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Full Paper

Convenient One-Pot Four-Component Synthesis of 6,8-Disubstituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]-pyrimidin-4(3*H*)-ones via a Triple Mannich Reaction

Ahmed F. M. EL-Mahdy,[A,B,C] *Hassan A. H. El-Sherief,*[A,C] *and Zainab A. Hozien*[A]

[A]Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt.
[B]Department of Materials and Optoelectronic Science, National Sun Yat-Sen University, Kaohsiung 80424, Taiwan.
[C]Corresponding authors. Email: ahmedelmahdy@mail.nsysu.edu.tw; hassan.elsherief@science.au.edu.eg

An efficient and simple one-pot four-component protocol has been developed and performed for the synthesis of 6,8-disubstituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones, involving a triple Mannich reaction of 6-amino-2-(ethylthio)pyrimidin-4(3*H*)-one, formaldehyde, primary amines, and alcohols. Secondary amines were also utilised instead of alcohols as Mannich nucleophiles, and a variety of functional groups and electronically varied reaction partners were tolerated. This one-pot reaction facilitated the generation of a library of pyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones in very good to excellent yields. The regioselectivity of this reaction was investigated using atomic charge calculations, and spectroscopic data confirmed that the triple Mannich products were 6,8-disubstituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones rather than the isomeric 3,6-disubstituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones. The structures of all compounds synthesised using the triple Mannich reaction were confirmed via spectroscopic and elemental analyses. The reaction mechanism was studied and confirmed by isolation of the intermediate.

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Introduction

Pyrimidopyrimidine derivatives represent an important class of annelated uracils that have received significant attention from researchers in the field of medicinal chemistry because of their close relation to purines and pteridine systems.[1–3] Most of them possess a diverse range of biological activities, such as antitumour,[4] antioxidant,[5] antiviral,[4,6] antibacterial,[7] antifungal,[8] and hepatoprotective activities.[9] The pyrimidopyrimidine derivatives have a wide range of pharmacological activities, such as vasodilation, bronchodilation, and antiallergic activities. Moreover, this type of heterocyclic compound exhibits potent inhibitory properties towards the 5-phosphoribosyl-1-pyrophosphate synthetase,[10] dihydrofolate reductase,[11] and tyrosine kinase domain.[12] Due to the aforementioned biological activities and medicinal utilities of pyrimidopyrimidines, these moieties have a significant contribution to drug discovery and medicinal applications.

In recent years, the goal of organic chemists has been to discover new biologically active moieties with minimum synthetic steps.[13–16] in addition, chemists aim to develop new methods that are rapid, efficient, high yielding, and environmentally benign. To achieve this goal, multi-component reactions (MCRs)—with at least three components interacting simultaneously in a one-pot synthetic step—have become the modern approach in place of more complicated multi-step reactions, which are accompanied by high cost, lower yields, and complex product isolation. MCRs greatly contribute to the possibility of efficiently generating a highly complex molecule in a single step, which would lead to shorter reaction times, higher yield, greater step-efficiency, and simpler purification procedures.[17,18] Accordingly, MCRs have attracted considerable attention in combinatorial synthesis,[19,20] medicinal chemistry, the pharmaceutical industry,[21,22], and modern drug discovery.[23–25] The Mannich reaction, one of the MCRs, is considered useful because of its effectiveness in the generation of carbon–carbon and carbon–nitrogen single bonds.[26] A condensation Mannich reaction is usually utilised in the amino-alkylation of various compounds with one or more active hydrogen atoms. On the other hand, a double Mannich reaction could occur when the starting compounds already have two adjacent active hydrogen atoms.[27–30] Recently, we established a new efficient strategy for the synthesis of triazolothiadiazine,[27] pyrimidothiadiazine,[28] pyrazolopyrimidine,[29] and thiadiazinobenzimidazole[30] derivatives in relatively high yields via double Mannich reactions. In addition, we reported an efficient quadruple Mannich reaction for the synthesis of 2,5,7,9,11-pentaazaphenalenes in excellent yields.[31]

To the best of our knowledge, there are few methods available for the synthesis of pyrimido[4,5-*d*]pyrimidinones via the double Mannich reaction of 6-aminouracil (R1 = H) or its corresponding N-1 substituted derivatives (R1 ≠ H) with primary amines and

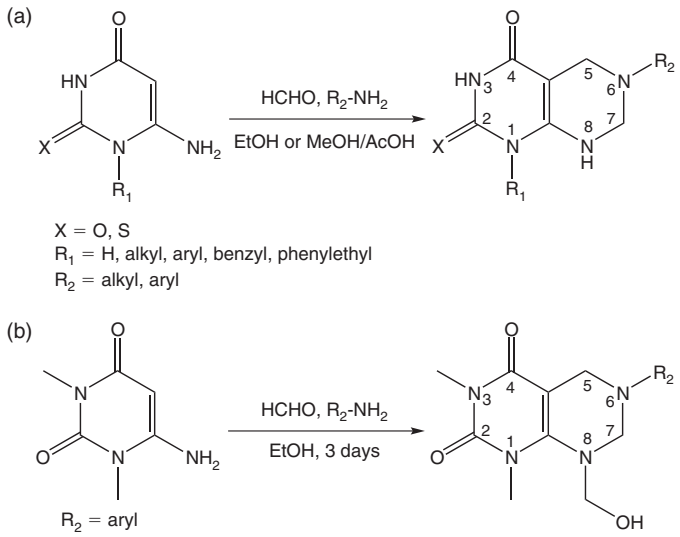
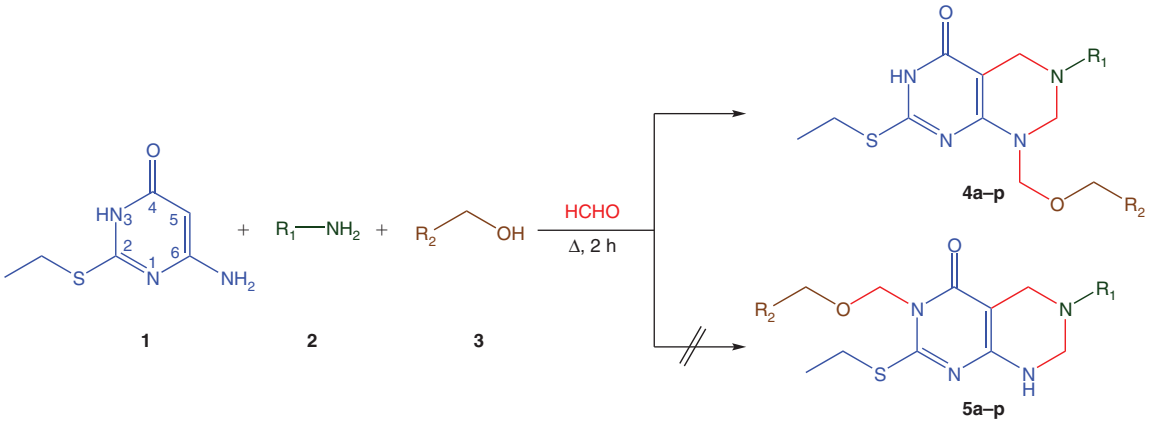


Fig. 1. Background for the synthesis of pyrimido[4,5-*d*]pyrimidinones via Mannich reaction.



4a–i, R_2 = CH_3 (**a**: R_1 = $CH_2CH_2CH_2CH_3$, **b**: R_1 = $CH_2CH(CH_3)_2$, **c**: R_1 = $CH_2C_6H_5$, **d**: R_1 = C_6H_5, **e**: R_1 = $C_6H_4OCH_3$-*p*, **f**: R_1 = $C_6H_4CH_3$-*p*, **g**: R_1 = C_6H_4OH-*P*, **h**: R_1 = C_6H_4Cl-*p*, **i**: R_1 = C_6H_4Br-*p*).

4j–p, R_2 = H (**j**: R = $CH_2CH(CH_3)_2$, **k**: R_1 = $CH_2C_6H_5$, **l**: R_1 = C_6H_5, **m**: R_1 = $C_6H_4OCH_3$-*p*, **n**: R_1 = $C_6H_4CH_3$-*p*, **o**: R_1 = C_6H_4Cl-*p*, **p**: R_1 = C_6H_4Br-*p*).

Scheme 1. Triple Mannich reaction of 6-amino-2-(ethylthio)pyrimidin-4(3*H*)-one in alcoholic solvent.

formaldehyde (Fig. 1a).[32–35] Furthermore, the 8-hydroxymethyl derivative of pyrimido[4,5-*d*]pyrimidinone was once prepared by reacting 6-amino-1,3-dimethyluracil with primary aromatic amines and formaldehyde in ethanol for 3 days (Fig. 1b).[36]

Interestingly, there are no reported methods for the synthesis of the 8-alkoxymethyl derivatives of pyrimido[4,5-*d*]pyrimidinone by either the Mannich reaction or other methods. Therefore, as part of our continued interest in the preparation of various heterocyclic compounds with pharmacological and biological activities, herein we report an efficacious and facile four-component protocol for the preparation of various 8-(alkoxymethyl)pyrimido[4,5-*d*]pyrimidinones (**4** and **8**) involving the triple Mannich reaction of 6-amino-2-(ethylthio) pyrimidin-4(3*H*)-one (**1**) with formaldehyde, primary amines **2**, and alcohols **3** or **7** under reflux for 2 h.

