Spiro Heterocycles

An Enantio- and Diastereoselective Mannich/Pictet–Spengler Sequence To Form Spiro[piperidine-pyridoindoles] and Application to Library Synthesis

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Abstract: A new tandem strategy based on a Mannich/Pictet–Spengler sequence has been developed and applied to the synthesis of a new small library (14 examples) of privileged compounds based on the spiro[piperidine-pyridoindole] core. The sequence proceeds by a diastereoselective Pictet–Spengler cyclization after condensation of several tryptamine derivatives

with three novel piperidin-4-ones containing the fluorinated substituents F, CF₃ and SF₅. The piperidin-4-ones were synthesized from readily available starting materials by an enantioselective multi-component organocatalytic Mannich reaction.

Introduction

Spirocyclic compounds have been increasingly exploited as lead compounds in the early phases of drug discovery due to their unique properties, such as intrinsic three-dimensionality, conformational restriction enhancing binding to a target and structural patentability.^[1] Over the past few years, various examples of natural compounds and synthetic drugs containing spiro-fused heterocycles have been discovered to possess relevant biological activities (Figure 1).^[2] In particular, nitrogen-containing spiro heterocycles have been identified as playing key roles in biological and pharmaceutical processes,^[3] rendering this framework an attractive building block for further research. Examples include ibololuteine, an iboga-type indole alkaloid isolated from the Apocynaceae family, fluspirilene, an antipsychotic drug used for the treatment of schizophrenia, and fenspiride hydrochloride, an antitussive drug.

Figure 1. Natural and synthetic active compounds containing the spiro-piperidine moiety.

In this regard, substituents at the 2- and 6-positions of the piperidine ring could be vital to modulate biological activity.^[4] Furthermore, it is well documented that the presence of fluorine atoms can greatly enhance the drug-likeness of small molecules. As a result of properties such as electronegativity, atom size and lipophilicity, the introduction of fluorine into small molecules can effectively alter their biological activity and bioavailability in comparison with their non-fluorinated counterparts.^[5,6]

Inspired by previous piperidinone syntheses by our group,^[7] and in conjunction with current work on spirocyclic compound libraries within the framework of the European Lead Factory,^[8] we herewith report an enantio- and diastereoselective reaction sequence for the synthesis of spiro[2,6-diaryl]piperidine-pyridoindole structures **7** and their utilization in the synthesis of a focused compound library also containing a variety of fluorine functionalities.

Results and Discussion

From a retrosynthetic point of view, the spiro[piperidine-pyridoindole] core of compounds **7** can be generated from piperidin-4-one **4** and substituted indole derivatives through a diastereoselective Pictet–Spengler reaction (Scheme 1). The enantiopure piperidin-4-one **4** can itself be diastereoselectively obtained from β -amino ketone **3** by an intramolecular organocatalysed Mannich reaction. Lastly, amino ketone **3** should be accessible through an enantioselective organocatalysed three-component Mannich reaction with commercially available *p*-anisidine, 3,4-dimethoxybenzaldehyde and acetone.

The forward synthesis commenced with the preparation of protected β -amino ketone **1**, as previously reported by our group.^[7] Compound **1** was obtained in 61 % yield and >99 % ee through a multi-component L-proline-catalysed Mannich reaction.^[7,9] We selected compound **1** for the synthesis of this

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Scheme 1. Retrosynthesis of the spiro[piperidine-4,1'-pyrido[3,4-b]indole] framework.

library due to the high relevance of the 3,4-dimethoxyphenyl group in nature and active drugs.^[10] From compound **1**, two possible synthetic routes for the synthesis of 2,6-disubstituted piperidin-4-ones were envisioned (Scheme 2). Early efforts were focused on the synthesis of *p*-methoxyphenyl (PMP) protected piperidinones **2** in a one-pot procedure by a Mannich cyclization.

Scheme 2. Strategy for the synthesis of piperidin-4-one.

This approach involved the synthesis of the scaffold, which proved a challenge owing to the high level of steric hindrance arising from the three contiguous substituents.^[11] In our efforts to synthesize product **2**, protected amine **1** was treated with several aldehydes in the presence of various catalysts and under a range of temperatures (see the Supporting Information). Unfortunately, none of these conditions led to the desired *N*-protected piperidin-4-one **2**. Owing to these difficulties, we then chose to synthesize the unprotected scaffold **4** with reduced steric hindrance (Scheme 2). To this end, the *N*-PMP amine **1** was deprotected by employing H_5IO_6 under acidic conditions to afford the corresponding product **3** in 46 % yield.^[12] Subsequently, the free amino ketone **3** was treated with triethylamine and 4-fluorobenzaldehyde to afford imine **5** ($\text{R} = \text{F}$). ^1H NMR analysis of the reaction mixture showed not only imine formation, but also the presence of a side-product, which could not be characterized, and the cyclized product **4A**. Several reaction

conditions were investigated to achieve the full conversion of imine **5** into the desired product **4A** (Table 1). The conditions previously reported by us^[7] for these types of cyclizations were unsuccessful (Table 1, Entry 4). After further investigation, we found that full conversion to the cyclized product **4A** could be achieved when using *L*-proline as the catalyst (Table 1, Entry 6).

Table 1. Reaction conditions employed to optimize the synthesis of **4A**.

Entry	Reagent (equiv.)	Solvent	T [°C]	Ratio 5/4A
1	Et_3N (1)	$\text{Et}_3\text{N}/1,2\text{-DCE}^{[a]}$	21–60	3.3:1
2	KOtBu (0.2)	THF	21–70	2:1
3	Et_3N (0.5)	1,2-DCE ^[a]	40	3.3:1
4	CSA (1.2)	1,2-DCE ^[a]	60	1.7:1
5	TFA (1.2)	CH_2Cl_2	21	0.3:1
6	<i>L</i> -proline (0.2)	MeCN	21	0:1

[a] 1,2-DCE = 1,2-dichloroethane.

In addition, ^1H NMR analysis of the reaction mixtures showed the existence of a slow equilibrium between imine **5** and cyclized product **4A** under certain conditions, which led to different ratios of products depending on the temperature. In this manner, we observed that at low temperatures the formation of **4A** was favoured, whereas at room temperature imines **5** and **6** were the major compounds in the reaction mixture. The presence of **5** and **6**, 4-fluorobenzaldehyde and 3,4-dimethoxybenzaldehyde confirmed the existence of an equilibrium between compounds **4A**, **5** and **6** (Scheme 3).

Scheme 3. Equilibria between **4a** and imines **5** and **6**.

Following the optimization of the two-step synthesis of **4A**, a one-pot procedure for the preparation of the cyclized product directly from **3** was investigated. Thus, amine hydrochloride **3** was treated with Et_3N and anhydrous Na_2SO_4 in the presence of catalytic amounts of *L*-proline to afford the cyclized product **4A** in 75 % yield. In the same way, two additional *cis*-2,6-diaryl-piperidin-4-ones, **4B** and **4C** containing CF_3 and SF_5 groups, were synthesized in yields of 38 and 28 %, respectively (Scheme 2).^[13] The mechanism for this diastereoselective cyclization by an intramolecular Mannich reaction is depicted in Scheme 4. First, the iminium ion species formed by the reaction of amine **3** and the corresponding aldehyde adopts the lowest-energy chair-like conformation in which the two hydrogen atoms are in pseudo-axial positions. Then the enamine, formed by *L*-proline and the ketone, attacks the iminium ion to form

Scheme 4. Mechanism for the diastereoselective cyclization reaction.

the final piperidin-4-one with a *cis* configuration with the two bulky aryl groups in equatorial positions. The *cis* stereochemistry of the products was confirmed by NOESY studies.

With the core scaffolds **4A–C** in hand, we focused on the development of a new library of spiro compounds based on the derivatization of the ketone by the classic Pictet–Spengler reaction.^[14] Initially, 3-methoxy-, 3,4-dimethoxy- and 3-fluorophenethylamine were selected as test substrates (Scheme 5).^[15]

Scheme 5. Reactions of the piperidin-4-ones **4A–C** with 2-phenylethylamines.

