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CINCHONA ALKALOID THIOUREA CATALYZED ASYMMETRIC SYNTHESIS AND ANTICANCER ACTIVITY EVALUATION OF TETRAHYDRO-β-SPIROOXINDOLES

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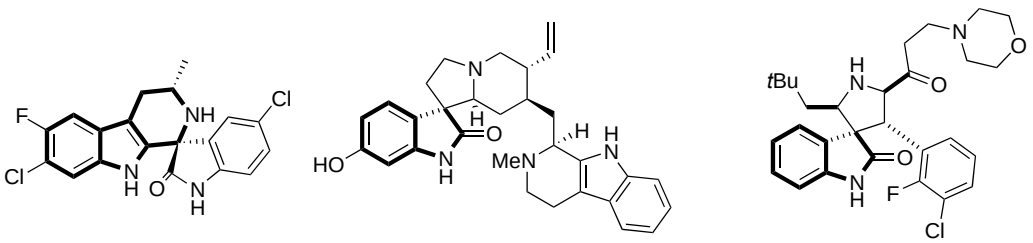
Abstract – Asymmetric synthesis and activity evaluation of tetrahydro-β-spirooxindole compounds is reported in this paper. Cinchona alkaloid thiourea has been utilized as catalyst for the asymmetric synthesis of tetrahydro-β-spirooxindoles, affording the desired products in moderate to good yields and with up to 94:6 er. Interestingly, the spirooxindoles exhibited moderate to good in vitro antitumor activity for A549 cells. Besides, the growth inhibitory activities of these selected compounds against normal lung cell CHL cells were further evaluated.

Tetrahydro-β-spirooxindoles are a class of useful heterocyclic compounds, which exhibit a broad spectrum of biological activities.[1] The multicyclic spiroindolinone scaffold is frequently utilized in medicinal chemistry where the chiral center and the spirocyclic-fused core of these structures supplements the deficiencies of flat heterocyclic compounds typically encountered in drug discovery programs (Figure 1). Some of these compounds are promising drug candidates for treating cancer,[2] tuberculosis,[3] malaria etc.[4] However, few synthetic methods have been developed for the construction of these skeletons. Due to their molecular complexity and spirocyclic quaternary carbon center, the synthetic methodology is still a significant challenge.[5] Although its asymmetric synthesis may be difficult, the construction of highly hindered, strained quaternary chiral central carbolines is indeed not a negligible task, especially in an enantioselective fashion.[6]

Asymmetric cycloaddition and cascade reaction have been proved to be powerful approaches to synthesize the spirooxindole framework.[7] However, most of these reports are limited to the pyrrolidin-3-yl-spirooxindoles or to all-carbon cycloalkyl-spirooxindoles.[8] To the best of our knowledge,

only few asymmetric cycloaddition reactions have been successfully applied in the synthesis of optically active tetrahydro-β-spirooxindoles catalyzed by (S)-BINOL-derived phosphoric acid.[9,12] Although BINOL acid catalysts have achieved great success in asymmetric reactions, complicated multistep reactions were employed to synthesize them.[10] The cinchona alkaloid derived catalysts play the same vital role in asymmetric reactions just like BINOL acids, and the synthesis of cinchona alkaloid catalysts are relatively simple compared to BINOL acids. However, there is still no report about cinchona alkaloid derivatives catalyzed asymmetric synthesis of tetrahydro-β-spirooxindoles. Therefore, to facilitate the exploration of the biological and medicinable utilities of tetrahydro-β-carboline derivatives, it is highly desirable to develop alternative efficient catalytic asymmetric methods for the synthesis of chiral quaternary tetrahydro-β-carbolines.[11] Encouraged by our earlier work on asymmetirc synthesis of enantioselective indole alkaloids,[13] herein, the catalyzation of facile cinchona alkaloid thiourea to asymmetric Pictet-Spengler reaction was reported, accessing a variety of highly hindered, strained spirocyclic quaternary chiral central carboline derivatives. Further investigation showed that these chiral carboline derivatives displayed moderate to good in vitro antitumor activity for lung carcinoma cells A549. Interestingly, some of these compounds showed weak cytotoxicity on normal lung cells CHL cell.



NITD609
antimalarial

strychnofoline
inhibitor mitosis

MI-63
anticancer

Figure 1. Examples of biological active indole alkaloid[4,12]

The investigations were initiated by screening various catalysts (Figure 2) for activation of tryptamine **1a** with chelating isatin **2a** (Table 1). As shown in Table 1, majority of the tested chiral Brønsted bases were proved to be efficient catalysts for this spirocyclization reaction, leading to the corresponding product **3a** in good yields. However, the enantioselectivity of this process is highly depended on the catalyst involved. Quinine- or quinidine-derived squaramide catalysts (**C1-C5**) showed poor enantioselectivity for this reaction, while thiourea catalysts achieved better er (enantiomeric ratio) values and **C7** turned out to be the optimal catalyst (Table 1, entries 1-7). Contrarily quinidine amine **C9** was failed to trigger to this process which indicated that the strong H-bonding donor group are crucial in catalysts for achieving high activity and enantioselectivity (Table 1, entry 9). Subsequently, the solvent was examined, and relevant results showed that the solvent remarkably affected the enantioselectivity of current reaction. DCE was

found to be efficient to produce **3a** with a slight decrease in er value, while other solvents, such as toluene, $CHCl_3$, THF, Et_2O, were failed to give enantioenriched **3a**, albeit in moderate enantioselectivity (Table 1, entries 10-15). It is worth noting that reducing the catalyst loading from 20 mol% to 10 mol% had influence on both yield and the enantioselectivity (Table 1, entry 16). Finally a slight decrease on either yield or enantioselectivity was observed when the reaction was carried out at 10 °C or without the use of 4 Å molecular sieves (Table 1, entries 17 and 18).

