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Gold(I)-Catalyzed Cascade Approach for the Synthesis of Tryptamine-Based Polycyclic Privileged Scaffolds as α_1-Adrenergic Receptor Antagonists

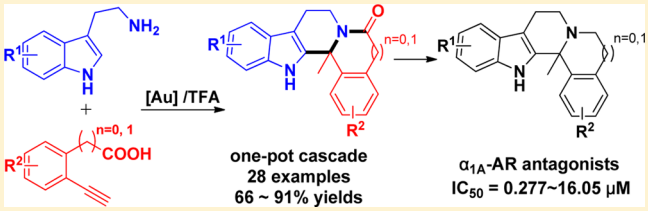
Zeng Li,[†,§] Jing Li,[‡,§] Nan Yang,[†] Ying Chen,[‡] Yu Zhou,[†] Xun Ji,[†] Lei Zhang,[†] Jinfang Wang,[†] Xin Xie,*[,‡] and Hong Liu*[,†]

[†]CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China

[‡]National Center for Drug Screening, CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

Supporting Information

ABSTRACT: An efficient and facile gold(I)-catalyzed one-pot cascade protocol has been developed for the synthesis of tryptamine-fused polycyclic privileged structures through the treatment of substituted tryptamines and 2-ethynylbenzoic acids or 2-ethynylphenylacetic acids. This strategy features the formation of one C−C bond and two C−N bonds with high yields and broad substrate tolerance. The selected reduced target molecules are validated to perform as α_1-adrenergic receptors antagonists. The most potent one, **4bh**, exhibits an IC_{50} value of 277 nM on α_{1A} subtype with a selectivity ratio of 15.8 over α_{1B} subtype.



INTRODUCTION

Indole alkaloids found in many natural and synthetic products have received appreciable attention in recent years because they often exhibit a wide range of biological activities.[1−5] Moreover, tryptamine-based molecules are generally considered as privileged structures with drug-like qualities and expectant effects for different types of diseases.[6−8] The top selling drugs tadalafil,[9,10] rizatriptan[11] and eletriptan[12] are tryptamine-based structures. Among the tryptamine-based polycyclic scaffolds, **LE300** analogues have been synthesized widely and exhibit quite potent affinities on drug targets such as dopamine receptors (DRs), serotonin receptors (5-HTRs), and α_1-adrenergic receptor (α_1-AR) (Figure 1).[13−18] Compound **1**, the precursor of **LE300** series, serves as an attractive leading scaffold with potent bioactivity on α_1-AR.[17,19] However, in the reported synthetic routes of these classes of compounds, some were limited by long routes, rigorous conditions, low atom economy, as well as limited substrate tolerance.[17−19] Thus, the development of new efficient synthetic strategies is in considerable demand.

In recent years, metal-catalyzed cascade reactions involving nucleophilic additions to C−C multiple bonds have been systematically studied.[20] Among them, gold(I) catalysts were explored widely in these types of reactions.[21−23] Moreover, enol lactones obtained by gold(I)-catalyzed cyclization of alkynoic acids are attractive because cascade reactions can take place after the formation of *N*-acyliminium ions followed by nucleophilic attacking from amine-tethered π nucleophiles.[24] To this end, gold-catalyzed one-pot cascade reactions have been accepted to be effective methods for the synthesis of polycyclic heterocycles in the works of pioneers and our research team.[24−31] Among those reported studies, linear alkynoic acids were often used. However, there are few reports about nonlinear alkynoic acids that are more inflexible, especially aromatic alkynoic acids. In this work, aromatic terminal alkynoic acids were used initially in a gold(I)-catalyzed sequential reaction.

Additionally, we expect our new strategy is useful for establishing diverse structures with potential biological effects. In the field of gold-catalyzed cascade synthesis or other new strategies for tryptamine polycyclic molecules,[32] few bioactive products were reported. Here, we present an efficient gold-catalyzed cascade reaction for the synthesis of tryptamine-fused polycyclic structures (Scheme 1). This strategy features the formation of one C−C bond and two C−N bonds in a one-pot operation with high yields and broad substrate tolerance. Attractively, novel classes of α_{1A}-AR selectivity antagonists that are potential anti-benign prostatic hyperplasia (BPH) agents[33−35] were obtained though simple reduction.

RESULTS AND DISCUSSION

Tryptamine (**1a**) and 2-ethynylbenzoic acid (**2a**) were chosen as model substrates to optimize the reaction conditions. Different combinations of catalysts, solvents, temperatures, and reaction times were investigated (Table 1). In our previous

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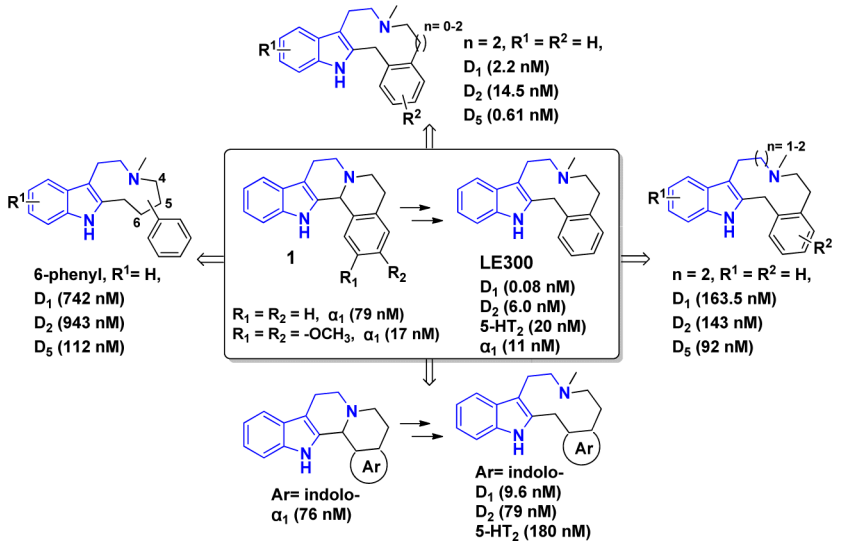
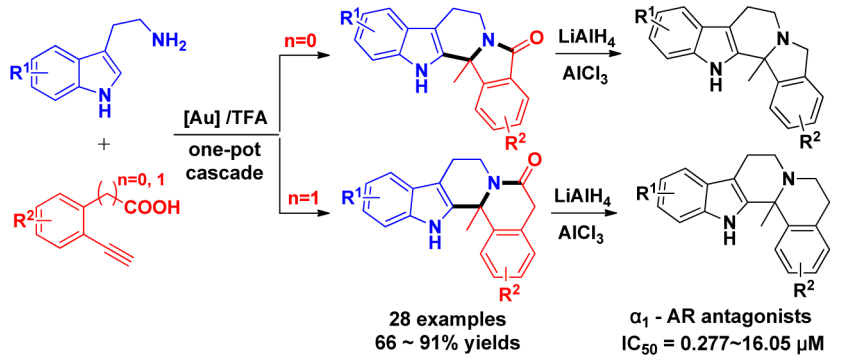


Figure 1. LE300 precursors, analogues, and their reported bioactivities (K_i).

Scheme 1. Synthesis of Tryptamine-Fused Polycyclic α_1-ARs Antagonists by Au-Catalyzed Tandem Reaction



work, it is found that some gold-complexes and/or silver salts were suitable for cascade transformation involving activation of alkynyl group.[29] Thus, Au catalysts I–III and $AgBF_4$ were first selected to explore the reaction condition at 90 °C for 4 h in a sealed tube using 1,2-dichloroethane (DCE) as the solvent. Surprisingly, moderate to good results were obtained (Table 1, entries 1–3). Among these attempts, Au catalyst III was found to be the most effective one, with an 81% yield of **3aa** (Table 1, entry 3). No significant improvements were obtained when the reaction temperatures were elevated to 110 °C using toluene as solvent or replacing $AgBF_4$ by $AgSbF_6$ (Table 1, entries 4–5). Only 53 or 25% yield of the products was obtained with Au catalyst III or $AgBF_4$, respectively (Table 1, entry 6–7). In previous experience, Ag salt was also treated as a Lewis acid and can be replaced by a Brönsted acid such as trifluoroacetic acid (TFA). The results told that TFA was a better choice with higher yield and a clearer reaction residue (Table 1, entry 8). Yield could be improved further to 87% by prolonging the reaction time to 6 h (Table 1, entry 9). However, no product was formed when TFA was used without any Au catalyst (Table 1, entry 10). Other Au catalysts (II and IV) with TFA were also screened (Table 1, entries 11 and 12). These results show that the combination of Au catalyst III and TFA was the best choice. In addition, polar solvents such as DMF, THF, and H_2O were employed, but disappointing results were obtained (Table 1, entries 13–15). It is known that microwave heating is an efficient way to enhance reaction rate, but it appeared to have a negative impact on the yield (Table 1, entry 16). Furthermore, decreasing the amount of **2a** to 1.0 equiv adversely affected the product yield, which fell down to 73% (Table 1, entry 17). Therefore, the optimal reaction condition was obtained when **1a** reacted with 1.2 equiv of **2a** in toluene with 5 mol % of Au catalyst III and 20 mol % of TFA in a sealed tube at 110 °C for 6 h.

Substrate scope of this cascade reaction was investigated under the optimized reaction condition. As summarized in Table 2, desired products **3aa–3ed** were achieved in good to excellent yields (75–91%) by treatment of various substituted tryptamines (**1a–1e**) with 2-ethynylbenzoic acids (**2a–2d**). Notably, the electronic nature of substituents on tryptamines had certain influence on the yield. When tryptamines were substituted by methyl- or methoxyl- groups, excellent yields were achieved (Table 2, entries 1–3). Conversely, introducing chloro- or fluoro-substitutions into tryptamines resulted in a decrease in yields (Table 2, entries 4 and 5). In addition, there were no significant influences on the yields if different substituents were introduced into 2-ethynylbenzoic acid (Table 2, entries 6–14). These results suggested that our protocol can be used for a broad range of substrates.

