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A prototype solid phase synthesis of pteridines and related heterocyclic compounds

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The development of a versatile solid phase synthesis of bicyclic polyaza heterocycles including pteridines, purines, and deazapurines is described. The strategy comprises the linking of a pre-formed pyrimidine through a thioether at the 2 or 4 position to a polystyrene resin, the cyclisation of the second ring, and the direct or oxidative cleavage of the product from the resin by nucleophilic substitution. This provides not only for substituent variation in the second ring, but also for variation at the site of cleavage. Limitations in the scope of the methodology are set by the intrinsic reactivity of pyrimidinyl 2- or 4-thioethers which, whilst undergoing ready nitration at C5, are surprisingly difficult to alkylate and acylate.

Introduction

Solid phase synthesis is well established as a major contributor to the discovery of novel biologically active compounds. Although deriving originally from oligopeptide synthesis many methods have now been described for the synthesis of heterocyclic systems.[1] Recent emphasis has been on so-called 'traceless linkers' to join the desired synthetic intermediates and products to the solid support so that cleavage can be accomplished without leaving a residue or trace of the linker. In that context, sulfur linkers have been attractive for heterocyclic synthesis because, if placed in a position adjacent to a pyridine-like nitrogen atom, they can be cleaved by nucleophilic aromatic substitution. In the case of pyrimidines, thioether linkers have been inserted, either by using thiol-substituted resins themselves[2] or by forming a thioether with a sulfur containing compound such as thiourea[3] or a pyrimidine thiol. After the appropriate substitution chemistry has been carried out, cleavage can be accomplished either by direct substitution with a suitable amine[4] or preferentially after oxidising the thioether to a sulfone.[2–4] In this way, multiply substituted pyrimidines[2,3] and aminopyridazines[4] have been prepared. Alternatively, cleavage can be carried out using Raney nickel to provide unsubstituted derivatives as has been done with pyrimido[4,5-*d*]pyrimidines, isomers of pteridines.[5] Purines with a wide variety of amino groups have also been prepared using thioether linkages.[6,7] Other chemistries based upon Rink resins,[8,9] tetrahydropyranyl ethers,[8,10] and silyl linkers[11] have been used to prepare various amino purines. At the outset of our studies, the only reported solid phase synthesis of a pteridine was a non-traceless synthesis of tetrahydropterins based upon Wang resin supported amino acid chemistry.[12] Recently, we have communicated the use of 2- and 4-thioether linked solid phase methods in the synthesis of pteridines.[13] Herein we report full details of our synthesis of pteridines together with its extension to the synthesis of purines, and related heterocyclic compounds of relevance to the study of pteridine biosynthesis and metabolism. These extensions include not only additional heterocyclic systems but also further cleavage methods. In this report we are concerned with achieving the maximum possible versatility in terms of the heterocyclic systems accessible and the largest possible number of points of diversity. Part of the enabling solution phase chemistry supporting this challenge has been described in previous papers.[14,15] The aim of the study is summarised in Fig. 1.

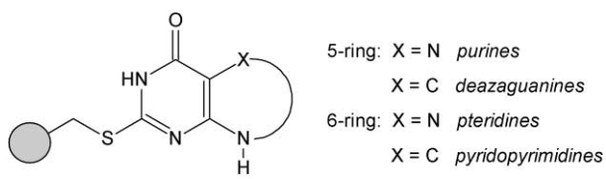

Fig. 1

Results and discussion

Solution phase chemistry underpinning the solid phase methodology

The first syntheses of highly functionalised pterins and deazapurines that we developed afforded compounds with the typical, naturally occurring 'amino-oxo' functionality in the pyrimidine ring. Although some protecting group strategies, notably involving dimethylaminoimino protecting groups, had proved successful,[15] none of these strategies readily transferred to the solid phase. In order to develop a traceless methodology, attention was focused on thioether linkers. The chemistry of thioether substituted pyrimidines in the preparation of C6 functionalised pteridines and deazaguanines has already been described.[14] In preliminary work[16] we investigated the synthesis of pteridines on Merrifield resins with thioether linkers; cleavage was attempted using cyanogen bromide but with complex outcomes. It was clear that the underlying heterocyclic chemistry of pyrimidylsulfanyl ethers was not understood well enough for the development of a successful solid phase synthesis. The range of available chemistry was therefore expanded in this study through the use of 4-amino-2-benzylsulfanylpyrimidin-6(1*H*)-one **1b** as the model substrate (Scheme 1). Although this compound does not react readily with C electrophiles, both it and the analogous pyrimidine thiol **1a**, smoothly undergo nitrosation with sodium nitrite and acetic acid in DMF to form **2a** and **2b** in yields in excess of 75%. Similarly, reduction of the nitroso group to the corresponding amines **3a** and **3b** was achieved using sodium dithionite in aqueous methanol in 80–97% yield. From the benzylsulfanyldiaminopyrimidine **3b** it was possible to access a number of key heterocyclic systems. Thus, treatment with biacetyl in DMF afforded the 6,7-dimethylpteridine **4b** (85%). Cyclisation with methyl orthoformate and acetic anhydride led to a new route to the 9-acetylpurine **5**,[17] which was hydrolysed to the corresponding purine **6** using molar aqueous sodium hydroxide (58%). Treatment of **3b** with

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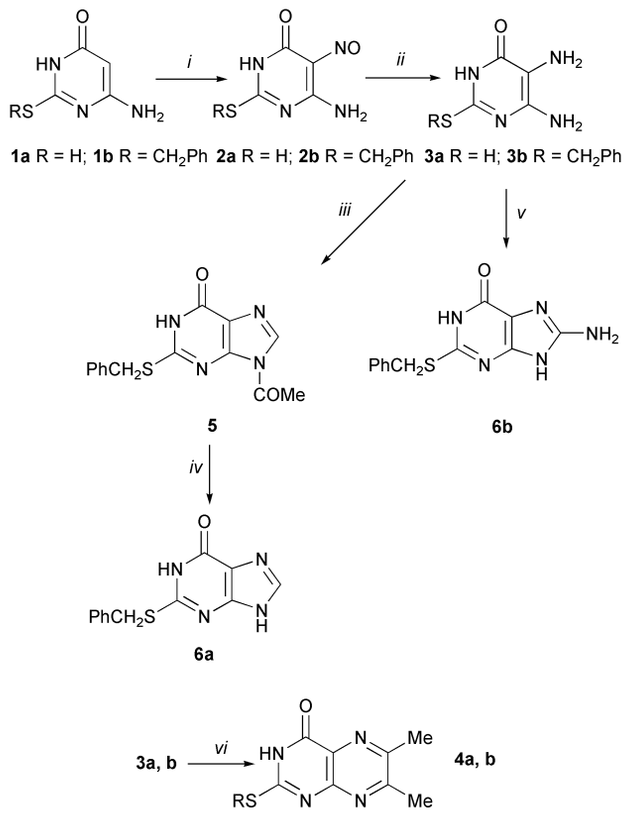
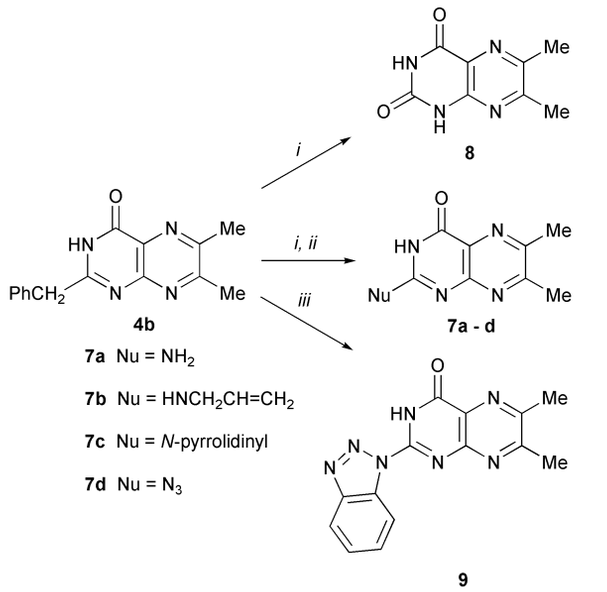


Scheme 1 *Reagents*: *i* $NaNO_2$–HOAc–DMF; *ii* $Na_2S_2O_4$–aq. MeOH; *iii* $(MeO)_3CH$–Ac_2O; *iv* aq. NaOH; *v* CNBr–ethanolic DMF; *vi* biacetyl–DMF.

cyanogen bromide in ethanolic DMF led directly to the 8-aminopurine **6b** (78%).[18] These reactions together with those that lead to deazaguanines described elsewhere[14] provide the basis in functional group modification chemistry and cyclisation chemistry to approach solid phase synthesis, provided that a suitable cleavage process can be developed.

Reactions described in the literature suggested that it would be possible to substitute the thioether in the pteridines and purines prepared directly using a range of primary and secondary amines.[2–4] In our hands, only one such reaction using **4b** as the test compound occurred in good yield, namely ammonolysis at 180° in a sealed tube which afforded the pterin **7a** in 90% yield. Under milder conditions, refluxing ethanol, allylamine and pyrrolidine led to partial substitution (25%) and compounds **7b** and **7c** were isolated and characterised. Since it had been shown that cleavage was more successful after oxidation to the corresponding sulfone, this method was investigated. It was quickly apparent that oxidation greatly increased reactivity because, when the test compound **4b** was oxidised with *m*-chloroperbenzoic acid, the sulfone was not isolated. Instead a high yield of the hydrolysis product, 6,7-dimethylpteridine-(1*H*,3*H*)-2,4-dione **8** was isolated (95%). The same product was obtained using OXONE® (78–88%).

