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# Metal-free [3+2+1]/[2+2+1] Biscyclization: Stereospecific Construction with Concomitant Functionalization of Indolizin-5(1*H*)-one

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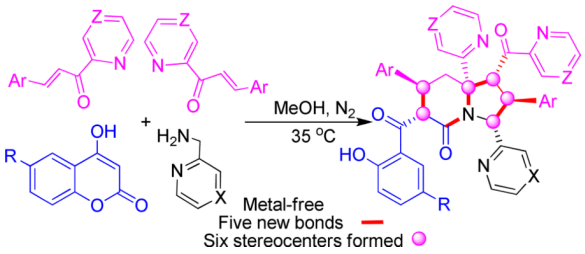
## Abstract




A metal-free [3+2+1]/[2+2+1] biscyclization strategy has been developed for the stereospecific construction with concomitant derivation of biologically significant indolizin-5(1*H*)-ones from simple and commercial starting materials. The transformations are notable because they can yield five new sigma bonds and six stereocenters including a quaternary carbon center in a single operation.

## INTRODUCTION

Azabicyclic ring systems are widely distributed in numerous natural products and synthetic compounds and exhibit a broad range of biological activities and pharmacological properties.[1] Among these systems, indolizin-5(1*H*)-one as an azabicyclic framework is well-represented, and this bicyclic core is frequently found in a number of biologically active natural alkaloids (Figure 1).[2] Moreover, indolizin-5(1*H*)-one derivatives would serve as cytotoxicity agents,[3] inhibitors of α-thrombin,[4] oligopeptidase inhibitors,[5] dipeptide mimetics,[6] integrin antagonists,[7] and inhibitors of aldosterone synthase.[8] Indolizin-5(1*H*)-ones have also been attractive synthetic targets because of their unique structures and

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**ASSOCIATED CONTENT**

**Supporting Information**

Copy of $^{1}H$ and $^{13}C$ NMR spectra for all products. X-ray CIF files for **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

powerful biological activities. Therefore, some research groups have devoted many efforts on the syntheses of these important products.[9]

In the meanwhile, indolizin-5(1*H*)-one bicyclic scaffolds have been proven to be key building block for the total synthesis of various indolizidine alkaloids.[10] Several approaches to bicyclic motifs have been developed, including the Schmidt reaction,[11] ring-closing metathesis reaction,[12] metal-catalyzed cycloaddition,[13] and Rh-catalyzed cyclization.[14] However, most of these approaches suffer from several noticeable drawbacks, such as the use of costly and toxic metal catalysts, multi-step procedures,[15] inaccessible substrates, and lack of effective derivation from the target skeleton. Thus, the development of metal-free strategies for the assembly and concomitant derivation of indolizin-5(1*H*)-ones from readily available starting materials with the aim of discovering new potentially interesting bioactive azabicyclic compounds would be a significant contribution to biomedical community.

In fact, creating molecular diversity and complexity from common and readily available reactants and forming various single and double bonds and rings in a single operation continue to be challenging in organic synthesis.[16] Multicomponent domino reactions (MDRs) have emerged as useful tools for this purpose; such reactions present many advantages over their classical counterparts, including high atom efficiency, minimizing time-consuming isolation of steps, and required high purity of precursors, etc.[17] Over the past few years, our group[18] and others[19] have developed various MDRs that can offer easy access to highly functionalized nitrogen-containing compounds of chemical and pharmaceutical interest. We recently discovered a novel $ABC_2$ type MDR[20] to give tricyclic pyrro[1,2-*a*]quinoline core of gephyrotoxin, an alkaloid isolated from the tropical frog *Dendrobates histrionicus*.[21] Considering the open-ring reaction of 4-hydroxy-2*H*-chrome-2-one treated with amine,[22] we hypothesized that the reactions of 4-hydroxy-2*H*-chromen-2-one, 3-aryl-1-(pyridin-2-yl)prop-2-en-1-one and pyridin-2-ylmethanamine or pyrazin-2-ylmethanamine will not only provide an efficient construction of bicyclic indolizin-5(1*H*)-one scaffolds, the parent core of Sessilifollamide J isolated from *Stemona sessilifolia*,[2h] but also provide a facile method of deriving this framework through simultaneous introduction of pyridine and pyrazine rings with biological importance.[23]

## RESULTS AND DISCUSSION

According to the analysis described above, we began our investigation of this multi-component domino reaction by first reacting 3-(4-chlorophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (**1a**), 4-hydroxy-2*H*-chromen-2-one (**2a**), and (pyridin-2-yl)methanamine (**3a**) to determine optimal conditions (Table 1). The catalyst-free model reaction was carried out at room temperature by using DMF as a solvent under inert gas protection. The desired compound **4a** was obtained after chromatographic separation in 55 % yield, and its structure was confirmed by $^1$H NMR, $^{13}$C NMR, and HRMS (Table 1, entry 1). We then examined the solvent effect of chemical yield. Compared with DMF, EtOH, $CH_3CN$, $CH_2Cl_2$, and THF, the use of anhydrous MeOH as a solvent provided optimal yield (Table 1, entry 3). To optimize the reaction conditions further, the optimal reaction temperature was determined. Results revealed that 35 °C is the optimal reaction temperature for the bicyclization reaction with highest yield of 79 % (Table 1, entry 8).

We next explored the scope of present multicomponent domino reactions under the above optimized conditions (Table 2). A range of 3-aryl-1-(pyridin-2-yl)prop-2-en-1-ones were smoothly converted into their corresponding products in good yields (Table 2, **entries 2–7**). When 3-aryl-1-(pyrazin-2-yl)prop-2-en-1-ones were used, the corresponding indolizin-5(1*H*)-ones were obtained (Table 2, **entries 8–10**). We then replaced pyridin-2-ylmethanamine (**3a**) with pyrazin-2-ylmethanamine for examination, and the target

compounds (Table 2, **entries 11, 12**) were formed in good yields of 80 % and 78 %, respectively. The use of either 4-hydroxy-6-methyl-2*H*-chromen-2-one or 6-bromo-4-hydroxy-2*H*-chromen-2-one in place of 4-hydroxy-2*H*-chromen-2-one (**2a**) also smoothly afforded the corresponding products under the same conditions (Table 2, **entries 13–18**). As shown in Table 2, for 3-aryl-1-(pyridin-2-yl)prop-2-en-1-ones and 4-hydroxy-2*H*-chromen-2-one, the electronic properties of both electron-donating groups and electron-withdrawing groups in the aryl substituent exerted very limited influence on the reactivity of reactants.

To confirm the stereochemistry of the indolizin-5(1*H*)-ones **4**, the relative stereo-configuration of a single crystal of **4a** was established by X-ray diffractional analysis. As shown in the crystal structure of **4a** (Figure S1 in Supporting Information), six stereocenters in the molecular structure and two aryl groups in anti-configuration have been successfully formed.