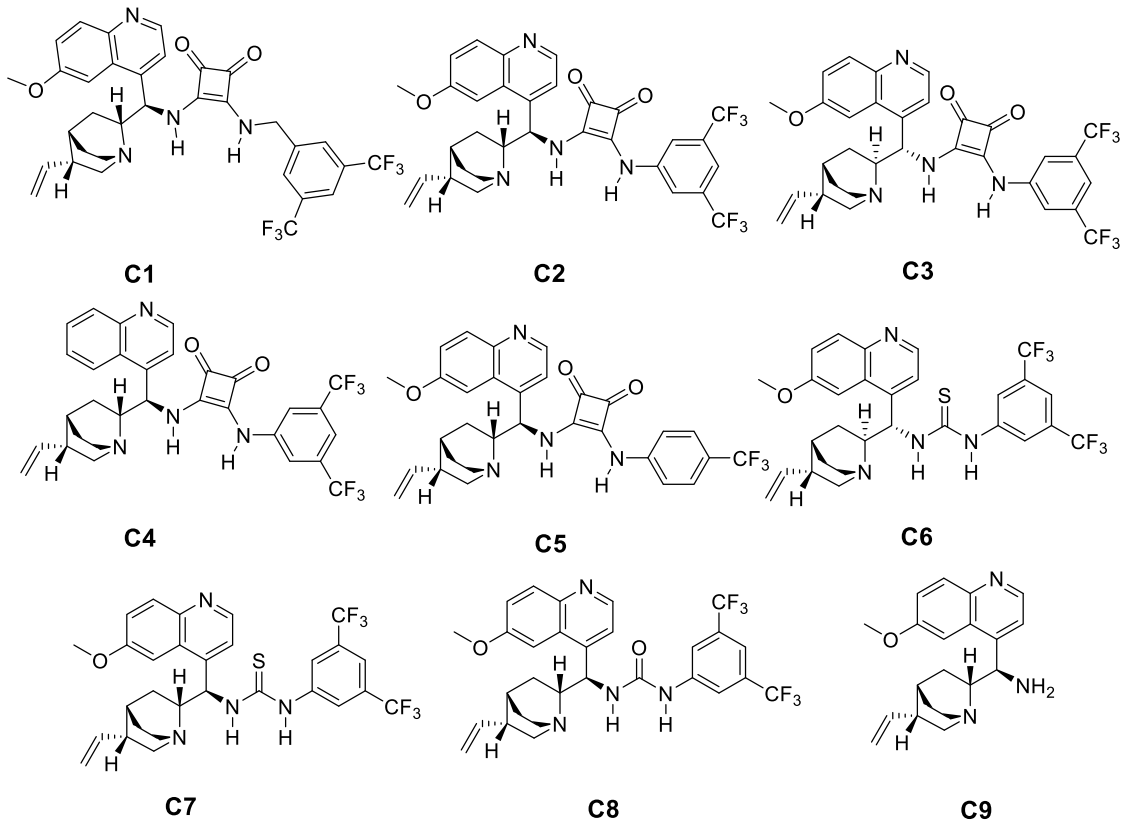
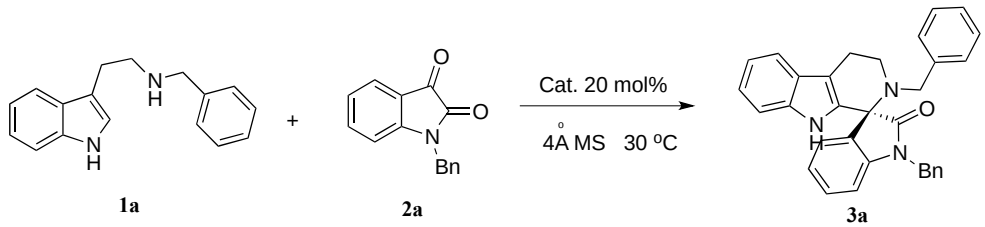


Figure 2. Different chiral Brønsted base catalysts

Table 1. Catalyst optimization for spiroindolone formation[a]



Entry	Catalyst	Solvent	Yield [a](%)	er [b]
1	C1	DCM	76	71:29
2	C2	DCM	83	63:37
3	C3	DCM	81	88:12
4	C4	DCM	90	65:35
5	C5	DCM	86	80:20

6	C6	DCM	77	85:15
7	**C7**	**DCM**	**85**	**94:6**
8	C8	DCM	67	88:12
9	C9	DCM	NR.	ND.
10	C7	DCE	69	87:13
11	C7	toluene	71	57:43
12	C7	$CHCl_3$	66	55:45
13	C7	Et_2O	74	47:43
14	C7	$PhCF_3$	71	79:21
15	C7	THF	76	51:49
16[d]	C7	DCM	81	77:23
17[e]	C7	DCM	84	92:8
18[f]	C7	DCM	62	92:8

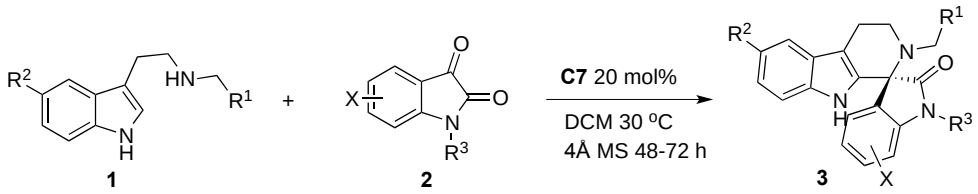
[a]Reaction performed with **3a** (0.3 mmol), **2a** (0.36 mmol) and catalyst (20 mol%) in solvent (2 mL). Reaction run from 48-72 h, monitored by TLC. [b]Isolated yield. [c]Enantioselectivity determined by HPLC analysis using chiral stationary phase. [d]10 mol% catalyst was used. [e]without 4Å MS(molecular sieves). [f]Reaction performed at 10 °C.

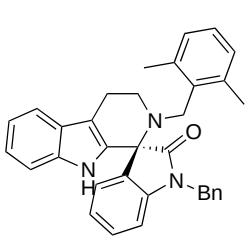
With the optimized reaction conditions in hand, the substrates scope of tryptamine were evaluated with various isatins subsequently. The represent results were summarized in the Table 2. Both the yield and the er values of the desired products were remarkably affected by the type of the tryptamine. The *N*-protected group R^1 significantly affect the yield and enantioselectivity of current protocols. A decreased er value was observed when phenyl (R^1) was replaced by other groups, such as 2,6-dimethylphenyl, 2-naphthyl and *o*-methoxyphenyl (**3b**, **3c**, **3g**). It is worth noting that spirocyclization reaction could not occur when the steric hindrance of substitute is large (**3f**). When R^1 is a heterocyclic ring (**3d**), moderate er value (77:23) was obtained.

