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Syntheses of highly functionalised 6-substituted pteridines

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Methods for the synthesis of polyfunctional 6-substituted pteridines from the corresponding 6-aldehydes are described. Alkene, ester, ketone, amide, cyano, oxime, bromo, methoxy and dihydroxy functional groups have all been introduced principally through improved methodologies for Wittig reactions using 2-thioalkyl-6-formylpteridines as substrates. Further modification of the alkenes derived from the Wittig reactions was difficult but selective conversion to the *vic*-diol was possible using ligand assisted catalysis with osmium tetraoxide. These methods are a component of an extensive methodology for the preparation of compounds that might serve as modulators of tetrahydrobiopterin activity or as inhibitors of dihydroneopterin aldolase.

Introduction

Inhibition of enzymes associated with the biosynthesis and activity of folate cofactors has been one of the most fruitful areas of drug discovery in the context of both anti-infective and anti-cancer drugs.[1] The principal target enzymes have been dihydropteroate synthase,[2] and dihydrofolate reductase, which continues to attract attention,[3] together with thymidylate synthase.[4] Despite these successes, the demand for anti-infective drugs that are effective against drug resistant strains of pathogens and for increasing selectivity in the action of anti-cancer drugs has encouraged the detailed study of other enzymes in the pathway.[5] Similarly, increasingly stringent criteria for the acceptability of agrochemicals have directed interest to enzymes of the folate pathway. There are several other enzymes involved in folate biosynthesis or in pteridine metabolism that conceivably might be therapeutic targets. Over the last few years, detailed structural and mechanistic studies have been undertaken with respect to several of the enzymes of the folate pathway including GTP-cyclohydrolase I,[6] dihydroneopterin aldolase,[7] 6-hydroxymethyl-dihydropteridine diphosphokinase,[8] and dihydropteroate synthase.[9] Similar studies have revealed details of the pathway *via* dihydropterin dehydratase and sepiapterin reductase to dihydrobiopterin[10] (Fig. 1). Tetrahydrobiopterin is also an obligatory cofactor for aromatic amino acid hydroxylation[11] and nitric oxide synthase.[12] Notably, all of the pterins involved in these reactions are highly functionalised at C6. Therefore, the availability of inhibitors or mechanistic probes depends upon synthetic methods for the preparation of related compounds with multiple functionality in C6 substituents. This paper describes a number of methods that lead to a variety of such substitution patterns at different oxidation levels and different positions. An additional point of significance is that modern medicinal chemistry makes great use of solid phase synthesis; the reactions described in this paper were developed to be transferable to chemistry on a solid support thereby making the preparation of 'intelligent libraries' possible.[13]

Results and discussion

Synthetic routes

One of the potentially most direct routes to highly functionalised 6-substituted pteridines is by the addition of organometallic reagents to pteridine 6-aldehydes or ketones which are readily available.[14] In order to carry out such reactions, it is essential to protect the 2-amino functional group. In our previous work,[15] we made extensive use of the formylimino protecting group and successfully carried out a number of Wittig reactions in moderate yield. To extend the range of products to 9-alcohols, the addition of diethylzinc to protected derivatives of pterin-6-carbaldehyde was attempted using β-aminosulfur catalysts. No reaction was observed with diethylzinc unless the 3–NH was also protected (with an allyl group) and in that case, a complex mixture was observed. Reasoning that the strongly electron-donating formylimino protecting group was deactivating the aldehyde, we investigated electron withdrawing protecting groups such as urethanes (BOC, FMOC, and ethoxycarbonyl) and more hydrophobic imines (benzylidene and 4-dimethylaminobenzylidene). In none of these cases was the required protected derivative obtained. Nevertheless, by use of 2-alkylthiopteridines, which were also of interest for the development of solid phase methodologies for the synthesis of fused pyrimidine derivatives,[16] four general or potential general synthetic routes to highly functionalised 6-substituted pteridines have been demonstrated. These are as follows: 1. cyanide catalysed *umpolung*, 2. Wittig reactions (in greatly improved variety and yield), 3. oxidation of products of Wittig reactions, and 4. α-nitrosation. It is notable, however, that in no case was a successful reaction carried out with an organometallic nucleophile whether the substrate was fully protected or not (see below).

The required 2-alkylthiopteridine 6-aldehydes were obtained by a modification of a route developed by Soyka and Pfleiderer[14] using methyl and benzyl as the alkyl groups attached to sulfur (Scheme 1). 6-Amino-2-mercaptopyrimidin-4(3*H*)-one **1** was alkylated with dimethyl sulfate or benzyl chloride to afford the thioethers **2a** and **2b** (97% and 96% respectively). 5-Nitrosation with sodium nitrite–acetic acid took place smoothly (**3a**, 85%; **3b**, 81%) and reduction of the nitroso group was best effected with sodium dithionite (**4a**, 86%; **4b**, 93%). The 5,6-diamino-2-alkylthiopyrimidinones **4a** and **4b** so prepared were condensed with D-arabinose phenylhydrazone to afford the pyranopteridines (**5a**, 59%; **5b**, 53%) as a mixture of stereoisomers. Finally, cleavage of the *gem*-diol with sodium periodate gave the required aldehydes (**6a**, 56%; **6b**, 72%).

In order to investigate the addition by organometallic reagents, methylthioether **6a** was further protected at N3 using BOC anhydride (**7a**, 36%) and allyl bromide (**7b**, 46%). As noted above, reactions with a variety of typical organometallic reagents (diethylzinc in the presence of catalyst, ethylmagnesium bromide, phenylmagnesium bromide, or *n*-butyllithium) were all unsuccessful, giving complex mixtures. It is possible that reactions at low temperature may be

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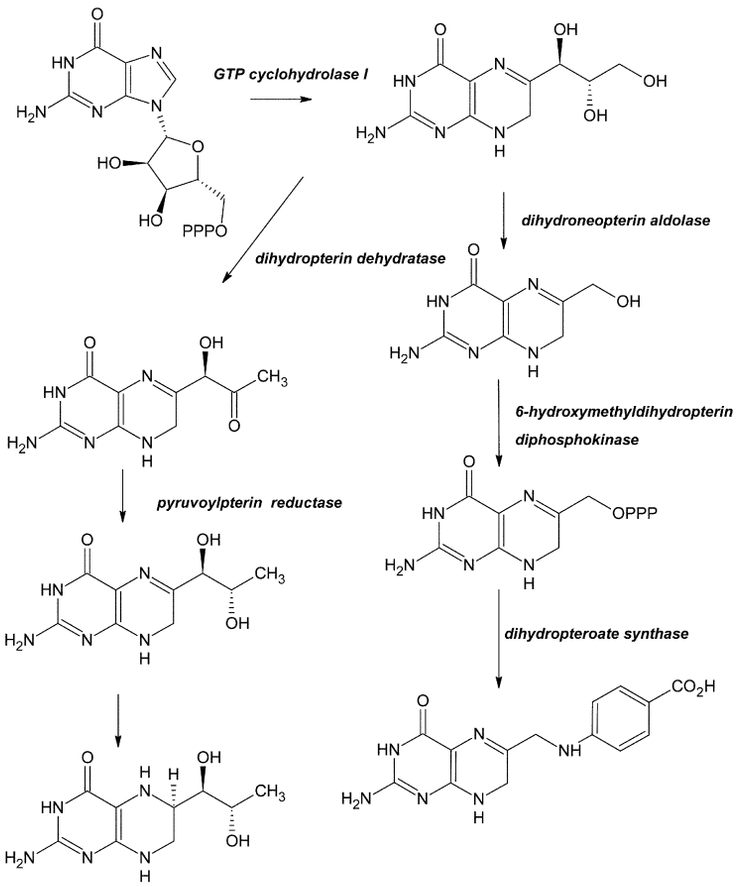
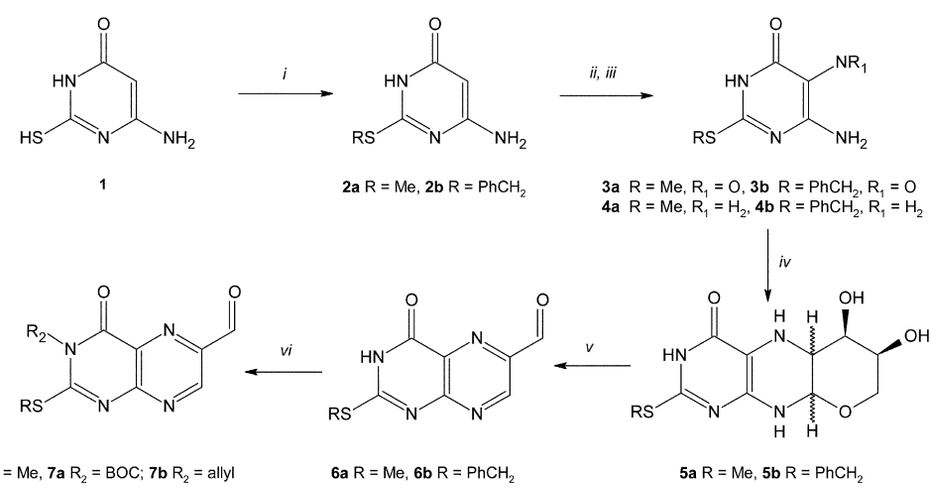
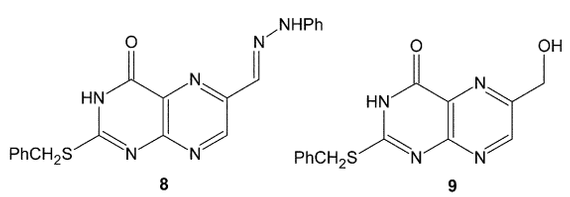


Fig. 1 Biosynthetic reactions involving highly functionalised 6-substituted pterins.

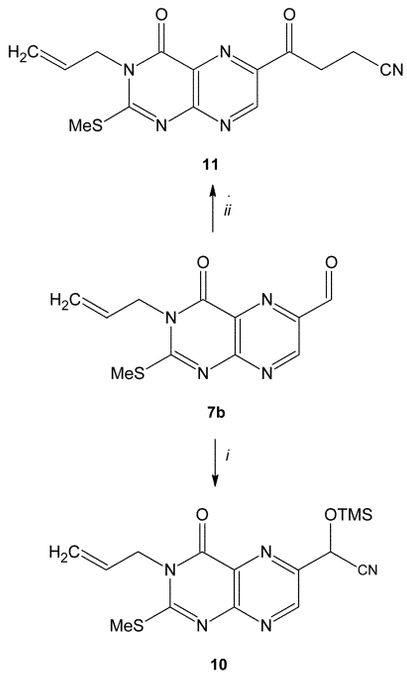


Scheme 1 *Reagents*: *i*, Me_2SO_4–NaOH or $PhCH_2Cl$–Et_3N; *ii*, $NaNO_2$–HOAc; *iii*, $Na_2S_2O_4$; *iv*, D-arabinose phenylhydrazone; *v*, $NaIO_4$; *vi*, BOC_2O–DMAP or allyl bromide–DMAP.

successful but the results were so discouraging that we wished to demonstrate that the reactivity of the 6-aldehydes in 2-alkylthiopteridine derivatives was indeed typical of aromatic aldehydes. To this end, we found that, using the 2-benzylthioether **6b** as substrate, the phenylhydrazone (**8**, 87%) and the primary alcohol (**9**, 83% using sodium borohydride) were both easily prepared.

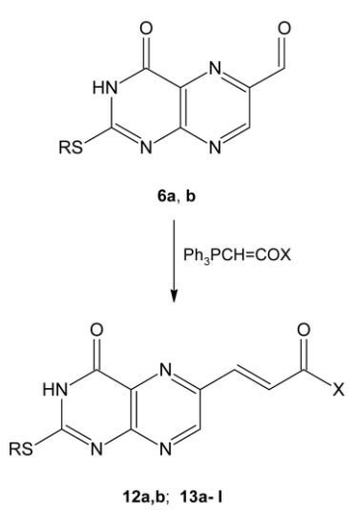


Approach 1. The above information allowed the first viable method to be investigated. 3-Allyl-protected pteridinecarbaldehyde **7b** was reacted with trimethylsilyl cyanide to afford the trimethylsilylcyanohydrin **10** in good yield (96%) (Scheme 2). However, the extension of the side chain by alkylation with reactive alkyl halides in the presence of strong bases following standard conditions caused extensive decomposition. Like organometallic reagents, strong bases (LDA, HMDS, or *n*-BuLi) appeared to be incompatible with these highly functionalised heterocyclic molecules. Fortunately, the use of catalytic quantities of sodium cyanide followed by the addition of acrylonitrile led to the Michael adduct **11** in satisfactory yield (66%). There is potential for the further development of this reaction using other soft electrophiles but the requirement for both 2- and 3-deprotection or modification is a disadvantage.



Scheme 2 *Reagents*: *i*, TMSCN; *ii*, NaCN then CH_2=CHCN.

Approach 2. With the success of the Wittig chemistry in our previous work in mind,[15] a more extensive series of Wittig reactions was investigated. Yields had been limited in our previous work due to the solubility and reactivity of the formylimino- and pivalamide-protected substrates. The ample demonstration of the reactivity of 2-alkylthiopteridine-6-carbaldehydes encouraged revisiting this reaction. Fifteen such examples have been demonstrated with yields generally in the range 60–80% (Scheme 3; Table 1). The acceptable functionality in the ylide includes aldehyde, ketone, ester, phenol, amide, vinyl bromide, and enol ether. In most cases, the required ylides were commercially available but in three cases (amide **14a**, vinyl bromides **14b** and **14c**, and enol ether **14d**) the reagents were prepared freshly before use following standard methods.[16] The yields in particular are a substantial improvement on those obtained previously[15] and the greatly improved solubility of the thioethers compared with the other derivatives greatly aids work-up and purification of products.

