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Synthesis of a Drug-Like Focused Library of Trisubstituted Pyrrolidines Using Integrated Flow Chemistry and Batch Methods

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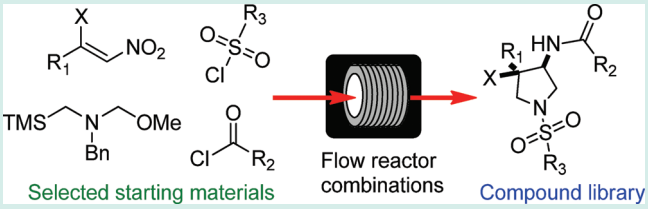
S Supporting Information

ABSTRACT: A combination of flow and batch chemistries has been successfully applied to the assembly of a series of trisubstituted drug-like pyrrolidines. This study demonstrates the efficient preparation of a focused library of these pharmaceutically important structures using microreactor technologies, as well as classical parallel synthesis techniques, and thus exemplifies the impact of integrating innovative enabling tools within the drug discovery process.



KEYWORDS: integrated flow, trisubstituted pyrrolidines, focused library

INTRODUCTION

One of the bottlenecks of current pharmaceutical research and development programmes is the continuous need for novel and structurally diverse chemical entities to run high-throughput screening (HTS) campaigns.[1] HTS is still one of the most powerful approaches available to identify new lead structures.[2] Given the low average HTS hit rates after confirmation it is desirable to screen large compound collections containing as many new scaffolds as possible in order to maximize the coverage of chemical space and increase the number of non related lead structures.[3] Classical synthesis approaches as used in the past have not delivered the quality and quantities of material necessary, often associated with low yielding and unreliable reactions requiring extensive reoptimization during subsequent resynthesis and scale up.[4] Furthermore, the time-consuming purifications needed after each reaction step waste not only resources but, moreover, delay the delivery of final compounds. Unquestionably, this has a massive impact on the time-lines and success rates of the early stages in the drug discovery process.[5]

Recently, we[6] and others[7] have addressed these issues by incorporating and applying enabling technologies to chemical synthesis.[8] In particular, flow chemical approaches have been found to be advantageous[9] because they allow not only for automation of operations, but also for improved heat and mass transfer leading to better control of chemical processes. In addition, reactions that were formerly avoided because of serious safety concerns[10] can now be performed conveniently in flow as only small quantities of reactive materials are within the reactor at a given time.

As part of our interest in the synthesis of heterocyclic systems with valuable substitution patterns[11] we recently reported on the flow synthesis of nitro-pyrrolidines prepared via dipolar cycloaddition reactions.[12] We have demonstrated that both stabilized and unstabilized azomethine ylides can be prepared in situ and used effectively to bring about the regio-controlled synthesis of these heterocycles. The [3 + 2] cycloaddition is a reaction particularly suited to flow as it is known to be associated with thermal runaway and delayed exotherms. In addition, as the resultant structures delivered by the reaction consist of orthogonally protected nitrogen functionalities, that is, a nitro group and a benzyl-protected pyrrolidine nitrogen, we applied the H-Cube hydrogenation system[13] to chemoselectively unmask these parent *N*-functionalities. Using Raney-Nickel (Raney Ni, a nickel−aluminium alloy) as the catalyst only the nitro group was reduced to the corresponding primary amine. Alternatively, when using in-line cartridges filled with palladium on carbon reduction of the nitro can be accomplished with simultaneous debenzylation. This strategy therefore allows for the stepwise unmasking and decoration of these key functional groups.

The pyrrolidine motif is an important pharmacophore possessing biological activity against a number of different targets and thus has found use in various advanced pharmaceutical research compounds and clinical candidates such as Factor Xa inhibitors (**1**),[14] NK_3 receptor antagonists (**2**),[15] DPP-IV inhibitors (**3**),[16] or MC4 receptor selective agonists (**4**, Figure 1).[17]

In this article, we wish to disclose the results of our efforts, which we directed toward the synthesis of a focused drug-like pyrrolidine library decorated with amide and sulfonamide appendages as part of our continuing corporate compound library building efforts. The introduction of these structures was based on the fact that both are well established as linkages to quickly diversify a common core structure allowing for the later evaluation of structure activity relationships. Furthermore, key features

