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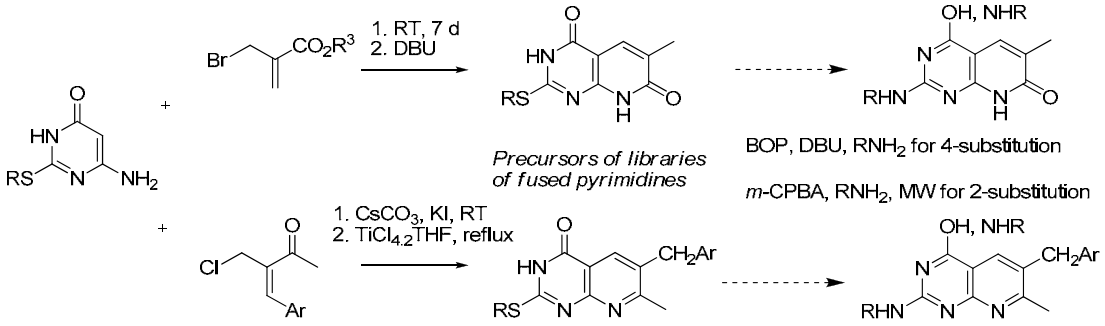
Jonathan Adcock, Colin L. Gibson, Judith K. Huggan, and Colin J Suckling*



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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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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.

Keywords: pyrimidines, Claisen allyl rearrangement, pyridopyrimidines, pteridines, diversity oriented synthesis, antiparasitic activity.

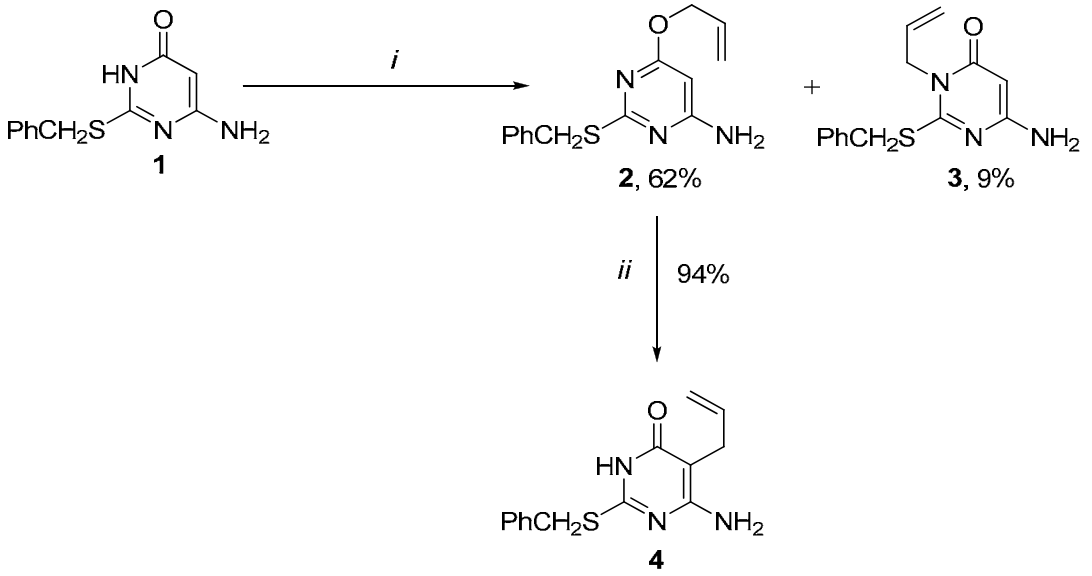
1. Introduction

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 reductase 1[5] 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 yield[8] 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 precursours for the Claisen allyl rearrangement would be available from O4 allyl ethers. Allyl rearrangements have been used in the synthesis of many natural 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

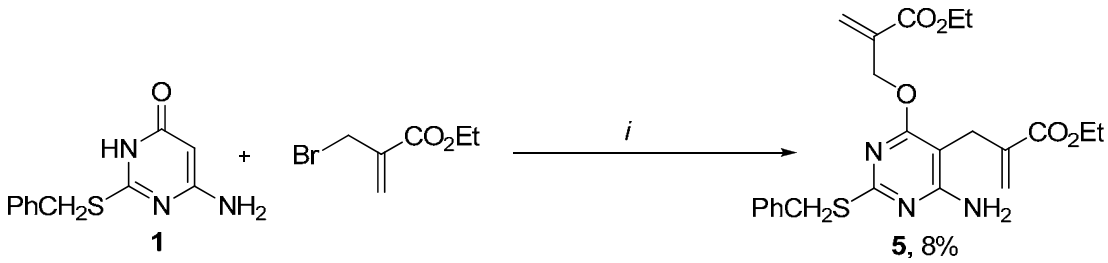
2.1 Claisen rearrangement

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.



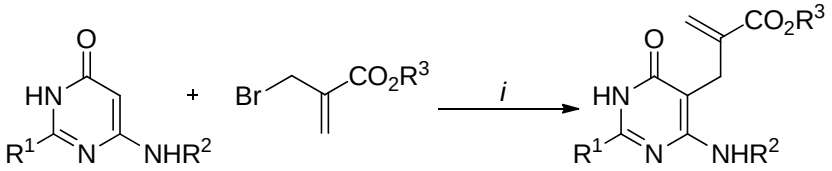
Scheme 1. Substitution by Claisen rearrangement. *Reagents and conditions*: *i*. DMF, K_2CO_3, 100 °C, 20 h; *ii*. 200 °C, 24 h

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 *di*substituted 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]



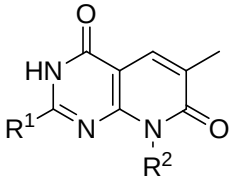
Scheme 2. Preparation of dialkylated pyrimidine **5** *Reagents and conditions: i*. DMF, K_2CO_3, 55 °C, 24h

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**, **7c**, **7d**) 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** – **6g**). 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** – **8e**).



1 R^1 = SBn, R^2 = H
7a R^1 = NH_2, R^2 = H
7b R^1 = SBn, R^2 = Me
7c R^1 = SBn, R^2 = CH_2Ph
7d R^1 = SBn, R^2 = CH_2CHCH_2

6a R^1 = SBn, R^2 = H, R^3 = Et, 46%
6b R^1 = SBn, R^2 = H, R^3 = H, 30%
6c R^1 = NH_2, R^2 = H, R^3 = Et, 83%
6d R^1 = NH_2, R^2 = H, R^3 = H 53%
6e R^1 = SBn, R^2 = Me, R^3 = Et, 33%
6f R^1 = SBn, R^2 = CH_2Ph, R^3 = Et, 33%
6g R^1 = SBn, R^2 = CH_2CHCH_2, R^3 = Et, 33%



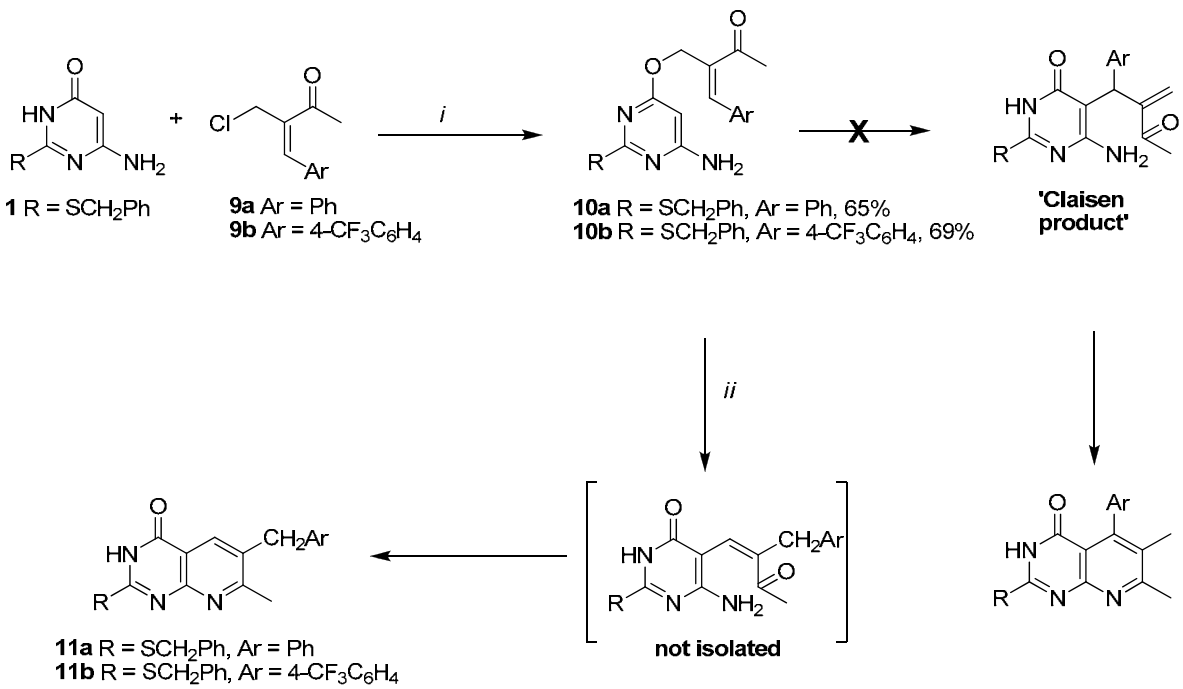
8a R^1 = SBn, R^2 = H, 98%
8b R^1 = NH_2, R^2 = H, 81%
8c R^1 = SBn, R^2 = Me, 96%
8d R^1 = SBn, R^2 = CH_2Ph, 96%
8e R^1 = SBn, R^2 = CH_2CHCH_2, 96%

Scheme 3. *Reagents and conditions: i*. DMF, r.t, 7 d; *ii*. TBD or DBU, MW, 100 °C, 30 min

