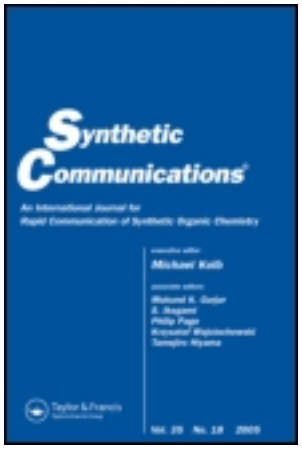

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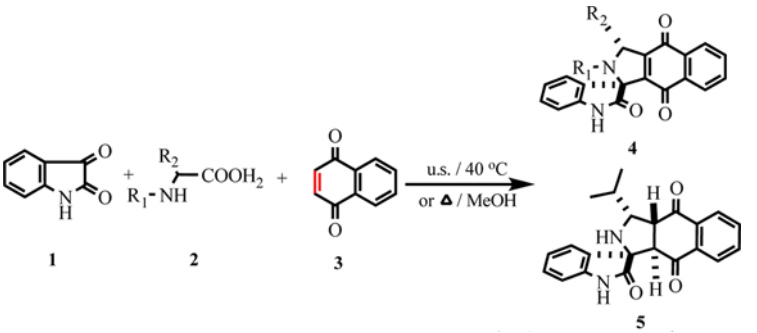
FACILE THREE-COMPONENT SYNTHESIS OF SPIROOXINDOLEPYRROLOLINE RING SYSTEMS VIA 1,3-DIPOLAR CYCLOADDITION WITH 1,4-NAPHTHOQUINONE

Hua Chen, Shun-Yi Wang, Xiao-Ping Xu, and Shun-Jun Ji
Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Material Sciences, Suzhou (Soochow) University, Suzhou, China

GRAPHICAL ABSTRACT



Abstract *1,3-Dipolar cycloadditions involving 1,4-naphthoquinone and an azomethine ylide generated from α-amino acids and isatins have been used in this reaction to afford the pyrrolidine-2-spiro-3′-oxindole* ***4*** *or* ***5*** *with moderate to excellent yields.*

Keywords α-Amino acids; 1,3-dipolar cycloaddition; isatin; 1,4-naphthoquinone

INTRODUCTION

The 1,3-dipolar cycloaddition reactions have attracted continuous attention as an efficient method for the preparation of heterocycles and natural products. Beyond the ability of the 1,3-dipolar cycloaddition reaction to produce heterocycles, its importance extends to two other areas of organic synthesis. First, the heteroatom-containing cycloadducts may be transformed into a variety of other functionalized organic molecules, whether cyclic or acyclic. Second, many 1,3-dipolar

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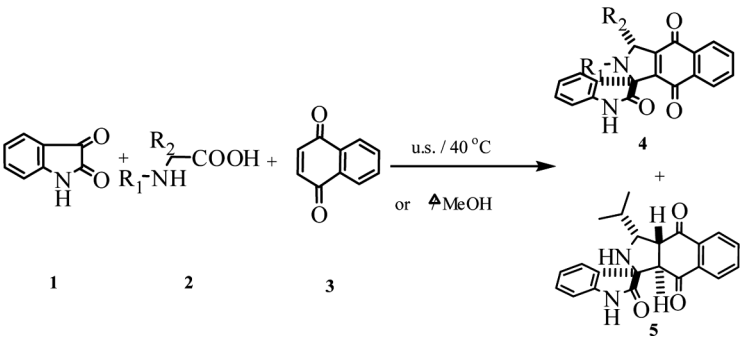
cycloadditions have the ability to generate rings (and the functionality derived from transformations of such rings) containing several contiguous stereocenters in one synthetic operation.[1] The pyrrolidino-2-spiro-3′-oxindole ring system can be found in several pharmacologically active alkaloids. Various strategies have been used to obtain these spiro compounds, such as oxidative rearrangement of β-carbolines and 1,3-dipolar cycloadditions.[2] Larger dipolarophiles, such as chalcones and phenyacetylene, have been used successfully in the three-component reaction of isatin, α-amino acids, and dipolarophiles.[3–6] In 2001, Azizian et al.[7] published a study of some reactions of proline (**2a**), isatin (**1a**), and *N*-arylmaleimide in refluxing ethanol, which are the conditions that yielded the pyrrolidine-2-spiro-3′-oxindole derivatives. Recently, Bergman et al.[8] performed 1,3-dipolar cycloadditions involving different dipolarophiles such as *N*-benzylmaleimide and an azomethine ylide prepared from the decarboxylative condensation between *N*-substituted α-amino acids and isatin under reflux at 90 °C in a mixture of methanol and water. This type reaction can also be performed under microwave conditions.[7] However, few of the reactions of 1,4-naphthoquinone as dipolarophiles have been reported in this type of reaction.[9]

