



Synthesis and reactivity of 3-amino-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-ones: development of a novel kinase-focussed library

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ABSTRACT

3-Amino-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-ones represent a potentially attractive heteroaromatic scaffold for drug-discovery chemistry. In particular, the arrangement of hydrogen bond donor and acceptor groups in the bicyclic core can fulfil the requirements for ATP competitive binding to kinase enzymes. Efficient and regioselective routes from simple starting materials to novel functionalised 3-amino-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-ones and related 3-amino-2*H*-pyrazolo[4,3-*c*]pyridines were explored and adapted for parallel synthesis, resulting in a library of compounds suitable for screening against kinases and other cancer drug targets. Methods for substituent variation at five distinct positions around the bicyclic core were devised to generate sets of compounds containing two- or three-point diversity.

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1. Introduction

Medicinal chemistry often relies on the synthesis of core chemical scaffolds, which can be further derivatised to improve their biological activity or pharmacokinetic properties. These scaffolds are often mono- or bicyclic aromatic heterocycles, which are relatively easy to make and functionalise.^{1,2} Similarities between scaffolds are evident when looking at inhibitors of particular classes of enzymes, which have very distinctive binding pockets. For example, ATP competitive kinase inhibitors tend to be structurally quite similar as the binding pocket is conserved across the entire class of enzymes.^{3,4} This leads to a number of problems, including similar scaffolds being identified multiple times in screening campaigns and therefore limiting access to new chemical space.^{5,6} There is therefore a need for new heterocyclic compounds to be synthesised for screening against new targets.² This would give novel start points for drug-discovery projects.

One problem with starting from a new scaffold can be a lack of knowledge of its reactivity, so more effort may be required in the synthesis of analogues. With this in mind, we describe here the development of a kinase-focussed library where exploration of the reactivity of scaffold was carried out in parallel with the library synthesis. The 3-amino-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-one scaffold (Fig. 1) was chosen because it contains multiple hydrogen bond donors and acceptors and could bind to protein targets in numerous

ways. In particular, the presence of several hydrogen bond donor-acceptor pairs in different spatial relationships renders the scaffold attractive as a potential ligand for the well-characterised ATP binding site in protein kinase enzymes.^{5,7} The scaffold also has a number of possible points at which it can be derivatised. Thus if a member of the library is found to be active against a particular protein target, the structure can be rapidly modified to find favourable interactions to improve the inhibitor's potency. This is extremely important in early drug discovery,⁸ and if the chemistry to functionalise the scaffold has already been developed, the process can be accelerated. At the outset of this project, limited prior reports on the syntheses of 3-amino-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-ones encouraged us that convenient routes to novel compounds in the library could be established.^{9–15} Although 3-amino-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-ones have not been previously investigated in the context of drug discovery, the simpler 3-amino-pyrazolo[4,3-*c*]pyridines have some precedent as inhibitors of kinase enzymes.^{16–18}

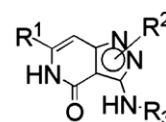


Figure 1. General structure of proposed 3-amino-1*H*-pyrazolo[4,3-*c*]pyridine-4(5*H*)-one kinase inhibitors.

Chemistry was developed to allow parallel syntheses of a library of scaffolds with two variable substituents starting from simple building blocks, and a further three positions for derivatisation

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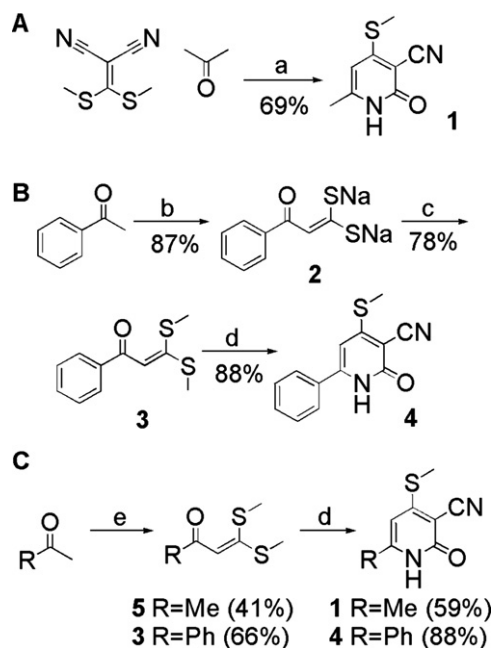
were explored. Importantly, the chemistry was developed to enable rapid preparation of analogues,¹⁹ with the incorporation of parallel synthesis procedures where possible.

2. Results and discussion

2.1. Scaffold synthesis—pyridone

There are sporadic reports of the syntheses of 3-amino-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-ones.^{9–15} Our first attempt at preparing the core revealed an unexpected misassignment of the structure yielded by one literature method.^{10,11} A more thorough investigation of the products of the reaction and possible mechanisms for their formations ensued.²⁰ Subsequently, an alternative route was adopted and successfully led to the desired scaffold.^{12–15} This synthesis involved the formation of a functionalized pyridone followed by condensation with hydrazine to install the fused pyrazole.

Two methods were used to make the pyridone ring. 6-Methylpyridone **1** was conveniently made by direct condensation of acetone and 2-(bis(methylthio)-methylene)malononitrile (Scheme 1A). For the production of 6-phenylpyridone **4**, acetophenone was converted to the bis(methylthio)but-3-en-2-one **3** and condensed with cyanoacetamide (Scheme 1B). This latter route could also be used to prepare **1**. This was of benefit as the same conditions could be employed to make both 6-alkyl- and 6-arylpyridones, and were altered to enable parallel synthesis (Scheme 1C). The disodium salt **2** was no longer isolated before methylation of the sulfurs, as in some cases the salt was hygroscopic. Rather, methanol and iodomethane were added directly to the reaction mixture. In addition the solvent was changed from toluene to the more volatile THF. This enabled the rapid parallel synthesis of a set of 12 pyridones bearing varied alkyl and aryl substituents at C-6.

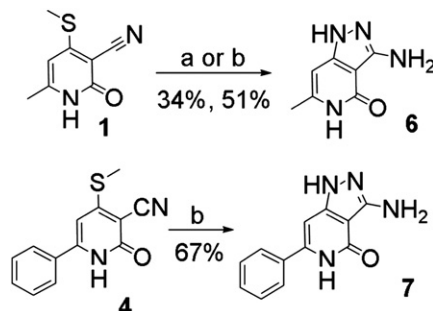


Scheme 1. (a) (i) KOH, wet DMSO, rt, 8 h (ii) HCl (aq); (b) NaO^tBu, CS₂, PhCH₃, 0 °C, 5 h; (c) MeI, MeOH, reflux, 15 min; (d) NaO^tPr, cyanoacetamide, ⁱPrOH, reflux, 50 min; (e) (i) CS₂, NaO^tBu, THF, 0 °C, 4 h, Ar; (ii) MeI, MeOH, reflux, 15 min.

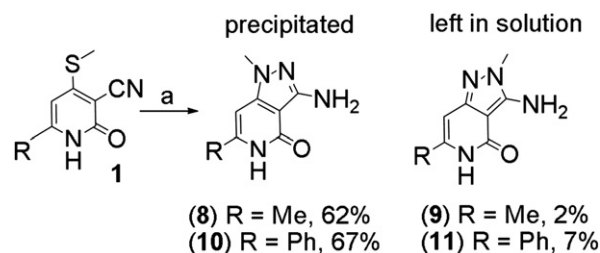
2.2. Scaffold synthesis—pyrazolopyridone

Fused, *N*-unsubstituted pyrazole rings, such as in **6**, had been introduced previously into 4-methylthio-3-cyano-2-pyridones

using hydrazine in ⁱPrOH and heating at reflux (Scheme 2).¹² We found that a faster reaction was obtained when the mixture was heated in the microwave in a sealed tube at higher temperatures. Although this reaction has not been reported for substituted hydrazines, similar conditions yielded the *N*-methylpyrazole compounds **8–11** (Scheme 3).



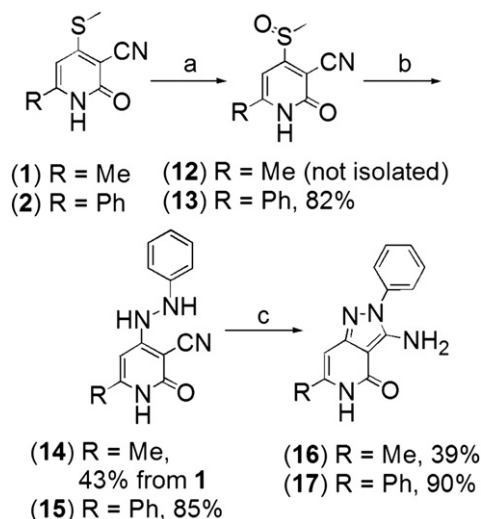
Scheme 2. (a) H₂N–NH₂, ⁱPrOH, reflux, 2 h; (b) H₂N–NH₂, ⁱPrOH, μW, 120 °C, 40 min.



Scheme 3. (a) H(Me)N–NH₂, Et₃N, ⁿBuOH, 150 °C, μW, 20 min.

The regiochemical outcome of the pyrazole forming reaction was predicted to depend on the nature of the hydrazine used, as had been shown for the reaction of substituted hydrazines with other scaffolds.^{21–24} In the case of methylhydrazine, both N1 and N2 substituted pyrazoles were often observed. Although electronic effects presumably favoured initial attack of the alkyl substituted, and thus more nucleophilic, nitrogen at C-4 of the pyridone to give the N1-substituted product, competing steric factors favoured N2 substitution. Fortunately, the N1 methylpyrazoles **8** and **10** precipitated from solution (Scheme 3). Substitution at N1 was always the major regioisomer from the reactions with methylhydrazine, but in cases where the N2 methyl isomer was also formed, it could be isolated by preparative TLC from the mother liquors. This synthesis was extended to multiple 4-methylthio-3-cyano-2-pyridone starting materials.

Although the reactions of methylhydrazine and hydrazine proceeded under simple microwave conditions, the reaction of phenylhydrazine was not as trivial due to its poor nucleophilicity. To promote reaction, the thiomethyl substituent was converted into a better leaving group.²⁵ The sulfur was oxidized with *m*-CPBA, making it more electron withdrawing and allowing the S_NAr to proceed, although a further acid catalysed cyclisation step was required to complete formation of the pyrazole ring (Scheme 4). The oxidation could be carefully controlled to produce either the sulfoxide or sulfone, by varying the stoichiometry of the oxidising agent. However, since both sulfoxide and sulfone reacted to give the desired products, it was generally more convenient to prepare mixtures during the oxidation and use these directly in the displacements. Applying these methods, a 36-membered library of compounds was synthesised in parallel with two points of variation; on the pyridone from 12 different methyl ketones and on the pyrazole from 3 hydrazines.



Scheme 4. (a) *m*-CPBA, EtOH, rt, 24 h; (b) $\text{H}_2\text{N}-\text{N}(\text{Ph})\text{H}$, $i\text{PrOH}$, reflux, 2 h; (c) HCl, dioxane, reflux, 3 h.

2.3. Scaffold synthesis—regiochemistry

The regiochemistry of substitution for the major and minor *N*-methyl isomers **10** and **11** was determined by ^1H NMR (NOESY) and confirmed by X-ray crystallography of **10** (Fig. 2). Likewise, NOESY and X-ray crystallography confirmed the regiochemistry of **17**.

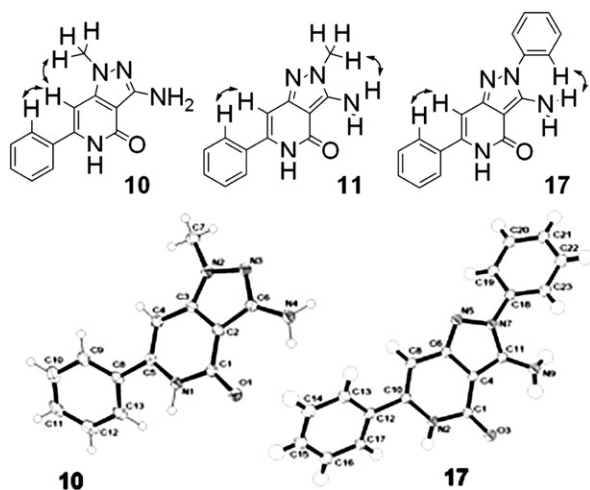
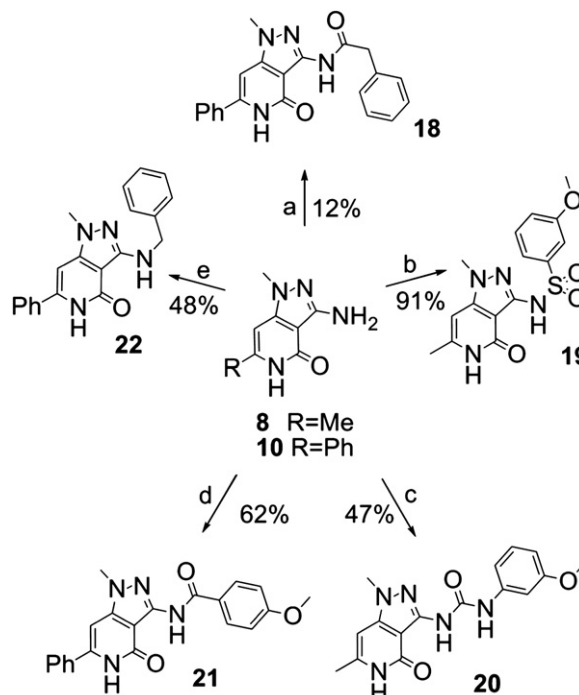


Figure 2. Structures of **10**, **11** and **17** (arrows show through space interactions between hydrogens as indicated by NOESY) and ORTEP representation of X-ray crystallographic structures for **10** and **17**.²⁶

2.4. Amine derivatisation

A number of different electrophiles could be reacted with the aminopyrazole motif of the *N*-methyl pyrazolopyridines such as **8** and **10**, although some reactions were more amenable to parallel synthesis than others (Scheme 5). Sulfonylation and reaction with isocyanates were high yielding and the resulting products were isolated by filtration requiring no further purification. Reductive amination and reactions with benzyl bromide and phenyl acetyl chloride did require purification due to the presence of by-products or double addition of the electrophiles. Reactions with acid anhydrides and acid chlorides needed excess reagent for complete reaction, which had to be removed during work-up. Parallel synthesis protocols for sulfonylation, urea formation and amidations using acid anhydrides were established for the dimethyl scaffold **8**. For

amide formation, the excess acid anhydride was removed by reaction with trisamine resin to capture the remaining anhydride and the resulting acid by-product was removed by filtration through a basic ion exchange resin. The scope of urea forming reactions was somewhat limited, presumably resulting from low nucleophilicity of the aminopyrazole. Although reactions with aryl isocyanates generally went well, no reaction was seen with the less electrophilic alkyl isocyanates. However, reactions with highly activated isocyanates also failed to give the desired product. For example, 4-cyanophenylisocyanate decomposed to form the bis-cyanophenyl urea rather than reacting on the amine.

