Colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.13 (d, J = 2.4 Hz, 1H), 7.37 (dd, J = 8.0, 2.4 Hz, 1H), 7.35-7.25 (m, 5H), 7.10 (d, J = 8.0 Hz, 1H), 4.78 (s, 2H), 3.47 (t, J = 6.8 Hz, 2H), 2.90 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 163.4, 137.1, 136.3, 133.1, 131.6, 130.9, 128.7, 128.5, 128.4, 128.1, 127.6, 50.5, 45.2, 27.5. ESI-HRMS: Calcd for $C_{16}H_{14}ClNNaO^+$ $[M+Na]^+$: 294.0656. Found: 294.0652.

2-(4-chlorophenethyl)isoindolin-1-one (2t-n)

Mp. 135-137 ºC (colorless plates, recrystallized from $CHCl_3$/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (d, J = 7.2 Hz, 1H), 7.51 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 7.45 (dd, J = 7.2, 7.2 Hz, 1H), 7.38 (d, J = 7.2 Hz, 1H), 7.27-7.24 (m, 2H), 7.19-7.16 (m, 2H), 4.22 (s, 2H), 3.85 (t, J = 7.2 Hz 2H), 2.97 (t, J = 7.2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 168.5, 141.0, 137.2, 132.8, 132.3, 131.2, 130.0, 128.7, 128.0, 123.6, 122.6, 50.5, 43.9, 34.2. ESI-HRMS: Calcd for $C_{16}H_{14}ClNNaO^+$ $[M+Na]^+$: 294.0656. Found: 294.0647. Anal. Calcd. for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.55; H, 5.47; N, 5.13.

Competition reaction (Table 2, Entry 4)

Synthesis and isolation of reaction products

To a solution of methyl 2-((benzyl(3-phenylpropyl)carbamoyl)oxy)benzoate (**1u**) (381.1 mg, 0.945 mmol) in dry dichloromethane (4.7 mL, 0.2 M), trifluoromethanesulfonic acid (0.84 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 28ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 1) to afford mixture of 2-(3-phenylpropyl)isoindolin-1-one and 2-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (218.8 mg, 0.871 mmol, total 92% yield). The mixture was purified again by the same method to afford 2-(3-phenylpropyl)isoindolin-1-one (**2u-m**) (178.9 mg, 0.712 mmol, 75% yield) and 2-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (**2u-n**) (39.5 mg, 0.157 mmol, 17% yield).

Product ratio analysis at 25 ºC (The 1st trial)

To a solution of trifluoromethanesulfonic acid (0.16 mL, 10 eq.) in dry dichloromethane (0.90 mL), solution of **1u** (73 mg, 0.18 mmol) in dry dichloromethane (0.90 mL, 0.2 M) was slowly added dropwise at 25 ºC for 15 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 3). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was roughly purified by column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 6 ~ 1 : 2) to afford mixture of **2u-m** and **2u-n** (40 mg, 0.16 mmol, total 87% yield). The ratio of the products was determined by ^{1}H NMR; **2u-m** : **2u-n** = 6.36 : 1.

Product ratio analysis at 25 ºC (The 2nd trial)

To a solution of trifluoromethanesulfonic acid (0.23 mL, 10 eq.) in dry dichloromethane (1.3 mL), solution of **1u** (106 mg, 0.26 mmol) in dry dichloromethane (1.3 ml, 0.2 M) was slowly added dropwise at 25 ºC for 7 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 3). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was roughly purified by column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 6 ~ 1 : 2) to afford mixture of mixture of **2u-m** and **2u-n** (53 mg, 0.21 mmol, total 80% yield). The ratio of the products was determined by ^{1}H NMR; **2u-m** : **2u-n** = 6.66 : 1.

2-(3-phenylpropyl)isoindolin-1-one (2u-m)

Colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (d, J = 7.6 Hz, 1H), 7.51 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.46-7.41 (m, 2H), 7.28-7.25 (m, 2H), 7.20-7.15 (m, 3H), 4.34 (s, 2H), 3.67 (t, J = 7.2 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.04-1.96 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 168.5, 141.3, 141.1, 133.0, 131.1, 128.4, 128.3, 128.0, 125.9, 123.6, 122.6, 49.8, 42.1, 33.1, 30.1. ESI-HRMS: Calcd for $C_{17}H_{17}NNaO^{+}$ $[M+Na]^{+}$: 274.1202. Found: 274.1224.

