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

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Abstract: A continuous flow process delivering key building-blocks for a series of BCP modulator libraries is reported. A dynamically mixed flow reactor has emerged as a pivotal technology in both synthetic and isolation phases enabling the processing of slurries and suspension whilst maintaining high productivity and reliability. Indeed, a key requirement of the synthesis is the rapid, large scale delivery of target compounds for progression into different lead optimization series. Accordingly, the common intermediates are employed herein to build a pyridazone based library (36 compounds) addressed at improving the lead potency and selectivity while further exploring the SAR of a new BCPs 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 regulating physiological and environmental stimuli in 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 target with potential applications in oncology as well as for the treatment of neurological and inflammatory diseases.[3] Indeed, numerous compounds have been disclosed to modulate bromodomain mediated protein-protein interactions also 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 block **1** and **2** (Figure 1).[5] The reported flow protocol featured a dynamically mixed reactor as enabling technology instrumental to process slurries and suspensions at scale redefining, moreover, the generation of solids in flow from a limitation into a designed in-line operation directed at improving the process safety and product quality.

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Supporting information is available from:

The major goal of this study is the rapid delivery of quantities of target compounds in order to sustain an advanced medicinal chemistry program. Herein, along with the detailed optimization of the multi-gram scale synthesis of key intermediates **1** and **2**, the synthesis of three lead development series based around the common 6-methyl-1-arylpyridazine nucleus (**A**-**C**, Figure 1) are reported and discussed.

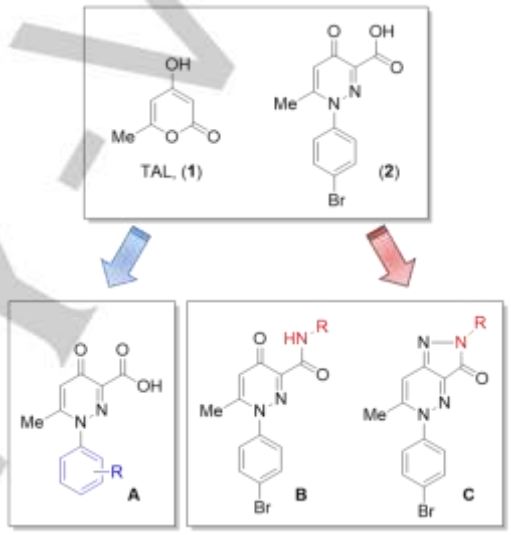
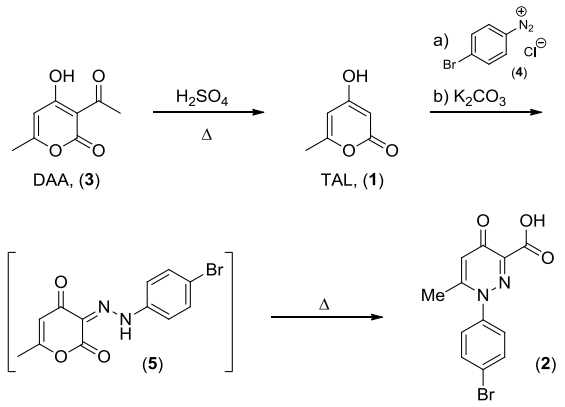


Figure 1. Building blocks (**1**, **2**) selected for the generation of a focused library designed around three general templates **A**-**C**.

Results and Discussion

Process Development

In the first phase of the study, we focused our attention on the process modelling and optimization of compound **1** and **2** aimed at developing scalable syntheses for their production. The selected approach for the preparation of compounds **1** and **2** comprises two practical synthetic steps starting from a sulfuric acid promoted deacylation of dehydroacetic acid (DAA, **3**, Scheme 1). The resulting triacetic acid lactone (TAL, **1**) is then reacted in a convergent process with a diazonium salt to form the intermediate hydrazone **9** which is directly submitted to an alkaline thermal rearrangement to yield the target structure **2** (Scheme 1). Whereas this strategy ensures acceptable reaction yields and batch purities at laboratory scales, it required a comprehensive re-optimisation in order to cope with several processing and isolation issues which emerged upon scaling-up the reactions. To translate the selected synthetic sequence into a flow-based process,[6] 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 typically 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 at 130 °C for 15-30 min, cooled and poured into 2.5 volumes of iced water. The mixture was stirred vigorously for 10-15 minutes and the resulting suspension filtered and dried. The desired TAL product (**1**) was obtained in variable isolated yields ranging from 68% to 80%. With the aim of translating the reaction to flow we directed our initial evaluation efforts at appraising the sulfuric acid concentration and heating temperature on the yield.

We immediately found that the amount of water present in the reaction mixture had a critical impact on determining the product speciation. Using a high water content changed the reaction outcome allowing two alternative products to be isolated and characterised (**6**, **7** Figure 2).