First, our studies were set in motion by exposing isatin to proline and 1,4-naphthoquinone, via anti-azomethine ylides, which attack the dipolarophiles **3** in methanol at 40–50 °C under ultrasounic radiation. The reaction flask was located in the water bath of the ultrasonic cleaner, and the temperature of the reaction system was controlled by adding H_2O. A facile reaction leading to the exclusive formation of 3-spiro[pyrrolidino-oxindoles] derivative **4a** occurred (Scheme 1).

The product **4a** was characterized by spectroscopic analysis. Final proof for the structure assigned for **4a** was derived from single-crystal x-ray analysis (Fig. 1). Compound **4a** also could be obtained in 89% yield under reflux conditions using a mixture of methanol and water as solvent (Table 1, entry 1). It was noted that no desired product was formed when the reaction was carried out at room temperature. Other amino acids such as L-tryptophan, L-isoleucine, L-penylalanine, and L-tryptophan (**2b–2d**) also could be used for this three-component reaction; the desired products **4b–4d** were obtained in good yields with high regio- and stereoselectivities (Table 1, entries 2–4). It was interesting that different types of product **5** were obtained in 78% yield when L-valine was used this reaction (Table 1, entry 5).



Scheme 1. The 1,3-dipolar of isatin, amino acids, and 1,4-naphthoquinone.

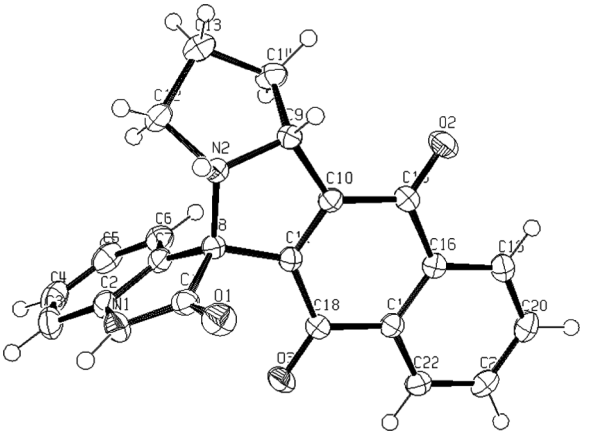
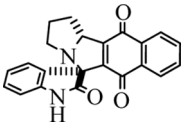
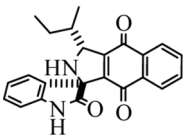
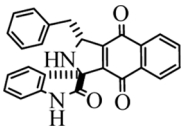
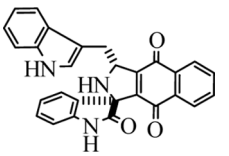
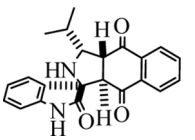