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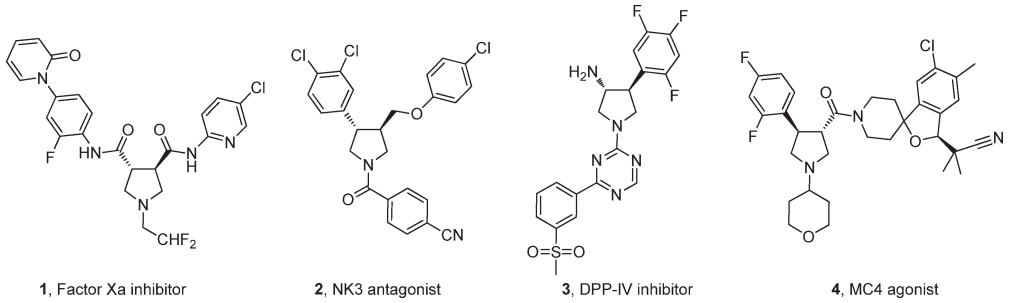
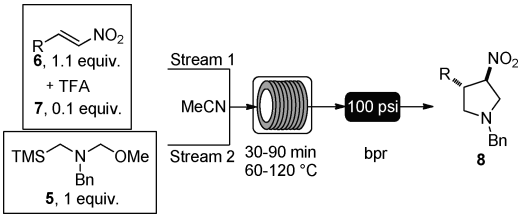


Figure 1. Recent examples of advanced pharmaceutical compounds containing a pyrrolidine substructure.

Scheme 1. General Flow Synthesis of Nitro-Pyrrolidine Building Blocks



of a compound such as solubility, lipophilicity and metabolic stability can be altered or adjusted readily.

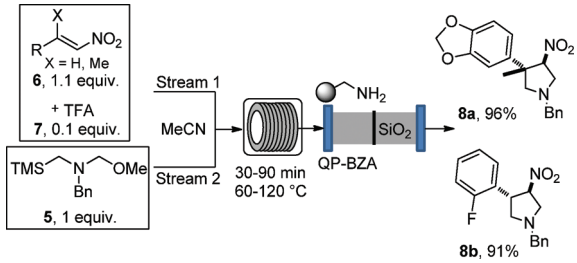
RESULTS AND DISCUSSION

To generate gram quantities of several nitro-pyrrolidine building blocks, we decided to use the commercially available *N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]benzylamine reagent (**5**) as dipole precursor in combination with different nitroalkenes **6** as dipolarophiles. Although we previously demonstrated that fluoride-loaded ion-exchange monoliths[18] can be used to generate the reactive dipole under mild conditions, it was felt that this method is less practical when rapid access to quantities of around 5 g is required. We, therefore, decided to use a catalytic quantity of TFA acid **7** (10 mol %) as an additive in the nitroalkene solution, which after mixing with the dipole precursor stream and directing into a heated flow coil would liberate the azomethine ylid required in the cycloaddition step (Scheme 1). Using the Vapourtec R2+/R4 flow system[19] for this initial reaction was found very beneficial as it allowed the convenient adjustment of parameters such as the temperatures and residence times independently for each substrate thereby maximizing conversion. In particular, the application of a back-pressure regulator allowed superheating of the dichloromethane solvent up to 170 °C enabling even those normally poorly reactive nitroalkenes to be utilized in this process.

Following the flow processing the reaction stream was collected and extracted with an aqueous solution of sodium bicarbonate giving the desired products in good yield (>80%) after drying and solvent removal.

In addition, a second method was established allowing for the direct generation of pure material by applying a series of scavengers placed in glass columns prior to the exit of the reactor. Despite slightly longer processing times this approach is attractive as it avoids conventional batch work-ups and moreover allows for telescoping of this synthesis directly into another reaction step. To achieve this in-line purification, a glass column filled with QP-BZA

Scheme 2. Flow Synthesis of 8a and 8b using an In-Line Work-Up



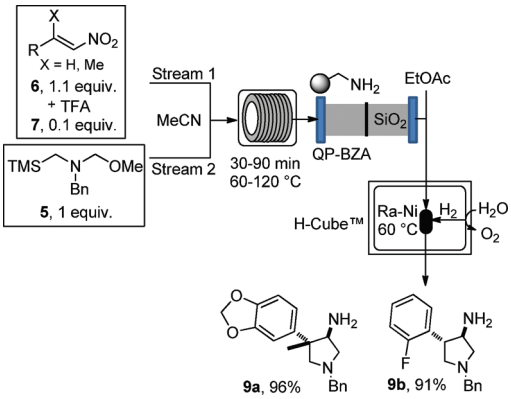
(QuadraPure QP-BZA is a polymer supported benzylamine equivalent, 1 equiv) and a short plug of silica gel (~2 g on a 2 mmol scale) was placed at the exit of the heated flow coil to remove excess nitroalkene, TFA, and colored impurities. This procedure was successfully applied to the synthesis of two further nitro-pyrrolidines as shown in Scheme 2.

To evaluate the potential benefits of flow chemistry in concert with immobilized scavengers to bring about in-line purification of the crude reaction mixture it was decided to process nitro-pyrrolidines **8a** and **8b** by using enabling technologies only. The conversion of nitro-pyrrolidines **8f**–**8j** (Scheme 5) using both flow and batch procedures will be discussed herein.

