Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 12294–12302
Tetrahedron

Efficient synthesis of 1,3,7-substituted xanthines by a safety-catch protection strategy

Matthew B. Allwood,[a] Booma Cannan,[b] Daan M. F. van Aalten[a] and Ian M. Eggleston[b,*]

[a]*Division of Biological Chemistry and Drug Discovery, College of Life Sciences, University of Dundee, Dundee DD1 5EH, UK*
[b]*Wolfson Laboratory of Medicinal Chemistry, Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK*

Received 26 July 2007; revised 11 September 2007; accepted 27 September 2007
Available online 29 September 2007

Abstract—An efficient synthesis of selectively *N*-substituted xanthine derivatives is described. Cyclocondensation of a suitably protected aminoimidazole with methyl-2-phenylthioethyl carbamate, followed by oxidation of sulfur to the sulfone, provides access to an orthogonally 1,7-protected xanthine, which may then be regioselectively alkylated and deprotected under mild conditions.

1. Introduction

Substituted xanthine derivatives are an important class of pharmacologically active compounds with well-known activity as adenosine receptor antagonists, phosphodiesterase inhibitors and inducers of histone deacetylase activity.[1] This has led to a wide range of medical applications including the treatment of asthma, bronchitis and chronic obstructive pulmonary disease, and their use as diuretics, cardiac stimulants and renal protective agents.[2] Very recently, xanthine derivatives such as caffeine, theophylline and pentoxifylline (Fig. 1) have been identified as micromolar inhibitors of bacterial family 18 chitinases,[3] thereby opening up potential applications for such molecules as fungicides and nematocides, and renewing interest in their use as asthma therapeutics.

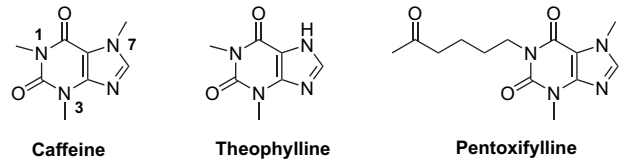
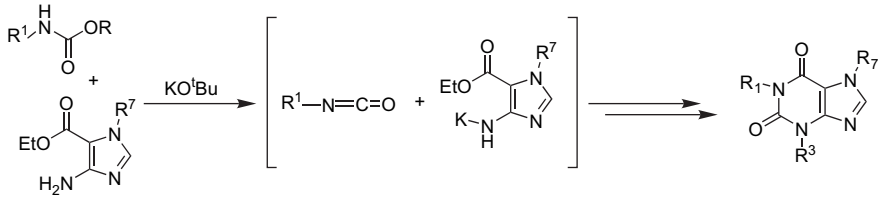


Figure 1.

As part of our studies in this area, we required an efficient route to xanthine derivatives, selectively substituted at the 1-, 3-, or 7-positions. Unfortunately, the synthesis of such compounds by the classic Traube[4] method from 6-aminouracils is both lengthy and incompatible with the introduction of complex *N*-substituents. An alternative approach is to use an imidazole starting material,[5] and in an interesting recent development, described by Zavialov,[6] the cyclocondensation of a metallated 4-amino-5-alkoxycarbonyl imidazole with in situ generated isocyanates that provide the N-1 substituent was reported (Scheme 1). Although this gives efficient access to the heterocyclic skeleton, and provides some scope for subsequent N-3 and N-7 modifications, a key drawback is that the N-1 substituent is fixed, thereby limiting further elaboration at this position, and is also restricted to simple alkyl or aralkyl groups that can withstand the strongly basic reaction conditions. In order to address these issues, we envisaged that a more flexible and powerful approach would be to generate an orthogonally protected xanthine via the Zavialov strategy



Scheme 1. Zavialov's[6] synthesis of substituted xanthine derivatives.

* Corresponding author. Tel.: +44 01225 383101; fax: +44 01225 386114; e-mail: ie203@bath.ac.uk

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.09.067

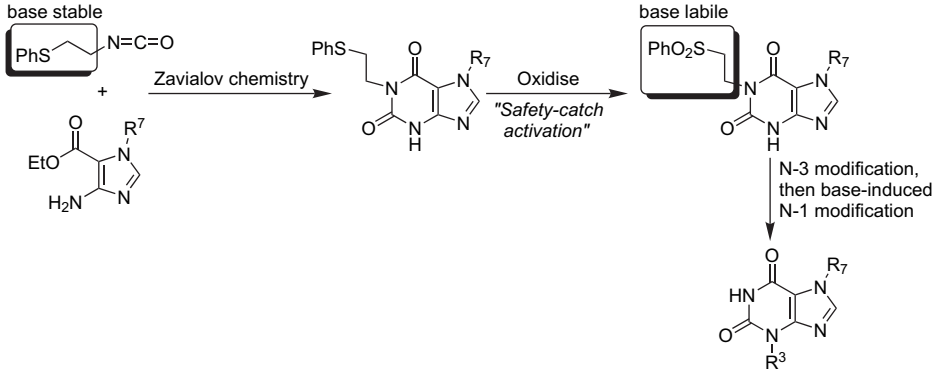
that might then be selectively deprotected and decorated at each nitrogen in turn. To achieve this goal, we have therefore devised a novel modification of this approach, that utilises a sacrificial N-1 substituent, which is stable to the basic cyclocondensation conditions, but may then be activated and released (safety-catch principle) in the presence of appropriate N-3 and N-7 protection or substitution once the ring system has been formed, and subsequently replaced as required. We describe herein the realisation of this principle and its application for the synthesis of various 1,3-, 1,7- and 1,3,7-substituted xanthine derivatives.

2. Results and discussion

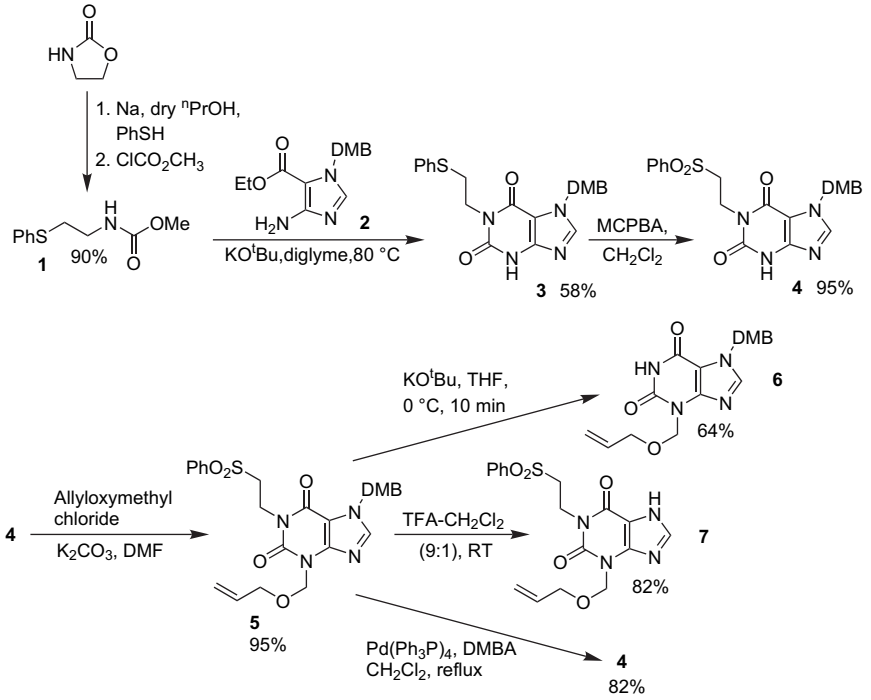
2.1. Synthesis of orthogonally protected xanthine derivatives

A promising candidate for the N-1 substituent in our projected xanthine synthesis was the 2-phenylthioethyl group. This was chosen since it was anticipated that it should be readily introducible into N-1 of the xanthine core via the appropriate isocyanate, produced in situ from a carbamate derivative, but might then be oxidised to the sulfone to provide a base-labile fragment. This approach, which is summarised in Scheme 2, was inspired by the safety-catch linker for peptide synthesis reported by Tesser,[7] and it was envisioned that such a protecting group strategy[8] would be entirely compatible with acid-labile N-7 protection such as PMB or DMB, and allyl-based N-3 protection, cleavable under neutral conditions by Pd(0) catalysis.

