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A Concise and Diversity-Oriented Strategy for the Synthesis of Benzofurans and Indoles via Ugi and Diels−Alder Reactions

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A one-pot synthesis of diverse benzofurans and indoles from readily available starting materials was achieved via the sequential Ugi four-component reaction, intramolecular Diels−Alder reaction, and oxidative aromatization.

Introduction

Benzofuran[1] and indole[2] are the basic units among a wide variety of naturally occurring products, and represent the most important structural classes in drug discovery. For example, both (+)-duocarmycin SA (**1**)[3a] and ellipticine (**2**)[3b] (Figure 1) are natural products with exceptionally potent antitumor activities. The naturally occurring khellinone (**3**)[3c] is an important lead compound for the development of voltage-gated potassium channel Kv1.3 blocker. Benzofuroyl pyrroloquinolone (**4**)[3d] is a potent and selective PDE5 inhibitor.

Over the past 10 years, diversity-oriented synthesis (DOS)[4] has acquired increasing attention in biomedical research. Therefore, development of efficient strategies to rapidly prepare structurally diverse small molecules, such as benzofurans and indoles, are imperative.

To date, syntheses of benzofurans and indoles generally require multiple-step synthesis and purification.[5] As a result, the construction of a diversity-oriented benzofuran or indole library is challenging. The domino process, which addresses issues of synthetic efficiency and reaction processing, provides an alternative route to the existing conventional syntheses.[6] Recently, we have directed considerable efforts at developing a DOS platform to make natural product-like compounds by domino reactions.[7]

The Ugi four-component reaction (Ugi-4CR)[8] is an example of a domino reaction which has been widely employed to construct complex structural frameworks with high efficiency. Therefore, as part of our strategy, we aimed to develop an approach that integrates Ugi-4CR and the intramolecular Diels−Alder (IMDA) reaction into a single synthetic process to construct benzofurans and indoles. We hoped that, on the basis of our rational design, the intermediate derived from Ugi-4CR could simultaneously undergo subsequent IMDA reaction to build up the desired frameworks, demonstrating the efficiency and multiplicative effect of Ugi-4CR.

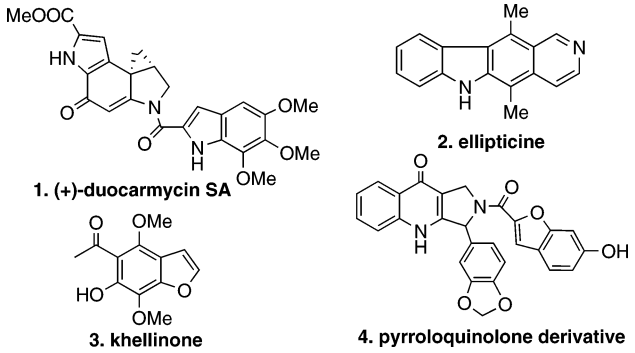

Figure 1. Biologically active indoles and benzofurans.

Despite recent advances in Ugi-4CR and IMDA reaction in complex molecules,[10] there is no report that associates the syntheses of tricyclic-based benzofurans and indoles with Ugi-4CR and IMDA reaction. Herein, we report our recent efforts to achieve a sequential reaction process of Ugi-4CR, IMDA reaction, and oxidative aromatization to construct heterotricyclic molecules in a one-pot operation, thereby providing an efficient approach to access a collection of small molecules having benzofuran and indole scaffolds with defined coordinates in chemical space.[11]

Results and Discussion

In this new scenario (Figure 2), intermediate **F** is expected to derive from its precursor **E** through an IMDA reaction, and **E** could be derived from **A**, **B**, **C**, and **D** by Ugi-4CR. We assumed intermediate **F** could easily undergo an H-shift to form the conjugated aromatic furan **G**, which would then undergo oxidative aromatization to afford product **H**. Synthetically, this proposed synthetic process could potentially be performed in the same reaction vessel, providing a format amenable for application in combinatorial synthesis.

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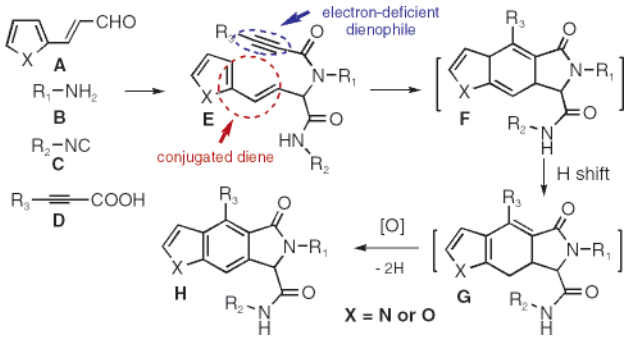
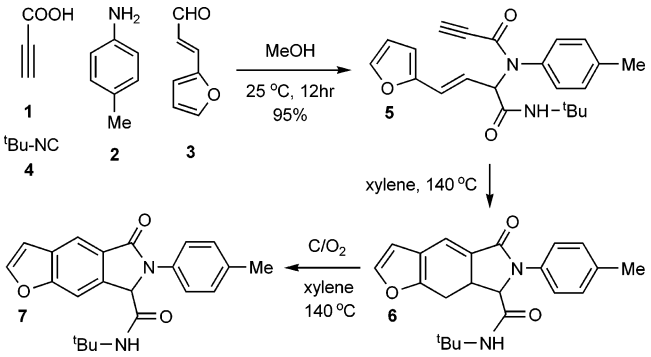


Figure 2. Synthetic analysis.