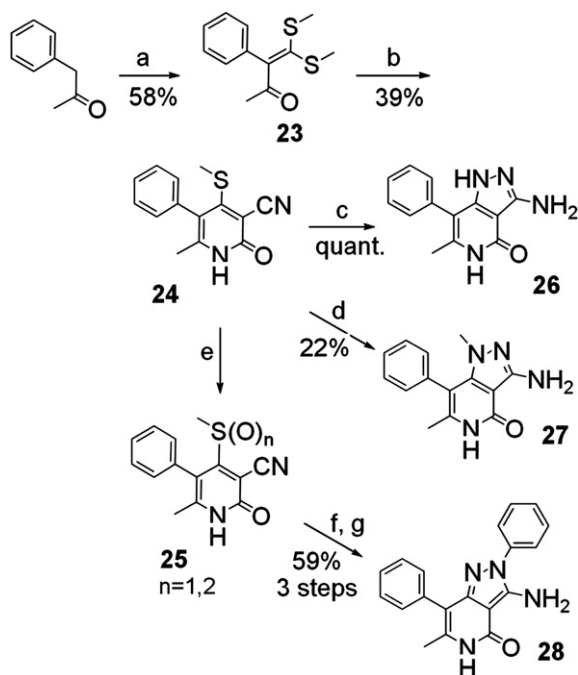


Scheme 5. (a) PhCH_2COCl , Et_3N , DCM, 0°C to rt; (b) $\text{ArS}(\text{O})_2\text{Cl}$, Py, rt, 24 h; (c) ArNCO , Py, rt; (d) $(\text{ArCO})_2\text{O}$, Py, 100°C , 24 h; (e) benzaldehyde, NaBH_3CN , AcOH, NaOAc, EtOH/ H_2O (1:1), rt.

Similar functionalisation of the *N*-phenyl and *N*-unsubstituted pyrazolopyridone scaffolds **17** and **6** was attempted but did not proceed successfully. In the case of **17** no reaction with sulfonyl chlorides was observed, ascribed to increased steric hindrance from the aryl substituent and a further reduction in amine nucleophilicity. For the *N*-unsubstituted scaffold **6**, mixtures of multiple products were observed on reaction with sulfonyl chlorides or acid anhydrides, presumed to result from the multiple reactive nitrogen atoms present.

2.5. C7 derivatisation—incorporation into scaffold

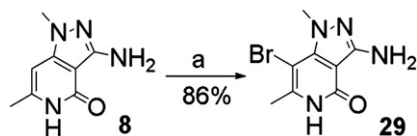
There are a number of possible approaches to adding functionality at the C7 position of the pyrazolopyridone scaffold. One is to introduce it during the first step of the synthesis. In the example shown (Scheme 6), 1-phenylpropan-2-one was used to place a phenyl group at the C7 position and allowed the synthesis of **26–28**. However this method was unsuccessful with substrates bearing alkyl groups at the same position, as the reaction of the bis-methylthio compound with cyanoacetamide yielded no pyridine product, possibly due to the lack of an electron withdrawing aryl group to raise the acidity of the α -protons, which have to be removed for the reaction to proceed. Syntheses of 5-alkylpyridones have been reported in the literature using the alternative route (Scheme 1A) described for compound **1**.¹⁵



Scheme 6. (a) (i) CS_2 , NaOtBu , THF, 0°C , 5 h; (ii) MeI, MeOH, reflux, 30 min; (b) $\text{NCCH}_2\text{CONH}_2$, NaOtPr , $^i\text{PrOH}$, 2 h; (c) $\text{H}_2\text{N-NH}_2$, $^i\text{PrOH}$, 120°C , μW , 40 min; (d) $\text{H}_2\text{N-N(Me)H}$, $^i\text{PrOH}$, 150°C , μW , 1 h; (e) $m\text{-CPBA}$, EtOH, rt, 18 h; (f) $\text{H}_2\text{N-N(Ph)H}$, $^i\text{PrOH}$, reflux, 2 h; (g) HCl, dioxane, reflux, 30 min.

2.6. C7 derivatisation—late stage addition to scaffold

A drawback of the approach shown in Scheme 6 was the need to carry out the entire synthesis for each different analogue. We therefore sought to add C7 functionality to the preformed scaffold and investigated bromination of the C7 position followed by palladium mediated coupling reactions. Bromination of **8** proceeded smoothly to form **29** in good yield (Scheme 7).



Scheme 7. (a) NBS, MeOH, reflux, 1 h.

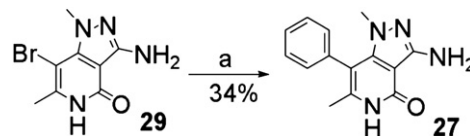
However, under standard Suzuki coupling conditions ($\text{Na}_2\text{CO}_3(\text{aq})$, $\text{Pd(PPh}_3)_4$, DME–EtOH) using **29** and phenylboronic acid, the main product formed was **8**, the debromination product (Table 1).

Table 1
Conditions for Suzuki coupling reactions to **29**

Catalyst	Temperature ($^\circ\text{C}$)	Solvent	Base	Time (h)	29 / 8 / 27 ^a
$\text{Pd(PPh}_3)_4$	105 (Thermal)	Dioxane	Na_2CO_3	24	100:0:0
$\text{Pd(PPh}_3)_4$	100 (μW)	DME/EtOH (50:50)	$\text{Na}_2\text{CO}_3(\text{aq})$	1	0:85:15
$\text{Pd(PPh}_3)_4$	100 (μW)	DME	Cs_2CO_3	1	75:14:11
$\text{Pd(PPh}_3)_4$	100 (μW)	Tol	Cs_2CO_3	1	70:15:15
$\text{Pd(PPh}_3)_4$	100 (μW)	Tol	K_3PO_4	1	56:22:22
$\text{Pd(PPh}_3)_4$	100 (μW)	Tol	NaOtBu	1	42:42:16
$\text{Pd(PPh}_3)_4$	130 (μW)	Tol	NaOtBu	1	13:13:74
$\text{Pd(PPh}_3)_4$	150 (μW)	Tol	NaOtBu	1	0:13:87
$\text{Pd(PPh}_3)_4$	150 (μW)	Tol/MeCN (95:5)	NaOtBu	1	0:13:87

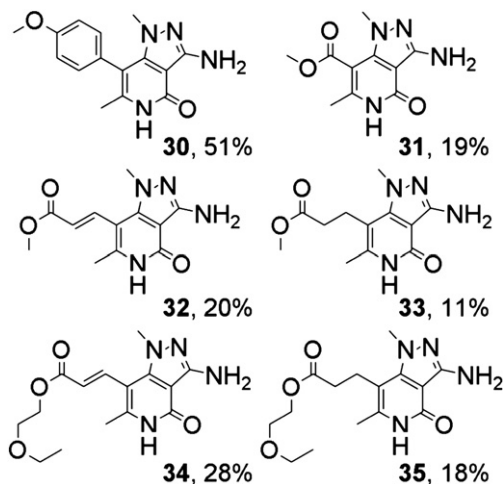
^a Conversion as measured by HPLC of crude reaction mixtures.

Subsequently it was found that the presence of any protic solvents in the reaction mixture led to significant debromination. Although different palladium sources and ligands made little difference to the yield, the use of a stronger base (NaOtBu) and higher temperature led to the formation of **27** as the main product (Scheme 8).



Scheme 8. (a) PhB(OH)_2 , $\text{Pd(PPh}_3)_4$, NaOtBu , toluene, 150°C , μW , 1 h.

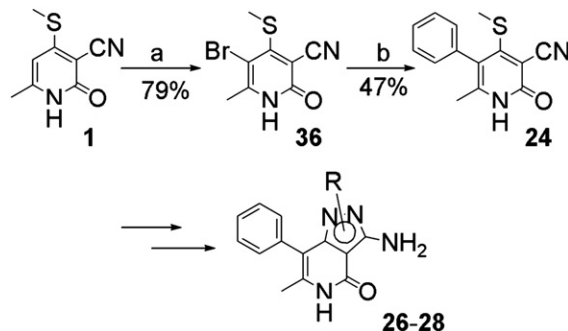
This method was used for other Suzuki couplings, for example, to form **30**. Methylpyrazole **8** was also a successful substrate for carbonylation reactions²⁷ and Heck coupling²⁸ to form **31–35** (Scheme 9). A simple hydrogenation could be used to remove the double bonds next to the ester groups of **32** and **34**. Although these reactions were not sufficiently high-yielding for parallel synthesis, a number of compounds with C7 substitution were made.



Scheme 9. Compounds made using palladium coupling reactions. Yields given from **29**.

2.7. C7 derivatisation—an alternative approach

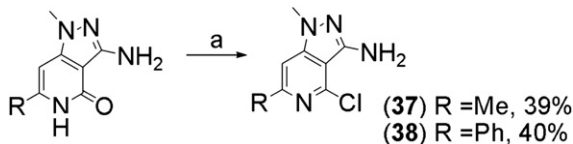
Although both **6** and **16** could also be brominated under the same conditions as **8**, the palladium coupling reactions failed to proceed. However, going back one step to the pyrazole **1** (Scheme 10), this could be brominated to give **36** and the couplings carried out before formation of the fused pyrazoles. Although the yields were generally low, some compounds inaccessible by the direct coupling route were made by this method.



Scheme 10. (a) NBS, MeOH, reflux, 1 h; (b) PhB(OH)_2 , $\text{Pd(PPh}_3)_4$, NaOtBu , toluene/MeCN (95:5), 150°C , μW , 1 h.

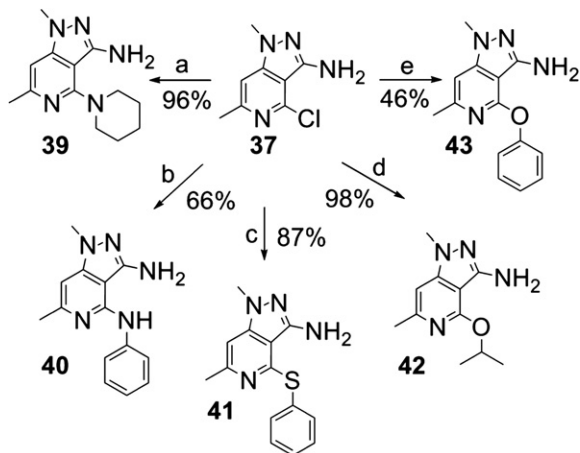
2.8. C4 derivatisation—chlorination and trial reactions

To derivatise at the C4 position, POCl₃ was used to form chloropyridines **37** and **38** from the pyridones (Scheme 11). This conversion was also successful for the phenylpyrazoles **16** and **17** using the same conditions.



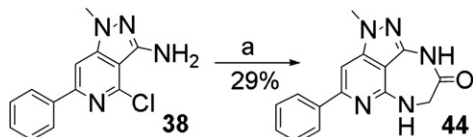
Scheme 11. (a) (i) POCl₃, 80 °C, 24 h; (ii) water, NaHCO₃.

A number of S_NAr reactions were attempted from **37** to give **39–43** (Scheme 12). Reactions with amine nucleophiles were carried out by microwave heating in ^tBuOH. Sulfur and oxygen nucleophiles in the presence of base also worked, although oxygen nucleophiles required the presence of an excess of the reagent and otherwise gave poor yields. Other trial reactions using amine nucleophiles were successful and a general work-up was developed using an acidic ion exchange resin column catch and release method to remove excess amine. This allowed parallel synthesis of 24 compounds.



Scheme 12. (a) Piperidine, ^tBuOH, 160 °C, μW, 30 min; (b) aniline, ^tBuOH, 160 °C, μW, 30 min; (c) PhSH, K₂CO₃, MeCN, reflux, 3 h; (d) NaOPr, ⁱPrOH, reflux, 18 h; (e) PhOH, Cs₂CO₃, DMSO, 130 °C, 18 h.

