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ORIGINAL ARTICLE

# Efficient and green synthesis of novel hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline derivatives

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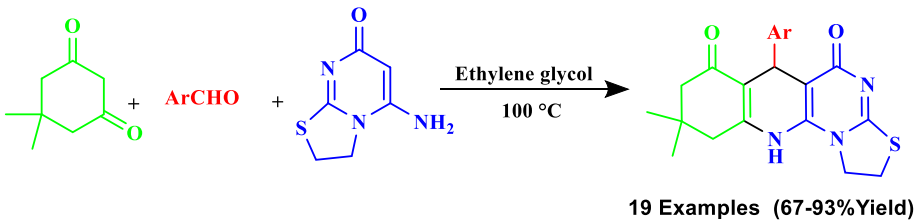
## Abstract

Herein, we report a catalyst-free, one-pot three-component reaction of 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one, aromatic aldehyde, and dimedone in ethylene glycol as a green solvent at 100 °C for the easy access of hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline. Catalyst-free, green solvent, simple procedure, mild reaction conditions, easy work-up procedure, and good to excellent yields are the significant advantages of this protocol.

### Graphical abstract




**Keywords** Three-component reaction · Catalyst-free synthesis · 5-Amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one · Hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinolines

## Introduction

Heterocyclic compounds are among the important heterocyclic compounds due to their presence in natural and synthetic products. Nitrogen-containing aromatic heterocyclic scaffolds are presented in many important organic compounds, which have relatively wide applications in various fields of technology, medicine, agriculture, dyes, and particularly in biologically active molecules [1–3].

Heterocyclic compounds containing nitrogen and sulfur atoms thiazolopyrimidine derivatives have attracted considerable attention due to their potent biological and pharmacological activities [4, 5]. These heterocyclic compounds display a broad range of biological activities such as antipsychotic, antimicrobial, anti-inflammatory, antioxidants, anti-HIV, antimicrobial, anticancer analgesic, anti-Parkinson's, and antibacterial [6–25]. These compounds have also been studied as a class of modulators for the transient receptor potential vanilloid-receptor 1(TRPV1) [26], phosphate inhibitors [27, 28], and acetylcholinesterase inhibitors [29, 30]. Moreover, thiadiazolo[3,2-*a*]pyrimidins are important heterocyclic cores since they exhibit engaging biological activities. For instance, molecule **A** has been used as an antiviral drug [31], compound **B** display antibacterial activity, and compound **C** has been used as antifungal drugs [32] (Fig. 1A–C).

Similarly, as an essential structural motif, the polyhydroquinoline (PHQ) ring is also found extensively in numerous pharmaceutically active compounds. PHQ exhibits various biological properties such as antitumor, antiatherosclerotic, vasodilator, geroprotective, bronchodilator, hepatoprotective activity, anticonvulsant, and bronchodilator, anti-inflammatory, hepatoprotective, neuroprotective, antidiabetic,

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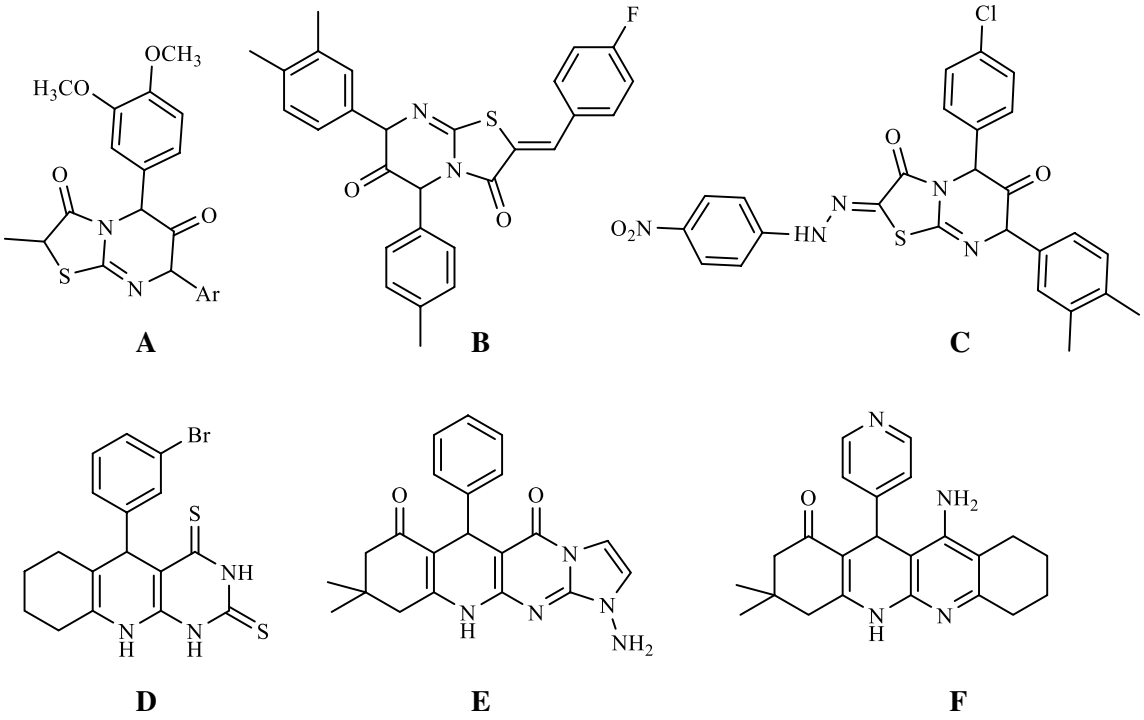



**Fig. 1** Biologically active thiazolopyrimidine and polycyclic 1,4-dihydropyridine derivatives

antihypertension, and antimutagenic activities [33–38]. Also, these drugs inhibit calcium ion penetration inside cells and afford a relaxation effect on cardiac muscle contractions, enhancing therapeutic success [39]. Figure 1 shows the significant potential of the PHQ derivative as a valuable drug candidate. For example, compound (D) is effective for the treatment of antitumor [40], and compounds (E) and (F) display antimicrobial and anti-Alzheimer activities, respectively [41, 42]. Besides the extensive therapeutic properties, PHQ scaffolds are also oxidized in the photocatalytic pathway leading to the development of pyridines [43].