The substituents on isatins have different effects on yield and enantioselectivities. Both 5-fluorine and 7-fluorine-substituted isatins provided higher er value than chlorine and bromine (**3h-3m**). The reaction of unsubstituted isatin (**3o**) with tryptamine could carry out with poor enantioselectivity (er value 61:39). *N*-acetylisatin could not make the reaction occur smoothly (**3q**). In order to determine the absolute configuration of the generated stereogenic center, the known compound *N*-debenzyl-**3o** was isolated and characterized. By comparison of the specific rotation value with the reported data,[9] the absolute configuration of the known *N*-debenzyl-3o can be assigned as S. Since none the bonds of stereogenic center has been broken during the following debenzylation reaction, the original configuration of **3o** is retained[11,14] the debenzylation product (see Supporting Information).

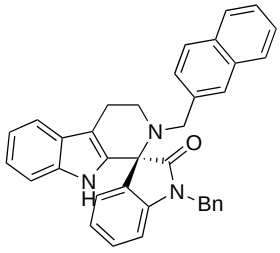
According to our previous work[13] and the recent report,[15] a plausible reaction mechanism has been depicted in Scheme 1 with **3a** as the model substrate. Firstly, **2a** was combined by the hydrogen bonds of the catalyst, then nucleophilic attack of **1a** to the activatied **2'** forms transition state **3.** Elimination of one molecule of water would generate ion pair **5**, which undergoes intramolecular Mannich reaction to form **6**. Proton shift in **6** yields product **3a** and release catalyst **C7**.

Table 2. Scope of isatins and tryptamine for the spirocyclization reaction[a]

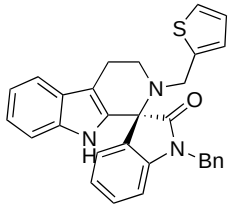




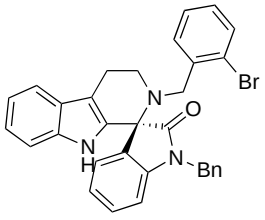
3b, Y:65%, er:78:22



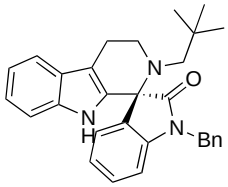
3c, Y:71%, er:70:30



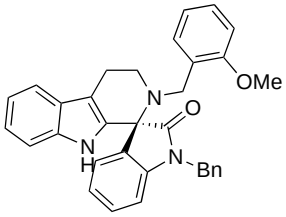
3d, Y:64%, er:77:23



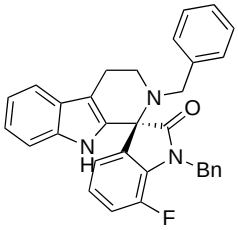
3e, Y:83%, er:77:23



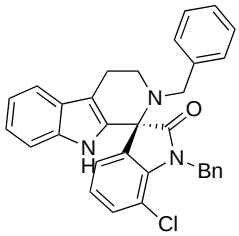
3f, NR.