According to the experimental outcomes, a mechanism hypothesis for this domino reaction is proposed as shown in Scheme 1. The first step of the mechanism is believed to be intermolecular Michael-addition between 4-hydroxy-2*H*-chromen-2-one (**2**) and 3-aryl-1-heteroarylprop-2-en-1-one (**1**) to generate intermediate **5**. Next, the intermediate **6** is formed by intermolecular nucleophilic addition of intermediate **5** to **3**, followed by an intramolecular nucleophilic addition to afford intermediate **7**. Intermediate **8** was formed *via* a ring-opening of **7** followed by dehydration to give intermediate **9**. The following step would involve intramolecular 1,4-addition or the one-step [3+2] cycloaddition to give trhe final product.

## CONCLUSION

We have developed a metal-free [3+2+1]/[2+2+1] biscyclization strategy for the synthesis of indolizidin-5(1*H*)-one bicyclic scaffolds. This methodology yields indolizidin-5(1*H*)-ones with different substituent groups from readily accessible commercial starting materials under one-pot multi-component systems. The transformations are notable because they can yield five new sigma bonds and six stereocenters including a quaternary carbon center.

## EXPERIMENTAL SECTION

### General information

All reactions were carried out in an nitrogen atmosphere and solvents were dried according to established procedures. Thin layer chromatography was performed on silica gel GF254 plates. Silica gel (300–400 mesh) was used for column chromatography. Melting points are uncorrected. $^{1}$H NMR spectra were measured on 400 MHz and $^{13}$C NMR spectra were recorded on 100 MHz in $CDCl_3$. IR spectra are reported in $cm^{-1}$. HRMS were performed on TOF mass spectrometer with an ESI source. The X-ray single-crystal diffraction was performed on CCD area detector.

### General procedure for synthesis of 4

A mixture of 3-aryl-1-(pyridin-2-yl)prop-2-en-1-ones or 3-aryl-1-(pyrazin-2-yl)prop-2-en-1-ones (**1**) (2.0 mmol) prepared according to the literature methods,[24] 4-hydroxy-2*H*-chromen-2-one or 4-hydroxy-6-methyl-2*H*-chromen-2-one or 6-bromo-4-hydroxy-2*H*-chromen-2-one (**2**) (1.0 mmol) and 2-(aminomethyl)pyridine or pyrazin-2-ylmethanamine (**3**) (1.0 mmol) was dissolved in 5 mL anhydrous methanol in a 25-mL 3-mouth flask, stirred with nitrogen incoming, heated to 35 °C progressively. The mixtures were stirred for a certain time (monitored by TLC). Then the solvent was removed in vacuum, and the residue

was separated by column chromatography on silica gel (petroleum ether/ethyl acetate 4:1 v/v) to afford the producrts **4**.

### 2,7-Bis(4-chlorophenyl)-6-(2-hydroxybenzoyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4a)

White solid (583 mg, 79% yield): m.p. 278–280 °C; IR (KBr): 3049, 1696, 1671, 1585, 1492, 1435, 1348, 1232, 1160, 1091, 1033, 1012, 993, 955, 867, 776, 751, 688, 607, 571 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.90 (s, 1H), 9.51 (d, *J* = 8.0 Hz, 1H), 8.73 (d, *J* = 4.8 Hz, 1H), 8.70–8.68 (m, 1H), 8.23 (d, *J* = 4.8 Hz, 1H), 8.02 (td, *J* = 8.0, 2.0 Hz, 1H), 7.77–7.71 (m, 2H), 7.50–7.42 (m, 2H), 7.35–7.23 (m, 3H), 7.19–7.15 (m, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.91–6.89 (m, 3H), 6.83–6.75 (m, 2H), 6.38 (d, *J* = 8.4 Hz, 2H), 5.62 (d, *J* = 12.8 Hz, 1H), 5.18 (d, *J* = 11.2 Hz, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.21–4.13 (m, 2H), 3.42 (dd, *J* = 14.4, 3.2 Hz, 1H), 3.28 (dd, *J* = 14.4, 11.2 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 200.6, 196.9, 168.8, 162.7, 160.3, 157.7, 154.2, 149.3, 148.7, 148.3, 141.5, 137.3, 136.9, 136.3, 136.2, 135.4, 133.2, 132.0, 129.7, 129.5, 128.8, 128.7, 128.4, 127.3, 124.0, 123.3, 122.9, 122.7, 122.3, 120.2, 118.9, 118.6, 74.4, 69.4, 61.5, 53.1, 50.1, 44.4, 39.6; HRMS (ESI) m/z: Calcd. for $C_{43}H_{32}Cl_2N_4O_4$ $[M+Na]^+$ 761.1698, found: 761.1707.

### 2,7-Bis(2-chlorophenyl)-6-(2-hydroxybenzoyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4b)

White solid (561 mg, 76% yield): m.p. 249–250 °C; IR (KBr): 3031, 1681, 1644, 1587, 1541, 1474, 1438, 1403, 1346, 1288, 1236, 1198, 1159, 1101, 1036, 995, 956, 886, 783, 749, 564 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.96 (s, 1H), 8.93 (d, *J* = 7.2 Hz, 1H), 8.60–8.59 (m, 2H), 8.26 (d, *J* = 4.0 Hz, 1H), 7.93–7.88 (m, 2H), 7.77 (td, *J* = 7.6, 1.6 Hz, 1H), 7.56–7.53 (m, 1H), 7.46 (td, *J* = 7.6, 1.6 Hz, 2H), 7.37 (ddd, *J* = 6.0, 4.8, 0.8 Hz, 1H), 7.32–7.27 (m, 2H), 7.21–7.10 (m, 5H), 7.07–6.98 (m, 4H), 6.79 (d, *J*= 7.6 Hz, 1H), 6.69–6.50 (m, 1H), 5.72 (d, *J* = 12.8 Hz, 1H), 5.46 (d, *J* = 9.6 Hz, 1H), 4.94 (dd, *J* = 10.8 Hz, 1H), 4.69 (dd, *J* = 12.4, 10.8 Hz, 1H), 3.76 (td, *J* = 10.8, 3.6 Hz, 1H), 2.99–2.88 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 202.3, 196.2, 168.2, 162.9, 158.9, 157.9, 155.5, 149.2, 148.1, 147.1, 138.9, 136.8, 136.6, 136.0, 135.9, 133.7, 131.5, 130.2, 130.0, 128.2, 127.9, 127.3, 127.0, 126.7, 125.8, 123.3, 122.6, 122.6, 122.4, 120.3, 118.7, 118.0, 74.3, 60.6, 56.0, 44.2, 36.9; HRMS (ESI) m/z: Calcd. for $C_{43}H_{32}Cl_2N_4O_4$ $[M+Na]^+$ 761.1698, found: 761.1726.

