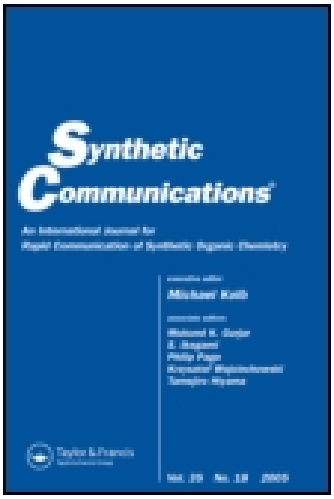

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Studies Towards the Synthesis of ATP Analogs as Potential Glutamine Synthetase Inhibitors

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STUDIES TOWARDS THE SYNTHESIS OF ATP ANALOGS AS POTENTIAL GLUTAMINE SYNTHETASE INHIBITORS

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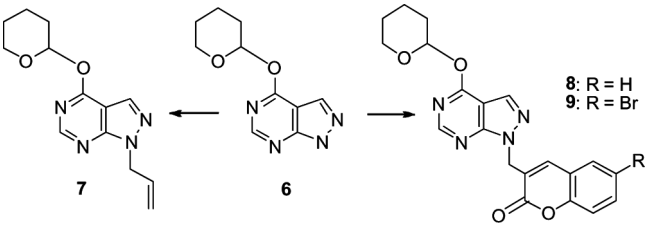
GRAPHICAL ABSTRACT



Abstract *In research directed at the development of adenine triphosphate (ATP) analogs as potential glutamine synthetase (GS) inhibitors, adenine and allopurinol derivatives have been synthesized either as novel ATP analogs or as scaffolds for the construction of such analogs.*

Keywords Adenine; allopurinol; Baylis–Hillman products; glutamine synthetase inhibitors

Although Tuberculosis (TB) has been viewed as a preventable disease, it remains a major international health challenge with the highest mortality rates being recorded in the poorest parts of the world. The problem has been exacerbated by the increased susceptibility of AIDS-infected patients to TB[1] and by the emergence of multidrug-resistant (MDR-TB)[2] and, very recently, extremely drug-resistant (XDR-TB) strains.[3–5] *Mycobacterium tuberculosis* (*M.tb.*) is the tubercle bacillus responsible for TB,[6,7] and the type II *M.tb.* glutamine synthetase enzyme (MTB-GS) has been shown to be essential, inter alia, for the formation of the cell wall of *M.tb.*[8] Adenine triphosphate (ATP; Fig. 1) is a critical GS substrate, and our research has focused on the development ATP mimics capable of binding to the active site of MTB-GS and thus inhibiting normal enzymatic function. The first step in exploring this hypothesis has involved the synthesis of such mimics, and in a collaborative program, we have

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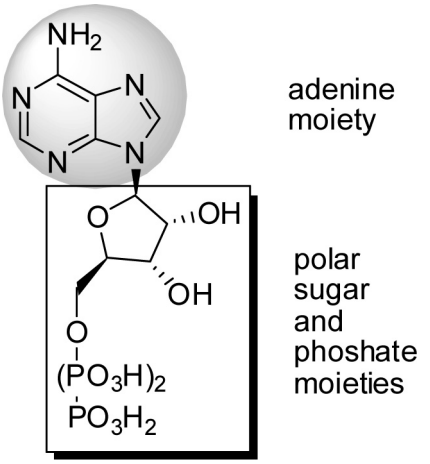
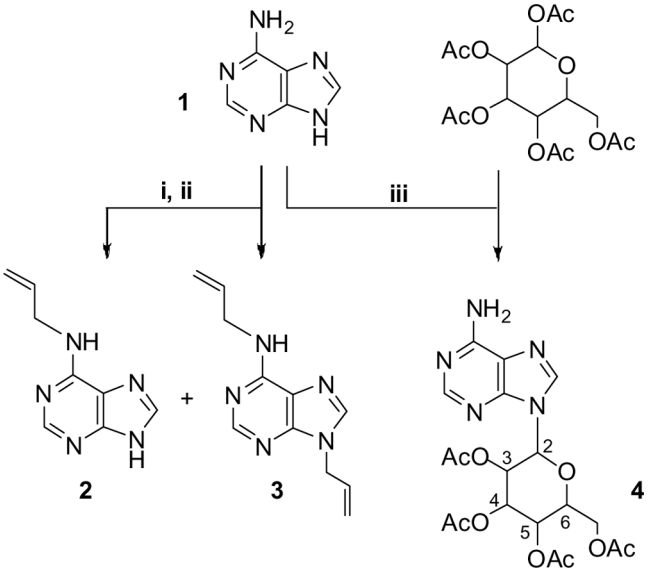


