ChemPubSoc Europe

DOI: 10.1002/ejoc.201600222

EurJOC European Journal of Organic Chemistry

Full Paper

Flow Chemistry

The Generation of a Library of Bromodomain-Containing Protein Modulators Expedited by Continuous Flow Synthesis

Paolo Filipponi[a] and Ian R. Baxendale*[a]

Abstract: A continuous flow process delivering key building blocks for a series of BCP modulator libraries is reported. A dynamically mixed flow reactor emerged as a pivotal technology in both synthesis and isolation phases enabling the processing of slurries and suspensions while maintaining high productivity and reliability. Accordingly, the synthesis of common intermediates in flow were employed to further build a pyridazone-based library (36 compounds) aimed at improving lead compound potency and selectivity while further enabling structure-activity relationship studies of a new BCP modulator family.

Introduction

The epigenetic biological network is orchestrated by several complex signalling pathways in which histone post translational modification plays a key role in encoding physiological and environmental stimuli and regulating chromatin architecture modifications.[1] Different proteins and protein complexes are directly or indirectly involved in transcription, replication and DNA repair processes, physically modifying histones (writers and erasers) or responding to specific histone marks (readers).[2] Among them, bromodomain-containing proteins (BCPs) have recently emerged as relevant therapeutic targets with potential applications in oncology and the treatment of neurological as well as inflammatory diseases.[3] Indeed, numerous compounds have been disclosed to modulate bromodomain-mediated protein–protein interactions thus demonstrating the drugability of new BCP family members.[4] However, despite the intense medicinal chemistry exploration that has already provided several promising scaffolds, additional work is required to define novel privileged structures for developing into bromodomain modulators with improved specificity and potency. In this context, we have recently devised a straightforward, large scale production, of key building blocks **1** and **2** (Figure 1).[5] The flow procedure utilises a dynamically mixed reactor instrumental to the processing of slurries and suspensions at scale redefining, the generation of solids in flow, from a limitation into a designed in-line operation directed at improving the process safety and product quality.[6]

A primary goal of this research is the rapid delivery of quantities of target compounds sufficient to support and sustain advanced medicinal chemistry programmes. Herein, along with detailed optimization of multi-gram scale synthesis of key intermediates **1** and **2**, the synthesis of three lead development series based on the 6-methyl-1-arylpyridazine nucleus (**A**–**C**, Figure 1) are reported.

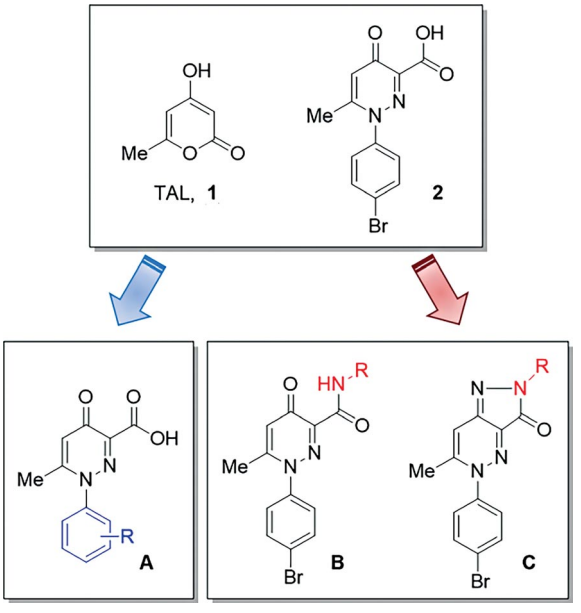


Figure 1. Building blocks **1** and **2** selected for generation of a focused library designed around three general templates **A**–**C**.

Results and Discussion

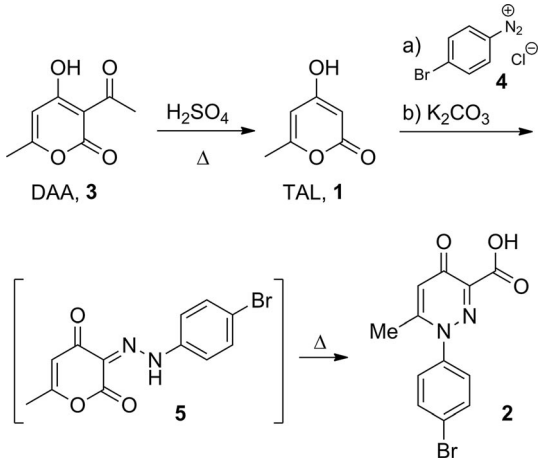
Process Development

In the first phase of the study, we focused our attention on the process modelling and optimization of compounds **1** and **2** aimed at developing scalable syntheses for their production. The selected approach to **1** and **2** entails two practical synthetic steps starting from a sulfuric acid-promoted deacylation of dehydroacetic acid (DAA, **3**, Scheme 1). The resultant triacetic acid lactone (TAL, **1**) is then reacted in a convergent process with a diazonium salt to form intermediate hydrazone **5** which is then

[a] *Department of Chemistry, University of Durham*
South Road, Durham, DH1 3LE, United Kingdom
E-mail: i.r.baxendale@durham.ac.uk
http://community.dur.ac.uk/i.r.baxendale/index.html

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201600222.

directly submitted to an alkaline thermal rearrangement to yield target structure **2** (Scheme 1). Whereas this strategy ensures acceptable reaction yields and batch purities when executed at laboratory scales, it required comprehensive re-optimisation to overcome several processing and isolation issues which became apparent upon scale up. In order to meet the required process standards in terms of efficiency and safety each step in the synthesis of compound **2** was individually analysed and optimised.



Scheme 1. Synthetic strategy adopted for the preparation of 4-hydroxy-6-methyl-2*H*-pyran-2-one (TAL, **1**) and 1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (**2**).

Deacylation of DAA (**3**) was initially performed as a batch process by dissolving the compound in 90 % H_2SO_4 at a concentration of 3.7 M. The solution was then heated to 130 °C for 15–30 min, cooled and poured into 2.5 volumes of ice water. The mixture was stirred vigorously for 10–15 min and the resulting suspension filtered and dried. Desired TAL product (**1**) was obtained in variable isolated yields ranging from 68 % to 80 %. We directed our initial evaluation efforts at appraising the impact of the sulfuric acid concentration and heating temperature on the resulting yield and product quality.

We immediately found that the amount of water present in the reaction mixture had a critical impact on product speciation (Table 1, Entries 1–9). The use of a higher water content changed the reaction outcome allowing two alternative products **6** and **7** to be isolated and characterised (Figure 2).

Consequently, symmetrical 3,5-dimethyl-4-pyrone (**6**) was recovered as the main component when performing the reaction in dilute (10 and 25 wt.-%), hot (> 100 °C) sulfuric acid. A reduction in the percentage of water corresponded to an increase in the presence of desired lactone **1** and a decrease in the amount of 2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxylic acid (**7**) formed (Table 1, Entries 1–4). A simple trend was also determined for temperature; experiments demonstrated that a deviation from an optimal setting of 130 °C translated to a decrease in yield and a requirement for prolonged reaction times (Table 1, Entries 9–13).

However, the principal reason for low isolated yields was determined to be inefficiencies in the workup step. This was demonstrated by the significant differences between the final isolated and ^{1}H-NMR determined yields (Table 1, Entries 7 and 8).

Table 1. Evaluation of the H_2SO_4 concentration and temperature effects on the deacylation yield.[a]

Entry	H_2SO_4 [%]	Temp. [°C]	H NMR yield[b] [%] 1	6	7	Isolated yield [%] 1
1	10	reflux	–	> 90	–	–
2	25	reflux	–	90	–	–
3	60	110	55	–	18	28
4	75	130	–	–	8	41
5	80	130	–	–	–	60
6	90	130	–	–	–	68
7	92.5	130	91	–	9	79
8	> 95	130	94	–	6	81
9	98[c]	130	100	–	0	–
10	98[c]	110	76	–	0	–
11	> 95	80	–	–	–	63[d]
12	> 95	150	–	–	–	66
13	> 95	180	–	–	–	55

[a] Reaction conditions: DAA (**3**, 15 mmol, 3.7 M), 15 min. [b] Analysis of a crude aliquot dissolved in D_2SO_4. [c] Reaction performed in D_2SO_4. [d] Yield referred to 4 h reaction time.

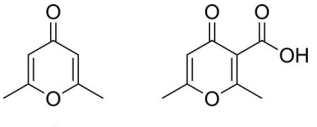


Figure 2. Principal by-products isolated in the synthesis of TAL (**1**): 3,5-dimethyl-4-pyrone (**6**) and 2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxylic acid (**7**).

Interestingly, we found no discernible decrease in the isolated yield at small scale when varying the volume of water used in the quench step nor when increasing the incubation time before filtration (Table 2; Entries 1–5). However, an increase in the amount of water used in the quench phase did translate to a beneficial effect on the quality of the precipitate produced. Using 7.5–10 volumes of water was found to be optimal producing a readily filtered, off-white, flocculent solid. By comparison, decreasing the amount of water used to quench the reaction had a negative impact with increasing scale and was found to produce a solid which rapidly agglutinated and became extremely difficult to filter and dry. This immediately became a process limiting issue as working reaction scales increased. We also noted the quench temperature required careful regulation; at elevated temperatures > 15 °C, as generated by the very exothermic mixing, side reactions occurred which affected the yield and purity (Table 2; Entries 6 and 7). This was again particularly noticeable at higher reaction scales where appreciable off-gassing was noted. Off-gassing was presumably the result of product hydrolysis and subsequent decarboxylation (Table 2, Entry 7).

We concluded from our explorative study that the use of concentrated (> 95 %) sulfuric acid and high temperature (130 °C) were key reaction attributes leading to excellent conversion. Furthermore, accurate control of the quenching parameters like temperature and mixing efficiencies (including the amount of water) emerged as critical aspects in ensuring high isolated yield and contributed significantly to the overall suc-

Table 2. Evaluation of the water volume on quenching efficiency.[a]

Entry	H_2O volumes	Incubation times [h]	Isolated yield [%]
1	2.5	2	80[b]
2	5	2	82[b]
3	7.5	2	79[b]
4	10	2	79[b]
5	10	12	78[b]
6	5	2	54[c]
7	5	2	47[d]

[a] Reaction conditions: DAA (**3**) (15 mmol, 3.7 M), H_2SO_4 > 95 %, 130 °C, 15 min. [b] The crude mixture was poured in iced water maintained at 0–5 °C. [c] The crude mixture was poured into ambient temperature water. [d] Addition of the crude mixture to 5 volumes of iced water over 10 min, internal temperature reached 26 °C.

cess of the process. Based upon these considerations, we envisaged gaining both operational safety and product processing benefits by implementing flow technologies, thus enabling gains in terms of containment, heat transfer (exotherm control) and improved mixing in both the synthetic and quenching steps. We therefore investigated the use of a dynamically mixed flow reactor selected for its ability to handle suspensions (Figure 3).[7]

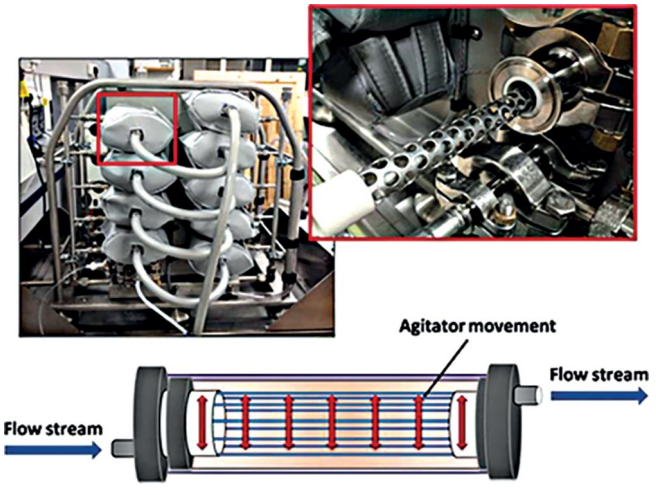
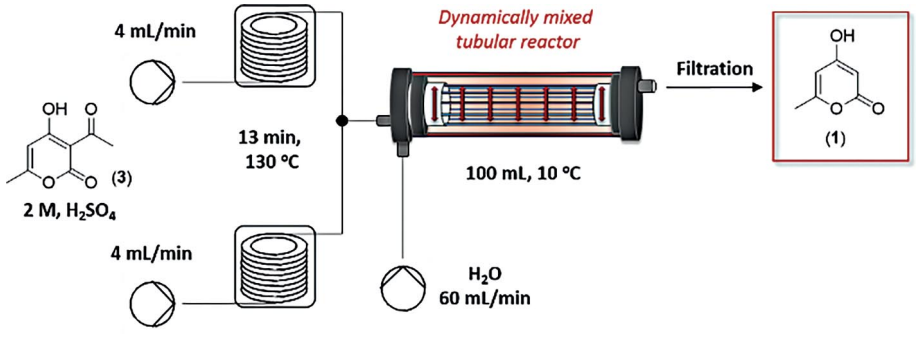


Figure 3. The AM Technology Coflore® ATR. The reactor has ten interconnected tubes with a total reactor volume of 1 L. All pipes are equipped with an internal dynamic mixer which generates a turbulent flow stream through lateral shacking.