Test reactions without catalyst failed to achieve full conversion into the corresponding imines. However, after thorough investigation (see the Supporting Information), the reactions in the presence of $\text{Ti}(\text{O}i\text{Pr})_4$ showed complete conversion. When performing the subsequent Pictet–Spengler reaction using both TFA and TfOH as promoters, however, no cyclized product was observed in any of the reactions.

Based on these preliminary results, the more reactive tryptamine was chosen as the model starting substrate (Table 2). The reactions of **4A–C** with tryptamine were carried out in dichloromethane in the presence of 4 Å molecular sieves, which smoothly afforded the imine intermediate. The addition of TFA at 0 °C then led to the diastereoselective formation of compounds **7Aa–Ca** in moderate yields (Table 2, Method A).

Further screening of the reaction conditions (see Table S7 in the Supporting Information) led us to conclude that optimal conversion into the imine could be achieved by the reaction of the selected amine with $\text{Ti}(\text{O}i\text{Pr})_4$ (1.3 equiv.) in the presence of Et_3N (1.2 equiv., only for substrates delivered as the hydrochloride salt) in THF at room temperature. As previously stated, the addition of TFA at 0 °C then successfully delivered the desired Pictet–Spengler cyclization products. It is important to note that in all cases initially a mixture of the piperidin-4-one and imine was formed, and full conversion into the imine could not be achieved. By using these conditions, compounds **7Ab–Cd** were synthesized in an average yield of 67 %. It is worth noting that TfOH was used as the acid in the synthesis of compounds **7Ad–Cd**. In these instances, the use of TFA in different amounts (2.2, 4.0 and 7.0 equiv.) was not sufficient for the cyclization to take place.^[16] The resulting molecules, which contain three N–H groups, were difficult to purify by standard silica gel column chromatography. For this reason, the products were isolated by inactivation of the silica with Et_3N . Moreover, after column chromatography, an additional washing step was performed with NH_4OH (25 % in water) to remove residual triethylammonium salts.

To explain the diastereoselectivity we propose a rationale that is in accordance with the known reactivity of cyclohexan-

Table 2. Scope of the Pictet–Spengler cyclization reaction.

[a] Method A: reaction carried out in CH_2Cl_2 in the presence of molecular sieves, followed by the addition of TFA. Method B: $\text{Ti}(\text{O}i\text{Pr})_4$ (1.3 equiv.) in THF followed by the addition of TFA or TfOH. [b] Yield given based on recovered starting material (BORSM) for compounds **7Ab–Cd**.

ones towards nucleophiles.^[17] The cyclization presumably proceeds through a chair-like transition state in which the indole ring exclusively attacks from the equatorial direction, which is the least hindered side (Scheme 6). 2D NMR studies (NOESY) confirmed the stereochemistry of products **7Aa–Cd**.

To extend this library of compounds and to further expand the scope of the synthetic strategy, we synthesized compound **12** from indole-2-carbaldehyde, and compound **13** by using a smaller pyrrole-based heterocycle (Schemes 7 and 8). First, the Pictet–Spengler precursors **9** and **11** were synthesized starting

Scheme 6. Rationale for the diastereoselectivity of the Pictet-Spengler cyclization reaction.

from the commercially available indole-2-carbaldehyde and pyrrole-2-carbaldehyde by Henry reactions with nitromethane.^[18] Next, the intermediate nitro alkene **8** was reduced by using LiAlH_4 in Et_2O for the synthesis of **9**, and nitro alkene **10** was reduced with a mixture of $\text{NaBH}_4/\text{NiCl}_2$ to give **11** (Scheme 7).^[19]

Scheme 7. Henry reaction and subsequent reduction for the synthesis of amines **9** and **11**.

Finally, precursors **9** and **11** were subjected to the previously optimized conditions in the presence of piperidin-4-one **4A** to afford the corresponding Pictet-Spengler products **12** and **13** in 52 % yield with complete diastereoselectivity in both cases (Scheme 8).

Scheme 8. Synthesis of spiro compounds **12** and **13**.

Conclusions

An enantio- and diastereoselective route for the synthesis of a new class of spirocyclic piperidine structures by means of a Mannich and Pictet-Spengler reaction sequence has been developed. Three new *cis*-2,6-disubstituted piperidin-4-one analogues containing fluorine functionalities were synthesized and

incorporated into the synthetic route. Finally, this methodology has been applied to the synthesis of a small library of compounds consisting of a total of 14 examples, all as single stereoisomers. Currently, the biological properties of these compounds are being evaluated in various assays.

Experimental Section

General Information: Full experimental details for the preparation of the compounds described herein, as well as details related to computational and mechanistic experiments, are provided in the Supporting Information. Reagents were obtained from commercial suppliers and used without purification. Standard syringe techniques were applied for the transfer of dry solvents and air- or moisture-sensitive reagents. TLC detection was performed with UV light and/or by charring at around 150 °C after dipping into a solution of either 2 % anisaldehyde in ethanol/ H_2SO_4 , $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ (25 g/L), or ninhydrin. Column or flash chromatography was carried out by using ACROS silica gel (0.035–0.070 mm, 60 Å pore diameter). IR spectra were recorded with an IR-ATR Bruker TENSOR 27 spectrometer. High-resolution mass spectra were recorded with a JEOL AccuTOF (ESI) or a MAT900 (EI, CI and ESI) spectrometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. NMR spectra were recorded at 298 K with a Varian Inova 400 (400 MHz), a Bruker Avance III 400 MHz, or a Bruker Avance III 500 MHz spectrometer in the solvent indicated. Chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (δ = 0.00 ppm) or CHD_2OD (δ = 3.31 ppm) as internal standard for ^1H NMR and CDCl_3 (δ = 77.16 ppm) or CD_3OD (δ = 49.00 ppm) as internal standard for ^{13}C NMR. Coupling constants are reported as *J* values in Hz. ^1H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublets, t = triplet, m = multiplet, br. = broad), coupling constants (Hz) and integration. The compounds were fully characterized by ^1H and ^{13}C NMR spectra and 2D gDQCOY, gHSQC, gHMBC and NOESY spectra.

(4S)-4-(3,4-Dimethoxyphenyl)-4-[(4-methoxyphenyl)amino]butan-2-one (1**):** 3,4-Dimethoxybenzaldehyde (10.5 g, 63.2 mmol), 4-anisidine (7.78 g, 63.2 mmol) and L-proline (1.5 g, 12.64 mmol) were added to a mixture of DMSO (45 mL) and acetone (180 mL). The resulting reaction mixture was stirred for 23 h. The reaction was then quenched with potassium phosphate buffer (0.5 M, pH 7, 100 mL). Subsequently, potassium phosphate buffer (0.5 M, pH 7, a total of 150 mL) was added in portions. The reaction mixture was cooled to 0 °C, and the product started to precipitate. After stirring for 20 min, the suspension was filtered and the residue was washed with water (0 °C, 50 mL). The product was dried in vacuo. The product was obtained as an off-white powder (19 g) and recrystallized from EtOAc to give white crystals (12.7 g, 38.5 mmol). Yield: 61 %. HPLC: *ee* >99 %, Chiralpak AD-H (250 × 4.6 mm), flow: 1.0 mL/min, heptane/propan-2-ol (80:20), retention time: **1**: 18.7 min, *ent*-**1**: 15.7 min. M.p. 147–151 °C. $[\alpha]_D^{20}$ = +2.4 (*c* = 0.41, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ = 6.91–6.86 (m, 2 H), 6.83–6.77 (m, 1 H), 6.72–6.66 (m, 2 H), 6.55–6.48 (m, 2 H), 4.69 (t, *J* = 6.5 Hz, 1 H), 3.84 (s, 6 H), 3.69 (s, 3 H), 2.88 (d, *J* = 6.5 Hz, 2 H), 2.10 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 207.5, 152.5, 149.3, 148.2, 141.1, 135.5, 118.3, 115.5, 114.8, 111.3, 109.6, 56.0, 55.9, 55.7, 55.3, 51.5, 30.9 ppm. FTIR: $\tilde{\nu}$ = 3385, 1708, 1510, 1253, 1235, 1139, 1027, 821 cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{38}\text{H}_{46}\text{N}_2\text{O}_8\text{Na}$ [*M* + *Na*]⁺ 352.15248; found 352.15248.

