Regioselective Synthesis of 5*H*-Thiazolo[3,2-*a*]pyrimidin-5-ones from Morita–Baylis–Hillman Adduct Acetates under Solvent-Free and Base-Free Conditions

Weihui Zhong, Baoming Guo, Fuliang Lin, Yongliang Liu, Weike Su*

Key Laboratory of Pharmaceutical Engineering of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. of China
Fax +86(571)88320752; E-mail: suweike@zjut.edu.cn

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Abstract: 5*H*-Thiazolo[3,2-*a*]pyrimidin-5-ones were easily prepared in good to excellent yields with high regioselectivity by nucleophilic addition of thiazol-2-amines to Morita–Baylis–Hillman adduct acetates, followed by cyclization and a thermo-sigmatropic shift procedure under solvent-free and base-free conditions.

Key words: fused-ring systems, heterocycles, α,β-unsaturated esters, thiazol-2-amines, solvent-free, base-free

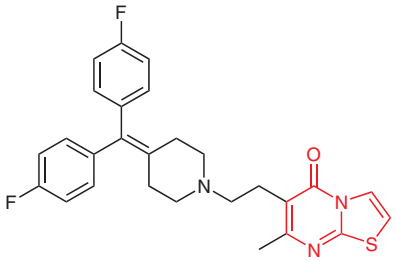


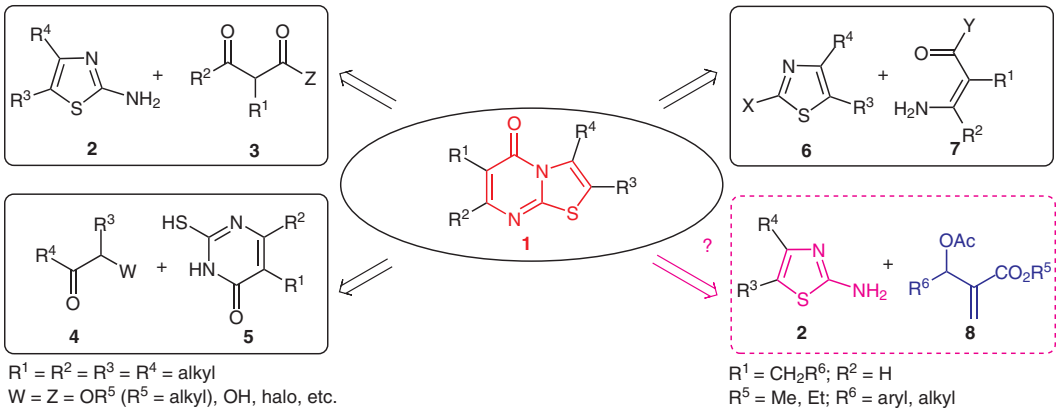
Figure 1 Structure of ritanserin

5*H*-Thiazolo[3,2-*a*]pyrimidin-5-ones are very important intermediates and widely used in pharmaceutical chemistry.[1] The compound ritanserin (Figure 1) has been described to have significant properties as a selective serotonin (5-HT_2) receptor antagonist. The starting materials in the reported synthetic routes for the 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one moiety remain synthetic bottlenecks.[2] During the last decades, several other researchers have focused on the synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones by different routes, but product yield and operational convenience have still remained a problem.[3]

The Baylis–Hillman reaction has proved to be a powerful tool for C–C bond-forming reactions, and has been used in an interesting series of densely functionalized molecules in operationally simple, one-pot, and completely atom-economical procedures.[4] Baylis–Hillman adducts can be widely used in organic synthesis and pharmaceutical chemistry.[5] During our previous studies towards the exploitation of the Baylis–Hillman reaction in heterocyclic chemistry to synthesize pharmaceutically valuable intermediates, we became aware that polyhydrochromenes, polyhydroquinolines, and 1,2,4-triazole derivatives are readily synthesized from Morita–Baylis–Hillman adduct acetates under solvent-free conditions.[6]

Today 'green chemistry' is becoming increasingly important. The synthesis of regioselective molecules is another important area, and the development of regioselective reactions that proceed under environmentally benign conditions is an extensively investigated field.[7]

Our approach to 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **1** is summarized by the retrosynthetic analysis under consideration of 'green chemistry' aspects shown in Scheme 1.



Scheme 1

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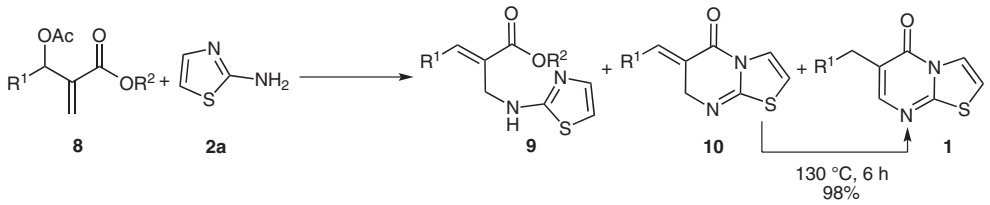
By analogy with our previous work, 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **1** and the relatively unstable intermediates 6-benzylidene-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **10** were formed by the reaction of thiazol-2-amine (**2a**) with the Morita–Baylis–Hillman adduct acetates **8** (Scheme 2).