Bi-functional reagents could be reacted with **37** to form a third fused ring as shown (Scheme 13). Thus glycine methyl ester was used as the nucleophile and also functioned as an electrophile reacting with the aminopyrazole to form the novel tricyclic scaffold **44**.

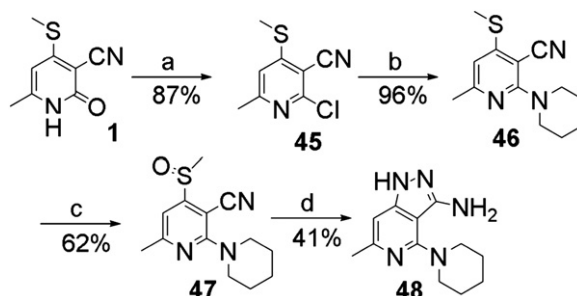


Scheme 13. (a) H₂NCH₂COOMe·HCl, Et₃N, ^tBuOH, 160 °C, μW, 30 min.

2.9. C4 derivatisation—alternative route

For the unsubstituted pyrazole **6**, although the POCl₃ chlorination seemed to yield some product by LCMS and ¹H NMR analysis, it quickly decomposed, so an alternative approach was sought. Reaction of the intermediate pyridone **1** with POCl₃ gave chloropyridine **45**, which then underwent S_NAr reactions before the

formation of the pyrazole (Scheme 14). A further step, sulfur oxidation, was required to overcome the pyridine's reduced electrophilicity resulting from replacement of the pyridine carbonyl by the electron donating amino group. Several examples using this sequence were demonstrated. Again, both the sulfoxide and sulfone reacted to form the desired product, so in most cases a mixture was taken through the synthesis.



Scheme 14. (a) (i) POCl₃, 80 °C, 24 h; (ii) NaHCO₃, water; (b) piperidine, ^tBuOH, 160 °C, μW, 30 min; (c) *m*-CPBA, EtOH, 6 h, rt; (d) H₂N–NH₂, ⁱPrOH, reflux, 6 h.

3. Conclusions

In summary, the syntheses of four distinct polysubstituted pyrazolopyridone scaffolds were developed (Fig. 3). Of the four synthetic sequences, three were amenable to medium-throughput parallel synthesis, although in some cases this was limited to specific starting materials. This chemistry enabled the synthesis of sets of compounds with two or three points of variation around the core scaffold. In total a library of approximately 200 novel compounds was prepared according to these methods, the biological characterisation of which will be reported separately. We have demonstrated how the pyrazolopyridone scaffold can be efficiently derivatised at several positions around the molecule. The ability to rapidly prepare analogues of the initial library is likely to be of benefit for the further investigation of pyrazolopyridone compounds arising as hits in targeted drug-discovery screens, enabling exploration of possible binding modes and improvements to the compound activity.

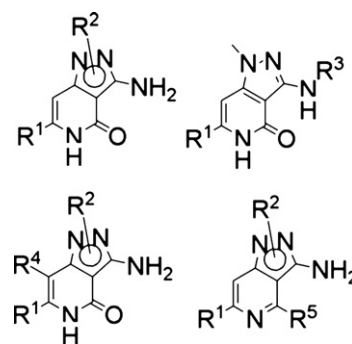


Figure 3. Summary of the substitution patterns accessible using parallel synthetic chemistry to prepare a library of approximately 200 compounds.

4. Experimental

4.1. General experimental

All reagents and anhydrous solvents were obtained from commercial suppliers and used without further purification. Infrared spectra were recorded on a Perkin–Elmer Spectrum RX-1 FT-IR spectrometer. ¹H and ¹³C nuclear magnetic resonance spectra were recorded at 500 MHz and 126 MHz, respectively, on Bruker

AMX500 spectrometers using an internal deuterium lock. Microanalysis was carried out by Warwick Analytical Service, and X-ray crystallography was carried out by the EPSRC UK National Crystallography Service at the University of Southampton. HPLC-MS analyses were performed on a Micromass LCT/Waters Alliance 2795 HPLC system with Phenomenex Gemini (PG) or Merck Chromolith SpeedROD (MC) columns at 22 °C, eluting with a MeOH/water gradient. UV detection was at 254 nm and ionisation was by positive or negative ion electrospray. Molecular weight scan range was 50–1000. HRMS values were determined on an Agilent 6210 ToF MS with a Phenomenex Gemini 3 μ C18 (3 cm $\times$ 4.6 mm i.d.) column.

Suitable crystals were selected and data collected on a Bruker Nonius KappaCCD Area Detector at the window of a Bruker Nonius FR591 rotating anode (Mo $K\alpha$ = 0.71073 Å) driven by COLLECT²⁹ and DENZO³⁰ software at 120 K. The structures were determined in SHELXS-97³¹ and refined using SHELXL-97.³² Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers 751882 and 751883. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.1.1. General method A: bis(methylthio)but-3-en-2-ones. NaO^tBu (2 equiv) in dry toluene was stirred at 0 °C under Ar for 10 min. The appropriate ketone (0.3 M) was added followed by CS₂ (1 equiv). The solution was stirred for a further 4 h at 0 °C whereupon the disodium salt was collected by filtration, washed using hexane and dried in a vacuum dessicator over silica. Dry MeOH (1 M) and MeI (2 equiv) were added to the salt. This solution was heated at reflux for 15 min. Water was added and the desired bis(methylthio)but-3-en-2-ones precipitated from the solution and were isolated by filtration unless otherwise stated.

4.1.2. General method B: pyridone formation from the bis(methylthio)but-3-en-2-ones. NaOⁱPr was made by the dissolution of sodium (1.1 equiv) in ⁱPrOH. To this was added cyanoacetamide (1 equiv) and the appropriate 1-substituted-4,4-bis(methylthio)but-3-en-2-ones (0.29 M). The mixture was stirred at reflux for 2 h and the solid formed was dissolved by the addition of water. The 4-(methylthio)-2-oxo-1,2-dihydropyridine-3-carbonitriles precipitated on neutralisation with 10% HCl solution and were isolated by filtration.

4.1.3. General method C: N-unsubstituted pyrazolopyridones. The appropriate 4-(methylthio)-2-oxo-1,2-dihydropyridine-3-carbonitriles were placed in a microwave reaction vessel with ⁱPrOH (0.25 M) and hydrazine hydrate (20 equiv). This mixture was heated at 120 °C for 40 min. The products precipitated on cooling and were collected by filtration unless otherwise stated.

4.1.4. General method D: N-methylpyrazolopyridones. The appropriate 4-(methylthio)-2-oxo-1,2-dihydropyridine-3-carbonitriles were placed in a microwave reaction vessel with ⁱPrOH (0.25 M) and methylhydrazine (5 equiv). The mixture was heated at 150 °C for 20 min. Over this time the products precipitated and were collected by filtration and the solid washed with cold ⁿBuOH.

4.1.5. General method E: oxidation of 4-(methylthio)pyridones. The appropriate 4-(methylthio)-2-oxo-1,2-dihydropyridine-3-carbonitrile (0.07 M) was stirred at rt in EtOH with *m*-CPBA ($\leq$ 77% by wt, 5 equiv) for 24 h. The product was isolated by filtration and taken on to the next step.

4.1.6. General method F: N-phenylpyrazolopyridones. The 4-(methylsulfinyl)-2-oxo-1,2-dihydropyridine-3-carbonitriles (0.25 M) and

phenylhydrazine (10 equiv) were stirred in ⁱPrOH at reflux for 2 h. The 6-methyl-2-oxo-4-(2-phenylhydrazinyl)-1,2-dihydropyridine-3-carbonitriles formed were collected by filtration. Where the compounds did not precipitate from ⁱPrOH, ether or ethyl acetate was used to aid precipitation of the product.

The 2-oxo-4-(2-phenylhydrazinyl)-1,2-dihydropyridine-3-carbonitriles (0.05 M) were isolated and cyclised by heating at reflux in 1 M HCl in dioxane for 2 h, whereupon the product precipitated out of solution as the HCl salt.

4.1.7. General method G: Suzuki couplings to 5-bromopyridin-2-ones and 7-bromo-1H-pyrazolo[4,3-*c*]pyridin-4(5H)-ones. The appropriate heteroaromatic bromide (0.06 M) and boronic acid (2.2 equiv) were stirred in toluene/MeCN (95:5) in a microwave vial for 5 min while bubbling Ar through the suspension. NaO^tBu (3 equiv) and Pd(PPh₃)₄ (0.05 equiv) were added and the mixture was stirred for a further 10 min while purging with Ar. The vial was sealed and heated in the microwave for 1 h at 150 °C. The solvent was removed in vacuo and the residue purified.

4.1.8. General method H: bromination of pyridin-2-ones and pyrazolo[4,3-*c*]pyridin-4(5H)-ones. The appropriate heteroaromatic compound (0.1 M) and *N*-bromosuccinimide (1.2 equiv) were stirred in refluxing MeOH for 1 h. The solvent was removed in vacuo and the residue was washed with water. The product was collected by filtration.

4.1.9. General method I: chlorination of pyridin-2-ones and pyrazolo[4,3-*c*]pyridin-4(5H)-ones. The appropriate heteroaromatic compound (0.12 M) was stirred in POCl₃ for 20 h at 80 °C. The yellow suspension was added to iced water (10 $\times$ POCl₃ volume). After leaving for 30 min to quench, NaHCO₃ was slowly added to neutralise the solution. The aqueous solution was extracted with CH₂Cl₂ (5 $\times$ 30 mL), the combined organic extracts were dried (Na₂SO₄) and the solvent was removed in vacuo to leave a pale yellow solid. Purification was carried out by flash column chromatography, eluting with EtOAc/Pet unless otherwise stated.

4.1.10. General method J: S_NAr displacements of 2-chloropyridines and 4-chloro-1H-pyrazolo[4,3-*c*]pyridines. The appropriate heteroaromatic chloride (0.45 M) and amine (3.1 equiv) in ⁿBuOH were heated in the microwave at 160 °C for 30 min. The resulting mixture was dissolved in MeOH/CH₂Cl₂ (50:50), absorbed on a prepared isolate SCX-2 ion exchange column and washed through with two column volumes of the solvent mixture. The product was released using 0.1 M NH₃ in MeOH and the solvent was removed in vacuo to give the products.

4.1.11. 6-Methyl-4-(methylthio)-2-oxo-1,2-dihydropyridine-3-carbonitrile (1)^{15,34}. **Method (i):** A mixture of 2-(bis(methylthio)methylene)malononitrile (2.00 g, 11.8 mmol), wet DMSO (35 mL), acetone (8.62 mL, 118 mmol) and ground KOH pellets (2.64 g, 47.1 mmol) was stirred at rt for 8 h. The brown suspension was poured into iced water (120 mL) then acidified with 10% HCl solution. The red-brown precipitate, which formed was collected by filtration and washed with hot MeOH to give **1** as a pale orange solid (1.46 g, 8.13 mmol, 69%).

Method (ii): General method A, using acetone (0.24 mL, 3.23 mmol). The disodium salt was not isolated. Instead, MeOH and MeI were added to the reaction mixture in toluene and this mixture was heated at reflux for 15 min. The solvent was removed in vacuo. The residue was partitioned between water (20 mL) and ethyl acetate (3 $\times$ 20 mL). The combined organic extracts were dried using brine followed by Na₂SO₄. Upon removal of the solvent, the brown oil was purified by recrystallisation from hexane to give pale brown needles of 4,4-bis(methylthio)but-3-en-2-one **5** (217 mg,

1.34 mmol, 41%); mp 66–69 °C (hexane) (lit. 67 °C; petrol ether)¹⁴; R_f =0.67 (10:90, MeOH/CH₂Cl₂); IR (Nujol mull, cm⁻¹) 1639 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H 2.20 (3H, s, C-CH₃), 2.45 (3H, s, S-CH₃), 2.48 (3H, s, S-CH₃), 6.05 (1H, s, C5-H); ¹³C NMR (126 MHz, (CD₃)₂CO) δ_C 14.6 (CH₃), 17.5, (CH₃), 30.2 (CH₃), 114.2 (CH), 162.2, 192.2; MS (ESI) m/z 163 (M+H)⁺; HRMS (M+H)⁺ calcd for C₆H₁₁OS₂=163.0246, found=163.0243; HPLC (PG) t_R =3.31 min; purity $\geq$ 95%.

4,4-Bis(methylthio)but-3-en-2-one (**5**) (200 mg, 1.23 mmol) was subjected to the conditions described in general method B to give **1** as a pale yellow solid (131 mg, 0.72 mmol, 59%). A sample was recrystallised from MeOH; mp 327–328 °C (MeOH) (lit. 325 °C; MeOH)³⁴; R_f =0.74 (10:90, MeOH/CH₂Cl₂); IR (Nujol mull, cm⁻¹) 2210 (CN), 1565 (C=O); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 2.26 (3H, s, C-CH₃), 2.57 (3H, s, S-CH₃), 6.28 (1H, s, CH), 12.21 (1H, br s, NH); ¹³C NMR (126 MHz, (CD₃)₂SO) δ_C 14.3, 19.1, 93.3, 101.4, 115.4, 151.2, 159.9, 164.0; MS (ESI) m/z 181 (M+H)⁺; HRMS (M+H)⁺ calcd for C₈H₉N₂OS=181.0436, found=181.0434; HPLC (PG) t_R =2.50 min; purity $\geq$ 95%. Anal. Calcd for C₈H₈N₂OS: C, 53.31; H, 4.47; N, 15.54%. Found C, 53.09; H, 4.34; N, 15.62%.