(4S)-4-Amino-4-(3,4-dimethoxyphenyl)butan-2-one Hydrochloride (3): Aqueous H₂SO₄ (1 M, 12.1 mL, 12.1 mmol) and H₅IO₆ (2.87 g, 12.6 mmol) were added to a solution of (4S)-4-(3,4-dimethoxyphenyl)-4-(4-methoxyphenylamino)butan-2-one (**1**; 4 g, 12.1 mmol) in MeCN/H₂O (1:1, 120 mL). The mixture was stirred at room temperature for 1.5 h, washed with CH₂Cl₂ (3 × 60 mL), and the resulting aqueous phase was diluted with CH₂Cl₂ (60 mL). The pH of the aqueous layer was brought to 9 by the addition of 5 M aqueous KOH under vigorous stirring. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 60 mL). The combined organic layers were dried with Na₂SO₄, and HCl/EtOAc (9.5 mL) was added. The resulting mixture was concentrated until the product precipitated. The product was isolated by filtration and dried in vacuo to afford **3** (1.44 g, 5.54 mmol) as a pale-yellow solid. Yield: 46 %. ¹H NMR (400 MHz, CD₃OD): δ = 7.03 (d, *J* = 1.8 Hz, 1 H), 7.00–6.96 (m, 2 H), 4.64 (t, *J* = 6.8 Hz, 1 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.20 (d, *J* = 6.8 Hz, 2 H), 2.20 (s, 3 H) ppm. ¹³C NMR (101 MHz, CD₃OD): δ = 207.5, 151.2, 150.9, 130.3, 121.1, 113.1, 112.1, 56.7, 56.5, 52.2, 47.6, 30.1 ppm. FTIR: ν̄ = 3395, 2936, 1709, 1515, 1264, 1143, 1018 cm⁻¹. HRMS (ESI): calcd. for [C₁₂H₁₈NO₃ + H]⁺ 224.12867; found 224.13151 (|Δ| = 12.69 ppm).

(3S)-4-(3,4-Dimethoxyphenyl)-4-[(E)-(4-fluorobenzylidene)-amino]butan-2-one (5): Triethylamine (0.44 mL, 3.18 mmol) and 4-fluorobenzaldehyde (0.34 mL, 3.18 mmol) were added to a solution of **3** (1.65 g, 6.36 mmol) in dry 1,2-dichloroethane (115 mL). The mixture was concentrated in vacuo. Dry 1,2-dichloroethane (110 mL) was added to the residue, and the mixture was concentrated again in vacuo. Dry 1,2-dichloroethane (110 mL) and triethylamine (0.44 mL, 3.18 mmol) were added to the resulting mixture, which was concentrated in vacuo. The mixture was dissolved in dry 1,2-dichloroethane (113 mL), and triethylamine (0.44 mL, 3.18 mmol) and 4-fluorobenzaldehyde (0.03 mL, 0.32 mmol) were added. The resulting mixture was concentrated in vacuo to afford the crude imine. ¹H NMR (400 MHz, CD₃OD): δ = 8.33 (s, 1 H), 7.77–7.70 (m, 2 H), 7.10–7.04 (m, 2 H), 6.98–6.93 (m, 2 H), 6.85–6.82 (m, 1 H), 4.85 (dd, *J* = 8.9, 4.2 Hz, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.21 (dd, *J* = 16.3, 8.9 Hz, 1 H), 2.89 (dd, *J* = 16.3, 4.2 Hz, 1 H), 2.11 (s, 3 H) ppm.

General Procedure for the Synthesis of Compounds 4A–C: A mixture of **3** (1.00 equiv.), triethylamine (1.00 equiv.), the corresponding aldehyde (1.00 equiv.), L-proline (0.20 equiv.) and anhydrous Na₂SO₄ (0.28 equiv.) in EtOH was stirred at room temperature under an inert gas for 3–4 h. Then the reaction was quenched with NH₄Cl (75 mL), and the aqueous layer was extracted with EtOAc (3 × 200 mL). The organic layers were combined and extracted with a solution 0.1 M HCl (3 × 200 mL). The combined aqueous layers were washed with EtOAc and neutralized with 1.0 M aqueous sodium hydroxide to pH 7–8. The aqueous layer was extracted with EtOAc (3 × 200 mL), saturated brine solution was added, and the organic layers were dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford compounds **4A–C**.

(2S,6R)-2-(3,4-Dimethoxyphenyl)-6-(4-fluorophenyl)piperidin-4-one (4A): According to the general procedure, the reaction of amino ketone hydrochloride **3** (2.5 g, 9.63 mmol) and 4-fluorobenzaldehyde afforded **4A** (2.4 g, 7.28 mmol) as an orange solid. Yield: 75 %. *R*_F = 0.50 (heptane/EtOAc, 1:1). ¹H NMR (400 MHz, CDCl₃): δ = 7.48–7.41 (m, 2 H), 7.08–7.02 (m, 2 H), 7.02–6.96 (m, 2 H), 6.85 (d, *J* = 8.1 Hz, 1 H), 4.05 (dd, *J* = 10.2, 4.5 Hz, 1 H), 4.01 (dd, *J* = 10.9, 3.7 Hz, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 2.66–2.50 (m, 4 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 208.1, 162.4 (d, *J* = 246.2 Hz), 149.3, 148.8, 138.6 (d, *J* = 3.1 Hz), 135.4, 128.3 (d, *J* = 8.1 Hz, 2 ×), 118.8, 115.7 (d, *J* = 21.3 Hz, 2 ×), 111.3, 109.7, 61.1,

60.6, 56.1, 50.7, 50.6 ppm. FTIR: ν̄ = 3305, 1710, 1509, 1264, 1232 cm⁻¹. HRMS (ESI): calcd. for [C₁₉H₂₀NO₃ + H]⁺ 330.15055; found 330.15190 (|Δ| = 4.11 ppm).

(2S,6R)-2-(3,4-Dimethoxyphenyl)-6-[4-(trifluoromethyl)phenyl]piperidin-4-one (4B): According to the general procedure, the reaction of amino ketone hydrochloride **3** (2.5 g, 9.63 mmol) and 4-(trifluoromethyl)benzaldehyde afforded **4B** (1.4 g, 3.70 mmol) as an orange solid. Yield: 38 %. *R*_F = 0.60 (heptane/EtOAc, 1:1). ¹H NMR (400 MHz, CDCl₃): δ = 7.66–7.56 (m, 4 H), 7.03–6.97 (m, 2 H), 6.85 (d, *J* = 8.1 Hz, 1 H), 4.14 (dd, *J* = 8.6, 7.0 Hz, 1 H), 4.03 (dd, *J* = 11.0, 3.6 Hz, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 2.68–2.53 (m, 4 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 207.5, 149.4, 148.9, 146.7 (q, *J* = 1.2 Hz), 135.2, 130.3 (q, *J* = 32.5 Hz), 127.1 (2 ×), 125.9 (q, *J* = 3.7 Hz, 2 ×), 122.7 (CF₃, indirect observation), 118.8, 111.3, 109.7, 61.1, 60.8, 56.1, 50.6, 50.3 ppm. HRMS (ESI): calcd. for [C₂₀H₂₁F₃NO₃ + H]⁺ 380.14735; found 380.14778 (|Δ| = 1.13 ppm).

