The application of flow microreactors to the preparation of a family of casein kinase I inhibitors†‡

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In this article we demonstrate how a combination of enabling technologies such as flow synthesis, solid-supported reagents and scavenging resins utilised under fully automated software control can assist in typical medicinal chemistry programmes. In particular automated continuous flow methods have greatly assisted in the optimisation of reaction conditions and facilitated scale up operations involving hazardous chemical materials. Overall a collection of twenty diverse analogues of a casein kinase I inhibitor has been synthesised by changing three principle binding vectors.

Introduction

Our greater understanding of the Human Genome and consequently the potential therapeutic targets available for modulation, has altered the way pharmaceutical research is conducted. The past practices involving opportunistic screening of vast compound libraries against many different targets in order to identify a hit compound has been supplemented by a more directed approach. Modern drug discovery tends to be a more iterative process which usually begins with a target orientated design phase and then proceeds to the synthesis of a small focused compound collection followed by biological evaluation.[1] The results and observations of these initial assays generate primary information concerning potency, selectivity, pharmacokinetic properties and other parameters which are reincorporated into the design loop to further the optimisation process (Fig. 1). As a result improving any step of the sequence immediately reduces the overall development time in this closed loop approach to drug discovery.[2]

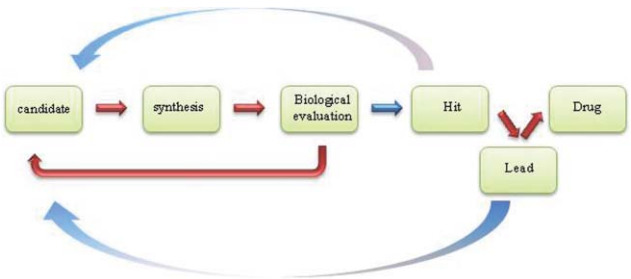

Fig. 1 The iterative cyclic drug design.

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While many high-throughput screening methods, computational modelling techniques and predictive software packages exist and have greatly aided medicinal discovery, the synthesis component can still sometimes constitute a significant bottle neck. Consequently, new thinking and alternative approaches for molecular assembly are required. Of these new enabling technologies continuous processing using chemical microreactors is proving to be particularly attractive.[3] While many groups have entered the area, few have addressed the key synthetic challenges in particular how to perform scalable multistep sequences capable of delivering clean product streams using direct in-line purification methods.

Here we show how some of the procedures and concepts developed in our laboratories[4] to solve these problems, can be applied to a particular medicinal chemistry programme.

The epsilon/delta isoforms of casein kinase I were chosen as a target enzyme since this Ser-Thr kinase is considered to be important in molecular pathways that regulate the circadian rhythm in mammalian systems.[5] Although the biology of the body's master clock is not fully understood at a molecular level, many groups are evaluating new medicinal agents which can selectively regulate epsilon/delta isoforms of this ubiquitous enzyme.[5–7] Such compounds could find application in a variety of treatments from sleep modulation to regulation of several mood disorders.[8] In this regard a particular class of substituted imidazo[1,2-*b*]pyridazine structures (Fig. 2) has recently been reported by Sanofi-Aventis as an inhibitor of casein kinase I-ε.[9] We considered that the preparation of analogues of this new therapeutic class of heterocyclic structure would provide an excellent opportunity to illustrate a series of automatable flow based chemical processing techniques. Herein, we describe the preparation of a small collection of imidazo[1,2-*b*]pyridazines using flow-assisted chemical processing techniques.

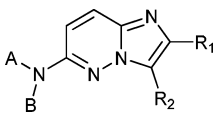
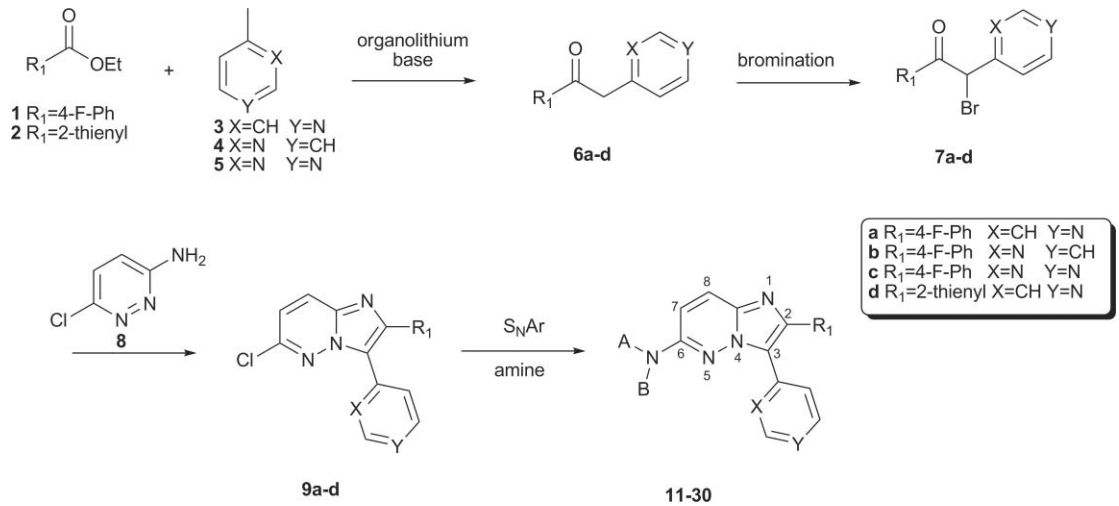


Fig. 2 General template of the imidazo[1,2-*b*]pyridazine core.



Scheme 1 General route to the target molecules.

Results and discussion

The proposed general synthetic route to the target class is shown in Scheme 1. By systematically varying the finger tip substituents at positions 2, 3 and 6 around the core imidazopyridazine structure a collection of twenty representative analogue compounds has been prepared.

