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Silica gel-promoted synthesis of multisubstituted spiroindolenines from tryptamines and γ-chloro-α,β-unsaturated ketones

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ABSTRACT

Here we report a one-pot synthesis of multisubstituted spiroindolenines from a series of tryptamine derivatives with γ-chloro-α,β-unsaturated ketones. The reaction sequence consists of base-induced condensation and silica gel-promoted intramolecular Michael addition. The target molecules are afforded in up to 90% yield with up to >20:1 diastereoselectivity.

1. Introduction

Spiroindolenine is a privileged molecular scaffold that is widely embedded in biologically active natural products and pharmaceutical agents (Fig. 1) [1]. Therefore, extensive efforts have been devoted in the selective synthesis of multisubstituted spiroindolenines [2]. Among the known synthetic strategies towards the spiroindolenine structures, the intramolecular dearomatization of indole derivatives has attracted broad interests [3,4]. The nucleophilic attack of the C3 position of the indole ring to an appropriately tethered electrophile provides the target spirocyclic molecules with high efficiency and selectivity. In 2017, our group reported an Ir-catalyzed asymmetric allylic dearomatization of bis(indol-3-yl) allylic carbonates by applying a desymmetrization strategy (Scheme 1a) [5]. The reaction afforded six-membered-ring spiroindolenines bearing three contiguous stereogenic centers in excellent yields, diastereo- and enantioselectivities. In order to broaden the scope of the desymmetrization strategy, we envisioned that dearomatization of bis(indol-3-yl) α,β-unsaturated ketones **1** might be achieved *via* an intramolecular Michael reaction by a Brønsted acid (Scheme 2) [6]. To our surprise, compounds **1** were found quite reactive under even weak acidic conditions. They were spontaneously transformed into the target molecules **4** during the purification by silica gel column chromatography. This discovery prompted us to develop a silica gel-promoted one-pot synthesis of multisubstituted spiroindolenines **4** from tryptamine derivatives **2** and γ-chloro-α,β-unsaturated ketones [7]. Herein, we report the results from this study.

2. Results and discussion

Our study commenced with the evaluation of the model reaction between N-benzyl-2,2-di(1*H*-indol-3-yl)ethan-1-amine **2a** and (*E*)-5-chloropent-3-en-2-one **3a**. The condensation of **2a** with **3a** occurred smoothly in the presence of KI and K_2CO_3 in acetone at room temperature. The crude residue containing **1aa** (obtained after a simple work-up, see the Experimental section for details) was next subjected to the silica gel-promoted Michael addition reaction (Table 1). It was found that the reaction proceeded well in CH_2Cl_2, $CHCl_3$ or toluene, but was less efficient in Et_2O, THF or dioxane (entries 1–6). The mesh size and resource of the silica gel did not influence the reaction outcome significantly. The target molecule was typically afforded as a mixture of two diastereoisomers (**4aa** and **4aa′**) in about 70% combined yield with 5:1 dr using CH_2Cl_2 as the solvent (entries 1, 7–9). Further variation of other reaction parameters suggested the optimal conditions of

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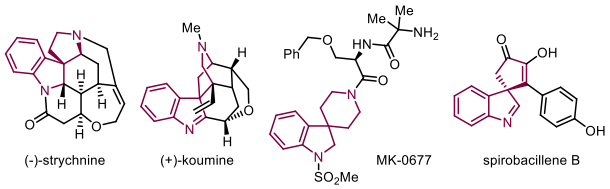
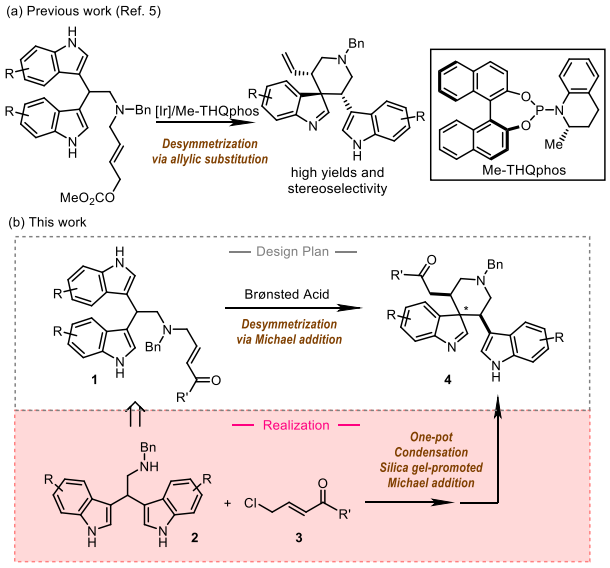
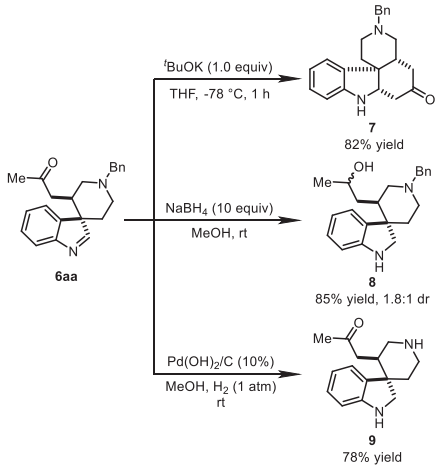


Fig. 1. Representative natural products and bioactive molecules containing spiroindolenine structures.



Scheme 1. Synthesis of Spiroindolenines via Desymmetrization Strategy.

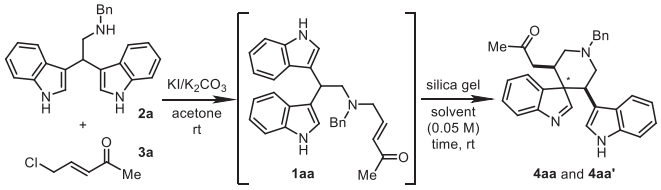


Scheme 2. Transformations of Product **6aa**.

the Michael addition as described in entry 13. The reaction was performed on a 0.2 mmol scale in CH_2Cl_2 (0.025 M) at room temperature for 1 h with silica gel II (100–200 mesh, 200 mg).

With the optimal conditions in hands, the scope of this reaction was next explored. Various bis(indol-3-yl) derived amines **2** and γ-chloro-α,β-unsaturated alkyl or aryl ketones **3** could participate the reactions, delivering the desired indol-3-yl substituted six-membered-ring spiroindolenines as a pair of separable diastereoisomers (**4** and **4′**), in reasonable to good combined yields

Table 1
Optimization of reactions Conditions[a].



entry	silica gel[b]	solvent	time (h)	yield (%)[c]	dr[d]
1	silica gel I	CH_2Cl_2	1	74	5:1
2	silica gel I	$CHCl_3$	1	70	5:1
3	silica gel I	Et_2O	8	65	3:1
4	silica gel I	THF	8	20	/
5	silica gel I	dioxane	8	/	/
6	silica gel I	toluene	1	68	4:1
7	silica gel II	CH_2Cl_2	1	74	5:1
8	silica gel III	CH_2Cl_2	1	69	5:1
9	silica gel IV	CH_2Cl_2	1	70	5:1
10[e]	silica gel II	CH_2Cl_2	2	68	3:1
11[f]	silica gel II	CH_2Cl_2	2	50	3:1
12[g]	silica gel II	CH_2Cl_2	1	63	4:1
13[h]	silica gel II	CH_2Cl_2	1	76	5:1

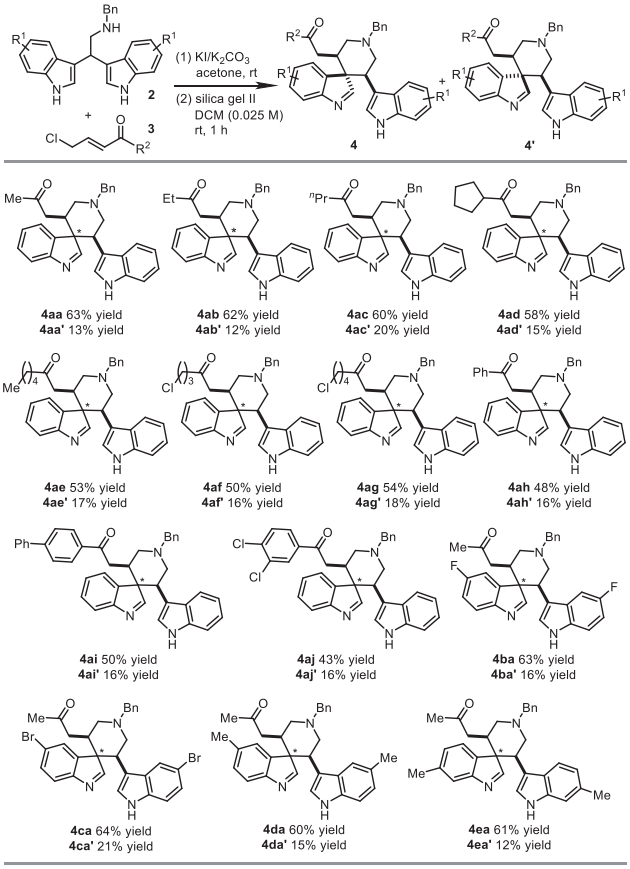
[a] Reaction conditions for step 1: **2a** (0.2 mmol), **3a** (1.2 equiv), K_2CO_3 (2 equiv), KI (1.2 equiv) in acetone (4 mL) at rt. Reaction conditions for step 2: Reaction residue of step 1, silica gel (200 mg) in solvent (4 mL) at rt.
[b] Silica gel I (300–400 mesh), silica gel II (100–200 mesh) and silica gel III (200–300 mesh) were purchased from Jiangyou Silicone Co., Ltd. Silica gel IV (230–400 mesh) was purchased from Silicycle Inc.
[c] Combined yield of two diastereoisomers.
[d] Determined by ^{1}H NMR spectra of the crude reaction mixture.
[e] Silica gel II (100 mg) was used.
[f] Silica gel II (50 mg) was used.
[g] In CH_2Cl_2 (2 mL).
[h] In CH_2Cl_2 (8 mL).

(52–85%), albeit with moderate diastereoselectivity (3:1–5:1 dr) (Table 2). The relative configurations of **4aa** and **4aa′** were determined by 2D NMR (See the SI for details), and those of other products were assigned by analogy. In each diastereoisomer of the products, both the alkyl ketone moiety and the unreacted indole ring adopt the *equatorial* position of the piperidine ring. The relative configurations of the quaternary carbon at the ring junction are different in **4** and **4'** (See the SI for details). Halogen atoms can be tolerated on the alkyl chain of **3** and also the indole ring of **2**, leaving possible handles for further derivations of the products. The reaction was readily scaled-up. Compounds **4aa** and **4aa′** could be obtained in 0.94 g (74% yield, 4:1 dr) from a 3 mmol-scale reaction under the standard conditions.

The reaction protocol is also compatible with tryptamine derivatives **5**. Under slightly modified conditions for the second step [in toluene at room temperature for 5 h with the silica gel I (300–400 mesh, 100 mg)], one-pot syntheses of spiroindolenines **6** were accomplished from the reactions of **5** with γ-chloro-α,β-unsaturated ketones **3** (Table 3). Notably, in all the cases, the target molecules were delivered in high yields (up to 90%) as a single diastereoisomer (>20:1 dr). The relative configuration of **6aa** was established by X-ray crystallographic analysis.

Spiroindolenine **6aa** was readily involved in a series of transformations (Scheme 2). In the presence of ^{t}BuOK as the base, an intramolecular Mannich reaction of **6aa** afforded tetracyclic spiroindoline **7** in 82% yield [8]. The methyl ketone and imine moieties of **6aa** were reduced in the presence of 10 equiv. of $NaBH_4$, leading to corresponding secondary alcohol **8** as a pair of diastereoisomers (85% yield, 1.8:1 dr). In addition, the hydrogenation of **6aa** by

Table 2
Substrate scope for Bis(indol-3-yl) Derivatives[a].



[a] Reaction conditions for step 1: **2** (0.2 mmol), **3** (1.2 equiv), K_2CO_3 (2 equiv), KI (1.2 equiv) in acetone (4 mL) at rt. Reaction conditions for step 2: Reaction residue of step 1, silica gel II (100-200 mesh, 200 mg) in CH_2Cl_2 (8 mL) at rt for 1 h. Isolated yields of **4** and **4'** are reported.

$Pd(OH)_2/C$ with the concomitant removal of the benzyl group delivered spiroindoline **9** in 79% yield.

3. Conclusions

In summary, we have developed a one-pot synthesis of multi-substituted spiroindolenines from tryptamine derivatives and γ-chloro-α,β-unsaturated ketones, employing the intramolecular Michael addition promoted by silica gel as the key step. The reaction features readily available starting materials, mild reaction conditions and operational simplicity. The synthetic utility of the products has been demonstrated by several useful transformations.

