2-(Benzylsulfanyl)-6-chloro-9-isopropylpurine, a Valuable Intermediate in the Synthesis of Diaminopurine Cyclin Dependent Kinase Inhibitors

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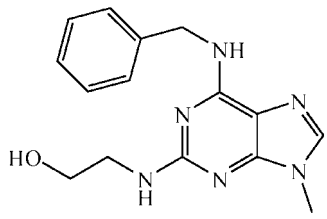
The synthetic potential of a novel precursor of 2,6-diaminopurine CDK inhibitors, 2-(benzylsulfanyl)-6-chloro-9-isopropylpurine, is described. The Traube purine synthesis was chosen to prepare the required 2-(benzylsulfanyl)hypoxanthine intermediate. Attempts to prepare its purin-6-yl methanesulfonic ester analogue failed. Conversion to the 6-chloropurine derivative enabled the introduction of arylamines in the presence of catalytic amounts of acid. Further chemical variety was introduced on the purine through a regioselective Mitsunobu *N*-9 alkylation. Oxidative cleavage of the 2-(benzylsulfanyl) leaving group with an aliphatic amine was implemented as previously reported. Purvalanol A, a potent CDK inhibitor, was synthesised using this methodology. The template and intermediates were fully characterised by modern spectroscopic techniques and single-crystal X-ray diffraction.

Introduction

Considerable attention has been devoted to the understanding of the cell cycle progression at the molecular level. A key class of cell cycle proteins are the Cyclin Dependent Kinases (CDKs).[1–3] Not only are these ubiquitous enzymes often found altered in proliferative disorders such as cancers but their natural inhibitors can also be strongly deregulated in tumours. After small molecular CDK inhibitors were shown to arrest cell proliferation and induce apoptosis in vitro but also in vivo,[4] several families of inhibitors were reported and optimised.[5–8] Olomoucine (**1**) was the original hit in the diaminopurine family and led to the discovery of Roscovitine (**2**) and Purvalanol A (**3**), the most potent purine based inhibitor to date.[7]

The synthesis of 2,6-diaminopurine CDK inhibitors traditionally relies on the base catalysed nucleophilic displacement of the corresponding dihalogenopurines with amines,[9,10] and several methodologies are available for their preparation.[11,12] However, the forcing conditions limit their versatility due to the low nucleophilicity of arylamines. We have found that 6-chloro-2-iodopurine[12] is unreactive with aniline and benzylamine in refluxing DMF in the presence of triethylamine for several days and that the reaction is very slow even in a sealed glass tube. More reactive leaving groups would allow the preparation of a wider range of diaminopurine CDK inhibitors. The oxidative cleavage of benzylsulfanyl by nucleophiles including deactivated anilines has been reported in the literature at the 2- and 6-positions of purines under milder conditions.[13,14] Furthermore, this particular thioether has also been successfully



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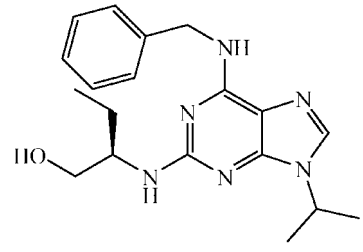

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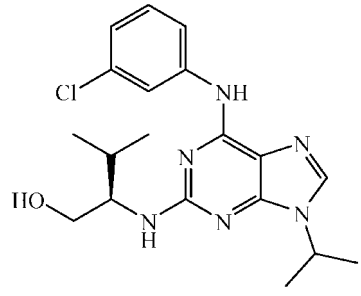

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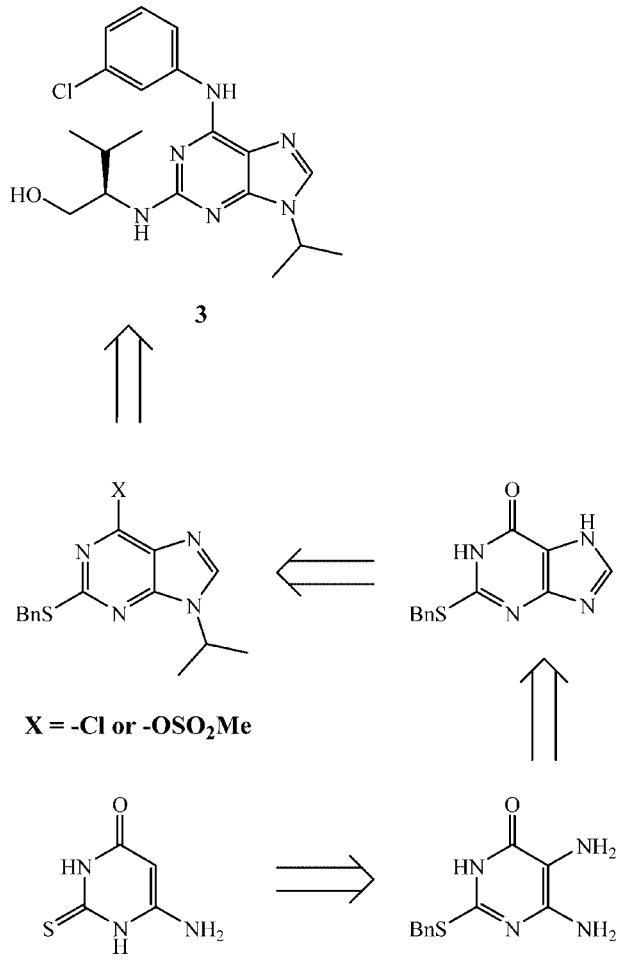
used as a traceless linker for the solid phase synthesis of pteridine and related purine heterocycles by Suckling et al.[14] Finally, the displacement of the mesylate leaving group with amines has been implemented on pyrimidinones[15] and is worth investigating on purines.

Hence, it appeared interesting to design the synthesis of novel purines bearing a combination of these moieties and to investigate the reactivity of such intermediates. The Traube synthesis was chosen to prepare the 2-substituted hypoxanthine from the 5,6-diaminopyrimidinone as described previously.[14] Since regioselective Mitsunobu alkylations on the *N*-9 position of hypoxanthines have also been reported[16] we postulated that subsequent conversion of the 6-oxo group into a suitable leaving group X could lead to the synthesis of potentially valuable diaminopurines such as Purvalanol A (see Scheme 1 below).



Scheme 1

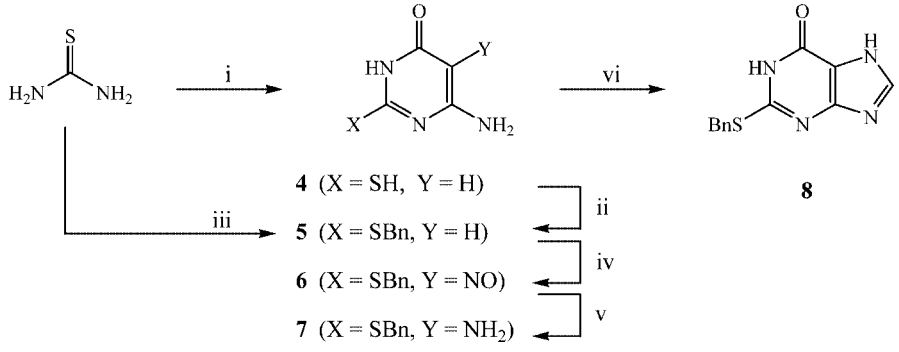
Results and Discussion

Traube Synthesis of 2-(Benzylsulfanyl)hypoxanthine (8)

When thiourea was treated with ethyl cyanoacetate in alkaline medium, followed by acidification with concentrated hydrochloric acid,[17] the 6-aminopyrimidinone **4** was obtained in near quantitative yield (see Scheme 2). Since the introduction of the benzyl moiety on the 2-thioxo group required deprotonation prior to nucleophilic attack on benzyl chloride, we opted for a one-pot cyclisation-benzylation in a sodium ethanoate solution, thus avoiding the isolation of 2-thiopyrimidinone **4**. Following *C*-5 nitrosation of the 2-(benzylsulfanyl)pyrimidinone (**5**) in 92% yield using the conditions described by Suckling et al.,[14] reduction with aqueous sodium dithionite in methanol[14] readily afforded the 5,6-diaminopyrimidinone **7** required for the Traube reaction. Treatment with triethyl orthoformate and hydrochloric acid in DMF afforded 2-(benzylsulfanyl)hypoxanthine (**8**) in good yield at room temperature.

