



Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701539

Link to VoR: <http://dx.doi.org/10.1002/ejoc.201701539>

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

Alejandra Riesco-Domínguez,^[a] Daniel Blanco-Ania,^[a] and Floris P. J. T. Rutjes^{*[a]}

Abstract: The advantages of performing reactions in continuous flow versus 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 are depicted in Figure 1. Trimeflur,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.

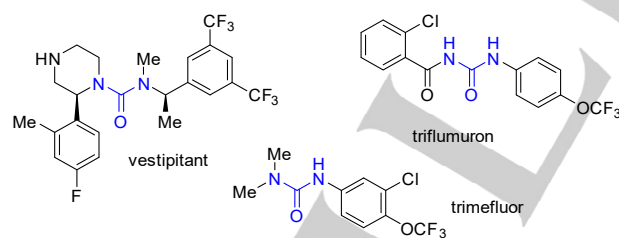
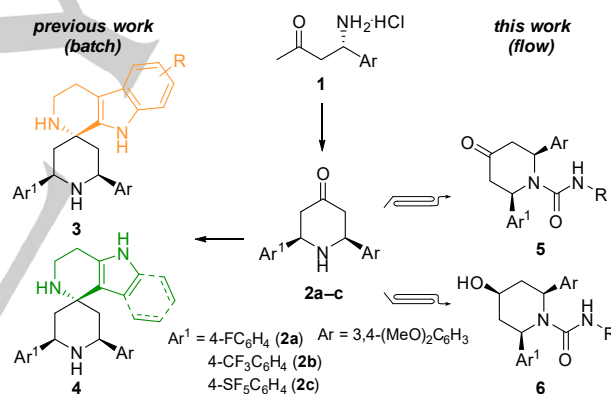


Figure 1. Biologically active compounds containing a urea group.

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 (**3** and **4**) under classic batch processes via a diastereoselective Pictet–Spengler cyclization.⁶

The inherent potential of this scaffold (**2a–c**) for derivatization combined with the advantages of flow chemistry for library synthesis⁸ (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).



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

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

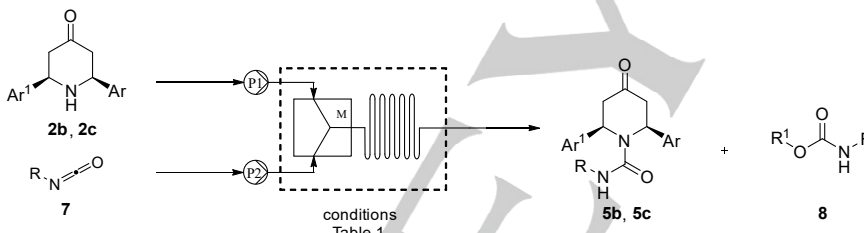
[a] A. Riesco-Domínguez, Dr. D. Blanco-Ania, Prof. dr. F. P. J. T. Rutjes
Institute for Molecules and Materials, Radboud University
Heyendaalseweg 135, 6525 AJ Nijmegen, the Netherlands
floris.rutjes@ru.nl
<http://www.ru.nl/syntheticorganicchemistry/>

FULL PAPER

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 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 explored the use of bulkier alcohols as solvent (*i*PrOH and

*t*BuOH) to avoid the formation of **8**. Thus, the reaction of piperidin-4-one **2c** with ethyl isocyanate (2.5 equiv) in the presence of propan-2-ol gave full conversion to urea **5cA** and less formation of the carbamate **8** (entry 9) whereas the formation of **8** was completely suppressed when *tert*-butyl alcohol was used (entry 10).¹⁰ With this result in hands, we tried to decrease the temperature of the reaction and the amount of isocyanate used. We confirmed that when using 2.0 equiv of ethyl isocyanate and temperatures between 25–35 °C full conversion was not reached (entries 11 and 12). Finally, we found that the use of 2.0 equiv of ethyl isocyanate at 50 °C in *t*BuOH were the suitable conditions to obtain full conversion to compound **5cA** (entry 13). Once the conditions for the synthesis of aliphatic ureas were optimized, we attempted the synthesis of the aryl derivatives. 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).

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



Entry	Substrate	7 (equiv)	Solvent	<i>t</i> (°C)	time (min)	Product	8	R	R ¹	Ratio 5/2/8 ^[a]	Flow rate (μL/min)
1	2b	7A (1.5)	MeCN	50	10	5bA	–	CH ₃ CH ₂	–	1:0.7:0 ^[b]	10.00
2	2b	7A (1.5)	MeCN	80	10	5bA	–	CH ₃ CH ₂	–	1:10:0	10.00
3	2b	7A (1.5)	MeCN	80	15	5bA	–	CH ₃ CH ₂	–	1:5.0:0	6.67
4	2b	7B (1.5)	1,2-DCE	80	15	5bB	–	(CH ₃) ₂ CH	–	1:6.0:0	6.67
5	2b	7B (1.5)	EtOH	80	10	5bB	8a	(CH ₃) ₂ CH	CH ₃ CH ₂	1:1.2:0.14	10.0
6	2b	7B (1.5)	EtOH	80	15	5bB	8a	(CH ₃) ₂ CH	CH ₃ CH ₂	1:0.15:0.31	6.67
7	2b	7B (2.0)	EtOH	80	17	5bB	8a	(CH ₃) ₂ CH	CH ₃ CH ₂	1:0.08:0.31	5.88
8	2c	7A (2.5)	EtOH	80	17	5cA	8b	CH ₃ CH ₂	CH ₃ CH ₂	1:0:0.92	5.88
9	2c	7A (2.5)	<i>i</i> PrOH	80	17	5cA	8c	CH ₃ CH ₂	(CH ₃) ₂ CH	1:0:0.6	5.88
10	2c	7A (2.5)	<i>t</i> BuOH	80	17	5cA	–	CH ₃ CH ₂	–	1:0:0 ¹⁰	5.88
11	2c	7A (2.0)	<i>t</i> BuOH	25	17	5cA	–	CH ₃ CH ₂	–	1:0.12:0 ¹¹	5.88
12	2c	7A (2.0)	<i>t</i> BuOH	35	17	5cA	–	CH ₃ CH ₂	–	1:0.10:0 ¹¹	5.88
13	2c	7A (2.0)	<i>t</i> BuOH	50	17	5cA	–	CH ₃ CH ₂	–	1:0:0 ¹¹	5.88

FULL PAPER

14	2b	7E (1.5)	EtOH	80	20	5bE	8d	2,4-F ₂ C ₆ H ₃	CH ₃ CH ₂	0:1:0.50	5.00
15	2b	7E (1.3)	1,2-DCE	80	17	5bE	–	2,4-F ₂ C ₆ H ₃	–	1:0:0	5.88

[a] Calculated by ¹H NMR of the fraction of the collected product. [b] Analyzed by ¹H NMR of the fraction of stabilization time.

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 hands, 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 directly by ¹H NMR from the fraction of collected product. This fraction always started after running three cycles of the stabilization time (see [SI] for experimental details).¹²

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%).