Accordingly, after demonstrating the prolonged stability of the DAA (**3**) starting material in H_2SO_4 (> 95 %) at ambient temperature, a 2 M stock solution was prepared and pumped using a Vapourtec E-series module into two parallel configured polar bear flow synthesisers[8] equipped with PTFE coil reactors (volume 52 mL, temperature 130 °C) (Scheme 2). The outflows from the twin reactors (8 mL/min) were combined at a Teflon™ T-piece and the stream directed into the first chamber of the Coflore ATR reactor (volume 100 mL, agitator frequency 4 Hz, temperature 5–10 °C). A secondary input of water (10 °C, delivered at 60 mL/min equating to 7.5 volumes) was added at right angles via a side arm connector of the first Coflore agitated chamber. The precipitate that formed was processed through the agitated reactor and dispensed onto a glass-sintered vacuum suction plate to facilitate filtration. The process was run continuously with periodic removal of the filtered material delivering very high productivity (116 g/h dry mass, 96 % yield). Consequently, while minimizing the safety issues of handling concentrated sulfuric acid, the devised flow configuration also ensured a nearly quantitative recovery of TAL which was easily isolated by filtration as an off white, fine powder.

Our next challenge was optimization and scale up of the synthesis of pyridazone **2** (Scheme 1). The selected approach involved a multi-step sequence using a base-catalyzed addition of lactone **1** (0.2 M) to a fleshly prepared aryl diazonium salt **4**. In batch, the resulting suspension was heated at reflux for 3 h to promote intramolecular cyclisation to rearranged hydrazone **5**. The dark red homogeneous mixture thus obtained was treated with activated charcoal and filtered. The filtrate was then acidified with concentrated HCl which induced precipitation of final product **2**. Again, performing this sequence at scale gave rise to several problems mainly related to processing times and safety.

For example, the initial coupling reaction (**1** + **4** → **5**; Scheme 1) is strongly exothermic (mixing acid/base solutions) and therefore requires the dropwise addition of the diazonium salt solution resulting in prolonged reaction times. This was additionally problematic since certain diazonium salts proved unstable and degraded over time to yield varying amounts of the corresponding phenols. Reaction scale up also increased the necessary addition time and, as a consequence, gave higher levels of impurities. A further issue was found to involve the selection of the alkali carbonate base needed to promote the



Scheme 2. Continuous flow set up for the synthesis and isolation of TAL (**1**).

rearrangement. At scale, copious CO_2 evolution, combined with the insolubility of hydrazone intermediate **5**, results in significant foaming with deleterious effects on mixing efficiency which further impacts reaction time. In response to these issues, we again designed a multistep flow process based upon the use of the ATR reactor due to its ability to process slurries and suspensions. The capabilities of this system enabled us to consequently take advantage of enhanced mixing and isothermal control offered by flow processing.

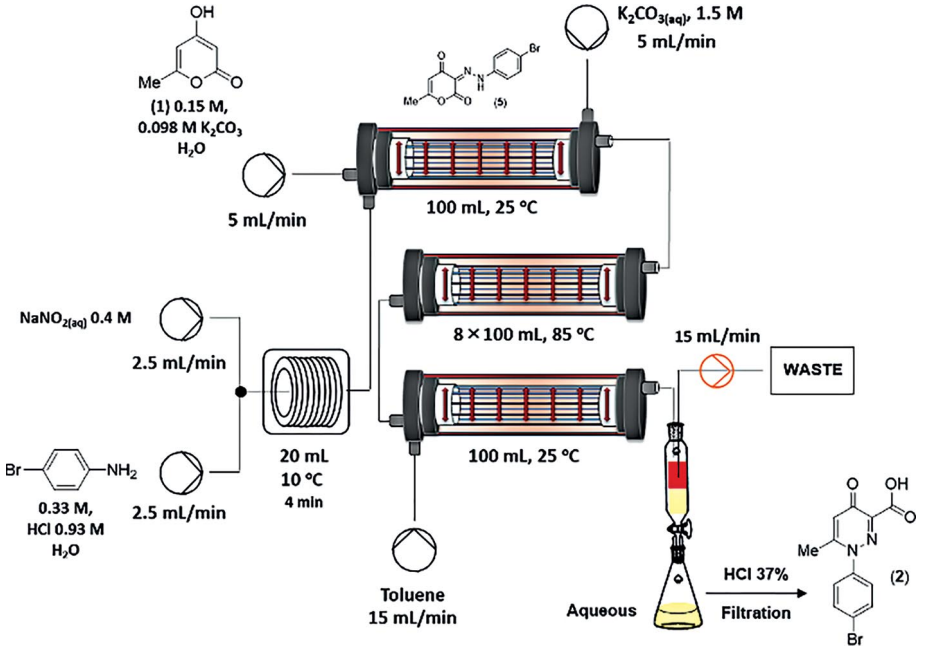
Diazonium Salt Coupling – 4-Bromoaniline Exemplification

Diazonium species **4** was prepared in situ as follows: a solution of $NaNO_2$ in water (0.4 M) was mixed at a T-connector with 4-bromoaniline (0.33 M) dissolved in aqueous HCl (0.93 M) and the combined flow stream then progressed through a 20 mL coil reactor (Scheme 3). This simple flow configuration worked well over a wide range of temperatures (–10 to 25 °C) delivering a continuous stream of desired diazonium salt **4** in quantitative conversion. The corresponding secondary input, a solution of TAL (**1**) was prepared by the addition of a substoichiometric quantity of K_2CO_3 (0.65 equiv.) which proved efficient at solubilizing **1** in an aqueous media. The base also sufficiently raised the pH to catalyze the subsequent diazonium coupling step (**1** + **4** → **5**). Therefore, the streams of TAL (**1**) and diazonium salt **4** could be blended together within the confines of the first 100 mL ATR reactor chamber (maintained at room temp.). Intermediate **5** could be easily processed with dynamic mixing using a residence time of 10 min. The outflowing suspension, if required, could be continuously filtered thus allowing isolation of compound **5** in almost quantitative yield and with high purity as a fine yellow powder.

It is worth noting that, relative to the original batch procedure, these flow conditions are much milder. As a consequence, we encountered less degradation of intermediate diazonium **4** (phenol formation) thereby allowing its relative stoichiometry to be reduced (1.1 equiv., cf. 2.5 equiv. in batch). In addition, the CO_2 evolution and associated foaming issues that proved highly problematic at scale in batch, were also diminished thereby increasing the efficiency of the reaction.

Although the optimized conditions proved highly beneficial for the first derivatization stage, the subsequent intramolecular cyclization (**5** → **2**) required more basic conditions. Therefore a successive injection of K_2CO_3 solution (1.5 M) was used to promote the conversion of hydrazone **5** to the final pyridazone **2**. In the final configuration the flow of feed **5** was mixed with a solution of K_2CO_3 (1.5 M) pumped at 5 mL/min. The combined flow stream was then processed through a further eight interconnected ATR chambers (temperature maintained at 85 °C) corresponding to a total residence time of approx. 53 min (note this compares to 3 h in batch) (Scheme 3).

In batch, we found that isolation of final material **2** necessitated treatment of the crude product solution with activated charcoal followed by acidification and filtration of the resulting solid. However, it was determined that the charcoal cleanup step as well as being a laborious operation was significantly less effective at scale; the final material isolated was still often contaminated with a dark red oily residue which furthermore affected the filtration process. We thus decided to implement an on-line extraction using the final ATR reactor chamber. A flow stream of toluene pumped at 15 mL/min was added and the biphasic mixture then processed through the final 100 mL in a dynamically agitated tube (residence time 3.3 min). The outflow was then collected into a settling tank (1.2 L); an extraction line continuously removed the organic phase which was directed to waste. The lower aqueous fraction was periodically drained, acidified with HCl (37 %), and finally, filtered. The recovered pale tan solid was then dried under vacuum to yield



Scheme 3. Continuous flow set up for the synthesis and isolation of 1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid (**2**).

desired pure product **2** in an overall 73 % yield. This multistep sequence had a productivity of 9.6 g/h.

Following the successful development of the flow process to prepare key building block **2** we used the same reactor configuration to generate a small derivative library (Figure 4). Pyranone **1** was therefore used as the starting material for the preparation of 13 additional compounds **8**–**14** characterised by different substituents at the phenyl moiety; all were isolated in good yield by means of acidification and filtration of the crude aqueous mixtures as described above.

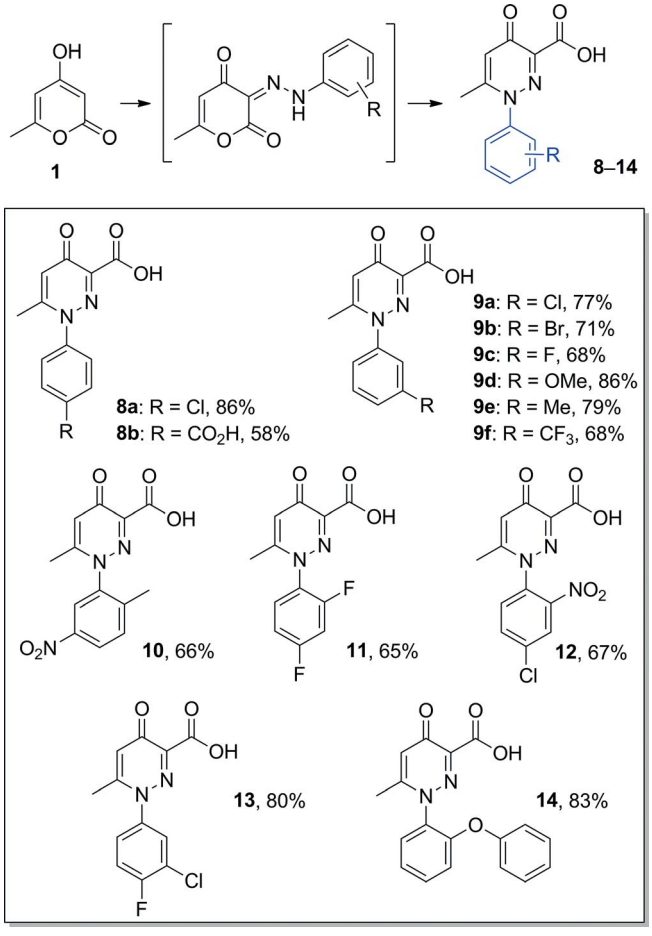


Figure 4. **A** series compounds synthesized by reacting TAL (**1**) with different substituted diazonium salts.

Library Construction

Our preliminary medicinal chemistry screening efforts had identified pyridazone framework **2** as a promising scaffold for evolution in a more advanced lead optimization study. In particular, its versatile structure was highly attractive due to its potential for late stage modifications providing different sites for chemical manipulation. Accordingly, we report here two exemplary lead development series (**B** and **C**, Figure 1) affording compounds for biological testing. It should be highlighted that library preparation was rapidly progressed due to the availability of bulk quantities of starting material **2** as furnished from the flow chemistry scale up described above.

The synthesis of the amide library **B** required the preliminary activation of the carboxylic acid moiety. This was easily achieved by treating compound **2** with 1,1′-carbonyldiimidazole (CDI) in MeCN for 1 h. The active amide was then mixed with desired amines and the reactions stirred overnight at ambient temperature. Several of the products precipitated thus allowing them to be directly filtered. Solids were then easily purified by two consecutive washings with MeCN and Et_2O respectively. This simple work-up procedure led to the isolation of pure products **15**–**18**, **20** in yields ranging from 42–77 %. In each case, additional materials could also be recovered by flash chromatography purification of the filtrates. Other compounds failed to precipitate and these products **19**, **21**–**23** required direct silica column purification, but again, could be isolated in high yields. As depicted in Figure 5, this synthetic method proved effective for a wide range of amines allowing for the synthesis of both aromatic and aliphatic amides with variable length side chains.

To gain additional insight in the structure–activity relationships of this new class of BCP modulators, and in line with