4.1.12. 3,3-Bis(methylthio)-1-phenylprop-2-en-1-one (**3**)^{14,35}. General method A, using acetophenone (0.97 mL, 8.33 mmol) to give pale yellow precipitate (1.12 g, 5.02 mmol, 66%). Purified by recrystallisation from EtOH to give bright yellow needles of **3** (1.06 g, 4.72 mmol, 57%); mp 89–93 °C (EtOH) (lit. 92.5–94 °C)³⁵; R_f =0.74 (50:50, EtOAc/hexane); IR (Nujol mull, cm⁻¹) 1667 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H 2.56 (3H, s, CH₃), 2.57 (3H, s, CH₃), 6.79 (1H, s, CH), 7.44–7.47 (2H, m, ArH), 7.50–7.53 (1H, m, ArH), 7.92–7.94 (2H, m, ArH); ¹³C NMR (126 MHz, CDCl₃) δ_C 15.2, 17.5, 110.3, 128.8, 129.7, 133.1, 140.6, 170.2, 187.6; MS (ESI) m/z 225 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₁H₁₃OS₂=225.0408, found=225.0406; HPLC (PG) t_R =4.41 min; purity $\geq$ 95%. Anal. Calcd for C₁₁H₁₂OS₂: C, 58.89; H, 5.39%. Found C, 58.70; H, 5.37%.

4.1.13. 4-(Methylthio)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (**4**)^{13,34}. General method B, using **3** (5.06 g, 22.5 mmol). The pale yellow solid formed was collected by filtration and washed with EtOAc to give **4** (4.82 g, 19.9 mmol, 88%). A sample was recrystallised from acetone/water (1:1); mp 292–293 °C (279–284 °C phase change) (acetone/water) (lit. 282 °C; MeOH)³⁴; R_f =0.50 (80:20, EtOAc/hexane); IR (Nujol mull, cm⁻¹) 2214 (CN), 1648 (C=O); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 2.70 (3H, s, CH₃), 6.58 (1H, br s, C5-H), 7.52–7.60 (3H, m, ArH), 7.84 (2H, d, J =7.0 Hz, ArH), 12.46 (1H, br s, NH); ¹³C NMR (126 MHz, (CD₃)₂SO) δ_C 13.9, 94.6, 100.1, 115.3, 127.8, 128.8, 131.2, 132.2, 150.3, 160.3, 163.9; MS (ESI) m/z 243 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₃H₁₁N₂OS=243.0592, found=243.0583; HPLC (PG) t_R =4.41 min; purity $\geq$ 95%.

4.1.14. 3-Amino-6-methyl-2H-pyrazolo[4,3-c]pyridin-4(5H)-one acetate (**6**)¹². General method C. Pale brown solid (67 mg, 0.41 mmol, 51%). A sample was recrystallised from AcOH; mp 314–317 °C (AcOH); (lit. 368 °C; AcOH)¹²; R_f =0.40 (20:80, MeOH/CH₂Cl₂); IR (Nujol mull, cm⁻¹) 3415 (NH₂), 3283 (NH), 1663 (C=O); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 1.91 (3H, s, CH₃COOH), 2.16 (3H, s, CH₃), 5.16 (2H, s, NH₂), 5.94 (1H, s, C7-H), 10.56 (1H, s, NH), 11.80 (1H, br s, NH); ¹³C NMR (126 MHz, (CD₃)₂SO) δ_C 18.8 (AcOH), 21.0, 91.1, 97.9, 141.6, 145.6, 152.2, 160.3, 172.0 (AcOH); MS (ESI) m/z 165 (M+H)⁺; HRMS (M+H)⁺ calcd for C₇H₉N₄O=165.0776, found=165.0779; HPLC (PG) t_R =1.30 min; purity $\geq$ 95%. Anal. Calcd for C₇H₈N₄O·AcOH·0.1(H₂O): C, 47.83; H, 5.44; N, 24.79%. Found C, 47.56; H, 5.64; N, 24.41%.

4.1.15. 3-Amino-6-phenyl-1H-pyrazolo[4,3-c]pyridin-4(5H)-one (**7**)¹². General method C. White crystalline solid (38 mg, 0.17 mmol, 67%); mp 321–323 °C (lit. 320 °C; AcOH)¹²; R_f =0.42

(10:90, MeOH/CH₂Cl₂); IR (Nujol mull, cm⁻¹) 3413 (NH₂), 1653 (C=O); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 5.21 (2H, br s, NH₂), 6.40 (1H, br s, C7-H), 7.43–7.48 (3H, m, ArH), 7.69–7.71 (2H, m, ArH), 10.81 (1H, br s, NH), 11.89 (1H, br s, NH); ¹³C NMR (126 MHz, (CD₃)₂SO) δ_C 90.5, 98.3, 126.8, 128.7, 129.2, 134.2, 143.2, 145.4, 152.1, 160.6; MS (ESI) m/z 227 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₂H₁₁N₄O=227.0933, found=227.0929; HPLC (PG) t_R =3.17 min; purity $\geq$ 95%. Anal. Calcd for C₁₂H₁₀N₄O·0.1(H₂O): C, 63.21; H, 4.51; N, 24.57%. Found C, 63.25; H, 4.22; N, 24.60%.

4.1.16. 3-Amino-1,6-dimethyl-1H-pyrazolo[4,3-c]pyridin-4(5H)-one (**8**) and 3-amino-2,6-dimethyl-2H-pyrazolo[4,3-c]pyridin-4(5H)-one (**9**). General method D. Compound **8**: small colourless crystals (244 mg, 1.37 mmol, 62%); mp 290–291 °C; R_f =0.57 (20:80, MeOH/CH₂Cl₂); IR (Nujol mull, cm⁻¹) 1635 (C=O); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 2.14 (3H, s, C-CH₃), 3.57 (3H, s, N-CH₃), 5.15 (2H, s, NH₂), 6.11 (1H, s, C7-H), 10.59 (1H, s, NH); ¹³C NMR (126 MHz, (CD₃)₂SO) δ_C 18.9, 34.6, 90.1, 98.1, 141.9, 144.7, 152.1, 159.9. MS (ESI) m/z 179 (M+H)⁺; HRMS (M+H)⁺ calcd for C₈H₁₁N₄O=179.0933, found=179.0931; HPLC (PG) t_R =2.04 min; purity $\geq$ 95%. Anal. Calcd for C₈H₁₀N₄O: C, 53.92; H, 5.66; N, 31.44%. Found C, 53.74; H, 5.63; N, 31.11%.

A second isomer was also isolated from the mother liquor by prep. TLC eluting with MeOH/CH₂Cl₂ (10:90) **9**: Pale brown powder (6.4 mg, 0.04 mmol, 2%); mp 229–233 °C (phase change 186 °C); R_f =0.50 (20:80, MeOH/CH₂Cl₂); IR (Nujol mull, cm⁻¹) 1628 (C=O); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 2.04 (3H, s, C-CH₃), 3.56 (3H, s, N-CH₃), 5.79 (1H, s, C7-H), 6.09 (2H, s, NH₂), 9.99 (1H, s, NH); ¹³C NMR (126 MHz, (CD₃)₂SO) δ_C 19.0, 34.0, 94.7, 95.1, 139.4, 146.3, 149.2, 161.1; MS (ESI) m/z 179 (M+H)⁺; HRMS (M+H)⁺ calcd for C₈H₁₁N₄O=179.0933, found=179.0931; HPLC (PG) t_R =1.78 min; purity $\geq$ 95%.

4.1.17. 3-Amino-1-methyl-6-phenyl-1H-pyrazolo[4,3-c]pyridin-4(5H)-one (**10**) and 3-amino-2-methyl-6-phenyl-2H-pyrazolo[4,3-c]pyridin-4(5H)-one (**11**). General method D. Compound **10**: cream coloured solid (482 mg, 2.01 mmol, 67%). A sample was recrystallised from AcOH; mp 255–259 °C (AcOH); R_f =0.71 (20:80, MeOH/CH₂Cl₂); IR (Nujol mull, cm⁻¹) 1641 (C=O); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 3.69 (3H, s, CH₃), 5.27 (2H, s, NH₂), 6.70 (1H, s, C7-H), 7.45–7.49 (3H, m, ArH), 7.74–7.78 (2H, m, ArH), 10.83 (1H, br s, NH); ¹³C NMR (126 MHz, (CD₃)₂SO) δ_C 34.8 (CH₃), 90.6 (CH), 98.6, 126.8 (CH), 128.6 (CH), 129.3 (CH), 134.1, 143.2, 144.6, 152.2, 160.2; MS (ESI) m/z 241 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₃H₁₃N₄O=241.1089, found=241.1078; HPLC (PG) t_R =3.55 min; purity $\geq$ 95%. Anal. Calcd for C₁₃H₁₂N₄O·0.1(H₂O): C, 64.50; H, 5.08; N, 23.14%. Found C, 64.68; H, 5.01; N, 22.85%.

A second isomer was isolated from the mother liquor by prep. TLC eluting with MeOH/CH₂Cl₂ (6:94) **11**: White solid (13 mg, 0.05 mmol, 7%); mp 253–256 °C; R_f =0.74 (20:80, MeOH/CH₂Cl₂); IR (Nujol mull, cm⁻¹) 1646 (C=O); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 3.62 (3H, s, CH₃), 6.22 (2H, s, NH₂), 6.35 (1H, br d, J =1.5 Hz, C7-H), 7.38–7.45 (3H, m, ArH), 7.66–7.68 (2H, m, ArH), 10.24 (1H, br s, NH); ¹³C NMR (126 MHz, (CD₃)₂SO) δ_C 34.3, 95.4, 95.6, 126.4, 128.6, 128.7, 134.8, 141.5, 146.5, 148.9, 161.3; MS (ESI) m/z 241 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₃H₁₃N₄O=241.1089, found=241.1085; HPLC (PG) t_R =3.62 min; purity $\geq$ 95%.

4.1.18. 4-(Methylsulfinyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (**13**). General method E. Bright yellow solid (87 mg, 0.33 mmol, 82%); mp 300–302 °C; IR (Nujol mull, cm⁻¹) 2216 (CN), 1668 (C=O), 1027 (S=O); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 2.96 (3H, s, CH₃), 7.05 (1H, br s, C5-H), 7.55–7.64 (3H, m, ArH), 7.89 (2H, d, J =7.0 Hz, ArH), 13.19 (1H, br s, NH); HMQC (500 MHz, (CD₃)₂SO, water) δ_C 41.2 (CH₃), (C7-H not observed), 127.8 (ArCH), 128.9 (ArCH), 131.8 (ArCH); MS (ESI) m/z 259 (M+H)⁺; HRMS (M+Na)⁺

calcd for $C_{13}H_{10}N_2O_2SNa=281.0355$, found=281.0353; HPLC (PG) $t_R=3.09$ min; purity $\geq 95\%$.

4.1.19. 3-Amino-6-methyl-2-phenyl-2H-pyrazolo[4,3-c]pyridin-4(5H)-one (16). General methods E and F. The product was isolated as the HCl salt by filtration as a white solid. This was dissolved in water (100 mL) and the solution was neutralised using saturated $NaHCO_3$ solution. The aqueous solution was extracted with CH_2Cl_2 (3×30 mL), the combined organic extracts dried (Na_2SO_4) and the solvent was removed in vacuo to leave **16** as a white solid (1.03 g, 4.27 mmol, 39%); mp 300–304 °C; $R_f=0.56$ (10:90, MeOH/ CH_2Cl_2); IR (Nujol, cm^{-1}) 3404 (NH₂), 3263, 3156 (NH), 1653 (C=O); 1H NMR (500 MHz, $(CD_3)_2SO$) δ_H 2.11 (3H, s, C-CH₃), 5.92 (1H, s, C7-H), 6.25 (2H, s, NH₂), 7.35–7.46 (1H, m, ArH), 7.54 (2H, dd, $J=7.5$, 7.5 Hz, ArH), 7.62 (2H, d, $J=7.5$ Hz, ArH), 10.22 (1H, s, NH); ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ_C 19.1, 94.6, 96.0, 123.3, 127.1, 129.3, 138.2, 140.9, 146.3, 150.4, 162.6; MS (ESI) m/z 241 (M+H)⁺; HRMS (M+H)⁺ calcd for $C_{13}H_{13}N_4O=241.1084$, found=241.1089; HPLC (PG) $t_R=3.28$ min; purity $\geq 95\%$. Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32%. Found C, 64.78; H, 4.96; N, 23.32%.