Initially, the experiments were performed in ethanol solution in the presence of triethylamine with Morita–Baylis–Hillman adduct acetate **8aα** (R^1 = 2-ClC_6H_4, R^2 = Me) and thiazol-2-amine (**2a**) as the substrates under different conditions; the results are summarized in Table 1. When the reaction mixture was stirred at room temperature for six hours, **10a** was the main product in a yield of 88% (Table 1, entry 1), but was partially transformed into product **1a** at a higher reaction temperature (entry 2). When the reaction was carried out for a prolonged time at 80 °C, a slightly higher yield was obtained (entry 3). For higher yields of **1a**, the reaction under refluxing solvents such as toluene and xylene was studied (entries 4 and 5), but the results were unsatisfactory.

Our previous studies indicated that solvent-free conditions may result in increased reaction efficiency. The reaction was tried under solvent-free conditions at room temperature for six hours, and a 91% yield of **10a** was isolated (Table 1, entry 6). Surprisingly, a similar result could also be obtained in the absence of triethylamine (entry 7); this implied that triethylamine is not essential for the reaction. To consider the steric effects on the reaction, **8aβ** was used as the starting material under the same conditions, and the corresponding product **10a** was formed in a yield of 65% (Table 2, entry 1), with an intermediate **9aβ** isolated from the residue. Other substrates **8** were also investigated under these solvent-free and base-free conditions, and the corresponding products **10b–f** were isolated in satisfying yields (Table 2, entries 2–6). When the reaction temperature was increased to 80 °C for three hours, a mixture of **1a** (47%) and **10a** (43%) was obtained (Table 1, entry 8), and when the reaction time was extended to six hours, a higher yield of **1a** (64%) was obtained (entry 9). This finding encouraged us to conduct the reaction at 130 °C under solvent-free and base-free conditions for six hours, and, as expected, only product **1a** was isolated (90% yield) (Table 1, entry 10). Thus, the transformation from product **10a** to **1a** can be carried out at 130 °C for six hours in 98% yield (Scheme 2). This straightforward route represents an original and regioselective pathway to these pharmaceutically valuable heterocycles.

With the optimal reaction conditions established, a representative class of Morita–Baylis–Hillman adduct acetates **8** was examined, and the full results are summarized in Table 3. All reactions proceeded smoothly under the optimized conditions to produce products **1** in moderate to



Scheme 2 The reaction of Morita–Baylis–Hillman adduct acetates **8** with thiazol-2-amine (**2a**) under various conditions

Table 1 The Reaction of Morita–Baylis–Hillman Adduct Acetate **8aα** (R^1 = 2-ClC_6H_4, R^2 = Me) with Thiazol-2-amine (**2a**) under Various Conditions[a]

Entry	Ratio **8aα**/**2a**/Et_3N	Solvent	Temp (°C)	Time (h)	Yield of **10a**[b] (%)	Yield of **1a**[b] (%)
1	1:1:1.2	EtOH	r.t.	6	88	–
2	1:1:1.2	EtOH	80	3	43	44[c]
3	1:1:1.2	EtOH	80	5	44	49[c]
4	1:1:1.2	toluene	110	3	25	55[c]
5	1:1:1.2	xylene	150	3	15	36[c]
6	1:1:1.2	none	r.t.	6	91	–
7	1:1:0	none	r.t.	6	90	–
8	1:1:0	none	80	3	43	47[c]
9	1:1:0	none	80	6	25	64[c]
10	1:1:0	none	130	6	–	90

[a] See also Scheme 2. Reagents and conditions: **8aα** (1.0 mmol), **2a** (1.0 mmol), Et_3N (0 or 1.2 mmol), solvent or solvent-free.
[b] Isolated yield of **10a** (R^1 = 2-ClC_6H_4) and **1a** (R^1 = 2-ClC_6H_4) based on **8aα** (R^1 = 2-ClC_6H_4, R^2 = Me).
[c] Isolated yields after purification by column chromatography (silica gel, CH_2Cl_2–MeOH, 30:1).

Table 2 Synthesis of 6-Benzylidene-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **10**[a]

Entry	Substrate **8**	R^1	R^2	Product **10**	Yield[b] (%)
1	**8aβ**	2-ClC_6H_4	Et	**10a**	65[c]
2	**8bα**	Ph	Me	**10b**	91
3	**8dα**	4-ClC_6H_4	Me	**10c**	91
4	**8eα**	2-Cl-6-FC_6H_3	Me	**10d**	86
5	**8fα**	4-FC_6H_4	Me	**10e**	87
6	**8hα**	3-$MeOC_6H_4$	Me	**10f**	80

[a] See also Scheme 2. Reagents and conditions: **8** (1.0 mmol), **2a** (1.0 mmol), no solvent, r.t., 6 h.
[b] Isolated yields of products **10** based on **8**.
[c] Product **9aβ** was isolated in 20% yield after column chromatography (silica gel, PE–EtOAc, 4:1).

high yields. A range of aryl- and hetaryl-substituted substrates **8**, with various steric and electronic influences, were examined. As shown in Table 3, aryl-substituted substrates **8** were found to be suitable for this transformation, generally providing the corresponding products **1** in good to excellent yields and regioselectivities. To investigate the steric effect of the ester moiety, an ethyl ester was used in place of the methyl ester; this resulted in decreased yields of **1** with increased bulk of the ester moiety (Table 3, entries 4–6), matching the results of our previous studies.[6]

Interestingly, the reaction of thiazol-2-amine **2a** with the Morita–Baylis–Hillman adduct acetate **8m**, derived from 3-methylbutanal and methyl acrylate, gave the normal product **1m**, rather than the Michael-addition-type products **11a** or **11b** (Scheme 3), analogously to our previous report.[6] The reactions of 4-methylthiazol-2-amine (**2b**) and 5-methylbenzothiazol-2-amine (**2c**) with acetates **8** were also examined, and the results are summarized in Table 4.

