Preparation of 9-Substituted Pyridine-Stretched Adenines and Hypoxanthines

Julia A. Crawford,[a] William Fraser,[b] Christopher A. Ramsden*[a]

[a] Lennard-Jones Laboratories, School of Physical and Geographical Sciences, Keele University, Keele, Staffordshire, ST5 5BG, UK
Fax +44(1782)712378; E-mail: c.a.ramsden@chem.keele.ac.uk

[b] School of Life and Health Sciences, Aston University, Aston Triangle, Birmingham, B4 7ET, UK

Received 27 November 2008

Abstract: 9-Methylsulfanyl pyridine-stretched adenine and hypoxanthine derivatives have been prepared via regioselective reaction of a 5-aminoimidazole with 2-(bis-methylsulfanylmethylene)malononitrile [$(NC)_2C{=}C(SMe)_2$]. The 9-methylsulfanyl substituent can be replaced by sequential oxidation and substitution by nucleophiles including amines.

Key words: 5-aminoimidazoles, *lin*-pyridoadenines, soft electrophiles, tricyclic heterocycles, pyridine-stretched purines

Several groups have investigated the modification of purine nucleosides by insertion of a third ring between the imidazole and pyrimidine fragments. The earliest investigation was undertaken by Leonard and co-workers who described the synthesis of the benzene-stretched adenosine analogue **1** (Figure 1).[1–4] Later, the 2′-deoxy-derivative **3** was prepared.[5] Subsequently, other groups have prepared tricyclic analogues[6–8] and aspects of this work have been reviewed.[9] We have been interested in preparing pyridine-stretched purine derivatives for some time, and have previously described the adenosine analogue **2** and the corresponding inosine analogue.[10] More recently, we prepared the 2′-deoxy analogues of adenosine **4** and inosine,[11] which have been incorporated into oligonucleotides and their duplex-forming properties investigated.[12] With the objective of providing access to a wider range of pyridine-stretched purine derivatives, we have investigated the preparation of 9-substituted derivatives of the general types **5** and **6** ($R^3 \neq H$) and now report the results of these studies.

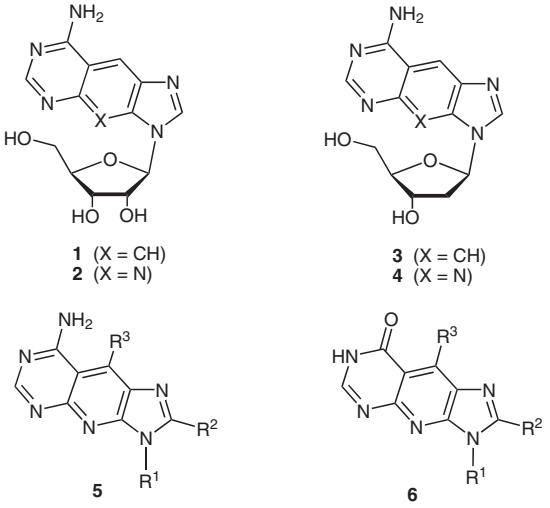


Figure 1

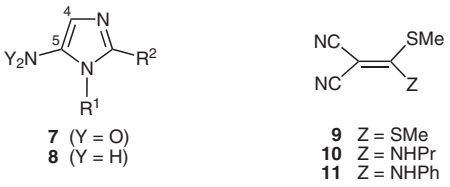


Figure 2

Two features of pyridine-stretched nucleosides may be advantageous: (i) the presence of the nitrogen atom in position 4 may enhance the stability of triplex-forming oligonucleotides (TFOs) targeted to DNA; (ii) their preparation via addition-elimination reactions of 5-aminoimidazoles may make them more easily accessible than the corresponding benzene-stretched derivatives. The 9-unsubstituted derivatives **2** and **4** were prepared via reaction of ethoxymethylene malononitrile [EMMN; $(NC)_2C{=}CHOEt$] with the appropriate 5-aminoimidazoles **8**, which were obtained by reduction of the 5-nitroimidazoles **7** (Figure 2).[10,11] The preparation of the 9-substituted derivatives **5** and **6** ($R^3 \neq H$) therefore requires a C-substituted analogue of EMMN that reacts selectively at the C-4 position of 5-aminoimidazoles **8**.

In an earlier study,[13,14] we showed that 5-aminoimidazoles[15] can react as either N- or C-nucleophiles and demonstrated a correlation between the position of the reaction and the softness of the electrophile, measured by the AM1 calculated LUMO energy. Thus, EMMN (LUMO –0.62 eV) gives exclusively C-adducts, whereas diethyl ethoxymethylenemalonate [EMME; $(EtO_2C)_2C{=}CHOEt$] (LUMO –0.27 eV) gives exclusively N-adducts. The general conclusion of our studies on a range of electrophiles was that reagents with a calculated (AM1) LUMO energy <–0.5 eV react predominantly at the C-4 position of 5-aminoimidazoles.[14] A C-substituted analogue of EMMN with a LUMO energy <–0.5 eV was therefore required in order to produce precursors of the 9-substituted derivatives **5** and **6**. Table 1 shows the AM1 calculated frontier orbital energies of selected electrophiles.

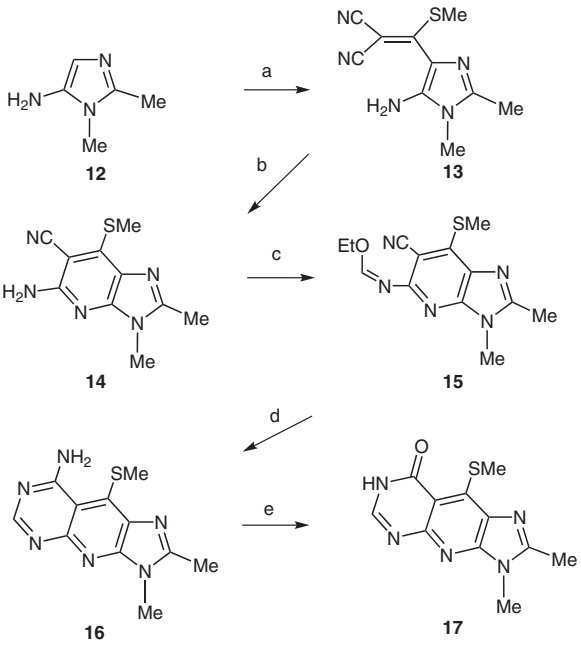
SYNTHESIS 2009, No. 8, pp 1271–1278
Advanced online publication: 25.03.2009
DOI: 10.1055/s-0028-1088028; Art ID: P13408SS

From Table 1 it is clear that introduction of a second ethoxy substituent into EMME (entries 2 and 4) will increase the LUMO energy and probably favour N-adduct formation. However, replacement of the ethoxy group by a methylsulfanyl substituent (entries 4 and 7) significantly reduces the LUMO energy, whilst the introduction of a second methylsulfanyl group (entry 8) leads to an electrophile with an exceptionally low energy LUMO. We therefore anticipated that 2-(bis-methylsulfanylmethylene)malononitrile [**9**; $(NC)_2C{=}C(SMe)_2$] would give C-adducts with 5-aminoimidazoles and thus provide access to 9-methylsulfanyl derivatives that can be further manipulated. Although we have not previously worked with the reagent **9**, it is readily prepared in good yield by reaction of malononitrile with carbon disulfide and methyl iodide in the presence of potassium fluoride.[16] The LUMO energy-lowering effect of an alkylsulfanyl substituent appears to be general: a similar effect is observed for the corresponding diesters (entries 1 and 3).