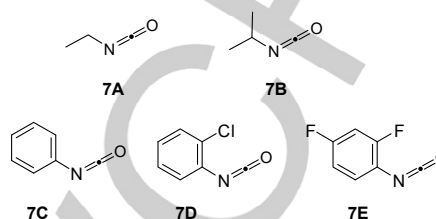
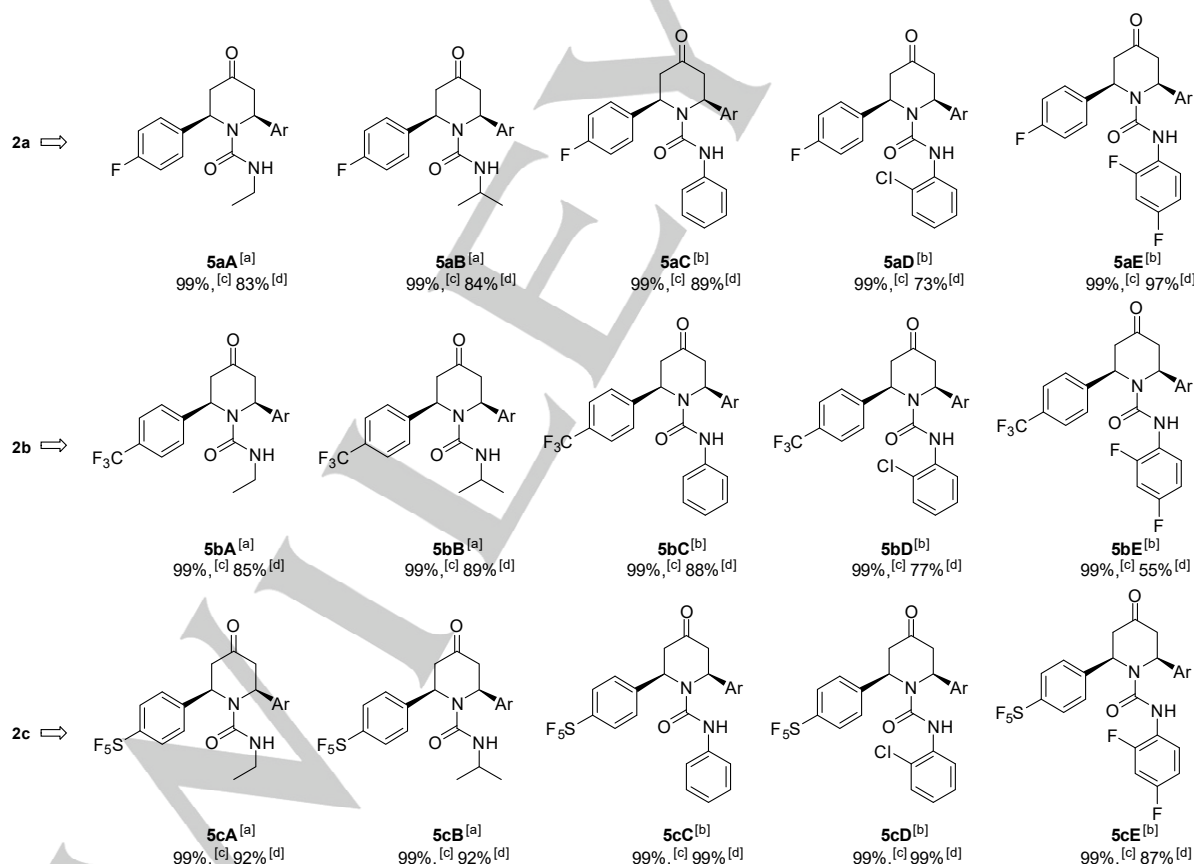


Figure 2. Isocyanates used for the generation of the library.

Table 2. Library of ureas **5aA–cE** based on the piperidin-4-one scaffold.



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

FULL PAPER

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.

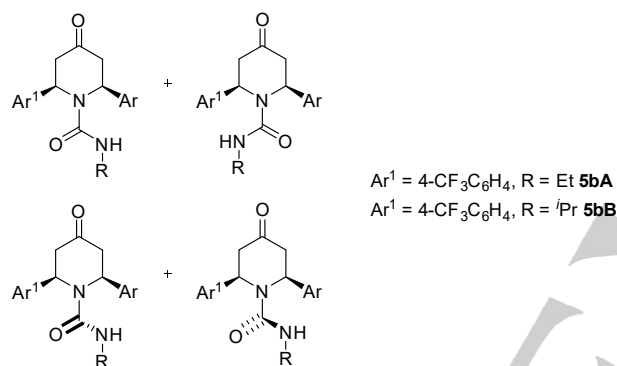
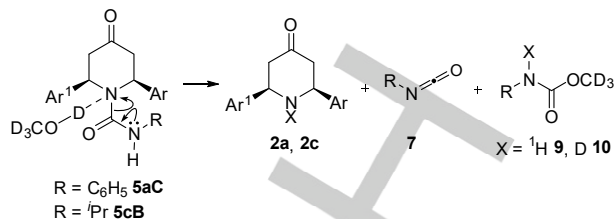


Figure 3. Rotamers and atropisomers of **5bA** and **5bB**.

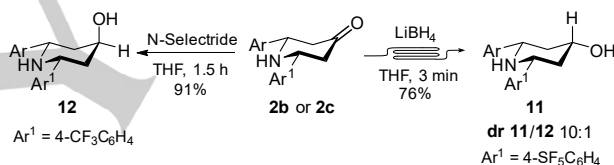
Optimization of these reactions to obtain full conversion was crucial because no further column chromatography was required. Purifying these poorly soluble ureas generally requires polar solvents such as MeOH, but in case of sterically congested ureas methanolysis¹³ may take place in the purification 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 CD_3OD 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).



Scheme 2. Methanolysis of ureas **5aC** and **5bC**.

We also studied the decomposition of the aliphatic urea **5bB**, 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 LiBH_4 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-Selectride¹⁴ to give alcohol **12**.¹⁵

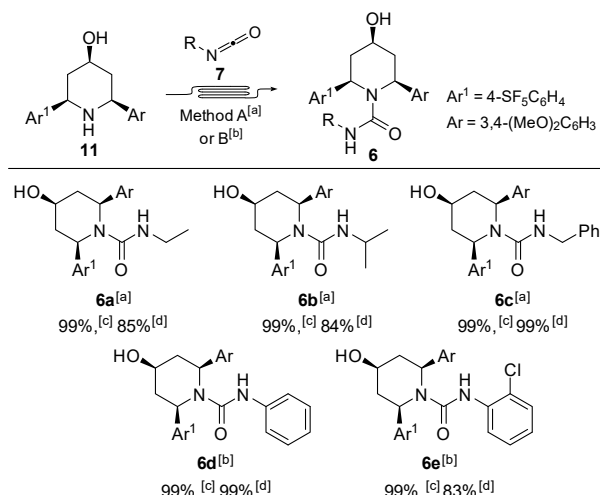


Scheme 3. Reduction of **2a** and **2c** with N-Selectride and LiBH_4 .

Then, we decided to perform the urea synthesis using as starting material amino alcohol **11** (Table 3). Initially, we performed the reaction between **11** and isocyanate **7B** using the conditions previously developed for aliphatic isocyanates ($^t\text{BuOH}$, 17 min and 50°C). We decreased the amount of **7B** to 1.0 equiv, to firstly test the reactivity of our hindered amine in the presence of the nucleophilic alcohol. We confirmed by ^1H NMR that only the amine group reacted with the isocyanate and therefore the corresponding carbamate was not observed. However, while using 1.0 equiv of isocyanate, a ratio **11/6b** 1:0.5 was obtained. Thus, we increased the amount of isocyanate **7B** to 1.5 equiv and full conversion to urea **6b** was achieved (84% yield). When we applied these conditions using ethyl (**7A**) and benzyl (**7F**) isocyanates, amino alcohol **11** was converted with full conversion to ureas **6a** and **6c**¹⁶ in 85 and 99% yield, respectively. Finally, two additional examples with aryl isocyanates (**7C** and **7D**) were synthesized. In this case, the use of 1.1 equiv of isocyanate in 1,2-DCE at 80°C was sufficient to reach full conversion to ureas **6d** and **6e**. For compounds **6a–e**, a 6:1 ratio of conformers was obtained.

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

FULL PAPER



[a] Reaction carried out in ^tBuOH at 50 °C in 17 minutes using 1.5 equiv of isocyanate. [b] Reaction carried out in 1,2-dichloroethane at 80 °C in 17 minutes using 1.1 equiv of isocyanate. [c] Conversion calculated by ¹H NMR of the fraction of collected product. [d] Isolated yield of the fraction of collected product.

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 correlation 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 H² and H⁶ (entries 1 and 5), but also for protons H⁴ and H⁷ (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, H² and H⁶. The clarification of these two products was done by NOESY studies.

Table 4. Chemical shifts (ppm) of atropisomers **13a** and **13b** in CDCl₃.

Entry	¹ H	ppm (13a)	ppm (13b)
1	H ²	4.89	4.36
2	H ³	2.11/1.84	2.20–2.10/2.00–1.89
3	H ⁴	4.43	4.16

4	H ⁵	2.70/2.00	2.37/2.20–2.10
5	H ⁶	5.65	5.12
6	H ⁷	3.80–3.70	3.58–3.49
7	H ⁸	0.88	0.72
8	H ⁹	0.74	0.60

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 reduced diastereoselectively the ketone group in flow in 3 min reaction time. Additional urea formation of amino alcohol **11** was also performed to create five different urea derivatives. NMR studies confirmed the formation of conformers caused by the hindered rotation around one of the single N–CO bonds of the urea. The elucidation of these species to be identified as either rotamers or atropisomers could not be clarified. This methodology could be applied to a wide range of substrates as a tool to prepare libraries of potentially bioactive molecules.