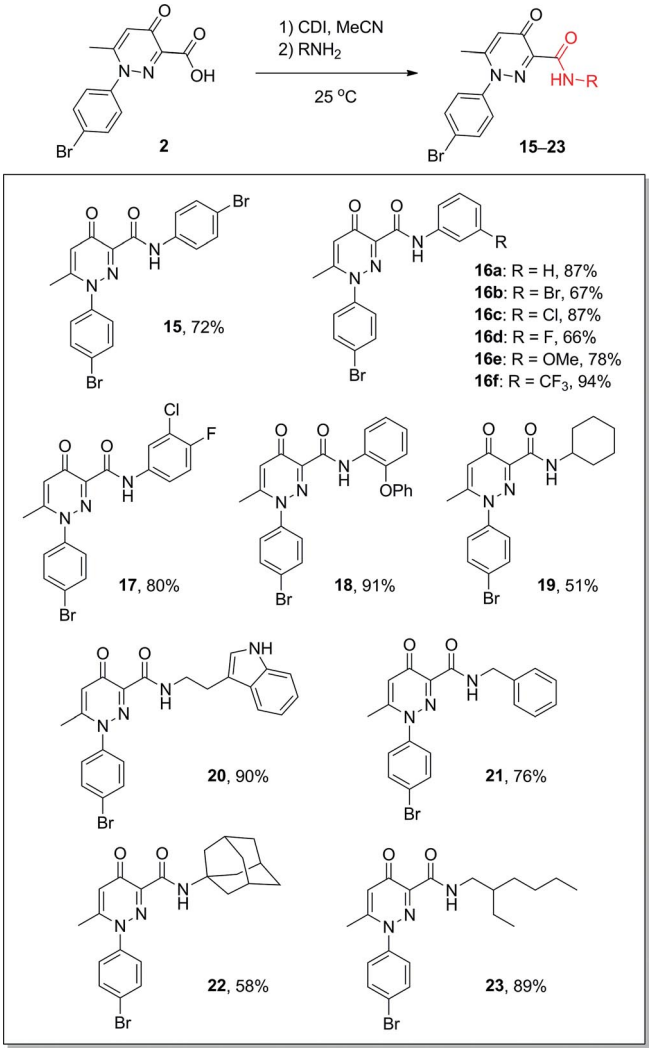
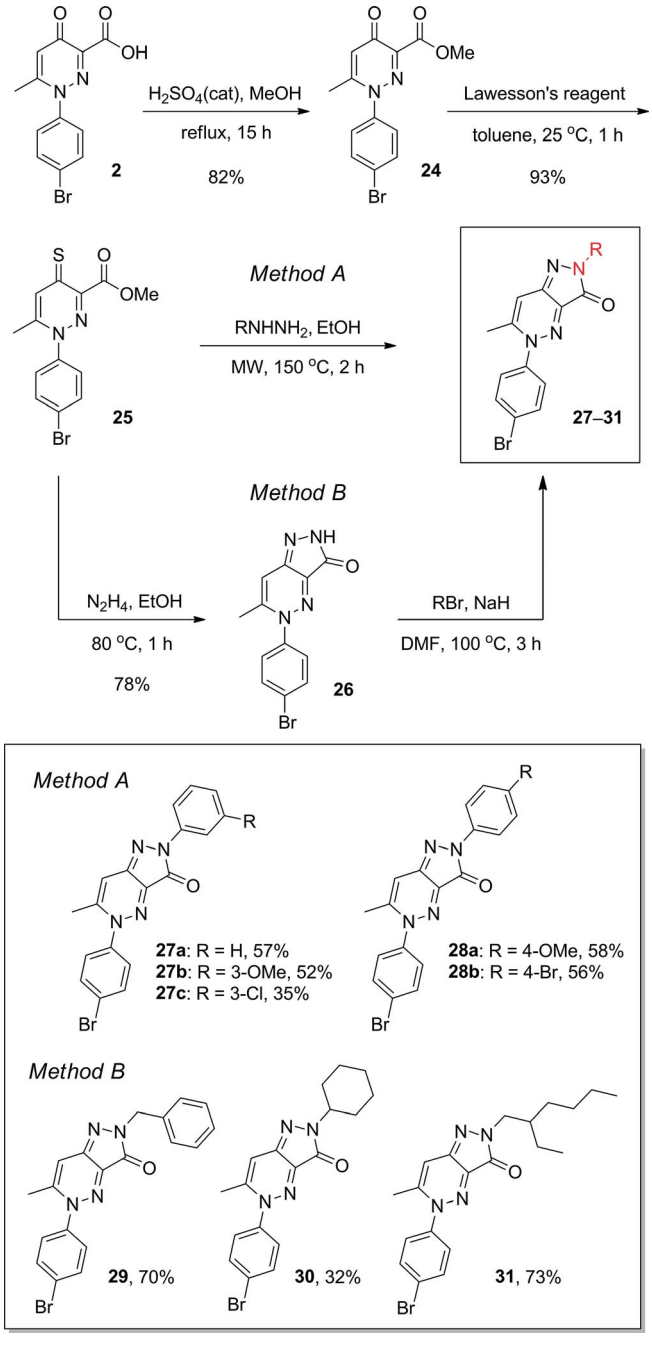


Figure 5. **B** series amide derivatives prepared starting from bulk-generated intermediate **2**.

a generally adopted medicinal chemistry strategy, we further designed a series of constrained derivatives (**C**, Figure 1). In particular, to develop a better understanding of the influence of amide orientation on both affinity and selectivity, we endeavored to lock the β-ketoamide moiety into a pyrazole structure. In this way, we achieved selective functionalization at the pyrazole *N-1* position thus delivering additional samples (**27**–**31**, Scheme 4) with a defined hydrophobic side chain orientation.

The synthesis of the fused pyrazolo[4,3-*c*]pyridazine motif initially required the preparation of a more reactive thioxo ester



Scheme 4. Synthetic strategy applied to preparation of **C** series pyrazolo[4,3-*c*]pyridazine derivatives **27**–**31**.

derivative **25**. Accordingly, after the esterification of starting material **2**, new intermediate **24** was treated with Lawesson's reagent in toluene. For the preparation of aryl derivatives **27**–**28**, resulting compound **25** was treated with different substituted hydrazines under microwave irradiation conditions at 150 °C for 2 h (Method A, Scheme 4). Despite these forcing reaction conditions, only moderate conversions could be achieved. However, the efficiency and levels of automation derived from the use of a microwave synthesizer, resulted in a general reduction in processing time relative to the batch procedure. For example, an essentially identical yield was obtained when preparing derivative **28a** by heating the reaction mixture at reflux albeit for 48 h.

Alternatively, benzyl and alkyl compounds **29**–**31** could be synthesized by initial condensation of thio derivative **25** with hydrazine in good overall isolated yields (Method B, Scheme 4). Subsequent *N*-functionalization of **26** with an alkyl bromide emerged as a valuable synthetic approach yielding example compounds **29**–**31** in moderate to excellent yields. The materials generated in this fashion could again be easily purified by column chromatography therein demonstrating the versatility of the scaffold to rapid and selective structural modification. All compounds generated herein have been submitted for extended biological evaluations as part of a wider European COST project initiative.[9]

Conclusions

Over the last few years, approaches to modulating bromodomain-mediated protein–protein interactions have emerged as one of the most promising interventional tactics behind epigenetic therapies. The novelty and potential of these biological targets have stimulated intense research efforts yielding many promising results, particularly in oncology. However, given the multi-regulatory behaviour of various bromodomains and BCPs, the development of a comprehensive understanding of their physio-pathological role demands continuous development of new, potent and selective pharmacological tools. Accordingly, we have developed a multi-gram scale flow synthesis of several building blocks (**1**, **2**, **8**–**14**, Figures 1, 4); these building blocks were instrumental for the rapid synthesis of focused BCP modulator libraries. The use of flow chemistry technologies has strongly impacted the research outcomes in terms of time, cost and manpower. Indeed, the devised process has delivered sufficient benefits to justify the initial development efforts enabling the continuous production of large quantities of target compounds without additional scale-up and re-optimization studies. The large scale availability as well as the synthetic versatility of produced building blocks facilitated expeditious generation of a compound collection based on the pyridazinone scaffold (**A**–**C**, Figure 1). These new BCP modulators are specifically designed to provide insight into how hydrophobic moieties influence both their potency and selectivity. We are confident that assays of their bioactivity, combined with their chemical diversity, will contribute to our understanding of their structure-activity relationship and pharmacological profiles. Moreover the results of these efforts will support ongoing research efforts to

better understand BCP biology and resulting therapeutic opportunities.

Experimental Section

Materials and Methods: All solvents were purchased from Fisher Scientific and used without further purification. Reagents were purchased from Alfa Aesar or Sigma Aldrich and used as received. Flow reactions were performed either with a Vapourtec (R-series and E-series) or a Polar Bear plus Flow™ or AM Technology Coflore® modules equipped with standard PTFE tubing (3.2 × 1.5 mm, o.d. × i.d) and connectors. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker Avance-400 instrument and are reported relative to $CDCl_3$ (δ = 7.26 ppm and δ = 77.2 ppm respectively) or [D$_6$]DMSO (δ = 2.50 ppm and δ = 39.5 ppm respectively). Data for ^{1}H-NMR are reported as follows: chemical shift (δ/ppm) [integration, multiplicity, coupling constant (Hz)]. Multiplicities are reported as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, t = triplet, q = quartet, m = multiplet, br. s = broad singlet. Data for ^{13}C-NMR are reported in terms of chemical shift (δ/ppm) and multiplicity (C, CH, CH_2 or CH_3). Data for ^{19}F-NMR were recorded using the above instrument at a frequency of 376 MHz using DMSO as an external standard. IR spectra were obtained with a Perkin–Elmer RX1 spectrometer (neat, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <51 % of tallest signal), medium (m, 51–70 % of tallest signal) or strong (s, > 71 % of tallest signal). Low and high resolution mass spectrometry were performed using the indicated techniques with either Waters LCT Premier XE or Waters TQD instruments equipped with an Acquity UPLC and a lock-mass electrospray ion source. For accurate mass measurements the deviation from the calculated formula is reported in mDa.

Multigram-Scale Flow Procedures

4-Hydroxy-6-methyl-2*H*-pyran-2-one (TAL, 1): Two solutions of 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**3**) (2 M) were individually pumped at 4 mL/min into two parallel coil reactors (52 mL) heated at 130 °C. The combined crude outflows fed, along with a stream of water (60 mL/min), a 100 mL Coflore® ATR reactor chamber cooled to 10 °C. The resulting suspension was filtered and the pale yellow solid dried under vacuum obtaining the pure title compound **1** in 96 % yield, m.p. 185.6 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.61 (s, 1 H), 5.96 (s, 1 H), 5.21 (s, 1 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 171.0 (C), 164.4 (C), 163.8 (C), 100.6 (CH), 88.6 (CH), 19.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2362.4 (w), 1658.1 (m), 1618.2 (m), 1538.5 (m), 1492.62 (m), 1255.2 (s), 1149.2 (m), 985.2 (s), 878.0 (m), 833.0 (s), 812.21 (s), 729.2 (m), 635.3 (m), 591.4 (s), 526.2 (s), 497.8 (s) cm^{-1}. LC-MS (ESI): 125.0 (M – H). HRMS (ESI): calculated for $C_6H_7O_3$ 127.0395, found 127.0389 (M + H, Δ = –0.6 mDa).

1-(4-Bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (2): Two solutions pumped at 2.5 mL/min were mixed in a T-piece before entering in a coil reactor (20 mL) cooled to 10 °C: one containing $NaNO_2$ 0.4 M and the second containing 4-bromoaniline (0.33 M) solubilised in aqueous HCl (0.93 M). The outflow was combined with a stream of **1** (0.15 M) dissolved in $K_2CO_{3(aq)}$ (0.098 M) and pumped at 5 mL/min. The resulting mixture was reacted at room temperature in the first chamber of the ATR reactor. A second stream of $K_2CO_{3(aq)}$ (1.5 M) was thus injected in the reactor at 5 mL/min and main stream processed into eight 100 mL dynamically mixed pipes heated at 85 °C. As the crude mixture enters the last reactor chamber it was mixed with a stream of toluene pumped at 15 mL/min. The biphasic solution that exited the reactor was separated. The water layer was acidified with HCl (37 %) and the suspension obtained filtered. The pale orange solid recovered was dried under reduced pressure obtaining the pure title compound **2** in 73 % yield, m.p. 214.0 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 15.55 (br. s, 1 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.12 (s, 1 H), 2.25 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 171.3 (C), 163.1 (C), 156.0 (C), 143.0 (C), 141.5 (C), 133.1 (2CH), 129.1 (CH), 124.0 (C), 120.6 (CH), 20.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1727.7 (m), 1566.3 (m), 1485.4 (s), 1337.9 (m), 1284.2 (m), 1218.8 (s), 1067.6 (s), 1015.6 (s), 909.7 (m), 839.7 (s), 794.1 (m), 738.1 (m), 641.0 (m) cm^{-1}. LC-MS (ESI): 307.1 (M – H). HRMS (ESI): calculated for $C_{12}H_{10}N_2O_3Br$ 308.9875, found 308.9882 (M + H, Δ = +0.7 mDa).

Compound Library Assembly

General Flow Procedure for the Preparation of A Derivatives 8–14: Compounds **8**–**14** were prepared following the flow procedure as described for compound **2** above.

1-(4-Chlorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (8a): Yield 86 %, white solid, m.p. 216.0–217.2 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 15.57 (br. s, 1 H), 7.72 (d, *J* = 9.6 Hz, 2 H), 7.68 (d, *J* = 9.6 Hz, 2 H), 7.13 (s, 1 H), 2.25 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 171.3 (C), 163.1 (C), 156.0 (C), 143.0 (C), 141.1 (C), 135.3 (C), 130.2 (CH), 128.8 (CH), 120.6 (CH), 20.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3046.5 (w), 1730.6 (s), 1619.5 (m), 1562.6 (m), 1485.4 (s), 1338.8 (m), 1288.1 (s), 1220.0 (s), 1085.2 (s), 1017.4 (s), 909.9 (m), 841.7 (s), 797.8 (m), 745.0 (m), 645.7 (m) cm^{-1}. LC-MS (ESI): 263.2 (M – H). HRMS (ESI): calculated for $C_{12}H_{10}N_2O_3Cl$ 265.0380, found 265.0392 (M + H, Δ = +1.2 mDa).

1-(4-Carboxyphenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (8b): Yield 58 %, pale orange solid, m.p. 243 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 15.35 (br. s, 1 H), 13.53 (br. s, 1 H), 8.16 (d, *J* = 8.5 Hz, 2 H), 7.76 (d, *J* = 8.5 Hz, 2 H), 7.12 (d, *J* = 0.8 Hz, 1 H), 2.27 (d, *J* = 0.8 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 171.2 (C), 166.7 (C), 163.1 (C), 155.7 (C), 145.4 (C), 143.1 (C), 132.8 (C), 131.1 (CH), 127.3 (CH), 120.7 (CH), 20.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2300–3200 (br., m), 1702.0 (s), 1594.6 (s), 1445.1 (s), 1413.5 (s), 1284.6 (s), 1247.5 (s), 1100.3 (m), 938.0 (m), 878.6 (m), 771.6 (m), 698.4 (s) cm^{-1}. LC-MS (ESI): 273.2 (M – H). HRMS (ESI): calculated for $C_{13}H_{11}N_2O_5$ 275.0668, found 275.0663 (M + H, Δ = –0.5 mDa).

