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Optimized scale up of 3-pyrimidinylpyrazolo[1,5-*a*]pyridine via Suzuki coupling; a general method of accessing a range of 3-(hetero)arylpyrazolo[1,5-*a*]pyridines

Paul A. Bethel, Andrew D. Campbell, Frederick W. Goldberg, Paul D. Kemmitt *, Gillian M. Lamont, Abid Suleman

AstraZeneca, Oncology iMed, Mereside, Alderley Park, Macclesfield SK10 4TG, UK

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ABSTRACT

We have developed an improved synthesis of 3-(hetero)aryl pyrazolo[1,5-*a*]pyridines (such as 3-(2,5-dichloropyrimidin-4-yl)pyrazolo[1,5-*a*]pyridine (**8**)) via an optimized synthesis and Suzuki coupling of 3-pyrazolo[1,5-*a*]pyridine boronic ester **10**. These conditions are applicable to both high throughput chemistry and large scale synthesis of these medicinally important compounds. The scope of this chemistry has been further extended to include the synthesis and coupling of a novel boronic ester, 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine (**43**).

1. Introduction

Many compounds containing 3-substituted pyrazolo[1,5-*a*]pyridines have been found to possess biological activity, with over 400 publications including this bicycle over the last 5 years.[1] Certain 3-substituted pyrazolo[1,5-*a*]pyridine derivatives have been shown to be effective adenosine A1 antagonists, e.g., FK-838 (**1**),[2] while others have been found to be effective as kinase inhibitors (e.g., **2**–**4**)[3–5] (Fig. 1). As part of ongoing discovery chemistry efforts, we were interested to investigate improvements to the synthetic methodology towards 3-arylpyrazolo[1,5-*a*]pyridines.

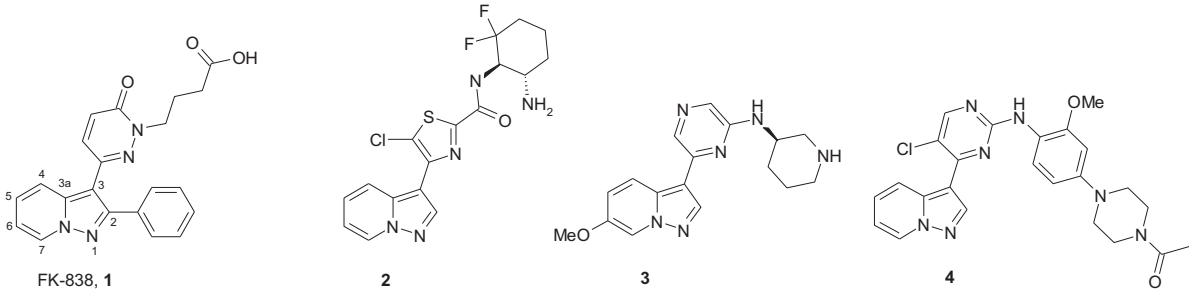

Fig. 1. Structures of some bioactive compounds containing a pyrazolo[1,5-*a*]pyridine motif.

1.1. Synthesis of 3-aryl and heteroaryl-pyrazolo[1,5-*a*]pyridines

3-Substituted pyrazolopyridines are typically made via a 1,3-dipolar cycloaddition between an azomethine imine **5** (formed by deprotonation of a 1-amino-pyridinium ion **6**) with an appropriate dipolarophile.[6] More recently their synthesis by a Michael reaction between vinylether **7** and 1-amino-pyridinium ion **6**, followed by a cyclization—oxidative aromatization sequence has been reported, Scheme 1.[7]

As part of an ongoing discovery campaign we required multi gram quantities of 3-(2,5-dichloropyrimidin-4-yl)pyrazolo[1,5-*a*]pyridine (**8**) as a key intermediate. We also wanted to be able to vary the 3-substituent by high throughput chemistry. Initially we followed the published route to compound **8**, which starts with the

* Corresponding author. Tel.: +44 (0) 1625 516128; e-mail address: paul.kemmitt@astrazeneca.com (P.D. Kemmitt).

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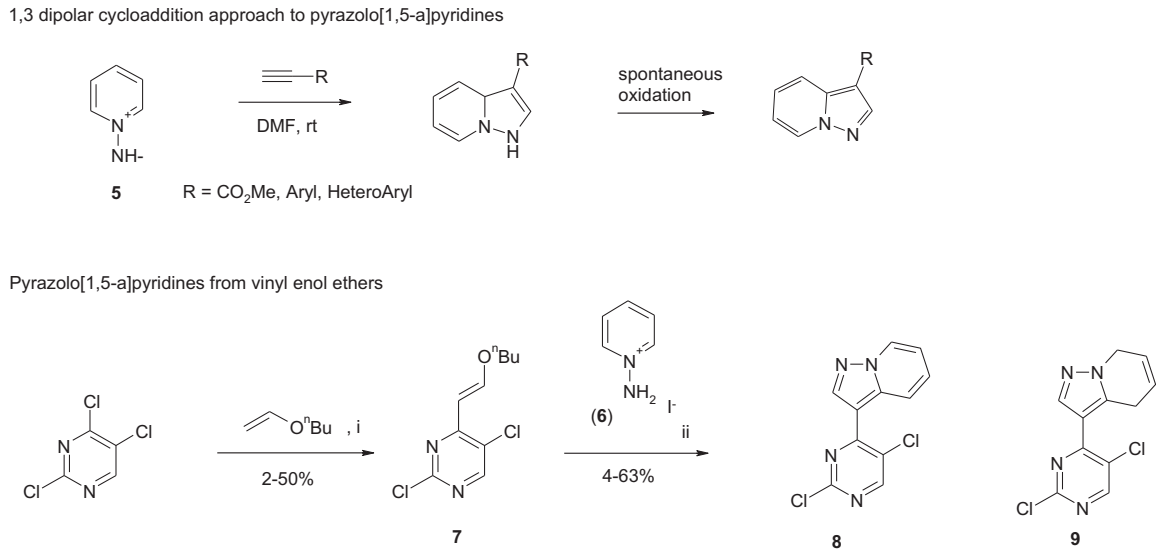


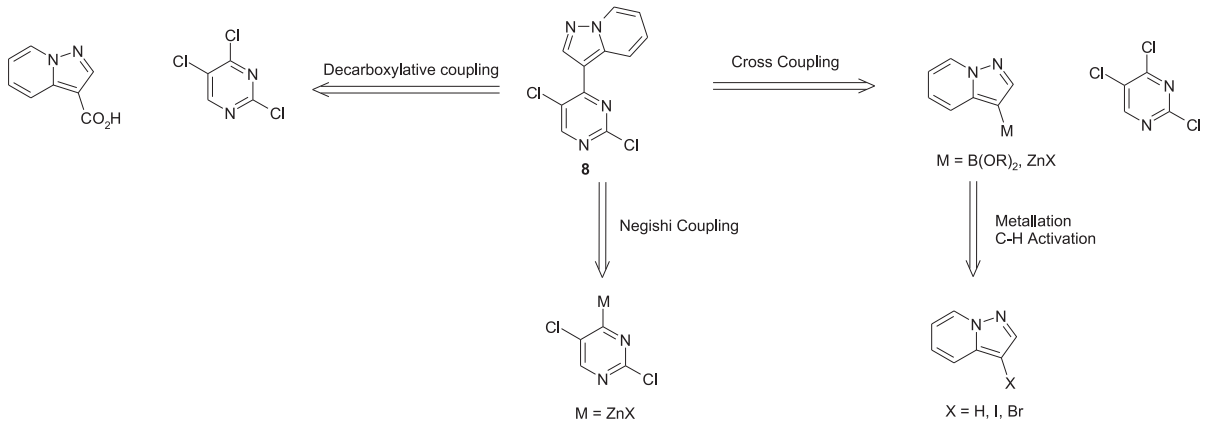
Scheme 1. Reported synthesis of pyrazolo[1,5-*a*]pyridines. Reagents and conditions: (i) 2 mol % $Pd(OAc)_2$, Et_3N, PEG-200 or 1,4 dioxane, 80 °C; (ii) DMF, K_2CO_3, rt, 6 h then 110 °C 2 h or modified conditions: K_2CO_3, (0.5 equiv), KOH (1 equiv), rt, 90 min, then 90 °C, 4 h.

Heck reaction of 2,3,5-trichloropyrimidine with *n*-butyl vinylether to make the enol ether **7** as the only regioisomer.[7] We found that the yield of this reaction could be improved by switching the solvent from PEG to dioxane, however, the reaction could never be driven to completion and it occasionally produced an exotherm (from 70 to 90 °C). Although the reaction to form the pyrazolopyridine core using modified conditions (KOH, K_2CO_3 in DMSO, Scheme 1) reduced the level of the unoxidized impurity **9**, we still found the reaction capricious and due to its poor solubility purification of the desired compound **8** was difficult.[7] Large scale synthesis using this chemistry was therefore problematic. In addition making derivatives would be cumbersome and not amenable to parallel synthesis. Likewise, using dipolar cycloaddition chemistry would require the synthesis of the acetylene starting materials.

