Expedient Microwave-Assisted Synthesis of 5-Benzoylamino-2-(aralkylsulfanyl)pyrimidin-4(3*H*)-ones

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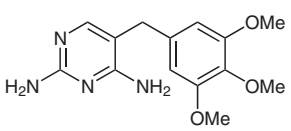
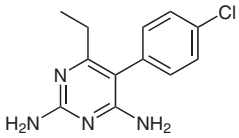
Abstract: A rapid and efficient microwave-assisted synthesis of novel 5-benzoylamino-2-(aralkylsulfanyl)pyrimidin-4(3*H*)-ones by rearrangement of 4-(1-ethoxyalkylidene)-2-phenyloxazol-5(4*H*)-ones in the presence of *S*-aralkyl-substituted isothiouronium halides and triethylamine is reported

Key words: microwave-assisted synthesis, azlactones, ring expansion, rearrangement, 2-(aralkylsulfanyl)pyrimidin-4(3*H*)-ones

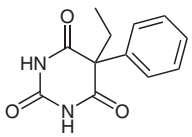
Polyfunctional pyrimidines play an important role in medicinal chemistry because of their different biological properties,[1–3] and various synthetic methods have been developed.[4] For instance, trimethoprim (**I**) and pyrimethamine (**II**) act as dihydrofolate reductase inhibitors and are valuable for antibacterial and antimalarial therapy (Figure 1). Barbiturates are well known as sedative, hypnotic, anxiolytic and anticonvulsant drugs with phenobarbital (**III**) being still the most widely used antiepileptic drug (AED) in the developing world and remaining a popular choice in many industrialized countries.[1] Dihydroalkyloxy-benzyl-oxopyrimidines (DABOs) have been characterized as strongly active nonnucleoside reverse transcriptase inhibitors (NNRTIs),[2] which, on structural modification, delivered *S*-DABO compounds (**IV**) as excellent anti-HIV agents with low cytotoxicity.[3]



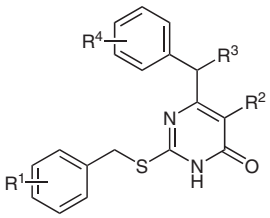
trimethoprim (**I**)



pyrimethamine (**II**)



phenobarbital (**III**)



S-DABOs (**IV**)

Figure 1 Selected biologically active polyfunctional pyrimidines

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Azlactones represent versatile building blocks for the synthesis of a great variety of multifunctional compounds.[5] Among the numerous different azlactones, 4-(ethoxymethylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one (**1a**) deserves particular interest as an intermediate in organic chemistry because of its ambivalent behavior towards nucleophiles.[5]

For example, the reaction of **1a** with benzylisothiouronium chloride (**2a**) in the presence of triethylamine has been reported to produce *N*-[2-(benzylsulfanyl)-6-oxo-1,6-dihydropyrimidin-5-yl]benzamide (**3a**) in 74% yield, although the assigned structural conformation of **3a** was only based on IR spectroscopy and microanalysis.[6]

During our studies on polyfunctional pyrimidines, we became interested in the transformation of **1a** into **3a** and developed an efficient microwave-assisted protocol for the targeted 5-benzoylamino-2-(aralkylsulfanyl)pyrimidin-4(3*H*)-one derivatives **3**, **4**, and **5**. After conducting the reaction of **1a** with benzylisothiouronium chloride according to literature[6] several times, we found that the reported yield (74%) could not be reproduced.

Due to higher efficiency, microwave-assisted reactions may offer a considerable advantage over conventional reaction conditions.[7] We therefore tried to optimize the formation of **3a** by means of microwave irradiation by monitoring the reaction using IR spectroscopy and TLC whilst varying the temperature and power. Best results (67% yield within five minutes) were achieved at high temperatures (see experimental). Moreover, **3a** was obtained in a pure crystalline state that was suitable for X-ray analysis by crystallization from methanol; this allowed the structure of **3a** to be proved unambiguously (Figure 2).[8]

By applying this method to the reaction of **1a** with the *S*-aralkyl-substituted isothiouronium halides **2b–g**, a set of novel benzoylamino-2-(aralkylsulfanyl)pyrimidin-4(3*H*)-