Results and Discussion

In the course of our on-going research on the synthesis of innovative heterocyclic scaffolds using the Mannich reaction, our efforts were directed to studying the behaviour of 6-amino-2-(ethylthio)pyrimidin-4(3*H*)-one (**1**) as a trifunctional nucleophile with both primary aliphatic and aromatic amines under Mannich reaction conditions. When compound **1** was treated with one equivalent of primary amine **2** and an excess of aqueous formaldehyde (35 %) in ethanol or methanol for 2 h, a single product with an undetermined structure was formed. Further analyses—NMR and mass spectrometry—as well as elemental analysis determined that the structure of this new product might have been either **4a**–**p** or **5a**–**p** (Scheme 1). The IR spectrum of the product obtained using isobutylamine in methanol lacked the amino (NH_2) absorption band and showed absorption bands at 3380 cm^{-1} for NH, 2975–2930 cm^{-1} for C–H aliphatic stretching, 1632 cm^{-1} for C=O stretching, 1567 cm^{-1} for C=N stretching, and 1488 cm^{-1} for C=C stretching. Surprisingly, the ^{1}H NMR (Fig. 2a) and ^{13}C NMR spectra (Fig. 2b) of the product indicated that one molecule of isobutylamine, three molecules of formaldehyde, and one molecule of methanol had reacted, confirming a triple Mannich reaction. Consequently,

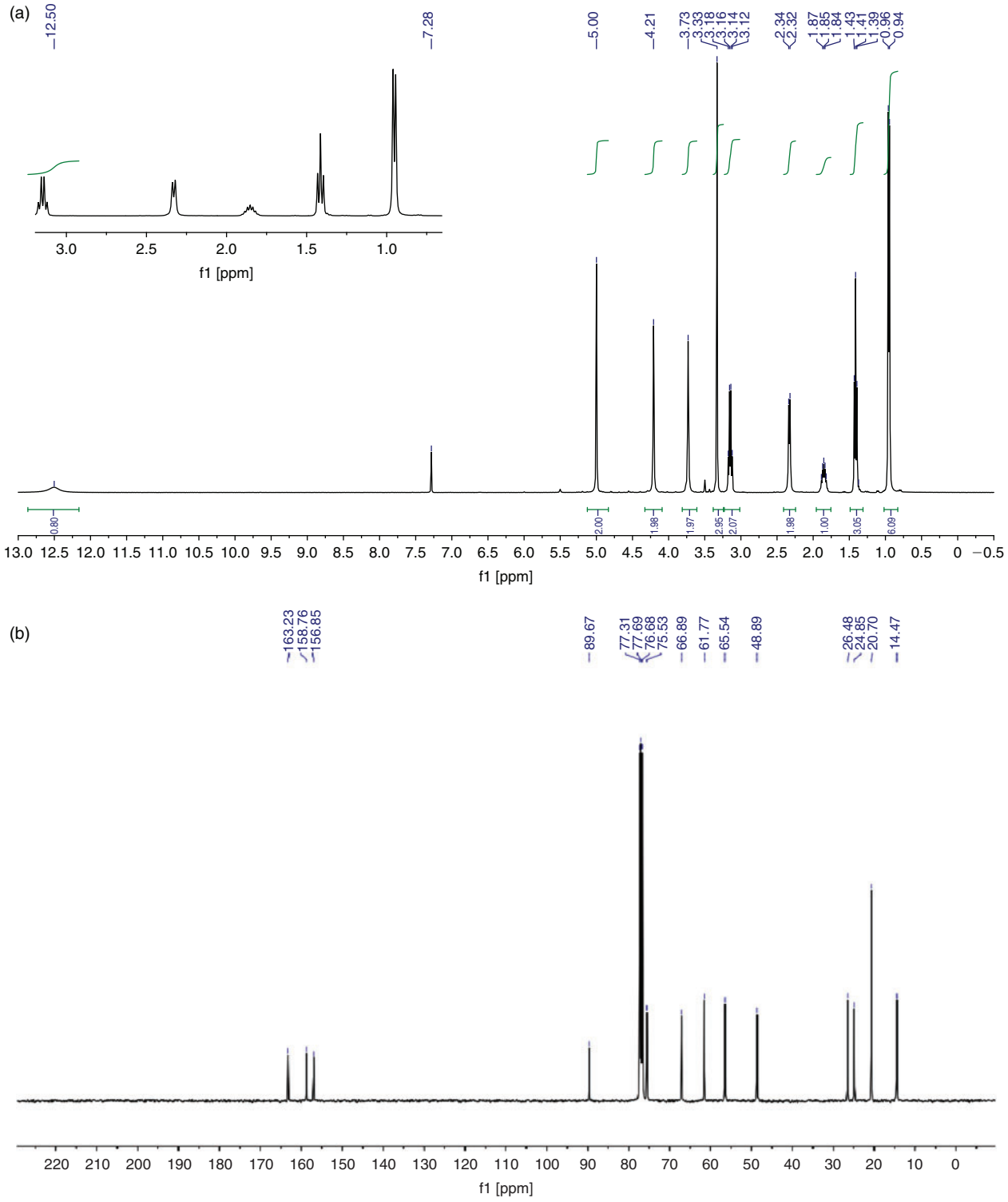
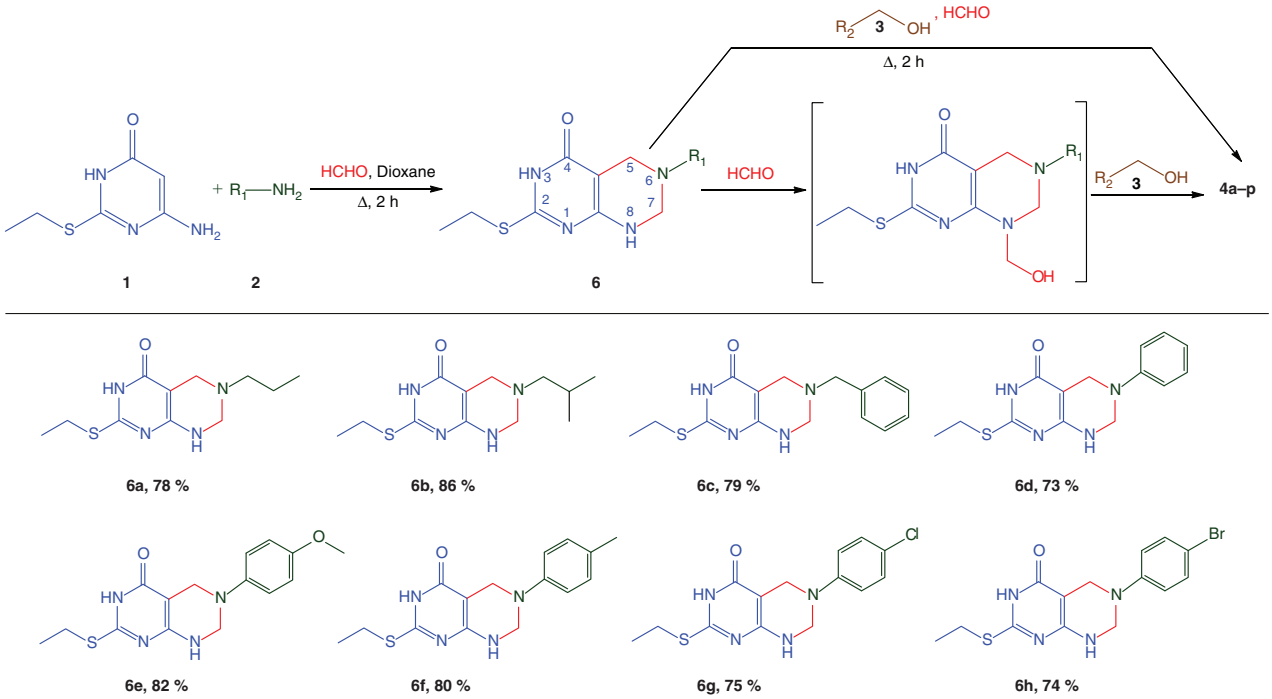


Fig. 2. ^{1}H NMR (a) and ^{13}C NMR (b) spectra of the triple Mannich product of isobutylamine in methanol.

the ^{1}H NMR spectrum of the new product was singularised by the appearance of a singlet signal at 12.50 ppm, which disappeared on deuteration and three single signals at 5.00, 4.21, and 3.73 ppm corresponding to the three methylene groups, in addition to the other protons for isobutyl, methoxy, and ethyl groups ($(CH_3)_2CHCH_2$, OCH_3, and SCH_2CH_3). On the other hand, its ^{13}C NMR spectrum was characterised by the presence of three signals for the methylene groups at 75.53, 66.89, and 48.89 ppm, as well as signals for the rest of the carbon atoms at the expected chemical shifts. The mass spectrum of the obtained product revealed a molecular ion peak at the *m/z* value of 313.56 [M + 1] and elemental analysis was found to be consistent with the theoretical values of the suggested structure **4a** or **5a**.

Formation of **4a**–**p** rather than **5a**–**p** isomers could be attributed to the following. First, the S-alkylated-6-aminouracil **1** is shown to exist in solution largely in the lactam form, and the



Scheme 2. The formation of the intermediates **6a**–**h** via a double Mannich reaction.

tautomeric hydrogen was found to be in position 3, as indicated by spectroscopic studies.[37–40] Second, the appearance of NH(3) at 12.89–11.92 ppm[41] supported the formation of **4a**–**p** rather than that of **5a**–**p**. Third, the differences in electron densities of the nitrogen atoms, N-3 and N-8, of the expected intermediate **6a**–**h** control the regioselectivity of the third Mannich step (Scheme 2). As per the atomic charge calculations of the intermediate **6a** (Fig. 3 and Table 1), the highest electron density value is located on N-8 (−0.64343) rather than N-3 (−0.63955). Furthermore, we observed that the obtained products completely dissolved in 5 % KOH alcoholic solution and completely reprecipitated upon addition of dilute acetic acid, in agreement with the suggested structure of the isomeric products **4a**–**p**. Consequently, based on the above data, the formation of products **5a**–**p** was ruled out, and the structures of the reaction products were assigned as the isomeric products **4a**–**p** (Scheme 2).

Finally, as reported, the double condensation Mannich reaction of 6-aminouracils with primary amines and formaldehyde occurred on the CH and NH_2 groups to provide the corresponding pyrimido[4,5-*d*]pyrimidin-4-ones.[32–35] These reported results support our hypothesis that the formed intermediates of this triple Mannich products are 2-(ethylthio)-6-substituted-pyrimido[4,5-*d*]pyrimidin-4-ones **6a**–**h** (Scheme 2), which could be easily transformed to their 8-hydroxymethyl derivatives followed by condensation with the solvent to afford the final isomeric products **4a**–**p** via a third Mannich step. This hypothesis is also supported by isolation of intermediates **6a**–**h** in 80–90 % yield upon refluxing a mixture of 6-amino-2-(ethylthio)pyrimidin-4(3*H*)-one (**1**), formaldehyde, and primary amines in dioxane as the aprotic solvent. Subsequently, the isolated intermediates **6a**–**h** were subjected to the third Mannich reaction with formaldehyde and a variety of alcohols to give **4a**–**p** in 73–86 % yield (Scheme 2). The IR and NMR spectra, melting points, and mixed melting points of the products were the same as those of products obtained from the direct interaction of 6-amino-2-(ethylthio)pyrimidin-4(3*H*)-one (**1**) with

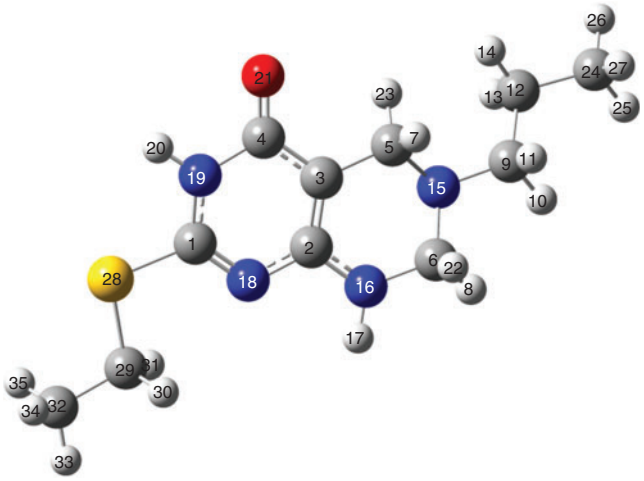


Fig. 3. The geometry structure of **6a**: grey (carbon), blue (nitrogen), red (oxygen), yellow (sulfur) and white (hydrogen).

formaldehyde and primary amines in alcohol. However, the 8-hydroxymethyl derivative could not be isolated.