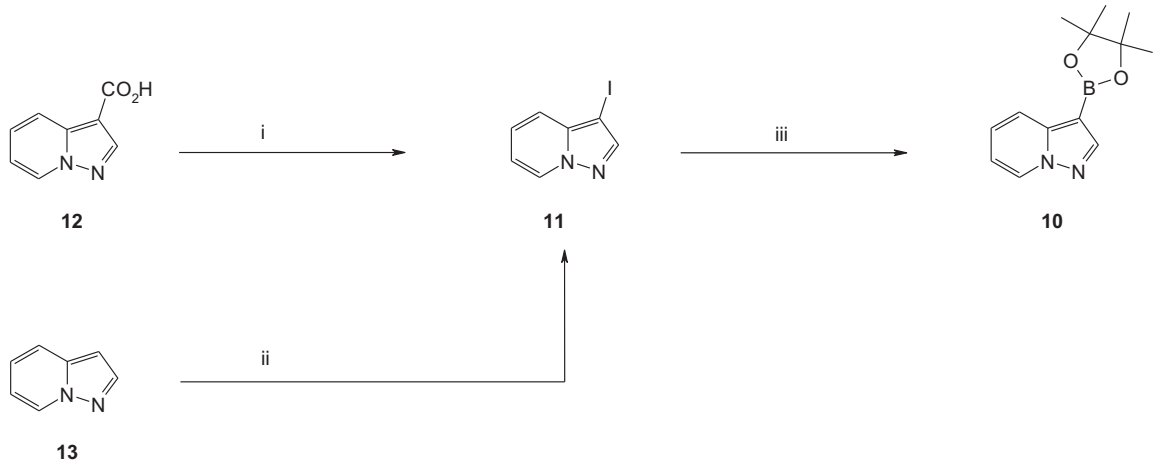
A number of alternative approaches were pursued from decarboxylative coupling,[8] Negishi Coupling,[9] C–H activation,[10] and the Suzuki (or Suzuki–Miyaura) reaction, Scheme 2. Due to the availability of reagents, robustness, and its suitablity to analogue synthesis, the Suzuki reaction is still the single most used reaction in the pharmaceutical industry for C–C bond formation.[11] It surprised us that despite the prevalence of this ring system this reaction has rarely been used to make analogues of pyrazolopyridines. Examples where it has been employed use a pyrazolopyridine halide and an appropriate boronic ester,[12] which thus limits the scope of coupling partner to stable, commercially available or synthesized boronic acids or esters. This would preclude the pyrimidine example in this case but also many medicinally relevant alternative heterocycles. There are only two publications reporting the synthesis of pyrazolopyridine boronic ester **10** and it was either isolated in a low 18% yield from a metal halogen exchange[3] or taken through crude after a Suzuki–Miyaura coupling with 4.5 mol % $Pd(OAc)_2$, 9 mol % tricyclohexylphosphine and bis(pinacolato)diboron.[13] Searching our own internal database found several failed attempts to isolate this boronic ester in acceptable yield and purity.[14] Consequently an improved synthesis of this reagent and optimized cross-coupling would have significant benefit and allow us to address the scalability concerns and improve the scope of analogue synthesis.

2. Results and discussion

Chavant et al.[15] have recently described a useful method of making functionalized aryl boronic esters on moderate scale from aryl iodides and ^{i}PrMgCl.LiCl. This requires the synthesis of 3-iodopyrazolo[1,5-*a*]pyridine (**11**), which was readily made in 75% yield by treatment of the corresponding carboxylic acid **12** with *N*-iodosuccinimide. To our knowledge this is the first direct conversion of a heteroaryl carboxylic acid to its iodide under these conditions and further work is underway to understand the scope of this methodology.[16] However, it was more convenient to prepare 3-



Scheme 2. Alternative strategies to 3-(2,5-dichloropyrimidin-4-yl)pyrazolo[1,5-*a*]pyridine (**8**).



Scheme 3. Synthesis of pyrazolo[1,5-*a*]pyridine-3-boronic ester (**10**). Reagents and conditions: (i) NIS, $NaHCO_3$, DMF, rt, 75%; (ii) NIS, MeCN, rt, 88%; (iii) ^{i}PrMgCl.LiCl, ^{i}PrOBPin, 5 °C, THF, 90%, or BuLi, ^{i}PrOBPin, −70 °C, THF, 50%.

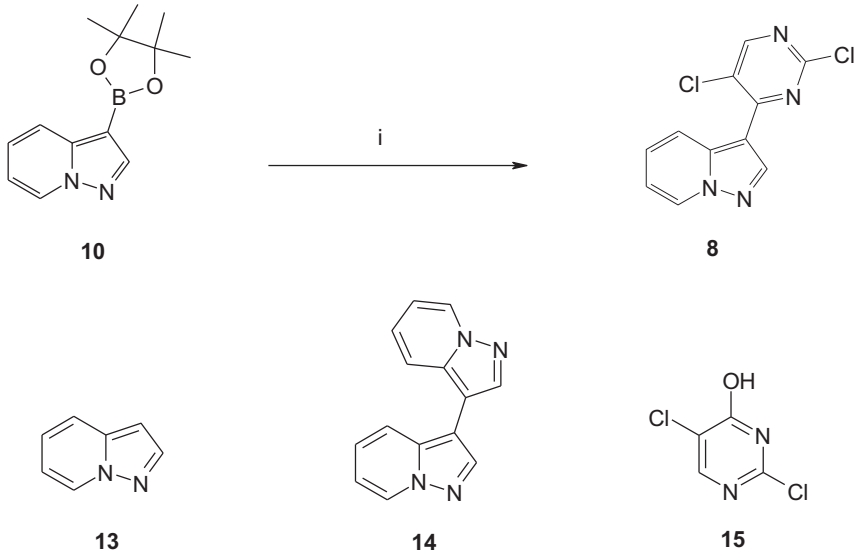
Table 1
Catalyst screen results

Catalyst system	Product/Internal standard after 5 h[a]	Isolated yield[b]
$Pd(dppf)Cl_2$	0.25	40%
$Pd(dtbpf)Cl_2$	0.30	31%
$Pd(OAc)_2$+S-Phos	0.04	n.d
$Pd(OAc)_2$+D*t*BPPS	0.31	n.d
$Pd(Amphos)Cl_2$	0.51	59%

[a] Relative yield measured by the ratio of product/internal standard (4,4′-di-*tert*-butylbiphenyl).
[b] After purification by chromatography, n.d not determined.

iodopyrazolo[1,5-*a*]pyridine (**11**) by direct iodination of the parent pyrazolo[1,5-*a*]pyridine (**13**).[17] Both of these procedures are an improvement of the only other published synthesis of this compound.[18] With access to the iodide we were now able to investigate the synthesis of the boronic ester **10**. We were pleased to find that by just using 1 equiv of ^{i}PrMgCl.LiCl we obtained 90% isolated yield of the desired boronic ester, Scheme 3. This has been carried out on up to 40 g without a significant drop off in yield and has been outsourced to a third party who has made 1 kg of this compound. This is a significant improvement over existing methods (vide supra) and is also better than the reaction of butyllithium with 3-iodopyrazolo[1,5-*a*]pyridine (**11**), which only formed the boronic ester (**10**) in 50% yield.[19]

An initial catalyst screen was carried out on the boronic ester (**10**) and 2,3,5-trichloropyrimidine with a range of common Suzuki catalysts, which would be available on scale. The reactions were carried out with 2M Na_2CO_3 in DME/water (4:1) and product formation was measured as a ratio of product over an internal standard (4,4′-di-*tert*-butylbiphenyl) where the higher ratio reflects higher product yield. The results are outlined in Table 1, $Pd(OAc)_2$ and S-Phos[20] gave the lowest conversion while $Pd(dppf)Cl_2$, $Pd(dtbpf)Cl_2$ and $Pd(OAc)_2$ with 3-(di-*tert*-butylphosphonium) propane sulfonate (D*t*BPPS)[21] were all similar. Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) ($Pd(Amphos)Cl_2$)[22] gave the highest yield. A number of key impurities were identified from this reaction. They were homocoupled pyrazole [1,5*a*]pyridine **14**, the product of protodeborylation (**13**) and hydrolysed chloropyrimidine **15**, Scheme 4. Impurities **13** and **15** were formed quickly during the Suzuki reaction and so a fast coupling process was needed to avoid these impurities becoming



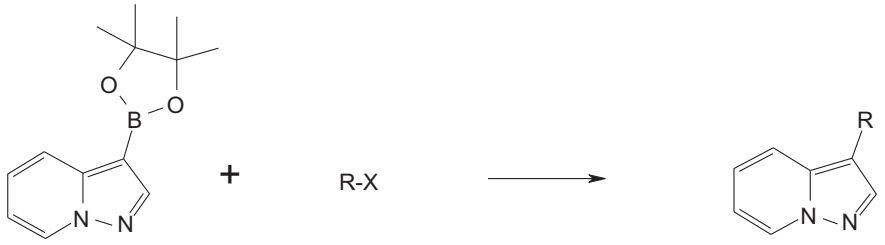
Scheme 4. Sythesis of 3-(2,5-dichloropyrimidin-4-yl)pyrazolo[1,5-*a*]pyridine (**8**). Reagents and conditions: (i) 6 mol % Catalyst and 2M Na_2CO_3 (2.2eq), 1 equiv boronic ester (**10**), 1.2 equiv trichloropyrimidine, DME/water (4:1) at 85 °C.

dominant. Varying the solvent (EtOH, tBuOH, DMA/water (4:1), toluene/water (4:1)) or base ($NaHCO_3$, CsF, DIPEA) failed to offer any improvement. Reducing the catalyst loading from 6 mol % to 3 mol % led to a reduction in product formation. To confirm these findings the reactions using Pd(dppf)Cl_2, Pd(d*t*bpf)Cl_2 and Pd(Amphos)Cl_2 were repeated and the isolated yields were 40%, 31% and 59%, respectively.

