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FULL PAPER

A Continuous Flow Strategy for the Facile Synthesis and Elaboration of Semi-Saturated Heterobicyclic Fragments

Nicola Luise, [a] Eleanor W. Wyatt, [a] Gary J. Tarver[a] and Paul G. Wyatt*[a]

Abstract: An efficient hydrogenation protocol under continuous flow conditions was developed for the synthesis of underrepresented semi-saturated bicyclic fragments containing highly sp^3-rich skeletons for fragment-based drug discovery (FBDD) programs. Excellent yields were generally achieved by using Pd/C (10% w/w) and RaNi at 25-150 °C under 4-100 bar of hydrogen pressure. The generated fragments, with appropriate physicochemical properties, present diverse hydrogen-bonding pharmacophores and useful vectors for their synthetic elaboration in the optimization stage. Successive, simple functionalizations in continuous flow were accomplished to demonstrate the opportunity to develop multi-step continuous flow synthesis of valuable starting points for FBDD campaigns. A conclusive quality control (QC) was essential to discard those structures that do not fit typical fragment library parameters.

Introduction

Since the seminal "SAR-by-NMR" paper published by Fesik *et al.* in 1996,[1] fragment-based drug-discovery (FBDD) has gained popularity among drug discovery practitioners and it is now deemed as a valid alternative to the more traditional high-throughput screening (HTS) approach.[2]

The application of FBDD to conventional and non-conventional targets has led to both clinically proven drug candidates and approved drugs, emphasizing its extensive application in the drug discovery arena.[3]

Recently, Rees *et al.* have defined guidelines that should be considered for the synthesis of fragments with optimal chemical properties for FBDD campaigns.[4] As an illustration, they reported an emblematic semi-saturated bicyclic fragment (dihydroisoquinolinone) synthesized in a few steps from a commercial available staring material and presenting polar functionalities, high sp^3-content and accessible vectors to be grown three dimensionally.[5] Concurrently and subsequently to Rees' work, we and others discussed the importance of designing fragments with higher shape diversity (sp^3-rich molecules) compared to the current "flat" fragment libraries, which prevent an efficient coverage of the theoretical chemical space.[6]

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Increasing the sp^3-content has been demonstrated to lead to an enhanced clinical success,[7] although attention should be paid to three dimensional (3D) character that can lead to increased complexity of ligands, diminishing the probability of binding to biological targets.[8] In this regard, as an extension of our previous work,[6a] we aimed to find a compromise by investigating the synthesis of semi-saturated bicyclic fragments, where some shape to improve physicochemical properties and to increase the number of possible points of growth is delivered by saturated heterocycles, which are fused to an unsaturated counterpart able to perform key interactions (e.g. H-bonds) with the biological target. Such bicyclic systems are embedded within the frameworks of many bioactive compounds (figure 1), underpinning the notion of building fragment libraries enriched in sp^3 character.[9]

We herein disclose the partial hydrogenation of fully unsaturated heterocycles to access semi-saturated bicyclic *N*-containing fragments under continuous flow conditions,[10] and their subsequent facile functionalization to access novel chemical space. Based on the paucity of protocols describing the continuous flow reduction of aromatic compounds to increase the saturation content,[11] we were encouraged to create an interface between FBDD and continuous flow synthesis aiming to generate a set of fragments that are either novel or known structures that otherwise would require more elaborate synthetic routes.

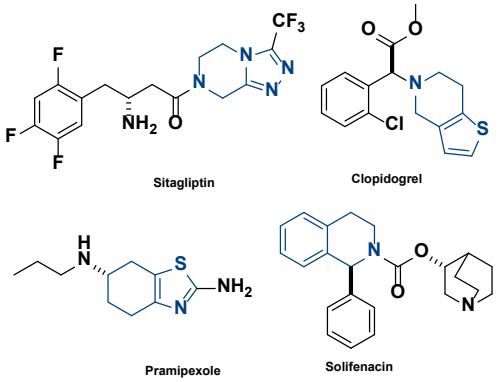
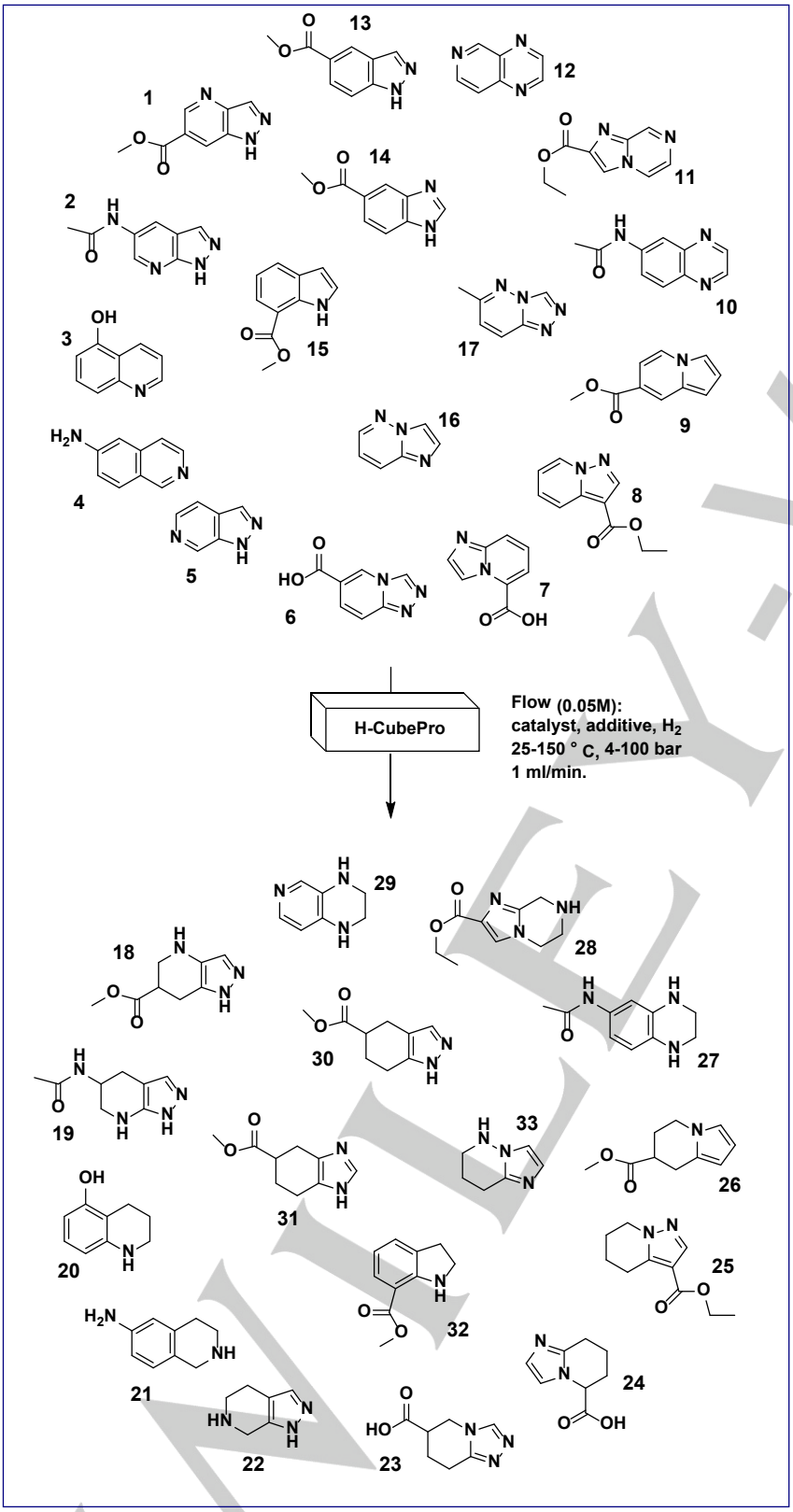


Figure 1. Bioactive molecules containing semi-saturated bicyclic moieties.

