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# New synthesis of 3,5-disubstituted-5*H*-thiazolo[3,2-α]pyrimidine via ring annulation of 3,4-dihydropyrimidin-2(1*H*)-thione using alkynyl(aryl)iodonium salts

Amol V. Shelke, Bhagyashree Y. Bhong, Nandkishor N. Karade *

*Department of Chemistry, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra 440 033, India*

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ABSTRACT

A transition metal-free protocol for the synthesis of biologically active thiazolo[3,2-*a*]pyrimidine derivatives has been achieved by the cyclocondensation of 3,4-dihydropyrimidin-2(1*H*)-thiones with alkynyl(aryl)iodonium tosylates. This reaction demonstrates another useful application of alkynyl(aryl)iodonium tosylates as synthon of alkynyl cation.

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The Biginelli reaction is a simple one pot three-component condensation of an aldehyde, β-ketoester, and urea or thiourea in the presence of a catalytic quantity of acid to produce 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs).[1] The dihydropyrimidinones and their derivatives exhibit a wide range of biological activities such as calcium channel modulators, mitotic kinesine inhibitors, adrenergic receptor antagonists, antibacterial, and antiviral agents.[2] Several biologically active marine alkaloids were also found to contain the dihydropyrimidinone-5-carboxylate core.[3] Most notable among them are batezelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors.[4] Owing to this remarkable pharmacological profile, there is a considerable interest in the decoration of all the six positions of DHPMs (N1, C2, N3, C4, C5, and C6) to produce low molecular weight 'drug like' compounds.[5] One of such structural post-modifications of 3,4-dihydropyrimidin-2(1*H*)-thiones is due to the presence of cyclic thiourea type moiety, leading to form highly elaborated skeletons with a potential pharmacological action.[6] In particular, when the reaction of 3,4-dihydropyrimidin-2(1*H*)-thiones is carried out with 1,2-dielectrophiles, the formation of ring annulation product, thiazolo[3,2-*a*]pyrimidine derivatives take place via C2–N3 linked centers.[7–11,6c] The synthesis of thiazolo[3,2-*a*]pyrimidine has recently gained importance due to diverse pharmacological activities such as anti-inflammatory, antiviral, antihypertensive, antimicrobial, and antibacterial.[7,8] They also serve as diacylglycerol (DG) kinase inhibitors, calcium antagonists, group 2 metabotropic glutamate receptor antagonists, and HIV-1 reverse transcriptase inhibitors.[8] Furthermore, some thiazolo[3,2-*a*]pyrimidines have been assigned as new acetylcholinesterase (AChE) inhibitors, especially for the treatment of Alzheimer's disease.[7a]

A variety of synthetic methods for the preparation of thiazolo[3,2-*a*]pyrimidine derivatives have been reported. One of the most common procedures involves the cyclization of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-thiones with halogen derived doubly electrophilic building blocks such as 2-bromo-ketones,[7] chloroacetic acid,[8] chloroacetyl chloride,[9] methyl chloroacetate,[10] and 1,2-dichloroethane[11] to form the C2–N3 linked thiazolo[3,2-*a*]pyrimidine derivatives (Fig. 1). Recently, an improved protocol involving in situ generation of α-bromo ketone from the reaction of ketone with 2 equiv of $Br_2$, followed by its subsequent trapping with 3,4-dihydropyrimidin-2(1*H*)-thiones has been reported to form thiazolo[3,2-*a*]pyrimidine derivatives.[6c] Another synthetic route for the preparation of these compounds is via C–S cross-coupling and 5-*endo*-*dig* cyclization sequence of 3,4-dihydropyrimidin-2(1*H*)-thiones with terminal alkynes.[12] This method utilizes CuCl (2 equiv), *N*,*N*′-dicyclohexylimidazolium chloride (2 equiv) as the ligand and $Et_3N$ (5 equiv) for the condensation of terminal alkyne (2 equiv) with 3,4-dihydropyrimidin-2(1*H*)-thiones under reflux conditions in toluene. The above discussed methods for the synthesis of thiazolo[3,2-*a*]pyrimidine derivatives utilize mainly halogen derived doubly electrophilic building blocks and terminal alkynes

* Corresponding author. Fax: +91 712 2532841.
*E-mail address:* nnkarade@gmail.com (N.N. Karade).