2-benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (2u-n)

Colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74-7.72 (m, 1H), 7.40-7.26 (m, 7H), 7.12-7.10 (m, 1H), 4.79 (s, 2H), 3.18 (t, J = 6.8 Hz, 2H), 2.72 (t, J = 6.8 Hz, 2H), 1.77 (tt, J = 6.8, 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.2, 138.1, 137.3, 136.0, 130.8, 128.7, 128.6, 128.3, 128.2, 127.5, 126.9, 50.3, 45.6, 30.2, 29.3. ESI-HRMS: Calcd for $C_{17}H_{17}NNaO^{+}$ $[M+Na]^{+}$: 274.1202. Found: 274.1196.

Competition reaction (Table 2, Entry 5)

Product ratio analysis at 25 ºC (The 1st trial)

To a solution of trifluoromethanesulfonic acid (0.61 mL, 10 eq.) in dry dichloromethane (3.4 mL), solution of methyl 2-(((4-chlorobenzyl)(3-phenylpropyl)carbamoyl)oxy)benzoate **(1v)** (299 mg, 0.683 mmol) in dry dichloromethane (3.4 mL) was slowly added dropwise at 25 ºC for 10 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 40 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 6 ~ 1 : 2) to afford inseparable mixture of 6-chloro-2-(3-phenylpropyl)isoindolin-1-one (**2v-n**) and 2-(4-chlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (**2v-m**) as colorless oil (the ratio was approximately 1 : 39.8)(170 mg, 0.596 mmol, total 87% yield).

Product ratio analysis at 25 ºC (The 2nd trial)

To a solution of trifluoromethanesulfonic acid (0.19 mL, 10 eq.) in dry dichloromethane (1.1 mL), solution of **1v** (93.5 mg, 0.214 mmol) in dry dichloromethane (1.1 mL) was slowly added dropwise at 25 ºC for 7 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 6 ~ 1 : 2) to afford inseparable mixture of **2v-n** and **2v-m** as colorless oil (the ratio was approximately 1 : 40.2) (46 mg, 0.161 mmol, total 75% yield).

The synthesis of authentic compound 2-(4-chlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (2v-m)

Since 2-(4-chlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (**2v-m**) could not be purified completely, authentic sample was synthesized. The starting material (2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one) was synthesized according to our previous literature.[8]

To the solution of 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (227 mg, 1.4 mmol) in tetrahydrofuran (2.0 mL), sodium hydride (82 mg, 50% dispersion in mineral oil) was added at 0 ºC and stirred for 10 min at 0 ºC under argon atmosphere. To the reaction solution, 4-chlorobenzyl bromide (427mg, 2.1 mmol) in tetrahydrofural (2.0 mL) was added and the reaction mixture was stirred at room temperature (20 ºC) for 24 hrs. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with ethyl acetate (50 mL). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 8 ~ 1 : 3) to afford 2-(4-chlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one **2v-m** as colorless oil (246 mg, 0.86 mmol, 61% yield).

2-(4-chlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (2v-m)

Mp. 96-97 ºC (colorless plates, recrystallized from $CHCl_3$/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.74 (dd, J = 7.6, 1.6 Hz, 1H), 7.41-7.28 (m, 6H), 7.14 (dd, J = 7.2, 1.2 Hz, 1H), 4.77 (s, 2H), 3.20 (t, J = 6.8 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H), 1.83 (p, J = 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.3, 137.3, 136.8, 135.8, 133.4, 130.9, 129.6, 128.8, 128.7, 128.3, 127.0, 49.7, 45.7, 30.2, 29.3. ESI-HRMS: Calcd for $C_{17}H_{16}ClNNaO^+$ $[M+Na]^+$: 308.0813. Found: 308.0803.

