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An efficient and facile synthesis of inhibitors for hepatitis C viral and *anti*-SARS agents: 4-aryl-5-cyano-1,6-dihydro-2-thiouracils

Liangce Rong · Shan Yin · Sheng Xia · Shimin Tao · Yanhui Shi · Shujiang Tu

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Abstract One-pot, multicomponent reaction for the synthesis of 4-aryl-5-cyano-1,6-dihydro-2-thiouracils via three-component from aromatic aldehydes, ethyl 2-cyanoacetate and *S*-benzylisothiourea hydrochloride (methyl carbamimidothioate sulfate) under methanol is described. These compounds have many drug activities, such as *anti*-hepatitis C viral, *anti*-Severe acute respiratory syndrome and *anti*-HIV-1 integrese activity. The advantages of this procedure include the short reaction time, mild reaction conditions and excellent yields.

Keywords Thiouracils · Three-component reaction · Heterocyclic compound · Cycloaddition · Drug activity

Introduction

It is well known that pyrimidione is an important intermediate in heterocyclic synthesis, and its skeleton exists in many natural or synthetic biologically active materials. Its derivatives are applied in various pharmaceutical and biochemical fields [1, 2]. Dihydropyrimidiones, the important derivatives of pyrimidione, are found in a wide range of biological activities such as anticancer [3], anti-HIV [4], antibacterial [5], antimalarial [6], antihypertensive [7], sedative hypnotics [8], anticonvulsant [9], antithyroid [10], antihistaminic agents [11] and antibiotics [12]. Thiouracils (thiopimidiones) are the contained sulfur atoms derivatives of dihydropyrimidiones [13]. According to the reported literature, thiouracils (thiopimidiones) derivatives have many medical and biological properties. They not only inhibit

L. Rong (✉) · S. Yin · S. Xia · S. Tao · Y. Shi · S. Tu
Jiangsu Key Laboratory of Green Synthetic Chemistry For Functional Materials, College of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou 221116, Jiangsu, People's Republic of China
e-mail: lcrong2005@yahoo.com

nucleic acid metabolism [14, 15] but also inhibit the formation of thyroid hormones, and they were also used for the treatment of hyperthyroidism and Basedow's disease [16]. Furthermore, a recent study revealed that thiopimidiones (thiouracils) derivatives could be applied as inhibitors for hepatitis C viral (*anti*-HCV) [17], and another paper reported that it has *anti*-HIV-1 integrese activity [18]. Ramajayam et al. [19] reported these compounds could be used as *anti*-severe acute respiratory syndrome agents. Taking into account their wide applicability, it is therefore very necessary to find effective methods for the synthesis of these compounds.

Multicomponent reactions (MCRs) [20–22], which can produce various compounds, provide one of the most efficient methods for the synthesis of structurally diverse organic compounds. Recently, this synthetic method was the preferred method for chemists to prepare organic compounds. Here, we report a facile and efficient multicomponent reaction to synthesize these active materials: 4-aryl-5-cyano-1, 6-dihydro-2-thiouracils.

Results and discussion

Ding [17] has reported the preparation of thiouracils derivatives. He first synthesized intermediate products: 5-cyano-4-oxo-6-aryl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine derivatives, then reacted intermediate products with benzyl bromides to give thiouracils derivatives. This total reaction time exceeded 20 h, but the main problem in this procedure was the by-products, i.e. S and N disubstituted pyrimidine derivatives could also be obtained. Chen [23] has reported synthesizing four similar compounds using two-step reaction procedures; however, the total reaction time was too long (more than 30 h) and the yields of products were too low (28–43%). So, we hope to discover a new procedure for synthesis of these compounds. In order to improve the yields of compounds, we design a one-pot, multicomponent reaction to prepare target products using aromatic aldehydes, ethyl 2-cyanoacetate, and *S*-benzylisothiorea hydrochloride as starting reactants.