Results and Discussion

After the seminal paper in 2005 by Ley *et al.*,[12] Thales Nanotechnology made a continuous flow hydrogenation reactor, named the H-cube, commercially available.[12] Multiple chemical reactions have been carried out in the H-cube over the last decade but, in the context of aromatic systems, only few published works reported the saturation of heterocycles.[11] Hence,



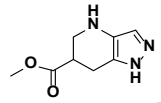
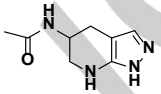
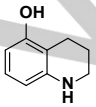
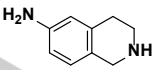
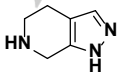
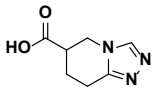
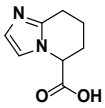
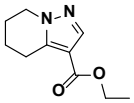
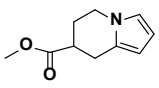
Scheme 1. Partial hydrogenation in the H-cube Pro system of fully unsaturated bicyclic heterocycles **1-17.**

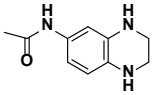
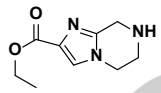
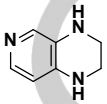
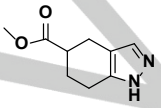
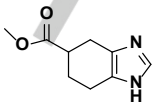
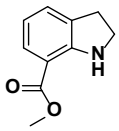
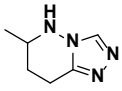
the application of this methodology to FBDD represent an exciting strategy to quickly deliver fragments and highly useful synthetic intermediates, especially considering the multitude of commercially available small unsaturated heterocycles that could act as ideal substrates.

To this end, commercially available compounds were selected based on their ability to deliver compounds compliant with the Drug Discovery Unit's (DDU) fragment library parameters (see supporting info) and conform to the "rule-of-three" (Ro3).[14] A remarkable variety of structures (e.g. carboaliphatic, heteroaliphatic, bridgehead heterocycles, etc.) can be accessed by adopting this approach and therefore it can be considered as a highly efficient synthetic tool to increase the libraries size for FBDD campaigns. In this respect, a set of semi-saturated bicyclic heterocycles (**18**-**33**) was afforded by hydrogenating various *N*-containing bicyclic aromatic compounds (**1**-**17**), made up of a 6-membered ring fused to either a 5- or 6-membered counterpart (Scheme 1). These scaffolds are functionalized with polar moieties useful for further elaboration and interaction with biological targets, but each of them also had to have alternative potential points of growth, which could be exploited for example *via* C-H activation reactions.[4][15] Moreover, fragments with stereocenters were intentionally synthesized as racemic mixture, in line with the widespread preference of screening racemates rather than pure enantiomers.[16] Functionalities either on the 5- or 6-membered cycles substantially modulated the reactivity of the scaffolds. Hence, temperature, pressure, reagents, solvents and catalyst were adapted to the specific characteristics of each scaffold.

Firstly, Pd/C (10% w/w) was selected as first choice catalyst, both because of its lower cost over other transition metal catalysts and its proven ability for reduction of heteroaromatic rings. Secondly, based on Knudsen *et al.*'s work,[17] a high temperature was maintained where possible, since it is beneficial for maximizing the lifetime of the catalyst. Finally, ethanol was chosen as the solvent and few equivalents of acetic acid were added both to suppress catalyst poisoning, due to secondary amine formation,[18] and to increase substrate reactivity and absorption onto the catalyst surface. Taking these considerations into

Table 1. Reaction conditions adopted for the partial hydrogenation of **1-17**.

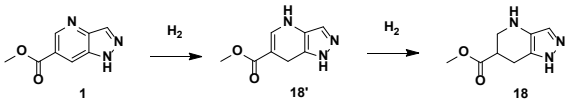
entry	catalyst	Temp.[°C]	Pressure [bar]	product	yield [%][a]
1	Pd/C [10%w/w]	70	70	 **18**	80[b]
2	"	"	"	"	85[b]
3	"	100	100	"	>99
4	"	"	"	**19** 	>99
5	"	25	4	 **20**	75[b]
6	RaNi	"	8	"	97
7	Pd/C [10%w/w]	80	80	**21** 	78[b]
8	"	"	"	**22** 	76[b]
9	"	100	100	**21**	>99
10	"	"	"	**22**	>99
11	"	50	50	 **23**	>99
12	"	"	"	 **24**	>99
13	"	"	"	 **25**	>99
14	"	"	"	**23**	12[b]
15	"	"	"	**24**	15[b]
16	"	25	8	**26** 	42[b]
17	RaNi	"	4	"	73[c] (77)[b]

18	Pd/C [10%w/w]	50	50	 **27**	>99
19	"	"	"	**28** 	>99
20	"	25	8	 **29**	73[b]
21	"	"	15	"	>99
22	"	100	100	 **30**	65[b]
23	"	"	"	**31** 	69[b]
24	"	"	"	**30**	74[b]
25	"	"	"	**31**	75[b]
26	Rh/C [5%w/w]	"	"	**30**	72[b]
27	"	"	"	**31**	75[b]
28	Pd/C [10%w/w]	150	"	**30**	84[c] (90)[b]
29	"	"	"	**31**	86[c] (91)[b]
30	"	25	30	 **32**	62[b]
31	"	40	50	"	75[b]
32	RaNi	"	"	"	96
33	Pd/C [10%w/w]	100	100	 **33**	86[b]
34	"	120	"	"	98
35	"	150	"	 **34**	55[b]

[a] Isolated yields after purification by isolute SCX or PE-AX column.
[b] conversion detected by HPLC-UV/Vis at 190nm and ^{1}H-NMR.
[c] isolated yields after flash chromatography.

account, the partial saturation of **1**-**17** was carried out in the H-cube. Gratifying, the hydrogenation in continuous flow gave the highly promising results depicted in table 1 and allowed us to access the desired fragments **18**-**33.**

The investigation was commenced by reducing **1**, which was solubilized in EtOH and reacted at 70 °C and 70 bar at flow rate of 1 ml/min (entry 1). An 80% conversion of **18** was achieved by using these conditions, although a better conversion was afforded after addition of water in a 1:5 ratio with ethanol. Water is an optimal solvent for hydrogenation and it was found to be beneficial for increasing solubility of both reagent and product (entry 2).[19] Finally, by increasing both temperature and pressure to 100 °C and 100 bar, respectively, we achieved complete conversion (entry 3). Conversely, a lower flow rate at 0.5ml/min did not significantly alter the final outcomes. Higher temperature and pressure were expected to work better since the electron withdrawing group (EWG) is meta to the nitrogen, leading to a stable vinylogous amide intermediate **18'** after addition of the first molecule of hydrogen (scheme 2).[20] Considering the positive result obtained by using water, it was decided to solubilize subsequent compounds in the water/ethanol (1:5) mixture.

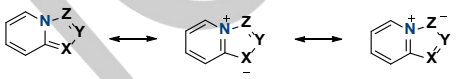


Scheme 2. Synthesis of **18** via stable formation of a vinylogous amide (**18'**).