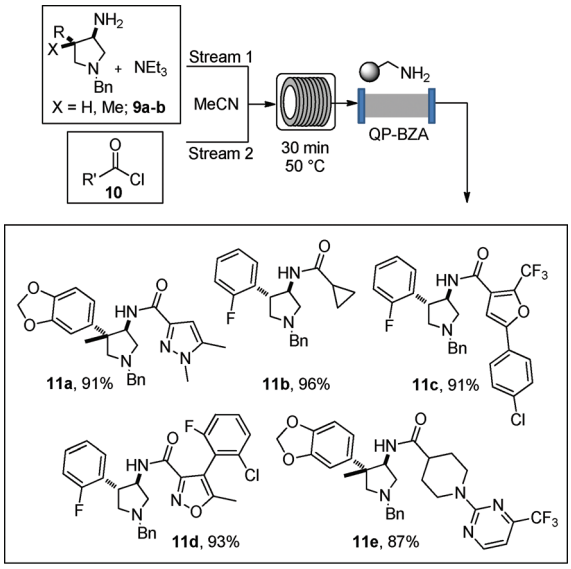
Flow Elaboration toward Amido-Sulfonamide Structures. As both compounds **8a** and **8b** could be isolated in purities greater than 95% following in-line purification it was anticipated that this initial cycloaddition step could be linked directly with a subsequent hydrogenation of the associated nitro groups. Thus the outlet of the reactor coil was connected in series with the H-Cube system utilizing a small cartridge filled with heterogeneous Raney Ni as the reduction catalyst. Pleasingly, it was found that telescoping both reactions gave the desired amino-pyrrolidines **9a** and **9b** in high yield and purity after only removal of the solvent (MeCN/EtOAc = 1:1, Scheme 3).

In the next step, the conversion of amines **9a** and **9b** into their amide derivatives was attempted using a simple flow setup where a stream containing the substrate and triethylamine (0.2 M in MeCN) was mixed with an acid chloride (0.2 M in MeCN) using a T-piece connector. The resulting combined flow stream was then directed through a continuous flow coil (CFC) reactor maintained at 50 °C prior to its passage through a column packed with QP-BZA to remove any unreacted acid chloride and to sequester hydrochloric acid. Starting from two different amine inputs five corresponding amides were obtained in high yield and purity (Scheme 4).

Scheme 3. Telescoped Sequence Starting with Nitroalkenes 6 to Pyrrolidines 9a and 9b



Scheme 4. Flow Amide Formation of Benzylated Building Blocks 11



To elaborate further the amides generated using the above procedure the benzyl protecting groups of certain selected structures were next removed using the H-Cube system in combination with cartridges filled with 10% Pd on carbon. This method worked extremely well when catalytic amounts of acetic acid were added to samples prepared in MeOH (0.1 M, 60 °C, full hydrogen mode). One interesting finding was that the aryl chloride of intermediate **11c** was additionally cleaved under these conditions. From previous studies on halogenated aromatic systems it is known that Pt-derived heterogeneous catalysts should give better selectivities in these systems.[20] However, initial attempts resulted in isolation of the dechlorinated amine as the sole product, consequently we did not investigate this system any further. Once the free pyrrolidines were isolated an analogous procedure to the one depicted in Scheme 4 was used to convert these structures to their corresponding sulfonamide products (**13a**−**c**). Again, a benzylamine resin was applied in-line to remove unreacted sulfonyl chloride giving a small selection of sulfonamide products after final solvent removal (Figure 2).

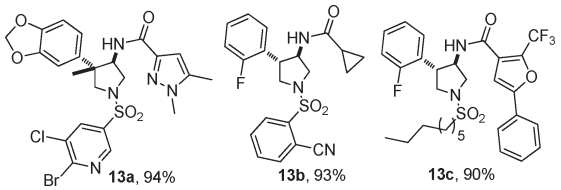


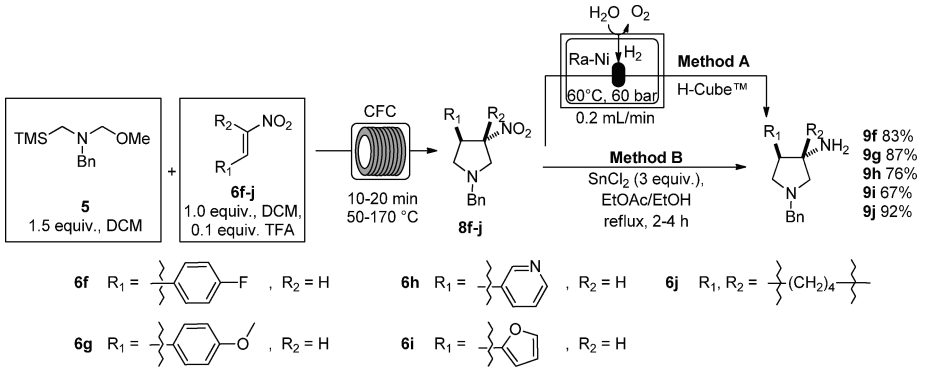
Figure 2. Sulfonamides **13a**−**c** prepared in flow.