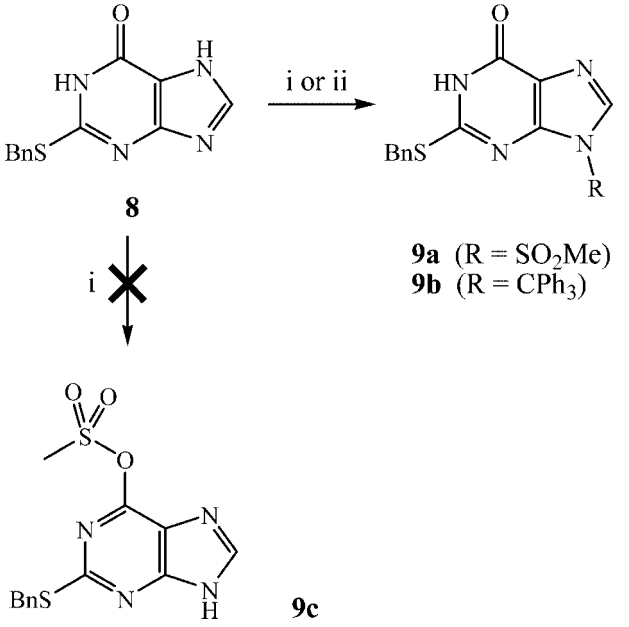
Attempted Synthesis of Purin-6-yl Methanesulfonates

Direct conversion of the hypoxanthine **8** into the purin-6-yl methanesulfonic ester with methanesulfonyl chloride in the presence of triethylamine[18] was not successful, although the NMR, MS and elemental analysis data of the isolated crystalline solid fitted perfectly with the proposed structure **9c**. Reaction with *m*-chloroaniline in THF resulted in the cleavage of the methylsulfonyl group, yielding a product that was characterised as the hypoxanthine precursor **8**. Single crystal diffraction studies confirmed the structure as being the *N*-9-sulfonyl derivative **9a** (see Scheme 3 below). A suitable protecting group was thus necessary for further functionalisation of the 6-oxo moiety. Tri-



Scheme 2. Conditions: i) ethyl cyanoacetate, EtONa, EtOH, Δ, then HCl (98%) ii) NaOH, EtOH, Δ, then BnCl iii) ethyl cyanoacetate, EtONa, EtOH, Δ, then BnCl (98%) iv) NaOH, $NaNO_2$, then AcOH (92%) v) $Na_2S_2O_{4(aq)}$, MeOH (97%), $HC(OEt)_3$, HCl, DMF (92%)

tylation was found regioselective as only the *N*-9-trityl **9b** was isolated in 61% yield after flash column chromatography as crystalline needles suitable for XRD studies (see Figure 1 and Figure 2).



Scheme 3. Conditions: i) $MeSO_2Cl$, NEt_3, DCM, 0 °C to room temp. (62%) ii) Ph_3CCl, NEt_3, DCM, 0 °C to room temp. (61%)

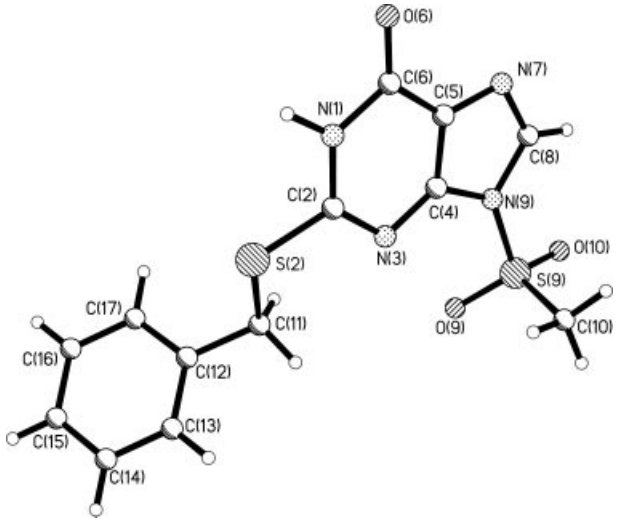


Figure 1. Crystal structure of hypoxanthines **9a**

In contrast to alkylation, sulfonylation of substituted hypoxanthines is known to occur frequently on the oxygen rather than on nitrogen.[18] It was thus assumed that reaction of hypoxanthine **9b** with methanesulfonyl chloride and triethylamine in dichloromethane would result in the desired *O*-mesyl compound. As shown in Scheme 4, we speculate that the *N*-methanesulfonamide product **10b** was obtained instead as reacting it with *m*-chloroaniline in refluxing THF[15] afforded the **9b** precursor exclusively. No crystal structure could be obtained for purine **10b** as the

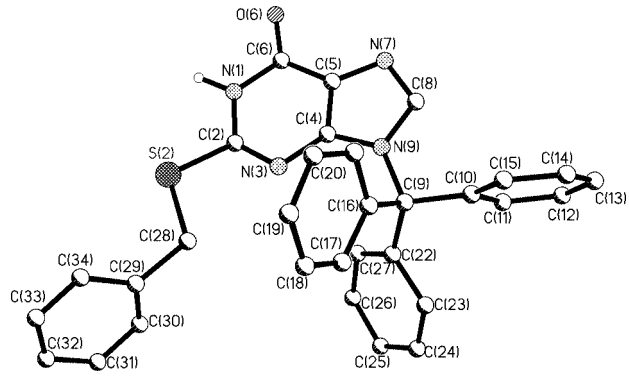
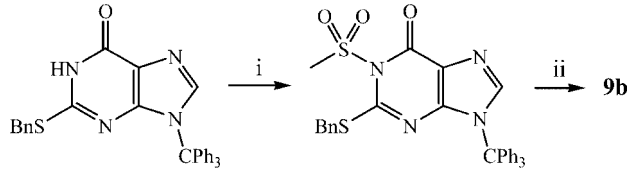


Figure 2. Crystal structure of hypoxanthines **9b**

product was isolated as a colourless oil. The preparation and reactivity of the *O*-tosyl derivative of **9b** with *m*-chloroaniline was not investigated as we developed an alternative strategy.