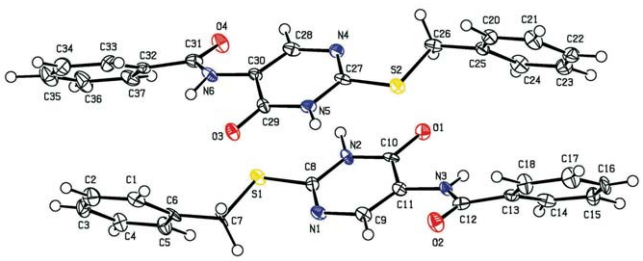
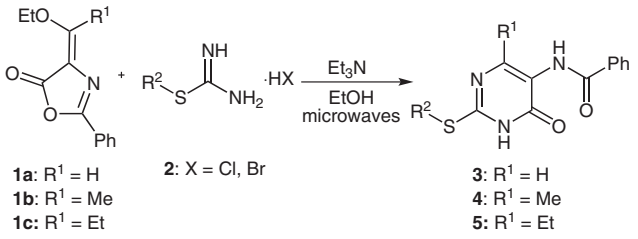


Figure 2 X-ray crystal structure of compound **3a** (illustrated as a dimer)



Scheme 1 Synthesis of 5-benzoylamino-2-(aralkylsulfanyl)pyrimidin-4(3*H*)-ones **3**–**5**

ones **3b**–**g** could be prepared in 64–73% yield (Scheme 1, Table 1).

Analogously, the easily available 4-(1-ethoxyalkylidene)-2-phenyloxazol-5(4*H*)-ones **1b** and **1c** furnished the desired 6-methyl-substituted 5-benzoylamino-2-(aralkylsulfanyl)pyrimidin-4(3*H*)-ones **4a**–**g** in 45–70% yield and the 6-ethyl-substituted 5-benzoylamino-2-(aralkylsulfanyl)pyrimidin-4(3*H*)-ones **5a**–**e** in 52–69% yield within only 5–10 minutes (Scheme 1, Table 1). Again, the reaction was monitored by IR spectroscopy and by TLC.

Structure determination of all synthesized compounds was based on IR, ^{1}H, and ^{13}C NMR spectroscopic data and on elemental analysis.

In conclusion, an efficient microwave-assisted synthetic method for 5-benzoylamino-2-(aralkylsulfanyl)pyrimidin-4(3*H*)-one derivatives **3**–**5** from 4-(1-ethoxyalkylidene)-2-phenyl-1,3-oxazol-5(4*H*)-ones **1** and *S*-aralkyl-substituted isothiouronium halides **2**, has been elaborated.

Melting points (uncorrected) were determined with an Electrothermal 9100 apparatus. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded with a Varian 800 FT-IR. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Bruker AMX 400 spectrometer using tetramethylsilane as internal standard and DMSO-d_6 as solvent. X-ray crystal analysis was performed with a Bruker Smart APEX CCD diffractometer with Mo K_α-radiation at 100 K. 4-(Ethoxymethylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one (**1a**) was purchased from Acros Organics. 4-(1-Ethoxyethylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one[9] (**1b**) and 4-(1-ethoxypropylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one[10] (**1c**) were prepared according to the literature. *S*-Benzylisothiouronium chloride (**2a**), *S*-(4-fluorobenzyl)isothiouronium bromide (**2b**), *S*-(2-chlorobenzyl)isothiouronium chloride (**2c**), *S*-(3-chloro)benzylisothiouronium chloride (**2d**), *S*-(4-chlorobenzyl)isothiouronium chloride (**2e**), *S*-(4-bromobenzyl)isothiouronium bromide (**2f**) and *S*-(4-methylbenzyl)isothiouronium bromide (**2g**) were prepared from thiourea and the respective aralkyl halide according to literature procedures.[11] Microwave-assisted syntheses of compounds **3**–**5** were carried out with a CEM Focused Microwave System, Model Discover.

Preparation of 3, 4 and 5; General Procedures

Compounds 3; Procedure A

4-(Ethoxymethylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one (**1a**; 217 mg, 1 mmol), the respective *S*-aralkyl-substituted isothiouronium halogenide **2** (1 mmol), Et_3N (200 mg, 2 mmol) and EtOH (5 mL) were added into a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar. The tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation (Discover mode; power: 150 W; ramp time: 30 sec.; hold time as indicated in Table 1; temperature: 100 °C; pressure: 10 bar; PowerMax-cooling mode). The reaction mixture was allowed to cool to r.t. and transferred to a round-bottomed flask. The solvent was evaporated, EtOH–H_2O (1:1, 10 mL) was added, and the precipitate was collected. Recrystallization from MeOH furnished analytically pure products.