Figure 1. Major structural features of ATP.

examined various approaches to their synthesis. These include (i) replacement of the adenine moiety (Fig. 1) by different heterocyclic sytems;[9] (ii) the use of "truncated" adenine derivatives;[10] and (iii) replacement of the polar sugar and triphosphate moieties in ATP by, for example, penta-acetylgluconyl or polyoxygenated alkylphosphonate groups.[9,10] In this communication, we report the results of preliminary studies directed toward the preparation of adenine and allopurinol derivatives.

It was anticipated that deprotonation of adenine followed by reaction with suitable electrophiles would afford novel ATP analogs or scaffolds for the construction of such analogs. When adenine **1** was treated with NaH in dimethylformamide (DMF),

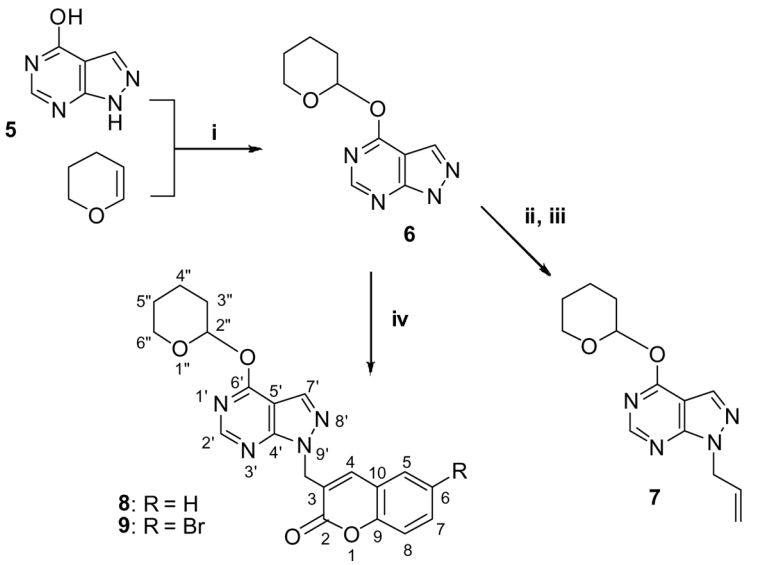


Scheme 1. *Reagents*: i) NaH, DMF; ii) $CH_2{=}CHCH_2Br$; iii) $SnCl_4$, CH_3CN.

