Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 9627–9634

Divergent cyclisations of 2-(5-amino-4-carbamoyl-1*H*-pyrazol-3-yl)acetic acids with formyl and acetyl electrophiles

Lynette A. Smyth,[a] Thomas P. Matthews,[a] Peter N. Horton,[b] Michael. B. Hursthouse[b] and Ian Collins[a,*]

[a]*Cancer Research UK Centre for Cancer Therapeutics, The Institute of Cancer Research, 15 Cotswold Road, Belmont, Surrey SM2 5NG, UK*
[b]*EPSRC UK National Crystallography Service, School of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, UK*

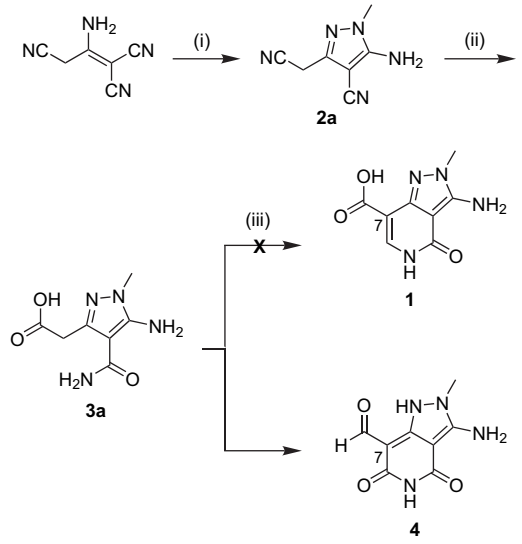
Received 17 May 2007; revised 25 June 2007; accepted 12 July 2007
Available online 19 July 2007

Abstract—The reaction of 2-(5-amino-4-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)acetic acid and triethylorthoformate did not give the expected dihydropyrazolo[4,3-*c*]pyridin-4-one product as described in literature, but formed an alternative cyclic imide product, fully characterised by NMR and X-ray crystallography. This mode of reaction was shown to be general to other 1-substituted-2-(5-amino-4-carbamoyl-1*H*-pyrazol-3-yl)acetic acids. The outcome of the cyclisation was highly sensitive both to the nature of the reagents used and also to the acidity of the reaction medium, such that a number of interesting bicyclic heterocycles could be produced in a controlled fashion from the single starting material. The major tautomeric forms of the bicyclic products in solution were found to vary according to their substitution pattern.

1. Introduction

Dihydropyrazolo[4,3-*c*]pyridin-4-ones are interesting compounds from the perspective of drug discovery, with potential for use as heterocyclic scaffolds in drug design. The target bicycle **1** contains a large number of hydrogen bond donors and acceptors that can bind proteins, as well as functional groups that can be used as points for further elaboration. Similar core structures are found in other biologically active molecules with a wide range of targets and effects.[1–5] As part of a programme to design and prepare libraries of heterocyclic compounds suitable for high-throughput screening against anti-cancer targets, we wished to investigate the synthesis and functionalisation of dihydropyrazolo[4,3-*c*]pyridin-4-ones related to **1**.

The synthesis of dihydropyrazolo[4,3-*c*]pyridin-4-ones bearing a carboxylate or similar substituent at C-7 has little precedence. Only one synthesis of **1** was reported in the literature,[6] starting from 2-(5-amino-4-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)acetic acid **3a** (Scheme 1). The product was characterised solely by UV, microanalysis and melting point. We attempted the synthesis of **1** by this route and obtained a product with similar properties. However, attempted functionalisation of the acid moiety of the product **1** was unsuccessful, prompting a more detailed structural analysis that revealed the structure to be different to that proposed in the literature. The use of ^{13}C NMR spectroscopy and X-ray crystallography led us to reassign the structure as the cyclic imide, **4**. Following this initial finding, we undertook a detailed study of the reactions of 2-(5-amino-4-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)acetic acid and



Scheme 1. Literature synthesis of the pyrazolopyridinone[6] (i) H_2N–$NHCH_3$, EtOH, reflux; (ii) NaOH, H_2O, reflux; (iii) (a) $(EtO)_3CH$, Ac_2O, reflux, (b) NaOH, H_2O, reflux.

Keywords: Cyclisation; One-carbon electrophile; Heterocycle; Divergent synthesis; Tautomerism.
* Corresponding author. Tel.: +44 208 722 4317; fax: +44 208 722 4126; e-mail: ian.collins@icr.ac.uk

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.07.034

close analogues with formyl and acetyl electrophilic reagents.

2. Results and discussion

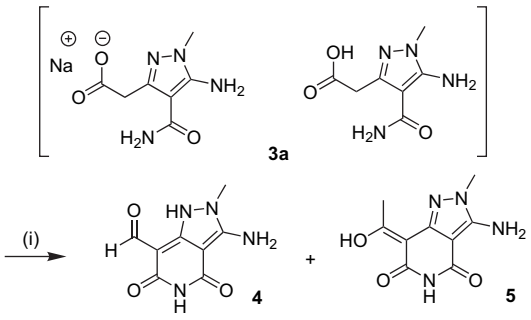
2.1. Reactions of 2-(5-amino-4-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)acetic acid (3a)

The synthesis of dihydropyrazolo[4,3-*c*]pyridinone **1** using the literature method[6] (Scheme 1) gave a product that had an identical UV spectrum (λ_{max} (0.1 M NaOH) 227, 237–246 (shoulder), 284, 332) and melting point (>350 °C) to that quoted. Mass spectrometry confirmed the molecular weight to be consistent with the anticipated product **1**. The ^{1}H NMR data could also be assigned to the expected structure, though many of the protons were exchangeable, leaving only two peaks (N–CH_3 and C–H), which could be reliably used for characterisation purposes.

Derivatisation of the acid was attempted but proved unsuccessful, so a more detailed analysis of the product assumed to be **1** was undertaken. Crystals of **1** were obtained by recrystallisation from DMSO, which were suitable for X-ray analysis. Although the crystals were twinned, the data were still sufficient to show the product to be **4** (Fig. 1) rather than the expected structure **1** (Scheme 1). The cyclic imide **4** adopted an interesting tautomeric form, with the pendant aldehyde in the keto form and accepting an intramolecular hydrogen bond from the pyrazole N(1)–H (N(1)–H⋯O(15)=2.33(3) Å), with the fused five-membered ring in a non-aromatic tautomer (see Fig. 1 for numbering). Additional intermolecular hydrogen bonding was observed, which potentially gives a more stable crystal lattice, and may explain the high melting point and poor solubility of compound **4**. Obtaining a ^{13}C NMR spectrum of **4** proved difficult due to its poor solubility (1.4 mg mL^{-1} in DMSO) and the slow relaxation times of some of the ^{13}C nuclei. After a number of attempts the presence of an aldehyde C–H was confirmed at δ 178 ppm by a DEPT experiment using an increased number of scans. There is more precedence for this type of structure, **4**, and there are a number of syntheses of cyclic imides in the literature, but only a few with a carbonyl group at the 7-position.[7–9]