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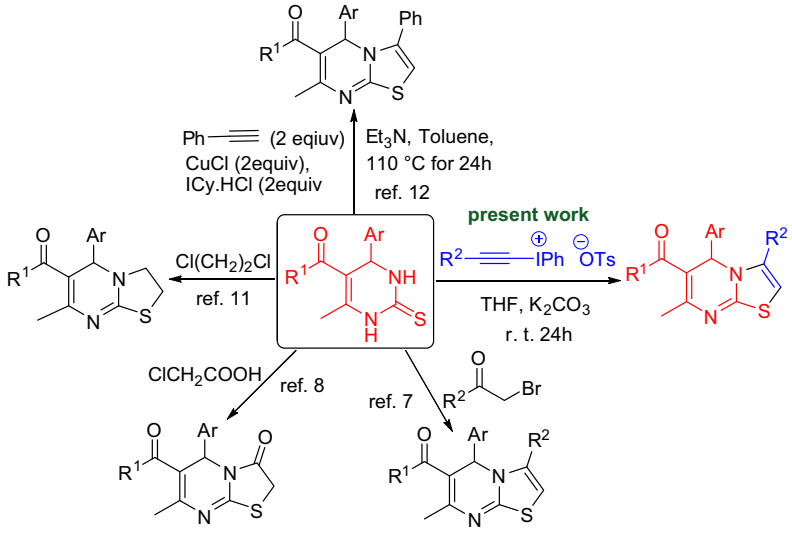


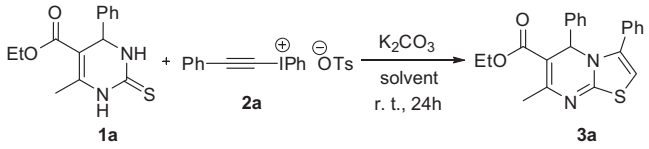

**Figure 1.** Methods of cyclocondensation of 3,4-dihydropyrimidin-2(1*H*)-thiones to form C2–N3 linked thiazolo[3,2-*a*]pyrimidine derivatives.

for cyclocondensation with 3,4-dihydropyrimidin-2(1*H*)-thiones. Herein, we wish to report the utilization of the alkynyl(aryl)iodonium salts as another source of building block for the ring annulation of 3,4-dihydropyrimidin-2(1*H*)-thiones to form thiazolo[3,2-*a*]pyrimidine derivatives under transition metal-free conditions.

The alkynyl(aryl)iodonium salts represent one of the useful and important classes of hypervalent iodine reagents, which show a wide range of applicability as a source of electrophilic acetylene equivalents, a change from the usual nucleophilic characteristics of acetylene.[13] The strong electron withdrawing properties of the iodonium group make alkynyl(aryl)iodonium salts to react via Michael-type conjugate addition reactions as well as Diels–Alder and other cycloadditions.[14] The good leaving group ability of iodobenzene moiety renders alkynyl(aryl)iodonium salts as powerful electrophilic alkynylating reagents toward various organic nucleophiles.[15]

In 1996, Wipf and Venkatraman reported a versatile method for the synthesis of thiazole by cyclocondensation of thioamides and alkynyl(aryl)iodonium mesylates under basic conditions.[16] The structural similarity of thioamides and 3,4-dihydropyrimidin-2(1*H*)-thiones led us to envisage that the reaction of the latter with doubly electrophilic alkynyl(aryl)iodonium tosylates could lead to form C2–N3 linked thiazolo[3,2-*a*]pyrimidine derivatives (Fig. 1).