Encouraged by these results, we focussed on evaluating the substrate scope of various aromatic or aliphatic amines **2** with regards to the triple Mannich reaction using ethanol as both reactant and solvent. The reaction was effective and produced the corresponding 6-substituted-8-(ethoxymethyl)-2-(ethylthio)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones **4a**–**i** in good-to-excellent yields (Scheme 3). It was noted that aliphatic amines (Scheme 3, **4a** and **4b**) gave higher yields than the aromatic amines (especially those with electron-withdrawing groups). Steric hindrance did not affect the yield when isobutylamine was utilised (Scheme 3, **4b**). Benzylamine also successfully generated the corresponding product in excellent yields (Scheme 3, **4c**). When aniline was reacted, the

Table 1. The atomic charge values of 6a

Atom	Number	Charge	Atom	Number	Charge
C	1	0.30968	**N(3)**	**19**	**−0.63955**
C	2	0.41801	H	20	0.45568
C	3	−0.26064	O	21	−0.65030
C	4	0.63705	H	22	0.19928
C	5	−0.26582	H	23	0.27053
C	6	−0.06695	C	24	−0.69903
H	7	0.22220	H	25	0.23376
H	8	0.24706	H	26	0.24725
C	9	−0.25879	H	27	0.23616
H	10	0.23542	S	28	0.27097
H	11	0.20631	C	29	−0.60002
C	12	−0.49163	H	30	0.26909
H	13	0.24726	H	31	0.27133
H	14	0.24142	C	32	−0.71543
N	15	−0.54763	H	33	0.25582
N(8)	**16**	**−0.64343**	H	34	0.24886
H	17	0.43708	H	35	0.24948
N	18	−0.57050			

corresponding product was obtained in good yield (Scheme 3, **4d**). We further noted that reaction of aromatic amines having electron-donating substituents generated products in higher yields than those with electron-withdrawing substituents. For example, *p*-methoxyaniline, *p*-methylaniline, and *p*-hydroxyaniline exhibited very good-to-excellent yields (Scheme 3, **4e**–**g**), whereas, *p*-chloroaniline and *p*-bromoaniline exhibited good yields (Scheme 3, **4h** and **4i**).

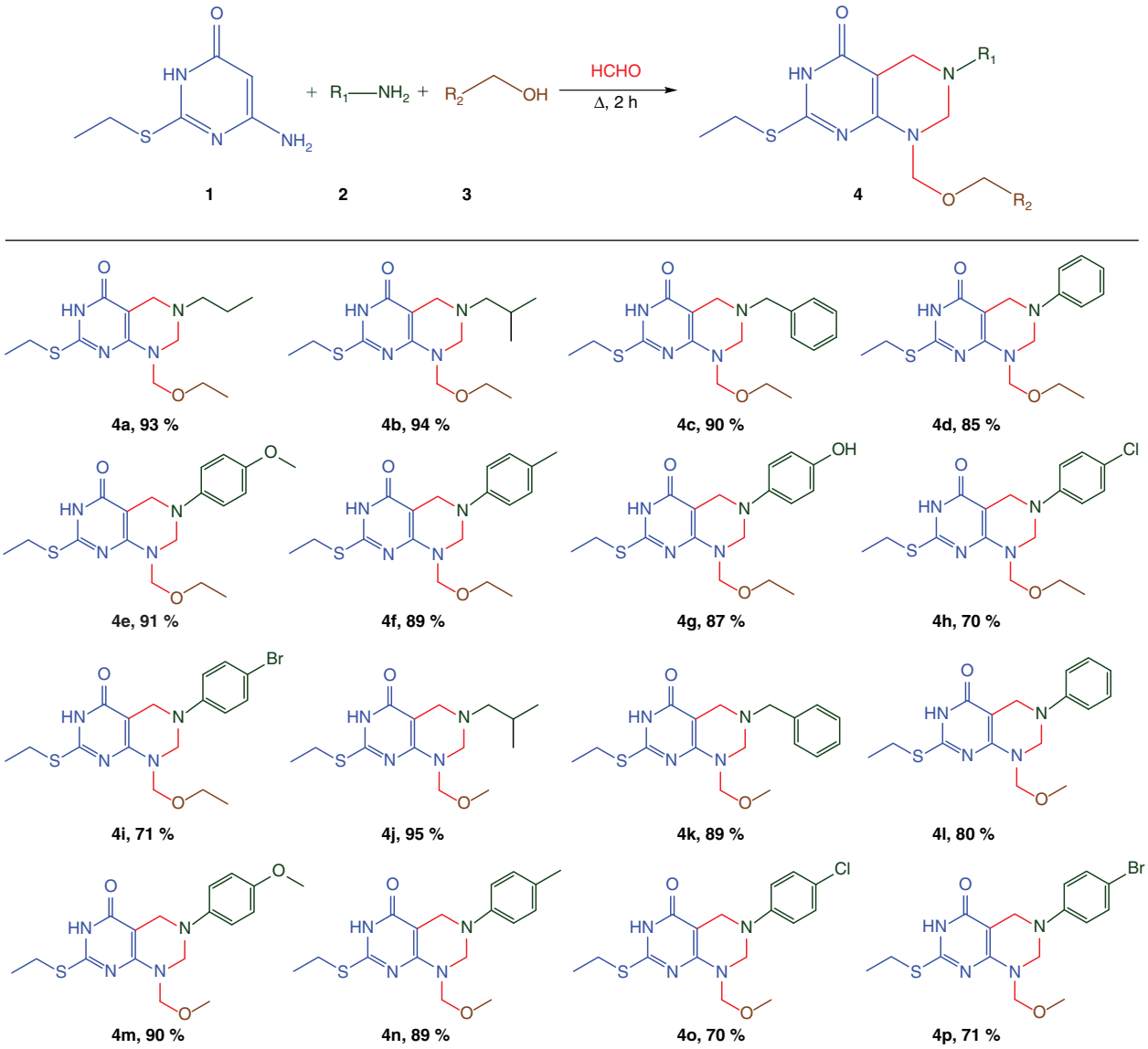
Furthermore, variation of the alcoholic solvent was also investigated under the same reaction conditions. 6-Amino-2-(ethylthio)pyrimidin-4(3*H*)-one (**1**) was subjected to a triple Mannich reaction with various primary aliphatic and aromatic amines **2b**–**i** and formaldehyde in methanol, and the results are summarised in Scheme 3. As expected, methanol took part in the reaction and the corresponding 6-substituted-8-(methoxymethyl)-2-(ethylthio)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones **4j**–**p** were obtained in very good-to-excellent yields (Scheme 3). The substrate scope study of various amines in methanol indicated that the bulky aliphatic amine, isobutylamine, generated the product in an excellent yield (Scheme 3, **4j**). Similarly, benzylamine generated an excellent yield of the product (Scheme 3, **4k**). Furthermore, as observed with ethanol as the solvent, aromatic amines such as aniline generated the product in yields lower than aliphatic amines (Scheme 3, **4l**). We also observed that aromatic amines with electron-donating substituents gave products in higher yields than those having electron-withdrawing substituents. *p*-Methoxyaniline and *p*-methylaniline exhibited very good-to-excellent yields (Scheme 3, **4m** and **4n**), while *p*-chloroaniline and *p*-bromoaniline showed good yields (Scheme 3, **4o** and **4p**). In general, the reaction proceeded with high efficiency and was completed within a short reaction time.

Moreover, to study the behaviour of the 6-amino-2-(ethylthio) pyrimidin-4(3*H*)-one (**1**) in terms of the triple Mannich reaction, we examined the utilisation of benzyl alcohol, piperidine, and morpholine as Mannich nucleophiles instead of ethanol or methanol (Scheme 4). The reaction of **1** with various primary amines, excess of formaldehyde (37 %), and benzyl alcohol in dioxane for 2 h directly generated 8-(benzyloxymethyl)-2-(ethylthio)-6-substituted-5,6,7,8-tetrapyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones **8a**–**d** in very high yields (Scheme 4). Similarly, when piperidine or morpholine was reacted with **1**, formaldehyde, and various primary amines under the same reaction conditions, the corresponding products 2-(ethylthio)-8-(piperidin-1-yl/morpholin-4-ylmethyl)-6-substituted-5,6,7,8-tetrapyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones **10a**–**d** were obtained in high yields (Scheme 4).

The structure of isolated compounds **8a**–**d** and **10a**–**d** were deduced based on the IR, NMR, and mass spectroscopic data, taking compounds **8a** and **10a** as examples. In the case of **8a**, the IR spectrum revealed massive absorption bands at 3050 cm^{-1} for C–H aromatic stretching, 2970–2951 cm^{-1} for C–H aliphatic stretching, 1633 cm^{-1} for C=O stretching, 1569 cm^{-1} for C=N stretching, and 1489 cm^{-1} for C=C stretching. The ^{1}H NMR spectrum was distinguished by the appearance of singlet signals at 5.05, 4.47, 4.14, and 3.63 ppm ascribed to the four methylene groups as well as the aromatic protons at the anticipated chemical shifts—which indicated the performance of the triple Mannich reaction. In addition, its ^{13}C NMR spectrum revealed the four methylene groups at 75.56, 69.86, 67.68, and 47.65 ppm. The mass spectrum of **8a** revealed the molecular ion peak at *m/z* 389.29 [M + 1]. While in the case of **10a**, the IR spectrum revealed massive absorption bands at 3052 cm^{-1} for C–H aromatic stretching, 2929–2853 cm^{-1} for C–H aliphatic stretching, 1635 cm^{-1} for C=O stretching, 1569 cm^{-1} for C=N stretching, and 1472 cm^{-1} for C=C stretching. The ^{1}H NMR spectrum revealed three singlet signals at 4.75, 4.18, and 4.13 ppm associated with the three methylene groups, in addition to peaks at 2.68–2.51 and 1.80–1.50 ppm for the piperidine moiety. The ^{13}C NMR spectrum of **10a** was distinguished by the appearance of peaks at 67.65, 66.84, and 65.42 ppm for the three methylene groups and other carbons for the piperidine moiety. The mass spectrum of **10a** revealed the molecular ion peak at *m/z* 416.67 [M + 1].