In the course of these investigations toward the synthesis of trisubstituted pyrrolidines, we found that flow techniques are very valuable to quickly and conveniently access these structures. As demonstrated in the cycloaddition/Raney Ni-reduction sequence, different flow reactors can be linked together to expedite the synthesis by avoiding the isolation of intermediates. Importantly, the flow sequences were performed in the presence of immobilized scavengers circumventing any time-consuming batch workup protocols.

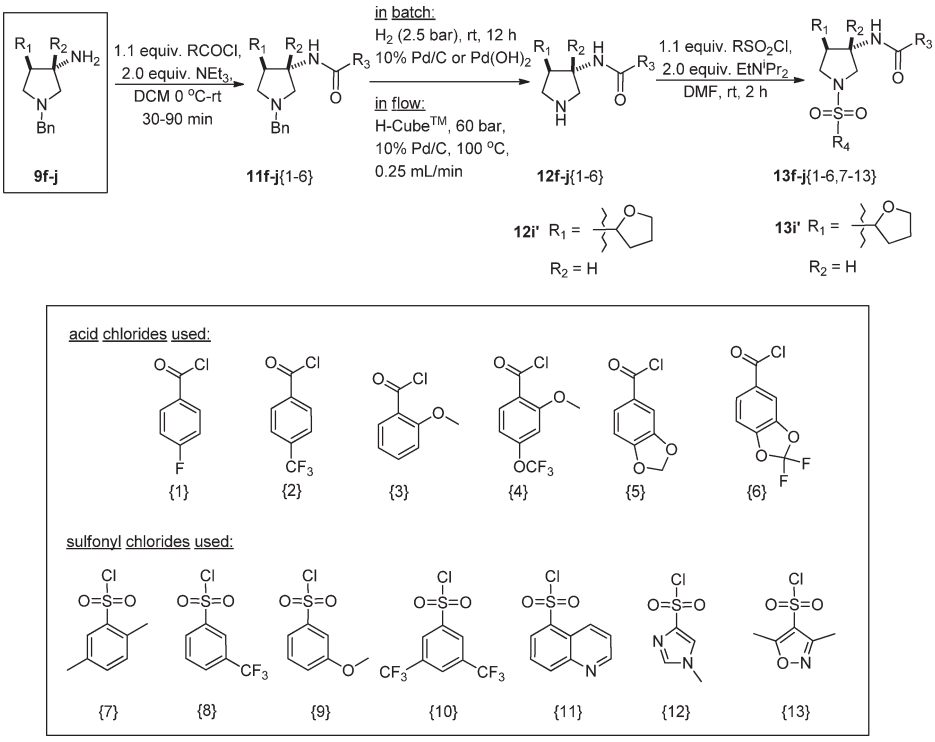
Focused Synthesis of a Drug-Like Pyrrolidine Library Using Flow and Parallel Synthesis Techniques. As an alternative approach to an exclusively flow-based synthesis scheme, we explored the synergistic combination of flow and classical batch techniques thereby making use of standard parallel synthesis tools available in nearly every well-equipped synthesis laboratory. The preparation of library compounds in a parallel array format is an established strategy in the pharmaceutical industry not only for the enrichment of corporate compound collections, but also the support of medicinal chemistry programs at various stages such as the hit-to-lead and the lead-optimization phase.[21]

The first step of the reaction sequence, the [3 + 2] cycloaddition outlined in Scheme 5, was conducted in flow because of the advantages discussed earlier such as better reaction control, easier scalability and the possibility for telescoping with the subsequent nitro reduction step. From the various methods that have been described for the preparation of azomethine ylides from *N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]benzylamine (**5**) we again chose a method employing catalytic amounts of TFA acid due to the relatively mild reaction conditions required.[22] Once more, the Vapourtec R2+/R4 flow system equipped with a PFA (polyfluoro acetate) coiled tube reactor (CFC, 10 mL) was used to perform this step. Two solutions were prepared; solution A contained a mixture of nitrostyrene (**6f**−**j**, 13.9 mmol, 1.0 equiv., 0.28 M) and TFA (1.39 mmol, 0.1 equiv., 0.028 M) in dichloromethane and solution B the *N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]benzylamine reagent (**5**, 20.8 mmol, 1.5 equiv. 0.42 M) also in dichloromethane. The two starting material solutions were introduced via reagent loops and pumped at equal flow rates to meet at a standard T-piece mixer. The optimal reaction conditions for nitro-olefins **6f**, **6g**, and **6i** were found to be a residence time of 10 min and a temperature of 50 °C. Higher reaction temperatures typically resulted in the formation of numerous unidentified side-products. Interestingly, when keeping the residence time constant at 10 min, the pyridine nitro-olefin **6h** required a slightly elevated temperature of 80 °C and the cyclohexene derivative **6j** was reacted at 170 °C to drive the reaction to completion. For all intermediates the crude reaction stream was collected into an aqueous solution of sodium hydrogen carbonate and extracted with dichloromethane providing the racemic nitro-pyrrolidine building blocks **8f**−**j** sufficiently clean to be used directly in the next reaction step. The advantage of using a flow reactor for this transformation was the