In addition to the various pharmacological and biological activities of PHQs, extra heterocycles with fused PHQs play a vital role in organic procedures and possess new biological and pharmacological activities.

Considering the finding mentioned above, our purpose was to develop new compounds with unique biological activities by improving hybrid molecules by combining different pharmacophore moieties. We attempted to synthesis one molecule involving both thiazolopyrimidine and PHQ, which may play an essential role in medicine and the organic field. In continuation to our research work [44], we present a catalyst-free, straightforward procedure for producing novel 9,9-dimethyl-6-phenyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8*H*)-dione derivatives in ethylene glycol via multicomponent reaction of 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one, aromatic aldehyde, and dimedone in the domino reaction. In this domino reaction, C–C (two) and C–N (one) bonds form one new ring that all reactants efficiently employed in the chemical transformation.

**Table 1** Optimization of reaction conditions for compound **4a**

| Entry | Solvent | Temperature (°C) | Catalyst | *Yield | Time (h) |
|---|---|---|---|---|---|
| 1 | Ethanol | Reflex | None | 35 | 24 |
| 2 | $H_2O$ | Reflex | None | 68 | 4 |
| 3 | Methanol | Reflex | None | 35 | 24 |
| 4 | n-Butanol | 110 | None | 25 | 24 |
| 5 | PEG-400 | 120 | None | 20 | 20 |
| 6 | DMF | Reflex | None | 10 | 20 |
| **7** | **Ethylene glycol** | **100** | **None** | **90** | **4** |
| 8 | Ethylene glycol | 100 | $Et_3N$ | 50 | 4 |
| 9 | Ethylene glycol | 100 | DABCO | 60 | 4 |
| 10 | Ethylene glycol | 100 | [a]$Fe_2O_3$ | 80 | 4 |
| 11 | Ethylene glycol | 100 | [b]$Fe_2O_3$ | 40 | 4 |
| 12 | Ethylene glycol | 90 | None | 75 | 4 |
| 13 | Ethylene glycol | 120 | None | 90 | 4 |
| 14 | Ethylene glycol | 130 | None | 90 | 4 |
| 15 | Solvent free | 110 | None | Trace | 24 |

Reaction condition: 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (1 mmol), *P*-nitro-benzaldehyde (1 mmol) and dimedone (1 mmol) in ethylene glycol (7 ml). *Isolated yield. [a]10 mmol%, [b]25 mol%

## Results and discussion

As a model reaction, we selected 5-amino-2,3-dihydro-7*H*-thiazolo [3,2-*a*] pyrimidin-7-one **1**, p-nitro benzaldehyde **2,** and dimedone **3**, to investigate critical parameters of domino reaction. The effect of different catalysts, solvents, and temperatures was examined (Table 1). The model reaction was performed in ethanol at 80 °C in catalyst-free conditions, and it gives the product **4a** in 35% yield within 24 h (Table 1, entry 1). Next, we investigated the influence of other solvents such as water, methanol, n-butanol, PEG-400, DMF, and ethylene glycol. It indicates that the yield of the product in ethylene glycol at 100 °C was improved (Table 1, entries 2–7). Different catalysts including $Et_3N$, DABCO, and $Fe_2O_3$ in ethylene glycol were tested at 100 °C, and the results have depicted that the highest value for the yield of the desired product has been obtained in ethylene glycol in the absence of catalyst (Table 1, entries 8–11). Then the reaction was screened at different temperatures, 90, 100, 120, and 130 °C, in ethylene glycol under catalyst-free conditions. It was observed that decreasing the temperature resulted in a low yield, whereas an increase in temperature did not improve product yield (Table 1, entries 7 and 12–14). The model reaction was also examined in neat conditions without catalyst at 100 °C but did not proceed even after 24 h (Table 1, entries 15). Thus, these results confirm that the reaction gave the best product yield in ethylene glycol under catalyst-free conditions at 100 °C (Table 1, entry 7).

Having the optimized reaction conditions in hand, the scope and generality of the protocol were subsequently studied by reacting a variety of aromatic aldehydes to obtain the corresponding 9,9-dimethyl-6-phenyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3] pyrimido[4,5-*b*]quinoline-5,7(8*H*)-diones (**4a-s**) with yields ranging from 67–93%. The results are depicted in Table 2.

The aldehydes containing electron-withdrawing substituents (such as Cl, Br, and $NO_2$) or electron-donating groups (such as Me, OH, and OMe) on the benzene ring proceeded easily to deliver the desired products in good-to-excellent yields (Table 2, 4a–s).

