



Diversity oriented synthesis: substitution at C5 in unreactive pyrimidines by Claisen rearrangement and reactivity in nucleophilic substitution at C2 and C4 in pteridines and pyrido[2,3-*d*]pyrimidines

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ABSTRACT

Diversity oriented synthesis of fused pyrimidines leads to scaffolds with many biological activities. In the case of the preparation of pyrido[2,3-*d*]pyrimidines from 2-alkylthiopyrimidines, the formation of a new carbon–carbon bond at C5 is required, a reaction, that is, very limited in scope. However Claisen type rearrangement of simple 4-allylic ethers affords C5 substituted pyrimidines readily; in cases with an ester substituent, rearrangement occurs at room temperature. Subsequent cyclisation to afford 6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-ones was achieved in high yield. Using allylic ethers derived from 3-chloromethyl-4-arylbut-3-en-2-ones as substrates, a new titanium[IV]chloride catalysed reaction affording 6-arylmethyl-7-methylpyrido[2,3-*d*]pyrimidines was discovered. In contrast, 2-alkylthiopteridines are readily available. In both cases, substitution at C2 and C4 to generate diversity has been carried out and the reactivity compared; yields of substitution products were generally higher with pteridine substrates. In biological assays unexpected hits were found for activity against the Gram positive bacterium, *Nocardia farcinia*, and against the parasite *Trypanosoma brucei brucei*, illustrating the value of diversity oriented synthesis in the discovery of biologically active compounds.

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1. Introduction

Whilst the synthesis of pteridines and related bicyclic nitrogen heterocycles is established,¹ the synthesis of their deaza analogues requires further development because most methods for the synthesis of such compounds have not been designed with the intention of creating highly diverse libraries of compounds as is required for modern medicinal chemistry in which multiple biological targets may be relevant. With emphasis on diversity oriented synthesis in our own studies, we have identified active compounds with respect to GTP cyclohydrolase 1,² dihydropterin diphosphokinase,³ dihydrofolate reductase,⁴ pteridine reductase⁵ and nitric oxide synthase.⁶ Several of these targets are significant clinically and the optimisation of activity requires the availability of more diverse libraries within the same basic structural skeleton. Our recent work, therefore, has emphasised maximising the number of easily variable sites, so that at least three variations are readily available from one synthetic stream. At the centre of these

developments has been the alkylthio substituent, either at C2 or C4 of a pyrimidine and we have established a prototype solid phase synthesis of pteridines using this linker, which proceeds through C5 nitrosation of the alkylthiopyrimidine.⁷ Extension of this chemistry to pyrido[2,3-*d*]pyrimidines and pyrrolo[2,3-*d*]pyrimidines requires carbon substitution to take place at C5 of the pyrimidine. Although a 2- or 4-alkylthio substituent gives access to diversity, via oxidation and nucleophilic displacement, the presence of the alkylthio substituent significantly reduces the reactivity of C5 to electrophiles compared with the more common 2-amino substituent such that carbon electrophiles, do not react. A significant exception is that when certain Michael acceptors are used, C5 substitution occurs in reduced yield⁸ and this chemistry has been developed to provide compounds with significant activity against *Trypanosoma brucei*.⁵ A further example of a successful C5 substitution of a 2-alkylthiopyrimidine is found in nucleoside analogue synthesis and involves Vilsmeier formylation.⁹ In contrast, halogen electrophiles substitute 2-alkylthiopyrimidines in high yield and provide suitable precursors for C5 carbon substitution.¹⁰ In view of the low reactivity of these intermolecular substitution reactions, we hypothesised that intramolecular C5 substitution might be successful and that suitable precursors for the Claisen allyl rearrangement would be available from O4 allyl ethers. Allyl rearrangements have been used in the synthesis of many natural

Abbreviations: BOP, (1-benzotriazolyl)oxy tris(dimethylamino) phosphonium hexafluorophosphate; *m*-CPBA, *m*-chloroperbenzoic acid; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

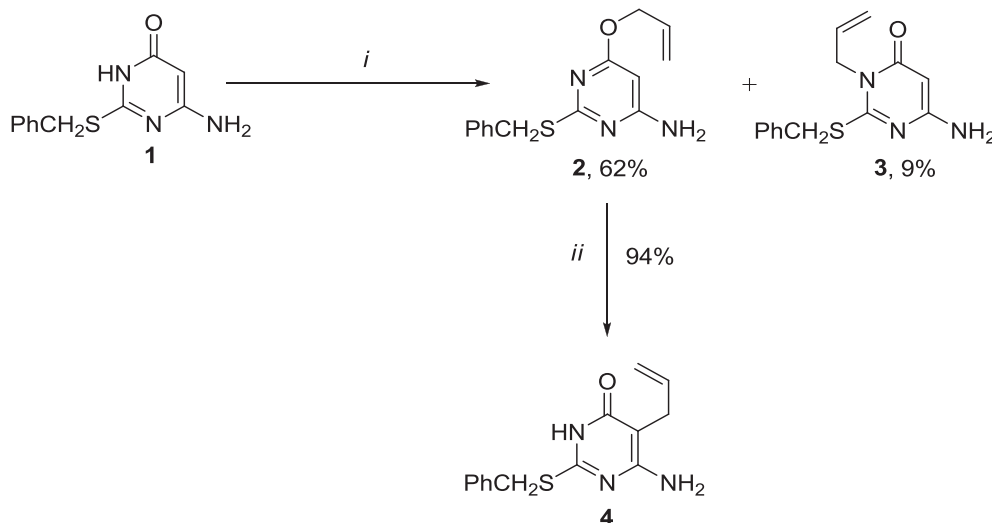
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products.¹¹ The Claisen rearrangement was first described in the pyrimidine series in 1961 but the reactions lacked functional groups for further transformations leading to fused pyrimidines.¹²

2. Results and discussion

2.1. Claisen rearrangement

To investigate further the Claisen rearrangement approach,¹² pyrimidine **1** was treated with allyl bromide in DMF in the presence of solid potassium carbonate to afford a mixture of the O4 and N3 allyl pyrimidines **2** (62%) and **3** (9%), which were separable by column chromatography. The O4 allylated pyrimidine **2** underwent quantitative Claisen rearrangement to afford **4** at 200 °C in the melt (Scheme 1); in previous work, reactions took place in high boiling solvents and gave only 20% yield.



Scheme 1. Substitution by Claisen rearrangement. Reagents and conditions: i. DMF, K₂CO₃, 100 °C, 20 h; ii. 200 °C, 24 h.

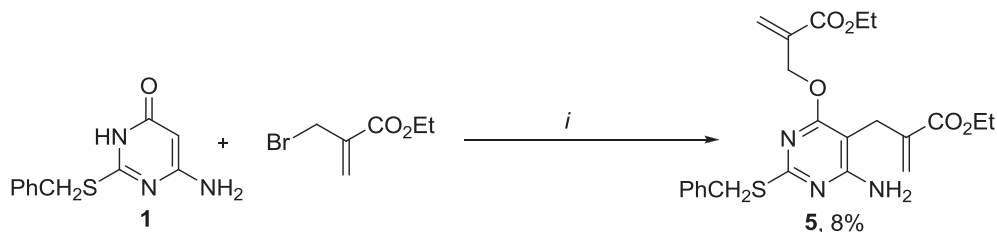
Cyclisation of **4** to either a pyrido[2,3-*d*]- or a pyrrolo[2,3-*d*]-pyrimidine proved unsuccessful using palladium catalysis.¹⁰ However, this cyclisation reaction was not a priority because the products of cyclisation of **4** would lack substituents in the newly formed ring, an outcome inappropriate for a diversity oriented synthesis; substituted allylic groups are necessary for library synthesis. In electrocyclic reactions, it is often found that the introduction of an electron withdrawing group to an alkene greatly increases the reaction rate.¹¹ By using ethyl bromomethylacrylate as the alkylating agent and pyrimidine **1**, two surprising results were obtained. Firstly, alkylation of the anion of **1** with ethyl bromomethylacrylate led directly to the disubstituted pyrimidine, **5** (Scheme 2); such a product could arise if rearrangement was exceptionally rapid and was followed by a subsequent O-alkylation. The structure of **5** was confirmed by X-ray crystallography.¹³

This reaction suggested that both allyl ether formation and rearrangement surprisingly had taken place at room temperature.

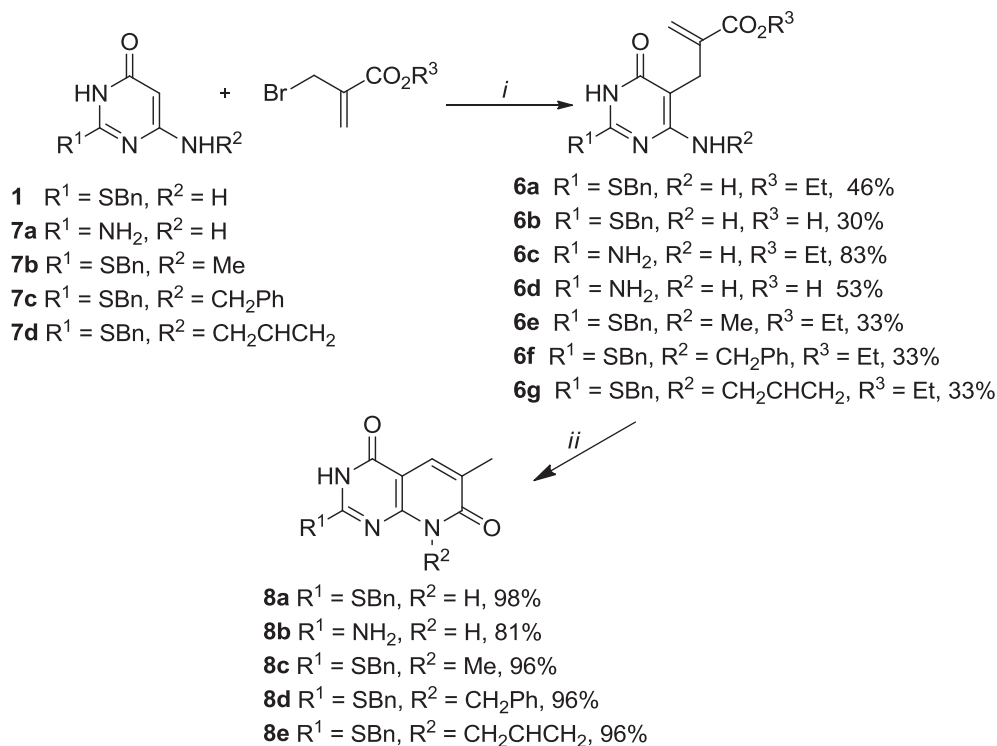
Pyrimidine **1** was therefore treated slowly over a period of days with ethyl bromomethylacrylate at room temperature in the absence of added base to afford the rearranged C5 alkylated product **6a** (46%). Similar reactions occurred between **1** and bromomethylacrylic acid to give **6b** (30%), as well as on the 2-aminopyrimidine **7a** to give **6c** and **6d** in 83 and 53% yield, respectively (Scheme 3). A set of 6-*N*-alkylpyrimidines (**7b–d**) was also prepared in a similar manner. As planned, the C5 alkylated products were cyclised with non-nucleophilic base to afford a set of pyrido[2,3-*d*]pyrimidine-7(8*H*)-ones (**6f–g**). Optimisation of the cyclisation conditions of the C5 alkylated Claisen rearrangement products **6** showed that triazabicyclodecane (TBD) was more effective than diazabicycloundecane (DBU) and yields of >80% were reproducibly obtained leading to a series of 2-alkylthiopyrido[2,3-*d*]-3(4*H*),7(8*H*)-diones (Scheme 3) from which a library of compounds through C2 substitution was generated (**8a–e**).

2.2. Lewis acid catalysed rearrangement and cyclisation

In principle, the bromomethylacrylate substitution and Claisen rearrangement leads to pyrido[2,3-*d*]pyrimidindiones with diversity at two positions and efforts were made to extend the reaction using more highly substituted acrylates without success. However the Claisen rearrangement route has further potential for the synthesis of diverse pyrido[2,3-*d*]pyrimidines if ketones are used in place of esters. β-Halomethyl arylidene ketones are readily available through the Baylis–Hillman reaction using methyl vinyl ketone and the appropriately substituted aldehyde.¹⁴ Such compounds **9a**, **9b** were found to react readily with the benzylthiopyrimidinone **1** in the presence of cesium carbonate to afford the O-alkyl products **10a,b** in 60–70% yield. Unlike the previous examples, these compounds are stable at room temperature and do not rearrange cleanly on thermolysis. Base catalysis via an N6 anion formed using sodium hydride or DBU did not



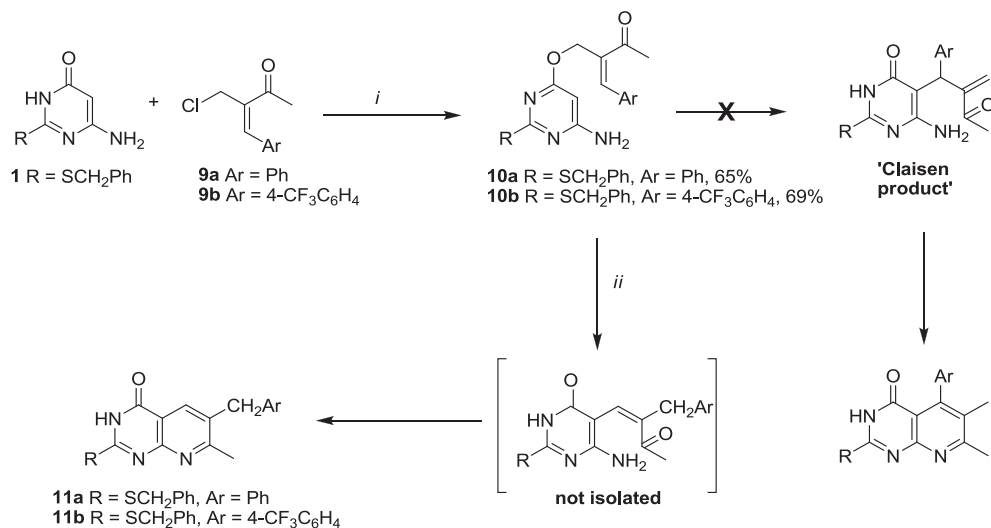
Scheme 2. Preparation of dialkylated pyrimidine **5**. Reagents and conditions: i. DMF, K₂CO₃, 55 °C, 24 h.



