Tetrahedron 68 (2012) 9713–9728

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Design and synthesis of 2(1*H*)-pyrazinones as inhibitors of protein kinases

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ARTICLE INFO

Article history:
Received 15 June 2012
Received in revised form 24 August 2012
Accepted 10 September 2012
Available online 13 September 2012

Keywords:
2(1*H*)-Pyrazinone
3-Benzyloxypyrazine
Suzuki
Kinase
Drug-like

ABSTRACT

Kinase enzymes play a key role in the development and progression of cancer. Inhibitors of deregulated kinases are effective small molecule anticancer drugs. The 2(1*H*)-pyrazinone heterocycle is a previously unexploited motif that can fulfil the structural requirements for ATP-competitive inhibition of kinases. Rapid solution-phase syntheses of novel 3,5- and 3,6-disubstituted-2(1*H*)-pyrazinones were developed through selective, sequential substitution of 2,5-dihalo-3-benzyloxypyrazine and 3,5-dihalo-2(1*H*)-pyrazinone intermediates. Palladium-catalysed cross-couplings and S_NAr reactions were used to introduce substituents chosen on the basis of the calculated physicochemical properties of the target pyrazinones. Representative compounds demonstrated good solubility, kinase inhibitory activity and antiproliferative activity in human tumour cells, confirming the suitability of this chemical class as a kinase-focused library.

1. Introduction

Cancer is one of the most frequent causes of death in developed countries and the identification of new therapies is an area of ongoing importance in biomedical research.[1,2] The genetic changes underlying the development of cancer often lead to deregulation of cell signalling pathways.[3,4] Protein kinases are critical components of many signal transduction cascades controlling cell growth, differentiation and survival, thus aberrant signalling by protein kinases can play a key role in cancer progression.[4,5] Protein kinases catalyse the transfer of the γ-phosphate from adenosine 5′-triphosphate (ATP) to protein substrates, with the target for phosphorylation usually being the oxygen atom of a serine, threonine or tyrosine hydroxyl.[6] It is now well established that inhibiting the catalytic activity of deregulated protein kinases can be an effective treatment for cancer, and much contemporary research is devoted to the discovery of new small molecule inhibitors.[5,7–12] High-throughput screening (HTS) has been one successful means of identifying new chemotypes with protein kinase inhibitory activity.[13–15] In particular, the design of screening libraries of compounds that are ATP-competitive has provided useful starting points for drug discovery.[8,16–20] As part of an anticancer drug discovery program, we have developed methods for the rapid synthesis of a library of novel 3,6- and 3,5-disubstituted 2(1*H*)-pyrazinones suitable for screening against kinase targets.

The choice of the 2(1*H*)-pyrazinone scaffold as the basis of a new screening library was initially suggested by the structure of the natural product ma'edamine A **1** (Fig. 1), which shows some kinase inhibitory activity (c-erbB-2 IC_{50}=11 μM),[21] and was refined through considering the requirements for the binding of ATP-competitive inhibitors to protein kinases.[5,6,8] ATP binds within a deep cleft in the protein kinase catalytic domain, where it forms two hydrogen bonds to backbone amides in the hinge-region, a flexible peptide chain linking the *N*- and *C*-terminal subdomains. Other important contacts occur between the hydroxyls of the ribose unit of ATP and polar residues in the kinase, and between the magnesium-chelated triphosphate group and the protein. While these pharmacophore points are conserved between different protein kinases, there are other areas adjacent to the position of ATP in the binding site, which vary more in composition and structure but are accessible to small molecule inhibitors. Pharmacophores incorporating these features have proved highly successful in guiding the discovery of new ATP-competitive kinase inhibitors.[11,22,23] We hypothesised that the 2(1*H*)-pyrazinone core would be capable of binding to the hinge-region while providing suitable vectors for the addition of further substituents (Fig. 2).

While to our knowledge no details of the structural biology of pyrazinone kinase inhibitors have been reported to date, the quinoxalin-2-one **2** (Fig. 1), which contains the 2(1*H*)-pyrazinone substructure within the bicycle has been found to be a potent CDK inhibitor.[24] The crystal structure of **2** bound to CDK2 showed that the donor (NH)—acceptor (C=O) motif of the fused pyrazinone can function as hypothesised here. Although the disubstituted 2(1*H*)-pyrazinone marine natural product ma'edamine A (**1**) shows some

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http://dx.doi.org/10.1016/j.tet.2012.09.039

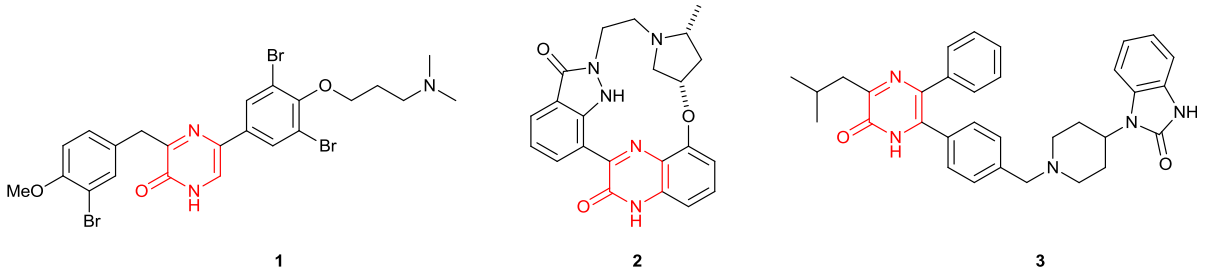


Fig. 1. Structures of 2(1*H*)-pyrazinone containing kinase inhibitors **1**, **2** and **3**.

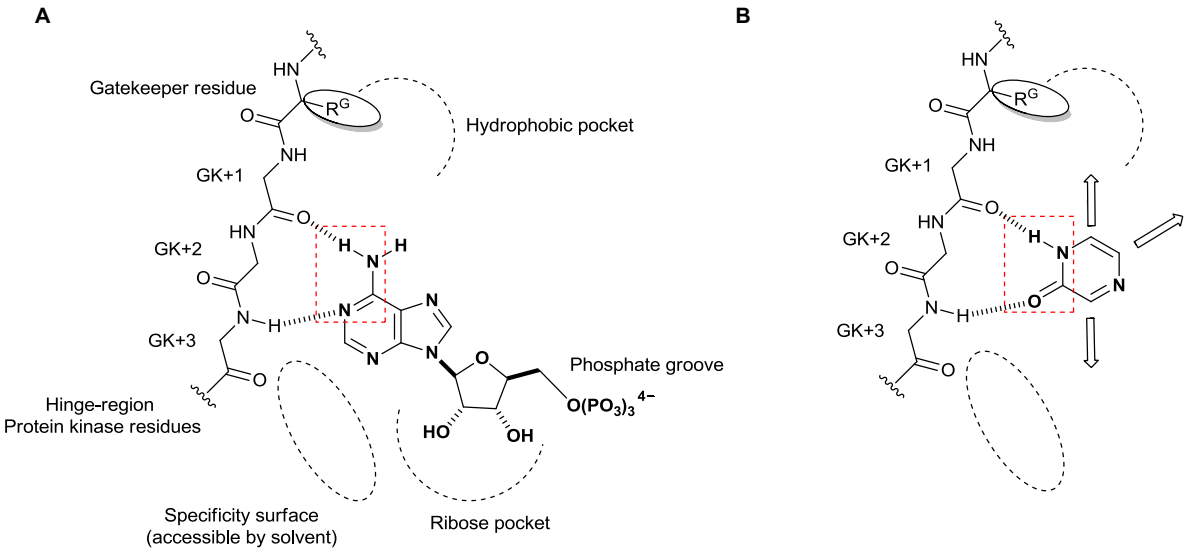


Fig. 2. Schematics of (A) ATP binding to protein kinases[22,23] and (B) the proposed alignment of the 2(1*H*)-pyrazinone scaffold within the binding site.

kinase inhibitory activity,[21] the mode of inhibition of the compound has not been established. A series of trisubstituted 2(1*H*)-pyrazinones, e.g., **3**, have been developed as inhibitors of the protein kinase PKB.[25] In this case, the compounds are known to be ATP-noncompetitive, allosteric inhibitors of the kinase, which bind to a distinct region away from the ATP-binding site.[26,27] Interestingly, the 2(1*H*)-pyrazinone motif also occurs in the dragmacidin family of marine natural products,[28–30] some of which are protein phosphatase inhibitors.

There are two main synthetic approaches to 2(1*H*)-pyrazinones:[31] making the ring by condensation[25,32,33] or preparing a functionalised ring with subsequent substitutions.[31c,34–39] For an example of the former, libraries of disubstituted pyrazinone PKB inhibitors related to **3** were produced by condensation of 1,2-diketones and 2-aminoacetamides, requiring chromatographic separation of the regioisomeric mixture arising from the ring forming reaction.[25] For our purpose, the second general approach was chosen as it was suited for parallel synthesis using sequential palladium-catalysed coupling and/or nucleophilic substitution reactions. Hoornaert and co-workers have published syntheses of highly substituted pyrazinones involving decoration of 3,5-dihalogenated pyrazinone scaffolds.[38,39] However, in many examples the pyrazinone N1 was substituted in the final products, whereas we required a free NH at this position in order to explore the hypothesised binding mode. Similar methodology has been successfully applied by Van der Eycken and colleagues to the solid phase synthesis of 3,5-disubstituted pyrazinones.[40,41] In these cases, N1 of the pyrazinone was used as the attachment point to the resin, thus releasing the free NH after cleavage in many cases. In addition, the Van der Eycken group have extended their methodology to the microwave assisted palladium coupling of 2(1*H*)-pyrazinones to give asymmetrically substituted pyrazines.[42] Interestingly, they observed that the formation of symmetrical 2,5-disubstituted pyrazines was difficult to control. In the total synthesis of the dragmacidins, Stoltz and co-workers demonstrated sequential palladium-catalysed couplings to a 2,5-dihalo-3-methoxypyrazine, followed later in the synthesis by removal of the 3-methoxy group using trimethylsilyl iodide to reveal the 2(1*H*)-pyrazinone.[35,37] Reasoning that masking of the pyrazinone carbonyl as a benzyloxy substituent would provide more options for removal of the protecting group, we initially chose to prepare a range of 2,5-dihalosubstituted 3-benzyloxypyrazines and investigate their suitability as starting materials for the parallel, solution phase synthesis of novel 3,6-di(hetero)aryl-2(1*H*)-pyrazinones. We subsequently extended our study to include previously unexplored sequential reactions on *N*-unsubstituted 3,5-dihalo-2(1*H*)-pyrazinones.

2. Results and discussion

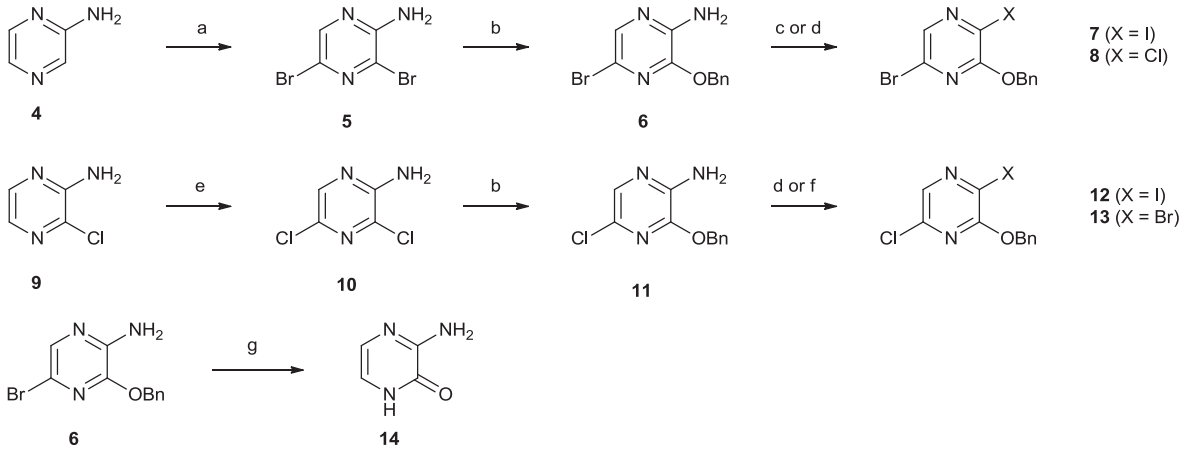
Two main factors were considered in selecting the substituents for the pyrazinone core in the proposed library. First, substituents were chosen containing a variety of peripheral hydrogen bonding, basic or lipophilic groups to interact with potential biological targets. Second, the physicochemical properties of the compounds were calculated to ensure that these were compatible with suggested criteria for 'drug-likeness' and 'lead-likeness' in small molecules.[10,43–48] Since medicinal chemistry optimisation of initial lead compounds often involves the addition of new functionality to improve potency or selectivity, it is logical that compounds for HTS libraries should be smaller than the average size of drugs, with lead-like compounds typically not larger than 350–400 MW and

with *Clog*P <3–4, although the exact values suggested for these cut-offs vary between research groups.[10,43–46]

Starting from commercially available 2-aminopyrazine **4** we prepared four different 2,5-dihalo-3-benzyloxypyrazine templates (**7**,[49] **8**, **12** and **13**) (Scheme 1). The templates were selected to possess different halide functionality and therefore potentially show different sequential reactivities, in particular towards palladium-catalysed cross-coupling reactions. Bromination of **4** using *N*-bromosuccinimide afforded 3,5-dibromopyrazin-2-amine **5**,[34,50] which reacted with the anion of benzyl alcohol to selectively substitute the bromine atom at the 3-position. The regiochemistry of the substitution was confirmed by hydrogenation of compound **6**[73] to obtain 3-aminopyrazin-2-one **14**[51] (Scheme 1). Transformation of the amino group of **6** into a halide was achieved through diazonium salt formation and halide substitution[35,52] using hydroiodic acid and sodium nitrite to give 3-(benzyloxy)-5-bromo-2-iodopyrazine **7**.[49] Alternatively, treatment of **6** with isoamyl nitrite and a mixture of copper(II) chloride/copper(I) chloride gave 3-(benzyloxy)-5-bromo-2-chloropyrazine **8**. 3,5-Dichloro-2-aminopyrazine **10**[75] was synthesised from 2-amino-3-chloropyrazine **9** using *N*-chlorosuccinimide. Displacement of the 3-chloro substituent gave 2-amino-5-chloro-3-benzyloxypyrazine **11**, which was converted into 5-chloro-2-iodo-3-benzyloxypyrazine **12** and 5-chloro-2-bromo-3-benzyloxypyrazine **13**, using a copper(II) bromide/copper(I) bromide mixture for the Sandmeyer reaction[52] to give **13**.

selectivity for, the mono-coupling products **15**, **16** or **18** was generally seen with electron-rich coupling partners, such as 4-methoxyphenyl- or *p*-tolylboronic acids. In this case, the initial reaction appears to be fast to give the mono-substituted product while subsequent reaction is presumably slower as a result of electron donation from the newly introduced aryl group reducing the reactivity towards oxidative addition of the palladium catalyst and reinforcing the selectivity. Despite extensive attempts to optimise the reactions further, general conditions for highly selective single Suzuki coupling to the templates **7**, **8**, **12** and **13** were not observed.