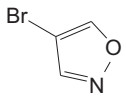
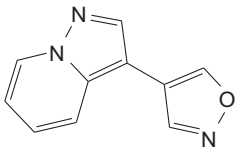
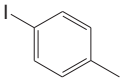
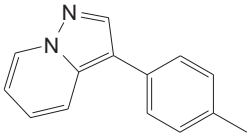
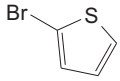
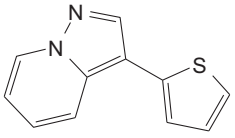
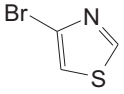
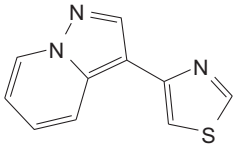
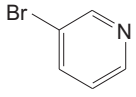
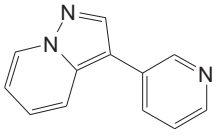
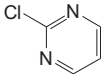
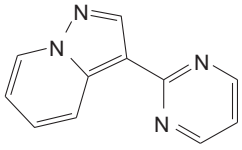
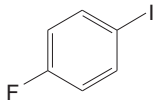
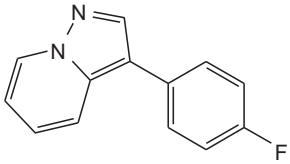
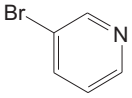
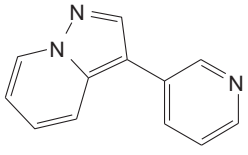
To replicate the heating profile of a large scale reactor, the reaction was slowly heated to 85 °C over 1 h and maintained at this temperature for 5 h. Pleasingly there was no loss of yield, when compared to the standard heating conditions (85 °C over 15 min). This has now successfully been scaled up to 25 g in house and has subsequently been outsourced to a third party. This represents the most efficient synthesis of 3-pyrimidinylpyrazolo[1,5-*a*]pyridine (**8**) to date, with an added advantage that the product precipitating from the reaction mixture facilitates purification.

With these conditions in hand we wanted to investigate the scope of the reaction towards a range of medicinally relevant 3-(hetero)aryl groups, as shown in Table 2. The design of the scoping set was primarily based on diversity, although we also ensured that we included the main ring systems reported in 3-(hetero)aryl pyrazolopyridine patent literature.[3–5,7,12,13] Thus we were able to demonstrate that the coupling worked for phenyl rings with an electronically diverse range of small substituents and for a series of aromatic heterocycles, including electron-deficient aromatic heterocycles that have previously proved difficult to couple. The yields varied from 20 to 71% with the exception of 3-chloropyrazole, which failed and 2-bromoimidazole, which only worked in 6% isolated yield.[23]

Table 2
Synthesis of 3-(het)aryl pyrazolo[1,5-*a*]pyridines derivatives by high throughput chemistry



10

R–X	Product (yield)	R–X	Product (yield)
	 **16** (24%)		 **21** (43%)
	 **17** (41%)		 **22** (42%)
	 **18** (50%)		 **23** (32%)
	 **19** (58%)		 **24** (44%)

(*continued on next page*)

Table 2 (*continued*)

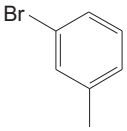
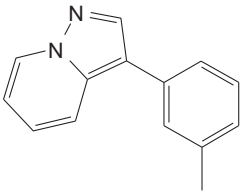
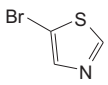
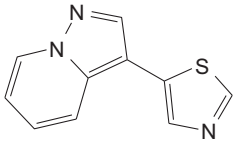
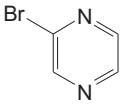
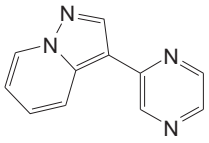
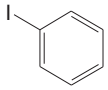
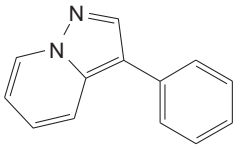
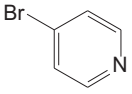
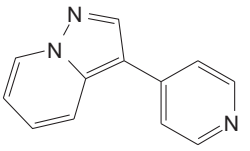
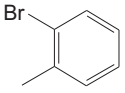
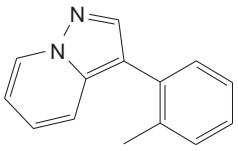
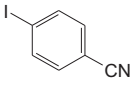
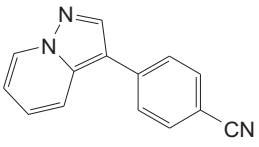
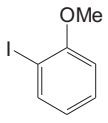
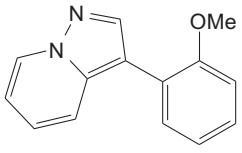
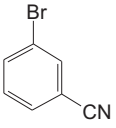
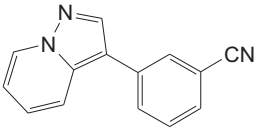
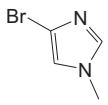
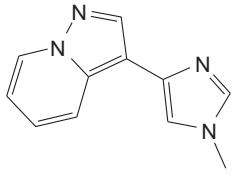
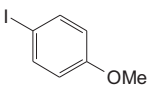
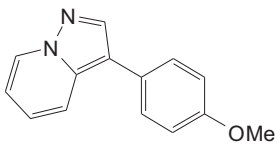
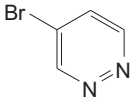
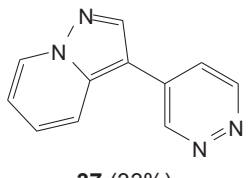
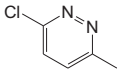
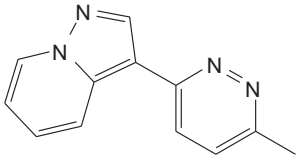
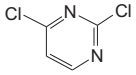
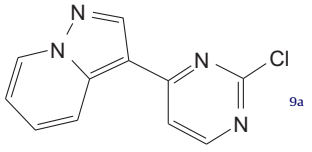
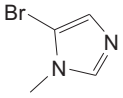
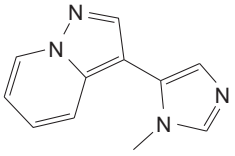
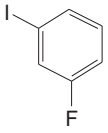
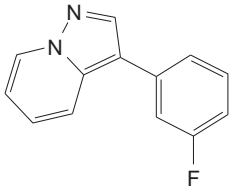
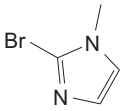
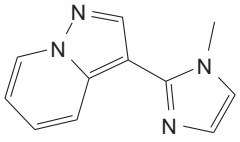
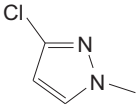
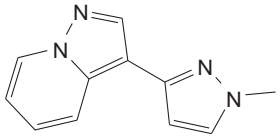
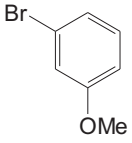
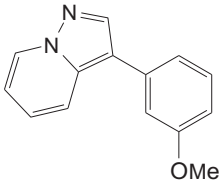
R–X	Product (yield)	R–X	Product (yield)
	 **20** (50%)		 **25** (41%)
	 **26** (41%)		 **33** (49%)
	 **27** (38%)		 **34** (44%)
	 **28** (63%)		 **35** (46%)
	 **29** (61%)		 **36** (21%)
	 **30** (59%)		 **37** (33%)

Table 2 (*continued*)

R–X	Product (yield)	R–X	Product (yield)
	 **31** (42%)		 **38**[9a] (49%)
	 **32** (36%)		 **39** (71%)
	 **40** (6%)		 **42** (0%)
	 **41** (51%)		

After the development of these robust conditions we extended the scope of this chemistry to the synthesis of a novel boronic ester **43** based on the fused pyrazolo ring system, 6,7-dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine. The boronic ester **43** was synthesized in four steps from methyl propiolate. The first step involved the addition of hydrazine hydrate to methyl propriolate to afford 1*H*-pyrazol-3(2*H*)-one (**44**) in good yield. Alkylation and cyclization with 1,3-dibromopropane gave the fused pyrazolo ring system **45**, which was carried through to iodide **46** before purification. Conversion to boronic ester **43** and subsequent Suzuki coupling with 2,3,5-trichloropyrimidine proceeded successfully, demonstrating the suitability of more complex boronic esters in this reaction, Scheme 5. Further work to fully optimize this sequence and expand the range of products is ongoing.