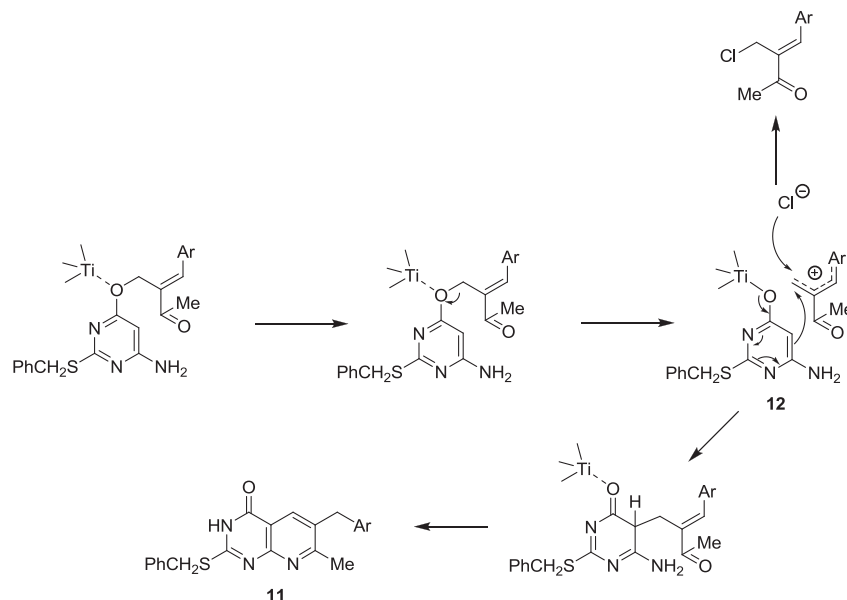
Scheme 3. Reagents and conditions: i. DMF, rt, 7 days; ii. TBD or DBU, MW, 100 °C, 30 min.

promote any reaction. Many metal complexes have been used to accelerate electrocyclic reactions including the Claisen rearrangement.^{11,15} Several Lewis acids were tested for their ability to promote rearrangement of the arylallyl ethers, **10**; boron trifluoride, magnesium dibromide, stannic chloride and zinc chloride failed but titanium tetrachloride (10 mol)^{16,17} induced both a rearrangement and concomitant cyclisation to afford the 6-arylmethylpyrido[2,3-*d*]pyrimidines **11a,b** in modest yield (Scheme 4). It is notable that these are not the expected products of Claisen rearrangement and subsequent cyclisation, which would be 5-aryl-6,7-dimethylpyrido[2,3-*d*]pyrimidines. Titanium tetrachloride catalysis has therefore caused the reaction to follow another course; the proposed mechanism for the reaction is shown in Scheme 5.

Increasing the molar proportion of titanium tetrachloride up to 50 mol% also failed to improve yields. Indeed the major product under conditions of higher concentration of titanium tetrachloride was the precursor Baylis–Hillman chloro-ketone, **9**. The occurrence of these competing reactions can be rationalised by a mechanism in which titanium tetrachloride generates an electrophile from the allyl ether, possibly with coordination also of the ketone carbonyl group to maintain an essentially intramolecular reaction. The initial coordination of titanium tetrachloride to the pyrimidyl ether would liberate chloride, which, at the higher concentrations, traps the intermediate delocalised allylic cation **12** reverting to the starting material **9**. Nevertheless, two new pyrido[2,3-*d*]pyrimidines **11** were obtained for investigation of the introduction of diversity by modifications at C2 and C4.



Scheme 4. Reagents and conditions: i. Cs_2CO_3 , KI, rt, 24 h; ii. $\text{TiCl}_4 \cdot 2\text{THF}$, THF, reflux, 3 days.

Scheme 5. Proposed mechanism for the synthesis of derivatives **11**.

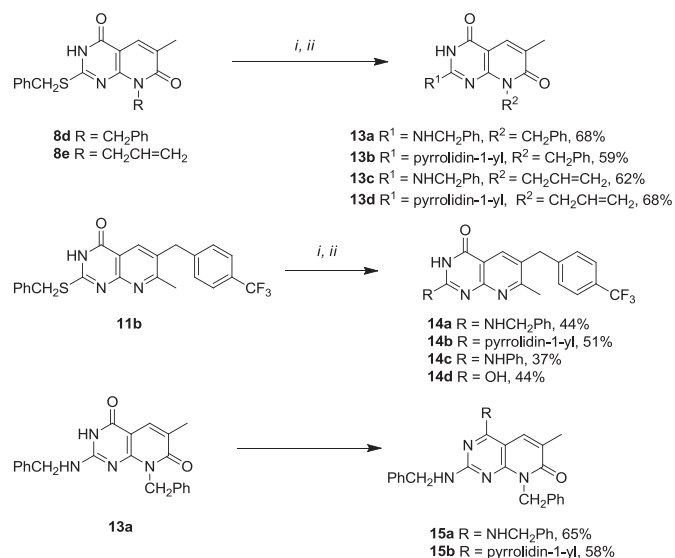
2.3. Diversification

Having established ring syntheses of pyrido[2,3-*d*]pyrimidines **11** from allyl ethers it was necessary to demonstrate diversification of these compounds at the 2-position. Two reactions were investigated, firstly oxidation of benzylthio substituents followed by nucleophilic substitution and secondly conversion of a 4-oxo substituent into a 4-aminoalkyl substituent using BOP (benzotriazole-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate) and the corresponding amine.¹⁸ The oxidation/substitution sequence is successful and in high yield (typically 85–95%) with pteridines and other compounds with electron deficient rings fused to pyrimidines.^{19–21} In many cases with pteridines as substrates, oxidation was not required before nucleophilic substitution of the alkylthio group. In this study, the range of examples has been extended to 4-aminoalkyl pteridines as substrates, the latter being available through BOP chemistry as noted above.¹⁸

At the other extreme of reactivity, pyrrolo[2,3-*d*]pyrimidines underwent substitution only after oxidation, under vigorous conditions and in much lower yields.⁵ It would be reasonable to expect that the reactivity of pyrido[2,3-*d*]pyrimidines to nucleophilic substitution after oxidation would lie between these two extremes and this indeed proved to be the case. The 7-oxopyrido[2,3-*d*]pyrimidines **8d** and **8e** gave **13a–d** in yields typically of 50–60%, somewhat greater than those for the pyrido[2,3-*d*]pyrimidines **11b** lacking the 7-oxo group, which afforded typically 35–55% yields of **14a–d** under the same conditions.

A further reaction of value in the diversification of oxo-heterocycles has been demonstrated by scientists from Wyeth who showed that oxo substituents in 4- and 7-positions especially could be converted into aminoalkyl substituents by treatment with BOP and the required amine.¹⁸ This reaction was successful with **13a** as a representative pyridopyrimidine substrate affording pentasubstituted pyrido[2,3-*d*]pyrimidines **15a** and **15b** in satisfactory yield (55–65%, Scheme 6).

In the pteridine series, both oxidative substitution and BOP-activated substitution were successful; the former gave a series of 2-alkylamino-4-oxopteridines (**17a–h**) in good yield and the latter, 4-aminoalkyl pteridines (**18a–f**) in acceptable to good yields (65–80%) (Scheme 7). That the order of substitution at C2 and C4



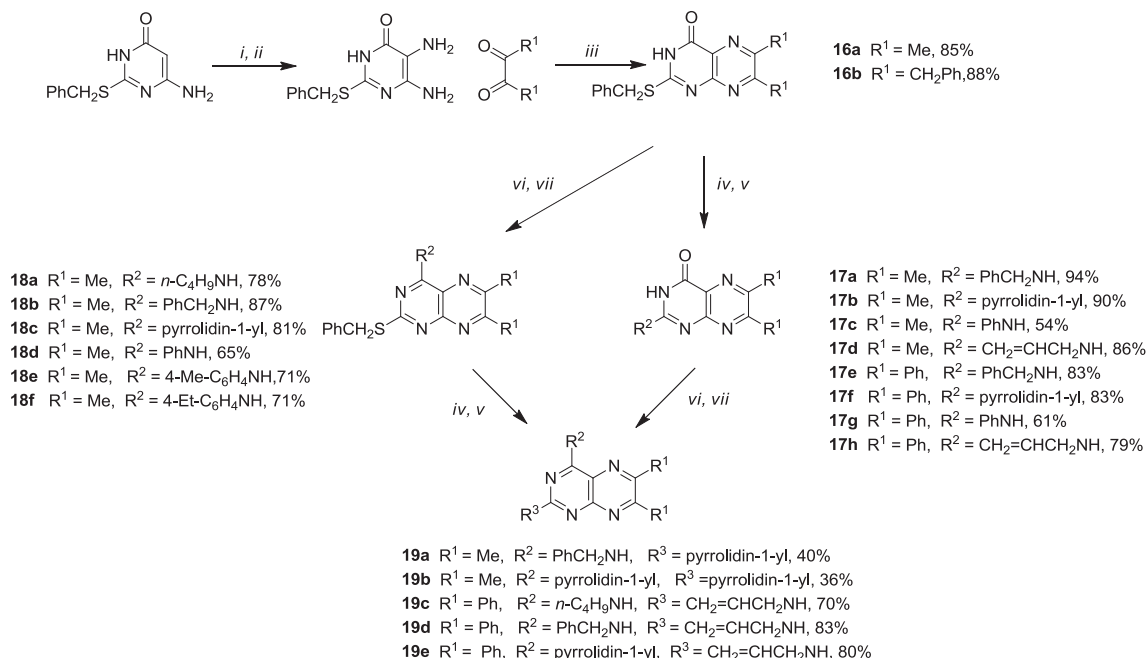
Scheme 6. Diversification reactions for pyrrolopyrimidines. Reagents and conditions: i, DMF, *m*-CPBA, rt, 3 h; ii, appropriate amine, MW, 110 °C, 1 h; iii, BOP, CHCN, rt, 10 min; iv, DBU, appropriate amine, rt, 48 h.

was not critical was shown by the successful oxidative substitution of the new 4-alkylaminopteridines by a variety of amines to give **19a–e** although yields were poorer for the BOP-mediated substitution (~30%).

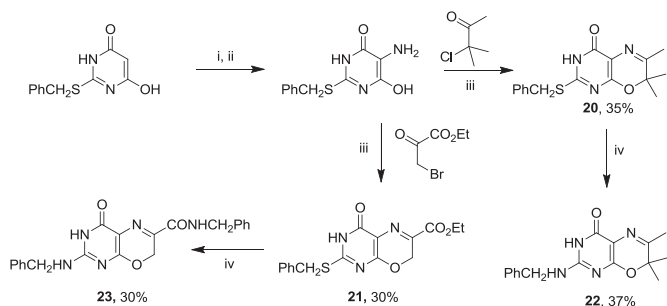
As a third example of a class of compounds for diversification, two pyrimido-oxazines, **20** and **21** were substituted directly with benzylamine without oxidative alkylation. In addition to substitution at C2, in the case of **21**, the C6 ester substituent underwent condensation affording the 6-benzylcarboxamide, **23** (Scheme 8). Direct substitution of methylthio groups in related pterins in moderate yield has been reported previously.²¹

2.4. Conclusions and biological activity

In summary, we find that of the fused pyrimidines we have examined in this and in previous work, alkylthiopteridines undergo nucleophilic substitution most readily.^{19,22} Thus in pteridines,



Scheme 7. Diversification reactions for pteridines. Reagents and conditions: i, HNO_2 ; ii, $\text{Na}_2\text{S}_2\text{O}_4$; iii, EtOH, reflux; iv, DMF, *m*-CPBA, rt, 3 h; v, appropriate amine, MW, 110 °C, 1 h; vi, BOP, CH_3CN , rt, 10 min; vii, DBU, appropriate amine, rt, 48 h.



Scheme 8. Diversification for pyrimido-oxazines. Reagents and conditions: i, HNO_2 ; ii, $\text{Na}_2\text{S}_2\text{O}_4$; iii, aq EtOH, NaOAc, reflux; iv PhCH_2NH_2 , MW, 110 °C, 1 h.

substitution after oxidation of the alkylthio group occurred at room temperature in 30–60% yield with water, azide, primary and secondary amines as nucleophiles. Pyrido[2,3-*d*]pyrimidines, as described above, are somewhat less reactive, requiring higher temperature and concentration of nucleophile to obtain a good yield. To a small extent, the 7-oxo group, which can assist in the delocalisation of charge in the intermediate in nucleophilic substitution, appears to give better yields. Pyrrolo[2,3-*d*]pyrimidines were the least reactive substrates requiring the use of neat amine as nucleophile and temperatures above 130 °C to effect substitution;^{5,23} this behaviour is consistent with the more electron rich pyrrole fused to the pyrimidine ring. In the pteridine series, substitution at C2 and C4 can be undertaken in either order using oxidation/substitution or BOP activation/substitution chemistry. Taken together, all of these methods provide access to a wide range of fused pyrimidines diversely substituted at a late stage in the pyrimidine ring.

We have described elsewhere how this approach has led to compounds with significant biological activity, especially in anti-parasitic applications.^{5,23} The biological activity of the compounds prepared in this study has been assessed in screens for antibacterial and antiparasitic properties. None of the pyrimido-oxazines was found to be active in any assay used. There was no significant antibacterial activity observed against *Staphylococcus aureus*, or *Escherichia coli*, but two of the 4-oxopteridines, **17g** and **17h** had

weak but measurable activity against the Gram positive bacterium, *Nocardia farcinia* (MIC=50 and 100 μM , respectively). On the other hand, several 4-amino substituted compounds were hits in a cell based assay against the parasite *T. brucei brucei*. In the pteridine series, both 2-alkylamino and 2-thiobenzyl compounds were active (**18a**, MIC=25 μM ; **18c**, 12.5; **18d**, 25; **18e**, 12.5; **18f**, 12.5; **19c**, 3.1; **19d**, 3.1; **19e**, 6.3); the most active compounds were the 2,4-dialkylamino compounds, **19c–e**. The pyridopyrimidin-2,4-dione **14d** was also a modest hit with a MIC of 25 μM . All of these compounds are, however, inferior as antiparasitic compounds to the pyrrolopyrimidines we have already described²³ because they have unacceptably high values of clog P (6–7). Nevertheless, the results reported here serve to illustrate the value of diversity oriented synthesis on heterocyclic templates in the discovery of biologically active compounds.