4. Experimental section

4.1. General

Unless stated, all reactions were carried out in flame-dried glassware under a dry argon atmosphere. All solvents were purified and dried according to standard methods prior to use. ^1H and ^{13}C NMR spectra were recorded on a Varian instrument (300 MHz and 75 MHz, 400 MHz and 100 MHz respectively) and internally referenced to tetramethylsilane signal or residual protio solvent signals. Data for ^1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). For HRMS analyses of new compounds, the species containing ^{35}Cl or ^{79}Br isotope(s) were measured.

4.2. General procedure for the preparation of *2*

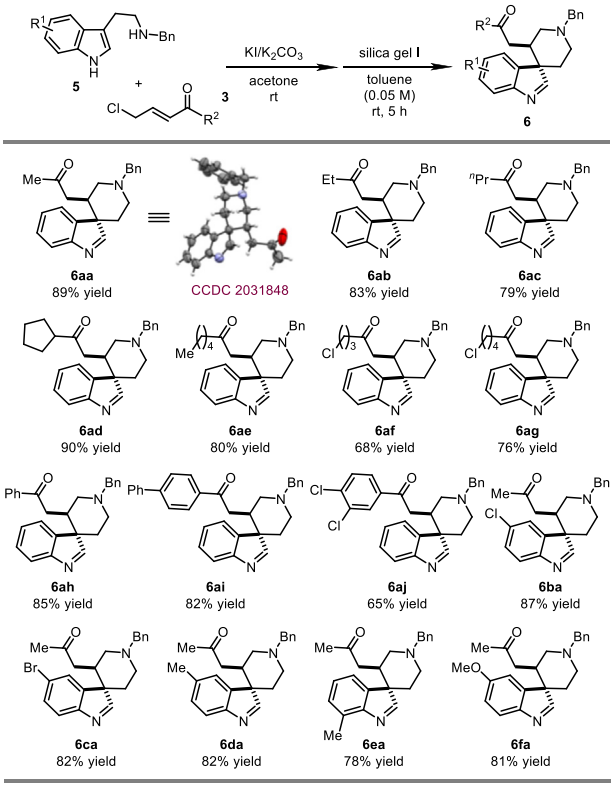
The synthesis of **2a**, **2b**, **2c**, **2d**, **2e** was accomplished via the following route according to reported procedures [5].

To a stirred solution of 2,2-di(*1H*-indol-3-yl)ethan-1-amine derivative (2.0 mmol) was added PhCHO (2.4 mmol) in MeOH (20 mL), and the mixture was stirred for 12 h at room temperature. Then the reaction mixture was cooled to 0 °C, and $NaBH_4$ (10 mmol) was added in portions. After the reaction was complete (monitored by TLC), the solvent was removed by rotary evaporation. Then the residue was purified by silica gel column chromatography (PE/EtOAc = 3/2) to afford the desired product **2**.

*4.2.1. N-benzyl-2,2-di(1H-indol-3-yl)ethan-1-amine (**2a**) beige solid, m.p. = 73.2–75.8 °C, 694.4 mg, 95% yield (2 mmol scale)*

^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 2H), 7.59 (d, J = 8.0 Hz, 2H),

Table 3
Substrate scope for tryptamine Derivatives.



[a] Reaction conditions for step 1: **5** (0.2 mmol), **3** (1.2 equiv), K_2CO_3 (2 equiv), KI (1.2 equiv) in acetone (4 mL) at rt. Reaction conditions for step 2: Reaction residue of step 1, silica gel I (300-400 mesh, 100 mg) in toluene (4 mL) at rt for 5 h. Isolated yields of **6** are reported.

7.36–7.18 (m, 7H), 7.15 (t, J = 7.4 Hz, 2H), 7.03 (t, J = 7.6 Hz, 2H), 6.94 (d, J = 1.2 Hz, 2H), 4.81 (t, J = 7.0 Hz, 1H), 3.84 (s, 2H), 3.40 (d, J = 7.2 Hz, 2H), 1.61 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 136.5, 128.3, 128.1, 126.9, 126.8, 122.0, 121.9, 119.5, 119.2, 117.9, 111.1, 53.8, 53.4, 34.5. IR (thin film): ν_{max} (cm^{-1}) = 3411, 3053, 1454, 1338, 1264, 1094, 1011, 733, 699; HRMS (ESI) calcd for $C_{25}H_{24}N_3$ $[M+H]^+$: 366.1965, Found: 366.1961.

*4.2.2. N-benzyl-2,2-bis(5-fluoro-1H-indol-3-yl)ethan-1-amine (**2b**) beige solid, m.p. = 65.3–68.5 °C, 714.7 mg, 89% yield (2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 2H), 7.30–7.18 (m, 7H), 7.12 (dd, J = 10.0, 2.4 Hz, 2H), 7.04 (d, J = 2.4 Hz, 2H), 6.88 (td, J = 8.8, 2.4 Hz, 2H), 4.64 (t, J = 7.2 Hz, 1H), 3.84 (s, 2H), 3.36 (d, J = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4 (d, J = 235.4 Hz), 139.6, 133.1, 128.3 (d, J = 27.4 Hz), 127.1, 127.0, 127.0, 123.8, 117.3 (d, J = 4.7 Hz), 111.8 (d, J = 9.8 Hz), 110.4 (d, J = 26.6 Hz), 104.4 (d, J = 23.7 Hz), 53.57, 52.46, 34.48. ^{19}F NMR (376 MHz, $CDCl_3$) δ −124.58 to −124.52 (m, 1F). IR (thin film): ν_{max} (cm^{-1}) = 3464, 1484, 1453, 1344, 1264, 1167, 1095, 936, 852, 797, 732, 700; HRMS (ESI) calcd for $C_{25}H_{22}F_2N_3$ $[M+H]^+$: 402.1776, Found: 402.1773.

*4.2.3. N-benzyl-2,2-bis(5-bromo-1H-indol-3-yl)ethan-1-amine (**2c**) white solid, m.p. = 159.8–161.2 °C, 941.9 mg, 90% yield (2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (m, 2H), 7.50 (s, 2H), 7.27–7.24 (m, 5H), 7.17 (d, J = 1.2 Hz, 4H), 6.94 (d, J = 2.0 Hz, 2H), 4.76 (t, J = 7.2 Hz, 1H), 3.87 (s, 2H), 3.33 (d, J = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 128.9, 128.8, 128.5, 128.0, 125.1, 124.1, 121.6, 114.9, 112.9, 112.8, 110.0, 52.1, 50.3, 33.0. IR (thin film): ν_{max} (cm^{-1}) = 3441, 2823, 1452, 1325, 1214, 1091, 862, 834, 789, 765; HRMS (ESI) calcd for $C_{25}H_{22}Br_2N_3$ $[M+H]^+$: 552.0175, Found: 552.0172.

*4.2.4. N-benzyl-2,2-bis(5-methyl-1H-indol-3-yl)ethan-1-amine (**2d**) beige solid, m.p. = 70.2–72.4 °C, 763.4 mg, 97% yield (2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 2H), 7.37 (s, 2H), 7.29–7.14 (m, 7H), 6.97 (dd, J = 8.0, 1.6 Hz, 2H), 6.82 (d, J = 2.4 Hz, 2H), 4.75 (t, J = 7.2 Hz, 1H), 3.84 (s, 2H), 3.35 (d, J = 7.2 Hz, 2H), 2.38 (s, 6H), 1.96 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 134.9, 128.3, 128.3, 128.2, 127.1, 126.8, 123.5, 122.3, 119.1, 117.2, 110.8, 53.5, 53.1, 34.3, 21.5. IR (thin film): ν_{max} (cm^{-1}) = 3408, 3028, 2832, 1453, 1264, 1094, 794, 732, 699; HRMS (ESI) calcd for $C_{27}H_{28}N_3$ $[M+H]^+$: 394.2278, Found: 394.2274.

*4.2.5. N-benzyl-2,2-bis(6-methyl-1H-indol-3-yl)ethan-1-amine (**2e**) beige solid, m.p. = 82.2–84.8 °C, 771.3 mg, 98% yield (2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.20 (s, 5H), 6.99 (s, 2H), 6.73 (d, J = 8.0, 2H), 6.70 (d, J = 1.6 Hz, 2H), 4.84 (t, J = 7.4 Hz, 1H), 3.71 (s, 2H), 3.27 (d, J = 7.6 Hz, 2H), 2.29 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.0, 134.4, 131.7, 129.2, 128.7,

128.1, 124.3, 122.2, 121.0, 118.8, 115.2, 111.4, 51.8, 50.5, 32.9, 21.5. IR (thin film): ν_{max} (cm^{-1}) = 3407, 2829, 1452, 1337, 1263, 1091, 1027, 799, 732, 699; HRMS (ESI) calcd for $C_{27}H_{28}N_3$ $[M+H]^+$: 394.2278, Found: 394.2274.

4.3. General procedure for the preparation of **3a**–**3g**

The synthesis of **3a**–**3g** was accomplished via the following route according to reported procedures [9].

To a stirred solution of acid chloride (2.0 mmol) and allyl chloride (4.0 mmol) in dichloromethane (4 mL) was added aluminum chloride (2.4 mmol) in portions over 10 min. The mixture was stirred for 2 h at 0 °C and for 1 h at room temperature and then poured onto crushed ice. The organic layer was separated, dried with Na_2SO_4, filtered and triethylamine (4 mL) was added. The mixture was refluxed for 2 h, cooled to room temperature. The solvents were removed under reduced pressure, Then the residue was purified by silica gel column chromatography (PE/EtOAc = 50/1) to afford the desired product.

4.3.1. (E)-4-chloro-1-cyclopentylbut-2-en-1-one (**3d**) brown liquid, 193.3 mg, 56% yield (2 mmol scale, 2 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (dt, J = 15.5, 6.1 Hz, 1H), 6.41 (dt, J = 15.5, 1.6 Hz, 1H), 4.20 (dd, J = 6.2, 1.5 Hz, 2H), 3.17–3.02 (m, 1H), 1.91–1.73 (m, 4H), 1.56–1.73 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6, 139.1, 130.8, 49.6, 43.0, 28.9, 26.0. ν_{max} (cm^{-1}) = 2953, 2868, 1695, 1670, 1632, 1449, 1359, 1288, 1252, 1200, 1110, 975, 713, 661; HRMS (ESI) calcd for $C_9H_{14}ClO$ $[M+H]^+$: 173.0728, Found: 173.0735.

4.3.2. (E)-1,7-dichlorohept-2-en-4-one (**3f**) brown liquid, 223.2 mg, 62% yield (2 mmol scale, 2 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (dt, J = 15.6, 6.0 Hz, 1H), 6.37 (dt, J = 15.6, 1.6 Hz, 1H), 4.21 (dd, J = 6.0, 1.6 Hz, 2H), 3.61 (t, J = 6.4 Hz, 2H), 2.80 (t, J = 7.0 Hz, 2H), 2.11 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 139.7, 131.3, 44.3, 42.8, 37.3, 26.2. ν_{max} (cm^{-1}) = 2961, 1699, 1676, 1635, 1439, 1410, 1372, 1323, 1293, 1210, 1103, 974, 708, 648; HRMS (ESI) calcd for $C_7H_{11}Cl_2O$ $[M+H]^+$: 181.0181, Found: 181.0182.

4.3.3. (E)-1,8-dichlorooct-2-en-4-one (**3g**) brown liquid, 253.5 mg, 65% yield (2 mmol scale, 2 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (dt, J = 15.5, 6.1 Hz, 1H), 6.36 (dt, J = 15.6, 1.6 Hz, 1H), 4.20 (dd, J = 6.0, 1.6 Hz, 2H), 3.56 (t, J = 6.0 Hz, 2H), 2.63 (t, J = 6.8 Hz, 2H), 1.87–1.72 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 139.4, 131.2, 44.5, 42.8, 39.7, 31.7, 20.9. ν_{max} (cm^{-1}) = 2956, 1699, 1676, 1635, 1444, 1409, 1370, 1289, 1254, 1104, 975, 723, 705, 648; HRMS (ESI) calcd for $C_8H_{13}Cl_2O$ $[M+H]^+$: 195.0338, Found: 195.0339.

4.4. General procedure for the preparation of **3h**–**3j**

The synthesis of **3h, 3i, 3j** was accomplished *via* the following route according to reported procedures [10].

A solution of aryl-substituted 2-bromoethanone (2.0 mmol) and PPh_3 (2.2 mmol) in THF (6 mL) was refluxed for 4 h. Upon cooling, volatiles were removed, the solid was re-dissolved in DCM and extracted with aq. NaOH (20% w/w in H_2O), washed with water, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by silica gel chromatography (EtOAc/*n*-hexane = 2/1) to afford the pure product.

A solution of aldehyde (2.0 mmol) and the Wittig reagent (2.2 mmol) in toluene (4 mL) was refluxed for 24 h. The mixture was cooled and extracted with EtOAc, washed with H_2O, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by silica gel chromatography (*n*-hexane/DCM = 2/1) to afford the pure product.