### 6-(2-Hydroxybenzoyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)-2,7-dip-tolylhexahydroindolizin-5(1*H*)-one (4c)

White solid (565 mg, 81% yield): m.p. > 300 °C; IR (KBr): 3011, 1694, 1667, 1589, 1515, 1405, 1341, 1157, 1034, 994, 953, 884, 856, 747, 666 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.97 (s, 1H), 9.54 (d, *J* = 7.2 Hz, 1H), 8.72 (s, 1H), 8.67 (s, 1H), 8.24 (s, 1H), 8.03–7.99 (m, 1H), 7.70 (s, 2H), 7.43–7.29 (m, 4H), 7.23–7.13 (m, 2H), 6.98–6.94 (m, 4H), 6.88–6.86 (m, 1H), 6.79–6.72 (m, 4H), 6.33 (d, *J* = 6.4 Hz, 2H), 5.66 (d, *J* = 12.8 Hz, 1H), 5.20 (d, *J* = 10.8 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.16–4.12 (m, 2H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.33–3.26 (m, 1H), 2.18 (s, 3H), 2.10 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 201.1, 197.2, 169.2, 162.59, 160.7, 158.2, 154.4, 149.1, 149.1, 148.6, 148.2, 140.2, 137.0, 136.8, 136.6, 136.0, 135.9, 135.7, 135.6, 133.9, 133.8, 129.9, 129.2, 128.9, 128.1, 127.2, 127.0, 124.0, 123.3, 122.6, 122.4, 122.3, 120.4, 118.8, 118.4, 74.5, 69.6, 61.6, 53.4, 50.4, 44.8, 40.0, 21.0, 20.8; HRMS (ESI) m/z: Calcd. for $C_{45}H_{38}N_4O_4$ $[M+Na]^+$ 721.2791, found: 721.2814.

### 6-(2-Hydroxybenzoyl)-2,7-bis(4-methoxyphenyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4d)

White solid (569 mg, 78% yield): m.p. 272–273 °C; IR (KBr): 3010, 1669, 1637, 1587, 1514, 1436, 1344, 1251, 1179, 1158, 1032, 827, 744, 622 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.98 (s, 1H), 9.54 (d, *J* = 7.6 Hz, 1H), 8.72 (d, *J* = 3.6 Hz, 1H), 8.68 (d, *J* = 4.4 Hz, 1H), 8.26 (d, *J* = 3.6 Hz, 1H), 8.01 (t, *J* = 7.6 Hz, 1H), 7.73–7.68 (m, 2H), 7.46–7.34 (m, 2H), 7.35–7.27 (m, 2H), 7.23–7.22 (m, 1H), 7.15–7.12 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.80–6.74 (m, 2H), 6.66 (d, *J* = 8.4 Hz, 2H), 6.46 (d, *J* = 8.8 Hz, 2H), 6.37 (d, *J* = 8.8 Hz, 2H), 5.63 (d, *J* =13.2 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.18–4.07 (m, 2H), 3.66 (s, 3H), 3.60 (s, 3H), 3.46–3.41 (m, 1H), 3.31–3.25 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 201.2, 197.3, 169.1, 162.6, 160.7, 158.7, 158.3, 157.8, 154.4, 149.2, 148.6, 148.2, 137.1, 136.70, 136.1, 136.0, 135.2, 129.9, 129.2, 128.8, 128.3, 127.0, 124.0, 123.3, 122.7, 122.5, 122.3, 120.4, 118.8, 118.4, 113.9, 113.6, 74.4, 69.6, 61.7, 55.1, 55.1, 53.513, 50.1, 44.8, 39.7; HRMS (ESI) m/z: Calcd. for $C_{45}H_{38}N_4O_6$ $[M+Na]^+$ 753.2689, found: 753.2720.

### 2,7-Bis(3,4-dimethoxyphenyl)-6-(2-hydroxybenzoyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4e)

White solid (624 mg, 79% yield): m.p. 242–243 °C; IR (KBr): 3049, 1696, 1672, 1586, 1518, 1491, 1451, 1435, 1404, 1438, 1269, 1159, 1091, 1031, 1072, 933, 886, 867, 853, 824, 786, 750, 662 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 12.00 (s, 1H), 9.55 (d, *J* = 8.0 Hz, 1H), 8.74–8.70 (m, 2H), 8.30 (d, *J* = 4.0 Hz, 1H), 8.03 (t, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 4.0 Hz, 2H), 7.49–7.42 (m, 2H), 7.32–7.28 (m, 2H), 7.25–7.22 (m, 1H), 7.17–7.14 (m, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.81–6.68 (m, 3H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.49 (s, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 6.10 (s, 1H), 6.04 (d, *J* = 8.0 Hz, 1H), 5.68 (d, *J* = 12.8 Hz, 1H), 5.18 (d, *J* = 11.2 Hz, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.18–4.07 (m, 2H), 3.74 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 3.54 (s, 3H), 3.54–3.50 (m, 1H), 3.36–3.29 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 201.2, 197.3, 169.0, 162.66, 160.86, 158.28, 154.37, 149.20, 148.59, 148.47, 148.22, 148.03, 147.31, 137.11, 136.79, 136.2, 136.0, 135.6, 129.6, 129.3, 127.1, 124.3, 123.6, 122.6, 122.5, 122.4, 120.4, 119.7, 119.4, 118.8, 118.5, 111.6, 111.2, 110.9, 110.8, 74.3, 69.6, 61.4, 55.7, 50.4, 44.5, 40.4; HRMS (ESI) m/z: Calcd. for $C_{47}H_{42}N_4O_8$ $[M+Na]^+$ 813.2900, found: 813.2907.

### 2,7-Bis(2,4-dichlorophenyl)-6-(2-hydroxybenzoyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4f)

White solid (645 mg, 80% yield): m.p. 246–247 °C; IR (KBr): 3057, 1680, 1647, 1587, 1474, 1438, 1406, 1345, 1313, 1281, 1251, 1233, 1197, 1160, 1106, 1046, 995, 954, 884, 863, 780, 746, 727, 688, 662, 619 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.89 (s, 1H), 8.81 (s, 1H), 8.59 (s, 2H), 8.27 (s, 1H), 7.94–7.91 (m, 2H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.52–7.47 (m, 1H), 7.41–7.30 (m, 3H), 7.20–7.03 (m, 8H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.74 (t, *J* = 8.0 Hz, 1H), 5.66 (d, *J* = 11.6 Hz, 1H), 5.45–5.38 (m, 1H), 4.91 (d, *J* = 10.8 Hz, 1H), 4.65 (t, *J* = 12.0 Hz, 1H), 3.77–3.72 (m, 1H), 2.93–2.77 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 201.8, 196.0, 167.9, 162.9, 158.6, 157.5, 155.3, 149.2, 148.1, 147.1, 137.5, 136.9, 136.8, 136.2, 136.1, 134.5, 134.4, 133.3, 131.5, 130.0, 129.8, 128.7, 127.7, 127.4, 126.8, 125.7, 123.4, 122.8, 122.6, 122.5, 120.2, 119.0, 118.2, 74.2, 55.6, 44.1, 36.3, 31.0; HRMS (ESI) m/z: Calcd. for $C_{43}H_{30}Cl_4N_4O_4$ $[M+Na]^+$ 831.0889, found: 831.0906.