**Table 1**
Optimization of reaction conditions




1a 2a 3a

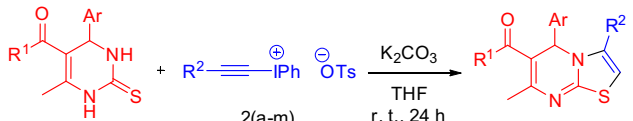
| Entry | **2a** (mmol) | Solvent | Yield of **3a**[a,b] (%) |
|---|---|---|---|
| 1 | 1 | $CHCl_3$ | 45 |
| 2 | 1 | $CH_2Cl_2$ | 42 |
| 3 | 1 | THF | 56 |
| 4 | 1.2 | $CHCl_3$ | 51 |
| 5 | 1.2 | $CH_2Cl_2$ | 53 |
| 6 | 1.2 | THF | 66 |
| 7 | 1.4 | $CHCl_3$ | 60 |
| 8 | 1.4 | $CH_2Cl_2$ | 57 |
| 9 | 1.4 | THF | 74 |

[a] Isolated yield.
[b] Reaction conditions: **1a** (1 mmol), **2a,** and $K_2CO_3$ (2.5 mmol).

The requisite alkynyl(aryl)iodonium tosylates were easily prepared from appropriate terminal alkynes and hydroxy(tosyloxy)iodobenzene using the literature methods.[17] We began our investigation with the model reaction of 4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thiones **1a** with phenyl(phenylethyny1)iodonium tosylate **2a** using $K_2CO_3$ as the base in different solvents such as $CH_2Cl_2$, $CHCl_3$, THF, and acetonitrile (Table 1). To our delight, the concept works nicely and the formation of **3a** took place in all the solvents. However, the maximum 74% yield of **3a** took place using 1.4 equiv of **2a** in THF after stirring at room temperature for 24 h (Table 1, entry 8).[18] In the absence of $K_2CO_3$, no formation of **3a** took place.

After optimization of the reaction conditions, the efficiency of the process was investigated with the cyclocondensation of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-thiones with different alkynyl(aryl)iodonium tosylates. As shown in Table 2, the presence of electron-donating and withdrawing substituents at C-4 aryl group of 3,4-dihydropyrimidin-2(1*H*)-thiones has little influence on the yields of cyclocondensation products. The alkynyl(aryl)iodonium

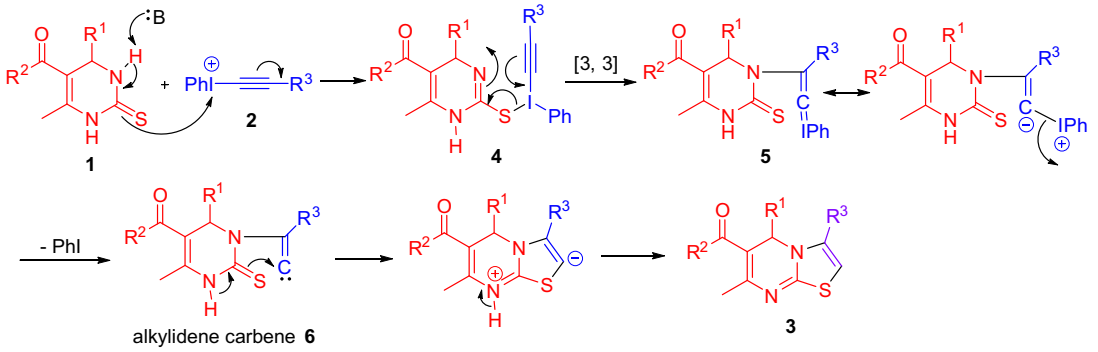
**Table 2**
Synthesis of thiazolo[3,2-*a*]pyrimidine derivatives using alkynyl(aryl)iodonium tosylates and 3,4-dihydropyrimidin-2(1*H*)-thiones[a]