To further explore the scope of this cascade reaction, we replaced 2-ethynylbenzoic acids with 2-ethynylphenylacetic acids (**2e–2h**). Correspondingly, six-membered ring products **3ae–3eh** were prepared in good yields (66–86%, Table 3). However, some of the yields fell down to 50% when these

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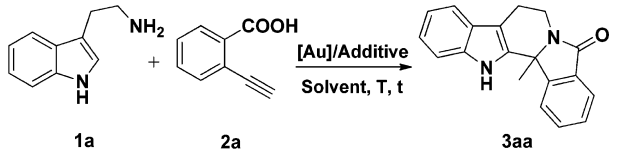
Table 1. Optimization of the Reaction Conditions[a]

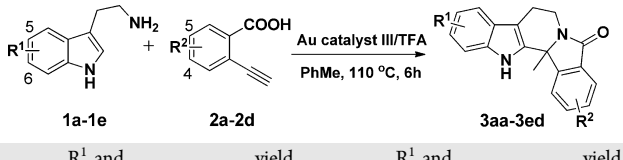


1a 2a 3aa

entry	[Au][b]/additive	solvent	T (°C)	t (h)	yield (%)[c]
1	Au catalyst I/$AgBF_4$	DCE	90	4	64
2	Au catalyst II/$AgBF_4$	DCE	90	4	77
3	Au catalyst III/$AgBF_4$	DCE	90	4	81
4	Au catalyst III/$AgBF_4$	PhMe	110	4	82
5	Au catalyst III/$AgSbF_6$	PhMe	110	4	72
6	Au catalyst III	PhMe	110	4	53
7	$AgBF_4$	PhMe	110	4	25
8	Au catalyst III/TFA	PhMe	110	4	85
9	**Au catalyst III/TFA**	**PhMe**	**110**	**6**	**87**
10	TFA	PhMe	110	6	0
11	Au catalyst II/TFA	PhMe	110	6	80
12	Au catalyst IV/TFA	PhMe	110	6	84
13	Au catalyst III/TFA	DMF	110	6	0
14	Au catalyst III/TFA	THF	100	6	51
15	Au catalyst III/TFA	H_2O	110	6	0
16	Au catalyst III/TFA	PhMe	120	0.5	40[d]
17	Au catalyst III/TFA	PhMe	110	6	73[e]

[a]**1a** (100 mg, 1.0 equiv), **2a** (1.2 equiv), Au catalyst (5 mol %), [Ag] (10 mol %), TFA (20 mol %). [b]Au catalyst I = $Au(PPh_3)Cl$; Au catalyst II = Au[tris(2,4-di-*tert*-butylphenyl)phosphite]Cl; Au catalyst III = Au[$P(t\text{-}Bu)_2$(*o*-biphenyl)][CH_3CN]SbF_6; Au catalyst IV = Au[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]Cl. [c]Isolated yield. [d]The reaction was performed under microwave irradiation at the power of 150 W. [e]**2a** was 1.0 equiv.

Table 2. Au(I)-Catalyzed Tandem Synthesis of 3aa−3ed[a]



1a-1e 2a-2d 3aa-3ed

entry	R^1 and R^2	products	yield (%)[b]	entry	R^1 and R^2	products	yield (%)[b]
1	R^1 = H, R^2 = H	**3aa**	87	8	R^1 = 5-OCH_3, R^2 = 4-F	**3cb**	88
2	R^1 = 5-OCH_3, R^2 = H	**3ba**	91	9	R^1 = 5-H, R^2 = 4-CH_3	**3ac**	85
3	R^1 = 5-CH_3, R^2 = H	**3ca**	91	10	R^1 = 5-OCH_3, R^2 = 4-CH_3	**3bc**	88
4	R^1 = 5-Cl, R^2 = H	**3da**	80	11	R^1 = 5-Cl, R^2 = 4-CH_3	**3dc**	78
5	R^1 = 6-F, R^2 = H	**3ea**	77	12	R^1 = 5-H, R^2 = 5-OCH_3	**3ad**	86
6	R^1 = 5-H, R^2 = 4-F	**3ab**	82	13	R^1 = 5-OCH_3, R^2 = 5-OCH_3	**3bd**	90
7	R^1 = 5-OCH_3, R^2 = 4-F	**3bb**	87	14	R^1 = 6-F, R^2 = 5-OCH_3	**3ed**	75

[a]**A** (100 mg, 1.0 equiv), **B** (1.2 equiv), Au catalyst III (5 mol %), TFA (20 mol %), PhMe (4 mL). [b]Isolated yield.

reactions were undertaken at 90 °C in DCE, suggesting that the generation of six-membered ring analogues is less favored on energetics and dynamics. Substrates **1** with electron-donating substituents were more beneficial to the yield than that of the substrates with electron-withdrawing substituents (Table 3, entries 15−19). On the other hand, different substituted 2-ethynylphenylacetic acids exhibited no obvious effect (Table 3, entries 20−28). Moreover, six-membered ring products show better solubility in organic solvents than the five-membered ones.

Furthermore, we have attempted to describe a reasonable mechanism by observing and identifying the key intermediates in the reaction process (Scheme 2). About 2−3 h after the transformation started, thin-layer chromatography (TLC) monitored a new intermediate point, which would be consumed when the reaction ended. The intermediate was identified as enol lactone **A**, which derived from alkynoic acid **2** via a gold-catalyzed intramolecular ring-closing approach as pioneer's report.[36] Besides, intermediate **A** can be obtained by reacting ethynylbenzoic acids **2** with gold catalysis in absence of tryptamine and TFA. It is apparent that the formation of **A** is a key node in this domino process, and it is also the reason why 1.2 equiv of **2** was more favorable than 1.0 equiv. Additionally, intermediate **B** was formed and separated when no TFA was added. Then intermediate **B** was treated only with TFA or $AgBF_4$ to afford target molecule **3** though the similar process reported formerly.[24,32] On the basis of these explorations, we deduced a reasonable path of the mechanism. Au catalyst activated the alkyne terminal of **2**, which then underwent an intramolecular cyclization with the carboxylic acid end to form **A**, followed by regeneration of the Au catalyst. Enol lactone **A** was attracted further by the primary amino group of tryptamine **1** to obtain the ammonolysis product **B**. Subsequently, **C** was formed under Brønsted acid (TFA) catalyzed *N*-acyliminium ion formation. Finally, C-2, the electron-rich carbon atom on indole, attacked the iminium ion through a nucleophilic process to give the target molecule **3**. Products **3aa** (Figure 2) and **3be** were recrystallized from mixed solvents of dichloromethane and methanol (70/30, v/v), and the structures were characterized using X-ray crystallography (see in the Supporting Information, CCDC deposition numbers: 931246, 931247).

To verify our expectation that this novel strategy could provide useful scaffold with attractive bioactivities, we reduced selected molecules to corresponding amines with $LiAlH_4$ and $AlCl_3$ (Scheme 3). Note that reduction could not happen easily if there is only reducing agent such as $LiAlH_4$ or BH_3 without $AlCl_3$. The X-ray crystallographic structure of target molecule **4aa** was solved (see in the Supporting Information, CCDC deposition number: 949954).

Bioactivities of target products **4aa−4bh** were tested on α_1-adrenergic receptors. The results were inspiring that most molecules exhibited good antagonism effects on calcium assays based on α_{1A}-AR, α_{1B}-AR overexpressed HEK293 cells with subtype selectivities (Table 4). The six-membered ring products **4ae−4bh** (IC_{50}: 0.277−4.188 μM) are more potent compared with five-membered ones **4aa−4dc** (IC_{50}: 4.232−16.05 μM). Additionally, the six-membered ring products exhibit better α_{1A} subtype selectivity over α_{1B} (α_{1B}/α_{1A} ratio: 1.6−15.8). The most active one, compound **4bh**, shows both the highest IC_{50} value of 277 nM on α_{1A} subtype and best

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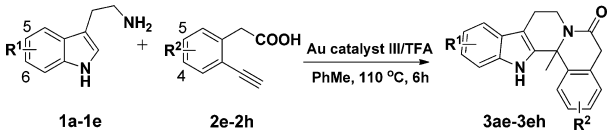
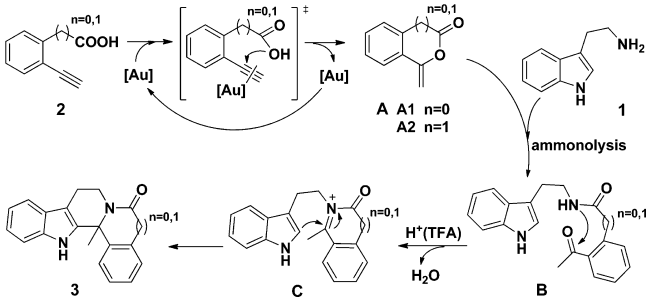
Table 3. Au(I)-Catalyzed Tandem Synthesis of 3ae−3eh[a]



entry	R^1 and R^2	product	yield (%)[b]	entry	R^1 and R^2	product	yield (%)[b]
15	R^1 = H	**3ae**	82	22	R^1 = 5-CH_3	**3cf**	76
	R^2 = H				R^2 = 5-Cl		
16	R^1 = 5-OCH_3	**3be**	85	23	R^1 = H	**3ag**	84
	R^2 = H				R^2 = 4-F		
17	R^1 = 5-CH_3	**3ce**	83	24	R^1 = 5-OCH_3	**3bg**	83
	R^2 = H				R^2 = 4-F		
18	R^1 = 5-Cl	**3de**	72	25	R^1 = 5-Cl	**3dg**	75
	R^2 = H				R^2 = 4-F		
19	R^1 = 6-F	**3ee**	69	26	R^1 = H	**3ah**	82
	R^2 = H				R^2 = 4-OCH_3		
20	R^1 = H	**3af**	80	27	R^1 = 5-OCH_3	**3bh**	82
	R^2 = 5-Cl				R^2 = 4-OCH_3		
21	R^1 = 5-OCH_3	**3bf**	86	28	R^1 = 6-F	**3eh**	66
	R^2 = 5-Cl				R^2 = 4-OCH_3		

[a]**A** (100 mg, 1.0 equiv), **B** (1.2 equiv), Au catalyst III (5 mol %), TFA (20 mol %), PhMe (4 mL). [b]Isolated yield.

Scheme 2. Reasonable Mechanism



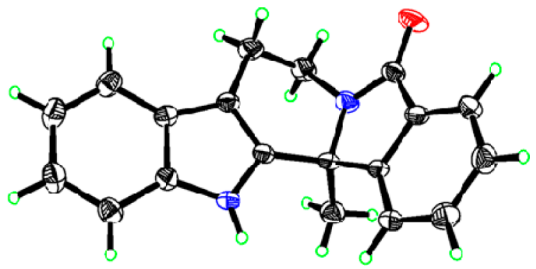


Figure 2. X-ray crystallographic structures of **3aa**.

subtype selectivity of 15.8. These results indicate that methoxyl groups are beneficial on activity and selectivity. Since selective α_{1A}-AR antagonists are successfully developed as anti-benign prostatic hyperplasia (BPH) drug agents such as brand named drugs Tamsulosin[37] and Silodosin,[35] these molecules are worthy of further optimization and development.