Table 1 Synthesis of 5-Benzoylamino-2-(aralkylsulfanyl)pyrimidin-4(3*H*)-ones **3**–**5**[a]

Product	R^1	R^2	Hold time (min)	Yield (%)
3a	H	Bn	5	67
3b	H	4-$FC_6H_4CH_2$	5	70
3c	H	2-$ClC_6H_4CH_2$	5	64
3d	H	3-$ClC_6H_4CH_2$	5	69
3e	H	4-$ClC_6H_4CH_2$	5	66
3f	H	4-$BrC_6H_4CH_2$	5	65
3g	H	4-$MeC_6H_4CH_2$	5	73
4a	Me	Bn	10	48
4b	Me	4-$FC_6H_4CH_2$	10	45
4c	Me	2-$ClC_6H_4CH_2$	10	55
4d	Me	3-$ClC_6H_4CH_2$	5	52
4e	Me	4-$ClC_6H_4CH_2$	10	56
4f	Me	4-$BrC_6H_4CH_2$	5	60
4g	Me	4-$MeC_6H_4CH_2$	10	70
5a	Et	Bn	10	52
5b	Et	4-$FC_6H_4CH_2$	5	60
5c	Et	3-$ClC_6H_4CH_2$	10	60
5d	Et	4-$BrC_6H_4CH_2$	5	69
5e	Et	4-$MeC_6H_4CH_2$	5	67

[a] Microwave-assisted synthesis of compounds **3**–**5** was carried out using a CEM Corporation Focused Microwave System, Model Discover. Parameters for compounds **3**–**5**: Discover mode; power: 150 W; ramp time: 0.5 min; temperature: 100 °C; pressure: 10 bar; PowerMax-cooling.

Compounds 4; Procedure B

4-(1-Ethoxyethylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one (**1b**; 463 mg, 2 mmol), the respective *S*-aralkyl-substituted isothiouronium halogenide **2** (2 mmol), Et_3N (400 mg, 4 mmol) and EtOH (5 mL) were reacted according to Procedure A. After completion, the solvent was evaporated, EtOH–H_2O (1:1, 15 mL) was added, and the precipitate was collected. Recrystallization from MeOH furnished analytically pure products.

Compounds 5; Procedure C

4-(1-Ethoxypropylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one (**1c**; 245 mg, 1 mmol), the respective *S*-aralkyl-substituted isothiouronium halogenide **2** (1 mmol), Et_3N (200 mg, 2 mmol) and EtOH (5 mL) were reacted according to Procedure A. After completion, the solvent was evaporated, EtOH–H_2O (1:1, 10 mL) was added, and the

precipitate was collected. Recrystallization from MeOH furnished analytically pure products.

***N*-[2-(Benzylsulfanyl)-6-oxo-1,6-dihydropyrimidin-5-yl]benzamide (3a)**
Yield: 227 mg (67%); colorless solid; mp 254 °C (Lit.[6] 251–253 °C).

IR (KBr): 3368, 1671, 1638 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.44 (s, 2 H, $ArCH_2$), 7.24–7.64 (m, 8 H, ArH), 7.94 (d, *J* = 7.3 Hz, 2 H, ArH), 8.55 (s, 1 H, ArH), 9.32 (br s, 1 H, NH), 13.25 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 32.7, 127.3, 127.4, 128.4, 128.5, 129.0, 131.9, 133.4, 137.0, 165.1.

Anal. Calcd for $C_{18}H_{15}N_3O_2S$: C, 64.08; H, 4.48; N, 12.45; S, 9.50. Found: C, 63.97; H, 4.56; N, 12.37; S, 9.67.

***N*-{2-[(4-Fluorobenzyl)sulfanyl]-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (3b)**
Yield: 250 mg (70%); colorless solid; mp 264 °C.