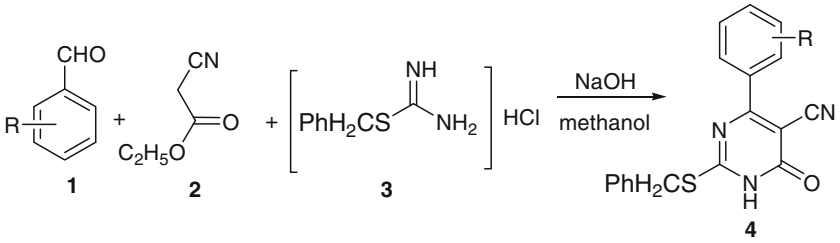
In our study, at first, we want to find a suitable synthesis condition to carry out this synthesis. 4-fluorobenzaldehyde **1a**, ethyl 2-cyanoacetate **2**, and *S*-benzylisothiourea hydrochloride **3** were chosen as the starting materials for the model reaction. The three reagents were reacted in the different solvents and used different catalysts. In our research, we found: when CH_3CN was used as solvent and Et_3N, $C_5H_{11}N$, K_2CO_3, Na_2CO_3, KOH, NaOH were used as catalysts, the reaction would not work. When CH_3OH or EtOH were used as solvents, the reactions could be brought out with different results. The results could be summarized as follows: when organic catalysts (Et_3N, $C_5H_{11}N$) were used, the reaction also would not work, but when weak inorganic base (K_2CO_3, Na_2CO_3) was used as catalyst, the reaction could be brought out with low yields. However, when a strong inorganic base such NaOH or KOH was used, the reaction could be carried out smoothly with high yields. Take into account the cost, toxicity and availability of catalysts and solvents, we chose NaOH and CH_3OH as the ideal catalyst and solvent to carry out theses synthesis. The optimized reaction results are listed in Table 1.

Table 1 Synthesis of **4a** in the presence of different catalysts and solvents

Entry	Solvent	Catalyst (1 mmol)	Yields (%)
1	CH_3CN	K_2CO_3	0
2	CH_3CN	Na_2CO_3	0
3	CH_3CN	Et_3N	0
4	CH_3CN	$C_5H_{11}N$	0
5	CH_3CN	NaOH	0
6	CH_3CN	KOH	0
7	CH_3OH	K_2CO_3	25
8	CH_3OH	Na_2CO_3	20
9	CH_3OH	Et_3N	0
10	CH_3OH	$C_5H_{11}N$	0
11	**CH_3OH**	**NaOH**	**89**
12	CH_3OH	KOH	83
13	EtOH	K_2CO_3	17
14	EtOH	Na_2CO_3	13
15	EtOH	Et_3N	0
16	EtOH	$C_5H_{11}N$	0
17	EtOH	NaOH	75
18	EtOH	KOH	70

Reagents and conditions: 4-fluorobenzaldehyde **1a** (1 mmol), ethyl 2-cyanoacetate **2** (1 mmol), *S*-benzylisothiourea hydrochloride **3** (1 mmol), NaOH (1 mmol) and solvent (10 mL)

Bold indicates the optimized reaction condition

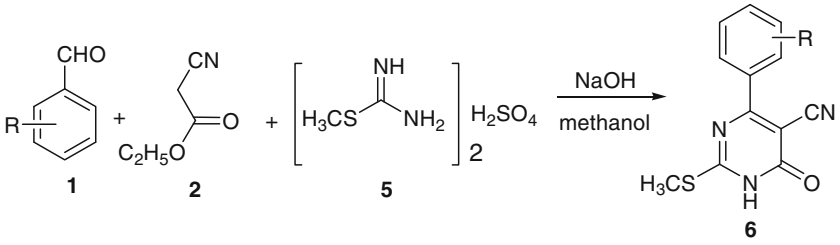


Scheme 1 Synthesis of 2-(benzylthio)-6-oxo-1,6-dihydropyrimidine

Using this optimized reaction condition, we used different aromatic aldehydes to react with ethyl 2-cyanoacetate and *S*-benzylisothiourea hydrochloride, and a series of 2-(benzylthio)-6-oxo-1,6-dihydropyrimidines could be gained with high yields (Scheme 1). The results of reactions are summarized in Table 2. As shown in Table 2, both electron-withdrawing (such as F, Cl, Br) or electron-donating substitute groups (CH_3–, CH_3O–) on aromatic aldehydes could give ideal results. We tried to use heterocyclic atom aldehydes, such as picolinaldehyde and isonicotinaldehyde, in this procedure, and we found that they were both suitable for synthesis of 2-(benzylthio)-6-oxo-1,6-dihydropyrimidines with good yields (**4n**, **4o**).

Table 2 Synthesis of 2-(benzylthio)-6-oxo-1,6-dihydropyrimidine

Entry	R	Products	Yields (%)
1	4-F	**4a**	89
2	3-Cl	**4b**	90
8	2,4-Cl_2	**4c**	96
9	3,4-Cl_2	**4d**	91
3	4-Br	**4e**	91
7	H	**4f**	90
4	4-CH_3	**4g**	90
5	4-CH_3O	**4h**	89
6	2-CH_3O	**4i**	87
10	3,4-$(CH_3)_2$	**4j**	94
11	3,4-$(CH_3O)_2$	**4k**	92
12	2,5-$(CH_3O)_2$	**4l**	89
13	3,4,5-$(CH_3O)_3$	**4m**	95
14	2-Pyridyl	**4n**	88
15	4-Pyridyl	**4o**	90