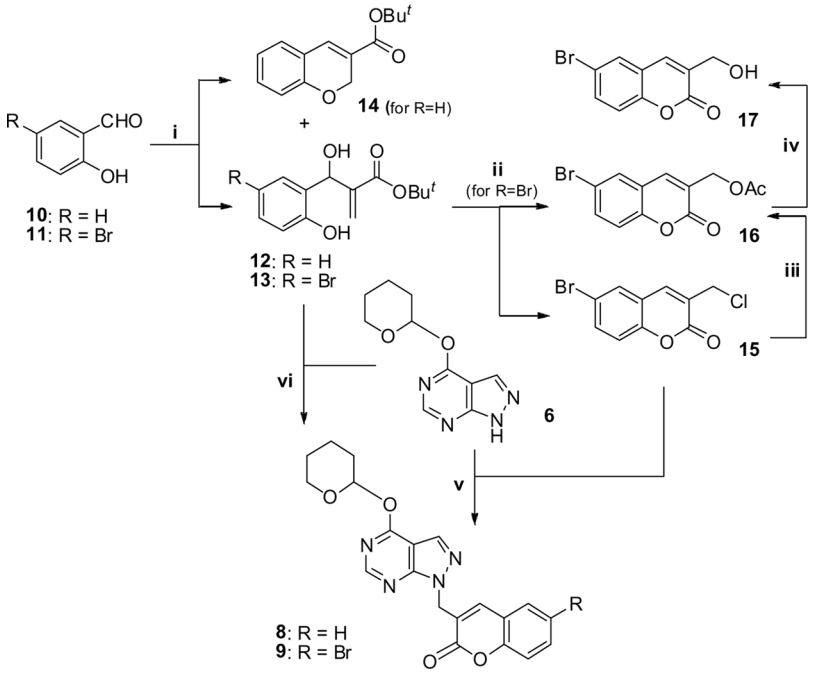
followed by allyl bromide (Scheme 1), both the monoallylated product **2** and the diallylated analog **3** were obtained in very poor yields (12% and 2% respectively), with monoallylation in the former compound occurring preferentially at the 6-amino group rather than on the purine nucleus at N-9. Preliminary attempts to couple deprotonated adenine with 2-(chloroethoxy)ethanol, acetoxyacetyl chloride, and chloroacetyl chloride all proved unsuccessful. However, $SnCl_4$-catalyzed *N*-glycosidation using specially prepared[11] penta-acetylated glucopyranose in acetonitrile[12] afforded 3,4,5-triacetoxy-6-acetoxymethyl-2-(6-aminopurin-9-yl)pyran **5** in 30% yield. NMR analysis of this product confirmed the presence of the anomeric proton, resonating at 5.88 ppm (0.4 ppm upfield of the corresponding signal in the penta-acetylated precursor), and the anomeric carbon, resonating at 80.3 ppm—an upfield shift of 8.8 ppm.

Attention was also given to the use of allopurinol **5** as a structural analog of adenine. Since it was again the intention to react the deprotonated heterocyclic substrate with various electrophiles, the allopurinol hydroxyl group was protected as the 2-pyranyl ether[13] to avoid competition between the NH and OH groups. The protected allopurinol **6** was deprotonated using sodium hydride in tetrahydrofuran (THF) and then treated with allyl bromide[14] under reflux to afford the *N*-allylated derivative **7** in 87% yield (Scheme 2). We had previously developed access to various coumarin derivatives using Baylis–Hillman methodology,[15] and it was decided to explore the use of 3-(chloromethyl)coumarins as alkylating agents to afford compounds **8** and **9**. The coumarin moiety is common in nature,[16] and has the potential to undergo nucleophilic ring opening.[17]

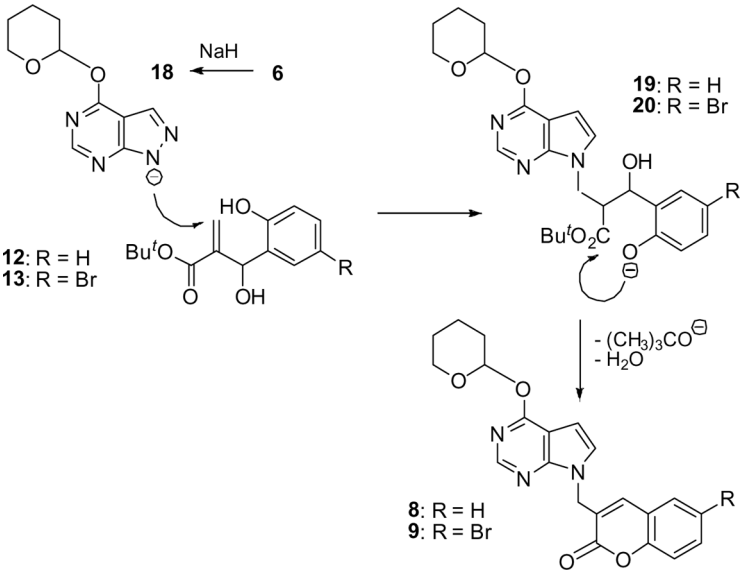
In the present study, the requisite Baylis–Hillman adducts **12** and **13** were obtained as outlined in Scheme 3, the former accompanied by a trace amount of the 2*H*-chromene-3-carboxylate ester **14**. Cyclization of the Baylis–Hillman adduct **13** in a refluxing mixture of HCl and CH_3COOH[15] yielded the desired 6-bromo-3-(chloromethyl)coumarin **15** in 31% yield together with two side products,