1(a-m) 2(a-m) 3(a-m)

| Entry | Ar | $R^1$ | $R^2$ | Product **3** | Yield[a] (%) |
|---|---|---|---|---|---|
| a | $C_6H_5$ | $CH_3CH_2O$ | $C_6H_5$ | **3a** | 74 |
| b | 4-$CH_3OC_6H_4$ | $CH_3CH_2O$ | $C_6H_5$ | **3b** | 79 |
| c | 3-$CH_3OC_6H_4$ | $CH_3CH_2O$ | $C_6H_5$ | **3c** | 76 |
| d | 4-$CH_3C_6H_4$ | $CH_3CH_2O$ | $C_6H_5$ | **3d** | 78 |
| e | 3,4-$(CH_3O)_2C_6H_3$ | $CH_3CH_2O$ | $C_6H_5$ | **3e** | 80 |
| f | 4-$ClC_6H_4$ | $CH_3CH_2O$ | $C_6H_5$ | **3f** | 71 |
| g | 2,5-$(CH_3O)_2C_6H_3$ | $CH_3CH_2O$ | $C_4H_9$ | **3g** | 77 |
| h | $C_6H_5$ | $CH_3CH_2O$ | $C_5H_{11}$ | **3h** | 73 |
| i | 4-$ClC_6H_4$ | $CH_3CH_2O$ | $C_5H_{11}$ | **3i** | 78 |
| j | 4-$CH_3C_6H_4$ | $CH_3$ | $C_6H_5$ | **3j** | 71 |
| k | 4-$CH_3C_6H_4$ | $CH_3$ | $C_4H_9$ | **3k** | 74 |
| l | 3-$CH_3OC_6H_4$ | $CH_3$ | $C_4H_9$ | **3l** | 69 |
| m | $C_6H_5$ | $CH_3$ | $C_4H_9$ | **3m** | 67 |

[a] Isolated yields after column chromatography.




**Scheme 1.** Mechanism of 3,5-disubstituted-5*H*-thiazolo[3,2-*a*]pyrimidine formation.

tosylates bearing an aromatic ring as well as alkyl substituents reacted very well to provide the cyclization products in good to high yields. All the products were characterized by IR, NMR, ($^1$H and $^{13}$C), and LCMS analysis (Supplementary data).[19]

The plausible reaction mechanism for the formation of thiazolo[3,2-*a*]pyrimidine derivatives is shown in Scheme 1.[16a] The nucleophilic sulfur of 3,4-dihydropyrimidin-2(1*H*)-thiones **1** can attack on electrophilic iodine of **2** to form **4** which undergoes [3,3]-hetero-Claisen rearrangement to furnish vinyliodonium ylide **5**. The tendency of **5** for the reductive elimination of iodobenzene may lead to form alkilidene carbene **6** as the intermediate which finally undergoes cyclization to yield **3**.

In conclusion, we have developed a mild, efficient, and transition metal-free protocol for the cyclocondensation of 3,4-dihydropyrimidin-2(1*H*)-thiones with alkynyl(aryl)iodonium tosylates to form thiazolo[3,2-*a*]pyrimidine derivatives in good yields. This transformation demonstrates other useful applications of alkynyl(phenyl)iodonium salts as synthon of alkynyl cation.

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## Supplementary data

Supplementary data associated (copies of IR, $^1$H NMR, $^{13}$C NMR spectra, and LCMS are provided for all the compounds synthesized) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.098.