Experimental Section

General information: Reagents were obtained from commercial suppliers and were used without purification. Standard syringe techniques were applied for the transfer of dry solvents and air- or moisture-sensitive reagents. Reactions were followed by ¹H NMR, and R_f values were obtained, using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254) with the indicated solvent mixture. Detection was performed with UV light, and/or by charring at ca. 150 °C after dipping into a solution of KMnO₄. Infrared spectra were recorded on an IR-ATR Bruker TENSOR 27 spectrometer. High-resolution or accurate mass measurement (Δm < 3mmu or 5ppm) were recorded on a JEOL AccuTOF-CS JMS-T100CS for Electrospray (spectra recorded in infusion in MeOH containing 50nM PPG-475 as internal mass-drift compensation standard) or JEOL AccuTOF-GCv JMS-T100GCv (GC/Electron Ionization MS, column bleeding at high temperature used as internal mass drift compensation standard) for methanolysis experiments. NMR spectra were recorded at 298 K on a Varian Inova 400 (400 MHz), Bruker Avance III 400 MHz or Bruker Avance III 500 MHz spectrometer in the solvent indicated. Chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (0.00 ppm) as internal standard for ¹H NMR; and CDCl₃ (77.16 ppm) as internal standard for ¹³C NMR. Coupling constants are reported as J values in hertz (Hz). ¹H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublets, quint = quintet, t = triplet, td = triplet of doublets, m = multiplet), coupling constants (Hz), and integration. Compounds were fully characterized by ¹H, ¹³C, COSY, HSQC, HMBC and NOESY. Reactions were carried out using the FlowStart Evo equipment and microreactors purchased by FutureChemistry (futurechemistry.com accessed Sep 11, 2017). 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 following equation 1:

$$\text{Stabilization Time} = 3 \times \text{Reactor Volume} / \text{Total Flow Rate} \quad (\text{Eq1})$$

For all reactions, products were analyzed from the collected fraction and therefore calculations and yields and based on this fraction.

FULL PAPER

General Procedure for the Synthesis of Alkyl Ureas 5aA, 5aB, 5bA, 5bB, 5cA and 5cB

Solution A: piperidin-4-one (**2a-c**, 1.0 equiv) dissolved in ^tBuOH (99.8–100.2 mM). **Solution B:** alkyl isocyanate (**7A** or **7B**, 2.0 equiv) dissolved in ^tBuOH (0.1 M). **Solution A** (1.96 μ L/min) was combined with **B** (3.92 μ L/min) inside the glass microreactor (internal volume: 100 μ L). The reaction was performed at 50 °C for 17 min.

(2S,6R)-2-(3,4-Dimethoxyphenyl)-N-ethyl-6-(4-fluorophenyl)-4-oxopiperidine-1-carboxamide 5aA

According to the general procedure, the reaction of piperidin-4-one **2a** (3.63 mg, 0.011 mmol) in ^tBuOH (99.8 mM) with **7A** afforded urea **5aA** (3.67 mg, 9.16 μ mol). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.39–7.31 (m, 2 H), 7.08–7.01 (m, 2 H), 6.80 (d, J = 8.2 Hz, 1 H), 6.75 (dd, J = 8.2, 2.1 Hz, 1 H), 6.64 (d, J = 2.1 Hz, 1 H), 6.00 (t, J = 5.4 Hz, 1 H), 5.22 (dd, J = 9.7, 4.9 Hz, 1 H), 4.40 (t, J = 5.2 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 Hz, 3 H). ¹³C NMR [101 MHz, δ (ppm), CDCl₃]: 207.8, 162.1 (d, J = 247.5 Hz), 159.1, 150.1, 149.0, 139.0 (d, J = 3.1 Hz), 134.9, 128.4 (d, J = 8.0 Hz), 117.9, 116.0 (d, J = 21.5 Hz), 111.4, 108.9, 56.1, 56.0, 52.4, 46.1, 43.6, 36.2, 15.2. FTIR [ν (cm⁻¹)]: 3420, 2967, 1722, 1639, 1511, 1264, 1228, 1025. HRMS [ESI (m/z)] calcd for (C₂₂H₂₅FN₂O₄ + Na)⁺ = 423.16906, found 423.16916 (Δ) = 1.0 ppm). *R*_F: 0.27 (heptane/AcOEt, 1:2). Yield: 83%.

(2S,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 (100.2 mM) with **7A** afforded urea **5bA** (4.74 mg, 0.011 mmol). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.66–7.60 (m, 2 H), 7.56–7.51 (m, 2 H), 6.80 (d, J = 8.2 Hz, 1 H), 6.75 (ddd, J = 8.2, 2.1, 0.5 Hz, 1 H), 6.54 (d, J = 2.1 Hz, 1 H), 6.20 (t, J = 5.2 Hz, 1 H), 5.12 (dd, J = 10.2, 4.9 Hz, 1 H), 4.44 (t, J = 5.2 Hz, 1 H), 3.86 (s, 3 H), 3.67 (s, 3 H), 3.23–3.11 (m, 3 H), 2.86 (dd, J = 18.4, 5.6 Hz, 1 H), 2.74 (dd, J = 17.5, 10.2 Hz, 1 H), 2.61 (dd, J = 17.5, 4.9 Hz, 1 H), 0.90 (t, J = 7.2 Hz, 3 H). ¹³C NMR [101 MHz, δ (ppm), CDCl₃]: 207.2, 159.1, 150.3, 149.2, 147.4, 134.6, 129.9 (indirect observation), 127.3, 126.1 (q, J = 3.6 Hz), 124.0 (q, J = 27.2 Hz), 117.9, 111.5, 108.7, 56.6, 56.1, 56.0, 52.3, 46.6, 42.9, 36.2, 15.2. FTIR [ν (cm⁻¹)]: 3422, 2970, 1722, 1635, 1517, 1327, 1264, 1238, 1123, 725. HRMS [ESI (m/z)] calcd for (C₂₃H₂₅F₃N₂O₄ + Na)⁺ = 473.16586, found 473.16547 (Δ) = 2.0 ppm). *R*_F: 0.28 (heptane/AcOEt, 1:2). Yield: 85%.

(2S,6R)-2-(3,4-Dimethoxyphenyl)-N-ethyl-4-oxo-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]piperidine-1-carboxamide 5cA

According to the general procedure, the reaction of piperidin-4-one **2c** (2.21 mg, 5.05 μ mol) in ^tBuOH (99.9 mM) with **7A** afforded urea **5cA** (2.37 mg, 4.66 μ mol). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.81–7.71 (m, 2 H), 7.55–7.49 (m, 2 H), 6.80 (d, J = 8.2 Hz, 1 H), 6.76 (dd, J = 8.2, 2.0 Hz, 1 H), 6.48 (d, J = 2.0 Hz, 1 H), 6.25 (t, J = 5.1 Hz, 1 H), 5.07 (dd, J = 10.3, 5.0 Hz, 1 H), 4.47 (t, J = 5.2 Hz, 1 H), 3.86 (s, 3 H), 3.66 (s, 3 H), 3.24–3.09 (m, 3 H), 2.88 (dd, J = 18.5, 5.8 Hz, 1 H), 2.72 (dd, J = 17.6, 10.4 Hz, 1 H), 2.61 (dd, J = 17.6, 5.0 Hz, 1 H), 0.91 (t, J = 7.2 Hz, 3 H). ¹³C NMR [101 MHz, δ (ppm), CDCl₃]: 206.9, 159.0, 153.1 (indirect observation), 150.4, 149.2, 147.2 (indirect observation), 134.4, 127.3, 126.7 (indirect observation), 117.9, 111.5, 108.5, 56.8, 56.1, 55.9, 51.9, 46.8, 42.7, 36.3, 15.2. FTIR [ν (cm⁻¹)]: 3431, 2925, 1723, 1643, 1518, 1264, 1239, 844. HRMS [ESI (m/z)] calcd for (C₂₂H₂₅F₅N₂O₄S + Na)⁺ = 531.13474, found 531.13535 (Δ) = 0.1 ppm). *R*_F: 0.26 (heptane/AcOEt, 1:2). Yield: 92%.