Scheme 3. Reduction of Products 3aa−3bh to 4aa−4bh

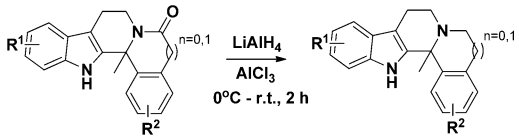


Table 4. IC_{50} of Calcium (Ca^{2+}) Mobilization Assays of 4aa−4bh as α_1- ARs Antagonists[a]

compds	precursors	α_{1A} IC_{50} ± SEM (μM)	α_{1B} IC_{50} ± SEM (μM)	selectivity α_{1B}/α_{1A}
4aa	**3aa**	12.36 ± 1.287	10.46 ± 1.147	0.8
4ba	**3ba**	16.05 ± 2.482	54.99 ± 6.190	3.4
4ca	**3ca**	5.025 ± 1.960	24.88 ± 2.678	5.0
4ac	**3ac**	4.232 ± 0.489	4.826 ± 0.152	1.1
4bc	**3bc**	13.09 ± 0.658	10.14 ± 2.391	0.8
4dc	**3dc**	5.357 ± 0.061	33.30 ± 12.56	6.2
4ae	**3ae**	2.290 ± 0.386	28.46 ± 3.942	12.4
4be	**3be**	2.876 ± 0.074	4.582 ± 1.152	1.6
4ce	**3ce**	0.514 ± 0.133	0.885 ± 0.190	1.7
4de	**3de**	3.451 ± 0.703	5.925 ± 0.470	1.7
4af	**3af**	1.687 ± 0.190	9.221 ± 1.030	5.5
4bf	**3bf**	4.188 ± 0.176	23.98 ± 1.124	5.7
4cf	**3cf**	2.083 ± 0.084	6.680 ± 0.507	3.2
4ah	**3ah**	0.496 ± 0.074	2.754 ± 0.518	5.6
4bh	**3bh**	0.277 ± 0.120	4.363 ± 0.413	15.8
Silodosin	–	0.002 ± 0.001	0.411 ± 0.087	168.2

[a]IC_{50} values (means ± SEM) were obtained based on the data from three separate experiments.

CONCLUSIONS

An efficient and facile method for the synthesis of tryptamine-fused polycyclic privileged structures has been developed via a gold(I)-catalyzed one-pot cascade protocol with good yields and broad substrate tolerance. In this work, aromatic terminal alkynoic acids were employed initially to build polycyclic structures with amine nucleophiles, and a reasonable mechanism has been demonstrated directly. Further reduction products were tested to perform as novel α_1-adrenergic receptors antagonists with good activities and subtype selectivities. It is a straightforward approach to construct novel polycyclic molecular architectures from very simple starting molecules. On the basis of the synthetic and bioactive studies of these structures, this strategy is powerful and meaningful in both organic synthesis and drug discovery, and we anticipate these novel compounds may find pharmaceutical applications after further investigations.

EXPERIMENTAL SECTION

Chemistry: General Methods. Commercially available reagents and solvents were used without further purification. Column chromatography was performed on silica gel. TLC was performed on silica gel GF254 plates. Melting points (mp) were measured in open capillary tubes, using a SGW X-4 melting point apparatus (−50 to 400 °C) and are uncorrected. ^1H and ^{13}C NMR spectras were obtained with TMS as internal standard. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multipet (m).

General Procedure for the Au(I)-Catalyzed One-Pot Cascade Reaction (3aa as an Example). *13b-Methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indol-5-one (**3aa**).* In a dry sealed

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tube, tryptamine (100 mg for each example, 0.62 mmol), 2-ethynylbenzoic acid (109 mg, 1.2 equiv), [Au{P(t-Bu)$_2$(*o*-biphenyl)}-{CH_3CN}]SbF_6 (24.1 mg, 0.05 equiv), and trifluoroacetic acid (14.2 mg, 0.2 equiv) were added with 4 mL of dry toluene. The tube was heated and stirred for 6 h in an oil bath at 110 °C before the solvent was removed in vacuo. The residue was purified by chromatography using a 75/25 mixture of petroleum ether and ethyl acetate as the eluent to obtain a white to light yellow solid powder **3aa** (157 mg, 87%): mp 246−250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67−8.51 (s, 1H), 7.94−7.84 (d, J = 7.6 Hz, 2H), 7.65−7.54 (s, 1H), 7.52−7.38 (d, J = 7.6 Hz, 2H), 7.40−7.29 (d, J = 8.0 Hz, 1H), 7.21−7.13 (t, J = 7.6 Hz, 1H), 7.13−7.03 (t, J = 7.4 Hz, 1H), 4.89−4.73 (dd, J = 13.8, 6.0 Hz, 1H), 3.52−3.33 (td, J = 12.8, 4.9 Hz, 1H), 3.05−2.92 (td, J = 13.5, 11.5, 6.1 Hz, 1H), 2.91−2.81 (dd, J = 15.7, 4.7 Hz, 1H), 1.99−1.87 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 167.2, 149.4, 136.2, 135.2, 132.3, 130.3, 128.6, 126.0, 123.2, 122.8, 121.6, 118.9, 118.4, 111.2, 106.4, 62.0, 35.5, 25.9, 21.5; LRMS (ESI-quadrupole) m/z [M + H]$^+$ 288.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd $C_{19}H_{17}N_2O^+$ 289.1340, found 289.1336.

*10-Methoxy-13b-methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]-indolizino[8,7-b]indol-5-one (**3ba**).* White powder, 153 mg, 91%: mp 249−252 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52−8.39 (s, 1H), 7.91−7.82 (t, J = 7.7 Hz, 2H), 7.64−7.54 (td, J = 7.5, 1.2 Hz, 1H), 7.50−7.43 (td, J = 7.4, 1.0 Hz, 1H), 7.25−7.18 (d, J = 8.8 Hz, 1H), 6.93−6.87 (d, J = 2.4 Hz, 1H), 6.85−6.77 (dd, J = 8.8, 2.4 Hz, 1H), 4.89−4.69 (m, 1H), 4.21−4.07 (q, J = 7.2 Hz, 1H), 3.89−3.74 (s, 3H), 3.47−3.34 (ddd, J = 13.4, 11.5, 5.0 Hz, 1H), 3.02−2.87 (ddd, J = 15.3, 11.4, 6.2 Hz, 1H), 2.84−2.77 (dd, J = 15.5, 4.6 Hz, 1H), 1.94−1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 154.4, 148.6, 135.5, 132.1, 131.3, 131.2, 128.8, 124.5, 121.1, 112.6, 111.8, 108.3, 100.7, 62.0, 55.9, 35.5, 29.7, 26.4, 21.8; LRMS (ESI-quadrupole) m/z [M + H]$^+$ 318.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd $C_{20}H_{19}N_2O_2^+$ 319.1441, found 319.1437.

*10,13b-Dimethyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino-[8,7-b]indol-5-one (**3ca**).* White powder, 158 mg, 91%: mp 253−258 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.31−11.08 (s, 1H), 8.34−8.19 (d, J = 8.4 Hz, 1H), 7.72−7.65 (t, J = 6.7 Hz, 2H), 7.52−7.46 (t, J = 7.4 Hz, 1H), 7.26−7.18 (d, J = 8.3 Hz, 1H), 7.17−7.10 (s, 1H), 6.94−6.82 (dd, J = 8.3, 1.7 Hz, 1H), 4.65−4.36 (dd, J = 13.4, 5.3 Hz, 1H), 3.41−3.35 (dd, J = 11.7, 4.7 Hz, 1H), 2.77 −2.68 (dd, J = 15.2, 4.2 Hz,), 2.69−2.59 (m, 1H), 2.33−2.26 (s, 3H), 1.83−1.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 169.5, 151.7, 137.5, 136.8, 134.5, 132.6, 130.9, 129.7, 128.5, 125.5, 125.4, 125.1, 120.3, 113.2, 108.2, 64.4, 37.8, 28.2, 23.8, 23.5; LRMS (ESI-quadrupole) m/z [M + H]$^+$ 302.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd $C_{20}H_{19}N_2O^+$ 303.1492, found 303.1482.

*10-Chloro-13b-methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]-indolizino[8,7-b]indol-5-one (**3da**).* White to light yellow powder, 133 mg, 80%: mp 247−251 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71−8.56 (s, 1H), 7.95−7.82 (dd, J = 7.6, 2.7 Hz, 2H), 7.68−7.55 (td, J = 7.6, 1.2 Hz, 1H), 7.55−7.43 (t, J = 7.5 Hz, 1H), 7.43−7.40 (d, J = 2.0 Hz, 1H), 7.25−7.19 (s, 1H), 7.18−7.06 (dd, J = 8.6, 2.1 Hz, 1H), 4.89−4.73 (dd, J = 13.4, 6.0 Hz, 1H), 3.48−3.37 (m, 1H), 3.01−2.86 (m, 1H), 2.84−2.75 (dd, J = 15.4, 4.9 Hz, 1H), 1.94−1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 148.4, 136.2, 134.6, 132.2, 131.1, 128.9, 127.8, 125.7, 124.5, 122.8, 121.2, 118.4, 112.1, 108.1, 62.0, 35.5, 26.3, 21.6; LRMS (ESI-quadrupole) m/z [M + H]$^+$ 322.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd $C_{19}H_{16}ClN_2O^+$ 323.0950, found 323.0949.

*11-Fluoro-13b-methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]-indolizino[8,7-b]indol-5-one (**3ea**).* White powder, 132 mg, 77%: mp 250−254 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.53−11.45 (s, 1H), 8.31−8.26 (d, J = 8.0 Hz, 1H), 7.74−7.65 (m, 2H), 7.53−7.47 (t, J = 7.5 Hz, 1H), 7.39−7.32 (dd, J = 8.7, 5.5 Hz, 1H), 7.16−7.10 (dd, J = 10.1, 2.4 Hz, 1H), 6.85−6.77 (ddd, J = 10.6, 8.8, 2.3 Hz, 1H), 4.53−4.45 (dd, J = 13.3, 5.7 Hz, 1H), 3.42−3.35 (dd, J = 13.1, 4.5 Hz, 1H), 2.80−2.71 (dd, J = 15.3, 4.3 Hz, 1H), 2.69−2.57 (m, 1H), 1.83−1.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 169.5, 162.7−159.7 (d, J_{C-F} = 234.2 Hz), 151.5, 138.5−138.3 (d, J_{C-F} = 12.5 Hz), 138.1, 134.6, 132.6, 131.0, 125.5, 125.2, 125.1, 122.2−121.4 (d, J_{C-F} = 10.5 Hz), 110.2−109.2 (d, J_{C-F} = 24.1 Hz), 108.9, 99.9−99.4 (d, J_{C-F} = 25.9 Hz), 64.3, 37.7, 28.1, 23.7; LRMS (ESI-quadrupole) m/z [M + H]$^+$ 306.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd $C_{19}H_{16}FN_2O^+$ 307.1241, found 307.1231.