3. Experimental

3.1. Instrumentation and general methods

NMR spectra were recorded on a Bruker Spectrospin spectrometer operating at 400 MHz for ^1H spectra and 100 MHz for ^{13}C spectra. The following abbreviations were used: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad. Coupling constants (*J*) are quoted in hertz. Chemical shifts are reported as parts per million relative to the residual protio solvent resonance spectra were determined using a Mattson 1000 FT spectrometer or a Nicolet Impact 400D FT spectrometer as a KBr disc. Mass spectra were measured on a JEOL JMS AX505 spectrometer at the University of Strathclyde using electrospray (ES), or chemical ionisation (CI) methods. Accurate mass was recorded at the University of Glasgow on Jeol JMS-7 MStation high resolution magnetic sector using electron impact (EI) or fast atom bombardment (FAB) ionisation. Melting points, where measurable, were determined on a Reichert hot stage apparatus and are uncorrected. Microanalysis is typically unreliable in polyazabicyclic compounds due to poor combustion even in the presence of a catalyst (WO_3); microanalytical data is reported where satisfactory and 400 MHz ^1H NMR spectra are included in the [Electronic Supplementary Data](#). TLC was

carried out on silica (Merck 0.25 mm 60 F₂₅₄) visualising the plates with either aqueous potassium permanganate solution or UV; whilst suitable for monitoring reactions and product purity, with these highly polar compounds, *R_f* values vary from run to run and have therefore not been given. Column chromatography was carried out using silica gel (230–400 mesh; 40–60 mm). All reagents were bought from Aldrich (Gillingham, Dorset, U.K.). Microwave reactions were carried out on a Biotage Initiator 2.0. HPLC was carried out on a Waters machine equipped with a 1525 binary HPLC pump, Waters 2487 dual λ absorbance detector, and Breeze software using Vydac protein and peptide C18 column, λ =254 nm. Gradient elution was with water/acetonitrile with or without trifluoroacetic acid.

3.2. Experimental procedures

3.2.1. 6-Amino-2-(benzylthio)pyrimidin-4(3H)-one **1**¹⁹. Compound **1** was prepared as previously described.

3.2.2. 6-(Allyloxy)-2-(benzylthio)-pyrimidin-4-amine **2 and 3-allyl-6-amino-2-(benzylthio)pyrimidin-4(3H)-one **3****. To 6-amino-2-(benzylsulfanyl)pyrimidin-4(3H)-one **1** (1.790 g, 7.67 mmol) in anhydrous DMF (20 mL) was added allyl bromide (700 μ L, 0.980 g, 8.03 mmol, 1.05 equiv) and potassium carbonate (1.24 g, 8.98 mmol, 1.17 equiv). The reaction mixture was left stirring at 100 °C for 20 h. The reaction mixture was cooled to room temperature, filtered under vacuum and the solvent evaporated under reduced pressure. The residue was dissolved in water (20 mL) and extracted with DCM (50 mL). The organic layers were combined, dried over MgSO₄ and concentrated under reduced pressure to give a pale yellow solid. The crude product was purified by column chromatography using ethyl acetate (100%) as eluant to give 6-(allyloxy)-2-(benzylthio)-pyrimidin-4-amine **2** as a pale yellow crystalline solid (0.924 g, 3.38 mmol, 62%) and 3-allyl-6-amino-2-(benzylthio)pyrimidin-4(3H)-one **3** as a white crystalline solid (0.127 g, 0.464 mmol, 9%).

Characterisation of **2**: mp 80–82 °C. ν_{max} (KBr): 3477, 3302, 3143, 1642, 1549, 1469, 1430, 1336, 1205, 984, 933, 815, 716, 696, 592 cm⁻¹; δ_{H} (DMSO-*d*₆): 4.30 (2H, s, CH₂S), 4.73 (2H, d, *J*=5.6 Hz, CH₂O), 5.20 (1H, d, *J*=10.8 Hz, CH=CH₂), 5.33 (1H, d, *J*=16.0 Hz, CH=CHH), 5.45 (1H, s, H-5), 5.94–6.04 (1H, m, CH=CH₂), 6.75 (2H, br s, NH₂), 7.21–7.31 (3H, m, C₆H₅), 7.39–7.41 (2H, m, C₆H₅); δ_{C} (DMSO-*d*₆): 33.8, 66.0, 81.9, 117.4, 126.9, 128.3, 128.8, 133.6, 138.6, 165.2, 168.3, 168.8. HRMS (EI): M⁺, found 273.0936. C₁₄H₁₅N₃O₅ requires 273.0936.

Characterisation of **3**: mp 167–174 °C (slow decomposition). ν_{max} (KBr): 3391, 3316, 3186, 1644, 1620, 1508, 1453, 1424, 1289, 1253, 1197, 1127, 1025, 913, 800, 635 cm⁻¹; δ_{H} (DMSO-*d*₆): 4.39 (2H, s, CH₂N), 4.45 (2H, s, CH₂S), 4.94 (1H, s, H-5), 5.01 (1H, d, *J*=17.6 Hz, CH=CHH), 5.12 (1H, d, *J*=10.4 Hz, CH=CH₂), 5.70–5.80 (1H, m, CH=CH₂), 6.57 (2H, br s, NH₂), 7.24–7.33 (3H, m, C₆H₅), 7.44–7.46 (2H, m, C₆H₅); δ_{C} (DMSO-*d*₆): 35.1, 44.3, 80.7, 116.8, 127.4, 128.4, 129.3, 132.1, 137.0, 160.5, 161.2 (\times 2). HRMS (EI): M⁺, found 273.0936. C₁₄H₁₅N₃O₅ requires 273.0936.

3.2.3. 5-Allyl-6-amino-2-(benzylthio)-4(3H)-pyrimidinone **4**. 6-(Allyloxy)-2-(benzylsulfanyl)-4-pyrimidinylamine **2** (0.310 g, 1.13 mmol) was heated to 200 °C under nitrogen for 24 h using a sand bath. The resulting brown solid was dissolved in methanol (15 mL) and filtered. The excess solvent was removed under reduced pressure and the resulting solid was purified by flash chromatography to yield the title compound **4** as a white solid (0.290 g, 1.06 mmol, 92%), mp 152–154 °C. ν_{max} (KBr): 3400, 3925, 1625, 1610, 1582, 1470, 1410, 1305, 1206, 1046, 934, 815, 717, 637, 593 cm⁻¹; δ_{H} (DMSO-*d*₆): 2.50 (2H, d, *J*=8.0 Hz, CH₂CH=), 4.72 (2H, s, CH₂S), 4.94 (1H, d, *J*=10.4 Hz, CH=CH₂), 5.05 (1H, d, *J*=16.0 Hz, CH=CH₂), 5.67–5.89 (1H, m, CH=CH₂), 6.26 (2H, br s, NH₂), 7.18–7.30 (3H, m, C₆H₅), 7.37–7.47 (2H, m,

C₆H₅), 11.66 (1H, br s, NH); δ_{C} (DMSO-*d*₆): 26.4, 33.1, 90.6, 114.2, 127.1, 128.3, 129.1, 135.4, 137.9. HRMS (EI): M⁺, found 273.0939. C₁₄H₁₅N₃O₅ requires 273.0936.

3.2.4. Ethyl 2-[(4-amino-2-(benzylsulfanyl)-6-[[2-(ethoxycarbonyl)-2-propenyl]oxy]5-pyrimidinyl)methyl]acrylate **5**. 6-Amino-2-(benzylthio)pyrimidin-4(3H)-one **1** (0.690 g, 2.95 mmol) was dissolved in DMF (12 mL, anhydrous) at room temperature under nitrogen. Ethyl 2-(bromomethyl)acrylate (610 μ L, 4.40 mmol, 1.50 equiv) and potassium carbonate (0.500 g, 3.62 mmol, 1.23 equiv) were added and the reaction mixture was stirred at 55 °C for 24 h. Once the reaction was complete (confirmed by TLC), the mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The subsequent yellow oil was dissolved in DCM, the organics were extracted with brine and dried over MgSO₄ and concentrated under reduced pressure to give a yellow oil. Purification of the crude product was achieved using column chromatography using ethyl acetate/hexane (1:1) as eluant. The title compound **5** was isolated as a white solid (0.114 g, 0.249 mmol, 8%), mp 110–112 °C. ν_{max} (KBr): 3407, 3323, 3191, 2991, 1707, 1652, 1572, 1493, 1474, 1444, 1401, 1376, 1316, 1264, 1158, 1050, 956, 855, 776, 563 cm⁻¹; δ_{H} (DMSO-*d*₆): 1.15–1.26 (6H, m, CH₃ \times 2), 3.33 (2H, s, CH₂=C(CO₂Et)CH₂), 4.09–4.20 (4H, m, CH₂ \times 2), 4.29 (2H, s, CH₂S), 4.98 (2H, s, CH₂O), 5.14 (1H, s, =CHH), 5.75 (1H, s, =CHH), 5.99 (1H, s, =CHH), 6.19 (1H, s, =CHH), 6.19 (2H, br s, NH₂), 7.19–7.31 (3H, m, C₆H₅), 7.39–7.41 (2H, m, C₆H₅); δ_{C} (DMSO-*d*₆): 13.9, 14.0, 24.4, 33.8, 60.3, 60.5, 63.5, 90.7, 123.1, 126.1, 126.8, 128.3, 128.8, 136.3, 137.0, 138.7, 163.4, 164.8, 165.4, 166.2, 166.2, 166.4. HRMS (ES): M+H⁺, found 458.1650. C₂₃H₂₇N₃O₅ requires 458.1671.

3.2.5. Ethyl 2-[(4-amino-2-(benzylsulfanyl)-1,6-dihydro-6-oxopyrimidin-5-yl)methyl]acrylate **6a**. 6-Amino-2-(benzylthio)pyrimidin-4(3H)-one **1** (0.520 g, 2.22 mmol) was dissolved in DMF (10 mL, anhydrous) to which ethyl 2-(bromomethyl)acrylate (310 μ L, 2.24 mmol) was added. The reaction mixture was then stirred under nitrogen for 7 days at room temperature prior to the concentration of excess solvent under reduced pressure. The resulting residue was purified by flash column chromatography using hexane/ethyl acetate (2:1) as eluant. The title compound **6a** was obtained as a white crystalline solid (0.340 g, 0.998 mmol, 44%), mp 160–162 °C. ν_{max} (KBr): 3483, 3368, 1693, 1614, 1475, 1438, 1333, 11,260, 1187, 1152, 1029, 953, 693 cm⁻¹; δ_{H} (DMSO-*d*₆): 1.27 (3H, t, *J*=7.6 Hz, CH₃), 3.18 (2H, s, CH₂C=), 4.19 (2H, q, *J*=7.6 Hz, CH₂CH₃), 4.34 (2H, s, CH₂S), 5.22 (1H, s, C=CH₂), 5.97 (1H, s, C=CH₂), 6.34 (2H, br s, NH₂), 7.21–7.34 (3H, m, C₆H₅), 7.43–7.46 (2H, m, C₆H₅), 11.70 (1H, br s, NH); δ_{C} (DMSO-*d*₆): 14.1, 24.7, 33.1, 60.2, 89.2, 122.7, 127.1, 128.4, 129.2, 137.3, 137.8, 160.4, 163.0, 166.8 (\times 2). HRMS (EI): M⁺, found 345.1149. C₁₇H₁₉N₃O₃S requires 345.1147.

Similarly prepared were:

3.2.6. 2-[(4-Amino-2-(benzylsulfanyl)-6-oxo-1,6-dihydro-5-pyrimidinyl)methyl]acrylic acid **6b**. From 6-amino-2-(benzylthio)pyrimidin-4(3H)-one **1** and 2-(bromomethyl)acrylic acid using 2 equiv of the latter added over 2 days and a further 5 days reaction in 30% yield, mp 157–159 °C. ν_{max} (KBr): 3444, 3003, 1705, 1642, 1552, 1320, 1207, 1017, 929, 843, 710 cm⁻¹; δ_{H} (DMSO-*d*₆): 3.07 (2H, s, CH₂C=), 4.31 (2H, s, CH₂S), 5.91 (1H, br s, C=CH₂), 6.33 (1H, br s, C=CH₂), 6.36 (2H, s, NH₂), 7.20–7.40 (3H, m, C₆H₅), 7.41–7.53 (2H, m, C₆H₅), 12.01 (1H, br s, NH); δ_{C} (DMSO-*d*₆): 34.0, 79.6, 124.7, 128.1, 128.6, 129.5, 137.5, 138.7, 158.3, 164.6, 166.2, 172.6. HRMS (EI): M⁺, found 317.0831. C₁₅H₁₅N₃O₃S requires 317.0834.

3.2.7. Ethyl 2-[(2,4-diamino-6-oxo-1,6-dihydro-5-pyrimidinyl)methyl]acrylate **6c**. From 2,6-diamino-4(3H)-pyrimidinone **7a** and ethyl 2-(bromomethyl)acrylate reacting for 3 days in 83% yield, mp 120–122 °C. ν_{max} (KBr): 3455, 3341, 3176, 1698, 1629, 1500, 1446,

1372, 1260, 1151, 1023, 779, 647 cm^{-1} ; δ_{H} (DMSO- d_6): 1.24 (3H, t, $J=7.1$ Hz, CH_3), 3.05 (2H, s, $\text{CH}_2\text{—C=}$), 4.14 (2H, q, $J=7.1$ Hz, CH_2CH_3), 5.26 (1H, d, $J=1.7$ Hz, $\text{CH}_2\text{=}$), 5.67 (2H, s, NH_2), 5.94 (1H, d, $J=1.7$ Hz, $\text{CH}_2\text{=}$), 6.02 (2H, br s, NH_2), 9.86 (1H, br s, NH); δ_{C} (DMSO- d_6): 14.2, 25.1, 60.2, 83.4, 122.6, 137.4, 152.3, 157.7, 161.8, 166.7. HRMS (EI): M^+ , found 238.1070. $\text{C}_{10}\text{H}_{14}\text{N}_4\text{O}_3$ requires 238.1066.

