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Library Synthesis in Flow

Continuous Flow Synthesis of Urea-Containing Compound Libraries Based on the Piperidin-4-one Scaffold

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Abstract: The advantages of performing reactions in continuous flow vs. the classic batch processes render flow chemistry a suitable technique for library synthesis. Inspired by our recent work to create fluorine-containing nitrogen heterocycles and by the potential of the urea group in drug design, we herewith describe the combination of both aspects in the continuous flow synthesis of two libraries of urea derivatives based on the piperidin-4-one scaffold.

Introduction

The urea group represents an important functionality in pharmaceutical and agrochemical products.[1] Urea-containing molecules possess an immense potential in drug design as a result of their capability for hydrogen binding to biomolecular targets.[2] Moreover, ureas are widely used in drug design for the modulation of several factors, such as selectivity, stability, toxicity and pharmacokinetic profile of lead molecules.[2] Examples of active compounds containing a urea unit are depicted in Figure 1. Trimefluor,[3] a selective pre- and post-emergence herbicide for use in cotton, and triflumuron,[4] a broad spectrum insecticide against chewing insects commercialized by Bayer CropScience, are examples of bioactive molecules containing a urea group. Another example of a urea-containing pharmaceutical is vestipitant,[5] a selective antagonist for the NK1 receptor.

Recently, we reported an enantio- and diastereoselective synthesis of piperidin-4-ones 2a–c from the enantiopure amino ketone 1 (Scheme 1).[6] Compounds 2a–c, containing three different fluorine functionalities (F, CF3 and SF5) to enhance their bioactivity and metabolic profile,[7] were synthesized and further derivatized into a novel library of spirocyclic compounds by the potential of the urea group in drug design, we herewith describe the combination of both aspects in the continuous flow synthesis of two libraries of urea derivatives based on the piperidin-4-one scaffold.

Scheme 1. Previously reported work (batch) and this work (flow) based on scaffolds 2a–c.

The inherent potential of this scaffold (2a–c) for derivatization combined with the advantages of flow chemistry for library synthesis[8] (including excellent heat exchange and fast mixing for better reaction control, automated small-scale optimization and rapid automated compound-library preparation) encouraged us to further develop a new class of urea derivatives in flow (5 and 6) based on scaffolds 2a–c (Scheme 1).

Figure 1. Biologically active compounds containing a urea group.

Results and Discussion

We started our investigations by testing the reactivity of our amines (2b and 2c) with alkyl isocyanates (ethyl [7A] or isopropyl isocyanate [7B], 1.5 equiv.) varying solvent, temperature and reaction time (see Table 1 for summarized results and Supporting Information [SI] for the entire optimization process). All reactions were carried out in a borosilicate glass reactor (channel width 600 μm, channel depth 500 μm and effective reactor volume 100 μL).[9] The microreactor was placed into a microreactor holder, which automatically aligns with the fluidic connections and makes contact with the temperature controlled...
metal plate in the microreactor holder. Then, the inlet modules were connected through the microreactor holder with the inlet ports of the microreactor and the outlet tubing was also placed at the outlet port. The tubing was connected to the syringes, which were connected to the pumps. The two solutions, one containing the piperidin-4-ones (2b or 2c) and the other one with the isocyanates 7 were pumped and brought together inside of the microreactor (Table 1). Initially, we used solvents such as MeCN or 1,2-dichloroethane in a temperature range of 50–80 °C and reaction times of 10–15 minutes (entries 1–4).

Low conversions to ureas 5bA and 5bB were obtained in all these cases and only a slightly higher conversion to 5bA (ratio 5bA/2b 1.0:7) was slightly achieved when we used MeCN at 50 °C (entry 1). The use of EtOH at 80 °C and a reaction time of 10 minutes provided a ratio of 1:1.2 for 5bB/2b (entry 5). An increase of the reaction time to 15 minutes (entry 6) gave higher conversion into product 5bB (1:0.15). By increasing the amount of isocyanate (2.0 and 2.5 equiv., entries 7 and 8, respectively), nearly full conversion to 5bB and full conversion to 5cA were obtained. However, carbamate 8 was also formed in the reaction mixture when EtOH was used as solvent, as a result of the nucleophilic attack of EtOH to the isocyanate. Therefore, we first explored the reaction of 2b with 2,4-difluorophenyl isocyanate (7E, 1.5 equiv.) at 80 °C in EtOH and a reaction time of 20 minutes; the reaction, however, did not show any conversion to product 5bE and it resulted in a mixture of 2b and carbamate 8 (ratio 2b/8d 1.0:50; entry 14).

By changing the solvent to 1,2-dichloroethane, and using 1.3 equiv. of isocyanate 7E, full conversion to compound 5bE was obtained (entry 15).