*2-Fluoro-13b-methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]-indolizino[8,7-b]indol-5-one (**3ab**).* White powder, 157 mg, 82%: mp 263−266 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.37−11.34 (s, 1H), 8.25−8.19 (dd, J = 9.0, 2.3 Hz, 1H), 7.80−7.75 (dd, J = 8.4, 5.1 Hz, 1H), 7.43−7.33 (m, 3H), 7.13−7.07 (t, J = 7.6 Hz, 1H), 7.03−6.95 (t, J = 7.4 Hz, 1H), 4.54−4.45 (dd, J = 13.3, 5.6 Hz, 1H), 3.46−3.39 (dd, J = 13.2, 4.6 Hz, 1H), 2.83−2.75 (dd, J = 15.4, 4.2 Hz, 1H), 2.73−2.62 (m, 1H), 1.87−1.85 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 166.6, 166.3−164.1 (d, J_{C-F} = 248.6 Hz), 152.6−152.0 (d, J_{C-F} = 10.0 Hz), 136.6, 134.9, 127.1, 126.4, 126.2−126.1 (d, J_{C-F} = 9.9 Hz), 122.2, 119.4, 118.9, 116.9−116.6 (d, J_{C-F} = 23.5 Hz), 111.7, 110.8−110.6 (d, J_{C-F} = 24.6 Hz), 107.1, 62.3, 36.0, 26.2, 21.8; LRMS (ESI-quadrupole) m/z [M + H]$^+$ 306.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd $C_{19}H_{16}FN_2O^+$ 307.1246, found 307.1241.

*2-Fluoro-10-methoxy-13b-methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indol-5-one (**3bb**).* White to light yellow powder, 162 mg, 87%: mp 270−275 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.20−11.17 (s, 1H), 8.22−8.16 (d, J = 8.9 Hz, 1H), 7.80−7.73 (dd, J = 7.9, 5.2 Hz, 1H), 7.40−7.32 (t, J = 8.8 Hz, 1H), 7.30−7.24 (d, J = 8.8 Hz, 1H), 6.91−6.87 (s, 1H), 6.77−6.71 (d, J = 8.7 Hz, 1H), 4.52−4.44 (m, 1H), 3.74−3.70 (s, 3H), 3.44−3.38 (m, 1H), 2.79−2.71 (dd, J = 15.1, 3.3 Hz, 1H), 2.69−2.59 (m, 1H), 1.85−1.80 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 166.6, 166.3−164.1 (d, J_{C-F} = 248.7 Hz), 153.8, 152.3−152.1 (d, J_{C-F} = 9.7 Hz), 135.5, 131.6, 127.1, 126.7, 126.2−126.1 (d, J_{C-F} = 9.9 Hz), 116.9−116.5 (d, J_{C-F} = 23.5 Hz), 112.4, 112.2, 110.9−110.4 (d, J_{C-F} = 24.8 Hz), 106.9, 100.8, 62.3, 55.8, 36.0, 26.3, 21.9; LRMS (ESI-quadrupole) m/z [M + H]$^+$ 336.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd $C_{20}H_{18}FN_2O_2^+$ 337.1352, found 337.1346.

*2-Fluoro-10,13b-dimethyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]-indolizino[8,7-b]indol-5-one (**3cb**).* White to light yellow powder, 163 mg, 88%: mp 273−277 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.23−11.18 (s, 1H), 8.24−8.17 (dd, J = 9.0, 2.3 Hz, 1H), 7.80−7.73 (dd, J = 8.4, 5.2 Hz, 1H), 7.42−7.30 (td, J = 8.3, 1.8 Hz, 1H), 7.29−7.24 (d, J = 8.3 Hz, 1H), 7.19−7.15 (s, 1H), 6.95−6.89 (dd, J = 8.2, 1.8 Hz, 1H), 4.53−4.44 (dd, J = 13.3, 5.3 Hz, 1H), 3.45−3.38 (m, 1H), 2.80−2.71 (m, 1H), 2.70−2.60 (m, 1H), 2.35−2.33 (s, 3H), 1.84−1.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 166.5, 166.2−164.0 (d, J_{C-F} = 248.8 Hz), 152.2−152.1 (d, J_{C-F} = 9.6 Hz), 134.9, 134.8, 127.8, 127.0, 126.5, 126.1−125.9 (d, J_{C-F} = 10.0 Hz), 123.6, 118.3, 116.7−116.5 (d, J_{C-F} = 23.6 Hz), 111.3, 110.7−110.4 (d, J_{C-F} = 24.5 Hz), 106.5, 62.1, 35.9, 26.1, 21.7, 21.5; LRMS (ESI-quadrupole) m/z [M + H]$^+$ 320.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd $C_{20}H_{18}FN_2O^+$ 321.1398, found 321.1391.

*2,13b-Dimethyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino-[8,7-b]indol-5-one (**3ac**).* White powder, 160 mg, 85%: mp 260−262 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.36−11.27 (s, 1H), 8.15−8.10 (s, 1H), 7.63−7.57 (d, J = 7.7 Hz, 1H), 7.41−7.36 (dd, J = 8.0, 2.6 Hz, 2H), 7.34−7.30 (d, J = 7.7 Hz, 1H), 7.12−7.04 (t, J = 7.4 Hz, 1H), 7.01−6.95 (t, J = 7.4 Hz, 1H), 4.53−4.46 (dd, J = 13.3, 5.7 Hz, 1H), 3.41−3.36 (dd, J = 13.0, 4.5 Hz, 1H), 2.80−2.73 (dd, J = 15.4, 4.4 Hz, 1H), 2.71−2.62 (m, 1H), 2.49−2.47 (s, 3H), 1.84−1.81 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 167.6, 150.1, 142.9, 136.5, 135.6, 129.8, 128.2, 126.4, 123.5, 123.4, 121.9, 119.2, 118.7, 111.6, 106.7, 62.2, 35.8, 26.4, 22.1, 21.8; LRMS (ESI-quadrupole) m/z [M + H]$^+$ 302.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd $C_{20}H_{19}N_2O^+$ 303.1492, found 303.1486.

*10-Methoxy-2,13b-dimethyl-7,8,13,13b-tetrahydro-5H-benzo-[1,2]indolizino[8,7-b]indol-5-one (**3bc**).* White to light yellow powder, 154 mg, 88%: mp 265−268 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.16−11.13 (s, 1H), 8.13−8.09 (s, 1H), 7.61−7.57 (d, J = 7.7 Hz, 1H), 7.34−7.29 (d, J = 7.7 Hz, 1H), 7.28−7.24 (d, J = 8.7 Hz, 1H), 6.89−6.86 (d, J = 2.5 Hz, 1H), 6.75−6.70 (dd, J = 8.8, 2.6 Hz, 1H), 4.52−4.45 (dd, J = 13.3, 5.7 Hz, 1H), 3.74−3.70 (s, 3H), 3.39−3.32 (m, 1H), 2.77−2.71 (dd, J = 15.3, 4.4 Hz, 1H), 2.68−2.59 (m, 1H), 2.49−2.45 (s, 3H), 1.83−1.79 (s, 3H); ^{13}C NMR (125 MHz,

DMSO) δ 167.6, 153.7, 150.1, 142.9, 136.2, 131.5, 129.8, 128.1, 126.7, 123.5, 123.3, 112.3, 111.9, 106.5, 100.6, 62.2, 55.7, 35.8, 26.4, 22.0, 21.9; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 332.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{21}H_{21}N_2O_2^+$ 333.1598, found 333.1589.

*10-Chloro-2,13b-dimethyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]-indolizino[8,7-b]indol-5-one (**3dc**).* White to light yellow powder, 135 mg, 78%: mp 260−264 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.57−11.52 (s, 1H), 8.13−8.10 (s, 1H), 7.63−7.57 (d, J = 7.7 Hz, 1H), 7.46−7.42 (s, 1H), 7.40−7.36 (d, J = 8.6 Hz, 1H), 7.36−7.31 (d, J = 7.7 Hz, 1H), 7.11−7.06 (d, J = 8.8 Hz, 1H), 4.51−4.45 (dd, J = 13.3, 5.9 Hz, 1H), 3.40−3.32 (m, 1H), 2.82−2.73 (dd, J = 15.4, 4.5 Hz, 1H), 2.69−2.60 (m, 1H), 2.50−2.47 (s, 3H), 1.84−1.80 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 167.6, 149.8, 143.0, 137.5, 135.00, 129.9, 128.2, 127.5, 123.9, 123.5, 123.4, 121.8, 118.1, 113.2, 106.78, 62.1, 35.6, 26.3, 22.1, 21.7; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 336.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{20}H_{18}ClN_2O^+$ 337.1108, found 337.1094.

*3-Methoxy-13b-methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]-indolizino[8,7-b]indol-5-one (**3ad**).* White to light yellow powder, 170 mg, 86%: mp 282−285 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.36−11.31 (s, 1H), 8.22−8.17 (d, J = 8.4 Hz, 1H), 7.40−7.34 (m, 2H), 7.30−7.25 (m, 1H), 7.21−7.18 (d, J = 2.4 Hz, 1H), 7.12−7.05 (m, 1H), 7.00−6.94 (d, J = 7.1 Hz, 1H), 4.56−4.46 (dd, J = 13.2, 5.3 Hz, 1H), 3.83−3.79 (s, 3H), 3.44−3.37 (dd, J = 12.4, 4.5 Hz, 1H), 2.82−2.74 (m, 1H), 2.73−2.63 (m, 1H), 1.83−1.81 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 167.4, 160.2, 142.0, 136.4, 135.9, 132.1, 126.3, 124.1, 121.9, 120.0, 119.2, 118.6, 111.5, 106.7, 106.3, 61.9, 56.0, 35.9, 26.3, 21.8; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 318.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{20}H_{19}N_2O_2^+$ 319.1441, found 319.1435.