Table 1 AM1 Calculated Frontier Orbital Energies of Electrophiles

Entry	Electrophile	LUMO (eV)	HOMO (eV)
1	$(EtO_2C)_2C{=}CHOEt$	–0.27	–10.15
2	$(NC)_2C{=}C(OEt)_2$	–0.29	–9.53
3	$(EtO_2C)_2C{=}CH.SMe$	–0.60	–9.05
4	$(NC)_2C{=}CHOEt$	–0.62	–10.05
5	$(NC)_2C{=}C(SMe)NHPr$	–0.71	–8.93
6	$(NC)_2C{=}C(SMe)NHPh$	–0.90	–8.87
7	$(NC)_2C{=}CHSMe$	–0.95	–9.11
8	$(NC)_2C{=}C(SMe)_2$	–1.31	–8.91

In these studies we have used 5-amino-1,2-dimethylimidazole (**12**) as a model compound. A solution of the amine **12** in tetrahydrofuran was generated by catalytic reduction (H_2/Pd/C) of 1,2-dimethyl-5-nitroimidazole (**7**; R^1 = R^2 = Me). The amine solution was filtered through Celite into a flask containing a five-fold excess of 2-(bis-methylsulfanylmethylene)malononitrile (**9**) and the mixture was stirred at 50 °C overnight. Workup gave a yellow-orange solid that, in accord with prediction, was identified as the C-adduct **13** (Scheme 1). The yield was 47%, based on the nitroimidazole starting material, and no other products were identified in the reaction mixture. An analytically pure sample (mp 197–198 °C) was prepared by flash chromatography and recrystallisation (EtOAc–MeOH). The structure of compound **13** was fully supported by its spectroscopic properties. In particular, the ^{1}H NMR spectrum showed a broad singlet (δ = 7.05 ppm) corresponding to the NH_2 group and the absence of an imidazole ring proton, which would be characteristic of the isomeric N-adduct. The constitution $C_{10}H_{11}N_5S$ was confirmed by mass spectrometry and elemental analysis.



Scheme 1 *Reagents and conditions*: (a) **9**, THF, 50 °C, 12 h (47% for 2 steps); (b) MeOH/H_2O, NaOH, 60 °C (87%); (c) $CH(OEt)_3$, PTSA·H_2O, 150 °C, 4 h (86%); (d) NH_3, EtOH, r.t., 1 h then reflux 12 h (85%); (e) 2M HCl, reflux, 2 h (74%).

Treatment of a methanol solution of the C-adduct **13** with aqueous sodium hydroxide at 60 °C resulted in cyclisation to the imidazo[4,5-*b*]pyridine **14** (mp 300 °C; 86%). Subsequent treatment with hot triethyl orthoformate gave the ethyl imidate **15** (mp 197–200 °C; 87%), which, upon reaction with hot ethanolic ammonia, gave the tricyclic amine **16** (mp 252–255 °C; 85%). The properties of the amine **16** were fully in accord with the proposed structure. The ^{1}H NMR spectrum showed C–CH_3, S–CH_3 and N–CH_3 singlets (δ = 2.66, 2.94 and 3.75 ppm, respectively), together with a broad NH_2 signal (δ = 8.32 ppm) and a single ring proton (δ = 8.40 ppm). The mass spectrum showed a strong molecular ion (*m*/*z* = 260). Compound **16** is an example of a 9-substituted pyridine-stretched adenine derivative, so the route shown in Scheme 1, employing the soft bis-methylsulfanyl electrophile **9**, therefore establishes a viable route to derivatives of this type. Treatment of compound **16** with hot 2 M HCl for two hours, gave the pyridine-stretched hypoxanthine derivative **17** (mp >350 °C; 74%), which was fully characterised.

Reaction of the ethyl imidate **15** with *n*-propylamine under various conditions gave only the amidine **18** and not the anticipated tricyclic *N*-(*n*-propyl)-derivative **19** (Figure 3). All attempts at cyclisation were unsuccessful, although similar cyclisations of 9-unsubstituted derivatives have been reported.[15]

Inspection of Table 1 reveals that amino-substituted electrophiles (entries 5 and 6) also have a low-energy LUMO and might be expected to react selectively to give C-adducts. In principle these reagents could provide a direct route to 9-amino derivatives, for example, **5** and **6**

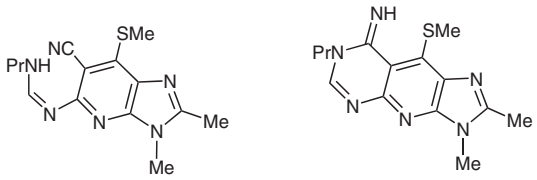


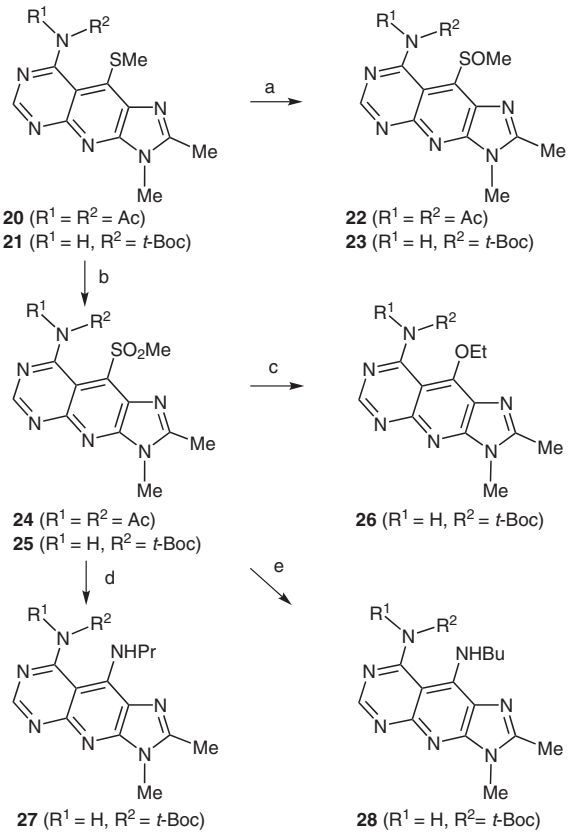
Figure 3

(R^3 = NHR). We therefore investigated the reactions of the reagents **10** and **11** with the aminoimidazole **12**, however, in neither case was any reaction detected under a variety of conditions. As might be expected, the nitrogen lone pair appears to reduce the reactivity of the electrophile and, although the LUMO energy is an indicator of regioselectivity, it is not a measure of reactivity. In order to prepare 9-amino derivatives we next investigated methods of modifying the 9-methylsulfanyl substituent.