Proposed Mechanism

Based on the experimental findings, a possible mechanism for the obtained compounds **4a**–**p**, **6a**–**h**, **8a**–**d**, and **10a**–**d** is illustrated in Scheme 5. In the first stage, the double condensation Mannich reaction proceeded through a typical condensation reaction between the primary amines with formaldehyde



Scheme 3. Synthesis of 8-(ethoxymethyl)-2-(ethylthio)pyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones **4a**–**i** and 8-(methoxymethyl)-2-(ethylthio)pyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones **4j**–**p** under triple Mannich reaction.

to form imines **11a**–**h**. The active centre (CH-3) of the starting compound **1** nucleophilically attacked the formed imines to provide the uncyclised intermediates **12a**–**h**. These intermediates then underwent a nucleophilic addition reaction with another formaldehyde molecule followed by an acid-catalysed dehydration and intramolecular cyclisation to generate the cyclised intermediates **6a**–**h**. Attack of the active nucleophilic centre (NH-8) with a third molecule of formaldehyde and then with ethanol, methanol, benzyl alcohol, or secondary amines resulted in the corresponding products **4a**–**i**, **4j**–**p**, **8a**–**d**, and **10a**–**d**, respectively.

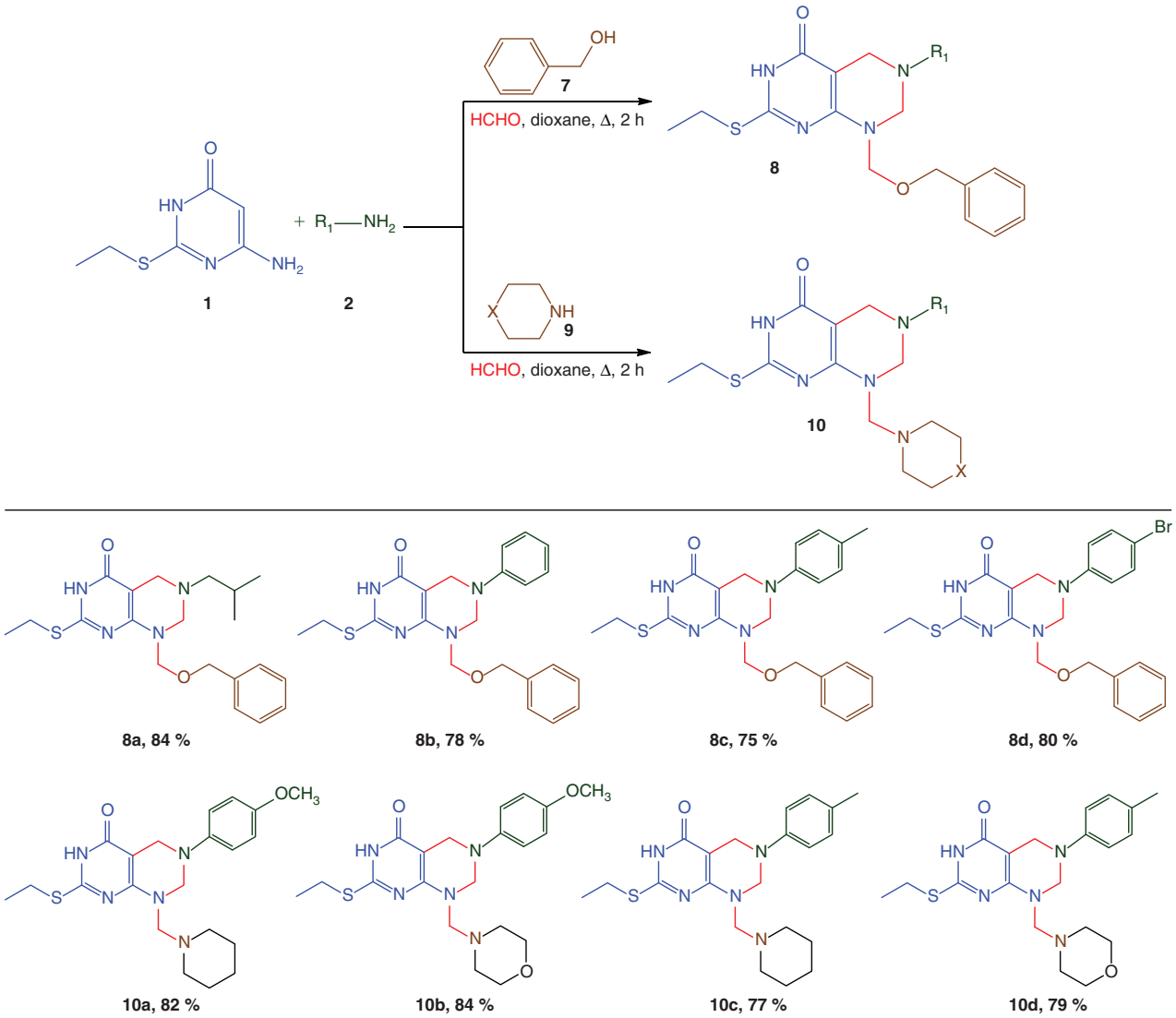
Conclusion

We have demonstrated a novel, regioselective, and highly effective one-pot four-component synthesis of 6,8-disubstituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones, involving a triple Mannich reaction of 6-amino-2-(ethylthio) pyrimidin-4(3*H*)-one, formaldehyde, primary amines, and alcohols. Ethanol and methanol were utilised as both solvents and reactants in the reaction process. The substrate scope for the various aromatic or aliphatic amines was investigated, and benzyl alcohol and secondary amines were utilised as Mannich nucleophiles instead of ethanol or methanol. Based on the atomic charge calculations and spectroscopic data, the reaction products were identified as 6,8-disubstituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones rather than the isomeric 3,6-disubstituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones. The products formed were easily isolated by filtration and then purified through recrystallisation using a suitable solvent. Further transformations of these functional pyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones could be utilised to construct a library of biologically active compounds for medicinal and pharmaceutical applications.

Experimental

Materials

All reagents and solvents were used directly from commercial sources.



Scheme 4. Synthesis of 8-(benzyloxymethyl)-2-(ethylthio)pyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones **8a**–**d** and 2-(ethylthio)-8-(piperidin-1-yl/morpholin-4-ylmethyl)pyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones **10a**–**d** under triple Mannich reaction.

Instrumentation

The melting points were measured on a Gallencamp melting point apparatus in open capillary tubes. The FT-IR spectra of the products were recorded on a Perkin–Elmer 1430 FT-IR spectrometer using KBr discs. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 400 NMR spectrometer or a Varian EM-390 90 MHz spectrometer using TMS as the internal standard and DMSO-d_6 or $CDCl_3$ as the solvent. The chemical shifts and coupling constants (*J*) were denoted as parts per million (ppm) and hertz (Hz), respectively. Elemental analyses were performed on a Perkin–Elmer 240-C analyser. Mass spectra of the products were measured on a JEOL JMS-600 mass spectrometer using a direct inlet system.

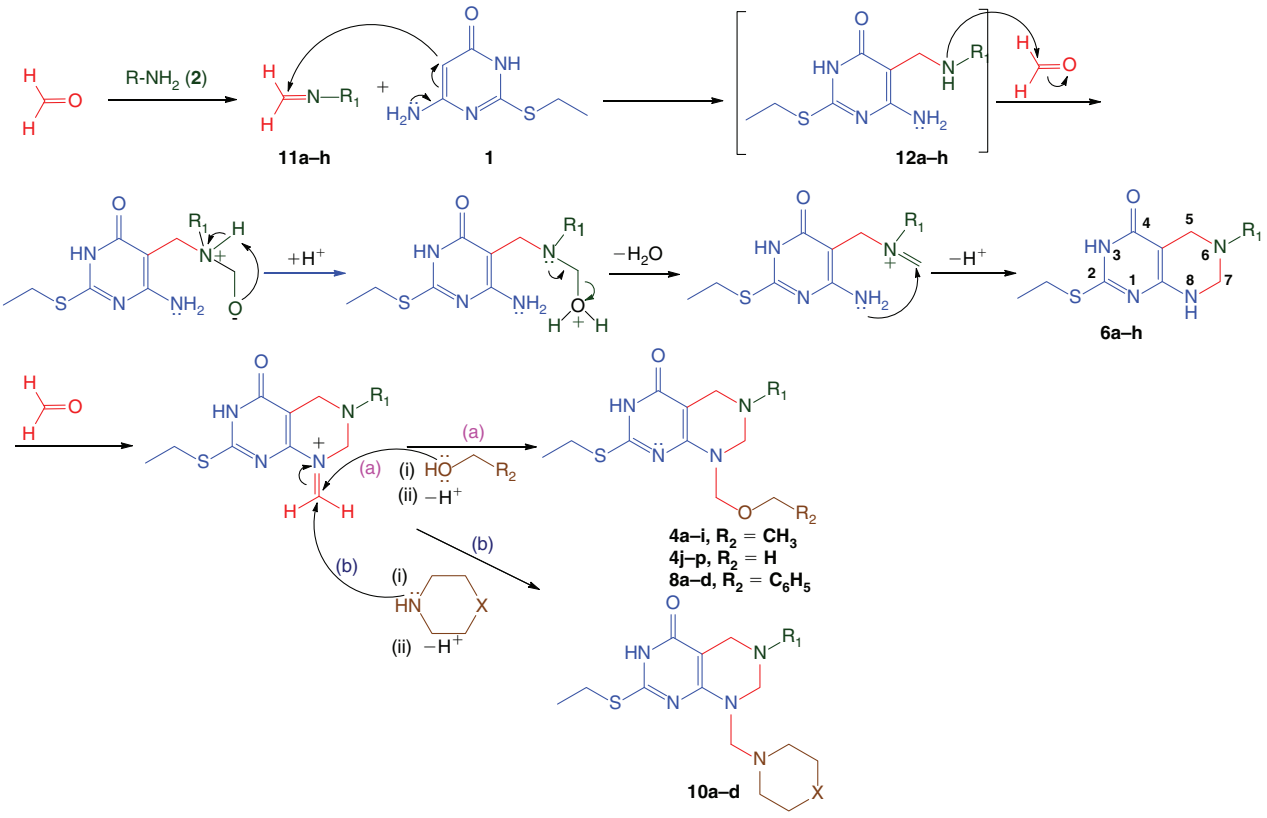
Synthetic Procedures

*6-Amino-2-(ethylthio)pyrimidin-4(3*H*)-one (**1**)*[41]

Ethyl iodide (12 mmol) was added dropwise into a solution of 6-amino-2-thioxo-2,3-dihydropyrimidin-4(*1H*)-one (6 mmol) in KOH (6.2 mmol) and then the reaction mixture was stirred at room temperature overnight. The obtained solid was collected by filtration, washed with petroleum ether, and then dried. The solid product was sufficiently pure to be used in the subsequent reactions without further purification. Yield: 85 %, white crystals (EtOH), mp 220–222°C (Lit.[41] 218–219°C). ν_{max}/cm^{-1} 3465 (NH), 3275–3260 (NH_2), 2926 (C–H aliphatic), 1659 (C=O), 1571 (C=N stretching), 1453 (C=C stretching). δ_H (90 MHz, DMSO-d_6) 11.80 (s, 1H, NH(3)), 6.45 (s, 2H, NH_2), 5.00 (s, 1H), 3.10 (q, *J* 18.0, 2H), 1.30 (t, *J* 18.0, 3H).