(2S,6R)-2-(3,4-Dimethoxyphenyl)-6-(4-fluorophenyl)-N-isopropyl-4-oxopiperidine-1-carboxamide 5aB

According to the general procedure, the reaction of piperidin-4-one **2a** (3.50 mg, 0.01 mmol) in ^tBuOH (99.8 mM) with **7B** afforded **5aB** (3.72 mg, 8.98 μ mol). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.40–7.31 (m, 2 H), 7.09–7.00 (m, 2 H), 6.80 (d, J = 8.2 Hz, 1 H), 6.75 (ddd, J = 8.2, 2.1, 0.6 Hz, 1 H), 6.67 (d, J = 2.1 Hz, 1 H), 5.95 (t, J = 5.5 Hz, 1 H), 5.23 (dd, J = 9.6, 4.9 Hz, 1 H), 4.29 (d, J = 7.2 Hz, 1 H), 3.88–3.80 (m, 1 H), 3.86 (s, 3 H), 3.74 (s, 3 H), 3.10 (dd, J = 18.2, 5.5 Hz, 1 H), 2.83 (dd, J = 17.7, 9.5 Hz, 1 H), 2.79 (dd, J = 18.2, 5.9 Hz, 1 H), 2.61 (dd, J = 17.6, 4.9 Hz, 1 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.83 (d, J = 6.5 Hz, 3 H). ¹³C NMR [101 MHz, δ (ppm), CDCl₃]: 207.8, 162.2 (d, J = 247.3 Hz), 158.4, 150.2, 149.0, 139.1 (d, J = 3.2 Hz), 135.1, 128.5 (d, J = 8.0 Hz), 117.9, 116.0 (d, J = 21.4 Hz), 111.4, 109.1, 56.1, 55.9, 52.5, 46.0, 43.7, 43.2, 23.3, 23.0. FTIR [ν (cm⁻¹)]: 3420,

2969, 1721, 1639, 1605, 1510, 1263, 1228, 1026, 854. HRMS [ESI (m/z)] calcd for (C₂₃H₂₇FN₂O₄ + Na)⁺ = 437.18471, found 437.18465 (Δ) = 1.4 ppm). *R*_F: 0.41 (heptane/AcOEt, 1:2). Yield: 84%.

(2S,6R)-2-(3,4-Dimethoxyphenyl)-N-isopropyl-4-oxo-6-[4-(trifluoromethyl)phenyl]piperidine-1-carboxamide 5bB

According to the general procedure, the reaction of piperidin-4-one **2b** (4.10 mg, 0.01 mmol) in ^tBuOH (100.2 mM) with **7B** afforded **5bB** (4.48 mg, 9.65 μ mol). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.66–7.60 (m, 2 H), 7.57–7.51 (m, 2 H), 6.80 (d, J = 8.2 Hz, 1 H), 6.75 (ddd, J = 8.2, 2.2, 0.5 Hz, 1 H), 6.55 (d, J = 2.1 Hz, 1 H), 6.16 (t, J = 5.2 Hz, 1 H), 5.11 (dd, J = 10.2, 4.9 Hz, 1 H), 4.33 (d, J = 7.2 Hz, 1 H), 3.88–3.82 (m, 1 H), 3.86 (s, 3 H), 3.68 (s, 3 H), 3.18 (dd, J = 18.4, 4.7 Hz, 1 H), 2.87 (dd, J = 18.4, 5.7 Hz, 1 H), 2.74 (dd, J = 17.5, 10.2 Hz, 1 H), 2.61 (dd, J = 17.5, 4.9 Hz, 1 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.82 (d, J = 6.5 Hz, 3 H). ¹³C NMR [101 MHz, δ (ppm), CDCl₃]: 207.2, 158.3, 150.3, 149.2, 147.5, 134.8, 129.9 (indirect observation), 127.3, 126.1 (q, J = 3.6 Hz), 122.5 (indirect observation), 117.9, 111.5, 108.7, 56.5, 56.1, 56.0, 52.3, 46.5, 43.3, 42.9, 23.3, 23.0. FTIR [ν (cm⁻¹)]: 3417, 2968, 1722, 1642, 1516, 1326, 1262, 1238, 1123, 767. HRMS [ESI (m/z)] calcd for (C₂₄H₂₇F₃N₂O₄ + Na)⁺ = 487.18151, found 487.18134 (Δ) = 1.5 ppm). *R*_F: 0.41 (heptane/AcOEt, 1:2). Yield: 89%.

(2S,6R)-2-(3,4-Dimethoxyphenyl)-N-isopropyl-4-oxo-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]piperidine-1-carboxamide 5cB

According to the general procedure, the reaction of piperidin-4-one **2c** (4.76 mg, 0.01 mmol) in ^tBuOH (99.9 mM) with **7B** afforded **5cB** (5.22 mg, 9.99 μ mol). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.78–7.73 (m, 2 H), 7.56–7.50 (m, 2 H), 6.80 (d, J = 8.2 Hz, 1 H), 6.75 (dd, J = 8.2, 2.1 Hz, 1 H), 6.49 (d, J = 2.1 Hz, 1 H), 6.22 (t, J = 5.1 Hz, 1 H), 5.04 (dd, J = 10.4, 5.0 Hz, 1 H), 4.36 (d, J = 7.2 Hz, 1 H), 3.86 (s, 3 H), 3.66 (s, 3 H), 3.18 (dd, J = 18.4, 4.3 Hz, 1 H), 2.89 (dd, J = 18.4, 5.7 Hz, 1 H), 2.71 (dd, J = 17.5, 10.4 Hz, 1 H), 2.60 (dd, J = 17.5, 5.0 Hz, 1 H), 0.99 (d, J = 6.5 Hz, 3 H), 0.82 (d, J = 6.5 Hz, 3 H). ¹³C NMR [101 MHz, δ (ppm), CDCl₃]: 206.9, 158.3, 152.9 (indirect observation), 150.4, 149.3, 147.4, 134.6, 127.3, 126.8–126.6 (m), 117.9, 111.5, 108.5, 56.8, 56.2, 55.9, 51.8, 46.8, 43.3, 42.6, 23.3, 23.0. FTIR [ν (cm⁻¹)]: 3421, 2970, 1723, 1642, 1517, 1263, 1238, 842. HRMS [ESI (m/z)] calcd for (C₂₃H₂₇F₅N₂O₄S + Na)⁺ = 545.15039, found 545.15003 (Δ) = 1.7 ppm). *R*_F: 0.45 (heptane/AcOEt, 1:2). Yield: 92%.

Synthesis and Full Characterization of Aryl Ureas 5aC–aE, 5bC–bE and 5cC–cE

Solution A: piperidin-4-one (**2a-c**, 1.0 equiv) dissolved in 1,2-DCE (78.5–102.5 mM). **Solution B:** aryl isocyanate (**7C**, **7D** or **7E**, 1.3 equiv) dissolved in 1,2-DCE (0.1 M). **Solution A** (2.56 μ L/min) was combined with **B** (3.32 μ L/min) inside the glass microreactor (internal volume: 100 μ L). The reaction was performed at 80 °C for 17 min.

(2S,6R)-2-(3,4-Dimethoxyphenyl)-6-(4-fluorophenyl)-4-oxo-N-phenylpiperidine-1-carboxamide 5aC

According to the general procedure, the reaction of piperidin-4-one **2a** (2.59 mg, 7.86 μ mol) in 1,2-DCE (88.9 mM) with **7C** afforded **5aC** (3.15 mg, 7.02 μ mol). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 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), 6.60 (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). ¹³C NMR [101 MHz, δ (ppm), CDCl₃]: 207.2, 162.3 (d, J = 247.8 Hz), 156.6, 150.6, 149.5, 138.6, 138.5 (d, J = 3.4 Hz), 134.3, 129.1, 128.6 (d, J = 8.0 Hz), 123.7, 120.0, 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. FTIR [ν (cm⁻¹)]: 3388, 2924, 1722, 1662, 1510, 1265, 1235, 1026, 754. HRMS [ESI (m/z)] calcd for (C₂₆H₂₅FN₂O₄ + Na)⁺ = 471.16906, found 471.16910 (Δ) = 1.1 ppm). *R*_F: 0.24 (heptane/AcOEt, 2:1). Yield: 89%.

