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Spiro Heterocycles

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

Alejandra Riesco-Domínguez,[a] Nick van der Zwaluw,[a] Daniel Blanco-Ania,[a] and Floris P. J. T. Rutjes*[a]

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, CF$_3$ and SF$_5$. 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 iboluteine, 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.

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-diarylpiperidine-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 enantipure 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
library due to the high relevance of the 3,4-dimethoxyphenyl group in nature and active drugs. 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.

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. 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$_3$IO$_6$ under acidic conditions to afford the corresponding product 3 in 46 % yield. Subsequently, the free amino ketone 3 was treated with triethylamine and 4-fluorobenzaldehyde under acidic conditions to afford the corresponding product 4 in 46 % yield. 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 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv.)</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Ratio 5/4A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_3$N (1)</td>
<td>H$_3$N/1,2-DCE$^a$</td>
<td>21-60</td>
<td>3.3:1</td>
</tr>
<tr>
<td>2</td>
<td>KOtBu (0.2)</td>
<td>THF</td>
<td>21-70</td>
<td>2.1</td>
</tr>
<tr>
<td>3</td>
<td>Et$_3$N (0.5)</td>
<td>1,2-DCE$^a$</td>
<td>40</td>
<td>3.3:1</td>
</tr>
<tr>
<td>4</td>
<td>CSA (1.2)</td>
<td>1,2-DCE$^a$</td>
<td>60</td>
<td>1.7:1</td>
</tr>
<tr>
<td>5</td>
<td>TFA (1.2)</td>
<td>CH$_2$Cl$_2$</td>
<td>21</td>
<td>0.3:1</td>
</tr>
<tr>
<td>6</td>
<td>L-proline (0.2)</td>
<td>MeCN</td>
<td>21</td>
<td>0:1</td>
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</table>

$^a$ 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).

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$_3$N and anhydrous Na$_2$SO$_4$ 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). 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 the desired 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 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).

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<td>1,2-DCE$^a$</td>
<td>40</td>
<td>3.3:1</td>
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<td>21</td>
<td>0.3:1</td>
</tr>
<tr>
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<td>L-proline (0.2)</td>
<td>MeCN</td>
<td>21</td>
<td>0:1</td>
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Scheme 3. Equilibria between 4A and imines 5 and 6.
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]

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 Ti(OiPr)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 Ti(OiPr)4 (1.3 equiv.) 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 Et3N. Moreover, after column chromatography, an additional washing step was performed with NH4OH (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-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–Ca.

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...
from the commercially available indole-2-carbaldehyde and pyrrole-2-carbaldehyde by Henry reactions with nitromethane.\cite{18} Next, the intermediate nitro alkenes 8 was reduced by using LiAlH₄ in Et₂O for the synthesis of 9, and nitro alkenes 10 was reduced with a mixture of NaBH₄/NiCl₂ to give 11 (Scheme 7).\cite{19}

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).

**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/H₂SO₄, (NH₄)₆Mo₇O₂4·4H₂O (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 CHD₂OD (δ = 49.00 ppm) as internal standard for 1H NMR and CDCl₃ (δ = 77.16 ppm) or CD₃OD (δ = 49.00 ppm) as internal standard for 13C 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 of doublets, t = triplet, m = multiplet, br. = broad), coupling constants (Hz) and integration. The compounds were fully characterized by 1H and 13C NMR spectra and 2D gDQCOSY, gHSQC, gHMBC and NOESY spectra.

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

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

**Scheme 8.** Synthesis of spiro compounds 12 and 13.
(4S)-4-Amino-4-(3,4-dimethoxyphenyl)butan-2-one Hydrochloride (3): Aqueous H$_2$SO$_4$ (1 m, 12.1 mL, 12.1 mmol) and H$_2$O$_2$ (2.87 g, 12.6 mmol) were added to a solution of (4S)-4-(3,4-dimethoxyphenyl)-4-(4-methoxyaminomethylene)butan-2-one (1; 4 g, 12.1 mmol) in MeCN/H$_2$O (1:1; 120 mL). The mixture was stirred at room temperature for 1.5 h, washed with CH$_2$Cl$_2$ (3 × 60 mL), and the resulting aqueous phase was diluted with CH$_2$Cl$_2$ (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 CH$_2$Cl$_2$ (3 × 60 mL). The combined organic layers were dried with Na$_2$SO$_4$, filtered and concentrated until 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: 75 %.