3.2.8. 2-((2,4-Diamino-1,6-dihydro-6-oxopyrimidin-5-yl)methyl)acrylic acid **6d.** From 2,6-diaminopyrimidin-4(3H)-one **7a** and 2-(bromomethyl)acrylic acid using 2 equiv of the latter added over 2 days and a further 5 days reaction in 53% yield, mp >230 °C. ν_{max} (KBr): 3378, 3199, 2972, 2758, 1707, 1647, 1604, 1511, 1419, 1282, 1237, 1193, 1116, 1091, 958, 808, 617, 550 cm^{-1} ; δ_{H} (DMSO- d_6): 2.45 (2H, s, $\text{CH}_2\text{—C=}$), 5.28 (1H, s, C=CH_2), 5.90 (1H, s, C=CH_2), 6.13 (2H, br s, NH_2), 7.08 (2H, br s, NH_2), 10.94 (1H, br s, NH), 11.22 (1H, br s, CO_2H); δ_{C} (DMSO- d_6): 24.2, 84.3, 122.7, 138.1, 152.0, 162.1, 162.3, 168.5. HRMS (EI): M^+ , found 211.0832. $\text{C}_8\text{H}_{10}\text{N}_4\text{O}_3$ requires 211.0831.

3.2.9. Ethyl 2-[[2-(benzylsulfanyl)-4-(methylamino)-6-oxo-1,6-dihydro-5-pyrimidinyl]methyl]acrylate **6e.** From 2-(benzylsulfanyl)-6-(methylamino)-4(3H)-pyrimidinone **7b** and ethyl 2-(bromomethyl)acrylate with a reaction time of 4 days in 33% yield, mp 171–173 °C. ν_{max} (KBr): 3503, 3367, 1670, 1618, 1483, 1452, 1370, 1181, 707 cm^{-1} ; δ_{H} (CDCl_3): 1.24 (3H, t, $J=7.1$ Hz, CH_3), 2.93 (3H, s, NHCH_3), 3.26 (2H, s, $\text{CH}_2\text{C=}$), 4.14 (2H, q, $J=7.1$ Hz, CH_2CH_3), 4.36 (2H, s, CH_2S), 5.85 (1H, d, $J=1.4$ Hz, $\text{CH}_2\text{=}$), 5.95 (1H, d, $J=1.4$ Hz, $\text{CH}_2\text{=}$), 6.12 (1H, m, NH), 7.18–7.33 (5H, m, C_6H_5), 12.48 (1H, br s, NH); δ_{C} (CDCl_3): 14.2, 24.5, 28.7, 34.5, 61.1, 92.7, 127.4, 127.7, 128.6, 128.9, 137.0, 137.6, 158.2, 160.1, 164.2, 169.0. HRMS (EI): M^+ , found 359.1303 requires $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$ 359.1304.

3.2.10. Ethyl 2-[[4-(benzylamino)-2-(benzylsulfanyl)-6-oxo-1,6-dihydro-5-pyrimidinyl]methyl]acrylate **6f.** From 2-(benzylsulfanyl)-6-(benzylamino)-4(3H)-pyrimidinone **7c** and ethyl 2-(bromomethyl)acrylate with four reaction in 33% yield, mp 168–171 °C. ν_{max} (KBr): 3478, 3165, 1774, 1661, 1559, 1534, 1459, 1205, 986 cm^{-1} ; δ_{H} (CDCl_3): 1.32 (3H, t, $J=7.1$ Hz, CH_3), 3.35 (2H, s, $\text{CH}_2\text{—C=}$), 4.11 (2H, q, $J=7.1$ Hz, CH_2CH_3), 4.25 (2H, d, $J=5.5$ Hz, CH_2NH), 4.45 (3H, s, CH_2S), 5.95 (1H, d, $J=1.5$ Hz, $\text{CH}_2\text{=}$), 6.04 (1H, d, $J=1.5$ Hz, $\text{CH}_2\text{=}$), 6.15 (1H, t, $J=5.5$ Hz, NHCH_2), 7.47–7.22 (10H, m, $2 \times \text{C}_6\text{H}_5$), 12.96 (1H, br s, NH). HRMS (FAB): $\text{M}^+ + \text{H}$, found 436.1694. $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$ requires 436.1695.

3.2.11. Ethyl 2-[[4-(allylamino)-2-(benzylsulfanyl)-6-oxo-1,6-dihydro-5-pyrimidinyl]methyl]acrylate **6g.** Compound **6g** as a pale yellow solid in 33% yield, mp 165–168 °C. ν_{max} (KBr): 3503, 3367, 1670, 1618, 1483, 1452, 1370, 1181, 707 cm^{-1} ; δ_{H} (CDCl_3): 1.31 (3H, t, $J=7.1$ Hz, CH_3), 3.37 (2H, s, $\text{CH}_2\text{—C=}$), 4.08–4.12 (2H, m, CH_2NH), 4.22 (2H, q, $J=7.1$ Hz, CH_2CH_3), 4.40 (2H, s, CH_2S), 5.12 (1H, d, $J=1.5$ Hz, $\text{CH}_2\text{=}$), 5.16 (1H, d, $J=1.5$ Hz, $\text{CH}_2\text{=}$), 5.85–5.94 (1H, m, CH=CH_2), 6.04 (1H, d, $J=1.6$ Hz, CH=CHH), 6.09 (1H, t, $J=5.7$ Hz, NHCH_2), 6.21 (1H, d, $J=1.6$ Hz, CH=CHH), 7.24–7.42 (5H, m, C_6H_5), 13.04 (1H, s, NH); δ_{C} (CDCl_3): 13.2, 23.4, 33.5, 43.0, 60.1, 91.9, 114.5, 126.4, 126.7, 127.6, 127.9, 134.4, 135.8, 136.5, 157.3, 158.3, 163.5, 167.9. HRMS (FAB): $\text{M}^+ + \text{H}$, found 386.1534. $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$ requires 386.1538.

3.2.12. 2-(Benzylsulfanyl)-6-(methylamino)-4(3H)-pyrimidinone **7b.** 2-(Benzylsulfanyl)-6-chloro-4(3H)-pyrimidinone (500 mg, 1.98 mmol) was dissolved in 2.0 M methylamine solution in THF (4.95 mL, 5 equiv). The solution was heated to 80 °C in a sealed tube and stirred for 48 h. The excess solvent was removed under reduced pressure and the residue was taken up in ethyl acetate. The solvent layer was washed with water (2×15 mL) and then saturated aqueous sodium bicarbonate solution (15 mL). The organic layer was then dried over MgSO_4 . The solvent was removed under reduced pressure and the residue was purified by flash

chromatography to yield the title product as a fine white powder (186 mg, 0.0752 mmol, 38%), mp >230 °C. ν_{max} (KBr): 3214, 3059, 1637, 1618, 1421, 1302, 1256, 1207, 1097, 978, 792, 711, 570 cm^{-1} ; δ_{H} (DMSO- d_6): 2.77 (3H, s, CH_3), 4.35 (2H, s, CH_2S), 4.81 (1H, s, H-5), 6.96 (1H, br d, —NHCH_3), 7.23–7.44 (5H, m, C_6H_5), 11.55 (1H, s, NH); δ_{C} (DMSO- d_6): 27.8, 33.1, 127.1, 128.4, 129.0, 137.9, 162.8, 164.0. HRMS (EI): M^+ , found 247.0776. $\text{C}_{12}\text{H}_{13}\text{N}_3\text{OS}$ requires 247.0779.

Similarly prepared were:

3.2.13. 6-(Benzylamino)-2-(benzylsulfanyl)-4(3H)-pyrimidinone **7c.** Compound **7c** as a white solid in 38% yield, mp 230 °C. ν_{max} (KBr): 3450, 3000, 2906, 2818, 1884, 1807, 1650, 1554, 1466, 1351, 1222, 1097, 984, 937, 829, 712, 552 cm^{-1} ; δ_{H} (DMSO- d_6): 4.14 (2H, s, CH_2N), 4.47 (2H, s, CH_2S), 4.90 (1H, s, H-5), 7.22–7.45 (11H, m, $\text{C}_6\text{H}_5 \times 2$ and NHCH_2), 11.54 (1H, s, NH); δ_{C} (DMSO- d_6): 34.3, 44.5, 126.8, 127.0, 127.1, 127.9, 128.3, 137.6, 138.2, 159.3, 162.4, 163.8. HRMS (FAB): $\text{M}^+ + \text{H}$, found 324.1174. $\text{C}_{18}\text{H}_{17}\text{N}_3\text{OS}$ requires 324.1171.

3.2.14. 6-(Allylamino)-2-(benzylsulfanyl)-4(3H)-pyrimidinone **7d.** Compound **7d** as a white solid in 37% yield, mp >230 °C. ν_{max} (KBr): 3214, 3059, 1637, 1618, 1421, 1302, 1256, 1207, 1097, 978, 792, 711, 570 cm^{-1} ; δ_{H} (DMSO- d_6): 3.88 (2H, m, —NH—CH_2), 4.34 (2H, s, CH_2S), 4.89 (1H, s, H-5), 5.10 (1H, d, $J=1.5$, $\text{—CH}_2\text{—CH=CH}_2$), 5.17 (1H, d, $J=1.5$, $\text{—CH}_2\text{—CH=CH}_2$), 5.80 (1H, m, $\text{—CH}_2\text{—CH=CH}_2$), 7.21 (1H, br s, NH), 7.42–7.23 (5H, m, C_6H_5), 11.54 (1H, s, —NH); δ_{C} (DMSO- d_6): 33.2, 42.4, 115.4, 115.6, 127.1, 128.4, 129.0, 134.4, 137.9, 159.2, 162.2, 163.3.

3.2.15. 2-(Benzylsulfanyl)-6-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione **8a.** Ethyl 2-[[4-amino-2-(benzylsulfanyl)-6-oxo-1,6-dihydro-5-pyrimidinyl]methyl]acrylate **6a** (0.100 g, 0.289 mmol) was dissolved in DMF (3 mL, anhydrous) to which 1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidine (0.089 g, 0.597 mmol, 2.2 equiv) was added. The reaction solution was then irradiated in the microwave apparatus at 100 °C for 30 min. The excess solvent was removed under reduced pressure and the resulting residue was dissolved in de-ionised water (10 mL). The reaction solution was adjusted to pH 6–7 using dil acetic acid, which caused a white precipitate to form. The precipitate was filtered off and washed with ether (2×10 mL) to yield the title compound **8a** as a white solid (0.085 g, 0.0283 mmol, 98%), mp >230 °C. ν_{max} (KBr): 3450, 3027, 2890, 1953, 1807, 1626, 1590, 1394, 1271, 959, 922, 790, 719, 571 cm^{-1} ; δ_{H} (DMSO- d_6): 2.01 (3H, s, CH_3), 4.43 (2H, s, CH_2S), 7.23–7.33 (3H, m, C_6H_5), 7.53–7.67 (2H, m, C_6H_5), 7.68 (1H, s, H-5), 12.27 (1H, br s NH), 12.73 (1H, br s, NH); δ_{C} (TFA): 14.1, 35.3, 102.9, 127.3, 127.8, 128.4, 128.7, 134.2, 137.6, 151.5, 164.2, 166.5. HRMS (FAB): $\text{M}^+ + \text{H}$, found 300.0816. $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_2\text{S}$ requires 300.0807.

Similarly prepared were:

3.2.16. 2-Amino-6-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione **8b.** Compound **8b** as a highly insoluble beige solid in 81% yield, mp >230 °C. ν_{max} (KBr): 3443, 3413, 3141, 1698, 1673, 1458, 1351, 1112, 841; δ_{H} (TFA): 2.32 (3H, s, CH_3), 8.12 (1H, s, H-5); δ_{C} (TFA): 16.4, 100.2, 130.1, 138.6, 145.5, 153.3, 161.3, 167.8.

3.2.17. 2-(Benzylsulfanyl)-6,8-dimethylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione **8c.** Compound **8c** as a white solid in 96% yield, mp >230 °C. ν_{max} (KBr): 2854, 1642, 1537, 1492, 1453, 1281, 1152, 988, 789, 701, 570 cm^{-1} ; δ_{H} (DMSO- d_6): 2.06 (3H, s, CCH_3), 3.62 (3H, s, NCH_3), 4.53 (2H, s, CH_2S), 7.26–7.48 (5H, m, C_6H_5), 7.74 (1H, s, H-5), 12.97 (1H, s, NH); δ_{C} (DMSO- d_6): 14.1, 35.3, 102.9, 127.3, 127.8, 128.4, 128.7, 134.2, 137.6, 151.5, 164.2, 166.5. HRMS (FAB): $\text{M}^+ + \text{H}$, found 314.0962. $\text{C}_{16}\text{H}_{16}\text{N}_3\text{O}_2\text{S}$ requires 314.0963.

3.2.18. 8-Benzyl-2-(benzylsulfanyl)-6-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione **8d.** Compound **8d** as a white solid in 96%

yield, mp >230 °C. ν_{\max} (KBr): 3452, 3183, 1642, 1629, 1588, 1465, 1264, 1098, 964, 951; δ_{H} (DMSO- d_6): 2.01 (3H, s, CH₃), 4.48 (2H, s, CH₂S), 5.35 (2H, s, CH₂N), 7.21–7.36 (10H, m, C₆H₅ × 2), 7.71 (1H, s, H-5), 12.98 (1H, s, NH); δ_{C} (DMSO- d_6): 16.6, 33.8, 43.9, 99.4, 120.6, 127.0, 127.3, 127.6, 128.0, 128.1, 128.3, 132.7, 138.1, 152.2, 160.8, 161.1, 165.3. HRMS (FAB): M⁺+H, found 390.1276. C₂₂H₁₉N₃O₂S requires 390.1276.