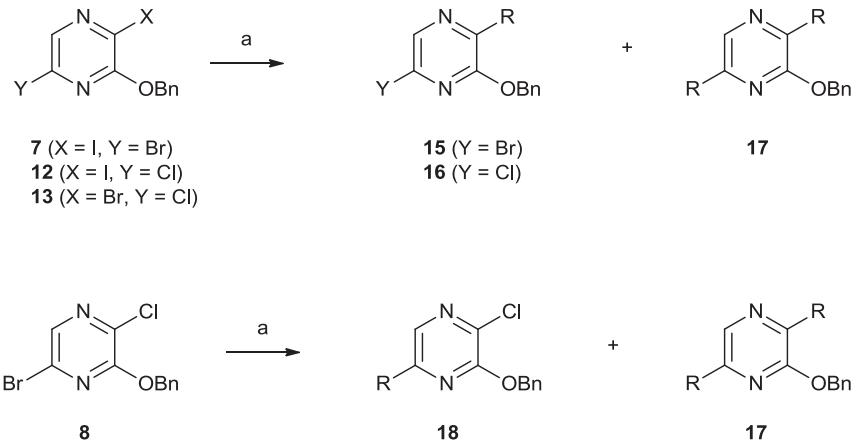
The lack of reliable control of mono-coupling and the dependence of the selectivity on the nature of the boronic acid building blocks limited the scope for a general combinatorial synthesis. However, the selectivity possible with 3-benzyloxy-5-bromo-2-chloropyrazine **8** and its regioisomer **13** with neutral and electron-rich boronic acids did provide an opportunity for parallel solution-phase synthesis. The two regioisomeric templates offered access to complementary 3,6-disubstitution patterns in the final pyrazinones, and thus to some extent overcame the limitations on the selective reaction of electron-poor arylboronic acids. The templates **8** and **13** were reacted on a multigram scale with 4-methoxyphenylboronic acid to afford monoarylpyrazines **19** and **20** in 70% and 61% yield, respectively (Scheme 3). Further Suzuki couplings were carried out on the chloropyrazines **19** and **20** with



Scheme 1. Synthesis of 2,5-dihalo-3-benzyloxypyrazines. Reagents and conditions: (a) NBS, DMSO, H_2O, 0 °C–rt, 16 h, 77%; (b) benzyl alcohol, NaH, THF, reflux, 10–24 h, 72% for **6**, 57% for **11**; (c) isoamyl nitrite, $CuCl_2$/CuCl (3:2), MeCN, rt, 3 h, 61% for **8**; (d) $NaNO_2$, HI, MeCN, H_2O, 50 °C, 21–24 h, 64% for **7**, 50% for **12**; (e) NCS, $CHCl_3$, reflux, 4 h, 76%; (f) isoamyl nitrite, $CuBr_2$/CuBr (3:2), MeCN, rt, 3 h, 48% for **13**; (g) H_2, Pd/C, EtOH, rt, 7 h, 20%.

With the 2,5-dihalopyrazine templates in hand, the regio- and chemoselectivity of Suzuki coupling reactions were investigated (Scheme 2). Tandem HPLC–mass spectrometry (LC–MS) of the crude reaction mixtures was used to monitor the conversion and product identities in the trial reactions, which although not quantitative in output, provided a rapid and direct means of analysis. An initial catalyst screen using pyrazine **7** and *p*-tolylboronic acid showed $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ formed the mono-coupled product **15** (Table 1), reacting as expected at the more reactive iodo centre. Absence of reaction or double coupling was observed with the remaining catalysts employed. Using $Pd(PPh_3)_2Cl_2$ with dihalopyrazines **8**, **12** and **13** led to formation of the expected mono addition products, however only pyrazine **12** reacted completely and selectively. As increasing the temperature was observed to give substantially increased amounts of diarylpyrazines, the temperature was reduced to 25 °C for a subsequent boronic acid screen in an effort to optimise mono adduct formation (Table 2). Of particular note was the variation in the degree and selectivity of the reaction with different boronic acid reagents. Greatest conversion to, and a varied set of (hetero)aromatic boronic acids or boronate esters (Scheme 3, Table 3). Although the reactions were performed successfully by heating at reflux for 18 h, microwave irradiation at 150 °C for 20 min was found to give similar yields in a much reduced time using $Pd(PPh_3)_4$ as the catalyst. For some less reactive coupling partners, a more active palladacyclic catalyst proved effective.[53]

Several methods were investigated for removal of the benzyloxy protecting groups. Although an acid-mediated reaction with trifluoroacetic acid at reflux was successful with some substrates, it proved unreliable and often low-yielding when generally applied. Using a dilute solution of trifluoroacetic acid (10% in dichloromethane) gave no reaction.[54] Hydrogenation removed the benzyl group but also reduced the pyrazinone ring to a piperazine. Use of the mild Lewis acid BCl_3SMe_2[55] gave no reaction, but treatment with 1 M boron trichloride in dichloromethane at rt for 30 min was found to cleanly produce the 2(1*H*)-pyrazinones (**38**–**54**) (Scheme 3, Table 4). The products were isolated by concentration of the crude reaction mixture and filtration through a short column of basic ion exchange



7 (X = I, Y = Br)
12 (X = I, Y = Cl)
13 (X = Br, Y = Cl)

15 (Y = Br)
16 (Y = Cl)

17

8

18

17

Scheme 2. Suzuki reaction of 2,5-dihalo-3-benzyloxypyrazines. Reagents and conditions: (a) $RB(OH)_2$ (5 equiv), 2 M aq Na_2CO_3, DME, Pd catalyst (10 mol %).

Table 1
Product distribution for Suzuki couplings to 2,5-dihalo-3-benzyloxypyrazines as a function of starting material, catalyst and temperature

Starting material	Catalyst	Product distribution[a]		
		Starting material (%)[b]	**15**, **16** or **18** (R=*p*-tolyl) (%)[b]	**17** (R=*p*-tolyl) (%)[b]
7	*trans*-$[(2\text{-tol})_3P]_2PdCl_2$	50	0	50
7	$PdCl_2(dppf)$	66	0	34
7	*trans*-$[(c\text{-hex})_3P]_2PdCl_2$	100	0	0
7	$Pd(PPh_3)_4$	75	25	0
7	$Pd(PPh_3)_2Cl_2$	8	77	15
8	$Pd(PPh_3)_2Cl_2$	55	45	0
12	$Pd(PPh_3)_2Cl_2$	0	100	0
13	$Pd(PPh_3)_2Cl_2$	60	33	7

[a] Percentage of product in crude reaction mixture as determined by HPLC analysis.
[b] Reaction in the presence of 5 equiv *p*-tolylboronic acid, 10 mol % catalyst, 2 M aq Na_2CO_3, DME, 50 °C, 24 h.

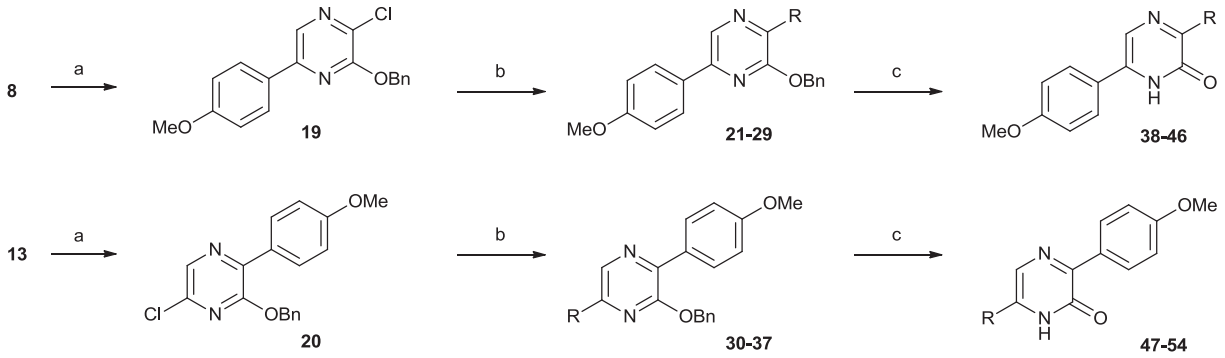
Table 2
Product distribution for Suzuki coupling of varied boronic acids to 2,5-dihalo-3-benzyloxypyrazines

Starting material	Boronic acid	Product distribution[a]		
		Starting material (%)[b]	**15**, **16**, or **18** (%)[b]	**17** (%)[b]
7	*p*-Tolylboronic acid	5	85	10
8	*p*-Tolylboronic acid	0	100	0
12	*p*-Tolylboronic acid	45	55	0
13	*p*-Tolylboronic acid	35	65	0
7	4-Methoxyphenylboronic acid	35	65	0
8	4-Methoxyphenylboronic acid	0	100	0
12	4-Methoxyphenylboronic acid	32	68	0
13	4-Methoxyphenylboronic acid	0	100	0
7	4-Chlorophenylboronic acid	40	30	30
8	4-Chlorophenylboronic acid	0	85	15
12	4-Chlorophenylboronic acid	32	32	36
13	4-Chlorophenylboronic acid	8	37	55
7	Pyridin-3-ylboronic acid	100	0	0
8	Pyridin-3-ylboronic acid	85	15	0
12	Pyridin-3-ylboronic acid	100	0	0
13	Pyridin-3-ylboronic acid	100	0	0

[a] Percentage of product in crude reaction mixture as determined by HPLC analysis.
[b] Reaction with $Pd(PPh_3)_2Cl_2$ (10 mol %), 2 M aq Na_2CO_3, DME, 25 °C, 24 h.

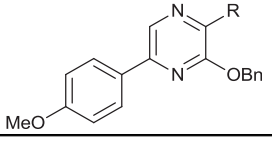
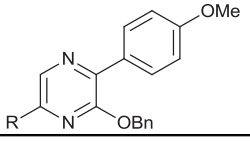
resin. Although the 4-methoxyphenyl groups were unaffected by the deprotection, in the case of the 2-methoxyphenyl derivative **37** the aryl ether was also cleaved to give phenol **54** in high yield.

Thus far, the focus was on 3,6-disubstituted pyrazinones with a linear relationship between the two aryl substituents. To provide compounds within the screening library with an alternative geometry, the 3,5-disubstitution pattern was also investigated. Starting from commercially available 2-amino-3-chloropyrazine (**9**), bromination followed by diazotization of the amine and hydrolysis of the diazonium salt[50] gave 5-bromo-3-chloropyrazin-2-one **56** (Scheme 4). Although selective couplings of arylstannanes with *N*-phenyl- and *N*-benzyl-3,5-dichloropyrazin-2-one have been reported,[56] Suzuki reactions of **56** failed to provide useful levels of regioselectivity with a range of catalysts, or resulted in low conversion of the starting material. However, reaction of the template with an excess of boronic acid was shown to give the simple 3,5-diaryl pyrazinones, such as the use of 4-methoxphenyl boronic acid to give **57** in 47% yield.



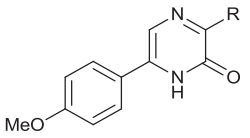
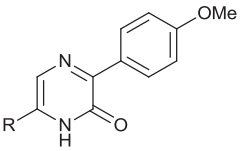
Scheme 3. Parallel synthesis of 2-benzyloxy-3,6-diarylpyrazines and 3,6-diarylpyrazin-2(1*H*)-ones. Reagents and conditions: (a) 4-methoxyphenylboronic acid, $Pd(PPh_3)_2Cl_2$, 2 M aq Na_2CO_3, DME, 50 °C, 16 h, 70% for **19**, 61% for **20**; (b) $RB(OR)_2$, $Pd(PPh_3)_4$ 6 mol %, 2 M aq Na_2CO_3, MeCN, 150 °C, microwave, 20 min or $RB(OR)_2$, 10 mol % palladacycle,[53] 2 M aq Na_2CO_3, DME, reflux, 4–40 h, 8–93%; (c) BCl_3, DCM, rt, 30 min, 8–98%.

Table 3
2-Benzyloxy-3,6-diarylpyrazine products from Suzuki coupling to templates **19** and **20**

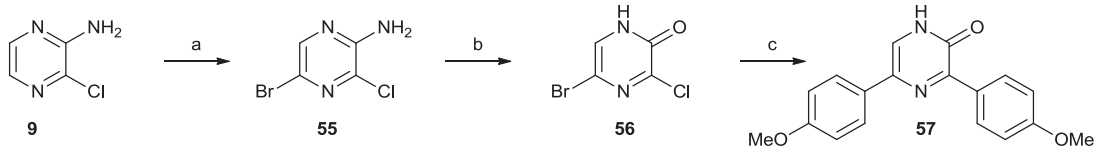
R				
	No.	Yield[a,b] (%)	No.	Yield[a,b] (%)
4-Methoxyphenyl	**21**	55[c]	—[d]	—
4-Methylphenyl	**22**	58[e]	**30**	51[e]
4-(Ethoxycarbonyl)-phenyl	**23**	53[e]	—	—
3-Pyridyl	**24**	60[c]	**31**	9
4-Hydroxyphenyl	**25**	49[c]	**32**	42[c]
3-Acetylaminophenyl	**26**	48[c]	—	—
4-Carbamoylphenyl	—	—	**33**	8[c]
Pyrazol-4-yl	—	—	**34**	59[c]
Pyrazol-3-yl	**27**	47[c]	**35**	60[c]
Thien-3-yl	**28**	62[c]	**36**	80[c]
4-(Morpholin-1-ylmethyl)-phenyl	**29**	93[c]	—	—
2-Methoxyphenyl	—	—	**37**	88[c]

[a] Isolated yield of purified material.
[b] Purity determined by HPLC >95%.
[c] Prepared according to general method A using $Pd(PPh_3)_4$ as catalyst.
[d] Reaction not performed.
[e] Prepared according to general method B using [2-[(dimethylamino-κN)methyl]phenyl-κC](tricyclohexylphosphine)(trifluoroacetato-κO)-palladium[53] as catalyst.

Table 4
Yields of 3,6-di(hetero)aryl-2(1*H*)-pyrazinones

R				
	No.	Yield[a,b] (%)	No.	Yield[a,b] (%)
4-Methoxyphenyl	**38**	95	—[c]	—
4-Methylphenyl	**39**	98	**47**	98
4-(Ethoxycarbonyl)phenyl	**40**	8	—	—
3-Pyridyl	**41**	47	**48**	39
4-Hydroxyphenyl	**42**	94	**49**	94
3-Acetylaminophenyl	**43**	64	—	—
4-Carbamoylphenyl	—	—	**50**	96
Pyrazol-4-yl	—	—	**51**	49
Pyrazol-3-yl	**44**	89	**52**	26
Thien-3-yl	**45**	94	**53**	94
4-(Morpholin-1-ylmethyl)-phenyl	**46**	61	—	—
2-Hydroxyphenyl	—	—	**54**[d]	92

[a] Isolated yield.
[b] Purity determined by HPLC >95%.
[c] Reaction not performed.
[d] Obtained from reaction of the 2-methoxyphenyl derivative **37**.

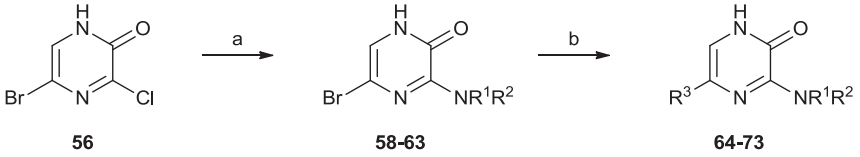


Scheme 4. Synthesis of 3,5-diaryl-2-(1*H*)-pyrazinones. Reagents and conditions: (a) NBS, $CHCl_3$, reflux, 16 h, 69%; (b) $NaNO_2$, concd H_2SO_4, H_2O, 0–40 °C, 1 h, 68%; (c) 4-methoxyphenylboronic acid (5 equiv), 0.5 M Na_2CO_3, $Pd(PPh_3)_4$, MeCN, MW 150 °C, 20 min, 47%.

In a more successful regioselective strategy, the halides of 5-bromo-3-chloropyrazin-2-one **56** were differentiated by S_NAr displacement of the 3-chloro substituent with amines to give the 5-bromo-3-amino-2(1*H*)-pyrazinones **58**–**63** (Scheme 5, Table 5). Selective S_NAr displacements of *N*-aryl- and *N*-alkyl-3,5-dihalopyrazin-2-ones are known,[57–60] but these reactions have not previously been reported on the simpler *N*-unsubstituted pyrazin-2-one substrates. Six-membered cyclic amines were chosen to give substituents with similar size to the (hetero)aryl groups present in the rest of the library. Subsequent Suzuki coupling with a range of boronic acids using bromides **58**–**63** provided a further library set for screening. Exemplars of this reaction sequence are shown in Table 5. Firstly, bromides **58**–**62** were found to couple successfully with 4-methoxyphenylboronic acid to give pyrazinones **64**–**68**. In addition, morpholine **63** was reacted with a range of boronic acids leading to the preparation of compounds **69**–**73** (Scheme 5, Table 5). Microwave heating was used for both the C–N and C–C bond forming steps, and the final compounds were purified by automated MPLC on silica gel. Yields from the Suzuki coupling were generally low to moderate, primarily as a consequence of the difficult isolation of pure product due to poor organic solvent solubility. However, the parallel procedure reliably and rapidly generated sufficient pure product for the purpose of building the screening library.