The compound structure was entirely elucidated by $^1$HNMR, $^{13}$CNMR, IR, mass spectroscopic data, and element analysis. For instance, in the $^1$H NMR spectrum of **4a**, the protons methyl group shows two singlets at 0.9 and 1.05 ppm. The dimedone moiety's diastereotopic protons of the methylene group showed an AB system at δ = 2.05 and 2.23 ppm ($J_{AB}$ = 16.2 Hz) for the methylene group. The methylene group protons of $CH_2S$ exhibited a triplet at δ = 3.5 ppm ($J$ = 7.5 Hz) and a multiplet at δ = 4.5 ppm corresponding to the methylene group protons of $CH_2N$. The methine group proton appeared a singlet at δ = 4.97 ppm. Four characteristic protons on the aldehyde ring appeared as two doublets at δ = 7.5, ppm ($J$ = 8.7 Hz) and δ = 8.1 ppm ($J$ = 8.7 Hz). Finally, the NH proton showed a singlet peak at 9.36 ppm. Its $^{13}$C NMR confirmed the structure of **4a**. Nineteen separate peaks were seen in agreement with the proposed structure. The peaks at δ = 194.8 and δ = 168 ppm indicated the presence of two carbonyl groups due to a keto and amid group in the proposed structure.

Based on the previously reported [45], a possible mechanism pathway for compound **4** was depicted in Scheme 1. In the beginning, the Knoevenagel condensation reaction between dimedone **3** and aldehyde **2** leads to **A**. Then, intermediate **A** undergoes Michael addition with 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one **1** to provide the intermediate B, which could isomerize to intermediate **C**. Intramolecular *N*-cyclization of **C** gave the compound **4**.

## Conclusion

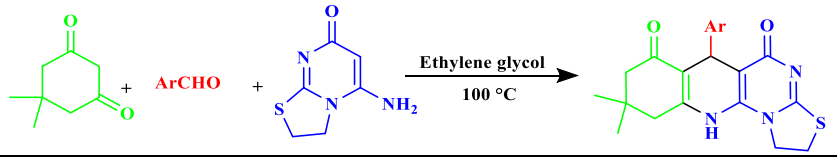
We successfully developed a green, mild, and clean process for producing the novel thiazolopyrimidoquinoline derivatives via domino reaction. The positive points for the presented approach are generality, efficiency, easy work-up, high-to-excellent yield, using green solvent, using readily and simple available starting materials, and catalyst-free condition.

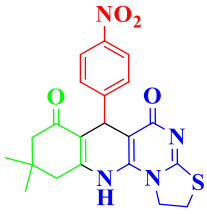
### Experimental

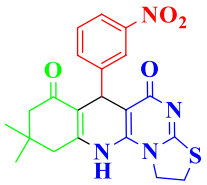
All reagents and solvents were purchased from Merck (Germany), and 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one was prepared according to the previously reported procedures, and their spectroscopic data were explained.[1] Melting points were recorded on an Electrothermal type 9100 melting point apparatus and are uncorrected. The IR spectra were obtained on an Avatar 370 FTIR Thermo-Nicolet spectrometer. $^1$H and $^{13}$C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analysis was performed by a Thermo Finnigan Flash EA microanalyzer.

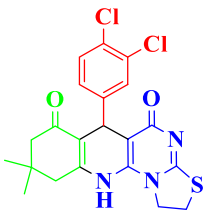
**General Procedure for the synthesis of 4a:** A mixture of 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (1 mmol), aryl aldehydes (1 mmol), and dimedone (1 mmol) in ethylene glycol (7 ml) as a green solvent at 100 °C was stirred. The reaction progress was monitored by thin-layer chromatography. After completion of the reaction, the

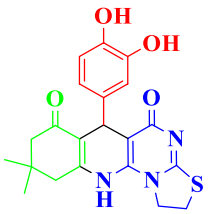
**Table 2** Synthesis of thiazolopyrimidoquinoline fused derivatives (**4a–q**)