The above results provided a possible explanation for the formation of compounds **1**, and this is shown in Scheme 4. The formation of compounds **1** might include a three-step successive reaction. Firstly, the reaction of Morita–Baylis–Hillman adduct acetates **8** with thiazol-2-amines **2**

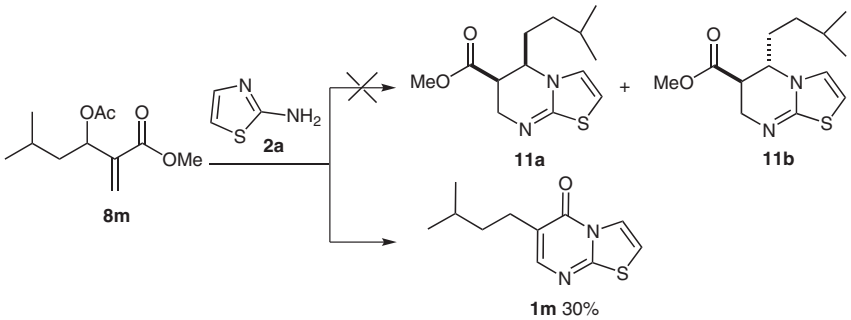
Table 3 Synthesis of 6-(Arylmethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **1**[a]

Entry	Substrate **8**	R^1	R^2	Time[b] (h)	Product **1**	Yield[c] (%)
1	**8aα**	2-ClC_6H_4	Me	6	**1a**	90
2	**8bα**	Ph	Me	4	**1b**	92
3	**8cα**	4-ClC_6H_4	Me	4	**1c**	82
4	**8aβ**	2-ClC_6H_4	Et	6	**1a**	65
5	**8bβ**	Ph	Et	5	**1b**	73
6	**8cβ**	4-ClC_6H_4	Et	5	**1c**	65
7	**8dα**	2-Cl-6-FC_6H_3	Me	3	**1d**	90
8	**8eα**	4-FC_6H_4	Me	4	**1e**	84
9	**8fα**	3-$MeOC_6H_4$	Me	4	**1f**	85
10	**8gα**	3,4-$Me_2C_6H_3$	Me	3	**1g**	91
11	**8hα**	3-$O_2NC_6H_4$	Me	4	**1h**	91
12	**8iα**	2-thienyl	Me	6	**1i**	65
13	**8jα**	2-furyl	Me	6	**1j**	60
14	**8kα**	4-methylthiazol-5-yl	Me	6	**1k**	61
15	**8lα**	2-chloro-3-quinolyl	Me	6	**1l**	62

[a] See also Scheme 2. Reagents and conditions: **8** (1.0 mmol), **2a** (1.0 mmol), no solvent, 130 °C.
[b] The reaction progress was monitored by TLC.
[c] Isolated yields of products **1** based on **8**.

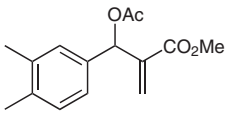
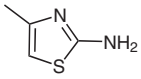
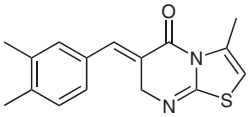
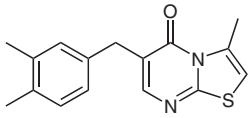
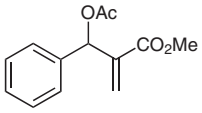
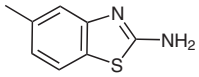
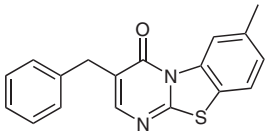
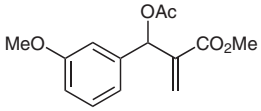
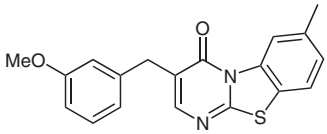
gives S_N2' intermediates **9**, which readily isomerize into **12**; cyclization follows to produce compounds **10**, which, finally, via a thermo-sigmatropic proton shift provide target compounds **1**.

In conclusion, we have developed a simple, efficient, and 'green' method for the synthesis of various 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **1** and benzylidene-6,7-dihydro-5*H*-thiazolo-[3,2-*a*]pyrimidin-5-ones **10** in high yields under solvent-free and base-free conditions. To the best of our knowledge, it is the first time that Morita–Baylis–Hillman adduct acetates have been applied under solvent-free and base-free conditions in the synthesis of heterocycles.

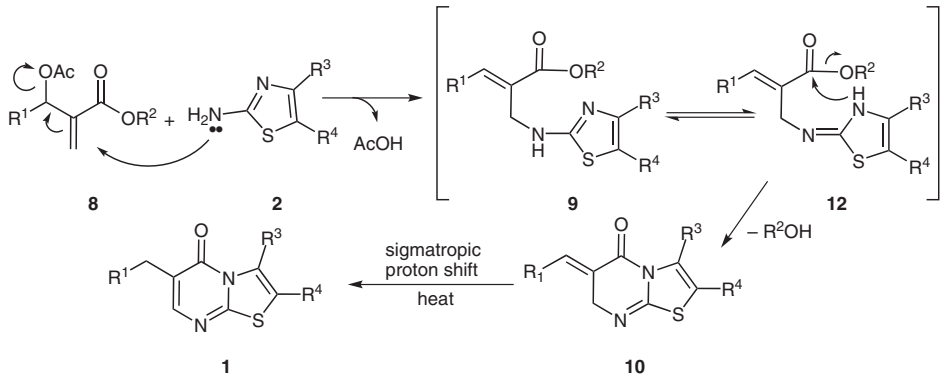


Scheme 3 *Reagents and conditions*: **8m** (1 equiv), **2a** (1 equiv), K_2CO_3 (1.1 equiv), 70 °C, 1 h, then 130 °C, 3 h.