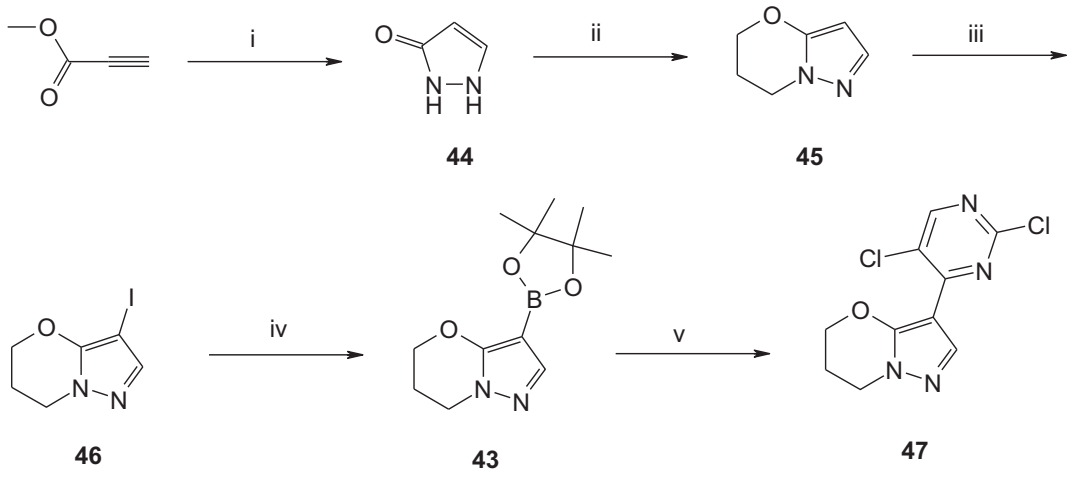
3. Conclusion

In summary, we have described an improved synthesis to 3-pyrazolo[1,5-*a*]pyridine boronic ester **10**, which has allowed us access to kilo quantities of this important building block. Its subsequent cross-coupling with 2,3,5-trichloropyrimidine has been optimized, robustly tested, scaled up in our labs and outsourced to a contract research organization. Ready access to this boronic ester has allowed us to examine the scope of the coupling with a range of halogenated (hetero)aromatic rings, including examples with electron-deficient heterocycles that were difficult to make using existing methodology. Finally these conditions have been applied to an efficient synthesis and coupling of a hitherto unreported boronic ester **43**.

4. Experimental

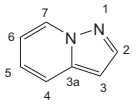
4.1. General methods

All solvents and chemicals used were reagent grade. $Pd(OAc)_2$, 3-(di-*tert*-butylphosphonium)propane sulfonate (D*t*BPPS), bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium-(II) ($Pd(Amphos)Cl_2$) and $Pd(dppf)Cl_2$, were purchased Aldrich. $Pd(dtbpf)Cl_2$ and S-Phos were purchased from Strem Chemicals, Inc. Anhydrous solvents tetrahydrofuran (THF), dimethoxyethane (DME) were purchased from Aldrich and used as such. Isopropylmagnesium chloride lithium chloride complex solution (1.3 M in THF) was purchased from Aldrich and titrated using L-menthol and 1,10-phenanthroline as indicator before use. Flash column chromatography was carried out using prepacked silica cartridges (from 4 g up to 330 g) from Crawford and eluted using an Isco Companion system. Preparative HPLC was carried out on a Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter,



Scheme 5. . 6,7-Dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine-3-boronic ester synthesis. Reagents and conditions: (i) $NH_2NH_2.H_2O$, MeOH, 95%; (ii) 1,3-Dibromopropane, K_2CO_3, DMF, 130 °C; (iii) NIS, MeCN, 29% over two steps; (iv) ^{i}PrMgCl.LiCl, ^{i}PrOBPin, 5 °C, THF, 46%; (v) 2,4,5-trichloropyrimidine, 2 M Na_2CO_3, 6 mol % Pd(Amphos)Cl_2, DME, 85 °C, 50%.

100 mm length (5–95% MeCN/1% NH_3 in H_2O). Catalytic screening experiments were assessed using a UPLC Waters Aquity Binary pump with sample manager, Aquity PDA and SQD Mass spectrometer. The solvents used 0.1% ammonium hydroxide (aq) and 0.1% ammonium hydroxide in acetonitrile. At a flow rate of 1 mL/min 1 uL of sample is injected onto a 50×2.1 1.7 μm Waters BEH column. Purity and characterization of compounds were established by a combination of liquid chromatography–mass spectroscopy (LC-MS), gas chromatography–mass spectroscopy (GC–MS) and NMR analytical techniques. Purities were all assessed to be 95% or more. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400, DRX 500 or AVANCE 700 spectrometer. Chemical shifts are reported in parts per million relative to solvent signal and coupling constant (*J*) values are reported in Hertz (Hz). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. Merck precoated thin layer chromatography (TLC) plates (silica gel 60 F254, 0.25 mm, art. 5715) were used for TLC analysis.



4.1.1. Pyrazolo[1,5-a]pyridine[17] ***(13)***. Sulfuric acid (50% v/v in water) (200 mL, 410.1 mmol) was added to ethyl pyrazolo[1,5-*a*] pyridine-3-carboxylate (78 g, 410.1 mmol) and the reaction was heated to reflux for 2 h 15 min. The reaction mixture was allowed to cool to room temperature and NaOH 50% w/w solution (350 mL) was added dropwise over 60 min while maintaining the temperature below 35 °C using an ice bath. This was then poured into water (1 L), further NaOH (50% w/w solution) (~75 mL) was added until the mixture was basic and the resultant suspension was stirred until everything dissolved. This was extracted with MTBE (3×250 mL), the combined organic extracts were washed with water (500 mL) and saturated brine (500 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to give the *title compound* (**13**, 44.6 g, 92%) as a yellow oil; δ_H(400 MHz, $CDCl_3$): 6.51 (1H, d, *J* 2 Hz, Ar*H*-3), 6.73 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.09 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.53 (1H, d, *J* 9 Hz, Ar*H*-4), 7.94 (1H, d, *J* 2 Hz, Ar*H*-2), 8.47 (1H, dd, *J* 7, 1 Hz, Ar*H*-7); δ_C(101 MHz, $CDCl_3$): 96.73, 111.60, 118.16, 123.14, 128.67, 140.16, 141.80; *m*/*z* (ES^+) 119 (100, MH^+); HRMS (ESI): MH^+, found 119.06036. $C_7H_7N_2$ requires 119.06037.

*4.1.2. 3-Iodopyrazolo[1,5-a]pyridine (**11**).*

4.1.2.1. From pyrazolo[1,5-a]pyridine-3-carboxylic acid. *N*-Iodosuccinimide (1.91 g, 8.51 mmol) was added to a stirred mixture of pyrazolo[1,5-*a*]pyridine-3-carboxylic acid (**12**, 1.15 g, 7.09 mmol) and $NaHCO_3$ (0.715 g, 8.51 mmol) in DMF (36 mL) and the resulting mixture was stirred at room temperature for 2 days. The reaction mixture was diluted with water (50 mL), extracted with EtOAc (3×125 mL), the organic extracts were combined, washed with saturated brine (100 mL), dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash chromatography (0–20% EtOAc/heptane) to give the *title compound* (**11**,1.3 g, 75%) as a brown oil, which solidified on standing.

4.1.2.2. From pyrazolo[1,5-a]pyridine ***13***. *N*-Iodosuccinimide (91 g, 403.18 mmol) was added portionwise over 10 min to a stirred solution of pyrazolo[1,5-*a*]pyridine (**13**, 43.3 g, 366.53 mmol) in acetonitrile (430 mL) at room temperature. The resulting mixture was stirred for 1 h, poured into water (2 L), stirred for 1 h and extracted with MTBE (2×800 mL). The organic extracts were combined and washed sequentially with 2 M NaOH (750 mL), 15% $Na_2S_2O_3$ (400 mL), and saturated brine (500 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product, 82.6 g. The crude product was purified by crystallisation from refluxing heptane (200 mL) to afford the *title compound* (**11**, 66.8 g) as a tan solid. The liquor was concentrated and purified by flash chromatography (DCM) to give a further 10.6 g of the *title compound*, (**11**) in an overall yield of 77.4 g, 87%; δ_H(400 MHz, $CDCl_3$): 6.80 (1H, td, *J* 7, 1 Hz Ar*H*-6), 7.17–7.22 (1H, m, Ar*H*-5), 7.48 (1H, d, *J* 9 Hz, Ar*H*-4), 7.96 (1H, s, Ar*H*-2), 8.46 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C(101 MHz, $CDCl_3$): 47.46, 112.49, 117.92, 124.67, 129.23, 141.02, 146.26; *m*/*z* (ES^+) 245 (100, MH^+); HRMS (ESI): MH^+, found 244.95695. $C_7H_6IN_2$ requires 244.95702.

*4.1.3. 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a] pyridine (**10**).*

4.1.3.1. Using isopropylmagnesium lithium chloride. Isopropylmagnesium lithium chloride (43.5 mL, 49.99 mmol, 1.15 M solution in THF) was added dropwise to a stirred solution of 3-iodopyrazolo[1,5-*a*]pyridine (**11**, 12.2 g, 49.99 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.30 mL, 74.99 mmol) in THF

(120 mL) at 5 °C (internal temperature kept below 10 °C), over a period of 10 min, under nitrogen. The resulting solution was stirred at 5 °C for 2 h and then concentrated under reduced pressure. The residue was diluted with DCM (50 mL), the suspension was filtered through a pad of silica, eluting with EtOAc (1000 mL) and evaporated to afford crude product, which was purified by flash chromatography (0–20% EtOAc/heptane) to give the *title compound* (**10**, 10.96 g, 90%) as a white solid; δ_H (400 MHz, $CDCl_3$): 1.36 (12H, s, 2×Me_2CO), 6.81 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.21 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.96 (1H, dt, *J* 9, 1 Hz, Ar*H*-4), 8.23 (1H, s, Ar*H*-2), 8.51 (1H, dt, *J* 7, 1 Hz, Ar*H*-7); δ_C(101 MHz, $CDCl_3$): 24.94 (4 CH_3), 83.12 (2C), 112.47, 120.09, 124.77, 128.82, 145.63, 148.77, C–B not seen; *m*/*z* (ES^+) 245 (100, MH^+); HRMS (ESI): MH^+, found 245.14558. $C_{13}H_{18}BN_2O_2$ requires 245.14558.