IR (KBr): 3369, 1674, 1643 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.43 (s, 2 H, $ArCH_2$), 7.11–7.99 (m, 9 H, ArH), 8.57 (s, 1 H, ArH), 9.30 (br s, 1 H, NH), 13.19 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 32.9, 115.2 (d, $^2J_{C–F}$ = 20.8 Hz), 127.4, 128.5, 131.0 (d, $^3J_{C–F}$ = 8.5 Hz), 131.9, 133.4 (d, $^4J_{C–F}$ = 3.1 Hz), 133.5, 161.3 (d, $^1J_{C–F}$ = 243.5 Hz), 165.1.

Anal. Calcd for $C_{18}H_{14}FN_3O_2S$: C, 60.83; H, 3.97; N, 11.82; S, 9.02. Found: C, 60.77; H, 4.22; N, 11.76; S, 9.12.

***N*-{2-[(2-Chlorobenzyl)sulfanyl]-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (3c)**
Yield: 237 mg (64%); colorless solid; mp 244 °C.

IR (KBr): 3368, 1670, 1639 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.53 (s, 2 H, $ArCH_2$), 7.27–8.00 (m, 9 H, ArH), 8.58 (s, 1 H, ArH), 9.30 (br s, 1 H, NH), 13.27 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 31.8, 127.3, 127.4, 128.5, 129.4, 129.4, 131.4, 131.9, 133.3, 133.5, 134.4, 165.1.

Anal. Calcd for $C_{18}H_{14}ClN_3O_2S$: C, 58.14; H, 3.79; N, 11.30; S, 8.62. Found: C, 57.99; H, 3.91; N, 11.22; S, 8.60.

***N*-{2-[(3-Chlorobenzyl)sulfanyl]-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (3d)**
Yield: 258 mg (69%); colorless solid; mp 237 °C.

IR (KBr): 3406, 1685, 1647 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.44 (s, 2 H, $ArCH_2$), 7.31–7.96 (m, 9 H, ArH), 8.56 (s, 1 H, ArH), 9.30 (br s, 1 H, NH), 13.24 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 32.9, 127.2, 127.4, 127.7, 128.5, 128.7, 130.2, 131.9, 132.8, 133.6, 139.9, 165.1.

Anal. Calcd for $C_{18}H_{14}ClN_3O_2S$: C, 58.14; H, 3.79; N, 11.30; S, 8.62. Found: C, 57.98; H, 3.86; N, 11.21; S, 8.60.

***N*-{2-[(4-Chlorobenzyl)sulfanyl]-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (3e)**
Yield: 245 mg (66%); colorless solid; mp 265 °C.

IR (KBr): 3367, 1676, 1645 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.43 (s, 2 H, $ArCH_2$), 7.35–7.98 (m, 9 H, ArH), 8.56 (s, 1 H, ArH), 9.30 (br s, 1 H, NH), 13.23 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 32.8, 127.3, 128.3, 128.5, 130.8, 131.9, 131.9, 133.5, 136.4, 154.8, 158.9, 165.1.

Anal. Calcd for $C_{18}H_{14}ClN_3O_2S$: C, 58.14; H, 3.79; N, 11.30; S, 8.62. Found: C, 58.01; H, 3.78; N, 11.25; S, 8.88.

***N*-{2-[(4-Bromobenzyl)sulfanyl]-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (3f)**
Yield: 271 mg (65%); colorless solid; mp 260 °C.

IR (KBr): 3365, 1676, 1645 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 4.41 (s, 2 H, $ArCH_2$), 7.35–7.99 (m, 9 H, ArH), 8.55 (s, 1 H, ArH), 9.30 (br s, 1 H, NH), 13.25 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 32.9, 120.4, 127.3, 128.5, 131.1, 131.2, 131.9, 133.5, 136.8, 165.1.

Anal. Calcd for $C_{18}H_{14}BrN_3O_2S$: C, 51.93; H, 3.39; N, 10.09; S, 7.70. Found: C, 51.91; H, 3.44; N, 10.12; S, 7.81.

***N*-{2-[(4-Methylbenzyl)sulfanyl]-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (3g)**
Yield: 257 mg (73%); colorless solid; mp 260 °C.

IR (KBr): 3363, 1642 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.27 (s, 3 H, CH_3), 4.39 (s, 2 H, $ArCH_2$), 7.13 (d, *J* = 7.8 Hz, 2 H, ArH), 7.31 (d, *J* = 8.1 Hz, 2 H, ArH), 7.45–7.66 (m, 3 H, ArH), 7.88–8.01 (m, 2 H, ArH), 8.56 (s, 1 H, ArH), 9.28 (br s, 1 H, NH), 13.21 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.6, 33.5, 127.4, 128.5, 128.9, 129.0, 131.9, 133.5, 133.8, 136.5, 165.1.