Scheme 1. Synthesis of Tricyclic Benzofuran **7**



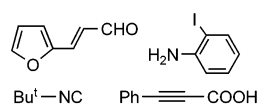
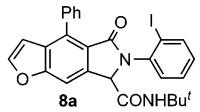
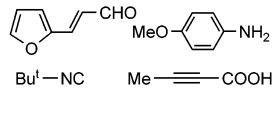
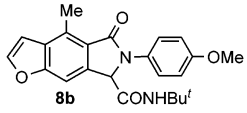
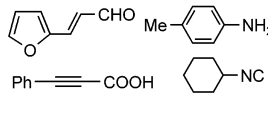
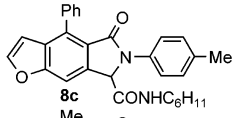
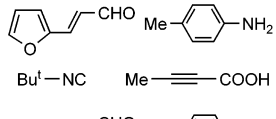
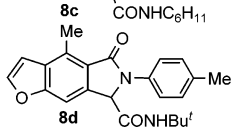
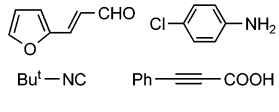
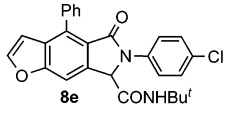
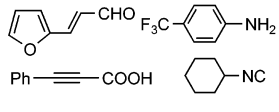
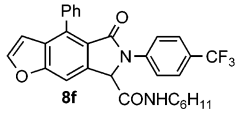
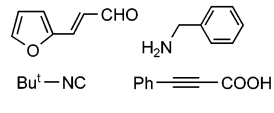
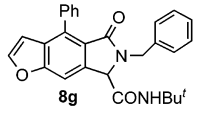
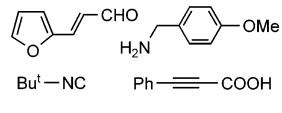
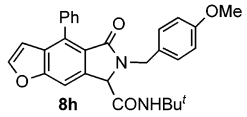
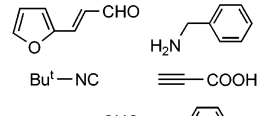
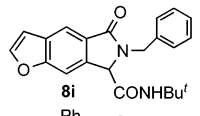
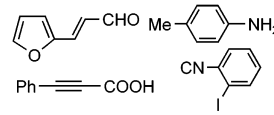
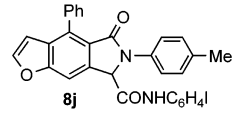
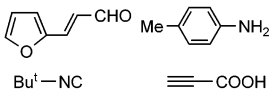
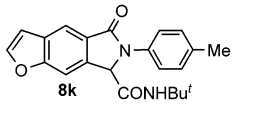
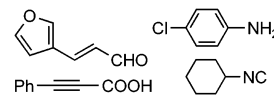
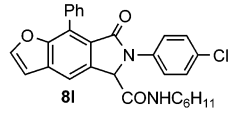
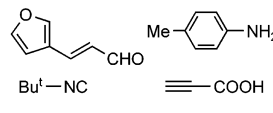
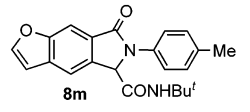
Initially, we chose a simple model to test the feasibility to synthesize benzofuran (Scheme 1). Hence, the commercially available propiolic acid **1**, arylamine **2**, furanoaldehyde **3**, and *tert*-butyl isonitrile **4** were mixed in methanol to give Ugi product **5** in 95% yield.[7b] Compound **5** was then heated to 80 °C in benzene; however, the expected IMDA reaction did not occur. Under forcing conditions, however, two new UV-active spots were observed on a TLC plate after heating at 140 °C in xylene for 10 h, which were later identified as **6** and **7** in 65% combined yield with a ratio of 4/1, respectively. The forcing conditions required for the IMDA reactions are somewhat surprising and are presumably due to the furan's aromaticity.[12] The formation of **7** under the thermal conditions reflects the feasibility of a direct synthesis of **7** from **5**. To this end, **5** was refluxed in toluene in the presence of activated carbon under positive oxygen pressure for 12 h,[13] and **7** was, indeed, obtained in 66% yield.

To achieve a one-pot reaction procedure, upon the termination of Ugi-4CR, the methanol was removed, and the residue was dissolved in xylene, then heated to 140 °C in the presence of positive oxygen pressure for 12 h. In this way, **7** was eventually obtained in 66% yield from simple substrates **1**, **2**, **3**, and **4**.

To assess the generality of this one-pot synthetic reaction, particularly in regard to the anticipated combinatorial library construction, 13 additional benzofurans were synthesized. To determine the efficiency profile, several commercially available arylamines, propiolic acids, and three types of isonitriles listed in Table 1 were screened to evaluate the scope of the reaction. Optimum yields were obtained by performing the reaction with an equal amount of amine, aldehyde, acid, and isocyanide.

In the initial experiments, most oxidative aromatizations were achieved by the active carbon/oxygen system. However, we subsequently showed that DDQ was a better oxidant in the oxidative aromatization and gave better yields. The final yields of the benzofuran derivatives after silica gel column chromatography are reported in Table 1, and the overall yields range from 45 to 80%, reflecting the chemical efficiency of each of the reactions involved (at least three reactions, >75% average yield).

Table 1. Synthesis of Benzofuran-Based Heterocycles

entry	substrates	product	yield (%)
1			86[a]
2			53[a]
3			82[a]
4			46[a]
5			87[a]
6			62[a]
7			73[a]
8			50[b]
9			56[a]
10			45[a]
11			66[b]
12			60[a]
13			48[a]

[a] Isolated yield based on DDQ oxidative aromatization. [b] Isolated yields based on activated carbon-mediated oxidative aromatization.

Table 2. Synthesis of Indole-Based Heterocycles

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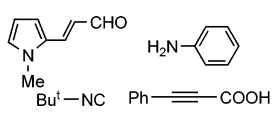
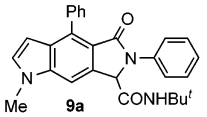
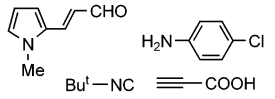
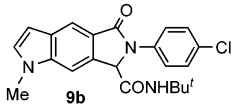
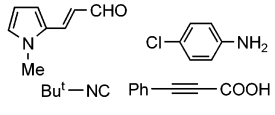
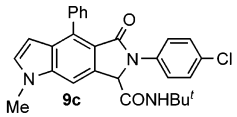
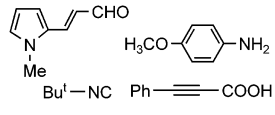
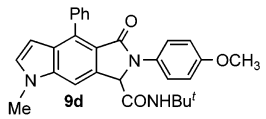
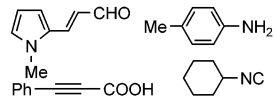
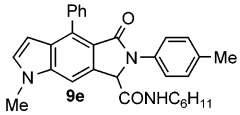
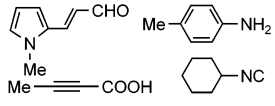
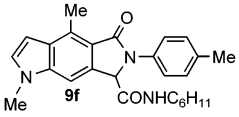
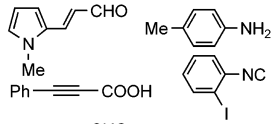
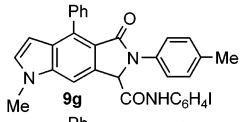
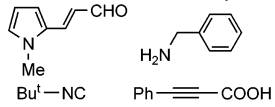
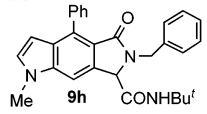
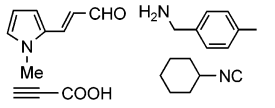
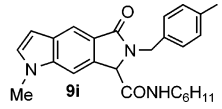
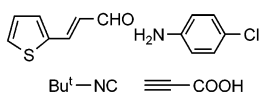
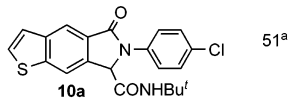
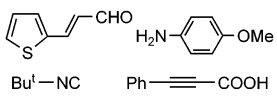
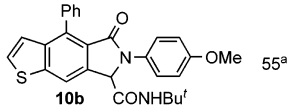
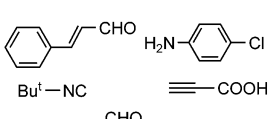
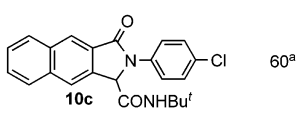
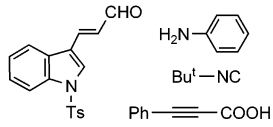
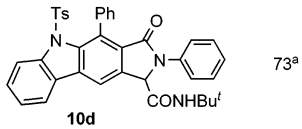
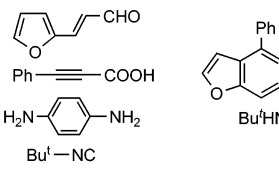
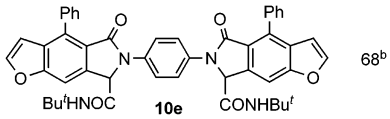
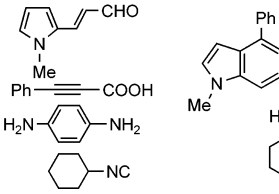
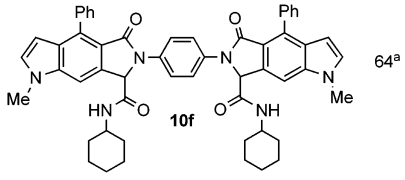
1		 **9a**	81[a]
2		 **9b**	72[a]
3		 **9c**	61[a]
4		 **9d**	75[a]
5		 **9e**	80[a]
6		 **9f**	45[a]
7		 **9g**	51[a]
8		 **9h**	52[b]
9		 **9i**	62[b]