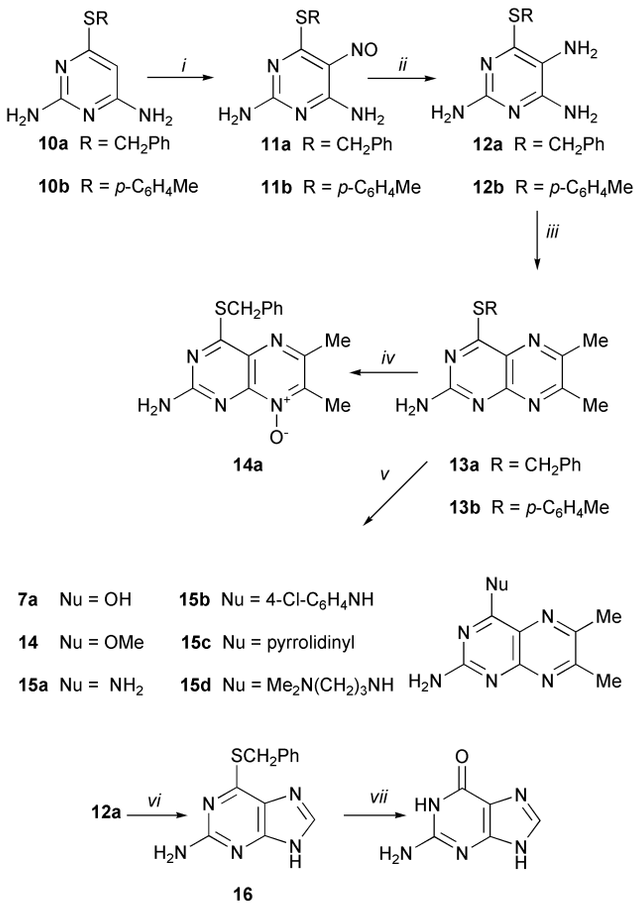
Tetrapropylammonium per-ruthenate with *N*-methylmorpholine *N*-oxide[19] caused substantial decomposition of the pteridine. Seeking to expand the cleavage methodology, we reasoned that activation of sulfur by halogenation would provide an alternative means of introducing a nucleophile at C-2. Accordingly, **4b** was treated with 1-chlorobenzotriazole;[20] cleavage duly occurred but benzotriazole itself was incorporated as the 2-substituent (**9**, not fully purified) (Scheme 2). This reaction demonstrated clearly that hydrolysis could be avoided and, if other *N*-chloroamines were used, additional access to diversity might be obtained. The most generally useful approach was found to be with dimethyldioxirane (DDO) as oxidising agent.[21] DDO was prepared freshly in anhydrous acetone and the concentration determined by UV spectroscopy.



Scheme 2 *Reagents*: *i* aq. DDO; *ii* DDO followed by Nu; *iii* *N*-chlorobenzotriazole.

It was found that with two to three equivalents of DDO, the thioether substrate was cleaved within two hours at room temperature. If anhydrous conditions were not employed, hydrolysis inevitably occurs affording **8**. On the other hand, after anhydrous oxidation without isolation of the sulfone, addition of a nitrogen nucleophile allowed the direct formation of the 2-amino compounds required. This reaction was successful with allylamine (**7b**, 79%), pyrrolidine (**7c**, 49%), and especially sodium azide (**7d**, 49%). This 2-azidopteridine **7d** was readily reduced to the 2-aminopteridine **7a** with sodium dithionite (65%). There were practical problems associated with the purification of these products and the removal of benzylsulfinic acid and the yields therefore cannot be considered to be optimal. However such difficulties should not arise on the solid phase.

Whilst the avoidance of the introduction of an oxo group at C2 was a problem, the introduction of such a group at C4 would be entirely satisfactory from the point of view of synthesis of pterins and guanine analogues. For this reason, the chemistry of pyrimidine-4-sulfanyl ethers was developed in parallel. The preparation of the sulfanyl ethers **10a** and **10b** (Scheme 3) has already been described.[22] As with the 2-substituted series, nitrosation (**11a**, **11b**; 74%, 77%), reduction (**12a**, **12b**; 74%, 90%), and cyclisation with biacetyl (**13a**, **13b**, 84%, 77%) all took place straightforwardly. Several reagents were investigated as cleavage reagents. Both hydrogen peroxide in acetic acid[23] and OXONE® failed to convert the thioether **13a** into a sulfone; instead the 8-*N*-oxide **14a** was obtained, the structure of which was suggested from its NMR spectrum and literature comparison.[24] As with the 2-thioethers, the best results were obtained using DDO but for a short time and at low temperature (−78 °C). In the absence of a stronger nucleophile, the pteridinedione **7a** was obtained (90%). Similarly to the case for the 2-thioether linkage, oxidative activation followed by addition of a nucleophile would provide an additional point of diversity. Thus DDO oxidation of **13a** followed by addition of the nucleophile and allowing the reaction to warm to room temperature gave good yields of a variety of 4-substituted pteridines: **7a**, OH, 90%; **14**, OMe, 74%; **15a**, NH_2, 89%; **15b**, 4-chloroaniline, 84%; **15c**, pyrrolidine, 92%; **15d**, 3-dimethylaminopropylamine, 71%. This new process was also applied to thioether **13b**, which behaved similarly in affording **7a** (89%) and **15b** (87%). This cleavage reaction is thus very effective in pteridines; the ease of reaction is consistent with the normally found preferential reaction at C4 compared with C2.



Scheme 3 *Reagents*: *i* $NaNO_2$–HOAc–DMF; *ii* $Na_2S_2O_4$–aq. MeOH; *iii* biacetyl; *iv* OXONE®; *v* for **7a** aq. DDO, for **14** DDO followed by MeOH, for **15a**–**d** DDO followed by Nu; *vi* $(EtO)_3CH$–Ac_2O, KOH; *vii* CH_3CO_2H–H_2O_2.

In the case of purines, the diaminopyrimidine **12a** was cyclised with ethyl orthoformate and acetic anhydride and the intermediate acetyl purine hydrolysed with potassium hydroxide to afford a novel route to the 5-benzylsulfanylpurine **16** in 70% yield.[25] In this case, *N*-oxide formation was not a problem and guanine itself was obtained by cleavage with hydrogen peroxide in acetic acid (64%) using our newly developed methodology.

Reactions on the solid phase

For linking the pyrimidine through 2-sulfanyl ethers, two chloromethyl resins were used. Type-A was a polystyrene residue cross linked with 2% divinylbenzene with a high loading of 6.05 mmol g^{-1} (courtesy Professor David Sherrington, Strathclyde). Type-B was a commercially available resin (Novabiochem) with lower cross linking (1%) and lower loading (1.94 mmol g^{-1}). Although the loading and physical properties of solid supports can be very important in the success of solid phase synthesis, in practice, there was no significant difference in handling between the two resins in our hands but higher reaction yields were usually obtained with resin type-B.

The resins were loaded with 6-amino-2-sulfanylpyrimidin-4(3*H*)-one by stirring in suspension in DMSO, in the presence of potassium iodide and potassium hydroxide. The data in Table 1 show the outcome of the sequence of reactions leading to the dimethylpteridinedione **8** which was used as a test case. Microanalysis was the primary analytical tool, although it was complicated with respect to precision by samples of resin that gained weight in air, presumably because of hygroscopy. The sequence of transformations was conveniently carried out using a mixed solvent system of DMF and water which made it possible to attain a reasonable degree of swelling and to use the inorganic nitrosating and reducing agents. Reaction times were standardised at between 20 and 24 h at temperatures from room temperature to 40 °C. Cyclisation with biacetyl required a higher temperature of 80 °C. After each reaction, the resin was washed with water and DMF and then twice successively with water, methanol, acetone, THF, and diethyl ether. Before analysis, the resin was dried under reduced pressure at 70 °C for 10 h.

With the synthetic reactions apparently successfully accomplished, the cleavage reactions discussed above were investigated. As expected, using the type-A resin, cleavage with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane led directly to the pteridinedione **8**, which was isolated and fully characterised. The cleavage took place in 25% yield from the resin bound final product. This is equivalent to 18% yield overall based upon the initial loading of the resin. Direct cleavage by ammonia and amines was also investigated:[2–4,26] 2-Amino **7a**, 2-allylamino **7b**, and 2-pyrrolidinyl **7c** derivatives were all isolated and identified but the harsh reaction conditions (sealed tube at 180 °C for **7a** and hot DMF for **7b** and **7c**) led to low yields and substantial decomposition. Cleavage of the product from resin type-B was investigated using DDO oxidation over 4–10 h at room temperature. Subsequent addition of a nucleophile (amine or azide ion to give **7d**) allowed 2-substitution to be demonstrated. Consistent with the solution phase results, this method was more efficient, the pteridinedione **8** being obtained in 45% yield on cleavage equivalent to 27% yield overall. Cleavage by oxidation and subsequent addition of a nitrogen nucleophile was also more effective than direct nucleophilic cleavage.

For linkage through 4-sulfanyl ethers, a commercially available thiol-functionalised Merrifield type resin (Novabiochem) was used; this material was 1% cross-linked and had a loading of 4 mmol g^{-1}. Table 2 shows the results of the loading, functional group modification, and cyclisation reactions successfully carried out under the same conditions as for the 2-sulfanyl resin. Again consistent with the solution phase experience, cleavage by oxidation followed by displacement with water gave the highest yield of the pteridinedione **8**; cleavage occurred in 50% yield which indicates 38% overall yield from the loaded resin.

Conclusion

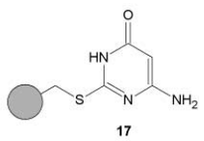
In this paper we have described the solution chemistry relevant to the establishment of a solid phase synthesis of pteridines and purines. We have reported new cleavage methods for 2-thioethers (using 1-chlorobenzotriazole) and the potential for additional diversity through the oxidative cleavage of 4-thioethers. These procedures have also been extended to the synthesis of purines. Taken with the results described in previous papers[13–16] the basis for the solid phase synthesis of 6-functionalised pteridines and 7-deazaguanines has also been established. Using the pteridinedione **8** as an example, a prototype solid phase methodology has been developed. There are clear limitations in the ability of this methodology with respect to cyclisation using carbon electrophiles at C5 of pyrimidine substrates and more work will be required to solve this problem. The exemplification of this prototype methodology for a range of heterocyclic products is now in hand.

Experimental

Instrumentation and general materials

NMR spectra were determined on a Bruker Spectrospin spectrometer operating at 400 MHz for ^1H spectra and 100 MHz for ^{13}C spectra. Chemical shifts are reported as ppm relative to TMS measured from the solvent resonance. *J* values are given in Hz. IR spectra were determined using a Mattson 1000 FT spectrometer or a Nicolet Impact 400D FT spectrometer. Mass spectra were measured on a JEOL JMS AX505 spectrometer. Microanalyses were carried out using a Perkin-Elmer Series II

Table 1 Solid phase synthesis using 2-sulfanyl ether linkage



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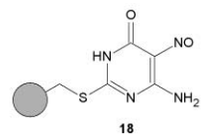

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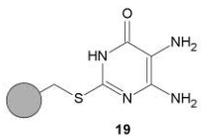

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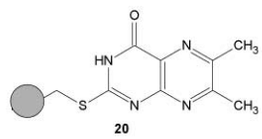

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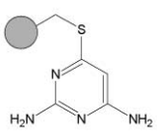
Sample	Resin type	%N	Loading/ mmol g^{-1}	Conversion (%)	Functional group (%)
17	A	12.27	2.91	79	79
	B	6.46	1.53	96	96
18	A	14.7	2.62	98	79
	B	7.71	1.37	94	90
19	A	13.01	2.32	85	67
	B	5.68	1.02	72	65
20	A	11.84	2.11	102	71
	B	5.21	0.93	96	64

Table 2 Solid phase synthesis using 4-sulfanyl linker



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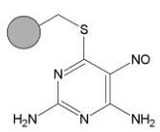

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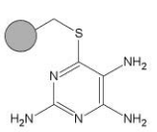

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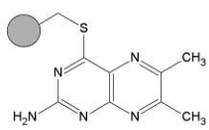

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Sample	%N	Loading/ mmol g^{-1}	Conversion (%)	Functional group (%)
21	13.25	2.37	85	85
22	14.67	2.09	95	81
23	13.35	1.91	88	71
24	12.65	1.81	104	76

instrument at the University of Strathclyde. UV spectra were determined using a Perkin-Elmer Lambda 2 spectrometer. Melting points, when measureable, were determined on a Reichert hot stage apparatus and are uncorrected. TLC was carried out on silica (Merck 0.25 mm 60 F_{254}). Column chromatography was carried out using silica gel (230–400 mesh; 40–60 μm). Reagents were bought from Aldrich (Gillingham, Dorset, UK).