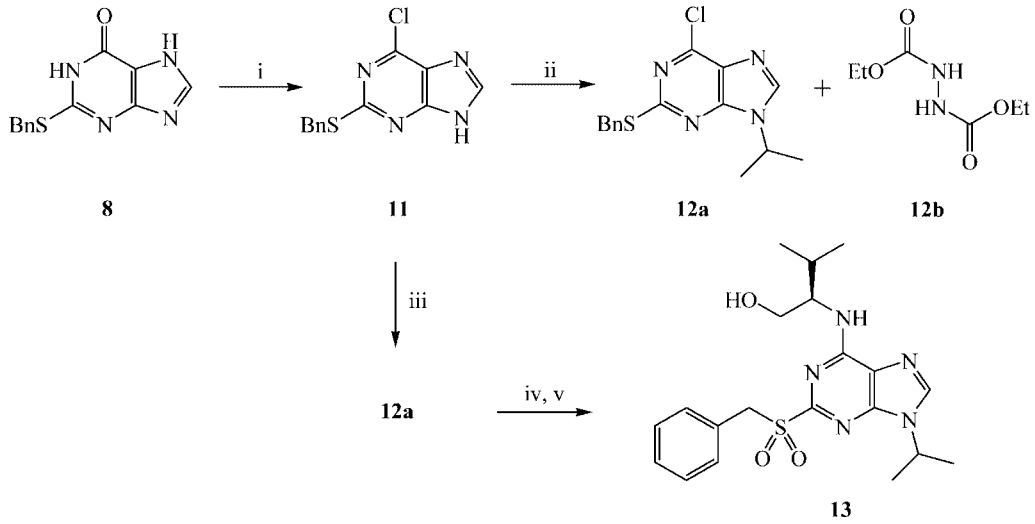


Scheme 4. Conditions: i) $MeSO_2Cl$, NEt_3, DCM, 0 °C to room temp. (98%) ii) *m*-chloroaniline, NEt_3, THF, Δ

Synthesis of Purvalanol A from 2-(Benzylsulfanyl)-6-chloropurine (11)

Chlorination of the hypoxanthine **8** under anhydrous conditions[19] gave the novel 6-chloropurine **11** following purification by chromatography in 89% yield. Reacting 6-chloropurine **11** under Mitsunobu conditions with propan-2-ol and diethyl azodicarboxylate-triphenylphosphane at −10 °C[20] only produced 20% of the desired *N*-9-isopropylpurine **12a** that was contaminated with the hydrazine by-product **12b**, as shown in Scheme 5 below; about 76% of the starting material was recovered. If the reaction is carried out at room temperature, a mixture of *N*-7- and *N*-9-isopropylpurines is obtained as reported previously[20] and their separation by chromatography is difficult. However, a regioselective and complete alkylation was implemented with the more reactive diisopropyl azodicarboxylate/triphenylphosphane system in THF at –50 °C. Following flash column chromatography, analytically pure trisubstituted purine **12a** was isolated as crystalline needles in 69% yield. HMBC NMR confirmed the regioselectivity of this alkylation since $^3J(^1H\text{-}^{13}C)$ correlations were observed between the tertiary isopropyl hydrogen –C*H*Me_2 (δ = 4.73 ppm) and the purine C4 (δ = 153.9 ppm) and C8 (δ = 145.0 ppm) carbon atoms. Single-crystal structure determination confirmed the results from the HMBC experiment (Figure 3).

Complete oxidation of the 2-benzylsulfanyl group of purine **12a** with *m*-chloroperbenzoic acid into the correspond-



Scheme 5. Conditions: i) $POCl_3$, DMA, NEt_4Cl, MeCN, 120 °C (89%) ii) Ph_3P, *i*PrOH, THF, –10 °C then DEAD, –10 °C to room temp. (20%) iii) Ph_3P, DIAD, THF, –50 °C then *i*PrOH, –50 °C to room temp. (69%), iv) $MgSO_4$, *m*-CPBA, DCM (100%) v) D-valinol, THF, Δ

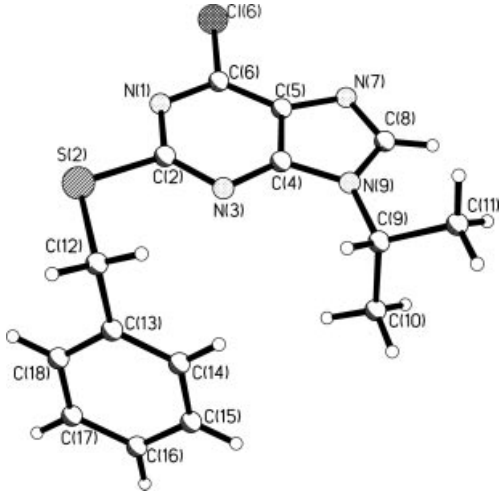


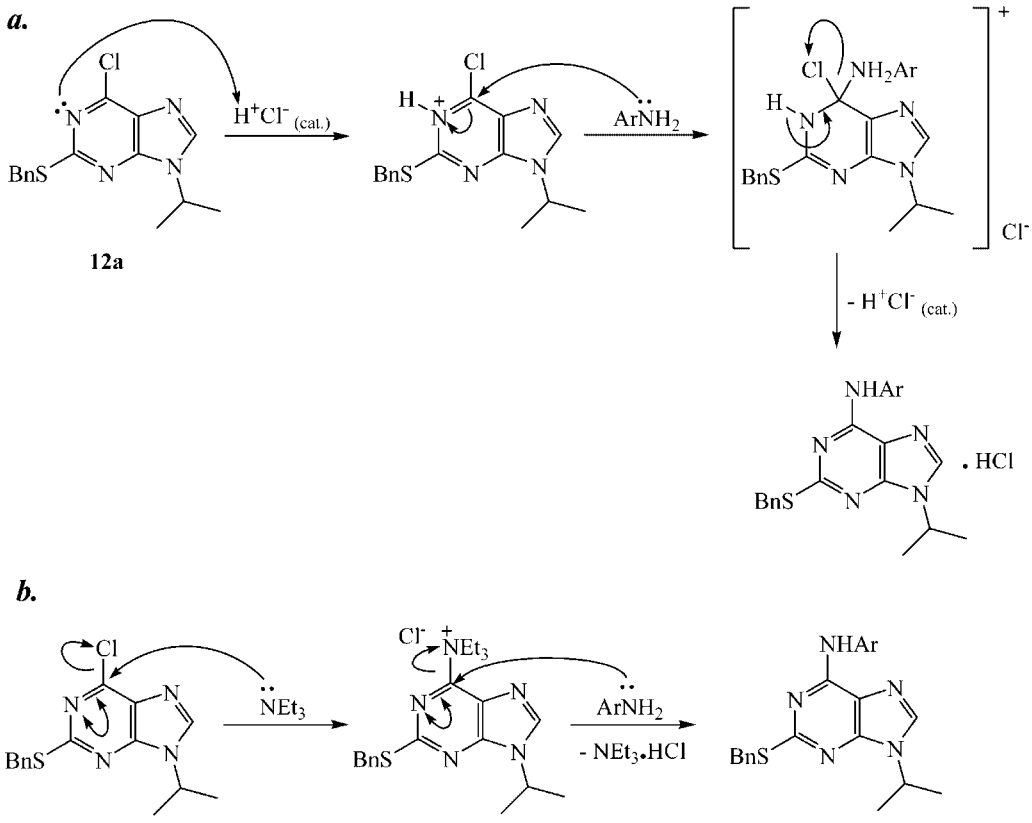
Figure 3. Crystal structure of purine **12a**

ing sulfone occurs at room temperature in dichloromethane in the presence of magnesium sulfate.[13] Suckling et al. reported the formation of 2-oxopurine under these conditions and recommended the use of dimethyldioxirane (DDO) as the best oxidising agent for 2-(benzylsulfanyl)purines.[14] No 2-oxopurine was isolated in our case and our procedure affords the desired 2-(benzylsulfonyl)purine as the main product. The reaction mixture was evaporated into a colourless solid that was used without further purification in the next reaction. Heating the sulfone in THF at 90 °C with D-valinol did not result in the nucleophilic displacement by the amino alcohol of the sulfonyl moiety as anticipated. Instead the corresponding 6-amino-2-(benzylsulfonyl)purine **13** was obtained and characterised by mass spectrometry (*m*/*z* 376.1437 thus $[M + H]^+$). This result was slightly unexpected as Suckling et al. reported that this group reacted at room temperature with aliphatic amines.