With the final conditions in hand, five isocyanates 7A–E (alkyl and aryl isocyanates with different substituents on the phenyl ring, Figure 2) were selected for the generation of a 15-compound library (Table 2). For all experiments, three fractions (stabilization time, collected product and residual) were collected in separated vials and final products were analyzed di-

Table 1. Optimization process for the synthesis of alkyl and aryl ureas 5b and 5c.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>7 [equiv.]</th>
<th>Solvent</th>
<th>t [°C]</th>
<th>time [min]</th>
<th>Product</th>
<th>R</th>
<th>R’</th>
<th>Ratio 5/2/8</th>
<th>Flow rate [μL/min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>7A (1.5)</td>
<td>MeCN</td>
<td>50</td>
<td>10</td>
<td>5bA</td>
<td>–</td>
<td>CH$_3$CH$_2$</td>
<td>1:0.70$^{[a]}$</td>
<td>10.00</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>7A (1.5)</td>
<td>MeCN</td>
<td>80</td>
<td>10</td>
<td>5bA</td>
<td>–</td>
<td>CH$_3$CH$_2$</td>
<td>1:1:0</td>
<td>10.00</td>
</tr>
<tr>
<td>3</td>
<td>2b</td>
<td>7A (1.5)</td>
<td>MeCN</td>
<td>80</td>
<td>15</td>
<td>5bA</td>
<td>–</td>
<td>CH$_3$CH$_2$</td>
<td>1:1.5:0</td>
<td>6.67</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>7B (1.5)</td>
<td>1,2-DCE</td>
<td>80</td>
<td>15</td>
<td>5bB</td>
<td>–</td>
<td>(CH$_3$)$_2$CH</td>
<td>1:6:0.0</td>
<td>6.67</td>
</tr>
<tr>
<td>5</td>
<td>2b</td>
<td>7B (1.5)</td>
<td>EtOH</td>
<td>80</td>
<td>10</td>
<td>5bB</td>
<td>8a</td>
<td>(CH$_3$)$_2$CH</td>
<td>1:1:2:0.14</td>
<td>10.0</td>
</tr>
<tr>
<td>6</td>
<td>2b</td>
<td>7B (1.5)</td>
<td>EtOH</td>
<td>80</td>
<td>15</td>
<td>5bB</td>
<td>8a</td>
<td>(CH$_3$)$_2$CH</td>
<td>1:1:0:15:0.31</td>
<td>6.67</td>
</tr>
<tr>
<td>7</td>
<td>2b</td>
<td>7B (2.0)</td>
<td>EtOH</td>
<td>80</td>
<td>17</td>
<td>5bB</td>
<td>8a</td>
<td>(CH$_3$)$_2$CH</td>
<td>1:0:08:0.31</td>
<td>5.88</td>
</tr>
<tr>
<td>8</td>
<td>2c</td>
<td>7A (2.5)</td>
<td>EtOH</td>
<td>80</td>
<td>17</td>
<td>5cA</td>
<td>8b</td>
<td>CH$_3$CH$_2$</td>
<td>1:1:0:92</td>
<td>5.88</td>
</tr>
<tr>
<td>9</td>
<td>2c</td>
<td>7A (2.5)</td>
<td>iPrOH</td>
<td>80</td>
<td>17</td>
<td>5cA</td>
<td>8c</td>
<td>CH$_3$CH$_2$</td>
<td>(CH$_3$)$_2$CH</td>
<td>1:0:0:6</td>
</tr>
<tr>
<td>10</td>
<td>2c</td>
<td>7C (2.5)</td>
<td>tBuOH</td>
<td>80</td>
<td>17</td>
<td>5cA</td>
<td>–</td>
<td>CH$_3$CH$_2$</td>
<td>1:1:0:0</td>
<td>5.88</td>
</tr>
<tr>
<td>11</td>
<td>2c</td>
<td>72 (2.0)</td>
<td>tBuOH</td>
<td>80</td>
<td>17</td>
<td>5cA</td>
<td>–</td>
<td>CH$_3$CH$_2$</td>
<td>1:1:0:1.2:0</td>
<td>5.88</td>
</tr>
<tr>
<td>12</td>
<td>2c</td>
<td>7C (2.0)</td>
<td>tBuOH</td>
<td>25</td>
<td>17</td>
<td>5cA</td>
<td>–</td>
<td>CH$_3$CH$_2$</td>
<td>1:1:0:1:0:0</td>
<td>5.88</td>
</tr>
<tr>
<td>13</td>
<td>2c</td>
<td>7D (2.0)</td>
<td>tBuOH</td>
<td>50</td>
<td>17</td>
<td>5cA</td>
<td>–</td>
<td>CH$_3$CH$_2$</td>
<td>1:1:0:1:0:0</td>
<td>5.88</td>
</tr>
</tbody>
</table>

$^{[a]}$ Calculated by $^1$H NMR of the fraction of the collected product. $^{[b]}$ Analyzed by $^1$H NMR of the fraction of stabilization time.
Table 2. Library of ureas 5aA–cE based on the piperidine-4-one scaffold.