Scheme 5. Flow [3 + 2] Cycloaddition of Nitro Olefins 6f−j and Subsequent Reduction of the Nitro Group in Intermediates 8f−j Providing Amino-Pyrrolidines 9f−j (Overall Yields Given)

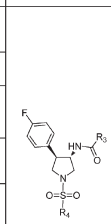
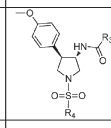
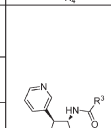
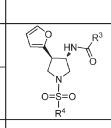
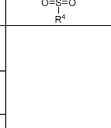
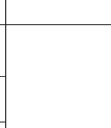


Scheme 6. Amidation of the Pyrrolidine Intermediates 9, Removal of the Benzyl Protection Group, and Final Transformation to the Target Sulfonamides 13



ease of scaling up either by continuous running or by the numbering up of the flow reactors. The reduction of the nitro group in the second reaction step was either conducted in flow by means of the H-Cube or for comparison by classical methods in batch. First, we examined the reduction of the nitro moiety in compounds **8h** and **8i** using the H-cube by evaluating the influence of solvent, concentration of the substrate, flow rate, temperature, type of catalyst and hydrogen pressure on product yield. Optimal results for a substrate concentration of 0.16 M were obtained in a mixture of ethyl acetate/ethanol (1:1) at a flow rate of 0.2 mL/min, 60 bar hydrogen pressure and a temperature of 60 °C with Raney Ni as the catalyst. As previously indicated, the use of Raney Ni enabled selective reduction of the nitro functionality without concomitant cleavage of the benzyl protecting group and was found to be a reliable and selective process for both building blocks. Importantly, it was noted that even traces of TFA from the cycloaddition reaction caused rapid inhibition of the catalyst and thus need to be carefully removed in order to avoid premature Raney Ni deactivation. As an alternative method to the reduction in flow, we explored the transformation of the nitro group of substrates **8f**, **8g**, and **8j** in batch. Because of safety concerns we did not want to employ Raney Ni in bulk amounts and thus opted for a less problematic reagent such as $SnCl_2$ that would also selectively reduce the nitro moiety without affecting the benzyl protection group. Heating substrates **8f**, **8g**, and **8j** in a mixture of ethyl acetate/ethanol (10:1) at reflux for 2−4 h resulted in their clean reduction to the corresponding amino compounds **9f**, **9g**, and **9j**, respectively. Interestingly, both methods, flow and batch,

Table 1. Overview of Prepared Library Members and Purification Data

Entry	Building block	R^3	R^4	Chemset	Yield[a] (%)	LC-MS[b] t_{Ret}/min	Purity[c]
1				**13f**{2,8}	10	2.22	> 98
2				**13f**{2,12}	17	1.95	> 98
3				**13f**{3,13}	17	2.07	> 98
4				**13f**{5,8}	6	2.29	> 98
5				**13f**{5,9}	7	2.06	> 98
6				**13f**{5,12}	3	1.78	> 98
7				**13f**{5,13}	3	2.01	> 98
8				**13g**{1,13}	18	2.06	> 98
9				**13h**{2,7}	3	1.93	> 98
10				**13h**{2,8}	4	1.95	> 98
11				**13h**{2,9}	5	1.80	86
12				**13h**{2,10}	3	2.09	> 98
13				**13h**{2,11}	5	1.72	> 98
14				**13i**{1,9}	15	2.26[d]	> 98
15				**13i**{1,13}	8	2.23[d]	> 98
16				**13j**{1,8}	8	2.15	> 98
17				**13j**{1,9}	11	2.04	> 98
18				**13j**{1,12}	14	1.73	> 98
19				**13j**{1,13}	9	2.04	> 98
20				**13j**{3,12}	9	1.74	> 98
21				**13j**{6,8}	28	2.23	86
22				**13j**{6,12}	13	1.89	> 98
23				**13j**{6,13}	21	2.15	97
24				**13i'**{2,7}	16	2.17	> 98
25				**13i'**{2,8}	28	2.16	> 98
26				**13i'**{2,12}	17	1.79	> 98
27				**13i'**{2,13}	18	2.05	95
28				**13i'**{6,8}	24	2.16	97
29				**13i'**{6,12}	19	1.79	96
30				**13i'**{6,13}	18	2.05	> 98

[a] Single-fraction yield after preparative HPLC purification. Compounds were isolated from the cleanest fraction only; individual fractions were not pooled. [b] Compounds were analyzed by an Agilent HP 1100 series analytical HPLC using a Gemini-NX C18, 110A, 50 × 4.6 mm column equipped with a Gilson Liquid Handler 215 autosampler, a Sedex ELSD 75 lightscatter, and a Dionex UVD 340S UV detector using acetonitrile/water as the mobile phase. [c] Determined by LC-MS (UV/vis at 254 nm). [d] Methanol/water was used as the mobile phase.

furnished the amino-pyrrolidine intermediates **9f**−**9j** after simple acid/base extraction in comparable purity and yield (67−92% over two steps). Whereas the H-Cube reduction would be clearly first choice for the transformation of smaller amounts of material (<5 g) or for rapid catalyst screening, the preparation of larger amounts might be more advantageous in batch with respect to processing time, although safety aspects and reduced waste production are clear benefits of the H-Cube method.

