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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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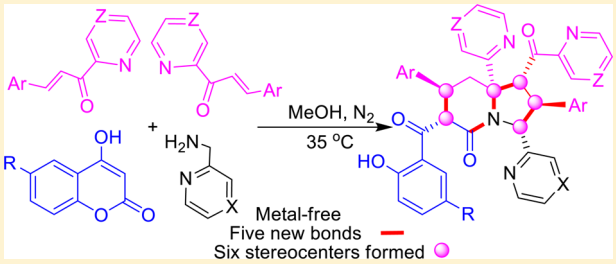
Supporting Information

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 σ 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]

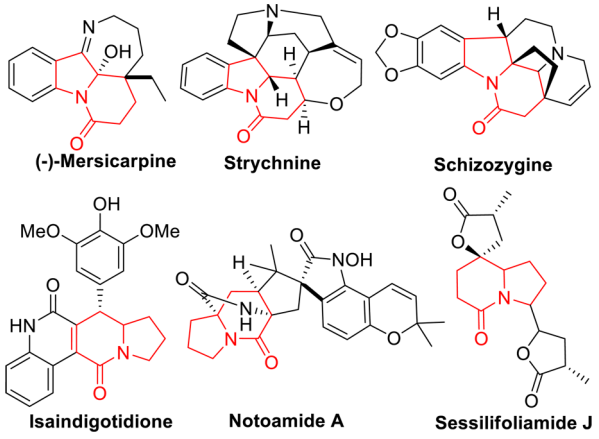


Figure 1. Representatives of natural products containing an indolizin-5(1*H*)-one core.

Indolizin-5(1*H*)-ones have also been attractive synthetic targets because of their unique structures and powerful biological activities. Therefore, some research groups have devoted much effort to the syntheses of these important products.[9]

In the meantime, 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, multistep 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

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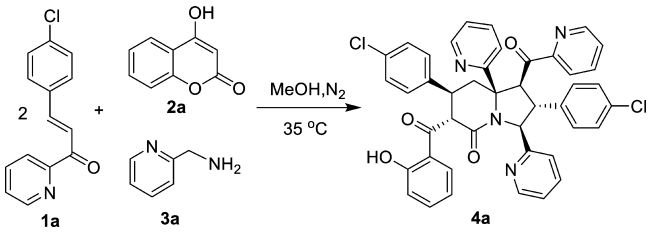
high purity of precursors, etc.[17] Over the past few years, our group[18] and others[19] have developed various MDRs that can offer easy access to highly functionalized nitrogen-containing compounds of chemical and pharmaceutical interest. We recently discovered a novel ABC_2-type MDR[20] to give a 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*-chromen-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 aessilifollamide J isolated from *Stemona sessilifolia*,[2] 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 multicomponent 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).

Table 1. Optimization of Conditions for the Model Reaction



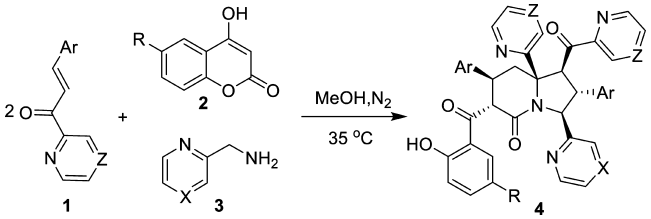
entry	solvent	T (°C)	time (h)	yield[a] (%)
1	DMF	25	16	55
2	EtOH	25	20	36
3	MeOH	25	18	64
4	CH_3CN	25	20	31
5	CH_2Cl_2	25	20	26
6	THF	25	20	NR
7	MeOH	30	18	73
8	MeOH	35	16	79
9	MeOH	45	16	70
10	MeOH	50	16	61

[a]Isolated yields.

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 the 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

Table 2. Synthetic Results of Products 4



entry	4	Ar	R	X/Z	yield[a] (%)
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	CH_3	CH/CH	79
18	**4r**	4-$CH_3OC_6H_4$	CH_3	CH/CH	77

[a]Isolated yields.