<table>
<thead>
<tr>
<th>Reaction carried out in tBuOH at 50 °C in 17 minutes using 2.0 equiv. of isocyanate.</th>
<th>Reaction carried out in 1,2-dichloroethane at 80 °C in 17 min using 1.3 equiv. of isocyanate.</th>
<th>Conversion calculated by 1H NMR of the fraction of collected product.</th>
<th>Isolated yield of the fraction of collected product.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5aA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;b&lt;/sup&gt; 83%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;d&lt;/sup&gt; 82%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;f&lt;/sup&gt; 97%&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>5aB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;b&lt;/sup&gt; 84%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;d&lt;/sup&gt; 89%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;f&lt;/sup&gt; 73%&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>5aC&lt;sup&gt;h&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;i&lt;/sup&gt; 89%&lt;sup&gt;j&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;k&lt;/sup&gt; 88%&lt;sup&gt;l&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;m&lt;/sup&gt; 77%&lt;sup&gt;n&lt;/sup&gt;</td>
</tr>
<tr>
<td>5aD&lt;sup&gt;h&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;i&lt;/sup&gt; 89%&lt;sup&gt;j&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;k&lt;/sup&gt; 90%&lt;sup&gt;l&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;m&lt;/sup&gt; 55%&lt;sup&gt;n&lt;/sup&gt;</td>
</tr>
<tr>
<td>5aE&lt;sup&gt;h&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;i&lt;/sup&gt; 87%&lt;sup&gt;j&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;k&lt;/sup&gt; 91%&lt;sup&gt;l&lt;/sup&gt;</td>
<td>99%,&lt;sup&gt;m&lt;/sup&gt; 87%&lt;sup&gt;n&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>[a]</sup> Reaction carried out in tBuOH at 50 °C in 17 minutes using 2.0 equiv. of isocyanate. <sup>[b]</sup> Reaction carried out in 1,2-dichloroethane at 80 °C in 17 min using 1.3 equiv. of isocyanate. <sup>[c]</sup> Conversion calculated by 1H NMR of the fraction of collected product. <sup>[d]</sup> Isolated yield of the fraction of collected product.

The reaction of piperidin-4-ones 2a–c with alkyl isocyanates 7A and 7B gave full conversions to products 5aA–cB in very good to excellent yields (83–92 %). We also obtained full conversions to ureas 5aC–cE when aryl isocyanates (7C–E) were used. Very good to excellent yields were obtained for compounds 5aC, 5aE, 5bC and 5cC–cE. Good yields were obtained for compounds 5aD and 5bD whereas compound 5bE was obtained with a moderate yield. The excess of isocyanates was removed in vacuo as much as possible so that only small amounts of the least volatile isocyanates remained in the reaction mixtures. The crude mixtures of compounds 5bA and 5bB showed the presence of a minor product in a 1:0.1 ratio according to their 1H NMR spectra. We attributed these mixtures to be either rotamers of the urea group or a possible mixture of atropisomers, with the carbamoyl group (almost) perpendicular to the piperidine ring (Figure 3), both caused by the congested 2,6-diphenylpiperidine-1-carboxamide framework. For ureas 5bC and 5bD, the ratio of the isomers could not be measured accurately whereas for the rest of ureas only one of both isomers was observed.

Figure 3. Rotamers and atropisomers of 5bA and 5bB.

Optimization of these reactions to obtain full conversion was crucial because no further column chromatography was required. Purifying these poorly soluble ureas generally requires polar solvents such as MeOH, but in case of sterically congested...
may take place in the purification process. In this case, methanolysis occurred because the nitrogen in the piperidine ring might not be fully conjugated anymore with the carbonyl and therefore MeOH can form a hydrogen bond with the nitrogen. To analyze the reactivity of these ureas in MeOH, we dissolved urea 5aC in CD3OD and monitored the mixture by 1H NMR (Scheme 2). We observed that compound 5aC was still present after 1–4 h, but after 19 h at room temperature compound 5aC transformed into piperidin-4-one 2a (protonated and deuterated substrates), phenyl isocyanate 7C and carbamates 9 and 10 (relative abundance 9/10 30:70). 1H NMR showed a mixture of compounds which was confirmed by GC–MS (Scheme 2).

We also studied the decomposition of the aliphatic urea 5cB, which also showed the presence of carbamates 9 and 10 (detected by GC–MS) and the starting material 2c (protonated and deuterated substrates).

Finally, a diastereoselective reduction of ketone 2c was carried out in flow using LiBH4 as reducing reagent to provide full conversion to a 10:1 mixture of piperidinols 11 and 12 (Scheme 3). The workup of this reaction was performed offline after the reaction mixture was completely collected in the corresponding vial. The reduction of ketone 2b was performed in batch using N-Selectride[14] to give alcohol 12.[15]

As previously mentioned, the presence of the conformers (rotamers or atropisomers) was caused by the hindered rotation around one of the single N–CO bonds of the urea.[17] NOESY experiments of compound 13a (the major product of reaction between alcohol 12 and isocyanate 7B) showed correlations between the NH of the urea with both benzylic protons (Table 4), indicating therefore the existence of atropisomerism (in case of rotamers, each rotamer would show only one corre-

