Concise routes to pyrazolo[1,5-*a*]pyridin-3-yl pyridazin-3-ones†‡

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Cycloaddition of pyridine *N*-imine with 6-alkyl-4-oxohex-5-ynoates followed by condensation with hydrazine provides concise access to pharmacologically active 6-(pyrazolo[1,5-*a*]pyridin-3-yl)pyridazinones. For the first time alkynyl heterocycles are also shown to be effective dipolarophiles for pyridine *N*-imine, and analogous compounds can be accessed directly in modest yields through the reaction of 6-(alkyn-1-yl)pyridazin-3-one derivatives.

Introduction

The pyrazolo[1,5-*a*]pyridine subunit appears in compounds displaying a considerable range of biological activities—in histamine H_3 receptor antagonists,[1] dopamine receptor ligands,[2] inhibitors of cyclooxygenase-2,[3] serotonin 5-HT_3 receptor antagonists,[4] P-glycoprotein inhibitors,[5] p38 kinase inhibitors,[6] phosphodiesterase (PDE) inhibitors,[7] and in compounds[8] with antiherpetic activity. In many of these compounds, the pyrazolopyridine unit is substituted at the 3-position. Pyrazolopyridines functionalized at this position with a pyridazin-3-one or 4,5-dihydropyridazin-3-one ring in particular have attracted recent interest because of their adenosine receptor antagonist activity, *e.g.* FK838,[9,10] and PDE inhibitory activity, *e.g.* KCA-1312,[11] Fig. 1.

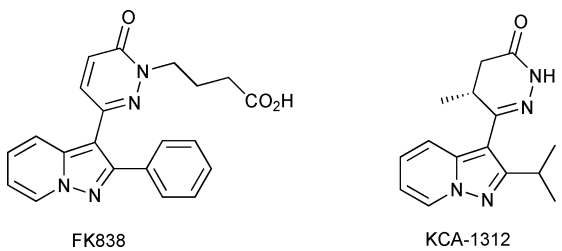
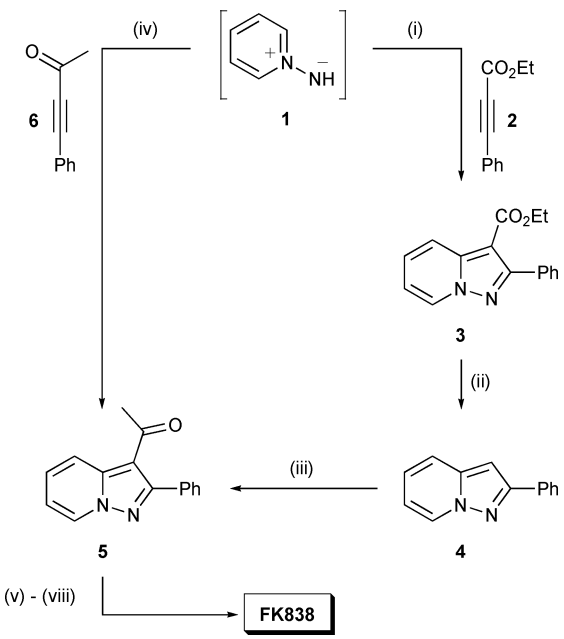


Fig. 1 Pharmacologically active 6-(pyrazolo[1,5-*a*]pyridin-3-yl)pyridazin-3-ones, FK838 and KCA-1312.

Synthesis of the pyrazolopyridine nucleus is routinely achieved *via* a 1,3-dipolar cycloaddition strategy that is well suited for the subsequent development of a 3-substituent. This is illustrated for FK838, Scheme 1, where cycloaddition of alkynoate **2** with pyridine *N*-imine (**1**), generated *in situ* by treatment of *N*-aminopyridinium iodide with base, afforded pyrazolopyridine **3** regioselectively.[10] In this case, decarboxylation of the 3-position followed by acetylation yielded acetylpyrazolopyridine **5**. A more concise route to **5** was developed on a pilot scale through cycloaddition of **1** with alkynone **6**, directly introducing the 3-acetyl substituent. The *N*-substituted pyridazinone of FK838 was subsequently built up from the methylketone over a number of steps.



Scheme 1 Representative synthesis of FK838.[10] *Reagents and conditions:* (i) *N*-aminopyridinium iodide, KOH, DMF, 32%; (ii) 47% aq. HBr, Δ, 95%; (iii) conc. H_2SO_4, Ac_2O, 41%; (iv) *N*-aminopyridinium iodide, KOH–CH_2Cl_2, H_2O, 93%; (v) $OHCCO_2H{\cdot}2H_2O$, AcOH, DMF, EtOAc, 65%; (vi) $N_2H_4{\cdot}H_2O$, Me_2NAc, 105–110 °C, 95%; (vii) $Br(CH_2)_3$-CO_2Et–$(PhCH_2NEt_3)Cl$, K_2CO_3, DMF, MeOH 55 °C; (viii) NaOH–H_2O, 89% over 2 steps.

As part of a programme to develop the PDE inhibitory activity of KCA-1312 and analogues, we required a concise route to 6-(pyrazolo[1,5-*a*]pyridin-3-yl)pyridazin-3-ones that would allow

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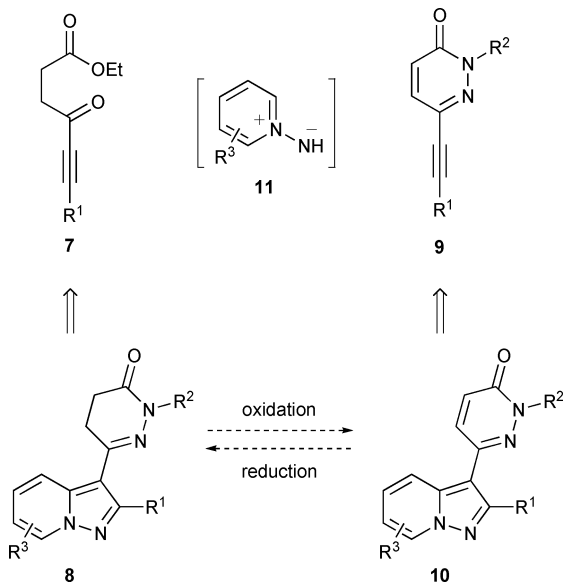
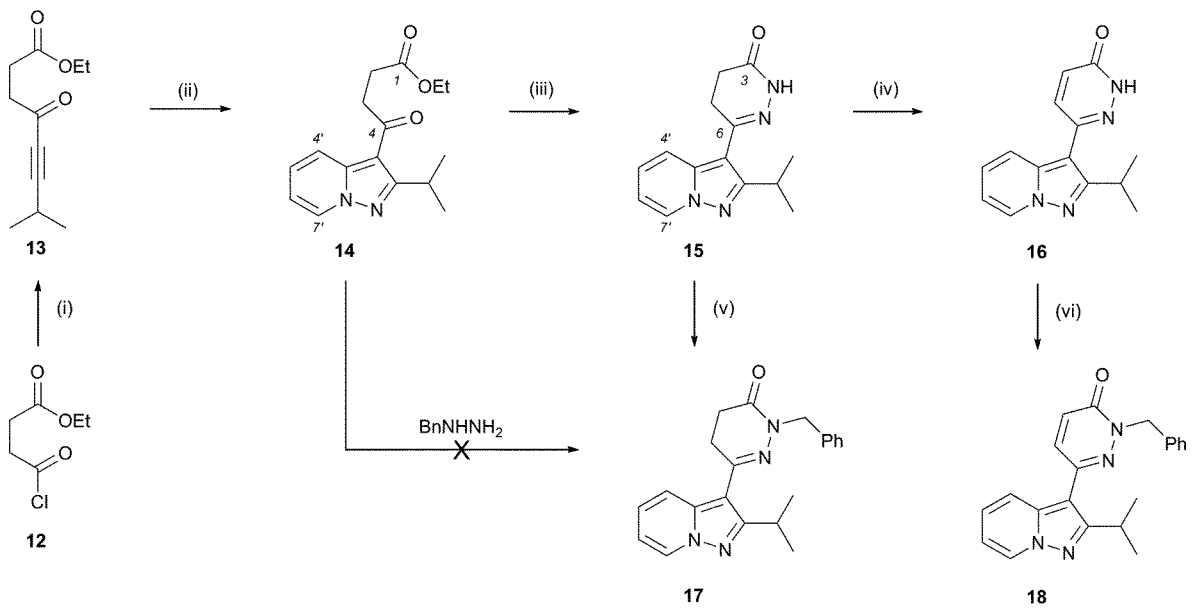


Scheme 2 Overall synthetic strategy.

series expansion for structure–activity relationship studies. While the pyridine *N*-imine cycloaddition is one of the most widely employed routes to pyrazolo[1,5-*a*]pyridines, it has been largely confined to reactions with simple alkynoates or alkynones such as **2** and **6** as the dipolarophiles.[12] We sought to apply the reaction with more advanced alkyne dipolarophiles that would minimize the number of steps required for introduction of the pyridazinone ring following pyrazolopyridine construction. It was envisaged that the cycloaddition of dipolarophiles of type **7** (Scheme 2), containing γ-keto ester functionality, would be straightforward. Subsequent condensation of the immediate cycloaddition product with hydrazine would then complete the formation of the dihydropyridazinone ring in just one additional step to form **8** (R^2 = H). We also considered that use of an alkynyl pyridazinone dipolarophile (**9**) might enable direct access to target compounds of type **10** in a single step. These routes might thus provide complementary access to both pyridazinone and dihydropyridazinone analogues whilst facilitating convenient multiple parallel synthesis of a wide range of pyridine ring-substituted variants through combination of the dipolarophile with a set of substituted pyridine *N*-imines (**11**). Reactions of alkynyl heterocycles as dipolarophiles in cycloadditions with pyridine *N*-imines have not, however, previously been reported in the literature. In this paper we present the first examples of such reactions and the utility of alkynes of types **7** and **9** for the synthesis of pharmacologically active 6-(pyrazolo[1,5-*a*]pyridin-3-yl)pyridazin-3-ones.

Results and discussion

Beginning with the alkynyl γ-keto ester approach, ethyl 7-methyl-4-oxooct-5-ynoate (**13**), Scheme 3, was prepared in a single step by reaction of ethyl succinyl chloride (**12**) with (3-methylbut-1-ynyl)magnesium bromide. Alkyne **13** underwent cycloaddition with pyridine *N*-imine satisfactorily when treated with a mixture of *N*-aminopyridinium mesitylenesulfonate[13] and K_2CO_3 in DMF at room temperature, affording pyrazolopyridine **14** in 56% yield. Subsequent condensation with hydrazine generated dihydropyridazinone **15** (92% yield), completing a concise 3-step sequence. Further derivatisation of the top ring was achieved by oxidation to the corresponding pyridazinone (**16**) and by alkylation to introduce a substituent at the N(2)-position (**17** and **18**). Attempts to access N(2)-substituted dihydropyridazinones by direct condensation of keto ester **14** with monosubstituted hydrazines (*e.g.* benzyl hydrazine) were unsuccessful however. The vinylogous amide character of the ketone renders it less susceptible to nucleophilic attack than the ester, and thus the



Scheme 3 *Reagents and conditions:* (i) (3-methylbut-1-ynyl)magnesium bromide, THF–Et_2O, 0 °C, 48%; (ii) *N*-aminopyridinium mesitylenesulfonate, K_2CO_3, DMF, 0 °C–rt, 56%; (iii) N_2H_4, AcOH (aq.), EtOH, Δ, 92%; (iv) Br_2 in AcOH, Δ, 73%; (v) NaH, BnBr, DMF, rt, 70%; (vi) Cs_2CO_3, BnBr, DMF, rt, 78%.