Using NMR coupling constant analysis and NOE measurements (for protons at the 3- and 4-position of the pyrrolidine ring) at different stages of the synthesis toward structures **9f**−**j** was found beneficial in order to ascertain the stereochemical integrity of the desired compounds, that is, trans relations if derived from (*E*)-nitro-olefins or cis relations if derived from nitro-olefin **6j**.

The amino-pyrrolidine building blocks **9f**−**j** were then decorated using a selected number of acid chlorides from the set of compounds shown in Scheme 6. It was not attempted to realize a full combinatorial library exemplifying all possible combinations, but rather using a number of selected pharmacophoric features to prepare a diverse set of compounds spanning a wide molecular property range.

Employing conventional parallel synthesis techniques, the pyrrolidine intermediates **9f**−**j** were dissolved in dichloromethane and treated with a slight excess of the acid chloride (1.1 equiv.) in the presence of triethylamine for 30−90 min (Scheme 6). The crude reaction mixtures were extracted with dichloromethane from a saturated solution of sodium hydrogen carbonate providing in most cases sufficiently clean amide products **11f**−**j** to be used directly in the consecutive reaction step. Only few intermediates, such as **11g**{*5*} or **11h**{*1*}, displayed a side-product profile that required further purification by medium pressure liquid chromatography (MPLC) over silica before they could be employed in the following reaction step. The debenzylation of the pyrrolidine core was again conducted most favorably in the H-Cube at a substrate concentration of 0.1 M using ethyl acetate/methanol (1:1) as the solvent mixture. Flow rates of 0.25 mL/min and 60 bar hydrogen pressure at 100 °C employing 10% Pd/C as a catalyst provided excellent results. However, the rather low flow rate that was required in many cases to ensure full conversion of the starting material could be considered a limiting factor for scale-up, particularly in cases where the larger H-Cube Midi system is not available. We also experienced issues scaling the reaction using the H-Cube Midi, which we found gave very inconsistent results delivering flow streams of variable conversion and in several cases producing additional byproduct. Thus, we also investigated classical reduction conditions using hydrogen gas in a pressurized glass vessel (2.5 bar) at 50 °C overnight employing 10% Pd/C in methanol, which provided equally good results. Interestingly, when using $Pd(OH)_2$ as a catalyst full reduction of the furan containing building blocks **11i**{*2*} and **11i**{*6*} to the corresponding tetrahydrofuran derivates **12i′**{*2*} and **12i′**{*6*}, respectively, was observed. Attempts to separate the diastereomeric mixtures were not undertaken as they coeluted under conventional HPLC conditions.

The sulfonylation steps were performed in parallel mode by treatment of building blocks **12f**−**i′**{1−6} (0.2 M in DMF) with the corresponding sulfonyl chlorides in the presence of Hünig's base (2.0 equiv.). After stirring at room temperature for 2 h, the crude reaction mixtures were purified by reverse phase preparative HPLC providing sufficient quantities of each target structure for further physicochemical analysis and biological profiling.

Table 2. Calculated Molecular Descriptors and Measured Physicochemical Properties