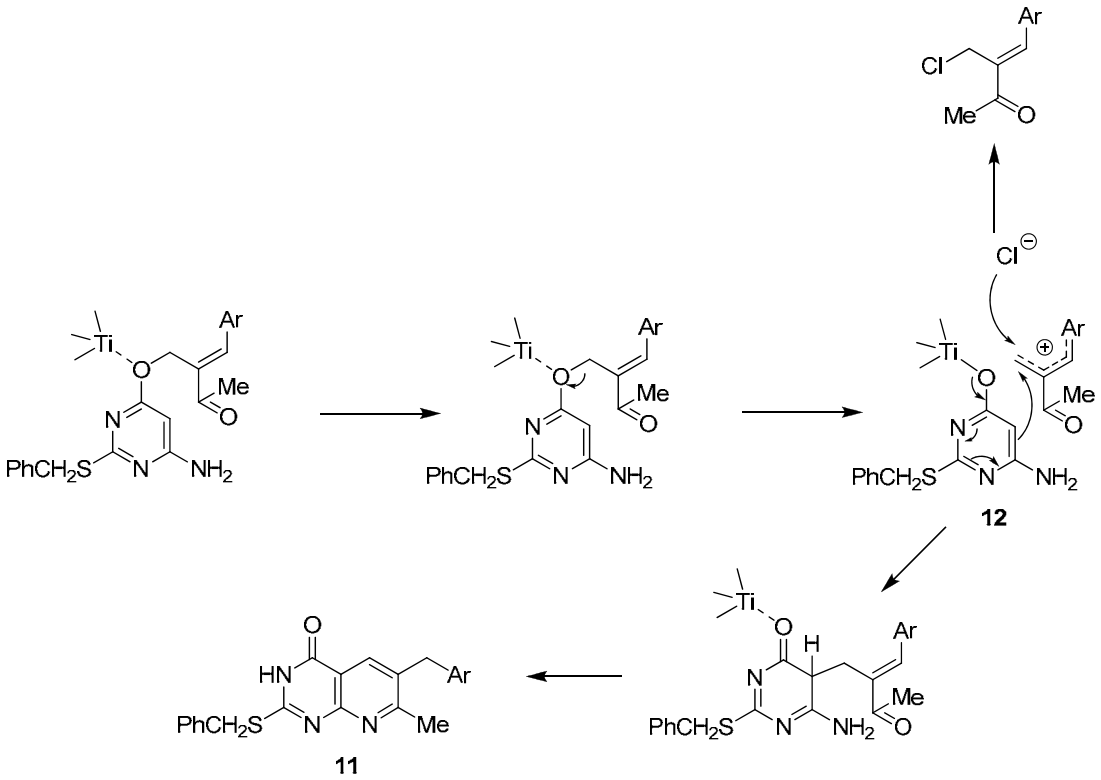
2.2 Lewis acid catalysed rearrangement and cyclisation

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**, **10b** 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 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**, **11b** 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**.



Scheme 4. *Reagents and conditions*: *i*. Cs_2CO_3, KI, r.t., 24 h; *ii*. $TiCl_4$.2THF, THF, reflux, 3 d



Scheme 5. Proposed mechanism for the synthesis of derivatives **11.** Ti was introduced as $TiCl_4.2THF$ in THF solution.

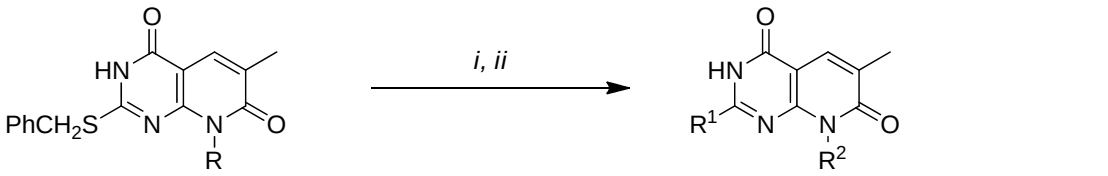
Increasing the molar proportion of titanium tetrachloride up to 50 mol.% also failed to improve yields. Indeed the major product under conditions of higher concentration of titanium tetrachloride was the precursor Baylis-Hillman chloroketone, **9**. The occurrence of these competing reactions can be 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.

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 substitutent using BOP (benzotriazole-1-yl-

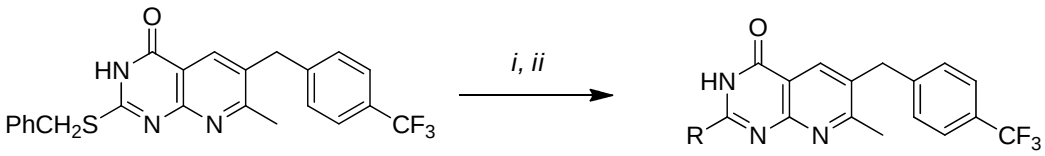
oxytris(dimethylamino)phosphonium hexafluorophosphate) and the corresponding amine.[18] The oxidation/substitution sequence is successful and in high yield (typically 85 – 95%) with pteridines and other compounds with electron deficient rings fused to pyrimidines.[19-21] In many cases with pteridines 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** – **13d** 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** – **14d** under the same conditions.



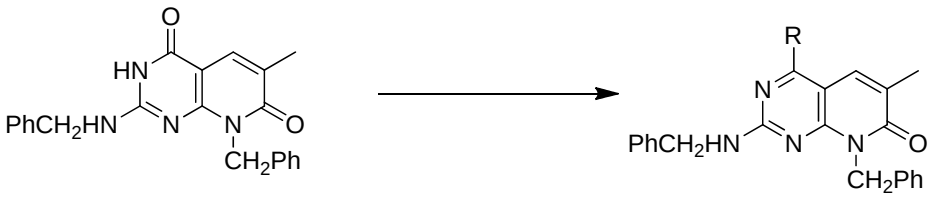
8d R = CH_2Ph
8e R = $CH_2CH{=}CH_2$

13a R^1 = $NHCH_2Ph$, R^2 = CH_2Ph, 68%
13b R^1 = pyrrolidin-1-yl, R^2 = CH_2Ph, 59%
13c R^1 = $NHCH_2Ph$, R^2 = $CH_2CH{=}CH_2$, 62%
13d R^1 = pyrrolidin-1-yl, R^2 = $CH_2CH{=}CH_2$, 68%



11b

14a R = $NHCH_2Ph$, 44%
14b R = pyrrolidin-1-yl, 51%
14c R = NHPh, 37%
14d R = OH, 44%



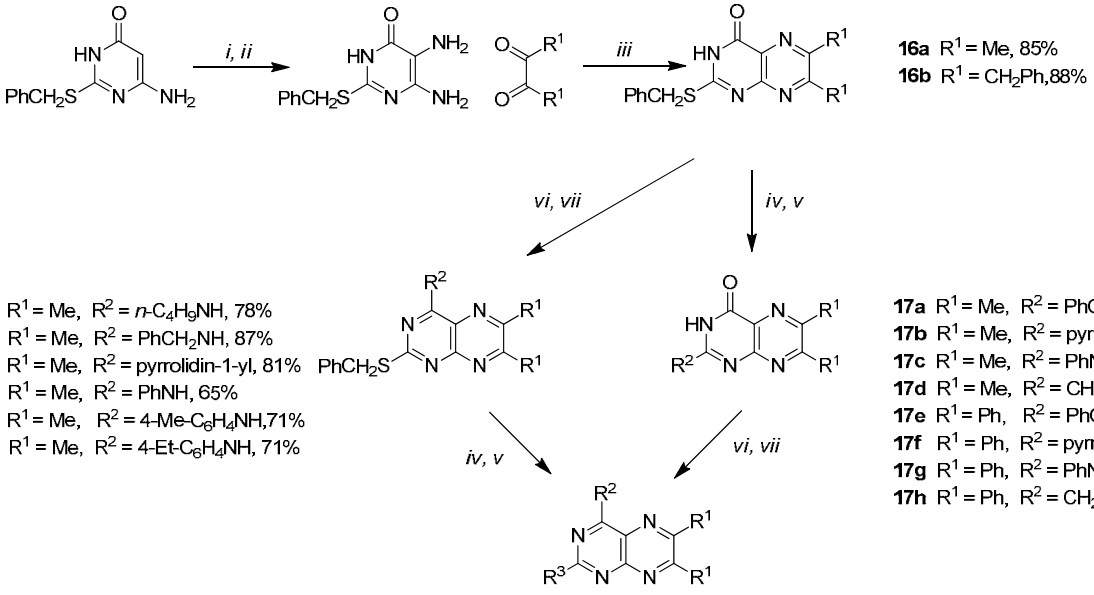
13a

15a R = $NHCH_2Ph$, 65%
15b R = pyrrolidin-1-yl, 58%

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

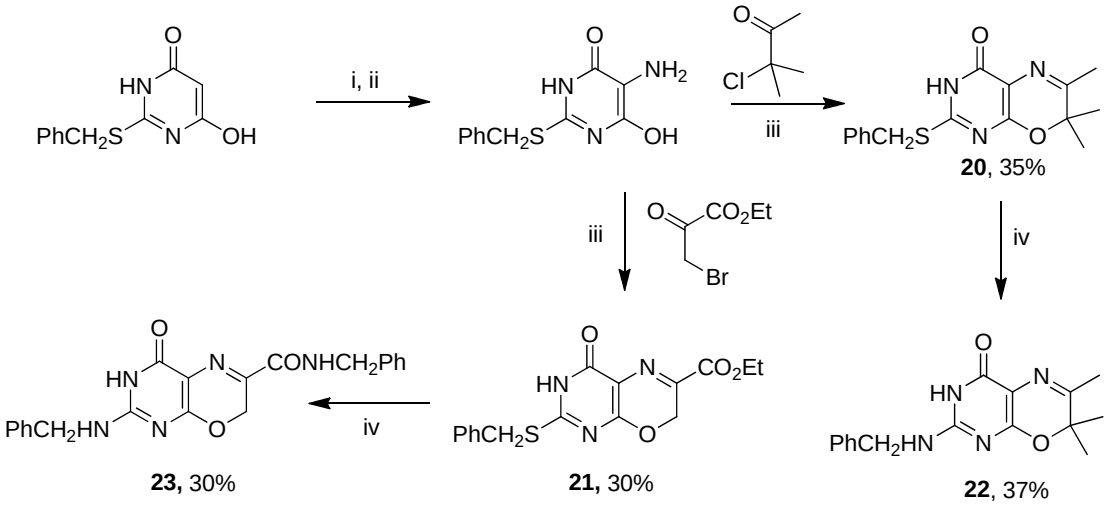
A further reaction of value in the diversification of oxo-heterocycles has been demonstrated by scientists from Wyeth who showed that oxo substituents in 4- and 7-positions especially could be converted into aminoalkyl substituents by treatment with BOP and the required amine.[18] This reaction was successful 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 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%).