unsubstituted terminus of the hydrazine reacts preferentially with the ester to form a hydrazide.‖ The route shown in Scheme 3 was amenable to multiple parallel synthesis of an extensive range of pyridine ring-substituted analogues through combination of the dipolarophile with a set of substituted pyridine *N*-imines (**11**) derived *in situ* from their parent *N*-aminopyridinium salts.†† The requisite salts are readily prepared in a single step by reaction of *O*-mesitylenesulfonylhydroxylamine with the appropriate pyridine.[12]

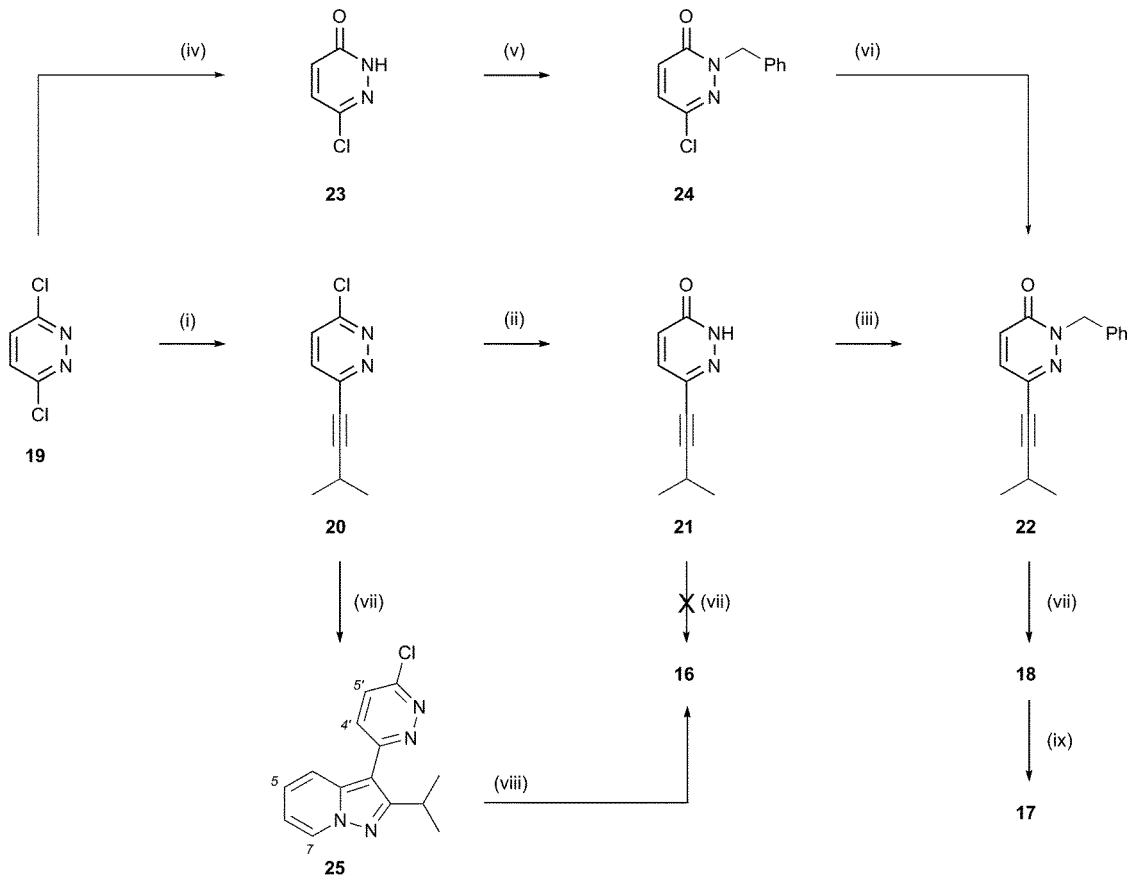
Attention was next focused upon alkynyl pyridazinone **21** as a dipolarophile, Scheme 4. This compound was prepared by Sonogashira coupling of 3-methyl-1-butyne with excess 3,6-dichloropyridazine (**19**) followed by treatment of the coupled product (**20**) with hot acetic acid and aqueous acetate. Attempts to achieve the cycloaddition of **21** with pyridine *N*-imine under the conditions employed for alkynone **13** (at room temperature in DMF) returned the dipolarophile unreacted. Under forcing conditions (at 120 °C) an intractable mixture of polar components was formed, and it was not possible to achieve the synthesis of pyrazolopyridine **16** by this route. However, the *N*-benzyl derivative (**22**) of alkynyl pyridazinone **21** proved more promising.

‖ D. R. Adams, R. W. Allcock, P. D. Bailey, I. D. Collier, Z. Jiang and K. M. Morgan, unpublished results.

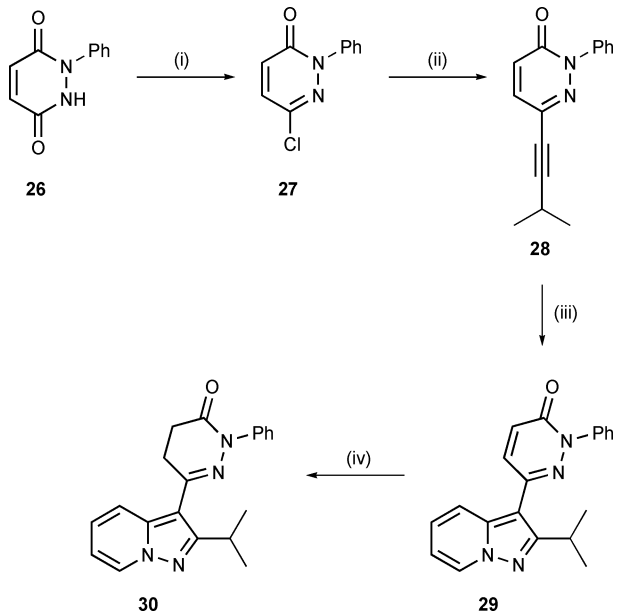
†† Detailed PDE inhibitory activities for our 6-(pyrazolo[1,5-*a*]pyridin-3-yl)pyridazin-3-one series will be presented elsewhere.

Compound **22** was prepared either by alkylation of **21** with benzyl bromide or by rearranging the synthetic sequence: beginning with hydrolysis of 3,6-dichloropyridazine (**19**) to 6-chloropyridazin-3(2*H*)-one (**23**),[14] followed by *N*-benzylation to **24**[15] and finally Sonogashira coupling with 3-methyl-1-butyne. Alkyne **22** was also unreactive with pyridine *N*-imine at room temperature. However, at elevated temperature (120 °C), treatment of **22** with *N*-aminopyridinium mesitylenesulfonate (2 equivalents) and K_2CO_3 in DMF over 48 h afforded pyrazolopyridine **18** in 26% yield. Alkynyl pyridazine **20** was also found to react under these conditions and afforded pyrazolopyridine **25** in 20% yield. Treatment of **25** with hot acetic acid and aqueous acetate afforded the pyridazinone (**16**), which had not been directly accessible from **21**. The use of a dipolarophile such as **22** necessarily gives rise to the pyridazinone product. Access to the dihydropyridazinone therefore requires reduction, which can be achieved by treatment with zinc in acetic acid, as illustrated for the conversion of **18** into **17**.

Similar chemistry with the *N*-phenyl analogue (**28**) of alkynyl pyridazine **22** afforded a concise route to pyrazolopyridines **29** and **30**, Scheme 5. In this case the acetylenic dipolarophile was prepared from pyridazinedione **26**.[16] Thus, chlorination of **26** with $POCl_3$ afforded chloropyridazinone **27**[17] and subsequent Sonogashira coupling with 3-methyl-1-butyne afforded alkyne **28** in 76% yield for the two steps. The cycloaddition reaction was



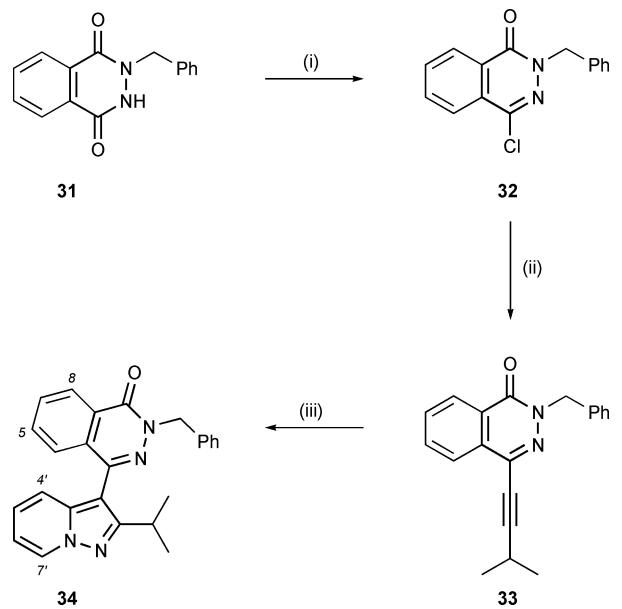
Scheme 4 *Reagents and conditions:* (i) 3-methyl-1-butyne (0.5 equiv.), $(i\text{-}Pr)_2NH$, Bu_4NI, CuI, $Pd(PPh_3)_4$, THF, 90 °C (sealed vessel), 53%; (ii) AcOH, NaOAc (aq.), reflux, 87%; (iii) K_2CO_3, BnBr, DMF, rt, 82%; (iv) AcOH, Δ, 95%; (v) Cs_2CO_3, BnBr, DMF, rt, 78%; (vi) 3-methyl-1-butyne, $(i\text{-}Pr)_2NH$, Bu_4NI, CuI, $Pd(PPh_3)_4$, THF, 80 °C (sealed vessel), 83%; (vii) *N*-aminopyridinium mesitylenesulfonate (2–3 equiv.), K_2CO_3, DMF, 120 °C; **25**, 20%; **16**, intractable mixture formed; **18**, 26%; (viii) AcOH, NaOAc (aq), Δ, 80%; (ix) Zn, AcOH, Δ, 56%.



Scheme 5 *Reagents and conditions:* (i) $POCl_3$, Δ, 77%; (ii) 3-methyl-1-butyne, $(i\text{-}Pr)_2NH$, Bu_4NI, CuI, $Pd(PPh_3)_4$, THF, 80 °C (sealed vessel), 99%; (iii) *N*-aminopyridinium mesitylenesulfonate (2 equiv.), K_2CO_3, DMF, 120 °C, 50%; (iv) Zn, AcOH, Δ, 84%.

conducted, as before, with *N*-aminopyridinium mesitylenesulfonate and K_2CO_3 in hot DMF, affording pyrazolopyridine **29** in 50% yield. Reduction of the latter with zinc in acetic acid efficiently gave the corresponding dihydropyridazinone (**30**; 84% yield).