*6,8-Disubstituted-2-(ethylthio)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones **4a**–**p***

General procedure: A solution of 6-amino-2-(ethylthio) pyrimidin-*4(3H)*-one (**1**) (3 mmol) in the corresponding alcohol **3** (5 mL) was added dropwise to a stirred solution of formaldehyde (35 wt-% in H_2O, 1 mL) and primary amines **2** (3 mmol) in alcohol **3** (20 mL) and the resulting reaction mixture stirred under reflux for 2 h. The reaction was monitored by thin-layer chromatography. After starting materials had been consumed, the reaction mixture was cooled and the separated precipitate was isolated by filtration, washed with alcohol, and then dried. The solid product was recrystallised from alcohol to afford the desired products **4a**–**p** in very good-to-excellent yields.



Scheme 5. Possible mechanism for the triple Mannich reaction of 6-amino-2-(ethylthio)pyrimidin-4(3*H*)-one (**1**).

*8-(Ethoxymethyl)-2-(ethylthio)-6-propyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4a**)*

Yield: 93 %, white crystals (EtOH), mp 140°C. ν_{max}/cm^{-1} 3400 (NH), 2959–2931 (C–H aliphatic), 1633 (C=O), 1570 (C=N stretching), 1489 (C=C stretching). δ_H (400 MHz, $CDCl_3$) 11.92 (s, 1H, NH(3)), 5.03 (s, 2H), 4.22 (s, 2H), 3.73 (s, 2H), 3.51 (q, *J* 7.0, 2H), 3.11 (q, *J* 7.3, 2H), 2.50 (t, *J* 7.0, 2H), 1.60 (m, *J* 7.0, 2H), 1.37 (t, *J* 7.0, 3H), 1.20 (t, *J* 7.0, 3H), 0.93 (t, *J* 7.0, 3H). δ_C (100 MHz, $CDCl_3$) 163.25, 158.78, 156.87, 89.70, 75.62, 66.97, 63.35, 54.85, 47.36, 24.88, 21.00, 15.11, 14.44, 11.72. *m*/*z* (EI, 70 eV) 313.26 [M + 1], 312.12 [M]. Anal. Calc. for $C_{14}H_{24}N_4O_2S$ (312.43): C 53.82, H 7.74, N 17.93, S 10.26. Found: C 53.01, H 7.92, N 18.11, S 10.14 %.

*8-(Ethoxymethyl)-2-(ethylthio)-6-isobutyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4b**)*

Yield: 94 %, white crystals (EtOH), mp 186–188°C. ν_{max}/cm^{-1} 3410 (NH), 2951–2928 (C–H aliphatic), 1633 (C=O), 1569 (C=N stretching), 1490 (C=C stretching). δ_H (400 MHz, $CDCl_3$) 12.64 (s, 1H, NH(3)), 4.95 (s, 2H), 4.11 (s, 2H), 3.62 (s, 2H), 3.44 (q, *J* 6.8, 2H), 3.05 (q, *J* 7.1, 2H), 2.21 (d, *J* 7.1, 2H), 1.75 (m, 1H), 1.31 (t, *J* 7.2, 3H), 1.11 (t, *J* 6.9, 3H), 0.86 (d, *J* 6.8, 6H). δ_C (100 MHz, $CDCl_3$) 163.26, 158.69, 156.97, 89.82, 75.54, 67.51, 63.32, 61.17, 47.77, 26.49, 24.88, 20.71, 15.12, 14.45. *m*/*z* (EI, 70 eV) 327.31 [M + 1], 326.34 [M]. Anal. Calc. for $C_{15}H_{26}N_4O_2S$ (326.46): C 55.19, H 8.03, N 17.16, S 9.82. Found: C 55.31, H 8.12, N 17.04, S 9.73 %.

*6-Benzyl-8-(ethoxymethyl)-2-(ethylthio)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4c**)*

Yield: 90 %, white crystals (EtOH), mp 182–184°C. ν_{max}/cm^{-1} 3380 (NH), 3069 (C–H aromatic), 2974–2932 (C–H aliphatic), 1685 (C=O), 1555 (C=N stretching), 1499 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 12.32 (s, 1H, NH(3)), 7.62–7.46 (m, 5H), 5.01 (s, 2H), 4.35 (s, 2H), 3.84 (s, 2H), 3.81 (s, 2H), 3.42 (q, *J* 8.0, 5.7, 2H), 3.13 (q, *J* 8.0, 2H), 1.31 (t, *J* 8.1, 3H), 1.06 (t, *J* 8.1, 3H). δ_C (100 MHz, DMSO-d_6) 163.35, 159.08, 156.96, 138.02, 129.10, 128.43, 127.35, 89.92, 75.56, 66.36, 63.34, 57.20, 47.75, 24.94, 14.95, 14.43. *m*/*z* (EI, 70 eV) 361.26 [M + 1], 360.38 [M]. Anal. Calc. for $C_{18}H_{24}N_4O_2S$ (360.47): C 59.97, H 6.71, N 15.54, S 8.90. Found: C 59.88, H 6.80, N 15.48, S 8.99 %.

*8-(Ethoxymethyl)-2-(ethylthio)-6-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4d**)*

Yield: 85 %, white crystals (EtOH), mp 176–178°C. ν_{max}/cm^{-1} 3446 (NH), 3052 (C–H aromatic), 2972–2925 (C–H aliphatic), 1645 (C=O), 1568 (C=N stretching), 1489 (C=C stretching). δ_H (90 MHz, DMSO-d_6) 12.10 (s, 1H, NH(3)), 7.40–6.80 (m, 5H), 5.05 (s, 2H), 4.95 (s, 2H), 4.15 (s, 2H), 3.30 (q, *J* 9.0, 2H), 3.10 (q, *J* 9.1, 2H), 1.20 (t, *J* 9.2, 3H), 1.00 (t, *J* 9.0, 3H). Anal. Calc. for $C_{17}H_{22}N_4O_2S$ (346.45): C 58.94, H 6.40, N 16.17, S 9.26. Found: C 58.69, H 5.46, N 16.30, S 9.57 %.

*8-(Ethoxymethyl)-2-(ethylthio)-6-(4-methoxyphenyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4e**)*

Yield: 91 %, white crystals (EtOH), mp 170–172°C. ν_{max}/cm^{-1} 3390 (NH), 3048 (C–H aromatic), 2971–2928 (C–H aliphatic), 1643 (C=O), 1568 (C=N stretching), 1513 (C=C stretching). δ_H (400 MHz, $CDCl_3$) 12.30 (s, 1H, NH(3)), 7.03 (d, *J* 8.5, 2H), 6.85 (d, *J* 7.9, 2H), 5.06 (s, 2H), 4.79 (s, 2H), 4.33 (s, 2H), 3.77 (s, 3H), 3.38 (q, *J* 6.9, 2H), 3.13 (q, *J* 7.4, 2H), 1.41 (t, *J* 7.4, 3H), 1.13 (t, *J* 6.9, 3H). δ_C (100 MHz, $CDCl_3$) 162.53, 158.96, 157.39, 154.51, 142.43, 119.61, 114.57, 90.43, 75.42,

65.90, 63.34, 55.53, 45.97, 24.98, 15.00, 14.78. *m/z* (EI, 70 eV) 377.17 [M + 1], 376.32 [M].

*8-(Ethoxymethyl)-2-(ethylthio)-6-*p*-tolyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4f**)*

Yield: 89 %, white crystals (EtOH), mp 172–174°C. ν_{max}/cm^{-1} 3380 (NH), 3047 (C–H aromatic), 2971–2924 (C–H aliphatic), 1636 (C=O), 1567 (C=N stretching), 1515 (C=C stretching). δ_H (400 MHz, $CDCl_3$) 12.10 (s, 1H, NH(3)), 6.94 (d, *J* 8, 2H), 6.68 (d, *J* 8, 2H), 4.91 (s, 2H), 4.69 (s, 2H), 4.24 (s, 2H), 3.30 (q, *J* 7.0, 2H), 3.05 (q, *J* 7.1, 2H), 2.19 (s, 3H), 1.34 (t, *J* 7.2, 3H), 1.07 (t, *J* 7.0, 3H). *m/z* (EI, 70 eV) 361.16 [M + 1], 360.14 [M]. Anal. Calc. for $C_{18}H_{24}N_4O_2S$ (360.47): C 59.97, H 6.71, N 15.54, S 8.90. Found: C 59.26, H 5.83, N 15.68, S 9.33 %.

*8-(Ethoxymethyl)-2-(ethylthio)-6-(4-hydroxyphenyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4g**)*

Yield: 87 %, brown crystals (EtOH), mp 200–202°C. ν_{max}/cm^{-1} 3370 (NH), 3349 (OH), 3051 (C–H aromatic), 2966–2928 (C–H aliphatic), 1643 (C=O), 1584 (C=N stretching), 1496 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 11.97 (s, 1H, NH (3)), 8.84 (s, 1H), 6.86 (d, *J* 8.1, 2H), 6.66 (d, *J* 7.9, 2H), 4.97 (s, 2H), 4.73 (s, 2H), 4.09 (s, 2H), 3.33 (q, *J* 8.0, 2H), 3.06 (q, *J* 8.2, 2H), 1.28 (t, *J* 8.2, 3H), 1.04 (t, *J* 8.2, 3H). δ_C (100 MHz, DMSO-d_6) 161.38, 159.48, 156.88, 151.97, 141.46, 119.40, 116.01, 89.96, 75.27, 65.45, 63.00, 46.09, 24.63, 15.44, 15.00. Anal. Calc. for $C_{17}H_{22}N_4O_3S$ (362.45): C 56.33, H 6.12, N 15.46, S 8.85. Found: C 56.30, H 6.48, N 15.19, S 8.94 %.