4.1.3.2. Using butyllithium. Butyllithium (1.6 M in hexanes) (1.9 mL, 3.10 mmol) was added dropwise to a stirred solution of 3-iodopyrazolo[1,5-*a*]pyridine (**11**, 504 mg, 2.07 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.3 mL, 6.20 mmol) in toluene (3.3 mL) and THF (0.8 mL) at −70 °C, under nitrogen. The resulting solution was stirred at −70 °C for 1 h and then removed from the cooling bath and allowed to stir at room temperature for 4 h. The reaction mixture was filtered through a pad of silica and washed through with EtOAc (250 mL) and evaporated to afford crude product. The crude product was purified by flash silica chromatography (0–20% EtOAc/heptane) to afford the *title compound* (**10**, 252 mg, 50%) as a colourless oil, which solidified on standing.

4.1.3.3. Representative example of a catalytic screening experiment. Reaction 1—Pd(dppf)Cl_2.

Reaction 2—Pd(d*t*bpf)Cl_2.

Reaction 3—Pd(OAc)$_2$+S-Phos.

Reaction 4—Pd(OAc)$_2$+D*t*BPPS.

Reaction 5—Pd(Amphos)Cl_2.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*]pyridine (**10**, 70 mg, 0.39 mmol), 4,4′-di-*tert*-butylbiphenyl (20 mg, 0.08 mmol) and the appropriate pre-catalyst (6 mol %) were placed in a tube in a Bohdan XT 24 position block under an atmosphere of nitrogen. Degassed DME (5 mL), 2,4,5-trichloropyrimidine (0.039 mL, 0.34 mmol) then 2M Na_2CO_3 (0.315 mL, 0.63 mmol) were then syringed into the tubes and the block was heated to 85 °C. The reactions were sampled after 20 min, 40 min, 90 min and 5 h by UPLC by syringing out 2 drops of the reaction mixture and diluting with methanol (1 mL).

*4.1.4. 3-(2,5-Dichloropyrimidin-4-yl)pyrazolo[1,5-a]pyridine[7] (**8**).*

4.1.4.1. Using Pd(dppf)Cl_2. (1,1′-Bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (104 mg, 0.13 mmol) was added to a degassed solution of 2,4,5-trichloropyrimidine (0.289 mL, 2.52 mmol), 2M Na_2CO_3 (2.3 mL, 4.61 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*]pyridine (**10**, 512 mg, 2.10 mmol) in DME (10 mL) and the resulting mixture was stirred at 85 °C for 1.5 h. The reaction mixture was allowed to cool, the precipitate was collected by filtration, washed with water (30 mL) and dried under vacuum at 50 °C to afford the *title compound* (**8**, 224 mg, 40%) as a yellow solid.

4.1.4.2. Using Pd(Amphos)Cl_2. Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (Pd(Amphos)Cl_2) (4.24 g, 5.99 mmol) was added to a degassed mixture of 2,4,5-trichloropyrimidine (13.72 mL, 119.7 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-*a*]pyridine (**10**, 24.35 g, 0.1 mol) and 2M Na_2CO_3 (110 mL, 219.46 mmol) in DME (500 mL) under nitrogen. The resulting mixture was stirred at 85 °C for 3 h and then allowed to cool to ambient temperature overnight. The precipitate was collected by filtration, washed with DME (150 mL) and water (3×250 mL) and dried under vacuum at 50 °C for 4 h to afford the *title compound* (**8**, 13.64 g) as a pale yellow solid. A precipitate developed in the aqueous filtrate, which was collected by filtration, stirred in acetone (250 mL) for ~5 min, filtered and dried under vacuum to afford further *title compound* (**8**, 2.01 g) as a cream solid. Overall yield 15.65 g, 59%; δ_H (400 MHz, DMSO): 7.28 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.67–7.77 (1H, m, Ar*H*-5), 8.56 (1H, d, *J* 9 Hz, Ar*H*-4), 8.80 (1H, s, Ar*H*-2), 8.96 (1H, d, *J* 7 Hz, Ar*H*-7), 9.08 (1H s, pyrimidine *H*); δ_C (176 MHz, DMSO at 70 °C): 105.78, 115.21, 119.81, 124.33, 128.86, 130.09, 139.76, 143.98, 157.33, 158.13, 159.44; *m*/*z* (ES^+) 265 (100, MH^+); HRMS (ESI): MH^+, found 265.00439. $C_{11}H_7Cl_2N_4$ requires 265.00423.

4.2. General procedure for parallel coupling

Reactions were carried out in a Bohdan XT 24 position block using the appropriate halide indicated.

2M Sodium carbonate (0.680 mL, 1.36 mmol) was added to a stirred mixture of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazolo[1,5-*a*]pyridine (**10**, 151 mg, 0.62 mmol), the appropriate halide (0.74 mmol) and bis(di-*tert*-butyl(4-dimethylaminophenyl) phosphine)dichloropalladium(II) (Pd(Amphos)Cl_2) (26.3 mg, 0.04 mmol) in DME (4 mL) under nitrogen. The resulting mixture was stirred at 80 °C for 4 h, allowed to cool, diluted with water (10 mL), extracted with EtOAc (2×25 mL) and the organic layer was evaporated to afford crude products. Unless otherwise stated the crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length, 5–95% MeCN/1% NH_3 in H_2O).

*4.2.1. 4-(Pyrazolo[1,5-a]pyridin-3-yl)isoxazole (**16**).* Using 4-bromoisoxazole; isolated the *title compound* (**16**, 28.1 mg, 24%) as a solid; δ_H (500 MHz, DMSO): 6.99 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.34–7.39 (1H, m, Ar*H*-5), 8.00 (1H, d, *J* 9 Hz, Ar*H*-4), 8.40 (1H, s, Ar*H*-2), 8.74 (1H, d, *J* 7 Hz, Ar*H*-7), 9.17 (1H, s, isoxazole C*H*O), 9.45 (1H, s, isoxazole C*H*N); δ_C(101 MHz, DMSO): 99.29, 111.86, 112.67, 117.33, 124.62, 129.23, 136.08, 140.31, 148.59, 152.94; *m*/*z* (ES^+) 186 (100, MH^+); HRMS (ESI): MH^+, found 186.06610. $C_{10}H_8N_3O$ requires 186.06619.

*4.2.2. 3-(Thiophen-2-yl)pyrazolo[1,5-a]pyridine (**17**).* Using 2-bromothiophene; isolated the *title compound* (**17**, 52.8 mg, 41%) as a gum; δ_H (500 MHz, DMSO): 6.98 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.16 (1H, dd, *J* 5, 4 Hz, thiophene), 7.34–7.39 (1H, m, Ar*H*-5), 7.40 (1H, dd, *J* 3, 1 Hz, thiophene), 7.49 (1H, dd, *J* 5, 1 Hz, thiophene), 7.94 (1H, dt, *J* 9, 1 Hz, Ar*H*-4), 8.34 (1H, s, Ar*H*-2), 8.74 (1H, dt, *J* 7, 1 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 105.94, 112.70, 117.12, 122.65, 123.26, 125.09, 127.92, 129.34, 134.25, 135.58, 139.90; *m*/*z* (ES^+) 201 (100, MH^+); HRMS (ESI): MH^+, found 201.04805. $C_{11}H_9N_2S$ requires 201.04810.

*4.2.3. 3-(Pyridin-3-yl)pyrazolo[1,5-a]pyridine (**18**).* Using 3-bromopyridine; isolated the *title compound* (**18**, 61 mg, 50%) as a solid; δ_H (500 MHz, DMSO): 7.05 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.43 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.53 (1H, ddd, *J* 8, 5, 1 Hz, pyridine), 8.08 (1H, dt, *J* 9, 1 Hz, pyridine), 8.15 (1H, ddd, *J* 8, 2, 2 Hz, Ar*H*-4), 8.51–8.55 (2H, m, Ar*H*-2 and pyridine), 8.83 (1H, dt, *J* 7, 1, Ar*H*-7), 9.00 (1H, dd, *J* 2, 1 Hz, pyridine); δ_C (101 MHz, DMSO): 108.15, 112.79, 117.16, 123.95, 125.29, 128.79, 129.47, 133.33, 136.34, 140.51, 146.85, 147.18; *m*/*z* (ES^+) 196 (100, MH^+); HRMS (ESI): MH^+, found 196.18689. $C_{12}H_{10}N_3$ requires 196.08692.

*4.2.4. 3-(4-Fluorophenyl)pyrazolo[1,5-a]pyridine (**19**).* Using 1-fluoro-4-iodobenzene; isolated the *title compound* (**19**, 77 mg, 58%) as an oil; δ_H (700 MHz, DMSO): 6.97 (1H, t, *J* 7 Hz, Ar*H*-6), 7.26–7.32

(2H, m, Ar*Ho*–F), 7.34 (1H, dd, *J* 9, 7 Hz, Ar*H*-5), 7.69–7.75 (2H, m, Ar*Hm*-F), 7.94 (1H, d, *J* 9 Hz, Ar*H*-4), 8.34 (1H, s, ArH-*2*), 8.73 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 110.63, 112.46, 115.79 (2C, d, *J* 21 Hz), 117.05, 124.74, 128.25 (2C, d, *J* 8 Hz), 129.18 (d, *J* 3 Hz), 129.31, 135.98, 140.26, 160.65 (d, *J* 243 Hz); *m*/*z* (ES^+) 213 (100, MH^+); HRMS (ESI): MH^+, found 213.08212. $C_{13}H_{10}FN_2$ requires 213.08225.