### 2,7-Bis(2,3-dimethoxyphenyl)-6-(2-hydroxybenzoyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4g)

White solid (593 mg, 75% yield): m.p. 264–266 °C; IR (KBr): 3049, 1670, 1632, 1585, 1478, 1434, 1399, 1338, 1264, 1223, 1160, 1089, 1067, 995, 872, 779, 746, 667, 617, 520

cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 11.98 (s, 1H), 9.69 (d, *J* = 8.0 Hz, 1H), 8.72 (s, 1H), 8.65 (s, 1H), 8.14 (s, 1H), 8.01 (t, *J* = 8.0 Hz, 1H), 7.65 (s, 2H), 7.50–7.26 (m, 4H), 7.18–7.11 (m, 2H), 6.87–6.78 (m, 5H), 6.68–6.67 (m, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 6.46–6.42 (m, 1H), 5.83 (d, *J* = 12.8 Hz, 1H), 5.36 (d, *J* = 11.2 Hz, 1H), 5.23 (d, *J* = 7.2 Hz, 1H), 4.70–4.66 (m, 2H), 4.47 (t, *J* = 12.0 Hz, 1H), 3.89 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.52 (s, 3H), 3.31 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 201.1, 197.4, 169.2, 162.6, 161.0, 158.7, 154.4, 152.7, 152.6, 149.1, 148.6, 148.5, 148.1, 146.7, 136.9, 136.5, 136.0, 135.9, 130.2, 130.0, 126.9, 123.7, 123.4, 123.3, 122.4, 122.4, 122.1, 121.2, 118.8, 118.4, 117.3, 111.6, 110.2, 74.4, 68.6, 60.8, 60.6, 60.5, 55.6, 55.5, 46.1, 44.4, 32.5, 32.5; HRMS (ESI) m/z: Calcd. for $C_{47}H_{42}N_4O_8$ $[M+Na]^+$ 813.2900, found: 813.2929.

### 2,7-Bis(4-bromophenyl)-6-(2-hydroxybenzoyl)-8*a*-(pyrazin-2-yl)-1-(pyrazine-2-carbonyl)-3-(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4h)

White solid (637 mg, 77% yield): m.p. > 300 °C; IR (KBr): 3046, 1697, 1632, 1591, 1574, 1488, 1437, 1395, 1338, 1302, 1245, 1206, 1157, 1073, 1055, 1010, 962, 859, 802, 748, 633, 610 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 11.82 (s, 1H), 10.00 (s, 1H), 9.13 (s, 1H), 8.74 (s, 1H), 8.66–8.62 (m, 3H), 8.33 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.37–7.26 (m, 5H), 7.16 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 3H), 6.75 (t, *J* = 8.0 Hz, 1H), 5.32–5.26 (m, 2H), 4.71 (d, *J* = 10.4 Hz, 1H), 4.21 (t, *J* = 12.0 Hz, 1H), 3.12–3.08 (m, 1H), 2.88–2.83 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 201.5, 195.5, 167.4, 163.0, 156.8, 154.0, 149.6, 149.0, 147.8, 147.6, 144.8, 144.2, 142.9, 141.8, 140.4, 137.1, 136.4, 136.3, 132.1, 131.9, 131.8, 129.8, 128.3, 124.7, 123.0, 121.5, 121.3, 120.1, 119.1, 118.3, 72.6, 70.5, 61.5, 57.0, 48.6, 43.9, 39.5; HRMS (ESI) m/z: Calcd. for $C_{41}H_{30}Br_2N_6O_4$ $[M+Na]^+$ 853.0572, found: 853.0567.

### 2,7-Bis(4-chlorophenyl)-6-(2-hydroxybenzoyl)-8*a*-(pyrazin-2-yl)-1-(pyrazine-2-carbonyl)-3-(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4i)

White solid (548 mg, 74% yield): m.p. 293–294 °C; IR (KBr): 3050, 1699, 1633, 1591, 1573, 1492, 1439, 1400, 1338, 1302, 1248, 1207, 1156, 1092, 1054, 962, 902, 880, 858, 824, 750, 716, 680, 665, 616 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 11.82 (s, 1H), 10.00 (s, 1H), 9.13 (d, *J* = 1.2 Hz, 1H), 8.74 (d, *J* = 2.4 Hz, 1H), 8.67–8.61 (m, 3H), 8.34 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.18–7.12 (m, 5H), 7.07 (d, *J* = 8.0 Hz, 3H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.74 (t, *J* = 7.6 Hz, 1H), 5.33–5.27 (m, 2H), 4.71 (d, *J* = 10.0 Hz, 1H), 4.25–4.19 (m, 1H), 3.15–3.09 (m, 1H), 2.90–2.81 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 201.5, 195.5, 167.4, 163.0, 156.8, 154.1, 149.6, 149.0, 147.8, 147.7, 144.8, 144.2, 142.8, 141.8, 139.9, 137.1, 136.2, 135.9, 133.3, 133.2, 131.8, 129.4, 129.2, 129.0, 128.0, 124.7, 122.9, 120.1, 119.1, 118.3, 72.6, 70.6, 61.6, 57.1, 48.5, 44.0, 39.4; HRMS (ESI) m/z: Calcd. for $C_{41}H_{30}Cl_2N_6O_4$ $[M+Na]^+$ 763.1603, found: 763.1626.

### 2,7-Bis(2,3-dimethoxyphenyl)-6-(2-hydroxybenzoyl)-8*a*-(pyrazin-2-yl)-1-(pyrazine-2-carbonyl)-3-(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4j)

White solid (650 mg, 82% yield): m.p. 228–229 °C; IR (KBr): 3044, 1698, 1587, 1480, 1387, 1270, 1158, 1090, 1016, 957, 891, 877, 861, 834, 817, 794, 742, 670, 666, 650, 625, 605 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 11.93 (s, 1H), 10.15 (s, 1H), 9.11 (s, 1H), 8.65 (s, 2H), 8.59 (s, 1H), 8.51 (s, 1H), 8.32 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.11–7.10 (m, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.92–6.84 (m, 3H), 6.79–6.65 (m, 5H), 5.48 (d, *J* = 12.8 Hz, 1H), 5.39 (d, *J* = 10.8 Hz, 1H), 5.01(d, *J* = 10.4 Hz, 1H), 4.52 (t, *J* = 11.2 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.51–3.48 (m, 1H), 3.45 (s, 3H), 3.33 (s, 3H), 2.81 (t, *J* = 13.2 Hz, 1H), 2.70 (d, *J* = 10.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl3): δ 202.3, 195.9, 168.0, 162.9, 158.1, 154.7, 152.8, 152.8, 149.5, 149.5, 148.4,

148.0, 147.2, 146.8, 144.8, 143.6, 142.7, 141.5, 136.6, 136.0, 134.5, 131.8, 130.8, 124.3, 123.8, 123.8, 122.5, 120.8, 120.3, 118.9, 118.8, 118.0, 111.6, 111.3, 73.0, 70.0, 61.1, 60.5, 60.3, 55.6, 55.0, 44.6, 44.5, 34.4; HRMS (ESI) m/z: Calcd. for $C_{45}H_{40}N_6O_8$ $[M+Na]^+$ 815.2805, found: 815.2816.