Initially reaction scoping and optimisation was conducted on a single derivative (R_1 = 4-fluorobenzene and R_2 = 4-picoline; *N*AB = piperazine **11**) with the information derived from these studies then being applied to the preparation of the additional members of the series. As a consequence the desired common heterocyclic intermediate **9a** was achieved *via* a 3 step sequence involving ketone formation, α-bromination and subsequent condensation with a 3-aminopyridazine **8**. In order to access this key fragment on multigram scale the initial organometallic substitution reaction had to be performed on at least a 50 mmol scale and thereby creating certain inherent handling issues.

Organolithium bases can be problematic at scale due to safety concerns regarding handling of large volumes of these reactive and sensitive reagents. Additionally problems involving the controlled addition of such species over extended periods of time and the opportunity for exothermic reactions leading to uncontrolled heating events can limit their application at scale. Over the past few years our group has pioneered several continuous flow procedures for the scale-up of potentially hazardous reactions.[10] For many of these examples it was necessary to overcome key technological challenges in regard to the reactor design prior to conducting the chemistries of interest. In this new project we defined at least two practical obstacles that needed to be solved early on in the program. Firstly, most reactions involving organolithium reagents must be performed at sub ambient temperatures (typically at temperatures between −78 and 0 °C). As commercially available low-temperature continuous flow reactors are not currently available we first needed to devise a method to maintain the low temperature environment for both the initial reagents and also to moderate the temperature of the chemical transformation itself. Secondly, we knew that the organolithium reagents could not be introduced directly through the high pressure pumps (ceramic heads with Vitron® seals) as this caused their rapid decomposition. Furthermore, temperature control of the precursor reagents would also be difficult over long periods of time. In order to circumvent these issues we devised a prototype "dual sample injection loop" reagent storage and delivery system. Although not optimal it was capable of performing the required task in a highly satisfactory manner.

The design of this new dual sample injection system employed one sample loop to supply the lithium base into the reactor while the second loop was being simultaneously loaded for later injection (Fig. 3). When the first sample loop had been fully injected (calibrated as a function of the sample loop volume and flow rate) the flow stream was immediately switched to engage the second sample loop while the original loop was automatically recharged using a liquid handling robot. This device could then effectively deliver a continuous flow of the organometallic base to the reactor. As organolithium reagents tend to be unstable at ambient temperature the two reagent loops were additionally cooled by submersion in a Dewar flask loaded with an ice/water (LiHMDS) or acetone/dry ice (*n*-BuLi) mixture. In this way even THF solutions of n-butyllithium were found to be quite easily dispensed over several hours of an extended reaction sequence.

Preparation of the first intermediate keto structure could be accomplished following the sequence depicted in Scheme 2. Although in order to simplify the experiment further we found that it was possible to premix the 4-picoline (**3**) with ethyl 4-fluorobenzoate (**1**) and to pump this mixture from a single reagent bottle meeting the LiHMDS solution added *via* the dual-loop system. The reagents were arranged to affect the deprotonation of the picoline (**3**) by combining in a static mixing tee then incubating in a 10 mL coiled flow reactor maintained at 0 °C. This mixture was then progressed through a further 20 mL flow coil warming to ambient temperature at a combined flow rate of 0.25 mL min^{-1} which resulted in an overall 2 h residence time. The reaction between the picolinate and the ester **1** rapidly reached completion in the second stage of the flow reactor. Finally, the product **6a** could be isolated in 94% yield and high purity by direct precipitation of the exiting flow stream into hexane. Employing a

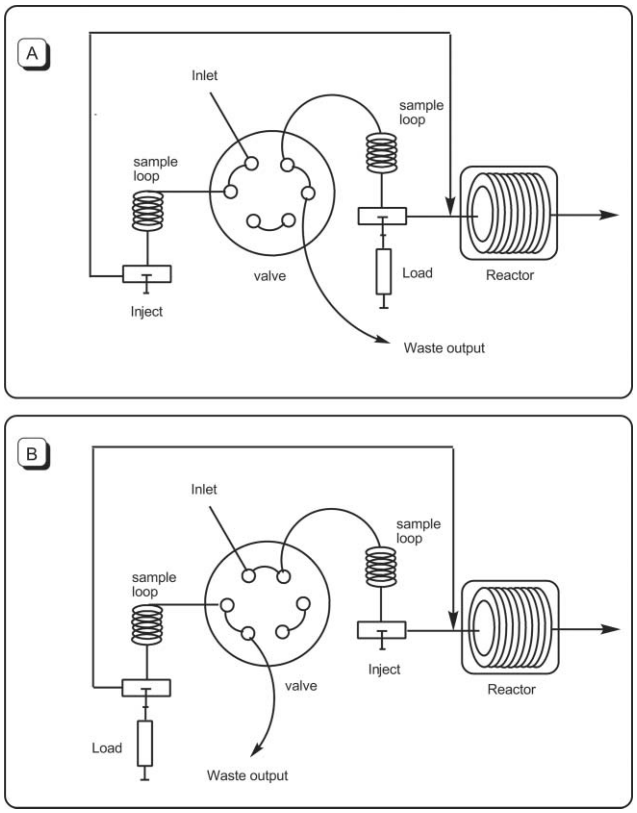
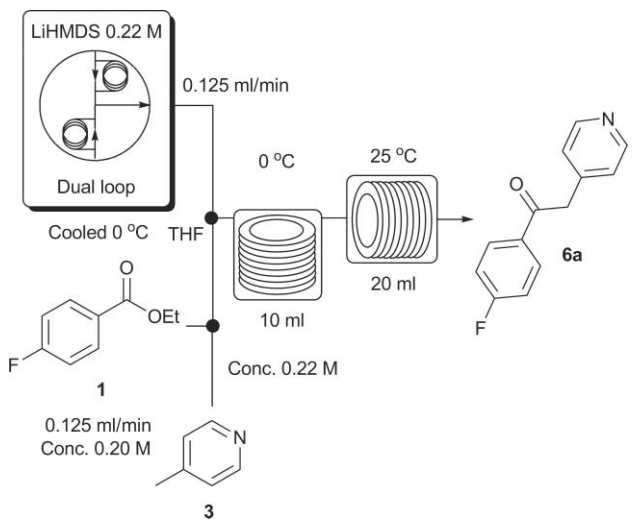


Fig. 3 Integrated continuous feed organometallic dual valve injection system.