[a] Isolated yield based on DDQ oxidative aromatization. [b] Isolated yields based on activated carbon-mediated oxidative aromatization.

To assemble indole-based heterocycles, pyrrole aldehydes were substituted for this one-pot reaction. Thus, under conditions identical to that of the benzofuran synthesis as listed in Table 1, an array of indole-based heterocycles were obtained in good yields. The results are listed in Table 2. We selected *N*-methyl-substituted pyrrole aldehydes in the reaction to prevent its potential decomposition at the oxidative aromatization step. It is worthwhile to point out that as in the case for **8h** synthesis (see entry 8 in Table 1), the two benzylamine-based Ugi products (see entries 8−9 in Table 2) gave low yields when DDQ was employed as an oxidative agent, presumably due to the oxidative debenzylation of *N*-benzylamines by DDQ during the process of oxidative aromatization.[14] Therefore, to obtain the high yielding products corresponding to **9h** and **9i**, we used active carbon/oxygen to carry out aromatization.

Having established the synthetic route to achieve the desired structures, we then proceeded to further expand the scope of this one-pot synthetic procedure by synthesizing six additional polycyclic molecules, as illustrated in Table 3. Two thiazole-based heterocylces (entries 1 and 2) were obtained in acceptable yields. When α,β-unsaturated aldehydes substituted with benzene or indoles were employed as substrates, two novel types of polycyclic heterocycles (see entries 3 and 4) were accomplished. Interestingly, the symmetrical benzofuran **10e** and indole **10f** (entries 5−6) could be obtained when 1,4-phenyldiamine was selected as the amine fragment, thus providing a convenient approach to the synthesis of benzofuran- or indole-based dimeric molecules.[15]

Table 3. Synthesis of Polycyclic Heterocycles

entry	substrates	product	yield (%)
1		 **10a**	51[a]
2		 **10b**	55[a]
3		 **10c**	60[a]
4		 **10d**	73[a]
5		 **10e**	68[b]
6		 **10f**	64[a]

[a] Isolated yield based on DDQ oxidative aromatization. [b] Isolated yields based on activated carbon-mediated oxidative aromatization.

In conclusion, we have developed a novel and efficient synthetic approach to construct heterocycles of benzofuran and indole by using a sequential Ugi reaction, IMDA reaction, and oxidative aromatization from simple and commercially available precursors. The synthetic protocol embodies a domino process and is accomplished in a one-pot process according to the chemical efficiency paradigm. We anticipate that this method may have interesting implications in the construction of diversified heterocyclic molecules and will find an application in the fields of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

Experimental Section

General Procedure for Ugi Reaction. To a solution of arylamine (1.0 mmol) in methanol (1.0 mL) was added aldehyde (1.0 mmol), and the reaction mixture was stirred at room temperature for 10 min. To this solution was added acetylenic acid (1.0 mmol), and the reaction mixture was stirred for 5 min, then isocyanide (1.0 mmol) was added,

and the reaction mixture was stirred for an additional 5 h to completion.

4-Furan-2-yl-2(propynoyl-*p*-tolylamino)-but-3-enoic Acid *tert*-Butylamide (5). After Ugi-4CR, the solvent was removed under vacuum, and the residue was then purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:8:8) to give product **5** (346 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.36 (s, 9H), 2.38 (s, 3H), 2.84 (s, 1H), 5.21−5.24 (d, J = 9.0 Hz, 1H), 6.00 (s, 1H), 6.08−6.17 (dd, J = 9.0, 15.9 Hz, 1H), 6.29−6.30 (d, J = 3.3 Hz, 1H), 6.36−6.38 (dd, J = 1.8, 3.6 Hz, 1H,), 5.42−5.47 (d, J = 15.9 Hz, 1H), 7.17−7.24 (m, 4H), 7.34 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 28.6, 51.7, 64.3, 76.0, 80.5, 109.5, 111.4, 120.1, 124.6, 129.4, 129.7, 136.7, 138.9, 142.7, 151.4, 153.5, 167.4. LRMS (EI), 364 (M^+). HRMS (EI) calcd for$C_{22}H_{24}N_2O_3$ (M^+), 364.1787; found, 364.1799.

5-Oxo-6-*p*-tolyl-6,7,7a,8-tetrahydro-5*H*-1-oxa-6-aza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (6). After Ugi-4CR, the solvent was removed under vacuum, xylene (30 mL) was added, and the mixture was stirred for 2 h at 140 °C under nitrogen. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:8:8) to give product **6** (182 mg, 50% yield as a pair of diastereoisomers) and product **7** (43 mg, 12% yield). The spectroscopic data for **6**: ^{1}H NMR (300 MHz, $CDCl_3$): 1.12 (s, 5.8H), 1.32 (s, 3.7H), 2.25 (m, 3.7H), 3.32−3.45 (m, 2H), 4.29−4.31 (m, 1H), 5.76 (s, 1H), 6.43 (d, J = 1.5 Hz, 1H), 7.23−7.29 (m, 3.4H), 7.36−7.39 (m, 2.6H), 7.52−7.55 (m, 0.7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 24.2, 27.0, 28.2, 29.6, 35.8, 38.8, 51.3, 51.9, 65.0, 67.0, 108.7, 117.9, 118.2, 120.0, 120.8, 123.2, 123.5, 129.5, 129.6, 135.0, 135.2, 135.5, 136.1, 142.7, 153.8, 153.9, 166.2, 166.3, 167.5, 168.8.