Table 4 Reactions of Thiazol-2-amine Derivatives **2b** and **2c** with Acetates **8**[a]

Entry	Substrate **8**	Substrate **2**	Product **10** or **1**	Yield[b] (%)
1[c]	**8gα** 	**2b** 	**10g** 	89
2	**8gα**	**2b**	**1n** 	87
3	**8bα** 	**2c** 	**1o** 	82
4	**8hα** 	**2c**	**1p** 	85

[a] Reagents and conditions: **8** (1 equiv), **2** (1 equiv), no solvent, no base, 130 °C, 3 h.
[b] Isolated yield based on **8**.
[c] Reagents and conditions: **8gα** (1 equiv), **2b** (1 equiv), no solvent, no base, r.t., 6 h.



Scheme 4 Proposed mechanism for the formation of 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones

Melting points were determined on a Büchi B-540 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet Aviatar-370 instrument; samples were prepared as KBr plates. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian 400-MHz spectrometer. Samples were prepared in $CDCl_3$ or DMSO-d_6 with TMS (δ = 0) as internal standard or in TFA-*d* (δ = 11.5) with 1,4-dioxane (δ = 3.85) as standard at r.t. Elemental analyses were carried out on a Vario EL III instrument. Mass spectra were obtained on a Thermo Finnigan LCQ-Advantage spectrometer. HRMS (EI) was carried out on an APEX (Bruker) mass III spectrometer. Analytical grade solvents and commercially available reagents were used as received. For chromatography, silica gel (200–300 mesh) purchased from Qingdao Haiyang Chemical Co., Ltd. was used. The Morita–Baylis–Hillman adduct acetates **8**[4b] and thiazol-2-amines **2**[8] were synthesized according to literature procedures.

(*E*)-6-Benzylidene-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones 10; General Procedure

A mixture of the appropriate acetate **8** (1 mmol) and thiazol-2-amine **2** (1 mmol) was stirred at r.t. for 6 h. The mixture was washed with EtOH (2 × 5 mL), filtered, and dried in vacuo to give the corresponding pure product **10**.

Ethyl (*E*)-3-(2-Chlorophenyl)-2-[(thiazol-2-ylamino)methyl]acrylate (9aβ); Typical Procedure

A mixture of **8aβ** (282 mg, 1 mmol) and **2a** (101 mg, 1 mmol) was stirred at r.t. for 6 h. The mixture was washed with EtOH (2 × 5 mL), filtered, and dried in vacuo; this gave pure product **10a**. Concentration of the filtrate and purification of the residue by column chromatography (silica gel, PE–EtOAc, 4:1) afforded **9aβ**.

6-(Arylmethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones 1; General Procedure

A magnetically stirred mixture of the appropriate acetate **8** (1 mmol) and thiazol-2-amine **2** (1 mmol) was heated to 130 °C under an atmosphere of N_2 for the amount of time indicated in Table 3. The mixture was washed with EtOH (2 × 5 mL), filtered, and dried in vacuo; this gave pure product **1**.

Ethyl (*E*)-3-(2-Chlorophenyl)-2-[(thiazol-2-ylamino)methyl]acrylate (9aβ)

Pale solid; mp 125.2–126.6 °C; R_f = 0.40 (PE–EtOAc, 4:1).

IR (KBr): 3141, 3045, 1704, 1602, 1507, 749, 715 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.62 (br, 1 H, N*H*), 3.72 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 3.98 (d, *J* = 1.0 Hz, 2 H, $NHCH_2$), 6.82 (d, *J* = 4.5 Hz, 1 H, NCH=C*H*S), 7.11 (d, *J* = 5.0 Hz, 1 H, SCH=C*H*N), 7.24–7.27 (m, 2 H, Ar*H*), 7.33 (s, 1 H, C*H*CC=O), 7.40 (d, *J* = 7.0 Hz, 1 H, Ar*H*), 7.41 (d, *J* = 7.0 Hz, 1 H, Ar*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.4, 32.0, 58.4, 109.9, 123.7, 124.1, 127.3, 128.6, 129.8, 131.9, 132.0, 134.4, 135.3, 163.8, 167.2.

MS (EI): *m*/*z* (%) = 321.1 [M^+], 241.1 (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{15}H_{15}ClN_2O_2S$: 322.0543; found: 322.0536.

(*E*)-6-(2-Chlorobenzylidene)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (10a)

Pale yellow solid; mp 201.7–202.5 °C; R_f = 0.35 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3141, 3045, 1647, 1602, 1507, 747, 718 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 5.16 (s, 2 H, CH_2), 6.92 (d, *J* = 4.4 Hz, 1 H, NCH=C*H*S), 7.29 (d, *J* = 4.5 Hz, 1 H, SCH=C*H*N), 7.40–7.48 (m, 3 H, Ar*H*), 7.57–7.60 (m, 1 H, Ar*H*), 7.66 (s, 1 H, COC=C*H*).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 47.1, 106.3, 125.3, 127.2, 129.4, 129.6, 130.4, 130.4, 131.3, 132.6, 133.3, 165.9, 172.6.

ESI-MS: *m*/*z* (%) = 277.2 [M^+ + 1] (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_9ClN_2OS$: 276.0124; found: 276.0126.