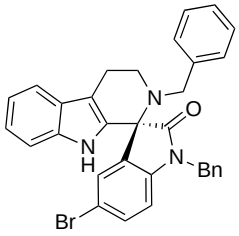
3g, Y:71%, er:78:22



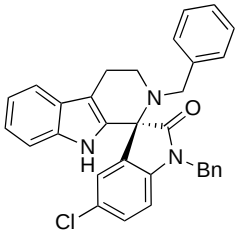
3h, Y:79%, er:78:22



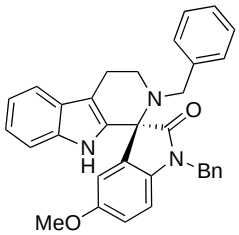
3i, Y:76%, er:73:27



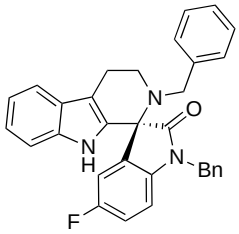
3j, Y:81%, er:80:20



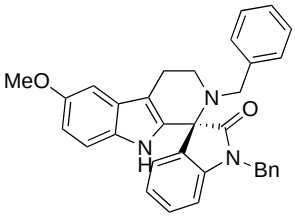
3k, Y:77%, er:70:30



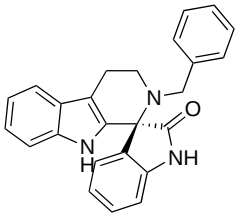
3l, Y:83%, er:81:19



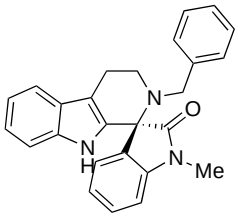
3m, Y:82%, er:82:18



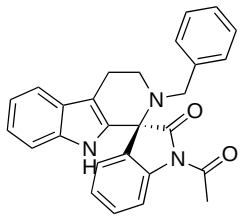
3n, Y:79%, er:86:14



3o, Y:67%, er:61:39



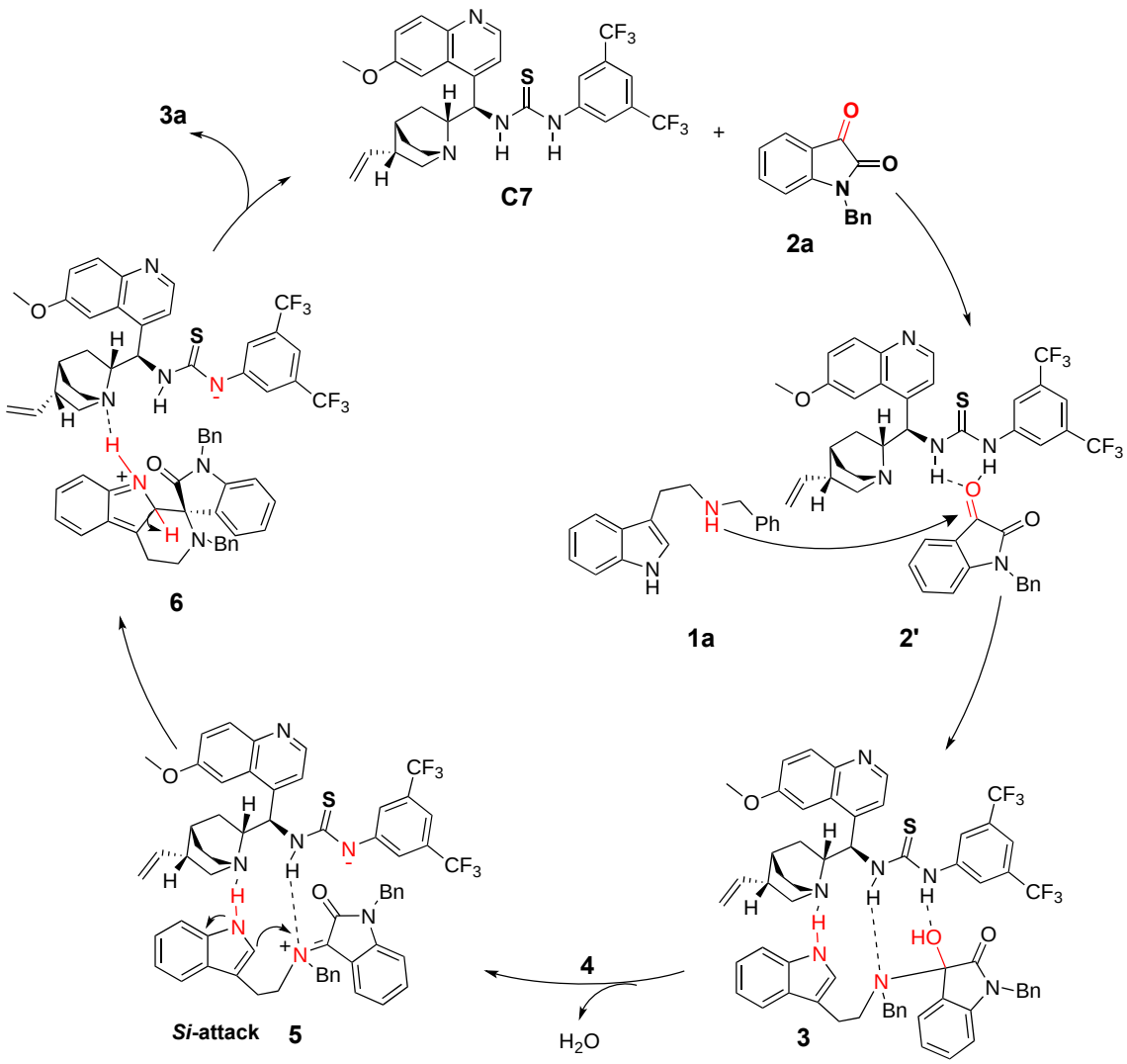
3p, Y:64%, er:54:46



3q, Y:trace, er:ND.

[a]Reaction performed with **1a** (0.3 mmol), **2a** (0.36 mmol) and catalyst (20 mol%) in solvent (2 mL), monitored by TLC. [b]Isolated yield. [c]Enantioselectivity determined by HPLC analysis using chiral stationary phase.

Previously the spirooxindoles scaffold displayed good in vitro antitumor activity. Therefore, the desired compounds were screened for their anticancer activity using MTT assay.[16] Standard anticancer drug camptothecin was used as positive control to validate the assay. Among them, six most active compounds (**3a**, **3g**, **3h**, **3i**, **3l**, **3m**) were found out by measuring their IC_{50} values against lung carcinoma cell A549 cells.[17]



Scheme 1. Plausible reaction mechanism

Compounds **3a**, **3h**, **3i**, **3l**, **3m** show better activity than **3g**, suggesting that the substituent R on the *N*-benzyltryptamine is less effective than that on the istain moiety. However, the difference in substitution on isatin shows a higher impact on the biological activity of molecules. Introduction of fluorine instead of chlorine improved the IC_{50} value from 28.86 μM to 5.90 μM, making **3m** the most active compound in this series (Figure 3A). Overall, the synthesized molecules, while displaying anticancer activity, showed weaker potency compared to camptothecin (see Supporting Information). To our delight, when the cytotoxicity of compounds on normal lung cells CHL was measured, it found that **3m** shows weak cytotoxictity on normal cells CHL cell (IC_{50}=118.20 μM) and selectivity for cancer cell A549 (Figure 3B). The compound 3m shows the optimum structural requirement for anticancer activity. The experimental results lead us to the identification of the tetrahydro-β-spirooxindole nucleus as an important structural feature to possess anticancer activity. Therefore, this compound will be further modified to discover more potent molecules.

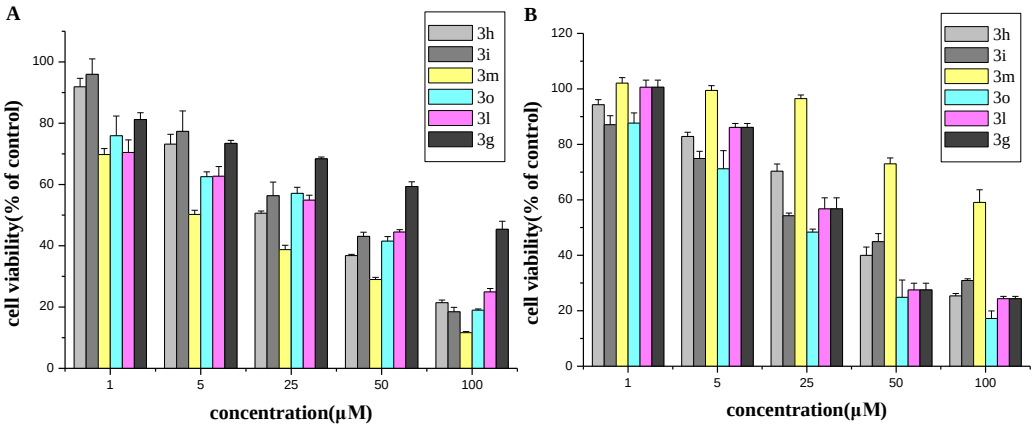


Figure 3. Anti-cancer activity and toxicity to A549 and CHL

In conclusion, we have presented a novel, mild and facile method for the synthesis of the chiral tetrahydro-β-spirooxindoles. The easily available cinchona alkaloid thiourea catalyst **C7** showed high efficiency, affording the desired products in moderate to good yields and er values. Some of the target compounds also display significant anticancer activity and weak cytotoxicity. This indicates the scope for screening the hitherto relatively unexplored tetrahydro-β-spirooxindole moiety in potential anticancer compounds.