During the production of the library, representative pyrazinones were tested for their kinase inhibitory activity. Compounds **38** and **57** were profiled against a diverse panel of 150 kinases,[63] and compounds **39** and **65** were assessed against a panel of 85 kinases[64] using radiometric (^{33}P-ATP) assay formats (Table 7). The analogues were screened at a concentration of 30 μM. Encouragingly, moderate activity (30–85% inhibition at 30 μM) was seen with these prototype ligands for a range of kinases, including targets in oncology, for example, Aurora-B[65] and PKB.[66] Although the potency of these inhibitors is low, the molecular weight is also low (292–308 Da). Inhibition (IC_{50}) in the 10–30 μM range would lead to ligand efficiencies of ca. 0.3 kcal mol^{-1} non-H $atom^{-1}$, which would indicate the hits to be viable for optimisation.[67,68] Interestingly, there was a variation in the pattern of inhibition between the different test compounds despite the simplicity and low molecular weight of the compounds, and the similar peripheral substituents in some cases. These results support the use of the library for kinase inhibitor screening.

To further establish the suitability of the library for screening, selected compounds were investigated for antiproliferative effects[69] in human tumour cell lines (Table 8). For instance, the 3,6-disubstituted pyrazinone **39** was cytotoxic to HCT116 colon cancer cells. The 3,5-disubstituted analogue **57** had weaker activity. This promising data suggests that the pyrazinones are cell penetrant, as would be predicted from their calculated physicochemical properties and measured solubilities, and validates the consideration of drug-likeness in the design of the library. However the observed antiproliferative activity cannot be assigned to any specific targets at this point, although it might be due in part to the inhibition of kinases in the cell. It is important to note that 3,5-(bisindolyl)-2(1*H*)-pyrazinones related to the dragmacidin natural products have shown a range of antiproliferative activities in human tumour cells.[70,71] Nevertheless, the initial assessment of physicochemical, biochemical and antiproliferative properties of the compounds supports their future use in high-throughput screening against kinase targets.



Scheme 5. Sequential chemoselective nucleophilic substitution and Suzuki coupling to 5-bromo-3-chloropyrazin-2-one **56**. Reagents and conditions: (a) NHR^1R^2, DIPEA, ^{n}BuOH, microwave 140 °C, 1 h, 53–91%; (b) $R^3B(OH)_2$, 0.5 M aq Na_2CO_3, $PdCl_2(dppf)$, MeCN, microwave 150 °C, 20 min, 8–99%.

To demonstrate the applicability of the sequential S_NAr and Suzuki reaction sequence to the preparation of 3,6-disubstituted pyrazinones, the 6-bromo-3-chloro-2-benzyloxypyrazine template **8** was deprotected with boron trichloride to give 6-bromo-3-chloropyrazin-2-one **74**. Reaction with morpholine and subsequently with 4-methoxyphenylboronic acid gave the 3,6-disubstituted pyrazinone **76** (Scheme 6).

Aqueous solubility studies were carried out on representative compounds with different substitution patterns (Table 6). Compound **65** was chosen as it contained a moderately basic *N*-methylpiperazine, which could enhance aqueous solubility, and indeed **65** was the most soluble analogue in neutral and acidic aqueous conditions. The 3,6-disubstituted pyrazin-2-ones **38** and **76** were the least soluble in methanol and pH 5 buffer, while the corresponding 3,5-disubstituted regioisomers **57** and **69** showed generally higher solubility. To be useful for in vitro biochemical screening and cellular assays, it was desirable that the library components should be soluble up to at least 100 μM in appropriate aqueous media.[61] For example, a molecular weight of ca. 300 with a concentration of 100 μM corresponds to a solubility of approximately 0.03 mg mL^{-1}. The data for the representative compounds indicates that even the less soluble reach this threshold and should therefore be suitable for screening.

3. Conclusions

A kinase-focused library of novel 3,5- and 3,6-disubstituted-2(1*H*)-pyrazinones for biochemical screening was synthesised by selective substitution of previously unreported 2,5-dihalo-3-benzyloxypyrazine and 3,5-dihalo-2(1*H*)-pyrazinone intermediates. Palladium-catalysed Suzuki cross-couplings to 2,5-dihalo-3-benzyloxypyrazines proceeded preferentially at the most reactive carbon–halogen bond, giving high chemoselectivity in the reaction of neutral and electron-rich boronic acids, but not with electron-

Table 5
Yields of the S_NAr products **58**–**62** and subsequent Suzuki products **64**–**73**

No.	X	R	Yield[a,b] (%)
58	–CH_2–	Br	91
59	–N(Me)–	Br	53
60	–CH(OH)–	Br	50
61	–CH(CO_2Me)–	Br	87
62	–CH(Ph)–	Br	88
63	–O–	Br	90
64	–CH_2–	4-Methoxyphenyl	99
65	–N(Me)–	4-Methoxyphenyl	38
66	–CH(OH)–	4-Methoxyphenyl	41
67	–CH(CO_2Me)–	4-Methoxyphenyl	17
68	–CH(Ph)–	4-Methoxyphenyl	18
69	–O–	4-Methoxyphenyl	20
70	–O–	4-Carbamoylphenyl	8
71	–O–	3-Pyridyl	12
72	–O–	4-Chlorophenyl	17
73	–O–	4-Acetylaminophenyl	23

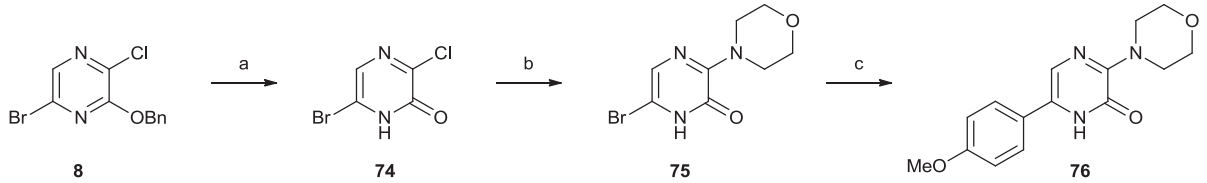
[a] Isolated yield of purified material.
[b] Purity determined by HPLC >95%.

of the core heterocycle as an ATP-mimetic, further studies of structure–activity relationships for specific kinases, or X-ray crystallographic studies on kinase-inhibitor complexes, are required to fully validate this hypothesis. The antiproliferative activity in cells seen for some compounds, while not necessarily due to kinase inhibition, gives confidence that the pyrazinones will be cell-penetrant, an essential property for drug discovery leads or tool compounds for studying intracellular kinase targets.[61] Further profiling of the library may give more insights on a possible mechanism of action for these compounds and other cytotoxic disubstituted pyrazinones.

4. Experimental

4.1. General experimental

Reagents and solvents were used as purchased from commercial suppliers unless otherwise stated. *N*-Bromosuccinimide (NBS) was purified by recrystallisation from water. Organic solutions were dried over Na_2SO_4. Reactions were carried out under an atmosphere of nitrogen. Microwave reactions were carried out in sealed glass vials using a Biotage Initiator microwave reactor. Ion exchange chromatography was performed using Isolute NH_2 and SCX-II resin cartridges. Flash column chromatography was performed on Merck silica gel 60 (0.015–0.040 mm). Automated MPLC was performed on a Biotage SP1 instrument using prepacked silica cartridges and UV-triggered fraction collection (254 nm). Melting points were recor-



8 74 75 76

Scheme 6. Synthesis of 6-(4-methoxyphenyl)-3-morpholinopyrazin-2(1*H*)-one **76**. Reagents and conditions: (a) BCl_3, DCM, RT, 48 h, 68%; (b) morpholine, DIPEA, ^{n}BuOH, microwave 140 °C, 1 h, 45%; (c) 4-methoxyphenylboronic acid, 0.5 M aq Na_2CO_3, MeCN, $PdCl_2$(dppf), microwave 150 °C, 20 min, 25%.

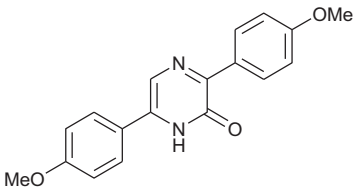
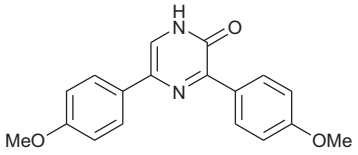
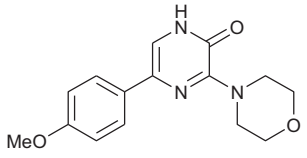
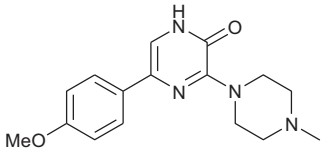
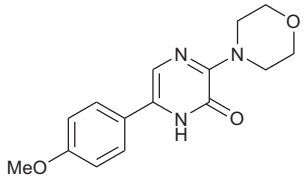
deficient reagents. Although this presents a limitation to the generality of the synthesis, it has been partly overcome by using two regioisomeric templates, 3-benzyloxy-5-bromo-2-chloropyrazine and 3-benzyloxy-2-bromo-5-chloropyrazine, which can compensate for the restriction to electron-rich boronic acids in the first coupling step. Although the synthetic route was mainly demonstrated here with 4-methoxyphenyl as one of the substituents, the extension to other groups can be envisaged. The application of a similar sequence to 5-bromo-3-chloropyrazin-2-one foundered on the lack of regioselectivity of the initial Suzuki coupling. However, better differentiation of the halogen substituents was achieved by nucleophilic substitution with amines, and was exploited in the parallel solution phase synthesis of 3-(aminoalkyl)-5-(hetero)aryl-2(1*H*)-pyrazinones. This sequence allows the alternative 3,5-disubstituted geometry of the pyrazinones to be quickly accessed, albeit with a differently constituted substituent set. Arguably, there are benefits to the incorporation of saturated nitrogen heterocycles into the library compounds, since these were found to have greater aqueous solubility than analogous diaryl substituted pyrazinones. We have previously found that the replacement of rigid aromatic spacers by conformationally flexible aliphatic rings gave more potent and selective inhibition of PKB by purine derivatives.[72]

Representative compounds from the library had appropriate solubility for use in biochemical and cell-based screens. The ability of such compounds to inhibit kinases provides support for pursuing 2(1*H*)-pyrazinones for this purpose. The potency was appropriate for the molecular weight of the compounds, suggesting the library would be capable of generating ligand efficient hits in screening. Although the library design was based on one specific binding mode

ded on a Reichert Thermovar apparatus. Infrared spectra were recorded on a Perkin–Elmer Spectrum RX-1 FT-IR spectrophotometer with the sample prepared as a thin film on NaCl discs. ^{1}H NMR spectra were recorded on Bruker AC250 or AV500a spectrometers at 250 MHz or 500 MHz, respectively, using an internal lock. ^{13}C NMR spectra were recorded on a Bruker AV500a spectrometer at 125 MHz using an internal lock. Chemical shifts (δ, parts per million) are reported relative to Me_4Si (δ=0) and/or referenced to the solvent in which they were measured. Coupling constants (J) are reported in hertz. GC–MS analyses were recorded on a Thermo Quest Finnigan Polaris Q instrument, using a Phenomenex Zebron 2.5 μm×15 m×0.25 mm column and a temperature gradient from 40 to 300 °C over 3 min. Combined HPLC-MS analyses were recorded using a Waters Alliance 2795 separations module, a Waters/Micromass LCT mass detector with electrospray ionisation, and a Waters 2487 Dual λ absorbance detector (λ=254 nm). HPLC analyses were performed using a Phenomenex Gemini C_{18} column (5 cm×4.6 mm i.d., 5 μm) and gradient elution of 10–90% MeOH/0.1% aqueous formic acid at a flow rate of 1 mL/min (run time of 6, 10 or 15 min as indicated) or a Merck Chromolith SpeedROD RP-18e column (5 cm×4.6 mm i.d.) and gradient elution of 10–90% MeOH/0.1% aqueous formic acid at a flow rate of 2 mL/min (run time of 3.5 min). HRMS analyses were performed using an Agilent 1200 series HPLC with an Agilent 6210 ToF mass spectrometer, referenced to caffeine (MH^+=195.087652), reserpine (MH^+=629.280657) and hexakis(1*H*,1*H*,3*H*-tetrafluoropentoxy) phosphazene (MH^+=922.009798).

4.1.1. 3,5-Dibromopyrazin-2-amine ***5***.[50] A solution of 2-aminopyrazine **4** (3.81 g, 40.1 mmol) in DMSO (80 mL) and water

Table 6
Solubility measurements of selected pyrazinones

No.	Structure	Medium	Solubility (mg mL^{-1})[a]
38		MeOH	0.13
		10% DMSO in H_2O	1.7
		H_2O pH=5	0.06
		H_2O pH=7.4	0.03[b]
57		MeOH	0.35
		10% DMSO in H_2O	2.5
		H_2O pH=5	0.15
		H_2O pH=7.4	0.11[b]
69		MeOH	1.8
		10% DMSO in H_2O	1.2
		H_2O pH=5	2.5
		H_2O pH=7.4	0.06[b]
65		MeOH	2.2
		10% DMSO in H_2O	1.3
		H_2O pH=5	3.5
		H_2O pH=7.4	0.15[b]
76		MeOH	0.2
		10% DMSO in H_2O	2
		H_2O pH=5	0.08
		H_2O pH=7.4	n.d.[c]

[a] Solubility determined by HPLC measurement of the concentration of a micro-membrane filtered saturated solution.
[b] Solubility determined by high-throughput filtration-based assay.[62]
[c] n.d.=not determined.

(2 mL) was stirred at 0 °C for 10 min. NBS (16.4 g, 92.2 mmol) was added portionwise to the solution over 50 min, keeping the temperature below 15 °C. The reaction mixture was warmed to rt and stirred for 16 h. The solution was poured into ice-water (250 mL) and stirred. The orange solid was collected by filtration and dried. The filtrate was extracted with ethyl acetate (200 mL). The organic layer was washed with 5% aqueous sodium carbonate (50 mL) and water (50 mL), then dried, filtered and concentrated. The combined material was recrystallised from water (200 mL) to give **5** (7.80 g, 77%) as a brown solid. (Found: C, 19.33; H, 1.10; N, 16.68; $C_4H_3N_3Br_2$ requires C, 19.00; H, 1.20; N, 16.62%); δ_H (250 MHz; $CDCl_3$) 5.08 (2H, br s, NH_2), 8.07 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 123.7, 123.9, 143.2, 151.9; LC–MS (15 min) *m/z* 256, 254, 252 (MH^+); HPLC t_R 4.45 min; purity 98%; (HRMS found: MH^+ *m/z* 251.8776; $C_4H_4{}^{79}Br_2N_3$ requires 251.8766).

4.1.2. 3-(Benzyloxy)-5-bromopyrazin-2-amine ***6***.[73] A suspension of sodium hydride (60% dispersed in mineral oil) (1.20 g, 29.7 mmol) in dry THF (50 mL) was stirred at rt for 10 min. Benzyl alcohol (3.10 mL, 29.9 mmol) was added and the mixture was stirred for 30 min, after which **5** (5.00 g, 19.8 mmol) was added. The reaction mixture was heated at reflux for 10 h then cooled and concentrated. The residual gum was washed with ethyl acetate (200 mL) and water (100 mL) and the mixture was filtered through Celite. The organic layer was separated, washed with brine (2×100 mL), dried, filtered and concentrated. Flash column chromatography on silica, eluting with 30% ethyl acetate in hexanes, gave **6** (4.00 g, 72%) as an orange solid. R_f (35% EtOAc/hexanes) 0.50; ν_{max} (thin film/cm^{-1}) 3411 (NH_2), 3019 (Ar CH), 929 (C–O); (found: C, 47.19; H, 3.52; N, 14.78. $C_{11}H_{10}N_3OBr$ requires C, 47.16; H, 3.60; N, 15.00%); δ_H (500 MHz; $CDCl_3$) 4.80 (2H, br s, NH_2), 5.41 (2H, s, OCH_2), 7.37–7.48 (5H, m, Ph), 7.68 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 69.0, 120.9, 128.5, 128.6, 128.6, 134.7, 135.7, 144.1, 147.0; LC–MS (6 min) *m/z* 280 (MH^+); HPLC t_R 4.03 min; purity 97%; (HRMS found: MH^+ *m/z* 280.0081; $C_{11}H_{11}{}^{79}BrN_3O$ requires 280.0080).