4.1.20. 3-Amino-2,6-diphenyl-2H-pyrazolo[4,3-c]pyridin-4(5H)-one (17). General method F: 2-Oxo-6-phenyl-4-(2-phenylhydrazinyl)-1,2-dihydropyridine-3-carbonitrile (**15**) was isolated as a pale yellow solid (480 mg, 1.59 mmol, 85%); 1H NMR (500 MHz, $(CD_3)_2SO$) δ_H 6.21 (1H, br s, C5-H), 6.73 (2H, d, $J=8.0$ Hz, ArH), 6.77 (1H, t, $J=7.5$ Hz, ArH), 7.19 (2H, dd, $J=8.0$, 7.5 Hz, ArH), 7.45–7.50 (3H, m, ArH), 7.61 (2H, d, $J=6.5$ Hz, ArH), 8.13 (1H, s, NH), 9.41 (1H, s, NH), 11.50 (1H, br s, NH); MS (ESI) m/z 303 (M+H)⁺; HPLC (PG) $t_R=4.40$ min purity $\geq 95\%$. After acid treatment of **15**, the resulting crude **17** was dissolved in the minimum amount of CH_2Cl_2 :MeOH (50:50), passed through a prepared isolate SCX-2 ion exchange column and washed through with two column volumes of the solvent mixture. The product was eluted in a 0.1 M solution of NH_3 in MeOH to give **17** a white solid on removal of the solvent (442 mg, 1.46 mmol, 90%); mp 250–253 °C; $R_f=0.20$ (10:90, MeOH/ CH_2Cl_2); IR (Nujol mull, cm^{-1}) 3430, 3344 (NH₂), 3097 (NH), 1659 (C=O); 1H NMR (500 MHz, $(CD_3)_2SO$) δ_H 6.34 (2H, s, NH₂), 6.46 (1H, s, C7-H), 7.41–7.48 (4H, m, ArH), 7.55 (2H, dd, $J=8.0$, 8.0 Hz, ArH), 7.65 (2H, dd, $J=8.5$, 1.0 Hz, ArH), 7.72 (2H, dd, $J=8.0$, 1.5 Hz, ArH), 10.44 (1H, s, NH); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 96.6, 97.4, 124.0, 126.1, 128.4, 129.2, 129.5, 129.9, 135.2, 137.7, 142.5, 145.8, 151.0, 162.2; MS (ESI) m/z 303 (M+H)⁺; HRMS (M+H)⁺ calcd for $C_{18}H_{15}N_4O=303.1240$, found=303.1247; HPLC (PG) $t_R=4.41$ min; purity $\geq 95\%$. Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53%. Found C, 71.46; H, 4.57; N, 18.55%.

4.1.21. N-(1-Methyl-4-oxo-6-phenyl-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-3-yl)-2-phenylacetamide (18). To a suspension of **10** (50 mg, 0.21 mmol) in CH_2Cl_2 (4.9 mL) at 0 °C was added phenylacetylchloride (0.061 mL, 0.54 mmol) and Et_3N (0.093 mL, 0.56 mmol). The mixture was stirred for 5 min at 0 °C, warmed to rt and stirred for 24 h. Water was added and the precipitated product was collected by filtration. Preparative TLC eluting with MeOH/ CH_2Cl_2 (10:90) gave **18** as a white solid (9 mg, 0.025 mmol, 12%); mp 267–268 °C; 1H NMR (500 MHz, $(CD_3)_2SO$) δ_H 3.73 (2H, s, CH₂), 3.90 (3H, s, N-CH₃), 6.90 (1H, s, C7-H), 7.25 (1H, t, $J=8.0$ Hz, ArH), 7.33 (2H, dd, $J=8.0$, 8.0 Hz, ArH), 7.38–7.41 (2H, br, ArH), 7.49–7.53 (3H, m, ArH), 7.79 (2H, dd, $J=7.5$, 1.5 Hz, ArH), 9.83 (1H, br s, NH), 11.16 (1H, br s, NH); HMQC (500 MHz, $(CD_3)_2SO$) δ_C 36.0 (N-CH₃), 42.5 (CH₂), 90.8 (CH), 126.7 (ArCH), 127.2 (ArCH), 127.3 (ArCH), 128.5 (ArCH), 129.3 (ArCH), 129.8 (ArCH); MS (ESI) m/z 359 (M+H)⁺; HRMS (M+H)⁺ calcd for $C_{21}H_{19}N_4O_2=359.1503$, found=359.1503; HPLC (PG) $t_R=4.28$ min; purity $\geq 95\%$.

4.1.22. N-(1,6-Dimethyl-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-3-yl)-3-methoxybenzenesulfonamide (19). 3-Methoxybenzene

sulfonyl chloride (45.3 mg, 0.22 mmol) and **8** (35.6 mg, 0.2 mmol) were stirred at rt in dry pyridine (1.2 mL) for 18 h. Water was added and **19** was collected by filtration as a white solid (63 mg, 0.18 mmol, 91%); IR (Nujol mull, cm^{-1}) 3584, 3113 (NH), 1652 (C=O), 1338, 1163 (S=O); 1H NMR (500 MHz, $(CD_3)_2SO$) δ_H 2.17 (3H, s, C-CH₃), 3.69 (3H, s, N-CH₃), 3.81 (3H, s, O-CH₃), 6.26 (1H, s, C7-H), 7.16 (1H, ddd, $J=8.0$, 2.5, 1.0 Hz, ArH), 7.43 (1H, dd, $J=8.0$, 8.0 Hz, ArH), 7.51 (1H, ddd, $J=8.0$, 1.5, 1.0 Hz, ArH), 7.56 (1H, dd, $J=2.5$, 1.5 Hz, ArH), 10.00 (1H, br s, NH), 10.93 (1H, br s, NH); ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ_C 18.8, 35.4, 55.5, 89.9, 102.6, 112.1, 118.7, 119.3, 129.8, 141.3, 142.2, 142.7, 145.3, 158.3, 159.0; MS (ESI) m/z 349 (M+H)⁺; HRMS (M+H)⁺ calcd for $C_{15}H_{17}N_4O_4S=349.0965$, found=349.0971; HPLC (PG) $t_R=3.44$; purity $\geq 95\%$. Anal. Calcd for $C_{15}H_{16}N_4O_4S \cdot 0.75(H_2O)$: C, 49.78; H, 4.87; N, 15.48%. Found C, 49.49; H, 4.78; N, 15.31%.

4.1.23. 1-(1,6-Dimethyl-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-3-yl)-3-(3-methoxyphenyl)urea (20). 3-Methoxyphenyl isocyanate (32.8 mg, 0.22 mmol) and **8** (35.6 mg, 0.2 mmol) were stirred at rt in dry pyridine (1.2 mL) for 18 h. Water was added and **20** was collected by filtration as a white solid (31 mg, 0.095 mmol, 47%); IR (Nujol mull, cm^{-1}) 3390, 3268 (NH), 1703, 1661, 1633 (C=O); 1H NMR (500 MHz, $(CD_3)_2SO$) δ_H 2.21 (3H, s, C-CH₃), 3.28 (3H, s, O-CH₃), 3.74 (3H, s, N-CH₃), 6.33 (1H, s, C7-H), 6.60 (1H, dd, $J=8.0$, 2.0 Hz, ArH), 6.99 (1H, dd, $J=8.0$, 2.0 Hz, ArH), 7.20 (1H, dd, $J=8.0$, 8.0 Hz, ArH), 7.24 (1H, br dd, $J=2.0$, 2.0 Hz, ArH), 8.21 (1H, s, NH), 9.78 (1H, s, NH), 11.06 (1H, br s, NH); ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ_C 19.0, 35.3, 55.0, 90.3, 99.6, 104.4, 107.9, 110.9, 129.6, 140.4, 143.1, 144.1, 144.6, 150.5, 159.3, 159.7; MS (ESI) m/z 328 (M+H)⁺; HRMS (M+H)⁺ calcd for $C_{16}H_{18}N_5O_3=328.1404$, found=328.1404; HPLC (PG) $t_R=4.36$; purity $\geq 95\%$. Anal. Calcd for $C_{16}H_{17}N_5O_3$: C, 58.71; H, 5.23; N, 21.39%. Found C, 58.34; H, 5.13; N, 21.77%.

4.1.24. 4-Methoxy-N-(1-methyl-4-oxo-6-phenyl-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-3-yl)benzamide (21). 4-Methoxybenzoic anhydride (215 mg, 0.75 mmol) and **10** (36 mg, 0.15 mmol) were stirred at 100 °C in dry pyridine (0.8 mL) for 24 h. The majority of the pyridine was removed by evaporation. Toluene was added and then evaporated in vacuo to remove the remaining pyridine as an azeotrope. The residue was dissolved in CH_2Cl_2 (2 mL) and stirred with PS-trisamine for 18 h. MeCN (2 mL) was added and the solution was passed through an isolate NH_2 ion exchange column. Two fractions were collected separately, the first by eluting with MeCN/ CH_2Cl_2 (50:50) and a second using MeOH. The solvent was removed to give **21** (35 mg, 0.09 mmol, 62%); IR (Nujol mull, cm^{-1}) 3398, 3170 (NH), 1654 (C=O); 1H NMR (500 MHz, $(CD_3)_2SO$) δ_H 3.85 (3H, s, O-CH₃), 3.94 (3H, s, N-CH₃), 6.91 (1H, s, C7-H), 7.08 (2H, d, $J=9.0$ Hz, ArH), 7.47–7.53 (3H, m, ArH), 7.78 (2H, dd, $J=8.0$, 1.5 Hz, ArH), 7.97 (2H, d, $J=9.0$ Hz, ArH), 10.04 (1H, s, NH), 11.10 (1H, s, NH); ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ_C 35.6, 55.4, 90.4, 105.1, 113.7, 125.1, 127.1, 128.7, 129.6, 129.6, 133.9, 142.8, 143.7, 145.2, 158.7, 162.1, 164.6; MS (ESI) m/z 375 (M+H)⁺; HRMS (M+H)⁺ calcd for $C_{21}H_{19}N_4O_3=375.1452$, found=375.1456; HPLC (PG) $t_R=4.42$; purity $\geq 95\%$. Anal. Calcd for $C_{20}H_{18}N_4O \cdot 0.4(H_2O)$: C, 62.23; H, 4.13; N, 14.51%. Found C, 61.91; H, 3.94; N, 14.25%.

4.1.25. 3-(Benzylamino)-1-methyl-6-phenyl-1H-pyrazolo[4,3-c]pyridin-4(5H)-one (22). To **10** (50 mg, 0.21 mmol) and benzaldehyde (0.17 mL, 1.7 mmol) in MeOH (6.0 mL), was added $NaCNBH_3$ (78.5 mg, 1.25 mmol). The white suspension was stirred at rt for 48 h. 1 M HCl (1.0 mL) was added and the mixture was stirred for a further 1 h, after which it was neutralised with 1 M NaOH, and the product extracted into EtOAc. The organics were washed with water (2×10 mL) and brine (10 mL) and dried over Na_2SO_4 . The solvent was removed in vacuo to leave a pale yellow oil.

Crystallisation from MeOH yielded **22** as a white solid (33 mg, 0.10 mmol, 48%); mp 228–231 °C; R_f =0.64 (10:90, MeOH/EtOAc); IR (Nujol mull, cm^{-1}), 1696 (C=O), 1641 (C=N); ^1H NMR (500 MHz, CDCl_3) δ_{H} 3.80 (3H, s, N-CH₃), 4.57 (2H, d, J =5.0 Hz, CH₂), 5.39 (2H, t, J =5.0 Hz, C3-NH), 6.34 (1H, s, C7-H), 7.30–7.47 (8H, m, ArH), 7.64–7.67 (2H, m, ArH), 9.92 (1H, br s, NH); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 35.2, 47.5, 90.5, 99.0, 126.5, 127.2, 128.0, 128.5, 129.0, 129.9, 134.4, 139.4, 144.0, 145.3, 153.7, 160.9; MS (ESI) m/z 331 (M+H)⁺; HRMS (M+H)⁺ calcd for C₂₀H₁₉N₄O=331.1559, found=331.1559; HPLC (PG) t_{R} =4.68 min; purity=90%.

4.1.26. 4,4-Bis(methylthio)-3-phenylbut-3-en-2-one (23)¹⁴. General method A from 1-phenylpropan-2-one using THF instead of toluene. The solvent was removed in vacuo to leave a yellow oil, which was dissolved in EtOAc, washed with water (2×30 mL), brine (1×30 mL) and dried (Na₂SO₄). Flash column chromatography eluting with EtOAc/hexane (90:10) gave **23** as a yellow oil (1.04 g, 4.37 mmol, 58%); R_f =0.79 (10:90, MeOH/CH₂Cl₂); IR (thin film, cm^{-1}) 1696 (C=O); ^1H NMR (500 MHz, (CD₃)₂CO) δ_{H} 2.18 (3H, s, S-CH₃), 2.24 (3H, s, S-CH₃), 2.41 (3H, s, C-CH₃), 7.27–7.40 (5H, m, ArH); ^{13}C NMR (126 MHz, (CD₃)₂CO) δ_{C} 17.6, 18.1, 30.3, 128.2, 128.5, 129.1, 136.9, 141.1, 146.2, 200.5; MS (ESI) m/z 239 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₂H₁₅OS₂=239.0559, found=239.0562; HPLC (PG) t_{R} =4.78 min; purity ≥95%.

4.1.27. 6-Methyl-4-(methylthio)-2-oxo-5-phenyl-1,2-dihydropyridine-3-carbonitrile (24). Method (i): General method B from **23**. Residual starting material was removed with a hexane wash to give **24** as a white solid (434 mg, 1.70 mmol, 39%).