Scheme 2. *Reagents*: i) PTSA, DMF; ii) NaH, DMF; iii) CH_2=$CHCH_2Br$; iv) See Scheme 3.



Scheme 3. *Reagents*: (i) $CH_2{=}CHCO_2Bu^t$, DABCO, $CHCl_3$; (ii) HCl, CH_3CO_2H; (iii) CH_3CO_2H; (iv) H_2O; (v) NaH, THF then **15**; (vi) NaH, THF, then **12** or **13**.



Scheme 4. Proposed mechanism for the formation of the allopurinol-coumarin products.

3-(acetoxymethyl)-6-bromocoumarin **16** (<2%) and 6-bromo-3-(hydroxymethyl)-coumarin **17** (7%). Formation of the acetate ester **16** may be attributed to direct conjugate addition by acetic acid on the substrate **13** and/or nucleophilic displacement of chloride in the major product **15** by acetate, while the formation of the alcohol **17** may be attributed to the hydrolysis of the ester **16** during workup (Scheme 3).

Two routes to the allopurinol-coumarin product **8** were followed (Scheme 3). In the first, the allopurinol ether **6** was deprotonated and reacted with 6-bromo-3-(chloromethyl)coumarin **15** using direct nuceophilic displacement, affording the required product **9** in 31% yield. In the second approach, use of the Baylis–Hillman adduct **13**, as the electrophile, involved a tandem conjugate addition–cyclization sequence to afford the product **9** in 14% yield. The second approach was also used to prepare compound **8** directly from the corresponding Baylis–Hillman adduct **12**. A mechanistic rationalization for the conjugate addition–cyclization sequence is outlined in Scheme 4. Thus, conjugate addition of the deprotonated alloprinol derivative **18** to the Baylis-Hillman adducts **12** and **13**, followed by intramolecular *trans*-esterification of the deprotonated aza-Michael adducts **18** and **19** and dehydration, is expected to afford products **8** and **9**, respectively. The conjugate addition of amines to Baylis–Hillman esters has been observed previously in our group.[18,19]

CONCLUSIONS

Although yields have not been optimized, the *N*-allylated derivatives **2** and **7**, the *N*-glycosylated derivative **4**, and the allopurinol-coumarin adducts **8** and **9** represent useful scaffolds for structural elaboration. The successful coupling of the protected allopurinol **6** to Baylis–Hillman adducts suggests that aza-Michael addition might well provide effective access to various *N*-substituted adenine and allopurinol systems. It is expected that this methodology and the potential of some of the products as glutamine synthetase inhibitors will be explored in future investigations.

EXPERIMENTAL

Low-resolution mass spectra (LRMS) were obtained on a Finnegan Mat GCQ spectrometer, whereas high-resolution mass spectra (HRMS) were recorded by the University of Witwatersrand Mass Spectrometry Unit. NMR spectra were recorded on a Bruker 400 MHz Avance spectrometer and were referenced using solvent signals (δ_H: 7.26 ppm for residual $CHCl_3$; δ_C: 77.0 ppm for $CDCl_3$). Melting points were determined using a hot-stage apparatus and are uncorrected. The penta-acetylated glucose,[11] the allopurinol 2-pyranyl ether **6**,[13] the Baylis–Hillman adducts **12** and **13**,[15] and the coumarin derivatives **14** and **15**[15,18] are known. Synthetic methods and the characterization of new compounds prepared in this study are detailed.