Reduction of pyridine **2**, bearing an acylated nitrogen whose electron pair can be delocalized onto both the carbonyl and the aromatic ring, under the abovementioned reaction conditions yielded the partial saturated fragment **19** (entry 4). These parameters were thought to be excessively harsh for the 5-hydroxyquinoline **3**, hence lower temperature and pressure were employed. Pyridine was found much more reactive than the previous systems and even room temperature and 4 bar were effective for partially converting **3** to the desired bicyclic system **20** (entry 5). However, partial saturation of the benzene ring was detected too and we opted for a milder catalyst. Pleasingly, switching to a RaNi catalyst promoted the complete conversion of **3** to **20** at room temperature and 8 bar, without generation of oversaturated side products (entry 6).

Next, we examined the reduction of **4** and **5**, bearing a pyridine nitrogen two bonds away from the fused benzene and pyrazole, respectively. High temperature and pressure expedited the conversion to **21** and **22** (entries 9 and 10) compared to milder conditions (entries 7 and 8), which could not drive the reaction to completion.

For the aza-indolizines **6**-**8**, 50-60 °C and 50-60 bar were sufficient to afford **23**-**25** (entries 11, 12 and 13). This higher reactivity might be due to the significant contribution of the pyridinium moiety in two of the three main mesomeric structures of **6**-**8** (scheme 3) compared to previous examples,[21] considering that the electron-withdrawing effect of the carboxylic derivatives, placed in a different position on the rings, plays a minor role. It has to be emphasized that **6** and **7** were not soluble in the typical 5:1 mixture of water/ethanol, but when acetic acid was replaced by sodium hydroxide the resulting salts were more soluble and could be treated in continuous flow. However, we observed that when more than one equivalent of sodium hydroxide was employed, the catalyst activity was generally diminished and nearly completely compromised with 4-6 equivalents (entries 14 and 15). For the indolizine **9**, the EWG para to the nitrogen seems to have a more significant role, since complete saturation of the six-membered ring occurred at room temperature and 8-10 bar. However, these conditions led to a partial conversion of the five membered ring to the reduced derivative (entry 16). Thus, it was decided to replace Pd/C (10% w/w) with a RaNi catalyst, and the highest yield was afforded when the hydrogenation was performed at room temperature and 4 bar, leading to a 73% yield of **26** along with an oversaturated side product and recovery of starting material (entry 17).



Scheme 3. Representation of the pyridinium moiety in two of the three main mesomeric structures of indolizine derivatives.

We next investigated the synthesis of the piperazine derivatives **27**-**29** from intermediates **10**-**12**. Interestingly, hydrogenation of **10** using 50 bar and 50 °C led to **27** without detectable oversaturated products (entry 18), and the same parameters also delivered **28** from the partial saturation of the bridgehead pyrazine **11** (entry 19). Compound **29** was generated by selective hydrogenation of pyrazine over pyrimidine of **12**, and to avoid generation of side products we investigated its synthesis by using milder conditions. At room temperature and 8 bar, partial conversion of **12** into **29** (entry 20) was observed, but by doubling the pressure and maintaining the temperature at 25 °C complete and selective saturation of the pyrazine ring was afforded (entry 21).

Subsequently, we examined the partial reduction of indazole **13** and benzimidazole **14**, which showed similar reactivity. At 100 °C and 100 bar, partial conversion was achieved (entry 22 and 23), whereas a slight improvement in conversion was detected by replacing water with EtOAc (entry 24 and 25). Switching to Rh/C (5% w/w) did not accelerate the conversion (entry 26 and 27), so the next attempt was carried out with Pd/C (10% w/w) at higher temperature. Raising the temperature from 100 °C to 150 °C led to a ≈ 90% conversion (entry 28 and 29).

The flow hydrogenation of **15** was initially tried with a Pd/C (10% w/w) catalyst under mild reaction conditions. At 30 °C and 30 bar, **15** was partially converted into the desired fragment **32** (entry 30), however oversaturated side products were produced at higher temperature and pressure (entry 31). Thus, it was decided to circumvent such problem by using RaNi, and generation of the indoline **32** was successfully achieved at 40 °C and 50 bar (entry 32).

Finally, the reduction of the pyridazine derivative **16** required the use of Pd/C (10% w/w) catalyst, 100 bar and 120 °C for full conversion (**33**) (entry 33). In contrast, the more hindered pyridazine **17** required harsher reaction conditions. Increasing the reaction temperature up to 150 °C enabled a 55% conversion (**34**) and recovery of **17** (30%), along with **34'** (11%) and **34"** (4%) (entry 35). Running the reduction of **17** at milder conditions with

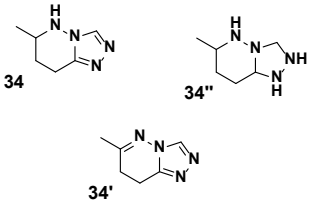
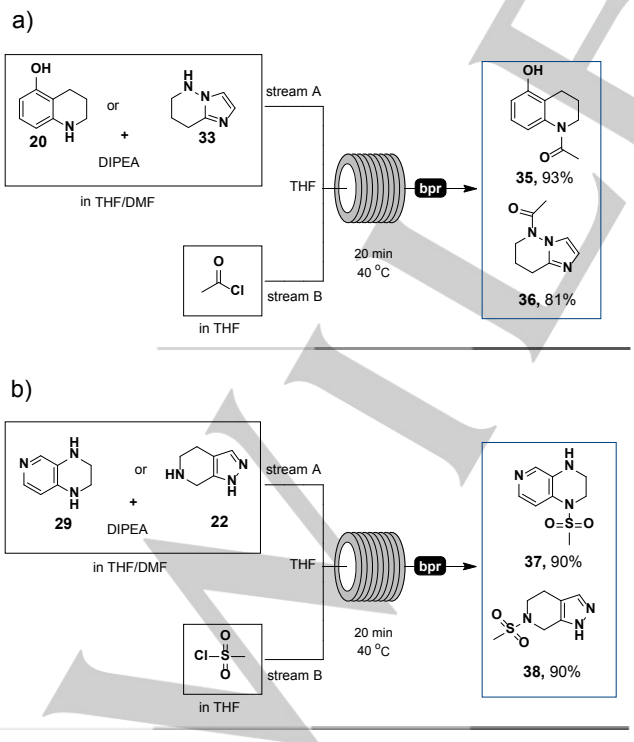


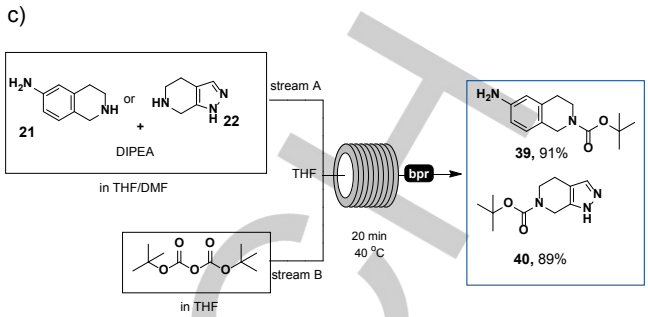
Figure 2. Main products from the hydrogenation of **17**.

Rh/C (5% w/w) was not beneficial for alleviating the oversaturation issue. **34** was discovered to be prone to oxidation at room temperature to give **34'**, consequently we did not investigate this optimization any further (figure 2).

Following the partial hydrogenation in the H-Cube, some selected fragments were further functionalized in a PTFE coil reactor (Vapourtec RS-200) with a series of simple reactions to demonstrate the synthetic utility of installed handles for creating other fragments.