The synthesis of authentic compound 6-chloro-2-(3-phenylpropyl)isoindolin-1-one (2v-n)

Since 6-chloro-2-(3-phenylpropyl)isoindolin-1-one (**2e-n**) could not be isolated, authentic sample was synthesized. The starting compound 3-(4-bromophenyl)propan-1-amine was synthesized according to the literature.[15]

To the mixture of 3-(4-bromophenyl)propan-1-amine (562 mg, 2.62 mmol) and triethylamine (0.50 mL) in dry dichloromethane (6.0 mL), Boc_2O (692.2 mg, 3.17 mmol) was added at 0 ºC and stirred at 20 ºC for 18 hrs. The reaction was quenched by NaOHaq (2M, 10 mL) and the whole was extracted with dichloromethane (50 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 6) to afford tert-butyl (3-(4-bromophenyl)propyl)carbamate as colorless oil (**4v-n**) (722 mg, 2.30 mmol, 88% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 4.60 (brs, 1H), 3.13 (q, J = 6.4 Hz, 2H), 2.58 (t, J = 7.2 Hz, 2H), 1.83-1.73 (m, 2H), 1.44 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 155.9, 140.5, 131.4, 130.1, 119.6, 85.1, 79.1, 40.0, 32.4, 31.5, 28.4, 27.3. ESI-HRMS: Calcd for $C_{14}H_{20}BrNNaO_2^+$ $[M+Na]^+$: 336.0570. Found: 336.0576.

To the solution of **4v-n** (445 mg, 1.42 mmol), tetrabuthyl ammonium iodide (70 mg, 0.19 mmol, 0.13 eq) and 4-chlorobenzyl bromide (584 mg, 2.84 mmol, 2 eq) in tetrahydrofuran (3.0 mL), sodium hydride (109 mg, 50% dispersion in mineral oil) was added at 0 ºC. The reaction mixture was stirred at 50 ºC for 2 days. After cooling, the reaction was quenched by water (20 mL) and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 10) to afford mixture of tert-butyl (3-(4-bromophenyl)propyl)(4-chlorobenzyl)carbamate and byproducts (488 mg). The crude mixture was dissolved in dry dichloromethane (2.0 mL) and was added trifluoroacetic acid (1.0 mL). The reaction solution was stirred at 20 ºC for 20 hours. The reaction was quenched by Na_2CO_3aq (0.7 M, 30 mL) and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give 3-(4-bromophenyl)-*N*-(4-chlorobenzyl)propan-1-amine **5e-n** as pale yellow solid (371 mg, 1.09 mmol, 77% for 2 steps).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39-7.36 (m, 2H), 7.31-7.22 (m, 4H), 7.03-7.00 (m, 2H), 3.74 (s, 2H), 2.65-2.58 (m, 4H), 2.52 (brs, 1H), 1.82-1.75 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 140.8, 138.0, 132.9, 131.4, 130.1, 129.6, 128.5, 119.6, 53.0, 48.4, 32.8, 31.1. ESI-HRMS: Calcd for $C_{16}H_{18}BrClN^+$ $[M+H]^+$: 338.0306. Found: 338.0303.

A solution of **5v-n** (371 mg, 1.09 mmol), dimethyl 2,2'-(carbonylbis(oxy))dibenzoate) (314 mmol, 0.951 mmol) in tetrahydrofuran (3.0 mL) was added to a 5-mL Biotage microwave bial with a Teflon coated stirring bar. The bial was sealed and heated at 100 ºC for 3 hrs. After cooling, the solvent of the reaction mixture was evaporated under reduced pressure to give a crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6 ~ 1 : 3) to afford methyl 2-(((3-(4-bromophenyl)propyl)(4-chlorobenzyl)carbamoyl)oxy)benzoate (**6v-n**) (344 mg, 0.666 mmol, 70% yield as colorless oil (based on dimethyl 2,2'-(carbonylbis(oxy))dibenzoate))).
^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 8.00-7.97 (m, 1H), 7.56-7.51 (m, 1H), 7.39-7.27 (m, 7H), 7.16-7.10 (m, 1H), 7.04-7.01 (m, 2H), 4.66 (s, 1H), 4.50 (s, 1H), 3.82 (s, 1.5H), 3.80 (s, 1.5 H), 3.43-3.32 (m, 2H), 2.59 (t, J = 7.6 Hz, 2H), 2.01-1.84 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 165.1, 155.0, 154.3, 151.0, 140.5, 140.3, 136.0, 135.9, 133.5, 133.4, 131.5, 131.4, 130.1, 130.0, 129.5, 129.0, 128.8, 128.7, 128.6, 128.2, 125.6, 124.0, 123.8, 119.7, 119.6, 52.0, 50.5, 50.4, 47.0, 46.5, 32.4, 32.3, 29.4, 28.9. ESI-HRMS: Calcd for $C_{25}H_{23}BrClNNaO_4^+$ $[M+Na]^+$: 538.0391. Found: 538.0389.