(2S,6R)-2-(3,4-Dimethoxyphenyl)-4-oxo-N-phenyl-6-[4-(trifluoromethyl)phenyl]piperidine-1-carboxamide 5bC

According to the general procedure, the reaction of piperidin-4-one **2b** (2.1 mg, 5.54 μ mol) in 1,2-DCE (82.8 mM) with **7C** afforded **5bC** (2.43 mg, 4.87 μ mol). ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 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,

FULL PAPER

$J = 17.5, 4.8$ Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), CDCl_3]: 206.6, 156.7, 150.7, 149.7, 146.7, 138.5, 133.9, 130.2 (indirect observation), 129.1, 127.4, 126.2 (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. FTIR [$\bar{\nu}$ (cm^{-1})]: 3391, 2939, 1722, 1663, 1597, 1517, 1442, 1327, 1265, 1238, 755. HRMS [ESI (m/z)] calcd for ($\text{C}_{27}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_4 + \text{Na}$) $^+$ = 521.16586, found 521.16560 ($|\Delta| = 1.6$ ppm). R_f : 0.70 (heptane/AcOEt, 1:2). Yield: 88%.

(2S,6R)-2-(3,4-Dimethoxyphenyl)-4-oxo-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]-N-phenylpiperidine-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 mM) with **7C** afforded **5cC** (3.22 mg, 5.79 μmol). ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 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), 6.90–6.86 (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). ^{13}C NMR [101 MHz, δ (ppm), CDCl_3]: 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. FTIR [$\bar{\nu}$ (cm^{-1})]: 3389, 2926, 1725, 1663, 1598, 1518, 1265, 1238, 844. HRMS [ESI (m/z)] calcd for ($\text{C}_{26}\text{H}_{25}\text{F}_5\text{N}_2\text{O}_4\text{S} + \text{Na}$) $^+$ = 579.13474, found 579.13534 ($|\Delta| = 0.1$ ppm). R_f : 0.22 (heptane/AcOEt, 2:1). Yield: 99%.

(2S,6R)-N-(2-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-6-(4-fluorophenyl)-4-oxopiperidine-1-carboxamide 5aD

According to the general procedure, the reaction of piperidin-4-one **2a** (2.4 mg, 7.28 μmol) in 1,2-DCE (90.2 mM) with **7D** afforded **5aD** (2.58 mg, 5.34 μmol). ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 8.09 (dd, $J = 8.2, 1.5$ Hz, 1 H), 7.44–7.37 (m, 2 H), 7.25–7.17 (m, 2 H), 7.11–7.04 (m, 2 H), 7.02 (s, 1 H), 6.98–6.90 (m, 1 H), 6.85 (dd, $J = 8.2, 1.9$ Hz, 1 H), 6.82 (d, $J = 8.2$ Hz, 1 H), 6.73 (d, $J = 1.9$ Hz, 1 H), 6.15 (t, $J = 5.6$ Hz, 1 H), 5.50 (dd, $J = 9.3, 5.1$ Hz, 1 H), 3.86 (s, 3 H), 3.75 (s, 3 H), 3.17 (dd, $J = 18.3, 5.6$ Hz, 1 H), 2.94 (dd, $J = 17.7, 9.3$ Hz, 1 H), 2.88 (dd, $J = 18.4, 5.6$ Hz, 1 H), 2.73 (dd, $J = 17.7, 5.1$ Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), CDCl_3]: 207.2, 162.3 (d, $J = 247.7$ Hz), 156.5, 150.2, 149.3, 138.0 (d, $J = 3.2$ Hz), 135.8, 133.7, 129.0, 128.6 (d, $J = 8.1$ Hz), 127.5, 124.0, 123.1, 122.3, 118.5, 116.3 (d, $J = 21.5$ Hz), 111.7, 109.2, 56.2, 56.1, 53.0, 46.2, 43.8. FTIR [$\bar{\nu}$ (cm^{-1})]: 3365, 2931, 1723, 1666, 1510, 1306, 1264, 1026. HRMS [ESI (m/z)] calcd for ($\text{C}_{26}\text{H}_{24}\text{ClF}_2\text{N}_2\text{O}_4 + \text{Na}$) $^+$ = 505.13063, found 505.13076 ($|\Delta| = 0.3$ ppm). R_f : 0.35 (heptane/AcOEt, 2:1). Yield: 73%.

(2S,6R)-N-(2-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-4-oxo-6-[4-(trifluoromethyl)phenyl]piperidine-1-carboxamide 5bD

According to the general procedure, the reaction of piperidin-4-one **2b** (1.98 mg, 5.22 μmol) in 1,2-DCE (82.8 mM) with **7D** afforded **5bD** (2.15 mg, 4.03 μmol). ^1H NMR [500 MHz, δ (ppm), CDCl_3]: 8.09 (dd, $J = 8.3, 1.5$ Hz, 1 H), 7.67–7.63 (m, 2 H), 7.60–7.56 (m, 2 H), 7.25–7.19 (m, 2 H), 7.04 (s, 1 H), 6.95 (ddd, $J = 8.1, 7.4, 1.5$ Hz, 1 H), 6.86 (dd, $J = 8.3, 2.1$ Hz, 2 H), 6.82 (d, $J = 8.3$ Hz, 1 H), 6.65 (d, $J = 2.1$ Hz, 1 H), 6.31 (t, $J = 5.4$ Hz, 1 H), 5.43 (dd, $J = 9.7, 5.1$ Hz, 1 H), 3.85 (s, 3 H), 3.70 (s, 3 H), 3.22 (dd, $J = 18.5, 5.1$ Hz, 1 H), 2.94 (dd, $J = 18.5, 5.7$ Hz, 1 H), 2.87 (dd, $J = 17.6, 9.7$ Hz, 1 H), 2.74 (dd, $J = 17.6, 5.1$ Hz, 1 H). ^{13}C NMR [126 MHz, δ (ppm), CDCl_3]: 206.4, 156.4, 150.2, 149.3, 146.3, 135.6, 133.2, 130.2 (q, $J = 32.7$ Hz), 128.9, 127.4, 127.2, 126.1 (q, $J = 3.6$ Hz), 124.1, 123.7 (q, $J = 27.5$ Hz, indirect observation), 123.1, 122.2, 118.5, 111.7, 108.8, 56.6, 56.0, 55.9, 52.8, 46.5, 43.0. FTIR [$\bar{\nu}$ (cm^{-1})]: 3356, 2961, 1724, 1666, 1593, 1517, 1439, 1327, 1263, 1234, 1124, 754. HRMS [ESI (m/z)] calcd for ($\text{C}_{27}\text{H}_{24}\text{ClF}_3\text{N}_2\text{O}_4 + \text{Na}$) $^+$ = 555.12689, found 555.12901 ($|\Delta| = 2.8$ ppm). R_f : 0.33 (heptane/AcOEt, 2:1). Yield: 77%.

(2S,6R)-N-(2-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-4-oxo-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]piperidine-1-carboxamide 5cD

According to the general procedure, the reaction of piperidin-4-one **2c** (3.4 mg, 7.77 μmol) in 1,2-DCE (78.5 mM) with **7D** afforded **5cD** (4.6 mg, 7.78 μmol). ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 8.09–8.05 (m, 1 H), 7.79–7.75 (m, 2 H), 7.58–7.53 (m, 2 H), 7.24–7.20 (m, 2 H), 7.05 (s, 1 H), 6.96 (ddd, $J = 8.2, 7.3, 1.5$ Hz, 1 H), 6.87 (dd, $J = 8.2, 2.1$ Hz, 1 H), 6.83 (d, $J = 8.2$ Hz, 1 H), 6.60 (d, $J = 2.1$ Hz, 1 H), 6.32 (t, $J = 5.4$ Hz, 1 H), 5.40 (dd, $J =$

9.7, 5.1 Hz, 1 H), 3.85 (s, 3 H), 3.68 (s, 3 H), 3.21 (dd, $J = 18.6, 5.0$ Hz, 1 H), 2.94 (dd, $J = 18.6, 5.8$ Hz, 1 H), 2.86 (dd, $J = 17.6, 9.7$ Hz, 1 H), 2.74 (dd, $J = 17.6, 5.1$ Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), CDCl_3]: 206.3, 156.4, 153.3 (indirect observation), 150.4, 149.5, 146.4, 135.6, 133.2, 129.1, 127.6, 127.4, 127.0–126.8 (m), 124.3, 123.2, 122.4, 118.6, 111.8, 108.7, 56.9, 56.2, 56.0, 52.5, 46.7, 42.9. FTIR [$\bar{\nu}$ (cm^{-1})]: 3360, 2961, 2838, 2258, 1725, 1686, 1593, 1517, 1440, 1306, 1263, 1234, 1145, 1027, 842, 751. HRMS [ESI (m/z)] calcd for ($\text{C}_{26}\text{H}_{24}\text{ClF}_5\text{N}_2\text{O}_4\text{S} + \text{Na}$) $^+$ = 613.09632, found 613.09446 ($|\Delta| = 3.02$ ppm). Yield: 99%.