Scheme 7. Diversification reactions for pteridines. *Reagents and conditions*: *i,* HNO_2; *ii*, $Na_2S_2O_4$; *iii,* EtOH, reflux; *iv,* DMF, *m*-CPBA, r.t., 3 h; *v,* appropriate amine, MW, 110 °C, 1 h; *vi*, BOP, CH_3CN, r.t., 10 min; *vii*, DBU, appropriate amine, r.t., 48 h.

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]



Scheme 8. Diversification for pyrimidooxazines. *Reagents and conditions*: *i*, HNO_2; *ii*, $Na_2S_2O_4$; *iii*, aq. EtOH, NaOAc, reflux; i *iv* $PhCH_2NH_2$, MW, 110 °C, 1 h.

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, 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 antiparasitic 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 *Trypanosoma 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 a also modest hit with a MIC of 25 μM. All of these compounds are, however, inferior as antiparasitic compounds to the pyrrolopyrimidines we have already described [23] because they have unacceptably high values of clogP (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 ^{1}H 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 Hz. Chemical shifts are reported as ppm 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 were 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 ^{1}H NMR spectra are included in the Electronic Supplementary Information†. TLC was carried out on silica (Merck 0.25 mm 60 F_{254}) 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(3*H*)-one 1[19] 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(3*H*)-one 3:

To 6-amino-2-(benzylsulfanyl)pyrimidin-4(3*H*)-one **1** (1.790 g, 7.67 mmol) in anhydrous DMF (20 mL) was added allyl bromide (700 μl, 0.980 g, 8.03 mmol, 1.05 eq.) and potassium carbonate (1.24 g, 8.98 mmol, 1.17 eq.). 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 $MgSO_4$ 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(3*H*)-one **3** as a white crystalline solid (0.127 g, 0.464 mmol, 9%).

Characterisation of **2**: m.p. 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, CH_2S), 4.73 (2H, d, J = 5.6 Hz, CH_2O), 5.20 (1H, d, J = 10.8 Hz, C*H*=CH_2), 5.33 (1H, d, J = 16.0 Hz, CH=CH*H*), 5.45 (1H, s, H-5), 5.94 – 6.04 (1H, m, C*H*=CH_2), 6.75 (2H, br s, NH_2), 7.21 – 7.31 (3H, m, C_6H_5), 7.39 – 7.41 (2H, m, C_6H_5); 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. $C_{14}H_{15}N_3OS$ requires 273.0936.

Characterisation of **3**: m.p. 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, CH_2N), 4.45 (2H, s, CH_2S), 4.94 (1H, s, H-5), 5.01 (1H, d, J = 17.6 Hz, CH=CH*H*), 5.12 (1H, d, J = 10.4 Hz, C*H*=CH_2), 5.70 – 5.80 (1H, m, C*H*=CH_2), 6.57 (2H, br s, NH_2), 7.24 – 7.33 (3H, m, C_6H_5), 7.44 – 7.46 (2H, m, C_6H_5); 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 (x2). HRMS (EI): M^+, found 273.0936. $C_{14}H_{15}N_3OS$ requires 273.0936.

3.2.3 5-Allyl-6-amino-2-(benzylthio)-4(3*H*)-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%), m.p. 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, C*H*$_2$CH=), 4.72 (2H, s, CH_2S), 4.94 (1H, d, J = 10.4 Hz, CH=C*H*$_2$), 5.05 (1H, d, J = 16.0 Hz, C*H*=CH_2), 5.67 – 5.89 (1H, m, C*H*=CH_2), 6.26 (2H, br s, NH_2), 7.18 – 7.30 (3H, m, C_6H_5), 7.37 – 7.47 (2H, m, C_6H_5), 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. $C_{14}H_{15}N_3OS$ 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(3*H*)-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 µl, 4.40 mmol, 1.50 eq.) and potassium carbonate (0.500 g, 3.62 mmol, 1.23 eq.) 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 $MgSO_4$ 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%), m.p. 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, CH_3 x 2), 3.33 (2H, s, CH_2=C(CO_2Et)CH_2), 4.09 – 4.20 (4H, m, CH_2 x 2), 4.29 (2H, s, CH_2S), 4.98 (2H, s, CH_2O), 5.14 (1H, s, =CH*H*), 5.75 (1H, s, =CH*H*), 5.99 (1H, s, =CH*H*), 6.19 (1H, s, =CH*H*), 6.19 (2H, br s, NH_2), 7.19 – 7.31 (3H, m, C_6H_5), 7.39-7.41 (2H, m, C_6H_5); 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. $C_{23}H_{27}N_3O_5S$ 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(3*H*)-one **1** (0.520 g, 2.22 mmol) was dissolved in DMF (10 mL, anhydrous) to which ethyl 2-(bromomethyl)acrylate (310 µl, 2.24 mmol) was added. The reaction mixture was then stirred under nitrogen for 7 d 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%), m.p. 160 – 162 ^oC. ν_{max} (KBr): 3483, 3368, 1693, 1614, 1475, 1438, 1333, 11260, 1187, 1152, 1029, 953, 693 cm^{-1}; δ_H (DMSO-d_6): 1.27 (3H, t, *J* = 7.6 Hz, CH_3), 3.18 (2H, s, CH_2C=), 4.19 (2H, q, *J* = 7.6 Hz. C$H_2$$CH_3$), 4.34 (2H, s, CH_2S), 5.22 (1H, s, C=CH_2), 5.97 (1H, s, C=CH_2), 6.34 (2H, br s, NH_2), 7.21 – 7.34 (3H, m, C_6H_5), 7.43 – 7.46 (2H, m, C_6H_5), 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 (x 2). HRMS (EI): M^+, found 345.1149. $C_{17}H_{19}N_3O_3S$ 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(3*H*)-one **1** and 2-(bromomethyl)acrylic acid using 2 eq. of the latter added over 2 d and a further 5 d reaction in 30% yield, m.p. 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, CH_2-C=), 4.31 (2H, s, CH_2S), 5.91 (1H, br s, C=CH_2), 6.33 (1H, br s, C=CH_2), 6.36 (2H, s, NH_2), 7.20 – 7.40 (3H, m, C_6H_5), 7.41 – 7.53 (2H, m, C_6H_5), 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. $C_{15}H_{15}N_3O_3S$ 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(3*H*)-pyrimidinone **7a** and ethyl 2-(bromomethyl)acrylate reacting for 3 d in 83% yield, m.p. 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, CH_2-C=), 4.14 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 5.26 (1H, d, *J* = 1.7 Hz, CH_2=), 5.67 (2H, s, NH_2), 5.94 (1H, d, *J* = 1.7 Hz, CH_2=), 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. $C_{10}H_{14}N_4O_3$ 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(3*H*)-one **7a** and 2-(bromomethyl)acrylic acid using 2 eq of the latter added over 2 d and a further 5 d reaction in 53 % yield, m.p. >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, CH_2-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. $C_8H_{10}N_4O_3$ 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(3*H*)-pyrimidinone **7b** and ethyl 2-(bromomethyl)acrylate with a reaction time of 4 d in 33% yield, m.p. 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, NHC*H*$_3$), 3.26 (2H, s, CH_2C=), 4.14 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 4.36 (2H, s, CH_2S), 5.85 (1H, d, *J* = 1.4 Hz, CH_2=), 5.95 (1H, d, *J* = 1.4 Hz, CH_2=), 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 $C_{18}H_{21}N_3O_3S$ 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(3*H*)-pyrimidinone **7c** and ethyl 2-(bromomethyl)acrylate with 4 reaction in 33% yield, m.p. 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, CH_2-C=), 4.11 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 4.25 (2H, d, *J* = 5.5 Hz, C*H*$_2$NH), 4.45 (3H, s, CH_2S), 5.95 (1H, d, *J* = 1.5 Hz, CH_2=), 6.04 (1H, d, *J* = 1.5 Hz, CH_2=), 6.15 (1H, t, *J* = 5.5 Hz, $NHCH_2$), 7.47 – 7.22 (10H, m, 2 x C_6H_5), 12.96 (1H, br s, NH). HRMS (FAB): M^++H, found 436.1694. $C_{24}H_{25}N_3O_3S$ requires 436.1695.

3.2.11 Ethyl 2-{[4-(allylamino)-2-(benzylsulfanyl)-6-oxo-1,6-dihydro-5-pyrimidinyl] methyl} acrylate 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, CH_2-C=), 4.08 – 4.12 (2H, m, C*H*$_2$NH), 4.22 (2H, q, *J* = 7.1 Hz, C*H*$_2$$CH_3$), 4.40 (2H, s, CH_2S), 5.12 (1H, d, *J* = 1.5 Hz, CH_2=), 5.16 (1H, d *J* = 1.5 Hz, CH_2=), 5.85 – 5.94 (1H, m, C*H*=CH_2), 6.04 (1H, d, *J* = 1.6 Hz, CH=CH*H*), 6.09 (1H, t, *J* = 5.7 Hz, N*H*CH_2), 6.21 (1H, d, *J* = 16 Hz, CH=C*H*H), 7.24 – 7.42 (5H, m, C_6H_5), 13.04 (1H, s, NH); δ_C ($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): M^++H, found 386.1534. $C_{20}H_{23}N_3O_3S$ requires 386.1538.

3.2.12 2-(Benzylsulfanyl)-6-(methylamino)-4(3*H*)-pyrimidinone 7b

2-(Benzylsulfanyl)-6-chloro-4(3*H*)-pyrimidinone (500 mg, 1.98 mmol) was dissolved in 2.0 M methylamine solution in THF (4.95 mL, 5 eq). The solution was heated to 80 °C in a sealed tube and stirred for 48 hours. 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 x 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%), m.p: >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, bd, -N*H*CH_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. $C_{12}H_{13}N_3OS$ requires 247.0779.