To a solution of **6v-n** (253 mg, 0.490 mmol) in dry dichloromethane (2.45 mL, 0.2 M), trifluoromethanesulfonic acid (0.44 mL, 10 eq.) was added at 0 ºC. The mixture was stirred at 20 ºC under argon atmosphere for 2 hours. Then the mixture was quenched with 30 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 2) to afford 2-(3-(4-bromophenyl)propyl)-6-chloroisoindolin-1-one (**7v-n**) (91.5 mg, 0.251 mmol, 51% yield) as white solids.
Mp. 138-139 ºC (colorless plates, recrystallized from $CHCl_3$/hexane)
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.80 (d, J = 2.0 Hz, 1H), 7.48 (dd, J = 8.0, 2.0 Hz, 1H), 7.38-7.26 (m, 3H), 7.07 (d, J = 8.0 Hz, 2H), 4.31 (s, 2H), 3.64 (t, J = 7.2 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.96 (p, J = 7.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 167.2, 140.1, 139.1, 134.6, 134.4, 131.44, 131.38, 130.0, 123.9, 123.8, 119.8, 49.5, 42.1, 32.5, 29.8. ESI-HRMS: Calcd for $C_{17}H_{15}BrClNNaO^+$ $[M+Na]^+$: 385.9918. Found: 385.9908.

The solution of 2-(3-(4-bromophenyl)propyl)-6-chloroisoindolin-1-one (43 mg, 0.12 mmol) and palladium on activated charcoal (5.5 mg, 10% Pd, 54% wet with water for safety) in methanol (2.0 mL) was stirred under hydrogen atmosphere (1 atm) for 3 hours. Then the solution was filtered and evaporated to give crude oil. The crude mixture was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 6 ~ 1 : 2) to afford 6-chloro-2-(3-phenylpropyl)isoindolin-1-one **2v-n** (25 mg, 0.089 mmol, 75% yield).

The ^{1}H NMR spectrum of 6-chloro-2-(3-phenylpropyl)isoindolin-1-one was consistent with the minor product of competition experiment.

6-chloro-2-(3-phenylpropyl)isoindolin-1-one (2v-n)
Mp. 104-105 ºC (colorless cubes, recrystallized from $CHCl_3$/hexane)
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.80 (d, J = 8.0 Hz, 1H), 7.47 (dd, J = 8.0, 2.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.28-7.24 (m, 2H), 7.19-7.16 (m, 3H), 4.31 (s, 2H), 3.65 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H), 1.99 (p, J = 7.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 167.2, 141.1, 139.1, 134.7, 134.3, 131.3, 128.4, 128.3, 126.0, 123.9, 123.8, 49.5, 42.2, 33.1, 29.9. ESI-HRMS: Calcd for $C_{17}H_{16}ClNNaO^+$ $[M+Na]^+$: 308.0813. Found: 308.0841.

Competition reaction (Table 2, Entry 6))

Product ratio analysis at 25 ºC (The 1st trial)

To a solution of trifluoromethanesulfonic acid (0.37 mL, 10 eq.) in dry dichloromethane (2.1 mL), solution of methyl 2-(((4-chlorobenzyl)(4-phenylbutyl)carbamoyl)oxy)benzoate **(1w)** (198 mg, 0.438 mmol) in dry dichloromethane (2.1 mL) was slowly added dropwise at 25 ºC for 20 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 30 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 6 ~ 1 : 2) to afford inseparable mixture of 6-chloro-2-(4-phenylbutyl)isoindolin-1-one (**2w-m**) and 2-(4-chlorobenzyl)-3,4,5,6-tetrahydrobenzo[c]azocin-1(2H)-one (**2w-n**) as colorless oil (the ratio was approximately 1.48 : 1) (77.4 mg, 0.258 mmol, total 59% yield). The separation of the mixture was achieved *via* HPLC (PEGASIL Silica SP100, 20 x 250 mm) eluting with AcOEt / hexane = 1 : 1 as eluent at a flow rate of 5.0 mL / min using a loading of 10 mg / injection. The UV absorption was measured at 260 nm.