4.4.1. (E)-1-([1,1′-biphenyl]-4-yl)-4-chlorobut-2-en-1-one (**3i**) white solid, m.p. = 112.4–114.1 °C, 231.0 mg, 45% yield (2 mmol scale, 3 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.48 (t, J = 7.4 Hz, 2H), 7.44–7.38 (m, 1H), 7.21–7.25 (m, 1H), 7.10 (dt, J = 15.2, 5.6 Hz, 1H), 4.32 (d, J = 5.6, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.2, 145.9, 141.4, 139.7, 135.9, 129.3, 129.0, 128.3, 127.5, 127.3, 127.3, 43.3. ν_{max} (cm^{-1}) = 1667, 1616, 1598, 1402, 1337, 1293, 1258, 1228, 1207, 1003, 732, 697; HRMS (ESI) calcd for $C_{16}H_{13}ClNaO$ $[M+Na]^+$: 279.0547, Found: 279.0553.

4.4.2. (E)-4-chloro-1-(3,4-dichlorophenyl)but-2-en-1-one (**3j**) white solid, m.p. = 44.6–46.5 °C, 234.0 mg, 47% yield (2 mmol scale, 3 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.10–7.04 (m, 2H), 4.29–4.25 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.2, 142.7, 137.7, 136.7, 133.3, 130.8, 130.5, 127.5, 126.4, 43.0. ν_{max} (cm^{-1}) = 3067, 1673, 1626, 1582, 1556, 1417, 1387, 1292, 1274, 1209, 1029, 972, 732, 675; HRMS (ESI) calcd for $C_{10}H_8Cl_3O$ $[M+H]^+$: 248.9635, Found: 248.9635.

4.5. General procedure for the preparation of **4** and **4'**

To a stirred solution of tryptamine derivative (0.2 mmol) and γ-chloro-α,β-unsaturated ketone (0.24 mmol) in acetone (4 mL) was added K_2CO_3 (0.4 mmol, 55 mg) and KI (0.24 mmol, 40 mg) at room temperature. After the reaction was complete (monitored by TLC), the crude reaction mixture was filtrated with Celite and washed with DCM, the solvent was removed under reduced pressure. Then the residue was re-dissolved in DCM and washed with water. The organic layer was dried over Na_2SO_4, and concentrated.

To a stirred solution of this residue in DCM (8 mL) was added silica gel (100–200 mesh, 200 mg). The reaction mixture was stirred at room temperature. After completion, the residue was filtrated and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc = 2/1 to 1/2) to afford the product.

4.5.1. 1-((3R,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)propan-2-one (**4aa**) beige solid, m.p. = 112.4–114.8 °C, 56.4 mg, 63% yield (0.2 mmol scale)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.65 (s, 1H), 7.60–7.53 (m, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.44–7.37 (m, 3H), 7.36–7.22 (m, 4H), 7.14–7.02 (m, 3H), 5.64 (s, 1H), 4.13 (dd, J = 12.0, 3.0 Hz, 1H), 3.83 (AB, J_{AB} = 13.2 Hz, 1H), 3.73 (AB, J_{BA} = 13.2 Hz, 1H), 3.35–3.25 (m, 1H), 3.06 (td, J = 12.0, 4.0 Hz, 2H), 2.82 (t, J = 12.0 Hz, 1H), 2.57 (t, J = 11.6 Hz, 1H), 1.87 (s, 3H), 1.66 (dd, J = 18.2, 8.2 Hz, 1H), 1.53 (dd, J = 18.2, 3.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7, 178.6, 157.8, 138.6, 137.6, 134.7, 129.0, 128.5, 128.3, 127.2, 127.0, 125.4, 125.2, 121.9, 121.7, 120.5, 119.4, 117.8, 112.5, 110.9, 65.2, 62.6, 55.3, 54.2, 42.5, 37.2, 34.5, 30.3. IR (thin film): ν_{max} (cm^{-1}) = 3056, 2923, 2810, 1712, 1355, 1264, 1159, 1099, 1026, 1014, 738, 701; HRMS (ESI) calcd for $C_{30}H_{30}N_3O$ $[M+H]^+$: 448.2383, Found: 448.2390.

4.5.2. 1-((3S,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)propan-2-one (**4aa′**) beige solid, m.p. = 101.2–103.5 °C, 11.6 mg, 13% yield (0.2 mmol scale)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.13 (s, 1H), 7.43–7.34 (m, 4H), 7.34–7.27 (m, 3H), 7.27–7.20 (m, 1H), 7.14–7.01 (m, 3H),

6.96 (td, J = 6.8, 0.8 Hz, 1H), 6.90–6.80 (m, 1H), 4.01 (dd, J = 12.4, 3.6 Hz, 1H), 3.80 (AB, J_{AB} = 13.2 Hz, 1H), 3.66 (AB, J_{BA} = 13.2 Hz, 1H), 3.24–3.12 (m, 3H), 2.73 (t, J = 12.0 Hz, 1H), 2.38 (t, J = 11.4 Hz, 1H), 1.93 (dd, J = 17.2, 9.2 Hz, 1H), 1.73 (s, 3H), 1.46 (dd, J = 17.6, 3.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.6, 174.3, 155.0, 140.6, 137.6, 134.9, 129.0, 128.3, 128.1, 127.2, 126.7, 126.5, 122.0, 121.5, 120.7, 120.5, 118.8, 118.4, 112.9, 110.7, 65.6, 62.8, 58.6, 57.9, 41.6, 40.1, 38.3, 30.0. ν_{max} (cm^{-1}) = 3056, 2922, 2807, 1714, 1548, 1494, 1456, 1340, 1264, 1163, 908, 731, 699; HRMS (ESI) calcd for $C_{30}H_{30}N_3O$ $[M+H]^+$: 448.2383, Found: 448.2381.

*4.5.3. 1-((3R,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)butan-2-one (**4 ab**) beige solid, m.p. = 84.3–86.6 °C, 60.7 mg, 62% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.74 (s, 1H), 7.58–7.53 (m, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.42–7.36 (m, 3H), 7.35–7.22 (m, 4H), 7.10–7.03 (m, 3H), 5.63 (d, J = 2.0 Hz, 1H), 4.12 (dd, J = 12.0, 3.6 Hz, 1H), 3.83 (AB, J_{AB} = 13.2 Hz, 1H), 3.72 (AB, J_{BA} = 13.2 Hz, 1H), 3.35–3.25 (m, 1H), 3.08–3.01 (m, 2H), 2.82 (t, J = 12.0 Hz, 1H), 2.58 (t, J = 11.4 Hz, 1H), 2.08 (q, J = 3.2 Hz, 2H), 1.63 (dd, J = 17.6, 8.0 Hz, 1H), 1.51 (dd, J = 17.6, 4.0 Hz, 1H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5, 178.6, 157.8, 138.6, 137.5, 134.7, 129.0, 128.5, 128.3, 127.2, 127.0, 125.4, 125.1, 121.8, 121.6, 120.5, 119.3, 117.8, 112.5, 110.9, 65.3, 62.6, 55.3, 54.3, 41.3, 37.2, 36.2, 34.7, 7.6. ν_{max} (cm^{-1}) = 2920, 1708, 1561, 1455, 1341, 1099, 693, 917, 738, 699; HRMS (ESI) calcd for $C_{31}H_{32}N_3O$ $[M+H]^+$: 462.2540, Found: 462.2549.

*4.5.4. 1-((3S,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)butan-2-one (**4 ab′**) beige solid, m.p. = 78.5–80.8 °C, 11.8 mg, 12% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.90 (s, 1H), 7.42–7.35 (m, 4H), 7.35–7.28 (m, 3H), 7.26–7.22 (m, 1H), 7.14–7.04 (m, 3H), 7.01–6.95 (m, 1H), 6.95–6.89 (m, 1H), 6.65 (d, J = 2.8 Hz, 1H), 4.01 (dd, J = 12.0, 3.6 Hz, 1H), 3.81 (AB, J_{AB} = 13.2 Hz, 1H), 3.65 (AB, J_{BA} = 13.2 Hz, 1H), 3.23–3.16 (m, 3H), 2.74 (t, J = 12.0 Hz, 1H), 2.45–2.36 (m, 1H), 2.08–1.95 (m, 1H), 1.94–1.83 (m, 2H), 1.45 (dd, J = 17.2, 3.2 Hz, 1H), 0.78 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4, 174.3, 155.0, 140.6, 137.5, 134.9, 129.0, 128.4, 128.1, 127.2, 126.8, 126.5, 122.1, 121.6, 120.7, 120.5, 118.9, 118.5, 113.1, 110.7, 65.7, 62.8, 58.5, 58.0, 40.4, 40.1, 38.4, 36.1, 7.5. ν_{max} (cm^{-1}) = 3052, 2925, 1712, 1548, 1494, 1456, 1373, 1342, 1264, 731, 700; HRMS (ESI) calcd for $C_{31}H_{32}N_3O$ $[M+H]^+$: 462.2540, Found: 462.2536.

*4.5.5. 1-((3R,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)pentan-2-one (**4ac**) beige solid, m.p. = 95.6–97.8 °C, 57.0 mg, 60% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.67 (s, 1H), 7.58–7.54 (m, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.43–7.37 (m, 3H), 7.36–7.21 (m, 4H), 7.12–7.02 (m, 3H), 5.64 (d, J = 2.4 Hz, 1H), 4.13 (dd, J = 12.0, 3.6 Hz, 1H), 3.83 (AB, J_{AB} = 13.2 Hz, 1H), 3.73 (AB, J_{BA} = 13.2 Hz, 1H), 3.35–3.26 (m, 1H), 3.08–3.01 (m, 2H), 2.82 (t, J = 12.0 Hz, 1H), 2.58 (t, J = 11.8 Hz, 1H), 2.06 (t, J = 7.4, 2H), 1.63 (dd, J = 17.8, 8.2 Hz, 1H), 1.51 (dd, J = 17.8, 4.2 Hz, 1H), 1.46–1.37 (m, 2H), 0.77 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 178.6, 157.9, 138.6, 137.6, 134.7, 129.0, 128.5, 128.3, 127.2, 127.0, 125.4, 125.1, 121.9, 121.7, 120.5, 119.4, 117.8, 112.5, 110.9, 65.3, 62.6, 55.3, 54.2, 45.0, 41.7, 37.2, 34.6, 17.0, 13.5. ν_{max} (cm^{-1}) = 2959, 2923, 2874, 2807, 1706, 1562, 1455, 1373, 1339, 738, 699; HRMS (ESI) calcd for $C_{32}H_{34}N_3O$ $[M+H]^+$: 476.2696, Found: 476.2706.

*4.5.6. 1-((3S,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)pentan-2-one (**4ac′**) beige solid, m.p. = 70.7–73.6 °C, 19.0 mg, 20% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 7.92 (s, 1H), 7.42–7.36 (m, 4H), 7.35–7.28 (m, 3H), 7.26–7.22 (m, 1H), 7.14–7.04 (m, 3H), 6.98 (m, J = 7.2 Hz, 1H), 6.92 (t, J = 7.2, 1H), 6.65 (d, J = 2.4 Hz, 1H), 4.01 (dd, J = 12.0, 3.6 Hz, 1H), 3.81 (AB, J_{AB} = 13.2 Hz, 1H), 3.65 (AB, J_{BA} = 13.2 Hz, 1H), 3.22–3.14 (m, 3H), 2.73 (t, J = 12.2 Hz, 1H), 2.40 (t, J = 11.8 Hz, 1H), 2.03–1.80 (m, 3H), 1.44 (dd, J = 17.4, 3.0 Hz, 1H), 1.37–1.22 (m, 2H), 0.70 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9, 174.2, 155.1, 140.6, 137.6, 134.9, 129.0, 128.3, 128.1, 127.2, 126.8, 126.5, 122.1, 121.6, 120.7, 120.5, 118.9, 118.5, 113.1, 110.7, 65.7, 62.8, 58.6, 58.0, 44.8, 40.7, 40.1, 38.3, 17.0, 13.5. ν_{max} (cm^{-1}) = 3055, 2962, 2877, 2807, 1709, 1619, 1548, 1455, 1341, 1263, 1098, 1066, 1011, 734, 700; HRMS (ESI) calcd for $C_{32}H_{34}N_3O$ $[M+H]^+$: 476.2696, Found: 476.2694.

*4.5.7. 2-((3R,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)-1-cyclopentylethan-1-one (**4ad**) beige solid, m.p. = 98.8–101.4 °C, 58.0 mg, 58% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.71 (s, 1H), 7.57–7.54 (m, 1H), 7.47–7.42 (m, 1H), 7.41–7.36 (m, 3H), 7.35–7.21 (m, 4H), 7.10–7.03 (m, 3H), 5.63 (d, J = 2.4 Hz, 1H), 4.12 (dd, J = 12.0, 3.6 Hz, 1H), 3.83 (AB, J_{AB} = 13.2 Hz, 1H), 3.71 (AB, J_{BA} = 13.2 Hz, 1H), 3.36–3.27 (m, 1H), 3.03 (dt, J = 12.0, 3.2 Hz, 2H), 2.82 (t, J = 12.0 Hz, 1H), 2.59 (t, J = 11.6 Hz, 1H), 2.54–2.44 (m, 1H), 1.68 (dd, J = 17.6, 8.0 Hz, 1H), 1.62–1.39 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 178.6, 157.9, 138.6, 137.6, 134.7, 129.0, 128.4, 128.3, 127.2, 127.0, 125.4, 125.1, 121.8, 121.6, 120.5, 119.3, 117.8, 112.5, 110.8, 65.3, 62.7, 55.3, 54.4, 51.4, 41.0, 37.3, 34.6, 28.9, 28.6, 25.8. ν_{max} (cm^{-1}) = 2963, 2927, 2873, 2807, 1706, 1563, 1454, 1373, 1340, 1097, 1047, 738, 699; HRMS (ESI) calcd for $C_{34}H_{36}N_3O$ $[M+H]^+$: 502.2853, Found: 502.2859.