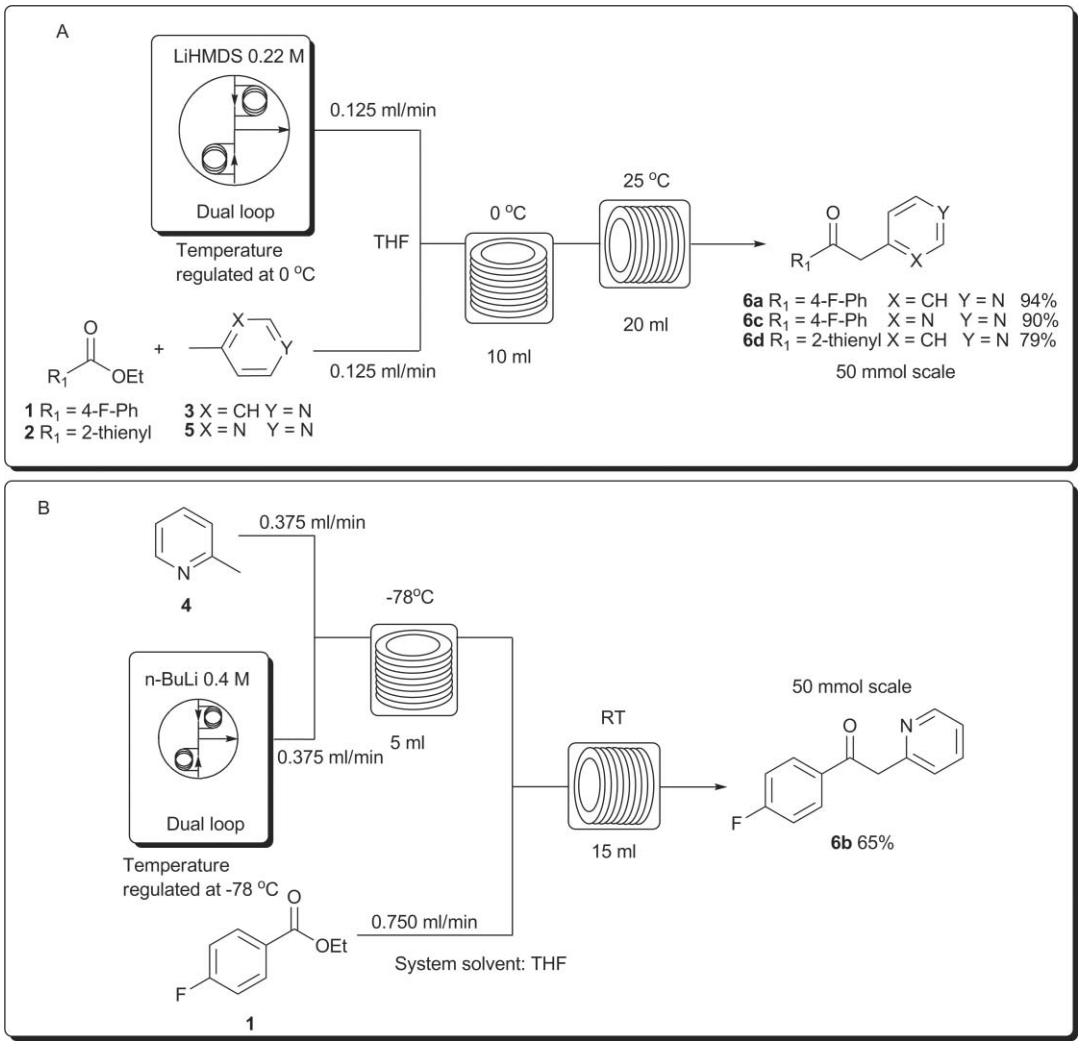


Scheme 2 Organometallic deprotonation and substitution.

flow rate of 0.25 mL min^{-1} a throughput of 1.5 mmol of **6a** could be processed per hour. Doubling the flow rate to 0.5 mL min^{-1} however resulted in a significantly lower isolated yield of only 63%. Alternatively, by increasing the reactor volume to 120 mL and maintaining the same residence time higher quantities of up to 6 mmol h^{-1} of product could be achieved again in excellent yield (>90%).