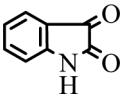
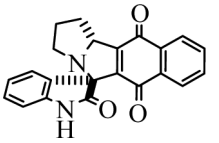
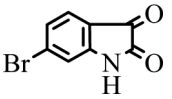
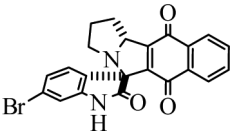
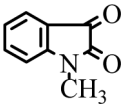
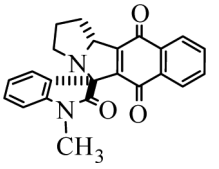
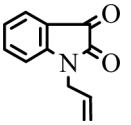
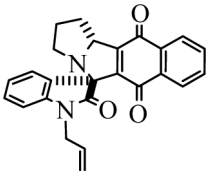
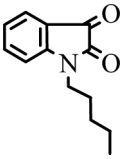
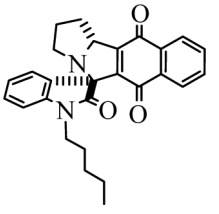
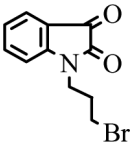
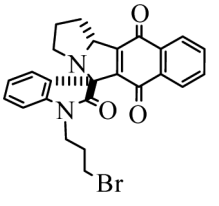
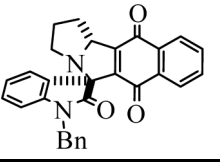
Figure 1. The x-ray crystal structure of **4a**.

Table 1. Three-component reaction between isatin **1a** with different α-amino acids and **3**[a]

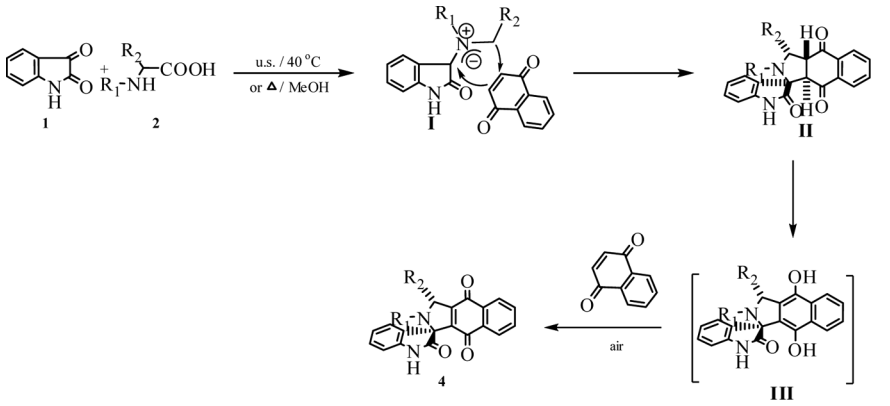
Entry	Amino acids		Products		Time (h)	Yield (%)[b]
1	L-Proline	**2a**		**4a**	1.5 1.5[c]	98 89
2	L-Isoleucine	**2b**		**4b**	5	80
3	L-Penylalanine	**2c**		**4c**	0.3	81
4	L-Tryptophan	**2d**		**4d**	5	88
5	L-Valine	**2e**		**5**	1	78

[a]All reactions were carried out in methanol under sonic waves.
[b]Isolated yields.
[c]The reaction was carried out in methanol under reflux conditions.

Table 2. The reaction of isatin **1a–g** with L-proline and **3**[a]

Entry	Isatin		Products		Time (h)	Yield (%)[b]
1		**1a**		**4a**	2	98
2		**1b**		**4e**	1	72
3		**1c**		**4f**	1.5	85
4		**1d**		**4g**	0.4	76
5		**1e**		**4h**	1	81
6		**1f**		**4i**	0.3	70
7		**1g**		**4j**	0.5	90

[a]All reactions were performed in methanol under sonic waves.
[b]Chemical yields are given for the isolated product.



Scheme 2. The plausible mechanism.

Finally, we also performed a similar three-component reaction of substituted isatins with L-proline and **3**, giving the desired products. The results are listed in Table 2. N-Benzylisatin **1 g** with **2a** and **3** afforded **4j** in 90% yield under sonic conditions (Table 2, entry 7).