EXPERIMENTAL

All reactions were carried out in oven-dried glassware with magnetic stirring under air unless otherwise mentioned. All other reagents were used without purification as commercially available. All reactions were monitored by thin layer chromatography. Purification of reaction products were carried out by flash chromatography on silica gel. Chemical yields refer to pure isolated substances. Solvents were purified and dried according to standard methods prior to use. Powdered 4Å molecular sieves were activated at 200 °C for 2 h. ^{1}H NMR spectra were recorded on 500 MHz or 600 MHz spectrometer. The chemical shifts were reported relative to internal standard TMS(0) in $CDCl_3$. The following abbreviations may be used to describe peak patterns where appropriate: br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. ^{13}C NMR spectra were recorded on 125 MHz or 150 MHz spectrometer, referred to the internal solvent signals (77.0 for $CDCl_3$). Analytical HPLC was recorded on a HPLC machine equipped with Agilent 1100 series quaternary pump with a UV diode array detector. The chiral stationary phase was Daicel Chiralcel AD-H and OD-H column. Optical rotations were determined using a Rudolph Autopol V polarimeter at 25 °C. Melting points were determined using a Büchi B-540 capillary melting point apparatus on the pure major component.

General procedure for the preparation of compounds 3

A mixture of *N*-protected tryptamine **1** (0.05 mmol), aldehyde **2** (0.06 mmol), catalyst **C7** (20 mol%), 4Å molecular sieves (0.1-0.2 g, powdered) in 2.0 mL DCM was stirred at 30 °C. The reaction was monitored with TLC. After the reaction was completed, the reaction mixture was directly purified by flash column chromatography (EtOAc / petroleum ether = 1/15 to 1/3, with 2% TEA) to give the desired product **3**.

(*S*)-1,2'-Dibenzyl-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3a)

This product was obtained in 85% yield as a white solid after chromatography and 94:6 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=80:20, 0.8 mL/min, λ=225 nm, t(minor)=17.81 min, t(major)=36.60 min]. $[\alpha]_D^{25}$ -51.2 (c 1.0, CH_2Cl_2); mp 262-265 °C. HRMS (ESI-TOF) calcd for $C_{32}H_{28}N_3O[M+H]^+$: 470.2241; Found: 470.2247. ^{1}H NMR (600 MHz, $CDCl_3$) 2.84-2.87 (m, 1H), 2.92-2.97 (m, 1H), 3.03-3.06 (m, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 3.53 (d, *J* = 12.0 Hz, 1H), 3.79-3.84 (m, 1H), 5.36 (d, *J* = 12.0 Hz, 1H), 5.47 (d, *J* = 12.0 Hz, 1H), 7.02 (m, 1H), 7.07 (br, 1H), 7.10-7013 (m, 1H), 7.14 (d, *J* = 6.0 Hz, 2H), 7.2-7.26 (m, 2H), 7.28-7.31 (m, 6H), 7.33-7.35 (m, 2H), 7.39 (d, *J* = 6.0 Hz, 2H), 7.54 (d, *J* = 6.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.0, 139.5, 139.1, 137.7, 136.6, 133.4, 132.4, 130.5, 128.7, 128.3, 128.2, 127.6, 127.3, 127.2, 127.1, 124.7, 124.2, 122.5, 119.7, 118.7, 115.7, 112.1, 110.9, 66.4, 54.6, 44.9, 43.7, 21.4.

(*S*)-1-Benzyl-2'-(2,6-dimethylbenzyl)-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3b)

This product was obtained in 65% yield as a white solid after chromatography and 78:22 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major)=9.60 min, t(minor)=15.17 min]. $[\alpha]_D^{25}$ -63.1 (c 1.0, CH_2Cl_2); mp 271-274 °C. HRMS (ESI-TOF) calcd for $C_{34}H_{32}N_3O[M+H]^+$: 498.2540; Found: 498.2544. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.30 (S, 6H), 2.77-2.81 (m, 2H), 2.84-2.87 (m, 1H), 3.41 (d, *J* = 12.0 Hz, 1H), 3.79 (d, *J* = 12.0 Hz, 1H), 3.88-3.92 (m, 1H), 4.89 (d, *J* = 18.0 Hz, 1H), 4.99 (d, *J* = 18.0 Hz, 1H), 6.87 (d, *J* = 12.0 Hz, 1H), 6.96 (d, *J* = 12.0 Hz, 2H), 7.02-7.04 (m, 1H), 7.05-7.06 (m, 2H), 7.06-7.08 (m, 3H), 7.11 (s, 1H), 7.26-7.28 (m, 2H), 7.29 (d, *J* = 6.0 Hz, 1H), 7.31 (d, *J* = 6.0 Hz, 1H), 7.39 (d, *J* = 6.0 Hz, 2H), 7.49-7.51 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.6, 143.6, 138.9, 136.6, 136.2, 134.2, 131.2, 129.9, 129.2, 128.9, 128.3, 127.9, 127.8, 127.2, 127.19, 126.3, 123.2, 122.2, 119.6, 118.7, 112.4, 111.0, 109.3, 67.5, 48.0, 44.0, 41.8, 21.7, 20.7.

(*S*)-1-Benzyl-2'-(naphthalen-2-ylmethyl)-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3c)

This product was obtained in 71% yield as a white solid after chromatography and 70:30 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major)=15.16 min, t(minor)=40.36 min]. $[\alpha]_D^{25}$ -37.1 (c 1.07, CH_2Cl_2); mp 254-257 °C. HRMS (ESI-TOF) calcd for $C_{36}H_{30}N_3O[M+H]^+$: 520.2383; Found: 520.2386. ^{1}H NMR (600 MHz, $CDCl_3$)

δ 2.85-2.87 (m, 1H), 2.92-2.93 (m, 1H), 3.08-3.10 (m, 1H), 3.67 (s, 2H), 3.88-3.91 (m, 1H), 4.19-4.22 (m, 1H), 4.89 (d, *J* = 18.0 Hz, 1H), 5.04 (d, *J* = 18.0 Hz, 1H), 6.88 (d, *J* = 12.0 Hz, 1H), 7.07-7.10 (m, 3H), 7.12-7.14 (m, 2H), 7.27-7.31 (m, 2H), 7.34-7.36 (m, 2H), 7.41-7.45 (m, 5H), 7.52 (d, *J* = 12.0 Hz, 1H), 7.74-7.77 (m, 2H), 7.79-7.81 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.7, 143.4, 136.9, 136.6, 136.1, 133.3, 132.9, 131.0, 129.9, 129.0, 128.0, 127.9, 127.8, 127.7, 127.66, 127.2, 127.0, 126.7, 126.0, 125.6, 123.8, 122.3, 119.6, 118.7, 112.0, 110.9, 109.5, 69.1, 66.7, 54.7, 43.9, 43.6, 21.6.