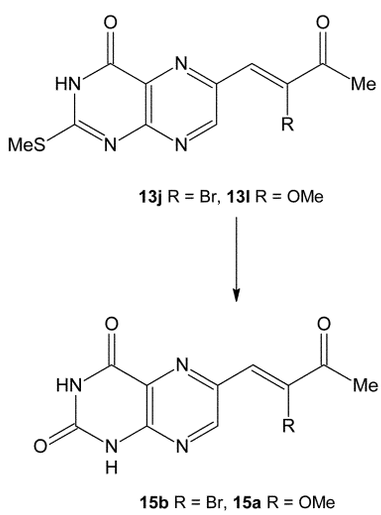


Scheme 3 Wittig reactions of petridine-6-carbaldehydes. For structures of **12** and **13**, see Table 1.

Approach 3. The logical extension to the ready availability of pteridine-6-alkenes is the further functionalisation of the alkene, in particular through hydroxylation bearing in mind the functionality in the enzyme substrates (Fig. 1). Of the products of the Wittig reactions, the bromo **13j** and the methoxy **13l** already contain additional functionality and their stability towards hydrolysis was investigated. Base-catalysed hydrolysis can be envisaged through nucleophilic attack at C10 in a Michael-type addition in which negative charge accumulates on N5. This reaction was, however, not observed in aqueous solution at up to 60 °C. The vinyl ether in **13l** would be expected to undergo hydrolysis in aqueous acid but this reaction was not observed either. Instead, the 2-alkylthio substituent was hydrolysed by 1 M aqueous hydrochloric acid to the corresponding 2-oxo derivative with the vinyl ether intact (**15a**, 85%) (Scheme 4). The bromoalkene **13j** reacted similarly affording **15b** (76%). The facile cleavage of the 2-alkylthio groups was not totally unexpected, especially in the context of developments towards solid state synthesis.[17] However in terms of preparing highly functionalised 6-substituted pteridines with substituents other than 2-oxo, it proved to be a disadvantage.

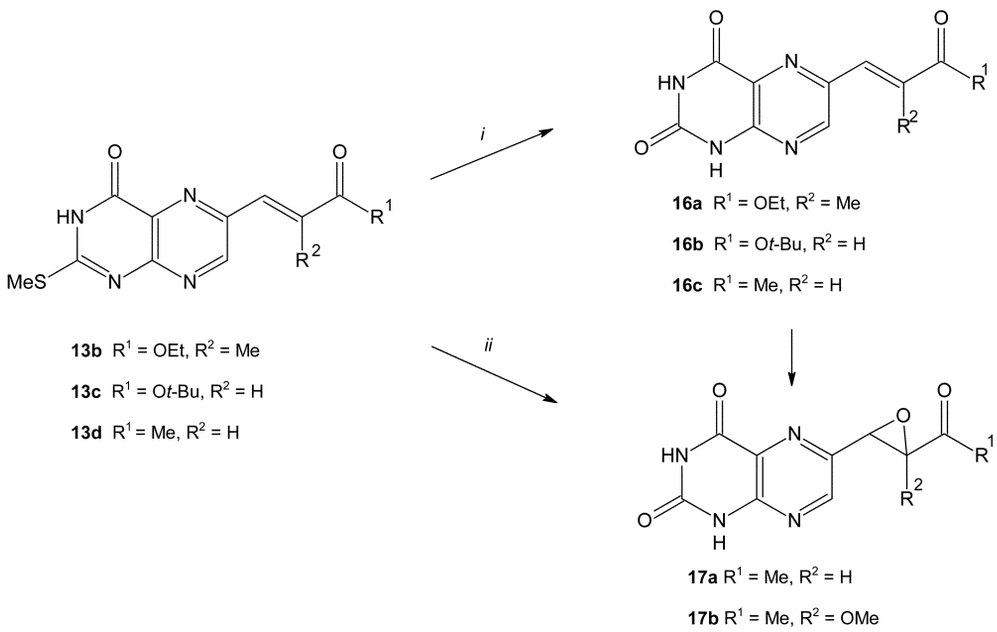
Table 1 Wittig reactions of 2-alkylthio-6-formylpteridines **6a**,**b** with reagents Ph_3P=R

Substrate	Reagent R	Product	Yield (%)
6b	$CHCO_2Me$	**12a**	52
6b	$C(Me)CO_2Me$	**12b**	82
6a	$CHCO_2Me$	**13a**	78
6a	$C(Me)CO_2Me$	**13b**	76
6a	$CHCO_2t$-Bu	**13c**	62
6a	CHCOMe	**13d**	71
6a	$CHCO(2\text{-}HOC_6H_4)$	**13e**	81
6a	CHCHO	**13f**	71
6a	$CHCOCH_2CO_2Et$	**13g**	15
6a	$CHCOCO_2Et$	**13h**	29
6a	$CHCONH_2$ (**14a**)	**13i**	13
6a	CBrCOMe (**14b**)	**13j**	71
6a	$CBrCO_2t$-Bu (**14c**)	**13k**	75
6a	C(OMe)COMe (**14d**)	**13l**	96



Scheme 4 Hydrolysis of methylthio groups in substituted alkenes **13j** and **13l**.

After unsuccessful reactions with a number of reagents (hydrogen peroxide, *m*-chloroperbenzoic acid) a thorough investigation of epoxidation using dimethyldioxirane (DDO, freshly prepared) demonstrated that it is possible to oxidise many alkenes (Table 1) to the corresponding epoxides under suitable conditions. It seems that the alkylthio group is more reactive than the alkene (which bears two electron withdrawing substituents) and, with four equivalents of DDO[18] at room temperature, the only product isolated was the 2-oxo-6-alkene (**16a**–**c**) with no trace of epoxide (Scheme 5). When greater ratios of DDO : substrate were used, the epoxide was detectable by NMR. With eight equivalents of DDO at 0° for seven days, a

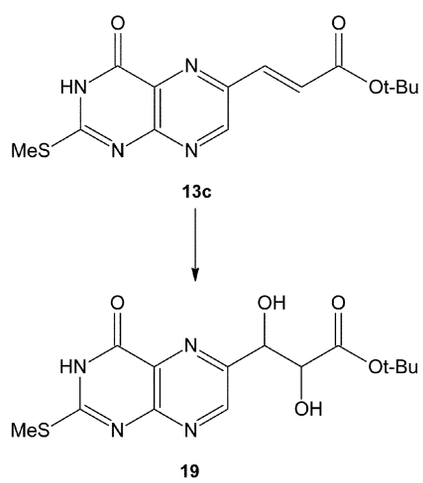


Scheme 5 Epoxidation reactions of 6-substitituted pteridine alkenes. *Reagents*: *i*, DDO 4 eq., RT, 3 d; *ii*, DDO, 8e q. 7 d, 0 °C.

good yield of 2-oxo-6-epoxide was prepared (**17a**, 93%) and was separable from the alkene. In the case of an analogous methylthioether (**13l**), the product 2-oxo-6-epoxide (**17b**, 64%) was obtained in only 16 h but was found to be unstable. The presumed route by which the 2-oxo substituent is formed in these oxidation reactions is by rapid oxidation to the 2-sulfone followed by hydrolysis. With solid phase synthesis in mind and the possibility that an additional site of diversity could be introduced by attack at C2 by nucleophiles other than water, allyl amine was tested. In two examples (**13b**,**c**), oxidation with DDO (4 equivalents) followed by the addition of allylamine afforded the 2-allylamines (**18a**,**b**) in modest yields (30%, 27%). Since allyl groups can be converted by hydrogenolysis into amino groups, this reaction opens the way to the synthesis of highly functionalised 6-substituted pterins.

The route described above is nevertheless cumbersome and lengthy. It was still important to investigate further the direct oxidation of the now accessible pteridinyl alkenes. Metal catalysed dihydroxylation reactions have been significant transformations for many years[19] and have been shown to be successful in cases of alkenes bearing electron withdrawing groups.[20] The reactions of high valent ruthenium and osmium compounds were therefore studied. Surprisingly, both the 2-methylthioethers **13b** and **13c** were resistant to oxidation by osmium tetraoxide (generated *in situ*) and flash dihydroxylation using ruthenium trichloride. However ligand assisted hydroxylation [21] using AD-mix-β successfully formed the *vic*-dihydroxy **19** derivative of **13c** in acceptable yield after a reaction time of several days (Scheme 6). The NMR spectroscopic properties of the product showed a complete absence of resonances associated with the α,β-unsaturated system and new resonances at δ 5.12 and 4.31 corresponding to the CH and δ 6.18 and 5.39 to the OH protons of the new secondary alcohols. Supporting data was obtained from ^{13}C NMR and high resolution mass spectroscopy. A bonus of this result is that it should be possible to obtain diols enantioselectively and this will be investigated. Although the absolute stereochemistry of the product **19** remains to be defined, the relative configuration of the diol can be deduced as *threo* on the basis of the known configuration of the alkene **13c** (*E*) and the stereochemical course of hydroxylation (*cis*).

Approach 4. 7-Oxopterins are significant natural products[22] and the synthesis of complex polyfunctional derivatives is also of interest in the context of the reactions of compounds shown

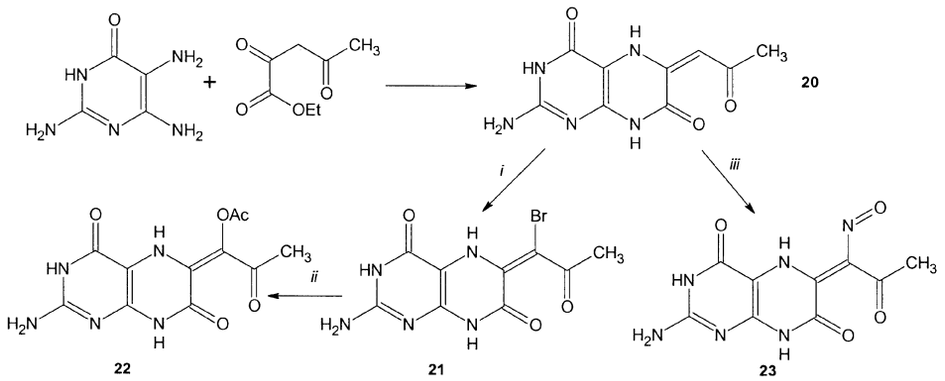


Scheme 6 Dihydroxylation of pteridinylalkene **13c** using AD-mix-β.

in Fig. 1. To exemplify a further possible strategy, we attempted to repeat an old synthesis of ichthyopterin[23] via the 9-acetoxy derivative **22** (Scheme 7). 2,5,6-Triaminopyrimidin-4(3*H*)-one was condensed with ethyl 2,4-dioxopentanoate in the presence of triethylamine to afford the pterin **20** in 64% yield. From the NMR spectrum, it was clear that this compound existed in the 6-*exo*-methylene tetrahydropterin tautomer (δ_H 6.10 (C9)). Bromination in acetic acid gave the unstable bromide **21**, which was treated with potassium acetate in the attempted preparation of **22**. Satisfactory samples for further transformation were not obtained. An alternative and very effective method of functionalisation at C9 was, however, discovered. Treatment of **20** with sodium nitrite in acetic acid afforded the 9-nitrosopterin **23** in good yield (86%). This reaction is of interest because it introduces another heteroatom (nitrogen) and provides direct access to a higher oxidation state at C9. Both of these features have potential for further development.

Conclusion

The experiments described above show that it is practical to synthesise a wide variety of pteridines with highly functionalised 6-substituents in a variety of oxidation states and positions. Both oxygen and nitrogen can be introduced. The reactions described also connect strongly with solid state approaches to the synthesis of bicyclic pyrimidine derivatives.[24]



Scheme 7 *Reagents*: i, Br_2–HOAc; *ii*, KOAc; *iii*, $NaNO_2$–HOAc.

Conventionally, it would not be expected that such highly polar molecules would have any useful biological properties. However, we and others have recently found that tetrahydrobiopterin and analogues can exert a direct effect through nitric oxide production.[25] The further investigation of such compounds is clearly justified. A more logical development of biologically active compounds would exploit the diversity available at C6 to define better the binding requirements of a target enzyme. Such a structure–activity relationship would then in principle be transposable to a series of compounds in which the substitution pattern in the pyrimidine ring was modified to make it less polar or for further alternative ring systems to replace the pyrimidine and/or pyrazine. The success of antifolates in anti-cancer therapy emphasises the validity of this approach.[26]

Experimental

Instrumentation and general materials

NMR spectra were recorded 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. 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 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). Ylides for Wittig reactions were bought from Lancaster Synthesis (Morecambe, UK) or Acros Organics (Loughborough, UK). All other reagents were bought from Aldrich (Gillingham, Dorset, UK).