*4.2.5. 3-m-Tolylpyrazolo[1,5-a]pyridine (**20**).* Using 1-bromo-3-methyl-benzene; isolated the *title compound* (**20**, 64.8 mg, 50%) as an oil; δ_H (700 MHz, DMSO): 2.39 (3H, s, *Me*), 6.96 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.10 (1H, d, *J* 8 Hz, Ph), 7.31–7.33 (1H, m, Ar*H*-5), 7.35 (1H, t, *J* 8 Hz, Ph), 7.48 (1H, d, *J* 8 Hz, Ph), 7.51 (1H, s, Ph), 7.97 (1H, d, *J* 9 Hz, Ar*H*-4), 8.34 (1H, s, Ar*H*-2), 8.72 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 21.09, 111.62, 112.41, 117.35, 123.49, 124.63, 126.63, 126.95, 128.89, 129.32, 132.61, 136.01, 138.13, 140.25; *m*/*z* (ES^+) 209 (100, MH^+); HRMS (ESI): MH^+, found 209.10728. $C_{14}H_{13}N_2$ requires 209.10732.

*4.2.6. 3-p-Tolylpyrazolo[1,5-a]pyridine (**21**).* Using 1-iodo-4-methylbenzene; isolated the *title compound* (**21**, 57.5 mg, 43%) as a solid; δ_H (700 MHz, DMSO):2.35 (3H, s, Ar*Me*), 6.94 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.28 (2H, d, *J* 8 Hz, Ph), 7.31 (1H, dd, *J* 8, 7 Hz, Ar*H*-5), 7.58 (2H, d, *J* 8 Hz, Ph), 7.94 (1H, d, *J* 9 Hz, Ar*H*-4), 8.32 (1H, s, Ar*H*-2), 8.72 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 20.67, 111.59, 112.30, 117.27, 124.44, 126.29 (2C), 129.27, 129.56 (2C), 129.81, 135.07, 135.93, 140.05; *m*/*z* (ES^+) 209 (100, MH^+); HRMS (ESI): MH^+, found 209.10722. $C_{14}H_{13}N_2$ requires 209.10732.

*4.2.7. 4-(Pyrazolo[1,5-a]pyridin-3-yl)thiazole (**22**).* Using 4-bromothiazole; isolated the *title compound* (**22**, 52.2 mg, 42%) as a solid; δ_H (700 MHz, DMSO): 6.98 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.37 (1H, dd, *J* 9, 7 Hz, Ar*H*-5), 7.95 (1H, d, *J* 2 Hz, thiazole CC*H*S), 8.28 (1H, d, *J* 9 Hz, Ar*H*-4), 8.52 (1H, s, Ar*H*-2), 8.73 (1H, d, *J* 7 Hz, Ar*H*-7), 9.24 (1H, d, *J* 2 Hz, thiazole NC*H*S); ^{13}C NMR δ_C (101 MHz, DMSO): 106.97, 110.78, 112.67, 118.50, 124.74, 129.12, 136.34, 140.42, 148.84, 154.11; *m*/*z* (ES^+) 202 (100, MH^+); HRMS (ESI): MH^+, found 202.04323. $C_{10}H_8N_3S$ requires 202.04334.

*4.2.8. 3-(Pyrimidin-2-yl)pyrazolo[1,5-a]pyridine (**23**).* Using 2-chloropyrimidine; isolated the *title compound* (**23**, 39.1 mg, 32%) as a solid; δ_H (700 MHz, DMSO): 7.10 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.26 (1H, t, *J* 5 Hz, pyrimidine, CH*CH*CH), 7.49–7.55 (1H, m, Ar*H*-5), 8.56 (1H, d, *J* 9 Hz, Ar*H*-4), 8.69 (1H, s, Ar*H*-2), 8.82 (2H, d, *J* 5 Hz, pyrimidine, C*H*CH*CH*), 8.83 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 110.72, 113.60, 117.51, 119.42, 126.66, 129.63, 138.60, 142.85, 157.37 (2C), 161.42; *m*/*z* (ES^+) 197 (100, MH^+); HRMS (ESI): MH^+, found 197.08203. $C_{11}H_9N_4$ requires 197.08217.

*4.2.9. 3-(Pyridin-3-yl)pyrazolo[1,5-a]pyridine (**24**).* Using 3-bromopyridine; isolated the *title compound* (**24**, 56.3 mg, 44%) as a solid; δ_H (700 MHz, DMSO): 7.01 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.35–7.42 (1H, m, Ar*H*-5), 7.48 (1H, dd, *J* 8, 5 Hz, pyridine), 8.03 (1H, d, *J* 9 Hz, Ar*H*-4), 8.11 (1H, dt, *J* 8, 2, pyridine), 8.47–8.51 (2H, m, Ar*H*-2 and pyridine), 8.78 (1H, d, *J* 7 Hz, Ar*H*-7), 8.95 (1H, d, *J* 2 Hz, pyridine); δ_C (101 MHz, DMSO): 108.15, 112.80, 117.17, 123.96, 125.30, 128.79, 129.47, 133.33, 136.34, 140.52, 146.85, 147.18; *m*/*z* (ES^+) 196 (100, MH^+); HRMS (ESI): MH^+, found 196.08681. $C_{12}H_{10}N_3$ requires 196.08693.

*4.2.10. 5-(Pyrazolo[1,5-a]pyridin-3-yl)thiazole (**25**).* Using 5-bromothiazole; isolated the *title compound* (**25**, 52.6 mg, 41%) as a gum; δ_H (700 MHz, DMSO): 7.03 (1H, td, *J* 7, 1 Hz, Ar*H*-5), 7.43 (1H, dd, *J* 9, 7 Hz, Ar*H*-5), 7.95 (1H, d, *J* 9 Hz, Ar*H*-4), 8.25 (1H, s, thiazole), 8.42 (1H, s, Ar*H*-2), 8.78 (1H, d, *J* 7 Hz, Ar*H*-7), 9.06 (1H, s, thiazole); δ_C (101 MHz, DMSO): 102.15, 113.05, 116.95, 125.64, 129.30, 129.48, 136.09, 138.23, 140.69, 151.28; *m*/*z* (ES^+) 202 (100, MH^+); HRMS (ESI): MH^+, found 202.04321. $C_{10}H_8N_3S$ requires 202.04334.

*4.2.11. 3-(Pyrazin-2-yl)pyrazolo[1,5-a]pyridine (**26**).* Using 2-bromopyrazine; isolated the *title compound* (**26**, 50.7 mg, 41%) as a solid; δ_H (700 MHz, DMSO): 7.09 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.49 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 8.41 (1H, d, *J* 3 Hz, pyrazine*H*), 8.50 (1H, d, *J* 9 Hz, Ar*H*-4), 8.61–8.66 (1H, m, pyrazine*H*), 8.83 (1H, d, *J* 7 Hz, Ar*H*-7), 8.85 (1H, s, Ar*H*-2), 9.21 (1H, d, *J* 2 Hz, pyrazine*H*); δ_C (101 MHz, DMSO): 108.03, 113.66, 119.17, 126.43, 129.55, 137.84, 140.47, 141.05, 141.58, 143.94, 148.86; *m*/*z* (ES^+) 197 (100, MH^+); HRMS (ESI): MH^+, found 197.08203. $C_{11}H_9N_4$ requires 197.08217.

*4.2.12. 3-(Pyridin-4-yl)pyrazolo[1,5-a]pyridine (**27**).* Using 4-bromopyridine; isolated the *title compound* (**27**, 46 mg, 38%) as a solid; δ_H (700 MHz, DMSO): 7.03–7.08 (1H, m, Ar*H*-6), 7.46 (1H, dd, *J* 8, 7 Hz, Ar*H*-5), 7.74 (2H, dd, *J*5, 2 Hz, pyridine), 8.15 (1H, d, *J* 9 Hz, Ar*H*-4), 8.58 (2H, dd, *J*5, 2 Hz, pyridine), 8.61 (1H, s, Ar*H*-2), 8.81 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 108.64, 113.16, 117.44, 120.28 (2C), 126.13, 129.78, 136.69, 140.10, 141.23, 150.09 (2C); *m*/*z* (ES^+) 196 (100, MH^+); HRMS (ESI): MH^+, found 196.08679. $C_{12}H_{10}N_3$ requires 196.08692.

*4.2.13. 4-(Pyrazolo[1,5-a]pyridin-3-yl)benzonitrile (**28**).* Using 4-iodobenzonitrile; the product, which was purified by flash chromatography (0–50% EtOAc/heptane) to give the *title compound* **28**, 84.8 mg, 63% as a solid; δ_H (400 MHz, DMSO): 7.04 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.44 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.86–7.9 (2H, m, Ph), 7.92–7.96 (2H, m, Ph), 8.09 (1H, dt, *J* 9, 1 Hz, Ar*H*-4), 8.56 (1H, s, Ar*H*-2), 8.80 (1H, dt, *J* 7, 1 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 107.71, 109.88, 113.13, 117.29, 119.09, 126.03, 126.47 (2C), 129.73, 132.86 (2C), 136.45, 137.73, 141.20; *m*/*z* (ES^+) 220 (100, MH^+); HRMS (ESI): MH^+, found 220.08687. $C_{14}H_{10}N_3$ requires 220.08692.