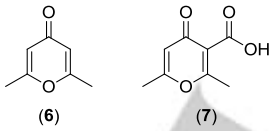


Figure 2. Principal by-products isolated in the synthesis of TAL (**1**): 3,5-dimethyl-4-pyrone (**6**) and 2,6-dimethyl-4-oxo-*4H*-pyran-3-carboxylic acid (**7**).

The symmetrical 3,5-dimethyl-4-pyrone (**6**) was recovered as the main component when performing the reaction in dilute (10, 25, 60 wt%), hot (>100 °C) sulfuric acid. A reduction in the percentage of water corresponded to an increase in the presence of the parent lactone; 2,6-dimethyl-4-oxo-*4H*-pyran-3-carboxylic acid (**7**) (Table 1, entries 1-3). A simple trend was also determined for temperature; experiments demonstrated that a deviation from the optimal setting (130 °C) translated to a decrease in yield and prolonged reaction times (Table 1, entries 9-13).

However, the principle reason for low isolated yields was determined to be inefficiencies in the workup sequence. This was demonstrated by the significant differences between the final isolated and ^{1}H-NMR determined yield (Table 1, Entries 4 and 5).

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

Entry	H_2SO_4	Temp.(°C)	H-NMR yield[b]			Isolated Yield (**1**)
			1	**6**	**7**	
1	25%	reflux	-	90%	-	-
2	10%	reflux	-	>90%	-	-
3	60%	110	55%	-	10%	28%
4	75%	130	-	-	-	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] Determined 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.

Interestingly we found no discernible decrease in the isolated yield 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 white flocculent solid. By comparison decreasing the amount of water had a negative impact producing a solid which rapidly agglutinates and became extremely difficult to filter and dry. This immediately became a process limiting issue as the working scale increased. We also noted the quench temperature required careful regulation as at elevated temperatures >15 °C as generated by the very exothermic mixing side reactions occurred which affected the yield and purity (Table 2; entries 6-7). This was particularly noticeable at higher reaction scales were appreciable off gassing was noted presumably from hydrolysis of the product and its subsequent decarboxylation (Table 2, entry 7).

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

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

[a] Reaction conditions: DAA (**3**) (15 mmol, 3.7 M), H_2SO_4 >95%, 130 °C, 15 min. [b] Quenching: the crude mixture was poured in iced water maintained at 0-5 °C. [c] Addition of the crude mixture to ambient temperature water. [d] Reaction conditions: DAA (**3**) (4 mol, 3.7 M), H_2SO_4 >95%, 130 °C, 15 min. Addition of the crude mixture to 5 volumes of iced water over 10 minutes, internal temperature reaches 26 °C.

We concluded from our explorative study that the use of concentrated (>95%) sulfuric acid at high temperature (130 °C) were key reaction attributes leading to excellent conversion. Furthermore accurate control of the quenching parameters like temperature and mixing efficiency (including the amount of water) emerged as critical aspects in ensuring a high isolated yield and contributed significantly to the overall success of the process. Based upon these considerations we envisaged to gain both operational safety and product processing benefits by implementation of flow technologies, gaining profitable 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]

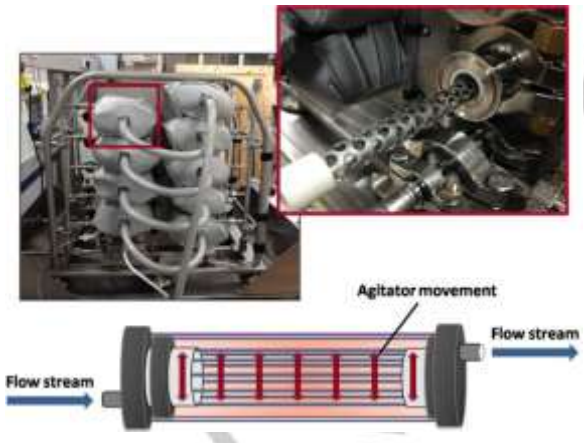
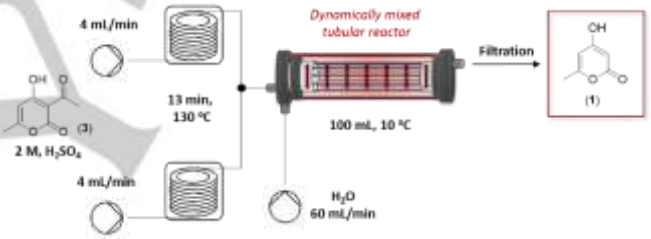


Figure 3. The AM Technology Coflore® ATR. The reactor has ten interconnected tubes with a total reactor volume of 1 L. All pipes are equipped with an internal dynamic mixer which generates a turbulent flow stream through lateral shacking.