6-(*N*-Allylamino)purine 2 and 9-Allyl-6-(*N*-allylamino)purine 3

NaH (60% dispersion in mineral oil; 100 mg, 4.0 mmol) was added, in small portions to permit controlled evolution of hydrogen, to a stirred solution of adenine **1** (300 mg, 2.2 mmol) in dry DMF (20 mL) under nitrogen at 0 °C. Allyl bromide

(230 μL, 2.7 mmol) was then added through a septum, and the resulting solution was refluxed for ca. 6 h. The reaction was quenched by the addition of water (25 mL). The solvent was evaporated in vacuo, and the aqueous residue was extracted with $CHCl_3$ (2×25 mL). The organic extracts were combined, washed sequentially with saturated aqueous $NaHCO_3$ (2×50 mL), water (2×50 mL), and brine (2×50 mL). The aqueous washings were extracted with $CHCl_3$, and the organic layers were combined and dried (anhydrous $MgSO_4$). The solvent was evaporated in vacuo, and the residue was flash chromatographed [on silica; elution with EtOH–EtOAc (1:20)] to afford two fractions.

6-(*N*-Allylamino)purine 2. Yellow solid (45 mg, 12%), mp 165–167 °C (found $\mathbf{M}^+$: 175.085842. $C_8H_9N_5$ requires, *M*: 175.085795); ν_{max} (solid deposit/cm^{-1}) 3382 (NH); δ_H/ppm (400 MHz; $CDCl_3$) 4.91 (2H, d, $J = 5.8$ Hz, CH_2CH), 5.25 (1H, d, $J = 17.1$ Hz, $CH_2CH{=}CH_Z$), 5.35 (1H, d, $J = 10.2$ Hz, $CH_2CH{=}CH_E$), 6.07 (1H, tdd, $J = 16.1$, 10.4 and 5.8 Hz, CH_2CH), 8.43 (1H, s, Ar-H), 8.70 (1H, s, Ar-H), 10.01 (1H, d, $J = 10.0$ Hz, 6-NH), and 11.12 (1H, d, $J = 9.4$ Hz, 9-NH); δ_C/ppm (100 MHz; $CDCl_3$) 46.1 (CH_2CH), 119.6, 120.4, 131.2, 144.2, 149.3, 151.9 and 152.5 ($CH{=}CH_2$ and Ar-C).

9-Allyl-6-(*N*-allylamino)purine 4. Yellow solid (8.0 mg, 2.0%), mp 103–105 °C (found $\mathbf{M}^+$: 215.118412. $C_{11}H_{13}N_5$ requires, *M*: 215.117096); ν_{max} (thin film/cm^{-1}) 3383 (NH); δ_H/ppm (400 MHz; $CDCl_3$) 4.80 (4H, d, $J = 5.3$ Hz, $2 \times CH_2CH$), 5.19 (2H, m, $CH{=}CH_2NH$), 5.30 (2H, d, $J = 8.0$ Hz, $CH{=}CH_2$), 6.02 (2H, m, $2 \times CH_2CH$), 7.77 (1H, s, Ar-H) and 8.40 (1H, s, Ar-H); δ_C/ppm (100 MHz; $CDCl_3$) 45.7 ($2 \times CH_2CH$), 116.4, 118.9, 119.6, 131.9, 134.3, 139.7, 152.5, 153.2 and 154.7 ($CH{=}CH_2$ and Ar-C).