General method for the nitrosation at C-5 of sulfanylpyrimidines

The appropriate pyrimidine (1 eq.) was partially dissolved in a solution of sodium hydroxide (1 eq.) in water at room temperature. A solution of sodium nitrite (1.2 eq.) in water was added. The solution was then acidified by the gradual addition of glacial acetic acid. A white precipitate formed almost immediately, which gradually turned blue on stirring at room temperature for the given time. The precipitate was collected by filtration, and washed with water and ether to afford the corresponding nitroso compound as an intensely coloured solid.

6-Amino-5-nitroso-2-sulfanyl-4(3*H*)-pyrimidinone 2a. Obtained using a solution of 6-amino-2-sulfanyl-4(3*H*)-pyrimidinone **1a** (18 g, 126 mmol) and sodium hydroxide (5.1 g, 127 mmol) in water (350 mL), sodium nitrite (10.35 g, 140 mmol) and acetic acid (35 mL). Reaction time: 2 days. Yield of **2a**: 77% (16.8 g, 97.7 mmol) as a blue crystalline solid, mp > 240 °C. δ_H(DMSO) 7.68 (1H, br s, N(6)H), 11.21 (1H, br s, N(6)H), 12.01 (1H, br s, N(3)H), 12.53 (1H, s, S(2)H). δ_C(DMSO) 140.80 (C-5), 143.02 (C-6), 159.78 (C-4), 176.87 (C-2). ν_{max}(KBr) 3055, 2866, 1689, 1646, 1276, 1169, 768, 584, 525, 502 cm^{-1}. LRMS (FAB) found: 173 (M + 1).

6-Amino-2-(benzylsulfanyl)-5-nitroso-4(3*H*)-pyrimidinone 2b. Obtained using a solution of 6-amino-2-(benzylsulfanyl)-4(3*H*)-pyrimidinone **1b** (21.5 g, 92 mmol) and sodium hydroxide (5.10 g, 127 mmol) in water (350 mL), sodium nitrite (7.77 g, 113 mmol) and acetic acid (35 mL). Reaction time: 2 days. Yield of **2b**: 81% (19.5 g, 75 mmol) as an intense blue crystalline solid, mp 185–187 °C. HRMS (FAB; NBA–glycerol matrix) found: 263.0586, $C_{11}H_{11}N_4O_2S$ (M + 1) requires 263.0603. δ_H(DMSO) 4.44 (2H, s, C(7)H_2), 7.24–7.33 (3H, m, 2 × C(10)H, C(11)H), 7.41–7.48 (2H, m, 2 × C(9)H), 9.04 (1H, br s, 1 × NH_2), 11.22 (1H, br s, 1 × NH_2), 12.72 (1H, br s, N(3)H). δ_C(DMSO) 34.68 (C-7), 128.30 (C-11), 129.37 (2 × C-10), 130.13 (2 × C-9), 137.88 (C-8), 144.06 (C-5), 147.86 (C-2), 162.78 (C-6), 168.81 (C-4). ν_{max}(KBr) 3401 (br), 3233, 3068, 1685, 1668, 1557, 1498 (N=O), 1464, 1319, 1277, 1189 cm^{-1}. λ_{max}(MeOH) 343, 283 nm.

6-(Benzylsulfanyl)-5-nitroso-2,4-pyrimidinediamine 11a. Obtained using a solution of 6-(benzylsulfanyl)-2,4-pyrimidinediamine **10a** (10 g, 43.1 mmol) and sodium hydroxide (1.7 g, 43.1 mmol) in water (80 mL), sodium nitrite (3.45 g, 50 mmol) and acetic acid (15 mL). Reaction time: 2 days. Yield of **11a**: 74% (8.35 g, 31.99 mmol) as an intense purple solid, mp 230–233 °C (dec.). HRMS (FAB) found: 262.0769, $C_{11}H_{12}N_5OS$ (M + 1) requires 262.0763. δ_H(DMSO) 4.46 (2H, s, C(7)H_2), 7.18–7.32 (3H, m, 2 × C(10)H, C(11)H), 7.48–7.50 (2H, m, 2 × C(9)H), 7.98 (1H, br s, 1 × N(2)H_2), 8.07 (1H, br s, 1 × N(2)H_2), 8.12 (1H, d, J = 2.8, 1 × N(4)H_2), 9.71 (1H, d, J = 2.8, 1 × N(4)H_2). δ_C(DMSO) 32.83 (C-7), 127.50 (C-11), 128.85 (2 × C-9), 129.78 (2 × C-10), 138.6 (C-8), 145.84 (C-5), 149.73 (C-4), 161.29 (C-2), 181.11 (C-6). ν_{max}(KBr) 3484, 3310, 3147, 1666, 1630, 1542 (N=O), 1254, 1146, 1017 cm^{-1}.

6-[(4-Methylphenyl)sulfanyl]-5-nitroso-2,4-pyrimidinediamine 11b. Obtained using a solution of 6-[(4-methylphenyl)sulfanyl]-2,4-pyrimidinediamine **10b** (10 g, 43.1 mmol) and sodium hydroxide (1.7 g, 43.1 mmol) in water (80 mL), sodium nitrite (3.45 g, 50 mmol) and acetic acid (15 mL). Reaction time: 2 days. Yield of **11b**: 77% (8.67 g, 33.21 mmol) as an

intense purple solid, mp 180–185 °C (dec.). HRMS (FAB) found: 262.0770, $C_{11}H_{12}N_5OS$ (M + 1) requires 262.0763. δ_H(DMSO) 2.36 (SH, s, C(11)H_3), 7.27–7.52 (4H, m, 2 × C(8)H and 2 × C(9)H), 7.59 (1H, br s, NH), 7.83 (1H, br s, NH), 8.15 (1H, br s, NH), 9.69 (1H, br s, NH). δ_C(DMSO) 21.31 (C-11), 124.76 (C-7), 130.22 (2 × C-8), 136.06 (2 × C-9), 139.37 (C-10), 145.34 (C-5), 149.44 (C-4), 161.46 (C-2), 181.69 (C-6). ν_{max}(KBr) 3323, 3137, 1649, 1578, 1273, 1027 cm^{-1}.

General method for the conversion of 5-nitrosopyrimidines into 5-aminopyrimidines

A solution of sodium dithionite (20 mmol) in water (25 mL) was added to a suspension of the appropriate 5-nitrosopyrimidine (10 mmol) in methanol (25 mL) at room temperature. After stirring for the given time, the precipitate went from coloured to colourless. The precipitate was collected by filtration and washed with water, acetone and ether.

5,6-Diamino-2-sulfanyl-4(3*H*)-pyrimidinone 3a. Obtained using a solution of sodium dithionite (10 g, 57.5 mmol) in water (80 mL) and 6-amino-5-nitroso-2-sulfanyl-4(3*H*)-pyrimidinone **2a** (5 g, 29 mmol) in methanol (80 mL). Reaction time: 40 min. Yield of **3a**: 79% (3.64 g, 23 mmol) as a colourless solid, mp > 240 °C. HRMS (FAB) found: 159.0341, $C_4H_7N_4OS$ (M + 1) requires 159.0341. δ_H(DMSO) 5.69 (2H, s, NH_2), 11.81 (1H, br s, SH). δ_C(DMSO) 102.81 (C-5), 141.01 (C-6), 158.39 (C-4), 168.02 (C-2). ν_{max}(KBr) 3403 (NH_2), 3311 (NH_2), 1634, 1583, 1271, 1184, 552 cm^{-1}.

5,6-Diamino-2-(benzylsulfanyl)-4(3*H*)-pyrimidinone 3b. Obtained using a solution of sodium dithionite (1.60 g, 9.20 mmol) in water (16 mL) and 6-amino-2-(benzylsulfanyl)-5-nitroso-4(3*H*)-pyrimidinone **2b** (0.42 g, 1.60 mmol) in methanol (16 mL). Reaction time: 40 min. Yield of **3b**: 98% (0.39 g, 1.57 mmol) as a colourless crystalline solid, mp 185–187 °C. HRMS (FAB; NBA–glycerol matrix) found: 249.0810, $C_{11}H_{13}N_4OS$ (M + 1) requires 249.0810. δ_H(DMSO) 4.31 (2H, s, C(7)H_2), 5.82 (2H, br s, NH_2), 7.21–7.31 (3H, m, 2 × C(10)H, C(9)H), 7.40–7.46 (2H, m, 2 × C(9)H). δ_C(DMSO) 33.98 (C-7), 106.84 (C-5), 127.45 (C-11), 128.74 (2 × C-10), 129.43 (2 × C-9), 138.57 (C-8), 148.20 (C-6), 149.22 (C-2), 157.71 (C-4). ν_{max}(KBr) 3465 (br), 3366, 3346, 1654, 1626, 1521, 1495, 1465, 1355, 1221 cm^{-1}. λ_{max}(MeOH) 298 nm.

6-(Benzylsulfanyl)-2,4,5-pyrimidinetriamine 12a. Obtained using a solution of sodium dithionite (10 g, 57.5 mmol) in water (60 mL) and 6-(benzylsulfanyl)-5-nitroso-2,4-pyrimidinediamine **11a** (5 g, 19.1 mmol) in methanol (60 mL). Reaction time: 1.5 hours. Yield of **12a**: 74% (3.5 g, 14.2 mmol) as a colourless crystalline solid, mp 175–177 °C (lit.[25] 177–178 °C). HRMS (FAB) found: 248.0973, $C_{11}H_{14}N_5S$ (M + 1) requires 248.0970. δ_H(DMSO) 4.32 (2H, s, C(7)H_2), 5.43 (2H, br s, NH_2), 6.0 (2H, br s, NH_2), 7.18–7.29 (3H, m, 2 × C(10)H, C(11)H), 7.34–7.39 (1H, m, 2 × C(9)H). δ_C(DMSO) 32.76 (C-7), 112.72 (C-5), 127.01 (C-11), 128.63 (2 × C-9), 129.34 (2 × C-10), 139.73 (C-8), 150.35 (C-4), 155.70 (C-2), 157.09 (C-6). ν_{max}(KBr) 3402 (NH_2), 3151, 1635, 1609, 1546, 1425, 897, 694 cm^{-1}.