*3,10-Dimethoxy-13b-methyl-7,8,13,13b-tetrahydro-5H-benzo-[1,2]indolizino[8,7-b]indol-5-one (**3bd**).* White powder, 165 mg, 90%: mp 281−285 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.17−11.14 (s, 1H), 8.20−8.14 (d, J = 8.4 Hz, 1H), 7.29−7.23 (m, 2H), 7.21−7.18 (d, J = 2.5 Hz, 1H), 6.89−6.86 (d, J = 2.4 Hz, 1H), 6.74−6.69 (dd, J = 8.7, 2.4 Hz, 1H), 4.54−4.45 (dd, J = 13.2, 5.3 Hz, 1H), 3.83−3.79 (s, 3H), 3.73−3.71 (s, 3H), 3.43−3.36 (m, 1H), 2.80−2.71 (dd, J = 15.1, 4.3 Hz, 1H), 2.71−2.61 (m, 1H), 1.81−1.78 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 167.4, 160.2, 153.7, 142.1, 136.6, 132.1, 131.5, 126.7, 124.1, 120.0, 112.2, 111.8, 106.7, 106.2, 100.6, 61.9, 56.0, 55.7, 35.9, 26.4, 21.9; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 348.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{21}H_{21}N_2O_3^+$ 349.1548, found 349.1537.

*11-Fluoro-3-methoxy-13b-methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indol-5-one (**3ed**).* White to light yellow powder, 141 mg, 75%: mp 275−278 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.46−11.44 (s, 1H), 8.17−8.14 (d, J = 8.4 Hz, 1H), 7.38−7.34 (dd, J = 8.5, 5.5 Hz, 1H), 7.28−7.24 (dd, J = 8.4, 2.4 Hz, 1H), 7.20−7.17 (d, J = 2.3 Hz, 1H), 7.14−7.10 (dd, J = 10.0, 2.1 Hz, 1H), 6.85−6.79 (d, J = 8.9 Hz, 1H), 4.51−4.45 (dd, J = 13.2, 5.7 Hz, 1H), 3.82−3.78 (s, 3H), 3.39−3.32 (dd, J = 24.3, 4.1 Hz, 1H), 2.78−2.72 (dd, J = 15.4, 4.2 Hz, 1H), 2.68−2.61 (m, 1H), 1.81−1.77 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 167.4, 160.3, 160.2−158.3 (d, J_{C-F} = 234.9 Hz), 141.8, 136.5, 136.4−136.2 (d, J_{C-F} = 12.7 Hz), 132.1, 124.1, 123.2, 120.0, 119.8−119.5 (d, J_{C-F} = 10.0 Hz), 107.7−107.3 (d, J_{C-F} = 24.4 Hz), 106.7, 106.5, 97.8−97.5 (d, J_{C-F} = 25.4 Hz), 61.8, 56.0, 35.8, 26.2, 21.8; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 336.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{20}H_{18}FN_2O_2^+$ 337.1347, found 337.1336.

*14b-Methyl-8,9,14,14b-tetrahydroindolo[2′,3′:3,4]pyrido[2,1-a]-isoquinolin-6(5H)-one (**3ae**).* White powder, 149 mg, 82%: mp 245−250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21−9.15 (s, 1H), 7.61−7.56 (d, J = 7.9 Hz, 1H), 7.56−7.50 (m, 2H), 7.31−7.23 (q, J = 7.7 Hz, 2H), 7.22−7.15 (m, 3H), 5.18−5.12 (dd, J = 13.1, 3.3 Hz, 1H), 3.97−3.90 (d, J = 19.5 Hz, 1H), 3.81−3.74 (d, J = 19.6 Hz, 1H), 3.12−3.03 (dd, J = 12.4, 3.6 Hz, 1H), 2.90−2.82 (d, J = 15.2 Hz, 1H), 2.75−2.66 (m, 1H), 1.93−1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 139.3, 136.1, 134.4, 131.5, 128.1, 127.8, 126.9, 126.5, 124.0, 122.3, 119.8, 118.6, 111.1, 111.0., 61.1, 38.7, 38.2, 27.3, 21.1; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 302.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{20}H_{19}N_2O^+$ 303.1492, found 303.1482.

*11-Methoxy-14b-methyl-8,9,14,14b-tetrahydroindolo[2′,3′:3,4]-pyrido[2,1-a]isoquinolin-6(5H)-one (**3be**).* White powder, 149 mg, 85%: mp 149−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.10 (s, 1H), 7.47−7.43 (d, J = 7.7 Hz, 1H), 7.38−7.31 (d, J = 8.6 Hz, 1H), 7.28−7.25 (d, J = 7.0 Hz, 1H), 7.23−7.19 (d, J = 7.3 Hz, 2H), 7.00−6.98 (d, J = 2.4 Hz, 1H), 6.93−6.88 (dd, J = 8.8, 2.4 Hz, 1H), 5.16−5.09 (ddd, J = 12.9, 4.7, 1.8 Hz, 1H), 3.95−3.88 (d, J = 19.4 Hz, 1H), 3.88−3.86 (s, 3H), 3.80−3.73 (d, J = 19.7 Hz, 1H), 3.11−3.04 (m, 1H), 2.84−2.82 (dd, J = 3.9, 1.8 Hz, 1H), 2.81−2.78 (dd, J = 4.0, 1.7 Hz, 1H), 2.77−2.67 (m, 1H), 1.88−1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 154.3, 139.2, 135.1, 131.6, 131.0, 128.2, 127.8, 127.0, 126.9, 123.8, 112.5, 111.8, 111.0, 100.5, 61.0, 55.9, 38.6, 38.0, 27.5, 21.1; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 333.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{21}H_{21}N_2O_2^+$ 333.1598, found 333.1595.

*11,14b-Dimethyl-8,9,14,14b-tetrahydroindolo[2′,3′:3,4]pyrido-[2,1-a]isoquinolin-6(5H)-one (**3ce**).* White powder, 151 mg, 83%: mp 146−151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57−8.50 (s, 1H), 7.50−7.46 (d, J = 8.2 Hz, 1H), 7.39−7.36 (d, J = 8.2 Hz, 1H), 7.36−7.35 (s, 1H), 7.29−7.25 (t, J = 7.0 Hz, 1H), 7.23−7.18 (m, 2H), 7.11−7.07 (dd, J = 8.2, 1.7 Hz, 1H), 5.15−5.09 (dd, J = 12.9, 3.2 Hz, 1H), 3.96−3.87 (d, J = 19.6 Hz, 1H), 3.80−3.72 (d, J = 19.6 Hz, 1H), 3.10−3.02 (td, J = 12.2, 3.5 Hz, 1H), 2.86−2.78 (dd, J = 15.1, 1.7 Hz, 1H), 2.75−2.66 (m, 1H), 2.50−2.47 (s, 3H), 1.91−1.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 139.3, 134.4, 134.3, 131.6, 129.2, 128.2, 127.8, 126.8, 126.8, 123.9, 123.8, 118.3, 110.7, 110.7, 61.0, 38.6, 38.1, 27.4, 21.4, 21.1; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 316.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{21}H_{21}N_2O^+$ 317.1648, found 317.1638.

*11-Chloro-14b-methyl-8,9,14,14b-tetrahydroindolo[2′,3′:3,4]-pyrido[2,1-a]isoquinolin-6(5H)-one (**3de**).* White powder, 125 mg, 72%: mp 169−173 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.82−11.75 (s, 1H), 7.55−7.52 (s, 1H), 7.50−7.45 (d, J = 8.5 Hz, 1H), 7.45−7.37 (d, J = 8.5 Hz, 1H), 7.30−7.24 (d, J = 2.5 Hz, 2H), 7.24−7.18 (d, J = 8.2 Hz, 1H), 7.17−7.10 (d, J = 8.3 Hz, 1H), 4.94−4.85 (dd, J = 12.4, 4.5 Hz, 1H), 4.14−4.01 (d, J = 19.5 Hz, 1H), 3.69−3.56 (d, J = 19.4 Hz, 1H), 2.96−2.74 (m, 2H), 2.53−2.40 (m, 1H), 1.85−1.80 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 169.2, 139.8, 137.2, 134.9, 132.6, 128.2, 127.9, 127.4, 126.7, 124.3, 123.8, 121.7, 117.9, 113.2, 109.5, 61.2, 38.2, 38.2, 26.5, 21.3; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 336.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{20}H_{18}ClN_2O^+$ 337.1102, found 337.1091.

*12-Fluoro-14b-methyl-8,9,14,14b-tetrahydroindolo[2′,3′:3,4]-pyrido[2,1-a]isoquinolin-6(5H)-one (**3ee**).* White powder, 124 mg, 69%: mp 195−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97−8.88 (s, 1H), 7.54−7.40 (m, 2H), 7.30−7.25 (d, J = 7.5 Hz, 1H), 7.24−7.15 (m, 3H), 6.98−6.90 (td, J = 9.6, 2.2 Hz, 1H), 5.16−5.09 (dd, J = 12.8, 4.5 Hz, 1H), 3.96−3.89 (d, J = 19.7 Hz, 1H), 3.80−3.73 (d, J = 19.7 Hz, 1H), 3.11−3.02 (td, J = 12.1, 3.4 Hz, 1H), 2.85−2.78 (dd, J = 15.3, 2.0 Hz, 1H), 2.75−2.66 (m, 1H), 1.92−1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 161.1−158.2 (d, J_{C-F} = 238.2 Hz), 138.8, 135.8−135.5 (d, J_{C-F} = 12.7 Hz), 134.3, 131.1, 127.9, 127.6, 126.6, 123.4, 122.8, 119.1−118.9 (d, J_{C-F} = 10.3 Hz), 110.7, 108.3−107.8 (d, J_{C-F} = 24.5 Hz), 97.5−96.9 (d, J_{C-F} = 26.3 Hz), 60.7 38.2, 37.7, 27.1, 20.7; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 321.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{20}H_{18}FN_2O^+$ 321.1398, found 321.1394.

*3-Chloro-14b-methyl-8,9,14,14b-tetrahydroindolo[2′,3′:3,4]-pyrido[2,1-a]isoquinolin-6(5H)-one (**3af**).* White powder, 168 mg, 80%: mp 250−253 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 11.58−11.55 (s, 1H), 7.50−7.43 (m, 3H), 7.42−7.40 (d, J = 2.3 Hz, 1H), 7.31−7.26 (dd, J = 8.5, 2.2 Hz, 1H), 7.17−7.13 (t, J = 7.7 Hz, 1H), 7.06−7.01 (t, J = 7.4 Hz, 1H), 4.92−4.86 (dd, J = 12.8, 3.1 Hz, 1H), 4.12−4.06 (d, J = 19.1 Hz, 1H), 3.71−3.65 (d, J = 19.6 Hz, 1H), 2.94−2.86 (td, J = 12.2, 2.8 Hz, 1H), 2.83−2.78 (d, J = 15.1 Hz, 1H), 2.49−2.42 (m, 1H), 1.83−1.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 168.8, 139.2, 136.5, 135.3, 135.0, 132.4, 127.8, 126.5, 126.4, 126.3, 121.9, 119.2, 118.6, 111.7, 109.8, 60.9, 38.4, 37.8, 26.4, 21.3; LRMS (ESI-

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quadrupole) m/z $[M + H]^+$ 336.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{20}H_{18}ClN_2O^+$ 337.1102, found 337.1096.