Product ratio analysis at 25 ºC (The 2nd trial)

To a solution of trifluoromethanesulfonic acid (0.21 mL, 10 eq.) in dry dichloromethane (1.2 mL), solution of **1w** (105 mg, 0.238 mmol) in dry dichloromethane (1.2 mL) was slowly added dropwise at 25 ºC for 7 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 30 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 6 ~ 1 : 2) to afford inseparable mixture of **2w-m** and **2w-n** as colorless oil (the ratio was approximately 1.45 : 1) (34.8 mg, 0.116 mmol, total 50% yield).

6-chloro-2-(4-phenylbutyl)isoindolin-1-one (2w-m)

Mp. 57-61 ºC (white powder, recrystallized from $CHCl_3$/hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.80 (d, J = 2.0 Hz, 1H), 7.47 (dd, J = 8.0, 2.0 Hz, 1H), 7.34 (dd, J = 8.0, 0.4 Hz, 1H), 7.28-7.24 (m, 2H), 7.19-7.15 (m, 3H), 4.28 (s, 2H), 3.64-3.60 (m, 2H), 2.66 (t, J = 6.8 Hz, 2H), 1.70-1.67 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 167.1, 141.9, 139.2, 134.8, 134.3, 131.3, 128.4, 128.3, 125.8, 123.8, 123.8, 49.5, 42.3, 35.4, 28.5, 27.8.

HPLC (chiral column: PEGASIL Silica SP100, 20 x 250 mm; solvent: ethyl acetate/hexane = 1/1; flow rate: 5.0 mL/min; detection: at 300 nm): t_R = 23.2 min. ESI-HRMS: Calcd for $C_{18}H_{18}ClNNaO^+$ $[M+Na]^+$: 322.0969. Found: 322.0964.

2-(4-chlorobenzyl)-3,4,5,6-tetrahydrobenzo[c]azocin-1(2H)-one (2w-n)

Colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.45 (dd, J = 7.6, 1.2 Hz, 1H), 7.36 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.31 (s, 4H), 7.27 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 5.38 (dd, J = 14.8, 1.2 Hz, 1H), 4.14 (d, J = 14.8 Hz, 1H), 3.20-3.14 (m, 1H), 3.08-3.03 (m, 1H), 2.83 (dd, J = 13.2, 7.2 Hz, 1H), 2.74-2.68 (m, 1H), 2.13-2.06 (m, 1H), 1.78-1.62 (m, 2H), 1.55-1.44 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 171.5, 140.2, 136.0, 135.2, 133.3, 130.4, 129.6, 129.3, 128.8, 127.5, 126.6, 47.7, 46.5, 32.4, 27.8, 26.0.

HPLC (chiral column: PEGASIL Silica SP100, 20 x 250 mm; solvent: ethyl acetate/hexane = 1/1; flow rate: 5.0 mL/min; detection: at 300 nm): t_R = 21.0 min. ESI-HRMS: Calcd for $C_{18}H_{18}ClNNaO^+$ $[M+Na]^+$: 322.0969. Found: 322.0963.