5-Oxo-6-*p*-tolyl-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (7). After Ugi-4CR, the solvent was removed under vacuum, the residue was mixed with activated carbon (200 mg) and xylene (30 mL), and the reaction mixture was heated at 140 °C for 2 h under a balloon pressure of oxygen. The activated carbon was filtered off, the filtrate was concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:8:8) to give product **7** (239 mg, 66% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.12 (s, 9H), 2.37 (s, 3H), 5.54 (s, 1H), 5.62 (s, 1H), 6.87−6.88 (d, J = 2.4 Hz, 1H), 7.23−7.26 (d, J = 8.4 Hz, 2H), 7.66−7.69 (d, J = 8.4 Hz, 2H), 7.73−7.74 (d, J = 2.1 Hz, 1H), 7.88 (s, 1H), 8.07 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 28.2, 51.6, 65.5, 106.0, 107.1, 117.4, 120.2, 126.2, 129.0, 129.9, 135.0, 135.5, 136.9, 146.9, 157.7, 167.0, 167.9. LRMS (EI): 362 (M^+). HRMS (EI): calcd for $C_{22}H_{22}N_2O_3$ (M^+), 362.1630; found, 362.1648.

6-(2-Iodophenyl)-5-oxo-4-phenyl-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (8a). After Ugi-4CR, the solvent was removed under vacuum, and the residue was dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen atmosphere, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was refluxed under nitrogen for an additional 12 h. The reaction mixture was cooled first, diluted with EtOAc (30 mL), and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:12:12) to give product **8a** (473 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.27 (s, 9H), 5.55 (s, 1H), 6.05 (br, 1H), 6.83 (d, J = 2.1 Hz, 1H), 7.04−7.09 (m, 1H), 7.38−7.49 (m, 5H), 7.60−7.63 (m, 2H), 7.72−7.73 (d, J = 2.1 Hz, 1H), 7.79 (s, 1H), 7.91−7.94 (d, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.6, 52.0, 66.1, 98.7, 105.1, 106.9, 127.7, 128.1, 129.1, 129.4, 129.8, 130.2, 134.3, 135.5, 139.3, 140.1, 146.8, 157.1, 166.9, 168.0. LRMS (EI): 550 (M^+). HRMS (EI) calcd for $C_{27}H_{23}N_2O_3I$ (M^+), 550.0753; found, 550.0752.

6-(4-Methoxyphenyl)-4-methyl-5-oxo-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (8b). After Ugi-4CR, the solvent was removed under vacuum, and the residue was dissolved in dichloromethane (1 mL) and diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was refluxed under nitrogen for another 12 h. After cooling again to room temperature, the reaction mixture was diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:5) to give product **8b** (208 mg, 53% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.13 (s, 9H), 2.91 (s, 3H), 3.84 (s, 3H), 5.46 (d, J = 0.9 Hz, 1H), 5.56 (s, 1H), 6.92−6.93 (m, 1H), 6.96−6.99 (dd, J = 2.4, 7.2 Hz, 2H), 7.64−7.67 (dd, J = 2.4, 7.2 Hz, 2H),7.72 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 28.3, 51.5, 55.4, 65.1, 103.6, 105.6, 114.5, 122.2, 129.6, 131.1, 132.3, 137.6, 146.1, 156.7, 156.9, 167.3, 168.8. LRMS (EI): 392 (M^+). HRMS (EI) calcd for $C_{23}H_{24}N_2O_4$ (M^+), 392.1736; found, 392.1732.

5-Oxo-4-phenyl-6-*p*-tolyl-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-7-carboxylic Acid Cyclohexylamide (8c). After Ugi-4CR, the solvent was removed under vacuum, and the residue was dissolved in dichloromethane (1 mL), then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and then the mixture was refluxed under nitrogen for another 12 h. After cooling again to room temperature, the mixture was diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous phase was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:6) to give product **8c** (380 mg, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 0.79−

0.80 (m, 2H), 0.97−1.06 (m, 1H), 1.13−1.26 (m, 2H), 1.47−1.63 (m, 5H), 2.31 (s, 3H), 3.62−3.65 (m, 1H), 5.64 (s, 1H), 5.85 (s, 1H), 6.71−6.72 (d, J = 1.2 Hz, 1H), 7.14−7.17 (d, J = 8.4 Hz, 2H) 7.42−7.54 (m, 4H), 7.58−7.61 (d, J = 8.4 Hz, 2H), 7.65−7.66 (d, J = 1.2 Hz, 1H), 7.81 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 24.2, 24.3, 25.1, 32.2, 32.3, 48.3, 63.8, 105.3, 106.7, 120.3, 121.4, 127.8, 128.2, 129.5, 129.7, 129.9, 134.5, 134.8, 135.0, 135.3, 137.9, 146.8, 156.9, 167.1, 167.3. LRMS (EI): 464 (M^+). HRMS (EI): calcd for$C_{30}H_{28}N_2O_3$ (M^+), 464.2100; found, 464.2087.

4-Methyl-5-oxo-6-*p*-tolyl-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (8d). After Ugi-4CR, the solvent was removed under vacuum, and the residue was dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was then refluxed under nitrogen for another 12 h. After cooling again to room temperature, the mixture was diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous phase was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, the and residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:10:10) to give product **8d** (175 mg, 46% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.13 (s, 9H), 2.36 (s, 3H), 2.84 (s, 3H), 5.46 (d, J = 0.3 Hz, 1H), 5.68 (s, 1H), 6.89−6.90 (dd, J = 0.9, 2.1 Hz, 1H), 7.20−7.23 (d, J = 8.4 Hz, 2H), 7.63−7.66 (d, J = 8.4 Hz, 2H), 7.70−7.71 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 20.8, 28.2, 51.5, 64.9, 103.5, 105.6, 120.3, 122.4, 129.6, 132.3, 134.7, 135.6, 137.6, 146.0, 156.8, 167.3, 168.8. LRMS (EI): 376 (M^+). HRMS (EI): calcd for $C_{23}H_{24}N_2O_3$ (M^+), 376.1787; found, 376.1777.

6-(4-Chlorophenyl)-5-oxo-4-phenyl-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (8e). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was then refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the reaction mixture was diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous phase was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (CH_2Cl_2) to give product **8e** (380 mg, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.14 (s, 9H), 5.42 (s, 1H), 5.54 (s, 1H), 6.77−6.78 (dd, J = 2.4, 0.9 Hz, 1H), 7.34−7.38 (d, J = 9.3 Hz, 2H), 7.50−7.57 (m, 5H), 7.73−7.77 (m, 3H), 7.89 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 51.7, 64.5, 105.1, 106.6, 121.2, 127.9, 128.4, 129.3, 129.8, 130.0, 134.5, 135.4, 136.8, 137.8, 147.0, 157.2, 166.8, 167.3. LRMS (EI): 458 (M^+). HRMS (EI): calcd for $C_{27}H_{23}N_2O_3Cl$ (M^+), 458.1397; found, 458.1393.

5-Oxo-4-phenyl-6-(4-trifluoromethylphenyl)-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-7-carboxylic Acid Cyclohexylamide (8f). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and then the mixture was refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the mixture was diluted with EtOAc (30 mL) and washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and then was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:6) to give product **8f** (321 mg, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 0.73−0.91 (m, 2H), 0.98−1.06 (m, 1H), 1.15−1.29 (m, 2H), 1.47−1.65 (m, 5H), 3.63−3.69 (m, 1H), 5.55−5.57(d, J = 8.1 Hz, 1H), 5.69 (d, J = 0.9 Hz,1H), 6.76−6.77 (dd, J = 2.1, 0.9 Hz, 1H), 7.47−7.65 (m, 6H), 7.72−7.73 (d, J = 2.4 Hz, 1H), 7.87−7.88 (d, J = 2.4 Hz, 1H), 7.39−7.96 (d, J = 8.7 Hz, 2H), 7.81 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.3, 24.4, 25.1, 32.3, 48.5, 63.8, 105.3, 106.7, 106.8, 119.3, 120.4, 126.4, 126.8, 127.9, 128.4, 129.9, 134.4, 135.6, 137.6, 141.1, 147.1, 157.2, 166.6, 167.6. LRMS (EI): 518 (M^+). HRMS (EI): calcd for $C_{30}H_{25}N_2O_3F_3$ (M^+), 518.1817; found, 518.1834.