1-(3-Bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (9a): Yield 77 %, off white solid, m.p. 222.6 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 15.55 (br. s, 1 H), 7.96 (t, *J* = 2.0 Hz, 1 H), 7.85 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1 H), 7.69 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1 H), 7.59 (t, *J* = 8.0 Hz, 1 H), 7.12 (d, *J* = 0.7 Hz, 1 H), 2.27 (d, *J* = 0.7 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 171.3 (C), 163.1 (C), 156.0 (C), 143.3 (C), 143.0 (C), 133.7 (CH), 132.0 (CH), 129.9 (CH), 126.2 (CH), 122.4 (C), 120.6 (CH), 20.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3073.9 (w), 1735.9 (s), 1606.4 (m), 1580.9 (s), 1515.1 (s), 1464.1 (s), 1417.1 (s), 1265.3 (s), 1107.0 (m), 887.9 (m), 802.0 (s), 641.6 (s) cm^{-1}. LC-MS (ESI): 307.1 (M – H). HRMS (ESI): calculated for $C_{12}H_{10}N_2O_3Br$ 308.9875, found 308.9871 (M + H, Δ = –0.4 mDa).

1-(3-Chlorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (9b): Yield 71 %, white solid, m.p. 194.9–196.2 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 15.54 (br. s, 1 H), 7.86–7.83 (m, 1 H), 7.74–7.70 (m, 1 H), 7.69–7.62 (m, 2 H), 7.12 (d, *J* = 0.8 Hz, 1 H), 2.27 (d, *J* = 0.8 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 171.3 (C), 163.1 (C), 155.9 (C), 143.3 (C), 143.0 (C), 134.2 (C), 131.8

(CH), 130.9 (CH), 127.1 (CH), 125.8 (CH), 120.6 (CH), 20.8 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1737.9 (s), 1610.4 (m), 1584.6 (s), 1504.4 (s), 1470.0 (s), 1110.7 (m), 965.4 (m), 892.1 (s), 789.7 (s), 671.8 (s), 644.1 (s) cm^{-1}. LC-MS (ESI): 263.2 (M – H). HRMS (ESI): calculated for $C_{12}H_{10}N_2O_3Cl$ 265.0380, found 265.0384 (M + H, Δ = +0.4 mDa).

1-(3-Fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (9c): Yield 68 %, white solid, m.p. 106.2–108.4 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 15.53 (br. s, 1 H), 7.73–7.62 (m, 2 H), 7.56–7.48 (m, 2 H), 7.12 (d, *J* = 0.8 Hz, 1 H), 2.27 (d, *J* = 0.8 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 171.2 (C), 163.1 (C), 162.3 (d, *J* = 247.5 Hz, CF), 155.9 (C), 143.3 (d, *J* = 10.2 Hz, C), 143.1 (C), 132.0 (d, *J* = 9.0 Hz, CH), 123.4 (d, *J* = 3.3 Hz, CH), 120.5 (CH), 117.9 (d, *J* = 20.8 Hz, CH), 114.8 (d, *J* = 24.8 Hz, CH), 20.8 (CH_3) ppm. ^{19}F NMR (376 MHz, [D_6]DMSO): δ = –110.44 (s) ppm. IR (neat): $\tilde{\nu}$ = 3067.8 (w), 1714.0 (m), 1598.9 (s), 1485.1 (s), 1418.3 (m), 1342.4 (m), 1290.9 (m), 1210.4 (s), 1196.1 (s), 1038.1 (m), 896.5 (s), 881.4 (s), 771.9 (s), 697.5 (m), 647.6 cm^{-1}. LC-MS (ESI): 247.2 (M – H). HRMS (ESI): calculated for $C_{12}H_{10}N_2O_3F$ 249.0675, found 249.0679 (M + H, Δ = +0.4 mDa).

1-(3-Methoxyphenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (9d): Yield 86 %, dark brown solid, m.p. 186.2 °C (dec.). ^1H NMR (400 MHz, [D_6]DMSO): δ = 15.71 (br. s, 1 H), 7.53 (t, *J* = 8.1 Hz, 1 H), 7.26 (t, *J* = 2.2 Hz, 1 H), 7.15–7.22 (m, 2 H), 7.14 (d, *J* = 0.9 Hz, 1 H), 3.82 (s, 3 H), 2.27 (d, *J* = 0.7 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 171.4 (C), 163.1 (C), 160.4 (C), 156.1 (C), 143.3 (C), 142.5 (C), 131.0 (CH), 120.6 (CH), 118.8 (CH), 116.6 (CH), 112.5 (CH), 56.1 (CH_3), 20.8 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1738.3 (s), 1605.3 (s), 1515.3 (s), 1475.7 (s), 1434.4 (s), 1236.8 (s), 1019.6 (s), 983.8 (s), 861.9 (s), 797.1 (s), 689.8 (m) cm^{-1}. LC-MS (ESI): 259.2 (M – H). HRMS (ESI): calculated for $C_{13}H_{13}N_2O_4$ 261.0875, found 261.0874 (M + H, Δ = –0.1 mDa).

6-Methyl-4-oxo-1-(*m*-tolyl)-1,4-dihydropyridazine-3-carboxylic Acid (9e): Yield 79 %, cream solid, m.p. 204.4–205.1 °C (dec.). ^1H NMR (400 MHz, [D_6]DMSO): δ = 15.74 (br. s, 1 H), 7.55–7.48 (m, 1 H), 7.46–7.39 (m, 3 H), 7.14 (d, *J* = 0.8 Hz, 1 H), 2.41 (s, 3 H), 2.26 (d, *J* = 0.8 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 171.3 (C), 163.1 (C), 156.1 (C), 142.6 (C), 142.3 (C), 140.1 (C), 131.3 (CH), 129.9 (CH), 127.1 (CH), 123.7 (CH), 120.7 (CH), 21.2 (CH_3), 20.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3065.5 (w), 1732.1 (m), 1608.3 (m), 1514.1 (s), 1471.0 (s), 1440.4 (s), 1279.1 (s), 1221.1 (s), 1102.5 (m), 999.5 (s), 888.8 (s), 801.3 (s), 643.1 (s) cm^{-1}. LC-MS (ESI): 243.2 (M – H). HRMS (ESI): calculated for $C_{13}H_{13}N_2O_3$ 245.0926, found 245.0935 (M + H, Δ = +0.9 mDa).

6-Methyl-4-oxo-1-[3-(trifluoromethyl)phenyl]-1,4-dihydropyridazine-3-carboxylic Acid (9f): Yield 68 %, orange solid, m.p. 129.3–130.4 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 15.52 (br. s, 1 H), 8.16 (s, 1 H), 7.97–8.05 (m, 2 H), 7.88 (t, *J* = 7.9 Hz, 1 H), 7.13 (s, 1 H), 2.26 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 171.3 (C), 163.1 (C), 156.0 (C), 143.2 (C), 131.6 (CH), 131.3 (CH), 130.8 (q, *J* = 33 Hz), 127.6 (q, *J* = 4 Hz, CH), 124.2 (q, *J* = 4 Hz, CH), 123.9 (q, *J* = 271 Hz, CF_3), 120.6 (CH), 20.9 (CH_3) ppm. ^{19}F NMR (376 MHz, [D_6]DMSO): δ = –61.2 (s) ppm. IR (neat): $\tilde{\nu}$ = 1738.0 (m), 1609.1 (m), 1475.3 (s), 1439.9 (s), 1325.1 (s), 1165.7 (s), 1129.4 (s), 1103.1 (s), 1068.1 (s), 819.2 (s), 702.8 (s), 618.5 (s) cm^{-1}. LC-MS (ESI): 297.2 (M – H). HRMS (ESI): calculated for $C_{13}H_{10}N_2O_3F_3$ 299.0644, found 299.0649 (M + H, Δ = +0.5 mDa).

6-Methyl-1-(2-methyl-5-nitrophenyl)-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (10): Yield 66 %, cream solid, m.p. 200.1–201.5 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 15.42 (br. s, 1 H), 8.61 (d, *J* = 2.4 Hz, 1 H), 8.40 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.81 (d, *J* = 8.5 Hz, 1 H), 7.13 (d, *J* = 0.9 Hz, 1 H), 2.20 (s, 3 H), 2.19 (d, *J* = 0.7 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 171.3 (C), 163.0 (C), 156.1 (C), 146.8 (C), 144.0 (C), 143.3 (C), 141.2 (C), 133.3 (CH), 125.7 (CH), 123.2 (CH), 120.6 (CH), 20.1 (CH_3), 17.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1732.0 (s), 1596.8 (m), 1527.5 (m), 1443.5 (s), 1347.5 (s), 1284.4 (s), 1077.1 (m), 892.2 (m), 840.4 (m), 737.6 (s), 645.5 (m) cm^{-1}. LC-MS (ESI): 288.2 (M – H). HRMS (ESI): calculated for $C_{13}H_{12}N_3O_5$ 290.0777, found 290.0776 (M + H, Δ = –0.1 mDa).

1-(2,4-Difluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (11): Yield 65 %, pale brown solid, m.p. 194.0 °C (dec.). ^1H NMR (400 MHz, [D_6]DMSO): δ = 15.08 (s, 1 H), 7.89 (td, *J* = 8.9, 5.8 Hz, 1 H), 7.71 (ddd, *J* = 10.4, 8.9, 2.8 Hz, 1 H), 7.40 (dddd, *J* = 9.1, 8.1, 2.8, 1.4 Hz, 1 H), 2.22 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 170.8 (C), 163.5 (dd, *J* = 253.0, 12.1 Hz, CF),163.1 (C), 156.9 (dd, *J* = 253.0, 12.1 Hz, CF), 156.1 (C), 145.1 (C), 131.0 (d, *J* = 10.6 Hz, CH), 126.3 (dd, *J* = 12.7, 4.1 Hz, C), 120.2 (CH), 113.5 (dd, *J* = 23.0, 3.7 Hz, CH), 106.3 (dd, *J* = 27.6, 23.3 Hz, CH), 19.9 (CH_3) ppm. ^{19}F NMR (376 MHz, [D_6]DMSO): δ = –104.93 (d, *J* = 9.0 Hz), –118.21 (d, *J* = 9.0 Hz) ppm. IR (neat): $\tilde{\nu}$ = 1732.4 (s), 1599.4 (s), 1502.8 (s), 1470.9 (s), 1272.8 (m), 1251.9 (m), 1148.6 (m), 1091.0 (m), 966.0 (m), 940.0 (m), 893.9 (m), 859.7 (s), 739.8 (m), 611.3 (s) cm^{-1}. LC-MS (ESI): 265.2 (M – H). HRMS (ESI): calculated for $C_{12}H_9N_2O_3F_2$ 267.0581, found 267.0584 (M + H, Δ = +0.3 mDa).

1-(4-Chloro-2-nitrophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (12): Yield 67 %, tan solid, m.p. 221.2–221.8 °C (dec.). ^1H NMR (400 MHz, [D_6]DMSO): δ = 15.18 (br. s, 1 H), 8.52 (d, *J* = 2.4 Hz, 1 H), 8.17 (dd, *J* = 8.5, 2.4 Hz, 1 H), 8.09 (d, *J* = 8.5 Hz, 1 H), 7.06 (d, *J* = 0.8 Hz, 1 H), 2.27 (d, *J* = 0.8 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 170.5 (C), 163.0 (C), 155.9 (C), 145.4 (C), 144.9 (C), 136.8 (C), 135.9 (CH), 133.4 (C), 131.8 (CH), 127.0 (CH), 120.2 (CH), 20.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1732.3 (s), 1596.7 (m), 1533.5 (s), 1515.1 (s), 1475.5 (s), 1342.4 (s), 1297.4 (m), 1154.2 (m), 1119.0 (m), 969.4 (m), 866.4 (s), 846.5 (m), 762.2 (s) cm^{-1}. LC-MS (ESI): 308.2 (M – H). HRMS (ESI): calculated for $C_{12}H_9N_3O_5Cl$ 310.0231, found 310.0228 (M + H, Δ = –0.3 mDa).

1-(3-Chloro-4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (13): Yield 80 %, cream solid, m.p. 214.1–214.9 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 15.46 (br. s, 1 H), 8.05 (dd, *J* = 6.6, 2.4 Hz, 1 H), 7.85–7.51 (m, 2 H), 7.10 (d, *J* = 0.9 Hz, 1 H), 2.26 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 171.2 (C), 163.1 (C), 158.4 (d, *J* = 250.5 Hz, CF), 156.1 (C), 143.2 (C), 139.0 (d, *J* = 3.6 Hz, C), 129.7 (CH), 128.2 (d, *J* = 8.3 Hz, CH), 120.9 (d, *J* = 19.2 Hz, C), 120.5 (CH), 118.3 (d, *J* = 22.7 Hz, CH), 20.8 (CH_3) ppm. ^{19}F NMR (376 MHz, [D_6]DMSO): δ = –113.33 (s) ppm. IR (neat): $\tilde{\nu}$ = 1730.9 (s), 1621.8 (s), 1470.4 (s), 1415.4 (s), 1265.7 (s), 1220.0 (s), 1063.5 (s), 1011.6 (s), 892.0 (s), 828.2 (s), 707.9 (s) cm^{-1}. LC-MS (ESI): 281.2 (M – H). HRMS (ESI): calculated for $C_{12}H_9N_2O_3FCl$ 283.0286, found 283.0284 (M + H, Δ = –0.2 mDa).

6-Methyl-4-oxo-1-(2-phenoxyphenyl)-1,4-dihydropyridazine-3-carboxylic Acid (14): Yield 83 %, dark brown solid, m.p. 170.4–171.2 °C. ^1H NMR (400 MHz, [D_6]DMSO): δ = 15.17 (br. s, 1 H), 7.73 (d, *J* = 7.8 Hz, 1 H), 7.62 (t, *J* = 7.9 Hz, 1 H), 7.30–7.45 (m, 3 H), 7.19 (t, *J* = 7.4 Hz, 1 H), 6.95–7.15 (m, 4 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 171.1 (C), 163.0 (C), 156.5 (C), 155.3 (C), 151.9 (C), 143.6 (C), 132.8 (CH), 132.4 (C), 130.7 (CH), 129.2 (CH), 125.3 (CH), 124.7 (CH), 120.2 (CH), 119.8 (CH), 119.2 (CH), 20.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1739.5 (m), 1583.5 (m), 1488.4 (s), 1451.9 (s), 1235.7 (s), 1021.9 (m), 871.4 (s), 766.3 (s), 690.4 (s) cm^{-1}. LC-MS (ESI): 345.1 $[M + Na]^+$. HRMS (ESI): calculated for $C_{18}H_{15}N_2O_4$ 323.1026, found 323.1036 (M + H, Δ = +1 mDa).