3,4,5-Triacetoxy-6-acetoxymethyl-2-(6-aminopurin-9-yl)pyran 4

Tin tetrachloride (1.0 mL, 9.3 mmol) was added to a stirred solution of adenine **1** (0.5 g, 4 mmol) and acetylated glucose[11] (1.4 g, 3.5 mmol) in acetonitrile (20 mL), and the reaction mixture was refluxed under argon for ca. 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL). The solvent was evaporated in vacuo, and the aqueous residue extracted with EtOAc (2×25 mL). The organic extracts were combined and washed sequentially with saturated aqueous $NaHCO_3$ (2×50 mL) and brine (2×50 mL). The aqueous washings were extracted with EtOAc, and the organic layers were combined and dried (anhydrous $MgSO_4$). The solvent was evaporated in vacuo, and flash chromatography of the residual oil [on silica; elution with EtOH-$CHCl_3$ (1:19)] afforded 3,4,5-triacetoxy-6-acetoxymethyl-2-(6-aminopurin-9-yl)pyran **4** as yellow crystals (510 mg, 30%), mp 63–65 °C (found $\mathbf{M}^+$: 465.14892. $C_{19}H_{23}N_5O_9$ requires, *M*: 465.14958); ν_{max} (solid deposit/cm^{-1}) 3339 (NH_2) and 1744 (C=O); δ_H/ppm (400 MHz; $CDCl_3$) 2.00–2.08 (12H, series of singlets, $4 \times CH_3$), 4.02–5.58 [6H, series of multiplets, CH_2 and pyran 3-,4-,5- and 6-H], 5.76 (2H, s, NH_2), 5.88 (1H, d, $J = 9.5$ Hz, pyran 2-H), 8.00 (1H, s, Ar-H) and 8.36 (1H, s, Ar-H); δ_C/ppm (100 MHz; $CDCl_3$) 20.1, 20.5, 20.6, and 20.7 ($5 \times CH_3$), 61.6 (CH_2), 67.9 (C-5), 70.4 (C-3), 72.9 (C-4), 75.1 (C-6), 80.3 (C-2), 119.2, 138.3, 150.7, 153.4 and 155.4 (Ar-C), 169.0, 169.4, 169.8 and 170.5 ($4 \times C{=}O$).

7-Allyl-4-(tetrahydropyran-2-yloxy)pyrazolo[3,4-*d*]pyrimidine 7

NaH (60% dispersion in mineral oil; 40 mg, 0.91 mmol) was added in small portions to a stirred solution of protected allopurinol **6**[13] (200 mg, 0.91 mmol) in dry THF (50 mL) under nitrogen to permit controlled evolution of hydrogen. Allyl bromide (80 μL, 0.91 mmol) was then added through a septum, and the resulting solution was refluxed for ca. 6 h. The reaction was quenched by the addition of water (50 mL). The solvent was evaporated in vacuo, and the aqueous residue was extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined and washed sequentially with water (2 × 100 mL) and brine (2 × 100 mL). The aqueous washings were extracted with CH_2Cl_2, and the organic layers were combined and dried (anhydrous $MgSO_4$). Evaporation of the solvent in vacuo afforded 7-allyl-4-(tetrahydropyran-2-yloxy)pyrazolo[3,4-*d*]-pyrimidine **7** as a pale yellow solid (210 mg, 87%), mp 60–62 °C (found $\mathbf{M}^+$: 260.12774. $C_{13}H_{16}N_4O_2$ requires, *M*: 260.12733); δ_H/ppm (400 MHz; $CDCl_3$) 1.61–4.10 [8H, series of multiplets, $(CH_2)_4$], 4.61 (2H, m, $CH_2CH{=}CH_2$), 5.21 (1H, d, $CH_2CH{=}CH_Z$), 5.28 (1H, dd, $CH_2CH{=}CH_E$), 5.83 (1H, dd, OCHO), 5.94 (1H, tdd, $CH{=}CH_2$), 7.94 (1H, s, Ar-H) and 8.12 (1H, s, Ar-H); δ_C/ppm (100 MHz; $CDCl_3$) 22.7 (C-5′), 24.9 (C-4′), 29.3 (C-3′), 47.8 ($CH_2CH{=}CH_2$), 68.2 (C-6′), 82.9 (OCHO), 106.3, 118.9, 132.1, 135.8, 149.0, 151.7 and 156.8 ($CH{=}CH_2$ and Ar-C).