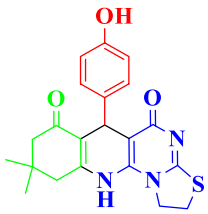


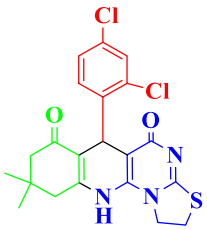


4a, 90%

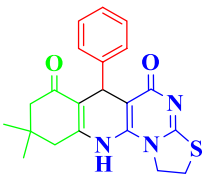

4b, 93%

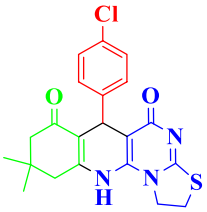

4c, 82%

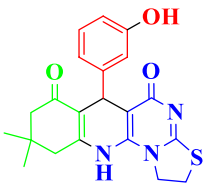

4d, 77%

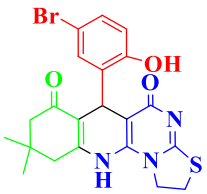

4e, 90%

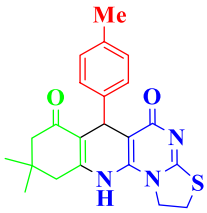

4f, 85%

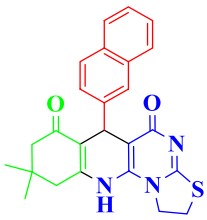

4g, 84%

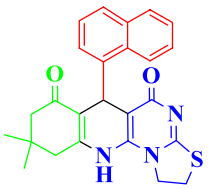

4h, 80%

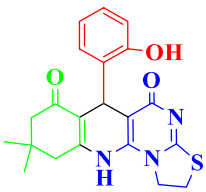

4i, 84%

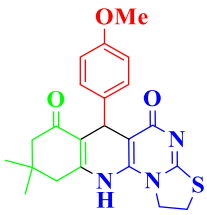

4j, 87%

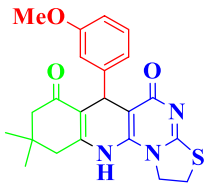

4k, 70%

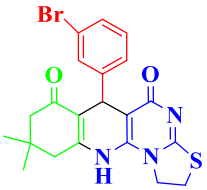

4l, 69%

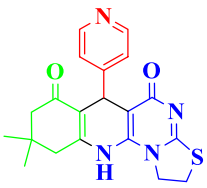

4m, 67%

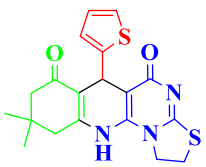

4n, 74%


4o, 81%


4p, 78%


4q, 72%

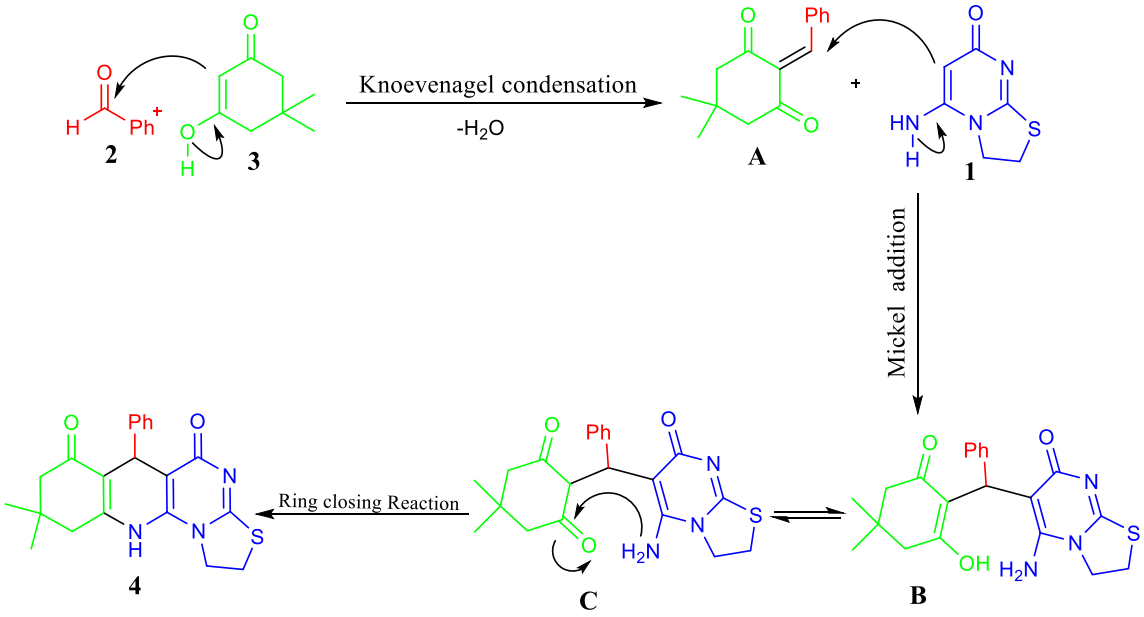

4r, 89%


4s, 91%

reaction mixture was purred to distill water. The precipitated product was filtered and washed with ethanol (20 ml) to give the pure product.

9,9-Dimethyl-6-(4-nitrophenyl)-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4a**).

White powder; (0.39 g, 90%) mp = 318–320 °C. IR (KBr) ($\upsilon_{max}$/cm$^{-1}$): 1648, 1594 (2 C=O). $^{1}$H NMR (300.13 MHz,




**Scheme 1** The probable mechanism for the formation of compounds **4**

DMSO-$d_6$): δ (ppm) 0.90 (3H, s, $CH_3$), 1.05 (3H, s, $CH_3$), 2.05, 2.23 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.56 (2H, $S_{br}$, CO–$CH_2$), 3.57 (2H, t, J = 7.5 Hz, S–$CH_2$), 4.43–4.60 (2H, m, N–CH2), 4.97(1H, s, CH), 7.52 (2H, d, J = 8.7 Hz, ArH), 8.10 (2H, d, J = 8.7 Hz, ArH), 9.36 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.2, 27.0, 29.3, 32.5, 35.1, 40.1, 50.3, 51.0, 96.0, 110.7, 123.3, 129.6, 143.3, 146.1, 150.6, 154.1, 164.9, 168.0, 194.8 (C=O). MS: (m/z, %): 424 ($M^+$, 5), 420 (60), 403 (20), 371 (31), 298 (48), 101 (68), 44 (35), 29 (87). Ana. Calcd for $C_{21}H_{20}N_4O_4S$: C: 59.42; H: 4.75; N: 13.20 found C: 59.71; H: 4.51; N: 13.33.

9,9-Dimethyl-6-(3-nitrophenyl)-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4b**).

White powder; (0.4 g, 94%) mp = 315–316 °C; IR (KBr) ($\upsilon_{max}$/$cm^{-1}$): 1654, 1578 (2 C=O). $^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.93 (3H, s, $CH_3$), 1.07 (3H, s, $CH_3$), 2.05, 2.25 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.59 (2H, $S_{br}$, CO–$CH_2$), 3.54–3.58 (2H, $t_{br}$, S–$CH_2$), 4.47–4.57 (2H, m, N–$CH_2$), 4.98 (1H, s, CH), 7.49–8.08 (4H, m, ArH), 9.39 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.2, 26.8, 29.5, 32.6, 34.9, 40.1, 50.3, 51.0, 96.3, 110.8, 121.4, 122.8, 129.6, 135.1, 143.3, 147.8, 148.7, 150.8, 164.9, 168.1, 194.9 (C=O). MS: (m/z, %): 424 ($M^+$, 5), 420 (60), 403 (20), 371 (31), 298 (48), 29 (87). Ana. Calcd for $C_{21}H_{20}N_4O_4S$ C: 59.42; H: 4.75; N: 13.20 found C: 59.63; H: 4.01; N: 13.93.