Similarly prepared were:

3.2.13 6-(Benzylamino)-2-(benzylsulfanyl)-4(3*H*)-pyrimidinone 7c as a white solid in 38% yield, m.p: 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, C_6H_5 x 2 and N*H*CH_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): M^++H, found 324.1174. $C_{18}H_{17}N_3OS$ requires 324.1171

3.2.14 6-(Allylamino)-2-(benzylsulfanyl)-4(3*H*)-pyrimidinone 7d as a white solid in 37% yield, m.p: >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-C*H*$_2$), 4.34 (2H, s, CH_2S), 4.89 (1H, s,

H-5), 5.10 (1H, d, *J* = 1.5, -CH_2-CH=CH_2), 5.17 (1H, d, *J* = 17.5, -CH_2-CH=CH_2), 5.80 (1H, m , -CH_2-C*H*=*C*H_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(3*H*,8*H*)-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-2*H*-pyrimido[1,2-*a*]pyrimidine (0.089 g, 0.597 mmol, 2.2 eq.) 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 x 10 mL) to yield the *title compound* **8a** as a white solid (0.085 g, 0.0283 mmol, 98%), m.p. > 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): M^++H, found 300.0816. $C_{15}H_{14}N_3O_2S$ requires 300.0807.

Similarly prepared were:
3.2.16 2-Amino-6-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione 8b as a highly insoluble beige solid in 81% yield, m.p. > 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(3*H*,8*H*)-dione 8c as a white solid in 96% yield, m.p. >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): M^++H, found 314.0962. $C_{16}H_{16}N_3O_2S$ requires 314.0963.

3.2.18 8-Benzyl-2-(benzylsulfanyl)-6-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione 8d as a white solid in 96% yield, m.p. > 230 °C. ν_{max} (KBr): 3452, 3183, 1642, 1629, 1588, 1465, 1264, 1098, 964, 951 δ_H (DMSO-d_6): 2.01 (3H, s, CH_3), 4.48 (2H, s, CH_2S), 5.35 (2H, s, CH_2N), 7.21 – 7.36 (10H, m, C_6H_5 x 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. $C_{22}H_{19}N_3O_2S$ requires 390.1276.

3.2.19 8-Allyl-2-(benzylsulfanyl)-6-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione 8e

as a white solid in 96% yield, m.p. > 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, CH_3), 4.47 (2H, s, CH_2S), 4.91 (2H, d, *J* = 2.1 Hz, C*H*$_2$-CH=), 4.95 (1H, dd, *J* = 17.2, 1.6 Hz, CH=CH*H*), 5.07 (1H, dd, *J* = 10.3, 1.6 Hz, CH=C*H*H), 5.86 – 5.93 (1H, m, C*H*=CH_2), 7.25 – 7.42 (5H, m, C_6H_5), 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. $C_{18}H_{17}N_3O_2S$ 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(3*H*)-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 eq.), 3-(chloromethyl)-4-phenyl-3-buten-2-one[15] (0.250 g, 1.28 mmol, 1.2 eq.) and potassium iodide (0.035 g, 0.214 mmol, 0.2 eq.) 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 $MgSO_4$, 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%), m.p. 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 ($CDCl_3$): 2.49 (3H, s, CH_3), 4.32 (2H, s, CH_2S), 4.67 (2H, br s, NH_2), 5.15 (2H, s, OCH_2), 5.53 (1H, s, H-5), 7.17 – 7.44 (10H, m, C_6H_5 x 2), 7.82 (1H, s, C=CH); δ_C ($CDCl_3$): 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. $C_{22}H_{21}N_3O_2S$ 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(3*H*)-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 eq.), 3-(chloromethyl)-4-(4-trifluoromethylphenyl)-3-buten-2-one[15] (0.267 g, 1.28 mmol, 1.2 eq.) and potassium iodide (0.035 g, 0.214 mmol, 0.2 eq.) 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 dried over $MgSO_4$, 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%), m.p. 145 – 147 °C. ν_{max} (KBr): 3477, 3366, 1651, 1625, 1578, 1454, 1424, 1325, 1300, 1195, 1123, 1069, 704 cm^{-1}; δ_H ($CDCl_3$): 2.50 (3H, s, CH_3) 4.31 (2H, s, CH_2S), 4.72 (2H, br s, NH_2), 5.10 (2H, s, OCH_2), 5.51 (1H, s, H-5), 7.18 – 7.66 (9H, m, C_6H_5 and C_6H_4), 7.78 (1H, s, C=CH); δ_C ($CDCl_3$): 26.4, 35.0, 60.1, 83.4, 125.7, 125.7 (CF_3), 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. $C_{23}H_{20}F_3N_3O_2S$ requires 459.1228.

3.2.22 6-Benzyl-2-(benzylsulfanyl)-7-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-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 d under nitrogen. The excess solvent was removed under reduced pressure and the resulting residue was washed with saturated aqueous $NaHCO_3$ solution (2 x 10 mL) and de-ionised water (2 x 10 mL). The organic layer was dried over $MgSO_4$, 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%), m.p. 181 – 183 °C. ν_{max} (KBr): 3437, 1709, 1662, 1638, 1541, 1186, 797, 700 cm^{-1}; δ_H ($CDCl_3$): 2.65 (3H, s, CH_3), 4.12 (2H, s, CCH_2), 4.68 (2H, s, SCH_2) 7.53 - 7.12 (10H, m, C_6H_5 x 2), 8.23 (1H, s, H-5), 10.00 (1H, s, NH); δ_C ($CDCl_3$): 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. $C_{22}H_{20}N_3OS$ requires 374.1327.

3.2.23 2-(Benzylsulfanyl)-7-methyl-6-[4-(trifluoromethyl)benzyl] pyrido[2,3-*d*]pyrimidin-4(3*H*)-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 d under nitrogen. The excess solvent was removed under reduced pressure and was washed with saturated aqueous $NaHCO_3$ solution. The reaction mixture was filtered and partitioned between water and ethyl acetate. The ethyl acetate layer was dried over $MgSO_4$, filtered under reduced pressure and the solvent was removed under reduced pressure. The *title compound* **11b** was re-crystallised from methanol as a white solid (0.055 g, 0.0125 mmol, 23%), m.p. 195 – 198 °C. ν_{max} (KBr): 3027, 2922, 1682, 1570, 1411, 1325, 1164, 1066, 805, 699 cm^{-1}; δ_H ($CDCl_3$): 2.63 (3H, s, CH_3), 4.15 (2H, s, CH_2C), 4.68 (2H, s, CH_2S), 7.23 –

7.58 (9H, m, C_6H_5 and C_6H_4), 8.26 (1H, s, H-5), 11.57 (1H, s, NH); δ_C ($CDCl_3$): 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. $C_{23}H_{18}F_3N_3OS$ requires 441.1123.

3.2.24 8-Benzyl-2-(benzylamino)-6-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione 13a
8-Benzyl-2-(benzylsulfanyl)-6-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-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 eq.) 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%), m.p. > 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, CH_3), 4.51 (2H, d, J = 5.5 Hz, NHCH_2), 5.37 (2H, s, NCH_2), 7.18 – 7.24 (10H, m, C_6H_5 x 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. $C_{22}H_{20}N_4O_2$ requires 373.1665.

Similarly prepared were:
3.2.25 8-Benzyl-6-methyl-2-(1-pyrrolidinyl)pyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione 13b as a beige solid in 59% yield, m.p. > 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, CH_2CH_2), 2.01 (3H, s, CH_3), 3.46 (4H, s, CH_2N x 2), 5.37 (2H, s, CH_2N), 7.18-7.33 (5H, m, C_6H_5), 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. $C_{19}H_{20}N_4O_2$ requires 367.1659.

3.2.26 8-Allyl-2-(benzylamino)-6-methylpyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-dione 13c as a beige solid in 62% yield, m.p. > 230 °C. δ_H (DMSO-d_6): 1.98 (3H, s, CH_3), 4.53 (2H, d, J = 5.9, CH_2NH), 4.75 (2H, d, J = 5.9, CH_2-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=CH_2), 7.24 -7.34 (5H, m, C_6H_5), 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. $C_{18}H_{18}N_4O_2$ 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 as a beige solid 64% yield, m.p. > 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, CH_2CH_2), 1.99 (3H, d, *J* = 1.1 Hz, CH_3), 3.50 (4H, t, *J* = 6.8 Hz, CH_2N x 2), 4.81 (2H, dd, *J* = 7.0, 1.4 Hz, C*H*$_2$-CH=), 5.06 (1H, t, *J* = 1.5 Hz, CH=CH*H*), 5.09 (1H, dd, *J* = 12.0, 1.5 Hz, CH=C*H*H), 5.85 – 5.95 (1H, m, C*H*=CH_2), 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. $C_{15}H_{18}N_4O_2$ 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 $NaHCO_3$ solution (2 x 5 mL) and water (2 x 5 mL). The organic layer way then dried over $MgSO_4$ and was purified by HPLC to yield the *title compound* **14a** as a white solid (0.021 g, 0.0495 mmol, 44%), m.p. 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, CH_3), 4.22 (2H, s, CH_2C), 4.66 (2H, d, *J* = 5.8 Hz, C*H*$_2$NH), 7.26 – 7.70 (9H, m, C_6H_5 and C_6H_4), 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. $C_{23}H_{19}F_3N_4O$ 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 $NaHCO_3$ solution (2 x 5 mL) and water (2 x 5 mL). The organic layer way then dried over $MgSO_4$ and purified by HPLC to