6-Bromo-3-(chloromethyl)coumarin 15, 3-(Acetoxymethyl)-6-bromocoumarin 16, and 6-Bromo-3-(hydroxymethyl)coumarin 17

A mixture of *t*-butyl 3-(5-bromo-2-hydroxyphenyl)-3-hydroxy-2-methylene propanoate **13** (2.0 g, 6.1 mmol), concentrated HCl (10 mL), and glacial acetic acid (10 mL) was boiled under reflux for 2.5 h. The reaction mixture was allowed to cool to room temperature. Ice-cold water (40 mL) was then added and the reaction mixture was stirred for 30 min. The mixture was allowed to stand at 0 °C for 24 h, and the pink solid was filtered off and flash chromatographed [on silica; elution with hexane–EtOAc (7:3)] to afford three products.

6-Bromo-3-(chloromethyl)coumarin 15. White powder (0.52 g, 31%), mp 102–104 °C (lit.[15] 104–106 °C).

3-(Acetoxymethyl)-6-bromocoumarin 16. White powder (33 mg, 1.8%), mp 119–121 °C (found $\mathbf{M}^+$: 297.966202. $C_{12}H_9^{81}BrO_4$ requires, *M*: 297.96637); ν_{max} (solid deposit/cm^{-1}) 1720 (C=O), δ_H/ppm (400 MHz; $CDCl_3$) 2.16 (3H, s, CH_3), 5.06 (1H, d, CH_2), 7.22 (1H, d, 8-H), 7.61 (1H, dd, 7-H) and 7.64 (2H, m, 5-H and 4-H); δ_C (100 MHz; $CDCl_3$) 20.8 (CH_3), 60.9 (CH_2), 117.2, 118.4, 120.3, 125.0, 130.2, 134.5, 138.9 and 152.3 (Ar-C), 159.5 and 170.4 (2 × C=O).

6-Bromo-3-(hydroxymethyl)coumarin 17. White powder (0.11 g, 7.3%), mp 147–149 °C (found: $\mathbf{M}^+$, 253.959816. $C_{10}H_7^{79}BrO_3$ requires, *M*: 253.95781); ν_{max} (solid deposit/cm^{-1}) 3409 (OH) and 1632 (C=O); δ_H/ppm (400 MHz; DMSO-d_6) 4.36 (2H, m, CH_2), 5.52 (1H, t, OH), 7.37 (1H, d, 8-H), 7.71 (1H, dd, 7-H), 7.94 (1H, d, 4-H) and 8.05 (1H, d, 5-H); δ_C (100 MHz; DMSO-d_6) 58.1 (CH_2), 116.1, 118.2, 121.0, 130.1, 130.5, 133.3, 135.6 and 151.3 (Ar-C) and 159.1 (C=O).

7-[(2*H*-Chromen-2-on-3-yl)methyl]-4-(tetrahydropyran-2-yloxy)-pyrazolo[3,4-*d*]pyrimidine 8