The realisation of the synthetic concept is shown in Scheme 3. Carbamate **1**[9] was generated in 90% yield by a one-pot procedure, by the treatment of 2-oxazolidinone with thiophenol and sodium propoxide in dry propanol to form 2-phenylthioethylamine,[10] followed by in situ trapping with methyl chloroformate. The carbamate **1** and aminoimidazole **2**[11] were then treated with KO^{t}Bu in diglyme at 80 °C, according to the method of Zavialov.[6] This gave the desired

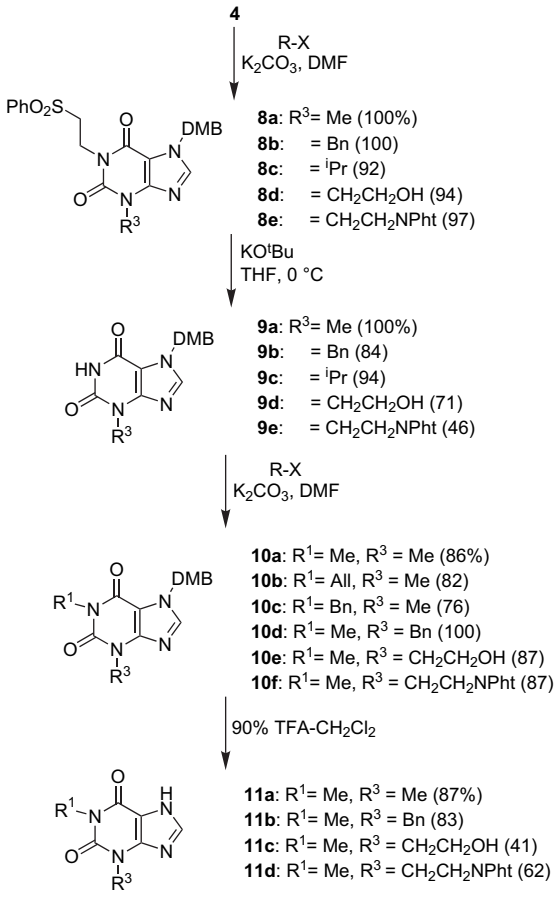


Scheme 2. Xanthine synthesis using a 2-phenylthioethyl safety-catch.



Scheme 3. Safety-catch synthesis and orthogonal protection strategy for the xanthine scaffold.

1,7-substituted xanthine **3** in 58% yield.[12] Subsequent treatment of **3** with *m*-CPBA in CH_2Cl_2 then gave the required N-1 activated intermediate **4** in 95% yield. Finally, treatment of **4** with allyloxymethyl chloride in DMF in the presence of K_2CO_3 gave the triply protected derivative **5**, in 95% yield. Selective removal of each *N*-protecting group in turn, under mild conditions, was confirmed by treatment with, respectively, KO^{t}Bu (N-1), TFA (N-7) and $Pd(PPh_3)_4$, with *N*,*N*-dimethylbarbituric acid (*N*,*N*-DMBA) as the allyl scavenger (N-3).[13] In each case the desired partially protected xanthines **4**, **6** and **7** were generated in good to excellent yields. PMB was also interchangeable for DMB for the N-7 protection, when introduced via the corresponding imidazole derivative, however, its removal required much more forcing conditions (refluxing TFA, three days[14]).



Scheme 4. Synthesis of 1,3-xanthines via alkylation and safety-catch cleavage of **4** (yields in parentheses).

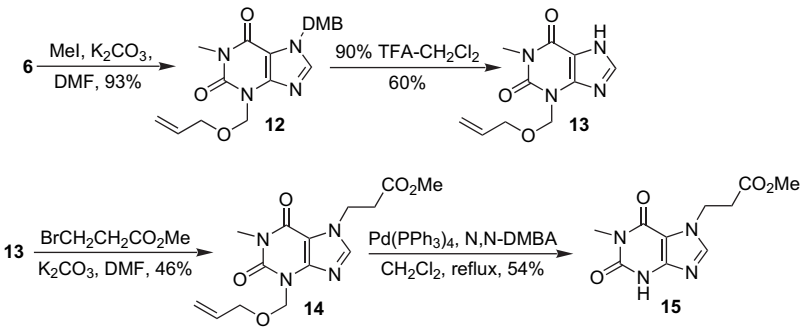
2.2. Synthesis of selectively 1,3-substituted xanthine derivatives

Having established an efficient preparation of doubly protected xanthine **4**, its potential for the preparation of various 1,3-substituted (theophylline-like) xanthine derivatives was explored. As shown in Scheme 4, alkylation of **4** at N-3 with simple aliphatic and functionalised electrophiles proceeded in excellent yields, followed by treatment with KO^{t}Bu to give N-1 deprotected derivatives **9**. These could then be alkylated as before, followed by cleavage of DMB protection by treatment with TFA in CH_2Cl_2, to give selectively 1,3-substituted compounds **11** in good overall yields. Importantly, this approach removes the need to use isocyanates, or precursors thereof, for the introduction of the N-1 grouping for each desired 1,3-decorated analogue at an early stage of the synthesis. This not only widens the scope of possible N-1 substituents, but also allows maximum flexibility for additional modification at other sites on the xanthine scaffold.

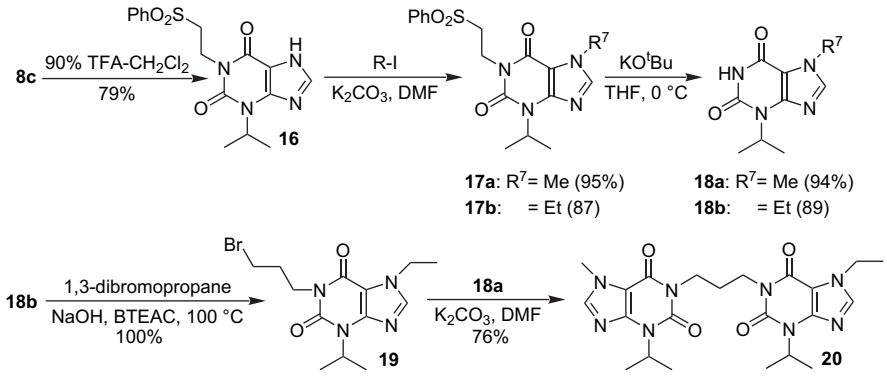
2.3. Synthesis of selectively 1,7- and 1,3,7-substituted xanthine derivatives

The safety-catch protection strategy exemplified above also provides flexible and efficient routes to a range of disubstituted xanthines with the less common 1,7-[15] and 3,7-substitution[16] patterns, as well as 1,3,7-trisubstituted derivatives, all starting from a single intermediate such as **4**, or triply orthogonally protected derivative **5**. Scheme 5 shows how **6**, obtained by base-mediated deprotection of **5**, was employed to provide a convenient and direct route to the 1,7-substituted (paraxanthine-like) derivative **15**, which is not readily accessible by the classic Traube method.

Similarly, sequential elaboration, as previously outlined of the N-1, N-7-orthogonally protected synthon **8c**, derived from **4**, gave rise to the novel 3, 7-decorated intermediates **18a** and **18b**, with high efficiency in each step (Scheme 6). Coupling of the two units through N-1 via a three-carbon spacer was then achieved as follows. Monoalkylation of **18b** with 1,3-dibromopropane to give **19** was effected in quantitative yield under phase transfer conditions using benzyltriethylammonium chloride (BTEAC);[17] then **19** was combined with **18a** in the usual way to generate the unsymmetrical



Scheme 5. Preparation of 1,7-xanthines.



Scheme 6. Preparation of novel 1,3,7-substituted xanthines.

dixanthine **20** in 76% yield. Such compounds (so-called 'dicaffeines') have previously attracted interest as models for stacking of nucleic acid bases,[18] and have recently also been identified as potent inhibitors of family 18 chitinases, showing similar π–π interactions with indolyl moieties in the protein.[3b] Preparation of such a compound by existing methods that do not allow exchange of the xanthine N-1 substituent,[4–6]would potentially require two successive cyclocondensations using two different specifically functionalised imidazole or aminopurine derivatives.

3. Summary

We have developed a highly efficient route to selectively *N*-functionalised xanthine derivatives, based on an orthogonal safety-catch protection strategy. The key N-1 2-phenylsulfonylethyl-protected intermediates may be simply and efficiently alkylated or deprotected in the presence of acid-labile or other suitable N-3/N-7 protection to generate a wide range of novel functionalised xanthines, either as synthons for more elaborate purine-like heterocycles,[19] or possible drug leads. In this context, the scope that our method provides for introducing novel N-1 substituents by standard alkylation or Mitsunobu chemistry[20] should further expand the range of application of these scaffolds in medicinal chemistry.

4. Experimental

4.1. General

All the reactions were carried out using oven-dried glassware under an atmosphere of argon. THF was dried by distillation from sodium/benzophenone under argon. CH_2Cl_2 and diglyme were dried by distillation from calcium hydride under argon. All other reagents and solvents were obtained from commercial sources without further purification. Thin layer chromatography was performed on silica gel (60 F_{254} Merck) pre-coated on aluminium sheets. Visualisation was accomplished by quenching of UV fluorescence at 254 nm, staining with vanillin or ninhydrin solutions, or iodine. Flash chromatography was performed on columns of silica gel (Fluorochem, Silica Gel 60, 40–60 μm).

Melting points were recorded on an Electrothermal IA9000 series digital melting point apparatus, using open capillaries, and are quoted uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer at 300 MHz, or a Bruker Avance 500 spectrometer at 500 MHz. ^{13}C NMR were recorded on the Avance 500 at 125 MHz. High resolution electrospray mass spectra were recorded on a Bruker MicroTOF instrument.

4.1.1. General procedures. *N-1 deprotection—General Procedure A*. A solution of the protected xanthine in dry THF (3 mL/mmol) was cooled in an ice–salt bath, and KO^{t}Bu (2 equiv) was added (the reaction mixture darkens immediately). When no further starting material was detectable by TLC (5–10 min), the reaction mixture was quenched with saturated aq NH_4Cl and the organic layer was separated. The aqueous layer was re-extracted twice with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography (0–5% MeOH/CH_2Cl_2).