It was thus necessary to introduce the aniline of Purvalanol A at the 6-position of purine **12a** prior to the oxidative cleavage of the benzylsulfanyl moiety with D-valinol at the 2-position. Although the traditionally used base catalysed conditions[21] with arylamines failed in our hands to yield the 6-anilinopurine, even in a sealed tube, we found that the reaction proceeded to completion in the presence of catalytic amounts of concentrated hydrochloric acid after 24 hours in refluxing *tert*-butyl alcohol or *n*-butanol at ambient pressure. Purine **14** was isolated after neutralisation with triethylamine, extraction of the reaction mixture with dichloromethane then flash column chromatography in 98% yield (see Scheme 6). We believe that the reaction is driven by the loss of aromaticity upon protonation with the acid catalyst at the *N*-1 position of the purine.[22] Nucleophilic substitution with the aniline enables the regain of aromaticity through the elimination of the catalyst to generate the hydrochloride salt of purine **14**. In contrast, the base catalysed nucleophilic substitution with trimethylamine is known to generate a trimethylpurin-6-ylammonium chloride intermediate,[23,24] that further reacts with primary and secondary aliphatic or aromatic amines as shown in Scheme 6.

Catalysed Nucleophilic Substitution of the Purine 12a

Oxidation of the 2-benzylsulfanyl group with *m*-chloroperbenzoic acid (*m*-CPBA) was readily accomplished as previously and afforded the purine intermediate **15** in near quantitative yield (Scheme 7). Finally, nucleophilic substitution with D-valinol was successful in a sealed Parr bomb at 160 °C in *n*-butanol in the presence of *N*,*N*-diisopropylethylamine (Hünig's base). Purvalanol A **3** was isolated following flash column chromatography in 86% yield. Given that the displacement of the 6-Cl of 6-chloro-2-fluoropurine with *m*-chloroaniline was reported by Schultz et al.[7] to occur only in a sealed tube at 140 °C in only 56% yield, and that the displacement of 2-chloro, 2-iodo or 2-fluoro with

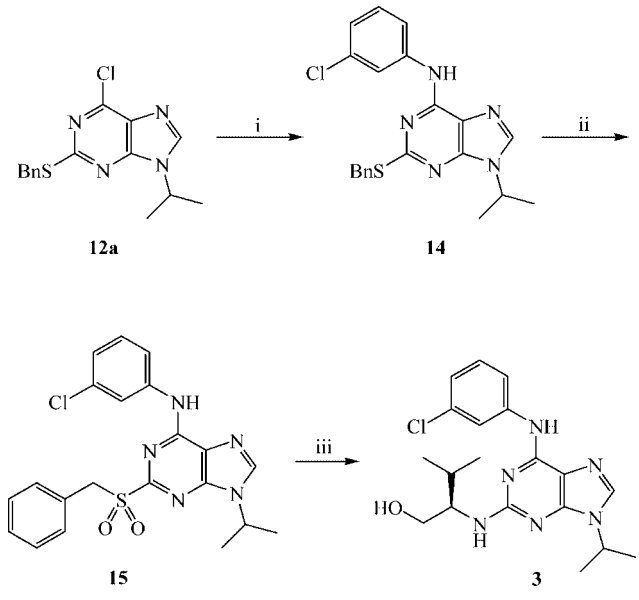


Scheme 6. Proposed mechanism for the acid (***a***.) and base (***b***.) catalysed nucleophilic substitution of purine **12a**

aliphatic amines are incomplete, our results compare very favourably with the reactivity of dihalogenopurines.

Conclusions

Although our investigations to prepare a 2,6-diaminopurine precursor bearing a 6-mesylate leaving group have been unsuccessful, the novel 2-(benzylsulfanyl)-6-chloro-9-isopropylpurine **12a** has been prepared from 2-(benzylsulfanyl) hypoxanthine and represents a valuable intermediate in the synthesis of new 2,6-diaminopurine CDK inhibitors. Purvalanol A was synthesised in 3 high yielding steps from this new purine template, including an interesting and complete acid catalysed nucleophilic displacement of the 6-Cl by *m*-chloroaniline at ambient pressure. Oxidation of the benzylsulfanyl moiety occurs readily at room temperature with *m*-CPBA in dichloromethane in the presence of magnesium sulfate while the final sulfone cleavage by D-valinol required forcing conditions in a Parr bomb but was nevertheless complete. Hence this new methodology constitutes an interesting and efficient alternative to dihalogenopurines for the synthesis of Purvalanol A analogues.



Scheme 7. Conditions: i) *m*-chloroaniline, $HCl_{(cat)}$, *n*BuOH, 120 °C (98%) ii) $MgSO_4$, *m*-CPBA, DCM (100%) iii) D-valinol, $EtN(iPr)_2$, *n*BuOH, 160 °C (86%)

Experimental Section

N,*N*-Dimethylaniline (DMA), ethanol, acetonitrile and dichloromethane were freshly distilled from calcium hydride, tetrahydrofuran (THF) and diethyl ether from sodium-benzophenone and hexane from sodium. Other solvents and reagents were used as received from BDH, Acros, Aldrich or Lancaster. Flash column chromatography was performed on silica gel 60_A (35–70μ) from Fluorochem Ltd. 0.20 mm aluminium backed sheets of silica 60_{254} from Aldrich were used for thin-layer chromatography and visualised under UV

light at 254 nm or after exposure to aqueous potassium permanganate. ^{1}H NMR spectra were recorded with a Bruker Avance 300 MHz or with a Jeol 270 MHz using the residual solvent peak as an internal reference. Chemical shifts δ are given in parts per million (ppm). Coupling constants, *J*, are given in Hz. ^{13}C NMR spectra were recorded with the above spectrometers, operating at 75.4 and 67.9 MHz respectively. Additional Pendant, HMBC and HMQC experiments were performed for full assignment where necessary. IR spectra were run with a FTIR Perkin–Elmer 2000 instrument as KBr pellets. Mass spectra were either performed by the St Andrews Analytical Services or by the EPSRC Mass Spectrometry Service at the University of Wales, Swansea, using electron impact (EI), chemical ionisation (CI) or electrospray (ESI) ionisation techniques. Elemental analyses were performed by the St Andrews Analytical Services within the School of Chemistry.

2-(Benzylsulfanyl)-7*H*-purin-6-one (8): To a stirred suspension of the 5,6-diaminopyrimidinone **7** (59.52 g, 0.24 mol) in dimethylformamide (100 mL) was added under nitrogen triethyl orthoformate (350 mL, 2 mol) and concentrated hydrochloric acid (10 mL). Stirring of the resulting dark red solution under nitrogen was continued for 2 days. The yellowish precipitate was filtered off, washed with water and recrystallised from ethanol to yield after drying the 2-substituted hypoxanthine **8** as colourless needles (56.97 g, 92%), m.p. 260 °C (ref.[14] 263–265 °C); R_f [DCM/MeOH, 95:5] = 0.14. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 4.43 (s, 2 H, PhCH_2S–), 7.21–7.32 (m, 3 H, aromatics), 7.42–7.45 (s, 2 H, aromatics), 8.05 (broad s, 1 H, 8-H), 12.50 (broad s, 1 H, NH) ppm. ^{13}C NMR (75.4 MHz, [D$_6$]DMSO, 25 °C): δ = 33.9 (s, PhCH_2S–), 115.1 (s, purine C-5), 127.3 (s, Ph C-4′), 128.4 (s, Ph C-2′), 129.1 (s, Ph C-3′), 136.8 (s, Ph C-1′), 139.1 (s, purine C-8), 151.4 (s, purine C-4), 154.9 (s, purine C-2), 156.5 (s, purine C-6) ppm. MS (ESI$^-$): *m*/*z* = 257 [M – H], $C_{12}H_{10}N_4OS$ requires 258.05753. IR (KBr disc, cm^{-1}): $\tilde{\nu}$ = 3104 s, 2890 m, 284 m, 1682 vs, 1572 s, 1536 m, 1514 m, 1494 m, 1452 s, 1386 m, 1359 s, 1266 w, 1225 s, 1153 m, 1116 m, 1071 w, 1027 w, 959 m, 912 w, 858 w, 818 w, 785 m, 775 w, 762 w, 696 s, 670 w, 614 w, 565 w, 536 w. $C_{12}H_{10}N_4OS$: calcd. C 55.80, H 3.90, N 21.69, S 12.41; found C 55.69, H 3.72, N 21.56, S 12.13