To enable more comprehensive studies on the reactions of **3a**, we sought an alternative purification method that avoided the use of toxic $Pb(OAc)_2$ and H_2S as originally described.[6] A simpler purification, used for compounds related to **3a**, involved acidification of the reaction mixture with aq HCl and collection of the precipitated free acid.[11] However, when **3a** isolated by this means was reacted with triethylorthoformate and acetic anhydride a mixture of two compounds was produced (Scheme 2). One of these was shown to be **4**, having identical HPLC retention time and NMR data, while the other (**5**) had a molecular weight of M+14 corresponding to the addition of a methylene group. The two compounds proved inseparable by either silica chromatography or recrystallisation, due to poor solubility, but NMR data supported the hypothesis that a compound with an additional methyl group was present, with an extra peak at δ 2.56 ppm (integration 3H) seen in the ^{1}H NMR spectrum. The structure of the new product was later confirmed by X-ray crystallography as pyrazolo[4,3-*c*]pyridinedione **5** (Fig. 2) following the development of a synthetic route to produce **5** as a single compound (see below).

X-ray analysis was carried out on a good quality crystal of compound **5** resulting in two independent molecules in the asymmetric unit. Structurally they are almost identical and both show that they adopted a different tautomeric form



Scheme 2. A mixture of the sodium salt and free acid of **3a** yielded two products: (i) (a) $(EtO)_3CH$, Ac_2O, reflux, (b) NaOH, H_2O, reflux (64%, **4**:**5**=4:1).

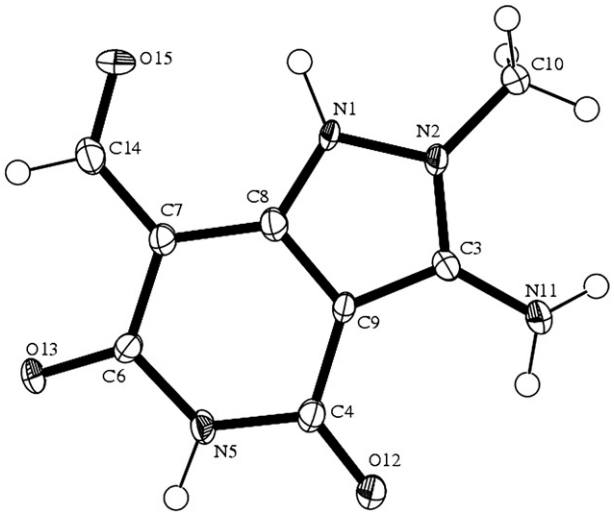


Figure 1. ORTEP[10] representation of the X-ray crystal structure of **4**.

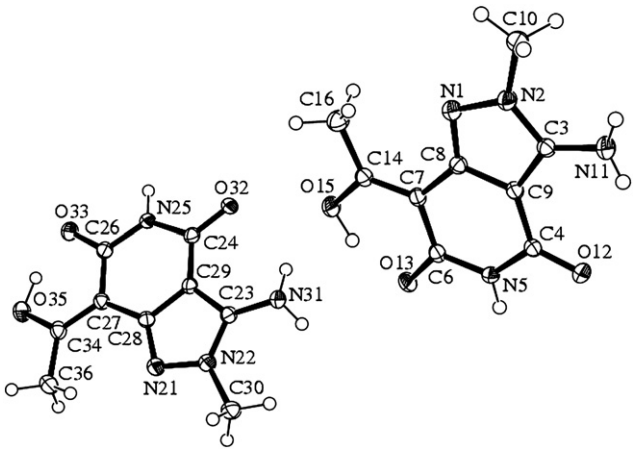


Figure 2. ORTEP[10] representation of the X-ray crystal structure of **5**.

compared to **4**, with the pendant methyl ketone in the enol tautomer (bond length C(14)–O(15)=1.331(2) Å, C(34)–O(35)=1.329(2) Å for **5** vs 1.232(2) Å for **4**) and the fused pyrazole ring in the unprotonated aromatic tautomer. Also the Fourier difference map does suggest that there is only a hydrogen atom attached to the enol oxygen (O15, O35) forming an intramolecular hydrogen bond to the imide oxygen (O13, O33, respectively).

We deduced that formation of a second product was due to the persistence of the sodium salt of **3a** when this intermediate was isolated by the modified procedure. On hydrolysis of **2**, the sodium salt of **3a** precipitated from solution. The mixture was acidified with HCl and the solid was collected by filtration. However, we observed that the salt of **3a** did not completely redissolve during the acidification process before the free acid began to precipitate. Thus the compound taken to the next reaction would likely have been a mixture of the free base and the sodium salt (Scheme 2). The pH of the reaction mixture for the next step would therefore have been altered to some extent and may have prevented the orthoester from being activated completely, allowing competition from the anhydride. It is well known that activation of orthoesters is highly pH dependent and requires the presence of H^+ ions.[12,13] In our case the resulting difference in pH may be small, but the major source of acid is pyrazole acetic acid **3a** itself and so the quantity of the free acid present in the reaction is critical.

The possibility that the presence of the sodium salt might alter the pH and subsequently the reaction outcome was confirmed by taking some of the mixture of **3a** and **3a** sodium salt, recrystallising it from water and acetic acid to guarantee the formation of the free acid, and repeating the reaction with triethylorthoformate and acetic anhydride from the original procedure. This time only one product, **4**, was formed.

2.2. Selective synthesis of 4 and 5 and other related bicyclic heterocycles

The mixture of products obtained with the mixture of free acid and sodium salt of **3a** was attributed to a competition between the reaction of the orthoester, making **4**, and the acetic anhydride, giving **5**. Therefore, to prepare them separately, orthoesters and anhydrides, which would react to give the same products were used. By using triethylorthoformate and acetic-formic anhydride,[14] **4** was synthesized, and by using trimethyl orthoacetate and acetic anhydride, **5** was the sole product formed (Scheme 3). These selective conditions were successful regardless of whether pure acid **3a** or a mixture of the free acid and sodium salt of **3a** was used. The selective synthesis of **5** allowed the isolation of crystals suitable for X-ray structural determination (Fig. 2).