3.2.19. 8-Allyl-2-(benzylsulfanyl)-6-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione 8e. Compound **8e** as a white solid in 96% yield, mp >230 °C. ν_{\max} (KBr): 2854, 1642, 1537, 1492, 1453, 1281, 1152, 988, 789, 701, 570 cm⁻¹; δ_{H} (DMSO- d_6): 2.00 (3H, s, CH₃), 4.47 (2H, s, CH₂S), 4.91 (2H, d, J =2.1 Hz, CH₂–CH=), 4.95 (1H, dd, J =17.2, 1.6 Hz, CH=CHH), 5.07 (1H, dd, J =10.3, 1.6 Hz, CH=CHH), 5.86–5.93 (1H, m, CH=CH₂), 7.25–7.42 (5H, m, C₆H₅), 7.75 (1H, s, H-5), 12.99 (1H, s, NH); δ_{C} (DMSO- d_6): 16.8, 33.8, 43.4, 99.8, 116.3, 125.1, 127.4, 128.6, 128.8, 131.3, 133.0, 136.8, 151.8, 160.5, 161.3, 162.2. HRMS (FAB): M⁺+H, found 340.1119. C₁₈H₁₇N₃O₂S requires 340.1120.

3.2.20. 3-([6-Amino-2-(benzylsulfanyl)-4-pyrimidinyl]oxy)methyl-4-phenyl-3-buten-2-one 10a. 6-Amino-2-(benzylsulfanyl)pyrimidin-4(3H)-one **1** (0.250 g, 1.07 mmol) was dissolved in DMF (15 mL, anhydrous) to which cesium carbonate (0.348 g, 1.07 mmol, 1.0 equiv), 3-(chloromethyl)-4-phenyl-3-buten-2-one¹⁵ (0.250 g, 1.28 mmol, 1.2 equiv) and potassium iodide (0.035 g, 0.214 mmol, 0.2 equiv) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then filtered and partitioned between water and ethyl acetate. The ethyl acetate layer was then dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography to yield the *title compound 10a* as a pale yellow solid (0.273 g, 0.70 mmol, 65%), mp 146–148 °C. ν_{\max} (KBr): 3476, 3350, 3230, 1964, 1643, 1626, 1514, 1425, 1396, 1300, 1270, 1196, 1035, 803, 759, 700 cm⁻¹; δ_{H} (CDCl₃): 2.49 (3H, s, CH₃), 4.32 (2H, s, CH₂S), 4.67 (2H, br s, NH₂), 5.15 (2H, s, OCH₂), 5.53 (1H, s, H-5), 7.17–7.44 (10H, m, C₆H₅ × 2), 7.82 (1H, s, C=CH); δ_{C} (CDCl₃): 27.0, 34.7, 60.4, 82.8, 135.3, 136.0, 139.5, 146.0, 166.1, 169.2, 169.7, 199.4. HRMS (EI): M⁺, found 391.1356. C₂₂H₂₁N₃O₂S requires 391.1354.

3.2.21. 3-([6-Amino-2-(benzylsulfanyl)-4-pyrimidinyl]oxy)methyl-4-[4-(trifluoromethyl)phenyl]-3-buten-2-one 10b. 6-Amino-2-(benzylsulfanyl)pyrimidin-4(3H)-one **1** (250 mg, 1.07 mmol) was dissolved in DMF (15 mL, anhydrous) to which cesium carbonate (0.348 g, 1.07 mmol, 1.0 equiv), 3-(chloromethyl)-4-[4-(trifluoromethyl)phenyl]-3-buten-2-one¹⁵ (0.267 g, 1.28 mmol, 1.2 equiv) and potassium iodide (0.035 g, 0.214 mmol, 0.2 equiv) was added. The reaction mixture was then filtered and partitioned between water and ethyl acetate. The ethyl acetate layer was dried over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography to yield the *title compound 10b* as a white powder (0.340 g, 0.074 mmol, 69%), mp 145–147 °C. ν_{\max} (KBr): 3477, 3366, 1651, 1625, 1578, 1454, 1424, 1325, 1300, 1195, 1123, 1069, 704 cm⁻¹; δ_{H} (CDCl₃): 2.50 (3H, s, CH₃), 4.31 (2H, s, CH₂S), 4.72 (2H, br s, NH₂), 5.10 (2H, s, OCH₂), 5.51 (1H, s, H-5), 7.18–7.66 (9H, m, C₆H₅ and C₆H₄), 7.78 (1H, s, C=CH); δ_{C} (CDCl₃): 26.4, 35.0, 60.1, 83.4, 125.7, 125.7 (CF₃), 127.0, 128.3, 128.8, 129.7, 137.5, 137.9, 138.0, 142.5, 164.1, 169.0, 170.5, 198.2. HRMS (EI): M⁺, found 459.1232. C₂₃H₂₀F₃N₃O₂S requires 459.1228.

3.2.22. 6-Benzyl-2-(benzylsulfanyl)-7-methylpyrido[2,3-d]pyrimidin-4(3H)-one trifluoroacetate salt 11a. 3-([6-Amino-2-(benzylsulfanyl)-4-pyrimidinyl]oxy)methyl-4-phenyl-3-buten-2-one **10a** (0.250 g, 0.639 mmol) was dissolved in THF (20 mL, anhydrous) to which titanium tetrachloride complex 1:2 THF (0.021 g, 0.0628 mmol) was added. The reaction was refluxed for 3 days

under nitrogen. The excess solvent was removed under reduced pressure and the resulting residue was washed with saturated aqueous NaHCO₃ solution (2 × 10 mL) and de-ionised water (2 × 10 mL). The organic layer was dried over MgSO₄, filtered under reduced pressure and the solvent was removed under reduced pressure. The resulting residue was purified by HPLC to yield the *title compound 11a* as a white solid (0.042 g, 0.112 mmol, 18%), mp 181–183 °C. ν_{\max} (KBr): 3437, 1709, 1662, 1638, 1541, 1186, 797, 700 cm⁻¹; δ_{H} (CDCl₃): 2.65 (3H, s, CH₃), 4.12 (2H, s, CCH₂), 4.68 (2H, s, SCH₂), 7.53–7.12 (10H, m, C₆H₅ × 2), 8.23 (1H, s, H-5), 10.00 (1H, s, NH); δ_{C} (CDCl₃): 19.9, 35.7, 37.7, 114.4, 127.4, 127.9, 128.6, 128.6, 129.3, 129.3, 134.3, 135.1, 136.5, 141.2, 152.8, 160.1, 162.3, 165.5. HRMS (EI): M⁺, found 374.1330. C₂₂H₂₀N₃OS requires 374.1327.

3.2.23. 2-(Benzylsulfanyl)-7-methyl-6-[4-(trifluoromethyl)benzyl]pyrido[2,3-d]pyrimidin-4(3H)-one 11b. 3-([6-Amino-2-(benzylsulfanyl)-4-pyrimidinyl]oxy)methyl-4-[4-(trifluoromethyl)phenyl]-3-buten-2-one **10b** (0.250 g, 0.544 mmol) was dissolved in THF (20 mL, anhydrous) to which titanium tetrachloride complex 1:2 THF (0.018 g, 0.054 mmol) was added. The reaction was refluxed for 3 days under nitrogen. The excess solvent was removed under reduced pressure and was washed with saturated aqueous NaHCO₃ solution. The reaction mixture was filtered and partitioned between water and ethyl acetate. The ethyl acetate layer was dried over MgSO₄, filtered under reduced pressure and the solvent was removed under reduced pressure. The *title compound 11b* was recrystallised from methanol as a white solid (0.055 g, 0.0125 mmol, 23%), mp 195–198 °C. ν_{\max} (KBr): 3027, 2922, 1682, 1570, 1411, 1325, 1164, 1066, 805, 699 cm⁻¹; δ_{H} (CDCl₃): 2.63 (3H, s, CH₃), 4.15 (2H, s, CH₂C), 4.68 (2H, s, CH₂S), 7.23–7.58 (9H, m, C₆H₅ and C₆H₄), 8.26 (1H, s, H-5), 11.57 (1H, s, NH); δ_{C} (CDCl₃): 23.7, 35.5, 38.4, 113.2, 125.4, 125.8, 127.9, 128.8, 128.9, 129.3, 128.8, 132.1, 136.6, 142.4, 157.2, 159.0, 163.2, 166.0. HRMS (EI): M⁺, found 441.1126. C₂₃H₁₈F₃N₃OS requires 441.1123.

3.2.24. 8-Benzyl-2-(benzylamino)-6-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione 13a. 8-Benzyl-2-(benzylsulfanyl)-6-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione **8d** (0.050 g, 0.128 mmol) was dissolved in DMF (3 mL, anhydrous) to which *m*-CPBA (0.066 g, 0.39 mmol, 3 equiv) was added and the mixture was stirred under nitrogen for 3 h at room temperature. The excess solvent was removed under reduced pressure and the residue was dissolved in benzylamine (2.0 mL, 18.31 mmol) and heated in the microwave at 110 °C for 1 h. The excess solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography to yield the *title compound 13a* as a pale yellow solid (0.033 g, 0.088 mmol, 68%), mp >230 °C. ν_{\max} (KBr): 3351, 3316, 2987, 1677, 1648, 1589, 1176, 1049, 949 cm⁻¹; δ_{H} (DMSO- d_6): 2.00 (3H, s, CH₃), 4.51 (2H, d, J =5.5 Hz, NHCH₂), 5.37 (2H, s, NCH₂), 7.18–7.24 (10H, m, C₆H₅ × 2), 7.18–7.24 (1H, m, NH), 7.66 (1H, s, H-5), 11.44 (1H, s, NH); δ_{C} (DMSO- d_6): 14.5, 43.7, 44.0, 95.7, 120.1, 126.7, 126.9, 127.2, 127.6, 128.1, 132.0, 137.8, 138.9, 153.4, 154.6, 161.0, 163.1. HRMS (FAB): M⁺+H, found 373.1662. C₂₂H₂₀N₄O₂ requires 373.1665.

Similarly prepared were:

3.2.25. 8-Benzyl-6-methyl-2-(1-pyrrolidinyl)pyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione 13b. Compound **13b** as a beige solid in 59% yield, mp >230 °C. ν_{\max} (KBr): 3342, 2987, 2852, 1668, 1652, 1441, 1216, 1062, 925 cm⁻¹; δ_{H} (DMSO- d_6): 1.89 (4H, s, CH₂CH₂), 2.01 (3H, s, CH₃), 3.46 (4H, s, CH₂N × 2), 5.37 (2H, s, CH₂N), 7.18–7.33 (5H, m, C₆H₅), 7.67 (1H, s, H-5), 11.16 (1H, s, NH); δ_{C} (DMSO- d_6): 16.6, 24.7, 44.0, 46.2, 94.6, 119.6, 126.8, 127.8, 128.1, 132.2, 138.1, 150.7, 154.3, 161.1, 163.3. HRMS (FAB): M⁺+H, found 337.1667. C₁₉H₂₀N₄O₂ requires 367.1659.

3.2.26. 8-Allyl-2-(benzylamino)-6-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione 13c. Compound **13c** as a beige solid in 62% yield,

mp >230 °C; δ_{H} (DMSO- d_6): 1.98 (3H, s, CH₃), 4.53 (2H, d, $J=5.9$, CH₂NH), 4.75 (2H, d, $J=5.9$, CH₂–CH=), 4.94 (1H, dd, $J=17.2$, 1.5 Hz, CH=CHH), 4.95 (1H, dd, $J=10.3$, 1.5 Hz, CH=CHH), 5.75–5.84 (1H, m, CH=CH₂), 7.24–7.34 (5H, m, C₆H₅), 7.63 (1H, s, H-5), 11.11 (1H, s, NH); δ_{C} (DMSO- d_6): 16.5, 43.1, 43.9, 95.5, 116.6, 120.2, 127.0, 128.3, 131.7, 133.0, 138.8, 152.8, 154.3, 160.3, 162.7. HRMS (FAB): M⁺+H, found 323.1510. C₁₈H₁₈N₄O₂ requires 323.1508.

3.2.27. 8-Allyl-6-methyl-2-(1-pyrrolidinyl)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione **13d.** Compound **13d** as a beige solid 64% yield, mp >230 °C. ν_{max} (KBr): 3161, 2962, 1683, 1652, 1605, 1547, 1524, 1378, 1205, 986 cm⁻¹; δ_{H} (DMSO- d_6): 1.92 (4H, t, $J=6.8$ Hz, CH₂CH₂), 1.99 (3H, d, $J=1.1$ Hz, CH₃), 3.50 (4H, t, $J=6.8$ Hz, CH₂N × 2), 4.81 (2H, dd, $J=7.0$, 1.4 Hz, CH₂–CH=), 5.06 (1H, t, $J=1.5$ Hz, CH=CHH), 5.09 (1H, dd, $J=12.0$, 1.5 Hz, CH=CHH), 5.85–5.95 (1H, m, CH=CH₂), 7.63 (1H, d, $J=1.1$ Hz, H-5), 11.02 (1H, s, NH); δ_{C} (DMSO- d_6): 16.5, 24.7, 43.0, 46.8, 95.4, 116.8, 119.5, 132.0, 133.1, 150.6, 154.1, 161.1, 162.9. HRMS (FAB): M⁺+H, found 287.1505. C₁₅H₁₈N₄O₂ requires 287.1508.