Anal. Calcd for $C_{19}H_{17}N_3O_2S$: C, 64.94; H, 4.88; N, 11.96; S, 9.12. Found: C, 64.84; H, 4.83; N, 11.92; S, 9.06.

***N*-[2-(Benzylsulfanyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl]benzamide (4a)**
Yield: 338 mg (48%); colorless solid; mp 264 °C.

IR (KBr): 3270, 1665, 1640 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.18 (s, 3 H, CH_3), 4.42 (s, 2 H, $ArCH_2$), 7.22–7.63 (m, 8 H, ArH), 7.97 (d, *J* = 7.3 Hz, 2 H, ArH), 9.60 (br s, 1 H, NH), 12.93 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.4, 33.7, 127.2, 127.6, 128.3, 128.3, 129.0, 131.6, 133.7, 137.3, 165.2.

Anal. Calcd for $C_{19}H_{17}N_3O_2S$: C, 64.94; H, 4.88; N, 11.96; S, 9.12. Found: C, 64.87; H, 5.09; N, 11.99; S, 9.28.

***N*-{2-[(4-Fluorobenzyl)sulfanyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (4b)**
Yield: 332 mg (45%); colorless solid; mp 286 °C.

IR (KBr): 3269, 1665, 1638 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.18 (s, 3 H, CH_3), 4.41 (s, 2 H, $ArCH_2$), 7.08–7.20 (m, 2 H, ArH), 7.45–7.63 (m, 5 H, ArH), 7.97 (d, *J* = 7.3 Hz, 2 H, ArH), 9.58 (br s, 1 H, NH), 12.92 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.4, 32.8, 115.1 (d, $^2J_{C–F}$ = 21.1 Hz), 127.6, 128.3, 131.1 (d, $^3J_{C–F}$ = 8.3 Hz), 131.6, 133.7, 161.3 (d, $^1J_{C–F}$ = 243.8 Hz), 165.2.

Anal. Calcd for $C_{19}H_{16}FN_3O_2S$: C, 61.78; H, 4.37; N, 11.37; S, 8.68. Found: C, 61.92; H, 4.48; N, 11.38; S, 8.28.

***N*-{2-[(2-Chlorbenzyl)sulfanyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (4c)**
Yield: 425 mg (55%); colorless solid; mp 272 °C.

IR (KBr): 3259, 1670, 1638 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.20 (s, 3 H, CH_3), 4.52 (s, 2 H, $ArCH_2$), 7.28–7.70 (m, 7 H, ArH), 7.97 (d, J = 7.3 Hz, 2 H, ArH), 9.61 (br s, 1 H, NH), 12.96 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.3, 31.8, 127.2, 127.6, 128.3, 129.4, 131.5, 133.3, 133.7, 134.7, 165.2.

Anal. Calcd for $C_{19}H_{16}ClN_3O_2S$: C, 59.14; H, 4.18; N, 10.89; S, 8.31. Found: C, 59.09; H, 4.32; N, 10.84; S, 8.07.

***N*-{2-[(3-Chlorobenzyl)sulfanyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (4d)**
Yield: 402 mg (52%); colorless solid; mp 256 °C.

IR (KBr): 3269, 1665, 1638 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.18 (s, 3 H, CH_3), 4.41 (s, 2 H, $ArCH_2$), 7.29–7.63 (m, 7 H, ArH), 7.97 (d, J = 7.6 Hz, 2 H, ArH), 9.59 (br s, 1 H, NH), 12.96 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.3, 33.0, 127.1, 127.6, 127.8, 128.3, 129.0, 130.1, 131.5, 132.7, 133.7, 140.2, 165.2.

Anal. Calcd for $C_{19}H_{16}ClN_3O_2S$: C, 59.14; H, 4.18; N, 10.89; S, 8.31. Found: C, 59.15; H, 4.24; N, 10.86; S, 7.94.

***N*-{2-[(4-Chlorobenzyl)sulfanyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (4e)**
Yield: 433 mg (56%); colorless solid; mp 287 °C.