We proposed the mechanism of the reaction of 1,4-naphthoquinone, α-amino acids, and isatins as shown in Scheme 2. At first, the intermediate anti-ylide **I** was formed by mixing α-amino acid and isatin under ultrasonic or reflux conditions. Followed the regio- and stereoselective cycloaddition of **I** with 1,4-naphthoquinone, cycloaddition product **II** was formed. In most cases, the initial addition product **II** tautomerized to the hydronaphthquinone **III**, which subsequently underwent rapid oxidation under air conditions, resulting in the formation of the desired product **4** (Scheme 2).

In conclusion, a series of 3-spiro[pyrrolidino-oxindoles] derivatives can be obtained via 1,3-dipolar cycloadditions of isatins, α-amino acids, and 1,4-naphthoquinone. We have unraveled some interesting reactivity profiles of the 1,4-naphthoquinone, thus achieving novel three-component reactions that offer a simple and efficient route to the synthesis of highly functionalized 1,4-naphthoquinone and pyrrolidinyl derivatives. It is interesting to note that a wide range of biologically active molecules contain naphthoquinone and pyrrolidinyl moieties. It is anticipated that the work presented in this article will arouse much interest in the area of 1,3-dipolar cycloaddition of 1,4-naphthoquinone.

EXPERIMENTAL

Melting points were recorded on an Electrothermal digital melting-point apparatus and are uncorrected. ^{1}H NMR (400-MHz) spectra were recorded on a Varian Mercury spectrometer in $CDCl_3$. Infrared (IR) spectra were obtained on a Nicolet Fourier transform (FT)–IR 500 spectrophotometer using KBr pellets. High-resolution mass spectra were obtained using a gas chromatography time-of-flight (GCT-TOF) mass spectrometry instrument.

General Procedure for Synthesis of 4

A mixture of isatin **1a** (0.147 g, 1 mmol), L-proline **2a** (0.115 g, 1 mmol), and 1,4-naphthoquinone **3** (0.158 g, 1 mmol) was irradiated in the presence of ultrasound in methanol (6 mL) at about 40 °C until the disappearance of the starting **3** (monitored by thin-layer chromatography, TLC). After standing 1 h, the reaction mixture was washed by cool water (2×25 mL) and cool ethanol (2×0.5 mL). The crude mixture was recrystallized from hot methanol to afford the pure product **4a** (0.349 g, yield: 98%).

Selected Data

Compound 4a. Orange-yellow needles; mp 221–223 °C; IR (KBr): ν 726, 762, 1030, 1121, 1470, 1590, 1612, 1666, 1738, 2889, 2967, 3169 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.72–1.78 (m, 1H, CH), 2.02–2.04 (m, 2H, CH_2), 2.47–2.50 (m, 1H, CH), 2.79–2.83 (m, 2H, CH_2), 5.07 (t, 1H, CH, $J = 7.6$ Hz), 6.94–7.03 (m, 3H), 7.33 (t, 1H, $J = 7.6$ Hz), 7.66–7.75 (m, 2H), 7.82 (br, s, 1H, NH), 7.90 (d, 1H, $J = 8.4$ Hz), 8.12 (d, 1H, $J = 6.8$ Hz). HRMS found: m/z 356.1169(M^+); calcd. for $C_{22}H_{16}N_2O_3$: M, 356.1161.