6-[(4-Methylphenyl)sulfanyl]-2,4,5-pyrimidinetriamine 12b. Obtained using a solution of sodium dithionite (10 g, 57.5 mmol) in water (80 mL) and 6-[(4-methylphenyl)sulfanyl]-5-nitroso-2,4-pyrimidinediamine **11b** (8 g, 30.6 mmol) in methanol (80 mL). Reaction time: 1.5 hours. Yield of **12b**: 90% (6.78 g, 27.45 mmol) as a colourless crystalline solid, mp 155–157 °C. HRMS (FAB) found: 248.0966, $C_{11}H_{14}N_5S$ (M + 1) requires 148.0970. δ_H(DMSO) 2.25 (3H, s, C(11)H_3), 7.11–7.27 (4H, m, 2 × C(8)H and 2 × C(9)H), 7.31 (2H, br s, NH_2). δ_C(DMSO) 21.04 (C-11), 121.27 (C-5), 128.77 (C-7), 130.52 (2 × C-8), 130.87 (2 × C-9), 135.64 (C-10), 154.02 (C-4), 157.47 (C-2), 161.85 (C-6). ν_{max}(KBr) 3401, 3196, 1632, 1509, 1118, 995, 810, 621 cm^{-1}.

General method for the cyclisation of di- or triaminopyrimidines into pteridines using biacetyl

The appropriate di- or triaminopyrimidine (4 mmol) was dissolved in DMF (20 mL) and biacetyl (8 mmol) was added. The solution was stirred for 5 hours at 100 °C, and then the solvent was evaporated under reduced pressure. The resulting orange oil was triturated with ether. The resulting solid was filtered and washed with ether to yield the corresponding 6,7-dimethylpteridine.

6,7-Dimethyl-2-sulfanyl-4(3*H*)-pteridinone 4a. Obtained using 5,6-diamino-2-sulfanyl-4(3*H*)-pyrimidinone **3a** (0.58 g, 3.67 mmol) in DMF (20 mL) and biacetyl (0.63 g, 7.34 mmol). Yield of **4a**: 67% (0.51 g, 2.45 mmol), mp 225–229 °C. HRMS (FAB) found: 209.0498, $C_8H_9N_4OS$ (M + 1) requires 209.0497. δ_H(DMSO) 2.52 (3H, s, C(10)H_3), 2.55 (3H, s, C(9)H_3), 12.60 (1H, br s, N(3)H), 13.09 (1H, br s, SH). δ_C(DMSO) 21.87 (C-9), 22.74 (C-10), 126.12 (C-4a), 147.18 (C-6), 150.43 (C-7), 154.72 (C-8a), 159.04 (C-4), 175.54 (C-2). ν_{max}(KBr) 3424 (NH), 1694, 1546, 1374, 1352, 1136, 537, 455 cm^{-1}.

2-(Benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone 4b. Obtained using 5,6-diamino-2-(benzylsulfanyl)-4(3*H*)-pyrimidinone **3b** (1 g, 4.03 mmol) in DMF (20 mL) and biacetyl (0.7 g, 8 mmol). Yield of **4b**: 85% (1.02 g, 3.44 mmol), mp > 240 °C. HRMS (EI) found: 298.0889, $C_{15}H_{14}N_4OS$ requires 298.0888. δ_H(DMSO) 2.57 (3H, s, C(14)H_3), 2.60 (3H, s, C(15)H_3), 4.52 (2H, s, C(9)H_2), 7.24–7.47 (5H, m, 2 × C(11)H, 2 × C(12)H, C(13)H), 12.95 (1H, br s, N(3)H). δ_C(DMSO) 22.17 (C-14), 23.03 (C-15), 34.28 (C-9), 127.78 (C-13), 128.92 (2 × C-11), 128.99 (C-10), 129.45 (2 × C-12), 137.18 (C-6), 151.96 (C-7), 152.99 (C-4a), 159.08 (C-8a), 159.58 (C-2), 160.71 (C-4). ν_{max}(KBr) 3168, 1692 (C=O), 1576, 1559, 1385, 1167, 962, 823, 721, 701, 465 cm^{-1}.

4-(Benzylsulfanyl)-6,7-dimethyl-2-pteridinamine 13a. Obtained using 6-(benzylsulfanyl)-2,4,5-pyrimidinetriamine **12a** (1 g, 4.05 mmol) in DMF (20 mL) and biacetyl (0.7 g, 8 mmol). Yield of **13a**: 84% (1.01 g, 3.4 mmol), mp 208–210 °C. HRMS (FAB) found: 298.1136, $C_{15}H_{16}N_5S$ (M + 1) requires 298.1126. δ_H(DMSO) 2.46 (3H, s, C(15)H_3), 2.52 (3H, s, C(14)H_3), 4.45 (2H, s, C(9)H_2), 7.22–7.31 (3H, m, C(13)H, 2 × C(12)H), 7.29 (2H, br s, NH_2), 7.48–7.50 (2H, m, 2 × C(11)H). δ_C(DMSO) 22.10 (C-15), 23.62 (C-14), 32.50 (C-9), 126.16 (C-4a), 127.42 (C-13), 128.73 (2 × C-12), 129.61 (2 × C-11), 138.23 (C-10), 148.09 (C-6), 153.30 (C-7), 161.16 (C-8a), 161.66 (C-2), 172.95 (C-4). ν_{max}(KBr) 3467 (NH_2), 3286, 1636, 1559, 1532, 1407, 1167, 934, 643 cm^{-1}.

6,7-Dimethyl-4-[(4-methylphenyl)sulfanyl]-2-pteridinamine 13b. Obtained using 6-[(4-methylphenyl)sulfanyl]-2,4,5-pyrimidinetriamine **12b** (1 g, 4.05 mmol) in DMF (20 mL) and biacetyl (0.7 g, 8 mmol). Yield of **13b**: 77% (0.93 g, 3.13 mmol), mp 147–150 °C. HRMS (FAB) found: 298.1135, $C_{15}H_{16}N_5S$ (M + 1) requires 298.1126. δ_H(DMSO) 2.36 (3H, s, C(13)H_3), 2.58 (3H, s, C(15)H_3), 2.61 (3H, s, C(14)H_3), 7.27–7.53 (4H, m, 2 × C(10)H and 2 × C(11)H), 7.49 (2H, br s, NH_2). δ_C(DMSO) 21.32 (C-13), 22.21 (C-15), 23.65 (C-14), 123.71 (C-4a), 125.58 (C-9), 130.51 (2 × C-10), 135.52 (2 × C-11), 139.87 (C-12), 149.69 (C-6), 149.92 (C-7), 158.96 (C-8a), 162.54 (C-2), 175.98 (C-4). ν_{max}(KBr) 3325, 3194, 1649, 1591, 1562, 1415, 1169, 1016, 805 cm^{-1}.

2-(Benzylsulfanyl)-1,9-dihydro-6*H*-purin-6-one 6a

5,6-Diamino-2-(benzylsulfanyl)-4(3*H*)-pyrimidinone **3b** (0.5 g, 2 mmol), trimethyl orthoformate (5 mL, 4.4 mmol) and acetic

anhydride (5 mL) were heated to reflux for 2.5 hours. The solution was evaporated under reduced pressure, the residue dissolved in sodium hydroxide solution (1 M, 10 mL) and methanol (10 mL) and heated for 10 min on a steam bath. The pH of the solution was brought to 3.8 with acetic acid, filtered, and washed with water to yield the title compound **6a** as a white solid (0.3 g, 1.16 mmol, 58%), mp > 240 °C (lit.[27] 263–265 °C). HRMS (FAB) found: 259.0645, $C_{12}H_{11}N_4OS$ (M + 1) requires 259.0654. δ_H(DMSO) 4.44 (2H, s, C(10)H_2), 7.23–7.33 (3H, m, 2 × C(13)H, C(14)H), 7.43–7.45 (2H, m, C(12)H), 8.02 (1H, s, C(8)H), 12.77 (1H, br s, NH). δ_C(DMSO) 34.31 (C-10), 127.65 (C-14), 128.77 (C-4), 128.85 (2 × C-13), 129.49 (2 × C-12), 137.65 (C-11, C-4), 140.05 (C-8), 155.53 (C-6), 156.68 (C-2). ν_{max}(KBr) 3424 (NH), 3103, 2886, 1679 (C=O), 1574, 1458, 1360, 1227, 962, 785, 695 cm^{-1}.

8-Amino-2-(benzylsulfanyl)-1,9-dihydro-6*H*-purin-6-one 6b

5,6-Diamino-2-(benzylsulfanyl)-4(3*H*)-pyrimidinone **3b** (0.5 g, 2 mmol) was dissolved in a mixture of ethanol (10 mL) and DMF (20 mL). To this stirring mixture, cyanic bromide (0.25 g, 2.3 mmol) was added and the reaction mixture was left stirring overnight at room temperature. The solvents were removed under reduced pressure and the residue was dissolved in the minimum quantity of ethanol and absorbed on top of a chromatographic silica gel column. Elution with 4 : 1 ethyl acetate–methanol, and evaporation of the relevant fractions gave the title compound **6b** as a light green solid (0.4 g, 1.46 mmol, 73%), mp 245–247 °C. HRMS (FAB) found: 274.0762, $C_{12}H_{12}N_5OS$ (M + 1) requires 274.0763. δ_H(DMSO) 4.30 (2H, s, C(10)H_2), 7.01 (2H, br s, C(8)NH_2), 7.20–7.30 (5H, m, 2 × C(12)H, 2 × C(13)H, C(14)H), 7.40 (1H, s, N(9)H), 7.42 (1H, s, N(1)H). δ_C(DMSO) 35.14 (C-10), 114.32 (C-5), 127.72 (C-14), 129.16 (2 × C-12), 129.83 (2 × C-13), 139.40 (C-11), 154.07 (C-4), 158.92, 160.40, 162.84 (C-2, C-8, C-6). ν_{max}(KBr) 3333 (NH_2), 3178, 1621, 1546, 1233, 968, 701 cm^{-1}.