6-(3,4-Dichlorophenyl)-9,9-dimethyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4c**).

White powder; (037 g, 82%) mp = 325–327 °C; IR (KBr) ($\upsilon_{max}$/$cm^{-1}$): 1651, 1569 (2 C=O).$^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.92 (3H, s, $CH_3$), 1.05 (3H, s, $CH_3$), 2.06, 2.23 (AB system, 2H, $J_{AB}$ = 15.9 Hz), 2.61 (2H, $S_{br}$, CO–$CH_2$), 3.57 (2H, t, J = 7.8 Hz, S–$CH_2$), 4.43–4.59 (2H, m, N–$CH_2$), 4.83 (1H, s, CH), 7.23 (1H, dd, J = 8.1 Hz, J = 2.1 Hz, ArH), 7.42 (1H, d, J = 2.1, ArH), 7.47 (1H, d, J = 8.1 Hz, ArH), 9.32 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.2, 26.9, 29.4, 32.6, 34.3, 40.1, 50.4, 51.0, 96.1, 110.8, 128.7, 128.8, 130.2, 130.6, 143.2, 147.5, 150.5, 164.8, 168.1, 194.9. MS: (m/z, %): 448 ($M^+$, 40), 446 (60), 298 (100), 240 (21), 29 (83). Ana. Calcd for $C_{21}H_{19}Cl_2N_3O_2S$ C: 56.26; H: 4.27; N: 9.37 found C: 56.12; H: 4.25; N: 9.63.

6-(3,4-Dihydroxyphenyl)-9,9-dimethyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4d**).

Yellow powder; (0.32 g, 77%) mp = 350 °C <; IR (KBr) ($\upsilon_{max}$/$cm^{-1}$): 3255 (OH),1646, 1607 (2 C=O). $^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.96 (3H, s, $CH_3$), 1.06 (3H, s, $CH_3$), 2.06, 2.21 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.53 (2H, $S_{br}$, CO–$CH_2$), 3.54–3.59 (2H, $t_{br}$, S–$CH_2$), 4.42–4.54 (2H, m, N–$CH_2$), 4.73 (1H, s, CH), 6.45 (1H, dd,J = 8.1 Hz, J = 1.8 Hz, ArH), 6.54 (1H, d, J = 8.1, ArH), 6.7 (1H, d, J = 1.8), 8.53 (1H, s, OH), 8.61 (1H, s, OH), 9.13 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.1, 27.1, 29.5, 32.5, 32.9, 40.8, 50.7, 50.8, 97.6, 112.3,115.2, 116.1, 118.7, 137.9, 142.6, 143.7, 144.7, 149.3, 164.0, 168.2, 194.9 (C=O). MS: (m/z, %) 297 (100), 242 (80), 215 (15), 187 (10), 109 (60), 85 (11), 64

(29), 29 (100). Ana. Calcd for $C_{21}H_{21}N_3O_4S$: C: 61.30; H: 5.14; N:10.2. found C: 60.90; H: 4.80; N: 9.81.

6-(4-Hydroxyphenyl)-9,9-dimethyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4e**).

White powder; (0.36 g, 90%) mp = 307–309 °C; IR (KBr) ($\upsilon_{max}/cm^{-1}$): 3263 (OH), 1649,1607 (2 C=O). $^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.92 (3H, s, $CH_3$), 1.05 (3H, s, $CH_3$), 2.05, 2.20 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.52 (2H, $S_{br}$, CO–$CH_2$), 3.54 (2H, t, J = 8.1 Hz, S–$CH_2$), 4.42–4.57 (2H, m, N–$CH_2$), 4.78 (1H, s, CH), 6.57 (1H, d, J = 8.7 Hz, ArH), 7.03 (1H, d, J = 8.4 Hz, ArH), 9.10 (1H, s, OH), 9.18 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.1, 27.0, 29.5, 32.5, 33.0, 40.1, 50.6, 50.9, 97.5, 112.2, 114.7, 129.0, 137.3, 142.8, 149.5, 155.8, 164.1, 168.3, 194.9 (C=O). MS: (m/z, %): 395 ($M^+$,7), 297 (100), 269 (22), 242 (95), 214 (60), 187 (45), 129 (29), 94 (93), 66 (92), 39 (93) 29 (64). Ana. Calcd for $C_{21}H_{21}N_3O_3S$ C: 63.78; H: 5.35; N: 10.63. found C: 63.89; H: 5.27; N: 10.33.

6-(2,4-Dichlorophenyl)-9,9-dimethyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4f**).

White powder; (0.39 g, 85%) mp = 295–297 °C; IR (KBr) ($\upsilon_{max}/cm^{-1}$): 1662,1641 (2 C=O). $^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm), 0.89 (3H, s, $CH_3$), 1.04 (3H, s, $CH_3$), 1.96, 2.20 (AB system, 2H, $J_{AB}$ = 15.9 Hz), 2.5 (2H, $S_{br}$, CO–$CH_2$), 3.57 (2H, t, J = 7.8 Hz, S–$CH_2$), 4.5 (2H, m, N–$CH_2$), 5.09 (1H, s, CH), 7.27 (1H, dd, J = 8.1 Hz, J = 2.1 Hz, ArH), 7.33 (1H, d, J = 8.1 Hz, ArH), 7.35 (1H, d, J = 2.1 Hz, ArH), 9.25 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.1, 26.8, 29.5, 32.3, 34.1, 40.1, 50.4, 50.9, 96.1, 110.7, 1267, 128.6, 131.2, 133.9, 134.1, 142.8, 143.4, 150.4, 164.7, 167.9, 194.7 (C=O). MS: (m/z, %): 411 (15), 408 (30), 391 (8), 371 (8), 299 (62), 240 (3), 144 (7), 86 (12), 56 (20), 41 (60), 36 (70), 30 (100). Ana. Calcd for $C_{21}H_{19}Cl_2N_3O_2S$ C: 56.26; H: 4.27; N: 9.37 found C: 56.70; H: 4.25; N: 9.63.