### 2,7-Bis(4-chlorophenyl)-6-(2-hydroxybenzoyl)-1-picolinoyl-3-(pyrazin-2-yl)-8*a*-(pyridin-2-yl) hexahydroindolizin-5(1*H*)-one (4k)

White solid (591 mg, 80% yield): m.p. > 300 °C; IR (KBr): 3048, 1667, 1584, 1527, 1592, 1447, 1435, 1342, 1291, 1260, 1234, 1158, 1092, 1034, 1014, 909, 882, 824, 788, 696, 663, 647, 618, 572, 522 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.82 (s, 1H), 8.95 (d, *J* = 7.6 Hz, 1H), 8.62–8.60 (m, 2H), 8.39 (d, *J* = 2.4 Hz, 1H), 8.21–8.18 (m, 2H), 7.90 (td, *J* = 8.0, 1.6 Hz, 1H), 7.69–7.65 (m, 2H), 7.38–7.35 (m, 1H), 7.28–7.24 (m, 1H), 7.19– 7.17 (m, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.72–6.68 (m, 1H), 6.33 (d, *J* = 8.4 Hz, 2H), 5.57 (d, *J* = 12.8 Hz, 1H), 5.21 (d, *J* = 11.2 Hz, 1H), 4.20 (d, *J* = 10.8 Hz, 1H), 4.22–4.10 (m, 2H), 3.36–3.23 (m, 2H); $^{13C}$ NMR (100 MHz, $CDCl_3$): δ 199.5, 195.5, 168.0, 161.7, 159.0, 153.0, 152.6, 147.7, 147.5, 144.5, 142.9, 142.8, 140.1, 136.2, 135.9, 135.5, 133.5, 132.9, 131.2, 128.4, 128.4, 128.1, 127.6, 127.4, 126.4, 122.0, 121.5, 121.3, 119.0, 117.9, 117.7, 73.3, 66.0, 60.6, 51.9, 49.0, 43.2, 38.8; HRMS (ESI) m/z: Calcd. for $C_{42}H_{31}Cl_2N_5O_4$ $[M+Na]^+$ 762.1651, found: 762.1630.

### 2,7-Bis(2,3-dimethoxyphenyl)-6-(2-hydroxybenzoyl)-1-picolinoyl-3-(pyrazin-2-yl)-8*a*-(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4l)

White solid (617 mg, 78% yield): m.p. 290–291 °C; IR (KBr): 2936, 1691, 1627, 1584, 1480, 1444, 1409, 1366, 1335, 1307, 1287, 1263, 1220, 1161, 1089, 1063, 1038, 997, 966, 945, 907, 860, 825, 795, 749, 683, 618 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 12.00 (s, 1H), 8.77 (d, *J* = 8.0 Hz, 1H), 8.57 (d, *J* = 4.0 Hz, 2H), 8.37 (d, *J* = 2.4 Hz, 1H), 8.29 (d, *J* = 4.0 Hz, 1H), 8.26 (s, 1H), 7.94–7.89 (m, 2H), 7.75 (td, *J* = 8.0, 1.6 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.37–7.34 (m, 1H), 7.31–7.26 (m, 1H), 7.21 (dd, *J* = 7.2, 4.8 Hz, 1H), 6.90–6.84 (m, 3H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.72–6.62 (m, 4H), 5.69 (d, *J* = 12.8 Hz, 1H), 5.40 (d, *J* = 10.8 Hz, 1H), 4.99 (d, *J* = 10.8 Hz, 1H), 4.40 (dd, *J* = 12.4, 11.2 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.56 (s, 3H), 3.50 – 3.43 (m, 1H), 3.35 (s, 3H), 2.94 – 2.85 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) : δ 202.9, 196.5, 168.7, 162.8, 159.3, 155.6, 154.7, 152.8, 148.3, 148.1, 147.1, 147.0, 145.2, 143.9, 143.2, 136.7, 136.5, 135.8, 135.0, 131.8, 130.5, 126.6, 125.4, 124.2, 124.0, 122.6, 122.4, 120.6, 120.4, 119.4, 118.8, 117.9, 111.6, 111.3, 74.4, 67.6, 60.5, 60.3, 60.2, 55.6, 56.0, 55.4, 44.4, 44.2, 35.0; HRMS (ESI) m/z: Calcd. for $C_{46}H_{41}N_5O_8$ $[M+Na]^+$ 814.2853, found: 814.2825.

### 6-(5-Bromo-2-hydroxybenzoyl)-2,7-bis(4-chlorophenyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4m)

White solid (669 mg, 82% yield): m.p. 287–289 °C; IR (KBr): 3049, 1671, 1587, 1570, 1493, 1468, 1435, 1412, 1346, 1287, 1174, 1093, 1048, 1014, 899, 857, 826, 779, 747, 697, 626 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.64 (s, 1H), 9.81 (d, *J* = 8.0 Hz, 1H), 8.88 (d, *J* = 4.0 Hz, 1H), 8.68 (d, *J* = 4.0 Hz, 1H), 8.27 (d, *J* = 4.0 Hz, 1H), 8.11–8.07 (m, 1H), 7.76–7.70 (m, 2H), 7.54–7.38 (m, 4H), 7.30–7.26 (m, 1H), 7.22–7.19 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 9.2 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 2H), 5.62 (d, *J* = 13.2 Hz, 1H), 5.18 (d, *J* = 8.8 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.15–4.07 (m, 2H), 3.44 (dd, *J* = 14.4, 3.2 Hz, 1H), 3.32–3.24 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 199.4, 196.8, 168.3, 161.2, 160.3, 157.3, 154.0, 149.7, 148.6, 148.4, 141.5, 138.7, 137.5, 136.8, 136.2, 135.1, 133.2, 132.5, 132.1, 129.5, 128.8, 128.6, 128.4, 127.3, 123.3, 123.3, 123.0, 122.7, 122.2, 121.3, 120.5, 110.6, 74.3, 69.0, 61.5,

53.6, 50.4, 44.5, 39.0; HRMS (ESI) m/z: Calcd. for $C_{43}H_{31}BrCl_2N_4O_4$ $[M+Na]^+$ 839.0803, found: 839.0764.