2-Amino-6,7-dimethyl-4(3*H*)-pteridinone 7a

a) From 4b using aqueous ammonia. 2-(Benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone **4b** (0.1 g, 0.33 mmol) and conc. NH_4OH (10 mL) were placed in a sealed tube and heated at 180 °C for 2 hours. After cooling to room temperature, water (20 mL) was added and the residue was filtered and washed with water and acetone. The crude product was recrystallised from aqueous ammonia (5 mL) to give the title compound **7a** (0.05 g, 0.26 mmol, 79%), mp > 260 °C. HRMS (FAB) found: 192.0878, $C_8H_{10}N_5O$ (M + 1) requires 192.0885. δ_H(TFA) 2.88 (3H, s, C(10)H_3), 2.90 (3H, s, C(9)H_3). δ_C(TFA) 21.75 (C-10), 23.81 (C-9), 124.30 (C-4a), 148.15 (C-8a), 154.11 (C-2), 157.38 (C-6), 161.40 (C-4), 167.96 (C-7). ν_{max}(KBr) 3264, 2847, 1689, 1547, 1515, 1273, 1179, 866, 686 cm^{-1}.

b) From 7d using sodium dithionite. To a suspension of 2-azido-6,7-dimethyl-4(3*H*)-pteridinone **7d** (0.1 g, 0.46 mmol) in methanol (7 mL) was added sodium dithionite (0.24 g, 1.38 mmol) in water (7 mL). The resulting reaction mixture was stirred and heated at 60 °C overnight, and then the solvent was removed under reduced pressure. The residue was taken in hot methanol (5 mL) filtered and washed with water. The resulting crude product was recrystallised from aqueous ammonia (5 mL) to give the required compound **7b** (0.057 g, 0.3 mmol, 65%). δ_H(DMSO) 2.48 (3H, s, C(10)H_3), 2.50 (3H, s, C(9)H_3), 6.68 (2H, br s, NH_2), 11.20 (1H, br s, N(3)H).

2-(Allylamino)-6,7-dimethyl-4(3*H*)-pteridinone 7b

a) From 4b and allylamine. 2-(Benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone **4b** (0.25 g, 0.84 mmol) and allylamine (0.47 g, 8.4 mmol) were heated to reflux in ethanol (20 mL) at 85 °C for 96 hours. Then the solution was evaporated under reduced pressure and the residue dissolved in the minimum quantity of methanol and adsorbed into the top of a chromatography silica gel column and eluted with ethyl acetate–methanol (5 : 1) to yield the title compound as a yellow solid (0.11 g, 0.48 mmol, 57%), mp > 240 °C. HRMS (FAB) found: 232.1208, $C_{11}H_{14}N_5O$ (M + 1) requires 232.1198. δ_H(DMSO) 2.48 (3H, s, C(13)H_3), 2.5 (3H, s, C(12)H_3), 3.99 (2H, s, C(9)H_2), 5.12 (1H, d, J = 10.2, 1 × C(11)H_2), 5.22 (1H, d, J = 17.2, 1 × C(11)H_2), 5.89–5.99 (1H, m, C(10)H), 6.71 (1H, br s, NH), 11.17 (1H, br s, N(3)H). δ_C(DMSO) 21.68 (C-12), 22.89 (C-13), 42.85 (C-9), 115.92 (C-11), 126.35 (C-6), 135.29 (C-10), 147.5 (C-4a), 152.15 (C-7), 155.6 (C-8a), 158.73 (C-2), 161.16 (C-4). ν_{max}(KBr) 3283 (NH), 2922 (CH), 1691 (C=O), 1619, 1560, 1492, 1220, 1039, 698, 620, 563 cm^{-1}. λ_{max}(MeOH) 348, 278, 225 nm.

b) From 4b using DDO and allylamine. A solution of dimethyldioxirane (DDO) in acetone (0.056 M, 20 mL, 1.12 mmol) was added to 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone **4b** (0.1 g, 0.33 mmol) and stirred at room temperature for 3 hours. The solution was evaporated under reduced pressure and the yellow residue was dissolved again in DMF (15 mL) and allylamine (50 mg, 0.87 mmol) was added. The mixture was stirred at 80 °C for 40 hours, whereupon it was evaporated to dryness under reduced pressure and purified by silica gel column chromatography eluting with ethyl acetate–methanol (5 : 1), to give the title compound **7b** as a yellow solid (60 mg, 0.26 mmol, 79%).

6,7-Dimethyl-2-(1-pyrrolidinyl)-4(3*H*)-pteridinone 7c from 4b and pyrrolidine

2-(Benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone **4b** (0.5 g, 1.68 mmol) and pyrrolidine (0.59 g, 8.4 mmol) were heated under reflux in ethanol (20 mL) at 85 °C for 96 hours. Then the solution was evaporated under reduced pressure and the residue was dissolved in the minimum quantity of methanol and adsorbed into the top of a chromatography silica gel column and eluted with ethyl acetate–methanol (4 : 1) to yield the title compound **7c** (0.2 g, 0.82 mmol, 49%), mp > 240 °C. HRMS (FAB) found: 246.1361, $C_{12}H_{16}N_5O$ (M + 1) requires 246.1355. δ_H(DMSO) 1.92 (4H, t, J = 6.5, C(10)H_2, C(11)H_2), 2.47 (3H, s, C(14)H_3), 2.49 (3H, s, C(13)H_3), 3.50 (4H, t, J = 6.5, C(9)H_2, C(12)H_2), 11.33 (1H, br s, N(3)H). δ_C(DMSO) 21.68 (C-13), 22.92 (C-14), 25.20 (C-10, C-11), 47.27 (C-9, C-12), 125.31 (C-6), 146.98 (C-4a), 150.59 (C-7), 155.68 (C-8a), 158.83 (C-2), 162.21 (C-4). ν_{max}(KBr) 3442, 3158 (NH), 2962 (CH), 1685 (C=O), 1605, 1560, 1520, 1398, 1271, 984, 822, 732, 518 cm^{-1}. λ_{max}(MeOH) 358, 286, 228 nm.

Synthesis of 2-azido-6,7-dimethyl-4(3*H*)-pteridinone 7d from 4b by DDO oxidation and sodium azide

A solution of dimethyldioxirane (DDO) in acetone (0.1 M, 20 mL, 2 mmol) was added to 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone **4b** (0.25 g, 0.84 mmol) and stirred for 3 hours at room temperature. The solution was evaporated under reduced pressure, the residue was dissolved in DMF (15 mL) and sodium azide (100 mg, 1.54 mmol) was added. The solution was stirred for a further 15 hours at room temperature and then the solution evaporated under reduced pressure. The residue was dissolved in water (20 mL) and barium hydroxide (1 mmol) was added. After stirring the solution for 10 min, it was filtered and evaporated to yield the title compound **7d** (0.145 g, 0.67 mmol, 49%), mp > 240 °C. HRMS (FAB) found: 218.0784, $C_8H_8N_7O$ (M + 1) requires 218.0790. δ_H(DMSO) 2.27 (3H, s, C(9)H_3), 2.34 (3H, s, C(10)H_3), 11.85 (1H, s, N(3)H). δ_C(DMSO) 20.66 (C-9), 21.84 (C-10), 130.87 (C-6), 137.77 (C-4a), 150.72 (C-7), 151.47 (C-2), 159.2 (C-8a), 169.62 (C-4). ν_{max}(KBr) 3385 (NH), 2134 (N≡N), 2038, 1606, 1446, 1206, 641 cm^{-1}. λ_{max}(MeOH) 342, 266, 204 nm.

6,7-Dimethyl-2,4(1*H*,3*H*)-pteridinedione 8

a) From 4b with potassium hydrogen persulfate (OXONE®). A solution of OXONE® ($KHSO_5$) (0.618 g, 2 mmol) in water (10 mL) was added at 0 °C to 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone **4b** (0.3 g, 1 mmol) in methanol (10 mL). The resulting cloudy slurry was stirred for 4 hours at room temperature and evaporated to dryness under reduced pressure. The product was separated from the salt by dissolving it in methanol (20 mL) and filtering the salt from the solution. Evaporation of the methanol yielded the title compound **8** (0.17 g, 0.88 mmol, 88%), mp > 260 °C (lit.[28] > 360 °C). HRMS (FAB) found: 193.0725, $C_8H_9N_4O_2$ (M + 1) requires 193.0726. δ_H(DMSO) 2.50 (3H, s, C(9)H_3), 2.52 (3H, s, C(10)H_3), 11.47 (1H, br s, N(1)H), 11.65 (1H, br s, N(3)H). δ_C(DMSO) 21.56 (C-9), 22.56 (C-10), 124.14 (C-4a), 147.62 (C-6), 148.45 (C-2), 150.29 (C-8a), 158.1 (C-7), 161.44 (C-4). ν_{max}(KBr) 3435, 3178, 3089, 1727 (C=O), 1690 (C=O), 1566, 1395, 1276, 1213, 831, 559, 441 cm^{-1}. λ_{max}(MeOH) 275, 207 nm.

b) From 4b with *m*-CPBA. A solution of *m*-chloroperbenzoic acid (0.5 g, 2 mmol) in dichloromethane (15 mL) was added to 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone **4b** (0.2 g, 0.67 mmol) and the resulting mixture was stirred for 4 hours at room temperature. The solution was evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with ethyl acetate–methanol (4 : 1) to yield the title compound **8** as a pale yellow solid (0.1 g, 0.53 mmol, 78%).

Synthesis of 2-(1*H*-1,2,3-benzotriazol-1-yl)-6,7-dimethyl-4(3*H*)-pteridinone 9

A solution of freshly prepared 1-chlorobenzotriazole (0.31 g, 2 mmol) in methanol (10 mL) was added in portions to 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone **4b** (0.3 g, 1 mmol) in methanol (20 mL) and molecular sieves (4 Å, 200 mg) at −78 °C. The solution was stirred for 2 hours, while the temperature was raised to room temperature. Evaporation of the solvents under reduced pressure and purification by silica gel column chromatography eluting with ethyl acetate–methanol (4 : 1) yielded the title compound **9** together with some impurities (0.15 g, 0.51 mmol, 25%). HRMS (FAB) found: 294.1102, $C_{14}H_{12}N_7O$ (M + 1) requires 294.1103. δ_H(DMSO 2.59 (6H, s, C(15)H_3, C(16)H_3), 7.46–7.50 (1H, m, C(11)H), 7.64–7.68 (1H, m, C(12)H), 8.12 (1H, d, *J* = 8.3, C(10)H), 8.76 (1H, d, *J* = 8.3, C(13)H). δ_C(DMSO) 22.10, 23.00 (C-15, C-16), 116.27 (C-13), 119.44 (C-10), 124.86 (C-11), 128.55 (C-12), 132.23 (C-14), 146.22 (C-6), 149.4, 152.4, 155.32, 157.21 (C-8a, C-2, C-4a, C-7), 171.95 (C-4). ν_{max}(KBr) 3413, 2925 (CH), 1658 (C=O), 1593, 1523, 1447, 1072, 949, 750, 472 cm^{-1}.

General method for the synthesis of benzylsulfanyl and (4-methylphenyl)sulfanyl pyrimidines from 6-chloro-2,4-pyrimidinediamine

To a suspension of 6-chloro-2,4-pyrimidinediamine (1 g, 6.94 mmol) and sodium hydroxide (0.35 g, 8 mmol) in ethanol (30 mL) and water (20 mL), the appropriate thiol (1.3 g, 10.46 mmol) was added. The reaction mixture was stirred at 80 °C overnight. The solution was concentrated by evaporation under reduced pressure, and water (20 mL) was added to the residue. The precipitate was collected by filtration, washed with water and diethyl ether, to afford the required product as a white solid.