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18. *General experimental procedure for the synthesis of thiazolo[3,2-a]pyrimidine:* To a stirred solution of appropriate 4-aryl-3,4-dihydropyrimidin-2(1*H*)-thiones (2 mmol) in THF (10 mL), $K_2CO_3$ (6 mmol) and alkynyl(aryl)iodonium tosylates (4.8 mmol) were added and the reaction mixture was allowed to stir at room temperature for 24 h. The progress of reaction was monitored by TLC. After completion of the reaction, THF was evaporated under reduced pressure. Water (10 mL) was added to the solid mass and the product was extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate layer was again washed with 3 N HCl (4 × 10 mL). The resultant acidic aqueous layer was then neutralized with saturated $NaHCO_3$ and the product was extracted with ethyl acetate (4 × 10 mL). The combined ethyl acetate layer was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to afford crude product, which was purified by column chromatography using silica gel (230–400 mesh) with petroleum ether and ethyl acetate (3:1) as eluent to afford thiazolo[3,2-*a*]pyrimidine derivatives **3** as yellow solid product.
19. *Characterization data for all the products:*
*Ethyl 7-methyl-3,5-diphenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate* (**3a**)*:* Yellow solid; mp 110–112 °C, $^1$H NMR 400 MHz ($CDCl_3$): $\delta$ 1.16 (t, *J* = 7.12 Hz, 3H), 2.46 (s, 3H), 4.07 (q, *J* = 7.2 Hz, 2H), 6.18 (s, 1H), 6.21 (s, 1H), 6.76 (d, *J* = 7.32 Hz, 2H), 7.05 (t, *J* = 7.3 Hz, 2H), 7.11 (d, *J* = 8.32, 3H), 7.39 (t, *J* = 7.36 Hz, 2H), 7.46 (t, *J* = 7.34 Hz, 1H); $^{13}$C NMR 100 MHz ($CDCl_3$): $\delta$ 14.25, 23.19, 29.71, 57.99, 59.86, 101.28, 103.37, 126.56, 128.22, 128.67, 128.87,

128.96, 129.39, 129.73, 139.85, 141.95, 166.20, 166.63; IR ($cm^{-1}$): 2970, 2917, 1737, 1673, 1567, 1455, 1362, 1225, 1078, 994, 698, 599; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{22}H_{20}N_2O_2S$: 76.12. Found: 377.05.

*Ethyl 5-(4-methoxyphenyl)-7-methyl-3-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3b**):* Yellow solid; mp 122–124 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 1.09 (t, *J* = 7.10 Hz, 3H), 4.12.383 (s, 3H), 3.61 (s, 3H), 3.97 (q, *J* = 7.12 Hz, 2H), 6.05 (s, 1H), 6.09 (s, 1H), 6.49 (d, *J* = 8.72 Hz, 2H), 6.59 (d, *J* = 8.72 Hz, 2H) 7.07 (d, *J* = 6.96 Hz, 2H), 6.31–6.41(m, 3H); $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 14.28, 23.43, 55.13, 57.37, 59.77, 101.39, 102.89, 113.42, 127.93, 128.67, 128.92, 129.63, 134.64, 139.81, 155.29, 159.24, 166.29, 166.81; IR ($cm^{-1}$): 3005, 2988, 1685, 1482, 1371, 1317, 1275, 1258, 1176, 1032, 763, 749, 694, 600; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{23}H_{22}N_2O_3S$: 406.14. Found: 407.10.

*Ethyl 5-(3-methoxyphenyl)-7-methyl-3-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3c**):* Yellow solid; mp 116–118 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 1.09 (t, *J* = 7.08 Hz, 3H), 2.37 (s, 3H), 3.48 (s, 3H), 3.99 (q, *J* = 7.04 Hz, 2H), 6.09 (s, 1H), 6.16 (s, 1H), 6.35 (d, *J* = 7.56 Hz, 1H), 6.57 (d, *J* = 8.04 Hz, 1H), 6.09 (t, *J* = 7.92 Hz, 1H), 7.06 (d, *J* = 7.24 Hz, 2H), 7.30–7.39 (m, 4H); $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 14.31, 23.51, 54.95, 57.78, 59.80, 100.98, 102.95, 111.61, 113.96, 118.87, 128.69, 128.91, 129.31, 129.61, 139.73, 143.54, 155.73, 159.18, 166.45, 166.75; IR ($cm^{-1}$): 2981, 2837, 1689, 1598, 1585, 1483, 1371, 1313, 1252, 1226, 1077, 1001, 765, 749, 694, 605; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{23}H_{22}N_2O_3S$: 406.14. Found: 407.05.