Table 3. Library of ureas 6a–e based on amino alcohol 11.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1H (ppm) (13a)</th>
<th>1H (ppm) (13b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H2 4.89</td>
<td>H2 4.36</td>
</tr>
<tr>
<td>2</td>
<td>H3 2.11–1.84</td>
<td>2H2–2.10–2.00–1.89</td>
</tr>
<tr>
<td>3</td>
<td>H2 4.43</td>
<td>4H 4.16</td>
</tr>
<tr>
<td>4</td>
<td>H3 2.70–2.00</td>
<td>2H2–2.37–2.20–2.10</td>
</tr>
<tr>
<td>5</td>
<td>H3 5.12</td>
<td>5H 5.12</td>
</tr>
<tr>
<td>6</td>
<td>H2 2.58–3.70</td>
<td>6H 3.58–3.49</td>
</tr>
<tr>
<td>7</td>
<td>H2 0.88</td>
<td>7H 0.72</td>
</tr>
<tr>
<td>8</td>
<td>H3 0.74</td>
<td>8H 0.60</td>
</tr>
</tbody>
</table>
lution with one benzylic proton.\(^{18}\) The assignment of the characteristic protons is depicted in Table 4. Chemical shifts of compounds 13a and 13b\(^{19}\) present a considerable difference, not only for the benzylic protons H\(^2\) and H\(^6\) (entries 1 and 5), but also for protons H\(^2\) and H\(^7\) (entries 3 and 6). We were also able to confirm that the major product of the stereoisomers was compound 13a, which showed a correlation between the NH proton of the urea and both benzylic protons, H\(^2\) and H\(^6\). The clarification of these two products was done by NOESY studies.

Conclusions

In summary, we have synthesized a small library of ureas in continuous flow. The reactions utilized for their syntheses were achieved in a reaction time of 17 min without further need of purification rendering drug-like molecules. Moreover, we have also diasteroselectively reduced the ketone group in flow in the solvent indicated. Chemical shifts are given in parts per million (ppm), with respect to the general procedure, the reaction of piperidin-4-one 2b (4.68 mg, 0.012 mmol) in tBuOH (99.8 mmol) with 7A afforded urea 5bA (4.74 mg, 0.011 mmol).\(^{18}\) 1H NMR (400 MHz, CDCl\(_3\): \(\delta = 7.66–7.60\) (m, 2 H), 7.56–7.51 (m, 2 H), 6.80 (d, \(J = 8.2 \text{ Hz}\), 1 H), 6.75 (dd, \(J = 8.2\), 2.1 Hz, 1 H), 6.64 (d, \(J = 2.1 \text{ Hz}\), 1 H), 6.00 (t, \(J = 5.4 \text{ Hz}\), 1 H), 5.22 (dd, \(J = 9.7\), 4.9 Hz, 1 H), 4.40 (t, \(J = 5.2 \text{ Hz}\), 1 H), 3.86 (s, 3 H), 3.73 (s, 3 H), 3.18–3.07 (m, 3 H), 2.88–2.73 (m, 2 H), 2.60 (dd, \(J = 17.6\), 4.9 Hz, 1 H), 0.88 (t, \(J = 7.2 \text{ Hz}\), 3 H) ppm.\(^{13}\) C NMR (101 MHz, CDCl\(_3\)): \(\delta = 207.8, 162.1\) (d, \(\delta = 247.5 \text{ Hz}\), 1 H), 159.1, 150.1, 149.0, 139.0 (d, \(J = 3.1\), 134.9, 128.4 (d, \(J = 8.0 \text{ Hz}\), 117.9, 116.0 (d, \(J = 21.5\), 111.4, 108.9, 56.1, 56.0, 52.4, 46.1, 43.6, 36.2, 15.2 ppm. FTIR: \(\nu = 3420, 2967, 1722, 1639, 1511, 1264, 1228, 1025 \text{ cm}–1.\)) HRMS [ESI (m/z)] calc. for (C\(_{22}\)H\(_{25}\)FN\(_2\)O\(_4\) + Na\(^+\)) = 423.16916, found 423.16916 (\(|\Delta| = 1.0 \text{ ppm}\). \(R_P\) = 0.27 (heptane/AcOEt, 1:2). Yield: 83 %.

(25,6R)-2-(3,4-Dimethoxyphenyl)-N-ethyl-4-oxo-6-(4-fluorophenyl)-1-carboxamide (5bA): According to the general procedure, the reaction of piperidin-4-one 2b (4.68 mg, 0.012 mmol) in tBuOH (99.8 mmol) with 7A afforded urea 5bA (4.74 mg, 0.011 mmol).\(^{18}\) 1H NMR (400 MHz, CDCl\(_3\): \(\delta = 7.66–7.60\) (m, 2 H), 7.56–7.51 (m, 2 H), 6.80 (d, \(J = 8.2 \text{ Hz}\), 1 H), 6.75 (dd, \(J = 8.2\), 2.1 Hz, 1 H), 6.54 (d, \(J = 2.1 \text{ Hz}\), 1 H), 6.20 (t, \(J = 5.2 \text{ Hz}\), 1 H), 5.12 (dd, \(J = 10.2, 4.9 \text{ Hz}\), 1 H), 4.44 (t, \(J = 5.2 \text{ Hz}\), 1 H), 3.86 (s, 3 H), 3.67 (s, 3 H), 3.23–3.11 (m, 3 H), 3.26 (dd, \(J = 18.4, 5.6 \text{ Hz}\), 1 H), 2.74 (dd, \(J = 17.5, 10.2 \text{ Hz}\), 1 H), 2.61 (dd, \(J = 17.5, 4.9 \text{ Hz}\), 1 H), 0.90 (t, \(J = 7.2 \text{ Hz}\), 3 H) ppm.\(^{13}\) C NMR (101 MHz, CDCl\(_3\)): \(\delta = 207.2, 159.1, 150.3, 149.2, 147.4, 143.9, 127.9\) (indirect observation), 125.7, 125.2, 122.2, 117.9, 115.5, 108.7, 56.1, 56.0, 52.8, 46.5, 35.7, 36.2, 15.2 ppm. FTIR: \(\nu = 3422, 2972, 1722, 1519, 1311, 1264, 1228, 1025 \text{ cm}–1.\)) HRMS [ESI (m/z)] calc. for (C\(_{23}\)H\(_{25}\)F\(_3\)N\(_2\)O\(_4\) + Na\(^+\)) = 473.16547, found 473.16547 (\(|\Delta| = 1 \text{ ppm}\). \(R_P\) = 0.28 (heptane/AcOEt, 1:2). Yield: 83 %.