N-7 deprotection—General Procedure B. A solution of the protected xanthine in 90% TFA/CH_2Cl_2 (10 mL/mmol) was stirred at rt for 24 h, or until no more starting material was detectable by TLC. The reaction mixture was evaporated under reduced pressure, and the residue was redissolved in CH_2Cl_2 (10 mL/mmol) and washed with saturated aq $NaHCO_3$. The organic layer was dried over $MgSO_4$ (the purple colouration that appears during the reaction is removed on filtration) and evaporated under reduced pressure. The crude product was purified by flash chromatography (0–5% MeOH/CH_2Cl_2).

N-3 deprotection—General Procedure C. A solution of the protected xanthine in dry CH_2Cl_2 (10 mL/mmol) was treated with *N*,*N*-DMBA (3 equiv), followed by tetrakis(triphenylphosphine)palladium(0) (5 mol %). The reaction mixture was heated at reflux for 24 h, and then it was diluted with CH_2Cl_2 (to 30 mL/mmol) and washed with H_2O. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography (0–80% EtOAc/CH_2Cl_2).

N-alkylation—General Procedure D. A suspension of the xanthine in dry DMF (5 mL/mmol) was treated with potassium carbonate (1 equiv), and the reaction mixture was allowed to stir at rt under Ar for 1 h. The alkyl halide (*1.2 equiv unless otherwise stated*) was then added gradually to the reaction mixture, and stirring was continued

overnight. If any starting material still remained, the reaction mixture was heated at 50 °C for 1 h to complete the reaction. The reaction mixture was then poured into H_2O (15 mL/mmol) and extracted with CH_2Cl_2 (2×10 mL/mmol). The organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure, co-evaporating with toluene to remove residual DMF. The crude product was then purified by flash chromatography (0–5% MeOH/CH_2Cl_2).

4.1.1.1. Methyl-2-phenylthioethyl carbamate (1).[9] A solution of sodium propoxide was prepared by the addition of sodium (1.94 g, 84 mmol) to dry ^{n}PrOH (250 mL). To the resulting solution was added thiophenol (13.1 g, 119 mmol), and the mixture was stirred at rt for 0.5 h. 2-Oxazolidinone (3.62 g, 41.6 mmol) was then added, and the resulting mixture was heated under reflux for 5 h, over which time a fine white precipitate formed. The reaction mixture was allowed to cool to rt with stirring and methyl chloroformate (5 mL, 64.5 mmol) was added. After 2 h stirring at rt, additional methyl chloroformate (5 mL, 64.5 mmol) and sodium methoxide (2.25 g, 41.6 mmol) were added and stirring was continued for a further 1.5 h. The reaction mixture was then evaporated under reduced pressure, and the residue was suspended in water (100 mL) and extracted with Et_2O (2×75 mL). The organic extracts were combined and dried over Na_2SO_4 and evaporated under reduced pressure. The crude product obtained was purified by flash chromatography (0–50% EtOAc/hexane), with positive fractions being recrystallised from hexane in two batches. This gave **1**[9] as a white crystalline solid (7.89 g, 90%). Mp 64–66 °C (lit.,[9] 66–67 °C); δ_H ($CDCl_3$, 300 MHz): 3.06 (2H, t, *J* 6.2, CH_2), 3.39 (2H, q, *J* 6.2, CH_2), 3.66 (3H, s, COOMe), 5.06 (1H, br s, NH), 7.14 (1H, t, *J* 7.5, Ar–H), 7.30 (2H, t, *J* 7.5, Ar–H), 7.38 (2H, d, *J* 7.5, Ar–H); δ_C ($CDCl_3$, 125 MHz): 33.9, 34.0, 52.2, 126.6, 129.1, 129.8, 134.9, 156.9; found (ES^+) 212.0743 $[M+H]^+$, $C_{10}H_{14}NO_2S$ requires 212.0740.

4.1.1.2. 7-(2,4-Dimethoxybenzyl)-1-(2-phenylthioethyl)-3,7-dihydropurine-2,6-dione (3). A solution of **1** (773 mg, 3.65 mmol) and **2** (930 mg, 3.05 mmol) in dry diglyme (13 mL) at 80 °C was treated with a solution of KO^{t}Bu (476 mg, 4.25 mmol) in diglyme (2 mL), added dropwise. The reaction mixture was stirred at 80 °C overnight, and then it was cooled to rt, poured into 5% citric acid (20 mL), and extracted with CH_2Cl_2. The organic extracts were washed with saturated aq $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure. Purification of the crude material by flash chromatography (0–90% EtOAc/CH_2Cl_2) gave **3** as a white solid (780 mg, 58%). Mp 155 °C; δ_H ($CDCl_3$, 500 MHz): 3.16 (2H, t, *J* 6.5, SCH_2), 3.72 (3H, s, OMe), 3.77 (2H, s, OMe), 4.21 (2H, t, *J* 6.5, N-1 CH_2N), 5.32 (2H, s, DMB CH_2), 6.39–6.42 (2H, m, DMB Ar–H), 7.06 (1H, t, *J* 7.4, SPh Ar–H), 7.09 (1H, d, *J* 8.1, DMB Ar–H), 7.18 (2H, t, *J* 7.4, SPh Ar–H), 7.37 (2H, d, *J* 7.4, SPh Ar–H), 7.39 (2H, d, *J* 8.1, DMB Ar–H), 7.61 (1H, s, C8 Ar–H), 11.62 (1H, br s, N-3 H); δ_C ($CDCl_3$, 125 MHz): 30.3, 40.3, 45.4, 55.5, 55.6, 98.8, 104.4, 115.4, 125.8, 128.2, 128.5, 128.9, 129.1, 132.2, 135.8, 137.9, 151.4, 155.5, 158.7, 161.8; found (ES^+) 439.1439 $[M+H]^+$, $C_{22}H_{23}N_4O_4S$ requires 439.1435.

4.1.1.3. 1-(2-Phenylsulfonylethyl)-7-(2,4-dimethoxybenzyl)-3,7-dihydropurine-2,6-dione (4). A solution of **3** (2.45 g, 55.9 mmol) in dry CH_2Cl_2 (200 mL) was treated with *m*-CPBA (2.42 g, 140 mmol). The reaction mixture was allowed to stir at rt for 15 min, after which time no starting material was visible by TLC. The reaction mixture was quenched by washing with saturated aq $NaHCO_3$ (100 mL), and the aqueous layer was then extracted with CH_2Cl_2 (3×100 mL). The organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure to give a white solid. Recrystallisation from CH_2Cl_2/hexane gave **4** as fine white needles (2.51 g, 95%). Mp 218 °C; δ_H ($CDCl_3$, 500 MHz): 3.59 (2H, t, *J* 7.1, SCH_2), 3.83 (3H, s, OMe), 3.87 (3H, s, OMe), 4.39 (2H, t, *J* 7.1, N-1 CH_2N), 5.39 (2H, s, DMB CH_2), 6.49–6.52 (2H, m, DMB Ar–H), 7.46–7.65 (5H, m, SO_2Ph), 7.71 (1H, s, H-8), 7.98 (2H, dt, *J* 8.2, 1.9, SO_2Ph Ar–H), 11.27 (1H, br s, N-3 H); δ_C ($CDCl_3$, 125 MHz): 34.6, 45.5, 52.9, 55.5, 55.6, 98.8, 104.5, 115.2, 128.1 (two signals), 129.3, 132.2, 133.8, 139.0, 141.7, 146.8, 150.8, 154.9, 158.7, 161.9; found (ES^+) 493.1155 $[M+Na]^+$, $C_{22}H_{22}N_4O_6SNa$ requires 493.1152.

Compound **4** was also obtained by N-3 deprotection of **6** on a 0.024 mmol scale, according to General Procedure C. The sample obtained in this way (9.3 mg, 82%) was indistinguishable from that described above.

4.1.1.4. 3-Allyloxymethyl-1-(2-phenylsulfonylethyl)-7-(2,4-dimethoxybenzyl)-3,7-dihydropurine-2,6-dione (5). A suspension of **14** (200 mg, 0.43 mmol) and potassium carbonate (59 mg, 0.43 mmol) in dry DMF (2 mL) was stirred under Ar at rt for 1 h. After this time, allyloxymethyl chloride[12] (54.3 mg, 0.51 mmol) was added and stirring was continued for a further 1.5 h, when no more **4** was detectable by TLC. The reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (2×50 mL). The organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. Purification of the residue by flash chromatography (0–30% EtOAc/CH_2Cl_2) gave **5** as a foaming syrup (220 mg, 95%). δ_H ($CDCl_3$, 500 MHz): 3.49 (2H, t, *J* 7.2, SCH_2), 3.73 (3H, s, OMe), 3.76 (3H, s, OMe), 4.07 (2H, dt, *J* 5.6, 1.3, O*C*H_2C=C), 4.32 (2H, t, *J* 7.2, N-1 CH_2N), 5.08 (1H, dt, *J* 7.8, 1.5, CH=C*H*$_2$), 5.22 (1H, dt, *J* 16.8, 1.5, CH=C*H*$_2$), 5.30 (2H, s, NCH_2OAll, DMB CH_2), 5.41 (2H, s, NCH_2OAll, DMB CH_2), 5.78–5.82 (1H, m, C*H*=CH_2), 6.37–6.43 (2H, m, DMB Ar–H), 7.41 (1H, d, *J* 8.3, DMB Ar–H), 7.44 (2H, t, *J* 7.5, SO_2Ph Ar–H), 7.55 (1H, t, *J* 7.5, SO_2Ph Ar–H), 7.57 (1H, s, H-8), 7.87–7.89 (2H, m, SO_2Ph Ar–H); δ_C ($CDCl_3$, 125 MHz): 35.2, 45.3, 52.9, 55.4, 55.5, 71.0, 72.2, 98.7, 104.3, 106.7, 115.7, 117.6, 128.1, 129.3, 132.1, 133.8, 133.9, 139.0, 142.2, 148.0, 151.1, 154.4, 158.6, 161.7; found (ES^+) 541.1749 $[M+H]^+$, $C_{26}H_{29}N_4O_7S$ requires 541.1751.