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 252479, for compound **4a**. Copies of this information may be obtained free of charge from the director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (e-mail: linstead@ccdc.cam.ac.uk or deposit@ccdc.cam.ac.uk; fax: +44 1223 336033). Structural parameters for **4a** MeOH are as follows: data collection: Rigaku Mercury CCD area detector; radiation: MoK, wavelength: $\lambda = 0.71070$ Å; crystal size: $0.50 \times 0.35 \times 0.12$ mm^3; $C_{23}H_{20}N_2O_4 \cdot C_3H_4O$, $Mr = 388.41$, monoclinic, space group p 21/c, $a = 13.684(3)$, $b = 8.0715(15)$, $c = 17.223(3)$ Å, $\alpha = 90.00$, $\beta = 99.624(4)$, $\gamma = 90.00$, $V = 1875.5(6)$ $Å^3$, $Z = 4$, Dcalc $= 1.376$ $g \cdot cm^{-3}$.

Compound 4b. Pink needles; mp 210–212 °C (dec); IR (KBr): ν 7710, 760, 1336, 1470, 1618, 1660, 1732, 2867, 2956, 3165, 3269 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ1.02 (d, 3H, CH_3, $J = 6.4$ Hz), 1.06 (d, 3H, CH_3, $J = 6.4$ Hz), 1.57–1.62 (m, 1H, CH), 1.91–1.92 (m, 1H, CH), 2.19 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 6.8$ Hz), 2.52 (br, s, 1H, NH), 4.99 (d, 1H, $J = 9.2$ Hz), 6.96 (d, 1H, $J = 7.6$ Hz), 7.05(t, 1H, $J = 7.6$ Hz), 7.17 (d, 1H, $J = 7.6$ Hz), 7.30 (d, 1H, $J = 7.6$ Hz), 7.66–7.75 (m, 2H), 7.90 (d, 1H, $J = 7.6$ Hz), 7.98 (br, s, 1H, NH), 8.10 (d, 1H, $J = 6.8$ Hz). HRMS found: m/z 372.1466 (M^+); calcd. for $C_{23}H_{20}N_2O_3$: M, 372.1474.

Compound 4c. Pink needles; mp 200–203 °C (dec); IR (KBr): ν 696, 740, 1264, 1470, 1621, 1687, 1705, 2868, 2960, 3067, 3180, 3290 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.35 (br, s, 1H, NH), 2.98–3.04 (m, 1H, CH), 4.03 (d, 1H, $J = 8.4$ Hz), 4.41–4.46 (m, 1H, CH), 5.07 (dd, 1H, CH, $J_1 = 7.2$ Hz, $J_2 = 8.0$ Hz), 6.35 (d, 1H, $J = 7.6$ Hz), 6.61 (t, 1H, $J = 7.6$ Hz), 6.74 (d, 1H, $J = 7.6$ Hz), 7.08 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 7.6$ Hz), 7.19 (dd, 1H, $J_1 = 6.8$ Hz, $J_2 = 7.6$ Hz), 7.28 (d, 2H, $J = 6.8$ Hz), 7.34 (d, 2H, $J = 6.8$ Hz), 7.43 (br, s, 1H, NH), 7.68–7.74 (m, 2H), 7.81 (t, 1H, $J = 7.6$ Hz), 8.14 (d, 1H, $J = 6.8$ Hz). HRMS found: m-1/z 405.1209 (M^+); calcd. for $C_{26}H_{18}N_2O_3$: M, 406.1317.

Compound 4d. Pink needles; mp 185–187 °C (dec); IR (KBr): ν 710, 740, 1180, 1471, 1619, 1665, 1738, 2909, 3283, 3407 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (br, s, 1H, NH), 3.38–3.50 (m, 1H, CH), 3.72–3.77 (m, 1H, CH), 5.29-5.32 (m, 1H, CH), 6.34 (d, 1H, $J = 7.2$ Hz), 6.80 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 7.2$ Hz), 6.85 (d, 2H, $J = 8.0$ Hz), 7.03–7.07(m, 2H), 7.16–7.21 (m, 2H), 7.28 (d, 2H, $J = 6.8$ Hz), 7.37 (d, 2H, $J = 8.0$ Hz), 7.62–7.65 (m, 2H), 7.69 (t, 1H, $J = 7.6$ Hz), 7.76 (t, 1H, $J = 7.2$ Hz), 8.10 (br, s, 1H, NH), 8.19 (d, 1H, $J = 6.4$ Hz). HRMS found: *m*-1/*m* 444.1303 (M^+); calcd. for $C_{28}H_{19}N_3O_3$: M, 445.1426.