Scheme 2 Synthesis of 2-(methylthio)-6-oxo-1,6-dihydropyrimidines

In order to expand this synthesis under similar conditions, methyl carbamimidothioate sulfate was used to replace *S*-benzylisothiourea hydrochloride to react with aromatic aldehydes and ethyl 2-cyanoacetate (Scheme 2). To our delight, we also found that all the reactions were carried out smoothly, and corresponding products 4-aryl-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile could be obtained with good yields. The results are summarized in Table 3. From Table 3, we can find that the reactions have very good applicability, and aromatic aldehydes with different substituent groups can give efficient results. Investigating the above reactions, we can come to the conclusion that CH_3OH and NaOH are the efficient conditions for the synthesis of these compounds under a multicomponent reaction. In these procedures, the reaction time was no more than 30 min.

The structures of all the products were confirmed on the basis of spectroscopic data, particularly ^{1}H NMR analysis and HRMS spectra. We take **4g** and **6f** as examples to analyze their structures. In **4g** ^{1}H NMR, its spectrum revealed a singlet signal at $\delta = 2.41$(3H), 4.54 (2H) ppm due to CH_3 and $PhCH_2$ protons. The triplet

Table 3 Synthesis of 2-(methylthio)-6-oxo-1,6-dihydropyrimidines

Entry	R	Products	Yields (%)
1	4-F	**6a**	86
2	3-Cl	**6b**	80
3	4-Cl	**6c**	88
4	3-Br	**6d**	90
5	4-Br	**6e**	92
6	4-CH_3	**6f**	90
7	4-CH_3O	**6g**	89
8	3,4-$(CH_3)_2$	**6h**	87

signal at $\delta = 7.27$ (1H, $J = 7.2$ Hz), 7.33 (2H, $J = 7.6$ Hz) ppm and doublet signals at 7.39 (2H, $J = 8.0$ Hz), 7.42 (2H, $J = 8.0$ Hz) and 7.87 (2H, $J =$ 8.4 Hz ppm were due to nine phenyl protons. In HRMS spectrum, the calculated *m/z* $[C_{19}H_{15}N_3OS\ (M + Na)^+]$ of **4g** is 356.0834, and the *m/z* found is 356.0831. The error value is only 0.82 ppm.

In **6f** ^{1}H NMR, its spectrum revealed a singlet signal at $\delta = 2.41$(3H), 2.61 (3H) ppm due to CH_3 and SCH_3 protons. The doublet signals at 7.39 (2H, $J = 8.0$ Hz), 7.90 (2H, $J = 8.0$ Hz) were due to four phenyl protons. In the HRMS spectrum, the calculated m/z $(C_{13}H_{11}N_3OS\ [M + Na]^+)$ of **6f** is 280.0521, and the *m/z* found is 280.0531. The error value is only 3.57 ppm. Although we have not found chemical shift of active H on nitrogen atoms in **4** or **6** ^{1}H NMR, we can see it in IR (about 3,400 cm^{-1}). This phenomenon can also be found in the literature [22].

Conclusions

In conclusion, we have expanded a facile and high efficiency one-pot reaction for the synthesis of 4-aryl-5-cyano-1,6-dihydro-2-thiouracils via the reaction of different aromatic aldehydes, ethyl 2-cyanoacetate and *S*-benzylisothiourea hydrochloride (methyl carbamimidothioate sulfate). Due to employing a one-pot, multicomponent reaction, this method offers several advantages including easy experimental work-up procedure and lower cost, and especially high yield of products in a short reaction time.

Experimental

Melting points were determined on XT-5 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a FT Bruker Tensor 27 spectrometer. ^{1}H NMR spectra were obtained from solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. Microanalyses were carried out using a Perkin-Elmer 2400 II analyzer. HRMS spectra were obtained with a Bruker microTOF-Q 134 instrument.

General procedure for the synthesis of 4-aryl-5-cyano-1,6-dihydro-2-thiouracils

The mixture of aromatic aldehydes **1** (1 mmol), ethyl 2-cyanoacetate **2** (1 mmol), *S*-benzylisothiorea hydrochloride **3** or methyl carbamimidothioate sulfate **5** (1 mmol), CH_3OH (10 mL) and NaOH (1 mmol) was put in a reaction flask at 70 °C about 30 min. After completion, the reaction mixture was poured into water, filtered, and then washed with water thoroughly. The products were dried and recrystallized from 95% ethanol.