4.1.1.5. 3-Allyloxymethyl-7-(2,4-dimethoxybenzyl)-3,7-dihydropurine-2,6-dione (6). Prepared from **5**, using General Procedure A. Scale: 0.317 mmol. Off-white solid (118 mg, 64%). Mp 156 °C; δ_H ($CDCl_3$, 500 MHz): 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 4.21 (2H, dt, *J* 5.6, 1.3, CH_2C=C), 5.18 (1H, dq, *J* 10.5, 1.5, All C=C*H*$_2$), 5.33 (1H, dq, *J* 17.2, 1.5, All C=C*H*$_2$), 5.40 (2H, s, DMB CH_2, N-3 CH_2O), 5.56 (2H, s, DMB CH_2, N-3 CH_2O), 5.88–5.93 (1H, m, C*H*=CH_2), 6.47–6.50 (2H, m, DMB Ar–H), 7.53 (1H, d, *J* 8.3, DMB Ar–H), 7.71 (1H, s, H-8), 8.83

(1H, s, N-1 H); δ_C ($CDCl_3$, 125 MHz): 45.4, 55.4, 55.5, 71.0, 71.5, 98.6, 104.3, 107.2, 115.7, 117.6, 132.2, 133.9, 142.5, 149.9, 151.0, 154.6, 158.6, 161.7; found (ES^+) 373.1504 $[M+H]^+$, $C_{18}H_{21}N_4O_5$ requires 373.1506.

4.1.1.6. 3-Allyloxymethyl-1-(2-phenylsulfonylethyl)-3,7-dihydropurine-2,6-dione (7). Prepared from **5**, using General Procedure B. Scale 0.127 mmol. White amorphous solid (41 mg, 82%). Mp 181 °C; δ_H ($CDCl_3$, 500 MHz): 3.57 (2H, t, *J* 6.6, SCH_2), 4.19 (2H, dt, *J* 5.6, 1.4, N-3 $CH_2C{=}C$), 4.51 (2H, t, *J* 6.6, N-1 CH_2), 5.19 (1H, dq, *J* 10.5, 1.5, N-3 $C{=}CH_2$), 5.31 (1H, dq, *J* 14.3, 1.6, N-3 $C{=}CH_2$), 5.58 (2H, s, NCH_2O), 5.87–5.93 (1H, m, $CH{=}CH_2$), 7.57 (2H, t, *J* 7.4, SO_2Ph Ar–H), 7.66 (1H, t, *J* 7.4, SO_2Ph Ar–H), 7.92–7.96 (3H, m, SO_2Ph Ar–H, H-8); δ_C ($CDCl_3$, 125 MHz): 35.2, 53.0, 71.2, 72.7, 106.9, 117.8, 127.9, 129.4, 133.8, 134.0, 139.2, 141.5, 148.5, 150.9, 155.5; found (ES^+) 413.0889 $[M+Na]^+$, $C_{17}H_{18}N_4O_5Na$ requires 413.0890.

The following compounds were prepared from **4** according to General Procedure D.

4.1.1.7. 1-(2-Phenylsulfonylethyl)-7-(2,4-dimethoxybenzyl)-3-methyl-3,7-dihydropurine-2,6-dione (8a). Using methyl iodide (3 equiv). Scale: 1.70 mmol. White solid (816 mg, quantitative). Mp 142 °C; δ_H ($CDCl_3$, 500 MHz): 3.39 (3H, s, N-3 Me), 3.51 (2H, t, *J* 7.2, N-1 CH_2), 3.73 (3H, s, OMe), 3.77 (3H, s, OMe), 4.32 (2H, t, *J* 7.2, N-1 CH_2N), 5.30 (2H, s, DMB CH_2), 6.38–6.42 (2H, m, DMB Ar–H), 7.38–7.44 (3H, m, DMB Ar–H, SO_2Ph Ar–H), 7.53 (1H, t, *J* 7.4, SO_2Ph Ar–H), 7.55 (1H, s, H-8), 7.87 (2H, d, *J* 7.4, SO_2Ph Ar–H); δ_C ($CDCl_3$, 125 MHz): 29.6, 35.2, 45.3, 52.9, 55.4, 55.5, 98.7, 104.3, 106.7, 115.9, 128.1, 129.2, 132.1, 133.7, 139.1, 142.0, 148.8, 151.0, 154.4, 158.6, 161.7; found (ES^+) 485.1492 $[M+H]^+$, $C_{23}H_{25}N_4O_6S$ requires 485.1489.

4.1.1.8. 1-(2-Phenylsulfonylethyl)-3-benzyl-7-(2,4-dimethoxybenzyl)-3,7-dihydro-purine-2,6-dione (8b). Using benzyl bromide. Scale: 0.956 mmol. White solid (560 mg, quantitative). Mp 58 °C; δ_H ($CDCl_3$, 500 MHz): 3.50 (2H, t, *J* 7.2, SCH_2), 3.73 (3H, s, OMe), 3.77 (3H, s, OMe), 4.32 (2H, t, *J* 7.2, CH_2N), 5.09 (2H, s, Bn CH_2, DMB CH_2), 5.29 (2H, s, Bn CH_2, DMB CH_2), 6.38–6.42 (2H, m, DMB Ar–H), 7.18–7.24 (3H, m, Ar–H), 7.34–7.38 (3H, m, Ar–H), 7.41 (1H, d, *J* 12.3, Ar–H), 7.49 (1H, t, *J* 7.5, Bn Ar–H, SO_2Ph Ar–H), 7.55 (1H, s, H-8), 7.92–7.84 (2H, m, Ar–H); δ_C ($CDCl_3$, 125 MHz): 35.3, 45.1, 46.5, 52.9, 55.4, 55.5, 98.7, 104.3, 106.7, 115.8, 127.9, 128.1, 128.6, 128.7, 129.2, 132.2, 133.7, 136.2, 139.0, 142.0, 148.4, 150.8, 154.4, 158.6, 161.7; found (ES^+) 561.1810 $[M+H]^+$, $C_{29}H_{29}N_4O_6S$ requires 561.1802.

4.1.1.9. 1-(2-Phenylsulfonylethyl)-7-(2,4-dimethoxybenzyl)-3-isopropyl-3,7-di-hydropurine-2,6-dione (8c). Using 2-iodopropane. Scale: 0.425 mmol. Colourless syrup (201 mg, 92%). δ_H ($CDCl_3$, 500 MHz): 1.44 (6H, d, *J* 7.0, $(CH_3)_2CH$), 3.50 (2H, t, *J* 7.2, SCH_2), 3.73 (3H, s, OMe), 3.78 (3H, s, OMe), 4.30 (2H, t, *J* 7.2, N-1 CH_2N), 5.01 (1H, q, *J* 7.0, N-3 C–H), 5.31 (2H, s, DMB CH_2), 6.37–6.43 (2H, m, DMB Ar–H), 7.39–7.45 (3H, m, DMB Ar–H, SO_2Ph Ar–H), 7.53–7.55 (2H, m, SO_2Ph Ar–H, H-8), 7.87 (2H, dt, *J* 7.1, 1.0, SO_2Ph Ar–H); δ_C ($CDCl_3$, 125 MHz): 19.7, 35.1, 36.5, 44.9, 48.4, 53.1, 55.4, 55.5, 98.6, 104.3, 107.1, 116.0, 128.1, 129.2, 132.2, 133.7, 139.1, 141.5, 148.2, 150.3, 154.5, 158.6, 161.6; found (ES^+) 535.1602 $[M+Na]^+$, $C_{25}H_{28}N_4O_6SNa$ requires 535.1622.

4.1.1.10. 1-(2-Phenylsulfonylethyl)-7-(2,4-dimethoxybenzyl)-3-(2-hydroxyethyl)-3,7-dihydropurine-2,6-dione (8d). Using 2-iodoethanol. Scale: 0.956 mmol. Foaming syrup (464 mg, 94%). δ_H ($CDCl_3$, 500 MHz): 3.08 (1H, t, *J* 5.7, OH), 3.49 (2H, t, *J* 6.9, CH_2S), 3.74 (3H, s, OMe), 3.78 (3H, s, OMe), 3.83 (2H, q, *J* 5.7, CH_2OH), 4.19 (2H, t, *J* 5.7, CH_2N), 4.33 (2H, t, *J* 6.9, N-1 CH_2N), 5.31 (2H, s, DMB CH_2), 6.39–6.43 (2H, m, DMB Ar–H), 7.40–7.46 (3H, m, DMB Ar–H, SO_2Ph Ar–H), 7.53–7.56 (2H, m, SO_2Ph Ar–H), 7.55 (1H, s, H-8), 7.89 (2H, dt, *J* 7.2, 1.3, SO_2Ph Ar–H); δ_C ($CDCl_3$, 125 MHz): 22.7, 31.4, 35.3, 45.3, 46.2, 52.9, 55.5 (two signals) 98.7, 104.3, 106.8, 115.6, 128.1, 129.2, 132.2, 133.8, 139.0, 141.8, 148.5, 151.4, 154.3, 158.6, 161.8; found (ES^+) 537.1390 $[M+Na]^+$, $C_{24}H_{26}N_4O_7SNa$ requires 537.1414.