(*S*)-1-Benzyl-2'-(thiophen-2-ylmethyl)-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3d)

This product was obtained in 64% yield as a white solid after chromatography and 77:23 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major)=14.59 min, t(minor)=29.78 min]. $[\alpha]_D^{25}$ +63.4 (c 1.0, CH_2Cl_2); mp 236-239 °C. HRMS (ESI-TOF) calcd for $C_{30}H_{26}N_3OS[M+H]^+$: 476.1856; Found: 476.1862. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.87-2.90 (m, 1H), 2.98-3.00 (m, 1H), 3.19-3.22 (m, 1H), 3.56 (d, *J* = 12.0 Hz, 1H), 3.82 (d, *J* = 12.0 Hz, 1H), 3.90-3.95 (m, 1H), 4.83 (d, *J* = 18.0 Hz, 1H), 4.98 (d, *J* = 18.0 Hz, 1H), 6.84 (d, *J* = 12.0 Hz, 1H), 6.88-6.90 (m, 2H), 7.03-7.07 (m, 2H), 7.08-7.11 (m, 3H), 7.18 (d, *J* = 6.0 Hz, 1H), 7.22-7.28 (m, 2H), 7.32-7.34 (m, 2H), 7.36-7.37 (m, 3H), 7.53-7.54 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.6, 143.2, 136.6, 136.1, 130.8, 129.9, 129.0, 128.0, 127.8, 127.2, 126.5, 125.6, 124.9, 123.9, 122.3, 119.7, 118.7, 112.0, 110.9, 109.4, 66.8, 49.90, 43.9, 21.4.

(*S*)-1-Benzyl-2'-(2-bromobenzyl)-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3e)

This product was obtained in 83% yield as a white solid after chromatography and 77:23 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major)=12.13 min, t(minor)=31.99 min]. $[\alpha]_D^{25}$ -73.1 (c 1.0, CH_2Cl_2); mp 224-245 °C. HRMS (ESI-TOF) calcd for $C_{32}H_{27}N_3OBr[M+H]^+$: 548.1332; Found: 548.1326. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.88-2.91 (m, 1H), 2.99-3.05 (m, 2H), 3.36 (d, *J* = 12.0 Hz, 1H), 3.92 (d, *J* = 12.0 Hz, 1H), 3.96-4.00 (m, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 6.82 (d, *J* = 12.0 Hz, 1H), 6.96-6.99 (m, 1H), 7.05-7.12 (m, 5H), 7.21-7.23 (m, 1H), 7.26-7.28 (m, 2H), 7.31-7.34 (m, 2H), 7.39 (d, *J* = 6.0 Hz, 2H), 7.44 (d, *J* = 6.0 Hz, 1H), 7.53-7.54 (m, 1H), 7.62 (d, *J* = 12.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 143.3, 136.6, 135.9, 132.5, 131.0, 129.9, 129.5, 129.4, 129.1, 128.3, 127.9, 127.7, 127.5, 127.2, 125.5, 123.9, 123.7, 122.4, 119.7, 118.7, 111.8, 110.9, 109.7, 66.7, 54.1, 44.4, 44.0, 21.5.

(*S*)-1-Benzyl-2'-(2-methoxybenzyl)-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3g)

This product was obtained in 85% yield as a white solid after chromatography and 94:6 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=80:20, 0.8 mL/min, λ=225 nm,

t(major)=15.62 min, t(minor)=31.21 min]. -40.2 (c 1.0, CH_2Cl_2); mp 232-236 °C. HRMS (ESI-TOF) calcd for $C_{33}H_{30}N_3O_2[M+H]^+$: 499.2331; Found: 500.2337. ^{1}H NMR (600 MHz, $CDCl_3$) 2.81-2.90 (m, 1H), 3.01-3.05 (m, 2H), 3.31-3.33 (m, 1H), 3.76 (s, 3H), 3.90-3.93 (m, 2H), 4.93-5.01 (m, 2H), 6.80-6.84 (m, 2H), 6.93-6.95 (t, *J* = 6.0 Hz, 1H), 7.01-7.12 (m, 5H), 7.28-7.31 (m, 2H), 7.34 (t, *J* = 6.0 Hz, 3H), 7.39-7.41 (m, 2H), 7.51-7.55 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.5, 157.6, 143.3, 136.6, 136.1, 131.4, 130.1, 129.6, 128.9, 127.8, 127.7, 127.7, 127.5, 127.3, 125.7, 123.5, 122.2, 120.43, 119.52, 118.6, 117.2, 111.9, 110.9, 110.1, 109.3, 66.9, 55.1, 48.23, 44.0, 43.9, 21.4.

(*S*)-1,2'-Dibenzyl-7-fluoro-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3h)

This product was obtained in 79% yield as a white solid after chromatography and 78:22 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=210 nm, t(major)=18.41 min, t(minor)=25.27 min]. $[\alpha]_D^{25}$ -56.7 (c 1.0, CH_2Cl_2); mp 271-274 °C. HRMS (ESI-TOF) calcd for $C_{32}H_{27}N_3OF[M+H]^+$: 488.2133; Found: 488.2119. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.90-2.91 (m, 1H), 2.95-2.97 (m, 1H), 3.07-3.09 (m, 1H), 3.52 (s, 2H), 3.83-3.88 (m, 1H), 5.06 (d, *J* = 12.0 Hz, 1H), 5.21 (d, *J* = 12.0 Hz, 1H), 7.04-7.10 (m, 3H), 7.14-7.16 (m, 3H), 7.17-7.19 (m, 2H), 7.31-7.35 (m, 4H), 7.36-7.40 (m, 3H), 7.49 (d, *J* = 6.0 Hz, 2H), 7.57 (d, *J* = 6.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 147.4 ($^1J_{C\text{-}F}$=243 Hz), 139.2, 137.3, 136.6, 130.5, 129.9 ($^3J_{C\text{-}F}$=9.0 Hz), 129.1, 128.8, 128.3, 128.2, 128.15 ($^4J_{C\text{-}F}$=1.5 Hz), 128.0, 127.1 ($^2J_{C\text{-}F}$=13.5 Hz), 124.4 ($^3J_{C\text{-}F}$=6.0 Hz), 122.4, 121.3, 119.7, 118.8, 117.9 ($^2J_{C\text{-}F}$=19.5 Hz), 112.0, 110.9, 67.1 ($^4J_{C\text{-}F}$=1.5 Hz), 54.7, 45.6, 45.6 ($^4J_{C\text{-}F}$=4.5 Hz), 43.6, 21.4.