*2-(Benzylthio)-4-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4a**)*

Melting point 193–194 °C; IR (KBr) *v*: 3,421, 2,220, 1,734, 1,660, 1,604, 1,539, 1,506, 1,473, 1,376, 1,243, 1,161, 1,000, 848, 784 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.55 (2H, s, $PhCH_2$–), 7.27 (1H, *t*, $J = 7.2$ Hz, ArH), 7.31–7.35 (2H, m, ArH), 7.41–7.46 (4H, m, ArH), 8.03 (2H, dd, $J = 5.6$ Hz, $J = 8.8$ Hz, ArH); Anal. Calcd. for $C_{18}H_{12}FN_3OS$: C 64.08, H 3.59, N 12.46. Found: C 63.96, H 3.60, N 12.41.

HRMS *m/z* calculated for $C_{18}H_{12}FN_3OS$ $[M + Na]^+$: 360.0583, found: 360.0585.

*2-(Benzylthio)-4-(3-chlorophenyl)- 6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4b**)*

Melting pioint 219–220 °C; IR (KBr) *v*: 3,430, 2,221, 1,731, 1,714, 1,694, 1,682, 1,652, 1,614, 1,583, 1,567, 1,519, 1,505, 1,455, 1,362 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.54 (2H, s, $PhCH_2$–), 7.28 (1H, *t*, $J = 7.2$ Hz, ArH), 7.34 (2H, *t*, $J = 7.2$ Hz, ArH), 7.43 (2H, d, $J = 8.4$ Hz, ArH), 7.62 (1H, *t*, $J = 8.0$ Hz, ArH), 7.70 (1H, d, $J = 8.4$ Hz, ArH), 7.88–7.91 (2H, m, ArH); Anal. Calcd. for $C_{18}H_{12}ClN_3OS$: C 61.10, H 3.42, N 11.88. Found: C 61.01, H 3.40, N 11.92.

HRMS *m/z* calculated for $C_{18}H_{12}ClN_3OS$ $[M + H]^+$: 354.0468, found: 354.0474.

*2-(Benzylthio)-4-(2,4-dichlorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4c**)*

Melting point 184–185 °C; IR (KBr) *v*: 3,416, 2,226, 1,678, 1,638, 1,586, 1,528, 1,474, 1,389, 1,365, 1,257, 1,107, 1,057, 1,002, 866, 781, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.43 (2H, s, $PhCH_2$–), 7.25–7.32 (3H, m, ArH), 7.37 (2H, dd, $J = 2.0$ Hz, $J = 8.4$ Hz, ArH), 7.62 (1H, d, $J = 8.4$ Hz, ArH), 7.68 (1H, d, $J = 8.4$ Hz, ArH), 7.89 (1H, d, $J = 2.0$ Hz, ArH); Anal. Calcd. for $C_{18}H_{11}Cl_2N_3OS$: C 55.68, H 2.86, N 10.82. Found: C 55.75, H 2.88, N 10.78.

HRMS *m/z* calculated for $C_{18}H_{11}Cl_2N_3OS$ $[M + H]^+$: 388.0078, found: 388.0077.

*2-(Benzylthio)-4-(3,4-dichlorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4d**)*

Melting point 192–193 °C; IR (KBr) *v*: 3,440, 1,760, 1,666, 1,537, 1,531, 1,471, 1,255, 1,209 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.53 (2H, s, $PhCH_2$–), 7.27

(1H, *t*, $J = 7.2$ Hz, ArH), 7.34 (2H, *t*, $J = 7.6$ Hz, ArH), 7.42 (2H, d, $J = 6.8$ Hz, ArH), 7.87 (1H, d, $J = 8.4$ Hz, ArH), 7.92 (1H, dd, $J = 2.0$ Hz, $J = 8.4$ Hz, ArH), 8.09 (1H, d, $J = 1.6$ Hz, ArH); Anal. Calcd. for $C_{18}H_{11}C_{l2}N_3OS$: C 55.68, H 2.86, N 10.82. Found: C 55.74, H 2.87, N 10.80.

HRMS *m/z* calculated for $C_{18}H_{11}C_{l2}N_3OS$ $[M + Na]^+$: 409.9898, found: 409.9887.

*2-(Benzylthio)-4-(4-bromophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4e**)*

Melting point 243–245 °C; IR (KBr) *v*: 3,435, 1,769, 1,650, 1,539, 1,521, 1,469, 1,369, 1,254, 1,210, 1,187, 1,119, 1,074, 998 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.54 (2H, s, $PhCH_2$–), 7.27 (1H, *t*, $J = 7.2$ Hz, ArH), 7.33 (2H, *t*, $J = 7.2$ Hz, ArH), 7.42 (2H, d, $J = 7.2$ Hz, ArH), 7.81 (2H, d, $J = 8.4$ Hz, ArH), 7.89 (2H, d, $J = 8.8$ Hz); Anal. Calcd. for $C_{18}H_{12}BrN_3OS$: C 54.28, H 3.04, N 10.55. Found: C 54.19, H 3.06, N 10.59.