*4.5.8. 2-((3S,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)-1-cyclopentylethan-1-one (**4ad′**) beige solid, m.p. = 79.4–82.4 °C, 15 mg, 15% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.07 (s, 1H), 7.42–7.35 (m, 4H), 7.34–7.27 (m, 3H), 7.26–7.21 (m, 1H), 7.13–7.02 (m, 3H), 6.97 (t, J = 7.0 Hz, 1H), 6.91 (t, J = 7.8 Hz, 1H), 4.01 (dd, J = 12.2, 3.4 Hz, 1H), 3.81 (AB, J_{AB} = 12.8 Hz, 1H), 3.64 (AB, J_{BA} = 13.2 Hz, 1H), 3.23–3.16 (m, 3H), 2.72 (t, J = 12.0 Hz, 1H), 2.46–2.33 (m, 2H), 1.93 (dd, J = 17.4, 8.6 Hz, 1H), 1.63–1.18 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.9, 174.3, 155.0, 140.6, 137.6, 134.9, 129.0, 128.3, 128.0, 127.2, 126.8, 126.5, 122.1, 121.5, 120.7, 120.5, 118.8, 118.5, 113.0, 110.7, 65.7, 62.8, 58.5, 58.1, 51.3, 40.1, 39.9, 38.1, 28.8, 28.1, 25.8, 25.8. ν_{max} (cm^{-1}) = 3056, 2949, 2868, 2805, 1705, 1548, 1494, 1455, 1370, 1342, 1263, 1097, 1012, 734, 699; HRMS (ESI) calcd for $C_{34}H_{36}N_3O$ $[M+H]^+$: 502.2853, Found: 502.2852.

*4.5.9. 1-((3R,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)butan-2-one (**4ae**) beige solid, m.p. = 72.6–74.4 °C, 53.0 mg, 53% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.68 (s, 1H), 7.57–7.54 (m, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.42–7.35 (m, 3H), 7.35–7.21 (m, 4H), 7.11–7.03 (m, 3H), 5.63 (d, J = 2.4 Hz, 1H), 4.13 (dd, J = 12.0, 3.6 Hz, 1H), 3.82 (AB, J_{AB} = 13.2 Hz, 1H), 3.72 (AB, J_{BA} = 13.2 Hz, 1H), 3.33–3.25 (m, 1H), 3.06–3.01 (m, 2H), 2.82 (t, J = 12.0 Hz, 1H), 2.57 (t, J = 11.6 Hz, 1H), 2.09–2.02 (m, 2H), 1.62 (dd, J = 18.0, 8.0 Hz, 1H), 1.50 (dd, J = 17.6, 4.0 Hz, 1H), 1.42–1.33 (m, 2H), 1.26–1.15 (m, 2H), 1.15–1.05 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2, 178.6, 157.9, 138.6, 137.6, 134.7, 129.0, 128.5, 128.3, 127.2, 127.0, 125.4, 125.1, 121.8, 121.7, 120.5, 119.4, 117.8, 112.5, 110.9, 65.3, 62.6, 55.3, 54.3, 43.1, 41.7, 37.2, 34.6, 31.2, 23.2, 22.3, 13.8. ν_{max} (cm^{-1}) = 2953, 2927, 2870, 1707, 1455, 1372, 1339, 1099, 738, 699; HRMS (ESI) calcd for $C_{34}H_{38}N_3O$ $[M+H]^+$: 504.3009, Found: 504.3016.

*4.5.10. 1-((3S,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)butan-2-one (**4ae′**) beige solid, m.p. = 75.2–77.8 °C, 17.0 mg, 17% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.88 (s, 1H), 7.42–7.35 (m, 4H), 7.35–7.27 (m, 3H), 7.26–7.22 (m, 1H), 7.15–7.03 (m, 3H), 6.98 (t, J = 7.0 Hz, 1H), 6.92 (t, J = 7.0 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 4.01 (dd, J = 12.0, 3.6 Hz, 1H), 3.81 (AB, J_{AB} = 13.2 Hz, 1H), 3.66 (AB, J_{BA} = 13.2 Hz, 1H), 3.22–3.14 (m, 3H), 2.73 (t, J = 12.2 Hz, 1H), 2.40 (t, J = 11.4 Hz, 1H), 2.02–1.94 (m, 1H), 1.91–1.82 (m, 2H), 1.44 (dd, J = 17.2, 3.2 Hz, 1H), 1.33–1.11 (m, 4H), 1.07–0.98 (m, 2H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1, 174.3, 155.1, 140.6, 137.6, 134.9, 129.0, 128.3, 128.1, 127.2, 126.8, 126.5, 122.1, 121.6, 120.7, 120.5, 118.9, 118.5, 113.1, 110.7, 65.7, 62.8, 58.6, 58.0, 43.0, 40.7, 40.1, 38.3, 31.1, 23.2, 22.3, 13.8. ν_{max} (cm^{-1}) = 3058, 3029, 2953, 2928, 1710, 1548, 1494, 1456, 1371, 1342, 1261, 1098, 1067, 1014, 737, 700; HRMS (ESI) calcd for $C_{34}H_{38}N_3O$ $[M+H]^+$: 504.3009, Found: 504.3008.

*4.5.11. 1-((3R,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)-3-chloropropan-2-one (**4af**) beige solid, m.p. = 70.7–72.8 °C, 51.0 mg, 50% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.62 (s, 1H), 7.58–7.48 (m, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.43–7.38 (m, 3H), 7.36–7.23 (m, 4H), 7.15–7.03 (m, 3H), 5.65 (d, J = 2.4 Hz, 1H), 4.13 (dd, J = 12.0, 3.6 Hz, 1H), 3.82 (AB, J_{AB} = 13.2 Hz, 1H), 3.74 (AB, J_{BA} = 13.2 Hz, 1H), 3.50–3.38 (m, 2H), 3.35–3.26 (m, 1H), 3.07–3.01 (m, 2H), 2.83 (t, J = 12.2 Hz, 1H), 2.59 (t, J = 11.8 Hz, 1H), 2.28–2.22 (m, 2H), 1.94–1.83 (m, 2H), 1.66 (dd, J = 17.6, 8.0 Hz, 1H), 1.54 (dd, J = 18.0, 4.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 178.6, 157.8, 138.5, 137.5, 134.7, 129.0, 128.6, 128.3, 127.3, 127.0, 125.4, 125.2, 121.9, 121.7, 120.5, 119.4, 117.8, 112.5, 110.9, 65.3, 62.7, 55.4, 54.2, 44.3, 41.9, 39.8, 37.2, 34.8, 26.0. ν_{max} (cm^{-1}) = 3337, 2972, 2924, 2887, 1713, 1454, 1377, 1087, 1046, 879, 741, 700; HRMS (ESI) calcd for $C_{32}H_{33}ClN_3O$ $[M+H]^+$: 510.2307, Found: 510.2314.

*4.5.12. 1-((3S,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)-3-chloropropan-2-one (**4af′**) beige solid, m.p. = 87.5–90.2 °C, 16.0 mg, 16% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.93 (s, 1H), 7.42–7.36 (m, 4H), 7.36–7.29 (m, 3H), 7.28–7.22 (m, 1H), 7.15–7.04 (m, 3H), 6.99 (t, J = 7.0 Hz, 1H), 6.93 (t, 7.0 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 4.02 (dd, J = 12.2, 3.4 Hz, 1H), 3.80 (AB, J_{AB} = 13.2 Hz, 1H), 3.68 (AB, J_{BA} = 13.2 Hz, 1H), 3.40–3.28 (m, 2H), 3.20–3.15 (m, 3H), 2.75 (t, J = 12.0 Hz, 1H), 2.42 (t, J = 12.4 Hz, 1H), 2.23–2.15 (m, 1H), 2.06–1.85 (m, 2H), 1.80–1.68 (m, 2H), 1.49 (dd, J = 17.0, 3.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5, 174.2, 155.1, 140.5, 137.5, 134.9, 129.0, 128.4, 128.2, 127.2, 126.8, 126.5, 122.2, 121.6, 120.7, 120.6, 118.9, 118.5, 113.0, 110.7, 65.7, 62.8, 58.6, 57.9, 44.2, 41.0, 40.1, 39.6, 38.4, 26.0. ν_{max} (cm^{-1}) = 3421, 3055, 2891, 2805, 2767, 1712, 1548, 1494, 1456, 1372, 1340, 1364, 735, 700; HRMS (ESI) calcd for $C_{32}H_{33}ClN_3O$ $[M+H]^+$: 510.2307, Found: 510.2305.

*4.5.13. 1-((3R,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)-3-chloropropan-2-one (**4 ag**) brown sticky oil, 56.6 mg, 54% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.68 (s, 1H), 7.58–7.54 (m, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.42–7.37 (m, 3H), 7.35–7.22 (m, 4H), 7.11–7.04 (m, 3H), 5.64 (d, J = 2.0 Hz, 1H), 4.12 (dd, J = 11.8, 3.4 Hz, 1H), 3.81 (AB, J_{AB} = 13.2 Hz, 1H), 3.73 (AB, J_{BA} = 13.2 Hz, 1H), 3.43 (t, J = 6.2 Hz, 2H), 3.34–3.21 (m, 1H), 3.06–3.00 (m, 2H), 2.83 (t, J = 12.0 Hz, 1H), 2.58 (t, J = 11.6 Hz, 1H), 2.09 (t, J = 7.0 Hz, 2H), 1.67–1.47 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 178.6, 157.8, 138.5, 137.6, 134.7, 129.0, 128.5, 128.3, 127.2, 127.0, 125.5, 125.2, 121.9, 121.7, 120.5, 119.4, 117.8, 112.5, 110.9, 65.3, 62.6, 55.4, 54.2, 44.5, 42.0, 41.7, 37.2, 34.7, 31.6, 20.7. ν_{max} (cm^{-1}) = 2928, 2808, 1708, 1456, 1339, 1216, 1098, 909, 736, 699; HRMS (ESI) calcd for $C_{33}H_{35}ClN_3O$ $[M+H]^+$: 524.2463, Found: 524.2475.

*4.5.14. 1-((3S,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)-3-chloropropan-2-one (**4 ag′**) brown sticky oil, 18.9 mg, 18% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.99 (s, 1H), 7.42–7.35 (m, 4H), 7.35–7.28 (m, 3H), 7.27–7.21 (m, 1H), 7.14–7.03 (m, 3H), 6.98 (t, J = 7.0 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 4.01 (dd, J = 12.0, 3.6 Hz, 1H), 3.79 (AB, J_{AB} = 13.2 Hz, 1H), 3.67 (AB, J_{BA} = 13.2 Hz, 1H), 3.38 (t, J = 6.4 Hz, 2H), 3.24–3.13 (m, 3H), 2.74 (t, J = 12.2 Hz, 1H), 2.41 (t, J = 12.4 Hz, 1H), 2.08–1.96 (m, 1H), 1.91–1.86 (m, 2H), 1.56–1.35 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 174.2, 155.0, 140.5, 137.6, 134.9, 129.0, 128.4, 128.1, 127.2, 126.8, 126.5, 122.2, 121.6, 120.7, 120.6, 118.9, 118.5, 113.0, 110.7, 65.7, 62.8, 58.6, 58.0, 44.5, 41.9, 40.8, 40.1, 38.3, 31.6, 20.7. ν_{max} (cm^{-1}) = 3048, 2886, 2806, 2766, 1710, 1548, 1493, 1455, 1371, 1341, 1264, 733, 700; HRMS (ESI) calcd for $C_{33}H_{35}ClN_3O$ $[M+H]^+$: 524.2463, Found: 524.2460.

*4.5.15. 2-((3R,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)-1-phenylethan-1-one (**4ah**) beige solid, m.p. = 93.1–95.2 °C, 48.9 mg, 48% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.68 (s, 1H), 7.64–7.60 (m, 2H), 7.59–7.54 (m, 1H), 7.50–7.44 (m, 2H), 7.44–7.28 (m, 8H), 7.26–7.22 (m, 1H), 7.13–7.03 (m, 3H), 5.67 (d, J = 2.4 Hz, 1H), 4.16 (dd, J = 12.2, 3.8 Hz, 1H), 3.86 (AB, J_{AB} = 13.6 Hz, 1H), 3.72 (AB, J_{BA} = 13.2 Hz, 1H), 3.49–3.42 (m, 1H), 3.18 (dd, J = 11.8, 4.2 Hz, 1H), 3.05 (dd, J = 11.6, 3.6 Hz, 1H), 2.85 (t, J = 12.0 Hz, 1H), 2.68 (t, J = 11.6 Hz, 1H), 2.16–2.12 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 178.5, 157.9, 138.7, 137.5, 136.6, 134.7, 133.1, 129.1, 128.6, 128.5, 128.4, 127.9, 127.2, 127.1, 125.5, 125.3, 121.9, 121.8, 120.6, 119.4, 117.9, 112.6, 110.9, 65.5, 62.7, 55.3, 54.4, 37.6, 37.4, 35.2. ν_{max} (cm^{-1}) = 2964, 1679, 1447, 1261, 1094, 1048, 1021, 799, 740, 689; HRMS (ESI) calcd for $C_{35}H_{32}N_3O$ $[M+H]^+$: 510.2540, Found: 510.2547.