6-Amino-2-(benzylthio)pyrimidin-4(3*H*)-one 2b

6-Amino-2-mercaptopyrimidin-4(3*H*)-one monohydrate **1** (8.0 g, 50 mmol) was suspended in a mixture of water (30 ml) and ethanol (50 ml). Triethylamine (10 g, 13.8 ml, 0.1 mol) was added, with stirring, and all the starting material dissolved. Benzyl chloride (6.4 ml, 7.0 g, 55 mmol) was added to the stirring solution. Within a few minutes, an exothermic reaction occurred with formation of a colourless precipitate. Stirring was continued for 30 min, and the mixture was cooled to 4 °C. After 20 min the precipitate was collected by filtration and washed with water and ether to afford the title compound as a white solid (11.2 g, 48 mmol, 96%), mp 248–253 °C. Found: (HREIMS): 233.0614. $C_{11}H_{11}N_3OS$ (M + 1) requires 233.0623. ν_{max}(KBr) 3448, 3300, 1638, 1602, 1448, 1570, 1220, 982, 821 cm^{-1}; δ_H(DMSO) 4.33 [2H, s, C(7)H_2], 4.96 [1H, s, C(5)H], 6.54 [2H, br s, N(12)H_2], 7.27 [3H, m, 2 × C(9)H & C(11)H], 7.42 [2H, s, 2 × C(10)H], 11.48 [1H, br s, N(3)H]; δ_C(DMSO) 33.7 [C(7)], 81.7 [C(5)], 127.45 [C(11)], 128.76 [C(9)], 129.47 [C(10)], 138.30 [C(8)], 162.62 [C(2)], 163.98 [C(4)], 165.03 [C(6)]; λ_{max}(DMF) 271 nm.

6-Amino-2-(methylthio)-5-nitrosopyrimidin-4(3*H*)-one 3a[27]

6-Amino-2-(methylthio)pyrimidin-4(3*H*)-one **2a** (20.0 g, 127 mmol) was dissolved in a solution of sodium hydroxide (5.10 g, 127 mmol) in water (350 ml) at room temperature. A solution of sodium nitrite (10.0 g, 145 mmol) was added. The yellow solution was then acidified by the gradual addition of glacial acetic acid (17.0 g, 283 mmol, 16.2 ml). A white precipitate formed almost immediately, which turned blue on leaving overnight at room temperature. The precipitate was collected by filtration, washed with water, methanol and ether (20.1 g, 108 mmol, 85%), mp >240 °C, lit.[27] decomp. >255 °C. Found: C, 32.3; H, 3.2; N, 30.1; S, 17.0. $C_5H_6N_4O_2S$ requires C, 32.25; H, 3.25; N, 30.09; S, 17.22%. Found (FABMS: NBA–glycerol matrix): 187.0305. $C_5H_7N_4O_2S$ (M + 1) requires 187.0290. ν_{max}(KBr) 3170 (br), 3004, 2896, 2723, 1683, 1631, 1555, 1504, 1472 cm^{-1}; δ_H(DMSO) 2.53 [3H, s, C(7)H_3], 9.04 [1H, br s, 1 × N(8)H], 11.26 [1H, br s, 1 × N(8)H], 12.67 [1H, br s, N(3)H]; δ_C(DMSO) 13.49 [C(7)], 143.40 [C(6)], 147.27 [C(5)], 161.53 [C(2)], 168.90 [C(4)]; λ_{max}(MeOH) 343, 270 nm.

6-Amino-2-(benzylthio)-5-nitrosopyrimidin-4(3*H*)-one 3b

6-Amino-2-(benzylthio)pyrimidin-4(3*H*)-one **2b** (21.5 g, 92 mmol) was partially dissolved in a solution of sodium hydroxide (5.10 g, 127 mmol) in water (350 ml) at room temperature. A solution of sodium nitrite (7.77 g, 113 mmol) was added. The yellow solution was then acidified by the gradual addition of glacial acetic acid (17.0 g, 283 mmol, 16.2 ml). A white precipitate formed almost immediately, which gradually turned blue on leaving stirring at room temperature for 7 days. The precipitate was collected by filtration, and washed with water and ether to afford the title compound as a blue solid (19.5 g, 75 mmol, 81%), mp 185–187 °C. Found (FABMS: NBA–glycerol matrix) 263.0586. $C_{11}H_{11}N_4O_2S$ (M + 1) requires 263.0603. ν_{max}(KBr) 3401 (br), 3233, 3068, 2905, 1685, 1668, 1626, 1557, 1498, 1464, 1450, 1331, 1319, 1282, 1277, 1189 cm^{-1}; δ_H(DMSO) 4.44 [2H, s, C(7)H_2], 7.28 [3H, m, 2 × C(9)H & C(11)H], 7.45 [2H, m, 2 × C(10)H], 9.04 [1H, br s, 1 × N(12)H], 11.22 [1H, br s, 1 × N(12)H], 12.72 [1H, br s, N(3)H]; δ_C(DMSO) 34.68 [C(7)], 128.30 [C(11)], 129.37 [C(10)], 130.13 [C(9)], 137.88 [C(8)], 144.06 [C(5)], 147.86 [C(2)], 162.78 [C(6)], 168.81 [C(4)]; λ_{max}(MeOH) 343, 283 nm.

5,6-Diamino-2-(methylthio)pyrimidin-4(3*H*)-one 4a

a) By reduction with ammonium sulfide.[27] Ammonium sulfide (10% aq. soln., 50 ml, 73 mmol) was heated on a steam bath. 6-Amino-2-(methylthio)-5-nitrosopyrimidin-4(3*H*)-one **3a** (22.7 g, 122 mmol) was added slowly. When the solution turned

red further ammonium sulfide (10% aq. pyrimidin-4(3*H*)-one, 50 ml, 73 mmol) was added and the solution was heated on the steam bath for 45 min. Sulfur separated after the reduction had proceeded for a few minutes. When the reduction was complete, as indicated by a yellow solution due to an excess of ammonium sulfide, the solution was concentrated to approx. 80 ml by heating over a Bunsen burner. The hot solution was then quickly filtered to remove the precipitated sulfur. On cooling, a white precipitate of **4a** formed which was collected by filtration and washed with water, acetone and ether (14.3 g, 83 mmol, 68%), mp 198–201 °C, lit.[27] 198 & 211 °C. Found (FAB: NBA–glycerol matrix): 173.0497. $C_5H_9N_4OS$ (M + 1) requires 173.0497. ν_{max}(KBr) 3447 (br), 3360, 3193, 1666, 1636, 1598, 1425, 1350, 1276 cm^{-1}; δ_H(DMSO) 2.44 [3H, s, C(7)H_3], 5.74 [2H, br s, NH_2]; δ_C(DMSO) 13.16 [C(7)], 105.60 [C(5)], 149.09 [C(2) or C(6)], 149.24 [C(2) or C(6)], 157.79 [C(4)]; λ_{max}(MeOH) 297 nm.

b) By reduction with sodium dithionite.[28] Powdered 6-amino-2-(methylthio)-5-nitrosopyrimidin-4(3*H*)-one **3a** (40.7 g, 219 mmol) was added to a stirring solution of sodium hydroxide (26.2 g, 655 mmol) in water (500 ml). Sodium dithionite (80.0 g, 463 mmol) was added slowly to the rapidly stirring suspension. Stirring was continued for 16 h at room temperature, the resulting mixture was cooled to 4 °C, and the white precipitate collected by filtration and washed with water. The title compound was obtained as a white solid (32.4 g, 188 mmol, 86%) identical to the compound characterised above.

5,6-Diamino-2-(benzylthio)pyrimidin-4(3*H*)-one 4b

A solution of sodium dithionite (1.60 g, 9.20 mmol) in H_2O (16 ml) was added to a suspension of 6-amino-2-(benzylthio)-5-nitrosopyrimidin-4(3*H*)-one **3b** (0.42 g, 1.60 mmol) in methanol (16 ml) at room temperature. After stirring for 40 min the precipitate went from blue to white. The precipitate was collected by filtration and washed with water, acetone and ether to afford **4b** as a white solid (369 mg, 1.49 mmol, 93%), mp 185–187 °C. Found (FABMS: NBA–glycerol matrix): 249.0810. $C_{11}H_{13}N_4OS$ (M + 1) requires 249.0810. ν_{max}(KBr) 3465 (br), 3366, 3346, 1654, 1626, 1598, 1558, 1521, 1495, 1465, 1355, 1221 cm^{-1}; δ_H(DMSO) 4.31 [2H, s, C(7)H_2], 5.82 [2H, br s, N(13)H_2], 7.26 [3H, m, 2 × C(9)H & C(11)H], 7.44 [2H, s, 2 × C(10)H]; δ_C(DMSO) 33.98 [C(7)], 106.84 [C(5)], 127.45 [C(11)], 128.74 [C(9)], 129.43 [C(10)], 138.57 [C(8)], 148.29 [C(2) or C(6)], 149.22 [C(2) or C(6)], 157.71 [C(4)]; λ_{max}(MeOH) 298 nm.

(6*R*,7*S*)-6,7-Dihydroxy-2-(methylthio)-3,5,5a,6,7,8,9a,10-octahydro-4*H*-pyrano[3,2-*g*]pteridin-4-one 5a

5,6-Diamino-2-(methylthio)pyrimidin-4(3*H*)-one **4a** (3.45 g, 20.0 mmol), freshly prepared D-arabinose phenylhydrazone[29] (6.00 g, 25.0 mmol) and HCl (5 M, 6 ml) were added to a MeOH–H_2O solution (360 ml, 1 : 1). When all the reagents had dissolved, the yellow solution was heated to reflux for 45 min. The resulting black solution was allowed to cool slowly to room temperature and then cooled to 0 °C. The brown precipitate was collected by filtration, washed with water, acetone and ether. The title compound was obtained as brown crystals, which consisted of a mixture of the 2 stereoisomers **a** and **b**, (3.38 g, 11.8 mmol, 59%), mp 223–226 °C, lit.[30] 247 °C. Found (FABMS: glycerol–NBA matrix): 287.0811. $C_{10}H_{15}N_4O_4S$ (M + 1) requires 287.0814. ν_{max}(KBr) 3298 (br), 2896, 2781, 2717, 1645, 1606, 1543, 1466, 1345, 1294, 1255 cm^{-1}; δ_H(DMSO) 2.41 & 2.44 [2 × 3H, 2 × s, C(11)H_3 of **a** & **b**], 3.06 [1H, br s, C(5a)H of **a**], 3.16 [1H, br s, C(5a)H of **b**], 3.54 [4H, m, C(8)H_2 of **a** & **b**], 3.74 [2H, m, C(6)H & C(7)H of **b**], 3.87 [1H, m, C(7)H of **a**], 3.98 [1H, br s, C(6)H of **a**], 4.15 [1H, br s, N(5)H of **b**], 4.28 [1H, d, *J* = 9.8 Hz, C(7)OH of **b**], 4.36 [br s, N(5)H of **a**], 4.59 [1H, d, *J* = 6.5, C(7)OH of **a**], 4.71 [1H, d, *J* = 4.9 Hz, C(9a)H of **a**], 4.84 [2H, m, C(9a)H & C(6)OH of **a**], 5.45 [1H, d, *J* = 5.44 Hz, C(6)OH of **b**], 7.21 [1H, d, *J* = 4.4 Hz, N(10)H of **a**], 7.70 [1H, d, *J* = 4.9 Hz, N(10)H of **b**], 12.04 [2H, br s, N(3)H of **a** and **b**]; δ_C(DMSO)[27] 13.24 [C(11) of **a** & **b**], 53.87 [C(5a) of **a**], 54.87 [C(5a) of **b**], 64.16 [C(7) of **a**], 65.39 [C(8) of **a**], 68.24 [C(7) of **b**], 68.48 [C(8) of **b**], 68.58 [C(6) of **a**], 68.76 [C(6) of **b**], 76.40 [C(9a) of **a**], 79.29 [C(9a) of **b**], 104.97 [C(4a) of **b**], 106.81 [C(4a) of **a**], 145.77 [C(10a) of **a**], 147.01 [C(10a) of **b**], 150.04 [C(2) of **a**], 152.26 [C(2) of **b**], 156.30 [C(4) of **a**], 156.79 [C(4) of **b**; λ_{max}(0.1 M NaOH) 272 nm.

(6*R*,7*S*)-2-(Benzylthio)-6,7-dihydroxy-3,5,5a,6,7,8,9a,10-octahydro-4*H*-pyrano[3,2-*g*]pteridin-4-one 5b

5,6-Diamino-2-(benzylthio)pyrimidin-4(3*H*)-one **4b** (3.50 g, 14.1 mmol), freshly prepared D-arabinose phenylhydrazone (4.14 g, 17.2 mmol) and HCl (5 M, 4 ml) were added to a MeOH–H_2O solution (240 ml, 1 : 1). When most of the reagents had dissolved, the solution was heated under reflux for 45 min. The resulting mixture was allowed to cool slowly to room temperature and then cooled to 0 °C. The precipitate was collected by filtration, washed with water, acetone and ether. The title compound **5b** was obtained as a pink solid which consisted of a 1 : 1 mixture of stereoisomers **a** and **b** (2.70 g, 7.5 mmol, 53%), mp >240 °C. Found (FAB: glycerol matrix): 287.0811. $C_5H_8N_3OS$ (M + 1) requires 287.0814. ν_{max}(KBr) 3576 (br), 3303, 2870, 2704, 1639, 1602, 1541, 1469, 1336, 1296, 1243 cm^{-1}; δ_H(DMSO)[27] 3.08 [1H, m, C(5a)H of **a**], 3.18 [1H, m, C(5a)H of **b**], 3.43 [2H, m, C(8)H_2 of **a**], 3.56 [5H, m, C(7)H of **a**, C(8)H_2, C(7)H & C(6)H of **b**], 3.71 [2H, m, N(5)H & C(6)H of **a**], 3.87 [1H, m, C(7)OH of **b**], 3.98 [1H, br s, N(5)H of **b**], 4.15 [1H, m, C(7)OH of **a**], 4.37 [5H, m, C(11)H_2 of **a**, C(11)H_2 & C(9a)H of **b**], 4.68 [1H, d, *J* = 4.8 Hz, C(9a)H of **a**], 4.86 [1H, m, C(6)OH of **a**], 5.32 [1H, m, C(6)OH of **b**], 7.28 [7H, m, N(10)H, 2 × C(13)H & C(15)H of **a**, 2 × C(13)H & C(15)H of **b**], 7.46 [4H, m, 2 × C(14)H of **a**, 2 × C(14)H of **b**], 12.00 [2H, br s, N(3)H of **a**, N(3)H of **b**]; δ_C(DMSO) [27] 33.90 & 33.96 [C(11) of **a** & **b**], 53.76 [C(5a) of **b**], 54.05 [C(5a) of **a**], 64.11 [C(7) of **a**], 65.36 [C(8) of **a**], 68.28 [C(7) of **b**], 68.47 [C(8) of **b**], 68.58 [C(6) of **a**], 68.73 [C(6) of **b**], 76.35 [C(9a) of **a**], 79.30 [C(9a) of **b**], 105.45 [C(4a) of **b**], 107.22 [C(4a) of **a**], 127.50 & 127.56 [C(15) of **a** & **b**], 128.76 & 128.79 [C(13) of **a** & **b**], 129.44 & 129.47 [C(14) of **a** & **b**], 138.22 & 138.39 [C(12) of **a** & **b**], 145.75 [C(10a) of **a**], 146.85 [C(10a) of **b**], 148.77 [C(2) of **a**], 150.73 [C(2) of **a**], 156.19 [C(4) of **a**], 156.72 [C(4) of **b**]; λ_{max}(MeOH) 317, 291 nm.