2-(Benzylsulfanyl)-9-(methylsulfonyl)hypoxanthine (9a): To a mixture of the hypoxanthine **8** (1 g, 3.86 mmol) and DMAP (30 mg, 0.23 mmol) in DCM (40 mL) was added triethylamine (6.4 mL, 45.8 mmol) at 0 °C under nitrogen. Methanesulfonyl chloride (0.45 mL, 5.70 mmol) was added dropwise and stirring under nitrogen was continued overnight at room temperature. The colourless precipitate was filtered off and washed once with cold DCM, then the filtrate was evaporated to full dryness into a yellow solid that was purified by flash column chromatography on silica gel using 2% MeOH in DCM to afford the 9-(methylsulfonyl)hypoxanthine **9a** as colourless needles (807 mg, 62%), decomposition at 200 °C; R_f = [DCM/MeOH, 95:5] 0.32. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ= 3.74 (s, 3 H, –SO_2CH_3), 4.47 (s, 2 H, PhCH_2S–), 7.21–7.34 (m, 3 H, Ph aromatics), 7.47–7.52 (m, 2 H, Ph aromatics), 8.24 (s, 1 H, hypoxanthine 8-H) ppm. ^{13}C NMR (75.4 MHz, [D$_6$] DMSO, 25 °C): δ = 34.5 (s, PhCH_2S–), 42.6 (s, –SO_2CH_3), 118.8 (s, hypoxanthine C-5), 127.8 (s, Ph C-2′), 128.9 (s, Ph C-3′), 129.5 (s, Ph C-4′), 137.1 (s, hypoxanthine C-8), 137.3 (s, Ph C-1′), 147.2 (s, hypoxanthine C-6), 156.8 (s, hypoxanthine C-4), 159.6 (s, hypoxanthine C-2) ppm. MS (EI): *m*/*z* = 337.0433 [M + H]$^+$, $C_{13}H_{13}N_4O_3S_2$ requires 337.0429. IR (KBr disc, cm^{-1}): $\tilde{\nu}$ = 3102 m, 3012 m, 2931 m, 2912 m, 1702 vs, 1542 m, 1467 w, 1375 s, 1323 m, 1262 w, 1227 m, 1183 s, 1154 m, 968 w, 873 w, 790 w, 763 m, 697 w, 671 m, 627 w, 580 w, 545 m, 513 w. $C_{13}H_{12}N_4O_3S_2$: calcd. C 46.42, H 3.60, N 16.66, S 19.06; found C 46.52, H 3.60, N 16.38, S 19.25. Crystals suitable for X-ray crystallography were obtained by recrystallisation from acetone.

2-(Benzylsulfanyl)-9-tritylhypoxanthine (9b): To a vigorously stirred suspension of the hypoxanthine **8** (5 g, 19.5 mmol) in anhydrous DCM (50 mL) was added triethylamine (4.6 mL, 29 mmol) under nitrogen. Following cooling to 0 °C, a solution of trityl chloride (8 g, 29 mmol) in anhydrous DCM (50 mL) was added dropwise. Stirring under nitrogen was continued for 24 hours at room temperature and the reaction was monitored by TLC. The solvent volume was reduced in vacuo to a few mL and purification of the crude reaction mixture by flash column chromatography on silica gel with 2.5% methanol in dichloromethane yielded the expected 9-tritylhypoxanthine **9b** as colourless crystalline needles (5.95 g, 61%), m.p. 268 °C; R_f [DCM/MeOH, 95:5] = 0.61. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 3.45 (s, 2 H, PhCH_2S–), 6.82–7.25 (m, 20 H, trityl and benzyl aromatics), 7.56 (s, 1 H, hypoxanthine 8-H), 12.44 (broad s, 1 H, amide NH) ppm. ^{13}C NMR (75.4 MHz, [D$_6$]DMSO, 25 °C): δ = 33.6 (s, PhCH_2S–), 74.8 (s, NCPh_3), 121.8 (s, purine C-5), 126.2 (s, Bn C-2′), 126.9 (s, trityl C-6′), 127.0 (s, trityl C-7′), 127.4 (s, Bn C-3′), 127.8 (s, Bn C-4′), 128.9 (s, trityl C-8′), 135.2 (s, Bn C-1′), 139.2 (s, purine C-8), 140.2 (s, trityl C-5′), 149.4 (s, purine C-6), 154.8 (s, purine C-4), 158.6 (s, purine C-2) ppm. MS (ESI$^+$): *m*/*z* = 501.1744 [M + H]$^+$, $C_{31}H_{25}N_4OS$ requires 501.1744. IR (KBr disc, cm^{-1}): $\tilde{\nu}$ = 3053 m, 3029 m, 3002 m, 2868 m, 2840 m, 1679 vs, 1599 m, 1561 s, 1541 s, 1494 s, 1467 m, 1443 s, 1407 w, 1349 s, 1316 m, 1244 m, 1205 vs, 1159 m, 1144 m, 1070 w, 1036 w, 1001 w, 954 w, 907 w, 872 m, 785 w, 776 w, 764 m, 751 s, 700 vs, 681 m, 670 m, 649 m, 609 m, 563 w, 553 m, 505 w. $C_{31}H_{24}N_4OS$: calcd. C 74.38, H 4.83, N 11.19, S 6.40; found C 74.52, H 5.25, N 11.30, S 6.89. Crystals suitable for X-ray crystallography were obtained by recrystallisation from layering a DCM solution with hexane.