IR (KBr): 3323, 3263, 1664, 1638 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.17 (s, 3 H, CH_3), 4.41 (s, 2 H, $ArCH_2$), 7.35–7.62 (m, 7 H, ArH), 7.97 (d, J = 7.3 Hz, 2 H, ArH), 9.58 (br s, 1 H, NH), 12.93 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.4, 32.9, 127.6, 128.3, 130.9, 131.5, 131.8, 133.7, 136.7, 165.2.

Anal. Calcd for $C_{19}H_{16}ClN_3O_2S$: C, 59.14; H, 4.18; N, 10.89; S, 8.31. Found: C, 59.11; H, 4.31; N, 10.83; S, 8.07.

***N*-{2-[(4-Bromobenzyl)sulfanyl]-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (4f)**
Yield: 516 mg (60%); colorless solid; mp 286 °C.

IR (KBr): 3327, 3264, 1664, 1638 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.17 (br s, 3 H, CH_3), 4.39 (s, 2 H, $ArCH_2$), 7.36–7.64 (m, 7 H, ArH), 7.97 (d, J = 7.1 Hz, 2 H, ArH), 9.57 (br s, 1 H, NH), 12.92 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.4, 32.9, 120.3, 127.6, 128.3, 131.2, 131.3, 131.5, 133.7, 137.1, 165.2.

Anal. Calcd for $C_{19}H_{16}BrN_3O_2S$: C, 53.03; H, 3.75; N, 9.76; S, 7.45. Found: C, 53.01; H, 3.87; N, 9.73; S, 7.14.

***N*-{4-Methyl-2-[(4-methylbenzyl)sulfanyl]-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (4g)**
Yield: 512 mg (70%); colorless solid; mp 274 °C.

IR (KBr): 3268, 1671, 1643 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.17 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 4.38 (s, 2 H, $ArCH_2$), 7.13 (m, J = 7.8 Hz, 2 H, ArH), 7.33 (m, J = 7.8 Hz, 2 H, ArH), 7.45–7.64 (m, 3 H, ArH), 7.97 (d, J = 7.6 Hz, 2 H, ArH), 9.58 (br s, 1 H, NH), 12.89 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.4, 20.6, 33.6, 127.6, 128.3, 128.9, 129.0, 131.5, 133.8, 134.1, 136.4, 165.2.

Anal. Calcd for $C_{20}H_{19}N_3O_2S$: C, 65.73; H, 5.24; N, 11.50; S, 8.77. Found: C, 65.68; H, 5.23; N, 11.46; S, 8.96.

***N*-[2-(Benzylsulfanyl)-4-ethyl-6-oxo-1,6-dihydropyrimidin-5-yl]benzamide (5a)**
Yield: 190 mg (52%); colorless solid; mp 239 °C.

IR (KBr): 3453, 3280, 1667, 1642 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.15 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 2.43–2.56 (m, 2 H, CH_2CH_3, overlapping with solvent signal), 4.45 (s, 2 H, $ArCH_2$), 7.22–7.62 (m, 8 H, ArH), 7.96 (d, J = 7.3 Hz, 2 H, ArH), 9.52 (s, 1 H, NH), 12.91 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 11.5, 26.0, 33.7, 127.2, 127.5, 128.3, 128.3, 128.9, 131.5, 133.8, 137.5, 165.6.

Anal. Calcd for $C_{20}H_{19}N_3O_2S$: C, 65.73; H, 5.24; N, 11.50; S, 8.77. Found: C, 65.46; H, 5.27; N, 11.40; S, 9.06.

***N*-{4-Ethyl-2-[(4-fluorobenzyl)sulfanyl]-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (5b)**
Yield: 231 mg (60%); colorless solid; mp 247 °C.

IR (KBr): 3277, 1670, 1642 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.15 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 2.43–2.54 (m, 2 H, CH_2CH_3, overlapping with solvent signal), 4.44 (s, 2 H, $ArCH_2$), 7.16 (t, J = 8.7 Hz, 2 H, ArH), 7.46–7.62 (m, 5 H, ArH), 7.97 (d, J = 7.3 Hz, 2 H, ArH), 9.54 (br s, 1 H, NH), 12.93 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 11.6, 26.0, 32.8, 115.1 (d, $^2J_{C–F}$ = 21.1 Hz), 127.6, 128.3, 130.9 (d, $^3J_{C–F}$ = 8.3 Hz), 131.6, 133.7, 133.8, 161.3 (d, $^1J_{C–F}$ = 243.8 Hz), 165.6.