2-(Methylthio)-4-oxo-3,4-dihydropteridine-6-carbaldehyde 6a[14]

A solution of $NaIO_4$ (16.10 g, 75.3 mmol) in H_2O (170 ml) was added dropwise to a suspension of **5a** (6.50 g, 22.7 mmol) in H_2O (200 ml) at 0–5 °C. Stirring was continued for 2 h. The grey precipitate was collected by filtration and washed with H_2O, acetone and ether. The beige solid was dried *in vacuo* at 120 °C for 4 h (2.83 g, 12.7 mmol, 56%), mp >240 °C, lit.[14] 258–261 °C. Found: C, 42.9; H, 2.6; N, 24.8; S, 14.7. $C_8H_6N_4O_2S$ requires C, 43.24; H, 2.72; N, 25.21; S, 14.43%. Found: (FABMS: glycerol matrix) 223.0273. $C_8H_7N_4O_2S$ (M + 1) requires 223.0290. ν_{max}(KBr) 3081 (br), 2902, 1728, 1696 (C=O), 1550, 1520, 1485, 1377, 1353, 1328, 1274, 1250 cm^{-1}; δ_H(DMSO) 2.63 [3H, s, C(9)H_3], 9.24 [1H, s, C(7)H], 10.07 [1H, s, C(10)H], 13.36 [1H, br s, N(3)H]; δ_C(DMSO) 13.81 [C(9)], 132.40 [C(4a)], 144.33 [C(6)], 148.38 [C(7)], 156.56 [C(2)], 159.98 [C(8a)], 165.37 [C(4)], 191.75 [C(10)]; λ_{max}(MeOH) 334, 277 nm.

2-(Benzylthio)-4-oxo-3,4-dihydropteridine-6-carbaldehyde 6b

A solution of sodium periodate (17.8 g, 83.2 mmol) in H_2O (180 ml) was added dropwise to a stirring suspension of **5b** (9.42 g, 26.0 mmol) in H_2O (200 ml) at room temperature. After 2 h the suspension was extracted with dichloromethane (4 × 100 ml). The combined organic extracts were dried ($MgSO_4$),

and concentrated under reduced pressure. The resulting solid was purified by flash column chromatography (gradient $CH_2Cl_2 \rightarrow CH_2Cl_2$: MeOH 97 : 3) to afford **6b** as a yellow solid (5.58 g, 18.7 mmol, 72%), mp 207–210 °C. Found (FABMS: glycerol matrix): 299.0591. $C_{14}H_{11}N_4O_2S$ (M + 1) requires 299.0603. ν_{max}(KBr) 3070, 3032, 2872, 2826, 1711, 1691 (C=O), 1577, 1546, 1529, 1492, 1453, 1373, 1288, 1245 cm^{-1}; $\delta_H(CDCl_3)$ 4.66 [2H, s, C(9)H_2], 7.32 [3H, m, 2 × C(11)H & C(13)H], 7.45 [2H, m, C(12)H], 9.44 [1H, s, C(7)H], 10.24 [1H, s, C(14)H], 11.63 [1H, br s, N(3)H]; $\delta_C(CDCl_3)$ 36.30 [C(9)], 128.37 [C(13)], 129.09 [C(11)], 129.54 [C(12)], 131.57 [C(4a)], 134.94 [C(10)], 144.94 [C(6)], 149.13 [C(7)], 156.93 [C(2)], 160.87 [C(8a)], 164.20 [C(4)], 190.86 [C(14)]; λ_{max}(MeOH) 340, 278 nm.

tert-Butyl 6-formyl-2-(methylthio)-4-oxo-4*H*-pteridine-3-carboxylate 7a

4-Dimethylaminopyridine (55 mg, 0.45 mmol) was added to a stirring suspension of 2-(methylthio)-4-oxo-3,4-dihydropteridine-6-carbaldehyde **6a** (100 mg, 0.45 mmol) in dichloromethane (10 ml) under a nitrogen atmosphere at room temperature. When all the reagents had dissolved, *tert*-butoxycarbonyl anhydride (196 mg, 0.90 mmol) was added to the orange solution, and the mixture was stirred at room temperature for 24 h. The red solution was then washed with 1 M HCl (3 × 25 ml), and brine. The organic solution was dried, treated with activated charcoal and concentrated *in vacuo*. The title compound was obtained as a red solid (51 mg, 0.16 mmol, 36%), mp 142–145 °C. Found (FABMS: glycerol matrix): 323.0807. $C_{13}H_{15}N_4O_4S$ (M + 1) requires 323.0814. ν_{max}(KBr) 2982, 2929, 2844, 1748, 1703 (C=O), 1572, 1530, 1471, 1456, 1372, 1363, 1262, 1161 cm^{-1}; $\delta_H(CDCl_3)$ 1.82 [9H, s, 3 × C(13)-H_3], 2.68 [3H, s, C(9)H_3], 9.48 [1H, s, C(7)H], 10.22 [1H, s, C(10)H]; $\delta_C(CDCl_3)$ 15.47 [C(13)], 28.57 [C(9)], 87.48 [C(12)], 126.81 [C(4a)], 131.99 [C(11)], 145.03 [C(6)], 149.31 [C(7)], 156.95 [C(2)], 165.61 [C(8a)], 176.95 [C(4)], 191.48 [C(10)]; $\lambda_{max}(CH_2Cl_2)$ 342, 315, 265 nm.

3-Allyl-2-(methylthio)-4-oxo-3,4-dihydropteridine-6-carbaldehyde 7b

2-(Methylthio)-4-oxo-3,4-dihydro-6-pteridinecarbaldehyde **6a** (1.00 g, 4.50 mmol) was added to a stirring solution of 4-dimethylaminopyridine (0.55 g, 4.50 mmol), triethylamine (0.46 g, 0.63 ml, 4.50 mmol) and allyl bromide (1.63 g, 1.17 ml, 13.5 mmol) in dichloromethane (20 ml) under a nitrogen atmosphere at room temperature. The orange solution was left stirring at room temperature for 48 h. The resulting black solution was washed with 1 M HCl (4 × 50 ml), and brine (30 ml). The organic solution was dried and treated with decolourising charcoal. The dichloromethane was removed under reduced pressure and the resulting yellow gum was purified twice by dissolving in the minimum of dichloromethane and precipitating **7b** as a yellow solid by the addition of hexane (0.56 g, 2.2 mmol, 48%), mp 105–107 °C. Found: C, 50.3; H, 3.8; N, 21.1; S, 12.4. $C_{11}H_{10}N_4O_2S$ requires C, 50.37; H, 3.84; N, 21.36; S, 12.23%. Found (FABMS: glycerol matrix): 263.0615. $C_{11}H_{11}N_4O_2S$ (M + 1) requires 263.0603. ν_{max}(KBr) 2986, 2947, 2840, 2365, 2344, 1703 (C=O), 1673, 1647, 1578, 1542, 1511, 1459, 1439, 1377, 1225 cm^{-1}; $\delta_H(CDCl_3)$ 2.79 [3H, s, C(9)H_3], 4.86 [2H, d, J = 1.36 Hz, C(11)H_2], 5.31 [2H, m, C(13)H_2], 5.93 [1H, m, C(12)H_2], 9.23 [1H, s, C(7)H], 10.27 [1H, s, C(10)H]; $\delta_C(CDCl_3)$ 16.01 [C(9)], 47.53 [C(11)], 120.66 [C(13)], 129.27 [C(12)], 130.48 [C(4a)], 145.00 [C(6)], 148.94 [C(7)], 155.08 [C(2)], 159.58 [C(8a)], 166.85 [C(4)], 191.09 [C(10)]; $\lambda_{max}(CH_2Cl_2)$ 340, 310, 275 nm.

2-(Benzylthio)-4-oxo-3,4-dihydropteridine-6-carbaldehyde phenylhydrazone 8

Phenylhydrazine (39 mg, 0.36 mmol) was added to a solution of 2-(benzylthio)-4-oxo-3,4-dihydropteridine-6-carbaldehyde **6b** (70 mg, 0.23 mmol) in methanol (10 ml) at room temperature. The solution was stirred overnight, whereupon an orange precipitate formed, which was collected by filtration and washed with methanol and ether (77 mg, 0.20 mmol, 87%), mp 198–201 °C. Found: C, 59.2; H, 4.4; N, 20.5; S, 8.0. $C_{20}H_{16}N_6OS \cdot H_2O$ requires C, 59.10; H, 4.46; N, 20.68; S, 7.89%. Found (FABMS: glycerol–NBA matrix): 389.1188. $C_{20}H_{17}N_6OS$ (M + 1) requires 389.1185. ν_{max}(KBr) 3241 (br), 3057, 2989, 2901, 2819, 1679, 1599, 1566, 1492, 1470, 1356, 1268 cm^{-1}; δ_H(DMSO) 4.54 [2H, s, C(9)H_2], 6.87 [1H, m, C(20)H], 7.36 [9H, m, 2 × C(11)H, 2 × C(12)H, C(13)H, 2 × C(18)H, 2 × C(19)H], 7.96 [1H, s, C(7)H], 9.42 [1H, s, C(14)H], 11.09 [1H, s, N(16)H], 13.07 [1H, br s, N(3)H]; δ_C(DMSO) 34.42 [C(9)], 113.17 [C(18)], 120.76 [C(20)], 127.89 [C(11) or C(12) or C(13) or C(19)], 128.99 [C(11) or C(12) or C(13) or C(19)], 129.64 [C(11) or C(12) or C(13) or C(19)], 129.75 [C(11) or C(12) or C(13) or C(19)], 131.25 [C(4a)], 133.95 [C(14)], 137.21 [C(10)], 144.45 [C(17)], 147.22 [C(7)], 148.62 [C(6)], 153.46 [C(2)], 159.47 [C(8a)], 160.78 [C(4)]; λ_{max}(MeOH) 409, 280 nm.

2-(Benzylthio)-6-(hydroxymethyl)pteridin-4(3*H*)-one 9

Sodium borohydride (15.4 mg, 0.41 mmol) was added to a stirring solution of 2-(benzylthio)-4-oxo-3,4-dihydropteridine-6-carbaldehyde **6b** (100 mg, 0.34 mmol) in THF–water (1 : 1 mixture, 10 ml) at room temperature under a nitrogen atmosphere. The yellow solution was stirred for 2 h and then acidified with HCl (1 M aq. solution, 5 ml). The volatiles were removed under reduced pressure and the resulting aqueous suspension was extracted with dichloromethane (4 × 15 ml). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to afford **9** as a green solid (84 mg, 0.28 mmol, 83%), mp 105–108 °C. Found (FABMS: glycerol matrix): 301.0765. $C_{14}H_{13}N_4O_2S$ (M + 1) requires 301.0759. ν_{max}(KBr) 3408 (br, OH & NH), 3188, 3064, 2957, 2922, 1706, 1686, 1578, 1534, 1495, 1452, 1365 cm^{-1}; δ_H(DMSO) 4.54 [2H, s, C(9)H_2], 4.72 [2H, s, C(14)H_2], 7.30 [3H, m, 2 × C(11)H & C(13)H], 7.50 [2H, m, 2 × C(12)H], 8.97 [1H, s, C(7)H], 13.12 [1H, br s, N(3)H]; δ_C(DMSO) 34.34 [C(9)], 63.06 [C(14)], 127.81 [C(13)], 128.91 [C(11)], 129.57 [C(12)], 130.95 [C(4a)], 137.21 [C(10)], 148.69 [C(7)], 153.79 [C(2)], 155.65 [C(6)], 160.73 [C(8a)], 164.87 [C(4)]; λ_{max}(MeOH) 281, 333 nm.