2-(Benzylsulfanyl)-6-chloropurine (11): To the thoroughly dried hypoxanthine **8** (500 mg, 1.93 mmol) and tetraethylammonium chloride (530 mg, 3.20 mmol) was added anhydrous acetonitrile (5 mL) then DMA (0.25 mL, 1.37 mmol) under nitrogen. Phosphorus oxychloride (1 mL, 11.9 mmol) was added dropwise under nitrogen and the reaction mixture was then refluxed for 30 minutes at 120 °C under nitrogen, to result in a orangish solution. Following cooling, pouring on to crushed ice (50 mL), then partition with DCM (3 × 35 mL), the organics were dried with potassium carbonate and the solvent volume was reduced to about 10 mL. Addition of hexane precipitated the 6-chloropurine **11** as a pale yellow solid (427 mg, 89%); m.p. 154 °C; R_f [DCM/MeOH, 95:5] = 0.29. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 4.49 (s, 2 H, PhCH_2S–), 7.26–7.38 (m, 3 H, aromatics PhCH_2S–), 7.50–7.52 (s, 2 H, aromatics PhCH_2S–), 8.59 (s, 1 H, purine 8-H) ppm. ^{13}C NMR (75.4 MHz, [D$_6$]DMSO, 25 °C): δ = 35.1 (s, PhCH_2S–), 114.7 (s, purine C-5), 127.5 (s, Ph C-4′), 128.8 (s, Ph C-2′), 129.4 (s, Ph C-3′), 137.8 (s, purine C-1′), 145.7 (s, purine C-8), 155.9 (s, purine C-4), 161.8 (s, purine C-6), 163.5 (s, purine C-2) ppm. MS (ESI$^-$): *m*/*z* = 275.0158 [M – H], $C_{12}H_8N_4SCl$ requires 275.0158. IR (KBr disc, cm^{-1}): $\tilde{\nu}$ = 3067 m, 3024 m, 2964 m, 2917 m, 2768 m, 2658 m, 2543 m, 1612 s, 1557 s, 1480 w, 1454 w, 1410 w, 1376 m, 1356 vs, 1292 m, 1262 vs, 1216 s, 1168 m, 1155 m, 1096 s, 1072s, 1017 s, 951 m, 865 m, 855 s, 800 s, 763 m, 698 m, 686 w, 677 w, 637 m, 622 w, 589 w, 565 w, 549 w. $C_{12}H_9ClN_4S$: calcd. C 52.08, H 3.28, N 20.25, S 11.59; found C 52.45, H 3.49, N 20.12, S 11.46.

2-(Benzylsulfanyl)-6-chloro-9-isopropylpurine (12a): To the thoroughly dried 6-chloropurine **11** (400 mg, 1.45 mmol) and triphenylphosphane (420 mg, 1.6 mmol) in a flame-dried round-bottomed Schlenk flask was added anhydrous THF (10 mL) and the

resulting solution was cooled to –50 °C. DIAD (0.33 mL, 1.6 mmol) was added dropwise under nitrogen at the same temperature with stirring continued for 15 minutes then 2-propanol (0.12 mL, 1.6 mmol) was added dropwise to the yellow mixture at –50 °C. The resulting solution was gradually warmed to room temperature and stirred for 3 days under nitrogen. Following evaporation to full dryness the oily residue was purified by flash column chromatography on silica gel using petroleum ether (40–60 °C), then EtOAc/Petroleum ether (1:1) to afford the 9-isopropylpurine **12a** as a pale yellow solid (320 mg, 69%); m.p. 76–78 °C; R_f [EtOAc/hexane, 2:1] = 0.38. ^{1}H NMR (300 MHz, MeOD, 25 °C): δ= 1.47 [d, ^3J(H,H) = 6.7 Hz, 6 H, methyls C(CH$_3$)$_2$], 4.28 (s, 2 H, PhCH$_2$S–), 4.73 (septet, $^3J_{H,H}$ = 6.7 Hz, 1 H, purine CHMe$_2$), 7.00–7.13 (m, 3 H, aromatics PhCH$_2$S–), 7.29–7.31 (m, 2 H, aromatics PhCH$_2$S–), 8.30 (s, 1 H, purine 8-H) ppm. ^{13}C NMR (75.4 MHz, MeOD, 25 °C): δ = 22.8 (s, methyl CHMe$_2$), 37.1 (s, PhCH$_2$S–), 50.2 (s, tertiary NCHMe$_2$), 128.6 (s, Ph C-4′), 129.8 (s, Ph C-2′), 129.9 (s, purine C-5), 130.4 (s, Ph C-2′), 139.2 (s, Ph C-1′), 145.4 (s, purine C-8), 151.3 (s, purine C-6), 153.9 (s, purine C-4), 166.5 (s, purine C-2) ppm. MS (ESI$^+$): *m*/*z* = 341.0602 [M + Na]+, $C_{15}H_{15}N_4SClNa$ requires 341.0604. IR (KBr disc, cm^{-1}): $\tilde{\nu}$ = 3106 m, 3083 m, 3050 m, 3026 m, 3022 m, 2975 m, 2925 m, 2864 m, 1780 w, 1733 w, 1693 w, 1588 vs, 1546 vs, 1495 vs, 1495 s, 1457 s, 1410 s, 1359 vs, 1240 s, 1211 s, 1186 s, 1156 s, 1132 s, 1104 s, 1081 m, 1025 m, 958 s, 895 wm, 868 s, 772 s, 703 m, 648 s, 622 s, 570 m, 565 m. $C_{15}H_{15}ClN_4S$: calcd. C 56.51, H 4.74, N 17.57, S 10.06; found C 56.97, H 4.78, N 17.53, S 10.40. Crystals suitable for X-ray crystallography were obtained by recrystallisation from hexane.

(2*R*)-[2-(Benzylsulfonyl)-9*H*-purin-6-ylamino]-3-methylbutan-1-ol (13): A mixture of *m*-chloroperbenzoic acid (284 mg, 1.15 mmol) and magnesium sulphate (400 mg, 3.33 mmol) in DCM (5 mL) was stirred overnight under nitrogen. Purine **12a** (122 mg, 0.38 mmol) was added and the mixture was stirred under nitrogen overnight. Following filtration of the precipitate and washing with DCM (50 mL), the filtrate was evaporated to full dryness into a pale yellow solid (MS (ESI$^-$): *m*/*z* = 349.0534 [M – H]; $C_{15}H_{14}ClN_4O_2S$ requires 349.0526). The crude 2-(benzylsulfonyl)purine was dissolved in anhydrous THF (10 mL) then D-valinol (223 mg, 2.16 mml) was added and the resulting solution was refluxed overnight at 90 °C under nitrogen and monitored by TLC. Evaporation to full dryness afforded a yellow solid that was purified by flash column chromatography on silica gel using 2–10% MeOH in DCM to afford the 6-aminopurine **13** as a colourless solid (80 mg, 44%); m.p. 176 °C; R_f [DCM/MeOH, 95:5] = 0.36. ^{1}H NMR (300 MHz, MeOD, 25 °C): δ = 0.95 (2d, $^3J_{H,H}$ = 6.9 Hz, 2 × 3 H, valinol methyl Me$_2$CH–), 1.44 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, methyl NCHMe$_2$), 2.00 [o, $^3J_{H,H}$ = 6.7 Hz, 1 H, valinol tertiary (CH$_3$)$_2$CH–], 3.21 (q, $^3J_{H,H}$ = 1.5 Hz, 1 H, valinol tertiary HOCH$_2$CHNH–), 3.70 (m, 2 H, valinol secondary HOCH$_2$CH–), 4.28 (dd, $^3J_{H,H}$ = 11.0 Hz and $^3J_{H,H}$ = 6.1 Hz, 1 H, valinol OH), 4.70 (d, $^3J_{H,H}$ = 4.9 Hz, 1 H, valinol NH), 4.78 [septet, $^3J_{H,H}$ = 6.7 Hz, 1 H, tertiary CH(CH$_3$)$_2$], 4.83 (s, 2 H, PhCH$_2$SO$_2$–), 7.10–7.13 (m, 3 H, aromatics PhCH$_2$SO$_2$–), 7.19–7.22 (m, 2 H, aromatics PhCH$_2$SO$_2$–), 8.11 (s, 1 H, purine 8-H) ppm. ^{13}C NMR (75.4 MHz, MeOD, 25 °C): δ = 19.2 (s, valinol methyl MeCH), 20.5 (s, valinol methyl MeCH), 22.4 (s, methyl NCHMe$_2$), 30.9 (s, valinol tertiary –CHMe$_2$), 50.5 (s, tertiary NCHMe$_2$), 59.1 (s, PhCH$_2$SO$_2$–), 59.6 (s, valinol HNCH–), 63.7 (s, valinol HOCH$_2$–), 129.5 (s, purine C-5), 130.1 (s, Ph C-4′), 131.5 (s, Ph C-2′), 132.7 (s, Ph C-3′), 135.9 (s, Ph C-1′), 146.7 (s, purine C-8), 154.3 (s, purine C-6), 156.9 (s, purine C-4), 159.8 (s, purine C-2) ppm. MS (ESI$^+$): *m*/*z* = 418.1918 [M + H]$^+$, $C_{20}H_{28}N_5O_3S$ requires 418.1913. IR (KBr disc, cm^{-1}): $\tilde{\nu}$ = 3504 m, 3292 m, 3066 m, 3034 m, 2964s, 2921s, 2874 m, 2811 m, 1871 w, 1623 vs, 1586 vs, 1460 m, 1409s, 1370 m, 1314 vs, 1284 vs, 1253 s, 1200 m, 1174 m, 1152 m, 1112 s, 1074 m, 965 m, 870 m, 802 w, 791 w, 777 w, 752 m, 716 w, 697 s, 671 m, 697 s, 631 m, 589 w, 577 w, 559 w, 512 s. $C_{20}H_{27}N_5O_3S$: calcd. C 57.53, H 6.52, N 16.77, S 7.68; found C 57.60, H 6.41, N 16.98, S 7.37.