*4.5.16. 2-((3S,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)-1-phenylethan-1-one (**4ah′**) beige solid, m.p. = 146.2–148.7 °C, 16.3 mg, 16% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.88 (s, 1H), 7.65–7.55 (m, 2H), 7.51–7.43 (m, 2H), 7.38 (d, J = 7.2 Hz, 3H), 7.35–7.27 (m, 5H), 7.27–7.21 (m, 1H), 7.15–7.02 (m, 3H), 6.98 (t, J = 7.0 Hz, 3H), 6.92 (t, J = 7.0 Hz, 3H), 6.68 (d, J = 2.0 Hz, 1H), 4.05 (dd, J = 12.2, 3.4 Hz, 1H), 3.85 (AB, J_{AB} = 13.2 Hz, 1H), 3.64 (AB, J_{BA} = 13.2 Hz, 1H), 3.41–3.28 (m, 2H), 3.20 (dd, J = 12.0, 3.2 Hz, 1H), 2.75 (t, J = 12.0 Hz, 1H), 2.54–2.40 (m, 2H), 2.03 (dd, J = 17.0, 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1, 174.3, 155.1, 140.6, 137.5, 136.4, 134.9, 133.1, 129.0, 128.4, 128.3, 128.2, 127.93, 127.2, 126.8, 126.5, 121.9, 121.6, 120.8, 120.6, 118.9, 118.5, 113.1, 110.7, 65.7, 62.8, 58.4, 58.1, 40.2, 38.8, 36.5. ν_{max} (cm^{-1}) = 3055, 2889, 2807, 2765, 1681, 1596, 1455, 1340, 1264, 1097, 1071, 1001, 733, 699; HRMS (ESI) calcd for $C_{35}H_{32}N_3O$ $[M+H]^+$: 510.2540, Found: 510.2537.

*4.5.17. 1-([1,1′-biphenyl]-4-yl)-2-((3R,3′S,5′R)-1′-benzyl-3′-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)ethan-1-one (**4ai**) beige solid, m.p. = 83.2–85.3 °C, 58.6 mg, 50% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.72–7.66 (m, 2H), 7.63 (s, 1H), 7.60–7.52 (m, 5H), 7.50–7.37 (m, 7H), 7.32 (t, J = 7.4 Hz, 3H), 7.26–7.20 (m, 1H), 7.15–7.03 (m, 3H), 5.67 (d, J = 2.4 Hz, 1H), 4.18 (dd, J = 12.0, 3.6 Hz, 1H), 3.87 (AB, J_{AB} = 13.2 Hz, 1H), 3.73 (AB, J_{BA} = 13.2 Hz, 1H), 3.52–3.40 (m, 1H), 3.20 (dd, J = 12.0, 4.0 Hz, 1H), 3.06 (dd, J = 12.0, 3.6 Hz, 1H), 2.86 (t,

J = 12.0 Hz, 1H), 2.71 (t, J = 11.6 Hz, 1H), 2.16 (d, J = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 178.5, 157.9, 145.7, 139.7, 138.6, 137.5, 135.3, 134.7, 129.0, 128.9, 128.6, 128.5, 128.3, 128.2, 127.2, 127.1, 127.0, 125.5, 125.3, 121.9, 121.8, 120.6, 119.4, 117.9, 112.6, 110.9, 65.5, 62.7, 55.2, 54.4, 37.6, 37.3, 35.3. ν_{max} (cm^{-1}) = 3052, 3032, 2923, 2808, 2361, 2339, 1677, 1602, 1453, 1263, 1097, 989, 731, 698; HRMS (ESI) calcd for $C_{41}H_{36}N_3O$ $[M+H]^+$: 586.2853, Found: 586.2861.

*4.5.18. 1-([1,1′-biphenyl]-4-yl)-2-((3S,3′S,5′R)-1′-benzyl-3'-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)ethan-1-one (**4ai′**) beige solid, m.p. = 113.1–114.8 °C, 18.7 mg, 16% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.89 (s, 1H), 7.71–7.63 (m, 2H), 7.61–7.52 (m, 4H), 7.49–7.42 (m, 3H), 7.39 (dd, J = 7.7, 1.5 Hz, 4H), 7.34–7.28 (m, 3H), 7.26–7.21 (m, 1H), 7.17–7.03 (m, 3H), 6.99 (t, J = 8.0 Hz, 1H), 6.93 (t, J = 8.0, 1H), 6.68 (d, J = 2.4 Hz, 1H), 4.06 (dd, J = 12.0, 3.6 Hz, 1H), 3.86 (AB, J_{AB} = 13.2 Hz, 1H), 3.65 (AB, J_{BA} = 13.6 Hz, 1H), 3.43–3.30 (m, 2H), 3.21 (dd, J = 11.8, 3.4 Hz, 1H), 2.76 (t, J = 12.2 Hz, 1H), 2.54–2.43 (m, 2H), 2.07 (dd, J = 16.8, 2.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8, 174.3, 155.2, 145.7, 140.7, 139.7, 137.6, 135.1, 134.9, 129.0, 128.9, 128.5, 128.3, 128.2, 127.2, 127.0, 126.8, 126.5, 121.9, 121.6, 120.8, 120.7, 118.9, 118.5, 113.1, 110.7, 65.8, 62.9, 58.5, 58.1, 40.2, 38.9, 36.6. ν_{max} (cm^{-1}) = 3056, 3031, 2923, 2807, 1678, 1603, 1455, 1341, 1267, 1221, 1190, 1098, 998, 739, 699; HRMS (ESI) calcd for $C_{41}H_{36}N_3O$ $[M+H]^+$: 586.2853, Found: 586.2851.

*4.5.19. 2-((3R,3′S,5′R)-1′-benzyl-3'-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)-1-(3,4-dichlorophenyl)ethan-1-one (**4aj**) beige solid, m.p. = 89.5–92.3 °C, 49.8 mg, 43% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.66 (s, 1H), 7.60–7.56 (m, 2H), 7.48–7.36 (m, 6H), 7.35–7.30 (m, 3H), 7.27–7.25 (m, 1H), 7.13–7.05 (m, 3H), 5.66 (d, J = 2.4 Hz, 1H), 4.17 (dd, J = 12.2, 3.8 Hz, 1H), 3.84 (AB, J_{AB} = 13.2 Hz, 1H), 3.75 (AB, J_{BA} = 13.2 Hz, 1H), 3.49–3.48 (m, 1H), 3.14–3.05 (m, 2H), 2.87 (t, J = 11.8 Hz, 1H), 2.68 (t, J = 11.8 Hz, 1H), 2.11–2.06 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 178.4, 157.9, 138.4, 137.7, 136.2, 134.8, 133.2, 130.6, 129.9, 129.0, 128.7, 128.4, 127.3, 127.1, 126.9, 125.5, 125.4, 122.0, 121.9, 120.6, 119.5, 117.9, 112.5, 110.9, 65.5, 62.7, 55.4, 54.3, 37.6, 37.4, 35.3. ν_{max} (cm^{-1}) = 3059, 2924, 2810, 1685, 1583, 1557, 1456, 1387, 1265, 1216, 1029, 736, 700; HRMS (ESI) calcd for $C_{35}H_{30}Cl_2N_3O$ $[M+H]^+$: 578.1760, Found: 578.1767.

*4.5.20. 2-((3S,3′S,5′R)-1′-benzyl-3'-(1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)-1-(3,4-dichlorophenyl)ethan-1-one (**4aj′**) beige solid, m.p. = 128.0–130.2 °C, 10.4 mg, 16% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.95–8.01 (m, 1H), 7.62 (s, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.39–7.34 (m, 4H), 7.34–7.21 (m, 5H), 7.12 (t, J = 7.4 Hz, 1H), 7.08–7.02 (m, 2H), 6.98 (t, J = 7.4 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.65 (s, 1H), 4.04 (dd, J = 12.2, 3.0 Hz, 1H), 3.82 (AB, J_{AB} = 13.2 Hz, 1H), 3.66 (AB, J_{BA} = 13.2 Hz, 1H), 3.34–3.15 (m, 3H), 2.76 (t, J = 12.2 Hz, 1H), 2.48 (t, J = 12.4 Hz, 1H), 2.35 (dd, J = 16.6, 9.4 Hz, 1H), 2.00 (dd, J = 16.6, 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0, 174.1, 155.0, 140.4, 137.6, 137.4, 135.7, 134.9, 133.0, 130.5, 129.9, 129.0, 128.3, 127.2, 126.9, 126.7, 126.6, 122.0, 121.6, 120.8, 120.7, 118.9, 118.4, 110.7, 65.7, 62.8, 58.5, 57.9, 40.1, 39.0, 36.6. ν_{max} (cm^{-1}) = 3052, 2809, 1687, 1583, 1553, 1456, 1264, 1030, 1010, 908, 730, 700; HRMS (ESI) calcd for $C_{35}H_{30}Cl_2N_3O$ $[M+H]^+$: 578.1760, Found: 578.1763.

*4.5.21. 1-((3R,3′S,5′R)-1′-benzyl-5-fluoro-3'-(5-fluoro-1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)propan-2-one (**4ba**) beige solid, m.p. = 86.2–88.9 °C, 60.9 mg, 63% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.82 (s, 1H), 7.53 (dd, J = 8.6, 2.2 Hz, 1H), 7.42–7.30 (m, 5H), 7.28–7.24 (m, 1H), 7.16 (dd, J = 9.6, 2.0 Hz, 1H), 7.08 (td, J = 8.8, 2.0 Hz, 1H), 7.00 (dd, J = 8.8, 4.4 Hz, 1H), 6.80 (td, J = 9.2, 2.4 Hz, 1H), 5.86 (d, J = 2.4 Hz, 1H), 3.99 (dd, J = 12.0, 3.6 Hz, 1H), 3.82 (AB, J_{AB} = 13.2 Hz, 1H), 3.72 (AB, J_{BA} = 13.2 Hz, 1H), 3.32–3.24 (m, 1H), 3.08 (dd, J = 12.0, 4.0 Hz, 1H), 3.01 (dd, J = 11.8, 3.8 Hz, 1H), 2.76 (t, J = 12.0 Hz, 1H), 2.49 (t, J = 11.8 Hz, 1H), 1.89 (s, 3H), 1.70 (dd, J = 18.2, 8.2 Hz, 1H), 1.53 (dd, J = 18.2, 3.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.3, 178.3 (d, J = 3.5 Hz), 160.5 (d, J = 246.0 Hz), 157.8 (d, J = 134.8 Hz), 153.7 (d, J = 2.3 Hz), 140.3 (d, J = 8.5 Hz), 137.4, 131.2, 128.9, 128.4, 127.3, 122.3, 122.2, 122.1, 115.1 (d, J = 23.5 Hz), 113.2 (d, J = 25.3 Hz), 112.5 (d, J = 4.9 Hz), 111.6 (d, J = 9.7 Hz), 110.5 (d, J = 26.5 Hz), 102.9 (d, J = 23.9 Hz), 66.0, 62.6, 54.9, 54.0, 42.5, 37.4, 34.4, 30.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.8 to −115.7 (m, 1F), −124.3 to −124.1 (m, 1F). ν_{max} (cm^{-1}) = 2964, 2899, 1713, 1628, 1585, 1455, 1362, 1257, 1165, 794, 736, 700; HRMS (ESI) calcd for $C_{30}H_{28}F_2N_3O$ $[M+H]^+$: 484.2195, Found: 484.2201.