(2S,6R)-N-(2,4-Difluorophenyl)-2-(3,4-dimethoxyphenyl)-6-(4-fluorophenyl)-4-oxopiperidine-1-carboxamide 5aE

According to the general procedure, the reaction of piperidin-4-one **2a** (2.30 mg, 6.98 μmol) in 1,2-DCE (87.6 mM) with **7E** afforded **5aE** (3.28 mg, 6.77 μmol). ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 8.01 (td, $J = 9.1, 5.9$ Hz, 1 H), 7.42–7.35 (m, 2 H), 7.12–7.05 (m, 2 H), 6.86–6.77 (m, 3 H), 6.74–6.67 (m, 2 H), 6.64 (d, $J = 1.8$ Hz, 1 H), 6.15 (t, $J = 5.4$ Hz, 1 H), 5.37 (dd, $J = 9.9, 4.9$ Hz, 1 H), 3.87 (s, 3 H), 3.72 (s, 3 H), 3.20 (dd, $J = 18.5, 5.1$ Hz, 1 H), 2.91 (dd, $J = 17.7, 9.9$ Hz, 1 H), 2.88 (dd, $J = 18.5, 5.6$ Hz, 1 H), 2.68 (dd, $J = 17.7, 4.9$ Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), CDCl_3]: 207.0, 162.3 (d, $J = 248.0$ Hz), 158.2 (dd, $J = 245.2, 11.4$ Hz), 156.4, 152.6 (dd, $J = 246.0, 12.0$ Hz), 150.3, 149.4, 138.1 (d, $J = 3.3$ Hz), 133.6, 128.6 (d, $J = 8.1$ Hz), 123.5 (dd, $J = 10.4, 3.8$ Hz), 122.7 (dd, $J = 9.0, 2.4$ Hz), 118.3, 116.3 (d, $J = 21.5$ Hz), 111.7, 111.1 (dd, $J = 21.6, 3.7$ Hz), 108.9, 103.4 (dd, $J = 26.7, 23.3$ Hz), 56.5, 56.10, 56.06, 52.6, 46.2, 43.4. FTIR [$\bar{\nu}$ (cm^{-1})]: 3379, 2936, 1721, 1665, 1534, 1511, 1256, 1228, 1025, 962, 849. HRMS [ESI (m/z)] calcd for ($\text{C}_{26}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_4 + \text{Na}$) $^+$ = 507.15021, found 507.15113 ($|\Delta| = 0.7$ ppm). R_f : 0.29 (heptane/AcOEt, 2:1). Yield: 97%.

(2S,6R)-N-(2,4-Difluorophenyl)-2-(3,4-dimethoxyphenyl)-4-oxo-6-[4-(trifluoromethyl)phenyl]piperidine-1-carboxamide 5bE

According to the general procedure, the reaction of piperidin-4-one **2b** (1.37 mg, 3.61 μmol) in 1,2-DCE (82.8 mM) with **7E** afforded **5bE** (1.07 g, 2.00 μmol). ^1H NMR [400 MHz, δ (ppm), CDCl_3]: 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 (ddd, $J = 11.0, 8.3, 2.8$ 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), 3.66 (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), 2.82 (dd, $J = 17.6, 10.6$ Hz, 1 H), 2.67 (dd, $J = 17.6, 4.9$ Hz, 1 H). ^{13}C NMR [101 MHz, δ (ppm), CDCl_3]: 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 (q, $J = 3.5$ Hz), 123.8 (q, $J = 27.0$ Hz, indirect observation), 123.4 (dd, $J = 10.4, 3.9$ Hz), 122.8 (dd, $J = 8.8, 2.3$ Hz), 118.4, 111.8, 111.2 (dd, $J = 21.6, 3.8$ Hz), 108.5, 103.5 (dd, $J = 26.6, 23.3$ Hz), 57.2, 56.1, 56.0, 52.3, 46.7, 42.7. FTIR [$\bar{\nu}$ (cm^{-1})]: 3381, 2927, 1723, 1667, 1611, 1535, 1518, 1327, 1257, 1126, 1026. HRMS [ESI (m/z)] calcd for ($\text{C}_{27}\text{H}_{23}\text{F}_5\text{N}_2\text{O}_4 + \text{Na}$) $^+$ = 557.14702, found 557.14825 ($|\Delta| = 1.2$ ppm). R_f : 0.31 (heptane/AcOEt, 2:1). Yield: 55%.

(2S,6R)-N-(2,4-Difluorophenyl)-2-(3,4-dimethoxyphenyl)-4-oxo-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]piperidine-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, δ (ppm), CDCl_3]: 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 (d, $J = 1.2$ 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, $J = 18.6, 4.1$ Hz, 1 H), 2.97 (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). ^{13}C NMR [126 MHz, δ (ppm), CDCl_3]: 206.2, 158.3 (dd, $J = 245.7, 11.4$ Hz), 156.4, 153.5–153.1 (m), 152.7 (dd, $J = 245.7, 11.5$ Hz), 150.6, 149.7, 146.5, 133.1, 127.4, 127.0–126.9 (m), 123.4 (dd, $J = 10.5, 3.7$ Hz), 122.9 (dd, $J = 9.0, 2.5$ Hz), 118.4, 111.8, 111.2 (dd, $J = 21.7, 3.6$ Hz), 108.3, 103.5 (dd, $J = 26.6, 23.3$ Hz), 57.4, 56.2, 55.9, 51.9, 46.9, 42.5. FTIR [$\bar{\nu}$ (cm^{-1})]: 3376, 2962, 1725, 1666, 1610, 1534, 1517, 1257, 843. HRMS [ESI (m/z)] calcd for ($\text{C}_{26}\text{H}_{23}\text{F}_7\text{N}_2\text{O}_4\text{S} + \text{H}$) $^+$ = 593.13395, found 593.13686 ($|\Delta| = 4.0$ ppm). HRMS [ESI (m/z)] calcd for ($\text{C}_{26}\text{H}_{23}\text{F}_7\text{N}_2\text{O}_4\text{S} + \text{Na}$) $^+$ = 615.11590, found 615.11657 ($|\Delta| = 0.2$ ppm). R_f : 0.25 (heptane/AcOEt, 2:1). Yield: 87%.

Synthesis and Full Characterization of Amino Alcohols 11 and 12

FULL PAPER

(2S,4R,6R)-2-(3,4-Dimethoxyphenyl)-6-[4-(pentafluoro- λ^6 -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 M solution in THF; 1.5 equiv) dissolved in THF (75 mM). **Solution A** (13.3 μ L/min) was combined with **B** (20 μ L/min) inside the glass microreactor (internal volume: 100 μ L). The reaction was performed at 21 °C for 3 min.

¹H NMR [500 MHz, δ (ppm), CDCl₃]: 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, J = 8.2 Hz, 1 H), 3.99–3.92 (m, 2 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.81 (dd, J = 11.3, 2.4 Hz, 1 H), 2.21–2.10 (m, 2 H), 1.62–1.46 (m, 2 H). **¹³C NMR** [126 MHz, δ (ppm), CDCl₃]: 153.0 (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, 69.9, 59.7, 59.4, 56.09, 56.07, 43.9, 43.8. **FTIR** [ν (cm⁻¹)]: 2936, 2839, 1517, 1262, 1232, 1027, 845, 815. **HRMS** [ESI (m/z)] calcd for (C₁₉H₂₂F₅NO₃S + H)⁺ = 440.13188, found 440.13125 (Δ) = 1.44 ppm. **Yield:** 76%.