entry	Chemset	MW g/mol	rule-of-5 alerts	clogP[a]	PSA[b] Å	logD[c]	Lysa[d] μg/mL	Pampa[e] Pe (10^{-6} cm/s) D/M/A	microsomal clearance[f] CL_{int} (μL/min/mg) mouse	human
1	**13f**{2,8}	560.5	2	6.23	57.2	>3.5[g]	<1.0	no result[h]	39	14
2	**13f**{2,12}	496.5	0	3.39	72.6	3.48	12	1.29 55/42/3	48	18
3	**13f**{3,13}	473.5	0	3.03	84.4	3.31	<1.0	12.84 17/73/10	390	219
4	**13f**{5,8}	487.5	0	3.09	97.5	>3.5[g]	<1.0	no result[i]	617	127
5	**13f**{5,9}	498.5	0	4.46	84.7	>3.5[g]	<1.0	0.92 43/55/2	1558	247
6	**13f**{5,12}	472.5	0	2.34	91.7	2.32	62	6.50 57/26/17	188	60
7	**13f**{5,13}	487.5	0	3.09	97.5	3.50	<1.0	1.45 35/63/2	1013	259
8	**13g**{1,13}	473.5	0	3.02	87.0	3.52	<1.0	4.37 31/63/6	881	241
9	**13h**{2,7}	503.5	1	4.70	67.2	4.30	<1.0	1.37 45/52/3	982	172
10	**13h**{2,8}	543.5	1	4.59	68.2	4.33	<1.0	0.00 45/55/0	107	19
11	**13h**{2,9}	505.5	1	3.87	76.7	4.03	<1.0	0.59 60/38/2	436	71
12	**13h**{2,10}	611.5	2	5.47	68.2	[j]	[j]	[j]	[j]	[j]
13	**13h**{2,11}	526.5	1	3.70	75.2	3.67	10	3.23 44/50/6	459	123
14	**13i**{1,9}	444.5	0	3.65	74.3	3.61	<1.0	2.61 49/45/6	532	299
15	**13i**{1,13}	433.5	0	2.28	87.1	3.07	23	0.00 96/4/0	216	260
16	**13j**{1,8}	470.5	1	5.65	54.9	4.12	<1.0	0.00 34/66/0	984	145
17	**13j**{1,9}	432.5	0	4.94	64.1	3.84	12	6.72 33/57/10	2774	686
18	**13j**{1,12}	406.5	0	2.81	70.0	1.47	270	[j]	205	43
19	**13j**{1,13}	421.5	0	3.13	76.3	3.20	55	9.82 39/45/16	1206	277
20	**13j**{3,12}	418.5	0	2.60	76.6	1.38	295	7.06 73/4/23	618	124
21	**13j**{6,8}	532.5	2	7.08	73.6	>3.5[g]	<1.0	1.01 25/74/1	464	224
22	**13j**{6,12}	468.5	0	4.24	89.1	2.52	315	9.60 59/17/24	241	77
23	**13j**{6,13}	483.5	0	4.99	95.0	4.16	<1.0	7.60 15/80/5	1172	515
24	**13i′**{2,7}	496.5	0	4.36	64.6	>3.5[g]	<1.0	0.00 31/69/0	2110	566
25	**13i′**{2,8}	536.5	1	4.25	65.6	>3.5[g]	<1.0	0.00 35/65/0	521	142
26	**13i′**{2,12}	472.5	0	1.41	80.9	1.92	260	6.57 75/3/22	33	16
27	**13i′**{2,13}	487.5	0	2.16	87.0	3.63	<1.0	4.60 52/37/11	379	196
28	**13i′**{6,8}	548.5	1	4.78	84.7	>3.5[g]	<1.0	3.31 27/69/4	417	85
29	**13i′**{6,12}	484.5	0	4.95	100.1	1.96	215	7.02 72/5/23	52	61
30	**13i′**{6,13}	499.5	0	2.69	105.7	3.62	<1.0	4.07 35/59/6	327	88

[a] Partition coefficients were calculated using clogP v4.94 (Daylight Chemical Information Systems, Irvine, CA). [b] Polar surface area. For three-dimensional descriptors, single molecular conformations were generated with Corina v3.46.[27] Surface, volume, size and form descriptors were calculated with Moloc (Gerber Molecular Design, Amden, Switzerland). [c] logD values were measured spectrophotometrically at pH = 7.4 in a 1-octanol/50 mM TAPSO buffer system containing 5% (v/v) DMSO. [d] Lyophilization solubility assay. Solubility was measured from lyophilized DMSO stock solutions spectrophotometrically at pH = 6.5 in a phosphate buffer. [e] Pampa (Parallel Artificial Membrane Permeation Assay): low: P*e* < 0.1, medium: 0.1 < P*e* < 1.0, high: P*e* > 1.0. Percentage distribution between donor (D), membrane (M), and acceptor (A) phase. [f] Microsomal clearance in human and mouse liver homogenate. High stability: CL_{int} < 15 μL/min/mg; medium stability: CL_{int} = 15−70 μL/min/mg; low stability: CL_{int} > 70 μL/min/mg. [g] No accurate logD determination possible due to low aqueous solubility. [h] Precipitation of compound. [i] Precipitation of reference compound. [j] Not determined.

During these studies, we elected not to invest the time in fully optimizing each individual reaction instead aiming to rapidly generate material and quickly obtain the analytically pure final compound. This strategy enabled us to accelerate our overall efforts by not only generating novel compounds in concert with selected data, but moreover gaining valuable information required as feedback in a second directed campaign aimed at the synthesis of improved compounds. Consequently, having identified the promising candidates further efforts were then invested to optimize both yields and efficiency of the molecules synthesis. From the 40 reactions initially started, 30 final compounds were isolated (Table 1).