6-Benzyl-5-oxo-4-phenyl-6,7-dihydro-5*H*-1-oxa-6-aza-s-indacene-7-carboxylic Acid *tert*-Butylamide (8g). After Ugi-4CR, the solvent was removed under vacuum, and the residue was dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was first cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was then refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the reaction mixture was diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 × 3), and the combined organic layer was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:10:10) to give product **8g** (320 mg, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.18 (s, 9H), 4.41−4.56 (d, J = 14.7 Hz, 1H), 4.79 (s, 1H), 4.99−5.04 (d, J = 14.7 Hz, 1H), 5.53 (s, 1H), 6.76−6.77 (d, J = 2.1 Hz, 1H), 7.26−7.34 (m, 5H), 7.47−7.62 (m, 4H), 7.67−7.68 (d, J = 2.1 Hz, 1H), 7.72 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1, 46.2, 51.2, 64.0, 104.8, 106.6, 120.8, 127.5, 127.7, 128.0, 128.5, 128.7, 129.0, 129.9, 134.4, 136.5, 139.1, 146.4, 156.5, 166.9, 168.9. LRMS (ESI): 439 (M + H^+).

6-(4-Methoxybenzyl)-5-oxo-4-phenyl-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (8h). After Ugi-4CR, the solvent was removed under

vacuum, the residue was mixed with activated carbon (200 mg) and xylene (30 mL), and the reaction mixture was heated at 140 °C for 2 h under a balloon pressure of oxygen. The activated carbon was filtered off, and the filtrate was concentrated. The residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:8:8) to give product **8h** (233 mg, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.20 (s, 9H), 3.78 (s, 3H), 4.32−4.37 (d, J = 14.4 Hz, 1H), 4.77 (s, 1H), 4.98−5.03 (d, J = 14.4 Hz, 1H), 5.51 (s, 1H), 6.77−6.78 (m, 1H), 6.83−6.86 (d, J = 8.7 Hz, 2H), 7.25−7.28 (d, J = 8.7 Hz, 2H), 7.48−7.62 (m, 5H), 7.69−7.73 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 45.9, 51.5, 55.3, 64.2, 105.1, 106.8, 114.4, 121.1, 127.8, 128.2, 128.7, 129.2, 130.1, 130.2, 134.7, 139.3, 146.6, 156.8, 159.4, 167.2, 169.2. LRMS (EI): 468 (M^+). HRMS (EI): calcd for $C_{29}H_{28}N_2O_4$ (M^+), 468.2049; found, 468.2048.

6-Benzyl-5-oxo-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (8i). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was then refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the reaction mixture was first diluted with EtOAc (30 mL), and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:5) to give product **8i** (203 mg, 56% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.18 (s, 9H), 4.46−4.51 (d, J = 15.0 Hz, 1H), 4.80 (s, 1H), 5.08−5.13 (d, J = 15.0 Hz, 1H), 5.72 (s, 1H), 6.84−6.85 (d, J = 1.8 Hz, 1H), 7.27−7.34 (m, 5H), 7.70−7.71 (d, J = 2.1 Hz, 1H), 8.00−8.01 (d, J = 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 46.5, 51.4, 65.0, 105.9, 107.1, 117.1, 125.6, 128.0, 128.6, 128.7, 129.0, 136.6, 138.0, 146.8, 157.4, 166.8, 169.8. LRMS (ESI): 363 ($M+H^+$).

5-Oxo-4-phenyl-6-*p*-tolyl-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-7-carboxylic Acid (2-iodophenyl)-amide (8j). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the mixture was diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:4:20) to give product **8j** (263 mg, 45% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 2.31 (s, 3H), 5.83 (d, J = 0.9 Hz, 1H), 6.75−6.80 (m, 2H), 7.18−7.20 (d, J = 8.4 Hz, 2H), 7.25−7.27 (m, 1H), 7.47−7.63 (m, 6H), 7.70−7.71 (d, J = 2.1 Hz, 1H), 7.75−7.76 (d, J = 1.8 Hz, 1H), 7.77 (s, 1H), 7.93 (s, 1H), 8.05 (s, 1H), 8.15−8.18 (dd, J = 8.4, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 64.3, 89.9, 105.5, 106.8, 120.5, 121.4, 121.5, 126.3, 127.8, 128.3, 129.1, 129.8, 129.9, 130.0, 134.5, 135.0, 135.3, 135.5, 137.0, 137.1, 138.7, 147.0, 157.0, 166.8, 167.1. LRMS (EI): 584 (M^+). HRMS (EI): calcd for $C_{30}H_{21}N_2O_3I$ (M^+), 584.0597; found, 584.0590.

6-(4-Chlorophenyl)-7-oxo-8-phenyl-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-5-carboxylic Acid Cyclohexylamide (8l). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL), and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the reaction mixture was first diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:5) to give product **8l** (290 mg, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 0.79−0.86 (m, 2H), 0.97−1.01 (m, 1H), 1.15−1.28 (m, 2H), 1.47−1.61 (m, 5H), 3.63−3.67 (m, 1H), 5.61 (s, 1H), 5.73−5.76 (d, J = 8.1 Hz, 1H), 6.85−6.86 (d, J = 2.1 Hz, 1H), 7.31−7.36 (m, 2H), 7.46−7.53 (m, 3H), 7.58−7.62 (m, 2H), 7.70−7.75 (m, 3H), 7.88 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.3, 24.4, 25.1, 32.3, 48.4, 63.6, 107.1, 114.1, 121.2, 122.5, 125.5, 127.7, 128.7, 129.2, 130.2, 130.4, 130.7, 132.3, 135.4, 136.6, 148.8, 153.2, 167.0, 167.5. LRMS (EI): 484 (M^+). HRMS (EI): calcd for $C_{29}H_{25}N_2O_3Cl$ (M^+), 484.1554; found, 484.1556.

7-Oxo-6-*p*-tolyl-6,7-dihydro-5*H*-1-oxa-6-aza-*s*-indacene-5-carboxylic Acid *tert*-Butylamide (8m). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the mixture was diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was first washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:12:12) to give product **8m** (174 mg, 48% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.11 (s, 9H), 2.37 (s, 3H), 5.53 (s, 1H), 5.55 (s, 1H), 6.88−6.89 (dd, J = 2.1, 0.6 Hz, 1H), 7.23 (s, 1H), 7.26−7.27 (d, J = 2.4 Hz, 1H), 7.66−7.69 (dd, J = 6.6, 1.8 Hz, 2H), 7.79−7.80 (d, J = 2.4 Hz, 1H), 7.97 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 28.2, 51.5, 65.5, 107.1, 115.1, 120.2, 127.7, 129.9, 132.6, 134.6, 135.0, 135.5, 148.2, 155.2, 167.3, 168.0.