Reaction of compound **16** with *n*-propylamine did not result in substitution of the thiomethyl group by the amine. It was therefore decided to oxidise the thioether to the methyl sulfone, which is a better leaving group. To avoid oxidation of the 8-amino group, N-protected derivatives were prepared. Reaction with either acetic anhydride or acetic anhydride/pyridine under various conditions gave the *N*,*N*-diacetyl derivative **20** (mp 178–183 °C). In one experiment, a very low yield of material (mp 218–220 °C) that appeared to be the mono-acetyl derivative was obtained, but attempts to repeat this by variation of method or work-up were unsuccessful. Attempts to remove one acetyl group using calcium carbonate in aqueous methanol[9] resulted in removal of both acetyl groups. We therefore decided to carry out further work on the diacetyl derivative **20**. The 8-amino group was also protected as the *tert*-butoxycarbonyl (*t*-Boc) derivative **21** [mp 167 °C (decomp.); 83%] by reaction with di-*tert*-butyl dicarbonate in 1,4-dioxane for six hours at 120 °C.

Oxidation of the *N*,*N*-diacetyl derivative **20** with one equivalent of 3-chloroperoxybenzoic acid (MCPBA) in dichloromethane at 0 °C gave a poor yield (11%) of the sulfoxide **22**. A similar procedure gave a better yield (63%) of the sulfoxide **23**. Both sulfoxides were fully characterized and showed the expected spectroscopic properties. Oxidation using two equivalents of MCPBA gave the sulfones **24** (mp 185–186 °C; 67%) and **25** [mp 100 °C (decomp.); 65%], respectively (Scheme 2). Further studies were carried out using the *t*-Boc-protected sulfone **25**, which was obtained in greater overall yield from the amine **16**.

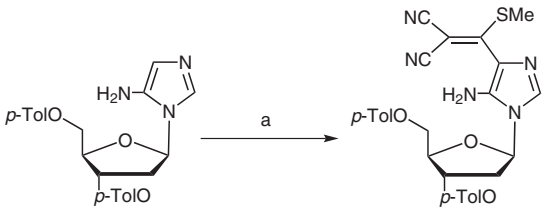
In order to demonstrate nucleophilic substitution of the methyl sulfonyl substituent, we initially reacted compound **25** with sodium ethoxide in ethanol at room temperature (Scheme 2). A single product was formed and, after chromatographic isolation in 24% yield, was identified as the 9-ethoxy derivative **26** [mp 204 °C (decomp.)]. ^{1}H NMR spectroscopy clearly showed the product contained an ethyl substituent (δ = 1.67 and 5.34 ppm) and the absence of a methyl sulfone signal (δ = ~3.9 ppm). Excellent yields of substitution products were obtained, without chromatography, when the sulfone **25** was reacted with alkylamines (Scheme 2). With *n*-propylamine in dichloromethane at room temperature (2 h), a 98% yield of the secondary amine **27** [mp 218 °C (decomp.)] was obtained. A similar procedure gave the *n*-butyl derivative **28** [mp 220 °C (decomp.)] in 93% yield. The use of 9-sulfones, for example **25**, therefore provides access to 8,9-diamino derivatives in the pyridine-stretched purine series.



20 (R^1 = R^2 = Ac)
21 (R^1 = H, R^2 = *t*-Boc)
22 (R^1 = R^2 = Ac)
23 (R^1 = H, R^2 = *t*-Boc)
24 (R^1 = R^2 = Ac)
25 (R^1 = H, R^2 = *t*-Boc)
26 (R^1 = H, R^2 = *t*-Boc)
27 (R^1 = H, R^2 = *t*-Boc)
28 (R^1 = H, R^2= *t*-Boc)

Scheme 2 *Reagents and conditions*: (a) MCPBA (1 equiv), CH_2Cl_2, 0 °C, 1.5 h (11% for **22**, 63% for **23**); (b) MCPBA (2 equiv), CH_2Cl_2, 0 °C, 4 h (67% for **24**, 65% for **25**); (c) NaOEt, EtOH, r.t., 30 min (24%); (d) *n*-$PrNH_2$, CH_2Cl_2, r.t., 2 h (98%); (d) *n*-$BuNH_2$, CH_2Cl_2, r.t., 2 h (93%).

The application of this methodology to the synthesis of 2′-deoxyribonucleotide analogues requires the reaction of 2-(bis-methylsulfanylmethylene)malononitrile (**9**) with 5-aminoimidazole **29**, to give the C-adduct **30** (Scheme 3). We have therefore made a preliminary investigation: reaction of the amine **29**[11] with electrophile **9** gave a single product which, after chromatography, was identified as the desired adduct **30** (mp 98–100 °C; 15%), which was fully characterised. The yield was low and requires optimisation, but the regioselectivity of the reaction demonstrates that this is a potential route to 9-substituted derivatives.



Scheme 3 *Reagents and conditions*: (a) **9**, THF, 50 °C, 12 h (15%).

IR spectra were obtained using a Thermo-Nicolet Avatar 370 FT-IR spectrometer. Mass spectra were obtained at the EPSRC National Mass Spectrometry Centre, University of Wales, Swansea, and were performed using either low-resolution electron impact (EI/LR), low-resolution electrospray (ES/LR) or high-resolution electrospray (ES/HR) ionisation techniques. Melting points were measured on a Stuart Scientific SMP3 melting point apparatus. NMR spectra were recorded on a Bruker Avance DPX300 NMR spectrometer in either $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are quoted as ppm relative to TMS as internal standard. Solvents were dried as follows: THF was heated under reflux over, and then distilled from, sodium wire and benzophenone; DMF was dried by distillation, and then standing over 4 Å molecular sieves; pyridine was refluxed over KOH and allowed to stand over 4 Å molecular sieves; 1,4-dioxane was refluxed over sodium and benzophenone, distilled off and stored over molecular sieves under a nitrogen atmosphere. Petroleum ether (PE), where used, had a boiling range of 60–80 °C. TLC was carried out on aluminium-backed 0.2 mm silica gel plates and visualised with 254 nm fluorescent indicator. Microanalyses were conducted through the Elemental Analysis Service at London Metropolitan University. AM1 calculations[17] were performed using the MOPAC programme in CS Chem3D (CambridgeSoft Corporation). Calculated frontier orbital energies vary with configuration but variations in the values recorded in Table 1 do not change the conclusions.

2-(Bis-methylsulfanylmethylene)malononitrile (**9**)[16] and 2-(methylsulfanyl-phenylaminomethylene) malononitrile (**11**)[18] were prepared by literature methods.

2-(Methylsulfanyl-propylaminomethylene)malononitrile (10)

2-(Bis-methylsulfanylmethylene)malononitrile (**9**; 4.00 g, 23.5 mmol) was dissolved in EtOH (25 mL) with stirring. *n*-$PrNH_2$ (1 mL, 11.8 mmol) was added dropwise over 1 h and the mixture was stirred overnight. The solvent was then removed under reduced pressure and the solid product was purified by column chromatography (CH_2Cl_2, 100% then MeOH–CH_2Cl_2, 5%) to give the product **10**.

Yield: 1.66 g (78%); pale-pink solid; mp 119–122 °C.