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 and 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 stereoconfiguration of a single crystal of **4a** was established by X-ray diffractional analysis. As shown in the crystal structure of **4a** (Figure S1, Supporting Information), six stereocenters in the molecular structure and two aryl groups in anticonfiguration 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

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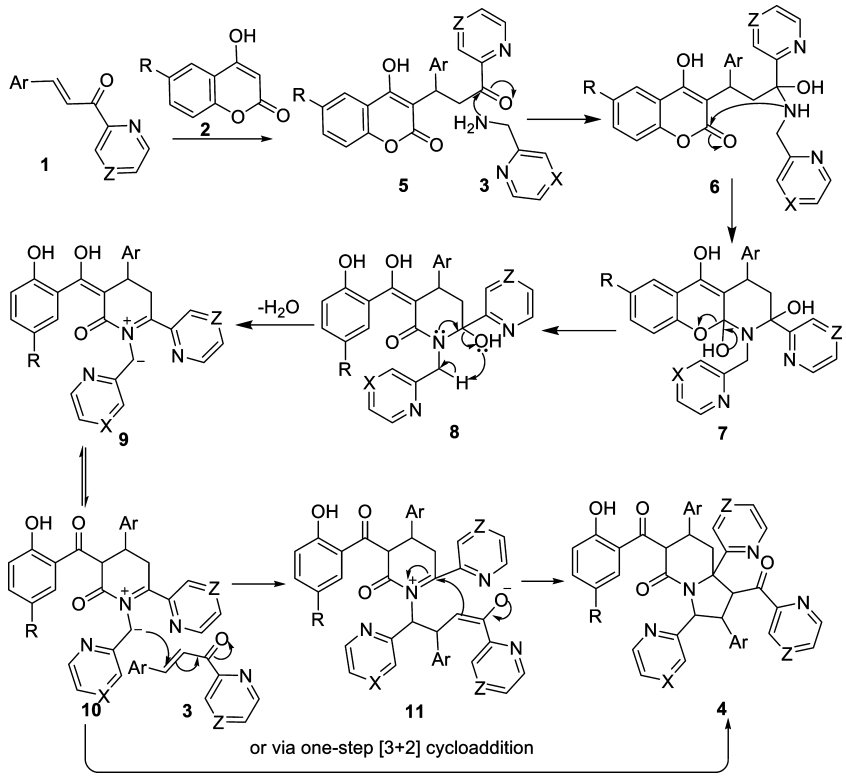
Scheme 1. Proposed Mechanism for the Synthesis of 4



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 multicomponent systems. The transformations are notable because they can yield five new σ bonds and six stereocenters including a quaternary carbon center.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under 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 a 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 of anhydrous methanol in a 25-mL three-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-3,8a-di(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4a**):* white solid (583 mg, 79% yield); mp 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}; ^{1}H 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-3,8a-di(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4b**):* white solid (561 mg, 76% yield); mp 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}; ^{1}H 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.

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*6-(2-Hydroxybenzoyl)-1-picolinoyl-3,8a-di(pyridin-2-yl)-2,7-di-p-tolylhexahydroindolizin-5(1H)-one (**4c**):* white solid (565 mg, 81% yield); mp >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-3,8a-di(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4d**):* white solid (569 mg, 78% yield); mp 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-3,8a-di(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4e**):* white solid (624 mg, 79% yield); mp 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-3,8a-di(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4f**):* white solid (645 mg, 80% yield); mp 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-3,8a-di(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4g**):* white solid (593 mg, 75% yield); mp 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}; ^1H 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)-8a-(pyrazin-2-yl)-1-(pyrazine-2-carbonyl)-3-(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4h**):* white solid (637 mg, 77% yield); mp >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}; ^1H 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)-8a-(pyrazin-2-yl)-1-(pyrazine-2-carbonyl)-3-(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4i**):* white solid (548 mg, 74% yield); mp 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}; ^1H 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)-8a-(pyrazin-2-yl)-1-(pyrazine-2-carbonyl)-3-(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4j**):* white solid (650 mg, 82% yield); mp 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}; ^1H 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, $CDCl_3$) 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,

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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)-8a-(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4k**): white solid (591 mg, 80% yield); mp >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); ^{13}C 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)-8a-(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4l**): white solid (617 mg, 78% yield): mp 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-3,8a-di(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4m**): white solid (669 mg, 82% yield); mp 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-3,8a-di(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4n**): white solid (596 mg, 76% yield); mp 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-3,8a-di(pyridin-2-yl)-2,7-di-p-tolylhexahydroindolizin-5(1H)-one (**4o**): white solid (644 mg, 83% yield); mp 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-3,8a-di(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4p**): white solid (654 mg, 81% yield); mp 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-3,8a-di(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4q**): white solid (594 mg, 79% yield); mp 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-3,8a-di(pyridin-2-yl)hexahydroindolizin-5(1H)-one (**4r**): white solid (573 mg, 77% yield); mp 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.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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