*Ethyl 7-methyl-3-phenyl-5-(p-tolyl)-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3d**):* Yellow solid; mp 130–132 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 1.17 (t, *J* = 7.12 Hz, 3H), 2.20 (s, 3H), 2.45 (s, 3H), 4.06 (q, *J* = 7.08 Hz, 2H), 6.14 (s, 1H), 6.15 (s, 1H), 6.65 (d, *J* = 8.08 Hz, 2H), 6.85 (d, 7.92 Hz, 2H), 7.14 (d, *J* = 6.88 Hz, 2H), 7.40 (t, 7.24 Hz, 2H), 7.46 (t, *J* = 6.66 Hz, 1H); $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 14.28, 21.12, 23.55, 57.56, 59.74, 101.29, 102.74, 126.44, 128.65, 128.86, 128.90, 129.60, 129.62, 137.79, 139.30, 139.80, 155.62, 166.47, 166.80; IR ($cm^{-1}$): 3090, 2924, 1737, 1680, 1573, 1469, 1362, 1312, 1227, 1176, 1072, 998, 788, 697, 656, 598; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{23}H_{22}N_2O_2S$: 390.14. Found: 391.05.

*Ethyl 5-(3,4-dimethoxyphenyl)-7-methyl-3-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3e**):* Yellow solid; mp 136–138 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 1.18 (t, *J* = 7.12 Hz, 3H), 2.47 (s, 3H), 3.54 (s, 3H), 3.77 (s, 3H), 4.08 (q, *J* = 8.56 Hz, 2H), 6.12 (d, *J* = 7.76 Hz, 2H), 6.17 (s, 1H), 6.49 (d, *J* = 8.32 Hz, 1H), 6.59 (d, *J* = 8.76 Hz, 1H), 7.18 (d, *J* = 6.56 Hz, 2H), 7.44 (m, 3H). $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 14.31, 23.58, 55.39, 55.70, 57.64, 59.77, 101.27, 102.84, 109.66, 110.77, 119.09, 128.70, 128.93, 129.50, 129.87, 134.99, 139.74, 148.01, 148.55, 155.49, 166.32, 166.87; IR ($cm^{-1}$): 2970, 1737, 1661, 1578, 1486, 1442, 1365, 1231, 1159, 1092, 1023, 809, 739, 697, 658, 610; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{24}H_{24}N_2O_4S$: 436.15. Found: 437.10.

*Ethyl 5-(4-chlorophenyl)-7-methyl-3-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3f**):* Yellow solid; mp 128–130 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 1.17 (s, 3H), 2.45 (s, 3H), 4.07 (q, *J* = 8.78 Hz, 2H), 6.15 (s, 1H), 6.20 (s, 1H), 6.68 (d, *J* = 8.48 Hz, 2H), 7.02 (d, *J* = 8.48 Hz, 2H), 7.13 (d, *J* = 7.0 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.48 (t, *J* = 7.36 Hz, 1H); $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 14.28, 22.48, 29.72, 57.36, 59.94, 100.95, 103.20, 128.02, 128.40, 128.79, 128.92, 129.32, 129.83, 133.92, 139.64, 140.60, 166.29, 166.61; IR ($cm^{-1}$): 2970, 2925, 1737, 1698, 1575, 1475, 1369, 1312, 1225, 1178, 1078, 1014, 996, 824, 770, 697, 654, 598; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{22}H_{19}ClN_2O_2S$: 410.09. Found: 411.05.