IR (KBr): 632, 864, 920, 1153, 1248, 1290, 1302, 1364, 1419, 1442, 1467, 1500, 1548, 2187, 2206, 2877, 2935, 2964, 3306 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.99 (t, *J* = 7.0 Hz, 3 H, $NHCH_2CH_2CH_3$), 1.67 (sext, *J* = 7.0 Hz, 2 H, $NHCH_2CH_2CH_3$), 2.68 (s, 3 H, SCH_3), 3.53 (q, *J* = 7.0 Hz, 2 H, $NHCH_2CH_2CH_3$), 6.31 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 11.00 ($NHCH_2CH_2CH_3$), 17.55 (SCH_3), 23.31 ($NHCH_2CH_2CH_3$), 48.33 ($NHCH_2CH_2CH_3$), 52.22 [$C(CN)_2$], 115.35 (CN), 115.64 (CN), 174.69 [C=$C(CN)_2$].

MS (EI/LR): *m*/*z* (%) = 181 (38) [M^+], 166 (9), 152 (18), 140 (13), 127 (15), 109 (12), 108 (19), 92 (58), 79 (15), 74 (22), 68 (22), 61 (63), 48 (25), 47 (33), 45 (40), 43 (75), 41 (100).

Anal. Calcd for $C_8H_{11}N_3S$: C, 53.01; H, 6.12; N, 23.18. Found: C, 52.93; H, 6.17; N, 23.05.

2-[(5-Amino-1,2-dimethyl-1*H*-imidazol-4-yl)methylsulfanylmethylene]malononitrile (13)

1,2-Dimethyl-5-nitroimidazole (**7**; $R^1 = R^2 = Me$; 1.58 g, 11.2 mmol) and 5% Pd/C catalyst (1.20 g) were placed in a flask with anhydrous THF (125 mL). The resulting mixture was hydrogenated at r.t. under atmospheric pressure, with vigorous stirring, over 2 h. The reaction was monitored by TLC (Et_2O), which showed complete consumption of all starting material. The product mixture was filtered through dry Celite, in an enclosed system under argon, into a flask containing 2-(bis-methylsulfanylmethylene)malononitrile (**9**; 9.64 g, 56.5 mmol). The reaction was stirred at 50 °C, under argon, overnight to give an orange-brown solution. The solvent was removed under reduced pressure at r.t. and the residue was treated with liquid nitrogen-chilled EtOAc (100 mL). The solution was then filtered to give a yellow-orange solid. The crude product **13** was used without further purification (yield over two stages 47%).

An analytical sample was prepared by dissolving the solid in a minimum amount of MeOH followed by flash column chromatography (EtOAc, 100%). The relevant fractions were combined and the solvent removed by rotary evaporation to give a yellow solid that was recrystallised (EtOAc–MeOH, 5:3) to give the product **13**.

Yield: 0.70 g (27%); brilliant yellow crystals; mp 197–198 °C.

IR (KBr): 1313, 1489, 1603, 2213, 2251, 3469 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.23 (s, 3 H, SCH_3), 2.49 (s, 3 H, CCH_3), 3.34 (s, 3 H, NCH_3), 7.05 (br s, 2 H, NH_2).

^{13}C NMR (DMSO-d_6): δ = 13.22 (CCH_3), 17.81 (SCH_3), 29.38 (NCH_3), 60.64 (methylene-C1), 113.70 (imidazole-C5), 116.85 (2 × CN), 143.52 (imidazole-C4), 147.64 (imidazole-C2), 164.26 (methylene-C2).

MS (EI/LR): *m*/*z* (%) = 233 (100) [M^+], 218 (8), 200 (22), 187 (21), 161 (17), 123 (4), 104 (10), 84 (22), 56 (63), 49 (29), 42 (24).

Anal. Calcd for $C_{10}H_{11}N_5S$: C, 51.48; H, 4.75; N, 30.02. Found: C, 51.53; H, 4.86; N, 29.84.

5-Amino-2,3-dimethyl-7-methylsulfanyl-3*H*-imidazo[4,5-*b*]pyridine-6-carbonitrile (14)

2-[(5-Amino-1,2-dimethyl-*1H*-imidazol-4-yl)methylsulfanylmethylene]malononitrile (**13**; 0.20 g, 0.86 mmol) was placed in a flask with MeOH (50 mL) and heated to 60 °C. NaOH (0.18 g) in H_2O (2 mL) was added to the reaction mixture. The reaction was followed by TLC (EtOAc–MeOH, 10:1) which, after 20 min, showed one fluorescent spot (R_f = 0.67). The mixture was cooled to r.t. and the precipitate was collected, recrystallised from DMF and identified as the product **14**.

Yield: 0.17 g (86%); off-white crystals; mp 300 °C.

IR (KBr): 517, 639, 899, 1370, 1425, 1488, 1560, 1585, 1648, 2202, 2931, 3338, 3412 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.45 (s, 3 H, CCH_3), 3.03 (s, 3 H, SCH_3), 3.54 (s, 3 H, NCH_3), 6.54 (br s, 2 H, NH_2).

^{13}C NMR (DMSO-d_6): δ = 14.38 (CCH_3), 16.74 (SCH_3), 28.64 (NCH_3), 83.63 (C-6), 117.20 (CN), 126.01 (C-1a), 144.52 (C-3a), 149.82 (C-2), 151.59 (C-7), 157.94 (C-5).

MS (EI/LR): *m*/*z* (%) = 233 (100) [M^+], 232 (24), 218 (9), 206 (11), 200 (25), 188 (12), 187 (27), 186 (15), 145 (13), 123 (12), 117 (12), 109 (18), 105 (23), 104 (44), 95 (21), 91 (45), 82 (44), 77 (56), 69 (34), 67 (43).

Anal. Calcd for $C_{10}H_{11}N_5S$: C, 51.48; H, 4.75; N, 30.02. Found: C, 51.33; H, 4.67; N, 29.90.

***N*-(6-Cyano-2,3-dimethyl-7-methylsulfanyl-3*H*-imidazo[4,5-*b*]pyridin-5-yl)formimidic Acid Ethyl Ester (15)**

5-Amino-2,3-dimethyl-7-methylsulfanyl-3*H*-imidazo[4,5-*b*]pyridine-6-carbonitrile (**14**; 5.96 g, 25.5 mmol), $CH(OEt)_3$ (500 mL) and $PTSA·H_2O$ (0.81 g, 4.3 mmol) were placed in a flask fitted with a Claisen head and condenser. The mixture was heated to 150 °C for 4 h, then activated carbon was then added and the hot mixture was filtered. The precipitate, which appeared on cooling, was collected and washed with a little Et_2O to give the product **15**.

Yield: 6.43 g (87%); fine colourless crystals; mp 197–200 °C.

IR (KBr): 1196, 1226, 1559, 1580, 1627, 2214, 2935 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.36 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2), 2.56 (s, 3 H, CCH_3), 3.11 (s, 3 H, SCH_3), 3.69 (s, 3 H, NCH_3), 4.37 (q, *J* = 7.0 Hz, 2 H, CH_3CH_2), 8.56 (s, 1 H, CHOEt).

^{13}C NMR (DMSO-d_6): δ = 13.84 (CCH_3), 13.98 (CH_3CH_2), 16.28 (SCH_3), 28.35 (NCH_3), 63.34 (CH_3CH_2), 94.81 (C-6), 115.78 (CN), 130.10 (C-1a), 144.19 (C-3a), 147.75 (C-2), 153.98 (C-7), 156.10 (EtOC=N), 160.45 (C-5).