Competition reaction (Table 2, Entry 7)

Product ratio analysis at 25 ºC

2-benzyl-3,4-dihydroisoquinolin-1(2*H*)-one (2x-m)

To a solution of methyl 2-((benzyl(phenethyl)carbamoyl)oxy)benzoate (**1x**) (215.0 mg, 0.552 mmol) in dichloromethane (2.8 ml, 0.2 M), trifluoromethanesulfonic acid (0.49 mL, 10 eq) was added. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 10 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 4) to afford 2-benzyl-3,4-dihydroisoquinolin-1(2*H*)-one (124.7 mg, 0.525 mmol, 95% yield) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.15 (dd, J = 7.6, 1.6 Hz, 1H), 7.42 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 7.38-7.25 (m, total 6H), 7.16 (dd, J = 7.6, 0.8 Hz, 1H), 4.80 (s, 2H), 3.49 (t, J = 6.8 Hz, 2H), 2.94 (t, J = 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 164.6, 138.0, 137.4, 131.7, 129.4, 128.6, 128.5, 128.0, 127.4, 127.0, 126.9, 50.4, 45.3, 28.0. ESI-HRMS: Calcd for $C_{16}H_{15}NNaO^+$ $[M+Na]^+$: 260.1046. Found: 260.1042.

Competition reaction (Table 2, Entry 8)

Product ratio analysis at 25 ºC

To a solution of trifluoromethanesulfonic acid (0.52 mL, 10 eq.) in dry dichloromethane (2.9 mL), solution of methyl 2-(((4-phenylbutyl)(5-phenylpentyl)carbamoyl)oxy)benzoate (**1y**) (274.5 mg, 0.580 mmol) in dry dichloromethane (2.9 mL) was slowly added dropwise at 25 ºC for 8 min. The mixture was stirred at 25 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 30 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: hexane = 1 : 6 ~ 1 : 2) to afford 2-(5-phenylpentyl)-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one (**2y-m**) as colorless oil (100 mg, 0.310mmol, 53% yield).

2-(5-phenylpentyl)-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one (2y-m)

Colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 (dd, J = 7.6, 1.2 Hz, 1H), 7.34-7.23 (m, 4H), 7.21-7.13 (m, 4H), 3.92 (ddd, J = 16.0, 10.0, 6.4 Hz, 1H), 3.21-3.10 (m, 2H), 3.08-3.01 (m, 1H), 2.77 (dd, J = 13.2, 7.2 Hz, 1H), 2.67-2.62 (m, 3H), 2.09-2.04 (m, 1H), 1.82-1.61 (m, 6H), 1.53-1.37 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 170.8, 142.5, 140.0, 135.9, 130.0, 129.1, 128.4, 128.2, 127.3, 126.4, 125.6, 47.2, 45.7, 35.8, 32.3, 31.2, 27.7, 27.2, 26.7, 26.5. ESI-HRMS: Calcd for $C_{22}H_{27}NNaO^+$ $[M+Na]^+$: 344.1985. Found: 344.2010.

V. Optimization of the reaction condition of 8-membered ring formation

Prior to investigate TfOH promoted cyclization reaction, we examined several methods for formation of 8-membered ring compounds (The results are summarized in Supporting Information, **Table S1**). The traditional conditions using $POCl_3$ as dehydrating reagent (Table S1, Entry 1) did not afford any cyclized product, only recovery of the starting material. When we tried Wang's conditions,[16] no cyclized product was obtained, but the urea compound was formed (Table S1, Entry 2).

In neat TfOH, the use of a methanol leaving group afforded cyclized product **2h** in 16% yield (Table S1, Entry 3), but the reaction required a high temperature and a long reaction time, which might account for the low yield. When Nakata's condition[3d] was employed for this medium-sized ring formation reaction, the cyclized product was obtained in 33% yield (Table S1, Entry 4). We assumed that intermolecular dimerization lowered the yield, so the reaction was conducted under diluted conditions, but the yield remained low (Table S1, Entry 5). Then we changed the leaving group to methyl salicylate, which can generate a carbamoyl cation at room temperature in strong acid. When Tf_2NH was employed as a strong acid, it did not afford the cyclized product at all, but the carbamate functionality was converted into an amino group (data not shown in Table S1). Finally, when TfOH was used (the same

condition as in our conventional method, Table S1, Entry 7), the cyclized product was obtained in 61% yield. Thus, we adopted this as the optimized condition.