Compound 4e. Pink needles; mp 253–255 °C; IR (KBr): ν 681, 724, 1083, 1450, 1606, 1661, 1724, 2880, 2964, 3213 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.61–1.678 (m, 1H, CH), 1.92–1.96 (m, 2H, CH_2), 2.39–2.42 (m, 1H, CH), 2.65–2.76 (m, 2H, CH_2), 4.98 (dd, 1H, CH, $J_1 = 8.4$ Hz, $J_2 = 7.6$ Hz), 6.74 (d, 1H, $J = 8.4$ Hz), 7.08 (d, 2H, $J = 8.4$ Hz), 7.61–7.70 (m, 3H), 7.90 (d, 1H, $J = 7.6$ Hz), 8.12 (d, 1H, $J = 6.8$ Hz). HRMS found: m/z 434.0038 (M^+); calcd. for $C_{22}H_{15}N_2O_3$ ^{79}Br: M, 434.0089.

Compound 4f. Pink needles; mp 220–221 °C; IR (KBr): ν 688, 761, 1084, 1132, 1494, 1609, 1665, 1712, 2863, 2970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.64–1.73 (m, 1H, CH), 1.90–1.94 (m, 2H, CH_2), 2.39–2.42 (m, 1H, CH), 2.71 (t, 2H, CH_2, $J = 6.8$ Hz), 3.24 (s, 3H, CH_3), 5.00 (dd, 1H, CH, $J_1 = 8.4$ Hz, $J_2 = 7.2$ Hz), 6.88–6.97 (m, 3H), 7.32 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 7.6$ Hz), 7.57–7.67 (m, 2H), 7.78 (d, 1H, $J = 7.6$ Hz), 8.12 (d, 1H, $J = 7.2$ Hz). HRMS found: *m*/*z* 370. 1333 (M^+); calcd. for $C_{23}H_{18}N_2O_3$: M, 370.1317.

Compound 4g. Pink needles; mp 193–195 °C (dec); IR (KBr): ν 758, 1176, 1356, 1466, 1609, 1667, 1723, 2873, 2970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.71–1.80 (m, 1H, CH), 1.98–2.02 (m, 2H, CH_2), 2.46–2.50 (m, 1H, CH), 2.79 (t, 2H, $J = 6.8$ Hz), 4.35–4.52 (m, 2H, CH_2), 5.08 (dd, 1H, CH, $J_1 = 8.4$ Hz, $J_2 = 7.6$ Hz), 5.28–5.46 (m, 2H), 5.89–5.97 (m, 1H, CH), 6.94–7.06 (m, 3H), 7.35 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 8.0$ Hz), 7.65–7.74 (m, 2H), 7.88 (d, 1H, $J = 7.6$ Hz), 8.11 (d, 1H, $J = 7.6$ Hz). HRMS found: *m*/*z* 396.1491 (M^+); calcd. for $C_{25}H_{20}N_2O_3$: M, 396.14741.

Compound 4h. Pink needles; mp 179–181 °C; IR (KBr): ν 754, 1137, 1335, 1357, 1466, 1609, 1666, 1728, 2868, 2933, 2951 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (dd, 3H, CH_3, $J_1 = 6.8$ Hz, $J_2 = 6.4$ Hz), 1.41 (s, 4H, $2CH_2$), 1.72–1.80 (m, 3H, CH, CH_2), 1.96–2.04 (m, 2H, CH_2), 2.44–2.51 (m, 1H, CH), 2.78 (dd, 2H, CH_2, $J_1 = 5.6$ Hz, $J_2 = 6.8$ Hz), 3.72–3.82 (m, 2H, CH_2), 5.05–5.09 (m, 1H, CH), 6.95–7.02 (m, 3H), 7.37 (dd, 1H, $J_1 = 6.8$ Hz, $J_2 = 7.6$ Hz), 7.64–7.74 (m, 2H), 7.87 (d, 1H, $J = 7.6$ Hz), 8.11 (d, 1H, $J = 6.4$ Hz). HRMS found: *m*/*z* 426.1934 (M^+); calcd. for $C_{27}H_{26}N_2O_3$: M, 426.1943.