HRMS *m/z* calculated for $C_{18}H_{12}BrN_3OS$ $[M + Na]^+$: 419.9782, found: 419.9774.

*2-(Benzylthio)-4-phenyl-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4f**)*

Melting point 191–193 °C (lit.[18] 202–204 °C); IR (KBr) *v*: 3,420, 2,220, 1,653, 1,539, 1,495, 1,474, 1,262, 1,213, 1,119, 1,002, 694 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.55 (2H, s, $PhCH_2$–), 7.27 (1H, *t*, $J = 7.2$ Hz, ArH), 7.32 (2H, *t*, $J = 6.8$ Hz, ArH), 7.43 (2H, *t*, $J = 6.8$ Hz, ArH), 7.57–7.63 (3H, m, ArH), 7.95 (2H, d, $J = 6.8$ Hz, ArH); Anal. Calcd. for $C_{18}H_{13}N_3OS$: C 67.69, H 4.10, N 13.16. Found: C 67.59, H 4.12, N 13.18.

HRMS *m/z* calculated for $C_{18}H_{13}N_3OS$ $[M + H]^+$: 320.0858, found: 320.0855.

*2-(Benzylthio)-6-oxo-4-p-tolyl-1,6-dihydropyrimidine-5-carbonitrile (**4g**)*

Melting point 224–225 °C (lit.[18] 229–232 °C); IR (KBr) *v*: 3,423, 2,221, 1,735, 1,639, 1,542, 1,471, 1,373, 1,225, 1,191, 1,140, 1,116, 998, 781, 703, 566 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.41 (3H, s, CH_3), 4.54 (2H, s, $PhCH_2$–), 7.27 (1H, *t*, $J = 7.2$ Hz, ArH), 7.33 (2H, *t*, $J = 7.6$ Hz, ArH), 7.39 (2H, d, $J = 8.0$ Hz, ArH), 7.42 (2H, d, $J = 8.0$ Hz, ArH), 7.87 (2H, d, $J = 8.4$ Hz, ArH); Anal. Calcd. for $C_{19}H_{15}N_3OS$: C 68.45, H 4.53, N 12.60. Found: C 68.54, H 4.51, N 12.64.

HRMS *m/z* calculated for $C_{19}H_{15}N_3OS$ $[M + Na]^+$: 356.0834, found: 356.0831.

*2-(Benzylthio)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4h**)*

Melting point 242–243 °C (lit.[18] 248–250 °C); IR (KBr) *v*: 3,421, 2,216, 1,747, 1,650, 1,601, 1,539, 1,507, 1,473, 1,370, 1,303, 1,262, 1,216, 1,180, 1,141, 1,024, 998 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.86 (3H, s, CH_3O), 4.55 (2H, s, $PhCH_2$–), 7.13 (2H, d, $J = 8.8$ Hz, ArH), 7.27 (1H, *t*, $J = 7.2$ Hz, ArH), 7.33 (2H, *t*, $J = 7.6$ Hz, ArH), 7.43 (2H, d, $J = 7.2$ Hz, ArH), 8.03 (2H, d, $J = 8.8$ Hz, ArH);

Anal. Calcd. for $C_{19}H_{15}N_3O_2S$: C 65.31, H 4.33, N 12.03. Found: C 65.40, H 4.32, N 11.99.

HRMS *m/z* calculated for $C_{19}H_{15}N_3O_2S$ $[M + H]^+$: 350.0963, found: 350.0947.

*2-(Benzylthio)-4-(2-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4i**)*

Melting point 189–190 °C; IR (KBr) *v*: 3,066, 2,221, 1,648, 1,601, 1,525, 1,491, 1,468, 1,253 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.85 (3H, S, CH_3O), 4.45 (2H, s, $PhCH_2$–), 7.09–7.13 (1H, m, ArH), 7.22 (1H, d, $J = 8.0$ Hz, ArH), 7.27–7.34 (3H, m, ArH), 7.39–7.44 (3H, m, ArH), 7.53–7.57 (1H, m, ArH); Anal. Calcd. for $C_{19}H_{15}N_3O_2S$: C 65.31, H 4.33, N 12.03. Found: C 65.41, H 4.32, N 12.00.

HRMS *m/z* calculated for $C_{19}H_{15}N_3O_2S$ $[M + Na]^+$: 372.0783, found: 372.0802.