LRMS (EI): 362 (M^+). HRMS (EI): calcd for $C_{22}H_{22}N_2O_3$ (M^+), 362.1630; found, 362.1629.

1-Methyl-5-oxo-4,6-diphenyl-1,5,6,7-tetrahydro-1,6-diaza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (9a). After Ugi-4CR, the solvent was removed under vacuum, and the residue was dissolved in dichloromethane (1 mL), then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was then refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the mixture was first diluted with EtOAc (30 mL) and then washed with NaOH (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:4) to give product **9a** (355 mg, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (s, 9H), 3.87 (s, 3H), 5.53 (s, 1H), 5.61 (s, 1H), 6.47−6.49 (d, J = 3.3 Hz, 1H), 7.14−7.18 (m, 2H), 7.36−7.41 (m, 2H), 7.45−7.54 (m, 3H), 7.60−7.62 (m, 2H), 7.71 (s, 1H), 7.77−7.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 33.3, 51.3, 64.4, 102.3, 102.4, 117.7, 120.1, 124.6, 127.6, 127.7, 129.1, 130.0, 131.0, 134.7, 134.7, 135.6, 138.3, 139.2, 168.0, 168.3. LRMS (EI): 437 (M^+). HRMS (EI): calcd for $C_{28}H_{27}N_3O_2$ (M^+), 437.2103; found, 437.2095.

6-(4-Chlorophenyl)-1-methyl-5-oxo-1,5,6,7-tetrahydro-1,6-diaza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (9b). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL), then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was then refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the reaction mixture was first diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL), then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:4) to give product **9b** (285 mg, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.13 (s, 9H), 3.86 (s, 3H), 5.51 (s, 1H), 5.58 (s, 1H), 6.63−6.64 (d, J = 3.3 Hz, 1H), 7.18−7.19 (d, J = 3.3 Hz, 1H), 7.38−7.41 (d, J = 9.0 Hz, 2H), 7.64 (s, 1H), 7.81−7.84 (d, J = 9.0 Hz, 2H), 8.12 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 33.4, 51.5, 65.6, 102.8, 102.9, 117.6, 120.7, 122.2, 129.3, 129.7, 129.8, 131.3, 133.4, 137.3, 134.0, 167.7, 169.1. LRMS (EI): 395 (M^+). HRMS (EI): calcd for $C_{22}H_{22}N_3O_2Cl$ (M^+), 395.1401; found, 395.1401.

6-(4-Chlorophenyl)-1-methyl-5-oxo-4-phenyl-1,5,6,7-tetrahydro-1,6-diaza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (9c). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was then refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the reaction mixture was first diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous phase was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:4) to give product **9c** (288 mg, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.13 (s, 9H), 3.89 (s, 3H), 5.45 (s, 1H), 5.53 (s, 1H), 6.47−6.48 (d, J = 3.3 Hz, 1H), 7.16−7.17 (d, J = 3.3 Hz, 1H), 7.33−7.36 (d, J = 9.0 Hz, 2H), 7.46−7.59 (m, 5H), 7.68 (s, 1H), 7.76−7.79 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 33.5, 51.6, 64.5, 102.4, 102.5, 117.5, 120.9, 127.7, 127.9, 129.2, 129.7, 130.2, 131.1, 134.5, 135.0, 135.5, 137.1, 139.3, 167.9, 168.4. LRMS (EI): 471 (M^+). HRMS (EI): calcd for $C_{28}H_{26}N_3O_2Cl$ (M^+), 471.1714; found, 471.1710.

6-(4-Methoxyphenyl)-1-methyl-5-oxo-4-phenyl-1,5,6,7-tetrahydro-1,6-diaza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (9d). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the reaction mixture was then refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the mixture was diluted with EtOAc (30 mL), then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:4) to give product **9d** (351 mg, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.12 (s, 9H), 3.80 (s, 3H), 3.86 (s, 3H), 5.55 (s, 2H), 6.48 (d, J = 3.0 Hz, 1H), 6.90−6.93 (d, J = 9.0 Hz, 2H), 7.14−7.15 (d, J = 3.3 Hz, 1H), 7.44−7.53 (m, 3H), 7.60−7.69 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 33.3, 51.3, 55.4, 64.7, 102.3, 102.4, 114.3, 117.8, 122.0, 127.5, 127.6, 129.9, 130.1, 130.8, 131.4, 131.5, 134.5, 134.8, 135.6, 139.1, 156.6, 168.2. LRMS (EI): 467 (M^+). HRMS (EI): calcd for $C_{29}H_{29}N_3O_3$ (M^+), 467.2209; found, 467.2202.

1-Methyl-5-oxo-4-phenyl-6-*p*-tolyl-1,5,6,7-tetrahydro-1,6-diaza-*s*-indacene-7-carboxylic Acid Cyclohexylamide (9e). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was then refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the reaction mixture was first diluted with EtOAc (30 mL), then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with

dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:4) to give product **9e** (382 mg, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 0.77−0.85 (m, 2H), 0.98−1.03 (m, 1H), 1.15−1.26 (m, 2H), 1.46−1.63 (m, 5H), 2.32 (s, 3H), 3.61−3.67 (m, 1H), 3.86 (s, 3H), 5.63 (s, 1H), 5.66 (s, 1H), 6.46−6.47 (dd, J = 3.6, 0.9 Hz, 1H), 7.13−7.18 (m, 3H), 7.41−7.52 (m, 3H), 7.57−7.67 (m, 4H), 7.70 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 34.2, 24.3, 25.0, 32.1, 32.2, 33.2, 48.1, 63.7, 102.2, 102.5, 115.6, 117.8, 120.0, 127.5, 127.6, 129.5, 129.9, 130.8, 134.1, 134.4, 134.5, 135.5, 135.7, 139.0, 168.1, 168.2. LRMS (EI): 477 (M^+). HRMS (EI): calcd for $C_{31}H_{31}N_3O_2$ (M^+), 477.2416; found, 477.2409.

1,4-Dimethyl-5-oxo-6-*p*-tolyl-1,5,6,7-tetrahydro-1,6-diaza-*s*-indacene-7-carboxylic Acid Cyclohexylamide (9f). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the reaction mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was then refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the reaction mixture was diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was first washed with brine (5 mL), then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:4) to give product **9f** (187 mg, 45% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 0.80−0.85 (m, 2H), 0.97−1.01 (m, 1H), 1.14−1.26 (m, 2H), 1.46−1.60 (m, 5H), 2.33 (s, 3H), 2.92 (s, 3H), 3.60−3.67 (m, 1H), 3.83 (s, 3H), 5.58 (d, J = 0.9 Hz, 1H), 5.76−5.79 (d, J = 8.4, 1H), 6.65−6.67 (dd, J_1 = 3.6, J_2 = 0.9 Hz, 1H), 7.14−7.15 (d, J = 3.3, 1H), 7.19−7.22 (d, J = 8.4, 2H), 7.52 (s, 1H), 7.67−7.70 (d, J = 8.4, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 20.8, 24.4, 24.5, 25.2, 32.3, 33.3, 48.2, 64.3, 101.0, 118.7, 120.0, 129.7, 130.0, 130.3, 132.0, 134.2, 134.4, 136.0, 138.7, 168.4, 170.0. LRMS (EI): 415 (M^+). HRMS (EI): calcd for $C_{26}H_{29}N_3O_2$ (M^+), 415.2260; found, 415.2255.