1H NMR (400 MHz, CD$_3$OD): δ = 2.45–2.41 (m, 2 H), 7.10–7.05 (m, 1 H), 7.05–6.99 (m, 1 H), 6.85 (d, J = 8.1 Hz, 1 H), 6.85–6.82 (m, 1 H), 4.85 (dd, J = 8.3, 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.

13C NMR (126 MHz, CDCl$_3$): δ = 60.6, 56.1, 56.1, 50.7, 50.6 ppm. FTIR: ν = 3305, 1710, 1509, 1264, 1232 cm$^{-1}$. HRMS (ESI): calcd. for [C$_{19}$H$_{20}$F$_3$NO$_3$ +H$^+$] $^+$ 380.14778; found 380.14778 (|Δ| = 0.27 ppm).

General Procedure for the Synthesis of Compounds 7Aa–Ca: A mixture of piperidine-4-one 4A–C (1.07 g, 1.45 mmol) and 1-ethyl-3-(1-ethoxy carbonyl)piperidine-4-carboxylic acid (EtOAc, 1.1 equiv.) was stirred at room temperature under an inert gas for 4 h. Then the reaction was quenched with NaHCO$_3$ solution, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The organic layers were washed with brine, dried with Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford compounds 4A–C.
calcd. for [C\textsubscript{29}H\textsubscript{30}FN\textsubscript{3}O\textsubscript{2} + H\textsuperscript{+}] = 472.23985; found 472.24003 (Δ|Δ| = 0.4 ppm).

(25,45,6R)-2-(3,4-Dimethoxyphenyl)-6-[4-(trifluoromethyl)-sulfanyl]phenyl]-2′,3′,4′,9′-tetrahydrospiro[pyriderin-4,1′-pyrido[3,4-b]indole] (7Ba): According to the general procedure, the reaction of piperidin-4-one 4A (50 mg, 0.12 mmol) afforded 7Bb (18 mg, 0.030 mmol). In this case, after applying the general procedure, the crude product was purified by a second column chromatography [heptane/EtOC/MeOH (2:4:4:1)]. The dried product was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (5 mL) and washed with aqueous NH\textsubscript{4}OH (5 mL). The aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 5 mL), and the combined organic layers were washed with brine, dried with Na\textsubscript{2}SO\textsubscript{4}, filtered and dried in vacuo to afford compounds 7Ab-Cb.

General Procedure for the Synthesis of Compounds 7Ab-Cb: A solution of Ti(OiPr\textsubscript{4})\textsubscript{4} (1.30 equiv) in dry THF (0.5 mL) was added to a mixture of piperidin-4-one 4A-\textsubscript{C} (1.00 equiv) and 6-methoxytryptamine (1.20 equiv) in dry THF (2 ml) at 21 °C under argon. After 6 h, THF (2.00 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 mixture was quenched with a saturated NaHCO\textsubscript{3} solution and the mixture diluted with EtOC. The layers were separated, and the organic phase was extracted with EtOC (3 ×). The combined organic layers were washed with brine, dried with Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated in vacuo. The crude product was purified by column chromatography [heptane/EtOC/MeOH (2:1) → EtOC/MeOH (10:1)]. The dried product was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (5 mL) and washed with aqueous NH\textsubscript{4}OH (5 mL). The aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 5 mL), and the combined organic layers were washed with brine, dried with Na\textsubscript{2}SO\textsubscript{4}, filtered and dried in vacuo to afford compounds 7Ab-Cb.
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 x). The combined organic layers were washed with brine, dried with Na₂SO₄ and filtered in vacuo. The crude product was purified by column chromatography [heptane/EtOAc (1:1) → 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 x 5 mL), and the combined organic layers were washed with brine, dried with Na₂SO₄ and filtered in vacuo to afford **7bc** (27.5 mg, 0.051 mmol) as a purple solid. Yield (BORMS): 74 %, Rf = 0.32 (EtOAc/Et, N, 8:1). \(^1\)H 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 (d, J = 8.6, 2.4 Hz, 1 H), 6.53 (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. \(^1^3\)C NMR (101 MHz, CDCl₃): δ = 149.6, 149.1, 148.3, 148.3, 140.3, 136.7, 130.9, 129.6 (q, J = 32.4 Hz, 128.2, 127.3 (2 x), 125.6 (q, J = 3.7 Hz, 2 x), 124.3 (q, J = 2720 Hz, C(6)), 119.1, 111.7, 111.5, 113.0, 108.3, 103.5, 56.7, 56.6, 56.1, 56.0, 53.4, 44.5, 44.3, 39.3, 23.1 ppm. FTIR: ν = 3364, 3305, 2931, 2856, 1591, 1599, 1509, 1233, 1140, 1024, 800 cm⁻¹. HRMS (ESI): calcd. for [C₃₀H₂₃F₂N₂O₇ + H]⁺ 538.23216; found 538.23175 (Δ |Δ| = 0.8 ppm).