(*E*)-6-Benzylidene-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (10b)

Pale yellow solid; mp 194.7–195.8 °C; R_f = 0.40 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3129, 3037, 1653, 1601, 1518, 750, 692 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 5.28 (s, 2 H, CH_2), 6.91 (d, *J* = 4.5 Hz, 1 H, NCH=C*H*S), 7.32 (d, *J* = 4.5 Hz, 1 H, SCH=C*H*N), 7.41–7.45 (m, 3 H, Ar*H*), 7.48–7.50 (m, 2 H, Ar*H*), 7.62 (s, 1 H, COC=C*H*).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 48.1, 106.6, 123.3, 129.2 (CH × 2), 129.3, 130.0, 130.4 (CH × 2), 135.1, 135.4, 166.6, 172.8.

ESI-MS: *m*/*z* (%) = 242.1 [M^+] (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_{10}N_2OS$: 242.0514; found: 242.0520.

(*E*)-6-(4-Chlorobenzylidene)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (10c)

Yellow solid; mp 228.9–229.8 °C; R_f = 0.30 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3137, 3062, 1634, 1591, 1482, 813 cm^{-1}.

^1H NMR (400 MHz, TFA-*d*): δ = 5.57 (s, 2 H, CH_2), 7.26 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.36–7.41 (m, 3 H, Ar*H*), 7.53 (d, *J* = 4 Hz, 1 H, SCH=C*H*N), 7.16 (s, 1 H, COC=C*H*).

^{13}C NMR (100 MHz, TFA-*d*): δ = 49.8, 115.2, 125.4, 130.4 (CH × 2), 131.9, 131.0, 132.5 (CH × 2), 140.0, 141.2, 147.7, 162.3.

ESI-MS: *m*/*z* (%) = 277 [M^+ + 1] (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_9ClN_2OS$: 276.0124; found: 276.0128.

(*E*)-6-(2-Chloro-6-fluorobenzylidene)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (10d)

Yellow solid; mp 235.2–235.6 °C; R_f = 0.35 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3136, 3094, 1655, 1609, 1505, 907, 790 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 4.85 (s, 2 H, CH_2), 6.94 (d, *J* = 4.5 Hz, 1 H, NCH=C*H*S), 7.28 (d, *J* = 4.5 Hz, 1 H, SCH=C*H*N), 7.36 (s, 1 H, COC=C*H*), 7.39 (t, *J* = 9 Hz, 1 H, Ar*H*), 7.47 (d, *J* = 7.5 Hz, 1 H, Ar*H*), 7.52 (dd, *J* = 7.0, 8.0 Hz, 1 H, Ar*H*).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 47.2 (d, *J* = 10.0 Hz), 106.6, 115.0 (d, *J* = 22.5 Hz), 120.7, 121.5 (d, *J* = 18.8 Hz), 125.7, 128.5, 129.5, 131.5, 133.8 (d, *J* = 5 Hz), 159.3 (d, *J* = 250 Hz), 165.5, 172.9.

MS (EI): *m*/*z* (%) = 294.1 [M^+] (5), 259.1 (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_8ClFN_2OS$: 294.0030; found: 294.0033.

(*E*)-6-(4-Fluorobenzylidene)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (10e)

Yellow solid; mp 226.3–228.5 °C; R_f = 0.30 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3141, 3043, 1644, 1584, 1523, 1506, 820, 705 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 5.26 (s, 2 H, CH_2), 6.92 (d, *J* = 4.5 Hz, 1 H, NCH=C*H*S), 7.31 (d, *J* = 4.5 Hz, 1 H, SCH=C*H*), 7.33 (d, *J* = 9 Hz, 2 H, Ar*H*), 7.51 (dd, *J* = 6, 9 Hz, 2 H, Ar*H*), 7.60 (s, 1 H, COC=C*H*N).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 47.6, 106.2, 115.7 (d, *J* = 21 Hz, CH × 2), 122.7, 129.5, 131.2, 132.2 (d, *J* = 8.7 Hz, CH × 2), 133.8, 161.2 (d, *J* = 246 Hz), 166.1, 172.4.

ESI-MS: *m*/*z* (%) 261.2 [M^+ + 1] (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_9FN_2OS$: 260.0420; found: 260.0426.

(*E*)-6-(3-Methoxybenzylidene)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (10f)

Yellow solid; mp 192.5–193.9 °C; R_f = 0.30 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3106, 3043, 1638, 1586, 1524, 1507, 821, 706 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.81 (s, 3 H, CH_3O), 3.81 (s, 3 H, CH_2), 6.91 (d, *J* = 4.8 Hz, 1 H, NCH=C*H*S), 6.99 (s, 1 H, Ar*H*), 7.00 (m, 2 H, Ar*H*), 7.35 (d, *J* = 4.8 Hz, 1 H, SCH=C*H*N), 7.40 (t, *J* = 8 Hz, 1 H, Ar*H*), 7.59 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 47.5, 55.1, 106.1, 114.4, 115.3, 122.0, 123.3, 129.5, 129.7, 134.9, 135.9, 159.3, 166.1, 172.3.

ESI-MS: *m*/*z* (%) = 273.4 [M^+ + 1] (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{14}H_{12}N_2O_2S$: 272.0619; found: 272.0624.

(*E*)-6-(3,4-Dimethylbenzylidene)-3-methyl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (10g)

Pale yellow solid; mp 162.3–163.7 °C; R_f = 0.35 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3182, 3121, 1705, 1592, 1512, 989 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.25 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 5.18 (s, 2 H, CH_2), 6.55 (d, *J* = 1.2 Hz, 1 H, CH_3C=C*H*S), 7.19 (d, *J* = 8 Hz, 1 H, Ar*H*), 7.25 (s, 1 H, Ar*H*), 7.26 (d, *J* = 7.2 Hz, 1 H, Ar*H*), 7.56 (s, 1 H, COC=C*H*).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.1, 19.2, 19.3, 46.1, 100.1, 120.6, 127.3, 129.8, 131.3, 132.3, 134.8, 136.6, 137.3, 137.5, 165.6, 172.4.