6-(Benzylsulfanyl)-2,4-pyrimidinediamine 10a. Obtained using benzylthiol. Yield of **10a**: 85% (1.37 g, 5.90 mmol), mp 144–146 °C (lit.[25] 146–148 °C). HRMS (FAB) found: 233.0871, $C_{11}H_{13}N_4S$ (M + 1) requires 233.0861. δ_H(DMSO) 4.26 (2H, s, C(7)H_2), 5.63 (1H, s, C(5)H), 6.01 (2H, s, NH_2), 6.20 (2H, s, NH_2), 7.20–7.40 (5H, m, 2 × C(9)H, 2 × C(10)H, C(11)H). δ_C(DMSO) 32.44 (C-7), 90.37 (C-5), 127.26 (C-11), 128.74 (2 × C-9), 129.29 (2 × C-10), 138.77 (C-8), 162.85 (C-4), 164.14 (C-2), 166.02 (C-6). ν_{max}(KBr) 3440 (NH_2), 3302, 1612, 1562, 1430, 1362, 787, 715 cm^{-1}.

6-[(4-Methylphenyl)sulfanyl]-2,4-pyrimidinediamine 10b. Obtained using 4-methylbenzenethiol. Yield of **10b**: 94% (1.51 g, 6.50 mmol), mp 240–242 °C. HRMS (EI) found: 232.0788, $C_{11}H_{12}N_4S$ requires 232.0783. δ_H(DMSO) 2.35 (3H, s, C(11)H_3), 5.08 (1H, s, C(5)H), 5.97 (2H, br s, NH_2), 6.18 (2H, br s, NH_2), 7.29 (2H, d, *J* = 7.8, 2 × C(8)H), 7.44 (2H, d, *J* = 7.8, 2 × C(9)H). δ_C(DMSO) 21.71 (C-11), 90.05 (C-5), 126.49 (C-7), 131.26 (2 × C-8), 136.36 (2 × C-9), 140.16 (C-10), 163.28 (C-4), 164.96 (C-2), 170.12 (C-6). ν_{max}(KBr) 3485 (NH_2), 3371, 1642, 1619, 1558, 1363, 899, 506 cm^{-1}.

4-(Benzylsulfanyl)-6,7-dimethyl-2-pteridinamine 8-oxide 14a. A solution of OXONE® ($KHSO_5$) (0.93 g, 3 mmol) in water (10 mL) was added at 0 °C to 4-(benzylsulfanyl)-6,7-dimethyl-2-pteridinamine **13a** (0.3 g, 1 mmol) in methanol (10 mL). The resulting cloudy slurry was stirred for 4 hours at room temperature and evaporated to dryness under reduced pressure. The product was separated from the salt by dissolving it in methanol (20 mL) and filtering. Evaporation of the methanol yielded the title compound **14a** (0.23 g, 0.73 mmol, 73%), mp > 240 °C. HRMS (FAB) found: 314.1068, $C_{15}H_{16}N_5OS$ (M + 1) requires 314.1076. δ_H(DMSO) 2.53 (3H, s, C(15)H_3), 2.61 (3H, s, C(14)H_3), 4.51 (2H, s, C(9)H_2), 7.24–7.27 (1H, m, C(13)H), 7.30–7.34 (2H, m, 2 × C(12)H), 7.51–7.53 (2H, m, 2 × C(11)H), 7.93 (2H, br s, NH_2). δ_C(DMSO) 22.17 (C-15), 23.58 (C-14), 32.82 (C-9), 126.00 (C-4a), 127.66 (C-13), 128.84 (2 × C-12), 129.71 (2 × C-11), 137.70 (C-10), 149.12 (C-8a), 149.88 (C-7), 158.16 (C-2), 162.41 (C-6), 176.21 (C-4).

General method for the cleavage of the 4-benzylsulfanyl group from 13a or the 4-[(4-methylphenyl)sulfanyl] group from 13b using DDO oxidation and a nucleophile

4-(Benzylsulfanyl)-6,7-dimethyl-2-pteridinamine **13a** or 6,7-dimethyl-4-[(4-methylphenyl)sulfanyl]-2-pteridinamine **13b** (0.25 g, 0.84 mmol) was added to a Suba-sealed flask with a magnetic stirring bar. The flask was immersed in an acetone–dry ice bath, and a 0.107 M solution of DDO in acetone (20 mL, 2.14 mmol) was added *via* a syringe to the stirring solution. After 15 min, the appropriate nucleophile was added *via* syringe, then the flask was removed from the dry ice bath, and left stirring for 40 min or until it reached room temperature. The solvent was removed under reduced pressure and the residue was dissolved in a small amount of diethyl ether and/or acetone and filtered to afford the required substituted compound.

2-Amino-6,7-dimethyl-4(3*H*)-pteridinone 7a. *From* **13a**: Obtained using water (5 mL) as nucleophile and leaving the reaction stirring at room temperature overnight. A pure sample was obtained by recrystallisation from aqueous ammonia. Yield of **7a**: 90% (0.145 g, 0.76 mmol) as a yellow amorphous solid, mp > 240 °C (lit.[24] > 300 °C). HRMS (EI) found: 191.0807, $C_8H_9N_5O$ (M^+) requires 191.0807. δ_H(TFA) 2.88 (3H, s, C(10)H_3), 2.90 (3H, s, C(9)H_3). δ_C(TFA) 21.75 (C-10), 23.81 (C-9), 124.30 (C-4a), 148.15 (C-8a), 154.11 (C-2), 157.38 (C-6), 161.40 (C-4), 167.96 (C-7). ν_{max}(KBr) 3263 (NH_2), 2847, 2771, 1687 (C=O), 1547, 1517, 1389, 1270, 1179, 867, 686, 518 cm^{-1}.

From **13b**: Obtained using water (5 mL) as nucleophile and leaving the reaction stirring at room temperature overnight. A pure sample was obtained by recrystallisation from aqueous ammonia. Yield of **7a**: 89% (0.142 g, 0.75 mmol) as a yellow amorphous solid.

4-Methoxy-6,7-dimethyl-2-pteridinamine 14. Obtained using methanol (4 mL) as nucleophile and leaving the reaction stirring at room temperature for a further 3 hours. Yield of **14**: 74% (0.127 g, 0.62 mmol) as a bright red solid, mp > 240 °C (lit.[29] 255–257 °C). HRMS (FAB) found: 206.1044, $C_9H_{12}N_5O$ (M + 1) requires 206.1042. δ_H(DMSO) 2.50 (3H, s, C(12)H_3), 2.54 (3H, s, C(11)H_3), 4.03 (3H, s, C(10)H_3), 7.08 (2H, s, NH_2). δ_C(DMSO) 22.04 (C-12), 23.45 (C-11), 54.61 (C-10), 120.15 (C-4a), 148.24 (C-6), 155.75 (C-7), 160.41, 161.20, 167.15 (C-8a, C-2, C-4). ν_{max}(KBr) 3486, 3339, 1627, 1597, 1547, 1448, 1223, 992, 821 cm^{-1}.

6,7-Dimethyl-2,4-pteridinediamine 15a. Obtained by bubbling NH_3 (gas) into the acetone solution for 5 min. Yield of **15a**: 89% (0.142 g, 0.75 mmol) as an orange crystalline solid, mp > 240 °C. HRMS (FAB) found: 191.1052, $C_8H_{11}N_6$ (M + 1) requires 191.1045. δ_H(TFA) 2.69 (3H, s, C(10)H_3), 2.72 (3H, s, C(9)H_3). δ_C(TFA) 23.11 (C-10), 23.46 (C-9), 121.83 (C-4a), 145.94 (C-8a), 156.49 (C-2), 158.46 (C-6, C-4), 166.88 (C-7). ν_{max}(KBr) 3443 (NH_2), 3307, 3154, 1667, 1624, 1583, 1543, 1447, 1342, 1232, 964, 821, 461 cm^{-1}.

***N*⁴-(4-Chlorophenyl)-6,7-dimethyl-2,4-pteridinediamine 15b.** *From* **13a**: Obtained using 4-chloroaniline (0.127 g, 1 mmol) in acetone (2 mL) as nucleophile. Yield of **15b**: 84% (0.21 g, 0.7 mmol) as an orange solid.

From **13b**: Obtained using 4-chloroaniline (0.129 g, 1 mmol) in acetone (2 mL) as nucleophile.

Yield of **15b**: 87% (0.22 g, 0.73 mmol), mp > 240 °C. HRMS (FAB) found: 301.0959, $C_{14}H_{14}N_6{}^{35}Cl$ (M + 1) requires 301.0969. δ_H(DMSO) 2.60 (3H, s, C(15)H_3), 2.63 (3H, s, C(14)H_3), 7.43 (2H, d, J = 8.8, 2 × C(11)H), 7.45 (2H, br s, NH_2), 8.06 (2H, d, J = 8.8, 2 × C(12)H), 10.26 (1H, s, N(9)H). δ_C(DMSO) 21.88 (C-13), 23.28 (C-14), 119.65 (C-10), 123.61 (2 × C-11), 127.84 (C-6), 128.71 (2 × C-12), 138.04 (C-13), 152.25 (C-7), 158.45, 160.18, 160.50 (C-8a, C-2, C-4). ν_{max}(KBr) 3478 (NH), 3096, 1687, 1589, 1554, 1490, 1090, 826, 466 cm^{-1}.

6,7-Dimethyl-4-(1-pyrrolidinyl)-2-pteridinamine 15c. Obtained using pyrrolidine (0.12 g, 1.69 mmol) as nucleophile. Yield of **15c**: 92% (0.19 g, 0.78 mmol) as a yellow crystalline solid. mp > 240 °C. HRMS (EI) found: 245.1517, $C_{12}H_{16}N_6$ (M^+) requires 245.1514. δ_H(TFA) 2.21–2.34 (4H, m, 2 × C(11)H_2), 2.78 (3H, s, C(13)H_3), 2.80 (3H, s, C(12)H_3), 4.10 (2H, t, J = 6.8, C(10)H_2), 4.65 (2H, t, J = 6.8, C(10)H_2). δ_C(TFA) 22.39 (C-13), 22.78 (C-12), 25.45 (1 × C-11), 28.37 (1 × C-11), 55.57 (1 × C-10), 57.35 (1 × C-10), 125.36 (C-4a), 146.68 (C-8a), 154.10 (C-2), 155.08, 156.17, 162.29 (C-6, C-4, C-7). ν_{max}(KBr) 3369 (NH_2), 3128, 1644, 1574, 1553, 1450, 1424, 1342, 1313, 820 cm^{-1}.