*4.2.14. 3-(Pyrazolo[1,5-a]pyridin-3-yl)benzonitrile (**29**).* Using 3-bromobenzonitrile; the product, which was purified by flash chromatography (0–50% EtOAc/heptane) to give the *title compound* (**29**, 83.2 mg, 61%) as a solid; δ_H (400 MHz, DMSO): 7.02 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.40 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.62–7.75 (2H, m, Ph), 8.02–8.13 (2H, m, Ph), 8.16 (1H, t, *J* 2 Hz, Ph), 8.51 (1H, s, Ar*H*-2), 8.77 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 109.53, 112.22, 112.90, 117.24, 118.83, 125.52, 129.25, 129.34, 129.51, 130.16, 130.71, 134.13, 136.26, 140.83; *m*/*z* (ES^+) 220 (100, MH^+); HRMS (ESI): MH^+, found 220.08687. $C_{14}H_{10}N_3$ requires 220.08692.

*4.2.15. 3-(4-Methoxyphenyl)pyrazolo[1,5-a]pyridine (**30**).* Using 1-iodo-4-methoxy-benzene; the product, which was purified by flash chromatography (0–50% EtOAc/heptane) to give the *title compound* (**30**, 86.8 mg, 59%) as a solid; δ_H (400 MHz, DMSO): 3.81 (3H, s, O*Me*), 6.92 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.01–7.06 (2H, m, Ph), 7.29 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.57–7.63 (2H, m, Ph), 7.90 (1H, d, *J* 9 Hz, Ar*H*-7), 8.27 (1H, s, Ar*H*-2), 8.70 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 55.13, 111.46, 112.20, 114.52 (2C), 117.19, 124.21, 125.13, 127.66 (2C), 129.19, 135.76, 139.87, 157.72; *m*/*z* (ES^+) 225 (100, MH^+); HRMS (ESI): MH^+, found 225.10216. $C_{14}H_{13}N_3$ requires 225.10224.

*4.2.16. 3-(6-Methylpyridazin-3-yl)pyrazolo[1,5-a]pyridine (**31**).* Using 3-chloro-6-methyl-pyridazine; the product, which was purified by flash chromatography (0–70% EtOAc/heptane) to give the *title compound* (**31**, 55.2 mg, 42%) as a solid; δ_H (400 MHz, DMSO): 2.63 (3H, s *Me*), 7.08 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.50 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.58 (1H, d, *J* 9 Hz, pyridazine), 8.07 (1H, d, *J* 9 Hz, pyridazine), 8.55 (1H, dt, *J* 9, 1 Hz, Ar*H*-4), 8.75 (1H, s, Ar*H*-2), 8.79–8.83 (1H, m, Ar*H*-7); δ_C (101 MHz, DMSO): 21.50, 108.19, 113.52, 119.66, 123.31, 126.26, 127.22, 129.41, 137.19, 141.33, 153.37,

156.43; *m*/*z* (ES^+) 211 (100, MH^+); HRMS (ESI): MH^+, found 211.09776. $C_{12}H_{11}N_4$ requires 211.09782.

*4.2.17. 3-(1-Methyl-1H-imidazol-5-yl)pyrazolo[1,5-a]pyridine (**32**).* Using 5-bromo-1-methyl-imidazole; isolated the *title compound* (**32**, 43.8 mg, 36%) as a solid; δ_H (500 MHz, DMSO): 3.67 (3H, s, N*Me*), 6.99 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.11 (1H, d, *J* 1 Hz, imidazole), 7.32 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.70 (1H, dt, *J* 9, 1 Hz, Ar*H*-4), 7.73 (1H, s, imidazole), 8.26 (1H, s, Ar*H*-2), 8.75 (1H, dt, *J* 7, 1 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 31.88, 100.14, 112.76, 117.10, 123.83, 124.73, 127.09, 129.04, 137.37, 138.78, 140.49; *m*/*z* (ES^+) 199 (100, MH^+); HRMS (ESI): MH^+, found 199.09775. $C_{11}H_{11}N_4$ requires 199.09782.

*4.2.18. 3-Phenylpyrazolo[1,5-a]pyridine (**33**).* Using iodobenzene; isolated the *title compound* (**33**, 58.7 mg, 49%) as a gum; δ_H (700 MHz, DMSO): 6.97 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.29 (1H, t, *J* 7 Hz, Ph), 7.34 (1H, dd, *J* 9, 7 Hz, Ar*H*-5), 7.47 (2H, t, *J* 8 Hz, Ph), 7.70 (2H, d, *J* 7 Hz, Ph), 7.98 (1H, d, *J* 9 Hz, Ar*H*-4), 8.37 (1H, s, Ar*H*-2), 8.74 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 111.57, 112.44, 117.24, 124.71, 125.92, 126.38 (2C), 129.00 (2C), 129.34, 132.74, 136.05, 140.27; *m*/*z* (ES^+) 195 (100, MH^+); HRMS (ESI): MH^+, found 195.09154. $C_{13}H_{11}N_2$ requires 195.09154.

*4.2.19. 3-o-Tolylpyrazolo[1,5-a]pyridine (**34**).* Using 1-bromo-2-methyl-benzene; isolated the *title compound* (**34**, 56.4 mg, 44%) as a gum; δ_H (700 MHz, DMSO): 2.29 (3H, s, *Me*), 6.94 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.22–7.30 (3H, m, Ph), 7.33–7.38 (2H, m, Ph), 7.51 (1H, d, *J* 9 Hz, Ar*H*-4), 8.13 (1H, s, Ar*H*-2), 8.73 (1H, d, *J* 7 Hz Ar*H*-7); δ_C (101 MHz, DMSO): 20.26, 110.96, 112.26, 117.03, 124.15, 125.97, 126.91, 129.03, 129.95, 130.53, 131.57, 135.90, 136.92, 141.39; *m*/*z* (ES^+) 209 (100, MH^+); HRMS (ESI): MH^+, found 209.10721. $C_{14}H_{13}N_2$ requires 209.10732.

*4.2.20. 3-(2-Methoxyphenyl)pyrazolo[1,5-a]pyridine (**35**).* Using 1-iodo-2-methoxy–benzene; isolated the *title compound* (**35**, 64.5 mg, 46%) as a gum; δ_H (400 MHz, DMSO): 3.82 (3H, s), 6.92 (1H, t, *J* 6 Hz, Ph), 7.05 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.14 (1H, dd, *J* 8, 1 Hz, Ph), 7.25 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.32 (1H, ddd, *J* 8, 7, 2 Hz, Ph), 7.47 (1H, dd, *J* 8, 2 Hz, Ph), 7.61–7.68 (1H, m, Ar*H*-4), 8.17 (1H, s, Ar*H*-2), 8.69 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 55.32, 108.13, 111.66, 112.06, 118.12, 120.72, 121.22, 123.77, 127.82, 128.96, 129.60, 136.83, 141.69, 156.04; *m*/*z* (ES^+) 225 (100, MH^+); HRMS (ESI): MH^+, found 225.10217. $C_{14}H_{13}N_2O$ requires 225.10224.

*4.2.21. 3-(1-Methyl-1H-imidazol-4-yl)pyrazolo[1,5-a]pyridine (**36**).* Using 4-bromo-1-methyl-imidazole; isolated the *title compound* (**36**, 26.4 mg, 21%) as a gum; δ_H (500 MHz, DMSO): 3.76 (3H, s, N*Me*), 6.92 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.28 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.53 (1H, d, *J* 1 Hz, imidazole), 7.70 (1H, s, imidazole), 8.15–8.21 (1H, m, Ar*H*-4), 8.27 (1H, s, Ar*H*-2), 8.68 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 32.91, 106.93, 111.99, 115.43, 118.59, 123.27, 128.74, 134.32, 135.53, 137.87, 138.68; *m*/*z* (ES^+) 199 (100, MH^+); HRMS (ESI): MH^+, found 199.09782. $C_{11}H_{11}N_4$ requires 199.09775.

*4.2.22. 3-(Pyridazin-4-yl)pyrazolo[1,5-a]pyridine (**37**).* Using 4-bromopyridazine; isolated the *title compound* (**37**, 40.5 mg, 33%) as a solid; δ_H (500 MHz, DMSO): 7.12 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.53 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 8.00 (1H, dd, *J* 6, 3 Hz, pyridazine), 8.26 (1H, dt, *J* 9, 1 Hz, Ar*H*-4), 8.80 (1H, s, Ar*H*-2), 8.87 (1H, dt, *J* 7, 1 Hz, Ar*H*-7), 9.15 (1H, dd, *J* 6, 1 Hz, pyridazine), 9.69 (1H, dd, *J* 3, 1 Hz, pyridazine); δ_C (101 MHz, DMSO): 105.20, 113.71, 117.59, 121.01, 126.94, 130.04, 131.24, 137.27, 141.73, 148.73, 151.26; *m*/*z* (ES^+) 197 (100, MH^+); HRMS (ESI): MH^+, found 197.08206. $C_{11}H_9N_4$ requires 197.08217.

*4.2.23. 3-(2-Chloropyrimidin-4-yl)pyrazolo[1,5-a]pyridine (**38**)*[9a]. Using 2,4-dichloropyrimidine; isolated the *title compound* (**38**, 70 mg, 49%) as a solid; δ_H (400 MHz, DMSO): 7.19 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.66 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.97 (1H, d, *J* 5 Hz, pyrimidine), 8.47–8.52 (1H, m, Ar*H*-4), 8.62 (1H, d, *J* 5 Hz, pyrimidine), 8.90 (1H, dd, *J* 7, 1 Hz, Ar*H*-7), 8.94 (1H, s, Ar*H*-2); δ_C (101 MHz, DMSO): 107.59, 114.59, 114.76, 119.26, 128.32, 130.08, 138.37, 143.35, 159.25, 160.23, 162.39; *m*/*z* (ES^+) 231 (100, MH^+); HRMS (ESI): MH^+, found 231.04327. $C_{11}H_8ClN_4$ requires 231.04320.