**General Procedure for the Synthesis of Compounds 7Ad–Cd:** A solution of Et₃N (1.20 equiv.) in dry THF (0.5 mL) was added to a mixture of piperedin-4-one **4A**–**4C** (1.00 equiv.) and 5-fluorotryptamine hydrochloride (2.00 equiv.) in dry THF (2 mL) at 21 °C under argon. After 4–7 h, TIOH (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 was warmed to 21 °C and stirred for 24.5 h.
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 x). 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 x 5 mL), and the combined organic layers were washed with brine, dried with Na₂SO₄, filtered and concentrated in vacuo to afford compounds 7Ad–Cd.

(25,45,6R)-2-(3,4-Dimethoxyphenyl)-6'-fluoro-6-(4-fluorophenyl)-2',3',4',9'-tetrahydropyridine-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 (Borsrm): 74%. Rₛ = 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), 6.90–6.78 (m, 3 H), 6.86 (dd, 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), 3.36 (s, 3 H), 3.25 (t, J = 3.8 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 = 45.2 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 x), 127.9 (d, J = 9.8 Hz), 119.0, 115.4 (d, J = 21.1 Hz, 2 x), 111.4 (d, J = 9.4 Hz), 111.2, 110.9, 109.9 (d, J = 26.0 Hz), 109.1 (d, J = 4.3 Hz), 103.4 (d, J = 23.2 Hz), 56.5, 56.3, 56.1, 53.3, 50.0, 45.0, 39.3, 23.2 ppm. FTIR: ν = 3362, 2930, 2838, 1601, 1508, 1225, 1139, 1025, 798 cm⁻¹. HRMS (ESI): calcd. for [C₂₉H₂₉F₂N₃O₂ + H⁺]⁺ 598.19536; found 598.19629 (Δ[Å] = 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-(1H-indol-2-yl)-ethan-1-amine (9) for 12 and 2-(1H-pyrryl-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 x 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 x 5 mL), and the combined organic layers were washed with brine, dried with Na₂SO₄, filtered and concentrated in vacuo to afford compounds 12 and 13.

(25,45,6R)-2-(3,4-Dimethoxyphenyl)-6'-fluoro-6-(4-fluorophenyl)-2',3',4',9'-tetrahydropyrolo[4,3-b]pyridine (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%. Rₛ = 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), 7.14–0.09 (m, 2 H), 7.08–0.03 (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 (s, 3 H), 2.62 (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 x), 125.1, 121.2, 119.5, 119.4, 119.0, 116.4, 115.2 (d, J = 21.1 Hz, 2 x), 111.3, 110.9, 110.4, 56.9, 56.6, 56.1 (2 x), 54.2, 44.8, 44.6, 38.7, 24.8 ppm. FTIR: ν = 3366, 2957, 2856, 1602, 1508, 1229, 1056, 763 cm⁻¹. HRMS (ESI): calcd. for [C₂₉H₂₉F₂N₃O₂S + H⁺]⁺ 472.42003; found 472.42094 (Δ[Å] = 1.92 ppm).
pounds described herein, characterization of new compounds and nitrogen heterocycles · Library synthesis · Multicomponent reactions · Enantioselectivity · Diastereoselectivity · Spiro compounds · Nitrogen heterocycles · Library synthesis · Multicomponent reactions

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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