(25,6R)-2-(3,4-Dimethoxyphenyl)-N-ethyl-4-oxo-6-[(4-trifluoromethyl)phenyl]piperidine-1-carboxamide (5bA): According to the general procedure, the reaction of piperidin-4-one 2b (4.68 mg, 0.012 mmol) in tBuOH (99.8 mmol) with 7A afforded urea 5bA (4.74 mg, 0.011 mmol).\(^{18}\) 1H NMR (400 MHz, CDCl\(_3\): \(\delta = 7.68–7.60\) (m, 2 H), 7.56–7.51 (m, 2 H), 6.80 (d, \(J = 8.2 \text{ Hz}\), 1 H), 6.75 (dd, \(J = 8.2\), 2.1 Hz, 1 H), 6.54 (d, \(J = 2.1 \text{ Hz}\), 1 H), 6.20 (t, \(J = 5.2 \text{ Hz}\), 1 H), 5.12 (dd, \(J = 10.2, 4.9 \text{ Hz}\), 1 H), 4.44 (t, \(J = 5.2 \text{ Hz}\), 1 H), 3.86 (s, 3 H), 3.67 (s, 3 H), 3.23–3.11 (m, 3 H), 3.26 (dd, \(J = 18.4, 5.6 \text{ Hz}\), 1 H), 2.74 (dd, \(J = 17.5, 10.2 \text{ Hz}\), 1 H), 2.61 (dd, \(J = 17.5, 4.9 \text{ Hz}\), 1 H), 0.90 (t, \(J = 7.2 \text{ Hz}\), 3 H) ppm.\(^{13}\) C NMR (101 MHz, CDCl\(_3\)): \(\delta = 207.2, 159.1, 150.3, 149.2, 147.4, 143.9, 129.9\) (indirect observation), 127.3, 126.1, 117.9, 115.5, 108.7, 56.1, 56.0, 52.3, 46.6, 42.9, 36.2, 15.2 ppm. FTIR: \(\nu = 3422, 2972, 1722, 1519, 1311, 1264, 1228, 1025 \text{ cm}–1.\)) HRMS [ESI (m/z)] calc. for (C\(_{23}\)H\(_{25}\)F\(_3\)N\(_2\)O\(_4\) + Na\(^+\)) = 473.16547, found 473.16547 (\(|\Delta| = 1 \text{ ppm}\). \(R_P\) = 0.28 (heptane/AcOEt, 1:2). Yield: 83 %.
According to the general procedure, the reaction of piperidin-4-one 2a (2.59 mg, 7.86 μmol) in 1,2-DCE (88.9 μmol) with 7C afforded 5aC (3.15 mg, 7.02 μmol). 1H NMR (400 MHz, CDCl3): δ = 7.45–7.38 (m, 2 H), 7.25–7.18 (m, 2 H), 7.12–7.05 (m, 2 H), 7.05–6.98 (m, 3 H), 6.89–6.83 (m, 2 H), 6.65 (d, J = 1.7 Hz, 1 H), 6.00 (s, 1 H), 6.19 (t, J = 5.3 Hz, 1 H), 5.35 (dd, J = 10.1, 4.9 Hz, 1 H), 3.89 (s, 3 H), 3.72 (s, 3 H), 3.21 (dd, J = 18.4, 4.9 Hz, 1 H), 2.95–2.85 (m, 2 H), 2.67 (dd, J = 17.6, 4.9 Hz, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 207.2, 162.3 (d, J = 247.8 Hz), 156.6, 150.6, 149.5, 138.6, 138.5 (d, J = 3.4 Hz), 134.9, 129.1, 128.6 (d, J = 8.0 Hz), 132.7, 130.0, 118.1, 116.3 (d, J = 21.4 Hz), 111.7, 108.9, 56.6, 56.2, 56.1, 52.3, 46.3, 43.4 ppm. FTIR: ʋ = 3388, 2924, 2722, 1650, 1526, 1235, 1026, 754 cm⁻¹. HRMS (EI/m/z) calcd. for (C$_{26}$H$_{32}$F$_{2}$N$_{2}$O$_{4}$Na$^+$) = 471.16906, found 471.16910 (|Δ| = 1.1 ppm). R$_p$ = 0.24 (heptane/AcOEt, 2:1). Yield: 89%.