4.1.1.11. 1-(2-Phenylsulfonylethyl)-7-(2,4-dimethoxybenzyl)-3-[3-(1,3-dioxo-1,3-di-hydroisoindol-2-yl)-propyl]-3,7-dihydropurine-2,6-dione (8e). Using 3-bromopropylphthalimide. Scale: 0.956 mmol. White solid (611 mg, 97%). Mp 60 °C; δ_H ($CDCl_3$, 500 MHz): 2.17 (2H, quintet, *J* 7.1, $CH_2CH_2CH_2$), 3.59 (2H, t, *J* 7.1, SCH_2), 3.77 (2H, t, *J* 7.1, N-3 CH_2N), 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 4.11 (2H, t, *J* 7.1, N-3 CH_2N), 4.38 (2H, t, *J* 7.1, N-1 CH_2N), 5.36 (2H, s, DMB CH_2), 6.47–6.51 (2H, m, DMB Ar–H), 7.49–7.53 (3H, m, DMB Ar–H, SO_2Ph Ar–H), 7.56 (1H, s, H-8), 7.62 (1H, t, *J* 7.5, SO_2Ph Ar–H), 7.73 (2H, dd, *J* 5.4, 3.0, Phth Ar–H), 7.84 (2H, dd, *J* 5.4, 3.0, Phth Ar–H), 7.97 (2H, d, *J* 7.5, SO_2Ph Ar–H); δ_C ($CDCl_3$, 125 MHz): 15.3, 27.0, 35.2, 35.6, 41.2, 45.2, 52.9, 55.4, 65.9, 98.7, 104.3, 106.7, 115.8, 123.2, 128.1, 129.2, 132.1, 132.2, 133.7, 134.0, 139.1, 142.0, 148.3, 150.6, 154.4, 158.6, 161.7, 168.3; found (ES^+) 658.1973 $[M+H]^+$, $C_{33}H_{32}N_5O_8S$ requires 658.1966.

The following compounds were prepared according to General Procedure A.

4.1.1.12. 7-(2,4-Dimethoxybenzyl)-3-methyl-3,7-dihydropurine-2,6-dione (9a). Using **8a**. Scale: 1.44 mmol. Pale yellow crystals, after recrystallisation from hot MeOH (468 mg, quantitative). Mp 182 °C; δ_H ($CDCl_3$, 500 MHz): 3.55 (3H, s, N–Me), 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 5.41 (2H, s, DMB CH_2), 6.47–6.50 (2H, m, DMB Ar–H), 7.52 (1H, d, *J* 8.2, DMB Ar–H), 7.69 (1H, s, H-8), 8.58 (1H, br s, N-1 H); δ_C ($CDCl_3$, 125 MHz): 29.0, 45.4, 55.4, 55.5, 98.7, 104.3, 107.1, 115.8, 132.2, 142.2, 150.6, 151.1, 154.6, 158.6, 161.7; found (ES^+) 339.1068 $[M+Na]^+$, $C_{15}H_{16}N_4O_4Na$ requires 339.1064.

4.1.1.13. 7-(2,4-Dimethoxybenzyl)-3-benzyl-3,7-dihydropurine-2,6-dione (9b). Using **8b**. Scale: 0.914 mmol. Fine white crystalline solid (301 mg, 84%). Mp 192 °C; δ_H ($CDCl_3$, 500 MHz): 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 5.24 (2H, s, Bn CH_2, DMB CH_2), 5.39 (2H, s, Bn CH_2, DMB CH_2), 6.47–6.50 (2H, m, DMB Ar–H), 7.25–7.28 (3H, m, Bn Ar–H), 7.30–7.53 (3H, m, Bn Ar–H, DMB

Ar–H), 7.69 (1H, s, H-8), 8.50 (1H, br, N1-H); δ_C ($CDCl_3$, 125 MHz): 45.2, 45.8, 55.4, 55.5, 98.6, 104.3, 107.2, 115.8, 127.8, 128.5, 128.7, 132.3, 136.3, 142.2, 150.2, 150.8, 154.6, 158.6, 161.7; found (ES^+) 415.1385 $[M+Na]^+$, $C_{21}H_{20}N_4O_4Na$ requires 415.1377.

4.1.1.14. 3-Isopropyl-7-methyl-3,7-dihydropurine-2,6-dione (9c). Using **8c**. Scale: 0.307 mmol. Off-white solid (60 mg, 94%). Mp 230 °C; δ_H ($CDCl_3$, 500 MHz): 1.60 (6H, d, *J* 6.9, $(CH_3)_2CH$), 3.99 (3H, s, N-7 Me), 5.15 (1H, septet, *J* 6.9, $(CH_3)_2CH$), 7.53 (1H, s, H-8), 8.42 (1H, br s, N-1 H); δ_C ($CDCl_3$, 125 MHz): 19.7, 33.5, 47.8, 108.6, 141.3, 150.5, 154.8, 174.2; found (ES^+) 231.0855 $[M+Na]^+$, $C_9H_{12}N_4O_2Na$ requires 231.0852.

4.1.1.15. 7-(2,4-Dimethoxybenzyl)-3-(2-hydroxyethyl)-3,7-dihydropurine-2,6-dione (9d). Using **8d**. Scale: 0.519 mmol. An additional equivalent of KO^{t}Bu was used due to the acidic hydroxyl proton. Off-white solid (128 mg, 71%). Mp 222 °C; δ_H ($CDCl_3$, 500 MHz): 3.31 (1H, t, *J* 5.3, OH), 3.73 (3H, s, OMe), 3.78 (3H, s, OMe), 3.87 (2H, q, *J* 5.3, N-3 CH_2OH), 4.27 (2H, t, *J* 5.3, CH_2N), 5.35 (2H, s, DMB CH_2), 6.38–6.42 (2H, m, DMB Ar–H), 7.42 (1H, d, *J* 8.3, DMB Ar–H), 7.56 (1H, s, H-8); δ_C ($CDCl_3$, 125 MHz): 28.1, 45.3, 46.3, 55.5, 62.0, 98.7, 104.3, 107.0, 115.8, 132.1, 141.5, 148.3, 152.2, 155.1, 158.6, 161.7; found (ES^+) 347.1360 $[M+H]^+$, $C_{16}H_{19}N_4O_5$ requires 347.1350.

4.1.1.16. 7-(2,4-Dimethoxybenzyl)-3-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propyl]-3,7-dihydropurine-2,6-dione (9e). Using **8e**. Scale: 0.826 mmol. Off-white amorphous solid (187 mg, 46%). Mp 164 °C; δ_H ($CDCl_3$, 500 MHz): 2.09 (1H, quintet, *J* 7.4, $CH_2CH_2CH_2$), 3.68–3.73 (5H, m, N-3 CH_2N, OMe), 3.76 (3H, s, OMe), 4.06 (2H, t, *J* 7.4, N-3 CH_2N), 5.28 (2H, s, DMB CH_2), 6.37–6.40 (2H, m, DMB Ar–H), 7.42 (1H, d, *J* 8.3, DMB Ar–H), 7.51 (1H, s, H-8), 7.63 (2H, dd, *J* 5.4, 3.0, Phth Ar–H), 7.75 (2H, dd, *J* 5.4, 3.0, Phth Ar–H), 8.09 (1H, br s, N-1 H); δ_C ($CDCl_3$, 125 MHz): 27.3, 35.8, 40.5, 45.3, 55.4, 55.5, 98.7, 104.3, 107.2, 115.8, 123.3, 132.1, 132.2, 133.9, 142.2, 150.1, 150.5, 154.5, 158.6, 161.7, 168.3; found (ES^+) 490.1716 $[M+H]^+$, $C_{25}H_{24}N_5O_6$ requires 490.1721.

The following compounds were prepared according to General Procedure D.

4.1.1.17. 7-(2,4-Dimethoxybenzyl)-1,3-dimethyl-3,7-dihydropurine-2,6-dione (10a). Using **9a** and methyl iodide (3 equiv). Scale: 0.316 mmol. White crystalline rosettes (90 mg, 86%). Mp 152 °C; δ_H ($CDCl_3$, 500 MHz): 3.43 (3H, s, N–Me), 3.57 (3H, s, N–Me), 3.81 (3H, s, OMe), 3.86 (3H, s, OMe), 5.44 (2H, s, DMB CH_2), 6.46–6.50 (2H, m, DMB Ar–H), 7.50 (1H, d, *J* 8.2, DMB Ar–H), 7.66 (1H, s, H-8); δ_C ($CDCl_3$, 125 MHz): 28.0, 29.7, 45.2, 55.4 (two signals), 76.8, 77.1, 77.3, 98.6, 104.2, 106.9, 116.0, 132.0, 141.8, 148.6, 151.7, 155.3, 158.6, 161.6; found (ES^+) 353.1234 $[M+Na]^+$, $C_{16}H_{18}N_4O_4Na$ requires 353.1220.