3-Chloro-11-methoxy-14b-methyl-8,9,14,14b-tetrahydroindolo-[2′,3′:3,4]pyrido[2,1-a]isoquinolin-6(5H)-one (**3bf**). White powder, 166 mg, 86%: mp 163−168 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 11.40−11.38 (s, 1H), 7.45−7.41 (d, J = 8.5 Hz, 1H), 7.41−7.40 (d, J = 2.0 Hz, 1H), 7.36−7.33 (d, J = 8.7 Hz, 1H), 7.31−7.26 (dd, J = 8.5, 1.9 Hz, 1H), 7.00−6.97 (d, J = 2.3 Hz, 1H), 6.80−6.76 (dd, J = 8.7, 2.4 Hz, 1H), 4.91−4.85 (dd, J = 12.8, 3.0 Hz, 1H), 4.11−4.04 (d, J = 19.5 Hz, 1H), 3.77−3.75 (s, 3H), 3.70−3.64 (d, J = 19.6 Hz, 1H), 2.94−2.84 (td, J = 12.2, 2.7 Hz, 1H), 2.80−2.75 (d, J = 15.0 Hz, 1H), 2.48−2.40 (ddd, J = 15.6, 11.9, 4.4 Hz, 1H), 1.81−1.80 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 168.7, 153.8, 139.2, 135.5, 135.3, 132.3, 131.5, 127.7, 126.6, 126.5, 126.4, 112.4, 112.0, 109.7, 100.4, 61.0, 55.7, 38.4, 37.8, 26.5, 21.4; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 366.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{21}H_{20}ClN_2O_2^+$ 367.1208, found 367.1197.

3-Chloro-11,14b-dimethyl-8,9,14,14b-tetrahydroindolo[2′,3′:3,4]-pyrido[2,1-a]isoquinolin-6(5H)-one (**3cf**). White powder, 154 mg, 76%: mp 285−188 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.42−11.40 (s, 1H), 7.43−7.41 (d, J = 8.5 Hz, 1H), 7.40−7.38 (s, 1H), 7.34−7.31 (d, J = 8.2 Hz, 1H), 7.29−7.26 (dd, J = 8.4, 1.9 Hz, 1H), 7.25−7.24 (s, 1H), 6.97−6.94 (d, J = 8.3 Hz, 1H), 4.89−4.83 (dd, J = 12.7, 3.1 Hz, 1H), 4.09−4.03 (d, J = 19.4 Hz, 1H), 3.68−3.63 (d, J = 19.5 Hz, 1H), 2.90−2.83 (td, J = 12.2, 2.7 Hz, 1H), 2.77−2.72 (d, J = 14.2 Hz, 1H), 2.46−2.38 (ddd, J = 15.5, 12.0, 4.4 Hz, 1H), 2.38−2.35 (s, 3H), 1.80−1.78 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 168.7, 139.2, 135.3, 135.0, 134.8, 132.3, 127.7, 127.7, 126.5, 126.5, 126.4, 123.4, 118.2, 111.4, 109.3, 61.0, 38.4, 37.8, 26.4, 21.6, 21.3; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 350.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{21}H_{20}ClN_2O^+$ 351.1259, found 351.1255.

3-Fluoro-14b-methyl-8,9,14,14b-tetrahydroindolo[2′,3′:3,4]-pyrido[2,1-a]isoquinolin-6(5H)-one (**3ag**). White powder, 167 mg, 84%: mp 255−260 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 11.60−11.58 (s, 1H), 7.51−7.48 (d, J = 8.7 Hz, 2H), 7.36−7.31 (t, J = 7.1 Hz, 1H), 7.25−7.20 (m, 1H), 7.19−7.10 (m, 2H), 7.07−7.02 (t, J = 7.9 Hz, 1H), 4.93−4.87 (dd, J = 12.8, 3.0 Hz, 1H), 4.06−4.00 (d, J = 19.7 Hz, 1H), 3.69−3.63 (d, J = 19.4 Hz, 1H), 2.95−2.87 (td, J = 12.2, 2.9 Hz, 1H), 2.83−2.79 (d, J = 13.8 Hz, 1H), 2.48−2.44 (m, 1H), 1.84−1.83 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 169.1, 162.1−159.8 (d, J_{C-F} = 240.9 Hz), 142.3−142.2 (d, J_{C-F} = 7.3 Hz), 136.5, 134.8, 130.0−129.9 (d, J_{C-F} = 8.0 Hz), 128.8, 126.3, 122.0, 119.3, 118.6, 114.7−114.5 (d, J_{C-F} = 21.0 Hz), 111.9−111.6 (d, J = 22.5 Hz), 111.7, 110.0, 61.1, 38.3, 37.4, 26.4, 21.3; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 320.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{20}H_{18}FN_2O^+$ 321.1398, found 321.1396.

3-Fluoro-11-methoxy-14b-methyl-8,9,14,14b-tetrahydroindolo-[2′,3′:3,4]pyrido[2,1-a]isoquinolin-6(5H)-one (**3bg**). White powder, 153 mg, 83%: mp 154−158 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 11.42−11.40 (s, 1H), 7.39−7.36 (d, J = 8.7 Hz, 1H), 7.35−7.31 (d, J = 6.3 Hz, 1H), 7.24−7.19 (dd, J = 10.7, 2.5 Hz, 1H), 7.16−7.10 (td, J = 8.5, 2.6 Hz, 1H), 7.00−6.99 (d, J = 2.3 Hz, 1H), 6.81−6.78 (dd, J = 8.7, 2.4 Hz, 1H), 4.92−4.87 (dd, J = 12.8, 3.0 Hz, 1H), 4.04−3.99 (d, J = 18.4 Hz, 1H), 3.76−3.76 (s, 3H), 3.68−3.62 (d, J = 19.4 Hz, 1H), 2.94−2.86 (td, J = 12.2, 2.9 Hz, 1H), 2.81−2.76 (d, J = 14.5 Hz, 1H), 2.48−2.41 (m, 1H), 1.82−1.81 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 169.1, 162.0−160.0 (d, J_{C-F} = 241.3 Hz), 153.8, 142.4−142.3 (d, J_{C-F} = 7.0 Hz), 135.3, 131.5, 130.0−129.9 (d, J_{C-F} = 7.8 Hz), 128.7, 126.6, 114.7−114.4 (d, J_{C-F} = 21.3 Hz), 112.4, 112.1, 111.8−111.6 (d, J_{C-F} = 24.2 Hz), 109.8, 100.5, 61.1, 55.7, 38.4, 37.4, 26.4, 21.4; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 350.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{21}H_{20}FN_2O_2^+$ 351.1503, found 351.1498.

11-Chloro-2-fluoro-14b-methyl-8,9,14,14b-tetrahydroindolo-[2′,3′:3,4]pyrido[2,1-a]isoquinolin-6(5H)-one (**3dg**). White powder, 137 mg, 75%: mp 103−106 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 11.84−11.81 (s, 1H), 7.58−7.55 (d, J = 2.1 Hz, 1H), 7.52−7.48 (d, J = 8.6 Hz, 1H), 7.37−7.33 (t, J = 7.2 Hz, 1H), 7.21−7.12 (m, 3H), 4.91−4.86 (dd, J = 12.8, 3.3 Hz, 1H), 4.06−3.99 (d, J = 19.5 Hz, 1H), 3.70−3.63 (d, J = 19.5 Hz, 1H), 2.94−2.86 (dd, J = 12.2, 2.3 Hz, 1H), 2.84−2.78 (d, J = 15.4 Hz, 1H), 2.48−2.41 (m, 1H), 1.85−1.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 169.1, 162.3−159.8 (d, J_{C-F} = 241.2 Hz), 142.0−141.9 (d, J_{C-F} = 7.1 Hz), 136.6, 135.0, 130.2−130.1 (d, J_{C-F} = 8.0 Hz), 128.8, 127.4, 124.0, 122.0, 118.1, 114.8−114.6 (d, J_{C-F} = 21.4 Hz), 113.4, 111.8−111.5 (d, J_{C-F} = 24.4 Hz), 110.1, 61.1, 38.3, 37.4, 26.4, 21.2; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 354.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{20}H_{17}ClFN_2O^+$ 355.1008, found 355.1003.

2-Methoxy-14b-methyl-8,9,14,14b-tetrahydroindolo[2′,3′:3,4]-pyrido[2,1-a]isoquinolin-6(5H)-one (**3ah**). White powder, 170 mg, 82%: mp 277−282 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.57−11.55 (s, 1H), 7.48−7.45 (d, J = 8.7 Hz, 2H), 7.20−7.17 (d, J = 8.3 Hz, 1H), 7.16−7.11 (t, J = 7.6 Hz, 1H), 7.04−7.00 (t, J = 7.8 Hz, 1H), 7.00−6.99 (d, J = 2.0 Hz, 1H), 6.87−6.84 (dd, J = 8.3, 2.6 Hz, 1H), 4.91−4.86 (dd, J = 12.5, 3.2 Hz, 1H), 3.97−3.89 (d, J = 19.1 Hz, 1H), 3.68−3.62 (s, 3H), 3.58−3.53 (d, J = 19.2 Hz, 1H), 2.91−2.82 (t, J = 11.8 Hz, 1H), 2.82−2.75 (d, J = 14.9 Hz, 1H), 2.46−2.41 (m, 1H), 1.81−1.78 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 169.6, 158.1, 141.3, 136.4, 135.3, 129.1, 126.3, 124.3, 121.8, 119.2, 118.5, 112.1, 111.8, 111.6, 109.7, 61.2, 55.4, 38.3, 37.4, 26.5, 21.4; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 332.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{21}H_{21}N_2O_2^+$ 333.1597, found 333.1590.