(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-6-[4-(trifluoromethyl)phenyl]piperidin-4-ol 12

N-Selectride (3.95 mL, 3.95 mmol, 1.0 M solution in THF) was added to a solution of piperidin-4-one **2b** (500 mg, 1.32 mmol) in dry THF (96 mL) at -78 °C. The reaction was stirred for 1 hour and it was quenched with H₂O (100 mL). The solution was allowed to reach 21 °C and then AcOEt was added. The organic layer was separated and the aqueous layer was extracted with AcOEt (3 \times 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered off and concentrated in vacuo. The residue was purified by SCX-2 column to afford amino alcohol **12** (456 mg, 1.20 mmol). **¹H NMR** [400 MHz, δ (ppm), CDCl₃]: 7.66–7.53 (m, 4 H), 7.04–6.97 (m, 2 H), 6.84 (d, J = 8.1 Hz, 1 H), 4.40–4.32 (m, 2 H), 4.25 (dd, J = 11.7, 2.7 Hz, 1 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 1.95–1.87 (m, 2 H), 1.86–1.70 (m, 2 H). **¹³C NMR** [101 MHz, δ (ppm), CDCl₃]: 149.4, 149.1, 148.4, 137.5 (indirect observation), 129.4 (indirect observation), 127.3, 125.5 (q, J = 3.7 Hz), 123.0 (indirect observation), 118.9, 111.3, 110.2, 66.2, 56.09, 56.07, 56.0, 55.7, 41.66, 41.65. **FTIR** [ν (cm⁻¹)]: 2936, 1517, 1465, 1326, 1263, 1163, 1123, 1067, 1027, 806. **HRMS** [ESI (m/z)] calcd for (C₂₀H₂₂F₃NO₃ + H)⁺ = 382.16300, found 382.16336 (Δ) = 0.94 ppm. **Yield:** 91%.

Synthesis and Full Characterization of Alkyl Ureas 6a–c

Solution A: compound **11** (1.0 equiv) dissolved in ^tBuOH (94.3–96.5 mM). **Solution B:** alkyl isocyanate (**7A**, **7B** or **7F**, 1.5 equiv) dissolved in ^tBuOH (0.1 M). **Solution A** (2.35 μ L/min) was combined with **B** (3.53 μ L/min) inside the glass microreactor (internal volume: 100 μ L). The reaction was performed at 50 °C for 17 min.

(2S,4R,6R)-2-(3,4-Dimethoxyphenyl)-N-ethyl-4-hydroxy-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]piperidine-1-carboxamide 6a

According to the general procedure, the reaction of amino alcohol **11** (2.37 mg, 5.39 μ mol) in ^tBuOH (94.6 mM) afforded urea **6a** (2.33 mg, 4.56 μ mol). **¹H NMR** [400 MHz, δ (ppm), CDCl₃]: 7.74–7.70 (m, 2 H), 7.70–7.65 (m, 2 H), 6.85 (dd, J = 8.3, 2.0 Hz, 1 H), 6.81 (d, J = 8.3 Hz, 1 H), 6.57 (d, J = 2.0 Hz, 1 H), 5.39 (t, J = 6.2 Hz, 1 H), 4.43 (t, J = 5.8 Hz, 1 H), 4.40 (dd, J = 11.7, 4.3 Hz, 1 H), 4.27–4.14 (m, 1 H), 3.86 (s, 3 H), 3.69 (s, 3 H), 2.93 (qd, J = 7.3, 5.4 Hz, 2 H), 2.43 (dt, J = 13.3, 6.2 Hz, 1 H), 2.24–2.10 (m, 2 H), 1.94 (dt, J = 13.5, 11.2 Hz, 1 H), 1.78 (d, J = 3.7 Hz, 1 H). **¹³C NMR** [101 MHz, δ (ppm), CDCl₃]: 160.7, 152.7 (indirect observation), 149.9, 148.9, 148.7 (indirect observation), 135.7, 128.1, 126.3–126.1 (m), 118.7, 111.4, 109.5, 65.8, 59.2, 56.1, 56.0, 55.3, 41.2, 37.8, 35.7, 14.8. **FTIR** [ν (cm⁻¹)]: 3414, 2937, 1627, 1517, 1263, 1140, 1027, 846, 594. **HRMS** [ESI (m/z)] calcd for (C₂₂H₂₇F₅N₂O₄S + Na)⁺ = 533.15094, found 533.15027 (Δ) = 1.26 ppm. **Yield:** 85%.

(2S,4R,6R)-2-(3,4-Dimethoxyphenyl)-4-hydroxy-N-isopropyl-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]piperidine-1-carboxamide 6b

According to the general procedure, the reaction of amino alcohol **11** (2.80 mg, 6.37 μ mol) in ^tBuOH (94.3 mM) afforded urea **6b** (2.76 mg, 5.34 μ mol). **¹H NMR** [400 MHz, δ (ppm), CDCl₃]: 7.73–7.68 (m, 2 H), 7.68–7.63 (m, 2 H), 6.86 (dd, J = 8.3, 2.0 Hz, 1 H), 6.81 (d, J = 8.2 Hz, 1 H), 6.62 (d, J = 2.1 Hz, 1 H), 5.19 (dd, J = 7.4, 5.1 Hz, 1 H), 4.36–4.28 (m, 2 H), 4.24–4.12 (m, 1 H), 3.86 (s, 3 H), 3.72 (s, 3 H), 3.60–3.50 (m, 1 H), 2.46–2.35 (m, 1 H), 2.21–2.08 (m, 2 H), 1.99–1.87 (m, 1 H), 0.75 (d, J = 6.5 Hz, 3 H), 0.61 (d, J = 6.5 Hz, 3 H). **¹³C NMR** [101 MHz, δ (ppm), CDCl₃]: 160.3, 152.7 (indirect observation), 149.8, 148.9, 148.4, 135.5, 128.2, 126.2–126.0 (m), 119.0, 111.4, 109.9, 66.2, 59.7, 56.2, 56.0, 42.4, 41.4, 38.4, 22.8, 22.5.

FTIR [ν (cm⁻¹)]: 3404, 2967, 1704, 1627, 1517, 1465, 1263, 1140, 1027, 844, 595. **HRMS** [ESI (m/z)] calcd for (C₂₃H₂₉F₅N₂O₄S + H)⁺ = 525.18464, found 525.18665 (Δ) = 3.82 ppm. **Yield:** 84%.

(2S,4R,6R)-N-Benzyl-2-(3,4-dimethoxyphenyl)-4-hydroxy-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]piperidine-1-carboxamide 6c

According to the general procedure, the reaction of amino alcohol **11** (2.00 mg, 4.55 μ mol) in ^tBuOH (96.5 mM) afforded urea **6c** (2.60 mg, 4.54 μ mol). **¹H NMR** [400 MHz, δ (ppm), CDCl₃]: 7.76–7.66 (m, 4 H), 7.21–7.12 (m, 3 H), 6.80 (dd, J = 8.2, 2.1 Hz, 1 H), 6.77–6.72 (m, 3 H), 6.54 (d, J = 2.1 Hz, 1 H), 5.44 (t, J = 6.1 Hz, 1 H), 4.80 (t, J = 5.6 Hz, 1 H), 4.47 (dd, J = 11.5, 4.2 Hz, 1 H), 4.27–4.19 (m, 1 H), 4.17 (dd, J = 14.8, 5.8 Hz, 1 H), 4.05 (dd, J = 14.8, 5.2 Hz, 1 H), 3.85 (s, 3 H), 3.63 (s, 3 H), 2.44 (dt, J = 13.1, 6.3 Hz, 1 H), 2.24 (dt, J = 14.4, 6.5 Hz, 1 H), 2.15 (dt, J = 13.5, 5.1 Hz, 1 H), 1.97 (dt, J = 13.7, 11.1 Hz, 1 H), 1.82 (d, J = 3.3 Hz, 1 H). **¹³C NMR** [101 MHz, δ (ppm), CDCl₃]: 160.5, 152.6 (indirect observation), 149.9, 148.9, 148.7, 138.4, 135.6, 128.5, 128.2, 127.3, 127.2, 126.3–126.2, 118.7, 111.5, 109.4, 65.6, 59.0, 56.1, 55.9, 55.2, 45.1, 40.9, 37.6. **FTIR** [ν (cm⁻¹)]: 3410, 2936, 1690, 1560, 1541, 1263, 1139, 1027, 842, 750, 595. **HRMS** [ESI (m/z)] calcd for (C₂₇H₂₉F₅N₂O₄S + Na)⁺ = 595.16659, found 595.16478 (Δ) = 3.04 ppm. **Yield:** 99%.

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:** aryl isocyanate (**7C–E**, 1.1 equiv) dissolved in 1,2-DCE (0.1 M). **Solution A** (2.80 μ L/min) was combined with **B** (3.08 μ L/min) inside the glass microreactor (internal volume: 100 μ L). The reaction was performed at 80 °C for 17 min.