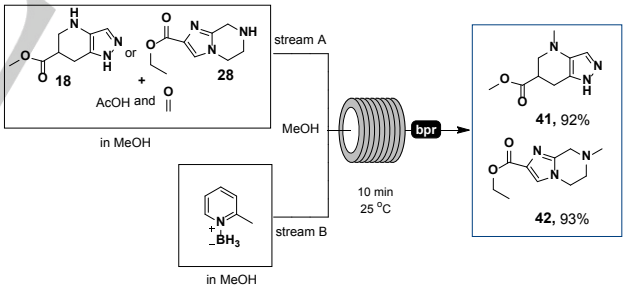
Initially, we attempted the conversion of amines **20** and **33** into their respective carboxamides **35** and **36**. A stream containing the amine substrate and DIPEA (0.1 M in THF/DMF 1:1) was mixed with acyl chloride (0.1 M in THF), and the resulting solution was reacted at 40 °C (scheme 4a). Similarly, amines **29** and **22** were transformed into their respective sulfonamides **37** and **38**, after treatment with methanesulfonyl chloride in continuous flow (scheme 4b). The same reaction conditions were found to be successful for the Boc protection of **21** and **22** to deliver **39** and **40,** as final fragments or useful intermediates for organic synthesis (scheme 4c).





Scheme 4. General flow synthesis of fragment **35** and **36** (a), **37** and **38** (b), **39** and **40** (c).

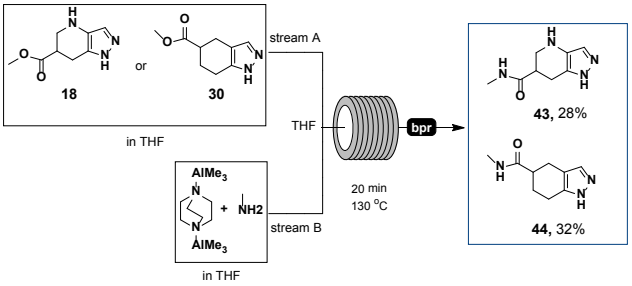
Next, the synthesis of tertiary amines by reductive amination was examined. There is literature precedent describing multiple ways of making amines by reductive amination,[22] but there are no studies based on the use of 2-picoline borane (Pic-BH_3) in continuous flow as a reducing agent. Sato *et al.* were the first to report the use of Pic-BH_3 in classical batch methodologies, showing its high reactivity, stability as a white solid and good solubility in MeOH and water,[23] an important aspect for continuous flow. Therefore, to explore the use of Pic-BH_3 for the methylation of secondary amines, a stream containing the substrate (**18** and **28**), formaldehyde and acetic acid (0.1 M in MeOH) was mixed with a solution of Pic-BH_3 in MeOH. Pleasingly, this unprecedented in continuous flow reduction gave a high yield of **41** and **42** when the reaction mixtures were passed through the reactor coil at 30 °C for 10 minutes (scheme 5).



Scheme 5. General flow synthesis of fragment **41** and **42**.

Finally, we attempted the possible aminolysis of fragments substituted with carboxylic esters in continuous flow at high temperature and pressure to deliver the respective secondary amides. The air-stable DABAL-Me_3 (adduct of $AlMe_3$ and DABCO) was selected to promote this chemical transformation. Its use has been described for both batch and microwave methodologies, however elevated temperature and pressure are generally required for the ester conversion into an amide, and this is a limitation for possible scale-up. Lee and co-workers have reported one of the few examples of this transformation in continuous flow as a validated strategy to scale-up amide synthesis.[24] Based on these results, we were interested in

derivatizing **18** and **30** in small scale, with the intention of exploring the utility of the approach. Generation of **43** and **44** was attempted in continuous flow, and the application of a back-pressure regulator allowed superheating of THF at a temperature higher than its boiling point. A THF solution of methylamine and DABAL-Me_3 was filtered and injected in the Vapourtec RS-200, followed by injection of the substrate (0.1 M in THF). The two streams were joined and reacted at 130 °C. A residence time of 5 minutes did not lead to conversion, whereas a longer residence time (20 min) gave **43** and **44** in 28% and 32% yield, respectively (scheme 6). These results were in line with Lee's work at 130 °C, and higher reaction yields could be achieved during the optimization process by using a tubular reactor packed with glass beads and heated at 170-190 °C.

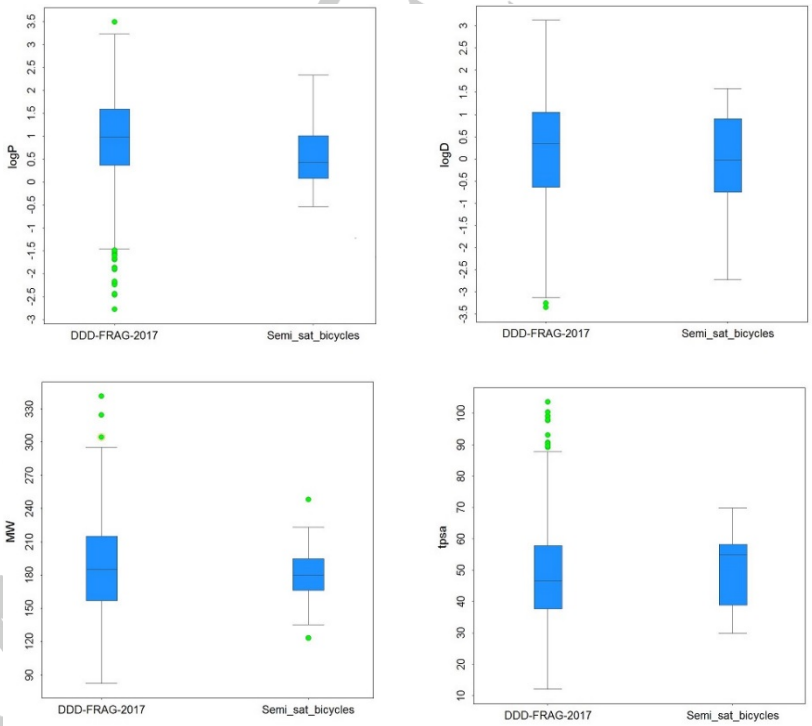


Scheme 6. General flow synthesis of fragment **43** and **44.**

Before adding fragments to our library, it was essential to run a quality control (QC) process, which has been extensively discussed elsewhere, to evaluate their purity, stability, solubility and tendency to aggregate.[6a][25] Following this analysis, compound **32, 26** and **36** were discarded, since they failed QC due to aggregation, stability and solubility issues, respectively.

Conclusions

In conclusion, we have developed the synthesis of a set of quality fragments with optimal physicochemical properties (figure 3) by using flow-based technology. The H-cube Pro was initially employed to partially hydrogenate fully aromatic systems (**1**-**17**) to yield semi-saturated bicyclic fragments (**18**-**33**), which represents a rapid strategy to access novel chemical space by increasing the sp^3 content. Next, we showed how possible functionalization (**35**-**44**) can be introduced by exploiting a simple variety of reactions in a second flow reactor (Vapourtec RS 200), underlining the opportunity for multi-step synthesis of semi-saturated small molecules.[26] These preliminary results demonstrate this strategy would be applicable to many other commercially available bicyclic heterocycles in order to support FBDD programs at various stages including enriching fragment libraries with optimal small molecules and efficiently facilitating hit optimization, and to deliver useful synthetic intermediates.