During these investigations two further bicyclic heterocycles, **6** and **7**, were prepared by simple adjustments to the reaction conditions (Scheme 3). On the omission of acetic anhydride from the standard reaction conditions, i.e., refluxing **3a** in triethylorthoformate, and adding catalytic amounts of acid, 2-(1-methyl-4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl) acetic acid **6** was obtained. This structure was confirmed by X-ray crystallography (Fig. 3). The formation of **6** is consistent with the role of acetic anhydride to temporarily protect the primary amine in the standard reaction conditions, allowing the amide and carboxylic acid to react. The *N*-acetyl group is removed in a

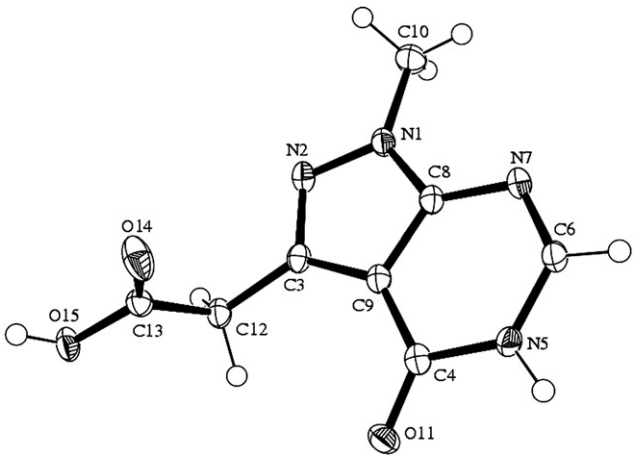
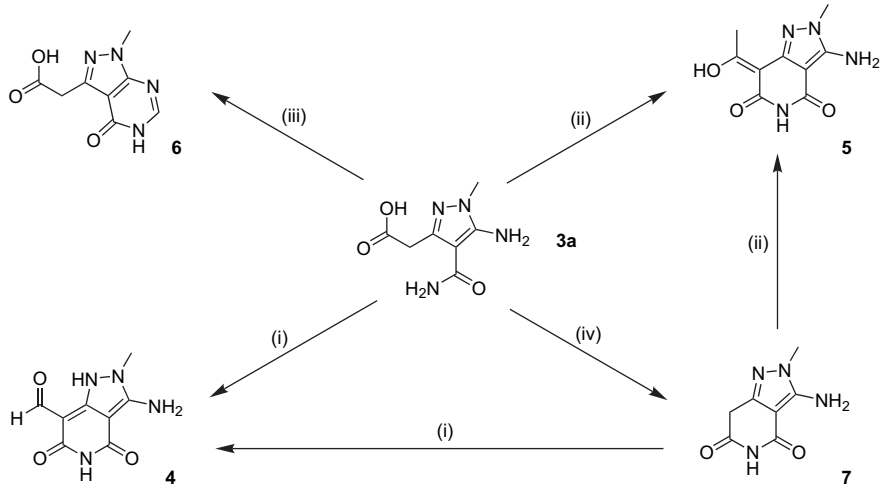


Figure 3. ORTEP[10] representation of the X-ray crystal structure of **6**.



Scheme 3. Simple changes in the reaction conditions led to a variety of products from **3a**. (i) (a) $(MeO)_3CH$, AcOCHO, reflux, (b) NaOH, H_2O, reflux (30% from **3a**, 38% from **7**); (ii) (a) $(MeO)_3CCH_3$, Ac_2O, reflux, (b) NaOH, H_2O, reflux, (c) HCl, H_2O, reflux (43% from **3a**, 30% from **7**); (iii) $(EtO)_3CH$, HCl, reflux (30%); (iv) HCl, reflux (77%).

separate base hydrolysis step during work up. In the absence of this temporary N-protection, the carbon electrophile reacted preferentially with the amino substituent and the amide. There is precedence in the literature for the formation of pyrazolo[3,4-*d*]pyrimidin-4-ones similar to **6** under related conditions, and these also exhibit biological activity.[15,16]

On removal of triethylorthoformate from the reaction mixture, **3a** reacted with acetic anhydride to give **5**, but the hydrolysis step proved problematic this time around and the yield was low. This seemed to be due to the slow removal of the acetyl group, requiring repetition of the base hydrolysis step.

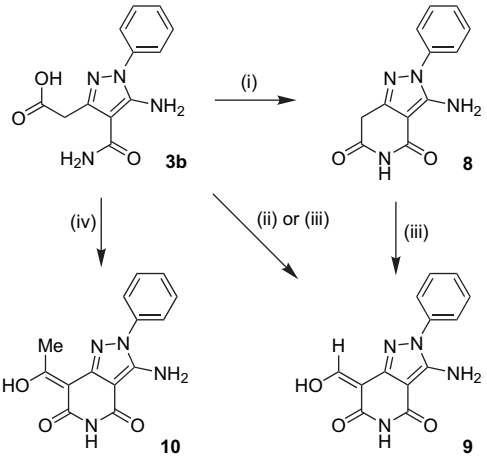
The dehydration product, **7**, was formed under acidic conditions as stated in the primary literature[6] but it was also possible that **7** could be an intermediate in the reactions to form **4** and **5**. Confirmation of this was obtained by subjecting **7** to the standard reaction conditions through which **4** and **5** were formed from **3a** (Scheme 3). This revealed that **7** was indeed converted selectively to either **4** or **5**, depending on the anhydride–orthoester combination. Thus, a possible path for the formation of the cyclic imides **4** and **5** is through initial dehydration of **3a**, with concomitant amine acylation, to give *N*-acylated **7**, which subsequently undergoes reaction with the carbon electrophile to introduce the pendant carbonyl functionality of **4** and **5**.

2.3. Reactions of 2-(5-amino-4-carbamoyl-1-phenyl-1*H*-pyrazol-3-yl)acetic acid (3b)

To investigate if the pattern of reactivity seen with the *N*-methyl substituted pyrazole **3a** would extend to other derivatives, similar reactions with the *N*-phenyl analogue **3b** were carried out. When reacted with acetic anhydride only, the dehydration product **8** precipitated from the reaction mixture. This was in contrast to the behaviour of the *N*-methyl analogue **3a**, which gave the ketone-bearing scaffold **5**. However, the formation of **8** can be rationalised if, as proposed from observations with **7**, the dehydration product is an intermediate in the reaction. In the case of the phenyl analogue **3b** this initial product **8** is not soluble and therefore precipitates rapidly from the reaction mixture. When the *N*-methyl pyrazole **3a** is reacted, the intermediate dehydration product **7** is more soluble and continues to react to give **5**.

Other reactions were also carried out using the *N*-phenyl analogue **3b**. In this case, using material isolated by the modified procedure (HCl precipitation) and reacting with acetic anhydride and triethylorthoformate, only product **9** was formed. This was attributed to the production of solely the pure, free acid **3b** in this instance, since during the purification all products were in solution and only precipitated upon addition of acid.

It was found that both **9** and **10** could be synthesised separately using the anhydride–orthoester combination discovered for the methyl analogue. Compound **9** was also prepared from imide **8** using the same conditions as for transformation from **3b** (Scheme 4). Importantly, with both *N*-methyl and *N*-phenyl pyrazole acetic acids **3a** and **3b**, in a variety of reaction conditions, we did not observe the formation of products consistent with the originally proposed dihydropyrazolo[4,3-*c*]pyridin-4-one structure.