Library Analysis. For the final library members **13f**−**i′** molecular descriptors such as molecular weight, rule-of-5-alerts,[23] clogP and polar surface area (PSA) values were calculated and are summarized in Table 2. In addition to these in silico calculated parameters, physicochemical properties including distribution coefficients (logD), solubility (lyophilization solubility assay, Lysa), passive membrane permeation (Pampa),[24] as well as metabolic stabilities in mouse and human microsomes have been determined. All these physicochemical parameters are routinely explored in the early discovery phase and their optimization is increasingly addressed in parallel to that of target affinity and selectivity. A balanced physicochemical profile is essential in

order to reduce the attrition rate of potential clinical candidates at a later stage of drug development.[25] The rule-of-five guidelines have emerged as a widely used in silico tool for library design as the risk of poor oral activity of a compound increases with the number of alerts. From the 30 final library members, 7 compounds (23%; entry 9, 10, 11, 13, 16, 25, 28) generated a single violation of the guidelines and only 3 compounds (10%; entry 1, 12, 21) showed two excepts as the molecular weight exceeded 500 Da or clogP values are greater 5. Both parameters are strongly influenced by the fluorine load of the molecule and thus it comes as no surprise that particularly structures **13f**{*2,8*}, **13h**{*2,10*}, and **13j**{*6,8*} containing 6, 9, and 5 fluorine atoms, respectively, display two alerts. From all side-chains explored, the imidazoyl {*12*} and isoxazolyl {*13*} moieties are the most efficient groups in conveying polarity to the final structure as demonstrated by examples **13i′**{*2,12*} and **13i′**{*2,13*} having the lowest clogP values of the entire library at 1.41 and 2.16. The majority of the compounds prepared (80%) display a PSA value lower than 90 $Å^2$ and thus should show a high to medium propensity to cross the blood-brain-barrier, which is a key requirement for central nervous system targets.[26] All library compounds are un-ionized at physiological pH as they do not contain any basic or acidic moieties. Thus, for all cases the correlation between clogP, which describes the partition coefficient of the uncharged molecule between a water and 1-octanol phase, and log*D* measured at neutral pH is excellent. The range of logD values spans from 1.38 (**13j**{*3,12*}) to 4.33 (**13h**{*2,8*}) and thus for most compounds is within a useful range, although for several library members such as **13f**{*2,8*} or **13j**{*6,8*} no accurate logD could be measured because of low aqueous solubility. In such cases a conservative lowest limit of 3.5 is stated. The aqueous solubility has been assessed using the lyophilization solubility assay (Lysa). A rather large number of compounds display low solubility in this assay, however, compounds bearing the heterocyclic imidazoyl {*12*} appendage such as **13f**{*5,12*}, **13j**{*1,12*}, **13j**{*3,12*}, and **13j**{*6,12*} are positive exceptions from this trend showing the highest solubilities within this series of up to 315 μg/mL for the latter. As expected an inverse correlation between high solubility and low logD is observed as evidenced by for instance **13j**{*3,12*} or **13j**{*6,12*}, respectively. With respect to passive permeation, almost all compounds showed high artificial membrane permeabilities (Pe values) and thus high diffusion rates, with only few exceptions, such as **13h**{*2,8*}, **13j**{*1,8*}, **13i′**{*2,7*}, and **13i′**{*2,7*} displaying a Pe value of 0.0×10^{-6} cm/s, but nevertheless they show in all cases high accumulation within the membrane. For a large number of compounds the metabolic stability in mouse microsomes is found to be low and thus clearly would require further optimization. Only few exceptions such as **13f**{*2,8*}, **13f**{*2,12*}, or **13i′**{*6,12*} display medium intrinsic clearance. In structures **13f** most likely the *p*-CF_3 moiety of the phenyl group in the amide vector (R^3 vector) together with the *p*-F atom of the phenyl group of the pyrrolidine core helps to effectively shield these metabolically potentially labile positions. For other structures containing the *p*-CF_3 phenyl moiety, but nevertheless showing low metabolic stability, most likely the site of metabolism is diverted to more vulnerable sites such as the R^1 vector. The metabolic trend found in mouse microsomes is very well paralleled in human microsomes, albeit lower absolute intrinsic clearance values are found. Again, **13f**{*2,8*} is the least metabolized compound displaying high stability, and a number of other library candidates such as **13f**{*2,12*}, **13f**{*5,12*}, **13f**{*1,12*}, **13h**{*2,8*}, and **13j**{*1,12*} show medium stability, respectively. In summary, it can be concluded that a number of key parameters such as logD, Lysa, Pampa, or microsomal stability can be well influenced by the nature of the side-chains attached to the pyrrolidine core, offering a range of possibilities for further adjustment of physicochemical properties.

CONCLUSION

In conclusion, we have demonstrated that the integrated use of flow chemistry and conventional batch methods facilitates the synthesis of drug-like libraries of compounds based upon the pyrrolidine scaffold. These complementary techniques exemplify the impact of harnessing the enabling tools in modern drug discovery processes.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and full characterization data for selected intermediates and library compounds is included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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