General Procedure for the Preparation of B Series Derivatives 15–23: To a suspension of **2** (500 mg, 1.62 mmol) in MeCN (6 mL),

1,1′-carbonyldiimidazole (1.9 mmol) was added and the mixture stirrred at room temperature for 1 h. The appropriate amine (2.4 mmol) was thus added and crude reacted for additional 15 h at room temperature. For those reactions leading to a substantial precipitation of the desired product, the crude mixture was filtered. The solid was washed with MeCN (2 mL) and Et_2O (2 × 4 mL) affording pure compounds **15**–**18**, **20**. The filtrate was dried under vacuum and the residue purified by flash chromatography (CH_2Cl_2/MeOH). Alternatively, in the case of negligible precipitation, the crude mixture was diluted with EtOAc (60 mL) and the organic washed with HCl (1 M, 25 mL), H_2O (25 mL) and finally with brine (25 mL). The separated organic layer was treated with Na_2SO_4 and dried under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH) affording pure compounds **19**, **21**–**23** in yield ranging from 51 % to 89 %.

***N*,1-Bis(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (15):** Yield 72 %, cream solid, m.p. 224.8–226.6 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.29 (s, 1 H), 7.84 (d, *J* = 8 Hz, 1 H), 7.67 (d, *J* = 8 Hz, 1 H), 7.61 (d, *J* = 8 Hz, 1 H), 7.56 (d, *J* = 8 Hz, 1 H) 6.92 (s, 1 H), 2.22 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.4 (C), 159.9 (C), 153.7 (C), 145.5 (C), 141.7 (C), 137.9 (C), 133.0 (CH), 132.4 (CH), 129.2 (2CH), 123.6 (C), 122.2 (2CH), 121.0 (CH), 116.3 (C), 20.6 (CH$_3$) ppm. IR (neat): $\tilde{\nu}$ = 3060.8 (w), 1686.7 (m), 1538.7 (m), 1484.8 (s), 1395.6 (w), 1069.6 (m), 1008.2 (m), 820.6 (s), 738.01 (m), 586.5 (w) 510.31 (s) cm^{-1}. LC-MS (ESI): 461.9 [M + H]. HRMS (ESI): calculated for $C_{18}H_{14}N_3O_2Br_2$ 461.9453, found 461.9451 (M + H, Δ = –0.2 mDa).

1-(4-Bromophenyl)-6-methyl-4-oxo-*N*-phenyl-1,4-dihydropyridazine-3-carboxamide (16a): Yield 87 %, white solid, m.p. 250.7–253.1 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.24 (s, 1 H), 7.84 (d, *J* = 8 Hz, 2 H), 7.69 (d, *J* = 8 Hz, 2 H), 7.62 (d, *J* = 8 Hz, 2 H), 7.38 (t, *J* = 8 Hz, 2 H), 7.14 (t, *J* = 8 Hz, 1 H), 6.92 (s, 1 H), 2.22 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.5 (C), 159.7 (C), 153.7 (C), 145.5 (C), 141.8 (C), 138.6 (C), 133.0 (CH), 129.5 (2CH), 129.2 (2CH), 124.7 (C), 123.6 (CH), 121.0 (CH), 120.2 (CH), 20.6 (CH$_3$) ppm. IR (neat): $\tilde{\nu}$ = 3028.4 (w), 1688.1 (s), 1538.8 (m), 1483.7 (m), 1285.7 (m) 1195.7 (w), 1010.7 (w), 854.4 (m), 760.4 (s), 692.7 (m), 586.7 (m), 554.8 (s), 509.6 (m) cm^{-1}. LC-MS (ESI): 384.0 [M + H]. HRMS (ESI): calculated for $C_{18}H_{15}N_3O_2Br$ 384.0348, found 384.0338 (M + H, Δ = –1.0 mDa).

***N*-(3-Bromophenyl)-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (16b):** Yield 67 %, cream solid, m.p. 207.0–209.5 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.31 (s, 1 H), 8.07 (s, 1 H), 7.84 (d, *J* = 8 Hz, 2 H), 7.61 (d, *J* = 8 Hz, 2 H), 7.57–7.54 (m, 1 H), 7.35–7.34 (m, 2 H), 6.93 (s, 1 H), 2.22 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.3 (C), 160.1 (C), 153.8 (C), 145.4 (C), 141.7 (C), 140.1 (C), 133.1 (CH), 131.5 (CH), 129.2 (CH), 127.4 (CH), 123.6 (C), 122.6 (CH), 122.23 (C), 121.1 (CH), 119.1 (CH), 20.6 (CH$_3$) ppm. IR (neat): $\tilde{\nu}$ = 2970.6 (w), 1687.37 (m), 1588.7 (m), 1476.0 (s), 1289.1 (w), 1194.6 (w), 1067.8 (m), 1006.6 (w), 870.21 (w), 837.7 (s), 766.0 (s), 732.41 (m), 675.0 (m), 561.7 (m), 509.0 (w) cm^{-1}. LC-MS (ESI): 461.9 [M + H]. HRMS (ESI): calculated for $C_{18}H_{14}N_3O_2Br_2$ 461.9453, found 461.9455 (M + H, Δ = +0.2 mDa).

1-(4-Bromophenyl)-*N*-(3-chlorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (16c): Yield 87 %, off white solid, m.p. 209.8–211.6 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.32 (s, 1 H), 7.94 (t, *J* = 1.9 Hz, 1 H), 7.84 (d, *J* = 8 Hz, 2 H), 7.62 (d, *J* = 8 Hz, 2 H), 7.52 (d, *J* = 8 Hz, 1 H), 7.41 (d, *J* = 8 Hz, 1 H), 7.20 (d, *J* = 8 Hz, 1 H), 6.93 (s, 1 H), 2.22 (s, CH$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.3 (C), 160.1 (C), 153.8 (C), 145.4 (C), 141.7 (C), 139.9 (C), 133.8 (CH), 133.1 (CH), 131.2 (CH), 129.2 (CH), 124.4 (C), 123.6 (C), 121.1 (CH), 119.8 (CH), 118.8 (CH), 20.6 (CH$_3$) ppm. IR (neat): $\tilde{\nu}$ = 2934.0 (w), 1695.6 (m), 1592.8 (m), 1547.0 (s), 1489.8 (m), 1398.9 (w) 1291.4 (w), 1193.6 (w), 1072.4 (m), 864.8 (m), 813.9 (w), 864.8 (m), 772.6 (s), 731.9 (m), 675.4 (s), 554.1 (s), 506.8 (m) cm^{-1}. LC-MS (ESI): 417.8 [M + H]. HRMS (ESI): calculated for $C_{18}H_{14}N_3O_2ClBr$ 417.9958, found 417.9960 (M + H, Δ = +0.2 mDa).

1-(4-Bromophenyl)-*N*-(3-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (16d): Yield 66 %, cream solid, m.p. 208.2–209.9 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.35 (s, 1 H), 7.84 (d, *J* = 8 Hz, 2 H), 7.73 (d, *J* = 8 Hz, 1 H), 7.62 (d, *J* = 8 Hz, 2 H), 7.45–7.36 (m, 2 H), 6.98 (t, *J* = 8 Hz, 1 H), 6.93 (s, 1 H), 2.22 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.3 (C), 162.6 (d, *J* = 241 Hz, CF), 160.1 (C), 153.8 (C), 145.4 (C), 141.7 (C), 140.2 (d, *J* = 11 Hz, C), 133.0 (2CH), 131.2 (d, *J* = 10 Hz, CH), 129.2 (2CH), 123.6 (C), 121.1 (CH), 116.1 (d, *J* = 3 Hz, CH), 111.2 (d, *J* = 21 Hz, CH), 107.2 (d, *J* = 26 Hz, CH), 20.6 (CH$_3$) ppm. IR (neat): $\tilde{\nu}$ = 3060.6 (w), 1691.6 (m), 1597.2 (s), 1557.5 (m), 1488.9 (s), 1293.6 (w), 1199.5 (m), 1142.8 (m), 1015.2 (w), 859.0 (s), 844.3 (s), 781.6 (m), 737.8 (m), 683.0 (m), 587.5 (m), 564.2 (m), 504.4 (w) cm^{-1}. LC-MS (ESI): 417.8 [M + H]. HRMS (ESI): calculated for $C_{18}H_{14}N_3O_2FBr$ 402.0253, found 402.0259 (M + H, Δ = +0.6 mDa).

1-(4-Bromophenyl)-*N*-(3-methoxyphenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (16e): Yield 78 %, off white solid, m.p. 188.5–189.4 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.21 (s, 1 H), 7.84 (d, *J* = 8 Hz, 2 H), 7.61 (d, *J* = 8 Hz, 2 H), 7.40 (s, 1 H), 7.28 (t, *J* = 8 Hz, 1 H) 7.18 (d, *J* = 8 Hz, 1 H), 6.92, (s, 1 H) 6.72 (d, *J* = 8 Hz, 1 H), 3.76 (s, 3 H), 2.22 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.5 (C), 160.1 (C), 159.7 (C), 153.7 (C), 145.4 (C), 141.8 (C), 139.7 (C), 133.0 (CH), 130.4 (CH), 129.2 (CH), 123.6 (C), 121.0 (CH), 112.5 (CH), 110.2 (CH), 106.0 (CH), 55.5 (CH$_3$), 20.6 (CH$_3$) ppm. IR (neat): $\tilde{\nu}$ = 2967.8 (w), 1683.3 (s), 1597.5 (m), 1557.7 (s), 1485.7 (m), 1413.6 (w), 1292.1 (w), 1216.7 (s), 1154.4 (m), 1012.9 (w), 851.6 (w), 815.1 (m), 738.21 (m), 681.8 (m), 626.6 (w), 583.6 (w), 555.3 (s), 504.9 (w) cm^{-1}. LC-MS (ESI): 411.9 (M – H). HRMS (ESI): calculated for $C_{19}H_{17}N_3O_3Br$ 414.0453, found 414.0457 (M + H, Δ = +0.4 mDa).

1-(4-Bromophenyl)-6-methyl-4-oxo-*N*-[3-(trifluoromethyl)-phenyl]-1,4-dihydropyridazine-3-carboxamide (16f): Yield 94 %, white solid, m.p. 201.2–202.4 °C (dec.). ^{1}H NMR (700 MHz, [D$_6$]DMSO): δ = 12.36 (s, 1 H), 8.18 (s 1 H), 7.82 (m, 3 H), 7.59 (m, 3 H), 7.46 (d, *J* = 7.7 Hz, 1 H), 6.90 (s, 1 H), 2.19 (s, 3 H) ppm. ^{13}C NMR (176 MHz, [D$_6$]DMSO): δ = 170.2 (C), 160.3 (C), 153.8 (C), 145.5 (C), 141.7 (C), 139.3 (C), 133.0 (CH), 130.8 (CH), 130.1 (q, *J* = 31.5 Hz, C), 129.2 (CH), 124.4 (q, *J* = 272 Hz, CF$_3$), 123.9 (C), 123.6 (CH), 121.05 (CH), 121.04 (q, *J* = 4 Hz, CH), 116.4 (q, *J* = 4 Hz, CH), 20.6 (CH$_3$) ppm. ^{19}F NMR (376 MHz, DMSO): δ = –61.35 (s) ppm. IR (neat): $\tilde{\nu}$ = 2973.0 (w), 1697.41 (m), 1614.7 (w), 1553.9 (m), 1488.8 (m), 1416.9 (w), 1327.51 (s), 1166.1 (s), 1123.9 (s), 1069.1 (m), 1014.2 (w), 837.8 (w), 734.22 (m), 695.9 (m), 588.2 (w), 559.9 (s), 506.05 (w) cm^{-1}. LC-MS (ESI): 452.0 [M + H]. HRMS (ESI): calculated for $C_{19}H_{14}BrF_3N_3O_2$ 452.0221, found 452.0222 (M + H, Δ = +0.1 mDa).

1-(4-Bromophenyl)-*N*-(3-chloro-4-fluorophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (17): Yield 80 %, off white solid, m.p. 206.1–208.5 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.30 (s, 1 H), 8.06 (dd, *J* = 6.4, 2 Hz, 1 H), 7.85 (d, *J* = 8 Hz, 2 H), 7.63–7.58 (m, 3 H), 7.43 (t, *J* = 9.2 Hz, 1 H), 6.92 (s, 1 H), 2.22 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.2 (C), 160.1 (C), 154.1 (d, *J* = 243 Hz, C), 153.8 (C), 145.4 (C), 141.7 (C), 135.8 (d, *J* = 3 Hz, C), 133.0 (CH), 129.2 (CH), 123.6 (C), 121.8 (CH), 121.1 (CH), 120.8 (d, *J* = 7.1 Hz, CH), 119.9 (d, *J* = 18.5 Hz, C), 117.7 (d, *J* = 22 Hz, CH), 20.6 (CH$_3$) ppm. ^{19}F NMR (376 MHz, DMSO): δ = –121.39 (s) ppm. IR (neat): $\tilde{\nu}$ = 2371.7 (w), 1695.5 (m), 1554.1 (m), 1487.0 (m), 1399.1 (w), 1212.1 (m), 1006.1 (w), 865.3 (w), 814.7 (m),

732.6 (m), 691.20 (m), 587.44 (w), 524.5 (s), 493.3 (w) cm^{-1}. LC-MS (ESI): 436.0 [M + H]. HRMS (ESI): calculated for $C_{18}H_{13}BrClFN_3O_2$ 435.9864, found 435.9871 (M + H, Δ = +0.7 mDa).