(2S,4R,6R)-2-(3,4-Dimethoxyphenyl)-4-hydroxy-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]-N-phenylpiperidine-1-carboxamide 6d

According to the general procedure, the reaction of amino alcohol **11** (2.57 mg, 5.85 μ mol) in 1,2-DCE (95.6 mM) afforded urea **6d** (3.26 mg, 5.84 μ mol). **¹H NMR** [400 MHz, δ (ppm), CDCl₃]: 7.80–7.76 (m, 2 H), 7.75–7.70 (m, 2 H), 7.20–7.14 (m, 2 H), 6.99–6.90 (m, 4 H), 6.87 (d, J = 8.2 Hz, 1 H), 6.56 (s, 1 H), 6.51 (d, J = 2.1 Hz, 1 H), 5.80 (t, J = 5.8 Hz, 1 H), 4.61 (dd, J = 12.0, 4.3 Hz, 1 H), 4.36–4.24 (m, 1 H), 3.88 (s, 3 H), 3.62 (s, 3 H), 2.58 (dt, J = 14.3, 6.9 Hz, 1 H), 2.37 (dt, J = 14.9, 5.4 Hz, 1 H), 2.18 (dt, J = 13.6, 5.1 Hz, 1 H), 2.03 (dt, J = 13.7, 11.6 Hz, 1 H), 1.89–1.85 (m, 1 H). **¹³C NMR** [101 MHz, δ (ppm), CDCl₃]: 157.6, 152.6 (indirect observation), 150.4, 149.3, 148.9, 138.5, 135.3, 129.0, 128.2, 126.4–126.2 (m), 123.6, 119.8, 118.5, 111.6, 109.1, 65.1, 59.1, 56.2, 55.9, 53.8, 41.0, 36.6. **FTIR** [ν (cm⁻¹)]: 3388, 2933, 2841, 1686, 1647, 1501, 1443, 1420, 1264, 1237, 1140, 1027, 843, 754. **HRMS** [ESI (m/z)] calcd for (C₂₆H₂₇F₅N₂O₄S + Na)⁺ = 581.15094, found 581.14995 (Δ) = 1.70 ppm. **Yield:** 99%.

(2S,4R,6R)-N-(2-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-4-hydroxy-6-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]piperidine-1-carboxamide 6e

According to the general procedure, the reaction of amino alcohol **11** (3.40 mg, 7.74 μ mol) in 1,2-DCE (105.0 mM) afforded urea **6e** (3.81 mg, 6.42 μ mol). **¹H NMR** [400 MHz, δ (ppm), CDCl₃]: 8.01 (dd, J = 8.6, 1.6 Hz, 1 H), 7.79–7.75 (m, 2 H), 7.75–7.70 (m, 2 H), 7.21–7.14 (m, 2 H), 6.97 (s, 1 H), 6.95–6.87 (m, 2 H), 6.82 (d, J = 8.3 Hz, 1 H), 6.61 (d, J = 2.2 Hz, 1 H), 5.83 (t, J = 6.0 Hz, 1 H), 4.85 (dd, J = 11.1, 4.8 Hz, 1 H), 4.39–4.37 (m, 1 H), 3.84 (s, 3 H), 3.65 (s, 3 H), 2.57 (dt, J = 14.4, 7.0 Hz, 1 H), 2.36 (dt, J = 14.9, 5.8 Hz, 1 H), 2.26 (dt, J = 13.9, 5.4 Hz, 1 H), 2.09 (dt, J = 13.9, 10.5 Hz, 1 H), 1.87 (d, J = 3.6 Hz, 1 H). **¹³C NMR** [101 MHz, δ (ppm), CDCl₃]: 157.1, 152.6 (indirect observation), 150.1, 149.1, 148.5, 135.8, 134.8, 129.0, 128.2, 127.5, 126.5–126.3 (m), 123.9, 123.0, 122.0, 119.0, 111.8, 109.2, 64.9, 58.3, 56.2, 56.0, 54.0, 40.8, 36.6. **FTIR** [ν (cm⁻¹)]: 3362, 2936, 2838, 2258, 1735, 1663, 1517, 1439, 1263, 1140, 1027, 843, 754. **HRMS** [ESI (m/z)] calcd for (C₂₆H₂₆ClF₅N₂O₄S + H)⁺ = 593.13002, found 593.12885 (Δ) = 1.98 ppm. **Yield:** 83%.

Synthesis and Full Characterization of Ureas 13a and 13b**(2S,4S,6R)-2-(3,4-Dimethoxyphenyl)-4-hydroxy-N-isopropyl-6-[4-(trifluoromethyl)phenyl]piperidine-1-carboxamide 13a and 13b**

Isopropyl isocyanate (**7B**; 0.01 mL, 0.12 mmol) was added to a solution of piperidin-4-ol **12** (46.2 mg, 0.12 mmol) in CH₂Cl₂ (1.2 mL) at 21 °C and the reaction was stirred for 20 hours. 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%.

FULL PAPER

13a: ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 7.59–7.49 (m, 4 H), 6.84–6.74 (m, 2 H), 6.64 (bs, 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), 4.33 (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), 2.15–2.07 (m, 1 H), 2.00 (dt, *J* = 15.0, 5.4 Hz, 1 H), 1.84 (dt, *J* = 14.9, 3.8 Hz, 1 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 0.74 (d, *J* = 6.4 Hz, 3 H). ¹³C NMR [101 MHz, δ (ppm), CDCl₃]: 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. FTIR [$\bar{\nu}$ (cm⁻¹)]: 3415, 2965, 2937, 1619, 1517, 1465, 1327, 1262, 1164, 1123, 1070, 1019, 808. HRMS [ESI (m/z)] calcd for (C₂₄H₂₉F₃N₂O₄ + Na)⁺ = 489.19771, found 489.19701 (Δ = 1.43 ppm).

13b: ¹H NMR [400 MHz, δ (ppm), CDCl₃]: 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). ¹³C NMR [101 MHz, δ (ppm), CDCl₃]: 160.4, 149.7, 148.8, 148.4, 135.6, 129.4 (indirect observation), 128.2, 125.4, 122.9 (indirect observation), 119.1, 111.3, 110.0, 66.3, 59.6, 56.7, 56.1, 56.0, 42.4, 41.2, 38.7, 22.8, 22.5. FTIR [$\bar{\nu}$ (cm⁻¹)]: 3414, 2930, 1620, 1517, 1465, 1325, 1263, 1164, 1122, 1027, 842. HRMS [ESI (m/z)] calcd for (C₂₄H₂₉F₃N₂O₄ + Na)⁺ = 489.19771, found 489.19688 (Δ = 1.70 ppm).

Acknowledgements

This work has been supported by the FP7 Marie Curie Actions of the European Commission via the ITN ECHONET Network (MCITN-2012-316379).

Keywords: continuous flow • nitrogen heterocycles • urea functionality • atropisomers • piperidin-4-one

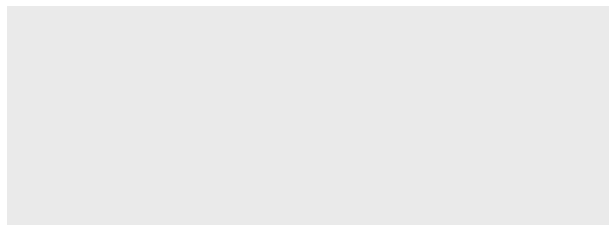
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- [9] Reactions were carried out using the FlowStart Evo equipment and microreactors purchased from FutureChemistry (futurechemistry.com accessed Sep 11, 2017).
- [10] 1,3-Diethylurea was obtained as a side product in the reaction mixture (ratio **5cA**/1,3-diethylurea 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 following equation 1:

$$\text{Stabilization Time} = 3 \times \text{Reactor Volume} / \text{Total Flow Rate (Eq 1)}$$
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- [15] The reduction of ketone **2** to alcohol **12** was unsuccessfully performed in flow.
- [16] 1,3-Dibenzylurea was present in the reaction mixture (ratio **6c**/1,3-dibenzylurea 1:0.15).
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- [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**.

FULL PAPER

Layout 2:

FULL PAPER

**Key Topic*** Library synthesis in flow*Alejandra Riesco-Domínguez, Daniel Blanco-Ania and Floris P. J. T. Rutjes****Page No. – Page No.****Title:** Continuous Flow Synthesis of Urea-Containing Compound Libraries Based on the Piperidin-4-one Scaffold.

Two libraries of ureas based on the piperidin-4-one scaffold have been developed in continuous flow and twenty drug-like compounds were synthesized in moderate to high yields.