(25,6R)-2-(3,4-Dimethoxyphenyl)-4-oxo-6-(4-tert-fluorophenyl)piperidine-1-carboxamide (5bC): According to the general procedure, the reaction of 5bC (2.1 mg, 5.54 μmol) in 1,2-DCE (82.8 μmol) with 7C afforded 5cC (2.43 mg, 4.87 μmol). 1H NMR (400 MHz, CDCl3): δ = 7.69–7.64 (m, 2 H), 7.62–7.57 (m, 2 H), 7.25–7.19 (m, 2 H), 7.06–6.99 (m, 3 H), 6.89–6.85 (m, 2 H), 6.64 (s, 1 H), 6.53–6.51 (m, 1 H), 6.41 (t, J = 5.0 Hz, 1 H), 5.22 (dd, J = 10.8, 4.8 Hz, 1 H), 3.89 (s, 3 H), 3.65 (s, 3 H), 3.29 (dd, J = 18.6, 4.1 Hz, 1 H), 2.98 (dd, J = 18.6, 5.8 Hz, 1 H), 2.80 (dd, J = 17.5, 10.8 Hz, 1 H), 2.66 (dd, J = 17.5, 4.8 Hz, 1 H) ppm. 13C NMR (101 MHz, CDCl3): δ = 206.6, 156.7, 150.7, 149.7, 146.7, 138.5, 133.9, 130.2 (indirect observation), 129.1, 127.4, 126.4 (q, J = 3.6 Hz), 125.9 (indirect observation), 123.9, 120.0, 118.1, 111.7, 108.6, 57.3, 56.2, 56.0, 51.9, 46.9, 42.6 ppm. FTIR: ʋ = 3391, 2939, 2722, 1663, 1597, 1517, 1442, 1327, 1265, 1238, 754 cm⁻¹. HRMS (ESI [m/z]) calcd. for (C$_{26}$H$_{32}$F$_{2}$N$_{2}$O$_{4}$Na$^+$) = 521.16586, found 521.16560 (|Δ| = 1.6 ppm). R$_p$ = 0.70 (heptane/AcOEt, 1:2). Yield: 88%.

(25,6R)-2-(3,4-Dimethoxyphenyl)-4-oxo-6-[4-(pentafluorophenoxy)-4-sulfanyl]phenyl-piperidine-1-carboxamide (5cC): According to the general procedure, the reaction of piperidin-4-one 2c (2.49 mg, 5.69 μmol) in 1,2-DCE (102.5 μmol) with 7C afforded 5dC (3.22 mg, 5.79 μmol). 1H NMR (400 MHz, CDCl3): δ = 7.81–7.75 (m, 2 H), 7.61–7.55 (m, 2 H), 7.25–7.20 (m, 2 H), 7.06–7.02 (m, 3 H), 6.90–6.88 (m, 2 H), 6.67 (s, 1 H), 6.49–6.47 (m, 1 H), 6.47–6.43 (m, 1 H), 5.16 (dd, J = 11.0, 4.9 Hz, 1 H), 3.89 (s, 3 H), 3.63 (s, 3 H), 3.28 (dd, J = 18.7, 3.7 Hz, 1 H), 3.00 (dd, J = 18.7, 5.9 Hz, 1 H), 2.77 (dd, J = 17.5, 11.0 Hz, 1 H), 2.66 (dd, J = 17.5, 4.9 Hz, 1 H) ppm. 13C NMR (101 MHz, CDCl3): δ = 206.3, 156.6, 153.4 (indirect observation), 150.9, 149.7, 146.9, 138.4, 133.8, 129.1, 127.4, 126.9–126.8 (m, 123.9, 120.1, 118.1, 111.7, 108.3, 57.6, 56.2, 55.9, 51.5, 47.0, 42.4 ppm. FTIR: ʋ = 3389, 2926, 1725, 1663, 1598, 1518, 1265, 1238, 844 cm⁻¹. HRMS (ESI [m/z]) calcd. for (C$_{26}$H$_{32}$F$_{2}$NF$_{2}$O$_{4}$Na$^+$) = 579.13474, found 579.13534 (|Δ| = 0.1 ppm). R$_p$ = 0.22 (heptane/AcOEt, 2:1). Yield: 99%.
(2S,6R)-N-(2-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-4-oxo-6-(4-trifluoromethyl)phenylpiperidine-1-carboxamide (5bD): According to the general procedure, the reaction of piperidin-4-one 2b (1.37 mg, 3.61 μmol) in 1,2-DCE (87.8 mM) with 7E afforded 5bE (1.07 g, 2.00 mmol). 1H NMR (400 MHz, CDCl3): δ = 8.01 (td, J = 9.1, 5.9 Hz; 1 H), 7.70–7.64 (m, 2 H), 7.60–7.55 (m, 2 H), 6.88–6.79 (m, 3 H), 6.73 (s, 1 H), 6.72 (dd, J = 11.0, 8.3, 2.8 Hz, 1 H), 6.54–6.52 (m, 1 H), 6.35 (t, J = 5.1 Hz; 1 H), 5.26 (dd, J = 10.5, 4.9 Hz, 1 H), 3.86 (s, 3 H), 3.36 (s, 3 H), 2.32 (dd, J = 18.6, 4.4 Hz, 1 H), 2.95 (dd, J = 18.6, 5.8 Hz, 1 H), 2.82 (dd, J = 17.6, 10.6 Hz, 1 H), 2.67 (dd, J = 17.6, 4.9 Hz, 1 H) ppm. 13C NMR (101 MHz, CDCl3): δ = 206.5, 156.4, 158.2 (d, J = 244.4 Hz, 152.3 (dd, J = 243.9, 11.6 Hz, 150.5, 149.6, 146.5, 133.2, 130.2 (indirect observation), 127.4, 126.2, 1126, 1026 cm⁻¹. HRMS [ESI (m/z)] calcld. for (C27H24ClF3N2O4 + Na)⁺ = 557.14702, found 557.14825 (Δ|I| = 1.2 ppm). Rf: 0.31 (heptane/AcOEt, 2:1).