1-(4-Bromophenyl)-6-methyl-4-oxo-*N*-(2-phenoxyphenyl)-1,4-dihydropyridazine-3-carboxamide (18): Yield 91 %, white solid, m.p. 253.7–254.9 °C (dec.). ^{1}H NMR (700 MHz, [D$_6$]DMSO): δ = 12.91 (s, 1 H), 8.51 (d, *J* = 7.7 Hz, 1 H), 7.81 (d, *J* = 7.7 Hz, 2 H), 7.57 (d, *J* = 7.7 Hz, 2 H), 7.36 (t, *J* = 7.7 Hz, 2 H), 7.17, (t, *J* = 7.7 Hz, 1 H), 7.13–7.08 (m, 2 H), 7.01 (d, *J* = 7.7 Hz, 2 H), 6.97 (d, *J* = 7.7 Hz, 1 H), 6.85 (s, 1 H), 2.15 (s, 3 H) ppm. ^{13}C NMR (176 MHz, [D$_6$]DMSO): δ = 170.9 (C), 159.3 (C), 157.1 (C), 153.6 (C), 145.9 (C), 143.7 (C), 141.8 (C), 133.0 (CH), 130.8 (CH), 130.4 (CH), 129.2 (CH), 125.1 (C), 124.7 (CH), 123.9 (CH), 123.6 (C), 121.7 (CH), 121.4 (CH), 119.5 (CH), 118.3 (CH), 20.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3066.3 (w), 1683.2 (m), 1592.3 (m), 1538.8 (m), 1480.5 (m), 1456.3 (s), 1218.0 (m), 1065.8 (w), 1011.1 (w), 854.9 (w), 748.1 (s), 737.0 (s), 686.9 (m), 560.6 (w), 508.3 (w) cm^{-1}. LC-MS (ESI): 475.9 [M + H]. HRMS (ESI): calculated for $C_{24}H_{19}BrN_3O_3$ 476.0610, found 476.0603 (M + H, Δ = –0.7 mDa).

1-(4-Bromophenyl)-*N*-cyclohexyl-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (19): Yield 51 %, white solid, m.p. 203.8–205.7 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.06 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 2 H) 7.57 (d, *J* = 8.8 Hz, 2 H), 6.81 (s, 1 H), 3.84–3.73 (m, 1 H), 2.17 (s, 3 H), 1.87–1.77 (m, 2 H), 1.71–1.62 (m, 2 H), 1.59–1.49 (m, 1 H), 1.43–1.18 (m, 5 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.7 (C), 160.4 (C), 153.1 (C), 145.2 (C), 141.8 (C), 133.0 (CH), 129.3 (CH), 123.5 (C), 120.8 (CH), 47.7 (CH), 32.6 (CH_2), 25.6 (CH_2), 24.5 (CH_2), 20.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2924.4 (m), 2850.1 (w), 1738.4 (w), 1684.3 (s), 1616.1 (m), 1527.0 (m), 1495.4 (m), 1207.4 (m), 1014.9 (m), 866.2 (s), 859.6 (s), 733.6 (m), 691.6 (w), 584.7 (w), 557.5 (m), 510.7 (m) cm^{-1}. LC-MS (ESI): 390.0 [M + H]. HRMS (ESI): calculated for $C_{18}H_{21}BrN_3O_2$ 390.0817, found 390.0824 (M + H, Δ = +0.7 mDa).

1-(4-Bromophenyl)-*N*-[2-(1*H*-indol-3-yl)ethyl]-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (20): Yield 90 %, off white solid, m.p. 276.5 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.88 (s, 1 H), 10.06 (t, *J* = 5.6 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 2 H), 7.61–7.54 (m, 3 H), 7.34 (d, *J* = 8 Hz, 1 H), 7.19 (s, 1 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 6.97 (t, *J* = 7.2 Hz, 1 H), 6.79 (s, 1 H), 3.60 (q, *J* = 6 Hz, 2 H), 2.94 (t, *J* = 7.2 Hz, 2 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.5 (C), 161.5 (C), 153.1 (C), 145.3 (C), 141.8 (C), 136.7 (C), 133.0 (CH), 129.3 (CH), 127.6 (C), 123.5 (C), 121.4 (CH), 120.8 (CH), 118.8 (CH), 118.7 (CH), 111.9 (C), 111.8 (CH), 40.0 (CH_2), 25.5 (CH_2), 20.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3254.3 (w), 1665.0 (s), 1612.4 (m), 1530.3 (m), 1487.0 (m), 1433.7 (w), 1359.8 (w), 1299.64 (w), 1069.0 (w), 1013.14 (m), 861.7 (m), 748.2 (s), 734.8 (m), 701.4 (m), 584.2 (w), 515.9 (m) cm^{-1}. LC-MS (ESI): 452.9 (M + 2 H). HRMS (ESI): calculated for $C_{22}H_{20}BrN_4O_2$ 451.0770, found 451.0762 (M + H, Δ = –0.8 mDa).

***N*-Benzyl-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (21):** Yield 76 %, off white solid, m.p. 202.4–203.9 °C (dec.). ^{1}H NMR (700 MHz, [D$_6$]DMSO): δ = 7.72 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 7 Hz, 2 H), 7.42 (d, *J* = 9 Hz, 2 H), 7.35 (t, *J* = 7.7 Hz, 2 H), 7.31 (t, *J* = 7 Hz, 1 H) 6.33 (s, 1 H), 3.94 (s, 2 H), 2.07 (s, 3 H) ppm. ^{13}C NMR (176 MHz, [D$_6$]DMSO): δ = 169.0 (C), 166.2 (C), 151.1 (C), 142.0 (C), 135.7 (C), 132.7 (CH), 129.3 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 122.5 (CH), 116.7 (C), 42.9 (CH_2), 20.8 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3048.7 (w), 1738.3 (w), 1649.5 (w), 1594.8 (s), 1579.7 (s), 1487.3 (m), 1396.1 (w), 1219.7 (m), 1068.4 (m), 1011.4 (w), 859.0 (w), 750.2 (m), 700.2 (s), 635.8 (m), 572.0 (w), 491.5 (m) cm^{-1}. LC-MS (ESI): 397.8 [M + H]. HRMS (ESI): calculated for $C_{19}H_{17}BrN_3O_2$, 398.0504, found 398.0507 (M + H, Δ = +0.3 mDa).

***N*-(Adamantan-1-yl)-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (22):** Yield 58 %, cream solid, m.p. 258.2–259.6 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.98 (s, 1 H), 7.81 (d, *J* = 8 Hz, 2 H), 7.57 (d, *J* = 8 Hz, 2 H), 6.79 (s, 1 H), 2.16 (s, 3 H), 2.10–1.94 (m, 9 H), 1.66 (s, 6 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.8 (C), 159.9 (C), 153.1 (C), 145.4 (C), 141.8 (C), 133.0 (CH), 129.3 (CH), 123.5 (C), 120.8 (CH), 51.6 (C), 41.5 (CH_2), 36.4 (CH_2), 29.2 (CH), 20.4 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3046.5 (w), 2899.0 (m), 2854.2 (w), 1690.2 (s), 1619.7 (m), 1554.1 (m), 1492.6 (m), 1412.7 (w), 1358.2 (w), 1214.6 (w), 1064.8 (w), 1016.3 (m), 869.4 (s), 844.2 (m), 732.6 (m), 695.6 (w), 570.4 (s), 505.9 (m) cm^{-1}. LC-MS (ESI): 442.1 [M + H]. HRMS (ESI): calculated for $C_{22}H_{25}BrN_3O_2$, 442.1130, found 442.1133 (M + H, Δ = +0.3 mDa).

1-(4-Bromophenyl)-*N*-(2-ethylhexyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide (23): Yield 89 %, white solid, m.p. 129.8–131.1 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.07 (t, *J* = 5.6 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 2 H), 7.58 (d, *J* = 8.8 Hz, 2 H), 6.81 (s, 2 H), 3.32–3.21 (m, 2 H), 2.17 (s, 3 H), 1.53–1.43 (m, 1 H), 1.36–1.21 (m, 8 H), 0.87 (t, *J* = 7.2 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 170.7 (C), 161.5 (C), 153.2 (C), 145.1 (C), 141.8 (C), 133.0 (CH), 129.3 (CH), 123.5 (C), 120.9 (CH), 41.6 (CH_2), 39.2 (CH), 31.0 (CH_2), 28.8 (CH_2), 24.4 (CH_2), 22.9 (CH_2), 20.5 (CH_3), 14.4 (CH_3), 11.3 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2959.4 (m), 2919.1 (m), 2858.4 (w), 1740.3 (m), 1677.7 (s), 1612.6 (m), 1538.7 (m), 1486.7 (m), 1464.5 (m), 1415.0 (m), 1377.9 (w), 1292.9 (w), 1208.8 (w), 1070.7 (w), 1011.8 (w), 867.9 (w), 735.3 (m), 75.4 (w), 585.5 (w), 512.5 (m) cm^{-1}. LC-MS (ESI): 420.0 [M + H]. HRMS (ESI): calculated for $C_{20}H_{27}BrN_3O_2$, 420.1287, found 420.1285 (M + H, Δ = –0.2 mDa).

Methyl 1-(4-Bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylate (24): Yield 82 %. To a suspension of **2** (10 g, 32.4 mmol) in MeOH (120 mL), H_2SO_4 95 % (0.2 mL) was added and the mixture refluxed for 15 h. The crude material was concentrated under reduced pressure and the residue diluted with CH_2Cl_2 (150 mL). The resulting solution was washed with $NaHCO_{3\ (ss)}$ (50 mL). The separated organic layer was treated with Na_2SO_4, filtered and dried under vacuum. The crude material was triturated in AcOEt (15–20 mL) and the suspension obtained was filtered. The solid was washed with Et_2O and dried yielding 8.6 g of pure titled compound as an off white powder, m.p. 171.3–172.7 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.79 (d, *J* = 8.8 Hz, 2 H), 7.57 (d, *J* = 8.8 Hz, 2 H), 6.66 (s, 1 H), 3.81 (s, 3 H), 2.13 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 167.5 (C), 163.6 (C), 152.9 (C), 148.3 (C), 141.4 (C), 133.0 (CH), 129.3 (CH), 123.4 (C), 119.9 (CH), 53.0 (CH_3), 20.8 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3027.2 (w), 2591.1 (w), 1739.6 (s), 1626.8 (m), 1487.0 (w), 1409.4 (w), 1380.2 (w), 1350.5 (w), 1314.3 (w), 1240.8 (m), 1203.6 (s), 1081.7 (m), 1014.3 (m), 861.4 (m), 848.2 (m), 798.4 (w), 761.1 (w), 733.3 (m), 713.3 (w), 592.2 (w), 571.0 (w), 513.8 (m), 473.3 (w), 422.3 (w) cm^{-1}. LC-MS (ESI): 323.5 [M + H]. HRMS (ESI): calculated for $C_{13}H_{12}BrN_2O_3$, 323.0031, found 323.0026 (M + H, Δ = –0.5 mDa).

Methyl 1-(4-Bromophenyl)-6-methyl-4-thioxo-1,4-dihydropyridazine-3-carboxylate (25): Yield 93 %. To a suspension of **24** (3 g, 9.3 mmol) in toluene (60 mL), Lawesson's reagent (3.75 g, 9.3 mmol) was added and the mixture stirred at room temperature for 1 h. The resulting orange suspension was filtered and the filtrate dried under vacuum. The residue was dissolved in CH_2Cl_2 and filtered through a silica gel pad (CH_2Cl_2) obtaining 2.93 g of pure title compound as a yellow powder, m.p. 166.3–167.6 °C (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.82 (d, *J* = 8.4 Hz, 2 H), 7.75 (s, 1 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 3.82 (s, 3 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 180.0 (C), 164.3 (C), 156.2 (C), 147.9 (C), 141.1 (C), 135.5 (CH), 133.1 (CH), 128.8 (CH), 123.9 (C), 53.2 (CH_3), 20.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2947.3 (w), 1750.3 (m), 1736.8 (s), 1567.1 (s), 1485.8 (m), 1436.2 (w), 1401.9 (w), 1273.4 (s), 1238.0 (m),

1149.4 (m), 1117.8 (s), 1078.2 (s), 1014.9 (s), 938.7 (w), 843.4 (m), 772.4 (m), 730.6 (w), 629.2 (w), 554.7 (w), 513.9 (w), 441.0 (w) cm^{-1}. LC-MS (ESI): 339.0 [M + H]. HRMS (ESI): calculated for $C_{13}H_{12}BrN_2O_2S$, 338.9803, found 338.9797 (M + H, Δ = –0.6 mDa).

5-(4-Bromophenyl)-6-methyl-2*H*-pyrazolo[4,3-*c*]pyridazin-3(5*H*)-one (26): Yield 78 %. To a solution of **25** (2 g, 5.9 mmol) in EtOH (50 mL), N_2H_4 1 M in THF (11.8 mL, 11.8 mmol) was added and the mixture refluxed for 1 h. The resulting black solution was dried under reduced pressure and the residue triturated in CH_2Cl_2 (5–10 mL). The suspension was filtered recovering 1.23 g of pure desired product as a dark brown powder. The filtrate was dried and purified by flash chromatography (CH_2Cl_2/MeOH) obtaining additional 180 mg of pure title compound, m.p. 294.8–295.5 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.92 (s, NH), 7.81 (d, *J* = 8.4 Hz, 2 H), 7.60 (d, *J* = 8.4 Hz, 2 H), 7.19 (s, 1 H), 2.17 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 160.9 (C), 143.2 (C), 142.3 (C), 140.9 (C), 135.7 (C), 132.9 (CH), 129.5 (CH), 123.3 (C), 110.8 (CH), 21.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3299.5 (w), 3252.6 (w), 1659.5 (m), 1609.0 (s), 1564.5 (m) 1388.4 (w), 1312.3 (w), 1141.2 (w), 1069.7 (w), 1014.4 (w), 846.3 (m), 779.5 (m), 724.9 (s), 677.1 (m), 582.2 (m), 549.2 (s), 491.0 (w), 415.6 (w) cm^{-1}. LC-MS (ESI): 305.1 [M + H]. HRMS (ESI): calculated for $C_{12}H_{10}BrN_4O$, 305.0038, found 305.0043 (M + H, Δ = +0.5 mDa).