Scheme 4. (i) Ac_2O, reflux (54%); (ii) (a) $(EtO)_3CH$, Ac_2O, reflux, (b) NaOH, H_2O, reflux (75%); (iii) (a) $(MeO)_3CH$, AcOCHO, reflux, (b) NaOH, H_2O, reflux (15% from **3b**, 57% from **8**); (iv) (a) $(MeO)_3CCH_3$, Ac_2O, reflux, (b) NaOH, H_2O, reflux, (c) HCl, H_2O, reflux (45%).

2.4. Comparison of ^{1}H and ^{13}C NMR data for the pyrazolopyridinediones 4, 5, 9 and 10

A good correlation of proton and carbon chemical shifts was observed between the bicyclic compounds **4**, **5**, **9** and **10** (Fig. 4) on comparison of the NMR data (Table 1), although it was noticed that the aldehyde carbon signal for **9** was at unusually high field, as was the C*H* signal for that aldehyde in the ^{1}H NMR. The differences in these signals between **9** and **4** correlated with those anticipated in the literature for

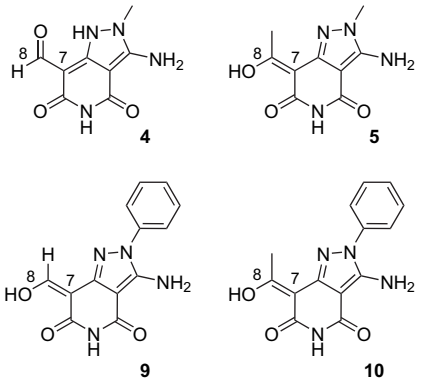


Figure 4. Predominant tautomers of compounds **4**, **5**, **9** and **10** based on X-ray crystal structures and NMR data.

Table 1. Selected ^{1}H and ^{13}C NMR signals for **4**, **5**, **9** and **10**

	4	5	9	10
^{1}H assignment[a]				
C8–CH_3	—[b]	2.56	—	2.59
N–CH_3	3.56	3.58	—	—
Ph	—	—	7.43–7.58	7.53–7.61
C7–*CH*	9.26	—	8.42	—
^{13}C assignment[c]				
C8–CH_3	—	22.6	—	22.9
N–CH_3	33.0	34.1	—	—
C=O	160.8, 166.2	159.6, 172.1	161.5, 166.6	160.1, 172.1
*C*8=O	178.4	182.3	165.4	183.3

[a] ^{1}H values in parts per million relative to DMSO=2.50 ppm.
[b] Signal not present.
[c] ^{13}C values in parts per million relative to DMSO=39.5 ppm.

the shift from a keto to enol tautomeric form[17] and indicated that the enol tautomer of **9** was prevalent in solution (Fig. 4). Thus while the *N*-methyl 7-aldehyde **4** is present as the keto tautomer both in the solid state and in the solution, the *N*-phenyl analogue **9** adopts the enol form in solution.

3. Conclusions

In summary, the reaction of 2-(5-amino-4-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)acetic acid (**3a**) and triethylorthoformate–acetic anhydride did not give the expected dihydropyrazolo[4,3-*c*]pyridin-4-one product, but rather a cyclic imide **4**. This led us to investigate the reactions of the starting material **3a** and the *N*-phenyl analogue **3b** further, revealing a number of modes of cyclisation to give interesting bicyclic heterocycles, which have been fully characterised. The major tautomers adopted by some of these bicyclic products in the solid phase and solution have been examined by X-ray crystallography and NMR, respectively. The keto–enol tautomerism of the pendant C-7 carbonyl functionality in compounds **4**, **5**, **9** and **10** was found to vary according to the substitution of the carbonyl and the nature of the pyrazole *N*-substituent. The outcome of the cyclisation of 1-substituted-2-(5-amino-4-carbamoyl-1*H*-pyrazol-3-yl)acetic acids **3a** and **3b** can be controlled by the combinations of formyl and acetyl electrophiles used and is also sensitive to the acidity of the reaction medium.

4. Experimental

4.1. General experimental

All reagents and anhydrous solvents were obtained from commercial suppliers and used without further purification. Infrared spectra were recorded on a Perkin–Elmer Spectrum RX-1 FTIR spectrometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded at 500 and 126 MHz, respectively, on Bruker AMX500 spectrometers using an internal deuterium lock. Microanalysis was carried out by Warwick Analytical Service, and X-ray crystallography was carried out by the EPSRC UK National Crystallography Service at the University of Southampton. HPLC–MS analyses were performed on a Micromass LCT/Water's Alliance 2795 HPLC system with a Supelco Discovery column at 22 °C, eluting with a MeOH–water gradient. UV detection was at 254 nm and ionisation was by positive or negative ion electrospray. Molecular weight scan range was 50–1000. Compound purities were determined from the HPLC data by comparison of the integrations of the plot of UV absorption versus retention time for the compound and any observed impurities. HRMS values were determined on a Micromass LCT/Water's Alliance 2795 system with a Supelco Discovery column at 22 °C, or on an Agilent 6210 TOF MS with a Phenomenex Gemini 3 μm C18 (3 cm×4.6 mm i.d.) column.

Suitable crystals were selected and data were collected on a Bruker Nonius KappaCCD Area Detector at the window of a Bruker Nonius FR591 rotating anode (Mo K= 0.71073 Å) driven by COLLECT1 and DENZO2 software at 120 K. The structures were determined in SHELXS-973 and refined using SHELXL-974.

Crystallographic data (excluding structural factors) for the structures in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers 646017, 646018, and 646019. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.1.1. 5-Amino-3-(cyanomethyl)-1-methyl-1*H*-pyrazole-4-carbonitrile (2a).[6] A suspension of 2-amino-1-propene-1,1,3-tricarbonitrile (2.00 g, 15.2 mmol) in EtOH (15 mL) was heated to reflux, whereupon it dissolved and was removed from the heat source. A solution of methylhydrazine (0.29 mL, 16.7 mmol) in EtOH (4.5 mL) was added dropwise and the resulting solution was heated at reflux for 45 min and then cooled. The small pale brown crystals were recrystallised (water) to give **2a** as pale yellow needles (1.29 g, 8.01 mmol, 53%); mp 178–179 °C; R_f=0.39 (80:20, EtOAc–Hex); IR (Nujol mull, cm^{-1}) 3351 (NH_2), 2216 (CN); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ_H 3.64 (3H, s, CH_3), 3.84 (2H, s, CH_2), 6.06 (2H, br s, NH_2); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ_C 16.9, 74.3, 113.9, 116.8, 143.0, 153.1; MS (ESI) *m*/*z* 162 (M+H)$^+$; HRMS (M+H)$^+$ calcd for $C_7H_8N_5$ 162.0780, found 162.0776; HPLC t_R=2.54 min; purity >99%. Anal. Calcd for $C_7H_7N_5$: C, 52.17; H, 4.38; N, 43.45%. Found: C, 52.00; H, 4.30; N, 43.26%.