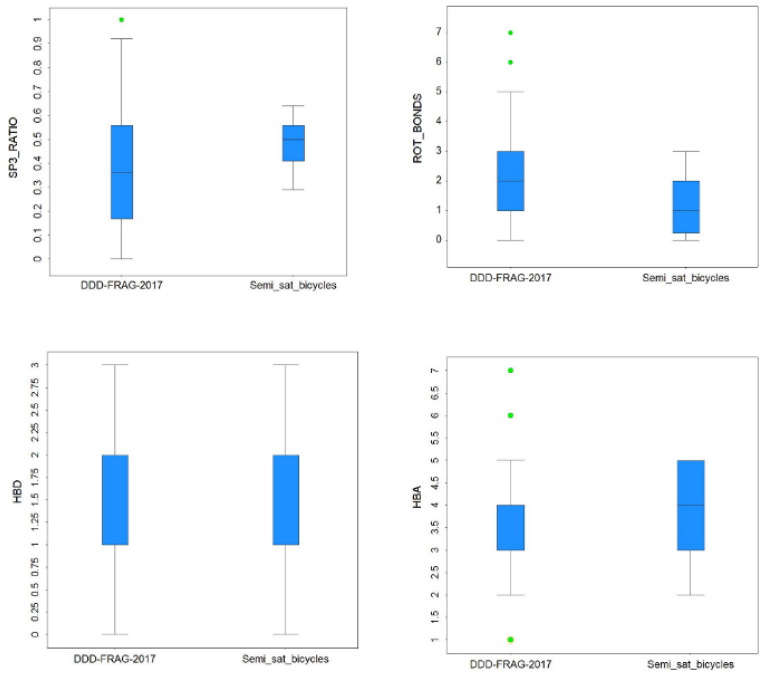


Figure 3. Box plots outlining the main physicochemical properties of fragments described in this work (Semi_sat_bicycles) against those of the DDU's fragment library (DDD-FRAG-2017).

Experimental procedure

General: Chemicals and solvents were purchased from Aldrich Chemical Co., Acros, TCI, and Fluorochem. Room temperature (rt) refers to ambient temperature. Temperatures of 0 °C were maintained using an ice-water bath. Temperatures below 0 °C were maintained using an acetone-cardice bath. Yields refer to chromatographically and spectroscopically pure compounds. Analytical thin-layer chromatograph (TLC) was performed on precoated TLC plates (layer 0.20 mm silica gel 60 with fluorescent indicated UV254, from Merck). Developed plates were air-dried and analyzed under a UV lamp (UV 254/365 nm) or sprayed with a potassium permanganate solution to visualize oxidizable substances. Flash column chromatography was performed using prepacked silica gel catridge (230–400 mesh, 40– 63 µm, from SiliCycle) using a Teledyne ISCO Combiflash Companion or Combiflash Retrieve. ^{1}H and ^{13}C NMR spectra were recorded either on a Bruker ARX-400 spectrometer (400 and 100 MHz for ^{1}H and ^{13}C NMR, respectively) or ARX-500 spectrometer (500 and 125 MHz for ^{1}H and ^{13}C NMR, respectively). Chemical shifts (δ) are reported in ppm relative to the residual solvent peak as internal reference and coupling constants (J) are reported in hertz (Hz). Data are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, integration. LC–MS analyses were performed with either an Agilent HPLC 1100 series connected to a Bruker Daltonics MicrOTOF. LC–MS chromatographic separations were conducted with a Waters XBridge C18 column, 50 mm × 2.1 mm, 3.5 µm particle size; mobile phase, water–acetonitrile mixture with 0.1% formic acid, or water–acetonitrile mixture with 0.1% ammonia; linear gradient from 80:20 to 5:95 over 6.0 minutes; flow rate of 0.5 mL min–1. High resolution electrospray measurements were performed on a Bruker Daltonics MicrOTOF mass spectrometer. HPLC purification was conducted using Waters AutoPurification System with 3100 Mass Detector, with the column used either Waters XBridge C18 preparative OBD column, 19 mm × 100 mm, 5 µm particle size, or Waters XSelect CSH C18 preparative OBD column, 19 mm × 100 mm, 5 µm particle size.

Partial hydrogenation in the H-cube. General procedure: A mixture of a 0.05 M solution of starting material in the appropriate solvent was pumped through the H-Cube Pro flow hydrogenator using CatCart (70 mm). The conversion was monitored by HPLC-UV/Vis analysis at 190 nm. After the continuous-flow hydrogenation, the solvents were removed under reduced pressure and the crude was purified either by isolute SCX-2 column eluting with a 2N solution of NH_3 in MeOH/ PE-AX column

eluting with a 1N HCl solution in water and MeCN or by flash chromatography. Then, volatiles were removed in vacuo to yield the desired semi-saturated bicyclic product.

methyl 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-b]pyridine-6-carboxylate (18): 1 (200mg, 1.105mmol) in EtOH (18ml), water (4ml) and AcOH (0.08ml), 10 % Pd/C cartridge, 100 bar H_2, 100° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield **18** (203mg, 1.093mmol, 99%) as a pale yellow solid. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.09 (s, 1H), 3.72 (s, 3H), 3.38 (d, *J* = 12.0 Hz, 2H), 3.16 (dd, *J* = 8.0, 12.2 Hz, 1H), 2.97 - 2.91 (m, 3H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 172.5, 124.8, 49.6, 43.6, 37.6, 21.6; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{11}N_3O_2$: 182.0924, found: 182.0932.

N-(4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b]pyridin-5-yl)acetamide (19): 2 (200mg, 1.11mmol) in EtOH (18ml), water (4ml) and AcOH (0.08ml), 10 % Pd/C cartridge, 50 bar H_2, 50° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield **19** (204mg, 1.10mmol, 99%) as a white solid.**^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.20 (s, 1H), 4.15 (ddd, *J* = 2.8, 6.9, 12.3 Hz, 1H), 4.18-4.12 (m, 1H), 3.10 (dd, *J* = 7.2, 11.6 Hz, 1H), 2.82 (dd, *J* = 5.3, 15.2 Hz, 1H), 2.53 (dd, *J* = 6.8, 15.2 Hz, 1H), 1.94 (s, 3H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 171.5, 152.3, 127.4, 99.04, 45.8, 44.1, 24.8, 21.2; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{12}N_4O$: 181.1084, found: 181.1102.

1,2,3,4-tetrahydroquinolin-5-ol (20): 3 (200mg, 1.34mmol) in EtOH (22ml), water (5ml) and AcOH (0.1ml), RaNi cartridge, 8 bar H_2, 25° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield **20** (199mg, 1.30mmol, 97%) as a yellow solid. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 6.71 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.10 - 6.05 (m, 2H), 3.16 (t, *J* = 5.4 Hz, 2H), 2.61 (t, *J* = 6.6 Hz, 2H), 1.93 - 1.85 (m, 2H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 155.0, 146.1, 126.0, 108.9, 106.6, 103.6, 41.1, 21.8, 20.3; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{11}NO$: 150.0913, found: 150.0922.

1,2,3,4-tetrahydroisoquinolin-6-amine (21): 4 (200mg, 1.35mmol) in EtOH (22ml), water (5ml) and AcOH (0.2ml), 10 % Pd/C cartridges, 70 bar H_2, 70° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield **21** (203mg, 1.33mmol, 99%) as a pale yellow solid. **^{1}H-NMR** (500 MHz, MeOD-d_4): δ 6.78 (d, *J*=8.1 Hz, 1H), 6.54 (dd, *J*=2.3, 8.1 Hz, 1H), 6.49 (d, *J*=2.3 Hz, 1H), 3.83 (s, 2H), 3.03 (t, *J*=6.0 Hz, 2H), 2.73 (t, *J*=6.0 Hz, 2H); **^{13}C NMR** (125 MHz, MeOD-d_4): δ 145.3, 134.6, 126.6, 124.4, 115.4, 113.8, 46.6, 43.1, 28.0; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{11}N_3O_2$: 149.1075, found: 149.1073.