*Ethyl 5-(2,5-dimethoxyphenyl)-7-methyl-3-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3g**):* Yellow solid; mp 144–146 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 1.12 (t, *J* = 12.72 Hz, 3H), 2.43 (s, 3H), 3.33 (s, 3H), 3.51 (s, 3H), 4.02 (q, *J* = 9.57 Hz, 2H), 6.03 (s, 1H), 6.35 (d, *J* = 2.96 Hz, 1H), 6.43 (s, 1H), 6.52 (d, *J* = 8.92 Hz, 1H), 6.61 (d, *J* = 8.88 Hz), 1H), 7.08 (d, *J* = 7.08 Hz, 2H), 7.36 (m, 3H); $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 14.12, 23.52, 54.60, 55.40, 55.50, 59.44, 99.96, 102.04, 111.31, 114.65, 114.72, 128.29, 128.75, 129.12, 130.10, 130.79, 139.99, 150.93, 152.76, 155.57, 166.82, 166.87; IR ($cm^{-1}$): 2970, 1737, 1665, 1571, 1454, 1365, 1318, 1263, 1217, 1079, 1014, 996, 922, 794, 716, 698, 606, 573; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{24}H_{24}N_2O_4S$: 436.15. Found: 437.10.

*Ethyl 7-methyl-3-pentyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3h**):* Yellow solid; mp 102–104 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 0.87 (t, *J* = 7.64 Hz, 3H), 1.52–1.36 (m, 8H), 1.42–1.46 (m, 1H), 1.53–1.60 (m, 1H), 2.17–2.26 (m, 1H), 3.37 (s, 3H), 4.15 (q, *J* = 7.46 Hz, 2H), 5.93 (s, 1H), 6.18 (s, 1H), 7.22–7.30 (m, 5H); $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 13.93, 14.45, 22.29, 23.85, 26.60, 27.34, 31.10, 57.50, 59.85, 99.56, 100.01, 126.28, 128.18, 128.73, 139.90, 143.02, 156.03, 166.92, 166.98; IR ($cm^{-1}$): 2955, 2926, 1737, 1693, 1665, 1591, 1474, 1369, 1321, 1242, 1207, 1007, 831, 756, 696, 669; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{21}H_{26}N_2O_2S$: 370.17. Found: 371.00.

*Ethyl 5-(4-chlorophenyl)-7-methyl-3-pentyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3i**):* Yellow solid; mp 110–112 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 0.88 (t, *J* = 7.0 Hz, 3H), 1.25–1.30 (m, 7H), 1.44–1.47 (m, 1H), 1.55–1.58 (m, 1H), 2.20–2.24 (m, 1H), 2.34–2.39 (m, 4H), 4.16 (q, *J* = 6.04 Hz, 2H), 5.96 (s, 1H), 6.16 (s, 1H), 7.24–7.28 (m, 4H); $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 13.90, 14.45, 22.29, 23.84, 26.55, 27.34, 29.71, 31.10, 56.94, 59.99, 99.79, 99.92, 127.70, 128.94, 134.02, 139.68, 141.41, 156.01, 166.80; IR ($cm^{-1}$): 2928, 2864, 1737, 1677, 1562, 1455, 1369, 1205, 1064, 1014, 973, 813, 729, 636, 588; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{21}H_{25}ClN_2O_2S$: 404.13. Found: 405.05.

*1-(7-Methyl-3-phenyl-5-(p-tolyl)-5H-thiazolo[3,2-a]pyrimidin-6-yl)ethanone (**3j**):* Yellow solid; mp 126–128 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 2.20 (s, 3H), 2.31 (s, 3H), 2.47 (s, 3H), 6.24 (s, 1H), 6.30 (s, 1H), 6.67 (d, *J* = 8.04 Hz, 2H), 6.86 (d, *J* = 7.92 Hz, 2H), 7.15 (d, *J* = 6.96 Hz, 2H), 7.41 (t, *J* = 7.32 Hz, 2H), 7.46 (d, *J* = 7.24 Hz, 1H); $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 14.16, 21.10, 22.72, 24.76, 29.39, 29.72, 31.47, 31.95, 57.20, 103.59, 112.46, 126.40, 128.98, 129.95, 137.83, 138.90, 140.35, 194.76; IR ($cm^{-1}$): 2916, 2848, 1737, 1611, 1462, 1369, 1311, 1228, 1177, 1062, 989, 941, 822, 696, 596; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{22}H_{20}N_2OS$: 360.13. Found: 361.05.