Method (ii): General method G from **36** (78 mg, 0.30 mmol) and phenylboronic acid. Purification was carried out by flash column chromatography eluting with MeOH/CH₂Cl₂ (6:94) to yield **24** as a pale brown solid (36 mg, 0.87 mmol, 47%); mp 323–325 °C (MeOH); R_f =0.48 (10:90, MeOH/CH₂Cl₂); IR (Nujol, cm^{-1}) 3282 (NH), 2216 (CN) 1644 (C=O); ^1H NMR (500 MHz, (CD₃)₂SO) δ_{H} 1.94 (3H, s, C-CH₃), 2.41 (3H, s, S-CH₃), 7.23–7.24 (2H, m, ArH), 7.38–7.46 (3H, m, ArH), 12.53 (1H, br s, NH); ^{13}C NMR (126 MHz, (CD₃)₂SO) δ_{C} 17.6, 18.3, 99.2, 116.0, 119.5, 128.2, 128.6, 130.8, 134.7, 147.8, 160.2, 161.6; MS (ESI) m/z 257 (M+H)⁺. HRMS (M+H)⁺ calcd for C₁₄H₁₃N₂OS=257.0743, found=257.0743; HPLC (MC) t_{R} =2.26 min; purity ≥95%.

4.1.28. 3-Amino-6-methyl-7-phenyl-1H-pyrazolo[4,3-c]pyridin-4(5H)-one (26)¹². General method C from **24** (15.1 mg, 0.059 mmol). Pale brown solid (14 mg, 0.059 mmol, quant.); mp 315–318 °C (dec) (lit. 312–314 °C (dec); AcOH)¹²; R_f =0.20 (10:90, MeOH/CH₂Cl₂); IR (Nujol mull, cm^{-1}) 3442, 3326 (NH₂), 3138 (NH), 1636 (C=O); ^1H NMR (500 MHz, (CD₃)₂SO) δ_{H} 2.03 (3H, s, C-CH₃), 5.20 (2H, br s, NH₂), 7.31–7.38 (3H, m, ArH), 7.44 (2H, dd, J =7.5, 7.5 Hz, ArH), 10.67 (1H, br s, NH), 11.44 (1H, br s, NH); HMQC (500 MHz, (CD₃)₂SO) δ_{C} 17.0 (C-CH₃), 127.6 (ArCH), 129.0 (ArCH), 130.6 (ArCH); MS (ESI) m/z 241 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₃H₁₃N₄O=241.1084, found=241.1089; HPLC (PG) t_{R} =3.22 min; purity ≥95%. Anal. Calcd for C₁₃H₁₂N₄O.0.2(H₂O): C, 64.03; H, 5.13; N, 22.97%. Found C, 64.33; H, 4.95; N, 22.57%.

4.1.29. 3-Amino-1,6-dimethyl-7-phenyl-1H-pyrazolo[4,3-c]pyridin-4(5H)-one (27). Method (i): General method D from **24** (102.5 mg, 0.40 mmol). On washing with a mixture of MeOH/CH₂Cl₂/DMSO the white solid remaining was found to be the desired product (**27**) (22 mg, 0.09 mmol, 22%).

Method (ii): General method G from 3-amino-7-bromo-1,6-dimethyl-1H-pyrazolo[4,3-c]pyridin-4(5H)-one (**29**) (30 mg, 0.12 mmol) and phenylboronic acid. Purification was carried out using semi-prep HPLC (20:80 MeCN/water, isocratic) and the solvent was removed in vacuo to leave **27** as a pale brown solid (10 mg,

0.04 mmol, 34%); mp >350 °C; R_f =0.63 (10:90, MeOH/CH₂Cl₂); IR (Nujol mull, cm^{-1}) 3385, 3314 (NH₂), 3134 (NH), 1645 (C=O); ^1H NMR (500 MHz, (CD₃)₂SO) δ_{H} 1.88 (3H, s, C-CH₃), 2.92 (3H, s, N-CH₃), 5.21 (2H, s, NH₂), 7.30–7.33 (2H, m, ArH), 7.41–7.50 (3H, m, ArH), 10.85 (1H, br s, NH); ^{13}C NMR (126 MHz, (CD₃)₂SO) δ_{C} 16.6, 36.7, 98.9, 105.4, 128.0, 128.7, 131.1, 134.4, 139.1, 143.1, 151.8, 159.6; MS (ESI) m/z 255 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₄H₁₅N₄O=255.1240, found=255.1242; HPLC (PG) t_{R} =3.84 min; purity ≥95%.

4.1.30. 3-Amino-6-methyl-2,7-diphenyl-2H-pyrazolo[4,3-c]pyridin-4(5H)-one (28). General methods E and F from **24** (76.8 mg, 0.30 mmol). White solid (62 mg, 0.18 mmol, 59%); mp 315–320 °C (dec); R_f =0.40 (10:90, MeOH/CH₂Cl₂); IR (Nujol mull, cm^{-1}) 3409, 3325 (NH₂), 3140 (NH), 1651 (C=O); ^1H NMR (500 MHz, (CD₃)₂SO) δ_{H} 2.05 (3H, s, CH₃), 6.26 (2H, br s, NH₂), 7.27–7.56 (10H, m, ArH), 10.34 (1H, br s, NH); ^{13}C NMR (126 MHz, (CD₃)₂SO) δ_{C} 17.0, 96.1, 108.4, 123.7, 126.6, 127.3, 127.9, 129.3, 130.5, 135.1, 136.9, 138.1, 146.6, 150.5, 160.9; MS (ESI) m/z 317 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₉H₁₇N₄O=317.1397, found=317.1400; HPLC (PG) t_{R} =4.47 min; purity ≥95%.

4.1.31. 3-Amino-7-bromo-1,6-dimethyl-1H-pyrazolo[4,3-c]pyridin-4(5H)-one (29). General method H from **8** (1.00 g, 5.61 mmol). Orange solid (1.23 g, 4.80 mmol, 86%); mp 243–245 °C (dec); R_f =0.55 (10:90, MeOH/CH₂Cl₂); IR (Nujol, cm^{-1}) 3416 (NH₂), 3267, 3187, 3127 (NH), 1651 (C=O); ^1H NMR (500 MHz, (CD₃)₂SO) δ_{H} 2.27 (3H, s, C-CH₃), 3.93 (3H, s, N-CH₃), 5.31 (2H, s, NH₂), 11.11 (1H, br s, NH); ^{13}C NMR (126 MHz, (CD₃)₂SO) δ_{C} 19.0, 37.3, 83.4, 99.9, 140.7, 140.9, 151.6, 158.9; MS (ESI) m/z 257 (⁷⁹Br), 259 (⁸¹Br) (M+H)⁺; HRMS (M+H)⁺ calcd for C₈H₁₀BrN₄O (⁷⁹Br)=257.0033, found=257.0034; HPLC (PG) t_{R} =3.22 min; purity ≥95%.

4.1.32. 3-Amino-7-(4-methoxyphenyl)-1,6-dimethyl-1H-pyrazolo[4,3-c]pyridin-4(5H)-one (30). General method J from **29** (30 mg, 0.12 mmol) and 4-methoxyphenylboronic acid. Purification was carried out using semi-prep. HPLC (gradient) to give **30** as a pale brown solid (17 mg, 0.06 mmol, 51%); mp 290–291 °C; R_f =0.56 (10:90, MeOH/CH₂Cl₂); IR (Nujol, cm^{-1}) 3397, 3311 (NH₂), 1652 (C=O); ^1H NMR (500 MHz, (CD₃)₂SO) δ_{H} 1.89 (3H, s, C-CH₃), 2.97 (3H, s, N-CH₃), 3.80 (3H, s, O-CH₃), 5.21 (2H, s, NH₂), 7.02 (2H, d, J =8.5 Hz, ArH), 7.21 (2H, d, J =8.5 Hz, ArH), 10.75 (1H, s, NH); ^{13}C NMR (126 MHz, (CD₃)₂SO) δ_{C} 16.6, 36.7, 55.1, 98.9, 105.0, 114.1, 126.2, 132.2, 139.4, 143.4, 151.8, 158.9, 159.5; MS (ESI) m/z 285 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₅H₁₆N₄O₂=285.1346, found=285.1349; HPLC (PG) t_{R} =3.85 min; purity ≥95%.

4.1.33. Methyl 3-amino-1,6-dimethyl-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]pyridine-7-carboxylate (31). Compound **29** (117 mg, 0.45 mmol), PPh₃ (47 mg, 0.18 mmol), Pd(OAc)₂ (20 mg, 0.09 mmol, 0.20 equiv) and K₂CO₃ (62 mg, 0.45 mmol) were stirred in DMSO and MeOH (9:1, 9.0 mL) whilst CO was bubbled through the suspension for 20 min. The mixture was then heated to 110 °C under 1 atm of CO overnight. After cooling, solids were removed by filtration and the filtrate purified by semi-prep. HPLC (gradient) to give **34** as a pale yellow solid (20 mg, 0.09 mmol, 19%); mp 252–254 °C. R_f =0.31 (10:90, MeOH/CH₂Cl₂); IR (Nujol, cm^{-1}) 3415 (NH₂), 3281, 3199 (NH), 1712, 1682 (C=O); ^1H NMR (500 MHz, (CD₃)₂SO) δ_{H} 2.28 (3H, s, C-CH₃), 3.52 (3H, s, N-CH₃), 3.84 (3H, s, O-CH₃), 5.30 (2H, s, NH₂), 11.12 (1H, br s, NH); ^{13}C NMR (126 MHz, (CD₃)₂SO) δ_{C} 17.4, 37.7, 52.0, 98.2, 99.1, 140.8, 145.6, 152.0, 159.1, 165.4; MS (ESI) m/z 237 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₀H₁₃N₄O₃=237.0982, found=237.0890; HPLC (MC) t_{R} =1.49 min; purity ≥95%.

4.1.34. (E)-Methyl 3-(3-amino-1,6-dimethyl-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-7-yl)acrylate (32). Compound **29** (300 mg,

1.17 mmol), PPh_3 (42.8 mg, 0.16 mmol), $\text{Pd}(\text{OAc})_2$ (18.3 mg, 0.08 mmol, 0.07 equiv), methyl acrylate (0.21 mL, 2.33 mmol) and Et_3N (0.49 mL, 3.50 mmol) were stirred in DMF (1.8 mL) in a microwave vial for 10 min while bubbling Ar through the suspension. The vial was sealed and heated in the microwave for 30 min at 150 °C. Water was added to the dark green mixture and a green-brown solid was obtained by filtration. Purification was carried out using flash column chromatography eluting with $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (10:90) to give **32** as a yellow solid (62 mg, 0.24 mmol, 20%); mp 278–280 °C; R_f =0.31 (10:90, $\text{MeOH}/\text{CH}_2\text{Cl}_2$); IR (Nujol, cm^{-1}) 3460 (NH_2), 3294, 3202, 3151 (NH), 1716, 1686 ($\text{C}=\text{O}$); ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{H} 2.27 (3H, s, C- CH_3), 3.70 (3H, s, N- CH_3), 3.74 (3H, s, O- CH_3), 5.29 (2H, s, NH_2), 6.10 (1H, d, J =16.0 Hz, CH), 7.77 (1H, d, J =16.0 Hz, CH), 11.02 (1H, s, NH); ^{13}C NMR (126 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{C} 17.5, 38.2, 51.5, 99.2, 100.5, 122.5, 137.8, 142.3, 142.4, 151.9, 159.1, 166.2; MS (ESI) m/z 263 ($\text{M}+\text{H}^+$); HRMS ($\text{M}+\text{H}^+$) calcd for $\text{C}_{12}\text{H}_{15}\text{N}_4\text{O}_3$ =263.1139, found=263.1142; HPLC (PG) t_{R} =3.02 min; purity $\geq$ 95%.

4.1.35. Methyl 3-(3-amino-1,6-dimethyl-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-7-yl)propanoate (33). Compound **32** (40 mg, 0.15 mmol) was dissolved in AcOH (20 mL) and the double bond was reduced using Pd/C and free flowing H_2 by running through an H-cube flow reactor at 0.9 mL/min two times at 25 °C. The AcOH was removed in vacuo, the residue was dissolved in water (50 mL) and neutralised with saturated NaHCO_3 solution. The aqueous solution was extracted with CH_2Cl_2 (3 $\times$ 20 mL), the organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo to leave **33** as a white solid (23 mg, 0.09 mmol, 57%); mp 275–279 °C; R_f =0.28 (10:90, $\text{MeOH}/\text{CH}_2\text{Cl}_2$); IR (Nujol, cm^{-1}) 3313 (NH_2), 1735 ($\text{C}=\text{O}$), 1644 ($\text{C}=\text{O}$); ^1H NMR (500 MHz, CDCl_3) δ_{H} 2.31 (3H, s, C- CH_3), 2.49–2.59 (2H, m, $\text{C}(\text{O})\text{CH}_2\text{CH}_2$), 2.98–3.10 (2H, m, $\text{C}(\text{O})\text{CH}_2$), 3.73 (3H, s, N- CH_3), 3.94 (3H, s, O- CH_3), 4.66 (2H, s, NH_2), 9.63 (1H, s, NH); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 16.7, 21.6, 34.7, 38.0, 51.9, 100.9, 102.7, 138.7, 144.6, 151.9, 160.6, 172.5; MS (ESI) m/z 265 ($\text{M}+\text{H}^+$); HRMS ($\text{M}+\text{H}^+$) calcd for $\text{C}_{12}\text{H}_{17}\text{N}_4\text{O}_3$ =265.1295, found=265.1300; HPLC (MC) t_{R} =1.50 min; purity $\geq$ 95%. Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_3 \cdot 0.2(\text{H}_2\text{O})$: C, 53.80; H, 6.17; N, 20.91%. Found C, 54.03; H, 6.00; N, 20.64%.