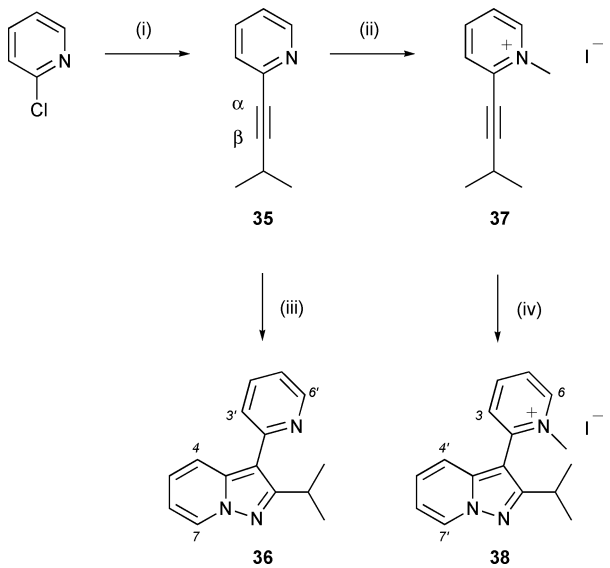
Alkynyl phthalazinone **33** was also found to be effective as a dipolarophile for pyridine *N*-imine, Scheme 6. This compound was prepared in two steps from phthalazinedione **31**[18] by chlorination with $POCl_3$ followed by Sonogashira coupling of the intermediate chloride (**32**) with 3-methyl-1-butyne. The yield (17%) for the



Scheme 6 *Reagents and conditions:* (i) $POCl_3$, Δ, 17%; (ii) 3-methyl-1-butyne, $(i\text{-}Pr)_2NH$, Bu_4NI, CuI, $Pd(PPh_3)_4$, THF, 80 °C (sealed vessel), 91%; (iii) *N*-aminopyridinium mesitylenesulfonate (2 equiv.), K_2CO_3, DMF, 100 °C, 40%.

first of these steps was compromised by some competing *N*-debenzylation under the reaction conditions with $POCl_3$. As with the preparation of alkynyl pyridazinones **22** and **28**, however, the Sonogashira coupling to **33** was efficient (91%), provided that a sealed reaction vessel was used to prevent loss of the volatile 3-methyl-1-butyne reactant. The cycloaddition step afforded pyrazolopyridine **34** in 40% yield when conducted under similar conditions to the preceding examples in hot DMF.

To test further the scope of the cycloaddition reaction of pyridine *N*-imine with alkynyl heterocycles, attention was turned to alkynyl pyridine **35**, prepared in 41% yield by Sonogashira coupling of 2-chloropyridine with 3-methyl-1-butyne (Scheme 7). Reaction of alkyne **35** with *N*-aminopyridinium mesitylenesulfonate (2 equiv.) and K_2CO_3 in DMF at 95 °C over 18 h afforded the target pyrazolopyridine (**36**) in just 3% yield together with 38% recovery of unreacted alkyne. At reduced temperature (80 °C) over 40 h the yield of pyrazolopyridine **36** rose to 10% with 53% recovery of unreacted alkyne, suggesting that the reaction outcome is compromised by competing degradation pathways at higher temperature.‡‡



Scheme 7 *Reagents and conditions:* (i) 3-methyl-1-butyne, $(i\text{-}Pr)_2NH$, CuI, $Pd(PPh_3)_4$, THF, 70 °C (sealed vessel), 41%; (ii) MeI, THF, 60 °C, 72%; (iii) *N*-aminopyridinium mesitylenesulfonate (2 equiv.), K_2CO_3 (4 equiv.), DMF, 80 °C, 10%; (iv) *N*-aminopyridinium mesitylenesulfonate (2 equiv.), K_2CO_3 (4 equiv.), DMF, 95 °C, 18 h, 39%.

As with the reactions of the alkynyl pyridazine and pyridazinone derivatives, the cycloaddition of alkynyl pyridine **35** proceeded with regiocontrol favouring exclusive formation of a product (**36**) in which the heterocycle from the dipolarophile is connected to the 3-position of the pyrazolopyridine. The alternative regioisomer

‡‡ Some unreacted dipolarophile was also recovered from the reactions of the two *N*-benzyl diazinones (**22** and **33**), though not from the reactions of the *N*-phenyl pyridazinone (**28**) or the chloropyridazine (**20**). Alkyne recovery was respectively 43% and 39% from the reactions of **22** and **33**, which were conducted with two equivalents of the *N*-aminopyridinium mesitylenesulfonate. Attempts to improve the yield of isolated product in these reactions with prolonged reaction times were ineffective. Use of larger excesses of *N*-aminopyridinium salt in the reaction complicated product isolation by generating quantities of tarry residue.

was not detected. The regiochemical outcome of this reaction was determined from the NOESY spectrum of **36** and confirmed by the acquisition of an X-ray crystal structure, Fig. 2. The regiochemical outcome for the cycloaddition of alkynyl pyridazinone **22** was similarly confirmed by acquisition of NOESY spectra and X-ray crystal structures for the product (**18**) and its reduced analogue (**17**). These structures also served to substantiate the regiochemistry assigned to the reaction of alkynone **13** with pyridine *N*-imine, Scheme 3.

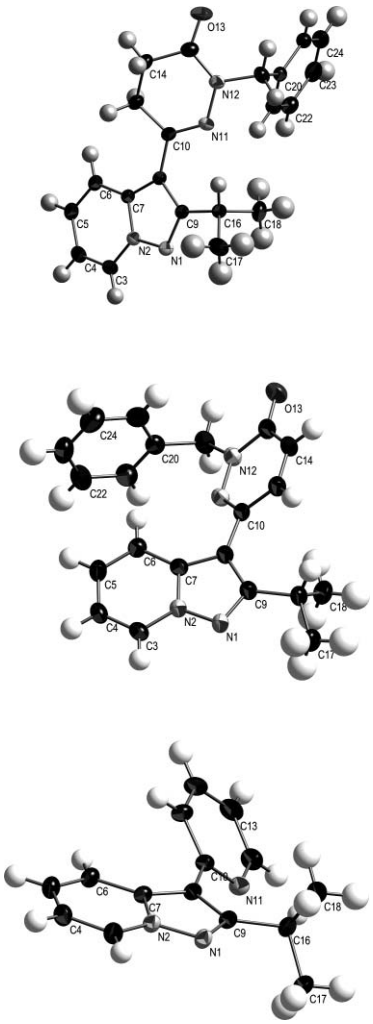


Fig. 2 X-Ray crystal structures of compounds **17** (top), **18** (middle) and **36** (bottom).

Cycloaddition reactions of alkynoate and alkynone dipolarophiles with pyridine *N*-imines are typically conducted within a temperature range of 0–25 °C. In contrast, cycloaddition of the alkynyl heterocycles presented here requires significantly elevated temperatures in order to proceed. This requirement was thought likely to reflect reduced dipolarophilic reactivity due to the comparatively modest electron demand exerted on the alkyne by the heterocycle. Increased electron demand in the heterocycle might therefore be expected to enhance the reactivity of the dipolarophile. In order to verify this expectation at a qualitative level, alkynyl pyridine **35** was quaternised with methyl iodide and the resulting alkynyl pyridinium salt (**37**) tested in the reaction with pyridine *N*-imine. When conducted under identical conditions to the reaction of alkynyl pyridine **35**, with *N*-aminopyridinium mesitylenesulfonate (2 equiv.) and K_2CO_3 in DMF at 95 °C over 18 h, a greatly improved 39% yield of the pyrazolopyridine product (**38**) was obtained from the cycloaddition step. However, the yields of the cycloaddition reactions of **35** and **37** were not improved with extended reaction times. Indeed, in the case of alkynyl pyridinium salt **37** the reaction time could be reduced substantially without significant reduction in the yield of pyrazolopyridine product. Thus, the yield of **38** was 37% when the reaction was conducted at 95 °C over the reduced duration of 2 h.

Examination of the ^{13}C chemical shifts for the alkyne carbons of compounds **35** and **37** suggests that quaternisation of the pyridine nitrogen exerts a substantial polarizing effect upon the alkyne, which may contribute to the improved reactivity of **37**. The alkyne α and β carbons of compound **35** give resonances at δ_C 80 and 96 respectively, whereas the corresponding carbons in alkynyl pyridinium salt **37** give signals at δ_C 71 and 117. The enhanced polarisation of alkyne **37** is also reflected in partial charge calculations, which give values of −0.130 and −0.109 for the α and β carbons respectively in alkyne **35** and values of −0.289 and −0.079 for the corresponding carbons in alkyne **37**.§§

Conclusions

In summary, concise routes to pharmacologically active 6-(pyrazolo[1,5-*a*]pyridin-3-yl)pyridazin-3-ones have been developed using alkynyl γ-keto ester and alkynyl pyridazinone dipolarophiles for cycloaddition with pyridine *N*-imines. Use of the alkynyl γ-keto ester in the cycloaddition furnishes the dihydropyridazinone following an additional hydrazine condensation step; the alkynyl pyridazinone affords the pyrazolopyridine-pyridazinone directly. Application of standard reduction and oxidation procedures permits pyridazinone–dihydropyridazinone ring interconversion. Previously reported reactions of pyridine *N*-imines have been confined to simple alkynone or alkynoate dipolarophiles. We show here for the first time that reactions with alkynyl heterocycles are feasible, albeit requiring elevated temperature. Although yields for the cycloaddition step are modest, the alkynyl heterocycles are readily prepared through robust Sonogashira coupling procedures and allow for very concise routes to pyrazolopyridines substituted at C-3 with a heterocycle.

Experimental

General details

Commercially available reagents from Aldrich, Avocado and Lancaster chemical companies were generally used as supplied without further purification. Tetrahydrofuran, diethyl ether and toluene were dried by distillation from sodium-benzophenone ketyl under argon. 'Light petroleum' refers to the fraction boiling between 40 °C and 60 °C. Anhydrous *N*,*N*-dimethylformamide was purchased from Aldrich and used as supplied from Sure/Seal™ bottles. With the exception of the pyridine *N*-imine cycloadditions, which were carried out in air to facilitate oxidation of the

§§ Partial charges calculated using standard semi-empirical AM1 methods within CAChe software.

immediate dihydropyrazolopyridine cycloadduct, reactions were routinely carried out under an inert atmosphere of argon or nitrogen. Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF_{254} (Art. 05554). Developed plates were visualized under ultraviolet light (254 nm) and/or alkaline potassium permanganate dip. Flash chromatography was performed using DAVISIL® silica (60 Å; 35–70 μm) from Fisher (cat. S/0693/60). Fully characterized compounds were chromatographically homogeneous.

Melting points were determined using a Stuart Scientific SMP10 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FT IR spectrometer. Spectra were recorded as potassium bromide discs, as solutions in $CHCl_3$, or as films between sodium chloride plates. Mass spectra were obtained on Kratos Concept IS EI (electron impact) and Fisons VG Quattro (electrospray) spectrometers. ^{1}H NMR spectra were recorded at 200 and 400 MHz on Bruker AC200 and DPX400 spectrometers; ^{13}C NMR spectra were recorded at 50 and 101 MHz on the same instruments. Chemical shifts are recorded in parts per million (δ in ppm) and are referenced against solvent signals (δ_C 77.16 for chloroform and δ_C 39.52 for methyl sulfoxide) for ^{13}C spectra and solvent residual resonances (δ_H 7.26 for chloroform and δ_H 2.50 methyl sulfoxide) for ^{1}H spectra.[19] Chemical shift values are accurate to ±0.01 ppm and ±0.1 ppm respectively. *J* values are given in Hz. Multiplicity designations used are: s, d, t, q, sept and m for singlet, doublet, triplet, quartet, septet and multiplet respectively. In ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups are assigned from DEPT. Elemental analyses were carried out by the analytical service of the Chemistry Department at Heriot-Watt University using an Exeter CE-440 Elemental Analyser.

Ethyl 7-Methyl-4-oxooct-5-ynoate (13)

(Part 1) 3-Methyl-1-butyne (11.2 g, 164 mmol) was dissolved in anhydrous THF (300 mL) and cooled to −15 °C (salt–ice bath) under argon. EtMgBr (3 M solution in Et_2O; 55 mL, 165 mmol) was added slowly over 40 min to give a golden brown homogenous solution. The mixture was allowed to attain 15 °C and was stirred at that temperature for 18 h. (Note: the alkynyl magnesium bromide may precipitate!). Further alkyne (*ca.* 2 mL, 20 mmol) was added; the mixture was heated at 45 °C for 1 h and then cooled to rt.