*4.5.22. 1-((3S,3′S,5′R)-1′-benzyl-5-fluoro-3'-(5-fluoro-1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)propan-2-one (**4ba′**) beige solid, m.p. = 113.4–115.6 °C, 15.5 mg, 16% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.07 (s, 1H), 7.42–7.37 (m, 2H), 7.36–7.30 (m, 2H), 7.27–7.20 (m, 2H), 7.12 (dd, J = 7.6, 2.4 Hz, 1H), 7.03–6.97 (m, 2H), 6.83–6.72 (m, 2H), 6.69 (d, J = 2.0 Hz, 1H), 3.85 (dd, J = 12.0, 3.6 Hz, 1H), 3.81 (AB, J_{AB} = 13.6 Hz, 1H), 3.65 (AB, J_{BA} = 13.2 Hz, 1H), 3.24 (dd, J = 11.8, 3.0, 1H), 3.18–3.07 (m, 2H), 2.72 (t, J = 12.2 Hz, 1H), 2.37 (t, J = 11.6 Hz, 1H), 1.98 (dd, J = 17.6, 9.6 Hz, 1H), 1.82 (s, 3H), 1.47 (dd, J = 17.6, 2.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.1, 173.9 (d, J = 3.5 Hz), 161.9 (d, J = 248.2 Hz), 157.5 (d, J = 235.7 Hz), 151.0 (d, J = 1.7 Hz), 142.9 (d, J = 8.7 Hz), 137.4, 131.4, 128.9, 128.4, 127.3, 127.0 (d, J = 9.7 Hz), 122.7, 121.5 (d, J = 9.0 Hz), 115.1 (d, J = 24.0 Hz), 112.8 (d, J = 4.8 Hz), 111.4 (d, J = 9.7 Hz), 110.3 (d, J = 26.5 Hz), 109.7 (d, J = 24.7 Hz), 103.3 (d, J = 24.0 Hz), 66.1 (d, J = 2.1 Hz), 62.7, 58.1, 57.6, 41.5, 40.5, 38.0, 30.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.28 to −114.33 (m, 1F), −124.4 to −124.5 (m, 1F). ν_{max} (cm^{-1}) = 2917, 2856, 1713, 1631, 1583, 1486, 1358, 1259, 1168, 791, 700, 668; HRMS (ESI) calcd for $C_{30}H_{28}F_2N_3O$ $[M+H]^+$: 484.2195, Found: 484.2208.

*4.5.23. 1-((3R,3′S,5′R)-1′-benzyl-5-bromo-3'-(5-bromo-1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)propan-2-one (**4ca**) beige solid, m.p. = 72.4–74.6 °C, 77.5 mg, 64% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.88 (s, 2H), 7.63 (d, J = 1.8 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.43–7.32 (m, 4H), 7.30–7.24 (m, 2H), 7.12 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 5.81 (d, J = 2.0 Hz, 1H), 4.00 (dd, J = 12.0, 3.6 Hz, 1H), 3.83 (AB, J_{AB} = 13.2 Hz, 1H), 3.74 (AB, J_{BA} = 13.6 Hz, 1H), 3.33–3.24 (m, 1H), 3.06 (dd, J = 12.0, 4.0 Hz, 1H), 3.00 (dd, J = 12.0, 3.6 Hz, 1H), 2.78 (t, J = 12.2 Hz, 1H), 2.50 (t, J = 11.6 Hz, 1H), 1.89 (s, 3H), 1.72 (dd, J = 18.0, 8.0 Hz, 1H), 1.52 (dd, J = 18.4, 4.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.2, 178.9, 156.6, 140.7, 137.3, 133.3, 131.7, 128.9, 128.6, 128.5, 128.4, 127.3, 124.9, 122.9, 121.9, 120.5, 119.2, 112.9, 112.4, 111.9, 66.0, 62.4, 54.9, 54.0, 42.5, 37.3, 34.4, 30.3. ν_{max} (cm^{-1}) = 2964, 2899, 2807, 1712, 1557, 1442, 1363, 1260, 1149, 1025, 882, 795, 736, 699; HRMS (ESI) calcd for $C_{30}H_{28}Br_2N_3O$ $[M+H]^+$: 604.0594, Found: 604.0595.

*4.5.24. 1-((3S,3′S,5′R)-1′-benzyl-5-bromo-3'-(5-bromo-1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)propan-2-one (**4ca′**) beige solid, m.p. = 143.3–146.0 °C, 25.4 mg, 21% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$ δ 8.57 (s, 1H), 7.91 (s, 1H), 7.61 (d,

J = 1.6 Hz, 1H), 7.45 (d, J = 1.2 Hz, 1H), 7.42–7.37 (m, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.27–7.24 (m, 2H), 7.14 (d, J = 8.4 Hz, 1H), 7.08 (dd, J = 8.6, 1.8 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 3.86 (dd, J = 17.2, 3.6 Hz, 1H), 3.82 (AB, J_{AB} = 13.6 Hz, 1H), 3.64 (AB, J_{BA} = 13.2 Hz, 1H), 3.30–3.21 (m, 1H), 3.19–3.05 (m, 2H), 2.71 (t, J = 12.0 Hz, 1H), 2.36 (t, J = 11.6 Hz, 1H), 1.99 (dd, J = 17.8, 9.8 Hz, 1H), 1.85 (s, 3H), 1.49 (dd, J = 17.8, 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.1, 174.4, 154.0, 142.9, 137.6, 133.5, 131.5, 128.8, 128.4, 128.3, 127.3, 125.5, 124.8, 122.1, 121.9, 121.23, 120.9, 112.6, 112.4, 112.1, 66.1, 62.6, 57.9, 57.6, 41.5, 40.3, 37.8, 30.1. ν_{max} (cm^{-1}) = 2923, 2809, 2361, 1714, 1452, 1356, 1261, 1168, 1100, 883, 823, 795, 737, 701; HRMS (ESI) calcd for $C_{30}H_{28}Br_2N_3O$ $[M+H]^+$: 604.0594, Found: 604.0594.

*4.5.25. 1-((3R,3′S,5′R)-1′-benzyl-5-methyl-3′-(5-methyl-1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)propan-2-one (**4da**) beige solid, m.p. = 81.6–84.1 °C, 57.1 mg, 60% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.52 (m, 2H), 7.43–7.30 (m, 6H), 7.29–7.24 (m, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4, 1H), 5.59 (d, J = 2.4 Hz, 1H), 4.07 (dd, J = 12.0, 3.6 Hz, 1H), 3.86 (AB, J_{AB} = 13.6 Hz, 1H), 3.76 (AB, J_{BA} = 13.2 Hz, 1H), 3.29–3.22 (m, 1H), 3.08–2.98 (m, 2H), 2.81 (t, J = 12.0 Hz, 1H), 2.58 (t, J = 11.6 Hz, 1H), 2.45 (s, 3H), 2.42 (s, 3H), 1.89 (s, 3H), 1.66 (dd, J = 18.2, 8.2 Hz, 1H), 1.55 (dd, J = 18.0, 4.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 177.7, 155.7, 138.8, 137.4, 134.9, 133.1, 129.1, 128.5, 128.3, 127.2, 126.4, 123.5, 121.1, 120.6, 117.6, 112.2, 110.5, 64.8, 62.5, 55.0, 53.9, 42.5, 37.4, 34.7, 30.3, 21.8, 21.5. ν_{max} (cm^{-1}) = 2918, 2361, 1713, 1563, 1454, 1364, 1262, 1166, 1097, 1027, 796, 734, 700; HRMS (ESI) calcd for $C_{32}H_{34}N_3O$ $[M+H]^+$: 476.2696, Found: 476.2703.

*4.5.26. 1-((3S,3′S,5′R)-1′-benzyl-5-methyl-3′-(5-methyl-1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)propan-2-one (**4da′**) beige solid, m.p. = 88.0–91.6 °C, 14.3 mg, 15% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.88 (s, 1H), 7.48–7.40 (m, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.31–7.23 (m, 2H), 7.21 (d, J = 7.6 Hz, 1H), 7.14 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.83 (d, J = 8.4, 1H), 6.61 (d, J = 2.4, 1H), 3.98 (dd, J = 12.2, 3.4 Hz, 1H), 3.84 (AB, J_{AB} = 13.2 Hz, 1H), 3.67 (AB, J_{BA} = 13.2 Hz, 1H), 3.31–3.07 (m, 3H), 2.70 (t, J = 12.0 Hz, 1H), 2.43–2.35 (m, 3H), 2.33 (s, 3H), 1.99 (dd, J = 17.6, 9.6 Hz, 1H), 1.81 (s, 3H), 1.52 (dd, J = 17.6, 2.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 173.4, 153.1, 140.8, 137.8, 136.4, 133.3, 128.9, 128.7, 128.3, 127.9, 127.2, 127.1, 123.1, 122.9, 120.7, 120.0, 118.3, 112.7, 110.3, 65.1, 62.7, 58.4, 57.9, 41.6, 40.1, 38.4, 30.1, 21.5. ν_{max} (cm^{-1}) = 3029, 2913, 2805, 2767, 1713, 1546, 1467, 1452, 1357, 1321, 1166, 1095, 820, 795, 734, 700; HRMS (ESI) calcd for $C_{32}H_{34}N_3O$ $[M+H]^+$: 476.2696, Found: 476.2693.

*4.5.27. 1-((3R,3′S,5′R)-1′-benzyl-6-methyl-3′-(6-methyl-1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)propan-2-one (**4ea**) beige solid, m.p. = 104.7–106.6 °C, 58.0 mg, 61% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.45–7.42 (m, 2H), 7.40–7.37 (m, 2H), 7.35–7.29 (m, 3H), 7.26–7.22 (m, 1H), 7.07 (d, J = 7.2 Hz, 1H), 6.93–6.88 (m, 2H), 5.59 (d, J = 2.0 Hz, 1H), 4.07 (dd, J = 12.0, 3.6 Hz, 1H), 3.81 (AB, J_{AB} = 13.2 Hz, 1H), 3.72 (AB, J_{BA} = 13.2 Hz, 1H), 3.28–3.21 (m, 1H), 3.06–3.00 (m, 2H), 2.78 (t, J = 12.0 Hz, 1H), 2.53 (t, J = 11.6 Hz, 1H), 2.42 (s, 4H), 2.37 (s, 3H), 1.88 (s, 3H), 1.64 (dd, J = 18.2, 8.2 Hz, 1H), 1.53 (dd, J = 18.0, 3.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 178.7, 158.2, 138.5, 137.6, 135.5, 135.1, 131.7, 129.0, 128.3, 127.2, 125.9, 125.0, 122.4, 121.2, 119.9, 117.5, 112.6, 110.9, 110.0, 64.9, 62.6, 55.5, 54.2, 42.5, 37.3, 34.6, 30.3, 21.5. ν_{max} (cm^{-1}) = 2914, 2806, 1711, 1620, 1560, 1452, 1339, 1157, 1099, 1050, 798, 748, 699, 664; HRMS (ESI) calcd for $C_{32}H_{34}N_3O$ $[M+H]^+$: 476.2696, Found: 476.2706.

*4.5.28. 1-((3S,3′S,5′R)-1′-benzyl-6-methyl-3′-(6-methyl-1H-indol-3-yl)spiro[indole-3,4′-piperidin]-5′-yl)propan-2-one (**4ea′**) beige solid, m.p. = 88.5–90.7 °C, 11.4 mg, 12% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.75 (s, 1H), 7.40–7.20 (m, 7H), 7.13 (s, 1H), 6.92 (d, J = 7.2 Hz, 1H), 6.83 (s, 1H), 6.77 (dd, J = 8.4, 0.8 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 3.95 (dd, J = 12.2, 3.8 Hz, 1H), 3.78 (AB, J_{AB} = 13.2 Hz, 1H), 3.64 (AB, J_{BA} = 13.2 Hz, 1H), 3.25–3.02 (m, 3H), 2.70 (t, J = 12.0 Hz, 1H), 2.35 (t, J = 11.6 Hz, 1H), 2.31 (s, 3H), 2.21 (s, 3H), 1.91 (dd, J = 17.6, 9.6 Hz, 1H), 1.75 (s, 3H), 1.46 (dd, J = 17.4, 3.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 174.5, 155.5, 138.0, 137.7, 135.5, 131.3, 129.0, 128.4, 127.4, 127.2, 124.8, 121.5, 121.3, 120.8, 120.1, 118.2, 113.1, 110.7, 65.2, 62.8, 58.8, 58.0, 41.7, 40.2, 38.7, 30.1, 21.5, 21.4. ν_{max} (cm^{-1}) = 2919, 2806, 1714, 1588, 1548, 1453, 1365, 1264, 1159, 1096, 799, 731, 699; HRMS (ESI) calcd for $C_{32}H_{34}N_3O$ $[M+H]^+$: 476.2696, Found: 476.2695.

*4.6. General procedure for the preparation of **6***

To a stirred solution of tryptamine derivative (0.2 mmol) and **2** (0.24 mmol) in acetone (4 mL) was added K_2CO_3 (0.4 mmol, 55 mg) and KI (0.24 mmol, 40 mg) at room temperature. The reaction mixture was stirred overnight. After the reaction was complete (monitored by TLC), the crude reaction mixture was filtrated with Celite and washed with DCM. The solvent was removed under reduced pressure. Then the residue was resolved in DCM and washed with water. The organic layer was dried over Na_2SO_4, and concentrated.

To a stirred solution of this residue was added silica gel (300–400 mesh, 100 mg) in toluene (4 mL). The reaction mixture was stirred overnight at room temperature. After completion, the residue was filtered and concentrated. The residue was purified by silica gel flash column chromatography (hexanes/EtOAc = 2/1 to 1/2) to afford the product.