9,9-Dimethyl-6-phenyl-1,2,6,9,10,11-hexahydro-5H-thiazolo[2',3':2,3]pyrimido[4,5-b]quinoline-5,7(8H)-dione (**4 g**).

white powder; (0.32 g, 84%) mp = 337–339 °C; IR (KBr) ($\upsilon_{max}/cm^{-1}$): 1650, 1580 (2 C=O). $^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.93 (3H, s, $CH_3$), 1.06 (3H, s, $CH_3$), 2.06, 2.23 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.55 (2H, $S_{br}$, CO–$CH_2$), 3.57 (2H, t, J = 8.1 Hz, S–$CH_2$), 4.42–4.58 (2H, m, N–$CH_2$), 4.88 (1H, s, CH), 7.07–7.27 (5H, m, ArH), 9.20 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.1, 27.0, 29.5, 31.0, 31.1, 32.6, 34.1, 50.5, 50.9, 97.1, 111.8, 126.2, 128.0, 128.2, 142.9, 146.6, 149.9, 161.3, 164.3, 168.1, 194.8 (C=O). MS: (m/z, %): 379 ($M^+$, 5), 375 (65), 298 (100), 290 (18), 29 (100). Ana. Calcd for $C_{21}H_{21}N_3O_2S$ C: 66.47; H: 5.58; N: 11.07 found C: 66.38; H: 5.25; N: 10.5.

6-(4-Chlorophenyl)-9,9-dimethyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4 h**).

White powder; (0.33 g, 80%) mp = 326–328 °C; IR (KBr) ($\upsilon_{max}/cm^{-1}$): 1650, 1565 (2 C=O). $^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.91 (3H, s, $CH_3$), 1.05 (3H, s, $CH_3$), 2.05, 2.22 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.54 (2H, $S_{br}$, CO–$CH_2$), 3.57 (2H, t, J = 7.8 Hz, S–$CH_2$), 4.44–4.56 (2H, m, N–$CH_2$), 4.85 (1H, s, CH), 7.25 (4H, s, ArH), 9.24 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.2, 27.0, 29.4, 32.5, 33.9, 40.1, 50.5, 50.9, 96.7, 111.4, 127.9, 130.1, 130.8, 143.0, 145.6, 150.1, 164.5, 168.1, 194.8 (C=O). MS: (m/z, %): 413($M^+$, 20), 298 (100), 241 (10), 43 (10), 29 (100). Ana. Calcd for $C_{21}H_{20}ClN_3O_2S$ C: 60.94; H: 4.87; N: 10.15 found: C: 61.14; H: 4.81; N: 9.53.

6-(3-Hydroxyphenyl)-9,9-dimethyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4i**).

White powder; (0.33 g, 84%) mp = 349–350 °C; IR (KBr) ($\upsilon_{max}/cm^{-1}$): 3311 (OH), 1655, 1616 (2 C=O). $^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.95 (3H, s, $CH_3$), 1.05 (3H, s, $CH_3$), 2.06, 2.22 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.54 (2H, $S_{br}$, CO–$CH_2$), 3.53–3.57 (2H, m, S–$CH_2$), 4.42–4.57 (2H, m, N–$CH_2$), 4.82 (1H, s, CH), 6.49 (1H, dd, J = , 7.8 Hz, J = 1.5 Hz, ArH), 6.66 (1H, d, J = 7.8 Hz, ArH), 6.71 (1H, $t_{br}$, J = 1.7 Hz, ArH), 6.96 (1H, t, J = 7.8 Hz, ArH), 9.14 (1H, s, NH), 9.23 (1H, s, OH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.1 ($CH_2$), 27.1 ($CH_3$), 29.5 ($CH_3$), 32.5 ($CH_2$), 33.8 (CH), 50.6 ($CH_2$), 50.9 ($CH_2$), 97.2 ($C_q$), 111.8 ($C_q$), 113.2 (CH), 115.5 (CH), 118.8 (CH), 128.9 (CH), 142.9 ($C_q$), 147.9 ($C_q$), 149.9 ($C_q$), 157.1 ($C_q$), 164.2 ($C_q$), 168.3 ($C_q$), 194.8($C_q$). MS: (m/z, %): 395($M^+$, 3), 391 (35), 298 (90), 240 (22), 215 (10), 93 (31), 65 (30), 59 (85), 29 (100). Ana. Calcd for $C_{21}H_{21}N_3O_3S$ C: 63.78; H: 5.35; N: 10.63. found C: 63.89; H: 5.27; N: 10.23.

6-(5-Bromo-2-hydroxyphenyl)-9,9-dimethyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4j**).