4.1.2. 5-Amino-3-(cyanomethyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (2b).[6] A suspension of 2-amino-1-propene-1,1,3-tricarbonitrile (2.00 g, 15.2 mmol) in EtOH (20 mL) was heated to reflux, whereupon it dissolved and was removed from the heat source. Phenylhydrazine (1.64 mL, 16.7 mmol) was added slowly, the solution heated at reflux for 15 min, and then cooled. The resulting small pale brown crystals were collected and washed with cold EtOH. Recrystallisation from EtOH gave **2b** as pale purple needles (1.39 g, 6.22 mmol, 41%); mp 166–167 °C; R_f=0.72 (80:20, EtOAc–Hex); IR (Nujol mull, cm^{-1}) 3328 (NH_2), 2218 (CN), 2216 (CN); ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ_H 3.99 (2H, s, CH_2), 6.31 (2H, br s, NH_2), 7.47–7.49 (1H, m, Ar*H*), 7.55–7.60 (4H, m, Ar*H*); ^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ_C 17.1, 75.1, 113.6, 116.6, 125.4, 129.4, 130.5, 138.3, 145.0, 153.0; MS (ESI) *m*/*z* 224 (M+H)$^+$; HRMS (M+H)$^+$ calcd for $C_{12}H_{10}N_5$ 224.0936, found 224.0942; HPLC t_R=4.40 min; purity >99%. Anal. Calcd for $C_{12}H_9N_5 \cdot 0.05(H_2O)$: C, 48.68; H, 3.47; N, 47.31%. Found: C, 48.47; H, 3.39; N, 47.14%.

4.1.3. 2-(5-Amino-4-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)acetic acid (3a).[6] A solution of 5-amino-3-(cyanomethyl)-1*H*-pyrazolidine-4-carbonitrile (**2a**) (400 mg, 2.48 mmol) and NaOH (200 mg, 5.00 mmol) in water (2.5 mL) was heated at reflux for 5 h. Purification was carried out by acidifying the cream coloured suspension to pH 5–6 with glacial AcOH. $Pb(OAc)_2$ (575 mg, 1.51 mmol) was dissolved in water (5 mL), heated and added to the reaction mixture. After heating at reflux for 15 min, the resulting white lead salt was collected by filtration and washed with cold water. The solid was suspended in boiling water (12.5 mL) and H_2S was bubbled through for 15 min, whereupon a black precipitate formed. The black solid was removed by filtration to give a clear solution from which colourless crystals of

3a precipitated (143 mg, 0.72 mmol, 29%); mp 205–208 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 3.47 (3H, s, CH_3), 3.57 (2H, s, CH_2), 6.08 (2H, s, amine NH_2), 6.78 (2H, s, amide NH_2), 12.78 (1H, br s, OH); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 33.7, 34.8, 96.3, 142.0, 149.9, 166.6, 172.1; MS (ESI) m/z 199 (M+H)$^+$; HRMS (M+H)$^+$ calcd for $C_7H_{11}N_4O_3$ 199.0831, found 199.0829; HPLC t_R=1.76 min; purity >99%. Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27%. Found: C, 42.45; H, 5.10; N, 28.07%.

Alternative purification (2.00 g scale):[10] the cream suspension formed following basic hydrolysis was cooled, neutralised with 10% HCl and collected by filtration to give **3a**, which was used without further purification (mixture of free acid and Na salt) (1.70 g, 8.57 mmol, 69%); mp 202–204 °C; R_f=0.68 (50:50, MeOH–CH_2Cl_2); IR (Nujol mull, cm^{-1}) 3397 (NH_2), 3200–3300 (br, NH), 1583 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 3.13 (2H, s, CH_2), 3.41 (3H, s, CH_3), 5.96 (2H, s, amine NH_2), 6.17 (1H, br s, amide NH_2), 10.36 (1H, br s, amide NH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 33.4 (*C*H_3), 39.3 (*C*H_2), 96.7, 145.1, 150.2, 167.8, 174.3; MS (ESI) m/z 199 (M+H)$^+$; HRMS (M+H)$^+$ calcd for $C_7H_{11}N_4O_3$ 199.0831, found 199.0830; HPLC t_R=1.76 min; purity >99%. Anal. Calcd for $0.9(C_7H_9N_4O_3Na)\cdot 0.1(C_7H_{10}N_4O_3)\cdot 1.2(H_2O)$: C, 35.09; H, 4.84; N, 23.38%. Found: C, 34.83; H, 4.60; N, 23.41%.

On recrystallisation of this white solid by dissolving in hot AcOH, clear crystals of **3a** were formed. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 3.47 (3H, s, CH_3), 3.57 (2H, s, CH_2), 6.08 (2H, s, amine NH_2), 6.78 (2H, s, amide NH_2), 12.78 (1H, br s, OH); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 33.7, 34.8, 96.3, 142.0, 149.9, 166.6, 172.1.

4.1.4. 2-(5-Amino-4-carbamoyl-1-phenyl-1*H*-pyrazol-3-yl)acetic acid (3b).[6,10] A solution of 5-amino-3-cyanomethyl-1-phenyl-pyrazolidine-4-carbonitrile (**2b**) (2.00 g, 8.97 mmol) in 10% NaOH aq (6.46 mL, 16.1 mmol) was heated at reflux for 50 min. The resulting brown solution was cooled and acidified to pH 3 with 10% HCl. *N*-Phenyl pyrazole acetic acid **3b** precipitated as a pale brown solid, which was collected by filtration and was used without further purification (1.81 g, 6.95 mmol, 77%); mp 186–187 °C; R_f=0.74 (50:50, MeOH–CH_2Cl_2); IR (Nujol mull, cm^{-1}) 3313 (NH_2), 3185 (amide), 1709 (C=O), 1640 (C=C), 1608 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 3.72 (2H, s, CH_2), 6.30 (2H, s, amine NH_2), 6.93 (2H, s, amide NH_2), 7.38 (1H, tt, J=7.0, 1.5 Hz, ArH), 7.50–7.55 (4H, m, ArH), 12.71 (1H, br s, OH); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 34.7, 97.1, 123.3, 127.1, 129.3, 137.9, 144.2, 149.9, 166.6, 172.0; MS (ESI) m/z 161 (M+H)$^+$; HRMS (M+H)$^+$ calcd for $C_{12}H_{13}N_4O_3$ 261.0988, found 261.0984; HPLC t_R=3.88 min; purity 95%. Anal. Calcd for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53%. Found: C, 55.03; H, 4.59; N, 21.14%.

4.1.5. 3-Amino-2-methyl-4,6-dioxo-2,4,5,6-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine-7-carbaldehyde (4).