(2S,6R)-2-(3,4-Dimethoxyphenyl)-6-[4-(pentafluoro-λ⁶-sulfanyl)phenyl]piperidin-4-one (4C): According to the general procedure, the reaction of amino ketone hydrochloride **3** (2.2 g, 8.61 mmol) and 4-(pentafluorosulfanyl)benzaldehyde afforded **4C** (1.07 g, 2.45 mmol) as a yellow solid. Yield: 28 %. *R*_F = 0.60 (heptane/EtOAc, 1:1). ¹H NMR (400 MHz, CDCl₃): δ = 7.79–7.74 (m, 2 H), 7.61–7.56 (m, 2 H), 7.03–6.96 (m, 2 H), 6.86 (d, *J* = 7.9 Hz, 1 H), 4.17–4.12 (dd, *J* = 8.3, 6.5 Hz, 1 H), 4.04 (dd, *J* = 11.0, 3.3 Hz, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 2.69–2.50 (m, 4 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 207.2, 153.7 (indirect observation), 149.4, 148.9, 146.6–146.5 (m), 135.1, 127.1 (2 ×), 126.7–126.5 (2 ×), 118.8, 111.3, 109.7, 61.1, 60.5, 56.1, 50.6, 50.2 ppm. FTIR: ν̄ = 1714, 1517, 829 cm⁻¹. HRMS (ESI): calcd. for [C₁₉H₂₁F₅NO₃S + H]⁺ 438.11623; found 438.11611 (|Δ| = 0.27 ppm).

General Procedure for the Synthesis of Compounds 7Aa–Ca: A mixture of piperidin-4-one **4A–C** (1.00 equiv.) and tryptamine (1.00 equiv. for the synthesis of **7Aa** and **7Ca** and 1.60 equiv. for the synthesis of **7Ba**) dissolved in CH₂Cl₂ in the presence of molecular sieves was stirred at 21 °C under an inert gas for the time indicated in each case. Then the solution was cooled to 0 °C, TFA (2.2 equiv.) was added and the reaction mixture was warmed to 21 °C and stirred for the time indicated in each case. The reaction was quenched with a saturated NaHCO₃ solution, and the aqueous layer was extracted with CH₂Cl₂ (3 ×). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered and concentrated in vacuo.

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6-(4-fluorophenyl)-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indole] (7Aa): According to the general procedure, the reaction mixture of piperidin-4-one **4A** (51.5 mg, 0.16 mmol) was stirred in CH₂Cl₂ (2.5 mL) overnight to form the imine. TFA (27 μL, 0.34 mmol) in CH₂Cl₂ (0.14 mL) was added, and the mixture was stirred for 48 h. The crude mixture was purified by column chromatography [heptane/EtOAc (4:1) → EtOAc] and ion-exchange column chromatography (ISOLUTE SCX-2) to afford compound **7Aa** (38.5 mg, 0.08 mmol) as a yellow solid. Yield: 52 %. *R*_F = 0.43 (EtOAc). ¹H NMR (500 MHz, CDCl₃): δ = 7.86 (br. s, 1 H), 7.49–7.44 (m, 3 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.13 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1 H), 7.10–7.06 (m, 1 H), 7.06–6.98 (m, 4 H), 6.83 (d, *J* = 8.2 Hz, 1 H), 4.50–4.43 (m, 1 H), 4.40 (dd, *J* = 10.9, 3.1 Hz, 1 H), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.26 (t, *J* = 5.7 Hz, 2 H), 2.75 (t, *J* = 5.7 Hz, 2 H), 2.08–1.93 (m, 4 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 162.1 (d, *J* = 244.7 Hz), 149.1, 148.4, 140.5, 139.4, 137.3, 135.6, 128.4 (d, *J* = 7.9 Hz, 2 ×), 127.6, 121.9, 119.5, 119.0, 118.3, 115.4 (d, *J* = 21.1 Hz, 2 ×), 111.3, 110.9, 110.2, 108.9, 56.6, 56.3, 56.1, 56.1, 53.3, 45.1, 45.1, 39.4, 23.3 ppm. FTIR: ν̄ = 3364, 2933, 2835, 1603, 1507, 1223, 1136, 1025, 804 cm⁻¹. HRMS (ESI):

calcd. for $[C_{29}H_{30}FN_3O_2 + H]^+$ 472.23985; found 472.24003 ($|\Delta| = 0.4$ ppm).

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6-[4-(trifluoromethyl)phenyl]-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indole] (7Ba): According to the general procedure, the reaction mixture of piperidin-4-one **4B** (100 mg, 0.26 mmol) was stirred, in the presence of 4 Å molecular sieves, in CH_2Cl_2 (5 mL) for 5 h to form the imine. TFA (44 µL, 0.57 mmol) in CH_2Cl_2 (0.25 mL) was added, and the mixture was stirred for 24 h. The crude product was purified by two column chromatographic procedures [heptane/EtOAc (3:1) → EtOAc/MeOH (10:1) and heptane/EtOAc (2:3) → EtOAc/MeOH (10:1)] to afford compound **7Ba** (56.6 mg, 0.11 mmol). Yield: 41 %. $R_F = 0.22$ (heptane/EtOAc, 2:3). 1H NMR (400 MHz, $CDCl_3$): $\delta = 7.84$ (br. s, 1 H), 7.67–7.55 (m, 4 H), 7.47 (d, $J = 7.7$ Hz, 1 H), 7.27 (dt, $J = 8.0, 0.9$ Hz, 1 H), 7.13 (ddd, $J = 8.1, 7.1, 1.3$ Hz, 1 H), 7.10–7.01 (m, 3 H), 6.84 (d, $J = 8.1$ Hz, 1 H), 4.54 (dd, $J = 10.5, 3.5$ Hz, 1 H), 4.42 (dd, $J = 10.4, 3.4$ Hz, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.34–3.20 (m, 2 H), 2.75 (t, $J = 5.7$ Hz, 2 H), 2.08–1.90 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 149.1, 149.0$ (q, $J = 1.0$ Hz), 148.4, 139.2, 137.3, 135.6, 129.6 (q, $J = 32.3$ Hz), 127.5, 127.2 (2×), 125.6 (q, $J = 3.7$ Hz, 2×), 124.3 (q, $J = 272.2$ Hz, CF_3), 122.0, 119.6, 118.9, 118.4, 111.3, 110.9, 109.0, 56.6, 56.4, 56.1 (2×), 53.2, 45.2, 45.0, 39.4, 23.3 ppm. FTIR: $\tilde{\nu} = 3367, 2931, 2835, 1628, 1507, 1223, 1153, 1025, 764$ cm^{-1} . HRMS (ESI): calcd. for $[C_{30}H_{32}F_3N_3O_2 + H]^+$ 522.23708; found 522.23684 ($|\Delta| = 0.5$ ppm).

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indole] (7Ca): According to the general procedure, the reaction mixture of piperidin-4-one **4C** (40 mg, 0.09 mmol) was stirred, in the presence of 4 Å molecular sieves, in CH_2Cl_2 (1.5 mL) for 5 h to form the imine. TFA (20 µL, 0.20 mmol) was added, and the mixture was stirred overnight. The crude product was purified by column chromatography [heptane/EtOAc (4:1) → EtOAc] to afford compound **7Ca** (24.4 mg, 0.042 mmol). Yield: 47 %. $R_F = 0.34$ (heptane/EtOAc, 2:3). 1H NMR (400 MHz, $CDCl_3$): $\delta = 7.89$ (s, 1 H), 7.75–7.69 (m, 2 H), 7.62–7.57 (m, 2 H), 7.48 (d, $J = 7.7$ Hz, 1 H), 7.27 (d, $J = 7.4$ Hz, 1 H), 7.14 (t, $J = 7.5$ Hz, 1 H), 7.11–7.01 (m, 3 H), 6.85 (d, $J = 8.1$ Hz, 1 H), 4.55 (dd, $J = 10.3, 2.9$ Hz, 1 H), 4.43 (dd, $J = 10.6, 2.7$ Hz, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.37–3.17 (m, 2 H), 2.76 (t, $J = 5.5$ Hz, 2 H), 2.12–1.91 (m, 4 H), 1.86 (br. s, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 152.9$ (quint, $J = 17.1$ Hz), 149.1, 148.8, 148.4, 139.1, 137.1, 135.6, 127.5, 127.1 (2×), 126.3 (quint, $J = 4.6$ Hz, 2×), 122.0, 119.5, 118.9, 118.4, 111.3, 110.9, 110.1, 109.0, 56.3 (2×), 56.1, 56.1, 53.2, 45.1, 44.8, 39.4, 23.2 ppm. FTIR: $\tilde{\nu} = 3373, 2934, 2838, 1592, 1515, 1232, 1138, 1027, 840$ cm^{-1} . HRMS (ESI): calcd. for $[C_{29}H_{31}F_5N_3O_2S + H]^+$ 580.20571; found 580.20471 ($|\Delta| = 1.73$ ppm).