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 MedChem module into two parallel configured polar bear flow synthesisers equipped with PTFE coil reactors (volume 52 mL, temperature 130 °C). 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 connector of the 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 (Scheme 2). The process was run continuously with periodic removal of the filtered material delivering a high productivity (116 g/h dry mass, 96% yield). Therefore, whilst minimizing the safety issues of handling concentrated sulfuric acid, the devised flow configuration also ensured a nearly quantitative recovering of the TAL easily isolated by filtration as an off white, fine powder.



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

Our next challenge was the optimization and scale up of the synthesis of pyridazone **2** (Scheme 1). The selected approach involved a multi-step sequence comprising a base catalyzed addition of lactone **1** (0.2 M) with a fleshly generated aryl diazonium salt **4**. In batch the resulting suspension was heated at reflux for three hours to promote the intramolecular cyclisation to the rearranged hydrazone **5**. The dark red homogenous 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.

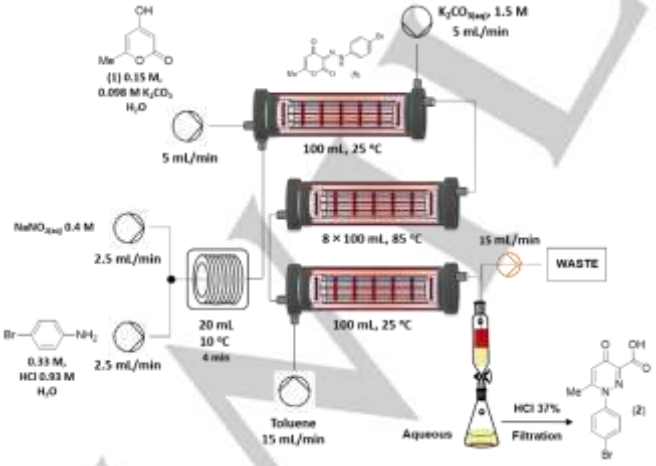
For example, the initial coupling reaction (**1**+**4**→**5**) is strongly exothermic (mixing acid/base solutions) and therefore requires the dropwise addition of the diazonium salt solution resulting in prolonged reaction times. This was additionally problematic as certain diazonium salts proved unstable and degraded over time to yield varying amounts of the corresponding phenols. Scaling up also increases the necessary addition time and as a consequence gives higher levels of impurity. A further issue was found upon scale up relating to the selection of the alkali carbonate base which promoted the

rearrangement. At scale copious CO_2 evolution combined with the insolubility of the hydrazone intermediate **5**, results in significant foaming with deleterious effects on mixing efficiency which impacted upon the reaction time. We thus designed a multistep flow process again based upon the use of the ATR reactor selected for its ability to process slurries and suspension whilst ensuring enhanced mixing and isothermal control.

Diazonium salt coupling

The 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 temperature (-10 °C to 25 °C) delivering a continuous stream of the 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 equivalents) 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 rt). The intermediate **5** could be easily processed under dynamic mixing with a residence time of 10 minutes. The outflow suspension, if required, could be continuously filtered allowing isolation of compound **5** in almost quantitative yield and high purity as a fine yellow powder.

It is worthy of note that in comparison to the original batch procedure these flow conditions are much milder. As a consequence we encountered less degradation of the 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 highly problematic at scale in batch were also diminished increasing the efficiency of the reaction.



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**).

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 8 interconnected ATR chambers (temperature maintained at 85 °C) corresponding to a total residence time of approx. 53 minutes (Scheme 3).

In batch we had found that isolation of the 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 by an dark red oily residue which furthermore affected the filtration process. We thus decided to implement an on-line extraction by using the final ATR reactor chamber. A flow stream of toluene pumped at 15 mL/min was added and the biphasic mixture processed through the final 100 mL dynamically agitated tube (residence time 3.3 min). The outflow was 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 dried under vacuum to yield the desired pure product **2** in an overall 73%. This multistep sequence had a productivity of 9.6 g/h.

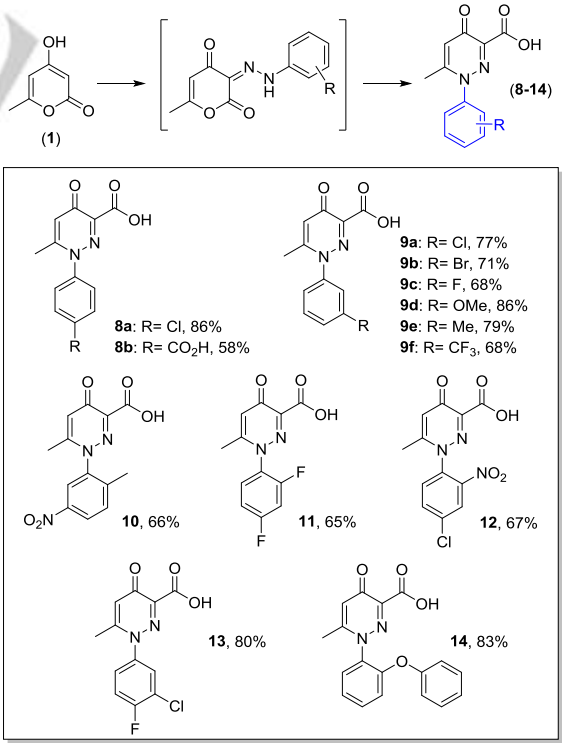


Figure 3. A series compounds synthesized by reacting TAL (**1**) with different substituted diazonium salts.