2-(Benzylsulfanyl)-6-(3-chlorophenylamino)-9-isopropylpurine (14): To a mixture of 6-chloropurine **12a** (250 mg, 0.79 mmol) in *n*-butanol (10 mL) was added *m*-chloroaniline (0.12 mL, 1.18 mmol) then concentrated hydrochloric acid (2 drops) and the solution was stirred at 120 °C for 24 hours. Following cooling of the resulting mixture and evaporation to full dryness into a dark oil, flash column chromatography on silica gel using petroleum ether (40–60 °C) then EtOAc/petroleum ether (1:1) afforded the 6-anilinopurine **14** as a pale yellow foam (316 mg, 98%); R_f [EtOAc/petroleum ether (40−60 °C), 1:1] = 0.19. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 1.52 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, methyl NCHMe$_2$), 4.42 (s, 2 H, PhCH$_2$S–), 4.76 (s, $^3J_{H,H}$ = 6.7 Hz, 1 H, tertiary NCHMe$_2$), 7.04 (ddd, $^3J_{H,H}$ = 3.1, $^3J_{H,H}$ = 2.0, $^3J_{H,H}$ = 1.0 Hz, 1 H, aniline H$_b$), 7.15–7.34 (m, 4 H, aromatics PhCH$_2$S– and aniline H$_d$), 7.38–7.45 (m, 2 H, aromatics PhCH$_2$S–), 7.81 (dd, $^3J_{H,H}$ = 7.7 Hz and $^3J_{H,H}$ = 3.1 Hz, 1 H, aniline H$_e$), 8.16 (dd, $^3J_{H,H}$ = 4.1 Hz and $^3J_{H,H}$ = 2.0 Hz, 1 H, aniline H$_c$), 8.32 (s, 1 H, purine H8), 10.18 (s, 1 H, aniline NH). ^{13}C NMR (75.4 MHz, [D$_6$]DMSO, 25 °C): δ = 22.4 (s, valinol methyl Me$_2$CH–), 35.0 (s, valinol tertiary –CHMe$_2$), 47.2 (s, PhCH$_2$S–), 118.4 (s, aniline C$_b$), 118.7 (s, purine C-5), 120.5 (s, aniline C$_f$), 123.6 (s, aniline C$_d$), 127.4 (s, Ph C-2′), 128.8 (s, Ph C-3′), 129.4 (s, Ph C-4′), 130.2 (s, aniline C$_c$), 134.9 (s, aniline C$_e$), 137.9 (s, purine C-8), 138.3 (s, Ph C-1′), 141.4 (s, aniline C$_a$), 150.7 (s, purine C-4), 151.5 (s, purine C-6), 164.9 (s, purine C-2) ppm. MS (ESI$^+$): *m*/*z* = 410.1221 [M + H]$^+$, $C_{21}H_{21}N_5SCl$ requires 410.1206. IR (KBr disc, cm^{-1}): $\tilde{\nu}$ = 3321 m, 3213 m, 3112 m, 3062 m, 3029 m, 2978 s, 2933 m, 1709 s, 1616 vs, 1575 vs, 1532 s, 1456 vs, 1372 s, 1325 s, 1286 s, 1268 s, 1223 m, 1197 m, 1164 m, 1132 m, 1098 m, 1077 m, 1029 s, 996 m, 948 m, 917 m, 898 w, 812 m, 788 s, 698 s, 661 m, 638 m, 610 m, 580, 564 w, 542 w, 513 w. $C_{21}H_{20}ClN_5S$: calcd. C 61.53, H 4.92, N 17.08, S 7.82; found C 61.87, H 4.74, N 17.42, S 7.52.

2-(Benzylsulfonyl)-6-(3-chlorophenylamino)-9-isopropylpurine (15): To a stirred mixture of magnesium sulphate (1.136 g, 9.47 mmol) and *m*-chloroperbenzoic acid (760 mg, 3.08 mmol) in anhydrous DCM was added a solution of the 2-(benzylsulfanyl)purine **14** (420 mg, 1.03 mmol) in DCM (10 mL) dropwise. Overnight stirring was continued overnight, then the precipitate was filtered off, washed thoroughly with DCM. The combined organics were evaporated to full dryness into a colourless solid that was purified by flash column chromatography on silica gel using EtOAc/petroleum ether (40−60 °C9 (1:1) at first to elute the *m*-chlorobenzoic acid, then with EtOAc/petroleum ether (3:1) to afford the 2-(benzylsulfonyl)purine **15** as a colourless foam (450 mg, 99%); m.p. 234 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 1.53 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, methyl NCHMe$_2$), 4.74 (s, 2 H, PhCH$_2$SO$_2$–), 4.89 [s, $^3J_{H,H}$ = 6.7 Hz, 1 H, tertiary NCH(CH$_3$)$_2$], 7.05 (ddd, $^3J_{H,H}$ = 7.9, $^3J_{H,H}$ = 1.8, $^3J_{H,H}$ = 0.8 Hz, 1 H, aniline H$_b$), 7.19−7.23 (m, 4 H, aromatics PhCH$_2$SO$_2$– and aniline H$_d$), 7.27–7.33 (m, 2 H, aromatics PhCH$_2$SO$_2$–), 7.61 (ddd, $^3J_{H,H}$ = 8.2 Hz and $^3J_{H,H}$ = 2.0 Hz and $^3J_{H,H}$ = 0.8 Hz, 1 H, aniline H$_e$), 7.87 (t, $^3J_{H,H}$ = 2.0 Hz, 1 H, aniline H$_e$), 7.98 (s, 1 H, purine H-8), 8.14 (s, 1 H, aniline NH) ppm. ^{13}C NMR (75.4 MHz, [D$_6$]DMSO, 25 °C): δ = 23.3 (s, methyl NCHMe$_2$), 48.2 (s, tertiary –NCHMe$_2$), 58.2 (s, PhCH$_2$SO$_2$–), 118.8 (s, aniline C$_b$), 120.8 (s, aniline C$_f$), 121.8 (s, aniline C$_d$), 121.9 (s, purine C-5), 124.6 (s, Ph C$_c$), 127.6 (s, Ph C-1′), 129.1 (s, Ph C-3′), 130.6 (s, Ph C-2′), 131.7 (s, Ph C-4′), 135.1 (s, aniline C$_e$), 139.4