4.1.5.1. Method A. A solution of 2-(5-amino-4-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)acetic acid (**3a**) (2.00 g, 10.1 mmol) in AcOCHO (29.88 mL), prepared in situ,[14] and $(MeO)_3CH$ (19.86 mL) was heated at reflux for 3 h. The resulting red-brown solution was cooled and the solvent was removed in vacuo. The brown solid was taken up in 10% NaOH aq (14 mL) and water (70 mL) and heated at reflux for 15 min. Glacial AcOH was added to the hot orange solution until it became turbid. On cooling, **4** precipitated as a bright orange solid (620 mg, 2.98 mmol, 30%).

4.1.5.2. Method B. A solution of 3-amino-2-methyl-2*H*-pyrazolo[4,3-*c*]pyridine-4,6(5*H*,7*H*)-dione (**7**) (30 mg, 0.17 mmol) in AcOCHO[14] (0.49 mL) and $(MeO)_3CH$ (0.33 mL) was heated at reflux for 3 h. The resulting brown solution was cooled and the solvent was removed in vacuo. The brown solid was suspended in THF (2 mL) and 5% HCl (2 mL) was added. The suspension was heated at reflux for 10 min and then cooled. The resulting pale orange solid (**4**) was collected by filtration (13 mg, 0.063 mmol, 38%); mp >350 °C (DMSO); IR (Nujol mull, cm^{-1}) 1668 (C=O), 1611 (C=O); UV (0.1 M NaOH, λ_{max}) 227, 237–246 (shoulder), 284, 332; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 3.56 (3H, s, CH_3), 7.12 (2H, s, NH_2), 9.26 (1H, s, CHO), 9.89 (1H, br s, NH); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 33.0 (*C*H_3), 89.0, 93.9, 147.3, 148.7, 160.8, 166.2, 178.4 (*C*H); MS (ESI) m/z 209 (M+H)$^+$; HRMS (M+H)$^+$ calcd for $C_8H_9N_4O_3$ 209.0675, found 209.0679; HPLC t_R=2.37 min; purity >99%. Anal. Calcd for $C_8H_8N_4O_3\cdot 0.1$ (AcOH): C, 45.99; H, 3.95; N, 26.16%. Found: C, 45.60; H, 3.73; N, 26.45%.

4.1.6. (*Z*)-3-Amino-7-(1-hydroxyethylidene)-2-methyl-2*H*-pyrazolo[4,3-*c*]pyridine-4,6(5*H*,7*H*)-dione (5).

4.1.6.1. Method A. A solution of 2-(5-amino-4-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)acetic acid (**3a**) (1.00 g, 5.05 mmol) in Ac_2O (13.0 mL) and $(MeO)_3CMe$ (10.0 mL) was heated at reflux for 3 h. The resulting brown solution was cooled and the solvent was removed in vacuo. The brown solid was taken up in 10% NaOH aq (6 mL) and water (30 mL) and heated at reflux for 15 min. Glacial AcOH was added to the hot orange solution until it was turbid. On cooling, a pink solid precipitated. The solid was collected by filtration, taken up in 5% HCl (18 mL) and THF (18 mL) and the suspension heated at reflux for 15 min. On cooling, the pink precipitate of **5** was isolated by filtration (487 mg, 2.19 mmol, 43%).

4.1.6.2. Method B. A solution of 3-amino-2-methyl-2*H*-pyrazolo[4,3-*c*]pyridine-4,6(5*H*,7*H*)-dione (**7**) (30 mg, 0.17 mmol) in Ac_2O (0.43 mL) and $(MeO)_3CMe$ (0.33 mL) was heated at reflux for 3 h. The resulting brown solution was cooled and the solvent was removed in vacuo. The brown solid was suspended in THF (2 mL) and 5% HCl (2 mL) and heated at reflux for 10 min. After cooling, the resulting orange solid (**5**) was collected by filtration (11 mg, 0.05 mmol, 30%); mp 299–301 °C (DMSO); IR (Nujol mull, cm^{-1}) 3135 (NH), 1662 (C=N), 1616 (C=O), 1599 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H 2.56 (3H, s, C–CH_3), 3.58 (3H, s, N–CH_3), 6.42 (2H, s, NH_2), 10.95 (1H, br s, NH); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 22.6 (*C*H_3), 34.1 (*C*H_3), 91.8, 94.4, 145.3, 147.8, 159.6, 172.1, 182.3; MS (ESI) m/z 223 (M+H)$^+$; HRMS (M+H)$^+$ calcd for $C_9H_{11}N_4O_3$ 223.0831, found 223.0829; HPLC t_R=3.89 min; purity >99%. Anal. Calcd for $C_9H_{10}N_4O_3\cdot 0.1$ (AcOH): C, 48.42; H, 4.59; N, 24.55%. Found: C, 48.05; H, 4.31; N, 24.45%.

4.1.7. 2-(1-Methyl-4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)acetic acid (6). A solution of 2-(5-amino-4-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)acetic acid (**3a**) (150 mg, 0.76 mmol) in $(EtO)_3CH$ (2.0 mL) with concd HCl (two drops) was heated at reflux for 3 h. A yellow-orange solid precipitated from the reaction mixture. On cooling, the solids were isolated by filtration to give **6** (48 mg, 0.23 mmol, 30%); mp 264–367 °C (217–219 °C, phase change) (AcOH); R_f=0.17 (50:50, MeOH–CH_2Cl_2); IR (Nujol mull, cm^{-1}) 1687 (C=O), 1584 (C=O); ^1H NMR (500 MHz, DMSO-d_6) δ_H 3.74 (2H, s, CH_2), 3.83 (3H, s, CH_3), 8.02 (1H, s, C*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 33.5 (*C*H_3), 34.7 (*C*H_2), 104.0, 143.0, 148.1 (*C*H), 152.2, 157.8, 171.1; MS (ESI) *m/z* 209 $(M+H)^+$; HRMS $(M+H)^+$ calcd for $C_8H_9N_4O_3$ 209.0675, found 209.0671; HPLC t_R=2.70 min; purity >99%. Anal. Calcd for $C_8H_8N_4O_3$: C, 46.16; H, 3.87; N, 26.91%. Found: C, 45.97; H, 3.85; N, 26.70%.