4.1.1.18. 1-Allyl-7-(2,4-dimethoxybenzyl)-3-methyl-3,7-dihydropurine-2,6-dione (10b). Using **9a** and allyl bromide. Scale: 0.379 mmol. Additional chromatography (10–20% EtOAc/CH_2Cl_2) was required to remove a polar impurity. White solid (92 mg, 82%). Mp 112 °C; δ_H ($CDCl_3$, 500 MHz): 3.49 (3H, s, N-3 Me), 3.72 (3H, s, OMe), 3.76 (3H, s, OMe), 4.57 (2H, dt, *J* 5.7, 1.4, $CH_2C{=}C$), 5.15 (1H, dt, *J* 9.6, 1.4, $CH{=}CH_2$), 5.19 (1H, dt, *J* 17.2, 1.4, $CH{=}CH_2$), 5.35 (2H, s, Bn CH_2), 5.84–5.88 (1H, m, $CH{=}CH_2$), 6.38–6.40 (2H, m, DMB Ar–H), 7.41 (1H, d, *J* 8.1, DMB Ar–H), 7.56 (1H, s, H-8); δ_C ($CDCl_3$, 125 MHz): 29.7, 43.4, 45.2, 55.4 (two signals), 98.6, 104.3, 106.9, 116.0, 117.4, 132.1, 132.4, 141.8, 148.8, 151.3, 154.9, 158.6, 161.6; found (ES^+) 357.1558 $[M+H]^+$, $C_{18}H_{21}N_4O_4$ requires 357.1557.

4.1.1.19. 1-Benzyl-7-(2,4-dimethoxy-benzyl)-3-methyl-3,7-dihydropurine-2,6-dione (10c). Using **9a** and benzyl bromide. Scale: 0.379 mmol. White amorphous solid (98 mg, 76%). Mp 126 °C; δ_H ($CDCl_3$, 500 MHz): 3.57 (3H, s, N-3 Me), 3.82 (3H, s, OMe), 3.84 (3H, s, OMe), 5.23 (2H, s, Bn CH_2, DMB CH_2), 5.45 (2H, s, Bn CH_2, DMB CH_2), 6.47–6.50 (2H, m, DMB Ar–H), 7.27 (1H, t, *J* 6.3, Bn Ar–H), 7.32 (2H, t, *J* 6.3, Bn Ar–H), 7.50–7.53 (3H, m, Bn Ar–H, DMB Ar–H), 7.63 (1H, s, H-8); δ_C ($CDCl_3$, 125 MHz): 29.7, 44.4, 45.2, 55.4, 55.5, 98.6, 104.3, 107.0, 116.0, 127.5, 128.4, 128.8, 132.0, 137.5, 141.8, 148.8, 151.6, 155.2, 158.6, 161.6; found (ES^+) 407.1695 $[M+H]^+$, $C_{22}H_{23}N_4O_4$ requires 407.1714.

4.1.1.20. 3-Benzyl-7-(2,4-dimethoxybenzyl)-1-methyl-3,7-dihydropurine-2,6-dione (10d). Using **9b** and methyl iodide (3 equiv). Scale: 0.204 mmol. White powder (108 mg, quantitative). Mp 179 °C; δ_H ($CDCl_3$, 500 MHz): 3.47 (3H, s, N-1 Me), 3.82 (3H, s, OMe), 3.90 (3H, s, OMe), 5.28 (2H, s, Bn CH_2, DMB CH_2), 5.43 (2H, s, Bn CH_2, DMB CH_2), 6.47–6.49 (2H, m, DMB Ar–H), 7.25–7.33 (3H, m, Bn Ar–H), 7.49–7.53 (3H, m, Bn Ar–H, DMB Ar–H), 7.68 (1H, s, H-8); δ_C ($CDCl_3$, 125 MHz): 28.1, 45.1, 46.6, 55.4, 55.5, 98.6, 104.2, 106.9, 116.1, 127.8, 128.5, 128.7, 132.1, 136.5, 141.8, 148.3, 151.5, 155.3, 158.6, 161.6; found (ES^+) 429.1543 $[M+Na]^+$, $C_{22}H_{22}N_4O_4Na$ requires 429.1533.

4.1.1.21. 7-(2,4-Dimethoxybenzyl)-3-(2-hydroxyethyl)-1-methyl-3,7-dihydropurine-2,6-dione (10e). Using **9d** and methyl iodide (3 equiv). Scale: 0.331 mmol. White solid (103 mg, 87%). Mp 174 °C; δ_H ($CDCl_3$/MeOD, 500 MHz): 3.33 (3H, s, N-1 Me), 3.73 (3H, s, OMe), 3.78 (3H, s, OMe), 3.80 (2H, t, *J* 5.5, CH_2N), 4.17 (2H, t, *J* 5.5, N-3 CH_2O), 5.32 (2H, s, DMB CH_2), 6.40–6.42 (2H, m, DMB Ar–H), 7.39 (1H, d, *J* 8.1, DMB Ar–H), 7.57 (1H, s, H-8); δ_C ($CDCl_3$, 125 MHz): 28.0, 45.3, 45.8, 55.3, 55.4, 60.2, 98.6, 104.3, 107.0, 115.6, 132.0, 141.5, 155.2, 158.6; found (ES^+) 361.1496 $[M+H]^+$, $C_{17}H_{21}N_4O_5$ requires 361.1506.

4.1.1.22. 7-(2,4-Dimethoxybenzyl)-3-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propyl]-1-methyl-3,7-dihydropurine-2,6-dione (10f). Using **9e** and methyl iodide (3 equiv). Scale: 0.204 mmol. Foaming syrup (89 mg, 87%). δ_H ($CDCl_3$, 500 MHz): 2.19 (2H, quintet, *J* 7.2, $CH_2CH_2CH_2$), 3.40 (3H, s, N–Me), 3.78–3.83 (5H, m, OMe, N-3 CH_2N), 3.86 (3H, s, OMe), 4.20 (2H, t, *J* 7.2, N-3 CH_2N), 5.41 (2H, s, DMB CH_2), 6.46–6.50 (2H, m, DMB Ar–H), 7.51 (1H, d, *J* 8.3, DMB Ar–H), 7.59 (1H, s, H-8), 7.72 (2H, dd, *J* 5.4, 2.4, Phth Ar–H), 7.84 (2H, dd, *J* 5.4, 2.4, Phth Ar–H); δ_C ($CDCl_3$, 125 MHz): 27.3, 28.0, 35.8, 41.3, 45.1, 55.4 (two

signals), 98.6, 104.2, 106.9, 116.0, 123.2, 132.0, 132.1, 133.9, 141.7, 148.1, 151.3, 155.3, 158.6, 161.6, 168.3; found (ES^+) 504.1879 $[M+H]^+$, $C_{26}H_{26}N_5O_6$ requires 504.1878.

The following compounds were prepared according to General Procedure B.

4.1.1.23. Theophylline (11a).[21] Using **10a**. Scale: 0.0908 mmol. White solid (14 mg, 87%). Mp 275 °C (lit.,[21] 276 °C).

4.1.1.24. 3-Benzyl-1-methyl-3,7-dihydropurine-2,6-dione (11b).[22] Using **10d**. Scale: 0.0738 mmol. White solid (16 mg, 83%). Mp 262 °C (lit.,[22] 263 °C).

4.1.1.25. 3-(2-Hydroxyethyl)-1-methyl-3,7-dihydropurine-2,6-dione (11c).[23] Using **10e**. Scale: 0.259 mmol. Pale yellow solid (22 mg, 41%). Mp 278 °C (lit.,[23] 268 °C, dec).

4.1.1.26. 3-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-propyl]-1-methyl-3,7-dihydropurine-2,6-dione (11d). Using **10f**. Scale: 0.0596 mmol. White solid (13.1 mg, 62%). Mp 198 °C; δ_H ($CDCl_3$, 500 MHz): 2.18 (2H, quintet, *J* 7.1, $CH_2CH_2CH_2$), 3.39 (3H, s, N-1 Me), 3.75 (2H, t, *J* 7.1, N-3 CH_2N), 4.21 (2H, t, *J* 7.1, N-3 CH_2N), 7.64 (2H, dd, *J* 5.5, 3.1, Phth Ar–H), 7.70 (1H, s, H-8), 7.76 (2H, dd, *J* 5.5, 3.1, Phth Ar–H), 12.49 (1H, br s, N-7 H); δ_C ($CDCl_3$, 125 MHz): 27.2, 28.5, 35.7, 41.7, 107.0, 123.3, 132.1, 134.0, 140.2, 148.5, 151.1, 156.1, 168.3; found (ES^+) 354.1183 $[M+H]^+$, $C_{17}H_{16}N_5O_4$ requires 354.1197.