Following the successful development of the flow process to prepare key building block **2** we were able to utilise the same reactor to generate a small derivative library (Figure 3). Pyranone **1** was therefore used as the starting material for the preparation of 13 materials **8**-**14** characterised by different substituents at the phenyl moiety all isolated in good yield by means of acidification and filtration of the crude aqueous mixtures as described above.

Library construction

Our preliminary medicinal chemistry screening had identified the 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 example lead development series (**B** and **C**, Figure 1) which generated compounds readily available for biological testing. It should be highlighted that the library preparation was rapidly progressed due to bulk quantities of the 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 **2** with 1,1'-carbonyldiimidazole (CDI) in MeCN for 1 h. The active amide was then mixed with the desired amine and the reaction stirred overnight at ambient temperature. Several of the products formed a precipitate allowing the product to be directly filtered. The solid was 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% to 77%. In each case additional material could also be recovered by flash chromatography purification of the filtrate. Other compounds gave negligible precipitation, these products **19**, **21**-**23** required direct silica column purification but again resulted in high yields of the coupled products. As depicted in Figure 4, 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.

In order to gain additional insight in the structure activity relationship of this new class of BCPs modulators and in line with a generally adopted medicinal chemistry strategy, we further designed a series of constrained derivatives (**C**, Figure 1). In particular, for the better understanding of the influence of the amide orientation on both affinity and selectivity, we planned to lock the β-ketoamide moiety into a pyrazole structure. In this way, we achieved a selective functionalization at the *N-1* position of the pyrazole portion 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 the more reactive thioxo ester derivative **25**. Accordingly, after the esterification of the starting material **2**, the new intermediate **24** was treated with Lawesson's reagent in toluene. For the preparation of aryl derivatives **27**-**28**, the resulting compound **25** was reacted with different substituted hydrazines under microwave irradiation at 150 °C for 2 h (*Method A*, Scheme 4). Despite the forcing reaction conditions only moderate conversions could be achieved. However, the efficiency and levels of automation derived from the use of a microwave synthesizer coupled with robot arm, resulted in a general reduction in processing time when compared with the batch procedure. For example, an essentially identical yield was obtained in preparing derivative **28a** by heating the reaction mixture at reflux for 48 h.