1-Methyl-5-oxo-4-phenyl-6-*p*-tolyl-1,5,6,7-tetrahydro-1,6-diaza-*s*-indacene-7-carboxylic Acid (2-Iodophenyl)-amide (9g). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was then refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the solvent was first diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:4) to give product **9g** (304 mg, 51% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 2.31 (s, 3H), 3.88 (s, 3H), 5.83 (s, 1H), 6.48−6.49 (d, J = 3.3 Hz,1H), 6.73−6.79 (dt, J = 1.5, 8.7 Hz 1H), 7.14−7.30 (m, 4H), 7.45−7.63 (m, 6H), 7.72 (s, 1H), 7.77−7.80 (d, J = 8.4 Hz, 1H), 8.11 (s, 1H), 8.18−8.21 (dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 33.4, 64.4, 89.9, 102.5, 102.7, 117.8, 120.3, 121.3, 126.2, 127.6, 127.8, 129.0, 129.8, 130.2, 130.3, 131.1, 133.7, 134.5, 135.1, 135.5, 135.7, 137.1, 138.8, 139.1, 167.9, 168.1. HRMS (EI): calcd for $C_{31}H_{24}N_3O_2I$ (M^+), 597.0913; found, 597.0910.

6-Benzyl-1-methyl-5-oxo-4-phenyl-1,5,6,7-tetrahydro-1,6-diaza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (9h). After Ugi-4CR, the solvent was removed under vacuum, the residue was mixed with activated carbon (200 mg) and xylene (30 mL), and the mixture was heated 140 °C for 2 h under a balloon pressure of oxygen. The activated carbon was filtered off, the filtrate was concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:4) to give product **9h** (235 mg, 52% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.16 (s, 9H), 3.81 (s, 3H), 4.41−4.46 (d, J = 14.7 Hz, 1H), 4.80 (s, 1H), 4.98−5.03 (d, J = 14.7 Hz, 1H), 5.56 (s, 1H), 6.47−6.49 (d, J = 3.3 Hz, 1H), 7.11−7.12 (d, J = 3.3 Hz, 1H), 7.25−7.34 (m, 5H), 7.45−7.54 (m, 4H), 7.61−7.64 (d, J = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 33.3, 46.6, 51.2, 64.4, 102.2, 102.5, 117.3, 127.6, 127.7, 127.8, 128.7, 128.9, 129.6, 130.2, 130.7, 134.2, 135.7, 136.1, 137.0, 138.9, 168.1, 170.4. LRMS (EI): 451 (M^+). HRMS (EI): calcd for $C_{29}H_{29}N_3O_2$ (M^+), 451.2260; found, 451.2258.

1-Methyl-6-(4-methylbenzyl)-5-oxo-1,5,6,7-tetrahydro-1,6-diaza-*s*-indacene-7-carboxylic Acid Cyclohexylamide (9i). After Ugi-4CR, the solvent was removed under vacuum, the residue was mixed with activated carbon (200 mg) and xylene (30 mL), and the mixture was heated to 140 °C for 2 h under a balloon pressure of oxygen. The activated carbon was filtered off, the filtrate was concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:2) to give product **9i** (257 mg, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 0.76−0.83 (m, 2H), 0.84−1.06 (m, 1H), 1.17−1.33 (m, 2H), 1.55−1.81 (m, 5H), 2.30 (s, 3H), 3.63−3.66 (m, 1H), 3.79 (s, 3H), 4.27−4.32 (d, J = 14.7 Hz, 1H), 4.87 (s, 1H), 5.19−5.24 (d, J = 14.7 Hz, 1H), 5.67−5.70 (d, J = 8.1 Hz, 1H), 6.61−6.62 (d, J = 3.6 Hz, 1H), 7.10−7.25 (m, 4H), 7.50 (s, 1H), 8.12 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 24.8, 25.3, 32.5, 32.9, 33.3, 46.0, 48.5, 64.0, 102.6, 103.4, 117.1, 122.1, 128.5, 129.4, 129.6, 131.0, 133.6, 134.8, 137.7, 139.5, 168.0, 171.2. LRMS (EI): 415 (M^+). HRMS (EI): calcd for $C_{26}H_{29}N_3O_2$ (M^+), 415.2260; found, 415.2249.

6-(4-Chlorophenyl)-5-oxo-6,7-dihydro-5*H*-1-thia-6-aza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (10a). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under a balloon pressure of nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the reaction mixture was refluxed under

nitrogen for an additional 12 h. After cooling again to room temperature, the reaction mixture was first diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous phase was extracted with dichloromethane (10 mL × 3), and the combined organic phase was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:6:6) to give product **10a** (203 mg, 51% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.15 (s, 9H), 5.56 (s, 1H), 5.59 (s, 1H), 7.41−7.46 (m, 3H), 7.58−7.60 (d, J = 5.7 Hz, 1H), 7.81−7.84 (dd, J = 2.1, 7.2 Hz, 2H), 8.27 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 51.8, 65.3, 116.6, 119.7, 121.0, 124.2, 127.4, 128.7, 129.4, 130.5, 135.1, 136.7, 140.4, 144.9, 166.6, 168.0. LRMS (EI): 398 (M^+). HRMS (EI): calcd for $C_{21}H_{19}N_2O_2SCl$ (M^+), 398.0856; found, 398.0852.

6-(4-Methoxyphenyl)-5-oxo-4-phenyl-6,7-dihydro-5*H*-1-thia-6-aza-*s*-indacene-7-carboxylic Acid *tert*-Butylamide (10b). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the reaction mixture was first diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous phase was extracted with dichloromethane (10 mL × 3), and the combined organic phase was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:6:6) to give product **10b** (259 mg, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.13 (s, 9H), 3.81 (s, 3H), 5.52 (s, 1H), 5.58 (d, J = 1.2 Hz, 1H), 6.91−6.94 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 0.9 Hz, 1H), 7.49−7.55 (m, 6H), 7.64−7.67 (d, J = 9.0 Hz, 2H), 8.31 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 51.6, 55.5, 64.4, 114.4, 115.9, 122.2, 124.0, 127.6, 127.7, 127.8, 128.1, 129.4, 130.5, 131.0, 135.5, 136.2, 136.8, 140.6, 144.1, 157.0, 167.2. LRMS (EI): 470 (M^+). HRMS (EI): calcd for $C_{28}H_{26}N_2O_3S$ (M^+), 470.1664; found, 470.1676.