4.1.36. (E)-2-Ethoxyethyl 3-(3-amino-1,6-dimethyl-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-7-yl)acrylate (34). Compound **29** (300 mg, 1.17 mmol), PPh_3 (42.8 mg, 0.16 mmol), $\text{Pd}(\text{OAc})_2$ (18.3 mg, 0.08 mmol, 0.07 equiv), ethylethoxyacrylate (0.34 mL, 2.33 mmol) and Et_3N (0.49 mL, 3.50 mmol) were stirred in DMF (1.8 mL) in a microwave vial for 10 min while bubbling Ar through the suspension. The vial was sealed and heated in the microwave for 30 min at 150 °C. Water was added to the dark green mixture and a green-brown solid was obtained by filtration. Purification was carried out using flash column chromatography eluting with $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (10:90). The solvent was removed in vacuo to yield **34** as a pale yellow solid (104 mg, 0.33 mmol, 28%); mp 242–243 °C; R_f =0.31 (10:90, $\text{MeOH}/\text{CH}_2\text{Cl}_2$); IR (Nujol, cm^{-1}) 3445 (NH_2), 3281, 3200, 3153 (NH), 1716, 1674 ($\text{C}=\text{O}$); ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{H} 1.11 (3H, t, J =7.0 Hz, OCH_2CH_3), 2.27 (3H, s, C- CH_3), 3.47 (2H, q, J =7.0 Hz, OCH_2CH_3), 3.62 (2H, t, J =5.0 Hz, $\text{C}(\text{O})\text{OCH}_2\text{CH}_2\text{O}$), 3.70 (3H, s, N- CH_3), 4.26 (2H, t, J =5.0 Hz, $\text{C}(\text{O})\text{OCH}_2\text{CH}_2\text{O}$), 5.27 (2H, s, NH_2), 6.10 (1H, d, J =16 Hz, $\text{C}(\text{O})\text{CH}=\text{CH}$), 7.78 (1H, d, J =16 Hz, $\text{C}(\text{O})\text{CH}=\text{CH}$), 11.01 (1H, s, NH); ^{13}C NMR (126 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{C} 15.0, 17.6, 38.2, 63.5, 65.6, 67.7, 99.2, 100.5, 122.3, 138.0, 142.4, 142.4, 151.9, 159.1, 165.8; MS (ESI) m/z 321 ($\text{M}+\text{H}^+$); HRMS ($\text{M}+\text{H}^+$) calcd for $\text{C}_{15}\text{H}_{21}\text{N}_4\text{O}_4$ =321.1557, found=321.1560; HPLC (MC) t_{R} =1.83 min; purity $\geq$ 95%.

4.1.37. 2-Ethoxyethyl 3-(3-amino-1,6-dimethyl-4-oxo-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-7-yl)propanoate (35). Compound **34**

(50 mg, 0.16 mmol) was dissolved in AcOH (20 mL) and the double bond was reduced using Pd/C and free flowing H_2 by running through an H-cube flow reactor at 0.9 mL/min two times at 25 °C. The AcOH was removed in vacuo, the residue was dissolved in water (50 mL) and neutralised with saturated NaHCO_3 solution. The aqueous solution was extracted with CH_2Cl_2 (3 $\times$ 20 mL), the organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo to leave **35** as a white solid (33 mg, 0.10 mmol, 66%); mp 216–219 °C; R_f =0.25 (10:90, $\text{MeOH}/\text{CH}_2\text{Cl}_2$); IR (Nujol, cm^{-1}) 3436 (NH_2), 3287, 3196, 3150 (NH), 1726, 1674 ($\text{C}=\text{O}$); ^1H NMR (500 MHz, CDCl_3) δ_{H} 1.22 (3H, t, J =7.0 Hz, CH_2CH_3), 2.32 (3H, s, C- CH_3), 2.47–2.63 (2H, m, C- $\text{CH}_2\text{CH}_2\text{C}(\text{O})$), 2.97–3.10 (2H, m, C- $\text{CH}_2\text{CH}_2\text{C}(\text{O})$), 3.54 (2H, q, J =7.0 Hz, CH_2CH_3), 3.64 (2H, t, J =5.0 Hz, $\text{C}(\text{O})\text{OCH}_2\text{CH}_2\text{O}$), 3.94 (3H, s, N- CH_3), 4.21 (2H, t, J =5.0 Hz, $\text{C}(\text{O})\text{OCH}_2\text{CH}_2\text{O}$), 4.66 (2H, s, NH_2), 10.18 (1H, br s, NH); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 15.1, 16.8, 21.5, 34.8, 38.0, 64.0, 66.7, 68.2, 100.9, 102.7, 138.7, 144.6, 151.9, 160.6, 172.1; MS (ESI) m/z 323 ($\text{M}+\text{H}^+$); HRMS ($\text{M}+\text{H}^+$) calcd for $\text{C}_{15}\text{H}_{23}\text{N}_4\text{O}_4$ =323.1714, found=323.1718; HPLC (MC) t_{R} =1.68 min; purity $\geq$ 95%. Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_4\text{O}_4$: C, 55.89; H, 6.88; N, 17.38%. Found C, 55.85; H, 6.87; N, 17.27%.

4.1.38. 5-Bromo-6-methyl-4-(methylthio)-2-oxo-1,2-dihydropyridine-3-carbonitrile (36). General method H from **1** (200 mg, 1.12 mmol). Cream solid (226 mg, 0.87 mmol, 79%); mp 271 °C (dec); R_f =0.66 (10:90, $\text{MeOH}/\text{CH}_2\text{Cl}_2$); IR (Nujol, cm^{-1}) 3289 (NH), 1645 ($\text{C}=\text{O}$); ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{H} 2.38 (3H, s, C- CH_3), 2.79 (3H, s, S- CH_3), 12.76 (1H, br s, NH); ^{13}C NMR (126 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{C} 18.4, 21.2, 99.9, 100.7, 115.4, 149.6, 159.7, 161.3; MS (ESI) m/z 259 (^{79}Br), 261 (^{81}Br) ($\text{M}+\text{H}^+$); HRMS ($\text{M}+\text{H}^+$) calcd for $\text{C}_8\text{H}_8\text{BrN}_2\text{OS}$ (^{79}Br)=258.9535, found=258.9543; HPLC (MC) t_{R} =1.84 min; purity $\geq$ 95%.

4.1.39. 4-Chloro-1,6-dimethyl-1H-pyrazolo[4,3-c]pyridin-3-amine (37). General method I from **8** (700 mg, 3.93 mmol). Purification was carried out by flash column chromatography, eluting with EtOAc/Pet (60:40), to yield **37** as a white solid (303 mg, 1.54 mmol, 39%); mp 172–174 °C; R_f =0.27 (60:40, EtOAc/Pet); IR (Nujol, cm^{-1}) 3450, 3294, 3197 (NH_2), 1611 ($\text{C}=\text{N}$); ^1H NMR (500 MHz, CDCl_3) δ_{H} 2.57 (3H, s, C- CH_3), 3.78 (3H, s, N- CH_3), 4.59 (2H, s, NH_2), 6.81 (1H, s, C7-H); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 24.3, 34.9, 101.6, 107.7, 143.4, 146.2, 147.5, 153.8; MS (ESI) m/z 197 (^{35}Cl), 199 (^{37}Cl) ($\text{M}+\text{H}^+$); HRMS ($\text{M}+\text{H}^+$) calcd for $\text{C}_8\text{H}_{10}\text{ClN}_4$ (^{35}Cl)=197.0589, found=197.0590; HPLC (MC) t_{R} =1.58 min; purity $\geq$ 95%.

4.1.40. 4-Chloro-1-methyl-6-phenyl-1H-pyrazolo[4,3-c]pyridin-3-amine (38). General method I from **10** (380 mg, 1.58 mmol). Purification was carried out by flash column chromatography, eluting with EtOAc/petrol (70:30), to yield **38** as a cream solid (162 mg, 0.63 mmol, 40%); mp 238–242 °C; R_f =0.33 (70:30, EtOAc/petrol); IR (Nujol, cm^{-1}) 3454, 3306, 3197 (NH_2); ^1H NMR (500 MHz, CDCl_3) δ_{H} 3.89 (3H, s, N- CH_3), 7.37 (1H, s, C7-H), 7.41–7.47 (1H, m, ArH), 7.47–7.52 (2H, m, ArH), 7.98–8.09 (2H, m, ArH); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} 35.1, 99.1, 108.1, 127.2, 128.8, 129.3, 138.2, 144.3, 146.3, 147.5, 153.8; MS (ESI) m/z 259 (^{35}Cl), 261 (^{37}Cl) ($\text{M}+\text{H}^+$); HRMS ($\text{M}+\text{H}^+$) calcd for $\text{C}_{13}\text{H}_{12}\text{ClN}_4$ (^{35}Cl)=259.0745, found=259.0747; HPLC (MC) t_{R} =2.41 min; purity $\geq$ 95%.

4.1.41. 1,6-Dimethyl-4-(piperidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-3-amine (39). General method J from **37** (20 mg, 0.10 mmol) and piperidine. White solid (24 mg, 0.10 mmol, 96%); mp 161–164 °C; R_f =0.48 (10:90, $\text{MeOH}/\text{CH}_2\text{Cl}_2$); IR (Nujol, cm^{-1}) 3368, 3303, 3212 (NH_2); ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{H} 1.54–1.59 (2H, m, $\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$), 1.65–1.70 (4H, m, $2 \times \text{N-CH}_2\text{-CH}_2$), 2.33 (3H, s, C- CH_3), 3.27–3.15 (4H, m, $2 \times \text{N-CH}_2\text{-CH}_2$), 3.63 (3H, s, N- CH_3), 4.93 (2H, s, NH_2), 6.67 (1H, s, C7-H); ^{13}C NMR (126 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{C} 24.2, 24.4, 25.4, 34.3, 50.9, 96.8, 100.6, 146.8, 147.7, 150.8, 157.6; MS

(ESI) m/z 246 ($M+H$)⁺; HRMS ($M+H$)⁺ calcd for $C_{13}H_{20}N_5=246.1713$, found=246.1709; HPLC (MC) $t_R=1.25$ min; purity $\geq 95\%$. Anal. Calcd for $C_{13}H_{19}N_5 \cdot 0.2(H_2O)$: C, 62.73; H, 7.86; N, 28.13%. Found C, 62.55; H, 7.69; N, 27.90%.

4.1.42. 1,6-Dimethyl-4-phenyl-1H-pyrazolo[4,3-c]pyridine-3,4-diamine (40). General method J from **37** (20 mg, 0.10 mmol) and aniline. Further purification by flash column chromatography, eluting with EtOAc/hexane (80:20), gave **40** as a yellow solid (17 mg, 0.067 mmol, 66%); mp 125–126 °C; $R_f=0.21$ (80:20, EtOAc/hexane); IR (Nujol, cm^{-1}) 3413, 3340 (NH₂), 3269, 3191 (NH); ¹H NMR (500 MHz, CDCl₃) δ_H 2.52 (3H, s, C-CH₃), 3.73 (2H, br s, NH₂), 3.78 (3H, s, N-CH₃), 6.48 (1H, s, C7-H), 7.03 (1H, t, $J=8.0$ Hz, ArH), 7.34 (2H, dd, $J=8.0, 8.0$ Hz, ArH), 7.46 (1H, s, NH), 7.71 (2H, d, $J=8.0$ Hz, ArH); ¹³C NMR (126 MHz, CDCl₃) δ_C 24.8, 34.8, 95.4, 100.4, 119.0, 122.1, 129.0, 140.7, 145.8, 147.1, 149.9, 153.5; MS (ESI) m/z 254 ($M+H$)⁺; HRMS ($M+H$)⁺ calcd for $C_{14}H_{16}N_5=254.1400$, found=254.1401; HPLC (MC) $t_R=1.25$ min; purity $\geq 95\%$.

4.1.43. 1,6-Dimethyl-4-(phenylthio)-1H-pyrazolo[4,3-c]pyridin-3-amine (41). Compound **37** (40 mg, 0.20 mmol), benzenethiol (50 μ L, 0.49 mmol) and K₂CO₃ (34 mg, 0.24 mmol) in MeCN (0.88 mL) were heated at reflux for 3 h. The resulting mixture was dissolved in MeOH/CH₂Cl₂ (50:50, 2 mL), absorbed on a prepared isolate SCX-2 ion exchange column and washed through with three column volumes of the solvent mixture. The product was released using 0.1 M NH₃ in MeOH and the solvent was removed in vacuo to give **41** as a pale yellow solid (48 mg, 0.18 mmol, 87%); mp 174–175 °C; $R_f=0.52$ (10:90, MeOH/CH₂Cl₂); IR (Nujol, cm^{-1}) 3448, 3302, 3200 (NH₂); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 2.33 (3H, s, C-CH₃), 3.70 (3H, s, N-CH₃), 5.39 (2H, s, NH₂), 7.04 (1H, s, C7-H), 7.32–7.44 (3H, m, ArH), 7.50 (2H, d, $J=7.0$ Hz, ArH); ¹³C NMR (126 MHz, (CD₃)₂SO) δ_C 24.5, 35.0, 101.3, 109.5, 128.6, 129.6, 131.5, 133.1, 145.2, 148.6, 150.2, 153.0; MS (ESI) m/z 271 ($M+H$)⁺; HRMS ($M+H$)⁺ calcd for $C_{14}H_{15}N_4S=271.1012$, found=271.1014; HPLC (MC) $t_R=1.52$ min; purity $\geq 95\%$. Anal. Calcd for $C_{14}H_{14}N_4S \cdot 0.2(H_2O)$: C, 61.38; H, 5.30; N, 20.45%. Found C, 61.59; H, 5.12; N, 20.07%.