Anal. Calcd for $C_{20}H_{18}FN_3O_2S$: C, 62.65; H, 4.73; N, 10.96; S, 8.36. Found: C, 62.36; H, 4.72; N, 10.87; S, 8.17.

***N*-{2-[(3-Chlorobenzyl)sulfanyl]-4-ethyl-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (5c)**
Yield: 239 mg (60%); colorless solid; mp 242 °C.

IR (KBr): 3269, 1671, 1643 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.15 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 2.43–2.53 (m, 2 H, CH_2CH_3, overlapping with solvent signal), 4.43 (s, 2 H, $ArCH_2$), 7.30–7.62 (m, 7 H, ArH), 7.96 (d, J = 7.6 Hz, 2 H, ArH), 9.54 (br s, 1 H, NH), 12.96 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 11.5, 26.0, 32.9, 127.1, 127.5, 128.3, 128.8, 130.1, 131.5, 132.7, 133.7, 140.5, 165.6.

Anal. Calcd for $C_{20}H_{18}ClN_3O_2S$: C, 60.07; H, 4.54; N, 10.51; S, 8.02. Found: C, 59.93; H, 4.48; N, 10.35; S, 7.78.

***N*-{2-[(4-Bromobenzyl)sulfanyl]-4-ethyl-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (5d)**
Yield: 307 mg (69%); colorless solid; mp 264 °C.

IR (KBr): 3445, 3273, 1674, 1641 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.14 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 2.42–2.54 (m, 2 H, CH_2CH_3, overlapping with solvent signal), 4.42 (s, 2 H, $ArCH_2$), 7.38–7.62 (m, 7 H, ArH), 7.96 (d, J = 7.3 Hz, 2 H, ArH), 9.53 (br s, 1 H, NH), 12.93 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 11.5, 26.0, 32.9, 120.2, 127.6, 128.3, 131.1, 131.2, 131.5, 133.8, 137.3, 165.6.

Anal. Calcd for $C_{20}H_{18}BrN_3O_2S$: C, 54.06; H, 4.08; N, 9.46; S, 7.22. Found: C, 54.33; H, 4.07; N, 9.44; S, 7.13.

***N*-{4-Ethyl-2-[(4-methylbenzyl)sulfanyl]-6-oxo-1,6-dihydropyrimidin-5-yl}benzamide (5e)**
Yield: 255 mg (67%); colorless solid; mp 249 °C.

IR (KBr): 3300, 1665, 1639 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.16 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 2.28 (s, 3 H, CH_3), 2.43–2.53 (m, 2 H, CH_2CH_3, overlapping with solvent signal), 4.40 (s, 2 H, $ArCH_2$), 7.13 (m, J = 7.8 Hz, 2 H, ArH), 7.33 (m, J = 7.8 Hz, 2 H, ArH), 7.47–7.62 (m, 3 H, ArH), 7.96 (d, J = 7.5 Hz, 2 H, ArH), 9.53 (br s, 1 H, NH), 12.88 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 11.5, 20.6, 26.0, 33.5, 127.6, 128.3, 128.8, 128.9, 131.5, 133.8, 134.3, 136.4, 165.6.

Anal. Calcd for $C_{21}H_{21}N_3O_2S$: C, 66.47; H, 5.58; N, 11.07; S, 8.45. Found: C, 66.46; H, 5.59; N, 11.01; S, 8.34.

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(8) CCDC 765698 contains the supplementary crystallographic data for the deposited structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Crystal data for compound **3a**: $C_{18}H_{15}N_3O_2S$; M_r = 337.40; orthorhombic; *Pca*2$_1$; *a* = 17.284(5), *b* = 5.8034(17), *c* = 31.641(9) Å; V = 3173.8(16) Å^3; T = 100 K; *Z* = 8; D_x = 1.412 Mg·m^{-3}; μ = 0.22 mm^{-1}; λ(Mo $K_α$) = 0.71073 Å; F(000) = 1408; 6062 independent reflections (R_{int} = 0.062), 4502 reflections with $I > 2δ(I)$; refinement method, full-matrix least-squares refinement on F^2; $R[F^2>2δ(F^2)]$ = 0.046, $wR(F^2)$ = 0.101, *S* = 1.06.

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