NaH (60% dispersion in mineral oil; 21 mg, 0.88 mmol) was added to a stirred solution of protected allopurinol **6** (110 mg, 0.49 mmol) in dry THF (10 mL) under nitrogen in small portions to permit controlled evolution of hydrogen. The resulting solution was refluxed for 1 h and then cooled to room temperature before adding *t*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylene propanoate **12** (120 mg, 0.49 mmol). The reaction mixture was refluxed for ca. 6 h. Water (30 mL) was added to quench the reaction. The organic solvent was evaporated in vacuo, and the aqueous residue was extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were washed sequentially with water (2×60 mL) and brine (2×60 mL). The aqueous washings were extracted with CH_2Cl_2, and the organic layers were combined and dried (anhydrous $MgSO_4$). Evaporation of the solvent in vacuo afforded a pale yellow solid, flash chromatography of which [on silica; elution with hexane–EtOAc (3:7)] afforded 7-[(2*H*-chromen-2-on-3-yl)methyl]-4-(tetrahydropyran-2-yloxy)pyrazolo[3,4-*d*]-pyrimidine **8** as a white powder (45 mg, 24%), mp 210–212 °C (found $\mathbf{M}^+$: 378.132008. $C_{20}H_{18}N_4O_4$ requires, *M*: 378.132805); ν_{max} (solid deposit/cm^{-1}) 1698 (C=O); δ_H/ppm (600 MHz; $CDCl_3$) 1.59–4.10 [8H, m, $(CH_2)_4$], 5.03 (2H, s, NCH_2), 5.84 (1H, dd, OCHO), 7.29 (2H, m, Ar-H), 7.52 (2H, m, Ar-H), 8.075 (1H, s, Ar-H), 8.078 (1H, s, Ar-H) and 8.46 (1H, s, Ar-H); δ_C/ppm (150 MHz; $CDCl_3$) 22.7 (C-5″), 24.8 (C-4″), 29.4 (C-3″), 45.7 (CH_2), 68.3 (C-6″), 82.8 (C-2″), 106.2, 116.6, 118.7, 121.9, 124.8, 128.5, 132.3, 135.6, 144.5, 150.2, 151.8, 153.7 and 157.4 (Ar-C) and 161.4 (C=O).

7-[(6-Bromo-2*H*-chromen-2-on-3-yl)methyl]-3-(tetrahydropyran-2-yloxy)-pyrazolo[3,4-*d*]pyrimidine 9

Method 1. NaH (60% dispersion in mineral oil; 24 mg, 0.99 mmol) was added to a stirred solution of protected allopurinol **6** (120 mg, 0.55 mmol) in dry THF (10 mL) under nitrogen in small portions to permit controlled evolution of hydrogen. The resulting solution was refluxed for 1 h and then cooled to room temperature before adding 6-bromo-3-(chloromethyl)chromen-2-one **15** (150 mg, 0.55 mmol). The reaction mixture was refluxed for ca. 6 h. Water (30 mL) was added to quench the reaction. The organic solvent was evaporated in vacuo, and the aqueous residue extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were washed sequentially with water (2×60 mL) and brine (2×60 mL). The aqueous washings were extracted with CH_2Cl_2, and the organic layers were combined and dried (anhydrous $MgSO_4$). Evaporation of the solvent in vacuo afforded a pale yellow solid, flash chromatography of which [on silica; elution with hexane–EtOAc (1:1)] afforded 7-[(6-bromo-2*H*-chromen-2-on-3-yl)methyl]-3-(tetrahydropyran-2-yloxy)pyrazolo[3,4-*d*]pyrimidine **9** as a white powder (77 mg, 31%), mp 210–212 °C (found $\mathbf{M}^+$: 458.041200. $C_{20}H_{17}^{81}BrN_4O_4$ requires, *M*: 458.04141); ν_{max} (solid deposit/cm^{-1}) 1720 (C=O); δ_H/ppm (400 MHz; $CDCl_3$) 1.60–4.10 [8H, series of multiplets, $(CH_2)_4$], 5.02 (1H, s, NCH_2), 5.83 (1H, dd, OCHO), 7.19 (1H, d, 8-H), 7.60 (1H, dd, 7-H), 7.66 (1H, d, 5-H), 8.00 (1H, s, Ar-H), 8.08 (1H, s, Ar-H), and 8.42 (1H, s, Ar-H); δ_C/ppm (100 MHz; $CDCl_3$) 22.7 (C-5″), 24.8 (C-4″), 29.3 (C-3″), 45.7 (NCH_2), 68.3

(C-6″), 82.8 (C-2″), 106.1, 117.4, 118.3, 120.2, 123.0, 130.7, 135.0, 135.6, 143.2, 150.0, 151.7, 152.4 and 157.3 (Ar-C), and 160.7 (C=O).

Method 2. The procedure described for the preparation of compound **8** was followed using the Baylis–Hillman adduct **13** and the protected allopurinol **6** to afford compound **9** in 14% yield.

ACKNOWLEDGMENTS

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