*4.6.1. 1-((3S,3′R)-1′-benzylspiro[indole-3,4′-piperidin]-3′-yl)propan-2-one (**6aa**) beige solid, m.p. = 99.1–101.4 °C, 59.2 mg, 89% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.65 (t, J = 7.4 Hz, 2H), 7.45–7.32 (m, 5H), 7.31–7.19 (m, 2H), 3.75 (AB, J_{AB} = 13.2 Hz, 1H), 3.62 (AB, J_{BA} = 13.2 Hz, 1H), 3.06–2.83 (m, 3H), 2.56 (td, J = 12.2, 2.6 Hz, 1H), 2.42–2.28 (m, 2H), 1.87 (s, 3H), 1.71 (dd, J = 18.4, 7.9 Hz, 1H), 1.54 (dd, J = 17.4, 3.6 Hz, 1H), 1.28 (dt, J = 13.4, 2.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7, 179.1, 156.3, 140.2, 137.9, 128.9, 128.3, 127.1, 125.4, 124.7, 121.7, 62.9, 59.5, 54.8, 48.4, 42.5, 33.4, 30.3, 29.7. IR (thin film): ν_{max} (cm^{-1}) = 2929, 2906, 2828, 2813, 1712, 1560, 1468, 1451, 1417, 1370, 1356, 1331, 1318, 1178, 961, 776, 754, 710; HRMS (ESI) calcd for $C_{22}H_{25}N_2O$ $[M+H]^+$: 333.1961, Found: 333.1965.

*4.6.2. 1-((3S,3′R)-1′-benzylspiro[indole-3,4′-piperidin]-3′-yl)butan-2-one (**6 ab**) brown oil, 57.5 mg, 83% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.65 (t, J = 7.0, 2H), 7.43–7.31 (m, 5H), 7.30–7.19 (m, 2H), 3.76 (AB, J_{AB} = 13.2 Hz, 1H), 3.62 (AB, J_{BA} = 13.2 Hz, 1H), 3.08–2.83 (m, 3H), 2.56 (td, J = 12.2, 2.6 Hz, 1H), 2.44–2.28 (m, 2H), 2.08 (q, J = 7.3 Hz, 2H), 1.69 (dd, J = 17.2, 8.0 Hz, 1H), 1.53 (dd, J = 17.6, 4.6 Hz, 1H), 1.27 (d, J = 12.8 Hz, 1H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4, 179.1, 156.2, 140.2, 137.8, 128.9, 128.2, 127.1, 125.3, 124.7, 121.7, 62.9, 59.5, 54.9, 48.4, 41.3, 36.2, 33.5, 29.9, 7.5. ν_{max} (cm^{-1}) = 2910, 1710, 1559, 1455, 1374, 1114, 1079, 990, 961, 752, 711; HRMS (ESI) calcd for $C_{23}H_{27}N_2O$ $[M+H]^+$: 347.2118, Found: 347.2124.

*4.6.3. 1-((3S,3′R)-1′-benzylspiro[indole-3,4′-piperidin]-3′-yl)pentan-2-one (**6ac**) brown oil, 57.0 mg, 79% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.65 (t, J = 7.0 Hz, 2H),

7.42–7.33 (m, 5H), 7.30–7.21 (m, 2H), 3.75 (AB, J_{AB} = 13.2 Hz, 1H), 3.62 (AB, J_{BA} = 13.2 Hz, 1H), 3.04–2.86 (m, 3H), 2.56 (td, J = 12.4, 2.8 Hz, 1H), 2.40–2.27 (m, 2H), 2.05 (t, J = 7.4 Hz, 2H), 1.68 (dd, J = 17.8, 8.2 Hz, 1H), 1.52 (dd, J = 17.6, 4.4 Hz, 1H), 1.45–1.36 (m, 2H), 1.29–1.26 (m, 1H), 0.77 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209, 179.1, 156.2, 140.2, 137.8, 128.9, 128.2, 127.1, 125.3, 124.7, 121.7, 63.0, 59.5, 54.8, 48.43, 45.0, 41.7, 33.5, 29.7, 16.9, 13.5. ν_{max} (cm^{-1}) = 2931, 2806, 1711, 1560, 1494, 1453, 1361, 1270, 1125, 1068, 1021, 962, 912, 735, 698; HRMS (ESI) calcd for $C_{24}H_{29}N_2O$ $[M+H]^+$: 361.2274, Found: 361.2284.

*4.6.4. 2-((3S,3′R)-1′-benzylspiro[indole-3,4′-piperidin]-3′-yl)-1-cyclopentylethan-1-one (**6ad**) brown oil, 69.6 mg, 90% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.65 (d, J = 8.0, 2H), 7.42–7.32 (m, 5H), 7.30–7.19 (m, 2H), 3.75 (AB, J_{AB} = 13.2 Hz, 1H), 3.62 (AB, J_{BA} = 13.2 Hz, 1H), 3.06–3.00 (m, 1H), 2.93–2.87 (m, 2H), 2.60–2.45 (m, 2H), 2.42–2.30 (m, 2H), 1.77–1.44 (m, 10H), 1.27 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1, 179.2, 156.3, 140.2, 137.9, 128.9, 128.2, 127.1, 125.3, 124.7, 121.6, 63.0, 59.6, 55.0, 51.3, 48.4, 41.1, 33.4, 29.8, 28.5, 25.7. ν_{max} (cm^{-1}) = 2946, 1706, 1560, 1451, 1368, 1025, 963, 747, 698, 655; HRMS (ESI) calcd for $C_{26}H_{31}N_2O$ $[M+H]^+$: 387.2431, Found: 387.2442.

*4.6.5. 1-((3S,3′R)-1′-benzylspiro[indole-3,4′-piperidin]-3′-yl)butan-2-one (**6ae**) brown oil, 60.0 mg, 80% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.65 (t, 6.8 Hz, 2H), 7.42–7.33 (m, 5H), 7.29–7.21 (m, 2H), 3.75 (AB, J_{AB} = 13.2 Hz, 1H), 3.62 (AB, J_{BA} = 13.2 Hz, 1H), 3.04–2.87 (m, 3H), 2.56 (td, J = 14.0, 2.0 Hz, 1H), 2.40–2.30 (m, 2H), 2.06 (t, J = 7.4 Hz, 2H), 1.68 (dd, J = 17.6, 7.6 Hz, 1H), 1.52 (dd, J = 17.6, 3.6 Hz, 1H), 1.41–1.33 (m, 2H), 1.29–1.17 (m, 3H), 1.14–1.06 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2, 179.2, 156.3, 140.3, 137.9, 128.9, 128.3, 127.1, 125.4, 124.8, 121.7, 63.0, 59.6 54.9, 48.5, 43.1, 41.7, 33.5, 31.1, 29.7, 23.2, 22.3, 13.8. ν_{max} (cm^{-1}) = 2927, 2806, 1711, 1560, 1453, 1362, 1269, 1109, 1073, 1025, 962, 912, 742, 698; HRMS (ESI) calcd for $C_{26}H_{33}N_2O$ $[M+H]^+$: 389.2587, Found: 389.2579.

*4.6.6. 1-((3S,3′R)-1′-benzylspiro[indole-3,4′-piperidin]-3′-yl)-3-chloropropan-2-one (**6af**) brown oil, 53.7 mg, 68% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.65 (t, J = 8.0 Hz, 2H), 7.43–7.33 (m, 5H), 7.29–7.22 (m, 2H), 3.74 (AB, J_{AB} = 13.2 Hz, 1H), 3.63 (AB, J_{BA} = 13.2 Hz, 1H), 3.48–3.39 (m, 2H), 3.06–2.96 (m, 1H), 2.94–2.88 (m, 2H), 2.57 (td, J = 12.0, 2.4 Hz, 1H), 2.42–2.30 (m, 2H), 2.27–2.23 (m, 2H), 1.91–1.84 (m, 2H), 1.72 (dd, J = 17.4, 7.4 Hz, 1H), 1.57 (dd, J = 17.8, 4.2 Hz, 1H), 1.34–1.23 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6, 179.1, 156.2, 140.0, 137.9, 128.9, 128.2, 127.1, 125.4, 124.7, 121.7, 62.9, 59.5, 54.7, 48.5, 44.2, 41.9, 39.7, 33.6, 29.7, 25.9. ν_{max} (cm^{-1}) = 2913, 2807, 2767, 1712, 1560, 1494, 1451, 1361, 746, 699; HRMS (ESI) calcd for $C_{24}H_{28}ClN_2O$ $[M+H]^+$:395.1885, Found: 395.1892.

*4.6.7. 1-((3S,3′R)-1′-benzylspiro[indole-3,4′-piperidin]-3′-yl)-3-chloropropan-2-one (**6 ag**) brown oil, 62.2 mg, 76% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.64 (t, J = 7.4 Hz, 2H), 7.44–7.31 (m, 5H), 7.30–7.19 (m, 2H), 3.74 (AB, J_{AB} = 13.2 Hz, 1H), 3.63 (AB, J_{BA} = 13.2 Hz, 1H), 3.43 (t, J = 6.4 Hz, 2H), 3.05–2.97 (m, 1H), 2.93–2.88 (m, 2H), 2.57 (td, J = 12.0, 2.4 Hz, 1H), 2.43–2.28 (m, 2H), 2.09 (t, J = 7.0 Hz, 2H), 1.77–1.46 (m, 6H), 1.34–1.24 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2, 179.1, 156.2, 140.1, 137.8, 129.0, 128.3, 128.3, 127.2, 125.4, 124.7, 121.7, 62.9, 59.5, 54.8, 48.5, 44.5, 42.0, 41.8, 33.6, 31.6, 29.7, 20.7.

ν_{max} (cm^{-1}) = 2936, 2911, 2806, 2766, 1710, 1560, 1494, 1452, 1363, 736, 699; HRMS (ESI) calcd for $C_{25}H_{30}ClN_2O$ $[M+H]^+$: 409.2041, Found: 409.2049.

*4.6.8. 2-((3S,3′R)-1′-benzylspiro[indole-3,4′-piperidin]-3′-yl)-1-phenylethan-1-one (**6ah**) brown oil, 67.1 mg, 85% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.67–7.59 (m, 3H), 7.48 (t, J = 7.6 Hz, 1H), 7.44–7.30 (m, 7H), 7.30–7.22 (m, 2H), 3.78 (AB, J_{AB} = 13.2 Hz, 1H), 3.61 (AB, J_{BA} = 13.2 Hz, 1H), 3.25–3.12 (m, 1H), 3.06 (dd, J = 11.6, 4.0 Hz, 1H), 2.90 (dt, J = 12.0, 4.0 Hz, 1H), 2.59 (td, J = 12.4, 2.4 Hz, 1H), 2.49 (t, J = 11.4 Hz, 1H), 2.37 (td, J = 13.2, 4.4 Hz, 1H), 2.29–2.07 (m, 2H), 1.38–1.23 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 179.0, 156.3, 140.3, 137.8, 136.6, 133.1, 129.0, 128.4, 128.3, 128.3, 127.9, 127.1, 125.5, 124.8, 121.9, 63.0, 59.7, 55.1, 48.4, 37.6, 34.1, 29.9. ν_{max} (cm^{-1}) = 2912, 2806, 1682, 1448, 1344, 1271, 1220, 990, 909, 730, 689; HRMS (ESI) calcd for $C_{27}H_{27}N_2O$ $[M+H]^+$: 395.2118, Found: 395.2125.

*4.6.9. 1-([1,1′-biphenyl]-4-yl)-2-((3S,3′R)-1′-benzylspiro[indole-3,4′-piperidin]-3′-yl)ethan-1-one (**6ai**) brown oil, 77.2 mg, 82% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.74–7.63 (m, 4H), 7.59–7.53 (m, 4H), 7.48–7.31 (m, 8H), 7.30–7.24 (m, 2H), 3.79 (AB, J_{AB} = 13.2 Hz, 1H), 3.62 (AB, J_{BA} = 13.2 Hz, 1H), 3.28–3.15 (m, 1H), 3.08 (dd, J = 11.7, 4.1 Hz, 1H), 2.91 (dt, J = 12.0, 3.6 Hz, 1H), 2.64–2.55 (m, 1H), 2.51 (t, J = 11.4 Hz, 1H), 2.43–2.33 (m, 1H), 2.22–2.14 (m, 1H), 1.37–1.21 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 179.1, 156.4, 145.7, 140.4, 139.8, 137.9, 135.4, 129.1, 128.9, 128.5, 128.4, 128.3, 128.2, 127.2, 127.2, 127.1, 125.6, 124.9, 121.9, 63.1, 59.8, 55.2, 48.5, 37.6, 34.3, 29.9. ν_{max} (cm^{-1}) = 3059, 2910, 2806, 1678, 1602, 1559, 1449, 1403, 1344, 991, 907, 727, 696; HRMS (ESI) calcd for $C_{33}H_{31}N_2O$ $[M+H]^+$: 471.2431, Found: 471.2434.