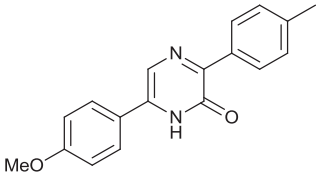
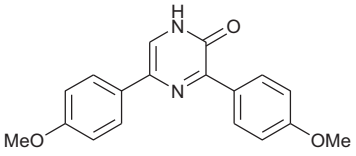
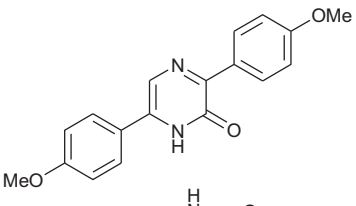
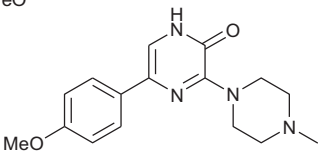
4.1.3. 3-(Benzyloxy)-5-bromo-2-iodopyrazine ***7***.[49] Aqueous 47% hydroiodic acid (4.80 mL, 27.0 mmol) was added to a stirred solution of **6** (0.500 g, 1.78 mmol) in acetonitrile (3.6 mL) and water (5.5 mL) at 0 °C. A solution of sodium nitrite (2.20 g, 31.9 mmol) in water (3.7 mL) was added dropwise. The reaction mixture was warmed to rt then heated at 50 °C for 24 h. The solution was basified to pH 12 with 20% aqueous sodium hydroxide (5 mL). The mixture was extracted with diethyl ether (3×30 mL) and the organic layer was washed with saturated aqueous sodium metabisulfite (40 mL) and brine (40 mL), dried, filtered and concentrated. Flash column chromatography on silica, eluting with 1:1 dichloromethane/hexanes, gave **7** (0.450 g, 64%) as a yellow oil. R_f (50% CH_2Cl_2/hexanes) 0.39; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 928 (C–O); δ_H (500 MHz; $CDCl_3$) 5.46 (2H, s, OCH_2), 7.37 (1H, t, *J* 7.0 Hz, ArH), 7.42 (2H, dd, *J* 7.0 Hz, ArH), 7.52 (2H, d, *J* 7.0 Hz, ArH), 8.10 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 70.3, 104.6, 128.0, 128.4, 128.6, 135.2, 135.8, 139.3, 158.1; LC–MS (15 min) *m/z* 393, 391 (MH^+); HPLC t_R 10.38 min; purity >99%; HRMS (found: MH^+ *m/z* 390.8950; $C_{11}H_9{}^{79}BrIN_2O$ requires 390.8937).

4.1.4. 3-(Benzyloxy)-5-bromo-2-chloropyrazine ***8***. A suspension of **6** (7.70 g, 27.5 mmol), copper(II) chloride (11.1 g, 82.6 mmol), copper(I) chloride (5.45 g, 55.1 mmol) in acetonitrile (77 mL) was stirred at rt for 10 min. Isoamyl nitrite (11.0 mL, 82.6 mmol) was added. The solution was stirred at rt for 3 h. Hydrochloric acid solution (1 M aq, 100 mL) was added and the mixture was extracted with diethyl ether (220 mL). The organic layer was dried, filtered and concentrated. Flash column chromatography on silica, eluting with 1:1 ethyl acetate/hexanes, gave **8** (5.00 g, 61%) as a yellow solid. Mp 269–272 °C; R_f (50% EtOAc/hexanes) 0.29; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 928 (C–O); δ_H (500 MHz; $CDCl_3$) 5.49 (2H, s, OCH_2), 7.37–7.44 (3H, m, ArH), 7.51 (2H, d, *J* 7.0 Hz, ArH), 8.07 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 70.0, 128.3, 128.6, 128.7, 133.8, 135.0, 136.3, 137.1, 155.2; GC–MS *m/z* 302, 300, 298 (M^+); GC t_R 4.19 min; purity >99%; HRMS (found: MH^+ *m/z* 298.9590; $C_{11}H_9N_2{}^{79}BrClO$ requires 298.9581).

4.1.5. 3,5-Dichloropyrazin-2-amine ***10***.[75] 2-Amino-3-chloropyrazine **9** (10.0 g, 77.2 mmol) was added to a stirred suspension of NCS (11.6 g, 86.9 mmol) in chloroform (73 mL). The reaction mixture was heated at reflux for 4 h. The solution was cooled and partitioned between chloroform (180 mL) and water (2×50 mL). The organic layer was dried, filtered and concentrated. Flash chromatography on silica, eluting with chloroform, gave **10** (9.66 g, 76%) as a pale yellow solid. Mp 200–202 °C; R_f ($CHCl_3$) 0.32; ν_{max} (thin film/cm^{-1}) 3411 (NH_2), 3019 (Ar CH); (found: C, 28.89; H, 1.71; N, 24.99; $C_4H_3N_3Cl_2$: 0.125(H_2O) requires C, 28.90; H, 1.97; N, 25.28%); δ_H (500 MHz; $CDCl_3$) 4.96 (2H, br s, NH_2), 7.90 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 131.4, 134.6, 140.0, 150.3; GC–MS *m/z* 167, 165, 163 (M^+), GC t_R 2.51 min; purity 98%; HRMS (found: MH^+ *m/z* 163.9782; $C_4H_4{}^{35}Cl_2N_3$ requires 163.9777).

4.1.6. 3-(Benzyloxy)-5-chloropyrazin-2-amine ***11***. Benzyl alcohol (7.60 mL, 73.2 mmol) was added slowly to a stirred suspension of sodium hydride (60% dispersed in mineral oil) (2.95 g, 73.2 mmol)

Table 7
Kinase inhibition by compounds **39** and **57** screened in a panel of 150 kinases, and compounds **38** and **65** screened in a panel of 85 kinases

No.	Structure	Kinase inhibition[a]	Kinase inhibition[b]
39		—	ABL2/ARG, CAMK2α, CAMK4, CDK4, CK1ε, CK2α, CK2α2, DAPK2, Fgr, FGFR4, HIPK3, IKKβ, PKCγ, TSSK2
57		—	DAPK2, FGFR4, MUSK
38		PKB-β, Aurora-B, SRPK1	PKB-α, PKB-β, S6K1, PKCα, PKD1, CAMK1, Aurora B, MELK, NEK6, SRPK1, FGF-R1, EPH-B3, NUAK1, HER4
65		PHK, PIM3	PKCα, PHK, CHK2, MELK, DYRK2, DYRK3, PIM1, PIM3, EPH-B3, HER4

[a] Inhibition of >60% at 30 μM concentration of test compound.
[b] Inhibition of >30% at 30 μM concentration of test compound.

Table 8
Antiproliferative activity of compounds **39** and **57**

No.	Cytotoxicity HCT116 cells (IC_{50}, μM)[a]	Cytotoxicity MV4-11 cells (IC_{50}, μM)[a]
39	3.2	n.d.[b]
57	30	20

[a] Single determination in MTT assay format.[69]
[b] n.d.=not determined.

in dry THF (122 mL). The mixture was stirred at rt for 10 min, after which **10** (7.30 g, 44.5 mmol) was added and the mixture was heated at reflux for 24 h. The cooled solution was concentrated, and ethyl acetate (500 mL) and water (200 mL) were added to the resulting gum. The mixture was filtered through Celite. The organic layer was separated, washed with brine (2×100 mL), dried, filtered and concentrated. Flash column chromatography on silica, eluting with 1:1 ethyl acetate/hexanes, gave a solid, which was recrystallised from water (200 mL) to give **11** (6.00 g, 57%) as an orange solid. Mp 285–287 °C (from water); R_f (50% EtOAc/hexanes) 0.41; ν_{max} (thin film/cm^{-1}) 3409 (NH_2), 3019 (Ar CH), 929 (C–O); (found: C, 56.19; H, 4.26; N, 17.65; $C_{11}H_{10}N_3OCl$ requires C, 56.06; H, 4.28; N, 17.83%); δ_H (500 MHz; $CDCl_3$) 4.77 (2H, br s, NH_2), 5.32 (2H, s, OCH_2), 7.30–7.39 (5H, m, Ph), 7.51 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 69.0, 128.5, 128.6, 128.6, 131.7, 131.9, 135.7, 143.8, 146.7; LC–MS (15 min) *m/z* 236 (MH^+) HPLC t_R 7.49 min; purity 99% HRMS (found: MH^+ *m/z* 236.0585; $C_{11}H_{11}{}^{35}ClN_3O$ requires 236.0585).

4.1.7. 3-(Benzyloxy)-5-chloro-2-iodopyrazine ***12****.* A solution of **11** (0.300 g, 1.27 mmol) in acetonitrile (2.5 mL), water (3.9 mL) and 47% aqueous hydroiodic acid (3.40 mL, 19.1 mmol) was stirred at 0 °C for 10 min. A solution of sodium nitrite (1.56 g, 22.6 mmol) in water (2.6 mL) was added dropwise to the reaction mixture, which was stirred at 0 °C for a further 10 min, then heated at 50 °C for 21 h. The cooled solution was basified with 20% aqueous sodium hydroxide (11 mL). The mixture was extracted with diethyl ether (3×50 mL) and the organic layer was washed with saturated aqueous sodium metabisulfite (50 mL) and brine (50 mL), dried, filtered and concentrated. Flash column chromatography on silica, eluting with 1:1 dichloromethane/hexanes, gave **12** (0.222 g, 50%) as a pale yellow solid. Mp 265–268 °C; R_f (50% CH_2Cl_2/hexanes) 0.55; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1014 (C–O); (found: C, 37.55; H, 2.21; N, 7.76; $C_{11}H_8N_2O_1Cl$: 0.25(H_2O) requires C, 37.64; H, 2.44; N, 7.98%); δ_H (500 MHz; $CDCl_3$) 5.38 (2H, s, OCH_2), 7.24–7.38 (3H, m, ArH), 7.43 (2H, d, *J* 7.0 Hz, ArH), 7.93 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 70.0, 126.9, 128.2, 128.5, 128.7, 134.9, 135.1, 144.2, 156.0; LC–MS (3.5 min) *m/z* 349, 347 (MH^+); HPLC t_R 2.95 min; purity 99%; HRMS (found: MH^+ *m/z* 346.9446; $C_{11}H_9{}^{35}ClIN_2O_3$ requires 346.9443).

4.1.8. 3-(Benzyloxy)-2-bromo-5-chloropyrazine ***13****.* Isoamyl nitrite (6.80 mL, 50.9 mmol) was added to a stirred suspension of **11** (4.00 g, 17.0 mmol), copper(I) bromide (4.87 g, 33.9 mmol) and copper(II) bromide (11.4 g, 50.9 mmol) in acetonitrile (48 mL) at rt. After 3 h the mixture was diluted with dilute hydrochloric acid (1 M aq, 200 mL) and extracted with ethyl acetate (2×200 mL). The organic extracts were dried, filtered and concentrated. Flash column chromatography on silica, eluting with 1:1 ethyl acetate/hexanes, gave **13** (2.44 g, 48%) as a white solid. Mp 274–278 °C; R_f (50% EtOAc/hexanes) 0.75; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1057 (C–O); (found: C, 43.94; H, 2.66; N, 9.20; $C_{11}H_8N_2OBrCl$ requires C, 44.11; H, 2.69; N, 9.35%); δ_H (500 MHz; $CDCl_3$) 5.48 (2H, s, OCH_2),

7.36–7.52 (5H, m, Ph), 7.98 (1H, s, 6-H); δ_C (125 MHz; DMSO-d_6) 70.2, 127.2, 128.5, 128.8, 129.0, 135.6, 135.8, 143.9, 156.1; GC–MS *m*/*z* 302, 300, 298 (M^+); GC t_R 4.35 min; purity >99%; HRMS (found: MH^+ *m*/*z* 298.9586; $C_{11}H_9{}^{79}Br^{35}ClN_2O$ requires 298.9581).

4.1.9. 3-Amino-pyrazin-2(1H)-one ***14***.[51] A solution of **6** (50.0 mg, 0.178 mmol), 10% w/w palladium on carbon (10.0 mg, 0.094 mmol) in ethanol (3 mL) was stirred at rt for 7.5 h under an atmosphere of hydrogen (1 atm). The mixture was filtered through a plug of Celite and concentrated. Purification by ion exchange chromatography on acidic resin, eluting with methanol then 1 M ammonia in methanol, gave **14** (4.0 mg, 20%) as a white solid. δ_H (500 MHz; CD_3OD) 6.57 (1H, d, *J* 4.5 Hz, Ar), 6.64 (1H, d, *J* 4.5 Hz, Ar); GC–MS *m*/*z* 111 (M^+); GC t_R 5.09 min.

4.1.10. 3-(Benzyloxy)-2-chloro-5-(4-methoxyphenyl)pyrazine ***19***. A solution of **8** (5.00 g, 16.7 mmol), 4-methoxyphenylboronic acid (3.85 g, 25.3 mmol), 2 M aq Na_2CO_3 (25.0 mL, 50.0 mmol), dichloro-bis-(triphenylphosphine)palladium(II) (1.20 g, 1.71 mmol) in dry DME (78 mL) was stirred at 50 °C for 16 h. Ethyl acetate (200 mL) was added and the organic layer washed with water (200 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were filtered through a plug of silica gel (6 g). The filtrate was concentrated. Flash column chromatography on silica, eluting with 1:1 dichloromethane/hexanes, gave **19** (3.83 g, 70%) as a yellow solid. Mp >300 °C; R_f (50% CH_2Cl_2/hexanes) 0.15; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1185 (C–O), 929 (C–O); (found: C, 65.86; H, 4.65; N, 8.36; $C_{18}H_{15}ClN_2O_2$ requires C, 66.16; H, 4.63; N, 8.57%); δ_H (500 MHz; $CDCl_3$) 3.90 (3H, s, OCH_3), 5.60 (2H, s, OCH_2), 7.02 (2H, d, *J* 9.0 Hz, ArH *o*- to OMe), 7.35–7.51 (5H, m, Ph), 7.94 (2H, d, *J* 9.0 Hz, ArH), 8.34 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 55.4, 68.7, 114.4, 127.8, 127.9, 128.2, 128.2, 128.6, 131.4, 134.7, 136.2, 147.9, 154.9, 161.2; GC–MS *m*/*z* 328, 326 (M^+); GC t_R 5.90 min; purity 99%; HRMS (found: MH^+ *m*/*z* 327.0899; $C_{18}H_{16}{}^{35}ClN_2O_2$ requires 327.0895).

4.1.11. 3-(Benzyloxy)-5-chloro-2-(4-methoxyphenyl)pyrazine ***20***. A solution of **13** (4.10 g, 13.7 mmol), 4-methoxyphenylboronic acid (3.14 g, 20.7 mmol), 2 M aq Na_2CO_3 (21.0 mL, 42.0 mmol), dichloro-bis-(triphenylphosphine)palladium(II) (0.960 g, 1.37 mmol) in dry DME (64 mL) was stirred at 50 °C for 16 h. Ethyl acetate (200 mL) was added and the organic layer was washed with water (200 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic extracts were filtered through a plug of silica gel. The filtrate was concentrated. Flash column chromatography on silica, eluting with 1:1 dichloromethane/hexanes, gave **20** (2.72 g, 61%) as an off-white solid. Mp >300 °C; R_f (50% CH_2Cl_2/hexanes) 0.18; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1177 (C–O), 929 (C–O); δ_H (500 MHz; $CDCl_3$) 3.79 (3H, s, OCH_3), 5.43 (2H, s, OCH_2), 6.89 (2H, d, *J* 9.0 Hz, ArH), 7.32–7.36 (3H, m, ArH), 7.41 (2H, d, *J* 7.0 Hz, ArH), 7.99 (2H, d, *J* 9.0 Hz, ArH), 8.15 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 52.8, 66.5, 111.2, 124.8, 125.6, 125.7, 126.0, 128.0, 132.4, 133.4, 138.2, 139.5, 153.3, 158.1; GC–MS *m*/*z* 328, 326 (M^+); GC t_R 5.72 min; purity 99%; HRMS (found MH^+: *m*/*z* 327.0896; $C_{18}H_{16}{}^{35}ClN_2O_2$ requires 327.0895).