### 6-(5-Bromo-2-hydroxybenzoyl)-2,7-bis(4-fluorophenyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4n)

White solid (596 mg, 76% yield): m.p. 247–248 °C; IR (KBr): 3046, 1670, 1585, 1510, 1348, 1231, 995, 831, 787, 745, 626 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.67 (s, 1H), 9.82 (d, *J* = 8.0 Hz, 1H), 8.87 (d, *J* = 8.0 Hz, 1H), 8.69 (d, *J* = 4.0 Hz, 1H), 8.28 (d, *J* = 4.0 Hz, 1H), 8.09 (t, *J* = 4.0 Hz, 1H), 7.76–7.71 (m, 2H), 7.54–7.37 (m, 4H), 7.30–7.26 (m, 1H), 7.20 (dd, *J* = 7.2, 5.2 Hz, 1H), 7.09 (dd, *J* = 8.4, 5.2 Hz, 2H), 6.87–6.79 (m, 3H), 6.72–6.64 (m, 3H), 6.43–6.40 (m, 2H), 5.63 (d, *J* = 12.8 Hz, 1H), 5.17 (d, *J* = 10.8 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.15–4.07 (m, 2H), 3.45 (dd, *J* = 7.2, 5.2 Hz, 1H), 3.31–3.25 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 199.6, 196.9, 168.4, 161.3, 160.4, 157.5, 154.1, 149.7, 148.7, 148.4, 138.7, 137.5, 136.9, 136.2, 132.6, 132.4, 132.3, 129.8, 129.7, 128.9, 128.8, 127.3, 123.4, 123.3, 123.0, 122.7, 122.3, 121.4, 120.5, 115.7, 115.4, 115.3, 115.0, 110.6, 74.3, 69.2, 61.6, 53.9, 50.4, 44.7, 39.0; HRMS (ESI) m/z: Calcd. for $C_{43}H_{31}BrF_2N_4O_4$ $[M+Na]^+$ 807.1394, found: 807.1395.

### 6-(5-Bromo-2-hydroxybenzoyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)-2,7-dip-tolylhexahydroindolizin-5(1*H*)-one (4o)

White solid (644 mg, 83% yield): m.p. 275–276 °C; IR (KBr): 3012, 1696, 1669, 1587, 1570, 1515, 1468, 1435, 1404, 1344, 1287, 1175, 1046, 995, 890, 819, 780, 747, 713, 689, 627 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.73 (s, 1H), 9.84 (d, *J* = 8.0 Hz, 1H), 8.86 (d, *J* = 4.4 Hz, 1H), 8.67 (d, *J* = 4.8 Hz, 1H), 8.29 (d, *J* = 4.0 Hz, 1H), 8.09 (t, *J* = 8.0 Hz, 1H), 7.74–7.68 (m, 2H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.47–7.36 (m, 3H), 7.28–7.26 (m, 1H), 7.17 (dd, *J* = 7.2, 5.2 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.79 (t, *J* = 8.0 Hz, 3H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.32 (d, *J* = 8.0 Hz, 2H), 5.68 (d, *J* = 12.8 Hz, 1H), 5.21 (d, *J* = 11.2 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.13–4.03 (m, 2H), 3.46 (dd, *J* = 14.4, 3.2 Hz, 1H), 3.33–3.26 (m, 1H), 2.20 (s, 3H), 2.13 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 200.0, 197.3, 168.9, 161.4, 160.9, 158.0, 154.5, 149.8, 148.9, 148.6, 140.4, 138.6, 137.5, 137.1, 136.9, 136.3, 136.0, 133.8, 132.9, 129.5, 129.2, 128.3, 127.4, 127.3, 123.6, 123.5, 123.0, 122.7, 122.5, 121.8, 120.6, 110.7, 74.7, 69.4, 61.8, 54.0, 51.0, 45.1, 39.6, 21.2, 21.0; HRMS (ESI) m/z: Calcd. for $C_{45}H_{37}BrN_4O_4$ $[M+Na]^+$ 799.1896, found: 799.1864.

### 6-(5-Bromo-2-hydroxybenzoyl)-2,7-bis(4-methoxyphenyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4p)

White solid (654 mg, 81% yield): m.p. 169–170 °C; IR (KBr): 3047, 1670, 1612, 1586, 1513, 1486, 1435, 1401, 1343, 1290, 1177, 1114, 1032, 995, 882, 828, 780, 746, 716, 688, 672, 618 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.75 (s, 1H), 9.85 (d, *J* = 8.0 Hz, 1H), 8.87 (d, *J* = 4.0 Hz, 1H), 8.68 (d, *J* = 4.0 Hz, 1H), 8.31 (d, *J* = 4.0 Hz, 1H), 8.10 (t, *J* = 8.0 Hz, 1H), 7.74–7.68 (m, 2H), 7.58 (d, *J* = 4.0 Hz, 1H), 7.48–7.45 (m, 1H), 7.42–7.36 (m, 2H), 7.30–7.26 (m, 1H), 7.18 (dd, *J* = 6.8, 4.8 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.69 (dd, *J* = 8.8, 1.6 Hz, 3H), 6.51 (d, *J* = 8.8 Hz, 2H), 6.38 (d, *J* = 8.8 Hz, 2H), 5.65 (d, *J* = 13.2 Hz, 1H), 5.21 (d, *J* = 10.8 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.13–4.02 (m, 2H), 3.68 (s, 3H), 3.63 (s, 3H), 3.49–3.44 (m, 1H), 3.33–3.26 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 199.88, 197.18, 168.65, 161.23, 160.72, 158.71, 157.86, 157.83, 154.24, 149.58, 148.66, 148.37, 138.46, 137.37, 136.70, 136.06, 135.25, 132.65, 129.24, 128.58, 128.31, 127.09, 123.43, 123.28, 122.84, 122.51, 122.25, 121.56, 120.37, 113.96, 113.62, 110.52, 74.38, 69.19, 61.72, 55.07, 55.05, 54.03, 50.43, 44.93, 39.09. HRMS (ESI) m/z: Calcd. for $C_{45}H_{37}BrN_4O_6$ $[M+Na]^+$ 831.1794, found: 831.1755.

### 2,7-Bis(4-chlorophenyl)-6-(2-hydroxy-5-methylbenzoyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4q)

White solid (594 mg, 79% yield): m.p. 254–255 °C; IR (KBr): 3050, 1695, 1667, 1588, 1491, 1435, 1411, 1338, 1293, 1247, 1171, 1091, 1051, 1013, 825, 779, 748, 698, 670, 620 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.64 (s, 1H), 9.71 (d, *J* = 7.6 Hz, 1H), 8.75 (d, *J* = 4.0 Hz, 1H), 8.69 (d, *J* = 4.8 Hz, 1H), 8.25 (d, *J* = 3.6 Hz, 1H), 8.03 (t, *J* = 8.0 Hz, 1H), 7.76–7.71(m, 2H), 7.51–7.42 (m, 2H), 7.28–7.25 (m, 1H), 7.20–7.17 (m, 1H), 7.15–7.12 (m, 4H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.93–6.88 (m, 3H), 6.72 (d, *J* = 9.2 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 2H), 5.64 (d, *J* = 12.8 Hz, 1H), 5.20 (d, *J* = 10.8 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.19–4.13 (m, 2H), 3.45 (dd, *J* = 14.4, 2.8 Hz, 1H), 3.32–3.25 (m, 1H), 2.29 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 200.0, 196.9, 168.9, 160.5, 160.4, 157.8, 154.1, 149.3, 148.7, 148.4, 141.7, 137.3, 137.1, 136.9, 136.3, 135.3, 133.2, 131.9, 129.8, 129.5, 128.8, 128.7, 128.4, 127.7, 127.3, 124.0, 123.3, 122.9, 122.7, 122.3, 119.7, 118.2, 74.4, 69.3, 61.5, 53.3, 50.4, 44.5, 39.2, 20.7; HRMS (ESI) m/z: Calcd. for $C_{44}H_{34}Cl_2N_4O_4$ $[M+Na]^+$ 775.1855, found: 775.1826.