*6-(4-Chlorophenyl)-8-(ethoxymethyl)-2-(ethylthio)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4h**)*

Yield: 70 %, pale yellow crystals (EtOH), mp 188–190°C. ν_{max}/cm^{-1} 3310 (NH), 3049 (C–H aromatic), 2970–2923 (C–H aliphatic), 1632 (C=O), 1567 (C=N stretching), 1493 (C=C stretching). δ_H (90 MHz, DMSO-d_6) 12.30 (s, 1H, NH(3)), 7.60 (d, *J* 9.0, 2H), 7.20 (d, *J* 9.0, 2H), 5.10 (s, 2H), 4.95 (s, 2H), 4.20 (s, 2H), 3.40 (q, *J* 7.0, 2H), 3.10 (q, *J* 7.0, 2H), 1.20 (t, *J* 7.1, 3H), 1.05 (t, *J* 7.1, 3H).

*6-(4-Bromophenyl)-8-(ethoxymethyl)-2-(ethylthio)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4i**)*

Yield: 71 %, pale yellow (EtOH), mp 174–176°C. ν_{max}/cm^{-1} 3250 (NH), 3051 (C–H aromatic), 2972–2926 (C–H aliphatic), 1624 (C=O), 1574 (C=N stretching), 1490 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 12.01 (s, 1H, NH(3)), 7.36 (d, *J* 7.1, 2H), 6.98 (d, *J* 7.1, 2H), 4.99 (s, 2H), 4.87 (s, 2H), 4.21 (s, 2H), 3.34 (q, *J* 7.0, 2H), 3.05 (q, *J* 7.0, 2H), 1.27 (t, *J* 7.0, 3H), 1.05 (t, *J* 7.0, 3H). δ_C (100 MHz, DMSO-d_6) 161.36, 159.74, 156.84, 148.27, 132.10, 119.43, 111.82, 89.81, 75.24, 63.93, 63.09, 45.28, 24.64, 15.40, 14.97. *m/z* (EI, 70 eV) 426.98 [Br^{81}, M + 1], 424.98 [Br^{79}, M + 1]. Anal. Calc. for $C_{17}H_{21}BrN_4O_2S$ (426.05): C 48.00, H 4.98, N 13.17, S 7.54. Found: C 48.11, H 4.89, N 13.22, S 7.47 %.

*2-(Ethylthio)-6-isobutyl-8-(methoxymethyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4j**)*

Yield: 95 %, white crystals (MeOH), mp 176–178°C. ν_{max}/cm^{-1} 3380 (NH), 2975–2930 (C–H aliphatic), 1632 (C=O), 1567 (C=N stretching), 1488 (C=C stretching). δ_H (400 MHz, $CDCl_3$) 12.50 (s, 1H, NH(3)), 5.00 (s, 2H), 4.21 (s, 2H), 3.73 (s, 2H), 3.33 (s, 3H), 3.16 (q, *J* 7.3, 2H), 2.34 (d, *J* 7.1, 2H), 1.85 (m, *J* 13.2, 6.6, 1H), 1.41 (t, *J* 7.3, 3H), 0.96 (d, *J* 6.5, 6H). δ_C (100 MHz, $CDCl_3$) 163.23, 158.76, 156.85, 89.67, 75.53, 66.89, 61.77, 56.54, 48.89, 26.48, 24.85, 20.70, 14.47. *m/z* (EI, 70 eV) 313.56 [M + 1], 312.25 [M]. Anal. Calc. for $C_{14}H_{24}N_4O_2S$ (312.43): C 53.82, H 7.74, N 17.93, S 10.26. Found: C 53.90, H 7.81, N 17.85, S 10.17 %.

*6-Benzyl-2-(ethylthio)-8-(methoxymethyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4k**)*

Yield: 89 %, white crystals (MeOH), mp 160–162°C. ν_{max}/cm^{-1} 3400 (NH), 3042 (C–H aromatic), 2974–2930 (C–H aliphatic), 1629 (C=O), 1559 (C=N stretching), 1487 (C=C stretching). δ_H (400 MHz, $CDCl_3$) 12.89 (s, 1H, NH(3)), 7.37–7.29 (m, 5H), 4.96 (s, 2H), 4.20 (s, 2H), 3.85 (s, 2H), 3.74 (s, 2H), 3.33 (s, 3H), 3.15 (q, *J* 7.1, 2H), 1.42 (t, *J* 6.9, 3H). δ_C (100 MHz, $CDCl_3$) 163.38, 159.05, 156.98, 138.00, 129.06, 128.42, 127.37, 89.83, 66.34, 57.14, 55.65, 47.64, 24.95, 14.44.

*2-(Ethylthio)-8-(methoxymethyl)-6-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4l**)*

Yield: 80 %, white crystals (MeOH), mp 204–206°C. ν_{max}/cm^{-1} 3410 (NH), 3051 (C–H aromatic), 2976–2926 (C–H aliphatic), 1640 (C=O stretching), 1566 (C=N stretching), 1489 (C=C). δ_H (400 MHz, DMSO-d_6) 12.07 (s, 1H, NH(3)), 7.25 (t, *J* 7.9, 2H), 7.03 (d, *J* 8.1, 2H), 6.83 (t, *J* 7.9, 1H), 4.97 (s, 2H), 4.88 (s, 2H), 4.22 (s, 2H), 3.12 (s, 3H), 3.06 (q, *J* 7.2, 2H), 1.28 (t, *J* 7.4, 3H). *m/z* (EI, 70 eV) 333.24 [M + 1], 332.26 [M]. Anal. Calc. for $C_{16}H_{20}N_4O_2S$ (332.42): C 57.81, H 6.06, N 16.85, S 9.65. Found: C 57.75, H 6.13, N 16.78, S 9.76 %.

*2-(Ethylthio)-8-(methoxymethyl)-6-(4-methoxyphenyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4m**)*

Yield: 90 %, white crystals (MeOH), mp 188–190°C. ν_{max}/cm^{-1} 3410 (NH), 3048 (C–H aromatic), 2975–2930 (C–H aliphatic), 1640 (C=O), 1569 (C=N stretching), 1488 (C=C stretching). δ_H (400 MHz, $CDCl_3$) 11.95 (s, 1H, NH(3)), 7.02 (d, *J* 8.4, 2H), 6.85 (d, *J* 8.5, 2H), 5.01 (s, 2H), 4.79 (s, 2H), 4.34 (s, 2H), 3.78 (s, 3H), 3.19–3.12 (m, 5H), 1.40 (t, *J* 7.2, 3H). δ_H (100 MHz, $CDCl_3$) 162.23, 158.84, 156.68, 154.50, 142.33, 119.60, 114.55, 90.62, 75.45, 66.04, 55.51, 45.96, 25.07, 14.40. *m/z* 363.18 [M + 1], 362.26 [M].

*2-(Ethylthio)-8-(methoxymethyl)-6-*p*-tolyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4n**)*

Yield: 89 %, white crystals (MeOH), mp 182–184°C. ν_{max}/cm^{-1} 3390 (NH), 3051 (C–H aromatic), 2969–2922 (C–H aliphatic), 1644 (C=O), 1568 (C=N stretching), 1487 (C=C stretching). δ_H (90 MHz, DMSO-d_6) 12.20 (s, 1H, NH(3)), 7.00 (s, 4H), 4.99 (s, 2H), 4.81 (s, 2H), 4.20 (s, 2H), 3.30–3.00 (m, 5H), 2.20 (s, 3H), 1.30 (t, *J* 7.0, 3H). *m/z* (EI, 70 eV) 347.11 [M + 1], 346.12 [M]. Anal. Calc. for $C_{17}H_{22}N_4O_2S$ (346.45): C 58.94, H 6.40, N 16.17, S 9.26. Found: C 57.49, H 5.72, N 16.27, S 9.51 %.

*6-(4-Chlorophenyl)-2-(ethylthio)-8-(methoxymethyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4o**)*

Yield: 70 %, pale yellow crystals (MeOH), mp 208–210°C. ν_{max}/cm^{-1} 3300 (NH), 3049 (C–H aromatic), 2971–2928

(C–H aliphatic), 1644 (C=O), 1567 (C=N stretching), 1495 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 12.10 (s, 1H, NH (3)), 7.27 (d, *J* 7.4, 2H), 7.05 (d, *J* 7.6, 2H), 4.96 (s, 2H), 4.88 (s, 2H), 4.21 (s, 2H), 3.25–3.05 (m, 5H), 1.30 (t, *J* 7.0, 3H). δ_C (100 MHz, DMSO-d_6) 161.39, 159.66, 156.90, 147.83, 129.26, 124.12, 118.94, 90.02, 76.97, 64.14, 55.45, 45.35, 24.68, 14.98. *m*/*z* (EI, 70 eV) 368.35 [Cl^{37}, M + 1], 366.27 [Cl^{35}, M + 1]. Anal. Calc. for $C_{16}H_{19}ClN_4O_2S$ (366.09): C 52.38, H 5.22, N 15.27, S 8.74. Found: C 52.43, H 5.14, N 15.19, S 8.81 %.

*6-(4-Bromophenyl)-2-(ethylthio)-8-(methoxymethyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**4p**)*

Yield: 71 %, pale yellow crystals (MeOH), mp 222–224°C. ν_{max}/cm^{-1} 3272 (NH), 3050 (C–H aromatic), 2972–2929 (C–H aliphatic), 1621 (C=O), 1574 (C=N stretching), 1491 (C=C stretching). δ_H (90 MHz, DMSO-d_6) 12.20 (s, 1H, NH(3)), 7.30 (d, *J* 7.0, 2H), 6.95 (d, *J* 7.0, 2H), 4.90 (s, 2H), 4.85 (s, 2H), 4.20 (s, 2H), 3.20 (s, 3H), 3.15 (q, *J* 7.0, 2H), 1.30 (t, *J* 7.0, 3H). Anal. Calc. for $C_{16}H_{19}BrN_4O_2S$ (412.04): C 46.72, H 4.66, N 13.62, S 7.80. Found: C 46.10, H 4.33, N 14.50, S 8.67 %.