Yellow powder; (0.42 g, 87%) mp = 278–278 °C; IR (KBr) ($\upsilon_{max}/cm^{-1}$): 1661, 1637 (2 C=O).$^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 1.10 (3H, s, $CH_3$), 1.11 (3H, s, $CH_3$), 2.10–2.28 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.6 (2H, AB system, J = 17.4 Hz, CO–$CH_2$), 3.59 (2H, t, J = 7.2 Hz, S–$CH_2$), 4.45–4.62 (2H, m, N–$CH_2$), 4.99 (1H, s, CH), 6.71 (1H, d, J = 8.7 Hz, ArH), 6.96 (1H, d, J = 2.5 Hz, ArH), 7.14 (1H, dd, J = 8.7 Hz, J = 2.5 Hz, ArH), 9.50 (1H, s, NH), 11. (1H, s, OH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.5 ($CH_2$), 26.9 ($CH_3$), 28.6 ($CH_3$), 29.8 (CH), 32.6 ($CH_2$), 50.3 ($CH_2$), 51.4 ($CH_2$), 63.2 ($C_q$), 96.9 ($CH_2$), 110.8 ($C_q$), 111.2 ($C_q$), 120.6 (CH), 130.4 (CH), 131.2 (CH), 136.4 ($C_q$), 144.3 ($C_q$), 151.4 ($C_q$), 154.2 ($C_q$), 165.4 ($C_q$), 171.1 ($C_q$), 194.6 ($C_q$). MS: (m/z, %): 473 ($M^+$, 2), 454 (5), 296

(100), 241 (80), 214 (20), 170 (55), 65 (40), 29 (50). Ana. Calcd for $C_{21}H_{20}BrN_3O_3S$ C: 53.17; H: 4.25; N: 8.86 found: C: 52.95; H: 4.22; N: 8.40.

9,9-Dimethyl-6-(p-tolyl)-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4 k**).

White powder; (0.28 g, 70%) mp = 316–318 °C; IR (KBr) ($\upsilon_{max}$/cm$^{-1}$): 1647, 1559 (2 C=O).

$^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.93 (3H, s, $CH_3$), 1.06 (3H, s, $CH_3$), 2.02–2.08 (2H, m, $CH_2$), 2.21 (3H, s, $CH_3$), 2.54 (2H, $S_{br}$, CO–$CH_2$), 3.56 (2H, t, J = 7.2 Hz, S–$CH_2$), 4.45–4.58 (2H, m, N–$CH_2$), 4.84 (1H, s, CH), 6.99 (2H, d, J = 7.8 Hz, ArH), 7.13 (2H, d, J = 7.8 Hz, ArH), 9.19 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 21.0, 21.2, 26.1, 27.0, 29.5, 32.5, 33.6, 50.6, 50.9, 97.3, 112.0, 128.1, 128.6, 135.1, 142.9, 143.7, 149.7, 164.2, 168.1, 194.8 (C=O). MS: (m/z, %): 393($M^+$, 5), 389 (23), 298 (58), 241 (3), 43 (11), 29 (100). Ana. Calcd for $C_{22}H_{23}N_3O_2S$ C: 67.15; H: 5.89; N: 10.68; found C: 66.99; H: 5.44; N: 10.98.

9,9-Dimethyl-6-(naphthalen-2-yl)-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4 l**).

White powder; (0.30 g, 69%) mp = 350 < °C. IR (KBr) ($\upsilon_{max}$/cm-*1*): 1641,1579 (2 C=O).$^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.91 (3H, s, $CH_3$), 1.06 (3H, s, $CH_3$), 2.04, 2.23 (AB system, 2H, $J_{AB}$ = 15.0 Hz), 2.58 (2H, $S_{br}$, CO–$CH_2$), 3.58 (2H, t, J = 7.5 Hz, S–$CH_2$), 4.45–4.61 (2H, m, N–$CH_2$), 5.03 (1H, s, CH), 7.41–7.82 (7H, m, ArH), 9.24 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 21.5, 26.1, 26.9, 29.5, 32.6, 34.4, 50.6, 50.9, 97.0, 111.7, 125.6, 126.1, 126.2, 127.4, 127.5, 127.7, 128.0, 132.1, 133.1, 143.0, 144.1, 150.0, 164.4, 168.1, 194.9 (C=O). MS: (m/z, %): 429($M^+$, 5), 423 (48), 366 (68), 340 (55), 297 (60), 240 (72), 126 (35), 59 (40), 44 (50), 29 (100). Ana. Calcd for $C_{25}H_{23}N_3O_2S$ C: 69.91; H: 5.40; N: 9.78. found C: 70.21; H: 5.14; N: 9.48.

9,9-Dimethyl-6-(naphthalen-1-yl)-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione.(**4 m**).

White powder; (0.28 g, 67%) mp = 277- 280 °C. IR (KBr) ($\upsilon_{max}$/cm$^{-1}$): 1651,1631 (2 C=O). $^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.85 (3H, s, $CH_3$), 1.04 (3H, s, $CH_3$), 1.93, 2.20 (AB system, 2H, $J_{AB}$ = 15.0 Hz), 2.55 (2H, $S_{br}$, CO–$CH_2$), 3.55 (2H, t, J = 7.5 Hz, S–$CH_2$), 4.43- 4.57 (2H, m, N–$CH_2$), 5.67 (1H, s, CH), 7.36–7.82 (7H, m, ArH), 9.31 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 22.6, 26.1, 26.7, 29.6, 32.4, 34.7, 50.5, 50.9, 98.9, 113.6, 125.3, 125.5, 125.8, 126.6, 126.7, 126.8, 127.9, 131.5, 133.2, 142.9, 145.9, 149.4, 164.2, 168.4, 194.9 (C=O). MS: (m/z, %): 429 ($M^+$, 5), 423(48), 396(10), 340 (55), 297 (60), 240 (72), 126 (35), 59 (40), 44 (50), 29 (100). Ana. Calcd for $C_{25}H_{23}N_3O_2S$ C: 69.91; H: 5.40; N: 9.78. found C: 70.09; H: 5.10; N: 8.95.