### 6-(2-Hydroxy-5-methylbenzoyl)-2,7-bis(4-methoxyphenyl)-1-picolinoyl-3,8*a*-di(pyridin-2-yl)hexahydroindolizin-5(1*H*)-one (4r)

White solid (573 mg, 77% yield): m.p. 172–173 °C; IR (KBr): 2927, 1672, 1612, 1587, 1514, 1436, 1399, 1342, 1251, 1177, 1091, 1032, 995, 828, 780, 746, 688, 671, 618 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 11.72 (s, 1H), 9.74 (d, *J* = 8.0 Hz, 1H), 8.74 (d, *J* = 4.0 Hz, 1H), 8.68 (d, *J* = 4.0 Hz, 1H), 8.28 (d, *J* = 4.0 Hz, 1H), 8.03 (t, *J* = 4.0 Hz, 1H), 7.73–7.68 (m, 2H), 7.48–7.44 (m, 1H), 7.42–7.39 (m, 1H), 7.26–7.24 (m, 1H), 7.17–7.11 (m, 3H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 4.0 Hz, 1H), 6.71– 6.67 (m, 3H), 6.48 (d, *J* = 8.0 Hz, 2H), 6.38 (d, *J* = 8.0 Hz, 2H), 5.65 (d, *J* = 12.0 Hz, 1H), 5.20 (d, *J* = 8.0 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.16–4.07 (m, 2H), 3.67 (s, 3H), 3.62 (s, 3H), 3.46 (dd, *J* = 14.8, 3.2 Hz, 1H), 3.31–3.25 (m, 1H), 2.29 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 200.6, 197.3, 169.3, 160.9, 160.4, 158.7, 158.3, 157.8, 154.3, 149.1, 148.7, 148.3, 137.0, 137.0, 136.7, 136.1, 135.4, 129.9, 129.2, 128.7, 128.3, 127.6, 127.1, 123.9, 123.4, 122.7, 122.5, 122.3, 119.9, 118.1, 114.0, 113.6, 74.4, 69.4, 61.7, 55.1, 55.0, 53.7, 50.3, 44.9, 39.2, 20.7; HRMS (ESI) m/z: Calcd. for $C_{46}H_{40}N_4O_6$ $[M+Na]^+$ 767.2846, found: 767.2870.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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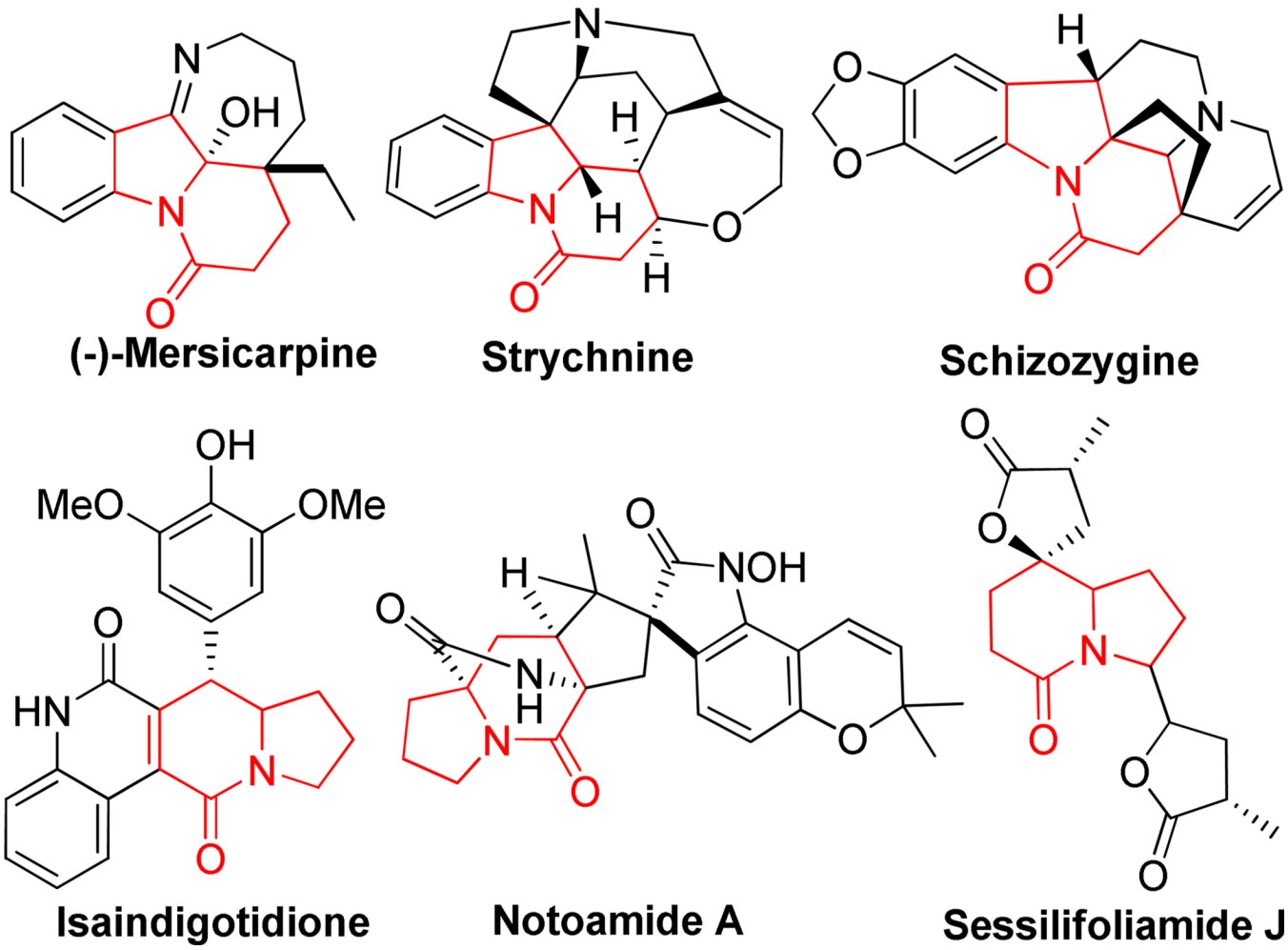
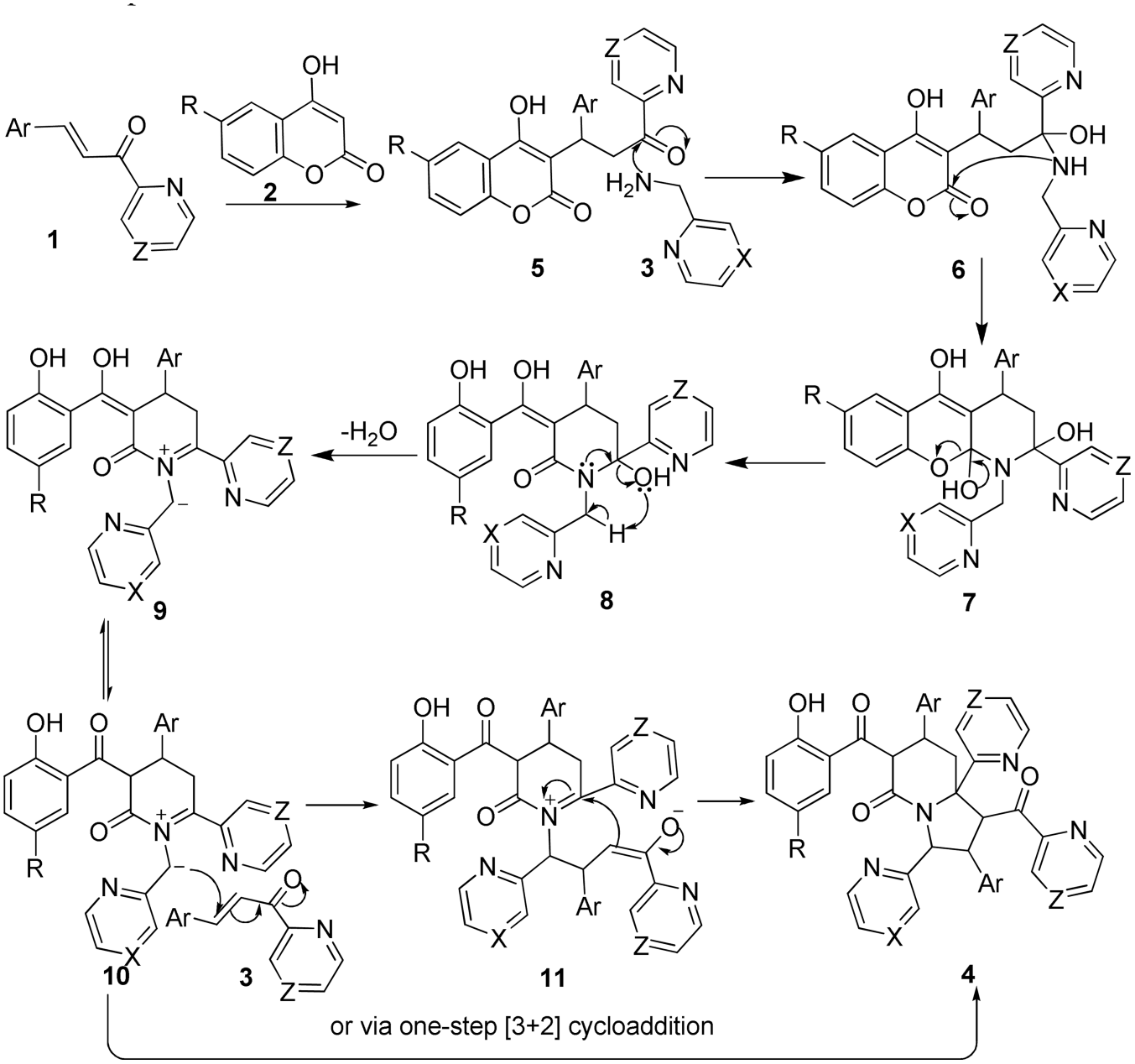