yield the *title compound* **14b** as a white solid (0.022 g, 0.0574 mmol, 51%), m.p. 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, CH_2CH_2), 2.41 (3H, s, CH_3), 3.50 (4H, t, *J* = 6.5 Hz, CH_2N x 2), 4.12 (2H, s, CH_2C), 7.40 (2H, d, *J* = 8.1 Hz, 2,6-CH of Ar), 7.67 (2H, d, *J* = 8.1 Hz, 3,5-CH_2 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. $C_{20}H_{19}F_3N_4O$ 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 eq.) 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 $NaHCO_3$ solution (2 x 5 mL) and water (2 x 5mL). The organic layer way then dried over $MgSO_4$ and purified by HPLC to yield the *title compound* **14c** as a white solid (0.017 g, 0.0414 mmol, 37%), m.p. 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, CH_3), 4.22 (2H, s, CH_2C), 7.14 – 7.23 (9H, m, C_6H_5 and C_6H_4), 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. $C_{22}H_{17}F_3N_4O$ 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 eq.) 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 $NaHCO_3$ solution (2 x 5 mL) and water (2 x 5 mL). The organic layer was then dried over $MgSO_4$ and purified by HPLC to yield the *title compound* **14d** as a white solid (0.018 mg, 0.0401 mmol, 35%), m.p. 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, CH_3), 4.16 (2H, s, CH_2C), 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. $C_{16}H_{12}F_3N_3O_2$ 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 eq.) were suspended in acetonitrile (10 mL, anhydrous) at room temperature. DBU (31 µl, 0.201 mmol, 1.5 eq) was added dropwise and the reaction solution became heterogeneous. After stirring for 10 min at room temperature, benzylamine (22 µl, 0.201 mmol, 1.5 eq) 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%), m.p. > 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, CH_3), 4.64 (2H, d, J = 6.3 Hz, CH_2NH), 4.79 (2H, d, J = 4.8 Hz, CH_2NH), 5.51 (2H, br s, NH x 2), 7.16 – 7.36 (15H, m, C_6H_5 x 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. $C_{29}H_{27}N_5O$ 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 eq.) were suspended in acetonitrile (10 mL, anhydrous) at room temperature. DBU (31 µl, 0.201 mmol, 1.5 eq.) was added dropwise and the reaction solution became heterogeneous. After stirring for 10 min at room temperature pyrrolidine (17 µl, 1.5 eq) 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%), m.p. > 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, CH_2CH_2), 2.03 (3H, s, CH_3), 3.73 (2H, t, J = 6.5, CH_2N), 4.24 (2H, t, J = 6.5, CH_2N), 4.80 (2H, d, J = 5.8, $C_6H_5CH_2NH$), 5.53 (2H, s, $C_6H_5CH_2N8$), 7.17 – 7.27 (10H, m, C_6H_5 x 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. $C_{26}H_{27}N_5O$ requires 426.2294.

3.2.34 2-(Benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone 16a

To a solution of 5,6-diamino-2-(benzylsulfanyl)-4(3*H*)-pyrimidinone (500 mg, 2.11 mmol) in ethanol (20 mL) was added biacetyl (353 µl, 4.02 mmol, 2 eq) dropwise at room temperature. The reaction mixture was refluxed at 80 °C for 24 hours. 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%) m.p. >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, CH_3), 2.61 (3H, s, CH_3), 4.52 (2H, s, CH_2S), 7.26 – 7.47 (5H, m, C_6H_5), 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. $C_{15}H_{14}N_4OS$ requires 299.0967.

3.2.35 2-(Benzylsulfanyl)-6,7-diphenyl-4(3*H*)-pteridinone 16b

To a solution of 5,6-diamino-2-(benzylsulfanyl)-4(3*H*)-pyrimidinone (1000 mg, 4.03 mmol) in ethanol (20 mL) was added benzil (1270 mg, 6.04 mmol, 1.5 eq) at room temperature. The reaction mixture was heated at 85 °C for 24 hours. 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%) m.p. >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, CH_2S), 7.26 – 7.51 (15H, m, C_6H_5 x 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. $C_{25}H_{18}N_4OS$ requires 423.1280.

3.2.36 2-(Benzylamino)-6,7-dimethyl-4(3*H*)-pteridinone 17a

2-(Benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone **16a** (100 mg, 0.335 mmol) was dissolved in dry DMF (3.0 mL). To this solution was added *m*-CPBA (3.0 eq, 1.01 mmol, 174 mg) and was stirred under nitrogen for 3 hours 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 hour. 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%) m.p. >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, CH_3), 2.48 (3H, s, CH_3), 4.59 (2H, d, J = 5.6 Hz, CH_2NH), 7.23 – 7.40 (5H, m, C_6H_5), 7.60 (1H, br s, CH_2NH), 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. $C_{15}H_{15}N_5O$ requires 282.1355.

Similarly prepared were:

3.2.38 6,7-Dimethyl-2-(1-pyrrolidinyl)-4(3*H*)-pteridinone 17b:

From 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone and pyrrolidine in 90% yield, m.p. >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, CH_2CH_2), 2.48 (3H, s, CH_3), 2.49 (3H, s, CH_3), 3.50 (4H, t, *J* = 6.1, CH_2N x 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): found 246.1351. $C_{12}H_{15}N_5O$ requires 246.1355.

3.2.39 2-Anilino-6,7-dimethyl-4(3*H*)-pteridinone 17c:

From 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone and aniline in 54% yield, m.p. >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, CH_3), 2.55 (3H, s, CH_3), 7.06 – 7.74 (5H, m, C_6H_5), 8.92 (1H, s, N*H*C_6H_5) 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. $C_{14}H_{13}N_5O$ requires 268.1198.

3.2.40 2-(Allylamino)-6,7-dimethyl-4(3*H*)-pteridinone 17d:

From 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone and allylamine in 86% yield, m.p. >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 x CH_3), 3.90 (2H, s, C*H*$_2$CH=), 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, CH_2C*H*=), 12.30 (1H, s, NH). HRMS (FAB): M^++Na, found 254.1020. $C_{11}H_{13}N_5ONa$ requires 254.1018;

3.2.41 2-(Benzylamino)-6,7-diphenyl-4(3*H*)-pteridinone 17e:

From 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone and benzylamine in 83% yield, m.p. >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, CH_2), 7.23 – 7.42 (16H, m, C_6H_5 x 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. $C_{25}H_{19}N_5O$ requires 406.1668.

3.2.42 6,7-Diphenyl-2-(1-pyrrolidinyl)-4(3*H*)-pteridinone 17f:

From 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone and pyrrolidine in 83% yield m.p. >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, CH_2CH_2), 3.57 (4H, t, *J* = 6.5 Hz, CH_2N), 7.30 – 7.43 (10H, m, C_6H_5), 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. $C_{22}H_{19}N_5O$ requires 370.1668.

3.2.43 2-Anilino-6,7-diphenyl-4(3*H*)-pteridinone 17g:

From 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone and aniline in 61% yield, m.p. >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, C_6H_5 x 3), 9.29 (1H, br s, N*H*CH_2), 11.29 (1H, s,); 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. $C_{24}H_{17}N_5O$ requires 392.1511.

3.2.44 2-(Allylamino)-6,7-diphenyl-4(3*H*)-pteridinone 17h:

From 2-(benzylsulfanyl)-6,7-diphenyl-4(3*H*)-pteridinone and allylamine in 79% yield, m.p. >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, NHC*H*$_2$-CH=), 5.15 (1H, dd, *J* = 10.3, 1.6 Hz, CH=CH*H*), 5.25 (1H, dd, *J* = 17.2, 1.6 Hz, CH=C*H*H), 5.94 – 5.99 (1H, m, CH_2-C*H*=), 6.94 (1H, s, NH), 7.30 – 7.43 (10H, m, C_6H_5 x 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. $C_{21}H_{17}N_5O$ requires 356.1511.

3.2.45 2-(Benzylsulfanyl)-*N*-butyl-6,7-dimethyl-4-pteridinamine 18a:

2-(Benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone **16a** (100 mg, 0.335 mmol) and BOP (196 mg, 0.443 mmol, 1.3 eq) were suspended in dry acetonitrile (10 mL). DBU (76 µl, 0.493 mmol, 1.5 eq) was then added dropwise and the reaction mixture became homogeneous. After stirring for 10 min at room temperature, butylamine (50 µl, 0.502 mmol, 1.5 eq) was added dropwise and the solution was stirred for a further 48 hours. 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%), m.p. >230 °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): M^++Na, found 376.1573. $C_{19}H_{23}N_5SNa$ requires 376.1572.

Similarly prepared were

3.2.46 *N*-Benzyl-2-(benzylsulfanyl)-6,7-dimethyl-4-pteridinamine 18b:

From 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone and benzylamine in 87% yield, m.p. >230 °C; ν_{max} (KBr): 3403, 3084, 2981, 1684, 1621, 1574, 1448, 1223, 909 cm^{-1}; δ_H (DMSO-d_6): 2.63 (6H, s, CH_3 x 2), 4.39 (2H, s, CH_2S), 4.71 (2H, d, J = 6.2, Hz, CH_2NH), 7.19 – 7.44 (10H, m, C_6H_5 x 2), 9.10 (1H, t, J = 6.2 Hz, CH_2NH); δ_C (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): M^++H, found 388.1593. $C_{22}H_{21}N_5S$ requires 388.1596.

3.2.47 2-(Benzylsulfanyl)-6,7-dimethyl-4-(1-pyrrolidinyl)pteridine 18c:

From 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone and pyrrolidine in 81% yield, m.p. >230 °C; ν_{max} (KBr): 3368, 3121, 2963, 1644, 1568, 1553, 1450, 1378, 1262, 820, 724 cm^{-1}; δ_H (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 (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): M^++H, found 352.1599. $C_{19}H_{21}N_5S$ requires 352.1596.

3.2.48 2-(Benzylsulfanyl)-6,7-dimethyl-*N*-phenyl-4-pteridinamine 18d:

From 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone and aniline in 65% yield, m.p. >230 °C; ν_{max} (KBr): 3451, 3096, 1681, 1574, 1541, 1483, 1241, 1090, 828, 741 cm^{-1}; δ_H (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, C_6H_5 x 2), 10.09 (1H, s, NH); δ_C (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): M^++H, found 374.1436.$C_{21}H_{19}N_5S$ requires 374.1439.