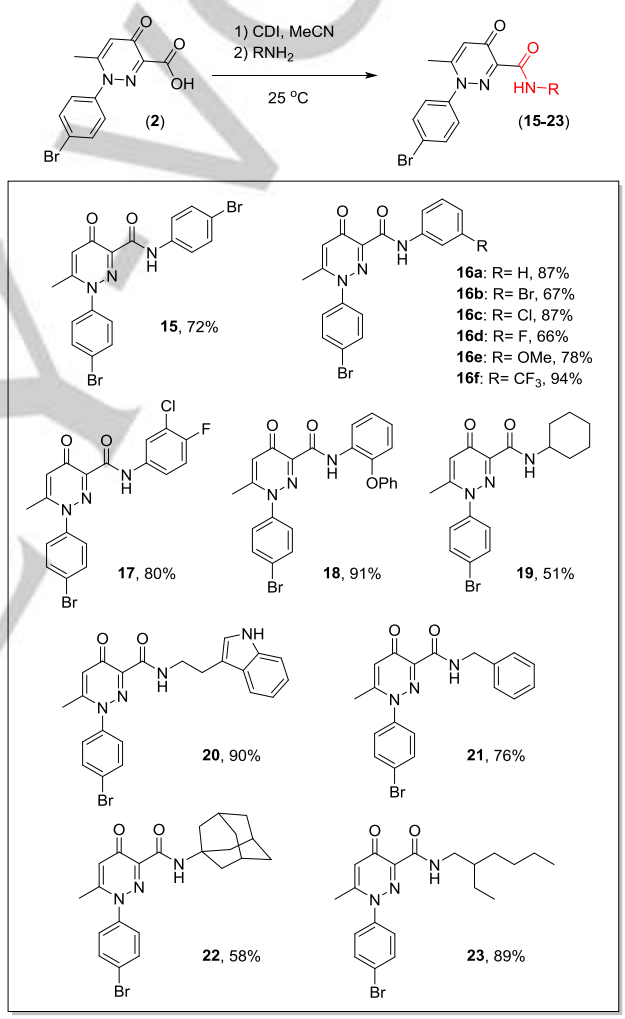
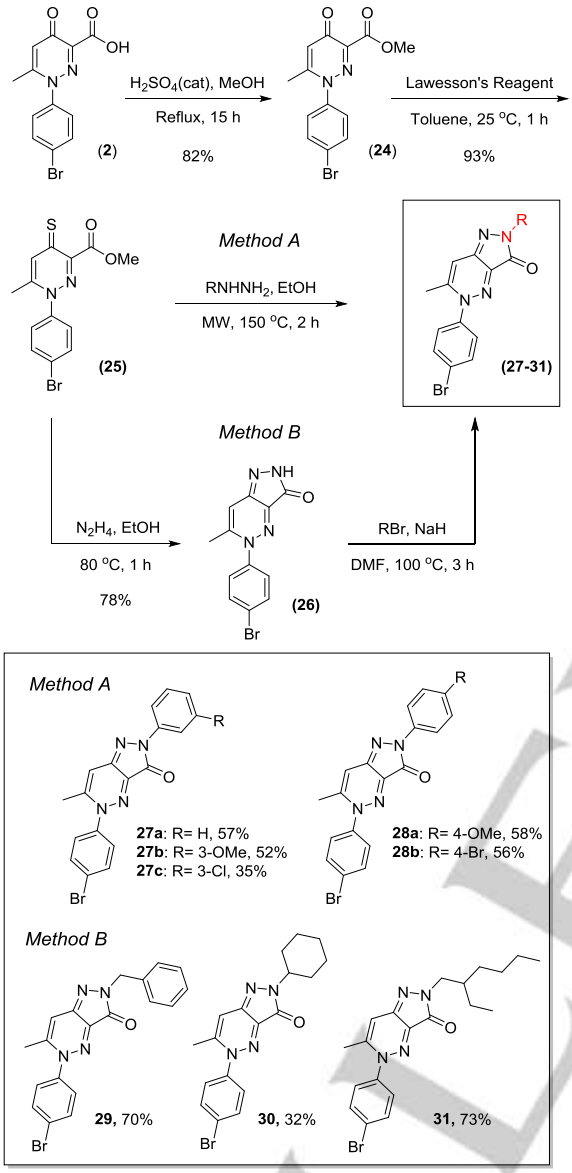


Figure 4. B series amide derivatives prepared starting from the intermediate **2**.

Alternatively the benzyl and alkyl compounds **29**-**31** could be synthesized by initial condensation of the thio derivative **25** with hydrazine in good overall isolated yield (*Method B*, Scheme 4). The subsequent *N*-functionalization of **26** with an alkyl bromide emerged as a valuable synthetic approach yielding compounds

29-**31** in moderate to excellent yield. The compounds could be easily purified by column chromatography. This again demonstrated the versatility of the scaffold to rapid and selective structural modification.



Scheme 4. Synthetic strategy adopted for the preparation of **C** series pyrazolo[4,3-c]pyridazine derivatives **27**-**31**.

Conclusions

Over the last year, the modulation of bromodomains mediated protein-protein interactions have emerged as one of the most promising intervention area for epigenetic therapies. The novelty and potential of these biological targets have stimulated intense research activity with many promising results particularly in oncology. However, consistently with the multi-regulatory behaviour of various bromodomains and BCPs, the comprehensive understanding of their physio-pathological role still demands the 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**, Figure 1) instrumental for the rapid synthesis of focused BCPs modulators 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 the produced building blocks allowed for an accelerated generation of a compound collection based upon the pyridazinone scaffold (**A**-**C**, Figure 1). These new BCPs modulators were specifically designed to provide insight on the hydrophobic moieties influence on both potency and selectivity. We are confident therefore that their biological assays combined with the chemical diversity explored, will contribute to extend their SAR and pharmacological profile, and, in general, will support the ongoing research efforts geared toward the better understanding of the BCPs biology and therapeutic potential.