ESI-MS: *m/z* (%) = 285.2 [M$^+$ + 1] (100).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{16}H_{16}N_2OS$: 284.0983; found: 284.0988.

6-(2-Chlorobenzyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1a)
Colorless crystals; mp 201.5–202.2 °C; R_f = 0.35 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3108, 3072, 1645, 1630, 1496, 721 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.77 (s, 2 H, CH_2), 7.26 (d, *J* = 4.8 Hz, 1 H, NC=C*H*S), 7.29–7.32 (m, 2 H, Ar*H*), 7.37 (dd, *J* = 3.6, 6.0 Hz, 1 H, Ar*H*), 7.47 (dd, *J* = 3.6, 5.6 Hz, 1 H, Ar*H*), 7.75 (d, *J* = 4.8 Hz, 1 H, SCH=C*H*N), 7.99 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.3, 109.7, 121.5, 125.3, 127.2, 128.3, 129.2, 131.3, 1313, 133.3, 135.7, 163.8, 166.2.

ESI-MS: *m/z* (%) = 277 [M$^+$ + 1] (100).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{13}H_9ClN_2OS$: 276.0124; found: 276.0128.

6-Benzyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1b)
Pale yellow crystals; mp 229.9–227.5 °C; R_f = 0.30 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3104, 3061, 1637, 1619, 1487, 698 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.87 (s, 2 H, CH_2), 7.21–7.98 (m, 6 H, Ar*H*), 7.73 (d, *J* = 4.4 Hz, 1 H, SCH=C*H*N), 8.16 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.5, 109.7, 123.3, 125.4, 126.2, 128.3 (CH × 2), 128.9 (CH × 2), 133.8, 138.7, 163.7, 166.5.

ESI-MS: *m/z* (%) = 243.2 [M$^+$ + 1] (100).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{13}H_{10}N_2OS$: 242.0514; found: 242.0519.

6-(4-Chlorobenzyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1c)
Gray solid; mp 237.8–238.6 °C; R_f = 0.35 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3135, 3108, 1642, 1595, 1482, 794, 729, 766 cm^{-1}.

^{1}H NMR (400 MHz, TFA-*d*, 1,4-dioxane): δ = 3.81 (s, 2 H, CH_2), 7.02 (d, *J* = 7.2 Hz, 2 H, Ar*H*), 7.15 (d, *J* = 7.2 Hz, 2 H, Ar*H*), 7.51 (d, *J* = 4.0 Hz, 1 H, NCH=C*H*S), 7.75 (d, *J* = 4 Hz, 1 H, SCH=C*H*N), 8.15 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, TFA-*d*, 1,4-dioxane): δ = 33.0, 117.4, 125.4, 128.0, 128.8, 130.0 (CH × 2), 131.0 (CH × 2), 133.1, 135.0, 138.1, 162.2.

ESI-MS: *m/z* (%) = 277 [M$^+$ + 1] (100), 279 (35).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{13}H_9ClN_2OS$: 276.0124; found: 276.0128.

6-(2-Chloro-6-fluorobenzyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1d)
Pale solid; mp 239.8–240.7 °C; R_f = 0.30 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3156, 3046, 1645, 1618, 1490, 720 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.80 (s, 2 H, CH_2), 7.25–7.33 (m, 2 H, NCH=C*H*S, Ar*H*), 7.41–7.45 (m, 2 H, Ar*H*), 7.73 (d, *J* = 4.4 Hz, 1 H, SCH=C*H*N), 7.76 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.9, 109.8, 114.6 (d, *J* = 23 Hz), 120.7, 123.2 (d, *J* = 18 Hz), 125.5 (d, *J* = 24 Hz), 129.5 (d, *J* = 18 Hz), 129.7, 132.5, 134.8 (d, *J* = 5 Hz), 161.1 (d, *J* = 246 Hz), 163.9, 166.1.

ESI-MS: *m/z* (%) = 295 [M$^+$ + 1] (100).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{13}H_8ClFN_2OS$: 294.0030; found: 294.0035.

6-(4-Fluorobenzyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1e)
Yellow solid; mp 241.5–242.8 °C; R_f = 0.30 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3113, 3067, 1638, 1614, 1484, 803 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.66 (s, 2 H, CH_2), 7.09–7.13 (m, 2 H, Ar*H*), 7.26 (d, *J* = 4.8 Hz, 1 H, NCH=C*H*S), 7.31–7.34 (m, 2 H, Ar*H*), 7.72 (d, *J* = 4.8 Hz, 1 H, SCH=C*H*N), 7.16 (s, 1 H, COC=C*H*N).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 32.7, 109.7, 114.9 (d, *J* = 21 Hz, CH × 2), 123.2, 125.3, 130.7 (d, *J* = 7 Hz, CH × 2), 133.8, 134.8, 160.9 (d, *J* = 240 Hz), 163.7, 166.4.

ESI-MS: *m/z* (%) = 261 [M$^+$ + 1] (100).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{13}H_9FN_2OS$: 260.0420; found: 260.0424.