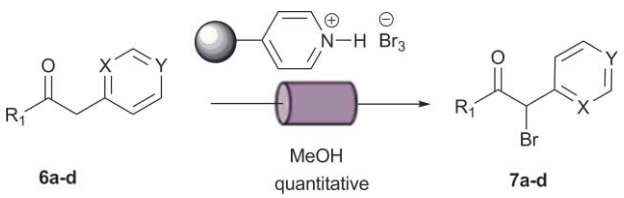
A virtually identical reaction sequence could be used for the preparation of the other 4-picoline analogue **6d** (79%) and 4-methylpyrimidine derivative **6c** (90%; Scheme 3A). However, it was discovered that the 2-picoline substrate **4** could not be fully deprotonated using LiHMDS instead *n*-butyllithium was required. In addition the ester **1** and 2-picoline (**4**) could not be premixed due to the competitive nucleophilic addition of the organolithium into the ester and so we were required to modify the procedure. In accordance with these new requirements *n*-butyllithium and 2-picoline (**4**) were initially brought together at a T-piece and allowed to react in a small 5 mL coiled reactor which was maintained at −78 °C. The resulting anion was then progressed to meet with a second matching stream of the ester **1** in a 15 mL coil reactor held at ambient temperature (Scheme 3B). A series of different calibration experiments were conducted using relationship fixed flow rates for the three different drive pumps in order to produce overall stoichiometic ratios of ester:picoline:*n*-BuLi at 1 : 1.5 : 2. The best results were obtained when *n*-butyllithium was introduced as a 0.4 M solution in THF and pumped at 0.375 mL min^{-1}. At this flow rate the 6.5 min residence time within the first coil reactor (5 mL) was more than adequate to permit the full deprotonation of the picoline under these flow conditions. Again, once optimised a facile scale-up could be achieved using the automated liquid handling procedures controlled by the auxiliary firmware and software driven protocols. These routines were additionally responsible for sequencing washing steps to clean the reactors at the end of the runs as well as determining valve switching times (load/inject of the base) and initiating safe shut down events if unexpected occurrences were encountered. This enabled confident unsupervised running of the reactors over extended periods of time facilitating gram quantity production of these key intermediates.

The second step in the synthesis was the α-bromination of these freshly prepared ketones **6a–d**. Bromine itself is commonly used to effect this transformation; however, due to its high reactivity and oxidising ability it is currently not compatible with many of the standard flow connectors, valve stators and seals generically used. Although we were aware that bromine can be handled in flow system[11] it would have required considerable modification of our apparatus to facilitate which we were reluctant to implement if an easier alternative could be found. Our long standing expertise in the preparation and application of solid-supported reagents[12] led us to experiment with a polymer-bound hydrobromide perbromide species.[13] After some initial experimentation we found that the desired monobrominated product **7a–d** could be attained cleanly in batch using methanol as the solvent at 25 °C and a 30 min reaction time. We were also aware through previous experience that in order to achieve quantitative yields of the α-brominated products the supplied resin required initial priming with a 0.2 M solution of hydrogen bromide in methanol at ambient temperature prior to its use. These batch reaction could then be easily scaled (>50 mmol) using just 1.1 equivalent of the freshly activated resin with the high purity products being readily isolated as the hydrobromide salt following only a simple filtration of the resin and evaporation of the solvent. Our next objective was to adapt these batch protocols to a flow based process. This was achieved by simply packing a glass cartridge with the perbromide resin and flowing a methanolic solution of the ketone through the column. Initially using low flow rates (< 0.25 mL min^{-1}) mixtures of the mono and dibrominated material were isolated. Indeed using very low flow rates only the dibrominated adduct was produced. However, by systematically ramping the flow rate an optimum



Scheme 3 The set-up for deprotonation using A: LiHMDS, B: *n*-BuLi in flow.

residence time of only 30 s gave quantitative conversion of the starting material to the monobrominated ketone albeit requiring a 5 equivalent excess of the resin owing to the fast flow rates used (Scheme 4). This demonstrates another powerful facet of flow based chemical processing where flow rates (residence times) can be tuned to furnish chemoselective reactions.[14]



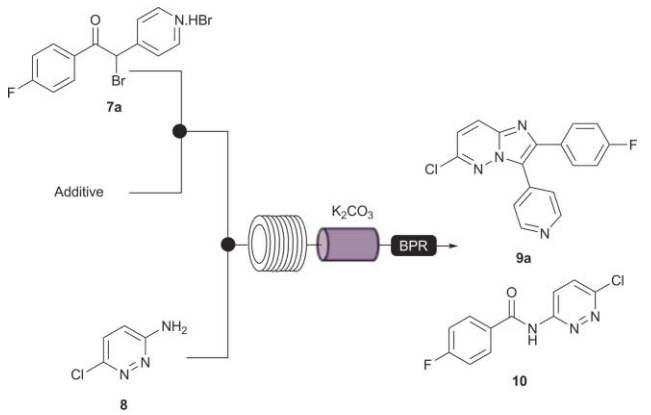
Scheme 4 Flow synthesis of α-bromomoketones.

The third step of the synthesis, the cyclocondensation reaction to generate the imidazopyridazine core has been reported to be both unreliable and low yielding giving only a modest 30%.[9] Furthermore, in the original literature conditions the reaction was performed in ethanol at 90 °C over 5.5 h making it difficult to directly scale without the use of a large pressure reactor.

We believed that the invention of a flow derived approach could offer several advantages. Firstly, it could be used to rapidly optimise the reaction further by quickly screening various reaction parameters such as residence times, temperatures and stoichiometric reagent ratios in an automated and labour-saving manner. Secondly, it could accommodate new improved reaction conditions involving superheated solvent system as these are readily tolerated by the flow chemistry equipment. Finally, the flow approach would enable a more linear and reliable scale-up to larger quantities of these key building blocks.