General Procedures for the Preparation of C Series Derivatives 27–31. Method A: To a suspension of **25** (200 mg, 0.59 mmol) in EtOH (8 mL), the opportune hydrazine (2.4 mmol) was added and crude reacted under microwave irradiation at 150 °C for 2 h. In the case when the hydrazine was in its hydrochloride salt form, DIPEA (3 mmol) was also added. The crude mixture was concentrated and the residue diluted with CH_2Cl_2 (60 mL). The resulting solution was washed with HCl (1 M, 2 × 30 mL), water and brine. The separated organic layer was treated with Na_2SO_4 and dried under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH (**27a**, **27b**, **28a**) or hexane/AcOEt (**27c**, **28b**) affording pure compounds in yields ranging from 35 % to 58 %.

Method B: To a 0 °C cooled solution of **26** (200 mg, 0.66 mmol) in DMF (8 mL), NaH (60 % w/w in paraffin, 0.98 mmol) was added and the mixture stirred under N_2 atmosfere for 30 min. The appropriate bromo derivative was thus added at 0 °C, the crude was slowly heated at 100 °C and reacted at this temperature for additional 4 h. After cooling at room temperature the resulting solution was diluted with CH_2Cl_2 (60 mL), washed with HCl (1 M, 4 × 40 mL), water and brine. The separated organic layer was treated with Na_2SO_4 and dried under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/MeOH affording pure compounds in yields ranging from 32 % to 73 %.

5-(4-Bromophenyl)-2-phenyl-6-methyl-2*H*-pyrazolo[4,3-*c*]pyridazin-3(5*H*)-one (27a): Yield 57 %, black solid, m.p. 266.1–267.4 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.16 (d, *J* = 8 Hz, 2 H), 7.85 (d, *J* = 8 Hz, 2 H), 7.64 (d, *J* = 8 Hz, 2 H), 7.48 (t, *J* = 8 Hz, 2 H), 7.39 (s, 1 H), 7.25 (t, *J* = 8 Hz, 1 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 157.7 (C), 145.3 (C), 142.2 (C), 140.7 (C), 139.7 (C), 136.6 (C), 133.0 (CH), 129.5 (CH), 129.4 (CH), 125.6 (CH), 123.6 (C), 119.2 (CH), 110.5 (CH), 21.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1670.8 (m), 1609.4 (m), 1483.8 (m), 1345.6 (m), 1294.9 (m), 1219.2 (w), 1147.4 (w), 1100.4 (w), 1064.6 (w), 1008.9 (w), 879.4 (w), 832.7 (w), 795.8 (w), 765.5 (s), 737.4 (w), 688.5 (s), 635.5 (w), 567.5 (w), 514.2 (w), 501.9 (w), 444.0 (w), 412.7 (w) cm^{-1}. LC-MS (ESI): 381.1 [M + H]. HRMS (ESI): calculated for $C_{18}H_{14}BrN_4O$, 331.0351, found 331.0339 (M + H, Δ = –1.2 mDa).

5-(4-Bromophenyl)-2-(3-methoxyphenyl)-6-methyl-2*H*-pyrazolo[4,3-*c*]pyridazin-3(5*H*)-one (27b): Yield 52 %, dark brown solid, m.p. 230.7–231.5 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.85 (d, *J* = 8 Hz, 2 H), 7.82–7.76 (m, 2 H), 7.64 (d, *J* = 8 Hz, 2 H), 7.40–7.36 (m, 2 H), 6.85–6.82 (m, 1 H) 3.81 (s, 3 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 160.0 (C), 157.8 (C), 145.4 (C), 142.2 (C), 140.8 (C), 140.7 (C), 136.6 (C), 133.0 (CH), 130.2 (CH), 129.5 (CH), 123.6 (C), 111.4 (CH), 111.2 (CH), 110.4 (CH), 104.8 (CH), 55.7 (CH_3), 21.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3053.2 (w), 2835.3 (w), 1671.4 (m), 1598.8 (s), 1566.5 (m), 1482.8 (m), 1429.7 (w), 1349.6 (w), 1313.7 (w), 1296.4 (w), 1244.3 (s), 1210.0 (w), 1153.5 (m), 1042.3 (m), 1008.2 (w), 88.5 (w), 846.4 (s), 809.7 (w), 785.4 (s), 719.9 (m), 685.6 (m), 635.6 (w),606.3 (w), 568.2 (m), 502.1 (m), 415.22 (w) cm^{-1}. LC-MS (ESI): 411.0 [M + H]. HRMS (ESI): calculated for $C_{19}H_{16}BrN_4O_2$, 411.0457, found 411.0456 (M + H, Δ = –0.1 mDa).

5-(4-Bromophenyl)-2-(3-chlorophenyl)-6-methyl-2*H*-pyrazolo[4,3-*c*]pyridazin-3(5*H*)-one (27c): Yield 35 %, brown solid, m.p. 238.2–238.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (t, *J* = 2.0 Hz, 1 H), 8.22 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.72 (d, *J* = 8.7 Hz, 2 H), 7.39 (t, *J* = 8.1 Hz, 1 H), 7.31 (d, *J* = 8.7 Hz, 2 H), 7.22 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.96 (s, 1 H), 2.29 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.8 (C), 143.6 (C), 141.7 (C), 141.1 (C), 140.2 (C), 135.8 (C), 134.6 (C), 133.0 (CH), 129.9 (CH), 128.2 (CH), 125.5 (CH), 124.3 (C), 119.5 (CH), 117.4 (CH), 110.2 (CH), 21.6 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3114.5 (w), 1674.9 (s), 1602.7 (s), 1572.2 (m), 1482.2 (m), 1429.1 (m),1353.15 (m), 1295.02 (m), 1267.11 (w), 1151.8 (w), 1065.9 (w), 1009.9 (w), 846.7 (w), 832.8 (m), 800.0 (w), 768.6 (m), 751.8 (m), 712.4 (m), 673.8 (m), 625.9 (w), 568.4 (w), 502.6 (m), 439.9 (w) cm^{-1}. LC-MS (ESI): 413.0 [M + H]. HRMS (ESI): calculated for $C_{18}H_{13}BrClN_4O$, 414.9961, found 414.9956 (M + H, Δ = –0.5 mDa).

5-(4-Bromophenyl)-2-(4-methoxyphenyl)-6-methyl-2*H*-pyrazolo[4,3-*c*]pyridazin-3(5*H*)-one (28a): Yield 58 %, dark brown solid, m.p. 208.4–210.2 °C. ^{1}H NMR (700 MHz, [D$_6$]DMSO): δ = 8.03 (d, *J* = 9.1 Hz, 2 H), 7.81 (d, *J* = 8.6 Hz, 2 H), 7.60 (d, *J* = 8.6 Hz, 2 H), 7.33 (s, 1 H), 7.01 (d, *J* = 9.1 Hz, 2 H), 3.76 (s, 3 H), 2.21 (s, 3 H) ppm. ^{13}C NMR (176 MHz, [D$_6$]DMSO): δ = 157.1 (C), 157.0 (C), 145.0 (C), 142.2 (C), 140.7 (C), 136.2 (C), 133.1 (C), 133.0 (CH), 129.4 (CH), 123.5 (C), 120.9 (CH), 114.4 (CH), 110.3 (CH), 55.8 (CH_3), 21.1 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3043.5 (w), 2841.2 (w), 1660.2 (m), 1602.4 (m), 1579.0 (w), 1564.1 (w), 1506.7 (m), 1481.2 (w), 1436.4 (w), 1402.2 (w), 1354.6 (w), 1294.6 (w), 1249.8 (m), 1220.8 (m), 1181.2 (w), 1149.2 (w), 1103.4 (w), 1069.4 (w), 1026.8 (m), 1008.3 (w), 894.9 (w), 879.6 (w), 831.0 (s), 802.2 (s), 735.7 (w), 675.5 (w), 608.4 (m), 555.7 (m), 524.9 (s), 412.5 (w) cm^{-1}. LC-MS (ESI): 411.1 [M + H]. HRMS (ESI): calculated for $C_{19}H_{16}BrN_4O_2$, 411.0457, found 411.0446 (M + H, Δ = –1.1 mDa).

2,5-Bis(4-bromophenyl)-6-methyl-2*H*-pyrazolo[4,3-*c*]pyridazin-3(5*H*)-one (28b): Yield 56 %, brown solid, m.p. 244.9–245.7 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.15 (d, *J* = 9.0 Hz, 2 H), 7.85 (d, *J* = 8.7 Hz, 2 H), 7.67 (d, *J* = 9.0 Hz, 2 H), 7.64 (d, *J* = 8.7 Hz, 2 H), 7.40 (s, 1 H), 2.25 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 157.8 (C), 145.6 (C), 142.1 (C), 140.5 (C), 138.9 (C), 136.9 (C), 133.0 (CH), 132.2 (CH), 129.4 (CH), 123.6 (C), 120.9 (CH), 117.6 (C), 110.6 (CH), 21.2 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1679.4 (w), 1611.5 (m), 1571.6 (w), 1482.9 (m), 1391.8 (w), 1340.0 (m), 1292.7 (w), 1215.7 (w), 1143.1 (w), 1068.5 (w), 1003.7 (w), 875.6 (w), 835.6 (s), 826.0 (s), 795.9 (m), 737.9 (w), 703.8 (m), 623.7 (m), 578.4 (m), 507.5 (s), 441.7 (w) cm^{-1}. LC-MS (ESI): 459.1 [M + H]. HRMS (ESI): calculated for $C_{18}H_{13}Br_2N_4O$, 458.9456, found 458.9450 (M + H, Δ = –0.6 mDa).

2-Benzyl-5-(4-bromophenyl)-6-methyl-2*H*-pyrazolo[4,3-*c*]pyridazin-3(5*H*)-one (29): Yield 70 %, brown solid, m.p. 189.2–191.4 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.83 (d, *J* = 8.6 Hz, 2 H), 7.61 (d, *J* = 8.6 Hz, 2 H), 7.42–7.18 (m, 6 H), 5.07 (s, 2 H), 2.19 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 158.2 (C), 144.1 (C), 142.3 (C),

140.2 (C), 138.0 (C), 135.1 (C), 133.0 (CH), 129.5 (CH), 128.9 (CH), 128.1 (CH), 127.7 (CH), 123.5 (C), 110.4 (CH), 48.6 (CH_2), 21.1 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3959.7 (w), 2928.9 (w), 1740.1 (w), 1665.8 (s), 1607.0 (s), 1585.7 (m), 1492.0 (m), 1383.8 (w), 1373.4 (w), 1326.7 (w), 1288.7 (w), 1209.3 (w), 1144.5 (w), 1071.3 (w), 1013.7 (w), 856.8 (w), 863.5 (w), 802.2 (w), 775.6 (w), 720.5 (m), 700.2(s), 617.9 (w), 538.1 (s), 496.1 (w), 415.5 (w) cm^{-1}. LC-MS (ESI): 395.1 [M + H]. HRMS (ESI): calculated for $C_{19}H_{16}BrN_4O$, 395.0507, found 395.0516 (M + H, Δ = +0.9 mDa).

5-(4-Bromophenyl)-2-cyclohexyl-6-methyl-2*H*-pyrazolo[4,3-*c*]-pyridazin-3(5*H*)-one (30): Yield 32 %, brown solid, m.p. 278.6–279.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.6 Hz, 2 H), 7.27 (s, 2 H), 6.95 (s, 1 H), 4.58–4.95 (m, 1 H), 2.27 (s, 3 H), 2.00–1.79 (m, 6 H), 1.77–1.68 (m, 1 H) 1.55–1.38 (m, 2 H), 1.34–1.19 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4 (C), 142.0 (C), 141.3 (C), 134.0 (C), 132.8 (CH), 128.2 (CH), 124.0 (C), 110.4 (CH), 53.3 (CH), 31.5 (CH_2), 25.6 (CH_2), 25.3 (CH_2), 21.5 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3036.8 (w), 2926.1 (w), 2852.4 (w), 1664.5 (s), 1615.7 (s), 1559.5 (m), 1483.1 (w), 1447.7 (w), 1379.1 (w), 1347.9 (w), 1310.8 (w), 1288.5 (w), 1208.4 (w), 1142.2 (w), 1069.8 (w), 1011.1 (w), 893.2 (w), 835.8 (m), 794.9 (w), 733.7 (w), 712.7 (w), 693.21 (w), 660.6 (w), 655.1 (w), 624.5 (w), 569.7 (w), 491.8 (w), 451.6 (w) cm^{-1}. LC-MS (ESI): 409.1 $[M + Na]^+$. HRMS (ESI): calculated for $C_{18}H_{20}BrN_4O$, 387.0820, found 387.0826 (M + H, Δ = +0.6 mDa).