4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (22): 5 (200mg, 1.62mmol) in EtOH (25ml), water (7ml) and AcOH (0.12ml), 10 % Pd/C cartridge, 100 bar H_2, 100° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield **22** (204mg, 1.60mmol, 99%) as a white solid.**^{1}H-NMR** (500 MHz, MeOD-d_4): δ 7.35 (s, 1H), 3.90 (s, 2H), 3.01 (t, *J* = 5.9 Hz, 2H), 2.64 (t, *J* = 5.9 Hz, 2H); **^{13}C NMR** (125 MHz, MeOD-d_4): δ 144.0, 127.4, 112.6, 43.1, 42.0, 20.5; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_6H_9N_3$: 124.0869, found: 124.0863.

5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-6-carboxylic acid (23): 6 (200mg, 1.20mmol) in EtOH (20ml), water (4ml) and 1M NaOH aq.sol. (1.2ml), 10 % Pd/C cartridge, 60 bar H_2, 60° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield **23** (202mg, 1.18mmol, 99%) as a white solid. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 8.37 (s, 1H), 4.27 (dd, *J* = 5.5, 12.6 Hz, 1H), 4.20 (dd, *J* = 8.1, 12.6 Hz, 1H), 3.04 (qd, *J* = 5.7, 11.5 Hz, 1H), 2.93 - 2.77 (m, 2H), 2.32 - 2.24 (m, 1H), 2.16 - 2.05 (m, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 173.0, 151.5, 143.5, 45.4, 21.6, 21.5, 19.4; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_7H_9N_3O_2$: 168.0768, found: 168.0770.

5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-5-carboxylic acid (24). 7 (200mg, 1.21mmol) in EtOH (20ml), water (4ml) and NaOH (1.2ml), 10 % Pd/C cartridge, 50 bar H_2, 50° C, 1 mL min^{-1} flow rate. Purification by isolute PE-AX column to yield **24** (202mg, 1.19mmol, 99%) as a white solid. **^{1}H-NMR** (500 MHz, DMSO-d_6) δ 14.08 (s, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 2.1 Hz, 1H), 5.21 (dd, *J* = 4.9, 4.9 Hz, 1H), 3.11 (ddd, *J* = 4.0, 5.7, 17.9 Hz, 1H), 3.04 - 2.95 (m, 1H), 2.30 - 2.26 (m, 2H), 2.03 - 1.96 (m, 1H), 1.76 - 1.65 (m, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 170.8, 163.4, 145.0, 122.6, 118.4, 57.6, 25.1, 21.2, 16.3; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{10}N_2O_2$: 167.0815, found: 167.0817.

ethyl 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-carboxylate (25): 8 (200mg, 1.03mmol) in EtOH (16ml) and water (4ml), 10 % Pd/C cartridge, 100 bar H_2, 100° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield **25** (202mg, 1.02mmol, 99%) as a pale yellow oil. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.80 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 3.04 (t, *J* = 6.4 Hz, 2H), 2.09 - 2.01 (m, 2H), 1.93 - 1.85 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 163.7, 144.0, 144.2, 110.2, 59.6, 22.6, 22.3, 19.0, 13.3; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{10}H_{14}N_2O_2$: 195.1128, found: 195.1138.

methyl 5,6,7,8-tetrahydroindolizine-7-carboxylate (26): 9 (200mg, 1.15mmol) in EtOH (18ml), water (5ml), RaNi cartridge, 4 bar H_2, 25° C, 1 mL min^{-1} flow rate. Purification by flash chromatography (EtOAc/Heptane, 15:85) to yield **26** (149mg, 0.83mmol, 73%) as a colourless oil. **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 6.55 (dd, *J* = 1.7, 1.7 Hz, 1H), 6.16 (dd, *J* = 3.1, 3.1 Hz, 1H), 5.89 (br, 1H), 4.12 (ddd, *J* = 3.3, 5.4, 12.3 Hz, 1H), 3.93 (dt, *J* = 4.7, 11.8 Hz, 1H), 3.76 (s, 3H), 3.16 (dd, *J* = 5.0, 15.7 Hz, 1H), 2.93 (dd, *J* = 11.2, 15.8 Hz, 1H), 2.84 - 2.76 (m, 1H), 2.36 - 2.29 (m, 1H), 2.15 - 2.05 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.6, 127.1, 118.7, 108.1, 104.6, 51.9, 44.2, 38.6, 26.5, 26.1; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_7H_9N_3$: 180.1019, found: 180.1023.

N-(1,2,3,4-tetrahydroquinoxalin-6-yl)acetamide (27): 10 (200mg, 1.047mmol) in EtOH (16ml), water (4ml) and AcOH (0.18ml), 10 % Pd/C cartridge, 70 bar H_2, 70° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield to yield **27** (202mg, 1.036mmol, 99%) as a yellow oil. **^{1}H-NMR** (500 MHz, DMSO-d_6): δ 9.32 (s, 1H), 6.70 (d, *J* = 2.3 Hz, 1H), 6.48 (dd, *J* = 2.3, 8.2 Hz, 1H), 6.24 (d, *J* = 8.2 Hz, 1H), 5.38 (s, 1H), 5.06 (s, 1H), 3.19 - 3.13 (m, 4H), 1.93 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 167.4, 134.5, 130.5, 130.3, 113.5, 108.8, 105.9, 40.9, 40.8, 24.2; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{10}H_{13}N_3O$: 192.1131, found: 192.1146.

ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-2-carboxylate (28): 11 (200mg, 1.025mmol) in EtOH (16ml), water (4ml) and AcOH (0.08ml), 10% Pd/C cartridge, 70 bar H_2, 70° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield **28** (202mg, 1.015mmol, 99%) as a pale yellow solid. **^{1}H-NMR** (500 MHz, MeOD-d_4): δ 7.69 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.06 (t, *J* = 5.6 Hz, 2H), 3.99 (s, 2H), 3.21 (t, *J* = 5.6 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, MeOD-d_4): δ 164.3, 145.7, 132.6, 126.4, 61.5, 46.3, 44.6, 43.3, 14.8; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{13}N_3O_2$: 196.1081, found: 196.1100.