The Vapourtec R2+/R4 platform[15] was selected to perform the optimisation of the reaction under the control of the Flow Commander software™. A 4-pump R series flow system with an autosampler was employed in which the first two pumps were used to deliver the starting materials while a third pump was used to introduce various additives and catalysts (Table 1). The software allows the user to define a basic set of explorable reaction parameters (such as residence time, temperature, stoichiometery, flow rates, *etc.*) which are used to automatically populate a sequence table as depicted by the screen shot in Fig. 4. Each reaction as well as its defined conditions are readily observed and can be scrolled through on screen as discrete editable

Table 1 The set-up and optimisation conditions for cyclisation in flow



Entry	Ratio[a]	Additive	T/°C	Time/min[b]	**9a** : **10** Ratio[d,e]
1	2	—	120	15	68 : 32
2	3	—	120	15	68 : 32
3	4	—	120	15	68 : 32
4	2	$BF_3{\cdot}Et_2O$	120	15	61 : 39
5	3	$BF_3{\cdot}Et_2O$	120	15	67 : 33
6	4	$BF_3{\cdot}Et_2O$	120	15	70 : 30
7	2	Et_3N	120	15	59 : 41
8	3	Et_3N	120	15	65 : 35
9	4	Et_3N	120	15	69 : 31
10	2	—	110	15	75 : 25
11	2	—	110	20	80 : 20
12	2	—	110	30	83 : 17
13	2	—	120	10	80 : 20
14	2	—	120	20	83 : 17
15[c]	2	—	130	5	81 : 19
16[c]	2	—	130	10	84 : 16
17[c]	2	—	130	15	82 : 18

[a] Ratio **9a** : **10**. [b] Residence time in the reactor. [c] In excess of 20% additional decomposed material was observed. [d] All α-bromoketone was consumed. [e] Calculated by HPLC.

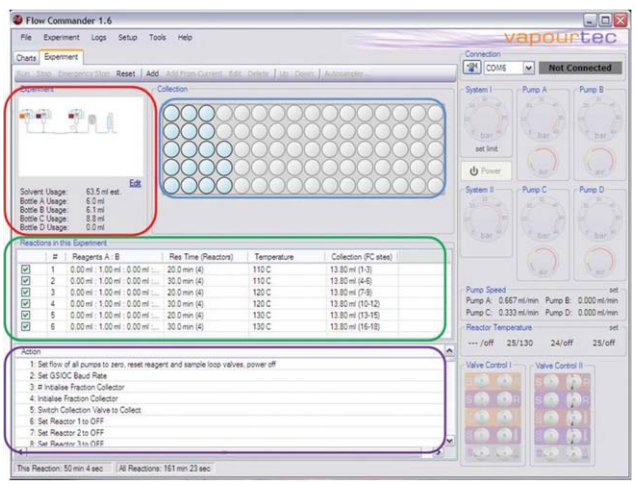


Fig. 4 Screen shot of automatically populated optimisation table: system set-up, fraction collector rack, reaction conditions, action list.

options. The graphical fraction collector simply highlights (colour coded; Cyan–to run, blue–finished) the position of the anticipated product output into a series of vials as laid out in real space ready for analysis.

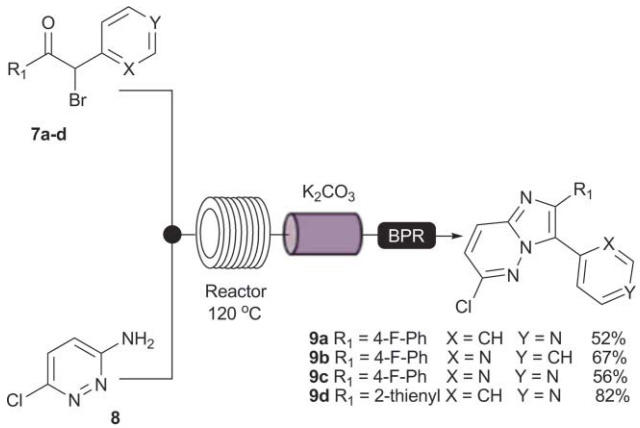
The software can also be used to predict the minimum amount of each reagent needed for the entire run based upon the reactor volume, column units and tubing dimensions. For example, with a proposed 5 mL flow coil reactor in the system, 2 mL of 0.1 M solution of the limiting reagent (bromoketone **7a**) equal to around 74 mg of the material would be necessary. Initial calculations suggested that in order to optimise at least three independent variables (namely, temperature, reaction time and reagent ratios in the presence or absence of an additive such as a Lewis acid or triethylamine) would require around twenty discrete experiments amounting to 1.5 g of the starting material. This is obviously a serious problem when valuable or proprietary starting materials are not readily available. Therefore to circumvent this problem it is necessary to use smaller microfluidic reactors to perform the initial DoE work.[16] Further work directed at addressing this issue is currently underway within our laboratory and will be reported in full shortly. In this current research all reactions were designed using the reaction time-stoichiometric mode of the Flow Commander software which eliminates the need for flow rate calculation. The required reaction time is supplied to the software and the resultant flow rates are calculated based on the machine specification. Table 1 shows the results of these optimisation experiments where all reactions were performed using DMF as the solvent.

Interestingly, the particular α-bromoketone **7a** proved problematic in its reactivity and we were unable to completely suppress the formation of a significant by-product **10**. However, from the table of data, entry 14 showed both high conversion and minimised by-product formation hence these conditions were selected for progressing material forward. It should be highlighted that the evaluation time for the above series of experiments took 14.7 h but required less than 30 min of manual user intervention with the resulting data being collected automatically. This therefore enabled the chemist to perform additional tasks whilst this process was being conducted.

In order to increase the scale of the reaction from the established analytical conditions to multigram quantities (10 mmol) we simply extended the reaction period. Unfortunately, despite an identical and reproducible HPLC indication, the isolated yield for the 4-picoline derivatives **9a** was only 52% following purification. Nevertheless this route provided gram quantities of the common imidazopyridazine intermediate which could then be taken on to the next step. Conducting the same transformation sequence on the other analogues gave improved isolated yields of up to 80% (Scheme 5).