3.2.28. 2-(Benzylamino)-7-methyl-6-[4-(trifluoromethyl)benzyl]pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **14a.** 2-(Benzylsulfanyl)-7-methyl-6-[4-(trifluoromethyl)benzyl]pyrido [2,3-*d*]pyrimidin-4(3*H*)-one **11b** (0.050 g, 0.113 mmol) was dissolved in THF (3 mL, anhydrous) to which *m*-CPBA (0.059 g, 0.342 mmol) was added. The reaction mixture was stirred at room temperature for 3 h under nitrogen. The excess solvent was removed and the residue was dissolved in benzylamine (2 mL, 18.31 mmol) and the solution was heated in a microwave at 110 °C for 1 h. The excess solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL) and washed with saturated aqueous NaHCO₃ solution (2 × 5 mL) and water (2 × 5 mL). The organic layer was then dried over MgSO₄ and was purified by HPLC to yield the *title compound* **14a** as a white solid (0.021 g, 0.0495 mmol, 44%), mp 201–203 °C. ν_{max} (KBr): 3335, 3193, 1672, 1561, 1523, 1493, 1351, 1292, 1131, 1039, 964 cm⁻¹; δ_{H} (DMSO- d_6): 2.54 (3H, s, CH₃), 4.22 (2H, s, CH₂C), 4.66 (2H, d, $J=5.8$ Hz, CH₂NH), 7.26–7.70 (9H, m, C₆H₅ and C₆H₄), 8.01 (1H, s, H-5), 8.39 (1H, br s, NH), 11.96 (1H, s, NH); δ_{C} (DMSO- d_6): 26.2, 35.6, 43.8, 99.5, 123.4, 125.5, 125.5, 127.2, 127.2, 128.5, 129.5, 130.4, 138.2, 143.7, 154.3, 158.0, 158.2, 158.4, 172.9. HRMS (FAB): M⁺+H, 425.1588. C₂₃H₁₉F₃N₄O requires 425.1589.

3.2.29. 7-Methyl-2-(1-pyrrolidinyl)-6-[4-(trifluoromethyl)benzyl] pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **14b.** 2-(Benzylsulfanyl)-7-methyl-6-[4-(trifluoromethyl)benzyl]pyrido [2,3-*d*]pyrimidin-4(3*H*)-one **11b** (0.050 g, 0.113 mmol) was dissolved in THF (3 mL, anhydrous) to which *m*-CPBA (0.059 g, 0.342 mmol) was added. The reaction mixture was stirred at room temperature for 3 h under nitrogen. The excess solvent was removed and the residue was dissolved in pyrrolidine (2.0 mL, 23.96 mmol) and the solution was heated in a microwave at 110 °C for 1 h. The excess solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL) and washed with saturated aqueous NaHCO₃ solution (2 × 5 mL) and water (2 × 5 mL). The organic layer was then dried over MgSO₄ and purified by HPLC to yield the *title compound* **14b** as a white solid (0.022 g, 0.0574 mmol, 51%), mp 205–207 °C. ν_{max} (KBr): 3177, 3061, 1720, 1621, 1553, 1414, 1328, 1217, 1042, 921 cm⁻¹; δ_{H} (DMSO- d_6): 1.90 (4H, t, $J=6.5$ Hz, CH₂CH₂), 2.41 (3H, s, CH₃), 3.50 (4H, t, $J=6.5$ Hz, CH₂N × 2), 4.12 (2H, s, CH₂C), 7.40 (2H, d, $J=8.1$ Hz, 2,6-CH of Ar), 7.67 (2H, d, $J=8.1$ Hz, 3,5-CH₂ of Ar), 7.88 (1H, s, H-5), 11.20 (1H, s, NH); δ_{C} (DMSO- d_6): 23.6, 25.4, 38.2, 47.0, 108.9, 125.6, 127.6, 128.8, 129.0, 136.1, 143.1, 150.2, 159.6, 164.3, 165.7. HRMS (FAB): M⁺+H, found 389.1584. C₂₀H₁₉F₃N₄O requires 389.1589.

3.2.30. 2-Anilino-7-methyl-6-[4-(trifluoromethyl)benzyl]pyrido[2,3-*d*]pyrimidin-4(3*H*)-one trifluoroacetate salt **14c.** 2-(Benzylsulfanyl)-7-methyl-6-[4-(trifluoromethyl)benzyl]pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **11b** (0.050 g, 0.113 mmol) was dissolved in THF (3 mL,

anhydrous) to which *m*-CPBA (0.059 g, 0.342 mmol, 3 equiv) was added. The reaction mixture was stirred at room temperature under nitrogen for 3 h. Aniline (2.0 mL, 21.95 mmol) was then added to the solution and heated in the microwave at 110 °C for 1 h. The excess solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL) and washed with saturated aqueous NaHCO₃ solution (2 × 5 mL) and water (2 × 5 mL). The organic layer was then dried over MgSO₄ and purified by HPLC to yield the *title compound* **14c** as a white solid (0.017 g, 0.0414 mmol, 37%), mp 199–201 °C. ν_{max} (KBr): 3288, 3020, 2934, 1643, 1578, 1462, 1381, 1320, 1215, 990, 739 cm⁻¹; δ_{H} (DMSO- d_6): 2.56 (3H, s, CH₃), 4.22 (2H, s, CH₂C), 7.14–7.23 (9H, m, C₆H₅ and C₆H₄), 8.37 (1H, s, H-5), 9.60 (1H, s, NH), 11.54 (1H, s, NH); δ_{C} (DMSO- d_6): 20.1, 35.9, 100.0, 121.2, 123.4, 124.2, 125.2, 125.5, 127.1, 127.3, 128.9, 129.3, 129.5, 137.6, 143.7, 151.5, 158.3, 158.5. HRMS (FAB): M⁺+H, found 411.1429. C₂₂H₁₇F₃N₄O requires 411.1433.

3.2.31. 7-Methyl-6-[4-(trifluoromethyl)benzyl]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione trifluoroacetate salt **14d.** 2-(Benzylsulfanyl)-7-methyl-6-[4-(trifluoromethyl)benzyl]pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **11b** (0.050 g, 0.113 mmol) was dissolved in THF (3 mL, anhydrous) to which *m*-CPBA (0.059 g, 0.342 mmol, 3 equiv) was added. The reaction mixture was stirred under nitrogen for 24 h at room temperature. The excess solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL) and washed with saturated aqueous NaHCO₃ solution (2 × 5 mL) and water (2 × 5 mL). The organic layer was then dried over MgSO₄ and purified by HPLC to yield the *title compound* **14d** as a white solid (0.018 mg, 0.0401 mmol, 35%), mp 210–212 °C. ν_{max} (KBr): 3318, 2931, 1661, 1621, 1567, 1506, 1465, 1298, 941, 767 cm⁻¹; δ_{H} (DMSO- d_6): 2.43 (3H, s, CH₃), 4.16 (2H, s, CH₂C), 7.41 (2H, d, $J=8.1$ Hz, 2,6-CH of Ar), 7.68 (2H, d, $J=8.1$ Hz, 3,5-CH of Ar), 7.97 (1H, s, H-5), 11.35 (1H, s, NH), 11.54 (1H, s, NH); δ_{C} (DMSO- d_6): 22.6, 36.5, 99.5, 107.63, 125.4, 129.0, 129.5, 136.5, 144.3, 150.4, 150.5, 162.4, 163.4. HRMS (FAB): M⁺+1, found 336.0966. C₁₆H₁₂F₃N₃O₂ requires 336.0960.

3.2.32. 8-Benzyl-2,4-bis(benzylamino)-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one **15a.** 8-Benzyl-2-(benzylsulfanyl)-6-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione **13a** (0.050 g, 0.134 mmol) and BOP (77 mg, 0.174 mmol, 1.3 equiv) were suspended in acetonitrile (10 mL, anhydrous) at room temperature. DBU (31 μ L, 0.201 mmol, 1.5 equiv) was added dropwise and the reaction solution became heterogeneous. After stirring for 10 min at room temperature, benzylamine (22 μ L, 0.201 mmol, 1.5 equiv) was added and the solution was stirred for a further 48 h. The excess solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography to yield the *title compound* **15a** as a pale yellow (0.040 g, 0.0867 mmol, 65%), mp >230 °C. ν_{max} (KBr): 3348, 3288, 3041, 2992, 1643, 1612, 1591, 1211, 1151, 989, 761 cm⁻¹; δ_{H} (DMSO- d_6): 2.03 (3H, d, $J=0.9$ Hz, CH₃), 4.64 (2H, d, $J=6.3$ Hz, CH₂NH), 4.79 (2H, d, $J=4.8$ Hz, CH₂NH), 5.51 (2H, br s, NH × 2), 7.16–7.36 (15H, m, C₆H₅ × 3), 7.85 (1H, s, H-5); δ_{C} (DMSO- d_6): 16.2, 44.3, 44.6, 91.1, 126.6, 126.8, 127.4, 127.6, 127.9, 128.2, 128.2, 128.9, 138.6, 139.5, 140.4, 155.3. HRMS (FAB): M⁺+H, found 462.2290. C₂₉H₂₇N₅O requires 462.2294.

3.2.33. 8-Benzyl-2-(benzylamino)-6-methyl-4-(1-pyrrolidinyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one **15b.** 8-Benzyl-2-(benzylsulfanyl)-6-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione **13a** (0.150 g, 0.134 mmol) and BOP (77 mg, 0.174 mmol, 1.3 equiv) were suspended in acetonitrile (10 mL, anhydrous) at room temperature. DBU (31 μ L, 0.201 mmol, 1.5 equiv) was added dropwise and the reaction solution became heterogeneous. After stirring for 10 min at room temperature pyrrolidine (17 μ L, 1.5 equiv) was added and the solution was stirred for a further 48 h at room temperature. The excess solvent was removed

under reduced pressure and the resulting residue was purified by flash column chromatography to yield the *title compound 15b* as an orange solid (0.033 g, 0.0775 mmol, 58%), mp >230 °C. ν_{\max} (KBr): 3348, 3128, 1682, 1557, 1458, 1435, 1388, 1329, 1213, 977 cm⁻¹; δ_{H} (DMSO-*d*₆): δ_{H} (DMSO-*d*₆): 2.01–1.85 (4H, m, CH₂CH₂), 2.03 (3H, s, CH₃), 3.73 (2H, t, *J*=6.5, CH₂N), 4.24 (2H, t, *J*=6.5, CH₂N), 4.80 (2H, d, *J*=5.8, C₆H₅CH₂NH), 5.53 (2H, s, C₆H₅CH₂N8), 7.17–7.27 (10H, m, C₆H₅ × 2), 7.17–7.27 (1H, br, NH), 7.85 (1H, s, H-5); δ_{C} (DMSO-*d*₆): 17.1, 25.5, 44.2, 44.9, 50.6, 93.1, 118.7, 126.8, 126.9, 127.7, 128.2, 128.4, 128.5, 133.1, 138.9, 141.2, 157.0, 160.0, 162.9. HRMS (FAB): M⁺+H, found 426.2296. C₂₆H₂₇N₅O requires 426.2294.

3.2.34. 2-(Benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone 16a. To a solution of 5,6-diamino-2-(benzylsulfanyl)-4(3H)-pyrimidinone (500 mg, 2.11 mmol) in ethanol (20 mL) was added biacetyl (353 μ L, 4.02 mmol, 2 equiv) dropwise at room temperature. The reaction mixture was refluxed at 80 °C for 24 h. The excess solvent was removed under reduced pressure and the resulting yellow solid was triturated with diethyl ether to yield the *title compound 16a* as a pale yellow solid (511 mg, 1.71 mmol, 85%), mp >230 °C. ν_{\max} (KBr): 2993, 2866, 1675, 1579, 1543, 1445, 1386, 1264, 1163, 959, 821, 717, 639, 516 cm⁻¹; δ_{H} (DMSO-*d*₆): 2.58 (3H, s, CH₃), 2.61 (3H, s, CH₃), 4.52 (2H, s, CH₂S), 7.26–7.47 (5H, m, C₆H₅), 12.95 (1H, s, NH); δ_{C} (DMSO-*d*₆): 21.8, 22.6, 33.8, 127.4, 128.5, 128.6, 129.1, 136.8, 152.6, 152.6, 158.8, 159.2, 160.4. HRMS (FAB): M⁺+H, found 299.0971. C₁₅H₁₄N₄OS requires 299.0967.

3.2.35. 2-(Benzylsulfanyl)-6,7-diphenyl-4(3H)-pteridinone 16b. To a solution of 5,6-diamino-2-(benzylsulfanyl)-4(3H)-pyrimidinone (1000 mg, 4.03 mmol) in ethanol (20 mL) was added benzil (1270 mg, 6.04 mmol, 1.5 equiv) at room temperature. The reaction mixture was heated at 85 °C for 24 h. The excess solvent was removed under reduced pressure and the resulting yellow solid was triturated with diethyl ether (10 mL) to yield the *title compound 16b* as a pale yellow solid (1.498 g, 3.25 mmol, 88%), mp >230 °C. ν_{\max} (KBr): 3165, 2988, 1664, 1573, 1559, 1423, 1378, 1167, 976, 723 cm⁻¹; δ_{H} (DMSO-*d*₆): 4.59 (2H, s, CH₂S), 7.26–7.51 (15H, m, C₆H₅ × 3), 13.17 (1H, s, NH); δ_{C} (DMSO-*d*₆): 34.0, 127.4, 128.1, 128.2, 128.6, 128.7, 129.1, 129.4, 129.6, 129.7, 129.8, 136.7, 137.8, 138.0, 150.4, 152.4, 156.8, 160.4, 160.8. HRMS (FAB): M⁺+H, found 423.1282. C₂₅H₁₈N₄OS requires 423.1280.

3.2.36. 2-(Benzylamino)-6,7-dimethyl-4(3H)-pteridinone 17a. 2-(Benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone **16a** (100 mg, 0.335 mmol) was dissolved in dry DMF (3.0 mL). To this solution was added *m*-CPBA (3.0 equiv, 1.01 mmol, 174 mg) and was stirred under nitrogen for 3 h at room temperature. The solvent was then removed under reduced pressure and the resulting solid was dissolved in benzylamine (2.0 mL, 18.31 mmol) and heated in the microwave at 110 °C for 1 h. The excess solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography to yield the *title compound 17a* as a yellow solid (89 mg, 0.316 mmol, 94%), mp >230 °C. ν_{\max} (KBr): 3413, 2925, 1666, 1590, 1535, 1447, 1414, 1268, 1036, 727 cm⁻¹; δ_{H} (DMSO-*d*₆): 2.47 (3H, s, CH₃), 2.48 (3H, s, CH₃), 4.59 (2H, d, *J*=5.6 Hz, CH₂NH), 7.23–7.40 (5H, m, C₆H₅), 7.60 (1H, br s, CH₂NH), 9.59 (1H, s, NH); δ_{C} (DMSO-*d*₆): 21.3, 22.5, 43.6, 126.1, 126.8, 127.1, 128.3, 139.3, 146.8, 153.1, 155.1, 158.0, 162.2. HRMS (FAB): M⁺+H, found 282.1353. C₁₅H₁₅N₅O requires 282.1355.