[3-Allyl-2-(methylthio)-4-oxo-3,4-dihydropteridin-6-yl]-[(trimethylsilyl)oxy]acetonitrile 10

Trimethylsilyl cyanide (0.07 ml, 55 mg, 0.55 mmol) was added to a stirring solution of 3-allyl-2-(methylthio)-4-oxo-3,4-dihydropteridine-6-carbaldehyde **7b** (120 mg, 0.46 mmol) in acetonitrile (7 ml) under a nitrogen atmosphere. The solution was heated at reflux under nitrogen for 24 h. The resulting red solution was concentrated under reduced pressure to afford **10** as a red solid (141 mg, 0.44 mmol, 96%), mp 84–88 °C (decomp.). Found (FAB: glycerol–NBA matrix): 362.1094. $C_{15}H_{20}N_5O_2SiS$ (M + 1) requires 362.1107. ν_{max}(KBr) 2966, 2928, 2392 (C≡N), 1706, 1647, 1572, 1467, 1436, 1389, 1323 cm^{-1}; $\delta_H(CDCl_3)$ 0.30 [9H, s, 3 × C(10)H_3], 2.78 [3H, s, C(11)H_3], 4.86 [2H, m, C(13)H_2], 5.35 [2H, m, C(15)H_2], 5.82 [1H, s, C(9)H], 5.95 [1H, m, C(14)H], 9.19 [1H, s, C(7)H]; $\delta_C(CDCl_3)$ 2.15 [C(10)], 15.87 [C(11)], 47.39 [C(13)], 64.01 [C(9)], 117.66 [C(12)], 120.37 [C(15)], 129.55 [C(14)], 148.03 [C(4a)], 148.85 [C(7)], 149.35 [C(6)], 153.31 [C(8a)], 159.84 [C(2)], 164.68 [C(4)]; $\lambda_{max}(CH_2Cl_2)$ 338, 304, 271 nm.

4-[3-Allyl-2-(methylthio)-4-oxo-3,4-dihydropteridin-6-yl]-4-oxobutanenitrile 11

Sodium cyanide (2 mg, 0.04 mmol) was added to a stirring solution of 3-allyl-2-(methylthio)-4-oxo-3,4-dihydropteridine-6-carbaldehyde **7b** (100 mg, 0.38 mmol) in anhydrous DMF (15 ml) under a nitrogen atmosphere at room temperature. The

solution was stirred for 2 h at 35 °C, whereupon an orange precipitate formed. Acrylonitrile (20.2 mg, 25 μl, 0.38 mmol) was then added and stirring continued for 3 h. Acetic acid (4 drops) was added to the solution and stirring continued for a further 5 min. The volatiles were removed under reduced pressure. The residue was dissolved in dichloromethane (1 ml) and precipitated with hexane (100 ml). The precipitate was collected by suction filtration and washed with hexane to afford the title compound as an orange solid (60 mg, 0.25 mmol, 66%), mp 97–99 °C (decomp.). Found (FABMS: glycerol–NBA matrix): 316.3589. $C_{14}H_{13}N_5O_2S$ (M + 1) requires 316.3595. ν_{max}(KBr) 2974, 2935, 2343 (C≡N), 1706, 1653, 1580, 1389 cm^{-1}; δ_H(DMSO) 2.70 [3H, s, C(9)H_3], 2.88 [2H, m, C(15)H_2], 3.11 [2H, m, C(14)H_2], 4.75 [2H, m, C(11)H_2], 5.28 [2H, m, C(13)-H_2], 5.93 [1H, m, C(12)H], 9.35 [1H, s, C(7)H]; δ_C(DMSO) 15.50 [C(11)], 19.81 [C(15)], 26.79 [C(14)], 46.98 [C(11)], 118.19 [C(13)], 121.05 [C(16)], 128.75 [C(4a)], 130.93 [C(12)], 141.71 [C(6)], 150.88 [C(7)], 154.00 [C(2)], 159.55 [C(8a)], 194.32 [C(10)].

Wittig reagents

(2-Amino-2-oxoethyl)(triphenyl)phosphonium chloride.[16a] A stirring solution of 2-chloroacetamide (1.90 g, 20.3 mmol) and triphenylphosphine (5.20 g, 19.8 mmol) in nitroethane (50 ml) was heated to 100 °C for 16 h under a nitrogen atmosphere. The resulting clear solution was then allowed to cool to room temperature. On standing at room temperature for 3 h a white precipitate formed which was collected by filtration and washed with nitroethane (5.93 g, 16.7 mmol, 84%), mp 222–226 °C, lit.[16a] 227–229 °C. Found: C, 64.5; H, 5.7; N, 3.8; Cl, 9.6; P, 8.3. $C_{20}H_{19}ClNOP{\cdot}H_2O$ requires C, 64.26; H, 5.66; N, 3.75; Cl, 9.48; P, 8.29%. ν_{max}(KBr) 3430, 3170, 2951, 2900, 1685, 1645, 1616, 1440, 1116, 755 cm^{-1}, δ_H(DMSO) 5.17 [2H, d, $J_{P\text{-}H}$ = 14.9 Hz, C(1)H_2], 7.61 [1H, br s, 1 × N(3)H_2], 7.80 [15H, m, 6 × C(5)H, 6 × C(6)H & 3 × C(8)H], 8.54 [1H, br s, 1 × N(3)H_2]; δ_C(DMSO) 31.56 [d, $J_{(P\text{-}C)}$ = 57.9 Hz, C(1)], 119.53 [d, $J_{(P\text{-}C)}$ = 88.7 Hz, C(4)], 130.33 [d, $J_{(P\text{-}C)}$ = 12.9 Hz, C(6)], 134.22 [d, $J_{(P\text{-}C)}$ = 10.7 Hz, C(5)], 135.13 [d, $J_{(P\text{-}C)}$ = 2.9 Hz, C(7)], 165.40 [d, $J_{(P\text{-}C)}$ = 4.9 Hz, C(2)].

2-(Triphenylphosphoranylidene)acetamide 14a.[16b] NaOH (1.00 M aq. soln., 6.00 ml, 6.00 mmol) was added to a stirring solution of (2-amino-2-oxoethyl)(triphenyl)phosphonium chloride (2.10 g, 5.90 mmol) in H_2O (50 ml) at 4 °C. The resulting precipitate was collected rapidly by filtration and washed with a little cold H_2O. The title compound was obtained as a white solid, which decomposed rapidly to triphenylphosphine oxide and acetamide in the presence of hydroxylic solvents. Also, the ^1H and ^{13}C NMR spectra in DMSO or $CDCl_3$ demonstrated that a mixture of triphenylphosphine oxide and acetamide were present. Hence, the title compound could only be confirmed by mass spectral analysis (1.49 g, 4.66 mmol, 79%), mp 153–155 °C (PPh_3O 156–158 °C, lit.[16a] 177–178 °C). Found (FABMS: glycerol matrix): 320.1204. $C_{20}H_{19}NOP$ (M + 1) requires 320.1204.

1-Bromo-1-(triphenylphosphoranylidene)acetone 14b. Bromine (0.50 g, 0.16 ml, 3.14 mmol) was added dropwise to a solution of 1-(triphenylphosphoranylidene)acetone (1.00 g, 3.14 mmol) in dichloromethane (20 ml) at room temperature. Aqueous sodium hydroxide (0.25 M, 14.0 ml, 3.50 mmol) was added and the resulting mixture was stirred vigorously at room temperature for 5 min. The organic layer was collected and the aqueous layer extracted with dichloromethane (2 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to obtain the title compound as a white solid (1.05 g, 2.64 mmol, 84%), mp 148–152 °C (decomp.). Found (FABMS: glycerol–NBA matrix): 397.0328. $C_{21}H_{19}$-OPBr (M^+) requires 397.0357. ν_{max}(KBr) 3020, 2940, 2846, 1732, 1106 cm^{-1}; δ_H($CDCl_3$) 2.34 [3H, s, C(3)H_3], 7.47 [6H, m, 6 × C(6)H], 7.55 [3H, m, 3 × C(7)H], 7.63 [6H, m, 6 × C(5)H]; δ_C($CDCl_3$) 26.77 [d, $J_{(P\text{-}C)}$ = 8.4 Hz, C(3)], 45.67 [d, $J_{(P\text{-}C)}$ = 117.63 Hz, C(1)], 126.27 [d, $J_{(P\text{-}C)}$ = 93.6 Hz, C(4)], 128.82 [d, $J_{(P\text{-}C)}$ = 12.6 Hz, C(5)], 132.29 [d, $J_{(P\text{-}C)}$ = 2.82 Hz, C(7)], 133.98 [d, $J_{(P\text{-}C)}$ = 9.8 Hz, C(6)], 189.17 [d, $J_{(P\text{-}C)}$ = 10.0 Hz, C(2)].

(1-Bromo-2-*tert*-butoxy-2-oxoethyl)(triphenyl)phosphonium bromide. Bromine (0.428 g, 0.14 ml, 2.68 mmol) was added dropwise to a solution of *tert*-butyl (triphenylphosphoranylidene)acetate (1.00 g, 2.66 mmol) in DME (20 ml) at room temperature. The resulting white precipitate was collected by filtration and washed with DME (1.19 g, 2.22 mmol, 83%), mp 148–150 °C. Found: C, 53.9; H, 4.7; Br, 29.6; P, 5.7. $C_{24}H_{25}Br_2O_2P$ requires C, 53.76; H, 4.70; Br, 29.80; P, 5.78%. ν_{max}(KBr) 3450, 2976, 2620, 1745, 1439, 1146, 1107, 692, 517 cm^{-1}; δ_H($CDCl_3$) 1.21 [9H, s, 3 × C(4)H_3], 7.74 [9H, m, 6 × C(7)H & 3 × C(8)H], 8.01 [6H, m, 6 × C(6)H], 8.65 [1H, d, $J_{P\text{-}H}$ = 8.6 Hz, C(1)H]; δ_C($CDCl_3$) 27.52 [C(4)], 38.30 [d, $J_{(P\text{-}C)}$ = 50.4 Hz, C(1)], 87.08 [C(3)], 117.47 [d, $J_{(P\text{-}C)}$ = 88.8 Hz, C(5)], 130.17 [d, $J_{(P\text{-}C)}$ = 13.2 Hz, C(6)], 134.91 [d, $J_{(P\text{-}C)}$ = 10.7 Hz, C(7)], 135.37 [d, $J_{(P\text{-}C)}$ = 3.1 Hz, C(8)], 162.19 [C(2)].

***tert*-Butyl bromo(triphenylphosphoranylidene)acetate 14c.** An aqueous solution of sodium hydroxide (0.25 M, 7.5 ml, 1.88 mmol) was added to a solution of (1-bromo-2-*tert*-butoxy-2-oxoethyl)(triphenyl)phosphonium bromide (1.00 g, 1.86 mmol) in H_2O (20 ml). The resulting cloudy suspension was extracted immediately with dichloromethane (3 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to obtain the title compound as a white solid (0.79 g, 1.74 mmol, 93%), mp 114–116 °C. Found (FAB: glycerol matrix): 455.0780. $C_{24}H_{25}O_2PBr$ (M + 1) requires 455.0776. ν_{max}(KBr) 3445, 2977, 1747, 1440, 1107 cm^{-1}; δ_H($CDCl_3$) 1.21 [9H, br s, 3 × C(4)H_3], 7.47 [6H, m, 6 × C(7)H], 7.56 [3H, m, 3 × C(8)H], 7.67 [6H, m, 6 × C(6)H]; δ_C($CDCl_3$) 28.62 [C(4)], 78.43 [C(3)], 127.19 [d, $J_{(P\text{-}C)}$ = 93.8 Hz, C(5)], 128.66 [d, $J_{(P\text{-}C)}$ = 12.4 Hz, C(6)], 132.31 [d, $J_{(P\text{-}C)}$ = 2.8 Hz, C(8)], 134.01 [d, $J_{(P\text{-}C)}$ = 9.7 Hz, C(7)].

1-Chloro-1-methoxyacetone.[16b] Copper bronze (200 mg, 3.15 mmol) was added to a stirring mixture of 1,1-dimethoxyacetone (23.6 g, 24.2 ml, 200 mol) and acetyl chloride (17.3 g, 15.7 ml, 220 mol) and heated under reflux for 1 h. The resulting black mixture was purified by distillation to afford the title compound as a yellow liquid (bp 70 °C, 260 mmHg) (15.4 g, 126 mmol, 63%). ν_{max}(thin film) 3451, 3011, 2943, 2843, 1734, 1109 cm^{-1}; δ_H($CDCl_3$) 2.24 [3H, s, C(3)H_3], 3.55 [3H, s, C(4)H_3], 5.51 [1H, s, C(1)H_3]; δ_C($CDCl_3$) 22.97 [C(3)], 57.64 [C(4)], 96.06 [C(1)], 197.77 [C(2)]. EIMS found: 122.9. $C_4H_8NClO_2$ (M^+) requires 122.0.

(1-Methoxy-2-oxopropyl)(triphenyl)phosphonium chloride. Triphenylphosphine (12.1 g, 46.1 mmol) was added to a stirring solution of 1-chloro-1-methoxyacetone (5.00 g, 40.8 mmol) in DME (30 ml). After stirring for 5 h at room temperature the resulting white precipitate was collected by filtration and washed with DME to afford the title compound as a white solid (12.3 g, 35.2 mmol, 86%), mp 136–136 °C. Found: C, 69.0; H, 5.8; P, 8.1. $C_{22}H_{22}ClO_2P$ requires C, 68.66; H, 5.76; P, 8.05%. ν_{max}(KBr) 3017, 2773, 2635, 2365, 2340, 1714, 1444, 1112, 1091, 760, 726, 693, 510 cm^{-1}; δ_H($CDCl_3$) 2.31 [3H, s, C(3)H_3], 3.71 [3H, s, C(8)H_3], 7.54 [6H, m, 6 × C(5)H], 7.67 [3H, m, 3 × C(7)H], 7.81 [6H, m, 6 × C(6)H], 8.67 [1H, d, $J_{P\text{-}H}$ = 10.1 Hz, C(1)H]; δ_C($CDCl_3$) 28.36 [d, $J_{(P\text{-}C)}$ = 3.6 Hz, C(3)], 63.30 [d, $J_{(P\text{-}C)}$ = 5.3 Hz, C(8)], 84.69 [d, $J_{(P\text{-}C)}$ = 64.7 Hz, C(1)], 117.83 [d, $J_{(P\text{-}C)}$ = 84.5 Hz, C(4)], 129.92 [d, $J_{(P\text{-}C)}$ = 12.8 Hz, C(6)], 134.58 [d, $J_{(P\text{-}C)}$ = 10.0 Hz, C(5)], 134.67 [d, $J_{(P\text{-}C)}$ = 3.2 Hz, C(7)], 205.16 [d, $J_{(P\text{-}C)}$ = 2.3 Hz, C(2)].