(*S*)-1,2'-Dibenzyl-7-chloro-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3i)

This product was obtained in 76% yield as a white solid after chromatography and 73:27 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major)=12.02 min, t(minor)=25.90 min]. $[\alpha]_D^{25}$ -63.4 (c 1.0, CH_2Cl_2); mp 266-267 °C. HRMS (ESI-TOF) calcd for $C_{32}H_{27}N_3OCl[M+H]^+$: 504.1832; Found: 504.1825. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.85-2.93 (m, 1H), 2.93-2.97 (m, 1H), 2.98-3.07 (m, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 3.53 (d, *J* = 12.0 Hz, 1H), 3.81-3.85 (m, 1H), 5.38 (d, *J* = 12.0 Hz, 1H), 5.47 (d, *J* = 12.0 Hz, 1H), 7.02-7.05 (m, 2H), 7.12-7.14 (m, 1H), 7.16-7.17 (m, 2H), 7.27-7.30 (m, 2H), 7.30-7.33 (m, 6H), 7.35-7.37 (m, 2H), 7.41 (d, *J* = 6.0 Hz, 2H), 7.55 (d, *J* = 6.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.4, 139.5, 137.7, 136.6, 132.4, 128.7, 128.3, 128.2, 127.6, 127.4, 127.2, 127.1, 124.7, 124.2, 122.5, 119.7, 118.8, 115.7, 112.2, 110.9, 100.0, 66.4, 54.7, 44.9, 43.2, 21.4.

(*S*)-1,2'-Dibenzyl-5-bromo-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3j)

This product was obtained in 81% yield as a white solid after chromatography and 80:20 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major)=14.61 min, t(minor)=22.76 min]. $[\alpha]_D^{25}$ -70.1 (c 1.0, CH_2Cl_2); mp 229-231 °C. HRMS

(ESI-TOF) calcd for $C_{32}H_{27}N_3OBr[M+H]^+$: 548.1332; Found: 548.1333. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.89-2.92 (m, 1H), 2.97-3.01 (m, 1H), 3.09-3.11 (m, 1H), 3.57-3.58 (m, 2H), 3.84-3.87 (m, 1H), 4.92-4.93 (m, 1H), 4.99-5.02 (m, 1H), 6.78 (d, *J* = 6.0 Hz, 1H), 7.13-7.14 (m, 4H), 7.36-7.37 (m, 5H), 7.40-7.42 (m, 5H), 7.51-7.52 (m, 1H), 7.58-7.60 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7, 142.3, 139.0, 136.7, 135.6, 132.7, 132.3, 130.2, 129.1, 128.6, 128.4, 128.3, 128.2, 127.7, 127.3, 127.1, 122.6, 119.8, 118.8, 116.6, 112.3, 111.0, 110.9, 67.0, 54.8, 44.1, 43.7, 21.4.

(*S*)-1,2'-Dibenzyl-5-chloro-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3k)

This product was obtained in 77% yield as a white solid after chromatography and 70:30 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major)=8.88 min, t(minor)=10.96 min]. $[\alpha]_D^{25}$ -57.2 (c 1.1, CH_2Cl_2); mp 264-267 °C. HRMS (ESI-TOF) calcd for $C_{32}H_{27}N_3OCl[M+H]^+$: 504.1837; Found: 504.1815. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.89-2.91 (m, 1H), 2.97-3.09 (m, 1H), 3.10-3.11 (m, 1H), 3.55-3.59 (m, 2H), 3.83-3.87 (m, 1H), 4.93 (d, *J* = 12.0 Hz, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 6.81 (d, *J* = 6.0 Hz, 1H), 7.14-7.16 (m, 2H), 7.17-7.19 (m, 2H), 7.22-7.27 (m, 1H), 7.28-7.30 (m, 1H), 7.36-7.37 (m, 6H), 7.39-7.41 (m, 4H), 7.58-7.59 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.9, 141.8, 139.0, 136.7, 135.7, 131.9, 130.2, 129.8, 129.3, 129.1, 128.4, 128.3, 128.2, 127.7, 127.3, 127.1, 125.8, 122.5, 119.8, 118.8, 112.3, 110.9, 110.5, 67.1, 54.7, 44.1, 43.7, 21.4.

(*S*)-1,2'-Dibenzyl-5-methoxy-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3l)

This product was obtained in 83% yield as a white solid after chromatography and 81:19 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major)=22.17 min, t(minor)=17.68 min]. $[\alpha]_D^{25}$ +43.9 (c 1.0, CH_2Cl_2); mp 292-295 °C. HRMS (ESI-TOF) calcd for $C_{33}H_{30}N_3O_2[M+H]^+$: 500.2333; Found: 500.2343. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.91-2.92 (m, 1H), 2.97-2.99 (m, 1H), 3.07-3.10 (m, 1H), 3.55-3.60 (m, 2H), 3.72 (s, 3H), 3.89-3.93 (m, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 12.0 Hz, 1H), 6.79-6.83 (m, 2H), 6.98-6.99 (m, 1H), 7.12-7.15 (m, 2H), 7.16-7.17 (m, 2H), 7.26-7.28 (m, 1H), 7.32-7.35 (m, 3H), 7.36-7.39 (m, 4H), 7.41 (d, *J* = 12.0 Hz, 1H), 7.57 (d, *J* = 12.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.1, 156.8, 139.5, 136.6, 136.55, 136.2, 131.3, 131.1, 128.9, 128.3, 128.28, 127.9, 127.8, 127.2, 127.1, 122.3, 119.6, 118.7, 115.1, 111.9, 111.5, 110.9, 110.1, 67.3, 55.8, 54.7, 44.0, 43.7, 21.4.