*2-(Ethylthio)-6-substituted-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones (**6a**–**h**)*

General procedure: A solution of 6-amino-2-(ethylthio) pyrimidin-4*(3H)*-one (**1**) (3 mmol) in dioxane (5 mL) was added dropwise to a stirred solution of formaldehyde (35 wt-% in H_2O, 1 mL) and primary amines **2** (3 mmol) in dioxane (20 mL) and then the reaction mixture was stirred under reflux for 2 h. The reaction was monitored by thin-layer chromatography. After starting materials had been consumed, the reaction mixture was cooled, concentrated under vacuum, and poured into ice-cold water. The precipitate that separated was isolated by filtration, washed with water, and then dried. The solid product was recrystallised from an appropriate solvent to generate the desired products **6a**–**h** in very good-to-excellent yields.

*2-(Ethylthio)-6-propyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**6a**)*

Yield: 78 %, white crystals (benzene/cyclohexane), mp 180–182°C. ν_{max}/cm^{-1} 3400–3260 (2 × NH), 2950–2867 (C–H aliphatic), 1632 (C=O), 1566 (C=N stretching), 1515 (C=C stretching). δ_H (400 MHz, $CDCl_3$) 12.01 (s, 1H, NH(3)), 5.42 (s, 1H, NH(8)), 4.42 (s, 2H), 3.92 (s, 2H), 3.10 (q, *J* 7.1, 2H), 2.50 (t, *J* 7.1, 2H), 71H), 1.60 (m, *J* 7.1, 2H), 1.39 (t, *J* 7.1, 3H), 0.93 (t, *J* 7.1, 3H). δ_C (100 MHz, $CDCl_3$) 162.92, 158.85, 152.92, 86.51, 65.04, 55.94, 47.43, 25.94, 21.04, 14.50, 11.79. Anal. Calc. for $C_{11}H_{18}N_4OS$ (254.35): C 51.94, H 7.13, N 22.03, S 12.61. Found: C 52.03, H 7.21, N 21.94, S 12.54 %.

*2-(Ethylthio)-6-isobutyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**6b**)*

Yield: 86 %, white crystals (benzene/cyclohexane), mp 210–212°C. ν_{max}/cm^{-1} 3411–3200 (2 × NH), 2954–2927 (C–H aliphatic), 1630 (C=O), 1566 (C=N stretching), 1485 (C=C stretching). δ_H (400 MHz, $CDCl_3$) 12.41 (s, 1H, NH(3)), 5.50 (s, 1H, NH(8)), 4.23 (s, 2H), 3.70 (s, 2H), 3.17 (q, *J* 6.9, 2H), 2.29 (d, *J* 6.9, 2H), 1.77 (m, *J* 13.2, 6.5, 1H), 1.43 (t, *J* 6.9, 3H), 0.93 (d, *J* 6.5, 3H). δ_C (100 MHz, $CDCl_3$) 162.67, 159.04, 156.80, 89.75, 67.45, 61.43, 47.51, 26.57, 24.94, 20.74, 14.40. *m*/*z* (EI, 70 eV) 289.49 [M + 1], 286.14 [M]. Anal. Calc. for $C_{12}H_{20}N_4OS$ (268.38): C 53.70, H 7.51, N 20.88, S 11.95. Found: C 53.81, H 7.43, N 20.95, S 11.88 %.

*6-Benzyl-2-(ethylthio)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**6c**)*

Yield: 79 %, white crystals (benzene/cyclohexane), mp 122–124°C. ν_{max}/cm^{-1} 3412–3180 (2 × NH), 3051 (C–H aromatic), 2951–2927 (C–H aliphatic), 1628 (C=O), 1570 (C=N stretching), 1490 (C=C stretching). δ_H (400 MHz, $CDCl_3$) 12.08 (s, 1H, NH(3)), 7.55–7.47 (m, 5H), 5.25 (s, 1H, NH(8)), 4.25 (s, 2H), 3.85 (s, 2H), 3.70 (s, 2H), 3.14 (q, *J* 7.0, 2H), 1.32 (t, *J* 7.0, 3H). δ_C (100 MHz, $CDCl_3$) 162.12, 159.05, 154.48, 138.02, 129.09, 128.38, 127.29, 87.40, 64.90, 59.84, 48.46, 24.93, 14.54.

*2-(Ethylthio)-6-phenyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**6d**)*

Yield: 73 %, white crystals (dioxane), mp 168–170°C. ν_{max}/cm^{-1} 3410–3200 (2 × NH), 3049 (C–H aromatic), 2952–2926 (C–H aliphatic), 1628 (C=O), 1559 (C=N stretching), 1496 (C=C stretching). δ_H (90 MHz, DMSO-d_6) 12.05 (s, 1H, NH(3)), 7.50–7.00 (m, 5H), 5.65 (s, 1H, NH(8)), 4.75 (s, 2H), 4.25 (s, 2H), 3.25 (q, *J* 7.0, 2H), 1.30 (t, *J* 7.2, 3H). Anal. Calc. for $C_{14}H_{16}N_4OS$ (288.37): C 58.31, H 5.59, N 19.43, S 11.12. Found: C 58.41, H 5.51, N 19.50, S 11.03 %.

*2-(Ethylthio)-6-(4-methoxyphenyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**6e**)*

Yield: 82 %, white crystals (dioxane), mp 144–146°C. ν_{max}/cm^{-1} 3415–3210 (2 × NH), 3052 (C–H aromatic), 2951–2929 (C–H aliphatic), 1632 (C=O), 1566 (C=N stretching), 1509 (C=C stretching). δ_H (90 MHz, DMSO-d_6) 12.03 (s, 1H, NH(3)), 7.15–6.9 (dd, *J* 7.1, 4H), 5.50 (s, 1H, NH(8)), 4.95 (s, 2H), 4.25 (s, 2H), 3.75 (s, 3H), 3.20 (q, *J* 7.2, 2H), 1.35 (t, *J* 7.2, 3H). δ_C (100 MHz, DMSO-d_6) 162.26, 158.42, 154.28, 142.25, 119.95, 114.65, 94.29, 68.04, 55.76, 45.17, 25.28, 14.60. *m*/*z* (EI, 70 eV) 419.67 [M + 1], 418.34 [M].

*2-(Ethylthio)-6-*p*-tolyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**6f**)*

Yield: 80 %, white crystals (dioxane), mp 280–284°C. ν_{max}/cm^{-1} 3431–3200 (2 × NH), 3051 (C–H aromatic), 29525–2928 (C–H aliphatic), 1635 (C=O), 1563 (C=N stretching), 1512 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 12.01 (s, 1H, NH(3)), 6.96 (d, *J* 7.3, 2H), 6.72 (d, *J* 7.3, 2H), 5.41 (s, 1H, NH(8)), 4.55 (s, 2H), 4.03 (s, 2H), 3.13 (q, *J* 7.3, 2H), 2.17 (s, 3H), 1.29 (t, *J* 7.3, 3H). δ_C (100 MHz, DMSO-d_6) 161.25, 159.99, 156.72, 146.65, 129.95, 129.76, 117.81, 89.77, 64.70, 45.28, 24.62, 20.49, 15.00. Anal. Calc. for $C_{15}H_{18}N_4OS$ (302.39): C 59.58, H 6.00, N 18.53, S 10.60. Found: C 59.69, H 5.92, N 18.60, S 10.51 %.

*6-(4-Chlorophenyl)-2-(ethylthio)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**6g**)*

Yield: 75 %, pale yellow crystals (dioxane), mp 244–246°C. ν_{max}/cm^{-1} 3411–3205 (2 × NH), 3049 (C–H aromatic), 2951–2928 (C–H aliphatic), 1631 (C=O), 1566 (C=N stretching), 1493 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 12.04 (s, 1H, NH(3)), 7.25–6.83 (dd, *J* 7.1, 4H), 5.42 (s, 1H, NH(8)), 4.64 (s, 2H), 4.14 (s, 2H), 3.12 (q, *J* 7.1, 2H), 1.27 (t, *J* 7.2, 3H). Anal. Calc. for $C_{14}H_{15}ClN_4OS$ (322.07): C 52.09, H 4.68, N 17.36, S 9.93. Found: C 52.21, H 4.75, N 17.27, S 9.85 %.

*6-(4-Bromophenyl)-2-(ethylthio)-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4(3H)-one (**6h**)*

Yield: 74 %, pale yellow (dioxane), mp 238–240°C. ν_{max}/cm^{-1} 3407–3200 (2NH), 3051 (C–H aromatic), 2951–2926 (C–H aliphatic), 1630 (C=O), 1566 (C=N stretching), 1492 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 12.05 (s, 1H, NH(3)), 7.28 (d, *J* 8.8, 2H), 6.79 (d, *J* 8.9, 2H), 5.42 (s, 1H, NH (8)), 4.64 (s, 2H), 4.10 (s, 2H), 3.11 (q, *J* 7.3, 2H), 1.28 (t, *J* 7.3, 3H). δ_C (100 MHz, DMSO-d_6) 161.24, 160.40, 156.75, 148.21, 132.14, 119.55, 112.23, 89.77, 64.08, 45.19, 24.66, 14.95. *m*/*z* (EI, 70 eV) 367.45 [Br^{79}, M + 1], 369.56 [Br^{81}, M + 1].

*Synthesis of 8-(Benzyloxymethyl)-2-(ethylthio)-6-substituted-5,6,7,8-tetrapyrimido[4,5-d]pyrimidin-4(3H)-ones (**8a**–**d**)*

General procedure: A solution of 6-amino-2-(ethylthio)pyrimidin-4*(3H)*-one (**1**) (3 mmol) in dioxane (5 mL) was added dropwise to a stirred solution of formaldehyde (35 wt-% in H_2O, 1 mL), primary amines **2** (3 mmol), and benzyl alcohol (**7**) (3 mmol) in dioxane (20 mL) and then the reaction mixture was stirred under reflux for 2 h. The reaction was monitored by thin-layer chromatography. After starting materials had been consumed, the reaction mixture was cooled, and the separated precipitate was isolated by filtration, washed with dioxane, and then dried. The solid product was recrystallised from dioxane to afford the desired products **8a**–**d** in very good-to-distinguished yields.