(s, aniline C_a), 141.3 (s, purine C-8), 147.8 (s, purine C-6), 151.9 (s, purine C-4), 158.5 (s, purine C-2) ppm. MS (ESI^+): *m/z* = 442.1114 $[M + H]^+$, $C_{21}H_{21}N_5O_2SCl$ requires 442.1104. IR (KBr disc, cm^{-1}): $\tilde{\nu}$ = 3568 m, 3342 m, 3215 m, 3096 w, 3030 w, 2987 w, 2931 w, 1646 s, 1618 m, 1600 m, 1571 vs, 1479 vs, 1456 m, 1421 m, 1363 m, 1334 m, 1297 vs, 1224 s, 1205 m, 1172 m, 1131 s, 1104 m, 1028 m, 995 m, 872 m, 792 m, 779 m, 713 s, 693 s, 682 m, 637 s, 584 m, 528 s, 521 m. $C_{21}H_{20}ClN_5O_2S$: calcd. C 57.07, H 4.56, N 15.85, S 7.26; found C 57.31, H 4.23, N 15.71, S 7.38

6-(3-Chlorophenylamino)-2-[(1*R*)-(2-hydroxy-1-isopropyl)ethylamino)]-9-isopropylpurine (3): To a solution of 2-(benzylsulfanyl) purine **15** (170 mg, 0.41 mmol) in *n*-butanol (10 mL) was added Hunig's base (0.5 mL, 90 mmol) and D-valinol (500 mg, 4.9 mmol). The resulting solution was heated at 160 °C in a Parr bomb for 24 hours. Following cooling down and evaporation to full dryness, the resulting oil was purified by flash chromatography on silica gel using 1−5% MeOH in DCM to afford Purvalanol A **3** as a colourless solid (137 mg, 86%); R_f [DCM/MeOH, 95:5] = 0.20. ^1H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 1.01 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, valinol methyl $CHMe_2$), 1.47 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, methyl $NCHMe_2$), 1.97 (m, $^3J_{H,H}$ = 6.7 Hz, 1 H, valinol tertiary $CHMe_2$), 3.60–3.71 (m, 1 H, valinol tertiary $NHCHCH_2OH$), 3.80−4.01 (m, 2 H, valinol methylene $NHCHCH_2OH$), 4.50 [sept, $^3J_{H,H}$ = 6.7 Hz, 1 H, tertiary $NCH(CH_3)_2$], 5.16 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, valinol NH), 6.92 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, aniline H_d), 7.13 (t, $^3J_{H,H}$ = 8.2 Hz, 1 H, aniline H_c), 7.41 (d, $^3J_{H,H}$ = 8.16 Hz, 1 H, aniline H_b), 7.70 (t, $^3J_{H,H}$ = 1.76 Hz, 1 H, aniline H_f), 7.97 (s, 1 H, purine H-8), 8.47 (broad s, 1 H, aniline NH) ppm. ^{13}C NMR (67. 9 MHz, $CDCl_3$, 25 °C): δ = 19.1 (s, valinol methyl $CHMe_2$), 19.5 (s, valinol methyl $CHMe_2$, 23.2 (s, methyl $NCH(CH_3)_2$), 46.6 [s, tertiary $NCH(CH_3)_2$], 30.0 (s, valinol tertiary Me_2CH), 59.5 (s, valinol tertiary NHCH), 64.7 (s, valinol secondary $HOCH_2CHNH$), 114.5 (s, purine C-5), 117.8 (s, aniline C_b), 119.8 (s, aniline C_f), 122.5 (s, aniline C_d), 131.3 (s, aniline C_c), 134.3 (s, aniline C_e), 135.1 (s, purine C-8), 140.8 (s, aniline C_a), 150.9 (s, purine C-4), 152.0 (s, purine C-6), 159.8 (s, purine C-2) ppm. MS (ESI^+): *m/z* = 389.1863 $[M + 1]^+$, $C_{19}H_{26}ClN_6O$ requires 389.1857. IR (KBr disc, cm^{-1}): $\tilde{\nu}$ = 3326 m, 3232 m, 3114 m, 2960 s, 2930 s, 2873 m, 1634 s, 1575 vs, 1480 s, 1422 m, 1362 m, 1336 m, 1031 m, 1248 m, 1172 w, 1132 m, 1080 m, 1028 m, 871 w, 777 m, 698 w, 640 m, 529 w. $C_{19}H_{25}ClN_6O$: calcd. C 58.68, H 6.48, N 21.61; found C 58.92, H 6.28, N 22.69.

X-ray Crystallography: Details of the structure determination are given in Table 1 and Table 2. X-ray diffraction measurements were made with graphite-monochromated Mo-K_α radiation (λ = 0.71073) at 125 K using a Siemens Smart diffractometer for compounds **9a** and **9b** and at 93 K using a Mo MM007 rotating anode generator with a Rigaku Saturn/Xstream for **12a**. Intensity data were collected accumulating area detector frames spanning a hemisphere of reciprocal space for all structures (data were integrated using the SAINT and CrystalClear programs for Bruker and Rigaku instruments respectively). All data were solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXTL). C–H hydrogen atoms were assigned isotropic displacement parameters and were constrained to idealised geometries. All calculations were made with SHELXTL[25].

CCDC-25261 to -25263 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Selected bond length [°] and angles [°] for purines **9a**, **9b** and **12a**

Purines	9a	9b	12a
Bond length			
N(1)–C(2)	1.366(3)	1.38(2)	1.359(4)
N(1)–C(6)	1.394(3)	1.38(2)	1.327(4)
C(2)–N(3)	1.314(3)	1.27(2)	1.329(4)
C(2)–S(2)	1.749(3)	1.78(2)	1.762(3)
C(4)–C(5)	1.378(4)	1.36(2)	1.403(4)
N(7)–C(8)	1.313(4)	1.34(2)	1.315(4)
Bond angle			
C(2)–N(1)–C(6)	125.2(2)	121.5(17)	116.3(2)
N(1)–C(2)–S(2)	114.31(19)	112.6(14)	111.2(2)
N(9)–C(4)–C(5)	104.4(2)	102.7(18)	105.6(2)
N(7)–C(5)–C(4)	112.4(2)	115.8(19)	111.0(2)
N(7)–C(5)–C(6)	129.7(2)	129(2)	122.4(3)
C(4)–N(9)–C(8)	106.1(2)	108.8(17)	105.5(2)

Table 2. Crystallographic data for purines **9a**, **9b** and **12a**

Purines	9a	9b	12a
Empirical formula	$C_{13}H_{12}N_4O_3S_2$	$C_{32.50}H_{27}Cl_3N_4OS$	$C_{15}H_{15}ClN_4S$
M	336.39	627.99	318.82
Crystal system	triclinic	monoclinic	monoclinic
Space group	$P\bar{1}$	*P*21/*c*	*P*21/*c*
a []	7.4495(15)	30.107(8)	8.676(3)
b []	7.4665(15)	10.225(3)	15.695(4)
c []	13.573(3)	19.879(5)	22.263(6)
α [°]	90.270(4)	90	90
β [°]	102.886(6)	100.062(5)	92.295(6)
γ [°]	95.404(4)	90	90
Z	2	8	8
μ [mm^{-1}]	0.381	0.407	0.388
Temperature [K]	125(2)	125(2)	93(2)
Reflections measured	4725	34933	22748
Independent reflections	2628	10895	5187
Final R_1, wR_2 [$I > 2\sigma(I)$]	0.0444, 0.1135	0.1431, 0.2264	0.0552, 0.1163

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