6-(3-Methoxybenzyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1f)
Gray solid; mp 204.0–204.8 °C; R_f = 0.35 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3104, 3025, 1637, 1606, 781, 705 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.65 (s, 2 H, CH_2), 3.73 (s, 3 H, CH_3O), 6.79 (dd, *J* = 2.8, 8.4 Hz, 1 H, Ar*H*), 6.82 (d, *J* = 9.2 Hz, 1 H, Ar*H*), 6.87 (s, 1 H, Ar*H*), 7.21 (t, *J* = 7.2 Hz, 1 H, Ar*H*), 7.26 (d, *J* = 4.4 Hz, 1 H, NCH=C*H*S), 7.73 (d, *J* = 4.4 Hz, 1 H, SCH=C*H*N), 8.13 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.5, 54.89, 109.7, 111.6, 114.8, 121.1, 123.3, 125.4, 129.3, 133.8, 140.2, 159.3, 163.7, 166.5.

ESI-MS: *m/z* (%) = 273 [M$^+$ + 1] (100).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{14}H_{12}N_2O_2S$: 272.0619; found: 272.0623.

6-(3,4-Dimethylbenzyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1g)
Pale yellow solid; mp 231.2–232.5 °C; R_f = 0.35 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3135, 1642, 1620, 1400, 766 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.18 (s, 6 H, CH_3), 3.58 (s, 2 H, CH_2), 6.98 (d, *J* = 7.5 Hz, 1 H, Ar*H*), 7.03 (s, 1 H, Ar*H*), 7.05 (d, *J* = 7.5 Hz, 1 H, Ar*H*), 7.24 (d, *J* = 4.5 Hz, 1 H, NCH=C*H*S), 7.72 (d, *J* = 4.5 Hz, 1 H, SCH=C*H*N), 8.06 (s, 1 H, COC=C*H*N).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.4, 19.9, 33.6, 110.1, 124.2, 125.9, 126.8, 129.9, 130.6, 134.1, 134.4, 136.3, 136.4, 164.1, 167.0.

ESI-MS: *m/z* (%) = 271 [M$^+$ + 1] (100).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{15}H_{14}N_2OS$: 270.0827; found: 270.0830.

6-(3-Nitrobenzyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1h)
Gray solid; mp 256.2–257.2 °C; R_f = 0.30 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3141, 3106, 1638, 1620, 1484, 796, 735 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.83 (s, 2 H, CH_2), 7.28 (d, *J* = 4.0 Hz, 1 H, NCH=C*H*S), 7.59 (t, *J* = 8.0 Hz, 1 H, Ar*H*), 7.71 (d, *J* = 4.0 Hz, 1 H, SCH=C*H*N), 7.78 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 8.09 (d, *J* = 4.0 Hz, 1 H, Ar*H*), 8.17 (s, 1 H, COC=C*H*N), 8.32 (s, 1 H, Ar*H*).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.7, 110.5, 121.8, 122.7, 124.0, 125.9, 130.2, 134.9, 136.3, 141.8, 148.3, 164.5, 166.9.

MS (EI): *m/z* (%) = 287.1 [M$^+$] (100), 257 (90), 241 (10).

HRMS (EI): *m/z* [M$^+$] calcd for $C_{13}H_9N_3O_3S$: 287.0365; found: 287.0366.

6-(2-Thienylmethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1i)
Gray solid; mp 192.5–193.2 °C; R_f = 0.30 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3144, 3062, 1645, 1618, 1488, 723 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.89 (s, 2 H, CH_2), 6.96 (m, 2 H, NCH=C*H*S, SC=C*H*), 7.28 (d, *J* = 4.8 Hz, 1 H, SCH=CH), 7.34 (t, *J* = 3.6 Hz, 1 H, SCH=C*H*), 7.76 (d, *J* = 4.4 Hz, 1 H, SCH=C*H*N), 8.27 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.7, 109.9, 122.8, 124.5, 125.4, 126.0, 126.9, 133.9, 140.8, 163.8, 166.2.

ESI-MS: *m*/*z* (%) = 249 [M^+ + 1] (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{11}H_8N_2OS_2$: 248.0078; found: 248.0081.

6-(2-Furylmethyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1j)
Orange solid; mp 179.2–180.9 °C; R_f = 0.30 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3135, 3041, 1643, 1609, 1520, 735 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.72 (s, 2 H, CH_2), 6.20 (d, *J* = 4 Hz, 1 H, OC=C*H*), 6.39 (dd, *J* = 4, 6 Hz, 1 H, OCH=C*H*), 7.28 (d, *J* = 4 Hz, 1 H, NCH=C*H*S), 7.55 (d, *J* = 4 Hz, 1 H, OCH=CH), 7.77 (d, *J* = 4 Hz, 1 H, SCH=C*H*N), 8.19 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.2, 106.9, 109.9, 110.6, 120.4, 125.4, 134.0, 141.9, 151.7, 163.9, 166.2.

MS (EI): *m*/*z* (%) = 232 [M^+] (100), 203 (60), 175 (15).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{11}H_8N_2O_2S$: 232.0306, found: 232.0311.

6-[(4-Methylthiazol-5-yl)methyl]-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1k)
Gray solid; mp 255.4–256.3 °C; R_f = 0.25 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3137, 3038, 1646, 1616, 1488, 766 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.37 (s, 3 H, CH_3), 3.83 (s, 2 H, CH_2), 7.28 (d, *J* = 4.8 Hz, 1 H, NCH=C*H*S), 7.76 (d, *J* = 4.8 Hz, 1 H, SCH=C*H*N), 8.21 (s, 1 H, COC=C*H*N), 8.84 (s, 1 H, N = C*H*S).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.7, 24.4, 109.9, 122.2, 125.4, 127.4, 133.7, 149.5, 150.9, 163.9, 166.1.