1,2,3,4-tetrahydropyrido[3,4-b]pyrazine (29): 12 (200mg, 1.48mmol) in EtOH (24ml), water (6ml), 10 % Pd/C cartridge, 15 bar H_2, 25° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield d **29** (204mg, 1.46mmol, 99%) as a pale yellow solid. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.50 (d, *J* = 5.9 Hz, 1H), 7.49 (s, 1H), 6.43 (d, *J* = 5.9 Hz, 1H), 3.44 (t, *J* = 4.7 Hz, 2H), 3.27 (t, *J* =4.7 Hz, 2H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 142.3, 138.7, 131.9, 130.0, 106.8, 40.3, 39.0; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_7H_9N_3$: 136.0869, found: 136.0868.

methyl 4,5,6,7-tetrahydro-1H-indazole-5-carboxylate (30): 13 (200mg, 1.11mmol) in EtOH (18ml), EtOAc (5ml), 10 % Pd/C cartridge, 100 bar H_2, 150° C, 1 mL min^{-1} flow rate. Purification by flash chromatography (EtOAc/Heptane, 55:45) to yield **30** (174mg, 0.93mmol, 84%) as a white solid. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.31 (s, 1H), 3.70 (s, 3H), 2.88 - 2.64 (m, 5H), 2.24 - 2.17 (m, 1H), 1.95 - 1.83 (m, 1H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 175.8, 142.8, 130.8, 113.0, 50.8, 40.1, 25.6, 22.8, 20.5; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{12}N_2O_2$: 181.0972, fund: 181.0994.

methyl 4,5,6,7-tetrahydro-1H-benzo[d]imidazole-5-carboxylate (31): 14 (200mg, 1.11mmol) in EtOH (18ml), EtOAc (5ml), 10 % Pd/C cartridge, 100 bar H_2, 150° C, 1 mL min^{-1} flow rate. Purification by flash chromatography (EtOAc/Heptane, 55:45) to yield **31** (176mg, 0.95mmol, 86%) as a white solid. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.53 (s, 1H), 3.72 (s, 3H), 2.88 - 2.80 (m, 3H), 2.68 - 2.61 (m, 2H), 2.25 - 2.18 (m, 1H), 1.96 - 1.89 (m, 1H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 175.5, 133.4, 128.0, 50.9, 39.9, 25.7, 24.6, 20.6; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{12}N_2O_2$: 181.0972, found: 181.0995.

methyl indoline-7-carboxylate (32): 15 (500mg, 1.13mmol) in EtOH (18ml), water (5ml) and AcOH (0.08ml), RaNi cartridge, 100 bar H_2, 100° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield **32** (196mg, 1.084mmol, 96%) as a pale yellow solid. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 0.8, 8.1 Hz, 1H), 7.16 (ddt, *J* = 1.1, 3.1, 3.5 Hz, 1H), 6.55 (dd, *J* = 7.1, 8.0 Hz, 1H), 6.07 - 6.07 (m, 1H), 3.86 (s, 3H), 3.71 (t, *J* = 8.5 Hz, 2H), 3.05 (t, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.1, 154.5, 130.9, 128.4, 127.8, 116.0, 107.8, 51.4, 46.8, 28.5; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{10}H_{11}N_1O_2$: 178.0863, found: 178.0880.

5,6,7,8-tetrahydroimidazo[1,2-b]pyridazine (33): 16 (200mg, 1.62mmol) in EtOH (25ml), water (7ml) and AcOH (0.11ml), 10 % Pd/C cartridge, 100 bar H_2, 100° C, 1 mL min^{-1} flow rate. Purification by isolute SCX-2 column to yield **33** (202mg, 1.59mmol, 98%) as a reddish solid. **^{1}H-NMR** (500 MHz, MeOD-d_4): δ 6.90 (d, *J* = 1.4 Hz, 1H), 6.78 (d, *J* = 1.4 Hz, 1H), 3.23 (td, *J* = 2.7, 5.4 Hz, 2H), 2.87 (t, *J* = 6.9 Hz, 2H), 2.01 - 1.95 (m, 2H); **^{13}C NMR** (125 MHz, MeOD-d_4): δ 139.6, 123.5, 116.8, 45.1, 21.6, 21.2; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{11}N_3O_2$: 124.0869, found: 124.0862.

Fragment functionalization in the Vapourtec RS-200. General procedure: A solution of staring material was injected in the reagent loop A of the Vapourtec RS-200. A solution of the reagent/s was injected in the reagent loop B. The two mixtures (A and B) were joined together and pumped with an appropriate anhydrous solvent (THF or MeOH) into a 10 ml PTFE coil reactor, equipped with a back pressure regulator, where the reaction took place. The collected material was concentrated in vacuo and purified by flash chromatography. The desired fractions were concentrated to dryness to afford the desired product.

1-(5-hydroxy-3,4-dihydroquinolin-1(2H)-yl)ethan-1-one (35): 20 (20mg, 0.134mmol) in THF:DMF (1:1) (2ml) and DIPEA (0.025ml, 0.147mmol) injected in the reagent loop A. Acyl chloride (0.0096ml, 0.134mmol) in THF (2ml) injected in the reagent loop B. 10 bar, 40° C, 0.5 mlL min^{-1}. Purification by flash chromatography (MeOH/DCM 7:93) to yield **35** (24mg, 0.124mmol, 93%) as a white solid. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.00 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.77 (s, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 3.74 (t, *J* = 6.1 Hz, 2H), 2.69 (t, *J* = 6.9 Hz, 2H), 2.20 (s, 3H), 1.97 - 1.88 (m, 2H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 171.1, 154.9, 139.9, 125.5, 119.2, 115.7, 111.3, 42.7, 23.1, 21.7, 20.1; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{11}H_{13}NO_2$: 192.1019, found: 192.1036.

1-(7,8-dihydroimidazo[1,2-b]pyridazin-5(6H)-yl)ethan-1-one (36): 33 (20mg, 0.16mmol) in THF:DMF (1:1) (2ml) and DIPEA (0.031ml, 0.178mmol) injected in the reagent loop A. Acyl chloride (0.013ml, 0.178mmol) in THF (2ml) injected in the reagent loop B. 10 bar, 40° C, 0.5 mlL min^{-1}. Purification by flash chromatography (MeOH/DCM 6:94) to yield **36** (19mg, 0.115mmol, 71%) as a white solid. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.33 (s, 1H), 6.90 (s, 1H), 3.93 (t, *J* = 4.1 Hz, 2H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.22 (s, 3H), 2.14 - 2.06 (m, 2H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 123.9, 118.6, 20.9, 20.7, 19.8; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{11}N_3O_2$: 166.0977, found: 166.0975.

1-(methylsulfonyl)-1,2,3,4-tetrahydropyrido[3,4-b]pyrazine (37): 29 (20mg, 0.148mmol) in DMF (2ml) and DIPEA (0.028ml, 0.162mmol) injected in the reagent loop A. Methanesulfonyl chloride (0.011ml, 0.148mmol) in DMF (2ml) injected in the reagent loop B. 10 bar, 40° C, 0.5 mlL min^{-1}. Purification by flash chromatography eluting (EtOAc/heptane 58:42) to yield **37** (28mg, 0.133mmol, 90%) as a pale yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.82 (d, *J* = 5.5 Hz, 1H), 7.40 (d, *J* = 5.5 Hz, 1H), 4.28 (s, 1H), 3.79 (t, *J* = 4.9 Hz, 2H), 3.42 (t, *J* = 4.9 Hz, 2H), 2.91 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 139.4, 137.5, 132.8, 129.6, 115.3, 74.7, 44.1, 40.2, 39.1; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{11}N_3O_2S$: 214.0645, found: 214.0662.

6-(methylsulfonyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine (38): 22 (20mg, 0.162mmol) in DMF:THF (1:1) (2ml) and DIPEA (0.031ml, 0.178mmol) injected in the reagent loop A.