*2-(Benzylthio)-4-(3,4-dimethylphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4j**)*

Melting point 186–188 °C; IR (KBr) *v*: 3,430, 2,220, 1,790, 1,769, 1,747, 1,715, 1,681, 1,668, 1,651, 1,538, 1,505, 1,373, 1,249 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.30 (3H, s, CH_3), 2.32 (3H, s, CH_3), 4.54 (2H, s, $PhCH_2$–), 7.28 (1H, *t*, $J = 7.2$ Hz, ArH), 7.33 (3H, *t*, $J = 7.2$ Hz, ArH), 7.43 (2H, d, $J = 7.2$ Hz, ArH), 7.70 (2H, d, $J = 4.4$ Hz, ArH); Anal. Calcd. for $C_{20}H_{17}N_3OS$: C 69.14, H 4.93, N 12.09. Found: C 69.38, H 4.90, N 12.13.

HRMS *m/z* calculated for $C_{20}H_{17}N_3OS$ $[M + H]^+$: 348.1171, found: 348.1143.

*2-(Benzylthio)-4-(3,4-dimethoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4k**)*

Melting point 217–219 °C; IR (KBr) *v*: 3,000, 2,223, 1,735, 1,702, 1,686, 1,664, 1,543, 1,364, 1,271, 1,207 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.76 (3H, s, CH_3O), 3.86 (3H, s, CH_3O), 4.58 (2H, s, $PhCH_2$–), 7.17 (1H, d, $J = 8.4$ Hz, ArH), 7.27 (1H, *t*, $J = 7.2$ Hz, ArH), 7.33 (2H, *t*, $J = 7.6$ Hz, ArH), 7.45 (2H, d, $J = 6.8$ Hz, ArH), 7.60 (1H, d, $J = 2.0$ Hz, ArH), 7.71 (1H, dd, $J = 2.0$ Hz, ArH); Anal. Calcd. for $C_{20}H_{17}N_3O_3S$: C 63.31, H 4.52, N 11.07. Found: C 63.25, H 4.50, N 11.09.

HRMS *m/z* calculated for $C_{20}H_{17}N_3O_3S$ $[M + H]^+$: 380.1069, found: 380.1062.

*2-(Benzylthio)-4-(2,5-dimethoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4l**)*

Melting point 208–209 °C; IR (KBr) *v*: 3,447, 2,226, 1,697, 1,656, 1,541, 1,499, 1,473, 1,412, 1,297, 1,265, 1,228, 1,187, 1,040, 1,012, 863, 816, 736, 694, 668 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.74 (3H, s, CH_3O), 3.80 (3H, s, CH_3O), 4.47 (2H, s, $PhCH_2$–), 7.01 (1H, d, $J = 2.4$ Hz, ArH), 7.10–7.17 (2H, m,

ArH), 7.27–7.33 (3H, m, ArH), 7.41 (2H, d, $J = 7.2$ Hz, ArH); Anal. Calcd. for $C_{20}H_{17}N_3O_3S$: C 63.31, H 4.52, N 11.07. Found: C 63.25, H 4.54, N 11.09.

HRMS *m/z* calculated for $C_{20}H_{17}N_3O_3S$ $[M + H]^+$: 380.1069, found: 380.1079.

*2-(Benzylthio)-4-(3,4,5-trimethoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4m**)*

Melting point 237–238 °C; IR (KBr) *v*: 3,445, 2,212, 1,656, 1,560, 1,505, 1,478, 1,467, 1,409, 1,366, 1,310, 1,271, 1,132, 1,123, 1,016, 1,004, 950, 781, 673 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.76 (3H, s, CH_3O), 3.80 (6H, s, $2XCH_3O$), 4.59 (2H, s, $PhCH_2$–), 7.27 (1H, *t*, $J = 7.2$ Hz, ArH), 7.31–7.34 (4H, m, ArH), 7.45 (2H, d, $J = 6.8$ Hz, ArH); Anal. Calcd. for $C_{21}H_{19}N_3O_4S$: C 61.60, H 4.68, N 10.26. Found: C 61.68, H 4.69, N 10.24.

HRMS *m/z* calculated for $C_{21}H_{19}N_3O_4S$ $[M + Na]^+$: 432.0994, found: 432.0995.