4.2. General procedures for the preparation of 2-(benzyloxy)-3,6-di(hetero)arylpyrazines 21–37

Method A: A mixture of the halopyrazine **19** or **20** (100 mg, 0.306 mmol), the (hetero)arylboronic acid or boronate ester (0.459 mmol, 1.5 equiv), sodium carbonate (45.0 mg, 0.425 mmol, 1.4 equiv) and tetrakis(triphenylphosphine)palladium (0) (23.0 mg, 0.019 mmol) in water (0.9 mL) and acetonitrile (3.4 mL) was heated in a microwave reactor using variable wattage to 150 °C for 20 min. The mixture was partitioned between ethyl acetate (50 mL) and water (40 mL). The organic layer was filtered through a short plug of silica gel (6 g) washing with ethyl acetate. The filtrate was concentrated. Where necessary, further purification was carried out by flash column chromatography on silica to give the coupled products; those which required chromatography have an associated R_f for the column eluant. The following compounds were prepared using Method A.

4.2.1. 2-(Benzyloxy)-3,6-bis-(4-methoxyphenyl)pyrazine ***21***. White solid; mp >300 °C; R_f (CH_2Cl_2) 0.33; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1033, 929; δ_H (500 MHz; $CDCl_3$) 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.65 (2H, s, OCH_2), 7.00 (2H, d, *J* 9.0 Hz, ArH), 7.04 (2H, d, *J* 9.0 Hz, ArH), 7.34–7.54 (5H, m, Ph), 8.03 (2H, d, *J* 9.0 Hz, ArH), 8.18 (2H, d, *J* 9.0 Hz, ArH), 8.65 (1H, s, 5-H); δ_C (125 MHz; $CDCl_3$) 55.3, 55.4, 67.9, 113.6, 114.3, 127.8, 128.0, 128.5, 128.9, 130.5, 132.2, 137.2, 139.8, 146.3, 156.1, 160.3, 160.8, two signals not observed; LC–MS (6 min) *m*/*z* 399 (MH^+); HPLC t_R 5.21 min; purity >99%; HRMS (found: MH^+ *m*/*z* 399.1701; $C_{25}H_{23}N_2O_3$ requires 399.1703).

4.2.2. 3-(Benzyloxy)-5-(4-methoxyphenyl)-2-(pyridin-3-yl)pyrazine ***24***. White solid. Mp >300 °C; R_f (50% EtOAc/hexanes) 0.23; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1029 (C–O), 929 (C–O); ^1H NMR δ_H (500 MHz; $CDCl_3$) 3.91 (3H, s, OCH_3), 5.67 (2H, s, OCH_2), 7.06 (2H, d, *J* 9.0 Hz, ArH), 7.35–7.53 (6H, m, Ph and pyridine 5-H), 8.06 (2H, d, *J* 9.0 Hz, ArH), 8.47 (1H, ddd, *J* 8.0, 1.0, 1.0 Hz, pyridine 4-H), 8.64 (1H, dd, *J* 5.0, 1.0 Hz, pyridine 6-H), 8.72 (1H, s, 6-H), 9.44 (1H, d, *J* 1.0 Hz, pyridine 2-H); δ_C (125 MHz; DMSO-d_6) 55.3, 67.8, 114.5, 123.3, 127.6, 128.0, 128.0, 128.3, 128.5, 131.3, 132.8, 135.8, 136.4, 136.7, 147.4, 149.4, 149.5, 156.1, 161.0; LC–MS (6 min) *m*/*z* 370 (MH^+); HPLC t_R 4.32 min; purity 99%; HRMS (found: MH^+ *m*/*z* 370.1558; $C_{23}H_{20}N_3O_2$ requires 370.1550).

4.2.3. 3-(Benzyloxy)-2-(4-hydroxyphenyl)-5-(4-methoxyphenyl)pyrazine ***25***. Off-white solid. Mp >300 °C; R_f (50% EtOAc/CH_2Cl_2) 0.10; ν_{max} (thin film/cm^{-1}) 3500–3200 (OH), 3019 (Ar CH), 928 (C–O); δ_H (500 MHz; $CDCl_3$) 3.91 (3H, s, OCH_3), 5.07 (1H, s, OH), 5.66 (2H, s, OCH_2), 6.92 (2H, d, *J* 8.0 Hz, ArH), 7.05 (2H, d, *J* 9.0 Hz, ArH), 7.34–7.54 (5H, m, Ph), 8.04 (2H, d, *J* 9.0 Hz, ArH), 8.12 (2H, d, *J* 8.0 Hz, ArH), 8.66 (1H, s, 6-H); δ_C (125 MHz; DMSO-d_6) 55.8, 67.8, 114.9, 115.5, 126.8, 128.3, 128.3, 128.4, 128.5, 128.9, 130.7, 132.6, 137.5, 139.7, 145.7, 155.8, 158.9, 161.0; LC–MS (6 min) *m*/*z* 385 (MH^+); HPLC t_R 4.59 min; purity 99%; HRMS (found: MH^+ *m*/*z* 385.1559; $C_{24}H_{21}N_2O_3$ requires 385.1552).

4.2.4. N-(3-(3-Benzyloxy-5-(4-methoxyphenyl)pyrazin-2-yl]phenyl) acetamide) ***26***. Yellow solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1684 (C=O), 928 (C–O); δ_H (500 MHz; $CDCl_3$) 2.20 (3H, s, CH_3), 3.91 (3H, s, OCH_3), 5.66 (2H, s, OCH_2), 7.05 (2H, d, *J* 9.0 Hz, ArH), 7.18 (1H, br s, NH), 7.32–7.56 (6H, m, ArH), 7.81 (1H, d, *J* 8.0 Hz, ArH), 7.96 (1H, d, *J* 8.0 Hz, ArH), 8.04 (2H, d, *J* 9.0 Hz, ArH), 8.09 (1H, s, ArH), 8.67 (1H, s, 6-H); LC–MS (6 min) *m*/*z* 426 (MH^+); HPLC t_R 4.30 min; purity 96%; HRMS (found: MH^+ *m*/*z* 426.1822; $C_{26}H_{24}N_3O_3$ requires 426.1812).

4.2.5. 3-(Benzyloxy)-2-(3-pyrazol-3-yl)-5-(4-methoxyphenyl)pyrazine ***27***. Pale yellow solid. Mp >300 °C; R_f (2:1 EtOAc/hexanes) 0.18; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 929 (C–O); δ_H (500 MHz; $CDCl_3$) 3.91 (3H, s, OCH_3), 5.69 (2H, s, OCH_2), 7.05 (2H, d, *J* 9.0 Hz, ArH), 7.05 (1H, br s, pyrazole 4-H), 7.40–7.57 (5H, m, Ph), 7.69 (1H, br s, pyrazole 5-H), 8.04 (2H, d, *J* 9.0 Hz, ArH), 8.64 (1H, s, 6-H); LC–MS (6 min) *m*/*z* 359 (MH^+); HPLC t_R 4.25 min; purity 99%; HRMS (found: MH^+ *m*/*z* 359.1506; $C_{21}H_{19}N_4O_2$ requires 359.1508).

4.2.6. 3-(Benzyloxy)-2-(thiophen-3-yl)-5-(4-methoxyphenyl)pyrazine ***28***. Pale yellow solid. Mp >300 °C; R_f (CH_2Cl_2) 0.71; ν_{max} (thin film/cm^{-1}) 3060, 3034 (Ar CH), 1024, 974; δ_H (500 MHz; $CDCl_3$) 3.90 (3H, s, OCH_3), 5.69 (2H, s, OCH_2), 7.04 (2H, d, *J* 7.0 Hz, ArH), 7.36–7.45 (3H, m, ArH and thienyl 3-H), 7.57 (2H, d, *J* 9.0 Hz, ArH) 8.00 (1H, d, *J* 7.5 Hz, thienyl 4-H), 8.00–8.04 (3H, m, ArH and thienyl

5-H), 8.27 (1H, s, thienyl 2-H), 8.64 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 55.4, 68.2, 114.4, 124.8, 126.7, 128.0, 128.1, 128.2, 128.2, 128.6, 128.8, 132.0, 136.0, 136.9, 137.4, 146.3, 155.6, 160.9; LC–MS (10 min) *m/z* 375 (MH^+); HPLC t_R 5.33 min; purity 99%; HRMS (found: MH^+ *m/z* 375.1164; $C_{22}H_{19}N_2O_2S$ requires 375.1162).

4.2.7. 4-(4-(3-Benzyloxy-5-(4-methoxyphenyl)pyrazin-2-yl)benzyl) morpholine ***29***. Pale yellow solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1034 (C–O), 929 (C–O); δ_H (500 MHz; $CDCl_3$) 2.50 (4H, br s, morpholine NCH_2), 3.70 (2H, s, NCH_2Ar), 3.74 (4H, br s, morpholine OCH_2), 3.91 (3H, s, OCH_3), 5.66 (2H, s, OCH_2), 7.05 (2H, d, *J* 9.0 Hz, ArH), 7.33–7.71 (7H, m, Ph and ArH), 8.04 (2H, d, *J* 9.0 Hz, ArH), 8.14 (2H, d, *J* 8.0 Hz, ArH), 8.68 (1H, s, 6-H); LC–MS (6 min) *m/z* 468 (MH^+); HPLC t_R 3.41 min; purity 98%; HRMS (found: MH^+ *m/z* 468.2283; $C_{29}H_{30}N_3O_3$ requires 468.2282).

4.2.8. 3-(Benzyloxy)-2-(4-methoxyphenyl)-5-(pyridin-3-yl)pyrazine ***31***. Yellow solid. Mp >300 °C; R_f (2:1 EtOAc/hexanes) 0.30; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 929 (C–O); (found: C, 74.39; H, 5.42; N, 11.12; $C_{23}H_{19}N_3O_2$ requires C, 74.78; H, 5.18; N, 11.37%); δ_H (500 MHz; $CDCl_3$) 3.79 (3H, s, OCH_3), 5.56 (2H, s, OCH_2), 6.91 (2H, d, *J* 7.0 Hz, ArH), 7.25–7.35 (5H, m, Ph), 7.43 (2H, d, *J* 7.0 Hz, ArH), 8.12 (1H, dd, *J* 8.0, 5.0 Hz, pyridine H), 8.22 (1H, ddd, *J* 8.0, 2.0, 2.0 Hz, pyridine H), 8.59 (1H, dd, *J* 5.0, 2.0 Hz, pyridine H), 8.62 (1H, s, 6-H), 9.21 (1H, d, *J* 2.0 Hz, pyridine H); δ_C (125 MHz; $CDCl_3$) 55.3, 68.2, 113.7, 123.6, 127.8, 128.0, 128.3, 128.6, 130.8, 132.0, 132.8, 133.8, 136.8, 141.9, 143.8, 148.1, 150.2, 156.4, 160.7; GC–MS *m/z* 369 (M^+); GC–MS t_R 6.90 min; purity 99%.

4.2.9. 3-(Benzyloxy)-2-(4-methoxyphenyl)-5-(4-hydroxyphenyl)pyrazine ***32***. Brown solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3400–3200 (OH), 3019 (Ar CH), 1020 (C–O), 929 (C–O); δ_H (500 MHz; $CDCl_3$) 3.88 (3H, s, OCH_3), 5.64 (2H, s, OCH_2), 5.70–5.80 (1H, br s, OH), 6.95 (2H, d, *J* 8.0 Hz, ArH), 7.00 (2H, d, *J* 7.0 Hz, ArH), 7.34–7.42 (3H, m, ArH), 7.53 (2H, d, *J* 8.0 Hz, ArH), 7.97 (2H, d, *J* 8.0 Hz, ArH), 8.16 (2H, d, *J* 7.0 Hz, ArH), 8.63 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 55.3, 67.9, 113.7, 115.9, 127.8, 127.9, 128.2, 128.4, 128.5, 128.9, 130.5, 132.1, 137.1, 139.9, 146.4, 156.1, 157.1, 160.3; LC–MS (6 min) *m/z* 385 (MH^+); HPLC t_R 4.53 min; purity 99%; HRMS (found: MH^+ *m/z* 385.1549; $C_{24}H_{21}N_2O_3$ requires 385.1552).

4.2.10. 4-(6-Benzyloxy-5-(4-methoxyphenyl)pyrazin-2-yl)benzamide ***33***. Green solid. Mp >300 °C; R_f (EtOAc) 0.46; ν_{max} (thin film/cm^{-1}) 3300 (NH_2), 3019 (Ar CH), 1684 (C=O), 929 (C–O); δ_H (500 MHz; DMSO-d_6) 3.84 (3H, s, OCH_3), 5.68 (2H, s, OCH_2), 7.07 (2H, d, *J* 9.0 Hz, ArH), 7.35–7.58 (5H, m, Ph), 8.04 (2H, d, *J* 9.0 Hz, ArH), 8.16 (2H, d, *J* 9.0 Hz, ArH), 8.27 (2H, d, *J* 9.0 Hz, ArH), 9.00 (1H, s, 6-H); δ_C (125 MHz; DMSO-d_6) 55.3, 67.7, 113.7, 126.2, 127.9, 128.0, 128.1, 128.2, 128.5, 130.4, 133.4, 134.5, 136.8, 138.0, 140.4, 144.7, 155.6, 160.2, 167.3; LC–MS (6 min) *m/z* 412 (MH^+); HPLC t_R 4.36 min; purity 98%; HRMS (found: MH^+ *m/z* 412.1657; $C_{25}H_{22}N_3O_3$ requires 412.1656).

4.2.11. 3-(Benzyloxy)-2-(4-methoxyphenyl)-5-(pyrazol-4-yl)pyrazine ***34***. Off-white solid. Mp >300 °C; R_f (50% EtOAc/CH_2Cl_2) 0.18; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1021 (C–O), 929 (C–O); δ_H (500 MHz; DMSO-d_6) 3.81 (3H, s, OCH_3), 5.59 (2H, s, OCH_2), 7.02 (2H, d, *J* 9.0 Hz, ArH), 7.31–7.41 (3H, m, ArH), 7.54 (2H, d, *J* 8.0 Hz, ArH), 8.07 (2H, d, *J* 9.0 Hz, ArH), 8.15 and 8.45 (2H, 2× br s, pyrazole CH), 8.63 (1H, s, 6-H), 13.20 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 55.2, 67.4, 113.6, 118.6, 127.8, 128.0, 128.4, 130.0, 131.4, 131.5, 132.3, 137.1, 137.7, 142.3, 155.6, 159.7; LC–MS (6 min) *m/z* 359 (MH^+); HPLC t_R 4.30 min; purity 97%; HRMS (found: MH^+ *m/z* 359.1502; $C_{21}H_{19}N_4O_2$ requires 359.1503).

4.2.12. 3-(Benzyloxy)-2-(4-methoxyphenyl)-5-(pyrazol-3-yl)pyrazine ***35***. White solid. Mp >300 °C; R_f (2:1 EtOAc/hexanes) 0.34; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 928 (C–O); δ_H (500 MHz; acetone-d_6) 3.87 (3H, s, OCH_3), 5.70 (2H, s, OCH_2), 7.01–7.03 (3H, m, ArH and pyrazole 4-H), 7.31–7.43 (3H, m, ArH), 7.61 (2H, d, *J* 8.5 Hz, ArH) 7.80 (1H, br s, pyrazole 5-H), 8.23 (2H, d, *J* 8.5 Hz, ArH), 8.84 (1H, s, 6-H), 12.50 (1H, br s, NH); δ_C (125 MHz; acetone-d_6) 55.6, 67.8, 104.8, 114.3, 124.4, 128.8, 129.0, 129.3, 131.4, 133.4, 138.2, 143.2, 146.4, 149.1, 157.0, 161.4, one signal not observed; GC–MS *m/z* 358 (M^+); GC–MS t_R 6.86 min; purity 99%; HRMS (found : MH^+ *m/z* 359.1510; $C_{21}H_{19}N_4O_2$ requires 359.1508).

4.2.13. 3-(Benzyloxy)-2-(4-methoxyphenyl)-5-(3-thiophenyl)pyrazine ***36***. Off-white solid. Mp >300 °C; R_f (CH_2Cl_2) 0.57; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1020 (C–O), 929 (C–O); δ_H (500 MHz; $CDCl_3$) 3.89 (3H, s, OCH_3), 5.64 (2H, s, OCH_2), 7.02 (2H, d, *J* 9.0 Hz, ArH), 7.36–7.47 (4H, m, ArH and thiophene 4-H), 7.54 (2H, d, *J* 7.0 Hz, ArH), 7.71 (1H, dd, *J* 5.0, 1.0 Hz, thiophene 5-H), 7.98 (1H, d, *J* 1.0 Hz, thiophene 2-H), 8.19 (2H, d, *J* 9.0 Hz, ArH), 8.60 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 55.3, 68.0, 113.7, 124.0, 125.8, 126.6, 127.9, 127.9, 128.4, 128.6, 130.6, 132.8, 137.1, 139.1, 140.4, 143.0, 156.2, 160.4; LC–MS (6 min) *m/z* 375 (MH^+); HPLC t_R 5.02 min; purity 99%; HRMS (found: MH^+ *m/z* 375.1164; $C_{22}H_{19}N_2O_2S$ requires 374.1162).