General Procedure for the Synthesis of Compounds 7Ab–Cb: A solution of $Ti(OiPr)_4$ (1.30 equiv.) in dry THF (0.5 mL) was added to a mixture of piperidin-4-one **4A–C** (1.00 equiv.) and 6-methoxytryptamine (1.20 equiv.) in dry THF (2 mL) at 21 °C under argon. After 6 h, TFA (2.20 equiv.) dissolved in dry THF (0.5 mL) was added at 0 °C, and the reaction mixture was warmed to 21 °C and stirred for 19–24 h. The reaction was quenched with a saturated $NaHCO_3$ solution and the mixture diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried with Na_2SO_4 , filtered and concentrated in vacuo. The crude product was purified by column chromatography [heptane/EtOAc (2:1) → EtOAc/MeOH (10:1)]. The dried product was dissolved in CH_2Cl_2 (5 mL) and washed with aqueous NH_4OH (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3× 5 mL), and the combined organic layers were washed with brine, dried with Na_2SO_4 , filtered and dried in vacuo to afford compounds **7Ab–Cb**.

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6-(4-fluorophenyl)-7'-methoxy-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indole] (7Ab): According to the general procedure, the reaction of piperidin-4-one **4A** (50 mg, 0.152 mmol) afforded **7Ab** (41.5 mg, 0.083 mmol). Yield (BORSM): 74 %. $R_F = 0.30$ (heptane/EtOAc/ Et_3N , 4:4:1). 1H NMR (400 MHz, $CDCl_3$): $\delta = 7.79$ (br. s, 1 H), 7.48–7.44 (m, 2 H), 7.33 (d, $J = 8.6$ Hz, 1 H), 7.05 (d, $J = 1.9$ Hz, 1 H), 7.03–6.98 (m, 3 H), 6.82 (d, $J = 8.3$ Hz, 1 H), 6.80 (d, $J = 2.2$ Hz, 1 H), 6.74 (dd, $J = 8.6, 2.2$ Hz, 1 H), 4.44 (dd, $J = 9.1, 4.9$ Hz, 1 H), 4.39 (dd, $J = 11.0, 2.9$ Hz, 1 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 3.24 (t, $J = 5.7$ Hz, 2 H), 2.70 (t, $J = 5.7$ Hz, 2 H), 2.06–1.92 (m, 4 H), 1.72 (br. s, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 162.1$ (d, $J = 245.0$ Hz), 156.4, 149.1, 148.3, 140.5, 138.2, 137.3, 136.4, 128.4 (d, $J = 7.9$ Hz, 2×), 122.0, 118.9, 118.8, 115.4 (d, $J = 21.2$ Hz, 2×), 111.2, 110.1, 108.9, 108.7, 95.1, 56.6, 56.3, 56.1 (2×), 55.9, 53.2, 45.1, 45.0, 39.4, 23.3 ppm. FTIR: $\tilde{\nu} = 3366, 2931, 2835, 1628, 1507, 1223, 1153, 1025, 764$ cm^{-1} . HRMS (ESI): calcd. for $[C_{30}H_{32}FN_3O_3 + H]^+$ 502.25093; found 502.25059 ($|\Delta| = 0.7$ ppm).

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-7'-methoxy-6-[4-(trifluoromethyl)phenyl]-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indole] (7Bb): According to the general procedure, the reaction of piperidin-4-one **4B** (50 mg, 0.132 mmol) afforded **7Bb** (56.0 mg, 0.102 mmol). Yield: 77 %. $R_F = 0.32$ (heptane/EtOAc/ Et_3N , 4:4:1). 1H NMR (500 MHz, $CDCl_3$): $\delta = 7.69$ (br. s, 1 H), 7.64–7.55 (m, 4 H), 7.34 (d, $J = 8.6$ Hz, 1 H), 7.06–7.01 (m, 2 H), 6.84 (d, $J = 8.2$ Hz, 1 H), 6.80 (d, $J = 2.2$ Hz, 1 H), 6.75 (dd, $J = 8.6, 2.2$ Hz, 1 H), 4.53 (dd, $J = 11.1, 2.3$ Hz, 1 H), 4.41 (dd, $J = 10.3, 3.5$ Hz, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.28–3.22 (m, 2 H), 2.71 (t, $J = 5.6$ Hz, 2 H), 2.05–1.89 (m, 4 H), 1.62 (br. s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 156.4, 149.1, 149.0, 148.4, 138.1, 137.3, 136.4, 129.6$ (q, $J = 32.3$ Hz), 127.2 (2×), 125.5 (q, $J = 3.7$ Hz, 2×), 124.3 (q, $J = 272.0$ Hz, CF_3), 122.0, 118.9, 118.8, 111.3, 110.2, 108.8, 108.7, 95.2, 56.6, 56.4, 56.1 (2×), 55.9, 53.2, 45.1, 44.9, 39.4, 23.3 ppm. FTIR: $\tilde{\nu} = 3369, 2926, 2835, 1619, 1515, 1260, 1097, 1066, 797$ cm^{-1} . HRMS (ESI): calcd. for $[C_{31}H_{32}F_3N_3O_3 + H]^+$ 552.24737; found 552.24740 ($|\Delta| = 0.1$ ppm).

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-7'-methoxy-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indole] (7Cb): According to the general procedure, the reaction of piperidin-4-one **4C** (50 mg, 0.114 mmol) afforded **7Cb** (18.1 mg, 0.030 mmol). In this case, after applying the general procedure, the crude product was purified by a second column chromatography [heptane/EtOAc (2:1) → EtOAc/MeOH (10:1)] and ion-exchange column chromatography (ISOLUTE SCX-2). The dried product was dissolved again in CH_2Cl_2 (5 mL) and washed with aqueous NH_4OH (5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3× 5 mL), and the organic layers were washed with brine, dried with Na_2SO_4 , filtered and dried in vacuo. Yield (BORSM): 56 %. $R_F = 0.28$ (heptane/EtOAc/ Et_3N , 4:4:1). 1H NMR (400 MHz, $CDCl_3$): $\delta = 7.73$ –7.70 (m, 2 H), 7.68 (br. s, 1 H), 7.61–7.57 (m, 2 H), 7.34 (d, $J = 8.6$ Hz, 1 H), 7.04 (d, $J = 2.0$ Hz, 1 H), 7.02 (dd, $J = 8.2, 2.0$ Hz, 1 H), 6.84 (d, $J = 8.2$ Hz, 1 H), 6.79 (d, $J = 2.2$ Hz, 1 H), 6.75 (dd, $J = 8.6, 2.2$ Hz, 1 H), 4.53 (dd, $J = 11.1, 2.2$ Hz, 1 H), 4.41 (dd, $J = 10.4, 3.5$ Hz, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.28–3.21 (m, 2 H), 2.71 (t, $J = 5.7$ Hz, 2 H), 2.04–1.87 (m, 4 H), 1.62 (br. s, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 156.5, 152.9$ (quint, $J = 17.6$ Hz), 149.1, 148.8, 148.5, 137.9, 137.1, 136.4, 127.1 (2×), 126.3 (quint, $J = 4.4$ Hz, 2×), 122.0, 118.9, 118.9, 111.3, 110.1, 108.9, 108.8, 95.2, 56.3 (2×), 56.1, 56.1, 55.9, 53.2, 45.1, 44.8, 39.4, 23.3 ppm. FTIR: $\tilde{\nu} = 3371, 2938, 2837, 1629, 1516, 1262, 1154, 1027, 823, 729$ cm^{-1} . HRMS (ESI): calcd. for $[C_{30}H_{32}F_5N_3O_3S + H]^+$ 610.21561; found 610.21628 ($|\Delta| = 1.1$ ppm).