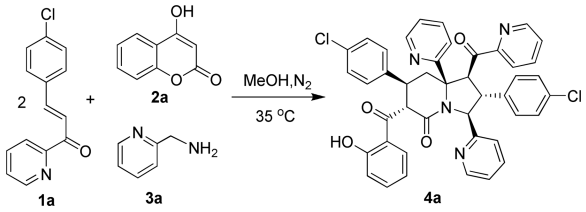

**Figure 1.**
Representatives of natural products containing an indolizin-5(1*H*)-one core




**Scheme 1.**
Proposed mechanism for the synthesis of 4

## Table 1

Optimization of conditions for the model reaction

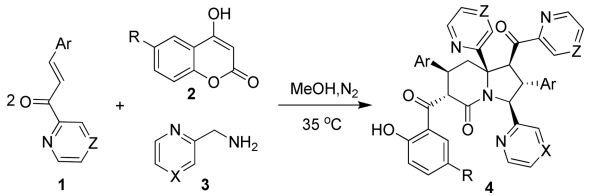



| Entry | Solvent | T / °C | Time / h | Yield / %[a] |
|---|---|---|---|---|
| 1 | DMF | 25 | 16 | 55 |
| 2 | EtOH | 25 | 20 | 36 |
| 3 | MeOH | 25 | 18 | 64 |
| 4 | $CH_3CN$ | 25 | 20 | 31 |
| 5 | $CH_2Cl_2$ | 25 | 20 | 26 |
| 6 | THF | 25 | 20 | NR |
| 7 | MeOH | 30 | 18 | 73 |
| 8 | MeOH | 35 | 16 | 79 |
| 9 | MeOH | 45 | 16 | 70 |
| 10 | MeOH | 50 | 16 | 61 |

[a]Isolated yields

**Table 2**

Synthetic results of products 4




| Entry | 4 | Ar | R | X/Z | Yield / % [b] |
|---|---|---|---|---|---|
| 1 | **4a** | 4-$ClC_6H_4$ | H | CH/CH | 79 |
| 2 | **4b** | 2-$ClC_6H_4$ | H | CH/CH | 76 |
| 3 | **4c** | 4-$CH_3C_6H_4$ | H | CH/CH | 81 |
| 4 | **4d** | 4-$CH_3OC_6H_4$ | H | CH/CH | 78 |
| 5 | **4e** | 3,4-$(CH_3O)_2C_6H_3$ | H | CH/CH | 79 |
| 6 | **4f** | 2,4-$Cl_2C_6H_3$ | H | CH/CH | 80 |
| 7 | **4g** | 2,3-$(CH_3O)_2C_6H_3$ | H | CH/CH | 75 |
| 8 | **4h** | 4-$BrC_6H_4$ | H | CH/N | 77 |
| 9 | **4i** | 4-$ClC_6H_4$ | H | CH/N | 74 |
| 10 | **4j** | 2,3-$(CH_3O)_2C_6H_3$ | H | CH/N | 82 |
| 11 | **4k** | 4-$ClC_6H_4$ | H | N/CH | 80 |
| 12 | **4l** | 2,3-$(CH_3O)_2C_6H_3$ | H | N/CH | 78 |
| 13 | **4m** | 4-$ClC_6H_4$ | Br | CH/CH | 82 |
| 14 | **4n** | 4-$FC_6H_4$ | Br | CH/CH | 76 |
| 15 | **4o** | 4-$CH_3C_6H_4$ | Br | CH/CH | 83 |
| 16 | **4p** | 4-$CH_3OC_6H_4$ | Br | CH/CH | 81 |
| 17 | **4q** | 4-$ClC_6H_4$ | CH3 | CH/CH | 79 |
| 18 | **4r** | 4-$CH_3OC_6H_4$ | $CH_3$ | CH/CH | 77 |

[b] Isolated yields