*4.2.24. 3-(3-Fluorophenyl)pyrazolo[1,5-a]pyridine (**39**).* Using 1-fluoro-3-iodo-benzene; Isolated the *title compound* (**39**, 81 mg, 71%) as a yellow oil; δ_H (400 MHz, DMSO): 6.99 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.05–7.14 (1H, m, Ph), 7.37 (1H, ddd, *J* 9, 7, 1 Hz, Ar*H*-5), 7.44–7.59 (3H, m, Ph), 8.03 (1H, dt, *J* 9, 1 Hz, Ar*H*-4), 8.46 (1H, s, Ar*H*-2), 8.77 (1H, dt, *J* 7, 1 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 110.34 (d, *J* 3 Hz), 112.48 (d, *J* 21 Hz), 112.72, 112.74 (d, *J* 22 Hz), 117.26, 122.20 (d, *J* 2 Hz), 125.26, 129.46, 130.90 (d, *J* 9 Hz), 135.17 (d, *J*=9 Hz), 136.13, 140.71, 162.74 (d, *J* 243 Hz); *m*/*z* (ES^+) 213 (100, MH^+); HRMS (ESI): MH^+, found 213.08228. $C_{13}H_{10}FN_2$ requires 213.08225.

*4.2.25. 3-(1-Methyl-1H-imidazol-2-yl)pyrazolo[1,5-a]pyridine (**40**).* Using 2-bromo-1-methyl-imidazole; isolated the *title compound* (**40**, 6.1 mg, 6%) of a colourless gum; δ_H (500 MHz, DMSO): 3.83 (3H, s, N*Me*), 6.98–7.05 (2H, m, Ar*H*-6 and imidazole), 7.20 (1H, d, *J* 1 Hz, imidazole), 7.33–7.4 (1H, m, Ar*H*-5), 8.21–8.28 (1H, m, Ar*H*-4), 8.44 (1H, s, Ar*H*-2), 8.73–8.78 (1H, dd, *J* 6, 1 Hz, Ar*H*-7); δ_C (176 MHz, DMSO): 33.86, 102.25, 113.19, 118.94, 121.68, 124.83, 127.37, 128.76, 137.88, 139.41, 140.73; *m*/*z* (ES^+) 199 (100, MH^+); HRMS (ESI): MH^+, found 199.09792. $C_{11}H_{11}N_4$ requires 199.09782.

*4.2.26. 3-(3-Methoxyphenyl)pyrazolo[1,5-a]pyridine (**41**).* Using 1-bromo-3-methoxy-benzene; Isolated the *title compound* (**41**, 72.6 mg, 51%) as a gum; δ_H (400 MHz, DMSO): 3.84 (3H, s, *Me*), 6.86 (1H, dd, *J* 8, 2 Hz, Ph), 6.96 (1H, td, *J* 7, 1 Hz, Ar*H*-6), 7.17–7.23 (1H, m, Ph), 7.26 (1H, d, *J* 8 Hz, Ph), 7.29–7.42 (2H, m), 7.97 (1H, d, *J* 9 Hz), 8.37 (1H, s, Ar*H*-2), 8.73 (1H, d, *J* 7 Hz, Ar*H*-7); δ_C (101 MHz, DMSO): 55.07, 111.51, 111.66, 111.84, 112.47, 117.30, 118.74, 124.80, 129.34, 130.05, 134.07, 136.11, 140.44, 159.82; *m*/*z* (ES^+) 225 (100, MH^+); HRMS (ESI): MH^+, found 225.10219. $C_{14}H_{13}N_2O$ requires 225.10224.

*4.2.27. 1H-Pyrazol-3(2H)-one (**44**).* Hydrazine hydrate (3.62 mL, 48.53 mmol) was added dropwise to a cooled (ice bath) solution of methyl propiolate (4.23 mL, 47.58 mmol) in methanol (40 mL). The reaction was allowed to stir for 30 min at room temperature. Brine (10 mL) was added and then the methanol was removed under vacuum. The remaining aqueous layer was extracted with EtOAc (4×75 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to yield the *title compound* (**44**, 3.82 g, 95%) as a cream solid; δ_H (400 MHz, DMSO): 5.44 (1H, d, *J* 2.27 Hz), 7.35 (1H, d, *J* 2.23 Hz), 9.50 (1H, br s, N*H*), 11.45 (1H, br s, N*H*); δ_C (101 MHz, DMSO): 89.25, 129.71, 160.73; *m*/*z* (ES^+) 85.04 (100, MH^+); HRMS (ESI): MH^+, found 85.03951. $C_3H_5N_2O$ requires 85.03964.

*4.2.28. 3-Iodo-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine (**46**).* 1*H*-Pyrazol-3(2*H*)-one (**44**, 5.11 g, 60.78 mmol) and potassium carbonate (29.4 g, 212.7 mmol) were heated to 130 °C in DMF (275 mL). 1,3-Dibromopropane (7.40 mL, 72.93 mmol) was added and the mixture was heated for 2 h and then concentrated. The residue was partitioned between DCM (200 mL) and water (100 mL) and the layers were separated. The aqueous layer was extracted with DCM (3×100 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude 6,7-*dihydro*-5*H*-*pyrazolo*[5,1-*b*][1,3]*oxazine* (**45**, 6.0 g) as a brown oil, which was used without further purification.

N-Iodosuccinimide (3.79 g, 16.84 mmol) was added portionwise to a solution of crude 6,7-dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine

(45, 1.9 g, 15.31 mmol) in acetonitrile (19 mL) at toom temperature and the reaction was stirred for 30 min. The reaction mixture was slowly poured into vigorously stirred water. Sodium thiosulphate solution was added and then the mixture was extracted with EtOAc (2×100 mL). The combined organic extracts were washed with water, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (0–2% MeOH/DCM) to give the title compound (46, 1.10 g, 29% for two steps) as a yellow waxy solid; δ_H (400 MHz, DMSO): 2.14–2.20 (2H, m), 4.09 (2H, t, *J* 6 Hz), 4.32–4.35 (2H, m), 7.29 (1H, s); δ_C (101 MHz, DMSO): 21.50, 36.03, 44.24, 66.38, 141.19, 150.88; *m*/*z* (ES^+) 251.03 (100, MH^+); HRMS (EI): M^+, found 249.9618. $C_6H_7N_2OI$ requires 249.960.

*4.2.29. 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine (**43**).* Isopropylmagnesium lithium chloride (3.08 mL, 4.00 mmol) was added dropwise to a stirred solution of 3-iodo-6,7-dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine (**46**, 1.0 g, 4.00 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 mL, 6.00 mmol) in THF (10 mL) at 5 °C, over a period of 10 min, under nitrogen. The resulting solution was stirred at 5 °C for 2 h and then concentrated in vacuo. The crude product was purified by flash silica chromatography (0–5% MeOH/DCM) to afford a pale yellow oil. Crystallisation from heptane yielded the *title compound* (**43**, 0.455 g, 45.5%) as a white solid; δ_H (400 MHz, DMSO): 1.22 (12H, s, 2×Me_2CO), 2.11–2.18 (2H, m, CH_2), 4.05 (2H, t, *J* 6.2 Hz, CH_2), 4.29–4.32 (2H, m, CH_2), 7.32 (1H, s, Ar); δ_C (101 MHz, DMSO): 21.11, 24.57 (4 CH_3), 43.60, 65.64, 82.32 (2C), 143.54, 156.26, C–B not seen; *m*/*z* (ES^+) 251.47(100, MH^+); HRMS (ESI): MH^+, found 251.15598. $C_{12}H_{20}BN_2O_3$ requires 251.15615.

*4.2.30. 3-(2,5-Dichloropyrimidin-4-yl)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine (**47**).* Bis(di-*tert*-butyl(4-dimethylaminophenyl) phosphine)dichloropalladium(II) (Pd(Amphos)Cl_2) (16.99 mg, 0.02 mmol) was added to a degassed mixture of 2,4,5-trichloropyrimidine (0.055 mL, 0.48 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6,7-dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine (43, 100 mg, 0.40 mmol) and 2 M sodium carbonate (0.440 mL, 0.88 mmol) in DME (2 mL) under nitrogen. The resulting mixture was stirred at 85 °C for 2 h and then allowed to cool to ambient temperature. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash silica chromatography (0–3% MeOH/DCM) to afford the title compound (47, 54 mg, 50%) as a white solid; δ_H (400 MHz, DMSO): δ 2.22–2.29 (2H, m, CH_2), 4.17 (2H, t, *J* 6.2 Hz, CH_2), 4.45–4.49 (2H, m, CH_2), 8.11 (1H, s, Ar), 8.72 (1H, s, Ar); δ_C (101 MHz, DMSO): 20.66, 44.06, 66.52, 97.85, 124.46, 138.83, 151.52, 157.27, 158.04, 159.22; *m*/*z* (ES^+) 271 (100, MH^+); HRMS (ESI): MH^+, found 271.01462. $C_{10}H_9Cl_2N_4O$ requires 271.01479.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.094. These data include MOL files and InChiKeys of the most important compounds described in this article.

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