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 on 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 x 1.5 mm, o.d. x i.d) and connectors.^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker Avance-400 instrument and are reported relative to $CDCl_3$ (δ 7.26 ppm and δ 77.2 ppm respectively) or DMSO-d6 (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 on the above instrument at a frequency of 376 MHz using DMSO as external standard. IR spectra were obtained by use of 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 on either Waters LCT Premier XE or Waters TQD instruments equipped with 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-2H-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 at 10 °C. The resulting suspension was filtered and the pale yellow solid dried under vacuum obtaining the pure title compound **1** in 92% yield.
Mp: 185.6 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 5.96 (s, 1H), 5.21 (s, 1H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.0 (C), 164.4 (C), 163.8 (C), 100.6 (CH), 88.6 (CH), 19.9 (CH_3). IR (neat): 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 at 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.
Mp: 214.0 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.55 (brs, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J*= 8.4 Hz, 2H), 7.12 (s, 1H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat):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 building

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, 86 %
Compound description: white solid. Mp: 216.0 - 217.2 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.57 (brs, 1H), 7.72 (d, *J* = 9.6 Hz, 2H), 7.68 (d, *J* = 9.6 Hz, 2H), 7.13 (s, 1H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat):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, 58 %.
Compound description: pale orange solid. Mp: 243 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.35 (br s, 1H), 13.53 (brs, 1H), 8.16 (d, *J*= 8.5 Hz, 2H), 7.76 (d, *J*= 8.5 Hz, 2H), 7.12 (d, *J* = 0.8 Hz, 1H), 2.27 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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, 77 %.
Compound description: off white solid. Mp: 222.6 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.55 (brs, 1H), 7.96 (t, *J* = 2.0 Hz, 1H), 7.85 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.69 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J*= 0.7 Hz, 1H), 2.27 (d, *J*= 0.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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, 71 %.
Compound description: white solid. Mp: 194.9 - 196.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.54 (brs, 1H), 7.86–7.83 (m, 1H), 7.74–7.70 (m, 1H), 7.69–7.62 (m, 2H), 7.12 (d, *J*= 0.8 Hz, 1H), 2.27 (d, *J*= 0.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat):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, 68 %.
Compound description: white solid. Mp: 106.2 - 108.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.53 (brs, 1H), 7.73 – 7.62 (m, 2H), 7.56 – 7.48 (m, 2H), 7.12 (d, *J*= 0.8 Hz, 1H), 2.27 (d, *J*= 0.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.44 (s). IR (neat): 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, 86 %.
Compound description: dark brown solid. Mp: 186.2 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.71 (brs, 1H), 7.53 (t, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 2.2 Hz, 1H), 7.15 - 7.22 (m, 2H), 7.14 (d, *J* = 0.9 Hz, 1H), 3.82 (s, 3H), 2.27 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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).

1-(*m*-tolyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid, 9e, 79 %.

Compound description: cream solid. Mp: 204.4 - 205.1 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.74 (brs, 1H), 7.55 – 7.48 (m, 1H), 7.46 – 7.39 (m, 3H), 7.14 (d, *J* = 0.8 Hz, 1H), 2.41 (s, 3H), 2.26 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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).

1-(3-(trifluoromethyl)phenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid, 9f, 68 %.
Compound description: orange solid. Mp: 129.3 - 130.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.52 (brs, 1H), 8.16 (s, 1H), 7.97-8.05 (m, 2H), 7.88 (t, *J* = 7.9 Hz, 1H), 7.13 (s, 1H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). ^{19}F NMR (376 MHz, DMSO-d_6) δ -61.2 (s). IR (neat): 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).

1-(2-methyl-5-nitrophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid, 10, 66 %.
Compound description: cream solid. Mp: 200.1 - 201.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.42 (brs, 1H), 8.61 (d, *J* = 2.4 Hz, 1H), 8.40 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.13 (d, *J* = 0.9 Hz, 1H), 2.20 (s, 3H), 2.19 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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, 65 %.
Compound description: pale brown solid. Mp: 194.0 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.08 (s, 1H), 7.89 (td, *J* = 8.9, 5.8 Hz, 1H), 7.71 (ddd, *J* = 10.4, 8.9, 2.8 Hz, 1H), 7.40 (dddd, *J* = 9.1, 8.1, 2.8, 1.4 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). ^{19}F NMR (376 MHz, DMSO-d_6) δ -104.93 (d, *J* = 9.0 Hz), -118.21 (d, *J* = 9.0 Hz). IR (neat): 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, 67 %.
Compound description: tan solid. Mp: 221.2 - 221.8 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.18 (brs, 1H), 8.52 (d, *J* = 2.4 Hz, 1H), 8.17 (dd, *J* = 8.5, 2.4 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 0.8 Hz, 1H), 2.27 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat):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, 80 %.
Compound description: cream solid. Mp: 214.1 - 214.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.46 (brs, 1H), 8.05 (dd, *J* = 6.6, 2.4 Hz, 1H), 7.85 – 7.51 (m, 2H), 7.10 (d, *J* = 0.9 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.33 (s). IR (neat):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).

1-(2-phenoxyphenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic acid, 14, 83%.
Compound description: dark brown solid. Mp: 170.4 - 171.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.17 (brs, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.30 - 7.45 (m, 3H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.95 - 7.15 (m, 4H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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 strirred 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) obtaining pure compounds **15**-**18**, **20**. The filtrate was dryed 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,** 72 %.
Compound description: cream solid. Mp: 224.8 - 226.6 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.67 (d, *J* = 8 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.56 (d, *J* = 8 Hz, 1H) 6.92 (s, 1H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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).