Synthesis of substrates

Synthesis of methyl methyl(4-phenylbutyl)carbamate (1a')

A solution of **3a** (shown in experimental section of the main text) (486 mg, 2.97 mmol), *N*,*N*-diisopropylethylamine (1.0 mL) and methyl chloroformate (319 mmol, 3.54 mmol, 1.2 eq) in tetrahydrofuran (2.0 mL) was stirred at 0 ºC for 10 min. Then the mixture was quenched with 30 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude solid mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: *n*-hexane = 1 : 3) to afford methyl methyl(4-phenylbutyl)carbamate **1a'** as colorless oil (645 mg, 2.92 mmol, 98% yield).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed (approximately 1 : 1 ratio at 25 ºC), δ (ppm): 7.29-7.25 (m, 2H, rotamer A and B), 7.19-7.16 (m, 3H, rotamer A and B), 3.68 (s, 3H, rotamer A and B), 3.27 (brs, 2H, rotamer A and B), 2.87 (brs, 1.5H, rotamer A), 2.84 (brs, 1.5H, rotamer B), 2.63 (t, J = 7.2 H, 2H, rotamer A and B), 1.58 (brs, 4H, rotamer A and B). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 157.0, 142.2, 128.4, 128.3, 125.7, 52.4, 48.8, 48.4, 35.6, 34.5, 33.8, 28.4, 27.4, 27.1. ESI-HRMS: Calcd for $C_{13}H_{19}NNaO_2^+$ $[M+Na]^+$: 244.1308. Found: 244.1308. Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.33; H, 8.41; N, 6.33.

Synthesis of (9H-fluoren-9-yl)methyl methyl(4-phenylbutyl)carbamate (1a")

A solution of **3a** (shown in experimental section of the main text) (215 mg, 1.32 mmol) and *N*-(9-Fluorenylmethoxycarbonyloxy)succinimide (467 mg, 1.39 mmol, 1.05 eq) in tetrahydrofuran-acetone-water (1:1:1 mixture (v/v), 6.0 mL) was stirred at room temperature for 14 hrs. Then the reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 mL). The whole was extracted with ethyl acetate (30 mL x 2) and the organic layer was washed with brine and dried over Na_2SO_4 and evaporated under reduced pressure to give crude oil. The crude product was purified by column chromatography (eluent: ethyl acetate : *n*-hexane = 1 : 6) to afford **1a"** as colorless oil (456 mg, 1.18 mmol, 90% yield).

^{1}H-NMR (400 MHz, $CDCl_3$), two rotamers (A and B) with respect to the amide bond were observed (approximately 1 : 1 ratio at 25 ºC), δ (ppm): 7.75 (d, J = 7.2 Hz, 2H), 7.58 (dd, J = 7.6, 7.6 Hz, 2H), 7.39 (dd, J = 7.6, 7.6 Hz, 2H), 7.31-7.25 (m, 4H), 7.19-7.16 (m, 3H), 4.49-4.39 (m, 2H), 4.24-4.21 (m, 1H), 3.30 (brs, 1H), 3.07 (brs, 1H), 2.86 (s, 1.5H), 2.84 (s, 1.5H), 2.64 (brs, 1H), 2.53 (brs, 1H), 1.59 (brs, 2H), 1.44-1.36 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$), two rotamers with respect to the amide bond were observed, δ (ppm): 156.3, 144.2, 142.2, 141.4, 128.4, 128.3, 127.6, 127.0, 125.8, 125.0, 124.8, 119.9, 67.2, 66.8, 48.9, 48.6, 47.4, 35.6, 34.6, 33.9, 28.4, 27.4, 27.1. ESI-HRMS: Calcd for $C_{26}H_{27}NNaO_2^+$ $[M+Na]^+$: 408.1934. Found: 408.1931.

Experimental procedures for the optimization

Condition 1: The mixture of **1a'** (95.5 mg, 0.432 mmol) in phosphoryl chloride (2.0 ml, 21 mmol) was refluxed for 2 hrs. Then the mixture was quenched with aqueous sodium carbonate (1M, 20 mL). The whole was extracted with ethyl acetate (50 mL x 2) and the organic layer was dried over sodium sulfate. The solution was evaporated to give starting material oil (76.6 mg, 80% recovery).