Yield: 55%.

(2S,6R)-N-(2,4-Difluorophenyl)-2-(3,4-dimethoxyphenyl)-4-oxo-6-(4-pentafluoro-λ₆-sulfanyl)phenylpiperidine-1-carboxamide (5cE): According to the general procedure, the reaction of piperidin-4-one 2c (1.87 mg, 4.27 μmol) in 1,2-DCE (82.9 mM) with 7E afforded 5cE (2.2 mg, 3.7 μmol). 1H NMR (400 MHz, CDCl3): δ = 8.00 (td, J = 9.1, 5.9 Hz; 1 H), 7.83–7.74 (m, 2 H), 7.60–7.52 (m, 2 H), 6.88–6.80 (m, 3 H), 6.79–6.68 (m, 2 H), 6.49 (dd, J = 12.1, 7.8 Hz, 1 H), 6.38 (t, J = 5.0 Hz; 1 H), 5.22 (dd, J = 10.7, 4.9 Hz, 1 H), 3.87 (s, 3 H), 3.65 (s, 3 H), 3.27 (dd, J = 18.6, 4.4 Hz, 1 H), 2.95 (dd, J = 18.6, 5.8 Hz, 1 H), 2.80 (dd, J = 17.6, 10.7 Hz, 1 H), 2.68 (dd, J = 17.6, 4.9 Hz, 1 H) ppm. 13C NMR (101 MHz, CDCl3): δ = 206.2, 156.3 (indirect observation), 150.4, 149.5, 146.4, 135.6, 133.2, 129.1, 127.4, 127.0–126.8 (m), 124.3, 122.4, 118.6, 111.8, 108.7, 56.9, 56.2, 50.5, 46.7, 42.9 ppm. FTIR: ν = 3360, 2962, 2714, 2653, 1517, 1440, 1306, 1234, 1145, 1027, 751 cm⁻¹. HRMS [ESI (m/z)] calcld. for (C26H24ClF3N2O4 + Na)⁺ = 593.13935, found 593.13686 (Δ|I| = 4.0 ppm) HRMS [ESI (m/z)] calcld. for (C27H24ClF3N2O4 + Cl⁻ + H⁺)⁻ = 615.11590, found 615.11657 (Δ|I| = 0.2 ppm). Rf: 0.25 (heptane/AcOEt, 2:1). Yield: 87%.

Synthesis and Full Characterization of Alcohols 11 and 12

(2S,4R,6R)-2-(3,4-Dimethoxyphenyl)-6-[4-(pentafluoro-λ₆-sulfanyl)phenyl]piperidin-4-ol (11): Solution A: piperidin-4-one 2c (8.4 mg, 0.019 mmol) dissolved in THF (50.3 mm). Solution B: LiBH₄ (2 mol solution in THF; 1.5 equiv.) dissolved in THF (75 mm). Solution A (13.33 μL) was combined with B (20 μL/min) inside the glass microreactor (internal volume: 100 μL). The reaction was performed at 21 °C for 3 min. 1H NMR (500 MHz, CDCl3): δ = 7.75–7.69 (m, 2 H), 7.57–7.52 (m, 2 H), 7.00 (d, J = 2.0 Hz, 1 H), 6.96 (dd, J = 8.2, 2.0 Hz, 1 H), 6.83 (d = 8.2 Hz, 1 H), 3.99–3.92 (m, 2 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.81 (d = 11.3, 2.4 Hz, 1 H), 2.21–2.10 (m, 2 H), 1.62–1.46 (m, 2 H) ppm. 13C NMR (126 MHz, CDCl3): δ = 150.3 (indirect observation), 149.2, 148.5, 148.2, 136.7, 127.2, 126.3 (quint, J = 4.0 Hz), 118.9, 111.2, 110.1, 69.6, 59.7, 59.4, 56.9, 56.0, 43.9, 43.8 ppm. FTIR: ν = 2936, 2839, 1517, 1262, 1232, 1027, 845, 815 cm⁻¹. HRMS [ESI (m/z)] calcld. for (C26H24F3ClN2SO4 + H+)⁺ = 440.13188, found 440.13125 (Δ|I| = 1.44 ppm). Yield: 76%.
Synthesis and Full Characterization of Alkyl Ureas 6a–c: Solution A: compound 11 (1.0 equiv.) dissolved in tBuOH (94.6–96.5 mm). Solution B: alkyl isocyanate (7A, 7B or 7F, 1.5 equiv.) dissolved in tBuOH (0.1 M). Solution A (2.35 μL/min) was combined with B (3.53 μL/min) inside the glass microreactor (internal volume: 3.05 μL, 0.01 mL, 0.12 mmol) was added to 6-sulfanyl)piperidine-1-carboxamide (3.08 μL/min) in 1,2-DCE (94.6–96.5 mm). Solution B: isocyanate (7A, 7B or 7F, 1.5 equiv.) dissolved in 1,2-DCE (94.6–96.5 mm). Solution A (2.35 μL/min) was combined with B (3.53 μL/min) inside the glass microreactor (internal volume: 100 μL). The reaction was performed at 80 °C for 17 min.