2,11-Dimethoxy-14b-methyl-8,9,14,14b-tetrahydroindolo-[2′,3′:3,4]pyrido[2,1-a]isoquinolin-6(5H)-one (**3bh**). White powder, 157 mg, 82%: mp 280−283 °C; ^{1}H NMR (500 MHz, DMSO) δ 11.39−11.36 (s, 1H), 7.36−7.33 (d, J = 8.8 Hz, 1H), 7.19−7.17 (d, J = 8.2 Hz, 1H), 6.99−6.96 (d, J = 2.3 Hz, 2H), 6.87−6.83 (dd, J = 8.1, 2.7 Hz, 1H), 6.79−6.75 (dd, J = 8.5, 2.5 Hz, 1H), 4.90−4.86 (dd, J = 12.4, 2.7 Hz, 1H), 3.94−3.89 (d, J = 19.2 Hz, 1H), 3.76−3.74 (s, 3H), 3.65−3.64 (s, 3H), 3.58−3.52 (d, J = 19.2 Hz, 1H), 2.89−2.82 (t, J = 11.6 Hz, 1H), 2.78−2.73 (d, J = 14.7 Hz, 1H), 2.46−2.38 (m, 1H), 1.79−1.76 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 169.6, 158.1, 153.7, 141.4, 135.8, 131.5, 129.0, 126.6, 124.3, 112.3, 112.1, 111.9, 111.7, 109.6, 100.4, 61.2, 55.7, 55.4, 38.3, 37.4, 26.5, 21.5; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 363.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{22}H_{23}N_2O_3^+$ 363.1703, found 363.1699.

12-Fluoro-2-methoxy-14b-methyl-8,9,14,14b-tetrahydroindolo-[2′,3′:3,4]pyrido[2,1-a]isoquinolin-6(5H)-one (**3eh**). White powder, 130 mg, 66%: mp 288−292 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.71−11.70 (s, 1H), 7.51−7.46 (dd, J = 8.6, 5.4 Hz, 1H), 7.26−7.19 (m, 2H), 6.99−6.97 (d, J = 2.6 Hz, 1H), 6.93−6.86 (m, 2H), 4.91−4.86 (dd, J = 12.6, 3.1 Hz, 1H), 3.97−3.90 (d, J = 19.2 Hz, 1H), 3.68−3.66 (s, 3H), 3.60−3.54 (d, J = 19.3 Hz, 1H), 2.92−2.83 (td, J = 12.3, 3.1 Hz, 1H), 2.82−2.77 (d, J = 15.2 Hz, 1H), 2.48−2.40 (m, 1H), 1.81−1.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 169.6, 160.6−158.2 (d, J_{C-F} = 234.0 Hz), 158.1, 141.3, 136.4−136.2 (d, J_{C-F} = 12.8 Hz), 135.8, 129.2, 124.3, 123.2, 119.8−119.6 (d, J_{C-F} = 10.4 Hz), 112.2, 111.7, 110.0, 107.8−107.5 (d, J_{C-F} = 24.5 Hz), 97.9−97.6 (d, J_{C-F} = 25.9 Hz), 61.2, 55.5, 38.2, 37.4, 26.5, 21.3; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 350.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{21}H_{20}FN_2O_2^+$ 351.1503, found 351.1495.

General Procedure for the Reduction of 3aa−3eh to 4aa−4bh (4aa as an Example). *13b-Methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indole* (**4aa**). In a dry two-necked bottle on ice bath, **3aa** (100 mg for each example, 0.35 mmol), $LiAlH_4$ (26.3 mg, 2.0 equiv), and $AlCl_3$ (92.5 mg, 2.0 equiv) were added under argon atmosphere. Dry THF (10 mL) was injected into the bottle, and the reaction was stirred and performed from 0 °C to room temperature for 2 h. THF was removed in vacuo followed by chromatography using a 65/35 mixture of petroleum ether and ethyl acetate as the eluent to obtain a white solid product **4aa** (82 mg, 86%): mp 162−166 °C; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.65 (s, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.31 (t, J = 7.2 Hz, 2H), 7.28 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.09 (t, J = 7.0 Hz, 1H), 4.24 (d, J = 12.7 Hz, 1H), 4.17 (d, J = 12.7 Hz, 1H), 3.54−3.46 (m, 1H), 3.22−3.13 (m, 1H), 2.64 (dd, J = 16.0, 3.9 Hz, 1H), 1.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 138.7, 136.4, 135.6, 127.1, 126.8, 126.7, 122.8, 121.4, 120.5, 119.0, 117.9, 110.4, 106.6, 64.1, 52.8, 41.2, 25.6, 15.8; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 274.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{19}H_{19}N_2^+$ 275.1542, found 275.1538.

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*10-Methoxy-13b-methyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]-indolizino[8,7-b]indole (**4ba**).* White powder, 87 mg, 91%: mp 146−151 °C; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.57 (s, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.1 Hz, 1H), 7.24−7.18 (m, 2H), 7.16 (d, *J* = 8.7 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.23 (d, *J* = 12.7 Hz, 1H), 4.15 (d, *J* = 12.7 Hz, 1H), 3.85 (s, 3H), 3.52−3.44 (m, 2H), 3.13 (ddd, *J* = 15.8, 11.5, 6.0 Hz, 1H), 2.59 (ddd, *J* = 16.0, 4.8, 1.3 Hz, 1H), 1.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 144.5, 138.6, 137.4, 130.7, 127.2, 127.1, 126.7, 122.8, 120.5, 111.1, 111.0, 106.4, 100.3, 64.2, 55.6, 52.8, 41.2, 25.6, 15.9; LRMS (ESI-quadrupole) *m*/*z* [M + H]$^+$ 305.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd $C_{20}H_{21}N_2O^+$ 305.1654, found 305.1650.

*10,13b-Dimethyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino-[8,7-b]indole (**4ca**).* White powder, 82 mg, 86%: mp 101−105 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (s, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.1 Hz, 1H), 7.19 (s, 2H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 4.20 (d, *J* = 12.7 Hz, 1H), 4.10 (d, *J* = 12.7 Hz, 1H), 3.47−3.36 (m, 2H), 3.11 (ddd, *J* = 15.8, 11.5, 6.0 Hz, 1H), 2.62−2.56 (m, 1H), 2.42 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 139.1, 136.9, 134.4, 128.8, 127.5, 127.4, 127.2, 123.3, 123.2, 121.0, 118.2, 110.5, 106.5, 64.7, 53.2, 41.6, 25.9, 21.4, 16.3; LRMS (ESI-quadrupole) *m*/*z* [M + H]$^+$ 289.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd $C_{20}H_{21}N_2^+$ 289.1699, found 289.1698.

*2,13b-Dimethyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]indolizino-[8,7-b]indole (**4ac**).* White powder, 79 mg, 83%: mp 94−97 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.12−7.04 (m, 3H), 7.00 (s, 1H), 4.18 (d, *J* = 12.7 Hz, 1H), 4.10 (d, *J* = 12.7 Hz, 1H), 3.50−3.42 (m, 2H), 3.13 (ddd, *J* = 17.2, 11.4, 6.1 Hz, 1H), 2.60 (dd, *J* = 15.8, 4.4 Hz, 1H), 2.31 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 142.0, 139.2, 137.3, 137.1, 136.0, 127.8, 127.2, 123.9, 121.7, 120.6, 119.4, 118.3, 110.8, 106.8, 64.3, 53.1, 41.6, 26.0, 21.3, 16.2; LRMS (ESI-quadrupole) *m*/*z* [M + H]$^+$ 289.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd $C_{20}H_{21}N_2^+$ 289.1699, found 289.1699.

*10-Methoxy-2,13b-dimethyl-7,8,13,13b-tetrahydro-5H-benzo-[1,2]indolizino[8,7-b]indole (**4bc**).* White powder, 81 mg, 85%: mp 96−98 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 (s, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.77 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.19 (d, *J* = 12.7 Hz, 1H), 4.11 (d, *J* = 12.7 Hz, 1H), 3.84 (s, 3H), 3.52−3.41 (m, 2H), 3.12 (ddd, *J* = 15.7, 11.4, 6.1 Hz, 1H), 2.57 (dd, *J* = 15.9, 3.7 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 142.2, 139.2, 138.1, 137.3, 131.2, 127.9, 127.6, 123.9, 120.7, 111.5, 111.4, 106.7, 100.7, 64.4, 56.0, 53.2, 41.7, 26.1, 21.3, 16.3; LRMS (ESI-quadrupole) *m*/*z* [M + H]$^+$ 319.9; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd $C_{21}H_{23}N_2O^+$ 319.1805, found 319.1801.

*10-Chloro-2,13b-dimethyl-7,8,13,13b-tetrahydro-5H-benzo[1,2]-indolizino[8,7-b]indole (**4dc**).* White powder, 77 mg, 80%: mp 96−100 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (s, 1H), 7.42 (s, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 1.6 Hz, 1H), 7.03 (s, 1H), 4.17 (d, *J* = 12.8 Hz, 1H), 4.11 (d, *J* = 12.7 Hz, 1H), 3.49−3.42 (m, 2H), 3.09 (ddd, *J* = 17.0, 11.1, 6.4 Hz, 1H), 2.58−2.52 (m, 1H), 2.33 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 139.3, 138.8, 137.5, 134.4, 128.4, 128.0, 125.0, 124.0, 121.8, 120.7, 118.0, 111.7, 106.7, 64.7, 53.2, 41.5, 26.0, 21.4, 16.1; LRMS (ESI-quadrupole) *m*/*z* [M + H]$^+$ 322.9; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd $C_{20}H_{20}ClN_2^+$ 323.1315, found 323.1310.

*14b-Methyl-5,6,8,9,14,14b-hexahydroindolo[2′,3′:3,4]pyrido[2,1-a]isoquinoline (**4ae**).* White powder, 83 mg, 87%: mp 104−107 °C; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 9.3 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 3.78−3.71 (m, 1H), 3.22 (ddd, *J* = 13.9, 6.2, 2.5 Hz, 1H), 3.14−3.08 (m, 3H), 3.03−2.95 (m, 1H), 2.76−2.68 (m, 2H), 1.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.9, 137.4, 135.6, 134.5, 130.0, 127.6, 126.7, 126.4, 125.8, 121.7, 119.5, 118.3, 110.9, 105.8, 58.2, 46.8, 45.4, 30.4, 28.8, 17.8; LRMS (ESI-quadrupole) *m*/*z* [M + H]$^+$ 289.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd $C_{20}H_{21}N_2^+$ 289.1699, found 289.1699.