Condition 2: To a solution of **1a'** (97.9 mg, 0.442 mmol) in phosphoryl chloride (2.0 ml, 21 mmol), phosphorus pentoxide (133.7 mg, 0.942 mmol) was added at room temperature The mixture was refluxed for 2 hrs. Then the mixture was quenched with aqueous sodium carbonate (1M, 20 mL). The whole was extracted with ethyl acetate (50 mL x 2) and the organic layer was dried over sodium sulfate. The solution was evaporated to give The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 1) to afford starting material oil (10.9 mg, 0.0492 mmol, 11% recovery) and

1,3-dimethyl-1,3-bis(4-phenylbutyl)urea **2a'** (28.7 mg, 0.0814 mmol, 37% yield) as colorless oil.

Cyclized product was not detected in the crude mixture.

1,3-dimethyl-1,3-bis(4-phenylbutyl)urea (2a')
Colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28-7.24 (m, 4H), 7.18-7.14 (m, 6H), 3.16-3.12 (m, 4H), 2.73 (s, 6H), 2.61 (t, J = 7.6 Hz, 4H), 1.62-1.55 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 165.4, 142.2, 128.32, 128.26, 125.7, 50.2, 36.6, 35.6, 28.6, 27.1. ESI-HRMS: Calcd for $C_{23}H_{32}N_2NaO^+$ $[M+Na]^+$: 375.2407. Found: 375.2404.

Condition 3: The mixture of **1a'** (126 mg, 0.57 mmol) and trifluoromethanesulfonic acid (3.2 mL, 50 eq) was stirred at 70 ºC under argon atmosphere for 67 hrs. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 1) to afford 2-methyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one **2a** (17 mg, 0.091 mmol, 16% yield) as colorless oil.

Condition 4: To a solution of **1a"** (99.3 mg, 0.258 mmol) in dry dichloromethane (4.4 ml, 0.06 M), phosphorus pentoxide (377.9 mg, 2.66 mmol) was added at 0 ºC. The mixture was stirred at 22ºC under argon atmosphere for 24 hrs. Then the mixture was quenched with aqueous sodium carbonate (1M, 50 mL) and the whole was extracted with dichloromethane (20 mL x 1) and ethyl acetate (50 mL x 2). The organic layer was washed with aqueous sodium hydroxide (2M, 10 mL x 2), brine (10 mL x 3). The solution was dried over sodium sulfate and filtered. The solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 1) to afford 2-methyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one **2a** (16.1 mg, 0.085 mmol, 33% yield) as colorless oil.

Condition 5: To a solution of **1a"** (62.1 mg, 0.161 mmol) in dry dichloromethane (13.7 ml, 0.012 M), phosphorus pentoxide (230.1 mg, 1.62 mmol) was added at 0 ºC. The mixture was stirred at 22 ºC under argon atmosphere for 24 hrs. Then the mixture was quenched with aqueous sodium carbonate (1M, 50 mL) and the whole was extracted with ethyl acetate (50 mL x 2). The organic layer was washed with aqueous sodium hydroxide (2M, 10 mL x 1), brine (10 mL x 1). The solution was dried over sodium sulfate and filtered. The solvent was evaporated to give a crude oil mixture. The crude product was purified by column chromatography (eluent: ethyl acetate: dichloromethane = 1 : 6 ~ 1 : 1) to afford 2-methyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one **2a** (11.2 mg, 0.0592 mmol, 31% yield) as colorless oil.

Condition 6: The solution of **1a** (64.5 mg, 0.20 mmol) and 1,1,1-trifluoro-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (1077 mg, 3.83 mmol, 19 eq) in dry dichloromethane was stirred at 20 ºC under argon atmosphere for 1 hr. Then the mixture was quenched with 20 mL of ice water and the whole was extracted with dichloromethane (30 mL x 2). The organic layer was dried over sodium sulfate and the solvent was evaporated to give a crude oil mixture. In the crude product, 2-methyl-3,4,5,6-tetrahydrobenzo[*c*]azocin-1(2*H*)-one was *not* observed by ^{1}H NMR.

ASSOCIATED CONTENT

Supporting Information

Supporting Figures, Tables, and NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org

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H. K. conceived the general idea and carried out all the experimental work. The manuscript was written by H.K. and T.O.

Notes

The authors declare no competing financial interest.

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