Similarly prepared were:

3.2.37. 6,7-Dimethyl-2-(1-pyrrolidinyl)-4(3H)-pteridinone 17b. From 2-(benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone and pyrrolidine in 90% yield, mp >230 °C. ν_{\max} (KBr): 3442, 3197, 2964, 1685, 1611, 1558, 1518, 392, 1270, 976 cm⁻¹; δ_{H} (DMSO-*d*₆): 1.91 (4H,

t, *J*=6.1 Hz, CH₂CH₂), 2.48 (3H, s, CH₃), 2.49 (3H, s, CH₃), 3.50 (4H, *t*, *J*=6.1, CH₂N × 2), 11.34 (1H, s, NH); δ_{C} (DMSO-*d*₆): 21.3, 22.5, 24.8, 46.9, 115.6, 129.0, 147.0, 150.3, 154.7, 162.3. HRMS (FAB): M⁺+H, found 246.1351. C₁₂H₁₅N₅O requires 246.1355.

3.2.38. 2-Anilino-6,7-dimethyl-4(3H)-pteridinone 17c. From 2-(benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone and aniline in 54% yield, mp >230 °C. ν_{\max} (KBr): 3318, 3013, 2922, 1663, 1590, 1454, 1405, 1323, 1232, 986, 741 cm⁻¹; δ_{H} (DMSO-*d*₆): 2.53 (3H, s, CH₃), 2.55 (3H, s, CH₃), 7.06–7.74 (5H, m, C₆H₅), 8.92 (1H, s, NHC₆H₅), 11.12 (1H, s, NH); δ_{C} (DMSO-*d*₆): 21.4, 22.5, 99.5, 119.9, 123.1, 126.9, 128.8, 138.3, 148.5, 149.1, 154.3, 158.7. HRMS (FAB): M⁺+H, found 268.1201. C₁₄H₁₃N₅O requires 268.1198.

3.2.39. 2-(Allylamino)-6,7-dimethyl-4(3H)-pteridinone 17d. From 2-(benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone and allylamine in 86% yield, mp >230 °C. ν_{\max} (KBr): 3278, 2934, 1688, 1621, 1546, 1498, 1312, 1225, 1064 cm⁻¹; δ_{H} (DMSO-*d*₆): 2.50 (6H, s, 2 × CH₃), 3.90 (2H, s, CH₂CH=), 5.02 (1H, dd, *J*=10.3, 1.6 Hz), 5.15 (1H, dd, *J*=17.2, 1.6 Hz), 5.93–5.99 (1H, m, CH₂CH=), 12.30 (1H, s, NH). HRMS (FAB): M⁺+Na, found 254.1020. C₁₁H₁₃N₅ONa requires 254.1018.

3.2.40. 2-(Benzylamino)-6,7-diphenyl-4(3H)-pteridinone 17e. From 2-(benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone and benzylamine in 83% yield, mp >230 °C. ν_{\max} (KBr): 3422, 3260, 3019, 1686, 1622, 1560, 1535, 1490, 1451, 1357, 1277, 1036, 727 cm⁻¹; δ_{H} (DMSO-*d*₆): 4.66 (2H, d, *J*=5.8 Hz, CH₂), 7.23–7.42 (16H, m, C₆H₅ × 3 and NH), 11.46 (1H, s, NH); δ_{C} (DMSO-*d*₆): 43.8, 127.0, 127.2, 127.4, 128.0, 128.1, 128.4, 129.0, 129.6, 138.2, 138.4, 138.8, 146.8, 152.8, 155.2, 156.5, 160.7. HRMS (FAB): M⁺+H, found 406.1665. C₂₅H₁₉N₅O requires 406.1668.

3.2.41. 6,7-Diphenyl-2-(1-pyrrolidinyl)-4(3H)-pteridinone 17f. From 2-(benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone and pyrrolidine in 83% yield, mp >230 °C. ν_{\max} (KBr): 3421, 3201, 2971, 1681, 1610, 1556, 1516, 1453, 1287, 980, 765 cm⁻¹; δ_{H} (DMSO-*d*₆): 1.95 (4H, *t*, *J*=6.5 Hz, CH₂CH₂), 3.57 (4H, *t*, *J*=6.5 Hz, CH₂N), 7.30–7.43 (10H, m, C₆H₅), 11.13 (1H, s, NH); δ_{C} (DMSO-*d*₆): 24.8, 47.1, 126.3, 127.9, 128.0, 129.0, 129.4, 129.6, 131.1, 138.4, 138.5, 146.1, 151.3, 154.7, 156.5, 162.0. HRMS (FAB): M⁺+H, found 370.1672. C₂₂H₁₉N₅O requires 370.1668.

3.2.42. 2-Anilino-6,7-diphenyl-4(3H)-pteridinone 17g. From 2-(benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone and aniline in 61% yield, mp >230 °C. ν_{\max} (KBr): 3423, 3089, 2924, 1729, 1641, 1539, 1492, 1313, 1185, 836, 781 cm⁻¹; δ_{H} (DMSO-*d*₆): 7.10–7.81 (15H, m, C₆H₅ × 3), 9.29 (1H, br s, NHCH₂), 11.29 (1H, s, NH); δ_{C} (DMSO-*d*₆): 120.3, 123.4, 128.0, 128.1, 128.2, 128.3, 128.8, 129.1, 129.5, 129.6, 138.2, 138.3, 147.8, 150.5, 154.5, 156.7. HRMS (FAB): M⁺+H, found 392.1509. C₂₄H₁₇N₅O requires 392.1511.

3.2.43. 2-(Allylamino)-6,7-diphenyl-4(3H)-pteridinone 17h. From 2-(benzylsulfanyl)-6,7-diphenyl-4(3H)-pteridinone and allylamine in 79% yield, mp >230 °C. ν_{\max} (KBr): 3288, 2931, 1685, 1623, 1563, 1496, 1287, 1095, 765 cm⁻¹; δ_{H} (DMSO-*d*₆): 4.07 (2H, m, NHCH₂–CH=), 5.15 (1H, dd, *J*=10.3, 1.6 Hz, CH=CHH), 5.25 (1H, dd, *J*=17.2, 1.6 Hz, CH=CHH), 5.94–5.99 (1H, m, CH₂–CH=), 6.94 (1H, s, NH), 7.30–7.43 (10H, m, C₆H₅ × 2), 11.41 (1H, s, NH); δ_{C} (DMSO-*d*₆): 42.5, 115.6, 127.3, 128.0, 128.0, 129.1, 129.4, 129.6, 134.8, 138.2, 146.7, 152.6, 155.2, 156.5, 160.6. HRMS (FAB): M⁺+H, found 356.1510. C₂₁H₁₇N₅O requires 356.1511.

3.2.44. 2-(Benzylsulfanyl)-*N*-butyl-6,7-dimethyl-4-pteridinamine 18a. 2-(Benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone **16a** (100 mg, 0.335 mmol) and BOP (196 mg, 0.443 mmol, 1.3 equiv) were suspended in dry acetonitrile (10 mL). DBU (76 μ L, 0.493 mmol, 1.5 equiv)

was then added dropwise and the reaction mixture became homogeneous. After stirring for 10 min at room temperature, butylamine (50 μ l, 0.502 mmol, 1.5 equiv) was added dropwise and the solution was stirred for a further 48 h. The excess solvent was removed under reduced pressure and the resulting residue was partitioned between ethyl acetate and water. The organic layer was dried over MgSO_4 and purified by flash chromatography to yield the *title compound 18a* as pale yellow solid (92 mg, 78%), mp $>230^\circ\text{C}$. ν_{max} (KBr): 3423, 3027, 2928, 1676, 1602, 1495, 1454, 1388, 750 cm^{-1} ; δ_{H} (CDCl_3): 0.98 (3H, t, $J=7.2$ Hz, CH_3), 1.40–1.50 (2H, m, CH_2), 1.66–1.73 (2H, m, CH_2), 2.64 (3H, s, CH_3), 2.71 (3H, s, CH_3), 3.63 (2H, t, $J=6.5$ Hz), 4.57 (2H, s, CH_2S), 6.93 (1H, m, NH) 7.22–7.48 (5H, m, C_6H_5); δ_{C} (CDCl_3): 11.8, 20.1, 22.3, 23.3, 31.4, 35.9, 40.7, 122.2, 127.0, 128.4, 128.4, 128.5, 129.2, 137.6, 150.1, 152.2, 159.1, 159.9, 171.6. HRMS (FAB): $\text{M}^+ + \text{Na}$, found 376.1573. $\text{C}_{19}\text{H}_{23}\text{N}_5\text{Na}$ requires 376.1572.

Similarly prepared were:

3.2.45. *N*-Benzyl-2-(benzylsulfanyl)-6,7-dimethyl-4-pteridinamine 18b. From 2-(benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone and benzylamine in 87% yield, mp $>230^\circ\text{C}$. ν_{max} (KBr): 3403, 3084, 2981, 1684, 1621, 1574, 1448, 1223, 909 cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$): 2.63 (6H, s, $\text{CH}_3 \times 2$), 4.39 (2H, s, CH_2S), 4.71 (2H, d, $J=6.2$, Hz, CH_2NH), 7.19–7.44 (10H, m, $\text{C}_6\text{H}_5 \times 2$), 9.10 (1H, t, $J=6.2$ Hz, CH_2NH); δ_{C} ($\text{DMSO}-d_6$): 22.0, 23.0, 34.4, 43.6, 121.6, 126.9, 127.3, 128.3, 128.4, 128.6, 128.7, 138.3, 138.9, 150.8, 151.7, 159.0, 160.3, 169.4. HRMS (FAB): $\text{M}^+ + \text{H}$, found 388.1593. $\text{C}_{22}\text{H}_{21}\text{N}_5\text{S}$ requires 388.1596.

3.2.46. 2-(Benzylsulfanyl)-6,7-dimethyl-4-(1-pyrrolidinyl)pteridine 18c. From 2-(benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone and pyrrolidine in 81% yield, mp $>230^\circ\text{C}$. ν_{max} (KBr): 3368, 3121, 2963, 1644, 1568, 1553, 1450, 1378, 1262, 820, 724 cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$): 2.02–1.86 (4H, m, CH_2CH_2), 2.56 (3H, s, CH_3), 2.59 (3H, s, CH_3), 3.67 (2H, t, $J=6.6$, Hz, CH_2N), 4.21 (2H, t, $J=6.6$, Hz, CH_2N), 4.44 (2H, s, CH_2S), 7.21–7.45 (5H, m, C_6H_5); δ_{C} ($\text{DMSO}-d_6$): 22.1, 22.7, 23.1, 26.4, 34.4, 49.8, 50.9, 123.5, 126.9, 128.4, 128.7, 138.5, 148.8, 153.3, 156.7, 158.4, 168.3. HRMS (FAB): $\text{M}^+ + \text{H}$, found 352.1599. $\text{C}_{19}\text{H}_{21}\text{N}_5\text{S}$ requires 352.1596.

3.2.47. 2-(Benzylsulfanyl)-6,7-dimethyl-*N*-phenyl-4-pteridinamine 18d. From 2-(benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone and aniline in 65% yield, mp $>230^\circ\text{C}$. ν_{max} (KBr): 3451, 3096, 1681, 1574, 1541, 1483, 1241, 1090, 828, 741 cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$): 2.68 (3H, s, CH_3), 2.70 (3H, s, CH_3), 4.45 (2H, s, CH_2S), 7.45–7.21 (10H, m, $\text{C}_6\text{H}_5 \times 2$), 10.09 (1H, s, NH); δ_{C} ($\text{DMSO}-d_6$): 22.0, 23.0, 34.5, 121.6, 122.0, 124.2, 126.9, 128.4, 128.5, 128.8, 138.0, 151.5, 152.0, 157.0, 160.8, 169.2. HRMS (FAB): $\text{M}^+ + \text{H}$, found 374.1436. $\text{C}_{21}\text{H}_{19}\text{N}_5\text{S}$ requires 374.1439.

3.2.48. 2-(Benzylsulfanyl)-6,7-dimethyl-*N*-(4-methylphenyl)-4-pteridinamine 18e. From 2-(benzylsulfanyl)-6,7-dimethyl-4(3H)-pteridinone and *p*-toluidine in 71% yield, mp $>230^\circ\text{C}$. ν_{max} (KBr): 3430, 3030, 2845, 1683, 1539, 1478, 1234, 1025, 697 cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$): 2.29 (3H, s, $\text{C}_6\text{H}_4\text{CH}_3$), 2.67 (3H, s, CH_3), 2.70 (3H, s, CH_3), 4.44 (2H, s, CH_2S), 7.17–7.77 (9H, m, C_6H_5 and C_6H_4), 10.03 (1H, s, NH); δ_{C} ($\text{DMSO}-d_6$): 20.5, 22.0, 23.0, 34.4, 121.6, 122.0, 127.0, 128.4, 128.8, 133.3, 135.6, 138.0, 151.4, 152.0, 156.9, 160.6, 169.2. HRMS (FAB): $\text{M}^+ + \text{H}$, found 388.1597. $\text{C}_{22}\text{H}_{21}\text{N}_5\text{S}$ requires 388.1596.