***N*-phenyl-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide, 16a,** 87%.
Compound description: white solid. Mp: 250.7 - 253.1 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 7.84), 7.69 (d, *J* = 8 Hz,

2H), 7.62 (d, *J* = 8 Hz, 2H), 7.38 (t, *J* = 8 Hz, 2H), 7.14 (t, *J* = 8 Hz, 1H), 6.92 (s, 1H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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,** 67%.
Compound description: cream solid. Mp: 207.0 - 209.5 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.07 (s, 1H), 7.84 (d, *J* = 8 Hz, 2H), 7.61 (d, *J* = 8 Hz, 2H), 7.57-7.54 (m, 1H), 7.35-7.34 (m, 2H), 6.93 (s, 1H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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).

***N*-(3-chlorophenyl)-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide, 16c,** 87%.
Compound description: off white solid. Mp: 209.8 - 211.6 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 7.94 (t, *J* = 1.9 Hz, 1H), 7.84 d, *J* = 8 Hz, 2H), 7.62 (d, *J* = 8 Hz, 2H), 7.52 (d, *J* = 8 Hz, 1H), 7.41 (d, *J* = 8 Hz, 1H), 7.20 (d, *J* = 8 Hz, 1H), 6.93 (s, 1H), 2.22 (s, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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).

***N*-(3-fluorophenyl)-*1*-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide, 16d,** 66%.
Compound description: cream solid. Mp: 208.2 - 209.9 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 1H), 7.84 (d, *J* = 8 Hz, 2H), 7.73 (d, *J* = 8 Hz, 1H), 7.62 (d, *J* = 8 Hz, 2H), 7.45 - 7.36 (m, 2H), 6.98 (t, *J* = 8 Hz, 1H), 6.93 (s, 1H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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).

***N*-(3-methoxyphenyl)-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide, 16e,** 78%.
Compound description: off white solid. Mp: 188.5 - 189.4 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 7.84 (d, *J* = 8 Hz, 2H), 7.61 (d, *J* = 8 Hz, 2H), 7.40 (s, 1H), 7.28 (t, *J* = 8 Hz, 1H) 7.18 (d, *J* = 8 Hz, 1H), 6.92, (s, 1H) 6.72 (d *J* = 8 Hz, 1H), 3.76 (s, 3H), 2.22 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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).

***N*-(3-(trifluoromethyl)phenyl)-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide, 16f,** 94%.
Compound description: white solid. Mp: 201.2 - 202.4 °C (decomposed). ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.36 (s, 1H), 8.18 (s 1H), 7.82 (m, 3H), 7.59 (m, 3H), 7.46 (d, *J* = 7.7 Hz, 1H), 6.90 (s, 1H), 2.19 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) 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, CH), 116.4 (q, *J* = 4, CH), 20.6 (CH_3). ^{19}F NMR (376 MHz, DMSO) δ -61.35 (s). IR (neat): 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).

***N*-(3-chloro-4-fluorophenyl)-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide, 17,** 80%.
Compound description: off white solid. Mp: 206.1 - 208.5 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 8.06 (dd, *J* = 6.4 Hz, 2 Hz, 1H), 7.85 (d, *J* = 8 Hz, 2H), 7.63-7.58 (m, 3H), 7.43 (t, J = 9.2 Hz, 1H), 6.92 (s, 1H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). ^{19}F NMR (376 MHz, DMSO) δ -121.39 (s). IR (neat): 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).

***N*-(2-phenoxyphenyl)-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide, 18,** 91%.
Compound description: white solid. Mp: 253.7 - 254.9 °C (decomposed). ^{1}H NMR (700 MHz, DMSO-d_6) δ 12.91 (s, 1H), 8.51 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 2H), 7.57 (d, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.17, (t, *J* = 7.7 Hz, 1H), 7.13-7.08 (m, 2H), 7.01 (d, *J* = 7.7 Hz, 2H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.85 (s, 1H), 2.15 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) 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). IR (neat): 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).

***N*-cyclohexyl-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide, 19,** 51%.
Compound description: white solid. Mp: 203.8 - 205.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (d, *J* = 7.6, 1H), 7.82 (d, *J* = 8.8, 2H) 7.57 (d, *J* = 8.8, 2H), 6.81 (s, 1H), 3.84-3.73 (m, 1H), 2.17 (s, 3H), 1.87 - 1.77 (m, 2H), , 1.71 - 1.62 (m, 2H), 1.59 - 1.49 (m, 1H), 1.43 - 1.18 (m, 5H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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).