***N*⁴-[3-(Dimethylamino)propyl]-6,7-dimethyl-2,4-pteridinediamine 15d.** Obtained using *N*,*N*-dimethyl-1,3-propanediamine (0.17 g, 1.66 mmol) as nucleophile. Yield of **15d**: 71% (0.16 g, 0.6 mmol) as an amorphous white solid, mp 197–199 °C. HRMS (FAB) found: 276.1926, $C_{13}H_{22}N_7$ (M + 1) requires 276.1937. δ_H(DMSO) 1.70–1.77 (2H, m, C(11)H_2), 2.15 (6H, s, 2 × C(14)H_3), 2.30 (2H, t, J = 6.8, C(12)H_2), 2.50 (6H, s, C(15)H_3, C(16)H_3), 3.48 (2H, q, J = 6.8, C(10)H_2), 6.41 (2H, br s, NH_2), 8.16 (1H, br s, N(9)H). δ_C(DMSO) 21.85 (C-16), 23.22 (C-15), 26.72 (C-11), 39.54 (C-10), 45.60 (2 × C-14), 57.71 (C-12), 120.11 (C-4a), 145.23 (C-6), 154.58 (C-7), 158.78, 160.58, 162.80 (C-8a, C-2, C-4). ν_{max}(KBr) 3374, 1641, 1582, 1439, 1338, 1220, 977, 822, 469 cm^{-1}.

6-(Benzylsulfanyl)-9*H*-purin-2-amine 16. 6-(Benzylsulfanyl)-2,4,5-pyrimidinetriamine **12a** (1.5 g, 6.07 mmol) was suspended in a 1 : 1 mixture (20 mL) of ethyl orthoformate and acetic anhydride. The solution was heated at reflux for 2–3 hours, and the excess solvent was removed under reduced pressure. The residue was covered with water (20 mL) and then solid potassium hydroxide was added until the solution was strongly basic. The solution was boiled, treated with charcoal, and filtered. The filtrate was neutralized with acetic acid and allowed to cool. The precipitate was filtered, washed with water, and dried at 70 °C to yield the desired purine **16** (1.1 g, 4.28 mmol, 70%), mp 208–210 °C (lit.[24] 212–214 °C). HRMS (FAB) found: 258.0802, $C_{12}H_{12}N_5S$ (M + 1) requires 258.0813. δ_H(DMSO) 4.55 (2H, s, C(10)H_2), 6.42 (2H, s, NH_2), 7.21–7.31 (3H, m, C(14)H, 2 × C(13)H), 7.45–7.47 (2H, m, 2 × C(12)H), 7.88 (1H, s, C(8)H), 12.51 (1H, br s, N(9)H). δ_C(DMSO) 31.47 (C-10), 124.04 (C-5), 127.32 (C-14), 128.73 (2 × C-13), 129.45 (C-8), 129.49 (2 × C-12), 139.08 (C-11), 152.26 (C-4), 158.37, 159.94 (C-2, C-6). ν_{max}(KBr) 3457, 3390 (NH), 1626, 1559, 1498, 1262, 914, 830, 703 cm^{-1}.

2-Amino-1,9-dihydro-6*H*-purin-6-one. 6-(Benzylsulfanyl)-9*H*-purin-2-amine **16** (0.2 g, 0.78 mmol) was stirred in a solution of acetic acid (10 mL) and hydrogen peroxide (30%, 1 mL). The solution mixture was heated to 60 °C for 4 hours, and then the solvent was evaporated under reduced pressure. The residue was washed with water (10 mL) and dried on air to afford the title compound (0.075 g, 0.49 mmol, 64%), mp > 260 °C (lit.[30] 365 °C). δ_H(DMSO) 6.90 (2H, br s, NH_2), 8.68 (1H, s, C(8)H), 11.40 (2H, br s, N(1)H, N(9)H). δ_C(DMSO) 109.26 (C-5), 137.25 (C-8), 151.24 (C-4), 154.35 (C-6), 154.98 (C-2). ν_{max}(KBr) 3324, 3120, 1677, 1625, 1573, 1272, 1150 cm^{-1}.

Solid phase reactions

Synthesis. *Preparation of resin **17** (type-A and type-B) – Loading*. Merrifield resin (12 mmol) was weighed into a 50 mL round bottom flask. To this was added potassium iodide (0.75 eq.), potassium hydroxide (1.2 eq.) and 6-amino-2-sulfanyl-4(3*H*)-pyrimidinone monohydrate **1a** (2.5 eq.) followed by DMSO (25 mL). The mixture was stirred with an overhead stirrer with the flask being placed in a pre-heated sand bath at 80 °C for 2 days. The mixture was filtered through a sinter and the resin was washed with DMF (2 × 20 mL), water (3 × 30 mL) and a double sequence of methanol (2 × 10 mL), acetone (2 × 10 mL), THF (10 mL) and ether (10 mL). The resin was dried at 70 °C/0.1 mmHg for 10 hours to give the functionalised resin **17**. Found resin A (6.05 mmol g^{-1}): C 58.62, H 5.44, N 12.27, Cl 4.47, S 9.51%, corresponding to 79% conversion, 2.91 mmol g^{-1}. Found resin B (1.98 mmol g^{-1}): C 74.63, H 6.57, N 6.46, S 5.33%, corresponding to 95% conversion, 1.53 mmol g^{-1}.

*Preparation of resin **18** (type-A and type-B) – Nitrosation*. Resin **17** (0.1 g) was placed in a 5 mL reaction vial containing a spin vane. DMF (3 mL) was added followed by a solution of sodium nitrite (5 eq.) in water (2 mL) and acetic acid (0.4 mL). The mixture was stirred for 24 hours at room temperature to give a green-blue resin. The mixture was filtered through a sinter and the resin was washed with DMF (2 × 20 mL), water (3 × 30 mL) and a double sequence of methanol (2 × 10 mL), acetone (2 × 10 mL), THF (10 mL) and ether (10 mL). The resin was dried at 70 °C/0.1 mmHg for 10 hours to give the nitroso polymer **18**. Found type-A: C 57.33, H 4.83, N 14.7, S 9.38%, corresponding to 97% conversion, 2.62 mmol g^{-1}. Found type-B: C 72.04, H 6.18, N 7.71, S 5.01%, corresponding to 93% conversion, 1.37 mmol g^{-1}.

*Preparation of resin **19** (type-A and type-B) – Reduction*. Resin **18** (0.15 g) was placed in a 5 mL reaction vial containing a spin vane. DMF (2 mL) was added followed by a solution of sodium hydrosulfide (5 eq.) in water (2 mL). The mixture was stirred for 20 hours at 40 °C to give a yellow resin. The mixture was filtered through a sinter and the resin was washed with DMF (2 × 20 mL), water (3 × 30 mL) and a double sequence of methanol (2 × 10 mL), acetone (2 × 10 mL), THF (10 mL) and ether (10 mL). The resin was dried (70 °C at 0.1 mmHg) for

10 hours to give the diamino polymer **19**. Found type-A (hygroscopic) C 55.06, H 5.25, N 13.01, S 10.67%, corresponding to 85% conversion, 2.32 mmol g^{-1}. Found type-B (hygroscopic): C 73.97, H 6.23, N 5.69, S 6.31%, corresponding to 72% conversion, 1.02 mmol g^{-1}.

*Preparation of resin **20** (type-A and type-B) – Cyclisation*. Resin **19** (0.12 g) was placed in a 5 mL reaction vial containing a spin vane. DMF (4 mL) was added followed by biacetyl (5 eq.). The mixture was stirred for 18 hours in a sand bath at 80 °C to give a dark brown resin. The mixture was filtered through a sinter and the resin was washed with DMF (2 × 20 mL), water (3 × 30 mL) and a double sequence of methanol (2 × 10 mL), acetone (2 × 10 mL), THF (10 mL) and ether (10 mL). The resin was dried (70 °C/0.1 mmHg) for 10 hours to give polymer **20**. Found type-A (hygroscopic): C 63.53, H 5.68, N 11.84, S 8.55%, corresponding to 101% conversion, 2.11 mmol g^{-1}. Found type-B (hygroscopic): C 79.23, H 6.54, N 5.21, S 5.67%, corresponding to 96% conversion, 0.93 mmol g^{-1}.

*Preparation of resin **21** – Loading*. A mercapto-functionalised Merrifield-type resin (Novabiochem, 2 g, 4 mmol g^{-1}, 8 mmol) was weighed into a 100 mL round bottom flask equipped with an overhead stirrer and nitrogen inlet. To this was added potassium iodide (1 g, 6 mmol), potassium hydroxide (0.45 g, 8 mmol) and 2,4-diamino-6-chloropyrimidine (2.9 g, 20 mmol) followed by DMSO (40 mL). The mixture was stirred with an overhead stirrer with the flask being placed in a pre-heated sand bath at 80 °C for 2 days. The mixture was filtered through a sinter and the resin was washed with DMSO (2 × 20 mL), water (3 × 30 mL) and a double sequence of methanol (2 × 10 mL), acetone (2 × 10 mL), THF (10 mL) and ether (10 mL). The resin was dried at 70 °C/0.1 mmHg for 10 hours to give the functionalised resin **21**. Found: C 69.32, H 6.28, N 13.25, S 7.75%, corresponding to 84% conversion, 2.37 mmol g^{-1}.

*Preparation of resin **22** – Nitrosation*. Resin **21** (0.2 g, 0.47 mmol) was placed in a 5 mL reaction vial containing a spin vane. DMF (3 mL) was added followed by a solution of sodium nitrite (0.1 g, 1.45 mmol) in water (2 mL) and acetic acid (0.4 mL). The mixture was stirred for 24 hours at room temperature to give a green-blue resin. The mixture was filtered through a sinter and the resin was washed with DMF (2 × 20 mL), water (3 × 30 mL) and a double sequence of methanol (2 × 10 mL), acetone (2 × 10 mL), THF (10 mL) and ether (10 mL). The resin was dried at 70 °C/0.1 mmHg for 10 hours to give the nitroso polymer **22**. Found: C 68.45, H 5.99, N 14.67, S 7.45%, corresponding to 95% conversion, 2.09 mmol g^{-1}.

*Preparation of resin **23** – Reduction*. Resin **22** (0.2 g, 0.42 mmol) was placed in a 5 mL reaction vial containing a spin vane. DMF (3 mL) was added followed by a solution of sodium hydrosulfide (0.36 g, 2.1 mmol) in water (2 mL). The mixture was stirred for 20 hours at 40 °C to give a yellow resin. The mixture was filtered through a sinter and the resin was washed with DMF (2 × 20 mL), water (3 × 30 mL) and a double sequence of methanol (2 × 10 mL), acetone (2 × 10 mL), THF (10 mL) and ether (10 mL). The resin was dried (70 °C/0.1 mmHg) for 10 hours to give the diamino polymer **23**. Found (hygroscopic) C 66.88, H 6.23, N 13.35, S 6.88%, corresponding to 88% conversion, 1.91 mmol g^{-1}.