MS (EI): *m*/*z* (%) = 289 (21) [M^+], 260 (100), 244 (46), 232 (15), 186 (12), 171 (10), 145 (12), 135 (12), 104 (19), 91 (15), 77 (13), 56 (57), 46 (12), 42 (18).

Anal. Calcd for $C_{13}H_{15}N_5OS$: C, 53.92; H, 5.22; N, 24.29. Found: C, 53.75; H, 5.00; N, 24.07.

2,3-Dimethyl-9-methylsulfanyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-ylamine (16)

N-(6-Cyano-2,3-dimethyl-7-methylsulfanyl-3*H*-imidazo[4,5-*b*]pyridin-5-yl)formimidic acid ethylester (**15**; 3.03 g, 10.5 mmol) was added to EtOH (300 mL) saturated with NH_3. The mixture was stirred at r.t. for 1 h and then heated under reflux overnight. The mixture was cooled in a freezer and the precipitate was collected and identified as the product **16**. An analytical sample was recrystallised from *i*-PrOH.

Yield: 2.31 g (85%); fine colourless crystals; mp 252–255 °C.

IR (KBr): 1346, 1401, 1429, 1455, 1500, 1521, 1551, 1576, 1638, 2360, 2937, 3075, 3282, 3434 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.66 (s, 3 H, CCH_3), 2.94 (s, 3 H, SCH_3), 3.75 (s, 3 H, NCH_3), 8.32 (br s, 2 H, NH_2), 8.40 (s, 1 H, CH).

^{13}C NMR (DMSO-d_6): δ = 14.45 (CCH_3), 19.48 (SCH_3), 28.27 (NCH_3), 105.43 (C8a), 133.47 (C-1a), 135.41 (C-3a), 150.56 (C-9), 155.78 (C-2), 155.90 (C-6), 157.88 (C-4a), 163.70 (C-8).

MS (EI): *m*/*z* (%) = 260 (88) [M^+], 254 (13), 245 (21), 234 (12), 233 (53), 227 (75), 218 (16), 214 (22), 212 (44), 210 (68), 204 (71), 197 (100), 187 (85), 179 (59), 169 (62).

Anal. Calcd for $C_{11}H_{12}N_6S$: C, 50.75; H, 4.65; N, 32.28. Found: C, 50.60; H, 4.44; N, 32.28.

2,3-Dimethyl-9-methylsulfanyl-3,7-dihydro-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-one (17)

2,3-Dimethyl-9-methylsulfanyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-ylamine (**16**; 1.00 g, 3.8 mmol) in 2 M HCl (100 mL) was heated under reflux for 2 h. The solution was cooled in an ice bath and basified with aq NH_3. The resulting precipitate was collected, washed with H_2O (15 mL), EtOH (15 mL) and Et_2O (25 mL) to give the product **17**.

Yield: 0.74 g (74%); colourless solid; mp >350 °C.

IR (KBr): 956, 1242, 1314, 1324, 1351, 1373, 1423, 1472, 1548, 1575, 1615, 1668, 2629, 2910, 3046 cm^{-1}.

^1H NMR (TFA): δ = 3.12 (s, 3 H, CCH_3), 3.15 (s, 3 H, SCH_3), 4.17 (s, 3 H, NCH_3), 9.56 (s, 1 H, CH).

^{13}C NMR (TFA): δ = 14.74 (CCH_3), 20.18 (SCH_3), 33.08 (NCH_3), 126.42 (C-8a), 149.03 (C-1a), 151.31 (C-3a), 154.42 (C-9), 155.07 (C-2), 161.66 (C-6), 161.99 (C-4a), 166.41 (C-8).

MS (EI): *m*/*z* (%) = 261 (31) [M^+], 228 (15), 187 (9), 105 (10), 91 (17), 77 (9), 56 (12), 44 (100).

Anal. Calcd for $C_{11}H_{11}N_5SO$: C, 50.56; H, 4.24; N, 26.80. Found: C, 50.54; H, 4.06; N, 26.65.

***N*-(6-Cyano-2,3-dimethyl-7-methylsulfanyl-3*H*-imidazo[4,5-*b*]pyridin-5-yl)-*N*′-propyl-formamidine (18)**

N-(6-Cyano-2,3-dimethyl-7-methylsulfanyl-3*H*-imidazo[4,5-*b*]pyridin-5-yl)formimidic acid ethyl ester (**15**; 0.50 g, 1.7 mmol) and *n*-$PrNH_2$ (0.70 mL, 8.5 mmol) in EtOH (25 mL) were allowed to stand at r.t. for 18 h. The solvent and excess amine were removed under reduced pressure. The solid residue was recrystallised (EtOAc–PE) and identified as the product **18**.

Yield: 0.31 g (58%); off-white crystals; mp 147–149 °C.

IR (KBr): 938, 959, 1151, 1195, 1250, 1349, 1373, 1423, 1475, 1574, 1615, 2212, 2873, 2929, 2958, 3243 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.97 (t, *J* = 7.5 Hz, 3 H, $NHCH_2CH_2CH_3$), 1.64 (m, 2 H, $NHCH_2CH_2CH_3$), 3.05 (s, 3 H, CCH_3), 3.34 (s, 3 H, SCH_3), 3.38 (q, *J* = 6.5 Hz, 2 H, $NHCH_2CH_2CH_3$), 3.62 (s, 3 H, NCH_3), 8.09 (d, *J* = 4.5 Hz, 1 H, CH), 8.52 (d, *J* = 4.5 Hz, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 11.44 ($NHCH_2CH_2CH_3$), 13.89 (CCH_3), 16.17 (SCH_3), 21.49 ($NHCH_2CH_2CH_3$), 28.07 (NCH_3), 42.16 ($NHCH_2CH_2CH_3$), 94.16 (C-6), 116.89 (CN), 128.27 (C-1a), 143.56 (C-3a), 148.16 (C-2), 152.30 (C-7), 153.21 (N=CN), 160.11 (C-5).

MS (EI): *m*/*z* (%) = 302 (26) [M^+], 287 (10), 269 (12), 244 (9), 200 (13), 187 (22), 56 (14).

Anal. Calcd for $C_{14}H_{18}N_6S$: C, 55.61; H, 6.00; N, 27.79. Found: C, 55.64; H, 5.79; N, 27.61.

***N*-Acetyl-*N*-(2,3-dimethyl-9-methylsulfanyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)acetamide (20)**

To a suspension of 2,3-dimethyl-9-methylsulfanyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-ylamine (**16**; 2.00 g, 7.7 mmol) in pyridine (27 mL), was added Ac_2O (20 mL). The mixture was heated under reflux for 2 h, then poured onto ice water (50 mL). The product was extracted into CH_2Cl_2 (2 × 50mL), dried ($MgSO_4$) and the solvent volume reduced by half (~20 mL). Et_2O (20 mL) was added and the solution was left to cool overnight. The precipitate was collected, dried under high vacuum at 100 °C, and identified as the product **20**.

Yield: 2.01 g (76%); fine yellow crystals; mp 178–183 °C.