3.2.49 2-(Benzylsulfanyl)-6,7-dimethyl-*N*-(4-methylphenyl)-4-pteridinamine 18e:

From 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-pteridinone and *p*-toluidine in 71% yield, m.p. >230 °C; ν_{max} (KBr): 3430, 3030, 2845, 1683, 1539, 1478, 1234, 1025, 697 cm^{-1}; δ_H (DMSO-d_6): 2.29 (3H, s, $C_6H_4CH_3$), 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 (DMSO-d_6): 20.5, 22.0, 23.0, 34.4, 121.6, 122.0, 127.0, 128.4, 128.8, 128.9, 133.3, 135.6, 138.0, 151.4, 152.0, 156.9, 160.6, 169.2. HRMS (FAB): M^++H, found 388.1597. $C_{22}H_{21}N_5S$ requires 388.1596.

3.2.50 2-(Benzylsulfanyl)-*N*-(4-ethylphenyl)-6,7-dimethyl-4-pteridinamine 18f:

From 2-(benzylsulfanyl)-6,7-dimethyl-4(3*H*)-and 4-ethylaniline in 71% yield, m.p. >230 °C. ν_{max} (KBr): 3424, 3026, 2942, 2853, 1678, 1513, 1495, 1392, 1259, 1012, 744 cm^{-1}; δ_H (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 (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): M^++H, found 402.1756. $C_{23}H_{23}N_5S$ requires 402.1752.

3.2.51 *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 eq) at room temperature and the reaction was stirred for 3 hours 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 hour 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%), m.p. >230 °C. ν_{max} (KBr): 3297, 2975, 1659, 1542, 1364, 1295, 981 cm^{-1}; δ_H (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 (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): M^++H, found 335.1987. $C_{19}H_{22}N_6$ requires 335.1984.

Similarly prepared was

3.2.52 6,7-Dimethyl-2,4-di(1-pyrrolidinyl)pteridine 19b

From 2-(benzylsulfanyl)-6,7-dimethyl-4-(1-pyrrolidinyl)pteridine **18 c** and pyrrolidine in 86% yield, m.p. >230 °C; ν_{max} (KBr): 3098, 2975, 1683, 1620, 1467,1346, 1234, 1082, 830 cm^{-1}; δ_H (DMSO-d_6): 1.90 (8H, s, CH_2CH_2 x 2), 2.46 (3H, s, CH_3), 2.48 (3H, s, CH_3), 3.51 (4H, s, CH_2N x 2), 3.68 (2H, s, CH_2N), 4.18 (2H, s, CH_2N); δ_C (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): M^++H, found 299.1987. $C_{16}H_{22}N_6$ requires 299.1984.

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

3.2.53 N^2-Allyl-N^4-butyl-6,7-diphenyl-2,4-pteridinediamine 19c

From 2-(allylamino)-6,7-diphenyl-4(3*H*)-pteridinone **17h** and *n*-butylamine in 70% yield, m.p. >230 °C. ν_{max} (KBr): 3283, 3080, 2974, 1691, 1616, 1560, 1492, 1220, 903, 735 cm^{-1}; δ_H (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, CH_2CH_2NH), 4.02 (2H, t, J = 5.6 Hz, CH_2CH=), 5.06 (2H, dd, J = 10.2, 1.6 Hz, CH=C*H*H), 5.18 (2H, dd, J = 17.2, 1.6 Hz, CH=CH*H*), 5.95 (1H, m, C*H*=CH_2), 7.29 – 7.44 (11H, m, C_6H_5 and NH) 8.16 (1H, s, NH). HRMS (FAB): M^++H, found 411.2298. $C_{25}H_{26}N_6$ requires 411.2297.

3.2.54 N^2-Allyl-N^4-benzyl-6,7-diphenyl-2,4-pteridinediamine 19d

From 2-(allylamino)-6,7-diphenyl-4(3*H*)-pteridinone **17h** and benzylamine in 83% yield, m.p. >230 °C. ν_{max} (KBr): 3310, 3054, 2986, 1663, 1621, 1446, 1421, 1263, 993, 895, 739 cm^{-1}; δ_H (DMSO-d_6): 4.01 (2H, s, $C_6H_5CH_2NH$), 4.75 (2H, d, *J* = 5.2, Hz, CH_2CH=) 5.05 (1H, dd, *J* = 10.0, 1.6 Hz, CH=C*H*H), 5.18 (1H, dd, *J* = 17.2, 1.6 Hz, CH=CH*H*), 5.94 (1H, m, C*H*=CH_2), 7.21 – 7.45 (16H, m, C_6H_5 x 3 and NH), 8.67 (1H, s, NH); δ_C (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): M^++H found 445.2136. $C_{28}H_{25}N_6$ requires 445.2141.

3.2.55 *N*-Allyl-6,7-diphenyl-4-(1-pyrrolidinyl)-2-pteridinamine 19e

From 2-(allylamino)-6,7-diphenyl-4(3*H*)-pteridinone **17h** and pyrrolidine in 80% yield, m.p: >230 °C. ν_{max} (KBr): 3304, 3063, 2951, 1696, 1612, 1439, 1412, 1249, 998, 755 cm^{-1}; δ_H (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, CH_2CH=), 4.26 (2H, t, *J* = 6.5, Hz, CH_2N), 5.06 (1H, dd, *J* = 10.3, 1.7 Hz, CH=C*H*H), 5.19 (1H, dd, *J* = 17.2, 1.7 Hz, CH=CH*H*), 5.91 – 6.00 (1H, m), 7.29 – 7.45 (11H, m, C_6H_5 x 2 and NH). HRMS (FAB): M^++H, found 409.2139. $C_{25}H_{24}N_6$ requires 409.2141.

3.2.56 2-(Benzylsulfanyl)-6,7,7-trimethyl-3,7-dihydro-4*H*-pyrimido[4,5-*b*][1,4]oxazin-4-one 20

2-(Benzylthio)-6-hydroxy-5-nitrosopyrimidin-4(3*H*)-one (300 mg, 1.14 mmol) was dissolved in ethanol (20 mL) to which sodium dithionite (496 mg, 2.85 mmol, 2.5 eq) 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 x 10 mL) and ether (2 x 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 eq) 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 eq) 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 x 10 mL) and dry ether (2 x 10 mL) to yield the *title compound* **20** as a beige solid (126 mg, 0.399 mmol, 35%), m.p. 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-CH_3 x 2), 2.07 (3H, s, 6-CH_3), 4.36 (2H, s, CH_2S), 7.41 – 7.20 (5H, m, C_6H_5), 12.63 (2H, br s, NH). HRMS (FAB): M^++H, found 316.1119. $C_{16}H_{17}N_3O_2S$ requires 316.1120.

Similarly prepared was:

3.2.57 Ethyl 2-(benzylsulfanyl)-4-oxo-3,7-dihydro-4*H*-pyrimido[4,5-*b*][1,4]oxazine-6-carboxylate 21

From 2-(Benzylthio)-6-hydroxy-5-nitrosopyrimidin-4(3*H*)-one reduced with sodium dithionite and ethyl bromopyruvate in 30% yield, m.p. 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, CH_3), 4.25 (2H, q, J = 7.1 Hz, CH_2), 4.40 (2H, s, CH_2S), 5.10 (2H, s, CH_2O), 7.42 – 7.25 (5H, m, C_6H_5), 13.00 (1H, br s, NH). HRMS (FAB): M^++H, found 346.0863. $C_{16}H_{15}N_3O_4S$ requires 346.0862.

3.2.58 2-(Benzylamino)-6,7,7-trimethyl-3,7-dihydro-4*H*-pyrimido[4,5-*b*][1,4]oxazin-4-one 22

2-(Benzylsulfanyl)-6,7,7-trimethyl-3,7-dihydro-4*H*-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 hour 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 x 5 mL) and water (2 x 5 mL). The organic layer was then dried over $MgSO_4$ and was purified by flash chromatography to yield the title product as a beige solid (44 mg, 0.148 mmol, 37%), m.p. >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, CH_3 x 2), 2.00 (3H, s, CH_3), 4.43 (2H, d, J = 6.3 Hz, CH_2NH), 7.15 (1H, br s, NH), 7.25 – 7.35 (5H, m, C_6H_5), 10.63 (1H, s, NH). HRMS (FAB): M^++H, found 299.1506. $C_{16}H_{18}N_4O_2$ requires 299.1508.

3.2.59 *N*-Benzyl-2-(benzylamino)-4-oxo-3,7-dihydro-4*H*-pyrimido[4,5-*b*][1,4]oxazine-6-carboxamide 23

Ethyl 2-(benzylsulfanyl)-4-oxo-3,7-dihydro-4*H*-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 hour 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 x 5 mL) and water (2 x 5 mL). The organic layer was then dried over $MgSO_4$ and the title product was recrystallised from methanol as an orange solid (34 mg, 0.088 mmol, 30%), m.p. >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, CH_2NH), 4.36 (2H, d, J = 5.9 Hz, CH_2NH), 5.00 (2H, s, CH_2O) 7.29 (10H, m, C_6H_5 x 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): M^++H, found 390.1570. $C_{21}H_{19}N_5O_3$ requires 390.1566.

4. Notes and references

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Electronic Supplementary Information (ESI) available: ^{1}H NMR spectra for most new compounds.

Abbreviations for reagents

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

Legends for figures.