4.1.44. 4-Isopropoxy-1,6-dimethyl-1H-pyrazolo[4,3-c]pyridin-3-amine (42). Sodium metal (30 mg) was dissolved in ⁱPrOH (2 mL) and **37** (20 mg, 0.10 mmol) was added and the resulting solution was heated at reflux overnight. To this solution was added water (10 mL) and the mixture was neutralised with NaHCO₃. The aqueous solution was extracted with CH₂Cl₂ (3 $\times$ 20 mL) and dried (Na₂SO₄). The solvent was removed in vacuo to leave **42** as a pale yellow solid (22 mg, 0.10 mmol, 98%); mp 99–101 °C; $R_f=0.40$ (80:20, EtOAc/Pet); IR (Nujol, cm^{-1}) 3485, 3294, 3197 (NH₂); ¹H NMR (500 MHz, CDCl₃) δ_H 1.40 (6H, d, $J=6.0$ Hz, OCH(CH₃)₂), 2.44 (3H, s, C-CH₃), 3.71 (3H, s, N-CH₃), 4.41 (2H, s, NH₂), 5.55 (1H, hept, $J=6.0$ Hz, OCH(CH₃)₂), 6.45 (1H, s, C7-H); ¹³C NMR (126 MHz, CDCl₃) δ_C 22.2, 24.7, 34.8, 68.0, 96.3, 98.2, 147.6, 148.2, 152.7, 157.8; MS (ESI) m/z 179 (($M-O^i$ Pr)+H)⁺; HRMS ($M+H$)⁺ calcd for $C_{11}H_{17}N_4O=221.1397$, found=221.1400; HPLC (MC) $t_R=1.75$ min; purity $\geq 95\%$. Anal. Calcd for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44%. Found C, 59.70; H, 7.28; N, 25.13%.

4.1.45. 1,6-Dimethyl-4-phenoxy-1H-pyrazolo[4,3-c]pyridin-3-amine (43). Compound **37** (40 mg, 0.20 mmol), phenol (21 mg, 0.22 mmol) and Cs₂CO₃ (73 mg, 0.22 mmol) in DMSO (0.23 mL) were heated in a sealed tube overnight at 130 °C. The resulting dark mixture was dissolved in MeOH/CH₂Cl₂ (50:50, 2 mL), absorbed on a prepared isolate SCX-2 ion exchange column and washed through with three column volumes of the solvent mixture. The product was released using 0.1 M NH₃ in MeOH and the solvent was removed. The product was purified by flash column chromatography, eluting with EtOAc/Pet (60:40), to give **43** as a pale brown solid

(24 mg, 0.094 mmol, 46%); mp 132–133 °C; $R_f=0.50$ (10:90, MeOH/CH₂Cl₂); IR (Nujol, cm^{-1}) 3461, 3295, 3173 (NH₂); ¹H NMR (500 MHz, CDCl₃) δ_H 2.40 (3H, s, C-CH₃), 3.79 (3H, s, N-CH₃), 4.49 (2H, s, NH₂), 6.61 (1H, br s, C7-H), 7.23 (1H, tt, $J=7.5, 1.0$ Hz, ArH), 7.26–7.30 (2H, m, ArH, overlaps with solvent peak), 7.42 (2H, dd, $J=7.5, 7.5$ Hz, ArH); ¹³C NMR (126 MHz, CDCl₃) δ_C 24.5, 34.9, 98.2, 98.8, 121.4, 124.6, 129.3, 147.8, 148.1, 152.8, 153.4, 156.9; MS (ESI) m/z 255 ($M+H$)⁺; HRMS ($M+H$)⁺ calcd for $C_{14}H_{15}N_4O=255.1240$, found=255.1242; HPLC (MC) $t_R=2.13$ min; purity $\geq 95\%$. Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03%. Found C, 66.01; H, 5.48; N, 21.97%.

4.1.46. 2-Methyl-4-phenyl-2,6,7,9-tetrahydro-1,2,5,6,9-pentaaza-benzo[cd]azulen-8-one (44). Compound **38** (130 mg, 0.50 mmol), methyl 2-aminoacetate hydrochloride (189 mg, 1.5 mmol) and Et₃N (0.14 mL, 1.0 mmol) in ⁿBuOH (1.1 mL) were heated in the microwave at 160 °C for 30 min. Water (30 mL) and CH₂Cl₂ (30 mL) were added to the resulting mixture. The two phases were separated and the aqueous fraction was washed with CH₂Cl₂ (2 $\times$ 30 mL). The organic fractions were combined, dried (Na₂SO₄) and the solvent was removed in vacuo. Flash column chromatography, eluting with MeOH/CH₂Cl₂ (5:95), gave **44** as a pale yellow solid. Recrystallised from MeOH (41 mg, 0.15 mmol, 29%); mp 270–275 °C (MeOH); $R_f=0.45$ (10:90, MeOH/CH₂Cl₂); IR (Nujol, cm^{-1}) 3666, 3352 (NH), 1683 (C=O); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 3.89 (3H, s, N-CH₃), 3.95 (2H, d, $J=3.5$ Hz, NH-CH₂), 7.27 (1H, t, $J=3.5$ Hz, NH-CH₂), 7.37–7.41 (1H, m, ArH), 7.42 (1H, s, C3-H), 7.43–7.49 (2H, m, ArH), 8.02–8.14 (2H, m, ArH), 11.02 (1H, s, NH); ¹³C NMR (126 MHz, (CD₃)₂SO) δ_C 35.1, 51.4, 92.6, 99.7, 126.7, 128.4, 128.4, 139.5, 141.3, 146.5, 151.9, 155.9, 168.5; MS (ESI) m/z 280 ($M+H$)⁺; HRMS ($M+H$)⁺ calcd for $C_{15}H_{14}N_5O=280.1193$, found=280.1194; HPLC (MC) $t_R=1.31$ min; purity $\geq 95\%$. Anal. Calcd for $C_{15}H_{13}N_5O \cdot 0.5(H_2O)$: C, 62.49; H, 4.89; N, 24.29%. Found C, 62.36; H, 4.58; N, 24.17%.

4.1.47. 2-Chloro-6-methyl-4-(methylthio)nicotinonitrile (45). General method I from **1** (700 mg, 3.88 mmol). On quenching **45** was isolated by filtration as a pale brown solid (672 mg, 3.38 mmol, 87%); mp 166–167 °C; $R_f=0.76$ (10:90, MeOH/CH₂Cl₂); IR (Nujol, cm^{-1}) 2231 (CN); ¹H NMR (500 MHz, CDCl₃) δ_H 2.59 (3H, s, CH₃), 2.60 (3H, s, CH₃), 6.92 (1H, s, C5-H); ¹³C NMR (126 MHz, CDCl₃) δ_C 14.5, 24.9, 104.5, 113.3, 116.2, 152.7, 158.7, 161.9; MS (ESI) m/z 199 (³⁵Cl), 201 (³⁷Cl) ($M+H$)⁺; HRMS ($M+H$)⁺ calcd for $C_8H_8ClN_2S=199.0091$, found=199.0094; HPLC (MC) $t_R=1.99$ min; purity $\geq 95\%$.

4.1.48. 6-Methyl-4-(methylthio)-2-(piperidin-1-yl)nicotinonitrile (46). General method J from **45** (120 mg, 0.60 mmol) and piperidine. Pale brown solid (143 mg, 0.58 mmol, 96%); mp 92–94 °C; $R_f=0.78$ (10:90, MeOH/CH₂Cl₂); IR (thin film, cm^{-1}) 2207 (CN); ¹H NMR (500 MHz, (CD₃)₂SO) δ_H 1.60 (6H, br s, N(CH₂CH₂)₂CH₂), 2.36 (3H, s, C-CH₃), 2.55 (3H, s, S-CH₃), 3.47–3.58 (4H, m, 2 $\times$ N-CH₂CH₂), 6.69 (1H, s, C5-H); ¹³C NMR (126 MHz, (CD₃)₂SO) δ_C 14.4, 24.6, 25.2, 26.0, 49.7, 89.0, 108.3, 116.8, 157.5, 160.2, 161.8; MS (ESI) m/z 248 ($M+H$)⁺; HRMS ($M+H$)⁺ calcd for $C_{13}H_{18}N_3S=248.1216$, found=248.1218; HPLC (MC) $t_R=2.70$ min; purity $\geq 95\%$.

4.1.49. 6-Methyl-4-(piperidin-1-yl)-1H-pyrazolo[4,3-c]pyridin-3-amine (48). Compound **46** (140 mg, 0.57 mmol) and *m*-CPBA ($\leq 77\%$ by wt, 381 mg, 1.70 mmol) in EtOH (5.4 mL) were stirred at rt for 6 h. To the resulting yellow solution was added water (10 mL) and saturated NaHCO₃ (10 mL). 6-Methyl-4-(methylsulfinyl)-2-(piperidin-1-yl)nicotinonitrile **47** precipitated from solution and was collected by filtration as a pale yellow solid (103 mg, 65%); MS (ESI) m/z 280 ($M+H$)⁺, HPLC (MC) $t_R=2.39$ min. A mixture of **47** (88 mg, 0.31 mmol) and hydrazine hydrate (0.30 mL, 6.68 mmol) in ⁱPrOH (1.7 mL) was stirred at reflux for

6 h. The resulting yellow solution was concentrated in vacuo and dissolved in MeOH/CH₂Cl₂ (50:50, 5 mL), absorbed on a prepared isolate SCX-2 ion exchange column and washed through with three column volumes of the solvent mixture. The product was released using 0.1 M NH₃ in MeOH and the solvent was removed in vacuo to leave a yellow oil. Flash column chromatography, eluting with MeOH/CH₂Cl₂ (10:90), gave **48** as a pale brown glass (30 mg, 0.13 mmol, 41%); mp 179–180 °C; R_f =0.27 (10:90, MeOH/CH₂Cl₂); IR (Nujol, cm⁻¹) 3442, 3356 (NH₂), 3142 (NH); ¹H NMR (500 MHz, CDCl₃) δ_H 1.65 (2H, quin, J =5.5 Hz, N(CH₂CH₂)₂CH₂), 1.76 (4H, tt, J =5.5, 5.5 Hz, 2×N-CH₂CH₂), 2.46 (3H, s, C-CH₃), 3.33 (4H, t, J =5.5 Hz, 2×N-CH₂CH₂), 4.41 (2H, s, NH₂), 6.58 (1H, s, C7-H), 9.34 (1H, br s, NH); ¹³C NMR (126 MHz, CDCl₃) δ_C 24.1, 25.6, 27.3, 52.8, 99.6, 102.6, 149.4, 150.5, 153.5, 160.4; MS (ESI) m/z 232 (M+H)⁺; HRMS (M+H)⁺ calcd for C₁₂H₁₈N₅=232.1557, found=232.1558; HPLC (MC) t_R =1.23 min; purity ≥95%. Anal. Calcd for C₁₂H₁₇N₅·0.33(H₂O): C, 60.75; H, 7.50; N, 29.52%. Found C, 61.05; H, 7.24; N, 29.33%.

4.2. Statistical data for the X-ray crystal structure determinations of **10** and **17**

	10	17
Empirical formula	C ₁₃ H ₁₂ N ₄ O	C ₁₈ H ₁₄ N ₄ O
Formula weight	240.27	302.33
Temperature	120(2) K	120(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Orthorhombic
Space group	C2/c	Pbca
Unit cell dimensions	$a=13.4275(7)$ Å, $b=7.1815(4)$ Å, $c=23.9546(10)$ Å $\alpha=90^\circ$, $\beta=102.587(2)^\circ$, $\gamma=90^\circ$	$a=14.7295(4)$ Å, $b=14.7023(4)$ Å, $c=26.7711(8)$ Å $\alpha=90^\circ$, $\beta=90^\circ$, $\gamma=90^\circ$
Volume	2254.4(2) Å ³	5797.5(3) Å ³
Z	8	16
Density (calculated)	1.416 mg/m ³	1.386 mg/m ³
Absorption coefficient	0.095 mm ⁻¹	0.090 mm ⁻¹
$F(000)$	1008	2528
Crystal	Cut shard; colourless	Slab; colourless
Crystal size	0.45×0.28×0.16 mm ³	0.34×0.12×0.05 mm ³
θ range for data collection	3.49–27.48°	3.01–27.48°
Reflections collected	11,796	26,155
Independent reflections	2582 [$R_{int}=0.0476$]	6537 [$R_{int}=0.0498$]
Completeness to $\theta=27.47^\circ$	99.7%	98.5%
Data/restraints/parameters	2582/0/177	6537/4/428
Goodness-of-fit on F^2	1.019	1.107
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1=0.0424$, $wR2=0.1001$	$R1=0.0654$, $wR2=0.1202$
R indices (all data)	$R1=0.0770$, $wR2=0.1170$	$R1=0.0912$, $wR2=0.1346$
Largest diff. peak and hole	0.230 and -0.212 e Å ⁻³	0.320 and -0.263 e Å ⁻³

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