4.1.1.27. 3-Allyloxymethyl-7-(2,4-dimethoxybenzyl)-1-methyl-3,7-dihydropurine-2,6-dione (12). Using **6** and methyl iodide (3 equiv), according to General Procedure D. Scale: 0.298 mmol. White solid (107 mg, 93%). Mp 128 °C; δ_H ($CDCl_3$, 500 MHz): 3.43 (3H, s, N–Me), 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 4.20 (2H, dt, *J* 5.6, 1.4, $OCH_2C{=}C$), 5.19 (1H, dt, *J* 11.7, 1.3, $C{=}CH_2$), 5.33 (1H, dt, *J* 7.2, 1.3, $C{=}CH_2$), 5.43 (2H, s, NCH_2O, DMB CH_2), 5.59 (2H, s, NCH_2O, DMB CH_2), 5.88–5.94 (1H, m, $CH{=}C$), 6.47–6.50 (2H, m, DMB Ar–H), 7.51 (1H, d, *J* 8.3, DMB Ar–H), 7.68 (1H, s, H-8); δ_C ($CDCl_3$, 125 MHz): 27.9, 45.2, 55.4, 71.0, 72.3, 98.7, 104.4, 107.0, 116.2, 117.3, 132.0, 134.1, 141.9, 148.0, 151.8, 155.4, 158.8, 161.7; found: (ES^+) 387.1654 $[M+H]^+$, $C_{19}H_{23}N_4O_5$ requires 387.1663.

4.1.1.28. 3-Allyloxymethyl-1-methyl-3,7-dihydropurine-2,6-dione (13). Using **12**, according to General Procedure B. Scale: 0.262 mmol. Glassy solid (37 mg, 60%). Mp 165 °C; δ_H ($CDCl_3$, 500 MHz): 3.52 (3H, s, N-1 Me), 4.26 (2H, dt, *J* 5.7, 1.2, $CH_2C{=}C$), 5.21 (1H, dq, *J* 10.5, 1.5, $C{=}CH_2$), 5.35 (1H, dq, *J* 17.3, 1.5, $C{=}CH_2$), 5.69 (2H, s, NCH_2O), 5.90–5.96 (1H, m, $CH{=}CH_2$), 7.93 (1H, s, H-8), 12.64 (1H, br s, N-7 H); δ_C ($CDCl_3$, 125 MHz): 28.5, 71.1, 72.7, 107.0, 117.7, 133.9, 140.5, 148.3, 151.6, 156.2; found (ES^-) 235.0834 $[M-H]^-$, $C_{10}H_{11}N_4O_3$ requires 235.0826.

4.1.1.29. 3-(3-Allyloxymethyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-yl)-propionic acid methyl ester (14). Using **13** and methyl 3-bromopropionate, according to General Procedure D. Scale: 0.137 mmol. Colourless oil (20.2 mg, 46%), after further chromatography (0–20% EtOAc/CH_2Cl_2). δ_H ($CDCl_3$, 500 MHz): 2.89 (2H, t, *J* 6.0, N-7 CH_2CO), 3.34 (3H, s, N–Me), 3.61 (3H, s, COOMe), 4.14 (2H, d, *J* 5.5, $OCH_2C{=}C$), 4.49 (2H, t, *J* 6.0, CH_2N), 5.11 (1H, dt, *J* 10.4, 1.2, $C{=}CH_2$), 5.25 (1H, dt, *J* 17.2, 1.2, $C{=}CH_2$), 5.52 (2H, s, NCH_2O), 5.80–5.86 (1H, m, $CH{=}CH_2$), 7.61 (1H, s, H-8); δ_C ($CDCl_3$, 125 MHz): 28.0, 34.7, 42.6, 52.1, 71.1, 72.3, 76.8, 77.1, 77.3, 106.6, 117.6, 134.0, 142.4, 148.4, 151.7, 155.2, 171.2; found (ES^+) 323.1340 $[M+H]^+$, $C_{14}H_{19}N_4O_5$ requires 323.1350.

4.1.1.30. 3-(1-Methyl-2,6-dioxo-1,2,3,6-tetrahydropurin-7-yl)-propionic acid methyl ester (15). Using **14**, according to General Procedure C. Scale: 0.053 mmol. Colourless syrup (7.2 mg, 54%). δ_H ($CDCl_3$, 300 MHz): 2.90 (2H, t, *J* 6.2, $CH_2CO_2CH_3$), 3.25 (3H, s, COOMe, N-1 Me), 3.62 (3H, s, COOMe, N-1 Me), 4.49 (2H, t, *J* 6.2, N-7 CH_2N), 7.65 (1H, s, H-8), 10.18 (1H, br s, N-3 H); δ_C ($CDCl_3$, 125 MHz): 27.5, 34.7, 42.7, 52.1, 106.5, 142.3, 147.3, 151.5, 155.6, 171.2; found (ES^+) 275.0746 $[M+Na]^+$, $C_{10}H_{12}N_4O_4Na$ requires 275.0751.

4.1.1.31. 1-(2-Phenylsulfonylethyl)-3-isopropyl-3,7-dihydropurine-2,6-dione (16). Using **8c**, according to General Procedure B. Scale: 1.01 mmol. White solid (290 mg, 79%). Mp 278 °C; δ_H (DMSO-d_6, 500 MHz) 1.52 (6H, d, *J* 6.9, $(CH_3)_2CH$), 3.69 (2H, t, *J* 7.4, SCH_2), 4.22 (2H, t, *J* 7.4, N-1 CH_2N), 5.07 (1H, septet, *J* 6.9, $(CH_3)_2CH$), 7.68–7.98 (5H, m, SO_2Ph), 8.10 (1H, s, H-8), 13.63 (1H, br s, N-7 H); δ_C (DMSO-d_6, 125 MHz): 19.4, 34.7, 47.4, 51.9, 107.2, 127.6, 129.4, 133.8, 138.7, 140.3, 147.5, 149.9, 153.7; found (ES^+) 385.0927 $[M+Na]^+$, $C_{16}H_{18}N_4O_4SNa$ requires 385.0941.

4.1.1.32. 1-(2-Phenylsulfonylethyl)-3-isopropyl-7-methyl-3,7-dihydropurine-2,6-dione (17a). Using **16** and methyl iodide, according to General Procedure D. Scale: 0.359 mmol. Granular white solid (128 mg, 95%). Mp 134 °C; δ_H ($CDCl_3$, 500 MHz): 1.57 (6H, d, *J* 6.5, $(CH_3)_2CH$), 3.56 (2H, t, *J* 7.1, SCH_2), 3.97 (3H, s, N-7 Me), 4.38 (2H, t, *J* 7.1, CH_2N), 5.14 (1H, septet, *J* 6.5, $(CH_3)_2CH$), 7.50 (1H, s, H-8), 7.58 (2H, t, *J* 8.5, SO_2Ph Ar–H), 7.66 (1H, t, *J* 8.5, SO_2Ph Ar–H), 8.00 (2H, d, *J* 8.5, SO_2Ph Ar–H); δ_C ($CDCl_3$, 125 MHz): 19.7, 33.6, 35.1, 48.5, 53.0, 108.0, 128.2, 129.3, 133.8, 139.0, 141.2, 148.4, 150.3, 154.7; found (ES^+) 377.1264 $[M+H]^+$, $C_{17}H_{21}N_4O_4S$ requires 377.1278.

4.1.1.33. 1-(2-Phenylsulfonylethyl)-3-isopropyl-7-ethyl-3,7-dihydropurine-2,6-dione (17b). Using **16** and ethyl iodide, according to General Procedure D. Scale: 0.359 mmol. Fluffy white solid (122 mg, 87%). Mp 148 °C; δ_H ($CDCl_3$, 500 MHz): 1.53 (3H, t, *J* 7.2, CH_2CH_3), 1.57 (6H, d, *J* 6.9, $(CH_3)_2CH$), 3.57 (2H, t, *J* 7.1, SCH_2), 3.43 (2H, q, *J* 7.2, CH_2CH_3), 4.40 (2H, t, *J* 7.1, N-1 CH_2N), 5.15 (1H, septet, *J* 6.9, N-3 $(CH_3)_2CH$), 7.55 (1H, s, H-8), 7.57–8.02 (5H, m, SO_2Ph); δ_C ($CDCl_3$, 125 MHz): 16.5, 19.7, 35.1, 42.3, 48.5, 53.1, 107.3, 128.2, 129.3, 133.8, 139.1, 134.0, 148.7, 150.3, 154.3; found (ES^+) 391.1453 $[M+H]^+$, $C_{18}H_{23}N_4O_4S$ requires 391.1435.

4.1.1.34. 3-Isopropyl-7-methyl-3,7-dihydropurine-2,6-dione (18a). Using **17a**, according to General Procedure A.

Scale: 0.307 mmol. Off-white solid (60 mg, 94%). Mp 230 °C; δ_H ($CDCl_3$, 500 MHz): 1.60 (6H, d, *J* 6.9, $(CH_3)_2CH$), 3.99 (3H, s, N-7 Me), 5.15 (1H, septet, *J* 6.9, $(CH_3)_2CH$), 7.53 (1H, s, H-8), 8.42 (1H, br s, N-1 H); δ_C ($CDCl_3$, 125 MHz): 19.7, 33.5, 47.8, 108.6, 141.3, 150.5, 154.8, 174.2; found (ES^+) 231.0855 $[M+Na]^+$, $C_9H_{12}N_4O_2Na$ requires 231.0852.