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6-(4-fluorophenyl)-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indol]-6'-ol (7Ac): Et₃N (25 μ L, 0.182 mmol) dissolved in dry THF (0.25 mL) and Ti(OiPr)₄ (58 μ L, 0.197 mmol) dissolved in dry THF (0.25 mL) were added to a mixture of **4A** (50 mg, 0.152 mmol) and 5-hydroxytryptamine hydrochloride (38.7 mg, 0.182 mmol) dissolved in dry THF (0.5 mL). After 30 min, additional Et₃N (25 μ L, 0.182 mmol) and THF (16.5 mL) were added. After 4.5 h, TFA (52 μ L, 0.668 mmol) dissolved in dry THF (0.5 mL) was added at 0 °C, and the reaction mixture was warmed to 21 °C and stirred for 21 h. The reaction was quenched with an aqueous saturated NaHCO₃ solution and the mixture diluted with EtOAc. The organic and aqueous phases were separated, and the aqueous phase was extracted with EtOAc (4 $\times$). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered and dried in vacuo. The crude product was dissolved in dry THF (2 mL), and 5-hydroxytryptamine hydrochloride (15.5 mg, 0.073 mmol), Et₃N (10 μ L, 0.073 mmol) in dry THF (0.5 mL) and Ti(OiPr)₄ (23.2 μ L, 0.079 mmol) were added. After 3 h, TFA (10.4 μ L, 0.134 mmol) was added at 0 °C, and the reaction mixture was warmed to 21 °C and stirred for 20.5 h. The reaction was quenched with an aqueous saturated NaHCO₃ solution and diluted with EtOAc. The organic and aqueous phases were separated, and the aqueous phase was extracted with EtOAc (4 $\times$). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered and dried in vacuo. The crude product was purified by column chromatography [EtOAc $\rightarrow$ EtOAc/MeOH (10:1)]. The dried product was dissolved in CH₂Cl₂ (5 mL) and washed with aqueous NH₄OH (2 $\times$ 5 mL). The combined aqueous layers were extracted with CH₂Cl₂ (3 $\times$ 10 mL), and the combined organic layers were washed with brine, dried with Na₂SO₄, filtered and dried in vacuo to afford **7Ac** (37.0 mg, 0.076 mmol) as a yellow solid. Yield (BORMS): 80 %. *R*_F = 0.32 (EtOAc/Et₃N, 8:1). ¹H NMR (500 MHz, CDCl₃): δ = 7.81 (br. s, 1 H), 7.45 (m, 2 H), 7.09 (d, *J* = 8.6 Hz, 1 H), 7.05 (d, *J* = 2.0 Hz, 1 H), 7.03–6.96 (m, 3 H), 6.84 (d, *J* = 2.4 Hz, 1 H), 6.81 (d, *J* = 8.2 Hz, 1 H), 6.67 (dd, *J* = 8.6, 2.4 Hz, 1 H), 4.44 (dd, *J* = 10.4, 3.6 Hz, 1 H), 4.39 (dd, *J* = 11.1, 2.6 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.22 (t, *J* = 5.7 Hz, 2 H), 2.63 (t, *J* = 5.7 Hz, 2 H), 2.10–1.93 (m, 4 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 162.1 (d, *J* = 245.2 Hz), 149.6, 149.1, 148.4, 140.6, 140.2 (d, *J* = 2.9 Hz), 137.1, 130.9, 128.5 (d, *J* = 7.9 Hz, 2 $\times$), 128.3, 119.0, 115.4 (d, *J* = 21.2 Hz, 2 $\times$), 111.5, 111.5, 111.3, 110.2, 108.4, 103.4, 56.7, 56.4, 56.1, 56.1, 53.4, 44.8 (2 $\times$), 39.3, 23.2 ppm. FTIR: $\tilde{\nu}$ = 3367, 2931, 2838, 1591, 1515, 1261, 1118, 1016, 800 cm⁻¹. HRMS (ESI): calcd. for [C₂₉H₃₀FN₃O₃ + H]⁺ 488.23454; found 488.23494 ($|\Delta|$ = 0.8 ppm).

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6-[4-(trifluoromethyl)phenyl]-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indol]-6'-ol (7Bc): Et₃N (22 μ L, 0.158 mmol) dissolved in dry THF (0.50 mL) and Ti(OiPr)₄ (50 μ L, 0.171 mmol) dissolved in dry THF (0.50 mL) were added to a mixture of **4B** (50 mg, 0.132 mmol) and 5-hydroxytryptamine hydrochloride (33.6 mg, 0.158 mmol) dissolved in dry THF (2 mL). After 7 h, TFA (22 μ L, 0.290 mmol) dissolved in dry THF (0.5 mL) was added at 0 °C, and the reaction mixture was warmed to 21 °C and stirred for 23 h. The reaction was quenched with an aqueous saturated NaHCO₃ solution and the mixture diluted with EtOAc. The organic and aqueous phases were separated, and the aqueous phase was extracted with EtOAc (4 h). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered and dried in vacuo. The crude product was dissolved in dry THF (1.5 mL), and 5-hydroxytryptamine hydrochloride (33.6 mg, 0.158 mmol), Et₃N (22 μ L, 0.158 mmol) in dry THF (0.5 mL) and Ti(OiPr)₄ (50 μ L, 0.171 mmol) were added. After 7 h, TFA (22 μ L, 0.290 mmol) dissolved in dry THF (0.5 mL) was added at 0 °C, and the reaction mixture was warmed to 21 °C and stirred for 24.5 h.

The reaction was quenched with an aqueous saturated NaHCO₃ solution and diluted with EtOAc. The organic and aqueous phases were separated, and the aqueous phase was extracted with EtOAc (3 $\times$). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered and dried in vacuo. The crude product was purified by column chromatography [heptane/EtOAc (1:1) $\rightarrow$ EtOAc/MeOH (10:1)]. The dried product was dissolved in CH₂Cl₂ (5 mL) and washed with aqueous NH₄OH (5 mL). The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 5 mL), and the combined organic layers were washed with brine, dried with Na₂SO₄, filtered and dried in vacuo to afford **7Bc** (27.5 mg, 0.051 mmol) as a purple solid. Yield (BORMS): 74 %. *R*_F = 0.32 (EtOAc/Et₃N, 8:1). ¹H NMR (400 MHz, CDCl₃): δ = 7.70 (br. s, 1 H), 7.62–7.55 (m, 4 H), 7.10 (d, *J* = 8.6 Hz, 1 H), 7.04 (d, *J* = 1.8 Hz, 1 H), 7.02 (dd, *J* = 8.2, 1.9 Hz, 1 H), 6.86 (d, *J* = 2.4 Hz, 1 H), 6.83 (d, *J* = 8.2 Hz, 1 H), 6.68 (dd, *J* = 8.6, 2.4 Hz, 1 H), 4.53 (dd, *J* = 10.7, 3.0 Hz, 1 H), 4.41 (dd, *J* = 10.7, 3.0 Hz, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.34–3.16 (m, 2 H), 2.66 (t, *J* = 5.7 Hz, 2 H), 2.19–1.91 (m, 5 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 149.6, 149.1, 148.5, 148.3, 140.3, 136.7, 130.9, 129.6 (q, *J* = 32.4 Hz), 128.2, 127.3 (2 $\times$), 125.6 (q, *J* = 3.7 Hz, 2 $\times$), 124.3 (q, *J* = 272.0 Hz, CF₃), 119.1, 111.7, 111.5, 111.3, 110.2, 108.3, 103.5, 56.7, 56.6, 56.1, 56.0, 53.4, 44.5, 44.3, 39.3, 23.1 ppm. FTIR: $\tilde{\nu}$ = 3364, 3305, 2931, 2836, 1591, 1509, 1223, 1140, 1024, 800 cm⁻¹. HRMS (ESI): calcd. for [C₃₀H₃₀F₃N₃O₃ + H]⁺ 538.23216; found 538.23175 ($|\Delta|$ = 0.8 ppm).