(*S*)-1,2'-Dibenzyl-5-fluoro-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3m)

This product was obtained in 82% yield as a white solid after chromatography and 82:18 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major)=14.39 min, t(minor)=36.66 min]. $[\alpha]_D^{25}$ -66.7 (c 1.0, CH_2Cl_2); mp 259-262 °C. HRMS (ESI-TOF) calcd for $C_{32}H_{27}N_3OF[M+H]^+$: 488.2133; Found: 488.2139. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.89-2.92 (m, 1H), 2.97-3.08 (m, 1H), 3.09-3.11 (m, 1H), 3.54-3.60 (m, 2H), 3.85-3.90 (m, 1H), 4.92 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 12.0 Hz, 1H), 6.81-6.83 (m, 1H), 6.97-7.01 (m, 1H), 7.12-7.18 (m, 5H),

7.34-7.39 (m, 5H), 7.40-7.42 (m, 4H), 7.58 (d, J = 6.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.1, 159.9 ($^1J_{C\text{-}F}$=241.5 Hz), 139.1 ($^4J_{C\text{-}F}$=1.5 Hz), 136.6, 135.8, 132.0, 130.3, 129.1, 128.4, 128.3, 128.2 ($^3J_{C\text{-}F}$=18.0 Hz), 127.7, 127.3, 127.1, 122.5, 119.7, 118.8, 116.3 ($^2J_{C\text{-}F}$=24.0 Hz), 113.4, 113.3 ($^2J_{C\text{-}F}$=24.0 Hz), 112.3, 110.9, 110.1 ($^3J_{C\text{-}F}$=9.0 Hz), 67.2 ($^4J_{C\text{-}F}$=1.5 Hz), 54.7, 44.1, 43.7, 21.4.

(*S*)-1,2'-Dibenzyl-6'-methoxy-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3n)

This product was obtained in 79% yield as a white solid after chromatography and 86:14 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major)=32.90 min, t(minor)=67.26 min]. $[\alpha]_D^{25}$ +43.7 (c 1.0, CH_2Cl_2); mp 242-246 °C. HRMS (ESI-TOF) calcd for $C_{33}H_{30}N_3O_2[M+H]^+$:500.2333; Found: 500.2326. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.81-2.83 (m, 1H), 2.91 (br, 1H), 3.04-3.05 (m, 1H), 3.48-3.54 (m, 2H), 3.83 (s, 3H), 3.86-3.87 (m, 1H), 4.88 (d, J = 12.0 Hz, 1H), 4.96 (d, J = 12.0 Hz, 1H), 6.75-6.77 (m, 1H), 6.83 (d, J = 12.0 Hz, 1H), 6.89-7.01 (m, 3H), 7.03-7.06 (m, 1H), 7.21-7.26 (m, 2H), 7.27-7.30 (m, 3H), 7.31-7.35 (m, 5H), 7.37 (d, J = 12.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 154.2, 143.4, 139.5, 136.1, 131.9, 131.7, 130.1, 129.8, 128.9, 128.3, 128.28, 127.9, 127.8, 127.6, 127.1, 125.5, 123.8, 112.2, 111.8, 111.7, 109.4, 100.8, 66.9, 56.2, 54.6, 44.2, 43.3, 21.9.

(*S*)-2'-Benzyl-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3o)

This product was obtained in 67% yield as a white solid after chromatography and 61:39 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major)=10.99 min, t(minor)=13.41 min]. $[\alpha]_D^{25}$ -37.4 (c 1.03, CH_2Cl_2); mp 201-204 °C. HRMS (ESI-TOF) calcd for $C_{25}H_{22}N_3O[M+H]^+$: 380.1757; Found: 380.1752. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.88-2.91 (m, 1H), 2.95-2.99 (m, 1H), 3.07-3.09 (m, 1H), 3.53 (d, J = 12.0 Hz, 1H), 3.58 (d, J = 12.0 Hz, 1H), 3.75-3.80 (m, 1H), 6.92-6.93 (m, 1H), 7.07-7.08 (m, 1H), 7.11-7.14 (m, 2H), 7.15-7.18 (m, 1H), 7.25-7.27 (m, 2H), 7.30-7.33 (m, 2H), 7.35-7.36 (m, 3H), 7.39-7.46 (m, 1H), 7.56 (d, J = 12.0 Hz, 1H), 8.68-8.73 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.5, 141.4, 139.4, 136.6, 130.7, 130.5, 129.8, 128.3, 128.28, 127.1, 125.8, 123.7, 122.3, 119.6, 118.7, 111.9, 111.0, 110.5, 110.4, 67.3, 54.5, 43.6, 21.4.

(*S*)-2'-Benzyl-1-methyl-2',3',4',9'-tetrahydrospiro[indoline-3,1'-pyrido[3,4-*b*]indol]-2-one (3p)

This product was obtained in 64% yield as a white solid after chromatography and 54:46 er value as determined by HPLC [Daicel Chiralpak AD-H, *n*-hexane/*i*-propanol=70:30, 0.8 mL/min, λ=225 nm, t(major=11.01 min, t(minor)=23.60 min]. $[\alpha]_D^{25}$ +23.1 (c 0.97, CH_2Cl_2); mp 204-205 °C. HRMS (ESI-TOF) calcd for $C_{26}H_{24}N_2O[M+H]^+$: 394.1865; Found: 394.1862. ^{1}H NMR (600 MHz, DMSO) δ 2.75-2.79 (m, 2H), 2.90-2.92 (m, 1H), 3.23 (s, 3H), 3.27 (d, J = 12.0 Hz, 1H), 3.31 (d, J = 12.0 Hz, 1H), 3.49-3.53 (m, 1H), 6.96-6.99 (m, 1H), 7.02-7.05 (m, 1H), 7.07-7.10 (m, 1H), 7.16-7.18 (m, 2H), 7.21-7.24 (m, 1H), 7.29-7.30 (m, 5H), 7.40-7.45 (m, 2H), 10.38 (s, 1H). ^{13}C NMR (150 MHz, DMSO)

δ 175.7, 145.1, 139.7, 136.9, 132.2, 130.4, 130.0, 128.7, 128.5, 127.5, 126.6, 124.8, 123.3, 121.7, 118.9, 118.3, 111.6, 109.8, 109.6, 66.9, 54.3, 43.9, 26.6, 21.7.

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17. IC_{50} values of other compounds see the Supporting Information for the detail.