IR (KBr): 1163, 1219, 1296, 1353, 1404, 1479, 1539, 1574, 1608, 1731, 2341, 2359, 2930, 3007 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.30 [s, 6 H, $NC(O)CH_3$], 2.66 (s, 3 H, CCH_3), 3.17 (s, 3 H, SCH_3), 3.86 (s, 3 H, NCH_3), 9.29 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 15.01 (CCH_3), 20.11 (SCH_3), 27.10 [2 × $NC(O)CH_3$] 28.93 (NCH_3), 115.15 (C-8a), 136.06 (C-1a), 138.28 (C-3a), 152.94 (C-9), 155.70 (C-2), 157.79 (C-6), 157.85 (C-4a), 160.60 (C-8), 171.67 [2 × $NC(O)CH_3$].

MS (EI): *m*/*z* (%) = 344 (3) [M^+], 301 (3), 269 (12), 255 (19), 245 (12), 227 (3), 171 (6), 135 (2), 94 (6), 82 (3), 56 (12), 43 (100).

Anal. Calcd for $C_{15}H_{16}N_6O_2S$: C, 52.31; H, 4.68; N, 24.40. Found: C, 52.43; H, 4.36; N, 24.19.

***tert*-Butyl (2,3-Dimethyl-9-methanesulfanyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)carbamate (21)**

2,3-Dimethyl-9-methylsulfanyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-ylamine (**16**; 1.00 g, 3.8 mmol) was suspended in anhydrous 1,4-dioxane (100 mL) and heated to 120 °C. When all the starting material had dissolved, Boc_2O (4.19 g, 19.2 mmol) was added and the solution was stirred for 5 h, after which time TLC (MeOH) showed that all starting material had reacted. The solvent was removed by evaporation and the resulting solid was treated with Et_2O (50 mL). The solid was collected, washed with further Et_2O (2 × 25 mL) and identified as the product **21**.

Yield: 1.15 g (83%); yellow solid; mp 167 °C (decomp.).

IR (KBr): 1060, 1152, 1248, 1305, 1353, 1372, 1426, 1505, 1580, 1697, 1758, 2923, 2976, 3422 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.61 [s, 9 H, $C(CH_3)_3$], 2.77 (s, 3 H, CCH_3), 2.87 (s, 3 H, SCH_3), 3.91 (s, 3 H, NCH_3), 9.10 (s, 1 H, CH), 11.49 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 15.08 (CCH_3), 20.74 (SCH_3), 28.25 [$O(CH_3)_3$], 28.97 (NCH_3), 82.21 [$(Me)_3CO$], 108.08 (C-8a), 131.27 (C-1a), 138.25 (C-3a), 149.79 (C-9), 151.74 (HNCOO), 156.09 (C-2), 156.46 (C-6), 158.64 (C-4a), 159.72 (C-8).

Anal. Calcd for $C_{16}H_{20}N_6O_2S$: C, 53.32; H, 5.59; N, 23.32. Found: C, 53.03; H, 5.43; N, 23.57.

***N*-Acetyl-*N*-(9-methanesulfinyl-2,3-dimethyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)acetamide (22)**

N-Acetyl-*N*-(2,3-dimethyl-9-methylsulfanyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)acetamide (**20**; 194 mg, 0.56 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. MCPBA (50–55%, 194 mg, 0.56 mmol) was added and the mixture was stirred for 1.5 h. The organic layer was then washed with sat. aq $NaHCO_3$ (2 × 20 mL) and H_2O (2 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude material was dissolved in EtOAc and the solvent volume was reduced until crystallisation began. After cooling, the solid was collected and identified as the product **22**.

Yield: 22 mg (11%); yellow crystals; mp 191–192 °C.

IR (KBr): 568, 599, 640, 685, 926, 867, 1006, 1040, 1067, 1157, 1230, 1301, 1369, 1423, 1475, 1514, 1577, 1616, 1698, 1720, 2922, 3006 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.12 (s, 3 H, $COCH_3$), 2.65 (s, 3 H, $COCH_3$), 2.88 (s, 3 H, CCH_3), 3.45 (s, 3 H, $SOCH_3$), 4.01 (s, 3 H, NCH_3), 9.46 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 15.97 (CCH_3), 26.76 [$NC(O)CH_3$], 28.15 [$NC(O)CH_3$], 29.69 (NCH_3), 40.86 ($SOCH_3$), 113.77 (C-8a), 136.33 (C-3a), 138.37 (C-1a), 156.00 (C-9), 156.36 (C-2), 156.82 (C-6), 160.42 (C-4a), 164.18 (C-8), 170.72 [$NC(O)CH_3$], 174.51 [$NC(O)CH_3$].

MS (EI): *m*/*z* (%) = 361 (3) [M + H^+], 345 (9), 303 (6), 277 (4), 255 (85), 246 (6), 200 (6), 120 (26), 119 (54), 111 (8), 97 (12), 77 (100).

Anal. Calcd for $C_{15}H_{16}N_6O_3S$: C, 49.99; H, 4.47; N, 23.32. Found: C, 49.73; H, 4.52; N, 23.06.

***tert*-Butyl (9-Methanesulfinyl-2,3-dimethyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)carbamate (23)**

Using the procedure described for the synthesis of compound **22**, compound **23** was obtained from *tert*-butyl (2,3-dimethyl-9-methanesulfanyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)carbamate (**21**; 1.00 g, 2.8 mmol).

Yield: 0.66 g (63%); pale-yellow, crystalline solid; mp 172 °C (decomp.).

IR (KBr): 749, 812, 839, 879, 927, 958, 1022, 1074, 1146, 1225, 1252, 1307, 1373, 1429, 1493, 1527, 1588, 1752, 2728, 2927, 2978, 3494 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.59 [s, 9 H, $C(CH_3)_3$], 2.79 (s, 3 H, CCH_3), 3.12 (s, 3 H, $SOCH_3$), 3.95 (s, 3 H, NCH_3), 9.22 (s, 1 H, CH), 12.28 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 15.56 (CCH_3), 28.66 [$OC(CH_3)_3$], 29.57 (NCH_3), 39.84 ($SOCH_3$), 82.18 [$(Me)_3CO$], 107.99 (C-8a), 134.44 (C-3a), 136.30 (C-1a), 151.54 (C-2), 153.33 (HNCOO), 157.30 (C-9), 158.27 (C-6), 158.81 (C-4a), 162.37 (C-8).

***N*-Acetyl-*N*-(9-methanesulfonyl-2,3-dimethyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)acetamide (24)**

N-Acetyl-*N*-(2,3-dimethyl-9-methylsulfanyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)acetamide (**20**; 2.00 g, 5.8 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. MCPBA (50–55%, 4.00 g, 11.6 mmol) was added and the mixture was stirred for 4 h. The organic layer was diluted with a further portion of CH_2Cl_2 (50 mL), washed with H_2O (2 × 100 mL) and dried ($MgSO_4$). After the solvent had been removed under reduced pressure, the crude solid was recrystallised from EtOAc and identified as the product **24**.

Yield: 1.51 g (67%); orange crystals; mp 185–186 °C.

IR (KBr): 537, 579, 640, 755, 933, 1009, 1038, 1122, 1152, 1211, 1236, 1259, 1310, 1353, 1366, 1404, 1426, 1485, 1517, 1561, 1577, 1623, 1706, 1733, 2924, 3016 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.48 (s, 6 H, $COCH_3$), 2.81 (s, 3 H, CCH_3), 3.83 (s, 3 H, SO_2CH_3), 3.98 (s, 3 H, NCH_3), 9.42 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 15.44 (CCH_3), 27.89 [$C(O)CH_3$], 29.36 (NCH_3), 48.90 (SCH_3), 112.17 (C-8a), 132.79 (C-3a), 132.83 (C-1a), 143.21 (C-2), 155.55 (C-9), 155.86 (C-6), 160.25 (C-4a), 163.78 (C-8), 173.18 [$C(O)CH_3$].