1-Methoxy-1-(triphenylphosphoranylidene)acetone 14d. An aqueous solution of sodium hydroxide (1.00 M, 8.00 ml, 8.00 mmol) was added to a solution of (1-methoxy-2-oxopropyl)(triphenyl)phosphonium chloride (3.00 g, 7.80 mmol) in H_2O (40 ml). The resulting cloudy suspension was extracted immediately with dichloromethane (3 × 30 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to obtain the title compound as a white solid (2.22 g, 6.37 mmol, 82%), mp 110–112 °C. Found (FAB: glycerol matrix): 349.1371. $C_{22}H_{22}O_2P$ (M + 1) requires 349.1357. ν_{max}(KBr) 3445, 3052, 2987, 2919, 2803, 1529, 1436, 1388, 1136, 1102, 720, 694 cm^{-1}; δ_H($CDCl_3$) 2.17 [3H, s, C(3)H_3], 3.18 [3H, s, C(8)H_3], 7.45 [6H, m, 6 × C(6)H], 7.55 [3H, m, 3 × C(7)H], 7.65 [6H, m, 6 × C(5)H]; δ_C($CDCl_3$) 23.21 [d, $J_{(P-C)}$ = 9.8 Hz, C(3)] 65.07 [C(8)], 100.77 [d, $J_{(P-C)}$ = 128.3 Hz, C(1)], 126.30 [d, $J_{(P-C)}$ = 88.9 Hz, C(4)], 129.14 [d, $J_{(P-C)}$ = 12.3 Hz, C(6)], 132.38 [d, $J_{(P-C)}$ = 2.8 Hz, C(7)], 134.06 [d, $J_{(P-C)}$ = 10.1 Hz, C(5)], 185.17 [d, $J_{(P-C)}$ = 28.5 Hz, C(2)],

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The general procedure is exemplified by the preparation of compound **12a** below. Pteridinecarbaldehyde **6a** was used in suspension in the stated solvent.

Methyl (2*E*)-3-[2-(benzylthio)-4-oxo-3,4-dihydropteridin-6-yl]prop-2-enoate 12a. Methyl (triphenylphosphoranylidene)-acetate (200 mg, 0.60 mmol) was added to a stirring solution of 2-(benzylthio)-4-oxo-3,4-dihydropteridine-6-carbaldehyde **6b** (167 mg, 0.56 mmol) in DME (10 ml) under a nitrogen atmosphere. The solution was stirred at room temperature for 5 h, whereupon a beige precipitate formed. The precipitate was collected by filtration and washed with DME and ether (102 mg, 0.29 mmol, 52%), mp 127–130 °C. Found: C, 57.6; H, 3.9; N, 15.7; S, 9.2. $C_{17}H_{14}N_4O_3S$ requires C, 57.62; H, 3.98; N, 15.81; S, 9.05%. Found (FABMS: glycerol–NBA matrix): 355.0862. $C_{17}H_{15}N_4O_3S$ (M + 1) requires 355.0865. ν_{max}(KBr) 3440, 3150, 2953, 1721, 1699, 1569, 1544, 1511, 1351 cm^{-1}; δ_H(DMSO) 3.78 [3H, s, C(17)H_3], 4.54 [2H, s, C(9)H_2], 7.02 [1H, d, J = 15.9 Hz, C(15)H], 7.30 [3H, m, 2 × C(11)H & C(13)H], 7.50 [2H, m, 2 × C(12)H], 7.81 [1H, d, J = 15.9 Hz, C(14)H], 9.25 [1H, s, C(7)H], 13.07 [1H, br s, N(3)H]; δ_C(DMSO) 34.48 [C(9)], 52.38 [C(17)], 123.51 [C(15)], 127.90 [C(13)], 128.98 [C(11)], 129.66 [C(12)], 132.54 [C(4a)], 137.18 [C(10)], 140.19 [C(14)], 145.89 [C(6)], 150.73 [C(7)], 154.76 [C(2)], 160.68 [C(8a)], 162.07 [C(4)], 166.40 [C(16)]; λ_{max}(MeOH) 365, 309, 260 nm.

Ethyl (2*E*)-3-[2-(benzylthio)-4-oxo-3,4-dihydropteridin-6-yl]-2-methylprop-2-enoate 12b. From ethyl 2-(triphenylphosphoranylidene)propanoate (200 mg, 0.55 mmol) and **6b** (150 mg, 0.50 mmol) over 24 h. The resulting yellow solution was concentrated under reduced pressure and purified by flash column chromatography (gradient: ethyl acetate⟶ethyl acetate : methanol 99 : 1). The product was contaminated with approximately 9% Ph_3PO (total yield 157 mg, 0.41 mmol, 82%), mp 156–159 °C. Found (FABMS: glycerol–NBA matrix): 383.1191. $C_{19}H_{19}N_4O_3S$ (M + 1) requires 383.1178. ν_{max}(KBr) 3435, 2943, 1722, 1699, 1569, 1544, 1506, 1345 cm^{-1}; δ_H(DMSO) 1.30 [3H, t, J = 7.1 Hz, C(19)H_3], 2.50 [3H, s, C(16)H_3], 4.32 [3H, q, J = 7.1 Hz, C(18)H_2], 4.61 [2H, s, C(9)H_2], 7.37 [3H, m, 2 × C(11)H & C(13)H], 7.60 [2H, m, 2 × C(12)H], 7.77 [1H, s, C(14)H], 9.12 [1H, s, C(7)H], 13.30 [1H, br s, N(3)H]; δ_C(DMSO) 14.53 [C(16)], 14.65 [C(19)], 34.44 [C(9)], 61.33 [C(18)], 127.88 [C(13)], 128.90 [C(11)], 129.57 [C(12)], 131.91 [C(15)], 134.03 [C(4a)], 134.78 [C(14)], 137.25 [C(10)], 148.14 [C(6)], 152.56 [C(7)], 153.27 [C(2)], 160.83 [C(8a)], 161.81 [C(4)], 167.80 [C(17)]; λ_{max}(MeOH) 369, 298 nm.

Methyl (2*E*)-3-[2-(methylthio)-4-oxo-3,4-dihydropteridin-6-yl]prop-2-enoate 13a. From methyl (triphenylphosphoranylidene)acetate (541 mg, 1.62 mmol) and 2-(methylthio)-4-oxo-3,4-dihydropteridine-6-carbaldehyde **6a** (300 mg, 1.35 mmol) in dichloromethane (20 ml) for 24 h (293 mg, 1.05 mmol, 78%), mp 186–189 °C. Found: C, 47.3; H, 3.6; N, 20.4; S, 11.6. $C_{11}H_{10}N_4O_3S$ requires C, 47.26; H, 3.62; N, 20.13; S, 11.52%. Found (FABMS: glycerol–NBA matrix): 279.0548. $C_{11}H_{11}N_4O_3S$ (M + 1) requires 279.0552. ν_{max}(KBr) 3443, 3067, 2922, 1721, 1700, 1577, 1549, 1353 cm^{-1}; δ_H(DMSO) 2.61 [3H, s, C(9)H_3], 3.78 [3H, s, C(13)H], 7.00 [1H, d, J = 16.0 Hz, C(11)H], 7.78 [1H, d, J = 16.0 Hz, C(10)H], 9.21 [1H, s, C(7)H], 13.21 [1H, br s, N(3)H]; δ_C(DMSO) 13.67 [C(9)], 52.36 [C(13)], 129.47 [C(11)], 132.32 [C(4a)], 140.05 [C(10)], 145.77 [C(6)], 150.57 [C(7)], 154.71 [C(2)], 160.32 [C(8a)], 162.87 [C(4)], 166.32 [C(12)]; λ_{max}(MeOH) 366, 307, 265 nm.

Ethyl (2*E*)-2-methyl-3-[2-(methylthio)-4-oxo-3,4-dihydropteridin-6-yl]prop-2-enoate 13b. From ethyl 2-(triphenylphosphoranylidene)propanoate (587 mg, 1.62 mmol) and **6a** (290 mg, 1.31 mmol) in dichloromethane (20 ml) at room temperature. After stirring for 2 h the resulting precipitate was collected by filtration and washed with dichloromethane (306 mg, 1.00 mmol, 76%), mp 201–203 °C. Found: C, 50.5; H, 4.6; N, 18.2; S, 10.6. $C_{13}H_{14}N_4O_3S$ requires C, 50.97; H, 4.61; N, 18.29; S, 10.47%. Found (FABMS: glycerol–NBA matrix): 307.0866. $C_{13}H_{15}N_4O_3S$ (M + 1) requires 307.0865. ν_{max}(KBr) 3435, 2907, 1721, 1700, 1564, 1548, 1348 cm^{-1}; δ_H(DMSO) 1.30 [3H, t, J = 6.9 Hz, C(15)H_3], 2.40 [3H, s, C(12)H_3], 2.60 [3H, s, C(9)H_3], 4.23 [2H, q, J = 6.9 Hz, C(14)H], 7.64 [1H, s, C(10)H], 8.98 [1H, s, C(7)H], 13.18 [1H, br s, N(3)H]; δ_C(DMSO) 13.65 [C(9)], 14.51 [C(15)], 14.64 [C(12)], 61.33 [C(14)], 131.68 [C(11)], 131.73 [C(10)], 134.83 [C(4)], 148.10 [C(6)], 152.53 [C(7)], 153.18 [C(2)], 160.31 [C(8a)], 162.41 [C(4)], 167.74 [C(12)]; λ_{max}(MeOH) 368, 302 nm.

***tert*-Butyl (2*E*)-3-[2-(methylthio)-4-oxo-3,4-dihydropteridin-6-yl]prop-2-enoate 13c.** From *tert*-butyl (triphenylphosphoranylidene)acetate (0.61 g, 1.62 mmol) and **6a** (0.30 g, 1.35 mmol) in dichloromethane (20 ml) over 15 min as a yellow solid (0.27 g, 0.84 mmol, 62%), mp 150–152 °C. Found: C, 52.4; H, 5.0; N, 17.2; S, 10.1. $C_{14}H_{16}N_4O_3S$ requires C, 52.49; H, 5.03; N, 17.49; S, 10.01%. Found (FABMS;: glycerol–NBA matrix): 321.1032. $C_{14}H_{17}N_4O_3S$ (M + 1) requires 321.1021. ν_{max}(KBr) 3440, 3138, 2979, 2936, 1716, 1580, 1549 cm^{-1}; δ_H(DMSO) 1.50 [9H, s, 3 × C(14)H_3], 2.61 [3H, s, C(9)H_3], 6.93 [1H, d, J = 15.9 Hz, C(11)H], 7.67 [1H, d, J = 15.9 Hz, C(10)H], 9.21 [1H, s, C(7)H], 13.20 [1H, br s, N(3)H]; δ_C(DMSO) 13.68 [C(9)], 28.16 [C(14)], 81.06 [C(13)], 125.82 [C(11)], 132.23 [C(4a)], 139.16 [C(10)], 146.06 [C(6)], 150.32 [C(7)], 154.59 [C(2)], 160.46 [C(8a)], 162.81 [C(4)], 165.13 [C(12)]; λ_{max}(MeOH) 366, 299 nm.

2-(Methylthio)-6-[(1*E*)-3-oxobut-1-enyl]pteridin-4(3*H*)-one 13d. From 1-(triphenylphosphoranylidene)acetone (1.12 g, 3.67 mmol) and **6a** (0.71 g, 3.20 mmol) in DMF (20 ml) over 45 min. The yellow product was precipitated by the addition of dichloromethane. (0.60 g, 2.27 mmol, 71%), mp >220 °C. Found: C, 49.9; H, 3.8; N, 21.1; S, 12.5. $C_{11}H_{10}N_4O_2S$ requires C, 50.37; H, 3.84; N, 21.36; S, 12.23%. Found (FABMS: glycerol–NBA matrix): 263.0604. $C_{11}H_{11}N_4O_2S$ (M + 1) requires 263.0603. ν_{max}(KBr) 3436, 3064, 3004, 2915, 1702, 1683, 1577, 1546, 1521, 1464, 1365, 1248 cm^{-1}; δ_H(DMSO) 2.42 [3H, s, C(9)H_3], 2.71 [3H, s, C(13)H_3], 7.28 [1H, d, J = 16.2 Hz, C(11)H], 7.83 [1H, d, J = 16.2 Hz, C(10)H], 9.28 [1H, s, C(7)H], 13.30 [1H, br s, N(3)H]; δ_C(DMSO) 13.67 [C(9)], 28.16 [C(13)], 131.98 [C(11)], 132.40 [C(4a)], 138.21 [C(10)], 146.40 [C(6)], 150.60 [C(7)], 154.64 [C(2)], 160.38 [C(8a)], 162.84 [C(4)], 198.37 [C(12)]; λ_{max}(MeOH) 372, 302 nm.