(Part 2) The alkynyl magnesium bromide solution from part 1 was cannulated over a period of 3 h into an ice-cooled solution of ethyl succinyl chloride (71.0 mL, 498 mmol) in anhydrous Et_2O (600 mL). The resulting pale yellow heterogenous mixture was quenched by addition of saturated NH_4Cl solution (20 mL), concentrated to 200 mL *in vacuo* and diluted with saturated $NaHCO_3$ solution (200 mL). The mixture was stirred for 1 h. The organic layer was then separated from the basic aqueous phase, washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the product as a red-brown oil. The crude product was subjected to flash column chromatography, eluting with light petroleum–EtOAc (10 : 1). Fractions containing the target material were combined, concentrated *in vacuo* and then distilled under reduced pressure through a 15 cm fractionating column (84–120 °C, 3 mmHg) to afford a yellow oil (26.3 g). This oil was then dissolved in THF (10 mL) and stirred with saturated $NaHCO_3$ solution (300 mL) for 1 h. The mixture was extracted with CH_2Cl_2 (100 mL); the separated organic phase was washed with brine, (50 mL), dried ($MgSO_4$) and evaporated to give to give the *title compound* (15.6 g; 48%) as a pale red oil in >90% purity: δ_H (200 MHz; $CDCl_3$) 1.20 (6 H, d, *J* 6.9, $CH(CH_3)_2$), 1.22 (3 H, t, *J* 7.1, OCH_2CH_3), 2.55–2.63 (2 H, m, CH_2-2), 2.69 (1 H, sept, *J* 6.9, $CH(CH_3)_2$), 2.79–2.88 (2 H, m, CH_2-3), 4.11 (2 H, q, *J* 7.1, OCH_2CH_3); δ_C (50 MHz; $CDCl_3$) 14.2 (OCH_2CH_3), 20.8 ($CH(CH_3)_2$), 21.9 ($CH(CH_3)_2$), 28.2 (CH_2-2), 40.1 (CH_2-3), 60.9 (OCH_2CH_3), 79.6 (C-5), 99.7 (C-6), 172.2 (C-1), 185.9 (C-4); *m*/*z* (EI) 196 (3%, M^+), 167 (6%, $M^+ - Et$), 151 (26%, $M^+ - OEt$), 129 (39%, $M^+ - C{\equiv}CCH(CH_3)_2$), 43 (100%, $C_3H_7^+$); (found: M^+, 196.1099. $C_{11}H_{16}O_3$ requires 196.1099).

Ethyl 4-(2-isopropylpyrazolo[1,5-*a*]pyridin-3-yl)-4-oxobutanoate (14)

Powdered K_2CO_3 (5.64 g, 40.8 mmol) was added to an ice-cooled solution of 1-aminopyridinium mesitylenesulfonate (6.00 g, 20.4 mmol) in DMF (150 mL) to afford a deep purple heterogenous mixture. After 15 min **13** (4.60 g, 23.4 mmol) was added and the mixture stirred for 1 h. The mixture was allowed to attain rt over 18 h and was then partitioned between brine (150 mL) and EtOAc (70 mL). The aqueous phase was further extracted with EtOAc (2 × 70 mL), and the combined organic extracts dried ($MgSO_4$) and evaporated. The residual oil was subjected to flash column chromatography (5 : 2 light petroleum–EtOAc) to afford the *title compound* (3.29 g; 56%) as a colourless powder: mp 72–73 °C (from EtOAc–light petroleum); ν_{max}(KBr)/cm^{-1} 2975, 2935, 1738, 1640, 1618, 1503, 1462, 1441, 1418, 1382, 1368, 1286, 1217, 1178, 1155, 1089, 1018, 998, 804, 763; δ_H (400 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1, OCH_2CH_3), 1.38 (6 H, d, *J* 6.9, $CH(CH_3)_2$), 2.77 (2 H, t, *J* 6.6, CH_2-2), 3.23 (2 H, t, *J* 6.6, CH_2-3), 3.78 (1 H, sept, *J* 6.9, $CH(CH_3)_2$), 4.15 (2 H, q, *J* 7.1, OCH_2CH_3), 6.88 (1 H, dt, $J_{6',4'}$ 1.3, $J_{6',5'}$ 6.9, $J_{6',7'}$ 6.9, H-6′), 7.37 (1 H, ddd, $J_{5',7'}$ 1.2, $J_{5',6'}$ 6.9, $J_{5',4'}$ 9.0, H-5′), 8.09 (1 H, dt, $J_{4',5'}$ 9.0, $J_{4',6'}$ 1.1, $J_{4',7'}$ 1.1, H-4′), 8.45 (1 H, dt, $J_{7',6'}$ 6.9, $J_{7',5'}$ 1.1, $J_{7',4'}$ 1.1, H-7′); δ_C (101 MHz; $CDCl_3$) 14.3 (OCH_2CH_3), 22.3 ($CH(CH_3)_2$), 27.9 ($CH(CH_3)_2$), 28.3 (CH_2-2), 37.0 (CH_2-3), 60.7 (OCH_2CH_3), 109.6 (C-3′), 113.4 (CH-6′), 119.2 (CH-4′), 127.9 (CH-5′), 129.3 (CH-7′), 141.8 (C-3a′), 164.1 (C-2′), 173.3 (C-1), 192.0 (C-4); *m*/*z* (EI) 288 (61%, M^+), 243 (52%, $M^+ - OEt$), 215 (55%, $M^+ - CO_2Et$), 187 (93%, $M^+ - CH_2CH_2CO_2Et$); (found: M^+, 288.1474. $C_{16}H_{20}N_2O_3$ requires 288.1474); (found C, 66.71; H, 7.03; N, 9.74. $C_{16}H_{20}N_2O_3$ requires: C, 66.65; H, 6.99; N, 9.72%).¶¶

6-(2-Isopropylpyrazolo[1,5-*a*]pyridin-3-yl)-4,5-dihydropyridazin-3(2*H*)-one (15)

Keto ester **14** (2.80 g, 9.71 mmol) was boiled for 18 h in a mixture of aqueous hydrazine buffered to pH 5 with AcOH (1.84 M in H_2NNH_2; 53 mL, 97.5 mmol) and EtOH (30 mL). The mixture

¶¶ NMR assignments for compounds **14**, **16**, **18**, **25**, **29** and **36** were supported by the acquisition of NOESY, HSQC and HMBC spectra; assignments for compounds **20** and **21** were supported by the acquisition of HSQC and HMBC spectra; assignments for salt **38** were supported by the acquisition of COSY, NOESY, HSQC and HMBC spectra; ^{13}C NMR assignments for compound **22** were supported by the acquisition of an HSQC spectrum. ^{1}H NMR spectra of salts **37** and **38** are shown in the accompanying ESI file.†

was then concentrated *in vacuo* to afford an aqueous slurry that was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$) and evaporated to give the crude product (2.45 g) as a buff powder. Trituration of the latter with hot Et_2O (50 mL) afforded the *title compound* (2.30 g; 92%) as a colourless powder: mp 211–212 °C (from EtOAc–light petroleum); ν_{max}(KBr)/cm^{-1} 3212, 3076, 2958, 1661, 1632, 1537, 1519, 1373, 1325, 1258, 1223, 951, 757, 736; δ_H (200 MHz; $CDCl_3$) 1.40 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 2.58–2.67 (2 H, m, CH_2-4), 3.00–3.09 (2 H, m, CH_2-5), 3.45 (1 H, sept, *J* 6.9, CH(CH$_3$)$_2$), 6.79 (1 H, dt, $J_{6',4'}$ 1.4, $J_{6',5'}$ 6.9, $J_{6',7'}$ 6.9, H-6′), 7.21 (1 H, ddd, $J_{5',7'}$ 1.2, $J_{5',6'}$ 6.9, $J_{5',4'}$ 8.9, H-5′), 7.78 (1 H, dt, $J_{4',5'}$ 8.9, $J_{4',6'}$ 1.1, $J_{4',7'}$ 1.1, H-4′), 8.43 (1 H, dt, $J_{7',6'}$ 6.9, $J_{7',5'}$ 1.1, $J_{7',4'}$ 1.1, H-7′), 8.58 (1 H, br s, NH); δ_C (50 MHz; 20% CD_3OD/$CDCl_3$) 22.2 (CH(*C*H$_3$)$_2$), 25.2 (CH_2), 26.0 (CH_2), 26.9 (*C*H(CH$_3$)$_2$), 105.0 (C-3′), 112.3 (CH-6′), 117.8 (CH-4′), 125.3 (CH-5′), 128.1 (CH-7′), 138.8 (C-3a′), 148.2 (C-6), 159.6 (C-2′), 167.9 (C-3); *m*/*z* (EI) 256 (34%, M$^+$), 198 (20%), 170 (13%), 184 (70%); (found: M$^+$, 256.1322. $C_{14}H_{16}N_4O$ requires 256.1324); (found C, 65.51; H, 6.25; N, 21.72. $C_{14}H_{16}N_4O$ requires: C, 65.61; H, 6.29; N, 21.86%).

6-(2-Isopropylpyrazolo[1,5-*a*]pyridin-3-yl)pyridazin-3(2*H*)-one (16)

Method 1. Bromine in AcOH (1 M; 22.0 mL, 22.0 mmol) was added dropwise over a period of 25 min to a solution of **15** (512 mg, 2.00 mmol) in AcOH (15 mL) at rt. The mixture was boiled for 30 min, then cooled, diluted with water (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 × 20 mL) followed by brine (15 mL) and then dried ($MgSO_4$) and evaporated. Trituration of the resulting yellow foam with Et_2O (3 × 2 mL) afforded the *title compound* (370 mg; 73%) as a colourless powder.

Method 2. A mixture of AcOH (20 mL), $NaOAc{\cdot}3H_2O$ (1.00 g, 2.00 mmol), water (1.00 mL) and **25** (380 mg, 1.39 mmol) was heated in an oil bath thermostatted at 120 °C for 5 h. Most of the AcOH was then removed by distillation at reduced pressure to afford a residue that was partitioned between EtOAc (50 mL) and saturated $NaHCO_3$ solution (50 mL). The organic phase was separated, further washed with saturated $NaHCO_3$ solution (2 × 50 mL), dried ($MgSO_4$) and evaporated. The resulting residue was recrystallised from $CHCl_3$–light petroleum to afford the *title compound* (282 mg; 80%) as a colourless crystalline solid: mp 221–222 °C (from $CHCl_3$–EtOAc–MeOH); ν_{max}(KBr)/cm^{-1} 3436, 3036, 2968, 2867, 1675, 1657, 1638, 1590, 1545, 1534, 1494, 1274, 1267, 1218, 1008; δ_H (400 MHz; $CDCl_3$) 1.38 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 3.41 (1 H, sept, *J* 6.9, CH(CH$_3$)$_2$), 6.74 (1 H, dt, $J_{6',4'}$ 1.4, $J_{6',5'}$ 6.9, $J_{6',7'}$ 6.9, H-6′), 7.10 (1 H, d, *J* 9.8, H-4), 7.13 (1 H, ddd, $J_{5',7'}$ 1.1, $J_{5',6'}$ 6.9, $J_{5',4'}$ 9.0, H-5′), 7.57 (1 H, d, *J* 9.8, H-5), 7.72 (1 H, dt, $J_{4',5'}$ 9.0, $J_{4',6'}$ 1.2, $J_{4',7'}$ 1.2, H-4′), 8.45 (1 H, dt, $J_{7',6'}$ 6.9, $J_{7',5'}$ 1.1, $J_{7',4'}$ 1.1, H-7′), 13.21 (1 H, br s, NH); δ_C (101 MHz; $CDCl_3$) 22.8 (CH(*C*H$_3$)$_2$), 27.0 (*C*H(CH$_3$)$_2$), 103.9 (C-3′), 112.3 (CH-6′), 117.4 (CH-4′), 125.2 (CH-5′), 128.8 (CH-7′), 130.0 (CH-4), 134.2 (CH-5), 139.1 (C-3a′), 142.3 (C-6), 159.5 (C), 161.8 (C); *m*/*z* (EI) 254 (64%, M$^+$), 239 (31%, M$^+$ − Me), 43 (100%, $C_3H_7^+$); (found: M$^+$, 254.1167. $C_{14}H_{14}N_4O$ requires 254.1168); (found C, 65.99; H, 5.43; N, 21.88. $C_{14}H_{14}N_4O$ requires: C, 66.13; H, 5.55; N, 22.03%).¶¶

2-Benzyl-6-(2-isopropylpyrazolo[1,5-*a*]pyridin-3-yl)-4,5-dihydropyridazin-3(2*H*)-one (17)

Method 1. NaH (60% w/w dispersion in oil; 30.0 mg, 0.750 mmol) was added to a solution of **15** (100 mg, 0.390 mmol) in anhydrous DMF (5 mL) under argon. The mixture was stirred for 1 h at rt after which time BnBr (1 M solution in DMF; 0.50 mL, 0.50 mmol) was added. The mixture was stirred for a further 90 min and then diluted with water (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried ($MgSO_4$) and evaporated. The residual oil was subjected to flash column chromatography (10 : 1 CH_2Cl_2–Et_2O) to afford the *title compound* (95.0 mg; 70%) as a colourless powder.