*1-(3-Butyl-7-methyl-5-(p-tolyl)-5H-thiazolo[3,2-a]pyrimidin-6-yl)ethanone (**3k**):* Yellow solid; mp 106–108 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 0.88 (t, *J* = 7.26 Hz, 3H), 1.34 (q, *J* = 7.29 Hz, 2H), 1.40–1.44 (m, 1H), 1.52–1.55 (m, 1H), 2.27 (s, 3H), 2.29–2.31 (m, 1H), 2.37 (s, 3H), 2.38 (s, 3H), 2.42–2.46 (m, 1H), 6.03 (s, 1H), 6.39 (s, 1H), 7.05 (d, *J* = 7.96 Hz, 2H), 7.16 (d, *J* = 8.12 Hz, 2H); $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 13.71, 21.12, 22.09, 25.08, 27.06, 28.29, 29.71, 31.71, 56.40, 100.52, 112.04, 126.16, 129.37, 137.85, 139.70, 140.76, 166.73, 194.24; IR ($cm^{-1}$): 2956, 2930, 1597, 1586, 1454, 1314, 1211, 1079, 1040, 957, 847, 759, 733, 694, 665; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{20}H_{24}N_2OS$: 340.16. Found: 341.00.

*1-(3-Butyl-5-(3-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)ethanone (**3l**):* Yellow solid; mp 114–116 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 0.88 (t, *J* = 7.26 Hz, 3H), 1.34 (p, *J* = 7.28 Hz, 2H), 1.43 (m, 1H), 1.54 (m, 1H), 2.30 (m, 1H), 2.38 (s, 3H), 2.39 (s, 3H), 2.44 (m, 1H), 3.74 (s, 1H), 6.04 (s, 1H), 6.44 (s, 1H), 6.75 (d, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 7.76 Hz, 2H), 7.16 (t, *J* = 7.86 Hz, 1H); $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 13.70, 22.07, 25.21, 27.01, 28.89, 31.67, 55.18, 56.27, 100.42, 111.63, 111.79, 113.31, 118.32, 129.72, 140.70, 144.01, 156.07, 159.72, 166.98, 194.27; IR ($cm^{-1}$): 2956, 2930, 1737, 1586, 1455, 1369, 1315, 1212, 1080, 1041, 958, 849, 747, 734, 695, 663; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{20}H_{24}N_2O_2S$: 356.16. Found: 357.00.

*1-(3-Butyl-7-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidin-6-yl)ethanone (**3m**):* Yellow solid; mp 126–128 °C, $^1H$ NMR 400 MHz ($CDCl_3$): $\delta$ 0.87 (t, *J* = 7.24 Hz, 3H), 1.33 (m, 2H), 1.41 (m, 1H), 1.54 (m, 1H), 2.28 (m, 1H), 2.38 (s, 6H), 2.43 (m, 1H), 6.03 (s, 1H), 6.44 (s, 1H), 7.26 (m, 5H); $^{13}C$ NMR 100 MHz ($CDCl_3$): $\delta$ 13.67, 22.04, 25.27, 27.01, 28.87, 31.67, 56.46, 100.35, 111.80, 126.16, 127.95, 128.67, 140.65, 142.61, 156.04, 167.02, 194.21; IR ($cm^{-1}$): 2956, 2929, 1607, 1552, 1458, 1369, 1315, 1211, 1083, 957, 827, 719, 695, 659, 612; MS (ESI) *m*/*z* $(M+H)^+$ Calcd for $C_{19}H_{22}N_2OS$: 326.15. Found: 326.90.