5-(4-Bromophenyl)-2-(2-ethylhexyl)-6-methyl-2*H*-pyrazolo[4,3-*c*]pyridazin-3(5*H*)-one (31): Yield 73 %, brown solid, m.p. 99.8–102.3 °C. ^{1}H NMR (700 MHz, [D_6]DMSO): δ = 7.86 (d, J = 7.6 Hz, 2 H), 7.65 (d, J = 7.8 Hz, 2 H), 7.29 (s, 1 H), 3.84–3.72 (m, 2 H), 2.24 (s, 3 H), 1.95–1.85 (m, 1 H), 1.41–1.20 (m, 8 H), 0.90 (s, 6 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 158.2 (C), 143.7 (C), 142.3 (C), 140.4 (C), 134.6 (C), 133.0 (CH), 129.5 (CH), 123.4 (C), 110.2 (CH), 48.1 (CH_2), 38.8 (CH), 30.5 (CH_2), 28.5 (CH_2), 23.8 (CH_2), 22.9 (CH_2), 21.1 (CH_3), 14.4 (CH_3), 10.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2956.3 (w), 2930.2 (w), 2870.7 (w), 1666.6 (s), 1606.0 (s), 1584.5 (w), 1485.5 (w), 1375.0 (w), 1279.6 (w), 1208.6 (w), 1167.2 (w), 1142.14 (w), 1066.6 (w), 1010.8 (m), 842.4 (m), 803.0 (w), 722.9 (w), 691.3 (m), 619.4 (w), 505.0 (w), 463.2 (w), 417.1 (w) cm^{-1}. LC-MS (ESI): 439.1 $[M + Na]^+$. HRMS (ESI): calculated for $C_{20}H_{26}BrN_4O$, 417.1290, found 417.1291 (M + H, Δ = 0.1 mDa).

Acknowledgments

The authors would like to thank AM Technology for the kind loan of their Coflore ATR 1 L Agitated Cell Reactor and for their invaluable technical support during the project. Financial support from the Royal Society of Chemistry (RSC) is also gratefully acknowledged. Furthermore, the authors are very grateful to A. S. Batsanov, D. S. Yufit (Department of Chemistry, Durham University) for solving the X-ray crystal structures of **2**, **6**, **7**, **16a**, **27a** and to A. Kenwright and J. A. Aguilar Malavia (Department of Chemistry, Durham University) for their technical contribution in the NMR study reported in Table 1.

Keywords: Synthetic methods · Flow reactors · Solids in flow · Protein–protein interactions · Nitrogen heterocycles · Structure–activity relationships · Medicinal chemistry

[1] a) M. S. Cheema, J. Ausió, *Genes* **2015**, *6*, 685–713; b) P. Sassone-Corsi, *Science* **2013**, *339*, 148–150; c) A. J. Bannister, T. Kouzarides, *Cell Res.* **2011**, *21*, 381–395; d) T. Bou Kheir, A. H. Lund, *Essays Biochem.* **2010**, *48*, 107–120; e) S. L. Berger, T. Kouzarides, R. Shiekhattar, A. Shilatifard, *Genes Dev.* **2009**, *23*, 781–783.

[2] a) A. Cabezas-Cruz, J. Lancelot, S. Caby, G. Oliveira, R. J. Pierce, *Front. Genet.* **2014**, *5*, 317; b) F. Coppedè, *Front. Genet.* **2014**, *5*, 220; c) C. H. Arrowsmith, C. Bountra, P. V. Fish, K. Lee, M. Schapira, *Nat. Rev. Drug Discovery* **2012**, *11*, 384–400; d) M. Tan, H. Luo, S. Lee, F. Jin, J. S. Yang, E. Montellier, T. Buchou, Z. Cheng, S. Rousseaux, N. Rajagopal, Z. Lu, Z. Ye, Q. Zhu, J. Wysocka, Y. Ye, S. Khochbin, B. Ren, Y. Zhao, *Cell* **2011**, *146*, 1016–1028; e) T. Kouzarides, *Cell* **2007**, *128*, 693–703.

[3] a) C. Y. Wang, P. Filippakopoulos, *Trends Biochem. Sci.* **2015**, *40*, 468–479; b) M. M. Perry, A. L. Durham, P. J. Austin, I. M. Adcock, K. F. Chung, *J. Biol. Chem.* **2015**, *290*, 9111–9121; c) K. A. Papavassiliou, A. G. Papavassiliou, *Trends Mol. Med.* **2014**, *20*, 477–478; d) R. Sanchez, J. Meslamani, M. M. Zhou, *Biochim. Biophys. Acta* **2014**, *1839*, 676–685; e) S. J. Conway, *ACS Med. Chem. Lett.* **2012**, *3*, 691–694; f) P. Filippakopoulos, S. Picaud, M. Mangos, T. Keates, J. P. Lambert, D. Barsyte-Lovejoy, I. Felletar, R. Volkmer, S. Müller, T. Pawson, A. C. Gingras, C. H. Arrowsmith, S. Knapp, *Cell* **2012**, *49*, 214–231; g) P. Filippakopoulos, S. Knapp, *FEBS Lett.* **2012**, *586*, 2692–2704; h) G. A. Josling, S. A. Selvarajah, M. Petter, M. F. Duffy, *Genes* **2012**, *3*, 320–343; i) M. A. Dawson, T. Kouzarides, B. J. P. Huntly, *New Engl. J. Med.* **2012**, *367*, 647–657; j) G. Zhang, R. Sanchez, M. M. Zhou, *J. Med. Chem.* **2012**, *55*, 7342–7345; k) R. K. Prinjha, J. Witherington, K. Lee, *Trends Pharmacol. Sci.* **2012**, *3*, 146–153; l) S. Muller, P. Filippakopoulos, S. Knapp, *Expert Rev. Mol. Med.* **2011**, *13*, e29; m) P. Filippakopoulos, J. Qi, S. Picaud, Y. Shen, W. B. Smith, O. Fedorov, E. M. Morse, T. Keates, T. T. Hickman, I. Felletar, M. Philpott, S. Munro, M. R. McKeown, Y. Wang, A. L. Christie, N. West, M. J. Cameron, B. Schwartz, T. D. Heightman, N. La Thangue, C. A. French, O. Wiest, A. L. Kung, S. Knapp, J. E. Bradner, *Nature* **2010**, *468*, 1067–1073.

[4] a) M. Brand, A. M. Measures, B. G. Wilson, W. A. Cortopassi, R. Alexander, M. Höss, D. S. Hewings, T. P. Rooney, R. S. Paton, S. J. Conway, *ACS Chem. Biol.* **2015**, *10*, 22–39; b) A. M. Taylor, R. G. Vaswani, V. S. Gehling, M. C. Hewitt, Y. Leblanc, J. E. Audia, S. Bellon, R. T. Cummings, A. Côté, J. C. Harmange, H. Jayaram, S. Joshi, J. M. Lora, J. A. Mertz, A. Neiss, E. Pardo, C. G. Nasveschuk, F. Poy, P. Sandy, J. W. Setser, R. J. Sims, Y. Tang, B. K. Albrecht, *ACS Med. Chem. Lett.* **2016**, *7*, 145–150; c) J. Bennett, O. Fedorov, C. Tallant, O. Monteiro, J. Meier, V. Gamble, P. Savitsky, G. A. Nunez-Alonso, B. Haendler, C. Rogers, P. E. Brennan, S. Müller, S. Knapp, *J. Med. Chem.* **2016**, *59*, 1642–1647; d) M. G. J. Baud, E. Lin-Shiao, M. Zengerle, C. Tallant, A. Ciulli, *J. Med. Chem.* **2016**, *59*, 1492–1500; e) M. Xu, A. Unzue, J. Dong, D. Spiliotopoulos, C. Nevado, A. Caflisch, *J. Med. Chem.* **2016**, *59*, 1340–1349; f) P. Chen, A. Chaikuad, P. Bamborough, M. Bantscheff, C. Bountra, C. Chung, O. Fedorov, P. Grandi, D. Jung, R. Lesniak, M. Lindon, S. Müller, M. Philpott, R. Prinjha, C. Rogers, C. Selenski, C. Tallant, T. Werner, T. M. Willson, S. Knapp, D. H. Drewry, *J. Med. Chem.* **2016**, *59*, 1410–1424; g) W. S. Palmer, G. Poncet-Montange, G. Liu, A. Petrocchi, N. Reyna, G. Subramanian, J. Theroff, A. Yau, M. Kost-Alimova, J. P. Bardenhagen, E. Leo, H. E. Shepard, T. N. Tieu, X. Shi, Y. Zhan, S. Zhao, M. C. Barton, G. Draetta, C. Toniatti, P. Jones, M. Geck Do, J. N. Andersen, *J. Med. Chem.* **2016**, *59*, 1440–1454; h) N. H. Theodoulou, P. Bamborough, A. J. Bannister, I. Becher, R. A. Bit, K. Hing Che, C. Chung, A. Dittmann, G. Drewes, D. H. Drewry, L. Gordon, P. Grandi, M. Leveridge, M. Lindon, A. Michon, J. Molnar, S. C. Robson, N. C. O. Tomkinson, T. Kouzarides, R. K. Prinjha, P. G. Humphreys, *J. Med. Chem.* **2016**, *59*, 1425–1439; i) P. G. Clark, L. C. Vieira, C. Tallant, O. Fedorov, D. C. Singleton, C. M. Rogers, O. P. Monteiro, J. M. Bennett, R. Baronio, S. Müller, D. L. Daniels, J. Méndez, S. Knapp, P. E. Brennan, D. J. Dixon, *Angew. Chem. Int. Ed.* **2015**, *54*, 6217–6221; *Angew. Chem.* **2015**, *127*, 6315; j) D. A. Hay, C. M. Rogers, O. Fedorov, C. Tallant, S. Martin, O. P. Monteiro, S. Müller, S. Knapp, C. J. Schofield, P. E. Brennan, *Med. Chem. Commun.* **2015**, *6*, 1381–1386; k) P. Bamborough, C. Chung, R. C. Furze, P. Grandi, A. Michon, R. J. Sheppard, H. Barnett, H. Diallo, D. P. Dixon, C. Douault, E. J. Jones, B. Karamshi, D. J. Mitchell, R. K. Prinjha, C. Rau, R. J. Watson, T. Werner, E. H. Demont, *J. Med. Chem.* **2015**, *58*, 6151–6178; l) E. H. Demont, C. Chung, R. C. Furze, P. Grandi, A. Michon, C. Wellaway, N. Barrett, A. M. Bridges, P. D. Craggs, H. Diallo, D. P. Dixon, C. Douault, A. J. Emmons, E. J. Jones, B. V. Karamshi, K. Locke, D. J. Mitchell, B. H. Mouzon, R. K. Prinjha, A. D. Roberts, R. J. Sheppard, R. J. Watson, P. Bamborough, *J. Med. Chem.* **2015**, *58*, 5649–5673; m) L. Drouin, S. McGrath, L. R. Vidler, A. Chaikuad, O. Monteiro, C. Tallant, M. Philpott, C. Rogers, O. Fedorov, M. Liu, W. Akhtar, A. Hayes, F. Raynaud,

S. Müller, S. Knapp, S. Hoelder, *J. Med. Chem.* **2015**, *58*, 2553–2559; n) L. Zhao, Y. Wang, D. Cao, T. Chen, Q. Wang, Y. Li, Y. Xu, N. Zhang, X. Wang, D. Chen, L. Chen, Y. Chen, G. Xia, Z. Shi, Y. Liu, Y. Lin, Z. Miao, J. Shen, B. Xiong, *J. Med. Chem.* **2015**, *58*, 1281–1297; o) S. Picaud, M. Strocchia, S. Terracciano, G. Lauro, J. Mendez, D. L. Daniels, R. Riccio, G. Bifulco, I. Bruno, P. Filippakopoulos, *J. Med. Chem.* **2015**, *58*, 2718–2736; p) X. Ran, Y. Zhao, L. Liu, L. Bai, C. Yang, B. Zhou, J. L. Meagher, K. Chinnaswamy, J. A. Stuckey, S. Wang, *J. Med. Chem.* **2015**, *58*, 4927–4939.

[5] P. Filipponi, A. Gioiello, I. R. Baxendale, *Org. Proc. Res. Dev.* **2016**, *20*, 371–375.

[6] a) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688–6728; *Angew. Chem.* **2015**, *127*, 6788; b) I. R. Baxendale, *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519–552; c) I. R. Baxendale, L. Brocken, C. J. Mallia, *Green Process Synth.* **2013**, *2*, 211–230; d) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384–6389; e) I. R. Baxendale, R. D. Braatz, B. K. Hodnett, K. F. Jensen, M. D. Johnson, P. Sharratt, J. P. Sherlock, A. J. Florence, *J. Pharm. Sci.* **2015**, *104*, 781–791; f) M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2015**, *11*, 1194–1219; g) R. M. Myers, D. E. Fitzpatrick, R. M. Turner, S. V. Ley, *Chem. Eur. J.* **2014**, *20*, 12348–12366; h) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849–8869.

[7] a) P. Salice, D. Fenaroli, C. C. De Filippo, E. Menna, G. Gasparini, M. Maggini, *Chimica Oggi-Chem. Today* **2012**, *30*, 37–39; b) E. Jones, K. McClean, S. Housden, G. Gasparini, I. Archer, *Chem. Eng. Res. Des.* **2012**, *90*, 726–731; c) R. Ashe, *Speciality Chemicals Magazine* **2012**, *32*, 38–39; d) D. L. Browne, B. J. Deadman, R. Ashe, I. R. Baxendale, S. V. Ley, *Org. Process Res. Dev.* **2011**, *15*, 693–697.

[8] See: http://www.cambridgereactordesign.com/polarbearplus/ website for details and D. L. Browne, M. Baumann, B. H. Harji, I. R. Baxendale, S. V. Ley, *Org. Lett.* **2011**, *13*, 3312–3315.

[9] Cost action designation number CM1106.

Received: February 25, 2016
Published Online: March 22, 2016