Scheme 1. Substitution by Claisen rearrangement.*Reagents and conditions*: *i*. DMF, K_2CO_3, 100 °C, 20 h; *ii*. 200 °C, 24 h

Scheme 2. Preparation of dialkylated pyrimidine **5** *Reagents and conditions: i*. DMF, K_2CO_3, 55 °C, 24h

Scheme 3. *Reagents and conditions: i*. DMF, r.t, 7 d; *ii*. TBD or DBU, MW, 100 °C, 30 min

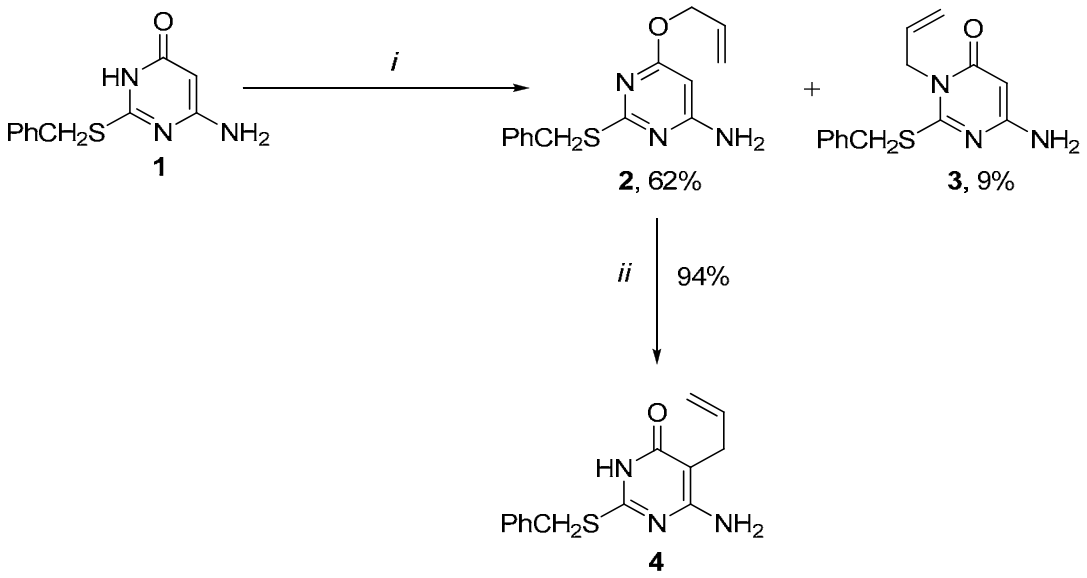
Scheme 4. *Regents and conditions*: *i*. Cs_2CO_3, KI, r.t., 24 h; *ii*. $TiCl_4$.2THF, THF, reflux, 3 d

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

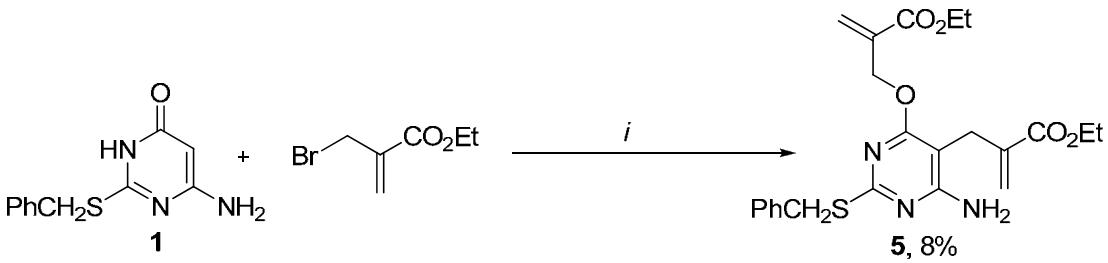
Scheme 6. Diversification reactions for pyrrolopyrimdines. *Reagents and conditions*: *i.* DMF, *m*-CPBA, r.t., 3 h; *ii,* appropriate amine, MW, 110 °C, 1 h; *iii*, BOP, CHCN, r.t., 10 min; *iv*, DBU, appropriate amine, r.t., 48 h.

Scheme 7. Diversification reactions for pteridines. *Reagents and conditions*: *i,* HNO_2; *ii*, $Na_2S_2O_4$; *iii,* EtOH, reflux; *iv,* DMF, *m*-CPBA, r.t., 3 h; *v,* appropriate amine, MW, 110 °C, 1 h; *vi*, BOP, CH_3CN, r.t., 10 min; *vii*, DBU, appropriate amine, r.t., 48 h.

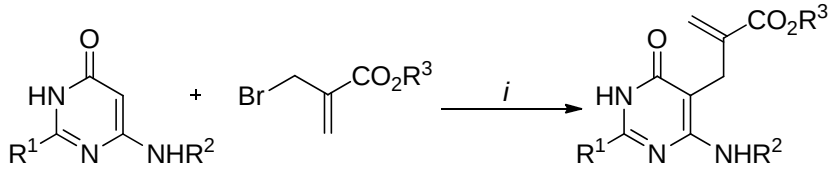
Scheme 8. Diversification for pyrimidooxazines. *Reagents and conditions*: *i*, HNO_2; *ii*, $Na_2S_2O_4$; *iii*, aq. EtOH, NaOAc, reflux; i *iv* $PhCH_2NH_2$, MW, 110 ^oC, 1 h.


O
HN
PhCH2S
N
NH2
1
i
O
N
PhCH2S
N
NH2
2, 62%
+
O
N
PhCH2S
N
NH2
3, 9%
ii
94%
O
HN
PhCH2S
N
NH2
4

Scheme 1

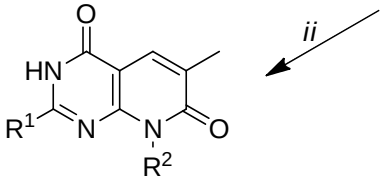


Scheme 2



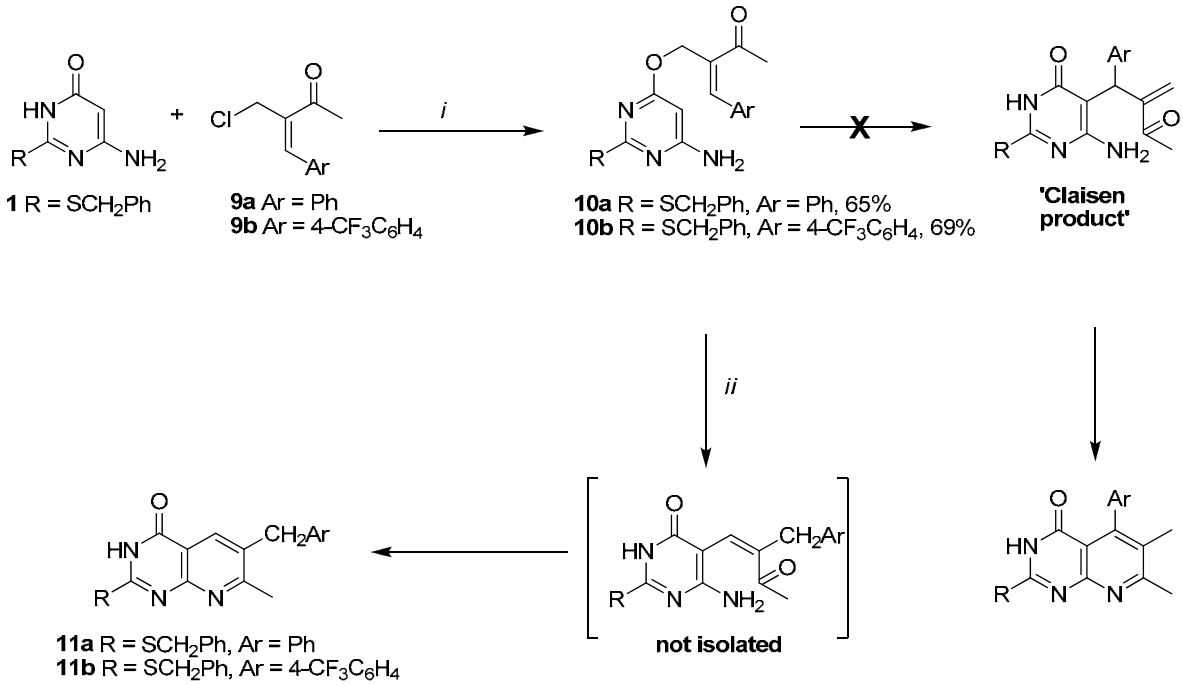
1 R^1 = SBn, R^2 = H
7a R^1 = NH_2, R^2 = H
7b R^1 = SBn, R^2 = Me
7c R^1 = SBn, R^2 = CH_2Ph
7d R^1 = SBn, R^2 = CH_2CHCH_2

6a R^1 = SBn, R^2 = H, R^3 = Et, 46%
6b R^1 = SBn, R^2 = H, R^3 = H, 30%
6c R^1 = NH_2, R^2 = H, R^3 = Et, 83%
6d R^1 = NH_2, R^2 = H, R^3 = H 53%
6e R^1 = SBn, R^2 = Me, R^3 = Et, 33%
6f R^1 = SBn, R^2 = CH_2Ph, R^3 = Et, 33%
6g R^1 = SBn, R^2 = CH_2CHCH_2, R^3 = Et, 33%

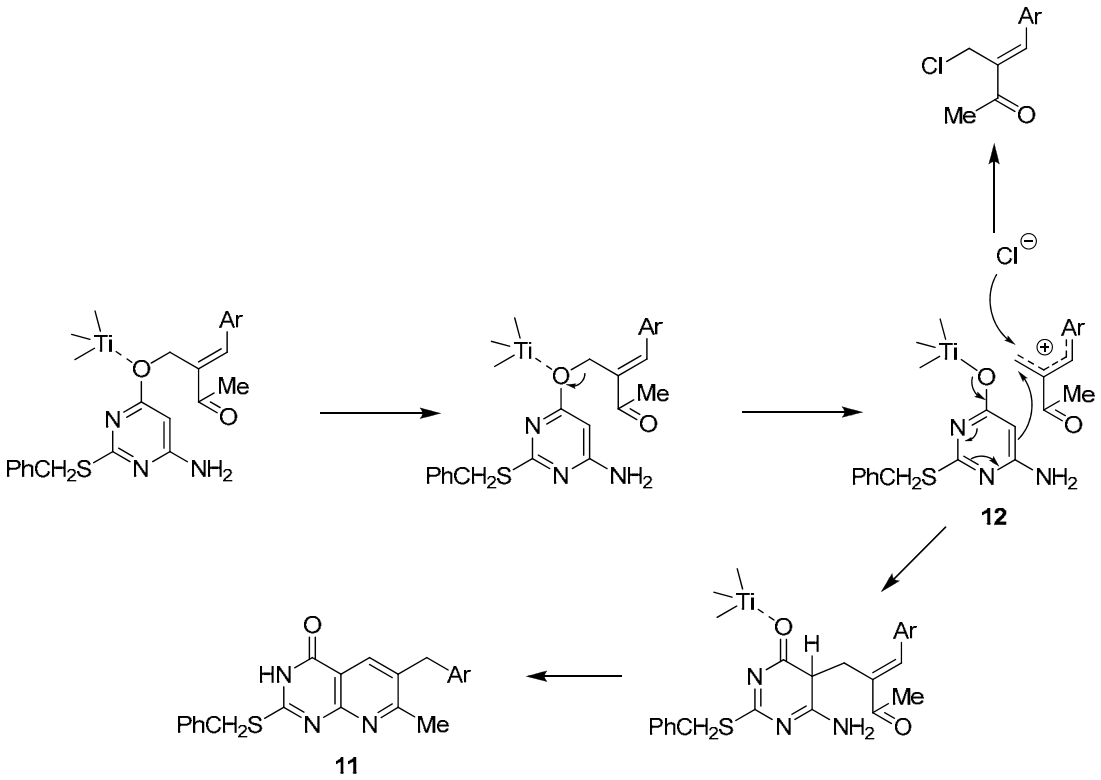


8a R^1 = SBn, R^2 = H, 98%
8b R^1 = NH_2, R^2 = H, 81%
8c R^1 = SBn, R^2 = Me, 96%
8d R^1 = SBn, R^2 = CH_2Ph, 96%
8e R^1 = SBn, R^2 = CH_2CHCH_2, 96%