*Preparation of resin **24** – Cyclisation*. Resin **23** (0.12 g, 0.23 mmol) was placed in a 5 mL reaction vial containing a spin vane. DMF (4 mL) was added followed by biacetyl (0.1 g, 1.16 mmol). The mixture was stirred for 18 hours in a sand bath at 80 °C to give a dark brown resin. The mixture was filtered through a sinter and the resin was washed with DMF (2 × 20 mL), water (3 × 30 mL) and a double sequence of methanol (2 × 10 mL), acetone (2 × 10 mL), THF (10 mL) and ether (10 mL). The resin was dried (70 °C/0.1 mmHg) for 10 hours to give polymer **24**.

Found: C 70.06, H 6.21, N 12.65, S 7.01%, corresponding to 104% conversion, 1.81 mmol g^{-1}.

Cleavage. ***7a** from resin **24** using DDO and water.* Resin **24** (0.3 g, 0.54 mmol) was suspended in an acetone solution of dimethyldioxirane (0.105 M, 25 mL, 2.62 mmol) at room temperature and stirred for 5 hours. Afterwards, the acetone solution was carefully removed from the flask and a further 25 mL of DDO solution in acetone was added. This was stirred at room temperature for 7 hours and then water (2 mL) was added. The solution was kept stirring for 5 hours at 40 °C, and then it was filtered, washing the resin extensively with methanol (30 mL) and conc aqueous ammonia (10 mL). All the filtrates were reunited, evaporated under reduced pressure, and the residue dissolved in conc. aqueous ammonia (10 mL). The title compound **7a** crystallised from the solution to give a yellow solid (52 mg, 0.27 mmol, 50%), mp > 260 °C. δ_H(TFA) 2.89 (3H, s, C(10)H_3), 2.91 (3H, s, C(9)H_3). δ_C(TFA) 21.75 (C-10), 23.81 (C-9), 124.30 (C-4a), 148.15 (C-8a), 154.11 (C-2), 157.38 (C-6), 161.40 (C-4), 167.96 (C-7). ν_{max}(KBr) 3265, 2842, 1689, 1547, 1519, 1389, 1179, 686, 517 cm^{-1}.

***7b** from cleavage of resin **20** (type-A) using allylamine.* Resin **20** (type-A, 0.2 g, 0.42 mmol) and allylamine (3 mL) were stirred in DMF (20 mL) at 100 °C for 72 hours. Then the resin was filtered off and washed with DMF (5 mL), water (5 mL) and methanol (5 mL). All the filtrates were reunited, evaporated under reduced pressure and purified by silica gel column chromatography eluting with ethyl acetate–methanol (5 : 1) (6 mg, 26 μmol, 6%), mp > 240 °C. δ_H(DMSO) 2.48 (3H, s, C(13)H_3), 2.49 (3H, s, C(12)H_3), 3.99 (2H, s, C(9)H_2), 5.12 (1H, d, J = 10.2, 1 × C(11)H_2), 5.22 (1H, d, J = 17.2, 1 × C(11)H_2), 5.90–5.97 (1H, m, C(10)H), 6.72 (1H, br s, NH), 11.17 (1H, br s, N(3)H). δ_C(DMSO) 21.69 (C-12), 22.91 (C-13), 42.83 (C-9), 115.93 (C-11), 135.28 (C-10), 152.16 (C-7), 161.12 (C-4).

***7b** from cleavage of resin **20** (type-B) using DDO and allylamine.* A solution of dimethyldioxirane (DDO) in acetone (0.09 M, 15 mL, 1.35 mmol) was added to the resin **20** (type-B, 0.3 g, 0.28 mmol) and stirred at room temperature for 3 hours. Then the acetone solution was carefully removed and a further 15 mL of the same solution were added. The resin was stirred for a further 5 hours, filtered and washed with acetone (10 mL), THF (10 mL) and ether (10 mL). After, the resin was suspended in DMF (10 mL), THF (5 mL) and allylamine (0.3 mL) were added. The mixture was stirred at 50 °C for 24 hours. Then, the resin was filtered off and washed with DMF (5 mL), water (5 mL) and methanol (5 mL). All the filtrates were reunited, evaporated under reduced pressure and purified by silica gel column chromatography eluting with ethyl acetate–methanol 5 : 1 to give the title compound as a yellow solid (22 mg, 95 μmol, 34%), mp > 240 °C. δ_H(DMSO) 2.48 (3H, s, C(13)H_3), 2.49 (3H, s, C(12)H_3), 3.99 (2H, s, C(9)H_2), 5.12 (1H, d, J = 10.2, 1 × C(11)H_2), 5.22 (1H, d, J = 17.2, 1 × C(11)H_2), 5.90–5.97 (1H, m, C(10)H), 6.72 (1H, br s, NH), 11.17 (1H, br s, N(3)H). δ_C(DMSO) 21.68 (C-12), 22.89 (C-13), 42.84 (C-9), 115.92 (C-11), 126.35 (C-6), 135.29 (C-10), 147.5 (C-4a), 152.15 (C-7), 155.6 (C-8a), 158.73 (C-2), 161.16 (C-4).

***7c** from cleavage of resin **20** (type-A) with pyrrolidine.* Resin **20** (type-A, 0.2 g, 0.42 mmol) and pyrrolidine (3 mL) were stirred in DMF (20 mL) at 100 °C for 72 hours. Then the resin was filtered off and washed with DMF (5 mL), water (5 mL) and methanol (5 mL). All the filtrates were reunited, evaporated under reduced pressure and purified by silica gel column chromatography eluting with ethyl acetate–methanol 5 : 1 (5 mg, 20 μmol, 5%), mp > 240 °C. The compound was identified by TLC analysis with an authentic sample.

***7c** from cleavage of resin **20** (type-B) using DDO and pyrrolidine.* A solution of dimethyldioxirane (DDO) in acetone (0.048 M, 15 mL, 0.72 mmol) and THF (7 mL) was added to the resin **20** (type-B, 0.3 g, 0.28 mmol) and stirred at room temperature for 3 hours. Then the acetone solution was carefully removed and a further 15 mL of the same solution were added. The resin was stirred for a further 5 hours, then filtered

and washed with acetone (10 mL), THF (10 mL) and ether (10 mL). Afterwards, the resin was suspended in DMF (10 mL) and THF (5 mL) and pyrrolidine (0.3 mL) was added. The mixture was stirred at 50 °C for 24 hours. Then, the resin was filtered off and washed with DMF (5 mL), water (5 mL) and methanol (5 mL). All the filtrates were reunited, evaporated under reduced pressure and purified by silica gel column chromatography eluting with ethyl acetate–methanol 5 : 1 to give the title compound as a yellow solid (30 mg, 0.12 mmol, 43%). mp > 240 °C. δ_H(DMSO) 1.92 (4H, t, J = 6.5, C(10)H_2, C(11)H_2), 2.48 (3H, s, C(14)H_3), 2.50 (3H, s, C(13)H_3), 3.50 (4H, t, J = 6.5, C(9)H_2, C(12)H_2), 11.34 (1H, br s, N(3)H). ν_{max}(KBr) 3440, 3159 (NH), 2962 (CH), 1685 (C=O), 1605, 1559, 1520, 1396, 1270, 984, 821, 732 cm^{-1}. λ_{max}(MeOH) 358, 286, 228 nm.

*7**d** from cleavage of resin **20** (type-B) using DDO and sodium azide.* A solution of dimethyldioxirane (DDO) in acetone (0.048 M, 15 mL, 0.72 mmol) and THF (7 mL) was added to the resin **20** (type-B, 0.3 g, 0.28 mmol) and stirred at room temperature for 3 hours. Then the acetone solution was carefully removed and a further 15 mL of the same solution were added. The resin was stirred for a further 5 hours, then filtered and washed with acetone (10 mL), THF (10 mL) and ether (10 mL). Afterwards, the resin was suspended in DMF (10 mL) and THF (5 mL), and sodium azide (0.1 g, 1.54 mmol) was added. The mixture was stirred at 50 °C for 24 hours. Then, the resin was filtered off and washed with DMF (5 mL), water (5 mL) and MeOH (5 mL). All the filtrates were reunited, evaporated under reduced pressure and re-dissolved in ethanol. The salt was filtered off the solution and the filtrate evaporated to yield the title compound (25 mg, 0.115 mmol, 41%), mp > 240 °C. δ_H(DMSO) 2.30 (3H, s, C(9)H_3), 2.35 (3H, s, C(10)H_3), 11.90 (1H, s, N(3)H). ν_{max}(KBr) 3380 (NH), 2137 (N≡N), 2041, 1605, 1448, 1206, 641 cm^{-1} . λ_{max}(MeOH) 342, 266, 205 nm.

***8** from cleavage of resin **20** (type-A) with m*-CPBA. Resin **20** (type-A, 0.10 g, 0.21 mmol) was suspended in dichloromethane (15 mL) and *m*-chloroperbenzoic acid (0.15 g, 0.6 mmol) was added. The mixture was stirred for 20 hours at room temperature and then the resin was filtered off and washed with dichloromethane (10 mL) and methanol (10 mL). All the filtrates were reunited, evaporated under reduced pressure, dissolved in ethyl acetate and absorbed into the top of a silica gel column and eluted with ethyl acetate (10 mg, 52 μmol, 25%), mp > 260 °C. δ_H(DMSO) 2.50 (3H, s, C(9)H_3), 2.52 (3H, s, C(10)H_3), 11.47 (1H, br s, N(1)H), 11.65 (1H, br s, N(3)H). δ_C(DMSO) 22.05 (C-9), 23.05 (C-10), 124.64 (C-4a), 148.12 (C-6), 148.94 (C-2), 150.78 (C-8a), 158.58 (C-7), 161.94 (C-4). λ_{max}(MeOH) 275, 207 nm.

***8** from cleavage of resin **20** (type-B) with DDO.* Resin **20** (type-B, 0.5 g, 0.46 mmol) was suspended in an acetone solution of dimethyldioxirane (0.11 M, 25 mL, 2.75 mmol) at room temperature and stirred for 5 hours. After, the acetone solution was carefully removed from the flask and a further 25 mL of DDO was added. This was stirred at room temperature for 7 hours and then water (2 mL) was added. The solution was kept stirring for 5 hours at 40 °C, and then it was filtered, washing the resin extensively with methanol. All the filtrates were reunited, evaporated and purified by flash silica gel column chromatography (ethyl acetate → ethyl acetate–methanol 4 : 1) (40 mg, 0.21 mmol, 45%), mp > 260 °C. δ_H(DMSO) 2.50 (3H, s, C(9)H_3), 2.52 (3H, s, C(10)H_3), 11.47 (1H, br s, N(1)H), 11.65 (1H, br s, N(3)H). δ_C(DMSO) 21.59 (C-9), 22.57 (C-10), 124.18 (C-4a), 147.66 (C-6), 148.50 (C-2), 150.29 (C-8a), 158.16 (C-7), 161.57 (C-4). ν_{max}(KBr) 3436, 3174, 3089, 1725 (C=O), 1689 (C=O), 1569, 1396, 1286, 831, 563 cm^{-1}. λ_{max}(MeOH) 275, 207 nm.

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