Synthesis and Full Characterization of Aryl Ureas 6d and 6e: Solution A: compound 11 (1.0 equiv.) dissolved in 1,2-DCE (95.6–105.0 mm). Solution B: aryly isocyanate (7C–E, 1.1 equiv.) dissolved in 1,2-DCE (0.1 M). Solution A (2.80 μL/min) was combined with B (3.08 μL/min) inside the glass microreactor (internal volume: 100 μL). The reaction was performed at 80 °C for 17 min.
(1.2 mL) at 21 °C and the reaction was stirred for 20 h. The solvent was removed under vacuo and the crude was purified by column chromatography (CH2Cl2 → CH2Cl2/MeOH, 10:1) to afford compounds 13a and 13b (21.5 mg, 0.046 mmol). Combined yield: 38%.

13a: 1H NMR (400 MHz, CDCl3): δ = 7.59–7.49 (m, 4 H), 6.84–6.74 (m, 2 H), 6.64 (br, s, 1 H), 5.65 (t, J = 5.4 Hz, 1 H), 4.90 (dd, J = 10.0, 4.1 Hz, 1 H), 4.43 (quint, J = 5.2 Hz, 1 H), 3.43 (d, J = 7.4 Hz, 1 H), 3.83 (s, 3 H), 3.82–3.71 (m, 1 H), 3.71 (s, 3 H), 2.76–2.64 (m, 1 H), 4.43 (quint, J = 3.8 Hz, 1 H), 0.89 (d, J = 15.9 Hz, 3 H) ppm. HRMS [ESI (m/z)] calcd. for (C24H29F3N2O4 + Na)+ = 489.19771, found 489.19688 (|Δ| = 1.43 ppm).

13b: 1H NMR (400 MHz, CDCl3): δ = 7.69–7.62 (m, 2 H), 7.61–7.54 (m, 2 H), 6.90–6.84 (m, 1 H), 6.81 (dd, J = 8.2, 0.8 Hz, 1 H), 6.67 (d, J = 1.9 Hz, 1 H), 5.12 (dd, J = 7.3, 5.2 Hz, 1 H), 4.36 (dd, J = 11.7, 3.9 Hz, 1 H), 4.32 (d, J = 7.5 Hz, 1 H), 4.23–4.11 (m, 1 H), 3.86 (s, 3 H), 3.73 (s, 3 H), 3.60–3.47 (m, 1 H), 2.41–2.33 (m, 1 H), 2.20–2.10 (m, 2 H), 2.01–1.91 (m, 1 H), 0.72 (d, J = 5.9 Hz, 3 H), 0.61 (d, J = 6.6 Hz, 3 H) ppm. 13C NMR (101 MHz, CDCl3): δ = 159.3, 149.7, 148.65–148.59 (m), 148.5, 136.1, 129.2 (q, J = 32.6 Hz), 127.4, 125.5 (q, J = 3.7 Hz), 122.8 (indirect observation), 118.3, 111.3, 109.6, 62.4, 56.0, 55.9, 54.1, 52.1, 42.8, 39.6, 36.1, 23.2, 22.9 ppm. FTIR: ν = 3415, 2965, 2937, 1619, 1517, 1465, 1327, 1262, 1164, 1123, 1070, 1019, 808 cm–1.

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Keywords: Continuous flow · Nitrogen heterocycles · Atropisomers · Nitrogen heterocycles · Compound Libraries

[9] Reactions were carried out using the FlowStart Evo equipment and micromixers purchased from FutureChemistry (futurechemistry.com accessed Sep 11, 2017).
[10] 1,3-Diethylurea was obtained as a side product in the reaction mixture (ratio 5cA/1,3-diethylurea 1:0.28).
[11] The presence of 1,3-diethylurea present was reduced (ratio 5cA/1,3-diethylurea 1:0.1).
[12] At very low flow rates, stabilization and pressure of the equipment may take long; therefore, a stabilization time is calculated and run before the collecting product fraction. The stabilization time is calculated in Equation (1), experimental section.
[15] The reduction of ketone 2 to alcohol 12 was unsuccessfully performed in flow.
[16] 1,3-Dibenzy lurea was present in the reaction mixture (ratio 6c/1,3-dibenzy lurea 1:0.15).
[18] We do not rule out the possibility of a mixture of rotamers because the 13C NMR chemical shift of the carbamoyl carbon is δ = 159.3 ppm and the IR stretching frequency of the C=O is at 1619 cm–1 in the IR (higher values would be expected if atropisomers were observed, although the absence of examples of this phenomenon in the literature makes the prediction of those values difficult).
[19] Compounds 13a and 13b were isolated after column chromatography of the reaction in batch of amino alcohol 12 and isopropyl isocyanate 7B.

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