*8-(Benzyloxymethyl)-2-(ethylthio)-6-isobutyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4(3H)-one (**8a**)*

Yield: 84 %, white crystals (dioxane), mp 154–156°C. ν_{max}/cm^{-1} 3410 (NH), 3050 (C–H aromatic), 2970–2951 (C–H aliphatic), 1633 (C=O), 1569 (C=N stretching), 1489 (C=C stretching). δ_H (400 MHz, $CDCl_3$) 12.28 (s, 1H, NH(3)), 7.29–7.18 (m, 5H), 5.05 (s, 2H), 4.47 (s, 2H), 4.14 (s, 2H), 3.63 (s, 2H), 2.92 (q, *J* 7.3, 2H), 2.27 (d, *J* 7.1, 2H), 1.77 (m, 1H), 1.24 (t, *J* 7.3, 3H), 0.85 (d, *J* 7.1, 6H). δ_C (100 MHz, $CDCl_3$) 162.98, 158.88, 156.82, 138.03, 128.39, 127.64, 127.45, 126.94, 89.98, 75.56, 69.86, 67.68, 61.21, 47.65, 26.46, 24.91, 20.72, 14.29. *m*/*z* (EI, 70 eV) 389.29 [M + 1], 388.30 [M]. Anal. Calc. for $C_{20}H_{28}N_4O_2S$ (388.53): C 61.83, H 7.26, N 14.42, S 8.25. Found: C 61.92, H 7.18, N 14.51, S 8.17 %.

*8-(Benzyloxymethyl)-2-(ethylthio)-6-phenyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4(3H)-one (**8b**)*

Yield: 78 %, white crystals (dioxane), mp 198–200°C. ν_{max}/cm^{-1} 3400 (NH), 2975–2927 (C–H aliphatic), 1632 (C=O), 1567 (C=N stretching), 1454 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 12.05 (s, 1H, NH(3)), 7.25–7.17 (m, 5H), 7.02 (m, 2H), 6.55 (m, 3H), 5.18 (s, 2H), 4.91 (s, 2H), 4.62 (s, 2H), 4.18 (s, 2H), 3.08 (q, *J* 8.7, 2H), 1.32 (t, *J* 8.7, 3H). δ_C (100 MHz, DMSO-d_6) 162.97, 158.68, 156.72, 150.21, 138.13, 129.62, 128.28, 127.53, 127.36, 126.84, 122.62, 115.52, 89.97, 75.65, 61.21, 59.85, 47.55, 25.01, 14.28.

*8-(Benzyloxymethyl)-2-(ethylthio)-6-p-tolyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4(3H)-one (**8c**)*

Yield: 75 %, white crystals (dioxane), mp 188–190°C. ν_{max}/cm^{-1} 3400 (NH), 3051 (C–H aromatic), 2972–2923 (C–H aliphatic), 1633 (C=O), 1570 (C=N stretching), 1489 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 12.02 (s, 1H, NH(3)), 7.35–7.24 (m, 5H), 7.04–6.90 (m, 4H), 5.12 (s, 2H), 4.87 (s, 2H), 4.40 (s, 2H), 4.17 (s, 2H), 2.95 (q, *J* 7.4, 2H), 2.18 (s, 3H), 1.21 (t, *J* 7.3, 3H). δ_C (100 MHz, DMSO-d_6) 161.41, 159.68, 156.81, 146.68, 138.74, 129.97, 129.34, 128.59, 128.00, 127.73, 117.58, 90.27, 75.57, 69.51, 64.69, 45.43, 24.58, 20.48, 14.89. *m*/*z* (EI, 70 eV) 423.42 [M + 1], 422.34 [M]. Anal. Calc. for $C_{23}H_{26}N_4O_2S$ (422.54): C 65.38, H 6.20, N 13.26, S 7.59. Found: C 65.27, H 6.29, N 13.35, S 7.67 %.

*8-(Benzyloxymethyl)-6-(4-bromophenyl)-2-(ethylthio)-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4(3H)-one (**8d**)*

Yield: 80 %, white crystals (dioxane), mp 204–206°C. ν_{max}/cm^{-1} 3428 (NH), 3052 (C–H aromatic), 2972–2923 (C–H aliphatic), 1633 (C=O), 1563 (C=N stretching), 1488 (C=C stretching). δ_H (90 MHz, DMSO-d_6) 12.15 (s, 1H, NH(3)), 7.20 (m, 5H), 6.95 (m, 4H), 5.10 (s, 2H), 4.85 (s, 2H), 4.35 (s, 2H), 4.15 (s, 2H), 2.95 (q, *J* 7.0, 2H), 1.25 (t, *J* 7.0, 3H). Anal. Calc. for $C_{22}H_{23}BrN_4O_2S$ (487.41): C 54.21, H 4.76, N 11.49, S 6.58. Found: C 54.16, H 4.68, N 11.56, S 6.65 %.

*2-(Ethylthio)-8-(piperidin-1-yl/morpholin-4-ylmethyl)-6-substituted-5,6,7,8-tetrapyrimido[4,5-d]pyrimidin-4(3H)-ones **10a**–**d***

General procedure: A solution of 6-amino-2-(ethylthio)pyrimidin-4*(3H)*-one (**1**) (3 mmol) in dioxane (5 mL) was added dropwise to a stirred solution of formaldehyde (35 wt-% in H_2O, 1 mL), primary amines **2** (3 mmol), and piperidine or morpholine (**7**) (3 mmol) in dioxane (20 mL) and then the reaction mixture was stirred under refluxed for 2 h. The reaction was monitored by thin-layer chromatography. After starting materials had been consumed, the reaction mixture was cooled, and the separated precipitate was isolated by filtration, washed with dioxane, and then dried. The solid product was recrystallised from dioxane to afford the desired products **10a**–**d** in very good-to-distinguished yields.

*2-(Ethylthio)-6-(4-methoxyphenyl)-8-(piperidin-1-ylmethyl)-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4(3H)-one (**10a**)*

Yield: 82 %, white crystals (dioxane), mp 194–196°C. ν_{max}/cm^{-1} 3350 (NH), 3052 (C–H aromatic), 2929–2853 (C–H aliphatic), 1635 (C=O), 1569 (C=N stretching), 1472 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 11.80 (s, 1H, NH(3)), 6.99 (d, *J* 9.0, 2H), 6.82 (d, *J* 8.9, 2H), 4.75 (s, 2H), 4.18 (s, 2H), 4.13 (s, 2H), 3.68 (s, 3H), 3.05 (q, *J* 8.9, 2H), 2.36 (t, *J* 9.0, 4H), 1.46–1.30 (m, 6H), 1.26 (t, *J* 8.9, 3H). δ_C (100 MHz, DMSO-d_6) 161.19, 159.29, 157.29, 153.91, 142.92, 119.12, 114.84, 88.65, 67.65, 66.84, 65.42, 55.71, 51.93, 46.14, 25.92, 24.51, 15.19. *m*/*z* (EI, 70 eV) 416.67 [M + 1], 415.34 [M].

*2-(Ethylthio)-6-(4-methoxyphenyl)-8-(morpholin-4-ylmethyl)-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4(3H)-one (**10b**)*

Yield: 84 %, white crystals (dioxane), mp 208–210°C. ν_{max}/cm^{-1} 3407 (NH), 3050 (C–H aromatic), 2920–2860 (C–H aliphatic), 1628 (C=O), 1560 (C=N stretching), 1496 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 11.83 (s, 1H, NH(3)), 6.99 (d, *J* 8.5, 2H), 6.83 (d, *J* 8.5, 2H), 4.77 (s, 2H), 4.20 (s, 2H), 4.13 (s, 2H), 3.68 (s, 3H), 3.53 (t, *J* 7.0, 4H), 3.04 (q, *J* 7.2, 2H), 2.36 (t, *J* 7.0, 4H), 1.29 (t, *J* 7.2, 3H). δ_C (100 MHz, DMSO-d_6) 161.23, 159.43, 157.25, 153.95, 142.83, 119.15, 114.86, 88.81,

67.08, 66.84, 66.57, 65.54, 55.72, 51.21, 45.95, 24.57, 15.13. Anal. Calc. for $C_{20}H_{27}N_5O_3S$ (417.53): C 57.53, H 6.52, N 16.77, S 7.68. Found: C 57.64, H 6.45, N 16.68, S 7.72 %.

*2-(Ethylthio)-8-(piperidin-1-ylmethyl)-6-*p*-tolyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**10c**)*

Yield: 77 %, white crystals (dioxane), mp 200–202°C. ν_{max}/cm^{-1} 3400 (NH), 3051 (C–H aromatic), 2923–2890 (C–H aliphatic), 1628 (C=O), 1567 (C=N stretching), 1494 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 11.95 (s, 1H, NH(3)), 7.00 (d, *J* 8.7, 2H), 6.92 (d, *J* 8.7, 2H), 4.49 (s, 2H), 4.14 (s, 4H), 2.99 (q, *J* 8.9, 2H), 2.32 (t, *J* 9.0, 4H), 2.15 (s, 3H), 1.43–1.34 (m, 6H), 1.24 (t, *J* 8.9, 3H). Anal. Calc. for $C_{21}H_{29}N_5OS$ (399.55): C 63.13, H 7.32, N 17.53, S 8.03. Found: C 63.05, H 7.40, N 17.46, S 8.12 %.

*2-(Ethylthio)-8-(morpholin-4-ylmethyl)-6-*p*-tolyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one (**10d**)*

Yield: 79 %, white crystals (dioxane), mp 214–216°C. ν_{max}/cm^{-1} 3395 (NH), 3052 (C–H aromatic), 2972–2922 (C–H aliphatic), 1629 (C=O), 1563 (C=N stretching), 1493 (C=C stretching). δ_H (400 MHz, DMSO-d_6) 11.88 (s, 1H, NH(3)), 7.00 (d, *J* 8.5, 2H), 6.91 (d, *J* 8.5, 2H), 4.79 (s, 2H), 4.16 (s, 2H), 4.13 (s, 2H), 3.50 (t, *J* 7.3, 4H), 2.98 (q, *J* 7.3, 2H), 2.32 (t, *J* 7.3, 4H), 2.15 (s, 3H), 1.21 (t, *J* 7.3, 3H). δ_C (100 MHz, DMSO-d_6) 161.21, 159.44, 157.25, 146.69, 129.97, 129.21, 117.55, 88.76, 67.03, 66.86, 66.60, 51.23, 45.55, 24.59, 20.56, 15.24. *m*/*z* (EI, 70 eV) 402.30 [M + 1], 401.29 [M].

Atomic Charge Calculations

The computational calculations of atomic charges were measured by using the natural population analysis method. The *Gaussian 09* software package with B3LYP functional and 6–31+G(d,p) basis set was used.[42]

Supplementary Material

FTIR, ^{1}H and ^{13}C NMR spectra of the synthesised compounds are available on the Journal's website.

Conflicts of Interest

The authors declare no conflicts of interest.

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