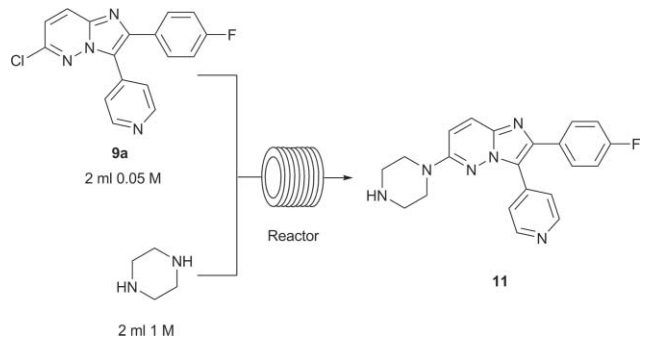
The final preparative step was the introduction of structural diversity by displacement of the chlorine substituent with different amines. Since the flow system was fully equipped with an autosampler/fraction collector unit it was proposed that we attempt to prepare a small collection of substitution products **11–29** in a fully automated fashion.

In the original synthesis of this compound class the substitution reaction was conducted in ethanol at 155 °C over 4 h and delivered only 26% yield for a typical reaction.[9] Flash heating has been shown to improve the overall yield and purity profile of many different transformations especially S_NAr reactions consequently and so we evaluated the influence of temperature on the outcome of the reaction.[17] Table 2 shows the results from a quick temperature and time screen.



Scheme 5 Flow synthesis of the imidazopyridazine cores.

Table 2 The set-up for S_NAr reaction in flow



Entry[a]	T/°C	Time/min[b]	Conversion[c]
1	172	30	46
2	163	60	66
3	177	30	30
4	177	60	95
5	177	100	100

[a] EtOH was used as the solvent. [b] Residence time in the reactor. [c] Conversion calculated by LC-MS.

Although it was immediately apparent that higher temperature and longer reaction times resulted in higher conversions in our system the use of a fixed maximum 250 psi backpressure regulator restricted the highest attainable temperature to 177 °C. At higher temperatures ethanol entered the gas phase leading to non reproducible results.

The conditions in entry 5 (Table 2) were selected to prepare the collection of compounds. The different imidazopyridazine cores **9a–d** and amine coupling partners were each loaded in sequence by the autosampler into corresponding 2 mL sample loops and combined in the reactor (Fig. 5). For each pairing 0.1 mmol of the imidazopyridazine (2 mL of 0.05 M solution) was reacted with 2.0 mL of 1.0 M solution of the amine. In this way a small array of twenty different analogues were prepared in a single experimental run representing variation of the amine, R1 and R2 substituents. The product streams from the reactor were collected (*via* the autosampler) into individual vials and a Biotage V-10[18] was used to remove the solvent and excess volatile amine. In most cases dissolution of the crude materials in dichloromethane and treatment with an isocyanate scavenger resin removed any residual non volatile amine to give the product in high purity following solvent removal. However, for the piperazine containing analogue **11** purification was best achieved by direct re-crystalisation from ethanol. Furthermore, compounds derived from **9c** required NMP as the solvent instead of ethanol due to the solubility of this precursor. Due to its boiling point, NMP could not be removed by the Biotage V10 and so the final compounds **26–30** were purified by a catch & release onto QP-SA a sulfonic acid resin,[19] washing the resin with methanol and releasing the products with an ammonia in methanol solution. The solvent could then be easily removed permitting isolation of the product in high purity after recrystallisation from ethanol. The final imidazopyridazine derivatives **11–30** were generally obtained in excellent purities (>95%) and moderate to good yields (Table 3).

Conclusion

In conclusion, we have demonstrated that flow chemistry methods can facilitate the preparation of medicinally relevant compounds. The programme reported above produced a small collection of inhibitors of casein kinase I using a four step sequence of reactions. The first of these used continuous flow methods to safely scale up a reaction utilizing organometallic bases at low temperature. Also we have shown for the first time the application of a dual loop system which enabled effective pumping of the organometallic reagents in a continuous fashion. The next step in the synthesis was facilitated by application of a solid-supported reagent to avoid using hazardous material and facilitate the reaction work up of the unstable monobrominated product. In the third step we used an automated flow device equipped with appropriate software to quickly optimise the conditions for the reaction which could be used directly on scale to deliver larger quantities of material. In addition an autosampler was used to perform automated S_NAr reactions to give a collection of diversified imidazopyridazine derivatives. Overall the sequence represents several practical and yield improvements over the conventional batch mode approach.

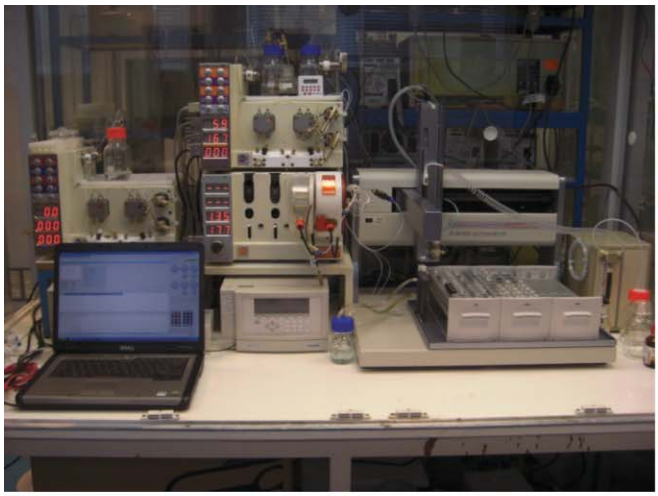
Experimental

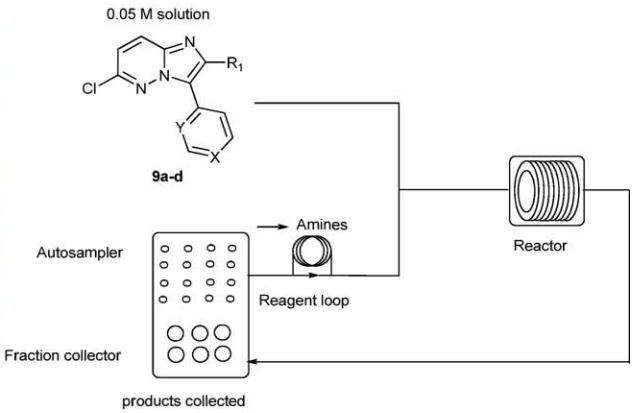
General procedures for flow synthesis of imidazo[1,2-*b*]pyridazine analogues of casein kinase 1 inhibitors:

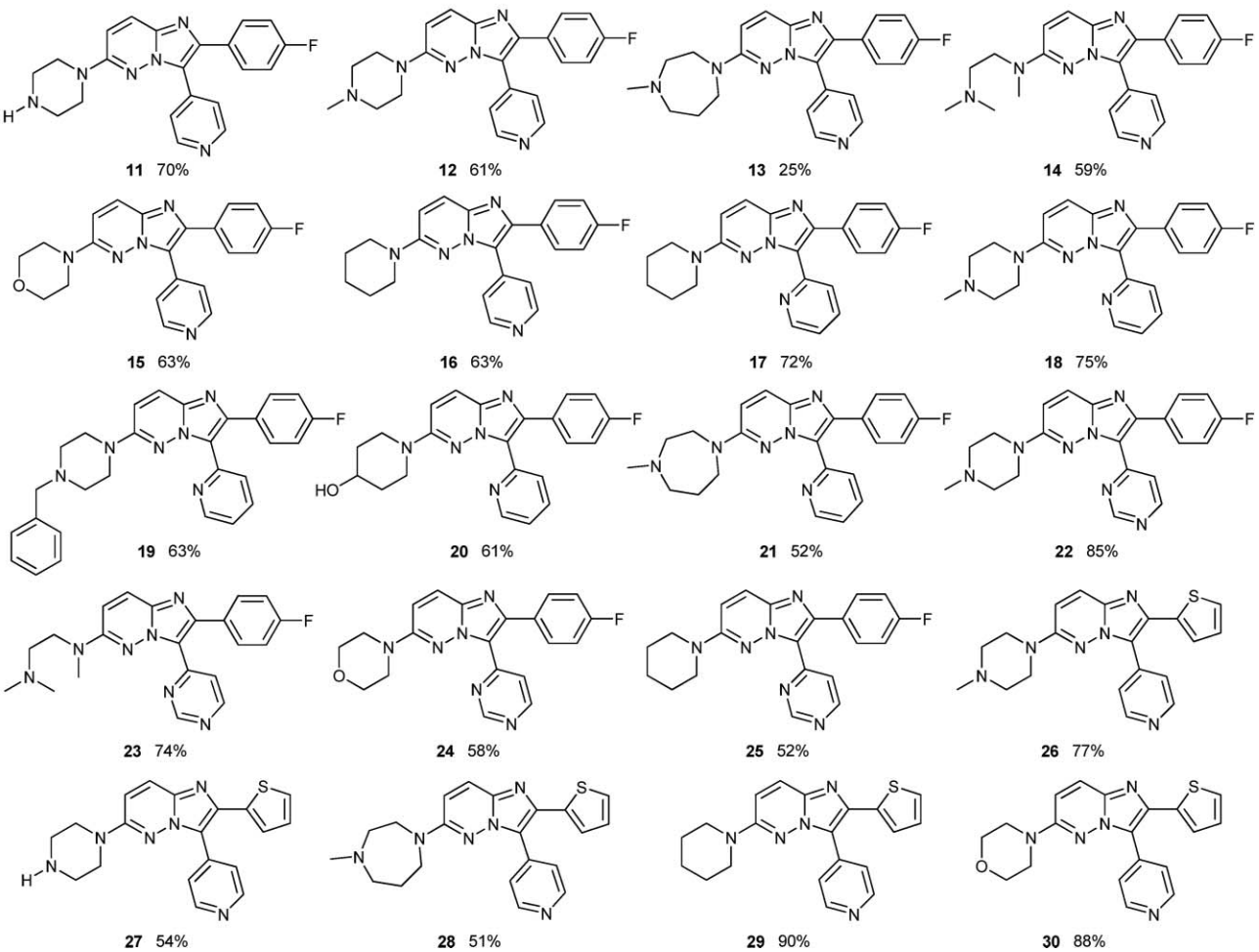
General method A for the synthesis of 1,2-diaryl-ethanone 6a,c,d

Aryl ester (60.0 mmol) and 4-methylpyridine or 4-methylpyrimidine (66.0 mmol) were mixed in THF and the volume was made up to 300 mL in a reagent bottle (Reagent stream 1). A sample of 10 mL of a 0.22 M solution of LiHMDS was injected into the first sample loop which was cooled to 0 °C (Reagent stream 2). Both reagent streams were pumped at 0.25 mL min^{-1} and combined in a static mixing-T before entering into a PTFE tubular coil reactor (10 mL) which was also cooled to 0 °C. The mixture exited the first reactor and entered a second PTFE flow coil reactor maintained at 25 °C. After 40 min sample loop 1 (part of the dual valve system) was switched to sample loop 2 which had been previously filled with 10 mL of LiHMDS (0.22 M in THF held at 0 °C.) and sample loop 1 was refilled with the aforementioned solution. This relay was repeated every 40 min as required. The output from the reactor was collected for 16 h (>50.0 mmol

Table 3 Preparation of potential casein kinase I inhibitors







processed) into hexane (250 mL) and the resulting precipitate was collected by filtration. The yellow solid was then dissolved in water (250 mL) and extracted into EtOAc (3 × 50 mL). The combined organic extract were dried over sodium sulfate and the solvent removed under reduced pressure to obtain the desired product.