***N*-*N*-(2-(1*H*-indol-3-yl)ethyl)-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide, 20,** 90%.
Compound description: off white solid. Mp: 276.5 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 10.06 (t, *J* = 5.6 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.61 - 7.54 (m, 3H), 7.34 (d, *J* = 8 Hz, 1H), 7.19 (s, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.79 (s, 1H), 3.60 (q, *J* = 6, 2H), 2.94 (t, *J* = 7.2, 2H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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+2H). 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,** 76%.
Compound description: off white solid. Mp: 202.4 - 203.9 °C (decomposed). ^{1}H NMR (700 MHz, DMSO-d_6) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 7 Hz, 2H), 7.42 (d, *J* = 9 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7 Hz, 1H) 6.33 (s, 1H), 3.94 (s, 2H), 2.07 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) 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). IR (neat): 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,** 58%.
Compound description: cream solid. Mp: 258.2 - 259.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.81 (d, *J* = 8 Hz, 2H), 7.57 (d, *J* = 8 Hz, 2H), 6.79 (s, 1H), 2.16 (s, 3H), 2.10-1.94 (m, 9H), 1.66 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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).

***N*-(2-ethylhexyl)-1-(4-bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxamide, 23,** 89%.
Compound description: white solid. Mp: 129.8 - 131.1 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (t, *J* = 5.6, 1H), 7.82 (d, *J* = 8.8, 2H), 7.58 (d, *J* = 8.8, 2H), 6.81 (s, 2H), 3.32 - 3.21 (m, 2H), 2.17 (s, 3H), 1.53 - 1.43 (m, 1H), 1.36 - 1.21 (m, 8H), 0.87 (t, *J* = 7.2, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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, 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.
Mp: 171.3 - 172.7 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 6.66 (s, 1H), 3.81 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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, 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 on a silica gel pad (CH_2Cl_2) obtaining 2.93 g of pure title compound as a yellow powder.
Mp: 166.3 - 167.6 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.75 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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, 78%.
To a solution of **25** (2 g, 5.9 mmol) in EtOH (50 mL), N_2H_4 1M 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.
Mp: 294.8-295.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, NH), 7.81 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.19 (s, 1H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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 CH_2Cl_2 (60 mL). The resulting solution was washed with HCl 1M (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 1M (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, 57%.
Compound description: black solid. Mp: 266.1 - 267.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, *J* = 8 Hz, 2H), 7.85 (d, *J* = 8 Hz, 2H), 7.64 (d, *J* = 8 Hz, 2H), 7.48 (t, *J* = 8 Hz, 2H), 7.39 (s, 1H), 7.25 (t, *J* = 8 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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, 52%.
Compound description: dark brown solid. Mp: 230.7 - 231.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, *J* = 8 Hz, 2H), 7.82-7.76 (m, 2H), 7.64 (d, *J* = 8 Hz, 2H), 7.40 - 7.36 (m, 2H), 6.85 - 6.82 (m, 1H) 3.81 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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, 35%.
Compound description: brown solid. Mp: 238.2 - 238.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (t, *J* = 2.0 Hz, 1H), 8.22 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.39 (t, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.22 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.96 (s, 1H), 2.29 (s, 3H). ^{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). IR (neat): 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, 58%.
Compound description: dark brown solid. Mp: 208.4 - 210.2 °C. ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.03 (d, *J* = 9.1 Hz, 2H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.33 (s, 1H), 7.01 (d, *J* = 9.1 Hz, 2H), 3.76 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) 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). IR (neat): 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, 56%.
Compound description: brown solid. Mp: 244.9 - 245.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, *J* = 9.0 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 9.0 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.40 (s, 1H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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).

5-(4-bromophenyl)-2-benzyl-6-methyl-2*H*-pyrazolo[4,3-*c*]pyridazin-3(5*H*)-one, 29, 70%.
Compound description: brown solid. Mp: 189.2 - 191.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.42-7.18 (m, 6H), 5.07 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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, 32%.
Compound description: brown solid. Mp: 278.6-279.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.6 Hz, 2H), 7.27 (s, 2H), 6.95 (s, 1H), 4.58-4.95 (m, 1H), 2.27 (s, 3H), 2.00-1.79 (m, 6H), 1.77-1.68 (m, 1H) 1.55-1.38 (m, 2H), 1.34-1.19 (m, 1H). ^{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). IR (neat): 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, 73%.
Compound description: brown solid. Mp: 99.8 - 102.3 °C. ^{1}H NMR (700 MHz, DMSO-d_6) δ 7.86 (d, *J* = 7.6 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.29 (s, 1H), 3.84-3.72 (m, 2H), 2.24 (s, 3H), 1.95-1.85 (m, 1H), 1.41-1.20 (m, 8H), 0.90 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) 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). IR (neat): 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).

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Keywords: bromodomain • flow • slurries • heterocycles • libraries.

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