3.2.49. 2-(Benzylsulfanyl)-*N*-(4-ethylphenyl)-6,7-dimethyl-4-pteridinamine 18f. From 2-(benzylsulfanyl)-6,7-dimethyl-4(3H)-and 4-ethylaniline in 71% yield, mp $>230^\circ\text{C}$. ν_{max} (KBr): 3424, 3026, 2942, 2853, 1678, 1513, 1495, 1392, 1259, 1012, 744 cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$): 1.18 (3H, t, $J=7.6$ Hz, CH_3), 2.59 (2H, q, $J=7.6$ Hz, CH_2), 2.67 (3H, s, CH_3), 2.70 (3H, s, CH_3), 4.44 (2H, s, CH_2S), 7.20–7.80 (9H, m, C_6H_5 and C_6H_4), 10.03 (1H, s, NH); δ_{C} ($\text{DMSO}-d_6$): 15.6, 22.0, 23.0, 27.6, 34.5, 121.6, 122.1, 126.9, 127.7, 128.4, 128.8, 135.8, 138.0, 139.8, 151.4,

152.0, 156.9, 160.7, 169.2. HRMS (FAB): $\text{M}^+ + \text{H}$, found 402.1756. $\text{C}_{23}\text{H}_{23}\text{N}_5\text{S}$ requires 402.1752.

3.2.50. *N*-Benzyl-6,7-dimethyl-4-(1-pyrrolidinyl)-2-pteridinamine 19a. 2-(Benzylsulfanyl)-6,7-dimethyl-4-(1-pyrrolidinyl)pteridine **18c** (100 mg, 0.285 mmol) was dissolved in dry DMF (3.0 mL). To this was added *m*-CPBA (147 mg, 0.852 mmol, 3.0 equiv) at room temperature and the reaction was stirred for 3 h under nitrogen. The excess solvent was removed and the residue was dissolved in benzylamine (2.0 mL, 18.31 mmol) and the solution was heated in a microwave for 1 h at 110°C . The excess solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography to yield the *title compound 19a* as a yellow solid (40 mg, 0.120 mmol, 42%), mp $>230^\circ\text{C}$. ν_{max} (KBr): 3297, 2975, 1659, 1542, 1364, 1295, 981 cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$): 1.93 (4H, s, CH_2CH_2), 2.47 (3H, s, CH_3), 2.48 (3H, s, CH_3), 3.95 (4H, br s, CH_2N), 4.58 (2H, d, $J=4.8$, CH_2NH), 6.84 (1H, br s, NH), 7.18–7.37 (5H, m, C_6H_5); δ_{C} ($\text{DMSO}-d_6$): 21.8, 22.5, 45.0, 50.2, 122.9, 126.8, 127.7, 128.5, 141.5, 144.0, 156.3, 157.3, 158.9, 161.1. HRMS (FAB): $\text{M}^+ + \text{H}$, found 335.1987. $\text{C}_{19}\text{H}_{22}\text{N}_6$ requires 335.1984.

Similarly prepared were:

3.2.51. 6,7-Dimethyl-2,4-di(1-pyrrolidinyl)pteridine 19b. From 2-(benzylsulfanyl)-6,7-dimethyl-4-(1-pyrrolidinyl)pteridine **18c** and pyrrolidine in 86% yield, mp $>230^\circ\text{C}$. ν_{max} (KBr): 3098, 2975, 1683, 1620, 1467, 1346, 1234, 1082, 830 cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$): 1.90 (8H, s, $\text{CH}_2\text{CH}_2 \times 2$), 2.46 (3H, s, CH_3), 2.48 (3H, s, CH_3), 3.51 (4H, s, $\text{CH}_2\text{N} \times 2$), 3.68 (2H, s, CH_2N), 4.18 (2H, s, CH_2N); δ_{C} ($\text{DMSO}-d_6$): 21.8, 22.8, 25.4, 46.8, 50.1, 122.3, 143.6, 156.3, 157.2, 158.5, 159.1. HRMS (FAB): $\text{M}^+ + \text{H}$, found 299.1987. $\text{C}_{16}\text{H}_{22}\text{N}_6$ requires 299.1984.

Prepared by the same method as **15a** and **15b** were:

3.2.52. *N*²-Allyl-*N*⁴-butyl-6,7-diphenyl-2,4-pteridinediamine 19c. From 2-(allylamino)-6,7-diphenyl-4(3H)-pteridinone **17h** and *n*-butylamine in 70% yield, mp $>230^\circ\text{C}$. ν_{max} (KBr): 3283, 3080, 2974, 1691, 1616, 1560, 1492, 1220, 903, 735 cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$): 0.93 (3H, t, $J=7.3$ Hz, CH_3), 1.31–1.40 (2H, m, CH_2), 1.60–1.67 (2H, m, CH_2), 3.63 (2H, q, $J=6.5$ Hz, $\text{CH}_2\text{CH}_2\text{NH}$), 4.02 (2H, t, $J=5.6$ Hz, $\text{CH}_2\text{CH}=\text{}$), 5.06 (2H, dd, $J=10.2$, 1.6 Hz, $\text{CH}=\text{CHH}$), 5.18 (2H, dd, $J=17.2$, 1.6 Hz, $\text{CH}=\text{CHH}$), 5.95 (1H, m, $\text{CH}=\text{CH}_2$), 7.29–7.44 (11H, m, C_6H_5 and NH) 8.16 (1H, s, NH). HRMS (FAB): $\text{M}^+ + \text{H}$, found 411.2298. $\text{C}_{25}\text{H}_{26}\text{N}_6$ requires 411.2297.

3.2.53. *N*²-Allyl-*N*⁴-benzyl-6,7-diphenyl-2,4-pteridinediamine 19d. From 2-(allylamino)-6,7-diphenyl-4(3H)-pteridinone **17h** and benzylamine in 83% yield, mp $>230^\circ\text{C}$. ν_{max} (KBr): 3310, 3054, 2986, 1663, 1621, 1446, 1421, 1263, 993, 895, 739 cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$): 4.01 (2H, s, $\text{C}_6\text{H}_5\text{CH}_2\text{NH}$), 4.75 (2H, d, $J=5.2$, Hz, $\text{CH}_2\text{CH}=\text{}$), 5.05 (1H, dd, $J=10.0$, 1.6 Hz, $\text{CH}=\text{CHH}$), 5.18 (1H, dd, $J=17.2$, 1.6 Hz, $\text{CH}=\text{CHH}$), 5.94 (1H, m, $\text{CH}=\text{CH}_2$), 7.21–7.45 (16H, m, $\text{C}_6\text{H}_5 \times 3$ and NH), 8.67 (1H, s, NH); δ_{C} ($\text{DMSO}-d_6$): 43.2, 43.3, 114.8, 126.7, 127.4, 127.8, 128.0, 128.2, 128.8, 129.5, 129.6, 136.0, 138.4, 138.9, 139.4, 144.8, 160.0, 161.4. HRMS (FAB): $\text{M}^+ + \text{H}$, found 445.2136. $\text{C}_{28}\text{H}_{25}\text{N}_6$ requires 445.2141.

3.2.54. *N*-Allyl-6,7-diphenyl-4-(1-pyrrolidinyl)-2-pteridinamine 19e. From 2-(allylamino)-6,7-diphenyl-4(3H)-pteridinone **17h** and pyrrolidine in 80% yield, mp $>230^\circ\text{C}$. ν_{max} (KBr): 3304, 3063, 2951, 1696, 1612, 1439, 1412, 1249, 998, 755 cm^{-1} ; δ_{H} ($\text{DMSO}-d_6$): 1.87–2.02 (4H, m, CH_2CH_2), 3.74 (2H, t, $J=6.5$ Hz, CH_2N), 4.02 (2H, d, $J=5.6$ Hz, $\text{CH}_2\text{CH}=\text{}$), 4.26 (2H, t, $J=6.5$, Hz, CH_2N), 5.06 (1H, dd, $J=10.3$, 1.7 Hz, $\text{CH}=\text{CHH}$), 5.19 (1H, dd, $J=17.2$, 1.7 Hz, $\text{CH}=\text{CHH}$), 5.91–6.00 (1H, m), 7.29–7.45 (11H, m, $\text{C}_6\text{H}_5 \times 2$ and NH). HRMS (FAB): $\text{M}^+ + \text{H}$, found 409.2139. $\text{C}_{25}\text{H}_{24}\text{N}_6$ requires 409.2141.

3.2.55. 2-(Benzylsulfanyl)-6,7,7-trimethyl-3,7-dihydro-4H-pyrimido [4,5-*bj*] [1,4]oxazin-4-one 20. 2-(Benzylthio)-6-hydroxy-5-nitroso

pyrimidin-4(3H)-one (300 mg, 1.14 mmol) was dissolved in ethanol (20 mL) to which sodium dithionite (496 mg, 2.85 mmol, 2.5 equiv) in water (20 mL) was added dropwise at room temperature and allowed to stir for 4 h. The flask was covered with aluminium foil to protect from light. A light yellow solid was precipitated, which was filtered and washed with water (2×10 mL) and ether (2×10 mL). The resulting solid was suspended in a 1:1 water/ethanol mixture (20 mL). 3-Chloro-3-methylbutan-2-one (206 mg, 1.5 equiv) in ethanol (10 mL) was then added to the suspension and this mixture was heated to reflux. After 15 min sodium acetate (112 mg, 1.2 equiv) in water (5 mL) was added dropwise and heating under reflux was continued for a further 3 h. The resulting mixture was allowed to cool to room temperature and then stored at 0 °C for 12 h. The resulting precipitate was filtered, washed with water (2×10 mL) and dry ether (2×10 mL) to yield the title compound **20** as a beige solid (126 mg, 0.399 mmol, 35%), mp 222–224 °C. ν_{\max} (KBr): 3424, 2981, 1658, 1561, 1312, 1239, 1121, 965, 705; cm^{-1} ; δ_{H} (DMSO- d_6): 1.44 (6H, s, 7-CH₃ ×2), 2.07 (3H, s, 6-CH₃), 4.36 (2H, s, CH₂S), 7.41–7.20 (5H, m, C₆H₅), 12.63 (2H, br s, NH). HRMS (FAB): $\text{M}^+ + \text{H}$, found 316.1119. C₁₆H₁₇N₃O₂S requires 316.1120.

Similarly prepared was:

3.2.56. Ethyl 2-(benzylsulfanyl)-4-oxo-3,7-dihydro-4H-pyrimido[4,5-b][1,4]oxazine-6-carboxylate **21**. From 2-(Benzylthio)-6-hydroxy-5-nitrosopyrimidin-4(3H)-one reduced with sodium dithionite and ethyl bromopyruvate in 30% yield, mp 205–207 °C. ν_{\max} (KBr): 3413, 3046, 2873, 1700, 1681, 1539, 1234, 1025, 721, 697 cm^{-1} ; δ_{H} (DMSO- d_6): 1.28 (3H, t, $J=7.1$ Hz, CH₃), 4.25 (2H, q, $J=7.1$ Hz, CH₂), 4.40 (2H, s, CH₂S), 5.10 (2H, s, CH₂O), 7.42–7.25 (5H, m, C₆H₅), 13.00 (1H, br s, NH). HRMS (FAB): $\text{M}^+ + \text{H}$, found 346.0863. C₁₆H₁₅N₃O₄S requires 346.0862.

3.2.57. 2-(Benzylamino)-6,7,7-trimethyl-3,7-dihydro-4H-pyrimido[4,5-b][1,4]oxazin-4-one **22**. 2-(Benzylsulfanyl)-6,7,7-trimethyl-3,7-dihydro-4H-pyrimido[4,5-b][1,4]oxazin-4-one **20** (100 mg, 0.32 mmol) was dissolved in benzylamine (2.0 mL, 18.31 mmol) and the solution was heated in a microwave for 1 h at 110 °C. The excess solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL) and washed with saturated sodium bicarbonate solution (2×5 mL) and water (2×5 mL). The organic layer was then dried over MgSO₄ and was purified by flash chromatography to yield the title product as a beige solid (44 mg, 0.148 mmol, 37%), mp >230 °C. ν_{\max} (KBr): 3425, 3283, 2992, 1643, 1551, 1213, 1303, 1239, 1091, 705 cm^{-1} ; δ_{H} (DMSO- d_6): 1.36 (6H, s, CH₃ ×2), 2.00 (3H, s, CH₃), 4.43 (2H, d, $J=6.3$ Hz, CH₂NH), 7.15 (1H, br s, NH), 7.25–7.35 (5H, m, C₆H₅), 10.63 (1H, s, NH). HRMS (FAB): $\text{M}^+ + \text{H}$, found 299.1506. C₁₆H₁₈N₄O₂ requires 299.1508.

3.2.58. N-Benzyl-2-(benzylamino)-4-oxo-3,7-dihydro-4H-pyrimido[4,5-b][1,4]oxazine-6-carboxamide **23**. Ethyl 2-(benzylsulfanyl)-4-oxo-3,7-dihydro-4H-pyrimido[4,5-b][1,4]oxazine-6-carboxylate **21** (100 mg, 0.29 mmol) was dissolved in benzylamine (2.0 mL, 18.31 mmol) and the solution was heated in a microwave for 1 h at 110 °C. The excess solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL) and washed

with saturated sodium bicarbonate solution (2×5 mL) and water (2×5 mL). The organic layer was then dried over MgSO₄ and the title product was recrystallised from methanol as an orange solid (34 mg, 0.088 mmol, 30%), mp >230 °C. ν_{\max} (KBr): 3423, 3005, 2873, 1701, 1669, 1539, 1234, 1025, 697 cm^{-1} ; δ_{H} (DMSO- d_6): 4.36 (2H, d, $J=6.4$ Hz, CH₂NH), 4.36 (2H, d, $J=5.9$ Hz, CH₂NH), 5.00 (2H, s, CH₂O), 7.29 (10H, m, C₆H₅ ×2), 7.52 (1H, s, NH), 8.69 (1H, s, NH), 10.95 (1H, s, NH); δ_{C} (DMSO- d_6): 42.1, 43.7, 63.1, 126.7, 127.1, 127.3, 127.4, 128.2, 128.4, 138.4, 139.4, 142.3, 153.8, 159.3, 162.0, 162.3. HRMS (FAB): $\text{M}^+ + \text{H}$, found 390.1570. C₂₁H₁₉N₅O₃ requires 390.1566.

Supplementary data

Electronic Supplementary Data (ESD) available: ¹H NMR spectra for most new compounds. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.03.011.

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