General method B for the synthesis of 1-(4-fluorophenyl)-2-pyridin-2-ylethanone 6b

A reagent bottle was charged with 2-picoline (90.0 mmol) and the voulme was made up to 300 mL with THF. A second reagent bottle was charged with ethyl 4-fluorobenzoate (60.0 mmol) and

the voulme was made up to 300 mL with THF. Two 10 mL aliquots of *n*-BuLi (0.4 M solution in hexanes) were injected into the dual sample loops (Sample loop 1 and 2) which were cooled to −78 °C. The solution from the reagent bottle 1 and sample loop 1 were pumped at 0.375 mL min^{-1} meeting at a T-piece and being directed into a PTFE coil reactor (5 mL) which was cooled to −78 °C. The ethyl 4-fluorobenzoate was pumped at 0.75 mL min^{-1} with a 6.5 min delay combining with the main flow stream at a T-piece. The resulting solution entered a second PTFE coiled reactor (15 mL) maintained at 25 °C. After 26 min sample loop 1 was switched to sample loop 2 and the original sample loop recharged with a solution of *n*-BuLi. This was repeated every 26 min as required. The entire output was collected for 11 h (50.0 mmol processed) and quenched with saturated aqueous NH_4Cl (50 mL) and water (150 mL) and extracted into EtOAc (3 × 100 mL). The combined organic extracts were dried over sodium sulfate and the solvent removed under reduced pressure to obtain a yellow solid **6b** as a keto-enol mixture (65%).

General method for the synthesis of 1,2-diaryl-2-bromoethanone 7a–d

Polymer-supported pyridine hydrobromide perbromide (16.5 g, 2.0 mmol g^{-1}) was pre-washed with 0.2 M solution of hydrogen bromide in methanol (50 mL). After filtration the resin was added to a solution of 1,2-diaryl-ethanone **6a–d** (30 mmol) in methanol (50 mL). The suspension was then mixed on an orbital shaker for 30 min before the resin was removed by filtration and the solvent evaporated under reduced pressure to obtain the product **7a–d** in quantitative yield.

General method for the synthesis of 1,2-diaryl-2-bromoethanone 7a–d under flow conditions

Polymer-supported pyridine hydrobromide perbromide (5.0 g, 2.0 mmol g^{-1}) was packed in a 150 × 100 mm glass chromatography column. The resin was activated by eluting with a 0.2 M solution of hydrogen bromide in methanol (50 mL) using the R2+/R4 system. The ketone (**6a–d**) (2.0 mmol) was dissolved in methanol to a volume of 10 ml in a reagent bottle. The solution was pumped directly through a pump head into the packed column at 0.65 mL min^{-1} (ambient temperature) resulting in an approximate residence time of 5 min. The output was collected for 30 min and the solvent removed to obtain α-bromoketones **7a–d** in quantitative yield.

General method for the synthesis of 6-chloro-2,3-diarylimidazo[1,2-*b*]pyridazine 9a–d

A solution of the appropriate 1,2-diaryl-2-bromoethanone **7a–d** (10 mmol) was prepared in DMF (100 mL). A stock solution of 3-amino-6-chloropyridazine (**8**) (20 mmol) also dissolved in DMF (200 mL) was prepared in a second reagent bottle. The two solutions were pumped at 0.167 and 0.333 mL min^{-1} respectively combining at a static microbore mixing tee. The flow stream next entered a PTFE flow coil reactor (10 mL) which was heated at 120 °C. The output was directed through a column packed with solid powdered K_2CO_3 (5 g) and the output collected for 11 h *via* a fraction collector controlled by the Flow Commander software. The crude reaction was crashed from solution by the addition of water and the resulting precipitate collected by filtration. The solid was dissolved in DCM and the mixture passed through a short plug of silica. The solvent was removed under reduced pressure to obtain the 6-chloro-2,3-diarylimidazo[1,2-*b*]pyridazine derivatives **9a–d**.

General method for the S_NAr replacement formation of compounds 11–30

A vial was charged with each of the 6-chloro-2,3-diarylimidazo-[1,2-*b*]pyridazine derivatives **9a–d** (1.0 mmol) and made up to 20 mL in volume in the required solvent (ethanol or NMP). Similarly, five different amines each in a separate vial (2.5 mmol in 2.5 mL) were prepared and placed in the corresponding locations in the autosampler. For each sequenced reaction, 2 mL of the pyridazine and amine solutions were pumped at 0.1 mL min^{-1} from sample loops. The two streams were combined at a static mixing tee and entered a stainless steel tubular reactor (20 mL) heated at 177 °C. The output flow was initially diverted to waste for 90 min and then the product stream collected for a further 70 min by the fraction collector. The reactor was automatically washed and the next reaction initiated. The whole procedure was scheduled and controlled by the Flow Commander software. The work up of the individual reactions at this stage varied depending on the solvent used and the nucleophilic amine employed. *Method A for compounds* **12–25**: The Biotage V-10 was used to remove the solvent and excess amine. The crude product was then dissolved in dichloromethane and treated with an isocyanate scavenger resin (3 eq.) to remove any residual non volatile amine to give the product in high purity after solvent removal. *Method B for compound* **11**: The Biotage V-10 was used to remove the solvent and excess amine and solid obtained was recrystallised from ethanol to yield compound **11**. *Method C for compounds* **26–30**: QP-SA (4 eq. based on the amine) was added to the reaction mixture, and was the suspension shaken for 2 h at ambient temperature. The resin was then filtered and washed with methanol (30 mL) and then treated with an ammonia in methanol solution (10 mL, 2.0 M). The solvent was removed under reduced pressure and the product was obtained in high purity following recrystallisation from ethanol.

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