4.2.14. 3-(Benzyloxy)-2-(4-methoxyphenyl)-5-(2-methoxyphenyl) pyrazine ***37***. Colourless oil. R_f (50% EtOAc/hexanes) 0.56; δ_H (500 MHz; $CDCl_3$) 3.89 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 5.64 (2H, s, OCH_2), 7.01 (2H, d, *J* 9.0 Hz, ArH), 7.06 (1H, d, *J* 7.0 Hz, ArH), 7.12–7.15 (1H, m, ArH), 7.34–7.44 (4H, m, ArH), 7.53 (2H, d, *J* 6.0 Hz, ArH), 8.0 (1H, dd, *J* 8.0, 2.0 Hz, ArH), 8.22 (2H, d, *J* 9.0 Hz, ArH), 8.98 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 55.3, 55.6, 67.9, 111.6, 113.6, 121.1, 125.5, 127.8, 127.9, 128.5, 130.4, 130.6, 130.9, 137.3, 137.6, 139.8, 144.9, 156.1, 157.6, 160.3, one signal not observed; LC–MS (6 min) *m/z* 399 (MH^+); HPLC t_R 5.08 min; purity 99%.

Method B: A mixture of the halopyrazine **19** or **20** (100 mg, 0.306 mmol), the (hetero)arylboronic acid or boronate ester (0.459 mmol, 1.5 equiv), aqueous sodium carbonate (2 M, 0.50 mL, 1.00 mmol) and [2-[(dimethylamino-κN)methyl]phenyl-κC](tricyclohexylphosphine)(trifluoroacetato-κO)-palladium[53] (20.0 mg, 0.031 mmol) in dry 1,2-dimethoxyethane (1.4 mL) was heated at reflux for 4–40 h until starting material was consumed. The mixture was partitioned between ethyl acetate (60 mL) and water (40 mL). The organic layer was filtered through a short plug of silica gel (6 g) washing with ethyl acetate. The filtrate was concentrated. Flash column chromatography on silica, eluting with mixtures of ethyl acetate/hexanes or dichloromethane/hexanes, gave the coupled products. The following compounds were prepared using method B.

4.2.15. 3-(Benzyloxy)-5-(4-methoxyphenyl)-2-(4-methylphenyl)pyrazine ***22***. White solid. Mp >300 °C; R_f (50% EtOAc/hexanes) 0.36; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1033 (C–O), 928 (C–O); δ_H (500 MHz; $CDCl_3$) 2.42 (3H, s, CH_3), 3.90 (3H, s, OCH_3), 5.65 (2H, s, OCH_2), 7.04 (2H, d, *J* 9.0 Hz, ArH), 7.27–7.54 (7H, m, ArH), 8.03 (2H, d, *J* 9.0 Hz, ArH), 8.08 (2H, d, *J* 9.0 Hz, ArH), 8.67 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 20.9, 55.3, 67.5, 114.4, 127.8, 128.1, 128.4, 128.6, 128.8, 129.0, 132.3, 132.7, 136.9, 138.5, 140.0, 146.2, 155.7, 160.9, one signal not observed; LC–MS (10 min) *m/z* 383 (MH^+); HPLC t_R 8.29 min; purity 99%; HRMS (found: MH^+ *m/z* 383.1757; $C_{25}H_{23}N_2O_2$ requires 383.1760).

4.2.16. 4-(3-Benzyloxy-5-(4-methoxyphenyl)pyrazin-2-yl)benzoic acid ethyl ester ***23***. White solid. Mp >300 °C; R_f (CH_2Cl_2) 0.32; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 929 (C–O); δ_H (500 MHz; $CDCl_3$) 1.43 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 3.91 (3H, s, OCH_3), 4.42 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 5.66 (2H, s, OCH_2), 7.06 (2H, d, *J* 9.0 Hz, ArH), 7.31–7.54 (5H, m, Ph), 8.06 (2H, d, *J* 9.0 Hz, ArH), 8.13 (2H, d, *J* 8.0 Hz, ArH),

8.26 (2H, d, *J* 8.0 Hz, ArH), 8.72 (1H, s, 6-H); δ_C (125 MHz; DMSO-d_6) 14.1, 55.4, 60.8, 67.7, 114.5, 127.5, 127.9, 127.9, 128.4, 128.5, 128.8, 128.9, 129.8, 132.7, 136.8, 137.4, 139.9, 147.5, 156.1, 161.0, 165.4; LC–MS (10 min) *m*/*z* 441 (MH^+); HPLC t_R 8.44 min; purity 96%; HRMS (found: MH^+ *m*/*z* 441.1812; $C_{27}H_{25}N_2O_4$ requires 441.1814).

4.2.17. 3-(Benzyloxy)-2-(4-methoxyphenyl)-5-(4-methylphenyl)pyrazine ***30***. White solid. Mp >300 °C; R_f (2:1 CH_2Cl_2/hexanes) 0.24; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 928 (C–O); (found: C, 78.49; H, 5.86; N, 7.16); $C_{25}H_{22}N_2O_2$ requires C, 78.51; H, 5.80; N 7.32%); δ_H (500 MHz; $CDCl_3$) 2.36 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 5.57 (2H, s, OCH_2), 6.91 (2H, d, *J* 9.0 Hz, ArH), 7.23 (2H, d, *J* 8.0 Hz, ArH), 7.25–7.42 (5H, m, Ph), 7.88 (2H, d, *J* 8.0 Hz, ArH), 8.09 (2H, d, *J* 9.0 Hz, ArH), 8.60 (1H, s, 6-H); δ_C (125 MHz; DMSO-d_6) 20.9, 55.2, 67.5, 113.6, 126.4, 127.7, 127.8, 127.9, 128.5, 129.6, 130.2, 132.6, 132.7, 136.9, 139.3, 139.4, 145.7, 155.5, 160.0; GC–MS *m*/*z* 382 (M^+); GC–MS t_R 6.92 min; purity 99%; (HRMS (found: *m*/*z* 383.1766; $C_{25}H_{23}N_2O_2$ requires 383.1754).

4.3. General procedure for the preparation of 3,6-di(hetero) arylpyrazin-2(1*H*)-ones 38–54

Boron trichloride in dichloromethane (1 M, 0.600 mL, 0.600 mmol) was added to a stirred solution of the appropriate 2-benzyloxy-3,6-di(hetero)arylpyrazine (**21**–**37**) (0.130 mmol) in dichloromethane (3.8 mL) at rt. After 30 min the reaction was quenched by the addition of methanol (30 mL) and stirred for 16 h. The mixture was concentrated. The crude product was redissolved in 9:1 dichloromethane/methanol and filtered through basic ion exchange resin. The filtrate was concentrated to give the 3,6-di(hetero)arylpyrazin-2(1*H*)-one product (**38**–**54**).

4.3.1. 3,6-Bis-(4-methoxyphenyl)-1H-pyrazin-2-one ***38***. Orange solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1636 (C=O), 1029 (C–O), 929 (C–O); δ_H (500 MHz; DMSO-d_6) 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 7.00 (2H, d, *J* 8.0 Hz, ArH), 7.06 (2H, d, *J* 8.0 Hz, ArH), 7.84–7.86 (2H, br d, *J* 7.0 Hz, ArH), 8.00 (1H, br s, 5-H), 8.33 (2H, br d, *J* 7.0 Hz, ArH), 12.45 (1H, br s, NH); LC–MS (3.5 min) *m*/*z* 309 (MH^+); HPLC t_R 2.70 min purity 98%; HRMS (found: MH^+ *m*/*z* 309.1237; $C_{18}H_{17}N_2O_3$ requires 309.1234).

4.3.2. 6-(4-Methoxyphenyl)-3-(4-methylphenyl)-1H-pyrazin-2-one ***39***. Bright yellow solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3446 (NH), 2994 (Ar CH), 1653 (C=O), 925 (C–O); (found: C, 73.04; H, 5.53; N, 9.13; $C_{18}H_{16}N_2O_2$.0.25 (H_2O) requires C, 72.83; H, 5.60; N, 9.44%); δ_H (500 MHz; $CDCl_3$) 2.44 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 7.07 (2H, d, *J* 9.0 Hz, ArH), 7.29 (2H, d, *J* 8.5 Hz, ArH), 7.74 (2H, d, *J* 8.5 Hz, ArH), 7.85 (1H, s, 6-H), 8.36 (2H, d, *J* 9.0 Hz, ArH); δ_C (125 MHz; $CDCl_3$) 20.9, 55.4, 114.4, 123.6, 128.1, 128.3, 128.4, 128.6, 131.0, 133.4, 138.6, 156.0, 160.7, one signal not observed; LC–MS (6 min) *m*/*z* 293 (MH^+); HPLC t_R 3.96 min; purity 99%; HRMS (found: MH^+ *m*/*z* 293.1290; $C_{18}H_{17}N_2O_2$ requires 293.1290).

4.3.3. 4-(5-(4-Methoxyphenyl)-3-oxo-3,4-dihydropyrazin-2-yl)benzoic acid ethyl ester ***40***. Bright yellow solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1684 (C=O), 1653 (C=O); δ_H (500 MHz; DMSO-d_6; 400 K) 1.40 (3H, t, *J* 8.0 Hz, CH_3), 3.89 (3H, s, OCH_3), 4.40 (2H, q, *J* 8.0 Hz, CH_2), 7.10 (2H, d, *J* 8.0 Hz, ArH), 7.92 (2H, d, *J* 9.0 Hz, ArH), 8.03 (2H, d, *J* 8.0 Hz, ArH), 8.148 (1H, s, 5-H), 8.46 (2H, d, *J* 9.0 Hz, ArH); LC–MS (6 min) *m*/*z* 351 (MH^+); HPLC t_R 4.24 min; purity 95%; HRMS (found: MH^+ *m*/*z* 351.1339; $C_{20}H_{19}N_2O_4$ requires 351.1345).

4.3.4. 6-(4-Methoxyphenyl)-3-(pyridin-3-yl)-1H-pyrazin-2-one ***41***. Yellow solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; DMSO-d_6); 3.85 (3H, s, OCH_3), 7.12 (2H, d, *J* 9.0 Hz, ArH), 7.95 (2H, *J* 9.0 Hz, ArH), 8.02 (1H, dd, *J* 8.0, 6.0 Hz, pyridine 5-H), 8.20 (1H, br s, 5-H), 8.87 (1H, br d, *J* 6.0 Hz, pyridine 4-H), 9.17 (1H, d, *J* 8.0 Hz, pyridine 6-H), 9.68 (1H, s, pyridine 2-H), 13.00 (1H, br s, NH); LC–MS (6 min) *m*/*z* 280 (MH^+); HPLC t_R 3.04 min; purity 99%; HRMS (found: MH^+ *m*/*z* 280.1086; $C_{16}H_{14}N_3O_2$ requires 280.1086).

4.3.5. 3-(4-Hydroxyphenyl)-6-(4-methoxyphenyl)-1H-pyrazin-2-one ***42***. Red solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; DMSO-d_6) 3.83 (3H, s, OCH_3), 6.85 (2H, d, *J* 9.0 Hz, ArH), 7.08 (2H, d, *J* 8.0 Hz, ArH), 7.85 (2H, d, *J* 9.0 Hz, ArH), 7.96 (1H, br s, 5-H), 8.23 (2H, d, *J* 8.0 Hz, ArH); δ_C (125 MHz; DMSO-d_6) 55.4, 114.1, 114.4, 114.8, 115.6, 124.0, 127.0, 128.2, 129.9, 143.7, 155.9, 158.7, 160.6; LC–MS (6 min) *m*/*z* 295 (MH^+); HPLC t_R 3.62 min; purity 99%; HRMS (found: MH^+ *m*/*z* 295.1078; $C_{17}H_{15}N_2O_3$ requires 295.1077).

4.3.6. N-(3-(5-(4-Methoxyphenyl)-3-oxo-3,4-dihydropyrazin-2-yl) phenyl)acetamide ***43***. Brown solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1684 (C=O), 1653 (C=O), 928 (C–O); δ_H (500 MHz; $CDCl_3$) 2.03 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 6.98 (2H, d, *J* 9.0 Hz, ArH), 7.30 (1H, br s, NH), 7.54 (2H, d, *J* 9.0 Hz, ArH), 7.59 (1H, dd, *J* 8.5, 9.0 Hz, ArH), 7.74 (1H, d, *J* 8.5 Hz, ArH), 7.85 (1H, d, *J* 9.0 Hz, ArH), 7.91 (1H, s, 5-H), 8.31 (1H, s, ArH), 11.32 (1H, br s, NH); LC–MS (6 min) *m*/*z* 336 (MH^+); HPLC t_R 3.61 min; purity 95%; HRMS (found: *m*/*z* 335.1267; $C_{19}H_{18}N_3O_3$ requires 335.1270).

4.3.7. 6-(4-Methoxyphenyl)-3-(pyrazol-3-yl)-1H-pyrazin-2-one ***44***. Orange solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; DMSO-d_6) 3.88 (3H, s, OCH_3), 7.04 (1H, d, *J* 8.0 Hz, pyrazole 4-H), 7.09 (2H, d, *J* 9.0 Hz, ArH), 7.71 (1H, d, *J* 8.0 Hz, pyrazole 5-H), 7.94 (2H, d, *J* 9.0 Hz, ArH), 8.20 (1H, s, 5-H); LC–MS (6 min) *m*/*z* 269 (MH^+); HPLC t_R 3.48 min; purity 95%; HRMS (found: MH^+ *m*/*z* 269.1038; $C_{14}H_{13}N_4O_2$ requires 269.1039).

4.3.8. 6-(4-Methoxyphenyl)-3-(thiophen-3-yl)-1H-pyrazin-2-one ***45***. Orange solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; DMSO-d_6) 3.83 (3H, s, OCH_3), 7.08 (2H, d, *J* 9.0 Hz, ArH), 7.59 (1H, dd, *J* 5.0, 3.0 Hz, thiophene 4-H), 7.85–7.88 (4H, m, ArH, thiophene 2-H, 5-H), 8.60 (1H, br s, 5-H), 12.60 (1H, br s, NH); LC–MS (6 min) *m*/*z* 285 (MH^+); HPLC t_R 4.03 min; purity 90%; HRMS (found: MH^+ *m*/*z* 285.0700; $C_{15}H_{13}N_2O_2S$ requires 285.0698).

4.3.9. 6-(4-Methoxyphenyl)-3-(4-(morpholin-1-ylmethyl)phenyl)-1H-pyrazin-2-one ***46***. Yellow solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 1005 (C–N), 929 (C–O); δ_H (500 MHz; DMSO-d_6) 2.38 (4H, broad s, morpholine CH_2), 3.50 (2H, s, NCH_2), 3.58 (4H, br s, morpholine CH_2), 3.83 (3H, s, OCH_3), 7.06 (2H, d, *J* 9.0 Hz, ArH), 7.36 (2H, d, *J* 8.0 Hz, ArH), 7.89 (2H, d, *J* 9.0 Hz, ArH), 8.05 (1H, s, 5-H), 8.29 (2H, d, *J* 8.0 Hz, ArH); LC–MS (6 min) *m*/*z* 378 (MH^+), 291 (MH^+-morpholine); HPLC t_R 2.41 min; purity 99%; HRMS (found: MH^+ *m*/*z* 378.1822; $C_{22}H_{24}N_3O_3$ requires 378.1812).

4.3.10. 3-(4-Methoxyphenyl)-6-(4-methylphenyl)-1H-pyrazin-2-one ***47***. Orange solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; DMSO-d_6) 2.38 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 7.01 (2H, d, *J* 9.0 Hz, ArH), 7.32 (2H, d, *J* 8.0 Hz, ArH), 7.79 (2H, d, *J* 8.0 Hz, ArH), 8.08 (1H, s, 5-H), 8.34 (2H, d, *J* 9.0 Hz, ArH); LC–MS (4 min) *m*/*z* 293 (MH^+); HPLC t_R 3.09 min; purity 96%; HRMS (found: MH^+ *m*/*z* 293.1287; $C_{18}H_{17}N_2O_2$ requires 293.1285).