Method 2. A mixture of Zn dust (5.4 mg, 83 μmol) and **18** (32.6 mg, 94.7 μmol) in AcOH (2 mL) was boiled for 10 h, adding further zinc dust (30.2 mg, 459 μmol) in increments until TLC indicated consumption of **18**. The mixture was then cooled, filtered through celite and evaporated to afford a residue that was partitioned between EtOAc (30 mL) and saturated $NaHCO_3$ solution (10 mL). The organic phase was separated, washed with additional volumes of $NaHCO_3$ solution (2 × 10 mL) followed by brine (3 × 10 mL), dried (Na_2SO_4) and evaporated. The resulting residue was subjected to flash column chromatography (gradient elution from 1 : 9 to 1 : 1 EtOAc–light petroleum) to afford the *title compound* (18.4 mg; 56%) as a colourless powder: mp 126–127 °C (from EtOAc–light petroleum); ν_{max}(KBr)/cm^{-1} 3088, 2970, 1668, 1532, 1397, 1377, 1220, 1138, 1028, 930, 755, 700; δ_H (200 MHz; $CDCl_3$) 1.34 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 2.61–2.69 (2 H, m, CH_2), 2.95–3.04 (2 H, m, CH_2), 3.36 (1 H, sept, *J* 6.9, CH(CH$_3$)$_2$), 5.04 (2 H, s, CH_2Ph), 6.72 (1 H, dt, $J_{6',4'}$ 1.4, $J_{6',5'}$ 6.9, $J_{6',7'}$ 6.9, H-6′), 7.08 (1 H, ddd, $J_{5',7'}$ 1.1, $J_{5',6'}$ 6.9, $J_{5',4'}$ 8.9, H-5′), 7.26–7.48 (6 H, complex overlapping m, H-4′ and Ph), 8.37 (1 H, dt, $J_{7',6'}$ 6.9, $J_{7',5'}$ 1.1, $J_{7',4'}$ 1.1, H-7′); δ_C (50 MHz; $CDCl_3$) 22.7 (CH(*C*H$_3$)$_2$), 26.0 (CH_2), 27.4 (*C*H(CH$_3$)$_2$), 27.5 (CH_2), 51.8 (*C*H$_2$Ph), 105.3 (C-3′), 112.2 (CH-6′), 118.2 (CH-4′), 125.2 (CH-5′), 127.4 (Ph *para*-CH), 128.5 (2× Ph CH), 128.6 (2× Ph CH), 128.8 (CH-7′), 138.0 (Ph C), 139.1 (C-3a′), 148.5 (C-6), 160.1 (C-2′), 165.2 (C-3); *m*/*z* (EI) 346 (30%, M$^+$), 255 (10%, M$^+$ − Bn); (found: M$^+$, 346.1818. $C_{21}H_{22}N_4O$ requires 346.1794), 303.1230 (0.42%, M$^+$ − C_3H_7 requires 303.1246); (found C, 72.52; H, 6.32; N, 16.06. $C_{21}H_{22}N_4O$ requires: C, 72.81; H, 6.40; N, 16.17%).¶¶

2-Benzyl-6-(2-isopropylpyrazolo[1,5-*a*]pyridin-3-yl)pyridazin-3(2*H*)-one (18)

Method 1. To a stirred solution of **16** (100 mg, 0.393 mmol) in anhydrous DMF (5 mL) under argon was added Cs_2CO_3 (380 mg, 1.17 mmol) followed by BnBr (1 M solution in DMF; 1.50 mL, 1.50 mmol). The mixture was stirred for 18 h at rt and then diluted with water (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried ($MgSO_4$) and evaporated. The residual oil was subjected to flash column chromatography (10 : 1 CH_2Cl_2–Et_2O) to afford the *title compound* (105 mg; 78%) as a colourless powder.

Method 2. A stirred mixture of 1-aminopyridinium mesitylenesulfonate[12] (350 mg, 1.19 mmol), **22** (304 mg, 1.20 mmol) and powdered K_2CO_3 (335 g, 2.40 mmol) in DMF

(12 mL) was heated at 120 °C for 24 h. Additional pyridinium salt (354 mg, 1.20 mmol) and K_2CO_3 (323 mg, 2.33 mmol) were then added and heating continued for a further 24 h. The mixture was subsequently evaporated to dryness and the resulting residue partitioned between CH_2Cl_2 (30 mL) and water (20 mL). The organic phase was separated, washed with water (20 mL) followed by brine (2 × 20 mL), dried ($MgSO_4$) and evaporated. The resulting residue was subjected to flash column chromatography (gradient elution from 3 : 7 to 3 : 2 EtOAc–light petroleum), affording the starting alkyne (129 mg, 511 μmol; 43%) followed by the *title compound* (109 mg, 316 μmol; 26%) as a pale yellow powder: mp 172–173 °C (from EtOAc); ν_{max}(KBr)/cm^{-1} 3088, 2968, 1662, 1589, 1533, 1506, 1321, 1030, 845, 746, 700; δ_H (400 MHz; $CDCl_3$) 1.36 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 3.34 (1 H, sept, *J* 6.9, C*H*(CH$_3$)$_2$), 5.40 (2 H, s, CH_2Ph), 6.74 (1 H, dt, $J_{6',4'}$ 1.4, $J_{6',5'}$ 6.9, $J_{6',7'}$ 6.9, H-6′), 7.02 (1 H, d, $J_{4,5}$ 9.6, H-4), 7.11 (1 H, ddd, $J_{5',7'}$ 1.1, $J_{5',6'}$ 6.9, $J_{5',4'}$ 9.0, H-5′), 7.27–7.37 (3 H, complex overlapping m, Ph *meta*-H and *para*-H), 7.44–7.49 (3 H, complex overlapping m, H-4′ and Ph *ortho*-H), 7.45 (1 H, d, $J_{5,4}$ 9.6, H-5), 8.41 (1 H, dt, $J_{7',6'}$ 6.9, $J_{7',5'}$ 1.1, $J_{7',4'}$ 1.1, H-7′); δ_C (101 MHz; $CDCl_3$) 22.7 (CH(*C*H$_3$)$_2$), 26.9 (*C*H(CH$_3$)$_2$), 55.1 (*C*H$_2$Ph), 104.1 (C-3′), 112.1 (CH-6′), 117.1 (CH-4′), 125.0 (CH-5′), 127.9 (Ph *para*-CH), 128.6 (2× Ph *meta*-CH), 128.8 (CH-7′), 129.1 (2× Ph *ortho*-CH), 130.3 (CH-4), 132.6 (CH-5), 136.7 (Ph C), 139.0 (C-3a′), 141.1 (C-6), 159.2 (C-3), 159.5 (C-2′); *m*/*z* (EI) 344 (100%, M$^+$), 253 (10%, M$^+$ − Bn), 91 (23%, $C_7H_7^+$); (found: C, 73.06; H, 5.77; N, 16.32. $C_{21}H_{20}N_4O$ requires C, 73.23; H, 5.85; N, 16.27%).¶¶

3-Chloro-6-(3-methylbut-1-ynyl)pyridazine (20)

A sealable, heavy-walled flask (~750 mL capacity) was charged with 3,6-dichloropyridazine (41.6 g, 279 mmol), Bu_4NI (37.0 g, 100 mmol), CuI (1.30 g, 6.83 mmol), $Pd(PPh_3)_4$ (1.66 g, 1.44 mmol), anhydrous THF (400 mL), 3-methyl-1-butyne (9.50 g, 140 mmol) and $^iPr_2NH$ (20.0 mL, 143 mmol). The flask was sealed and the mixture stirred magnetically in an oil bath thermostatted at 90 °C for 24 h [**SAFETY SCREEN**]. The flask was then cooled and opened; the mixture was diluted with light petroleum (600 mL) and passed through a column of Merck kieselgel 60H (120 mm diameter × 90 mm length), eluting with 1 : 1 EtOAc–light petroleum (2 L). The eluate was evaporated and the resulting dark brown residue subjected to flash column chromatography (30% EtOAc–light petroleum). Fractions containing the target material were evaporated and the resulting light brown powder crystallised from Et_2O–light petroleum to afford the *title compound* (13.4 g; 53%) as a colourless solid: mp 49–51 °C (Et_2O–light petroleum); ν_{max} ($CHCl_3$ film)/cm^{-1} 3099, 3067, 2981, 2238, 1560, 1395, 1145, 1067, 857; δ_H (200 MHz; $CDCl_3$) 1.28 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 2.83 (1 H, sept, *J* 6.9, C*H*(CH$_3$)$_2$), 7.44 (2 H, app. s, H-4 and H-5); δ_H (200 MHz; C_6D_6) 1.03 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 2.48 (1 H, sept, *J* 6.9, C*H*(CH$_3$)$_2$), 6.32 (1 H, d, *J* 8.8, H-4), 6.51 (1 H, d, *J* 8.8, H-5); δ_C (50 MHz; $CDCl_3$) 21.2 (*C*H(CH$_3$)$_2$), 22.2 (CH(*C*H$_3$)$_2$), 75.9 (*C*≡CCH), 102.7 (C≡*C*CH), 127.6 (CH-4), 131.7 (CH-5), 147.5 (C-6), 154.6 (C-3); δ_C (50 MHz; C_6D_6) 21.5 (*C*H(CH$_3$)$_2$), 22.4 (CH(*C*H$_3$)$_2$), 77.2 (*C*≡CCH), 101.7 (C≡*C*CH), 126.8 (CH-4), 131.0 (CH-5), 147.6 (C-6), 154.7 (C-3); *m*/*z* (EI) 180 (^{35}Cl; 100%, M$^+$), 179 (^{35}Cl; 64%, M$^+$ − H), 145 (37%, M$^+$ − Cl); (found: C, 59.87; H, 4.94; N, 15.55. $C_9H_9ClN_2$ requires C, 59.84; H, 5.02; N, 15.51%).¶¶

6-(3-Methylbut-1-ynyl)pyridazin-3(2*H*)-one (21)