2-(4-Chlorophenyl)-3-oxo-2,3-dihydro-1*H*-benzo[*f*]isoindole-1-carboxylic Acid *tert*-Butyl Amide (10c). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ was added, and the mixture was then refluxed under nitrogen for another 12 h. After cooling again to room temperature, the mixture was first diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed under vaccum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:5) to give product **10c** (235 mg, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.17 (s, 9H), 5.60 (s, 1H), 5.86 (s, 1H), 7.37−7.41 (d, J = 13.5 Hz, 2H), 7.46−7.63 (m, 2H), 7.81−7.85 (m, 3H), 7.92−7.96 (d, J = 12.3 Hz, 1H), 8.19−8.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 30.9, 51.8, 65.7, 121.1, 121.7, 125.1, 127.0, 128.1, 128.4, 128.5, 129.4, 129.5, 130.6, 133.3, 134.5, 135.9, 136.7, 166.8, 167.9. LRMS (EI): 392 (M^+). HRMS (EI): calcd for $C_{23}H_{21}N_2O_2Cl$ (M^+), 392.1292; found, 392.1275.

3-Oxo-2,4-diphenyl-5-(toluene-4-sulfonyl)-1,2,3,5-tetrahydropyrrolo[3,4-*b*]carbazole-1-carboxylic Acid *tert*-Butylamide (10d). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the mixture was then refluxed under nitrogen for an additional 12 h. After cooling again to room temperature, the reaction mixture was first diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous phase was extracted with dichloromethane (10 mL × 3), and the combined organic phase was washed with brine (5 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:1:5) to give product **10d** (458 mg, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (s, 9H), 2.25 (s, 3H), 5.55 (m, 2H), 6.90−6.93 (d, J = 8.1 Hz, 2H), 7.03−7.06 (d, J = 8.4 Hz, 2H), 7.18−7.23 (m, 1H), 7.38−7.59 (m, 9H), 7.72−7.75 (dd, J_1 = 1.2 Hz, J_2 = 8.7 Hz, 2H), 7.75−7.89 (m, 1H), 8.16−8.19 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 28.2, 51.6, 63.7, 113.1, 119.4, 120.5, 120.8, 125.3, 125.5, 126.3, 127.0, 127.8, 128.0, 128.7, 128.9, 129.3, 130.9, 133.6, 133.8, 134.2, 135.1, 137.8, 138.7, 140.2, 143.0, 144.1, 166.7, 166.8. LRMS (EI): 627 (M^+). HRMS (EI): calcd for $C_{38}H_{33}N_3O_4S$ (M^+), 627.2192; found, 627.2179.

6-(4-(7-(Cyclohexylcarbamoyl)-1-methyl-5-oxo-4-phenylfuryl[3,4-*f*]indol-6(1*H*,5*H*,7*H*)-yl)phenyl)-*N*-cyclohexyl-1,5,6,7-tetrahydro-1-methyl-5-oxo-4-phenylfuryl-[3,4-*f*]indole-7-carboxamide (10e). To a solution of *p*-phenyldiamine (0.5 mmol) in MeOH (3.0 mL) was added 3-(2-furyl)acrolein (1.0 mmol), and the reaction mixture was stirred at room temperature for 10 min after addition of phenylpropiolic acid (1.0 mmol). The reaction mixture was continually stirred for 5 min, followed by addition of *tert*-butyl isocyanide (1.0 mmol) in MeOH (2 mL). The reaction mixture was then stirred overnight. After the solvent was removed under vacuum, the residue was mixed with activated carbon (200 mg) and xylene (30 mL), and the reaction mixture was heated at 140 °C for 2 h with stirring under a balloon pressure of oxygen. The activated carbon was filtered off, the filtrate was concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:3:3) to give product **10e** (261.2 mg, 68% yield as a pair of diastereoisomers in a ratio of 1/1). The following are the spectroscopic data for the less polar compound. ^{1}H NMR (300 MHz, $CDCl_3$): 1.11 (s, 18H), 5.47 (s, 2H), 5.59 (s, 2H), 6.76 (d, J = 2.1 Hz, 2H), 7.50−7.56 (m, 12H), 7.72−7.73 (d, J = 2.4 Hz, 2H), 7.84

(s, 4H), 7.90 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 51.6, 64.4, 105.1, 106.8, 120.7, 121.2, 127.9, 128.3, 129.7, 130.0, 134.6, 135.0, 135.3, 137.9, 146.9, 157.1, 167.0, 167.3. LRMS (EI): 770 (M^+). The following spectroscopic data are for the polar compound. ^{1}H NMR (300 MHz, $CDCl_3$): 1.14 (s, 18H), 5.49 (d, J = 0.6 Hz, 2H), 5.53 (s, 2H), 6.75−6.76 (dd, J_1 = 0.9 Hz, J_2 = 2.4 Hz, 2H), 7.51−7.57 (m, 12H), 7.70−7.71 (d, J = 2.1 Hz, 2H), 7.83 (s, 4H), 7.87 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 51.7, 64.7, 105.1, 106.8, 120.5, 121.3, 127.9, 128.3, 129.7, 130.0, 134.7, 135.1, 135.3, 138.0, 146.9, 157.1, 167.1, 167.4. LRMS (EI): 770 (M^+).

6-(4-(7-(Cyclohexylcarbamoyl)-1-methyl-5-oxo-4-phenylpyrrolo[3,4-*f*]indol-6(1*H*,5*H*,7*H*)-yl)phenyl)-*N*-cyclohexyl-1,5,6,7-tetrahydro-1-methyl-5-oxo-4-phenylpyrrolo-[3,4-*f*]indole-7-carboxamide (10f). After Ugi-4CR, the solvent was removed under vacuum, and the residue was first dissolved in dichloromethane (1 mL) and then diluted with benzene (25 mL). After stirring at 50 °C for 4 h under nitrogen, the reaction mixture was cooled to room temperature, DDQ (227 mg, 1.0 mmol) was added, and the reaction mixture was then refluxed under nitrogen for another 12 h. After cooling again to room temperature, the mixture was first diluted with EtOAc (30 mL) and then washed with NaOH solution (1 M, 10 mL), followed by brine (10 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3), and the combined organic phase was washed with brine (5 mL), and then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/petroleum ether = 1:12:12) to give product **10f** (543 mg, 64% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 0.70−0.81 (m, 4H), 0.91−1.00 (m, 2H), 1.13−1.26 (m, 4H), 1.47−1.56 (m, 10H), 3.60−3.63 (m, 2H), 3.87 (s, 6H), 5.60−5.62 (m, 2H), 5.67 (s, 2H), 6.44−6.45 (d, J = 3.3 Hz, 2H), 7.13−7.14 (d, J = 3.3, 2H), 7.45−759 (m, 10H), 7.69 (s, 2H), 7.83 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 24.6, 25.1, 32.4, 32.5, 33.3, 48.4, 63.6, 102.4, 102.5, 117.7, 120.3, 127.6, 127.8, 130.1, 131.0, 134.4, 134.7, 135.0, 135.6, 139.2, 167.9, 168.3. LRMS (EI): 848 (M^+).

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Supporting Information Available. Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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