*11-Methoxy-14b-methyl-5,6,8,9,14,14b-hexahydroindolo-[2′,3′:3,4]pyrido[2,1-a]isoquinoline (**4be**).* White powder, 82 mg, 86%: mp 86−90 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.72 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.22 (td, *J* = 7.4, 1.1 Hz, 1H), 7.16 (dd, *J* = 12.3, 8.1 Hz, 2H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.85 (s, 3H), 3.75 (ddd, *J* = 13.8, 10.1, 5.8 Hz, 1H), 3.23 (ddd, *J* = 13.8, 6.2, 2.5 Hz, 1H), 3.17−3.06 (m, 3H), 2.97 (ddd, *J* = 16.1, 10.1, 6.2 Hz, 1H), 2.82−2.73 (m, 1H), 2.68 (ddd, *J* = 15.8, 5.8, 2.5 Hz, 1H), 1.93 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 139.4, 137.9, 133.9, 130.3, 129.5, 127.5, 126.2 125.9, 125.4, 111.1, 111.0, 105.1, 100.1, 57.8, 55.5, 46.3, 45.0, 29.9, 28.3, 17.4; LRMS (ESI-quadrupole) *m*/*z* [M + H]$^+$ 319.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd $C_{21}H_{23}N_2O^+$ 319.1806, found 319.1802.

*11,14b-Dimethyl-5,6,8,9,14,14b-hexahydroindolo[2′,3′:3,4]-pyrido[2,1-a]isoquinoline (**4ce**).* White powder, 86 mg, 90%: mp 85−88 °C; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.71 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.26 (s, 1H), 7.21 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.94 (dd, *J* = 8.1, 1.2 Hz, 1H), 3.73 (ddd, *J* = 13.9, 10.1, 5.8 Hz, 1H), 3.21 (ddd, *J* = 13.8, 6.2, 2.6 Hz, 1H), 3.15−3.06 (m, 3H), 2.96 (ddd, *J* = 16.1, 10.1, 6.2 Hz, 1H), 2.79−2.71 (m, 1H), 2.67 (ddd, *J* = 15.9, 5.8, 2.5 Hz, 1H), 2.42 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 137.6, 134.4, 134.0, 130.0, 128.7, 127.8, 126.6, 126.4, 125.9, 123.1, 118.1, 110.5, 105.3, 58.2, 46.8, 45.4, 30.4, 28.8, 21.5, 17.8; LRMS (ESI-quadrupole) *m*/*z* [M + H]$^+$ 303.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd $C_{21}H_{23}N_2^+$ 303.1856, found 303.1849.

*11-Chloro-14b-methyl-5,6,8,9,14,14b-hexahydroindolo[2′,3′:3,4]-pyrido[2,1-a]isoquinoline (**4de**).* White powder, 78 mg, 81%: mp 88−92 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 1.9 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.24 (t, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.07 (dd, *J* = 8.6, 2.0 Hz, 1H), 3.73 (ddd, *J* = 13.9, 10.0, 5.8 Hz, 1H), 3.26−3.17 (m, 1H), 3.14−3.08 (m, 3H), 2.98−2.91 (m, 1H), 2.81−2.74 (m, 1H), 2.66 (ddd, *J* = 15.9, 5.8, 2.6 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 138.5, 133.9, 133.5, 129.6, 128.2, 126.3, 126.1, 125.3, 124.6, 121.3, 117.4, 111.4, 105.2, 57.8, 46.2, 45.0, 29.8, 28.2, 17.2; LRMS (ESI-quadrupole) *m*/*z* [M + H]$^+$ 323.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd $C_{20}H_{20}ClN_2^+$ 323.1319, found 323.1314.

*3-Chloro-14b-methyl-5,6,8,9,14,14b-hexahydroindolo[2′,3′:3,4]-pyrido[2,1-a]isoquinoline (**4af**).* White powder, 80 mg, 84%: mp 94−99 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.9 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.13 (s, 1H), 6.94−6.91 (m, 1H), 6.80 (dd, *J* = 8.6, 2.1 Hz, 1H), 3.85 (s, 3H), 3.72−3.63 (m, 1H), 3.23−3.17 (m, 1H), 3.15−3.03 (m, 3H), 2.97−2.90 (m, 1H), 2.78−2.68 (m, 2H), 1.88 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 138.0, 137.3, 135.9, 131.9, 130.3, 129.1, 127.5, 126.9, 126.1, 111.2, 111.1, 105.6, 100.1, 57.6, 55.5, 46.3, 44.7, 29.8, 27.8, 17.6; LRMS (ESI-quadrupole) *m*/*z* [M + H]$^+$ 323.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd $C_{20}H_{20}ClN_2^+$ 323.1319, found 323.1313.

*3-Chloro-11-methoxy-14b-methyl-5,6,8,9,14,14b-hexahydroindolo[2′,3′:3,4]pyrido[2,1-a]isoquinoline (**4bf**).* White powder, 81 mg, 84%: mp 103−107 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (s, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.31−7.27 (m, 2H), 7.18−7.08 (m, 3H), 3.69 (ddd, *J* = 13.6, 9.6, 5.8 Hz, 1H), 3.20 (ddd, *J* = 13.8, 6.1, 3.1 Hz, 1H), 3.15−3.11 (m, 2H), 3.06−2.93 (m, 2H), 2.78−2.70 (m, 2H), 1.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 136.4, 136.0, 135.2, 131.9, 129.2, 127.1, 126.9, 126.1, 121.4, 119.2, 118.0, 110.4, 105.7, 57.6, 46.3, 44.7, 29.8, 27.9, 17.5; LRMS (ESI-quadrupole) *m*/*z* [M + H]$^+$ 353.0; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd $C_{21}H_{22}ClN_2O^+$ 353.1415, found 353.1413.

*3-Chloro-11,14b-dimethyl-5,6,8,9,14,14b-hexahydroindolo-[2′,3′:3,4]pyrido[2,1-a]isoquinoline (**4cf**).* White powder, 86 mg, 90%: mp 99−103 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.27 (s, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.14 (d, *J* = 2.2 Hz, 1H), 7.01−6.94 (m, 1H), 3.69

(ddd, J = 13.6, 9.6, 5.8 Hz, 1H), 3.20 (ddd, J = 13.8, 6.1, 3.0 Hz, 1H), 3.17−3.01 (m, 3H), 2.95 (ddd, J = 15.8, 9.6, 6.1 Hz, 1H), 2.77−2.69 (m, 2H), 2.44 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 136.5, 136.0, 133.6, 131.8, 129.1, 128.4, 127.3, 126.9, 126.1, 122.9, 117.7, 110.1, 105.2, 57.6, 46.3, 44.7, 29.8, 27.9, 21.0, 17.5; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 337.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{21}H_{22}ClN_2^+$ 337.1466, found 337.1462.

*2-Methoxy-14b-methyl-5,6,8,9,14,14b-hexahydroindolo-[2′,3′:3,4]pyrido[2,1-a]isoquinoline (**4ah**).* White powder, 84 mg, 88%: mp 99−103 °C; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.95 (s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.17 (s, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.07 (t, J = 7.2 Hz, 2H), 6.78 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H), 3.74−3.67 (m, 1H), 3.24−3.18 (m, 1H), 3.13−3.09 (m, 2H), 3.03−2.92 (m, 2H), 2.74−2.68 (m, 2H), 1.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 141.0, 137.1, 135.7, 130.8, 127.6, 126.5, 121.7, 119.4, 118.3, 112.8, 111.2, 110.9, 105.9, 58.4, 55.5, 46.8, 45.6, 30.3, 27.6, 17.9; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 319.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{21}H_{23}N_2O^+$ 319.1806, found 319.1804.

*2,11-Dimethoxy-14b-methyl-5,6,8,9,14,14b-hexahydroindolo-[2′,3′:3,4]pyrido[2,1-a]isoquinoline (**4bh**).* White powder, 82 mg, 85%: mp 84−87 °C; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.84 (s, 1H), 7.22−7.18 (m, 2H), 7.09 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 2.5 Hz, 1H), 6.83−6.79 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.78−3.70 (m, 1H), 3.27−3.21 (m, 1H), 3.16−3.12 (m, 2H), 3.07−2.95 (m, 2H), 2.76−2.68 (m, 2H), 1.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 154.1, 141.0, 138.1, 130.8, 128.0, 126.5, 112.8, 111.6, 111.4, 111.1, 105.7, 100.6, 58.4, 56.0, 55.5, 46.8, 45.6, 30.3, 27.7, 18.0; LRMS (ESI-quadrupole) m/z $[M + H]^+$ 349.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd $C_{22}H_{25}N_2O_2^+$ 349.1910, found 349.1907.

Pharmacology Studies: Chemicals and Reagents. Silodosin and Tamsulosin were purchased from J&K chemical (Shanghai, China), and phenylephrine was purchased from Tokoyokasei. Mammalian expression vectors encoding Gα16, α_{1A}AR, and α_{1B}AR were purchased from the UMR cDNA Resource Center.

Cell Culture and Transfection. HEK293 cells obtained from American Type Culture Collection were maintained in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 100 mg/L of penicillin, and 100 mg/L of streptomycin at 37 °C in a humidified atmosphere of 5% CO_2. HEK293 cells were cotransfected with plasmids encoding various α_1ARs and Gα16 by electroporation. To generate stable cell lines, transfected cells were seeded onto 10-cm dishes, and 1 mg/mL of G418 and 40 μg/mL of blasticidin were added to the culture medium 24 h later. The selection medium was changed every 3 days until colonies formed. A single colony was isolated, expanded, and tested with a calcium mobilization assay to confirm the expression and proper function of the transfected genes.

Calcium Mobilization Assay. Cells were seeded onto 96-well plates at a density of 3×10^4 cells/well and cultured overnight. Cells were then incubated with 2 μM Fluo-4 AM in HBSS (5.4 mM KCl, 0.3 mM Na_2HPO_4, 0.4 mM KH_2PO_4, 4.2 mM $NaHCO_3$, 1.3 mM $CaCl_2$, 0.5 mM $MgCl_2$, 0.6 mM $MgSO_4$, 137 mM NaCl, 5.6 mM D-glucose, and 250 μM sulfinpyrazone, pH 7.4) at 37 °C for 45 min. After a thorough washing, 50 μL of HBSS containing either antagonists or 1% DMSO (negative control) were added. After incubation at room temperature for 10 min, 25 μL of agonist (phenylephrine, final concentration at 50 nM) were dispensed into the well using a FlexStation III microplate reader (Molecular Devices), and intracellular calcium change was recorded at an excitation wavelength of 485 nm and an emission wavelength of 525 nm.

Data Analysis. Data were analyzed with GraphPad Prism software (GraphPad). Nonlinear regression analysis was performed to generate dose−response curves and calculate concentrations for 50% inhibition (IC_{50}) values. Means ± SEM were calculated using this software.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectras for all compounds, and crystallographic data for compounds **3aa**, **3be**, and **4aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xxie@mail.shcnc.ac.cn.

*E-mail: hliu@mail.shcnc.ac.cn.

Author Contributions

§Z. Li and J. Li contributed equally to this work.

Notes

The authors declare no competing financial interest.

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