*2-(Benzylthio)-4-(pyridin-2-yl)-6-oxo-1,6-dihydro pyrimidine-5-carbonitrile (**4n**)*

Melting point 211–213 °C; IR (KBr) *v*: 3,422, 2,217, 1,718, 1,671, 1,536, 1,480, 1,380, 1,321, 1,266, 1,242, 1,163, 1,118, 1,001, 774, 705 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.62 (2H, s, $PhCH_2$–), 7.27 (1H, *t*, $J = 7.2$ Hz, ArH), 7.34 (2H, *t*, $J = 7.2$ Hz, ArH), 7.47 (2H, *t*, $J = 6.8$ Hz, ArH), 7.63–7.67 (1H, m, ArH), 8.05–8.09 (1H, m, ArH), 8.26 (1H, d, $J = 8.0$ Hz, ArH), 8.76–8.78 (1H, m, ArH); Anal. Calcd. for $C_{17}H_{12}N_4OS$: C 63.73, H 3.78, N 17.49. Found: C 63.67, H 3.79, N 17.51.

HRMS *m/z* calculated for $C_{17}H_{12}N_4OS$ $[M + Na]^+$: 343.0630, found: 343.0641.

*2-(Benzylthio)-6-oxo-4-(pyridin-4-yl)-1,6-dihydro pyrimidine-5-carbonitrile (**4o**)*

Melting point 257–258 °C; IR (KBr) *v*: 3,432, 2,230, 1,701, 1,655, 1,561, 1,527, 1,498, 1,468, 1,266, 872, 714, 670, 659 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 4.55 (2H, s, $PhCH_2$–), 7.27 (1H, *t*, $J = 7.2$ Hz, ArH), 7.33 (2H, *t*, $J = 7.6$ Hz, ArH), 7.41 (2H, d, $J = 7.6$ Hz, ArH), 7.97 (2H, dd, $J = 1.6$ Hz, $J = 1.6$ Hz, ArH), 8.90 (2H, dd, $J = 1.2$ Hz, $J = 1.6$ Hz, ArH); Anal. Calcd. for $C_{17}H_{12}N_4OS$: C 63.73, H 3.78, N 17.49. Found: C 63.68, H 3.77, N 17.53.

HRMS *m/z* calculated for $C_{17}H_{12}N_4OS$ $[M + H]^+$: 321.0810, found: 321.0801.

*4-(4-Fluorophenyl)-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**6a**)*

Melting point > 280 °C; IR (KBr) *v*: 3,565, 2,851, 2,755, 2,224, 1,652, 1,602, 1,540, 1,505, 1,473, 1,382, 1,258, 1,228, 1,162, 1,002, 850, 786, 569, 700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.62 (3H, s, SCH_3), 7.43 (2H, *t*, $J = 8.8$ Hz, ArH), 8.06 (2H, dd, $J = 5.6$ Hz, $J = 8.8$ Hz, ArH); Anal. Calcd. for $C_{12}H_8FN_3OS$: C 55.16, H 3.09, N 16.08. Found: C 55.27, H 3.11, N 16.15.

HRMS *m/z* calculated for $C_{12}H_8FN_3OS$ $[M + Na]^+$: 284.0270, found: 284.0271.

*4-(3-Chlorophenyl)-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**6b**)*

Melting point 263–265 °C; IR (KBr) *v*: 3,444, 3,072, 3,024, 2,943, 2,714, 2,225, 1,653, 1,544, 1,526, 1,475, 1,382, 1,254, 1,216, 1,011, 895, 803, 783, 704, 679 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.61 (3H, s, SCH_3), 7.62 (1H, *t*, $J = 8.0$ Hz, ArH), 7.70 (1H, d, $J = 7.2$ Hz, ArH), 7.92 (1H, d, $J = 8.0$ Hz, ArH), 7.96 (1H, s, ArH); Anal. Calcd. for $C_{12}H_8ClN_3OS$: C 51.90, H 2.90, N 15.13. Found: C 51.77, H 2.89, N 15.16.

HRMS *m/z* calculated for $C_{12}H_8ClN_3OS$ $[M + Na]^+$: 299.9974, found: 299.9980.

*4-(4-Chlorophenyl)-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**6c**)*

Melting point > 300 °C; IR (KBr) *v*: 3,461, 3,089, 2,869, 2,759, 2,221, 1,664, 1,597, 1,547, 1,471, 1,435, 1,400, 1,381, 1,283, 1,254, 1,213, 1,186, 1,093, 1,003, 784, 687 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.61 (3H, s, SCH_3), 7.67 (2H, d, $J = 8.8$ Hz, ArH), 7.99 (2H, d, $J = 8.4$ Hz, ArH); Anal. Calcd. for $C_{12}H_8ClN_3OS$: C 51.90, H 2.90, N 15.13. Found: C 51.81, H 2.91, N 15.18.

HRMS *m/z* calculated for $C_{12}H_8ClN_3OS$ $[M + Na]^+$: 299.9974, found: 299.9982.