Compound 4i. Pink needles; mp 182–184 °C (dec); IR (KBr): ν 756, 1167, 1353, 1467, 1607, 1668, 1722, 2878, 1924, 2955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.72–1.79 (m, 1H, CH), 2.02–2.03 (m, 2H, CH_2), 2.38 (t, 2H, CH_2, $J = 6.8$ Hz), 2.47–2.49 (m, 1H, CH), 2.78–2.80(m, 2H, CH_2), 3.52–3.64 (m, 2H, CH_2), 3.85–4.05 (m, 2H, CH_2), 5.06 (dd, 1H, CH, $J_1 = 7.6$ Hz, $J_2 = 8.0$ Hz), 6.96 (d, 1H, $J = 6.4$ Hz), 7.03 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 7.6$ Hz), 7.11 (d, 1H, $J = 7.6$ Hz), 7.40

(dd, 1H, $J_1 = 6.8$ Hz, $J_2 = 7.6$ Hz), 7.65–7.74 (m, 2H), 7.86 (d, 1H, $J = 6.8$ Hz), 8.11 (d, 1H, $J = 7.6$ Hz). HRMS found: m/z 476.0742 (M^+); calcd. for $C_{25}H_{21}N_2O_3$ ^{79}Br: M, 476.0736.

Compound 4j. Pink needles; mp 178–180 °C (dec); IR (KBr): ν 694, 759, 1175, 1346, 1466, 1609, 1664, 1729, 2863, 2965, 3062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.72–1.80 (m, 1H, CH), 1.99–2.04 (m, 2H, CH_2), 2.46–2.49 (m, 1H, CH), 2.76–2.80 (m, 2H, CH_2), 4.92–5.11 (m, 3H), 6.76 (d, 1H, $J = 7.6$ Hz), 6.96–7.02 (m, 2H), 7.26–7.44 (m, 6H), 7.66–7.74 (m, 2H), 7.91 (d, 1H, $J = 7.6$ Hz), 8.12 (d, 1H, $J = 7.2$ Hz). HRMS found: m/z 446.1613 (M^+); calcd. for $C_{29}H_{22}N_2O_3$: M, 446.1630.

Compound 5. Pink needles; mp 180–182 °C; IR (KBr): ν 751, 1292, 1472, 1585, 1623, 1681, 1711, 2870, 2960, 3224, 3296 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (d, 3H, CH_3, $J = 6.4$ Hz), 1.20 (d, 3H, CH_3, $J = 6.0$ Hz), 2.35 (br, s, 1H, NH), 2.70–2.79 (m, 1H, CH), 3.55–3.59 (m, 1H, CH), 3.65–3.68 (m, 1H, CH), 4.10 (d, 1H, $J = 7.6$ Hz), 6.27 (d, 1H, $J = 7.6$ Hz), 6.52 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 7.2$ Hz), 6.75 (d, 1H, $J = 8.0$ Hz), 7.04 (ddt, 1H, $J_1 = 8.0$ Hz, $J_2 = 7.6$ Hz), 7.62–7.76 (m, 3H), 7.80 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 5.6$ Hz), 8.10 (d, 1H, $J = 8.0$ Hz). HRMS found: m/z 360.1481 (M^+); calcd. for $C_{26}H_{20}N_2O_3$: M, 360.1474.

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