MS (EI): *m*/*z* (%) = 377 (2) [M + H^+], 299 (4), 255 (35), 215 (4), 200 (7), 177 (4), 163 (4), 140 (4), 119 (9), 111 (18), 97 (24), 77 (100), 60 (12).

Anal. Calcd for $C_{15}H_{16}N_6O_4S$: C, 49.87; H, 4.28; N, 22.33. Found: C, 47.69; H, 4.05; N, 22.11.

***tert*-Butyl (9-Methanesulfonyl-2,3-dimethyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)carbamate (25)**

Using the procedure described for the synthesis of compound **24**, compound **25** was obtained from *tert*-butyl (2,3-dimethyl-9-methanesulfanyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)carbamate (**21**; 2.00 g, 5.5 mmol).

Yield: 1.42 g (65%); dark-gold, crystalline solid; mp 100 °C (decomp.).

IR (KBr): 774, 840, 1145, 1218, 1245, 1297, 1353, 1375, 1414, 1509, 1578, 1752, 2925, 2976, 3422 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.59 [s, 9 H, $C(CH_3)_3$], 2.79 (s, 3 H, CCH_3), 3.92 (s, 3 H, SO_2CH_3), 3.95 (s, 3 H, NCH_3), 9.16 (s, 1 H, CH), 10.03 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 15.69 (CCH_3), 28.53 [$OC(CH_3)_3$], 29.56 (NCH_3), 48.26 (SO_2CH_3), 82.44 [$(Me)_3CO$], 104.32 (C-8a), 132.17 (C-3a), 133.95 (C-1a), 150.91 (HNCOO), 154.93 (C-2), 155.97 (C-9), 156.83 (C-6), 157.16 (C-4a), 163.16 (C-8).

***tert*-Butyl (9-Ethoxy-2,3-dimethyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)carbamate (26)**

tert-Butyl (9-methanesulfonyl-2,3-dimethyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)carbamate (**25**; 0.50 g, 1.3 mmol) was dissolved in EtOH (50 mL) with stirring. Sodium metal (0.10 g, 2.5 mmol) was then added and the mixture was stirred for 30 min, at which point TLC (EtOAc–MeOH, 5:1) showed the dis-

appearance of the starting material and a new, slower running spot (R_f = 0.38). The EtOH was removed under reduced pressure and the residue was re-dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with H_2O (2 × 50 mL), dried ($MgSO_4$) and the solvent removed. The solid product was then purified by column chromatography (EtOAc–MeOH, 3:1) and the relevant fractions were combined to give compound **26**.

Yield: 0.11 g (24%); colourless solid; mp 204 °C (decomp.).

IR (KBr): 815, 949, 1016, 1060, 1109, 1143, 1241, 1356, 1369, 1380, 1466, 1507, 1555, 1597, 1624, 1663, 1751, 2973, 3342 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.58 [s, 9 H, $C(CH_3)_3$], 1.67 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 2.65 (s, 3 H, CCH_3), 3.86 (s, 3 H, NCH_3), 5.34 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 9.01 (s, 1 H, CH), 10.40 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 15.02 (OCH_2CH_3), 15.75 (CCH_3), 28.54 [$OC(CH_3)_3$], 29.26 (NCH_3), 72.23 (OCH_2CH_3), 82.10 [$(CH_3)_3CO$], 100.20 (C-8a), 122.51 (C-1a), 149.85 (C-3a), 152.39 (HNCOO), 155.45 (C-2), 155.63 (C-6), 157.21 (C-4a), 157.42 (C-8), 158.92 (C-9).

MS (EI): m/z (%) = 359 (14) [M + H^+], 259 (100), 244 (24), 222 (67), 204 (24), 192 (22), 176 (22), 150 (30), 148 (42), 135 (53), 122 (71), 100 (64), 98 (76), 84 (76), 72 (86).

HRMS (ES): m/z [M + H^+] calcd for $C_{17}H_{22}N_6O_3$: 359.1826; found: 359.1825.

tert-Butyl (2,3-Dimethyl-9-propylamino-3*H*-1,3,4,5,7-pentaazacyclopenta[*b*]naphthalen-8-yl)carbamate (27)

tert-Butyl (9-methanesulfonyl-2,3-dimethyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)carbamate (**25**; 0.86 g, 2.2 mmol) was dissolved in CH_2Cl_2 (75 mL). To this solution was added *n*-$PrNH_2$ (0.18 mL, 2.2 mmol) and stirring was maintained at r.t. for 2 h. The solvent was removed under reduced pressure and the resulting solid was dried under high vacuum at 70 °C for 12 h, to give the product **20**.

Yield: 0.80 g (98%); dark-yellow solid; mp 218 °C (decomp.).

IR (KBr): 1003, 1071, 1114, 1157, 1218, 1253, 1384, 1439, 1528, 1586, 1652, 1700, 2862, 2965, 3408 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.15 (t, J = 7.0 Hz, 3 H, $NHCH_2CH_2CH_3$), 1.53 [s, 9 H, $C(CH_3)_3$], 1.77 (m, 2 H, $NHCH_2CH_2CH_3$), 2.55 (s, 3 H, CCH_3), 3.74 (s, 3 H, NCH_3), 4.18 (q, J = 6.0 Hz, 2 H, $NHCH_2CH_2CH_3$), 8.05 (s, 1 H, CH), 11.63 (t, J = 6.0 Hz, 1 H, $NHCH_2CH_2CH_3$), 13.60 (br s, 1 H, Boc-NH).

^{13}C NMR ($CDCl_3$): δ = 11.82 ($NHCH_2CH_2CH_3$), 14.7 (CCH_3), 23.49 ($NHCH_2CH_2CH_3$), 28.57 [$OC(CH_3)_3$], 29.00 (NCH_3), 47.57 ($NHCH_2CH_2CH_3$), 80.24 [$(CH_3)_3CO$], 98.04 (C-8a), 120.13 (C-1a), 142.97 (C-3a), 148.94 (C-2), 149.19 (C-9), 151.78 (C-4a), 156.50 (C-6), 160.73 (HNCOO), 163.65 (C-8).

HRMS (ES): m/z [M + H^+] calcd for $C_{18}H_{26}O_2N_7$: 372.2142; found: 372.2149.

tert-Butyl (9-Butylamino-2,3-dimethyl-3*H*-1,3,4,5,7-pentaazacyclopenta[*b*]naphthalen-8-yl)carbamate (28)

Using the procedure described for the synthesis of compound **27**, compound **28** was obtained from *tert*-butyl (9-methanesulfonyl-2,3-dimethyl-3*H*-1,3,4,5,7-pentaaza-cyclopenta[*b*]naphthalen-8-yl)carbamate (**25**; 1.00 g, 2.6 mmol).

Yield: 0.91 g (93%); dark-orange solid; mp 220 °C (decomp.).