*4-(3-Bromophenyl)-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**6d**)*

Melting point 252–254 °C; IR (KBr) *v*: 3,410, 3,076, 3,025, 2,940, 2,765, 2,713, 2,224, 1,653, 1,543, 1,524, 1,473, 1,380, 1,252, 1,213, 1,116, 1,009, 883, 801, 782, 699, 663, 568 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.61 (3H, s, SCH_3), 7.55 (1H, *t*, $J = 8.0$ Hz, ArH), 7.83 (1H, dd, $J = 0.8$ Hz, $J = 8.4$ Hz, ArH), 7.95 (1H, d, $J = 8.0$ Hz, ArH), 8.09 (1H, s, ArH); Anal. Calcd. for $C_{12}H_8BrN_3OS$: C 44.74, H 2.50, N 13.04. Found: C 44.82, H 2.52; N 13.10.

HRMS *m/z* calculated for $C_{12}H_8BrN_3OS$ $[M + Na]^+$: 343.9469, found: 343.9460.

*4-(4-Bromophenyl)-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**6e**)*

Melting point > 300 °C; IR (KBr) *v*: 3,435, 3,011, 2,930, 2,873, 2,756, 2,226, 1,667, 1,540, 1,462, 1,455, 1,395, 1,380, 1,252, 1,212, 1,184, 1,119, 1,075, 1,012, 1,002, 826, 784 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.61 (3H, s, SCH_3), 7.80 (2H, d, $J = 8.8$ Hz, ArH), 7.91 (2H, d, $J = 8.4$ Hz, ArH); Anal. Calcd. for $C_{12}H_8BrN_3OS$: C 44.74, H 2.50, N 13.04. Found: C 44.80, H 2.54, N 13.11.

HRMS *m/z* calculated for $C_{12}H_8BrN_3OS$ $[M + Na]^+$: 343.9469, found: 343.9463.

*2-(Methylthio)-6-oxo-4-p-tolyl-1,6-dihydropyrimidine-5-carbonitrile (**6f**)*

Melting point > 290 °C; IR (KBr) *v*: 3,068, 2,935, 2,845, 2,752, 2,220, 1,651, 1,608, 1,573, 1,531, 1,505, 1,472, 1,456, 1,434, 1,417, 1,380, 1,257, 1,220, 1,187, 1,116, 1,001, 782 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.41 (3H, s, CH_3), 2.61 (3H, s, SCH_3), 7.39 (2H, d, $J = 8.0$ Hz, ArH), 7.90 (2H, d, $J = 8.0$ Hz, ArH); Anal. Calcd. for $C_{13}H_{11}N_3OS$: C 60.68, H 4.31, N 16.33. Found: C 60.80, H 4.34, N 16.36.

HRMS *m/z* calculated for $C_{13}H_{11}N_3OS$ $[M + Na]^+$: 280.0521, found: 280.0531.

*4-(4-Methoxyphenyl)-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**6g**)*

Melting point > 300 °C; IR (KBr) *v*: 3,444, 2,842, 2,754, 2,226, 1,651, 1,607, 1,575, 1,540, 1,506, 1,471, 1,456, 1,417, 1,382, 1,313, 1,258, 1,219, 1,177, 1,025, 998, 843, 786 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.62 (3H, s, SCH_3), 3.86 (3H, s, OCH_3), 7.13 (2H, d, $J = 9.2$ Hz, ArH), 8.04 (2H, d, $J = 8.8$ Hz, ArH); Anal. Calcd. for $C_{13}H_{11}N_3O_2S$: C 57.13, H 4.06, N 15.37. Found: C 57.24, H 4.09, N 15.41.

HRMS *m/z* calculated for $C_{13}H_{11}N_3O_2S$ $[M + Na]^+$: 296.0470, found: 296.0475.

*4-(3,4-Dimethylphenyl)-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**6h**)*

Melting point 266–268 °C; IR (KBr) *v*: 3,451, 3,022, 2,942, 2,864, 2,757, 2,220, 1,641, 1,546, 1,523, 1,472, 1,386, 1,257, 1,215, 1,186, 1,118, 1,022, 994, 931, 901, 837, 787, 680, 667, 568 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.30 (3H, s, CH_3), 2.31 (3H, s, CH_3), 2.61 (3H, s, SCH_3), 7.33 (1H, d, $J = 8.0$ Hz, ArH), 7.71 (1H, d, $J = 8.0$ Hz, ArH), 7.75 (1H, s, ArH); Anal. Calcd. for $C_{14}H_{13}N_3OS$: C 61.97, H 4.83, N 15.49. Found: C 61.85, H 4.87, N 15.44.

HRMS *m/z* calculated for $C_{14}H_{13}N_3OS$ $[M + Na]^+$: 294.0677, found: 294.0675.

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