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6-[4-(pentafluoro- λ^6 -sulfonyl)phenyl]-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indol]-6'-ol (7Cc): Et₃N (19 μ L, 0.137 mmol) dissolved in dry THF (0.5 mL) and Ti(OiPr)₄ (44 μ L, 0.149 mmol) dissolved in dry THF (0.5 mL) were added to a mixture of **4A** (50 mg, 0.114 mmol) and 5-hydroxytryptamine hydrochloride (29.2 mg, 0.137 mmol) in dry THF (2 mL). After 6 h, TFA (19 μ L, 0.251 mmol) dissolved in dry THF (0.5 mL) was added at 0 °C, and the reaction mixture was warmed to 21 °C and stirred for 20 h. The reaction was quenched with NaHCO₃ and the mixture diluted with EtOAc. The organic layer was separated, and the aqueous phase was extracted with EtOAc (4 $\times$). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered and dried in vacuo. The crude product was purified by column chromatography [heptane/EtOAc (1:1) $\rightarrow$ EtOAc/MeOH (10:1)], and the dried product was dissolved in CH₂Cl₂ (5 mL) and washed with aqueous NH₄OH (5 mL). The aqueous phase was extracted with CH₂Cl₂ (3 $\times$ 5 mL), and the combined organic layers were washed with brine, dried with Na₂SO₄, filtered and dried in vacuo to afford **7Cc** (32.4 mg, 0.054 mmol) as a purple solid. Yield (BORMS): 76 %. *R*_F = 0.37 (EtOAc/Et₃N, 8:1). ¹H NMR (500 MHz, CDCl₃): δ = 7.81 (br. s, 1 H), 7.71–7.66 (m, 2 H), 7.59–7.54 (m, 2 H), 7.08 (d, *J* = 8.6 Hz, 1 H), 7.04 (d, *J* = 1.9 Hz, 1 H), 7.01 (dd, *J* = 8.2, 1.9 Hz, 1 H), 6.84 (d, *J* = 2.4 Hz, 1 H), 6.82 (d, *J* = 8.3 Hz, 1 H), 6.67 (dd, *J* = 8.6, 2.4 Hz, 1 H), 4.54–4.50 (m, 1 H), 4.41 (dd, *J* = 11.2, 2.2 Hz, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.29–3.16 (m, 2 H), 2.62 (t, *J* = 5.6 Hz, 2 H), 2.13–1.90 (m, 5 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 153.0 (quint, *J* = 16.9 Hz), 149.6, 149.2, 148.5, 148.3, 140.2, 136.7, 130.9, 128.2, 127.2 (2 $\times$), 126.3 (quint, *J* = 4.2 Hz, 2 $\times$), 119.1, 111.7, 111.5, 111.3, 110.2, 108.4, 103.5, 56.5, 56.4, 56.1, 56.1, 53.3, 44.6, 44.3, 39.3, 23.1 ppm. FTIR: $\tilde{\nu}$ = 3367, 2961, 2839, 1592, 1516, 1260, 103, 799 cm⁻¹. HRMS (ESI): calcd. for [C₂₉H₃₀F₅N₃O₃S + H]⁺ 596.20116; found 596.20063 ($|\Delta|$ = 0.9 ppm).

General Procedure for the Synthesis of Compounds 7Ad–Cd: A solution of Et₃N (1.20 equiv.) in dry THF (0.5 mL) and a solution of Ti(OiPr)₄ (1.30 equiv.) in dry THF (0.5 mL) were added to a mixture of piperidin-4-one **4A–C** (1.00 equiv.) and 5-fluorotryptamine hydrochloride (1.20 equiv.) in dry THF (2 mL) at 21 °C under argon. After 4–7 h, TfOH (3.00 equiv. for **7Ad** and **7Bd** and 3.50 equiv. for **7Cd**) dissolved in dry THF (0.5 mL) was added at 0 °C, and the reaction

mixture was warmed to 21 °C and stirred for 22–25 h. The reaction was quenched with a saturated NaHCO₃ solution and the mixture diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography [heptane/EtOAc (2:1) → EtOAc/MeOH (10:1)], and the dried product was dissolved in CH₂Cl₂ (5 mL) and washed with aqueous NH₄OH (5 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic layers were washed with brine, dried with Na₂SO₄, filtered and dried in vacuo to afford compounds **7Ad–Cd**.

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6'-fluoro-6-(4-fluorophenyl)-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indole] (7Ad): According to the general procedure, the reaction of piperidin-4-one **4A** (50 mg, 0.152 mmol) afforded **7Ad** (46.1 mg, 0.094 mmol) as a yellow solid. Yield (BORMS): 74 %. *R*_F = 0.37 (heptane/EtOAc/Et₃N, 4:4:1). ¹H NMR (500 MHz, CDCl₃): δ = 7.93 (br. s, 1 H), 7.50–7.43 (m, 2 H), 7.20–7.16 (m, 1 H), 7.10 (dd, *J* = 9.4, 2.5 Hz, 1 H), 7.04 (d, *J* = 2.0 Hz, 1 H), 7.02–6.98 (m, 3 H), 6.86 (td, *J* = 9.2, 2.5 Hz, 1 H), 6.82 (d, *J* = 8.2 Hz, 1 H), 4.46–4.43 (m, 1 H), 4.40 (dd, *J* = 10.8, 3.1 Hz, 1 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 3.25 (t, *J* = 5.8 Hz, 2 H), 2.69 (t, *J* = 5.8 Hz, 2 H), 2.09–1.93 (m, 4 H), 1.72 (br. s, 2 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 162.1 (d, *J* = 245.2 Hz), 157.9 (d, *J* = 234.3 Hz), 149.1, 148.4, 141.4, 140.4, 137.1, 132.1, 128.4 (d, *J* = 7.9 Hz, 2 ×), 127.9 (d, *J* = 9.8 Hz), 119.0, 115.4 (d, *J* = 21.1 Hz, 2 ×), 111.4 (d, *J* = 9.4 Hz), 111.2, 110.1, 109.9 (d, *J* = 26.0 Hz), 109.1 (d, *J* = 4.3 Hz), 103.4 (d, *J* = 23.2 Hz), 56.6, 56.3, 56.1, 56.1, 53.3, 45.0, 45.0, 39.3, 23.2 ppm. FTIR: ν̄ = 3362, 2930, 2838, 1601, 1508, 1225, 1139, 1025, 798 cm⁻¹. HRMS (ESI): calcd. for [C₂₉H₂₉F₂N₃O₂ + H]⁺ 490.23155; found 490.23061 (|Δ| = 0.9 ppm).

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6'-fluoro-6-[4-(trifluoromethyl)phenyl]-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indole] (7Bd): According to the general procedure, the reaction of piperidin-4-one **4B** (50 mg, 0.132 mmol) afforded **7Bd** (21.9 mg, 0.041 mmol) as a yellow solid. In this case, after applying the general procedure, the crude product was purified for a second time by ion-exchange column chromatography (ISOLUTE SCX-2). The dried product was dissolved in CH₂Cl₂ (5 mL) and washed with aqueous NH₄OH (5 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic layers were washed with brine, dried with Na₂SO₄, filtered and dried in vacuo. Yield (BORMS): 37 %. *R*_F = 0.41 (heptane/EtOAc/Et₃N, 4:4:1). ¹H NMR (500 MHz, CDCl₃): δ = 7.94 (br. s, 1 H), 7.65–7.55 (m, 4 H), 7.20–7.15 (m, 1 H), 7.10 (dd, *J* = 9.4, 2.4 Hz, 1 H), 7.08–7.04 (m, 1 H), 7.06–7.00 (m, 1 H), 6.86 (td, *J* = 9.2, 2.6 Hz, 1 H), 6.83 (d, *J* = 8.3 Hz, 1 H), 4.57–4.52 (m, 1 H), 4.45–4.41 (m, 1 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 3.29–3.22 (m, 2 H), 2.70 (t, *J* = 5.5 Hz, 2 H), 2.09–1.92 (m, 4 H), 1.80 (br. s, 2 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 157.9 (d, *J* = 234.3 Hz), 149.2, 148.5, 148.4, 141.1, 136.8, 132.1, 129.7 (q, *J* = 32.6 Hz), 127.9 (d, *J* = 9.6 Hz), 127.3 (2 ×), 125.6 (q, *J* = 3.4 Hz, 2 ×), 124.3 (q, *J* = 271.5 Hz, CF₃), 119.0, 111.4 (d, *J* = 9.6 Hz), 111.3, 110.2, 110.0 (d, *J* = 26.0 Hz), 109.1 (d, *J* = 4.5 Hz), 103.4 (d, *J* = 23.2 Hz), 56.6, 56.5, 56.1, 56.1, 53.2, 44.6, 44.4, 39.3, 23.1 ppm. FTIR: ν̄ = 3362, 2935, 2837, 1586, 1514, 1261, 1017, 799 cm⁻¹. HRMS (ESI): calcd. for [C₃₀H₂₉F₄N₃O₂ + H]⁺ 540.22734; found 540.22741 (|Δ| = 0.1 ppm).