4.1.1.35. 3-Isopropyl-7-ethyl-3,7-dihydropurine-2,6-dione (18b). Using **17b**, according to General Procedure A. Scale: 0.218 mmol. Off-white solid (56 mg, 89%). Mp 160 °C; δ_H ($CDCl_3$, 500 MHz): 1.46 (3H, t, *J* 7.3, CH_2CH_3), 1.51 (6H, d, *J* 7.0, $(CH_3)_2CH$), 4.25 (2H, q, *J* 7.3, CH_2CH_3), 5.07 (1H, septet, *J* 7.0, $(CH_3)_2CH$), 7.49 (1H, s, H-8), 8.38 (1H, br s, N1-H); δ_C ($CDCl_3$, 125 MHz): 16.5, 19.7, 42.4, 47.8, 107.8, 140.1, 150.5, 154.5, 165.2; found (ES^+) 245.1016 $[M+Na]^+$, $C_{10}H_{14}N_4O_2Na$ requires 245.1009.

4.1.1.36. 1-(3-Bromopropyl)-7-ethyl-3-isopropyl-3,7-dihydropurine-2,6-dione (19). A stirred suspension of **18b** (30.3 mg, 0.136 mmol), NaOH (10.9 mg, 0.272 mmol) and BTEAC (0.9 mg, 0.0041 mmol) in 1,3-dibromopropane (1 mL) was heated at 100 °C for 3 h. The reaction mixture was subjected to a hot filtration, and the filtrate was evaporated under reduced pressure to give a yellow syrup. Purification by flash chromatography (0–1% MeOH/CH_2Cl_2) gave **19** as a pale yellow syrup (47.4 mg, quantitative). δ_H ($CDCl_3$, 500 MHz): 1.45 (3H, t, *J* 7.2, CH_2CH_3), 1.51 (6H, d, *J* 6.9, $(CH_3)_2CH$)), 2.18 (1H, quintet, *J* 7.0, $CH_2CH_2CH_2$), 3.39 (2H, t, *J* 7.0, N-1 CH_2N), 4.07 (2H, t, *J* 7.0, N-1 CH_2Br), 4.28 (2H, q, *J* 7.2, N-7 CH_2CH_3), 5.11 (1H, septet, *J* 6.9, $(CH_3)_2CH$), 7.49 (1H, s, H-8); δ_C ($CDCl_3$, 125 MHz): 16.6, 19.7, 30.7, 31.3, 40.3, 42.3, 48.4, 107.4, 139.8, 148.6, 150.7, 154.9; found (ES^+) 365.0577 $[M+Na]^+$, $C_{13}H_{19}N_4O_2BrNa$ requires 365.0584.

4.1.1.37. C_3-dicaffeine N-3, N-3′=$CH(CH_3)_2$; N-7=CH_3, N-7′=CH_2CH_3 (20). Using **18a** and **19**, according to General Procedure D. Scale: 0.115 mmol. Colourless syrup (40.9 mg, 76%). δ_H ($CDCl_3$, 500 MHz): 1.44 (3H, d, *J* 7.2, CH_2CH_3, 1.49 (6H, d, *J* 6.9, $(CH_3)_2CH$), 1.50 (6H, d, *J* 6.9, $(CH_3)_2CH$), 1.98 (2H, quintet, *J* 7.1, $CH_2CH_2CH_2$), 3.89 (3H, s, N-7 Me), 4.02–4.06 (4H, m, N-1 CH_2N), 4.26 (2H, q, *J* 7.2, CH_2CH_3), 5.06–5.12 (2H, m, $(CH_3)_2CH$), 7.40 (1H, s, H-8), 7.45 (1H, s, H-8); δ_C ($CDCl_3$):16.5, 19.7, 27.1, 33.5, 39.4 (2 signals), 42.2, 48.0, 48.2, 53.4, 107.5, 108.2, 139.6, 140.8, 148.2, 148.5, 150.7 (2 signals), 155.0, 155.4; [Found: (ES^+) 493.2288 $[M+Na]^+$, $C_{21}H_{28}N_8O_4Na$ requires 479.2282].

Acknowledgements

We thank the Wellcome Trust for a studentship (M.B.A.). D.M.F.vA. is a Wellcome Trust Senior Research Fellow.

References and notes

1. (a) Kalla, R. V.; Elzein, E.; Perry, T.; Li, X.; Palle, V.; Varkhedkar, V.; Gimbel, A.; Maa, T.; Zeng, D.; Zablocki, J. *J. Med. Chem.* **2006**, *49*, 3682–3692; (b) Lin, R.-Y.; Wu, B.-N.; Lo, Y.-C.; An, L.-M.; Dai, Z.-K.; Lin, Y.-T.; Tang, C.-S.; Chen, I.-J. *J. Pharmacol. Exp. Ther.* **2006**, *316*, 709–717; (c) Ito, K.; Lim, S.; Caramori, G.; Cosio, B.; Chung, K. F.; Adcock, I. M.; Barnes, P. J. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 8921–8926.
2. (a) Caramori, G.; Adcock, I. *Pulm. Pharmacol. Ther.* **2003**, *16*, 247–277; (b) Dal Piaz, V.; Giavannoni, M. P. *Eur. J. Med. Chem.* **2000**, *35*, 463–480; (c) Kiesman, W. F.; Zhao, J.; Conlon, P. R.; Dowling, J. E.; Petter, R. C.; Lutterodt, F.; Jin, X.; Smits, G.; Fure, M.; Jayaraj, A.; Kim, J.; Sullivan, G.; Linden, J. *J. Med. Chem.* **2006**, *49*, 7119–7131.
3. (a) Rao, F. V.; Andersen, O. A.; Vora, K. A.; DeMartino, J. A.; van Aalten, D. M. F. *Chem. Biol.* **2005**, *12*, 973–980; (b) Schuttelkopf, A. W.; Andersen, O. A.; Rao, F. V.; Allwood, M.; Lloyd, C.; Eggleston, I. M.; van Aalten, D. M. F. *J. Biol. Chem.* **2006**, *37*, 27278–27285.
4. Traube, W. *Chem. Ber.* **1900**, *33*, 3035–3056.
5. Bridson, P. K.; Wang, X. D. *Synthesis* **1995**, *8*, 855–858.
6. Zavialov, I. A.; Dahanukar, V. H.; Nguyen, H.; Orr, C.; Andrews, D. R. *Org. Lett.* **2004**, *6*, 2237–2240.
7. Tesser, G. I.; Buis, J. T. W. A. R. M.; Wolters, E. T. M.; Bothehelmes, E. G. A. M. *Tetrahedron* **1976**, *32*, 1069–1072.
8. For recent examples of a related safety-catch, see: (a) Fridkin, G.; Lubell, W. D. *J. Comb. Chem.* **2005**, *7*, 977–986; (b) Rambouts, F. J. R.; Fridkin, G.; Lubell, W. D. *J. Comb. Chem.* **2005**, *7*, 589–598.
9. Heine, H. W. *J. Am. Chem. Soc.* **1963**, *85*, 2743–2746.
10. Ishibashi, H.; Uekagi, M.; Sakai, M.; Takeda, Y. *Tetrahedron* **2001**, *57*, 2115–2120.
11. He, R. J.; Lam, Y. L. *J. Comb. Chem.* **2005**, *7*, 916–920.
12. Use of the corresponding *tert*-butyl carbamate (Annedi, S. C.; Li, W.; Samson, S.; Kotra, L. P. *J. Org. Chem.* **2003**, *68*, 1043–1049) gave a slightly improved yield in the cyclocondensation (59%). Methyl carbamate **1** was however preferred, as it is a crystalline compound, and more readily purified on a large scale.
13. Harding, S. J.; Jones, J. H. *J. Pept. Sci.* **1999**, *5*, 399–402.
14. Buckle, D. R.; Rockell, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 627–630.
15. Muller, C. E.; Shi, M.; Manning, M., Jr.; Muller, C. E.; Shi, M.; Manning, M., Jr.; Daly, J. W. *J. Med. Chem.* **1993**, *36*, 3341–3349.
16. Muller, C. E.; Thorand, M.; Qurishi, R.; Diekmann, M.; Jacobson, K. A.; Padgett, W. L.; Daly, J. W. *J. Med. Chem.* **2002**, *45*, 3440–3450.
17. Kalcheva, V. B.; Apostolova, T. M.; Anakieva, V. Z. *J. Prakt. Chem.* **1985**, *327*, 165–168.
18. Itahara, T.; Imamura, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 203–209.
19. Weyler, S.; Hayallah, A. M.; Muller, C. E. *Tetrahedron* **2003**, *59*, 47–54.
20. Beer, D.; Bhalay, G.; Dunstan, A.; Glen, A.; Haberthuer, S.; Moser, H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1973–1976.
21. Ebisuzaki, Y.; Boyle, P. D.; Smith, J. A. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1997**, *53*, 777–779.
22. Merlos, M.; Gomez, L.; Vericat, M. L.; Bartroli, J.; Garciarafanell, J.; Forn, J. *Eur. J. Med. Chem.* **1990**, *25*, 653–658.
23. Wells, J. N.; Garst, J. E.; Kramer, G. L. *J. Med. Chem.* **1981**, *24*, 954–958.