6-[(1*E*)-3-(2-Hydroxyphenyl)-3-oxoprop-1-enyl]-2-(methylthio)pteridin-4(3*H*)-one 13e. From 1-(2-hydroxyphenyl)-2-(triphenylphosphoranylidene)ethanone (500 mg, 1.26 mmol) and **6a** (234 mg, 1.05 mmol) in dichloromethane (20 ml) over 16 h. The yellow product was precipitated by the addition of DME (289 mg, 0.85 mmol, 81%), mp >230 °C. Found (FABMS: glycerol matrix): 341.0705. $C_{16}H_{13}N_4O_3S$ (M + 1) requires 341.0708. ν_{max}(KBr) 3436, 3071, 2894, 1694, 1637, 1575, 1544, 1348 cm^{-1}; δ_H(DMSO) 2.62 [3H, s, C(9)H$_3$], 7.02 [2H, m, C(15)H & C(17)H], 7.58 [1H, m, C(16)H], 7.84 [1H, d, *J* = 15.6 Hz, C(11)H], 8.04 [1H, m, C(18)H], 8.30 [1H, d, *J* = 15.6 Hz, C(10)H], 9.38 [1H, s, C(7)H], 11.96 [1H, s, C(14)OH], 13.25 [1H, br s, N(3)H]; δ_C(DMSO) 13.74 [C(9)], 118.15 [C(16)], 119.84 [C(17)], 122.02 [C(13)], 128.00 [C(11)], 131.14 [C(18)], 132.45 [C(4a)], 136.74 [C(16)H], 139.25 [C(10)], 146.43 [C(6)], 150.97 [C(7)], 154.72 [C(2)], 160.42 [C(8a)], 161.45 [C(14)], 163.01 [C(4)], 193.04 [C(12)]; λ_{max}(MeOH) 412, 316, 273 nm.

(2*E*)-3-[2-(Methylthio)-4-oxo-3,4-dihydropteridin-6-yl]prop-2-enal 13f. From (triphenylphosphoranylidene)acetaldehyde (537 mg, 1.76 mmol) and **6a** (361 mg, 1.62 mmol) in DMF (15 ml) over 1 h. The yellow product was precipitated by the addition of DME (286 mg, 1.15 mmol, 71%), mp 162–167 °C. Found (HREIMS): 248.0379. $C_{10}H_8N_4O_2S$ (M^+) requires 248.0368. ν_{max}(KBr) 3056, 3004, 2915, 1705, 1687, 1578, 1546, 1368, 1250 cm^{-1}; δ_H(DMSO) 2.60 [3H, s, C(9)H$_3$], 7.15 [1H, dd, *J* = 15.9 & 7.8 Hz, C(11)H], 7.89 [1H, d, *J* = 15.9 Hz, C(10)H], 9.26 [1H, s, C(7)H], 9.81 [1H, d, *J* = 7.8 Hz, C(12)H], 13.20 [1H, br s, N(3)H]; δ_C(DMSO) 13.79 [C(9)], 132.47 [C(11)], 132.58 [C(4a)], 147.98 [C(10)], 145.72 [C(6)], 150.43 [C(7)], 155.01 [C(4)], 161.14 [C(8a)], 164.41 [C(4)], 194.82 [C(12)]; λ_{max}(DMF) 358, 317 nm.

Ethyl (4*E*)-5-[2-(methylthio)-4-oxo-3,4-dihydropteridin-6-yl]-3-oxopent-4-enoate 13g. From ethyl 3-oxo-4-(triphenylphosphoranylidene)butanoate (843 mg, 2.16 mmol) and **6a** (400 mg, 1.80 mmol) in dichloromethane (20 ml) over 1 h. The yellow product was precipitated by the addition of DME as a mixture of two tautomers **a** and **b** (90 mg, 0.27 mmol, 15%), mp 219–221 °C. Found (FABMS: glycerol–NBA matrix): 335.0823. $C_{14}H_{15}N_4O_4S$ (M + 1) requires 335.0814. ν_{max}(KBr) 3440, 3083, 2997, 2915, 1693, 1651, 1582, 1550, 1350, 1241 cm^{-1}; δ_H(DMSO) 1.20 [3H, t, *J* = 7.1 Hz, C(16)H$_3$ of **a**], 1.25 [3H, t, *J* = 7.1 Hz, C(16)H$_3$ of **b**], 2.61 [6H, s, C(9)H$_3$ of **a** & C(9)H$_3$ of **b**], 3.96 [2H, s, C(13)H$_2$ of **a**], 4.13 [2H, q, *J* = 7.1 Hz, C(15)H$_2$ of **b**], 4.21 [2H, q, *J* = 7.1 Hz, C(15)H$_2$ of **a**], 5.59 [1H, s, C(13)H of **b**], 7.23 [1H, d, *J* = 15.8 Hz, C(11)H of **b**], 7.30 [1H, d, *J* = 16.1 Hz, C(11)H of **a**], 7.53 [1H, d, *J* = 15.8 Hz, C(10)H of **b**], 7.79 [1H, d, *J* = 16.1 Hz, C(10)H of **a**], 9.11 [1H, s, C(7)H of **a**], 9.19 [1H, s, C(7)H of **b**], 11.81 [1H, br s, C(12)OH], 13.21 [2H, br s, N(3)H of **a** & N(3)H of **b**]; δ_C(DMSO) 13.66 [C(9) of **b**], 13.70 [C(9) of **a**], 14.41 [C(16) of **a**], 14.47 [C(16) of **b**], 60.75 [C(15) of **a**], 61.04 [C(15) of **b**], 47.48 [C(13) of **a**], 94.81 [C(13) of **b**], 128.17 [C(11) of **b**], 130.58 [C(10) of **b**], 131.68 [C(11) of **a**], 132.23 [C(4a) of **b**], 132.53 [C(4a) of **a**], 138.96 [C(10) of **a**], 145.95 [C(6) of **a**], 147.63 [C(6) of **b**], 150.48 [C(7) of **a**], 150.87 [C(7) of **b**], 154.22 [C(2) of **a**], 154.79 [C(2) of **b**], 160.52 [C(8a) of **a** & C(8a) of **b**], 162.23 [C(12) of **b**], 167.54 [C(4) of **a** & C(4) of **b**], 167.77 [C(14) of **b**], 173.23 [C(14) of **a**], 193.40 [C(12) of **a**]; λ_{max}(MeOH) 389, 312 nm.

Ethyl (3*E*)-4-[2-(methylthio)-4-oxo-3,4-dihydropteridin-6-yl]-2-oxobut-3-enoate 13h. From ethyl 2-oxo-3-(triphenylphosphoranylidene)propanoate (813 mg, 2.16 mmol) and **6a** (400 mg, 1.80 mmol) in dichloromethane (25 ml) over 16 h. The yellow product was precipitated by the addition of DME (167 mg, 0.52 mmol, 29%), mp 190–192 °C. Found (FABMS: glycerol matrix): 321.0652. $C_{13}H_{13}N_4O_4S$ (M + 1) requires 321.0658. ν_{max}(KBr) 3433, 3082, 2989, 2911, 1736, 1694, 1581, 1518, 1356 cm^{-1}; δ_H(DMSO) 1.33 [3H, t, *J* = 7.1 Hz, C(15)H$_3$], 2.62 [3H, s, C(9)H$_3$], 4.34 [2H, q, *J* = 7.1 Hz, C(14)H], 7.79 [1H, d, *J* = 15.9 Hz, C(11)H], 7.92 [1H, d, *J* = 15.9 Hz, C(10)H], 9.23 [1H, s, C(7)H], 13.30 [1H, br s, N(3)H]; δ_C(DMSO) 13.72 [C(9)], 14.27 [C(15)], 62.53 [C(14)], 125.98 [C(11)], 132.74 [C(4a)], 141.50 [C(10)], 145.38 [C(6)], 151.70 [C(7)], 155.04 [C(2)], 160.41 [C(8a)], 161.74 [C(13)], 163.52 [C(4)], 183.06 [C(12)]; λ_{max}(MeOH) 396, 313 nm.

(2*E*)-3-[2-(Methylthio)-4-oxo-3,4-dihydropteridin-6-yl]prop-2-enamide 13i. From freshly prepared 2-(triphenylphosphoranylidene)acetamide **14a** (517 mg, 1.62 mmol) and **6a** (300 mg, 1.35 mmol) in dichloromethane (25 ml) under a nitrogen over 6 h. The product precipitated as an amorphous yellow solid (259 mg, 0.99 mmol, 73%), mp >230 °C. Found (FABMS: glycerol matrix): 264.0559. $C_{10}H_{10}N_5O_2S$ (M + 1) requires 264.0555. ν_{max}(KBr) 3401, 3337, 3188, 3060, 2997, 2805, 1705, 1688, 1572, 1546, 1521, 1350 cm^{-1}; δ_H(DMSO) 2.60 [3H, s, C(9)H$_3$], 7.19 [1H, d, *J* = 15.6 Hz, C(11)H], 7.30 [1H, s, 1 × N(13)H], 7.60 [1H, d, *J* = 15.6 Hz, C(10)H], 7.84 [1H, s, 1 × N(13)H], 9.03 [1H, s, C(7)H], 13.13 [1H, br s, N(3)H]; δ_C(DMSO) 13.69 [C(9)], 128.64 [C(11)], 132.24 [C(4a)], 134.86 [C(10)], 146.84 [C(6)], 150.42 [C(7)], 154.41 [C(2)], 160.62 [C(8a)], 162.34 [C(4)], 166.27 [C(12)]; λ_{max}(MeOH) 369, 302 nm.

6-[(1*Z*)-2-Bromo-3-oxobut-1-enyl]-2-(methylthio)pteridin-4(3*H*)-one 13j. From 1-bromo-1-(triphenylphosphoranylidene)-acetone **14b** (477 mg, 1.20 mmol) and **6b** (222 mg, 1.00 mmol) in DMF (10 ml) over 30 min. The product was isolated by concentration of the DMF solution and precipitation with dichloromethane (243 mg, 0.71 mmol, 71%), mp 191–194 °C (decomp.). Found: C, 39.0; H, 2.7; N, 16.1; S, 9.3; Br, 22.2. $C_{11}H_9N_4O_2SBr$ requires C, 38.72; H, 2.66; N, 16.42; S, 9.40; Br, 23.42%. Found (FABMS: glycerol–NBA matrix): 340.9704. $C_{11}H_{10}N_4O_2SBr$ (M + 1) requires 340.9708. ν_{max}(KBr) 3435, 3068, 2926, 1703, 1688, 1574, 1543, 1518, 1360, 1181 cm^{-1}; δ_H(DMSO) 2.62 [3H, s, C(9)H$_3$], 2.65 [3H, s, C(13)H$_3$], 8.41 [1H, s, C(10)H], 9.37 [1H, s, C(7)H], 13.24 [1H, br s, N(3)H]; δ_C(DMSO) 13.73 [C(9)], 26.77 [C(13)], 128.24 [C(11)], 132.28 [C(4a)], 137.77 [C(10)], 146.34 [C(6)], 151.17 [C(7)], 153.88 [C(2)], 160.08 [C(8a)], 163.52 [C(4)], 192.73 [C(12)]; λ_{max}(MeOH) 374, 310 nm.

***tert*-Butyl (2*Z*)-2-bromo-3-[2-(methylthio)-4-oxo-3,4-dihydropteridin-6-yl]prop-2-enoate 13k.** From *tert*-butyl bromo-(triphenylphosphoranylidene)acetate **14c** (738 mg, 1.62 mmol) and **6a** (300 mg, 1.35 mmol) in dichloromethane (15 ml) over 1 h. The product was isolated as an orange solid by evaporation of the dichloromethane and digestion of the residue with toluene (374 mg, 1.01 mmol, 75%), mp 94–97 °C. Found: C, 42.9; H, 2.6; N, 24.8; S, 14.7. $C_8H_6N_4O_2S$ requires C, 43.24; H, 2.72; N, 25.21; S, 14.43%. Found (FABMS: glycerol matrix): 223.0273. $C_8H_7N_4O_2S$ (M + 1) requires 223.0290. ν_{max}(KBr) 3441, 3070, 2928, 1715, 1689, 1578, 1520, 1361, 1180 cm^{-1}; δ_H(DMSO) 1.54 [9H, s, 3 × C(14)H$_3$], 2.62 [3H, s, C(9)H$_3$], 8.27 [1H, s, C(10)H], 9.37 [1H, s, C(7)H], 13.24 [1H, br s, N(3)H]; δ_C(DMSO) 13.70 [C(9)], 27.87 [C(14)], 83.93 [C(13)], 119.47 [C(11)], 132.21 [C(4a)], 136.47 [C(10)], 146.02 [C(6)], 150.89 [C(7)], 153.87 [C(2)], 160.12 [C(8a)], 161.32 [C(4)], 163.41 [C(12)]; λ_{max}(MeOH) 367, 308, 268 nm.

6-[(1*Z*)-2-Methoxy-3-oxobut-1-enyl]-2-(methylthio)pteridin-4(3*H*)-one 13l. From 1-methoxy-1-(triphenylphosphoranylidene)acetone **14d** (800 mg, 2.30 mmol) and **6a** (425 mg, 1.91 mmol) in dichloromethane (25 ml) over 4 h. The product precipitated as a yellow solid (538 mg, 1.84 mmol, 96%), mp >220 °C. Found (FABMS: glycerol matrix): 293.0703. $C_{12}H_{13}N_4O_3S$ (M + 1) requires 293.0708. ν_{max}(KBr) 3433, 3064, 2911, 1705, 1685, 1577, 1543 cm^{-1}; δ_H(DMSO) 2.47 [3H, s, C(13)H$_3$], 2.62 [3H, s, C(9)H$_3$], 3.84 [3H, s, C(14)H$_3$], 7.01 [1H, s, C(10)H], 9.34

[1H, s, C(7)H], 13.16 [1H, br s, N(3)H]; δ_C(DMSO) 13.66 [C(9)], 27.21 [C(13)], 59.96 [C(14)], 118.98 [C(10)], 132.16 [C(4a)], 147.01 [C(6)], 150.89 [C(7)], 153.15 [C(2)], 155.85 [C(11)], 160.38 [C(8a)], 162.24 [C(4)], 196.30 [C(12)]; λ_{max}(MeOH) 376, 323 nm.