4.3.11. 3-(4-Methoxyphenyl)-6-(pyridin-3-yl)-1H-pyrazin-2-one ***48***. Orange solid. Mp >300 °C; ν_{max}/cm^{-1} 3019 (ArH), 1653 (C=O); (500 MHz; DMSO-d_6; 400 K) δ_H 3.88 (3H, s, OCH_3), 7.03 (2H, d, *J*

9.0 Hz, ArH), 7.52 (1H, dd, *J* 8.0, 5.0 Hz, pyridine 5-H), 8.20 (1H, s, 5-H), 8.28 (1H, d, *J* 8.0 Hz, pyridine 4-H), 8.33 (2H, d, *J* 9.0 Hz, ArH), 8.68 (1H, dd, *J* 5.0, 1.0 Hz, pyridine 6-H), 9.13 (1H, d, *J* 1.0 Hz, pyridine 2-H); LC–MS (6 min) *m*/*z* 280 (MH^+); HPLC t_R 3.45 min; purity 99%; HRMS (found: MH^+ *m*/*z* 280.1083; $C_{16}H_{14}N_3O_2$ requires 280.1081).

4.3.12. 6-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)-1H-pyrazin-2-one ***49***. Red solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; $CDCl_3$) 3.81 (3H, s, OCH_3), 6.89 (2H, d, *J* 9.0 Hz, ArH), 7.00 (2H, d, *J* 8.0 Hz, ArH), 7.73 (2H, d, *J* 8.0 Hz, ArH), 8.08 (1H, s, 5-H), 8.33 (2H, d, *J* 9.0 Hz, ArH), 10.0 (1H, br s, NH or OH); LC–MS (6 min) *m*/*z* 295 (MH^+); HPLC t_R 3.73 min; purity 99%; HRMS (found: *m*/*z* 295.1076; $C_{17}H_{15}N_2O_3$ requires 295.1077).

4.3.13. 4-(5-(4-Methoxyphenyl)-6-oxo-1,6-dihydropyrazin-2-yl)benzamide ***50***. Yellow solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3450 (NH_2), 3019 (Ar CH), 1684 (C=O), 1653 (C=O), 929 (C–O); δ_H (500 MHz; DMSO-d_6; 400 K) 3.88 (3H, s, OCH_3), 7.05 (2H, br s, NH_2), 7.11 (2H, d, *J* 9.0 Hz, ArH), 7.91 (2H, d, *J* 9.0 Hz, ArH), 7.94 (2H, d, *J* 8.0 Hz, ArH), 8.12 (1H, s, 5-H), 8.38 (2H, d, *J* 8.0 Hz, ArH); LC–MS (6 min) *m*/*z* 322 (MH^+); HPLC t_R 3.10 min; purity 90%; HRMS (found: *m*/*z* 322.1190; $C_{18}H_{16}N_3O_3$ requires 322.1186).

4.3.14. 3-(4-Methoxyphenyl)-6-(pyrazol-4-yl)-1H-pyrazin-2-one ***51***. Orange solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; DMSO-d_6; 400 K) 3.86 (3H, s, OCH_3), 6.99 (2H, d, *J* 9.0 Hz, ArH), 7.83 (1H, s, 5-H), 8.21 (2H, s, pyrazole CH), 8.34 (2H, d, *J* 9.0 Hz, ArH); LC–MS (6 min) *m*/*z* 269 (MH^+); HPLC t_R 3.38 min; purity 98%; HRMS (found: *m*/*z* 269.1037; $C_{14}H_{13}N_4O_2$ requires 269.1033).

4.3.15. 3-(4-Methoxyphenyl)-6-(pyrazol-3-yl)-1H-pyrazin-2-one ***52***. Orange solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; DMSO-d_6; 400 K) 3.87 (3H, s, OCH_3), 6.92 (1H, d, *J* 3.0 Hz, pyrazole 4-H), 7.00 (2H, d, *J* 9.0 Hz, ArH), 7.77 (1H, d, *J* 3.0 Hz, pyrazole 5-H), 8.04 (1H, s, 5-H), 8.36 (2H, d, *J* 9.0 Hz, ArH); LC–MS (6 min) *m*/*z* 269 (MH^+); HPLC t_R 3.46 min; purity 98%; HRMS (found: *m*/*z* 269.1037; $C_{14}H_{13}N_4O_2$ requires 269.1033).

4.3.16. 3-(4-Methoxyphenyl)-6-(thiophen-3-yl)-1H-pyrazin-2-one ***53***. Orange solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; DMSO-d_6) 3.82 (3H, s, OCH_3), 7.01 (2H, d, *J* 9.0 Hz, ArH), 7.73 (2H, br s, thiophene 4-H, 2-H), 8.05 (1H, br s, 5-H), 8.31–8.36 (3H, m, ArH, thiophene 2-H); LC–MS (6 min) *m*/*z* 285 (MH^+); HPLC t_R 3.89 min; purity 98%; HRMS (found: *m*/*z* 285.0694; $C_{15}H_{13}N_2O_2S$ requires 285.0692).

4.3.17. 6-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-1H-pyrazin-2-one ***54***. Orange solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3250 (OH), 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; DMSO-d_6; 400 K) 3.88 (3H, s, OCH_3), 6.96 (1H, dd, *J* 7.0, 7.0 Hz, ArH), 7.01–7.04 (3H, m, ArH), 7.32 (1H, dd, *J* 7.0, 7.0 Hz, ArH), 7.74 (1H, d, *J* 7.0 Hz, ArH), 8.02 (1H, br s, 5-H), 8.33 (2H, d, *J* 9.0 Hz, ArH); LC–MS (6 min) *m*/*z* 295 (MH^+); HPLC t_R 3.94 min; purity 98%; HRMS (found: *m*/*z* 295.1084; $C_{17}H_{15}N_2O_3$ requires 295.1077).

4.3.18. 5-Bromo-3-chloro-pyrazin-2-amine ***55***.[74] A suspension of NBS (31.0 g, 173 mmol) and **9** (20.0 g, 154 mmol) in chloroform (140 mL) was heated at reflux for 16 h. The solution was cooled and washed with water (350 mL). The organic layer was filtered through Celite and concentrated to give **55** (22.0 g, 69%) as a brown solid. Mp 230–232 °C; ν_{max} (thin film/cm^{-1}) 3412 (NH_2), 3019 (Ar CH); δ_H (500 MHz; $CDCl_3$) 5.02 (2H, br s, NH_2), 8.05 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 123.5, 132.0, 142.9, 150.6; GC–MS *m*/*z* 211, 209, 207 (M^+); GC t_R 2.82 min; purity >99%; HRMS (found: MH^+ *m*/*z* 207.9280; $C_4H_4{}^{79}Br^{35}ClN_3$ requires 207.9272).

4.3.19. 5-Bromo-3-chloro-1H-pyrazin-2-one ***56***. A solution of **55** (9.00 g, 43.2 mmol) in concentrated sulfuric acid (35 mL) was added dropwise at 0 °C to a solution of sodium nitrite (3.52 g, 51.0 mmol) in concentrated sulfuric acid (20 mL). The solution was heated at 40 °C for 1 h, then cooled to rt and poured onto crushed ice (400 mL). The mixture was extracted with ethyl acetate (200 mL). The extract was dried, filtered and concentrated to give **56** (6.13 g, 68%) as a brown solid. Mp 175–177 °C; ν_{max}/cm^{-1} 3019 (ArH), 1653 (C=O); δ_H (500 MHz; CD_3OD) 7.72 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 114.2, 127.6, 146.4, 154.0; LC–MS (6 min) *m*/*z* 213, 211, 209 (MH^+); HPLC t_R 2.54 min purity >99%; HRMS (found: MH^+ *m*/*z* 208.9113; $C_4H_3{}^{79}Br^{35}ClN_2O$ requires 208.9112).

4.3.20. 3,5-Bis-(4-methoxyphenyl)-1H-pyrazin-2-one ***57***. A solution of **56** (50.6 mg, 0.242 mmol), sodium carbonate (35.6 mg, 0.336 mmol), 4-methoxyphenylboronic acid (182 mg, 1.20 mmol) and tetrakis(triphenylphosphine)palladium (0) (17 mg, 0.015 mmol) in water (0.7 mL) and acetonitrile (2.7 mL) was heated in a microwave reactor using variable wattage to 150 °C for 20 min. The mixture was partitioned between ethyl acetate (50 mL) and water (40 mL). The organic layer was filtered through a plug of silica gel (6 g). The filtrate was concentrated and purified by flash column chromatography on silica, eluting with ethyl acetate to give **57** (73 mg, 47%). Mp >300 °C; R_f (EtOAc) 0.16; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 972 (C–O), 929 (C-–O); δ_H (500 MHz; CD_3OD) 3.85 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 7.01 (2H, d, *J* 8.0 Hz, ArH), 7.02 (2H, d, *J* 9.0 Hz, ArH), 7.66 (1H, s, 6-H), 7.86 (2H, d, *J* 8.0 Hz, ArH), 8.46 (2H, d, *J* 9.0 Hz, ArH); LC–MS (6 min) *m*/*z* 309 (MH^+); HPLC t_R 4.11 min; purity 99%; HRMS (found: *m*/*z* 309.1243; $C_{18}H_{17}N_2O_3$ requires 309.1234).

4.4. General procedure for preparation of 5-bromo-3-(alkylamino)-1*H*-pyrazin-2-ones 58–63

A solution of **56** (1.50 g, 7.16 mmol), the appropriate secondary amine (8.59 mmol, 1.20 equiv) and diisopropylethylamine (1.50 mL, 8.59 mmol) in *n*-butanol (15 mL) was heated in a microwave reactor using variable wattage to 140 °C for 1 h. The mixture was concentrated and purified by flash column chromatography on silica, eluting with 9:1 dichloromethane/methanol, to give gave **58**–**63**.

4.4.1. 5-Bromo-3-(piperidin-1-yl)-1H-pyrazin-2-one ***58***. Brown solid. Mp 248–252 °C; R_f (50% EtOAc/hexanes) 0.54; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1647 (C=O); δ_H (500 MHz; $CDCl_3$) 1.60–1.70 (6H, br m, piperidine CH_2), 3.85–3.88 (4H, br m, piperidine NCH_2), 6.75 (1H, s, 6-H), 11.35 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 24.7, 26.0, 47.7, 114.1, 114.8, 151.2, 152.9; LC–MS (6 min) *m*/*z* 260, 258 (MH^+); HPLC t_R 3.83 min; purity 95%; HRMS (found: *m*/*z* 258.0236; $C_9H_{13}{}^{79}BrN_3O$ requires 258.0236).

4.4.2. 5-Bromo-3-(N-methylpiperazin-1-yl)-1H-pyrazin-2-one ***59***. Yellow solid; mp 285–288 °C; R_f (10% methanol/CH_2Cl_2) 0.25; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 1006 (C–N); δ_H (500 MHz; $CDCl_3$) 2.34 (3H, s, NCH_3), 2.51–2.53 (4H, br s, piperazine CH_2), 3.94–3.96 (4H, br s, piperazine CH_2), 6.77 (1H, s, 6-H); δ_C (125 MHz; $CDCl_3$) 46.0, 46.2, 114.5, 114.8, 150.9, 152.7, one signal not observed; LC–MS (6 min) *m*/*z* 275 (MH^+, 50%); 273 (MH^+, 50); HPLC (6 min) t_R 0.93 min; purity 99%; HRMS (found: *m*/*z* 273.0343; $C_9H_{14}{}^{79}BrN_4O$ requires 273.0345).

4.4.3. 5-Bromo-3-(4-hydroxypiperidin-1-yl)-1H-pyrazin-2-one ***60***. Brown solid. Mp 295–298 °C; R_f (10% MeOH/CH_2Cl_2) 0.29; ν_{max} (thin film/cm^{-1}) 3500–3300 (OH), 3019 (Ar CH), 1653 (C=O), 1265

(C–N); δ_H (500 MHz; $CDCl_3$) 1.52–1.68 (2H, m, NCH_2CH), 1.98–2.03 (2H, m, NCH_2CH), 3.43–3.51 (2H, m, NC*H*), 3.95–3.99 (1H, m, C*H*OH), 4.43–4.48 (2H, m, NC*H*), 6.75 (1H, s, 6-H), 10.80 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 34.4, 43.9, 67.6, 104.6, 114.3, 151.0, 152.4; LC–MS (6 min) *m*/*z* 276, 274 (MH^+); HPLC t_R 2.88 min; purity 99%; HRMS (found: *m*/*z* 274.0189; $C_9H_{13}{}^{79}BrN_3O_2$ requires 274.0186).

4.4.4. Methyl 1-(6-bromo-3-oxo-3,4-dihydropyrazin-2-yl)piperidine-4-carboxylate ***61***. Brown solid. Mp >300 °C; R_f (10% MeOH/CH_2Cl_2) 0.67; ν_{max} (thin film/cm^{-1}) 3019 (ArH), 1684 (C=O), 1653 (C=O); δ_H (500 MHz; $CDCl_3$) 1.81–1.86 (2H, m, NCH_2CH), 1.99–2.02 (2H, m, NCH_2CH), 2.59–2.61 (1H, m, C*H*CO_2Me), 3.08–3.14 (2H, m, NCH), 3.71 (3H, s, CO_2*Me*), 4.72 (2H, br d, *J* 14.0 Hz, NCH), 6.79 (1H, s, 6-H), 11.40 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 28.1, 41.1, 46.0, 51.8, 114.5, 114.9, 150.9, 152.5, 174.9; LC–MS (6 min) *m*/*z* 318, 316 (MH^+); HPLC t_R 3.56 min; purity 98; HRMS (found: 316.0283; $C_{11}H_{15}{}^{79}BrN_3O_3$ requires 316.0291).

4.4.5. 5-Bromo-3-(4-phenylpiperidin-1-yl)-1H-pyrazin-2-one ***62***. Brown solid. Mp >300 °C; R_f (10% MeOH/CH_2Cl_2) 0.71; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O); δ_H (500 MHz; DMSO-d_6) 1.62–1.70 (2H, m, NCH_2CH), 1.81–1.84 (2H, m, NCH_2CH), 2.77–2.82 (1H, m, C*H*Ph), 2.87–2.91 (2H, m, NC*H*), 4.91 (2H, br d, *J* 13.0 Hz, NCH), 6.91 (1H, s, 6-H), 7.17–7.31 (5H, m, Ph), 11.83 (1H, br s, NH); δ_C (125 MHz; DMSO-d_6) 32.8, 41.9, 46.4, 112.0, 115.8, 126.1, 126.7, 128.4, 145.8, 151.1, 151.3; LC–MS (6 min) *m*/*z* 336, 334 (MH^+); HPLC t_R 4.26 min; purity 98%; HRMS (found: *m*/*z* 334.0563; $C_{15}H_{17}{}^{79}BrN_3O$ requires 334.0549).

4.4.6. 5-Bromo-3-(4-morpholinyl)-1H-pyrazin-2-one ***63***. Yellow solid. Mp 285–288 °C; R_f (10% MeOH/CH_2Cl_2) 0.67; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O); δ_H (500 MHz; $CDCl_3$) 3.80–3.81 (4H, m, morpholine CH_2), 3.93–3.95 (4H, m, morpholine CH_2), 6.80 (1H, s, 6-H), 11.20 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 46.9, 66.8, 114.5, 115.1, 150.8, 152.6; LC–MS (6 min) *m*/*z* 260, 258 (MH^+); HPLC t_R 3.10 min; purity 99%; HRMS (found: *m*/*z* 260.0035; $C_8H_{11}{}^{79}BrN_3O_2$ requires 260.0029).

4.5. General procedure for preparation of 5-(hetero)aryl-3-(alkylamino)-2(1*H*)-pyrazinones 64–73

A mixture of the appropriate 5-bromo-3-(alkylamino)-2(1*H*)-pyrazinone **58**–**63** (0.366 mmol, 1 equiv), the appropriate (hetero) arylboronic acid or boronate ester (0.441 mmol, 1.2 equiv), sodium carbonate (55 mg, 0.509 mmol, 1.4 equiv) and Pd(dppf)Cl_2 (18 mg, 0.022 mmol) in water (1 mL) and acetonitrile (4.1 mL) was heated in a microwave reactor using variable wattage to 150 °C for 20 min. The mixture was partitioned between ethyl acetate (20 mL) and water (50 mL). The organic layer was separated and concentrated. Automated MPLC on silica, eluting with 9:1 dichloromethane/methanol, gave the products **64**–**73**.