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6'-fluoro-6-[4-(pentafluoro-λ⁶-sulfanyl)phenyl]-2',3',4',9'-tetrahydrospiro[piperidine-4,1'-pyrido[3,4-b]indole] (7Cd): According to the general procedure, the reaction of piperidin-4-one **4C** (50 mg, 0.114 mmol) afforded **7Cd** (27.6 mg, 0.046 mmol) as a yellow solid. Yield (BORMS): 52 %. *R*_F = 0.25 (heptane/EtOAc/Et₃N, 4:4:1). ¹H NMR

(500 MHz, CDCl₃): δ = 8.02 (br. s, 1 H), 7.71 (d, *J* = 8.8 Hz, 2 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 7.20–7.15 (m, 1 H), 7.10 (dd, *J* = 9.5, 2.5 Hz, 1 H), 7.04 (d, *J* = 2.0 Hz, 1 H), 7.02 (dd, *J* = 8.2, 2.0 Hz, 1 H), 6.87 (td, *J* = 9.1, 2.6 Hz, 1 H), 6.83 (d, *J* = 8.2 Hz, 1 H), 4.54 (dd, *J* = 7.6, 6.1 Hz, 1 H), 4.42 (dd, *J* = 11.0, 2.2 Hz, 1 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 3.31–3.20 (m, 2 H), 2.69 (t, *J* = 5.7 Hz, 2 H), 2.13–1.96 (m, 4 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 157.9 (d, *J* = 234.4 Hz), 153.0 (quint, *J* = 16.9 Hz), 149.2, 148.5, 148.4, 141.0, 136.8, 132.1, 127.9 (d, *J* = 9.6 Hz), 127.2 (2 ×), 126.3 (quint, *J* = 4.5 Hz, 2 ×), 119.0, 111.4 (d, *J* = 9.8 Hz), 111.3, 110.1, 110.0 (d, *J* = 26.6 Hz), 109.2 (d, *J* = 4.5 Hz), 103.4 (d, *J* = 23.4 Hz), 56.4, 56.3, 56.1 (2 ×), 53.2, 44.9, 44.6, 39.3, 23.2 ppm. FTIR: ν̄ = 3367, 2962, 2839, 1588, 1515, 1260, 1022, 795 cm⁻¹. HRMS (ESI): calcd. for [C₂₉H₂₉F₆N₃O₂S + H]⁺ 598.19536; found 598.19629 (|Δ| = 1.6 ppm).

General Procedure for the Synthesis of Compounds 12 and 13: Ti(OiPr)₄ was added to a mixture of piperidin-4-one **4A** (1.00 equiv.) and the amine [1.20 equiv., 2-(1*H*-indol-2-yl)ethan-1-amine (**9**) for **12** and 2-(1*H*-pyrrol-2-yl)ethan-1-amine (**11**) for **13**] in dry THF (3 mL) at 21 °C under argon. After 6 h, TFA (2.20 equiv.) was added at 0 °C, and the reaction mixture was warmed to 21 °C and stirred overnight. The reaction was quenched with a saturated NaHCO₃ solution (3 mL) and the mixture diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc (4 × 6 mL). The combined organic layers were washed with brine, dried with Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography [heptane/EtOAc (2:1) → EtOAc], and the dried product was dissolved in CH₂Cl₂ (5 mL) and washed with aqueous NH₄OH (5 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic layers were washed with brine, dried with Na₂SO₄, filtered and dried in vacuo to afford compounds **12** and **13**.

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6-(4-fluorophenyl)-2',3',4',5'-tetrahydrospiro[piperidine-4,1'-pyrido[4,3-b]indole] (12): According to the general procedure, the reaction of piperidin-4-one **4A** (15 mg, 0.05 mmol) afforded **12** (12 mg, 0.03 mmol). Yield: 52 %. *R*_F = 0.35 (EtOAc/Et₃N, 8:1). ¹H NMR (400 MHz, CDCl₃): δ = 7.88–7.75 (m, 2 H), 7.51–7.47 (m, 2 H), 7.31–7.27 (m, 1 H), 7.14–7.09 (m, 2 H), 7.08–7.03 (m, 2 H), 7.03–6.95 (m, 2 H), 6.85–6.80 (m, 1 H), 4.47–4.41 (m, 1 H), 4.40 (dd, *J* = 12.2, 2.2 Hz, 1 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 3.26 (t, *J* = 5.6 Hz, 2 H), 2.74 (t, *J* = 5.6 Hz, 2 H), 2.60–2.39 (m, 2 H), 1.92–1.82 (m, 2 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 162.0 (indirect observation), 149.0, 148.2, 140.0 (indirect observation), 137.9 (indirect observation), 132.5, 131.1, 128.5 (d, *J* = 7.8 Hz, 2 ×), 125.1, 121.2, 119.5, 119.4, 119.0, 116.4, 115.2 (d, *J* = 21.1 Hz, 2 ×), 111.3, 110.9, 110.4, 56.9, 56.6, 56.1 (2 ×), 54.2, 44.8, 44.6, 38.7, 24.8 ppm. FTIR: ν̄ = 3366, 2957, 2856, 1602, 1508, 1229, 1156, 1026, 763 cm⁻¹. HRMS (ESI): calcd. for [C₂₉H₃₁F₁N₃O₂ + H]⁺ 472.24003; found 472.24094 (|Δ| = 1.92 ppm).

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6-(4-fluorophenyl)-1',5',6',7'-tetrahydrospiro[piperidine-4,4'-pyrrolo[3,2-c]pyridine] (13): According to the general procedure, the reaction of piperidin-4-one **4A** (40 mg, 0.12 mmol) afforded **13** (22 mg, 0.062 mmol). Yield: 52 %. *R*_F = 0.45 (EtOAc/Et₃N, 8:1). ¹H NMR (400 MHz, CDCl₃): δ = 7.79 (br. s, 1 H), 7.49–7.39 (m, 2 H), 7.06–6.95 (m, 4 H), 6.82 (d, *J* = 8.2 Hz, 1 H), 6.60 (t, *J* = 2.7 Hz, 1 H), 6.06 (t, *J* = 2.7 Hz, 1 H), 4.33 (dd, *J* = 11.3, 3.5 Hz, 1 H), 4.29 (dd, *J* = 11.6, 2.9 Hz, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.20 (t, *J* = 5.8 Hz, 2 H), 2.58 (t, *J* = 5.8 Hz, 2 H), 2.07–1.79 (m, 4 H), 1.68 (br. s, 1 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 162.0 (d, *J* = 244.4 Hz), 149.0, 148.1, 141.1 (d, *J* = 3.0 Hz), 138.0, 128.4 (d, *J* = 7.9 Hz, 2 ×), 124.8, 118.9, 116.0, 115.1 (d, *J* = 21.1 Hz, 2 ×), 111.2, 110.9, 110.2, 104.5, 56.8, 56.5, 56.1 (2 ×), 53.5, 46.4, 46.3, 38.9, 24.3 ppm. FTIR: ν̄ = 3379, 2930,

2836, 1604, 1508, 1227, 1156, 1026, 765 cm⁻¹. HRMS (ESI): calcd. for [C₂₅H₂₉F₁₁N₃O₂ + H]⁺ 422.22438; found 422.22591 (Δ = 3.63 ppm).

Supporting Information (see footnote on the first page of this article): Full experimental details for the preparation of the compounds described herein, characterization of new compounds and ¹H and ¹³C NMR spectra.

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Keywords: Enantioselectivity · Diastereoselectivity · Spiro compounds · Nitrogen heterocycles · Library synthesis · Multicomponent reactions

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