4.1.8. 3-Amino-2-methyl-2*H*-pyrazolo[4,3-*c*]pyridine-4,6(5*H*,7*H*)-dione (7). A suspension of 2-(5-amino-4-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)acetic acid (**3a**) (100 mg, 0.51 mmol) and concd HCl (1.5 mL) was heated at 110 °C for 1 h. The mixture was cooled and the white solid (**7**) was collected by filtration (69 mg, 0.39 mmol, 77%); mp 290–292 °C (dec); R_f=0.60 (20:80, MeOH–CH_2Cl_2); IR (Nujol mull, cm^{-1}) 1696 (C=O), 1640 (C=O); ^1H NMR (500 MHz, DMSO-d_6) δ_H 3.51 (3H, s, CH_3), 3.63 (2H, s, CH_2), 10.73 (1H, s, N*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 31.9 (*C*H_3), 33.9 (*C*H_2), 91.8, 146.1, 148.0, 161.8, 171.2; MS (ESI) *m/z* 181 $(M+H)^+$; HRMS $(M+H)^+$ calcd for $C_7H_9N_4O_2$ 181.0726, found 181.0734; HPLC t_R=1.64 min; purity >99%. Anal. Calcd for $C_7H_8N_4O_2\cdot1.25(H_2O)$: C, 41.48; H, 5.22; N, 27.64%. Found: C, 41.51; H, 4.89; N, 27.32%.

4.1.9. 3-Amino-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine-4,6(5*H*,7*H*)-dione (8). A solution of 2-(5-amino-4-carbamoyl-1-phenyl-1*H*-pyrazol-3-yl)acetic acid (**3b**) (150 mg, 0.58 mmol) in Ac_2O (2.0 mL) was heated at reflux for 3 h. During this time, **8** precipitated as a pale yellow solid (76 mg, 0.31 mmol, 54%); mp 260–263 °C (AcOH); R_f=0.79 (20:80, MeOH–CH_2Cl_2); IR (Nujol mull, cm^{-1}) 3340 (NH_2), 1694 (C=O), 1621 (C=O); ^1H NMR (500 MHz, DMSO-d_6) δ_H 3.77 (2H, s, CH_2), 6.47 (2H, s, NH_2), 7.39–7.42 (1H, m, Ar*H*), 7.51–7.55 (4H, m, Ar*H*), 10.63 (1H, s, N*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 31.9 (*C*H_2), 92.7, 123.5 (*C*H), 127.5 (*C*H), 129.4 (*C*H), 137.6, 147.6, 148.1, 162.2, 171.1; MS (ESI) *m/z* 285 $(M+H)^+$; HRMS $(M+H)^+$ calcd for $C_{12}H_{11}N_4O_2$ 243.0882, found 243.0886; HPLC t_R=4.17 min; purity >99%. Anal. Calcd for $C_{12}H_{10}N_4O_2\cdot0.1$(AcOH): C, 59.03; H, 4.22; N, 22.57%. Found: C, 59.22; H, 4.13; N, 22.58%.

4.1.10. 3-Amino-4,6-dioxo-2-phenyl-2,4,5,6-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine-7-carbaldehyde (9).[6]

4.1.10.1. Method A. A solution of 2-(5-amino-4-carbamoyl-1-phenyl-1*H*-pyrazol-3-yl)acetic acid (**3b**) (100 mg, 0.39 mmol) in Ac_2O (1.15 mL) and $(EtO)_3CH$ (1.15 mL) was heated at reflux for 3 h. The resulting red solution was cooled and solvent was removed in vacuo. The brown solid was taken up in 10% NaOH aq (0.67 mL) and water (6.7 mL) and heated at reflux for 15 min. Glacial AcOH was added to the hot orange solution until it became turbid. On cooling, **9** precipitated as a pale yellow solid (78 mg, 0.29 mmol, 75%).

4.1.10.2. Method B. A solution of 2-(5-amino-4-carbamoyl-1-phenyl-1*H*-pyrazol-3-yl)acetic acid (**3b**) (1.00 g, 3.85 mmol) in AcOCHO (11.40 mL), prepared in situ,[14] and $(MeO)_3CH$ (7.57 mL) was heated at reflux for 3 h. The resulting red solution was cooled and solvent was removed in vacuo. The brown solid was taken up in 10% NaOH aq (6 mL) and water (30 mL) and heated at reflux for 15 min. Glacial AcOH was added to the hot orange solution until it became turbid. On cooling, **9** precipitated as a pale yellow solid (157 mg, 0.58 mmol, 15%).

4.1.10.3. Method C. A suspension of 3-amino-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine-4,6(5*H*,7*H*)-dione (**8**) (80 mg, 0.34 mmol) in AcOCHO (1.00 mL), prepared in situ,[14] and $(MeO)_3CH$ (0.67 mL) was heated at reflux for 3 h. The resulting red solution was cooled and solvent was removed in vacuo. The brown solid was taken up in 10% NaOH aq (0.5 mL) and water (6 mL) and heated at reflux for 15 min. Glacial AcOH was added to the hot orange solution until it became turbid. On cooling, **9** precipitated as a pale yellow solid (52 mg, 0.19 mmol, 57%); mp 273–275 °C (AcOH); R_f=0.73 (50:50, MeOH–DCM); IR (Nujol mull, cm^{-1}) 3162 (NH), 1683 (C=O), 1615 (C=O); ^1H NMR (500 MHz, DMSO-d_6) δ_H 6.58 (2H, s, NH_2), 7.43–7.46 (1H, m, Ar*H*), 7.53–7.58 (4H, m, Ar*H*), 8.42 (1H, s, C*H*O), 10.22 (1H, s, N*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 91.4, 98.4, 124.6 (*C*H), 128.0 (*C*H), 129.4 (*C*H), 136.8, 147.4, 147.7, 161.5 (*C*H), 165.4, 166.6; MS (ESI) *m/z* 271 $(M+H)^+$; HRMS $(M+H)^+$ calcd for $C_{13}H_{11}N_4O_3$ 271.0831, found 271.0834; HPLC t_R=2.97 min; purity >99%. Anal. Calcd for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.73; N, 20.73%. Found: C, 57.92; H, 3.76; N, 20.41%.

4.1.11. (*Z*)-3-Amino-7-(1-hydroxyethylidene)-2-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine-4,6(5*H*,7*H*)-dione (10). A solution of 2-(5-amino-4-carbamoyl-1-phenyl-1*H*-pyrazol-3-yl)acetic acid (**3b**) (450 mg, 1.73 mmol) in Ac_2O (3.95 mL) and $(MeO)_3CMe$ (5.06 mL) was heated at reflux for 3 h. The yellow solution was cooled and the solvent was removed in vacuo. The dark yellow solid was taken up into 10% NaOH aq (4 mL) and water (20 mL) and heated at reflux for 15 min. Glacial AcOH was added to the hot orange solution until it became turbid. On cooling, a pale yellow solid precipitated. The solid was collected by filtration and suspended in 5% HCl (8 mL) and THF (8 mL). The suspension was heated to reflux for 15 min. After cooling, the pale yellow solids of **10** were isolated by filtration (221 mg, 0.78 mmol, 45%); mp 264–266 °C (AcOH); R_f=0.77 (20:80, MeOH–CH_2Cl_2); IR (Nujol mull, cm^{-1}) 3200 (NH), 1705 (C=O), 1622 (C=N), 1575 (C=O); ^1H NMR (500 MHz, DMSO-d_6) δ_H 2.59 (3H, s, CH_3), 6.49 (2H, s, NH_2), 7.42 (1H, t, *J*=7.0 Hz, Ar*H*), 7.53–7.56 (2H, m, Ar*H*), 7.60–7.61 (2H, m, Ar*H*), 11.12 (1H, br s, N*H*); ^{13}C NMR (126 MHz, DMSO-d_6) δ_C 22.9 (*C*H_3), 92.6, 94.1, 123.5 (*C*H), 127.4 (*C*H), 129.4 (*C*H), 137.7, 146.7, 147.6, 160.1, 172.1, 183.3; MS (ESI) *m/z* 285 $(M+H)^+$; HRMS $(M+H)^+$ calcd for $C_{14}H_{13}N_4O_3$ 285.0988, found 285.0999; HPLC t_R=2.82 min; purity 97%. Anal. Calcd for $C_{14}H_{12}N_4O_3\cdot0.1$(AcOH): C, 58.76; H, 4.31; N, 19.30%. Found C: 58.74; H, 4.28; N, 19.24%.