Oxidation reactions

Ethyl (2*E*)-3-(2,4-dioxo-1,2,3,4-tetrahydropteridin-6-yl)-2-methylprop-2-enoate 16a. Ethyl (2*E*)-2-methyl-3-[2-(methylthio)-4-oxo-3,4-dihydropteridin-6-yl]prop-2-enoate **13b** (100 mg, 0.33 mmol) was added to a solution of freshly prepared DDO in acetone (0.040 M, 33 ml, 1.32 mmol) and stirred for 3 days at room temperature. Further DDO was added after 1 (0.040 M, 17 ml, 0.66 mmol) and 2 days (0.040 M, 17 ml, 0.66 mmol). The resulting solution was concentrated to dryness under reduced pressure and water (1 ml) added to the white residue. The mixture was stirred for 20 min at room temperature and then cooled to 0–4 °C. The white suspension was collected by suction filtration and washed with a little cold water and allowed to air dry (70 mg, 0.25 mmol, 78%), mp >235 °C. Found (FAB: glycerol–NBA matrix): 277.0933. $C_{12}H_{13}N_4O_4$ (M + 1) requires 277.0937. ν_{max}(KBr) 3450, 3190, 3094, 1734, 1701, 1548, 1342, 1226 cm^{-1}; δ_H(DMSO) 1.31 [3H, t, J = 7.1 Hz, C(14)H$_3$], 2.46 [3H, s, C(12)H$_3$], 4.27 [2H, q, C(13)H$_2$], 7.77 [1H, s, C(9)H], 9.24 [1H, s, C(7)H]; δ_C(DMSO) 14.55 [C(14)], 14.84 [C(12)], 61.55 [C(13)], 131.54 [C(9)], 134.27 [C(4a)], 136.87 [C(10)], 151.11 [C(6)], 152.15 [C(2)], 153.20 [C(7)], 156.63 [C(8a)], 161.55 [C(4)], 167.66 [C(11)]; λ_{max}(MeOH) 357, 286 nm.

***tert*-Butyl (2*E*)-3-(2,4-dioxo-1,2,3,4-tetrahydropteridin-6-yl)-prop-2-enoate 16b.** *tert*-Butyl (2*E*)-3-[2-(methylthio)-4-oxo-3,4-dihydropteridin-6-yl]prop-2-enoate **13c** (100 mg, 0.31 mmol) was added to a solution of freshly prepared DDO in acetone (0.052 M, 24 ml, 1.25 mmol) and stirred for 3 days at room temperature. Further DDO was added after 1 (0.052 M, 12 ml, 0.62 mmol) and 2 days (0.052 M, 12 ml, 0.62 mmol). The resulting solution was concentrated to dryness under reduced pressure and water (1 ml) added to the white residue. The mixture was stirred for 20 min at room temperature and then cooled to 0–4 °C. The white suspension was collected by suction filtration and washed with a little cold water and allowed to air dry (56 mg, 0.19 mmol, 62%), mp 132–134 °C. Found (FABMS: glycerol–NBA matrix): 291.1104. $C_{13}H_{15}N_4O_4$ (M + 1) requires 291.1093. ν_{max}(KBr) 3440, 3201, 3089, 2977, 2931, 2854, 1701, 1562, 1362, 1158 cm^{-1}; δ_H(DMSO) 1.50 [9H, s, 3 × C(12)H$_3$], 6.83 [1H, d, J = 15.9 Hz, C(10)H], 7.63 [1H, d, J = 15.9 Hz, C(9)H], 8.97 [1H, s, C(7)H]; δ_C(DMSO) 28.16 [C(13)], 80.90 [C(12)], 124.24 [C(10)], 128.09 [C(4a)], 139.14 [C(9)], 143.53 [C(6)], 148.74 [C(7)], 149.68 [C(2)], 150.16 [C(8a)], 160.94 [C(4)], 165.21 [C(11)]; λ_{max}(MeOH) 350, 286 nm.

6-[(1*E*)-3-Oxobut-1-enyl]pteridine-2,4(1*H*,3*H*)-dione 16c. 2-(Methylthio)-6-[(1*E*)-3-oxobut-1-enyl]pteridin-4(3*H*)-one **13d** (100 mg, 0.38 mmol) was added to a solution of freshly prepared DDO in acetone (0.055 M, 28 ml, 1.54 mmol) and stirred for 3 days at room temperature. Further DDO was added after 1 (0.055 M, 14 ml, 0.77 mmol) and 2 days (0.055 M, 14 ml, 0.77 mmol). The resulting solution was concentrated to dryness under reduced pressure and water (1 ml) was added to the white residue. The mixture was stirred for 20 min at room temperature and then cooled to 0–4 °C. The white suspension was collected by suction filtration and washed with a little cold water and allowed to air dry. 6-[(1*E*)-3-Oxobut-1-enyl]pteridine-2,4(1*H*,3*H*)-dione **16c** was isolated as a pure white solid (65 mg, 0.28 mmol, 74%), mp >220 °C. Found (FABMS: glycerol–NBA matrix): 233.0673. $C_{10}H_9N_4O_3$ (M + 1) requires 233.0675. ν_{max}(KBr) 3441, 3202, 2978, 2931, 2857, 1710, 1564, 1368, 1160 cm^{-1}; δ_H(DMSO) 2.44 [3H, s, C(12)H$_3$], 7.30 [1H, d, J = 16.3 Hz, C(10)H], 7.80 [1H, d, J = 16.3 Hz, C(9)H], 9.40 [1H, s, C(7)H]; δ_C(DMSO) 28.37 [C(12)], 133.70 [C(10)], 134.95 [C(4a)], 137.78 [C(9)], 149.55 [C(6)], 151.22 [C(7)], 153.51 [C(2)], 156.59 [C(8a)], 161.34 [C(4)], 165.13 [C(12)]; λ_{max}(DMF) 349, 298 nm.

6-(3-Acetyloxiran-2-yl)pteridine-2,4(1*H*,3*H*)-dione 17a. 2-(Methylthio)-6-[(1*E*)-3-oxobut-1-enyl]pteridin-4(3*H*)-one **13d** (100 mg, 0.38 mmol) was added to a solution of freshly prepared DDO in acetone (0.078 M, 39 ml, 3.04 mmol) and cooled to 4 °C for 7 days. The resulting solution was concentrated to dryness under reduced pressure and water (1 ml) added to the white residue. The mixture was stirred for 20 min at room temperature and then cooled to 0–4 °C. The white suspension was collected by suction filtration and washed with a little cold water and allowed to air dry. ^{1}H NMR analysis of the resulting solid indicated that it was composed of a mixture of the alkene **13d** and the epoxide **17a** in a ratio of 9 : 91 respectively. Thus, 6-(3-acetyloxiran-2-yl)pteridine-2,4(1*H*,3*H*)-dione **17a** was sufficiently pure to be completely characterized. Notably, **17a** decomposed within 5 days on storage at room temperature and had to be stored in the fridge under nitrogen (65 mg, 26 mmol, 69%), mp 124–126 °C. Found (FABMS: glycerol matrix): 249.0626. $C_{10}H_9N_4O_4$ (M + 1) requires 249.0624. ν_{max}(KBr) 3537, 3420, 3027, 2936, 1715, 1600, 1323, 1302, 1143 cm^{-1}; δ_H(DMSO) 2.22 [3H, s, C(12)H$_3$], 4.19 [1H, d, J = 1.9 Hz, C(9)H], 4.70 [1H, d, J = 1.9 Hz, C(9)H], 9.05 [1H, s, C(7)H]; δ_C(DMSO) 25.88 [C(12)], 55.98 [C(10)], 61.57 [C(9)], 134.22 [C(4a)], 149.17 [C(7)], 151.46 [C(6)], 153.57 [C(2)], 156.66 [C(8a)], 161.31 [C(4)], 203.69 [C(11)]; λ_{max}(MeOH) 330 nm.

***tert*-Butyl 2,3-dihydroxy-3-[4-oxo-2-(methylthio)-3,4-dihydropteridinyl]propanoate 19.** *tert*-Butyl [4-hydroxy-2-(methylthio)-pteridinyl]propenoate **13c** (15mg, 4.7 × 10^{-2} mmol) was dissolved in 1mL of 1:1 *t*-BuOH/H$_2$O and cooled to 0 °C. AD-mix *β* (70mg) was added and the solution stirred for 3 d at room temperature. The reaction was stopped by adding Na_2SO_3 until two clear phases were formed and no further gas was evolved. The organic layer was extracted with dichloromethane (3 × 1.5 mL). The aqueous layer was concentrated under reduced pressure. Methanol was added to the pale yellow residue and the solution was filtered and concentrated under reduced pressure again and purified by flash column chromatography (gradient: dichloromethane/methanol (9:1) then dichloromethane/methanol (8:2) then dichloromethane/methanol (1:1). Evaporation of the eluates containing pteridines afforded the required diol (10 mg, 2.82 × 10^{-2} mmol, 61%). Found: (FABMS) 355.1068; $C_{14}H_{19}N_4O_5S$ (M + 1) requires 355.1076. d$_H$ (DMSO): 1.42 [9H, s, 3 × C(14)H$_3$], 2.53 [3H, s, C(9)H$_3$], 4.32 [1H, m, C(10 or 11)H], 5.13 [1H, m, C(10 or 11)H], 5.40 [1H, d, J = 9.8Hz, C(10 or 11)OH], 6.18 [1H, d, J = 9.8Hz C(10 or 11)OH], 8.89 [1H, s, C(7)H] δ_C (DMSO): 13.67 [C(9)], 28.14 [C(14)], 74.30, 74.75 [C(10, 11)], 81.06 [C(13)], 130.32 [C(4a)], 149.06 [C(2)], 154.05, 155.02 [C(6, 7)], 161.64, 162.53 [C(4, 8a)], 171.25 [C(12)].

6-Oxopterins

2-Amino-6-(2-oxopropylidene)-5,8-dihydropteridine-4,7(3*H*,6*H*)-dione 20.[23] Ethyl 2,4-dioxovalerate (4.06 g, 25.7 mmol) in methanol (40 ml) was added to a solution of 2,5,6-triaminopyrimidin-4(3*H*)-one dihydrochloride (5.00 g, 23.3 mmol) in water (50 ml) and the resulting solution was heated on a steam bath for 20 min. Triethylamine (3.00 g, 4.13 ml, 29.6 mmol) was then added to the purple solution. After heating for a further 30 min a yellow precipitate had formed which, after cooling to room temperature, was collected by suction filtration and washed with water and acetone. The title compound was isolated as a yellow solid (3.50 g, 14.9 mmol, 64%), mp >230 °C. Found: C, 41.8; H, 4.3; N, 27.8. $C_9H_9N_5O_3.H_2O$ requires C, 42.69; H, 4.38; N, 27.66. Found

(FABMS: glycerol–NBA matrix): 236.07803. $C_9H_{10}N_5O_3$ (M + 1) requires 236.07836. ν_{max}(KBr) 3500, 3404, 3192, 3000, 1699, 1685, 1659, 1648, 1626, 1580, 1563, 1376, 1245 cm^{-1}; δ_H(DMSO) 2.20 [3H, s, C(11)H_3], 6.10 [1H, s, C(9)H], 6.58 [2H, br s, N(12)H_2], 11.07 [2H, br s, N(5)H & N(8)H], 12.44 [1H, br s, N(3)H]; δ_C(DMSO) 30.58 [C(11)], 95.99 [C(9)], 100.02 [C(4a)], 140.92 [C(6)], 144.24 [C(8a)], 152.39 [C(7)], 154.21 [C(4)], 155.10 [C(2)], 199.50 [C(10)]; λ_{max}(0.05N NaOH) 342, 280, 257 nm.

2-Amino-6-(1-nitroso-2-oxopropylidene)-5,8-dihydropteridine-4,7(3*H*,6*H*)-dione 23. Sodium nitrite (345 mg, 5.0 mmol) was added to a stirring suspension of 2-amino-6-(2-oxopropylidene)-5,8-dihydropteridine-4,7(3*H*,6*H*)-dione **20** (300 mg, 1.28 mmol) in water (20 ml). Glacial acetic acid (3.14 g, 3 ml, 52 mmol) was added and the resulting mixture was stirred at room temperature for 48 h. The resulting solution was concentrated to dryness under reduced pressure. Water (4 ml) was added to the residue and the resulting suspension collected by filtration. The title compound was isolated as an orange amorphous solid (290 mg, 1.1 mmol, 86%), mp >230 °C. Found (FABMS: glycerol–NBA matrix): 265.0682. $C_9H_{10}N_5O_3$ (M + 1) requires 265.0685. ν_{max}(KBr) 3440, 3272, 3145, 1663, 1540, 1392 cm^{-1}; δ_H(DMSO) 2.34 [3H, s, C(11)H_3], 6.40 [2H, br s, N(12)H_2], 11.58 [1H, br s, N(8)H], 11.71 [1H, br s, N(5)H], 12.71 [1H, br s, N(3)H]; δ_C(DMSO) 30.58 [C(11)], 95.99 [C(9)], 100.02 [C(4a)], 140.92 [C(6)], 144.24 [C(8a)], 152.39 [C(7)], 154.21 [C(4)], 155.10 [C(2)], 199.50 [C(10)]; λ_{max}(DMF) 419, 378 nm.

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