Chloropyridazine **20** (6.07 g, 33.6 mmol) was heated in a mixture of AcOH (140 mL), water (18 mL) and NaOAc·3H_2O (5.30 g) at 100 °C for 15 h. The mixture was then cooled and decanted into an ice-cooled solution of NaOH (100 g) in water (700 mL). The resulting alkaline solution was washed with CH_2Cl_2 (2 × 200 mL) and the organic phase discarded. The pH of the aqueous mixture was adjusted to ~6 by addition of conc. hydrochloric acid and it was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extract was dried ($MgSO_4$) and evaporated. The *title compound* (4.73 g; 87%) was isolated from the resulting residue as a colourless solid by flash column chromatography (50% EtOAc–light petroleum) followed by crystallisation from $CHCl_3$–light petroleum: mp 96–97 °C ($CHCl_3$–light petroleum); ν_{max}(KBr)/cm^{-1} 3468, 2976, 2925, 2233, 1682, 1648, 1585, 1547, 1442, 1005, 849, 657, 638; δ_H (200 MHz; $CDCl_3$) 1.27 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 2.79 (1 H, sept, *J* 6.9, C*H*(CH$_3$)$_2$), 6.95 (1 H, d, *J* 9.7, H-4), 7.28 (1 H, d, *J* 9.7, H-5), 12.65 (1 H, br s, NH); δ_C (50 MHz; $CDCl_3$) 21.0 (*C*H(CH$_3$)$_2$), 22.4 (CH(*C*H$_3$)$_2$), 75.0 (*C*≡CCH), 98.9 (C≡*C*CH), 129.6 (CH-4), 133.3 (C-6), 136.2 (CH-5), 161.5 (C-3); EIMS: *m*/*z* (EI) 162 (83%, M$^+$), 161 (100%, M$^+$ − H), 147 (71%, M$^+$ − CH_3), 133 (38%, M$^+$ − C_2H_5), 119 (33%, M$^+$ − C_3H_7); (found: C, 66.44; H, 6.19; N, 17.31. $C_9H_{10}N_2O$ requires C, 66.65; H, 6.21; N, 17.27%).¶¶

2-Benzyl-6-(3-methylbut-1-ynyl)pyridazin-3(2*H*)-one (22)

Method 1. To a stirred solution of **21** (3.92 g, 24.1 mmol) in anhydrous DMF (50 mL) was added powdered K_2CO_3 (13.5 g, 97.7 mmol) followed after 5 min by BnBr (3.50 mL, 29.4 mmol). After 30 min the mixture was diluted with water (850 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extract was dried ($MgSO_4$) and evaporated. The residual oil was subjected to flash column chromatography (4 : 7 EtOAc–light petroleum). Fractions containing the target material were evaporated and the resulting yellow solid crystallised from EtOAc–hexane to afford the *title compound* (4.98 g; 82%) as colourless needles.

Method 2. A sealable, heavy-walled flask (~100 mL capacity) was charged with **24**[15] (4.03 g, 18.3 mmol), Bu_4NI (6.99 g, 18.9 mmol), CuI (211 mg, 1.11 mmol), $Pd(PPh_3)_4$ (841 mg, 728 μmol), anhydrous THF (40 mL), 3-methyl-1-butyne (1.89 g, 27.7 mmol) and $^iPr_2NH$ (4.00 mL, 28.5 mmol). The flask was sealed and the mixture stirred magnetically in an oil bath thermostatted at 80 °C for 4 h [**SAFETY SCREEN**]. The flask was then cooled and opened; the mixture was evaporated to afford a residue that was dissolved in EtOAc (30 mL). The resulting solution was washed with water (2 × 20 mL), dried ($MgSO_4$) and evaporated. The residue was subjected to flash column chromatography (gradient elution from 1 : 9 to 1 : 4 EtOAc–light petroleum). Fractions containing the target material were evaporated and the resulting light brown residue crystallised from EtOAc–light petroleum to afford the *title compound* (3.83 g; 83%) as colourless needles: mp 85–87 °C (from EtOAc–light petroleum); ν_{max}(KBr)/cm^{-1} 3055, 2974, 2222, 1661, 1591, 1490, 1301, 1151, 938, 842, 731, 696; δ_H (200 MHz; $CDCl_3$) 1.26 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 2.78 (1 H, sept, *J* 6.9, C*H*(CH$_3$)$_2$), 5.30 (2 H, s, CH_2Ph), 6.84 (1 H, d, *J* 9.6, H-4), 7.17 (1 H, d, *J* 9.6, H-5), 7.22–7.46 (5 H, complex overlapping m, Ph); δ_C (50 MHz;

$CDCl_3$) 21.2 ($CH(CH_3)_2$), 22.5 ($CH(CH_3)_2$), 55.9 (CH_2Ph), 75.3 ($C{\equiv}CCH$), 98.7 ($C{\equiv}CCH$), 128.0 (Ph CH), 128.7 (2× Ph CH), 128.8 (2× Ph CH), 129.7 (CH-4), 132.3 (Ph C), 135.1 (CH-5), 136.0 (C-6), 159.2 (C-3); *m/z* (EI) 252 (100%, M^+), 237 (36%, $M^+ - CH_3$), 91 (79%, $C_7H_7^+$); (found: M^+, 252.1265. $C_{16}H_{16}N_2O$ requires 252.1263); (found: C, 75.86; H, 6.35; N, 11.10. $C_{16}H_{16}N_2O$ requires C, 76.16; H, 6.39; N, 11.10%).¶¶

3-(6-Chloropyridazin-3-yl)-2-isopropylpyrazolo[1,5-*a*]pyridine (25)

A stirred mixture of 1-aminopyridinium mesitylenesulfonate[12] (1.32 g, 4.47 mmol), **20** (254 mg, 1.41 mmol) and powdered K_2CO_3 (1.12 g, 8.08 mmol) in DMF (15 mL) was heated at 120 °C for 30 h. The mixture was then evaporated to dryness and the residue partitioned between EtOAc (50 mL) and water (50 mL). The organic phase was separated, washed with brine (50 mL), dried ($MgSO_4$) and evaporated. The resulting residue was subjected to flash column chromatography (2 : 3 EtOAc–light petroleum) to afford the *title compound* (78.0 mg; 20%) as a pale yellow powder: mp 147–148 °C (from hexane–EtOAc); ν_{max}(KBr)/cm^{-1} 3080, 2969, 1632, 1576, 1543, 1531, 1506, 1465, 1400, 1359, 1214, 1146, 1092, 771, 754; δ_H (200 MHz; $CDCl_3$) 1.38 (6 H, d, *J* 6.9, $CH(CH_3)_2$), 3.48 (1 H, sept, *J* 6.9, $CH(CH_3)_2$), 6.79 (1 H, dt, $J_{6,4}$ 1.4, $J_{6,5}$ 6.9, $J_{6,7}$ 6.9, H-6), 7.20 (1 H, ddd, $J_{5,7}$ 1.1, $J_{5,6}$ 6.8, $J_{5,4}$ 9.0, H-5), 7.49 (1 H, d, $J_{5',4'}$ 9.0, H-5′), 7.62 (1 H, d, $J_{4',5'}$ 9.0, H-4′), 7.99 (1 H, dt, $J_{4,5}$ 9.0, $J_{4,6}$ 1.2, $J_{4,7}$ 1.2, H-4), 8.43 (1 H, dt, $J_{7,6}$ 6.9, $J_{7,5}$ 1.1, $J_{7,4}$ 1.1, H-7); δ_C (50 MHz; $CDCl_3$) 22.6 ($CH(CH_3)_2$), 27.0 ($CH(CH_3)_2$), 104.4 (C-3), 112.8 (CH-6), 118.0 (CH-4), 125.9 (CH-5), 127.5 (CH-4′), 128.0 (CH-5′), 128.8 (CH-7), 139.6 (C-3a), 153.2 (C-6′), 155.6 (C-3′), 160.1 (C-2); *m/z* (EI) 272 (^{35}Cl; 19%, M^+), 271 (^{35}Cl; 18%, $M^+ - H$), 237 (44%, $M^+ - Cl$), 69 (100%); (found: C, 61.69; H, 4.69; N, 20.78. $C_{14}H_{13}ClN_4$ requires C, 61.65; H, 4.80; N, 20.54%).

6-(3-Methylbut-1-ynyl)-2-phenylpyridazin-3(2*H*)-one (28)

A sealable, heavy-walled flask (~50 mL capacity) was charged with **27**[17] (1.06 g, 5.13 mmol), Bu_4NI (2.08 g, 5.64 mmol), CuI (58.6 mg, 0.31 mmol), $Pd(PPh_3)_4$ (232 mg, 201 μmol), anhydrous THF (16 mL), 3-methyl-1-butyne (927 mg, 13.6 mmol) and $^iPr_2NH$ (1.00 mL, 7.13 mmol) under argon. The flask was sealed and the mixture was stirred magnetically in an oil bath thermostatted at 80 °C for 19 h [**SAFETY SCREEN**]. The flask was then cooled and opened; the mixture was filtered and the filtrate evaporated to afford a residue that was dissolved in EtOAc (15 mL). The resulting solution was washed with water (2 × 10 mL) followed by brine (2 × 10 mL), dried (Na_2SO_4) and evaporated. The residue was subjected to flash column chromatography (1 : 1 Et_2O–light petroleum gradient elution). Fractions containing the target material were evaporated to afford the *title compound* (1.22 g; 99%) as a buff powder: ν_{max}(KBr)/cm^{-1} 3300, 3045, 2970, 2237, 1677, 1589, 1312, 1198, 1022, 851, 767, 692; δ_H (200 MHz; $CDCl_3$) 1.26 (6 H, d, *J* 6.9, $CH(CH_3)_2$), 2.78 (1 H, sept, *J* 6.9, $CH(CH_3)_2$), 6.97 (1 H, d, *J* 9.6, H-4), 7.26 (1 H, d, *J* 9.6, H-5), 7.33–7.59 (5 H, complex overlapping m, Ph); δ_C (50 MHz; $CDCl_3$) 21.2 ($CH(CH_3)_2$), 22.5 ($CH(CH_3)_2$), 75.2 ($C{\equiv}CCH$), 99.2 ($C{\equiv}CCH$), 125.7 (2× Ph *ortho*-CH), 128.6 (Ph *para*-CH), 129.0 (2× Ph *meta*-CH), 130.7 (CH-4), 132.8 (C-6), 135.0 (CH-5), 141.4 (Ph CH), 159.0 (C-3); *m/z* (EI) 238 (65%, M^+), 223 (29%, $M^+ - CH_3$), 209 (11%, $M^+ - C_2H_5$), 195 (7%, $M^+ - C_3H_7$), 77 (100%, $C_6H_5^+$); (found: M^+, 238.1106. $C_{15}H_{14}N_2O$ requires 238.1106).