*4.6.10. 2-((3S,3′R)-1′-benzylspiro[indole-3,4′-piperidin]-3′-yl)-1-(3,4-dichlorophenyl)ethan-1-one (**6aj**) brown oil, 60.2 mg, 65% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.71–7.61 (m, 3H), 7.46–7.31 (m, 7H), 7.31–7.27 (m, 2H), 3.76 (AB, J_{AB} = 13.2 Hz, 1H), 3.64 (AB, J_{BA} = 13.2 Hz, 1H), 3.21–3.11 (m, 1H), 2.99 (dd, J = 11.6, 4.4 Hz, 1H), 2.92 (d, J = 11.6 Hz, 1H), 2.61 (t, J = 12.0 Hz, 1H), 2.47 (t, J = 11.4 Hz, 1H), 2.42–2.31 (m, 1H), 2.22–2.03 (m, 2H), 1.38–1.29 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2, 179.0, 156.2, 140.0, 137.8, 137.7, 136.1, 133.1, 130.6, 129.9, 129.0, 128.5, 128.3, 127.2, 126.9, 125.7, 124.8, 122.0, 63.0, 59.7, 54.9, 48.6, 37.6, 34.2, 29.8. ν_{max} (cm^{-1}) = 2929, 2910, 2807, 2772, 1684, 1583, 1555, 1265, 1028, 736, 698; HRMS (ESI) calcd for $C_{27}H_{25}Cl_2N_2O$ $[M+H]^+$:463.1338, Found: 463.1343.

*4.6.11. 1-((3S,3′R)-1′-benzyl-5-chlorospiro[indole-3,4′-piperidin]-3′-yl)propan-2-one (**6ba**) brown oil, 63.8 mg, 87% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.62–7.55 (m, 2H), 7.41–7.32 (m, 5H), 7.31–7.27 (m, 1H), 3.75 (AB, J_{AB} = 13.2 Hz, 1H), 3.63 (AB, J_{BA} = 13.2 Hz, 1H), 3.05–2.85 (m, 3H), 2.50 (td, J = 12.4, 2.4 Hz, 1H), 2.37–2.26 (m, 2H), 1.89 (s, 3H), 1.80–1.70 (m, 1H), 1.53 (dd, J = 18.0, 3.8 Hz, 1H), 1.33–1.25 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.3, 179.4, 154.7, 142.0, 137.7, 131.3, 128.9, 128.4, 128.3, 127.2, 125.1, 122.5, 62.8, 60.1, 54.7, 48.4, 42.5, 33.4, 30.3, 29.6. ν_{max} (cm^{-1}) = 2914, 2807, 2767, 1715, 1557, 1443, 1413, 1355, 1147, 826, 734, 699; HRMS (ESI) calcd for $C_{22}H_{24}ClN_2O$ $[M+H]^+$: 367.1572, Found: 367.1578.

*4.6.12. 1-((3S,3′R)-1′-benzyl-5-bromospiro[indole-3,4′-piperidin]-3′-yl)propan-2-one (**6ca**) brown oil, 67.4 mg, 82% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.77–7.73 (m, 1H), 7.57–7.50 (m, 2H), 7.41–7.32 (m, 4H), 7.31–7.25 (m, 1H), 3.76 (AB, J_{AB} = 13.2 Hz, 1H), 3.63 (AB, J_{BA} = 13.2 Hz, 1H), 3.06–2.86 (m, 3H), 2.50 (td, J = 12.0, 2.4 Hz, 1H), 2.33–2.27 (m, 2H), 1.89 (s, 3H), 1.76 (dd, J = 17.6, 8.0 Hz, 1H), 1.53 (dd, J = 17.6, 3.6 Hz, 1H), 1.33–1.21 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.3, 179.4, 155.2, 142.4, 137.7, 131.4, 128.9, 128.3, 127.9, 127.2, 122.9, 119.4, 62.8, 60.1, 54.7, 48.3, 42.5, 33.3, 30.3, 29.5. ν_{max} (cm^{-1}) = 2912, 2807, 2768, 1715, 1556, 1441, 1355, 1260, 1148, 1057, 1027, 910, 824, 732, 701; HRMS (ESI) calcd for $C_{22}H_{24}BrN_2O$ $[M+H]^+$: 411.1067, Found: 411.1062.

*4.6.13. 1-((3S,3′R)-1′-benzyl-5-methylspiro[indole-3,4′-piperidin]-3′-yl)propan-2-one (**6da**) brown oil, 51.3 mg, 74% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.40–7.30 (m, 5H), 7.29–7.25 (m, 1H), 7.18 (d, J = 7.6, 1H), 3.75 (AB, J_{AB} = 13.6 Hz, 1H), 3.63 (AB, J_{BA} = 13.2 Hz, 1H), 3.01–2.82 (m, 3H), 2.55 (td, J = 12.0, 2.1 Hz, 1H), 2.39 (s, 3H), 2.36–2.21 (m, 2H), 1.86 (s, 3H), 1.75–1.65 (m, 1H), 1.54 (dd, J = 17.6, 2.6 Hz, 1H), 1.28–1.21 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 178.1, 154.1, 140.4, 137.8, 135.2, 129.0, 128.8, 128.2, 127.1, 125.7, 121.2, 62.8, 59.3, 54.6, 48.3, 42.6, 33.5, 30.3, 29.8, 21.7. ν_{max} (cm^{-1}) = 2912, 2807, 2767, 1715, 1560, 1454, 1355, 1154, 966, 910, 822, 733, 699; HRMS (ESI) calcd for $C_{23}H_{27}N_2O$ $[M+H]^+$: 347.2118, Found: 347.2130.

*4.6.14. 1-((3S,3′R)-1′-benzyl-7-methylspiro[indole-3,4′-piperidin]-3′-yl)propan-2-one (**6ea**) brown oil, 54.1 mg, 78% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.46 (d, J = 7.2 Hz, 1H), 7.39–7.29 (m, 4H), 7.28–7.23 (m, 1H), 7.21 (d, J = 7.6, 1H), 7.12 (t, J = 7.6 Hz, 1H), 3.75 (AB, J_{AB} = 13.2 Hz, 1H), 3.61 (AB, J_{BA} = 13.2 Hz, 1H), 3.02–2.79 (m, 3H), 2.59 (s, 3H), 2.54 (dd, J = 12.0, 2.4 Hz, 1H), 2.39–2.25 (m, 2H), 1.88 (s, 3H), 1.80–1.62 (m, 1H), 1.54 (d, J = 17.2, 1H), 1.28–1.18 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8, 177.9, 154.6, 140.1, 137.9, 131.3, 129.7, 128.9, 128.3, 127.1, 125.3, 122.2, 62.9, 59.5, 54.7, 48.3, 42.6, 33.4, 30.3, 29.8, 16.9. ν_{max} (cm^{-1}) = 2912, 2807, 2767, 1714, 1562, 1452, 1358, 1265, 1157, 968, 912, 732, 699; HRMS (ESI) calcd for $C_{23}H_{27}N_2O$ $[M+H]^+$: 347.2118, Found: 347.2120.

*4.6.15. 1-((3S,3′R)-1′-benzyl-5-methoxyspiro[indole-3,4′-piperidin]-3′-yl)propan-2-one (**6fa**) brown oil, 58.7 mg, 81% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.41–7.31 (m, 4H), 7.30–7.26 (m, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 8.4, 2.4 Hz, 1H), 3.81 (s, 3H), 3.75 (AB, J_{AB} = 13.2 Hz, 1H), 3.62 (AB, J_{BA} = 13.2 Hz, 1H), 3.04–2.82 (m, 3H), 2.55 (t, J = 12.0 Hz, 1H), 2.40–2.25 (m, 2H), 1.89 (s, 3H), 1.73 (dd, J = 17.6, 8.4 Hz, 1H), 1.57 (d, J = 18.0 Hz, 1H), 1.34–1.25 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7, 177.0, 157.5, 149.9, 141.8, 137.6, 129.0, 128.2, 127.1, 121.7, 112.5, 111.8, 62.9, 59.4, 55.6, 54.3, 48.0, 42.5, 33.7, 30.3, 29.7. ν_{max} (cm^{-1}) = 2940, 2912, 2807, 2757, 1714, 1586, 1560, 1463, 1267, 1223, 1028, 732, 700; HRMS (ESI) calcd for $C_{23}H_{27}N_2O_2$ $[M+H]^+$: 363.2067, Found: 363.2072.

*4.7. Procedure for the preparation of **7** [8]*

To a stirred solution of **6aa** (0.2 mmol) was added KO^{t}Bu (0.2 mmol) under Ar in dry THF (3 mL) at −78 °C. After the reaction was completed (monitored by TLC), water was added to quench the reaction and the mixture was extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine, separated, dried over Na_2SO_4 and filtered. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (DCM/MeOH = 20/1 to 10/1) to afford the target product **7**.

*4.7.1. (4aR,7aS,12bS)-3-benzyl-1,2,3,4,4a,5,7a,8-octahydropyrido[3,4-d]carbazol-6(7H)-one (**7**) beige solid, m.p. = 138.1–140.8 °C, 54.5 mg, 82% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.26 (m, 6H), 7.04 (t, J = 7.6 Hz, 1H), 6.66 (t, J = 7.6 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 3.88 (dd, J = 6.8, 2.0 Hz, 1H), 3.77–3.66 (m, 3H), 2.92–2.75 (m, 3H), 2.70–2.52 (m, 3H), 2.24–2.06 (m, 3H), 2.03–1.88 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1, 150.3, 129.3, 129.3, 128.5, 128.3, 127.2, 127.0, 118.0, 110.1, 65.8, 62.9, 54.3, 48.8, 47.5, 47.0, 40.8, 38.4, 37.7. ν_{max} (cm^{-1}) = 2911, 2807, 1705, 1603, 1469, 1264, 1028, 733, 699; HRMS (ESI) calcd for $C_{22}H_{25}N_2O$ $[M+H]^+$: 333.1961, Found: 333.1964.

*4.8. Procedure for the preparation of **8***

To a stirred solution of **6aa** (0.2 mmol) was added $NaBH_4$ (2 mmol) under Ar in MeOH (2 mL) at room temperature. After the reaction was completed (monitored by TLC), silica gel was added to quench the reaction and filtered. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (DCM/MeOH = 20/1 to 10/1) to afford the target product **8**.

*4.8.1. 1-((3S,3′R)-1′-benzylspiro[indoline-3,4′-piperidin]-3′-yl)propan-2-ol (**8**) beige solid, m.p. = 55.6–57.3 °C, 57.2 mg, 85% yield, dr = 1.8:1 (determined by HPLC) (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 7.13 (d, J = 7.2 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.68 (td, J = 7.2, 3.2 Hz, 1H), 6.62 (dd, J = 7.6, 4.0 Hz, 1H), 4.02–3.42 (m, 6H), 3.27–3.22 (m, 1H), 2.85–2.75 (m, 3H), 2.47–1.93 (m, 3H), 1.75–1.65 (m, 1H), 1.62–1.30 (m, 2H), 1.09 (t, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8, 136.5, 129.54, 129.49, 128.4, 127.9, 127.8, 127.6, 127.5, 125.3, 125.3, 118.0, 118.0, 109.9, 109.8, 67.1, 64.8, 63.0, 59.6, 59.0, 55.1, 54.9, 49.5, 49.4, 47.2, 47.1, 39.5, 39.5, 38.4, 24.1, 23.8. ν_{max} (cm^{-1}) = 2962, 2925, 1603, 1487, 1460, 1246, 1267, 1124, 1064, 1026, 733, 699; HRMS (ESI) calcd for $C_{22}H_{29}N_2O$ $[M+H]^+$: 333.2274, Found: 333.2277.

*4.9. Procedure for the preparation of **9***

A solution of **6aa** (0.2 mmol) in MeOH (2 mL) was added $Pd(OH)_2/C$ (50 mg). Then the mixture was stirred under 1 atm H_2 at room temperature until TLC showed complete consumption of starting material. After removal of $Pd(OH)_2/C$, water was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine, separated, dried over Na_2SO_4 and filtered. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (DCM/MeOH = 20/1 to 10/1) to afford the target product **9**.

*4.9.1. 1-((3S,3′R)-spiro[indoline-3,4′-piperidin]-3′-yl)propan-2-one (**9**) sticky yellow oil, 38.1 mg, 78% yield (0.2 mmol scale)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.0 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.73 (t, J = 7.6 Hz, 1H), 6.65 (dd, J = 7.6, 1.1 Hz, 1H), 4.72 (s, 2H), 3.54 (d, J = 9.2 Hz, 1H), 3.30–3.23 (m, 2H), 3.13–2.98 (m, 2H), 2.90 (dd, J = 13.0, 8.6 Hz, 1H), 2.58 (dd, J = 17.6, 3.2 Hz, 1H), 2.45–2.39 (m, 1H), 2.28 (dd, J = 17.6, 9.2 Hz, 1H), 2.16–2.08 (m, 1H), 2.05 (s, 3H), 1.79–1.75 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6, 152.0, 132.0, 128.3, 125.3, 118.2, 109.9, 60.0, 46.6, 46.3, 42.4, 42.3, 37.7, 35.3, 30.5. ν_{max} (cm^{-1}) = 2921, 2850, 1706, 1604, 1487, 1462, 1356, 1263, 1171, 1155, 730, 699; HRMS (ESI) calcd for $C_{15}H_{21}N_2O$ $[M+H]^+$: 245.1648, Found: 245.1653.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131765.

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