5. Statistical data for the X-ray crystal structural determinations of 4–6

	4	5	6
Empirical formula	$C_8H_8N_4O_3$	$C_9H_{10}N_4O_3$	$C_8H_8N_4O_3$
Formula weight	208.18	222.21	208.18
Temperature	120(2) K	120(2) K	120(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Triclinic	Orthorhombic
Space group	$P2_1/n$	$P-1$	$Pbca$
Unit cell dimensions	a=6.8458(4) Å	a=7.21280(10) Å	a=14.4219(7) Å
	b=17.9414(9) Å	b=7.39940(10) Å	b=7.7902(2) Å
	c=7.3554(4) Å	c=17.7492(3) Å	c=15.6385(7) Å
	α=90°	α=79.6290(10)°	α=90°
	β=112.816(3)°	β=87.9050(10)°	β=90°
	γ=90°	γ=88.8590(10)°	γ=90°
Volume	832.73(8) Å^3	931.10(2) Å^3	1756.98(12) Å^3
Z	4	4	8
Density (calculated)	1.661 Mg/m^3	1.585 Mg/m^3	1.574 Mg/m^3
Absorption coefficient	0.131 mm^{-1}	0.123 mm^{-1}	0.124 mm^{-1}
F(000)	432	464	864
Crystal	Cut shard; light orange	Cut block; light orange	Rod; light yellow
Crystal size	0.07×0.06×0.04 mm^3	0.14×0.09×0.06 mm^3	0.40×0.05×0.04 mm^3
θ range for data collection	3.21–27.47°	3.22–27.48°	3.25–27.48°
Reflections collected	8634	17,879	13,231
Independent reflections	8635 [R_{int}=0.1030]	4237 [R_{int}=0.0302]	2010 [R_{int}=0.0531]
Completeness to θ=27.47°	99.5%	98.9%	99.6%
Data/restraints/parameters	8635/0/150	4237/1/317	2010/0/143
Goodness-of-fit on F^2	1.091	1.068	1.071
Final R indices [$F^2>2\sigma(F^2)$]	$R1$=0.1195, $wR2$=0.2728	$R1$=0.0483, $wR2$=0.1274	$R1$=0.0433, $wR2$=0.0950
R indices (all data)	$R1$=0.1731, $wR2$=0.3166	$R1$=0.0514, $wR2$=0.1299	$R1$=0.0588, $wR2$=0.1023
Largest diff. peak and hole	0.509 and −0.604 e Å^{-3}	0.781 and −0.279 e Å^{-3}	0.271 and −0.220 e Å^{-3}

Acknowledgements

We are grateful to The Institute of Cancer Research for funding (L.A.S.). This work was supported by Cancer Research UK [CUK], grant number C309/A8274. We thank Warwick Analytical Services Ltd and Jill Maxwell at the University of London for microanalysis data. We thank Dr. Amin Mirza and Mr. Meirion Richards for their expert assistance in the collection of NMR and MS data and Professor Keith Jones and Dr. Ted McDonald for their interest in this work and for helpful discussions. We also wish to acknowledge the use of the EPSRC Chemical Database Service at Daresbury.[18]

References and notes

1. Baraldi, P. G.; Tabrizi, M. A.; Preti, D.; Bovero, A.; Fruttarolo, F.; Romagnoli, R.; Zaid, N. A.; Moorman, A. R.; Varani, K.; Borea, P. A. *J. Med. Chem.* **2005**, *48*, 5001–5008.
2. Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Trincavelli, L.; Lucacchini, A. *J. Med. Chem.* **2000**, *43*, 3118–3124.
3. Markwalder, J. A.; Arnone, M. R.; Benfield, P. A.; Boisclair, M.; Burton, C. R.; Chang, C.-H.; Cox, S. S.; Czerniak, P. M.; Dean, C. L.; Doleniak, D.; Grafstrom, R.; Harrison, B. A.; Kaltenbach, R. F., III; Nugiel, D. A.; Rossi, K. A.; Sherk, S. R.; Sisk, L. M.; Stouten, P.; Trainor, G. L.; Worland, P.; Seitz, S. P. *J. Med. Chem.* **2004**, *47*, 5894–5911.
4. Shirai, A.; Ikeda, J. I.; Kawashima, S.; Tamaoki, T.; Kamiya, T. *J. Dermatol. Sci.* **2001**, *25*, 213–218.
5. Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819–1824.
6. Taylor, E. C.; Hartke, K. S. *J. Am. Chem. Soc.* **1959**, *81*, 2456–2464.
7. Elgemeie, G. H.; Ali, H. A.; Elghandour, A. H.; Abd Elaziz, G. W. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *164*, 189–197.
8. El-Sayed, A. A.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1801–1803.
9. Nair, M. D.; Mehta, S. R.; Kalbag, S. M. *Indian J. Chem.* **1967**, *5*, 464–466.
10. Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.
11. Sato, T. *J. Org. Chem.* **1959**, *24*, 963–966.
12. Bronsted, J. N.; Wynne-Jones, W. F. K. *Trans. Faraday Soc.* **1929**, *25*, 59–76.
13. DeWolfe, R. H.; Jensen, J. L. *J. Am. Chem. Soc.* **1963**, *85*, 3264–3268.
14. Fonseca, T.; Gigante, B.; Gilchrist, T. L. *Tetrahedron* **2001**, *57*, 1793–1799.
15. Gatta, F.; Luciani, M.; Palazzo, G. *J. Heterocycl. Chem.* **1989**, *26*, 613–618.
16. Petrie, C. R., III; Cottam, H. B.; McKernan, P. A.; Robins, R. K.; Revankar, G. R. *J. Med. Chem.* **1985**, *28*, 1010–1016.
17. O'Ferrall, R. A. M.; Murray, B. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2461–2470.
18. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746–749.