6-(2-Isopropylpyrazolo[1,5-*a*]pyridin-3-yl)-2-phenylpyridazin-3(2*H*)-one (29)

A stirred mixture of 1-aminopyridinium mesitylenesulfonate[12] (753 mg, 2.56 mmol), **28** (500 mg, 2.10 mmol) and powdered K_2CO_3 (597 mg, 4.32 mmol) in DMF (10 mL) was heated at 120 °C for 9 h. Additional pyridinium salt (506 mg, 1.72 mmol) and K_2CO_3 (535 mg, 3.87 mmol) were then added and heating continued for a further 12 h. The mixture was then evaporated to dryness and the resulting residue partitioned between EtOAc (75 mL) and water (40 mL). The organic phase was separated, washed with water (2 × 40 mL) followed by brine (4 × 40 mL), dried (Na_2SO_4) and evaporated. The residue was subjected to flash column chromatography (1 : 1 EtOAc–light petroleum) to afford the *title compound* (346 mg; 50%) as a pale yellow powder: mp 174–176 °C (from petroleum 60–80 °C); ν_{max}(KBr)/cm^{-1} 3053, 2969, 1670, 1590, 1527, 1476, 1310, 1043, 852, 745, 695; δ_H (400 MHz; $CDCl_3$) 1.43 (6 H, d, *J* 6.9, $CH(CH_3)_2$), 3.46 (1 H, sept, *J* 6.9, $CH(CH_3)_2$), 6.79 (1 H, dt, $J_{6',4'}$ 1.4, $J_{6',5'}$ 6.9, $J_{6',7'}$ 6.9, H-6′), 7.15 (1 H, d, $J_{4,5}$ 9.7, H-4), 7.20 (1 H, ddd, $J_{5',7'}$ 1.1, $J_{5',6'}$ 6.8, $J_{5',4'}$ 9.0, H-5′), 7.38–7.42 (1 H, complex m, Ph *para*-H), 7.48–7.53 (2 H, complex m, 2× Ph *meta*-H), 7.56 (1 H, d, $J_{5,4}$ 9.7, H-5), 7.70–7.72 (3 H, complex overlapping m, H-4′ and 2× Ph *ortho*-H), 8.45 (1 H, dt, $J_{7',6'}$ 7.0, $J_{7',5'}$ 1.0, $J_{7',4'}$ 1.0, H-7′); δ_C (50 MHz; $CDCl_3$) 22.8 ($CH(CH_3)_2$), 27.2 ($CH(CH_3)_2$), 103.9 (C-3′), 112.4 (CH-6′), 117.2 (CH-4′), 125.4 (2× *ortho*-CH and CH-5′), 128.2 (Ph *para*-CH), 128.9 (2× Ph *meta*-CH and CH-7′), 131.5 (CH-4), 132.8 (CH-5), 139.2 (C-3a′), 141.7 (C-6), 141.9 (Ph C), 159.2 (C-3), 159.7 (C-2′); *m/z* (EI) 330 (36%, M^+), 315 (9%, $M^+ - CH_3$), 197 (100%); (found: C, 72.48; H, 5.52; N, 16.69. $C_{20}H_{18}N_4O$ requires C, 72.71; H, 5.49; N, 16.96%).¶¶

6-(2-Isopropylpyrazolo[1,5-*a*]pyridin-3-yl)-2-phenyl-4,5-dihydropyridazin-3(2*H*)-one (30)

A mixture of Zn dust (51.6 mg, 789 μmol) and **29** (250 mg, 757 μmol) in AcOH (12 mL) was boiled for 37 h, adding further zinc dust (145 mg, 2.22 mmol) in increments until TLC indicated consumption of **29**. The mixture was then cooled, filtered through celite and evaporated to afford a residue that was partitioned between EtOAc (30 mL) and saturated $NaHCO_3$ solution (10 mL). The organic phase was separated, washed with additional volumes of $NaHCO_3$ solution (2 × 10 mL) followed by brine (3 × 10 mL), dried (Na_2SO_4) and evaporated. The resulting residue was subjected to flash column chromatography (3 : 2 Et_2O–light petroleum) to afford the *title compound* (212 mg; 84%) as a pale yellow powder: mp 129–130 °C (from petroleum 60–80 °C–EtOAc); ν_{max}($CHCl_3$ film)/cm^{-1} 3019, 2975, 1670, 1634, 1523, 1496, 1357, 1216, 753, 669; δ_H (200 MHz; $CDCl_3$) 1.42 (6 H, d, *J* 6.9, $CH(CH_3)_2$), 2.75–2.83 (2 H, complex m, CH_2), 3.10–3.18 (2 H, complex m, CH_2), 3.52 (1 H, sept, *J* 6.9, $CH(CH_3)_2$), 6.78 (1 H, dt, $J_{6',4'}$ 1.4, $J_{6',5'}$ 6.9, $J_{6',7'}$ 6.9, H-6′), 7.20 (1 H, ddd, $J_{5',7'}$ 1.1, $J_{5',6'}$ 6.8, $J_{5',4'}$ 9.0, H-5′), 7.21–7.30 (1 H, complex m, Ph *para*-H), 7.37–7.46 (2 H, complex m, 2× Ph *meta*-H), 7.58–7.65 (2 H, complex m, 2× Ph *ortho*-H), 7.80 (1 H, dt, $J_{4',5'}$ 9.0, $J_{4',6'}$ 1.2, $J_{4',7'}$ 1.2, H-4′), 8.42 (1 H, dt, $J_{7',6'}$ 6.9, $J_{7',5'}$ 1.1, $J_{7',4'}$ 1.1, H-7′); δ_C (101 MHz; $CDCl_3$)

22.8 (CH(CH$_3$)$_2$), 25.9 (CH$_2$), 27.7 (CH(CH$_3$)$_2$), 28.5 (CH$_2$), 105.2 (C-3′), 112.4 (CH-6′), 118.3 (CH-4′), 124.9 (2× Ph *ortho*-CH), 125.5 (CH), 126.5 (CH), 128.6 (2× Ph *meta*-CH), 129.0 (CH), 139.3 (C-3a′), 141.4 (Ph C), 149.7 (C-6), 160.4 (C-2′), 165.4 (C-3); *m*/*z* (EI) 332 (100%, M$^+$), 303 (23%, M$^+$ − C$_2$H$_5$); (found: C, 72.09; H, 5.99; N, 16.58; C$_{20}$H$_{20}$N$_4$O requires C, 72.27; H, 6.06; N, 16.86%).

2-Benzyl-4-chlorophthalazin-1(2*H*)-one (32)

Phthalazinedione **31**[17] (4.93 g, 19.5 mmol) was boiled in POCl$_3$ (70 mL). After 5 h the POCl$_3$ was removed by distillation. The residue was dissolved in EtOAc (30 mL) and washed with saturated NaHCO$_3$ (3 × 30 mL). The organic layer was then washed with brine (3 × 30 mL), dried (Na$_2$SO$_4$) and evaporated to give a brown solid that was subjected to flash column chromatography (1 : 9 EtOAc–light petroleum) to afford the *title compound* (905 mg; 17%) as a colourless powder: mp 99–101 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3033, 2958, 1656, 1578, 1495, 1344, 1295, 1128, 1074, 998, 767, 752, 682; δ_H (200 MHz; CDCl$_3$) 5.37 (2 H, s, CH_2Ph), 7.26–7.38 (3 H, complex overlapping m), 7.46–7.52 (2 H, complex m), 7.77–7.90 (2 H, complex overlapping m), 7.95–8.00 (1 H, complex m), 8.42–8.47 (1 H, complex m); δ_C (50 MHz; CDCl$_3$) 55.0 (*C*H$_2$Ph), 125.8 (CH), 127.7 (CH + C), 128.1 (CH), 128.7 (2× CH), 128.9 (2× CH), 132.7 (CH), 133.8 (CH), 136.4 (2× C), 137.8 (C), 158.9 (C); *m*/*z* (EI) 270 (^{35}Cl; 19%, M$^+$), 235 (44%, M$^+$ − Cl), 91 (38%, C$_7$H$_7^+$); (found: C, 66.50; H, 4.09; N, 10.14. C$_{15}$H$_{11}$ClN$_2$O requires C, 66.55; H, 4.03; N, 10.35%).

2-Benzyl-4-(3-methylbut-1-ynyl)phthalazin-1(2*H*)-one (33)

A sealable, heavy-walled flask (~100 mL capacity) was charged with **32** (3.07 g, 11.3 mmol), Bu$_4$NI (4.39 g, 11.9 mmol), CuI (141 mg, 740 μmol), Pd(PPh$_3$)$_4$ (524 mg, 453 μmol), anhydrous THF (50 mL), 3-methyl-1-butyne (2.74 g, 40.2 mmol) and ^{i}Pr$_2$NH (3.00 mL, 21.4 mmol). The flask was sealed and the mixture stirred magnetically in an oil bath thermostatted at 80 °C for 21 h [**SAFETY SCREEN**]. The flask was then cooled and opened; the mixture was evaporated to afford a residue that was dissolved in CH$_2$Cl$_2$ (30 mL). The resulting solution was washed with water (2 × 20 mL) followed by brine (2 × 20 mL), dried (Na$_2$SO$_4$) and evaporated. The residue was subjected to flash column chromatography (gradient elution from light petroleum to 1 : 9 EtOAc–light petroleum) to afford the *title compound* (3.12 g; 91%) as a colourless powder: mp 82–83 °C (from EtOAc–light petroleum); ν_{max}(KBr)/cm^{-1} 3090, 2972, 2873, 2230, 1661, 1607, 1582, 1454, 1348, 1301, 1112, 778, 701; δ_H (200 MHz; CDCl$_3$) 1.36 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 2.92 (1 H, sept, *J* 6.9, CH(CH$_3$)$_2$), 5.41 (2 H, s, CH_2Ph), 7.25–7.36 (3 H, complex overlapping m), 7.43–7.50 (2 H, complex m), 7.70–7.86 (2 H, overlapping m), 7.99–8.04 (1 H, complex m), 8.37–8.42 (1 H, complex m, CH); δ_C (50 MHz; CDCl$_3$) 21.4 (*C*H(CH$_3$)$_2$), 22.7 (CH(*C*H$_3$)$_2$), 55.5 (*C*H$_2$Ph), 73.6 (*C*≡CCH), 101.5 (C≡*C*CH), 126.4 (CH), 127.0 (CH), 127.6 (C), 127.8 (CH), 128.6 (2× Ph CH), 128.7 (2× Ph CH), 130.4 (C), 131.8 (CH), 132.7 (C), 133.4 (CH), 136.8 (C), 159.0 (C); *m*/*z* (EI) 302 (100%, M$^+$), 287 (4%, M$^+$ − CH$_3$), 91 (40%, C$_7$H$_7^+$), 77 (9%, C$_6$H$_5^+$); (found: M$^+$, 302.1451. C$_{20}$H$_{18}$N$_2$O requires 302.1419); (found: C, 79.05; H, 5.89; N, 9.19. C$_{20}$H$_{18}$N$_2$O requires C, 79.44; H, 6.00; N, 9.26%).

2-Benzyl-4-(2-isopropylpyrazolo[1,5-*a*]pyridin-3-yl)phthalizin-1(2*H*)-one (34)

A stirred mixture of 1-aminopyridinium mesitylenesulfonate[12] (498 mg, 1.69 mmol), **33** (503 mg, 1.66 mmol) and powdered K$_2$CO$_3$ (457 mg, 3.31 mmol) in DMF (16 mL) was heated at 100 °C for 20 h. Additional pyridinium salt (515 mg, 1.75 mmol) and K$_2$CO$_3$ (470 mg, 3.40 mmol) were then added and heating continued for a further 20 h. The mixture was then evaporated to dryness and the resulting residue partitioned between EtOAc (30 mL) and water (20 mL). The organic phase was separated, washed with water (20 mL) followed by brine (2 × 20 mL), dried (Na$_2$SO$_4$) and evaporated. The residue was subjected to flash column chromatography (gradient elution from light petroleum to 1 : 9 Et$_2$O–light petroleum), affording the starting alkyne (194 mg; 39%) followed by the *title compound* (262 mg; 40%) as a colourless powder: mp 198–199 °C (from MeOH); ν_{max}(KBr)/cm^{-1} 3040, 2958, 1651, 1581, 1532, 1350, 1302, 1256, 1158, 992, 766, 702; δ_H (200 MHz; CDCl$_3$) 1.24 (3 H, d, *J* 6.9, CH(CH_3)), 1.28 (3 H, d, *J* 6.9, CH(CH_3)), 3.11 (1 H, sept, CH(CH$_3$)$_2$), 5.36 (1 H, AB d, J_{gem} 13.8, CHHPh), 5.62 (1 H, AB d, J_{gem} 13.9, CHHPh), 6.77 (1 H, ddd, $J_{6',7'}$ 7.0, $J_{6',5'}$ 5.9, $J_{6',4'}$ 2.2, H-6′), 7.03–7.17 (2 H, complex overlapping m), 7.23–7.38 (3 H, complex overlapping m), 7.45–7.53 (3 H, complex overlapping m), 7.70 (1 H, td, *J* 7.2 and 1.6, H-6 or H-7), 7.78 (1 H, td, *J* 7.2 and 1.4, H-6 or H-7), 8.49 (1 H, dt, $J_{7',6'}$ 7.0, $J_{7',5'}$ 1.0, $J_{7',4'}$ 1.0, H-7′), 8.53–8.58 (1 H, complex m, H-8); δ_C (50 MHz; CDCl$_3$) 22.5 (CH(*C*H$_3$)), 23.0 (CH(*C*H$_3$)), 27.1 (*C*H(CH$_3$)$_2$), 54.9 (*C*H$_2$Ph), 102.8 (C-3′), 111.9 (CH-6′), 116.8 (CH-4′), 124.5 (CH), 126.7 (CH), 127.5 (CH), 127.8 (CH), 128.5 (C), 128.6 (2× Ph CH), 128.8 (CH), 128.9 (2× Ph CH), 130.4 (C), 131.7 (CH), 133.1 (CH), 137.2 (C), 140.1 (C), 140.8 (C), 159.2 (C), 160.8 (C); *m*/*z* (EI) 394 (100%, M$^+$), 91 (56%, C$_7$H$_7^+$); (found: M$^+$, 394.1793. C$_{25}$H$_{22}$N$_4$O requires 394.1778); (found: C, 75.78; H, 5.52; N, 14.18. C$_{25}$H$_{22}$N$_4$O requires C, 76.12; H, 5.62; N, 14.20%).