Methanesulfonyl chloride (0.014ml, 0.178mmol) in THF (2ml) injected in the reagent loop B. 10 bar, 40° C, 0.5 mlL min^{-1}. Purification by flash chromatography eluting (EtOAc/heptane 55:45) to yield **38** (29mg, 0.146mmol, 90%) as a white solid. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.44 (s, 1H), 4.41 (s, 2H), 3.52 (t, *J* = 5.8 Hz, 2H), 2.89 (s, 3H), 2.75 (t, *J* = 5.8 Hz, 2H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 142.3, 127.8, 112.2, 43.9, 43.3, 34.9, 20.5; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_7H_{11}N_3O_2S$: 202.0645, found: 202.0647.

tert-butyl 6-amino-3,4-dihydroisoquinoline-2(1H)-carboxylate (39): **21** (20mg, 0.135mmol) in DMF:THF (1:1) (2ml) and DIPEA (0.025ml, 0.135mmol) injected in the reagent loop A. Boc anhydride (30mg, 0.178mmol) in THF (2ml) injected in the reagent loop B. 10 bar, 40° C0.5 mlL min^{-1}. Purification by flash chromatography (EtOAc/Heptane 45:55) to yield **39** (30mg, 0.122mmol, 91%) as a pale yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.87 (d, *J* = 8.1 Hz, 1H), 6.52 (dd, *J* = 2.0, 8.1 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 4.45 (s, 2H), 3.68 - 3.53 (m, 4H), 2.72 (t, *J* = 5.8 Hz, 2H), 1.48 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.9, 144.8, 135.7, 127.1, 123.7, 114.7, 113.5, 79.5, 45.1, 41.2, 29.1, 28.5; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{14}H_{20}N_2O_2$: 249.1598, found: 249.1617.

tert-butyl 1,4,5,7-tetrahydro-6H-pyrazolo[3,4-c]pyridine-6-carboxylate (40): 22 (20mg, 0.162mmol) in DMF:THF (1:1) (2ml) and DIPEA (0.031ml, 0.178mmol) injected in the reagent loop A. Boc anhydride (39mg, 0.178mmol) in THF (2ml) injected in the reagent loop B. 10 bar, 40° C, 0.5 mlL min-1. Purification by flash chromatography (EtOAc/Heptane 45:55) to yield **40** (32mg, 0.144mmol, 89%) as a white solid.**^{1}H-NMR** (400 MHz, $CDCl_3$): δ 11.00 (s, 1H), 7.35 (s, 1H), 4.62 (s, 2H), 3.67 (t, *J* = 5.6 Hz, 2H), 2.66 (t, *J* = 5.6 Hz, 2H), 1.50 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.12, 113.61, 80.02, 42.57, 41.76, 28.45, 20.82; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{11}H_{17}N_3O_2$: 224.1394, found: 224.1396.

methyl 4-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-b]pyridine-6-carboxylate (41): 18 (20mg, 0.11mmol), formaldehyde (37 wt. %in water, 0.027ml, 0.33mmol), acetic acid (0.063ml, 1.10mmol) in MeOH (2ml) injected in the reagent loop A. 2-picoline-borane complex (11mg, 0.102mmol) in MeOH (2ml) injected in the reagent loop B. 10 bar, 25° C, 0.5 mlL min^{-1}. Purification by flash chromatography (MeOH/DCM 6:94) to yield **41** (19mg, 0.095mmol, 93%) as a white solid. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.10 (s, 1H), 3.71 (s, 3H), 3.17 - 3.05 (m, 2H), 2.93 - 2.87 (m, 3H), 2.65 (s, 3H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 173.7, 136.2, 132.1, 113.2, 53.7, 51.1, 40.8, 39.2, 22.7; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{13}N_3O_2$: 196.1081, found: 196.1102.

ethyl 7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-2-carboxylate (42): 28 (20mg, 0.102mmol), formaldehyde (37 wt. %in water, 0.025ml, 0.31mmol), acetic acid (0.058ml, 1.02mmol) in MeOH (2ml) injected in the reagent loop A. 2-picoline-borane complex (12mg, 0.101mmol) in MeOH (2ml) injected in the reagent loop B. 10 bar, 25° C, 0.5 mlL min^{-1}. Purification by flash chromatography (MeOH/DCM 8:92) to yield **42** (20mg, 0.095mmol, 94%) as a colourless oil. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.71 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.11 (t, *J* = 5.5 Hz, 2H), 3.64 (s, 2H), 2.90 (t, *J* = 5.5 Hz, 2H), 2.50 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 162.7, 144.1, 131.7, 124.6, 60.0, 52.3, 50.8, 44.1, 43.9, 13.3; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_{10}H_{15}N_3O_2$: 210.1238, found: 210.1263.

N-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-b]pyridine-6-carboxamide (43): 18 (20mg, 0.11mmol) in THF (2ml) injected in the reagent loop A. DABAL-$M3_3$ (22mg, 0.088mmol) and methylamine (2M in THF) (0.11ml, 0.22mmol) in THF (2ml) injected in the reagent loop B. 50 bar, 130° C, 0.5 mlL min^{-1}. The collected material was quenched with $NaHCO_3$ and purified by flash chromatography (MeOH/DCM 20:80) to yield **43** (5.6mg, 0.031mmol, 28%) as a white solid. **^{1}H-NMR** (400 MHz, MeOD-d_4): δ 7.10 (s, 1H), 3.28 (dd, *J* = 3.1, 12.0 Hz, 1H), 3.07 (dd, *J* = 10.2, 12.0 Hz, 1H), 2.90 - 2.87 (m, 2H), 2.75 (s, 3H), 2.73 - 2.64 (m, 1H); **^{13}C NMR** (100 MHz, MeOD-d_4): δ 175.3, 126.2, 45.8, 40.5, 24.9, 23.9; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_8H_{12}N_4O$: 181.1084, found: 181.1089.

N-methyl-4,5,6,7-tetrahydro-1H-indazole-5-carboxamide (44): 30 (20mg, 0.11mmol) in THF (2ml) injected in the reagent loop A. DABAL-$M3_3$ (22mg, 0.088mmol) and methylamine (2M in THF) (0.11ml, 0.22mmol) in THF (2ml) injected in the reagent loop B. 10 bar, 130° C, 0.5 mlL min^{-1}. The collected material was quenched with $NaHCO_3$ and purified by flash chromatography (EtOAc/Heptane 65:45) to yield **44** (6.3mg, 0.035mmol, 32%) as a white solid. **^{1}H-NMR** (125 MHz, MeOD-d_4): δ 7.30 (s, 1H), 2.83 - 2.60 (m, 6H), 2.55 - 2.46 (m, 1H), 2.12 - 2.03 (m, 1H), 1.92 - 1.82 (m, 1H); **^{13}C NMR** (125 MHz, MeOD-d_4): δ 177.4, 113.3, 42.1, 29.3, 26.5, 24.9, 23.4, 20.9; **HRMS** (ESI): $[M+H]^+$ calcd. for $C_9H_{13}N_3O$: 180.1132, found: 180.1139.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Flow reactions • hydrogenation • drug discovery • heterocycles • fused-ring systems

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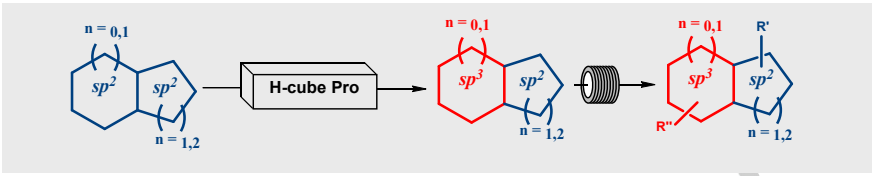

Key topic* Semi-saturated fragments

*Nicola Luise, Eleanor W. Wyatt, Gary J. Tarver and Paul G. Wyatt**

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A continuous flow strategy to readily synthesis and elaboration semi-saturated heterobicyclic fragments

Hydrogenation under continuous flow conditions was employed to deliver semi-saturated fragments, presenting ideal physicochemical properties and characterized by key motifs for both their synthetic elaboration and binding to biological targets. Their facile functionalization, in continuous flow, represents a valid opportunity for the multi-step synthesis of functionalized sp^3-rich fragments.