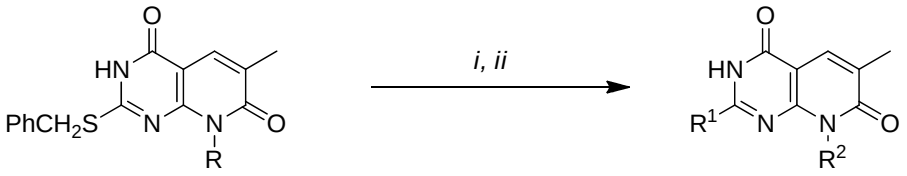
Scheme 3


1 R = SCH2Ph
9a Ar = Ph
9b Ar = 4-CF3C6H4
i
10a R = SCH2Ph, Ar = Ph, 65%
10b R = SCH2Ph, Ar = 4-CF3C6H4, 69%
'Claisen product'
ii
not isolated
11a R = SCH2Ph, Ar = Ph
11b R = SCH2Ph, Ar = 4-CF3C6H4

Scheme 4

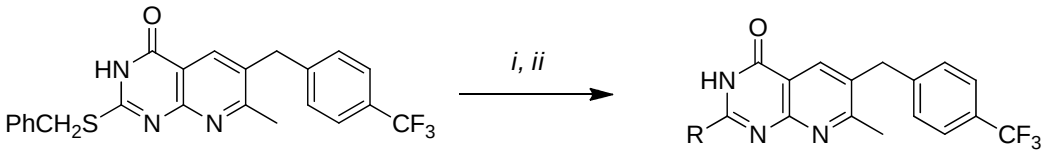


Scheme 5



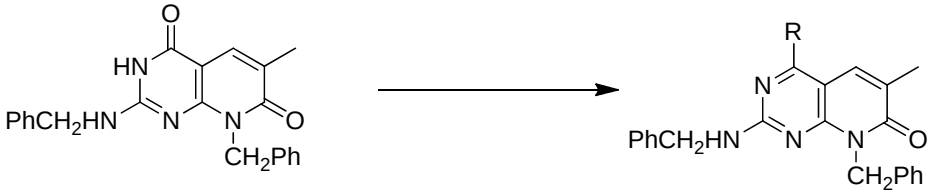
8d R = CH_2Ph
8e R = $CH_2CH{=}CH_2$

13a R^1 = $NHCH_2Ph$, R^2 = CH_2Ph, 68%
13b R^1 = pyrrolidin-1-yl, R^2 = CH_2Ph, 59%
13c R^1 = $NHCH_2Ph$, R^2 = $CH_2CH{=}CH_2$, 62%
13d R^1 = pyrrolidin-1-yl, R^2 = $CH_2CH{=}CH_2$, 68%



11b

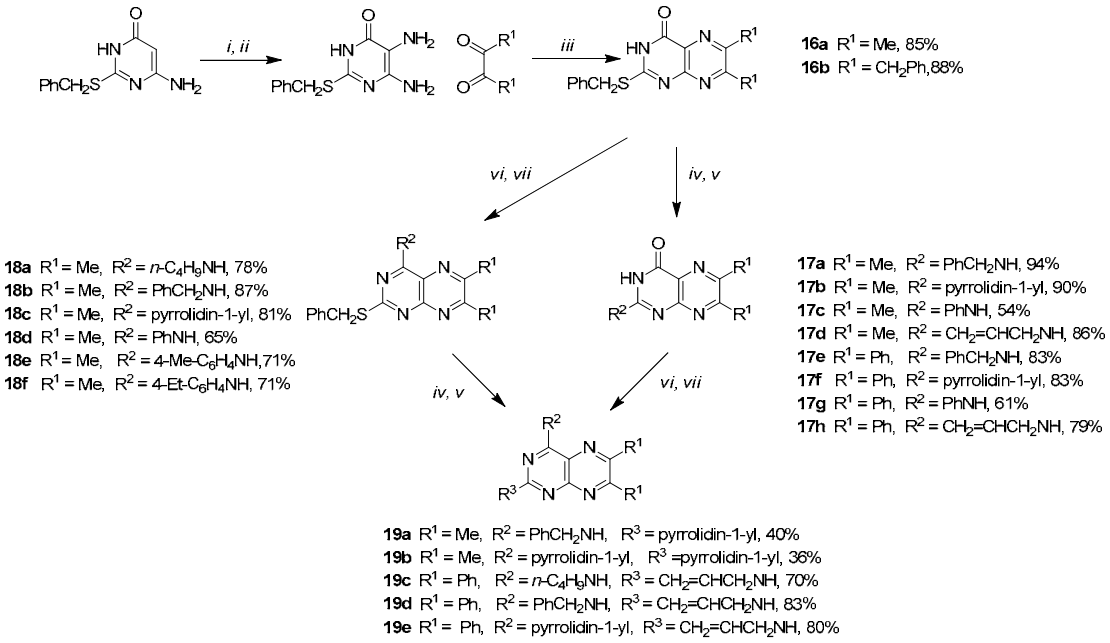
14a R = $NHCH_2Ph$, 44%
14b R = pyrrolidin-1-yl, 51%
14c R = NHPh, 37%
14d R = OH, 44%



13a

15a R = $NHCH_2Ph$, 65%
15b R = pyrrolidin-1-yl, 58%

Scheme 6



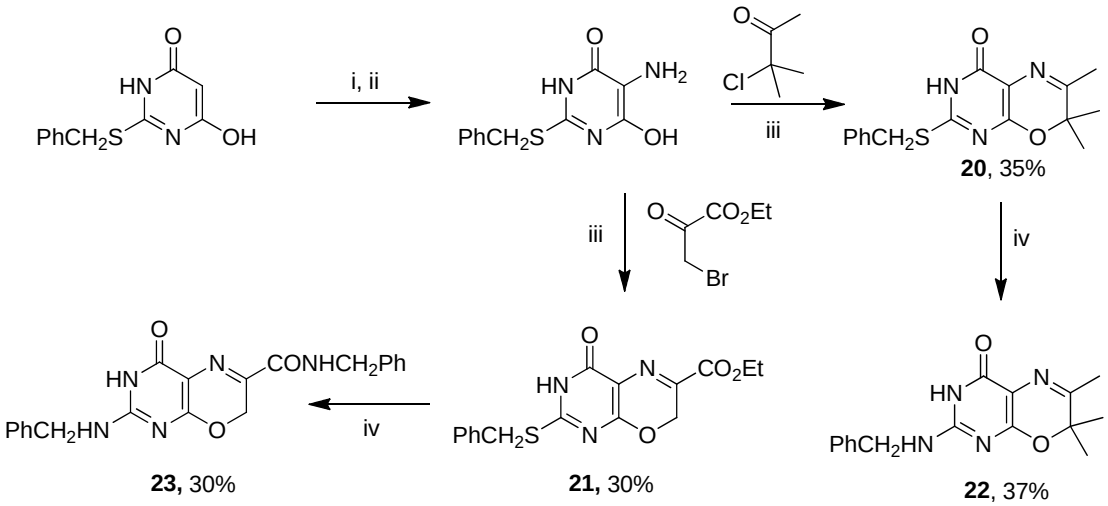
16a R^1 = Me, 85%
16b R^1 = CH_2Ph,88%

17a R^1 = Me, R^2 = $PhCH_2NH$, 94%
17b R^1 = Me, R^2 = pyrrolidin-1-yl, 90%
17c R^1 = Me, R^2 = PhNH, 54%
17d R^1 = Me, R^2 = CH_2=$CHCH_2NH$, 86%
17e R^1 = Ph, R^2 = $PhCH_2NH$, 83%
17f R^1 = Ph, R^2 = pyrrolidin-1-yl, 83%
17g R^1 = Ph, R^2 = PhNH, 61%
17h R^1 = Ph, R^2 = CH_2=$CHCH_2NH$, 79%

18a R^1 = Me, R^2 = *n*-C_4H_9NH, 78%
18b R^1 = Me, R^2 = $PhCH_2NH$, 87%
18c R^1 = Me, R^2 = pyrrolidin-1-yl, 81%
18d R^1 = Me, R^2 = PhNH, 65%
18e R^1 = Me, R^2 = 4-Me-C_6H_4NH,71%
18f R^1 = Me, R^2 = 4-Et-C_6H_4NH, 71%

19a R^1 = Me, R^2 = $PhCH_2NH$, R^3 = pyrrolidin-1-yl, 40%
19b R^1 = Me, R^2 = pyrrolidin-1-yl, R^3 =pyrrolidin-1-yl, 36%
19c R^1 = Ph, R^2 = *n*-C_4H_9NH, R^3 = CH_2=$CHCH_2NH$, 70%
19d R^1 = Ph, R^2 = $PhCH_2NH$, R^3 = CH_2=$CHCH_2NH$, 83%
19e R^1 = Ph, R^2 = pyrrolidin-1-yl, R^3 = CH_2=$CHCH_2NH$, 80%

Scheme 7



Scheme 8