2-(3-Methylbut-1-ynyl)pyridine (35)

A sealable, heavy-walled flask (~100 mL capacity) was charged with CuI (1.08 g, 5.67 mmol), Pd(PPh$_3$)$_4$ (227 mg, 196 μmol), anhydrous THF (50 mL), 2-bromopyridine (1.20 mL, 12.6 mmol), 3-methyl-1-butyne (1.08 g, 15.9 mmol) and ^{i}Pr$_2$NH (3.00 mL, 21.4 mmol). The flask was sealed and the mixture stirred magnetically in an oil bath thermostatted at 70 °C for 40 h [**SAFETY SCREEN**]. The flask was then cooled and opened; the mixture was evaporated to afford a residue that was partitioned between CH$_2$Cl$_2$ (75 mL) and water (75 mL). The organic phase was separated and washed with water (2 × 75 mL) followed by brine (2 × 20 mL), dried (MgSO$_4$) and evaporated. The residue was subjected to flash column chromatography (15 : 40 : 45 CH$_2$Cl$_2$–Et$_2$O–pentane) to afford the *title compound* (750 mg; 41%) as a pale yellow oil: ν_{max}(neat)/cm^{-1} 3053, 2972, 2933, 2235, 1584, 1464, 1428, 1322, 1149, 991, 780; δ_H (200 MHz; CDCl$_3$) 1.25 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 2.77 (1 H, sept, *J* 6.9, CH(CH$_3$)$_2$), 7.13 (1 H, ddd, $J_{5,4}$ 7.6, $J_{5,6}$ 4.9, $J_{5,3}$ 1.2, H-5), 7.33 (1 H, dt, $J_{3,4}$ 7.8, $J_{3,5}$ 1.1, $J_{3,6}$ 1.1, H-3), 7.56 (1 H, td, $J_{4,3}$ 7.7, $J_{4,5}$ 7.7, $J_{4,6}$ 1.8, H-4), 8.50 (1 H, ddd, $J_{6,5}$ 4.9, $J_{6,4}$ 1.7, $J_{6,3}$ 0.9, H-6); δ_C (50 MHz; CDCl$_3$) 21.0 (*C*H(CH$_3$)$_2$), 22.7 (CH(*C*H$_3$)$_2$), 79.6 (*C*≡CCH), 96.1 (C≡*C*CH), 122.3 (CH-5), 126.8 (CH-3), 136.1 (CH-4), 143.9 (C-2), 149.8 (CH-6); *m*/*z* (ESI) 146 (96%, M$^+$ + H),

130 (21%, $M^+ - CH_3$), 118 (93%, $M^+ - CHN$), 78 (70%, $C_5H_4N^+$); (found: M^+, 145.0903. $C_{10}H_{11}N$ requires 145.0892).

2-Isopropyl-3-(pyridin-2-yl)pyrazolo[1,5-*a*]pyridine (36)

A stirred mixture of 1-aminopyridinium mesitylenesulfonate[12] (596 mg, 2.02 mmol), **35** (158 mg, 1.09 mmol) and powdered K_2CO_3 (570 mg, 4.12 mmol) in DMF (12 mL) was heated at 80 °C for 40 h. The mixture was then evaporated to dryness and the residue partitioned between EtOAc (20 mL) and water (20 mL). The organic phase was separated, washed with brine (20 mL), dried ($MgSO_4$) and evaporated. The resulting residue was subjected to flash column chromatography (gradient elution from light petroleum to 7 : 3 EtOAc–light petroleum) to recover starting alkyne (83.0 mg; 53%) and afford the *title compound* (24.6 mg; 10%) as a pale yellow powder: mp 82–83 °C (from $CHCl_3$–hexane), ν_{max}(thin film)/cm^{-1} 3019, 2972, 1635, 1590, 1533, 1216, 756, 669; δ_H (400 MHz; $CDCl_3$) 1.42 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 3.63 (1 H, sept, *J* 6.9, CH(CH$_3$)$_2$), 6.75 (1 H, td, $J_{6,5}$ 6.9, $J_{6,7}$ 6.9, $J_{6,4}$ 1.4, H-6), 7.13–7.17 (2 H, overlapping m, H-5 and H-5′), 7.48 (1 H, br d, $J_{3',4'}$ 8.0, H-3′), 7.74 (1 H, td, $J_{4',3'}$ 7.8, $J_{4',5'}$ 7.8, $J_{4',6'}$ 1.9, H-4′), 7.91 (1 H, dt, $J_{4,5}$ 9.0, $J_{4,6}$ 1.2, $J_{4,6}$ 1.7, H-4), 8.44 (1 H, dt, $J_{7,6}$ 7.0, $J_{7,4}$ 1.1, $J_{7,5}$ 1.1, H-7), 8.71 (1 H, br d, $J_{6',5'}$ 4.8, H-6′); δ_C (101 MHz; $CDCl_3$) 22.9 (CH(*C*H$_3$)$_2$), 26.7 (*C*H(CH$_3$)$_2$), 109.2 (C-3), 112.0 (CH-6), 118.1 (CH-4), 120.5 (CH-5′), 123.0 (CH-3′), 124.6 (CH-5), 128.6 (CH-7), 136.4 (CH-4′), 139.6 (C-3a), 149.9 (CH-6′), 153.8 (C-2′), 159.5 (C-2); *m*/*z* (EI) 237 (91%, M^+), 236 (100%, $M^+ - H$), 222 (74%, $M^+ - CH_3$), 194 (26%, $M^+ - C_3H_7$), 78 (16%, $C_5H_4N^+$); (found: M^+, 237.1252. $C_{15}H_{15}N_3$ requires 237.1266); (found: C, 75.97; H, 6.34; N, 17.65. $C_{15}H_{15}N_3$ requires C, 75.92; H, 6.37; N, 17.71%).‡¶¶

1-Methyl-2-(3-methylbut-1-ynyl)pyridinium iodide (37)

A solution of methyl iodide (90.0 μL, 1.45 mmol) and **35** (200 mg, 1.38 mmol) in dry THF (2 mL) was heated at 60 °C for 1.5 h. Upon cooling and standing the mixture separated into two phases. The upper phase was decanted off and the lower phase pumped (0.1 mm Hg) to afford the *title salt* (283 mg; 72%) as a brown oil: ν_{max}(neat)/cm^{-1} 3041, 2974, 2223, 1618, 1509, 1457, 1270, 1180, 754; δ_H (200 MHz; $CDCl_3$) 1.21 (6 H, d, *J* 6.9, CH(CH_3)$_2$), 2.87 (1 H, sept, *J* 6.9, CH(CH$_3$)$_2$), 4.42 (3 H, s, NCH_3), 7.89–8.00 (2 H, overlapping m, H-3 and H-5), 8.52 (1 H, br td, $J_{4,3}$ 8.0, $J_{4,5}$ 8.0, $J_{4,6}$ 0.8, H-4), 9.42 (1 H, br d, $J_{6,5}$ 5.7, H-6); δ_C (50 MHz; $CDCl_3$) 21.6 (CH(*C*H$_3$)$_2$), 21.7 (*C*H(CH$_3$)$_2$), 47.9 (NCH_3), 71.4 (*C*≡CCH), 117.0 (C≡*C*CH), 126.6 (CH), 131.5 (CH), 138.0 (C-2), 145.3 (CH-4), 147.2 (CH-6); *m*/*z* (+ve ion ESI) 160 (100%, $C_{11}H_{14}N^+$), 117 (22%, $C_{11}H_{14}N^+ - C_3H_7$); *m*/*z* (−ve ion ESI) 127 (100%, I^-); (found: organic cation, 160.1120. $C_{11}H_{14}N^+$ requires 160.1121).¶¶

2-(2-Isopropylpyrazolo[1,5-*a*]pyridin-3-yl)-1-methylpyridinium iodide (38)

A stirred mixture of 1-aminopyridinium mesitylenesulfonate[12] (581 mg, 1.97 mmol), **37** (283 mg, 986 μmol) and powdered K_2CO_3 (555 mg, 4.01 mmol) in DMF (5 mL) was heated at 95 °C for 18 h. The mixture was then evaporated to dryness and the residue directly subjected to flash column chromatography (gradient elution from CH_2Cl_2 to 1 : 9 MeOH–CH_2Cl_2). Relevant fractions were combined, evaporated and the resulting residue triturated with 2 : 1 CH_2Cl_2–Et_2O to afford the *title salt* (146 mg; 39%) as a buff coloured powder: ν_{max}(thin film)/cm^{-1} 3019, 2972, 1632, 1530, 1216, 756, 754; δ_H (400 MHz; $CDCl_3$) 1.23 (3 H, d, *J* 6.9, CHCH_3), 1.30 (3 H, d, *J* 6.9, CHCH_3), 2.97 (1 H, sept, *J* 6.9, CH(CH$_3$)$_2$), 4.30 (3 H, s, NMe), 6.94 (1 H, td, $J_{6',5'}$ 6.9, $J_{6',7'}$ 6.9, $J_{6',4'}$ 1.3, H-6′), 7.36 (1 H, ddd, $J_{5',4'}$ 8.9, $J_{5',6'}$ 6.9, $J_{5',7'}$ 1.1, H-5′), 7.71 (1 H, dt, $J_{4',5'}$ 8.9, $J_{4',6'}$ 1.1, H-4′), 7.87 (1 H, dd, $J_{3,4}$ 7.9, $J_{3,5}$ 1.4, H-3), 8.14 (1 H, ddd, $J_{5,4}$ 7.7, $J_{5,6}$ 6.3, $J_{5,3}$ 1.4, H-5), 8.48 (1 H, d6, $J_{7'6,'}$ 7.0, $J_{7',4'}$ 1.0, $J_{7',5'}$ 1.0, H-7′), 8.55 (1 H, td, $J_{4,3}$ 7.9, $J_{4,5}$ 7.9, $J_{4,6}$ 1.2, H-4), 9.62 (1 H, br d, $J_{6,5}$ 6.2, H-6); δ_C (101 MHz; $CDCl_3$) 22.6 (CH*C*H$_3$), 22.9 (CH*C*H$_3$), 27.0 (*C*H(CH$_3$)$_2$), 47.2 (NMe), 98.9 (C-3′), 113.7 (CH-6′), 117.0 (CH-4′), 126.9 (CH-5), 127.6 (CH-5′), 129.2 (CH-7′), 131.5 (CH-3), 139.3 (C-3a′), 145.2 (CH-4), 148.5 (CH-6), 149.3 (C-2), 159.9 (C-2′); *m*/*z* (+ve ion ESI) 252 (100%, $C_{16}H_{18}N^+$); *m*/*z* (−ve ion ESI) 127 (100%, I^-); (found: organic cation, 252.1494. $C_{16}H_{18}N^+$ requires 252.1495).¶¶

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Notes and references

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