IR (KBr): 1041, 1157, 1264, 1367, 1585, 1700, 1718, 1621, 1646, 2867, 2924, 2964, 3439 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.99 (t, J = 7.0 Hz, 3 H, $NHCH_2CH_2CH_2CH_3$), 1.52 [s, 9 H, $C(CH_3)_3$], 1.62–1.76 (m, 4 H, $NHCH_2CH_2CH_2CH_3$ and $NHCH_2CH_2CH_2CH_3$), 2.54 (s, 3 H, CCH_3), 3.72 (s, 3 H, NCH_3), 4.21 (q, J = 6.0 Hz, 2 H, $NHCH_2CH_2CH_2CH_3$), 8.04 (s, 1 H, CH), 11.58 (br s, 1 H, $NHCH_2CH_2CH_2CH_3$), 13.62 (br s, 1 H, Boc-NH).

^{13}C NMR ($CDCl_3$): δ = 14.40 ($NHCH_2CH_2CH_2CH_3$), 14.68 (CCH_3), 20.29 ($NHCH_2CH_2CH_2CH_3$), 28.60 [$OC(CH_3)_3$], 29.00 (NCH_3), 32.28 ($NHCH_2CH_2CH_2CH_3$), 45.54 ($NHCH_2CH_2CH_2CH_3$), 80.22 [$(CH_3)_3CO$], 98.02 (C-8a), 120.13 (C-1a), 143.00 (C-3a), 148.91 (C-2), 149.20 (C-9), 151.77 (C-4a), 156.50 (C-6), 160.74 (HNCOO), 163.68 (C-8).

5-Amino-4-(1-methylsulfanyl-2,2-dicyanovinyl)-1-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-ribofuranosyl)imidazole (30)

1-(2′-Deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-5-nitroimidazole[11] (**29**; 3.00 g, 6.4 mmol), and 5% Pd/C catalyst (3.00 g) were placed in anhydrous THF (120 mL) and the mixture was hydrogenated at r.t. and atmospheric pressure, with vigorous stirring for 2 h. The solution was filtered through dry Celite, under argon, into a flask containing 2-(bis-methylsulfanylmethylene)malononitrile (**9**; 5.50 g, 32.3 mmol). The Celite was washed with a further portion of THF (120 mL). The reaction was stirred at 50 °C, under argon, overnight giving a dark-brown solution. The mixture was evaporated to dryness and the residue was treated with liquid nitrogen-chilled EtOAc (200 mL). The solution was then filtered to give the crude product, which was purified by column chromatography (CH_2Cl_2, 100% then MeOH–CH_2Cl_2, 1%). The relevant fractions were combined and evaporated to dryness to give the amine **30**.

Yield: 0.53 g (15%); brown crystalline solid; mp 98–100 °C.

IR (KBr): 752, 1102, 1178, 1209, 1270, 1311, 1377, 1449, 1486, 1508, 1544, 1578, 1611, 1720, 2209, 2923, 3035, 3329 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.30 (s, 3 H, SCH_3), 2.39 (s, 3 H, $ArCH_3$), 2.41 (s, 3 H, $ArCH_3$), 2.70 (m, 1 H, 2′-CH), 2.88 (m, 1 H, 2′-CH), 4.54 (m, 3 H, 5′-CH_2 and 4′-CH), 5.63 (d, J = 4.0 Hz, 1 H, 3′-CH), 6.19 (m, 1 H, 1′-CH), 7.18 (br s, 2 H, NH_2), 7.34 (d, J = 8.0 Hz, 2 × 2 H, ArH), 7.38 (d, J = 8.0 Hz, 2 H, 2 × ArH), 7.79 [s, 1 H, imidazole(2)-H], 7.88 (d, J = 8.0 Hz, 2 H, 2 × ArH), 7.97 (d, J = 8.0 Hz, 2 H, 2 × ArH).

^{13}C NMR (DMSO-d_6): δ = 17.61 (SCH_3), 21.09 (2 × $ArCH_3$), 36.08 (C-2′), 64.02 (C-5′), 64.40 (C-3′), 74.80 [$C(CN)_2$], 81.59 (C-1′), 82.73 (C-4′), 114.16 (imidazole-C4), 126.41 (2 × CN), 129.22 (2 × ArC), 129.30 (4 × ArC), 129.45 (4 × ArC), 132.29 (imidazole-C2), 143.82 (CCH_3), 144.04 (CCH_3), 145.42 (imidazole-C5), 165.08 (C=O), 165.38 (C=O), 167.13 [C=C(CN)$_2$].

MS (EI): m/z (%) = 558 (5) [M + H^+], 234 (52), 219 (10), 179 (13), 154 (43), 153 (15), 119 (27), 115 (58), 98 (100), 81 (85).

Anal. Calcd for $C_{29}H_{27}N_5O_5S$: C, 62.47; H, 4.88; N, 12.56. Found: C, 62.30; H, 4.65, N; 12.26.

Acknowledgment

We thank the EPSRC for a studentship (to J.A.C.) and the EPSRC National Mass Spectrometry Service for mass spectra.

References

(1) Leonard, N. J.; Sprecker, M. A.; Morrice, A. G. *J. Am. Chem. Soc.* **1976**, *98*, 3987.
(2) Scopes, D. I.; Barrio, J. R.; Leonard, N. J. *Science* **1977**, *195*, 296.
(3) Leonard, N. J.; Keyser, G. E. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 4262.
(4) Leonard, N. J. *Acc. Chem. Res.* **1982**, *15*, 128.
(5) Lessor, R. A.; Gibson, K. J.; Leonard, N. J. *Biochemistry* **1984**, *23*, 3868.

(6) Seley, K. L.; Januszczyk, P.; Hagos, A.; Zhang, L.; Dransfield, D. T. *J. Med. Chem.* **2000**, *43*, 4877.
(7) Minakawa, N.; Kojima, N.; Hikishama, S.; Sasaki, T.; Kiyosue, A.; Atsumi, N.; Ueno, Y.; Matsuda, A. *J. Am. Chem. Soc.* **2003**, *125*, 9970.
(8) Liu, H.; Gao, J.; Maynard, L.; Saito, Y. D.; Kool, E. T. *J. Am. Chem. Soc.* **2004**, *126*, 1102.
(9) Krueger, A. T.; Lu, H.; Lee, A. H. F.; Kool, E. T. *Acc. Chem. Res.* **2007**, *40*, 141.
(10) Humphries, M. J.; Ramsden, C. A. *Synthesis* **1999**, 985.
(11) Clayton, R.; Davis, M. L.; Fraser, W.; Li, W.; Ramsden, C. A. *Synlett* **2002**, 1483.
(12) Clayton, R.; Davis, M. L.; Fraser, W.; Ramsden, C. A. manuscript in preparation.
(13) Al-Shaar, A. H. M.; Gilmour, D. W.; Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2779.
(14) Al-Shaar, A. H. M.; Chambers, R. K.; Gilmour, D. W.; Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2789.
(15) Lythgoe, D. J.; Ramsden, C. A. *Adv. Heterocyl. Chem.* **1994**, *61*, 1.
(16) Mashraqui, S. H.; Hariharasubrahmanian, H. *J. Chem. Res.* **1999**, *8*, 492.
(17) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(18) Finnerty, J.; Mitschke, U.; Wentrup, C. *J. Org. Chem.* **2002**, *67*, 1084.