4.5.1. 5-(4-Methoxyphenyl)-3-(piperidin-1-yl)-1H-pyrazin-2-one ***64***. Brown solid. Mp >300 °C; R_f (10% MeOH/CH_2Cl_2) 0.43; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; $CDCl_3$) 1.69–1.74 (6H, m, piperidine CH_2), 3.83–3.89 (4H, m, piperidine NCH_2), 3.85 (3H, s, OCH_3), 6.94 (2H, d, *J* 9.0 Hz, ArH), 7.12 (1H, s, 6-H), 6.91 7.73 (2H, d, *J* 9.0 Hz, ArH), 11.95 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 25.0, 26.0, 47.8, 55.4, 110.5, 114.0, 126.2, 129.6, 132.4, 152.0, 153.0, 159.3; LC–MS (3.5 min) *m*/*z* 286 (MH^+); HPLC t_R 2.78 min; purity 95%; HRMS (found: *m*/*z* 286.1557; $C_{16}H_{20}N_3O_2$ requires 286.1550).

4.5.2. 5-(4-Methoxyphenyl)-3-(4-methylpiperazin-1-yl)-1H-pyrazin-2-one ***65***. Pale pink solid. Mp >300 °C; R_f (10% methanol/CH_2Cl_2) 0.24; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 929 (C–O); δ_H (500 MHz; $CDCl_3$) 2.39 (3H, s, NCH_3), 2.61–2.63 (4H, br m, piperazine CH_2), 3.85 (3H, s, OCH_3), 3.99–4.01 (4H, br m, piperazine NCH_2), 6.95 (2H, d, *J* 9.0 Hz, ArH), 7.12 (1H, s, 6-H), 7.72 (2H, d, *J* 9.0 Hz, ArH), 11.50 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 46.1, 46.3, 55.0, 55.4, 110.8, 114.1, 126.2, 129.3, 132.4, 151.4, 152.6, 159.4; LC–MS (3.5 min) *m*/*z* 301 (MH^+); HPLC t_R 1.49 min; purity 99%; HRMS (found: *m*/*z* 301.1659; $C_{16}H_{21}N_4O_2$ requires 301.1659).

4.5.3. 3-(4-Hydroxypiperidin-1-yl)-5-(4-methoxyphenyl)-1H-pyrazin-2-one ***66***. Brown solid. Mp >300 °C; R_f (10% MeOH/CH_2Cl_2) 0.40; ν_{max} (thin film/cm^{-1}) 3500–3460 (OH), 3019 (Ar CH), 1621 (C=O), 929 (C–O); δ_H (500 MHz; $CDCl_3$) 1.67–1.73 (2H, m), 2.04–2.08 (2H, m), 3.39 (2H, ddd, *J* 13.0, 10.0, 3.0 Hz, NCH_{ax}), 3.85 (3H, s, OCH_3), 3.97–3.99 (1H, m, C*H*OH), 4.53 (2H, br d, *J* 13.0 Hz, NCH_{eq}), 6.94 (2H, d, *J* 9.0 Hz, ArH), 7.12 (1H, s, 6-H), 7.71 (2H, d, *J* 9.0 Hz, ArH), 11.65 (1H, br s, NH); LC–MS (3.5 min) *m*/*z* 302 (MH^+); δ_C (125 MHz; $CDCl_3$) 34.4, 44.2, 55.4, 68.2, 110.7, 114.1, 126.2, 129.4, 132.4, 151.6, 152.7, 159.4; HPLC t_R 2.20 min; purity 98%; HRMS (found: *m*/*z* 302.1506; $C_{16}H_{20}N_3O_3$ requires 302.1499).

4.5.4. Methyl 1-(6-(4-methoxyphenyl)-3-oxo-3,4-dihydropyrazin-2-yl)piperidine-4-carboxylate ***67***. Brown solid. Mp >300 °C; R_f (10% MeOH/CH_2Cl_2) 0.38; ν_{max} (thin film/cm^{-1}) 2950 (CH), 1720 (C=O), 1643 (C=O), 1028; δ_H (500 MHz; $CDCl_3$) 1.89–1.97 (2H, m), 2.04–2.09 (2H, m), 2.61–2.68 (1H, m, C*H*CO_2Me), 3.11–3.17 (2H, m), 3.74 (3H, s, CO_2*Me*), 3.87 (3H, s, OCH_3), 4.75–4.89 (2H, m), 6.94–6.96 (2H, m, ArH), 7.16 (1H, s, 6-H), 7.72–7.74 (2H, m, ArH), 12.00 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 28.0, 41.5, 46.1, 51.8, 55.4, 111.1, 114.0, 126.2, 129.3, 132.5, 151.6, 153.0, 159.3, 175.3; LC–MS (3.5 min); *m*/*z* 344 (MH^+); HPLC t_R 3.0 min; purity 99%; HRMS (found: *m*/*z* 344.1613; $C_{18}H_{22}N_3O_4$ requires 344.1605).

4.5.5. 5-(4-Methoxyphenyl)-3-(4-phenylpiperidin-1-yl)-1H-pyrazin-2-one ***68***. Brown solid. Mp >300 °C; R_f (10% MeOH/CH_2Cl_2) 0.50; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 1265 (C–N), 929 (C–O); δ_H (500 MHz; DMSO-d_6) 1.69–1.78 (2H, m), 1.85–1.88 (2H, m), 2.78–2.85 (1H, m, C*H*Ph), 2.88–2.96 (2H, m), 3.77 (3H, s, OCH_3), 4.96–4.99 (2H, m), 6.95 (2H, d, *J* 9.0 Hz, ArH), 7.19–7.31 (5H, m, Ph, 6-H), 7.77 (2H, d, *J* 9.0 Hz, ArH), 11.86 (1H, br s, NH); δ_C (125 MHz; DMSO-d_6) 33.3, 42.6, 47.0, 55.5, 112.3, 114.3, 126.1, 126.6, 127.2, 128.9, 129.8, 129.9, 146.5, 151.8, 151.9, 158.9; LC–MS (3.5 min) *m*/*z* 362 (MH^+); HPLC t_R 3.13 min; purity 99%; HRMS (found: *m*/*z* 362.1860; $C_{22}H_{24}N_3O_2$ requires 362.1863).

4.5.6. 5-(4-Methoxyphenyl)-3-morpholino-1H-pyrazin-2-one ***69***. Yellow solid. Mp >300 °C; R_f (EtOAc) 0.31; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 928 (C–O); δ_H (500 MHz; $CDCl_3$) 3.86 (3H, s, OCH_3), 3.87–3.88 (4H, m, morpholine CH_2), 3.96–3.98 (4H, m, morpholine CH_2), 6.95 (2H, d, *J* 8.5 Hz, ArH), 7.08 (1H, s, 6-H), 7.69 (2H, d, *J* 8.5 Hz, ArH), 10.50 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 47.0, 55.4, 66.9, 110.8, 114.1, 126.2, 129.2, 132.3, 151.4, 152.3, 159.4; LC–MS (6 min) *m*/*z* 288 (MH^+); HPLC t_R 3.65 min; purity 99%; HRMS (found: *m*/*z* 288.1344; $C_{15}H_{18}N_3O_3$ requires 288.1343).

4.5.7. 4-(6-Morpholino-5-oxo-4,5-dihydropyrazin-2-yl)benzamide ***70***. Brown solid. Mp >300 °C; R_f (10% MeOH/CH_2Cl_2) 0.27; ν_{max} (thin film/cm^{-1}) 3420 (NH_2), 3019 (Ar CH), 1685 (C=O), 1653 (C=O); δ_H (500 MHz; DMSO-d_6) 3.71–3.73 (4H, m, morpholine CH_2), 3.80–3.83 (4H, m, morpholine CH_2), 7.32 (1H, br s, NH_2), 7.56 (1H, s, 6-H), 7.86 (2H, d, *J* 8.5 Hz, ArH), 7.90 (2H, d, *J* 8.5 Hz, ArH), 12.10 (1H, br s, NH); δ_C (125 MHz; DMSO-d_6) 46.9, 66.5, 115.3, 124.4, 128.2, 128.8, 132.8, 139.8, 151.6, 152.0, 168.1; LC–MS (3.5 min) *m*/*z* 301

(MH^+); HPLC t_R 2.10 min; purity 99%; HRMS (found: m/z 301.1291; $C_{15}H_{17}N_4O_3$ requires 301.1295).

4.5.8. 3-Morpholino-5-(pyridin-3-yl)-1H-pyrazin-2-one ***71***. Brown solid. Mp >300 °C; R_f (10% MeOH/CH_2Cl_2) 0.42; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1621 (C=O), 1265 (C–N); δ_H (500 MHz; DMSO-d_6) 3.71–3.73 (4H, m, morpholine CH_2), 3.82–3.84 (4H, m, morpholine CH_2), 7.40 (1H, dd, *J* 8.0, 5.0 Hz, pyridine 5-H), 7.58 (1H, s, 6-H), 8.19 (1H, ddd, *J* 8.0, 2.0, 1.5 Hz, pyridine 4-H), 8.46 (1H, dd, *J* 5.0, 1.5 Hz, pyridine 6-H), 9.05 (1H, d, *J* 2.0 Hz, pyridine 2-H), 12.12 (1H, br s, NH); δ_C (125 MHz; DMSO-d_6) 46.9, 66.5, 114.9, 123.9, 127.1, 132.1, 132.7, 146.4, 148.2, 151.9, 152.0; LC–MS (3.5 min) m/z 259 (MH^+); HPLC t_R 1.40 min; purity 99%; HRMS (found: m/z 258.1199; $C_{13}H_{15}N_4O_2$ requires 258.1190).

4.5.9. 3-Morpholino-5-(4-chlorophenyl)-1H-pyrazin-2-one ***72***. White solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 2960, 2856 (CH), 1641 (C=O); δ_H (500 MHz; DMSO-d_6) 3.71–3.73 (4H, m, morpholine CH_2), 3.80–3.82 (4H, br s, morpholine CH_2), 7.42 (2H, d, *J* 9.0 Hz, ArH), 7.50 (1H, s, 6-H), 7.87 (2H, d, *J* 9.0 Hz, ArH), 12.08 (1H, br s, NH); δ_C (125 MHz; DMSO-d_6) 46.9, 66.5, 114.5, 126.5, 128.4, 128.9, 131.8, 136.0, 151.6, 151.9; LC–MS (3.5 min) m/z 292 (MH^+); HPLC t_R 2.68 min; purity 99%; HRMS (found: m/z 292.0845; $C_{14}H_{15}ClN_3O_2$ requires 292.0847).

4.5.10. 3-Morpholino-5-(4-acetylaminophenyl)-1H-pyrazin-2-one ***73***. White solid. Mp >300 °C; ν_{max} (thin film/cm^{-1}) 3274 (NH), 3070 (Ar CH), 2976, 2854 (CH), 1652 (C=O); δ_H (500 MHz; DMSO-d_6) 2.04 (3H, s, Ac), 3.70–3.72 (4H, m, morpholine CH_2), 3.78–3.80 (4H, m, morpholine CH_2), 7.34 (1H, s, 6-H), 7.57 (2H, d, *J* 9.0 Hz, ArH), 7.74 (2H, d, *J* 9.0 Hz, ArH), 9.95 (1H, br s, AcNH), 11.93 (1H, br s, NH); δ_C (125 MHz; DMSO-d_6) 24.5, 46.9, 66.5, 113.2, 119.4, 125.1, 129.6, 131.8, 138.7, 151.6, 151.8, 168.6; LC–MS (3.5 min) m/z 315 (MH^+); HPLC t_R 1.93 min; purity 99%; HRMS (found: m/z 315.1448; $C_{16}H_{19}N_4O_3$ requires 315.1452).

4.5.11. 6-Bromo-3-chloro-1H-pyrazin-2-one ***74***. A solution of boron trichloride in dichloromethane (1 M; 24.0 mL, 24.0 mmol) was added to a stirred solution of **8** (1.44 g, 4.81 mmol) in dichloromethane (140 mL) at rt. After 48 h the mixture was concentrated. Flash column chromatography on silica, eluting with 9:1 dichloromethane/methanol, gave **74** (0.690 g, 68%) as a pale brown solid. Mp 178–181 °C; R_f (10% methanol/CH_2Cl_2) 0.18; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1521 (C=O); δ_H (500 MHz; DMSO-d_6) 8.02 (1H, s, 5-H), 13.75 (1H, br s, NH); LC–MS (3.5 min) m/z 213,,211, 209 (MH^+); HPLC t_R 1.79 min; purity 99%; HRMS (found: MH^+ m/z 208.9119; $C_4H_3{}^{79}Br^{35}ClN_2O$ requires 208.9112).

4.5.12. 6-Bromo-3-(morpholino)-1H-pyrazin-2-one ***75***. A solution of **74** (0.100 g, 0.477 mmol), morpholine (0.050 mL, 0.574 mmol) and diisopropylethylamine (0.098 mL, 0.572 mmol) in *n*-butanol (1 mL) was heated in a microwave reactor using variable wattage to 140 °C for 1 h. The cooled mixture was concentrated. Flash column chromatography on silica, eluting with 10% MeOH in dichloromethane, gave **75** (0.056 g, 45%) as a red solid. Mp 263–265 °C; R_f (10% methanol/CH_2Cl_2) 0.48; ν_{max} (thin film/cm^{-1}) 3019 (Ar CH), 1653 (C=O), 1022 (C–N); δ_H (500 MHz; $CDCl_3$) 3.81–3.84 (8H, br s, morpholine CH_2), 7.28 (1H, s, 5-H), 11.2 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 47.0, 66.8, 104.8, 124.0, 150.8, 153.2; LC–MS (3.5 min) m/z 262 (MH^+, 50%), 260 (MH^+, 50%); HPLC t_R 1.88 min, purity 95%; HRMS (found: m/z 260.0035; $C_8H_{11}{}^{79}BrN_3O_2$ requires 260.0029).

4.5.13. 6-(4-Methoxyphenyl)-3-(morpholino)-1H-pyrazin-2-one ***76***. A mixture of **75** (36.5 mg, 0.140 mmol), 4-methoxyphenylboronic acid (25.5 mg, 0.168 mmol), sodium carbonate (22.0 mg, 0.208 mmol) and Pd(dppf)Cl_2 (7.0 mg, 0.0086 mmol) in acetonitrile (1.6 mL) and water (0.4 mL) was heated at 150 °C in a microwave reactor for 20 min. The cooled mixture was concentrated. Flash column chromatography on silica, eluting with 10% MeOH in dichloromethane, followed by preparative TLC, eluting with 10% MeOH in dichloromethane, gave **120** (10.0 mg, 25%) as a yellow solid; R_f (10% methanol/CH_2Cl_2) 0.24; ν_{max} (thin film/cm^{-1}) 2960, 2854 (CH), 1635 (C=O); δ_H (500 MHz); (DMSO-d_6) 3.66–3.70 (8H, br m, morpholine CH_2), 3.79 (3H, s, OMe), 6.99 (2H, d, *J* 9.0 Hz, ArH), 7.19 (1H, s, 5-H), 7.59 (2H, d, *J* 9.0 Hz, ArH), 11.9 (1H, br s, NH); δ_C (125 MHz); (DMSO-d_6) 46.6, 55.2, 66.0, 114.2, 117.8, 123.8, 127.2, 129.4, 151.0, 152.4, 159.5; LC–MS (3.5 min) m/z 288 (MH^+); HPLC t_R 2.27 min, purity 99%; HRMS (found MH^+: m/z 288.1344; $C_{15}H_{18}N_3O_3$ requires 288.1343).

Acknowledgements

We thank Dr. A. Mirza and Mr. M. Richards for assistance in the spectroscopic characterisation of test compounds. We thank Professor K. Jones and Dr. E. McDonald for helpful conversations. This work was supported by funding from Cancer Research UK [CUK] grant numbers C309/A11566, C309/A8274 and C309/A8365, and The Institute of Cancer Research. We acknowledge NHS funding to the NIHR Biomedical Research Centre.

Supplementary data

Kinase panel selectivity data for compounds **38**, **39**, **57**, **65**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.09.039.

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