ESI-MS: *m*/*z* (%) 264 [M^+ + 1] (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{11}H_9N_3OS_2$: 263.0187; found: 263.0191.

6-[(2-Chloro-3-quinolyl)methyl]-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1l)
Yellow solid; mp >300 °C; R_f = 0.20 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3142, 3049, 1638, 1607, 1476, 758 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.93 (s, 2 H, CH_2), 7.28 (d, *J* = 4.8 Hz, 1 H, NCH=C*H*S), 7.65 (t, *J* = 7.2 Hz, 1 H, Ar*H*), 7.71 (d, *J* = 4.8 Hz, 1 H, SCH=C*H*N), 7.79 (t, *J* = 7.2 Hz, 1 H, Ar*H*), 7.97 (d, *J* = 10 Hz, 1 H, Ar*H*), 8.00 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 8.18 (s, 1 H, COC=C*H*N), 8.35 (s, 1 H, Ar*H*).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.3, 109.9, 120.8, 125.3, 127.3, 127.5, 127.6, 130.1, 130.3, 134.5, 139.2, 146.0, 149.1, 150.6, 164.1, 166.3.

ESI-MS: *m*/*z* (%) = 328 [M^+ + 1] (100), 329 (40).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{10}ClN_3OS$: 327.0233; found: 327.0236.

6-Isopentyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1m)
Brown crystals; mp 145.8–146.4 °C; R_f = 0.50 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3139, 2956, 1638, 1608, 1474 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 6 H, CH_3), 1.43 (q, *J* = 8 Hz, 2 H, $(CH_3)_2CHCH_2$), 1.55–1.60 (m, 1 H, $(CH_3)_2CH$), 2.46 (t, *J* = 8 Hz, 2 H, CH_2), 6.84 (d, *J* = 4.8 Hz, 1 H, NCH=C*H*S), 7.41 (d, *J* = 4.8 Hz, 1 H, SCH=C*H*N), 7.86 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4 (CH_3 × 2), 26.1, 27.8, 36.4, 109.5, 124.1, 126.1, 131.3, 163.6, 167.8.

ESI-MS: *m*/*z* (%) = 223 [M^+ + 1] (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{11}H_{14}N_2OS$: 222.0827; found: 222.0830.

6-(3,4-Dimethylbenzyl)-3-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (1n)
Yellow crystals; mp 201.4–203.1 °C; R_f = 0.25 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3170, 313102, 1638, 1605, 1487, 773 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.15 (s, 3 H, CH_3), 2.16 (d, *J* = 7.5 Hz, 3 H, CH_3), 2.36 (d, *J* = 7.5 Hz, 3 H, CH_3), 3.62 (s, 2 H, CH_2), 6.94 (s, 1 H, Ar*H*), 7.00 (s, 2 H, Ar*H*), 7.07 (s, 1 H, Ar*H*), 8.22 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 12.9, 18.9, 19.3, 33.2, 104.3, 122.6, 126.0, 129.1, 129.8, 131.9, 132.6, 133.5, 135.6, 136.5, 163.8, 166.1.

ESI-MS: *m*/*z* (%) = 285.2 [M^+ + 1] (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{16}H_{16}N_2OS$: 284.0983; found: 284.0986.

3-Benzyl-8-methyl-4*H*-benzothiazolo[3,2-*a*]pyrimidine-4-one (1o)
Green solid; mp 280.6–282.1 °C; R_f = 0.20 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3089, 1702, 1639, 1493, 702 cm^{-1}.

^1H NMR (400 MHz, TFA-*d*): δ = 2.47 (s, 3 H, CH_3), 3.99 (s, 2 H, CH_2), 7.19–7.29 (m, 5 H, Ar*H*), 7.54 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 7.68 (d, *J* = 7.6 Hz, 1 H, Ar*H*), 7.74 (s, 1 H, Ar*H*), 8.43 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, TFA-*d*): δ = 22.0, 35.3, 115.3, 125.8, 126.2, 130.1, 130.4, 131.1 (CH × 2), 131.4 (CH × 2), 133.4, 133.8, 136.3, 136.9, 144.9, 163.3, 164.6.

ESI-MS: *m*/*z* (%) = 307 [M^+ + 1] (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{14}N_2OS$: 306.0827; found: 306.0830.

3-(3-Methoxybenzyl)-8-methyl-4*H*-benzothiazolo[3,2-*a*]pyrimidine-4-one (1p)
Pale green solid; mp 226.0–227.2 °C; R_f = 0.25 (CH_2Cl_2–MeOH, 16:1).

IR (KBr): 3103, 3055, 1641, 1582, 1508, 823, 778 cm^{-1}.

^1H NMR (400 MHz, TFA-*d*): δ = 2.47 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 3.99 (s, 2 H, CH_2), 6.89–6.96 (m, 3 H, Ar*H*), 7.27 (t, *J* = 7.6 Hz, 1 H, Ar*H*), 7.55 (d, *J* = 8 Hz, 1 H, Ar*H*), 7.73 (s, 1 H, Ar*H*), 7.80 (d, *J* = 8.8 Hz, 1 H, Ar*H*), 8.61 (s, 1 H, COC=C*H*N).

^{13}C NMR (100 MHz, TFA-*d*): δ = 33.7, 35.2, 57.9, 115.3, 115.9, 118.5, 121.8, 125.6, 125.9, 126.4, 129.6, 133.0, 133.6, 134.0, 137.5, 139.0, 144.8, 160.8, 164.2.

ESI-MS: *m*/*z* (%) = 337 [M^+ + 1] (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{19}H_{16}N_2O_2S$: 336.0932; found: 336.0936.

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