6-(2-Hydroxyphenyl)-9,9-dimethyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)- dione.(**4n**).

white powder; (0.29 g, 74%) mp = 256–258 °C; IR (KBr) ($\upsilon_{max}$/cm$^{-1}$): 3134(OH), 1632, 1568 (2 C=O). $^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.98 (3H, s, $CH_3$), 1.08 (3H, s, $CH_3$), 2.07, 2.24 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.38–2.66 (2H, AB system, J = 17.2 Hz, CO–$CH_2$), 3.49 (1H, t, J = 7.2 Hz, S–CH), 3.57 (1H, t, J = 7.2 Hz, S–CH), 4.32–4.48 (2H, m, N–$CH_2$), 5.04 (1H, s, CH), 6.69–6.74 (1H, m, ArH), 6.80 (1H, s, OH), 6.87–7.00 (2H, m, ArH), 7.10–7.15 (1H, m, ArH), 10.72. (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.1, 27.0, 29.5, 31.0, 31.2, 32.6, 34.1, 50.6, 50.9, 97.1, 111.8, 126.2, 128.0, 128.2, 142.9, 146.6, 149.9, 161.3, 164.3, 168.1, 194.8. MS: (m/z, %): 395 ($M^+$,15), 297 (100), 242 (100), 214 (60), 94 (100), 66 (93), 29 (67). Ana. Calcd for $C_{21}H_{21}N_3O_3S$ C: 63.78; H: 5.35; N: 10.63 found: C: 64.12; H: 5.22; N: 10.17.

6-(4-Methoxyphenyl)-9,9-dimethyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4o**).

White powder; (0.33 g, 81%) mp = 246–248 °C; IR (KBr) ($\upsilon_{max}$/cm$^{-1}$): 1660, 1643 (2 C=O). $^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.93 (3H, s, $CH_3$), 1.05 (3H, s, $CH_3$), 2.05, 2.22 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.53 (2H, $S_{br}$, CO–$CH_2$), 3.56 (2H, t, J = 7.5 Hz, S–$CH_2$), 3.68 (3H, s, $OCH_3$), 4.42–4.59 (2H, m, N–$CH_2$), 4.81 (1H, s, CH), 6.74 (2H, d, J = 8.7 Hz, ArH), 7.13 (2H, d, J = 8.7 Hz, ArH), 9.16 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.1, 27.0, 29.5, 32.5, 33.2, 50.6, 50.8, 55.3, 63.2, 97.4, 112.0, 113.4, 129.1, 138.9, 142.7, 149.6, 157.8, 164.1, 168.1, 194.8 (C=O). MS: (m/z, %): 409 ($M^+$, 23), 407 (42), 376 (5), 346 (5), 302 (60), 43 (11), 29 (100). Ana. Calcd for $C_{22}H_{23}N_3O_3S$ C: 57.11; H: 9.59; N: 33.30; found C: 56.81; H: 9.79; N: 33.98.

6-(3-methoxyphenyl)-9,9-dimethyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4p**).

White powder; (0.32 g, 78%) mp = 237–238 °C; IR (KBr) ($\upsilon_{max}$/cm$^{-1}$): 1659, 1611 (2 C=O).$^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.95 (3H, s, $CH_3$), 1.06 (3H, s, $CH_3$), 2.07, 2.23 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.54 (2H, $S_{br}$, CO–$CH_2$), 3.56 (2H, t, J = 7.6 Hz, S–$CH_2$), 3.69 (3H, s, $OCH_3$), 4.40–4.56 (2H, m, N–$CH_2$), 4.85 (1H, s, CH), 6.66–7.13 (4H, m, ArH), 9.20 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.1, 27.0, 29.5, 32.5, 33.9, 50.6, 50.9, 55.2, 63.2, 97.0, 111.0, 111.6, 114.6, 120.5, 129.0, 142.9, 148.1, 150.1, 159.2, 164.2, 168.1, 194.8. MS: (m/z, %): 409($M^+$, 23), 407 (42), 376 (5), 346 (5), 299 (100),

43 (11), 29 (100). Ana. Calcd for $C_{22}H_{23}N_3O_3S$ C: 57.11; H: 9.59; N: 33.30; found C: 57.32; H: 9.69; N: 33.84.

6-(3-Bromophenyl)-9,9-dimethyl-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-b]quinoline-5,7(8H)-dione (**4q**).

White powder; (0.33 g, 72%) mp = 334–336 °C; IR (KBr) ($\upsilon_{max}/cm^{-1}$): 1651, 1582 (2 C=O).$^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.94 (3H, s, $CH_3$), 1.06 (3H, s, $CH_3$), 2.07, 2.24 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.56 (2H, $S_{br}$, CO–$CH_2$), 3.57 (2H, t, J = 7.6 Hz, S–$CH_2$), 4.39–4.59 (2H, m, N–$CH_2$), 4.83 (1H, s, CH), 7.15–7.39 (4H, m, ArH), 9.25 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.1, 26.9, 29.4, 32.6, 34.4, 50.4, 50.9, 96.5, 111.2, 121.4, 127.3, 129.1, 130.4, 131.0, 143.0, 149.2, 150.3, 164.6, 168.0, 194.8 MS: (m/z, %): 457 ($M^+$, 60), 428 (10), 397 (10), 373 (10), 299 (100), 243 (15), 76 (10), 28 (100). Ana. Calcd for $C_{21}H_{20}BrN_3O_2S$ C: 55.03; H: 4.40; N: 9.17. found C: 55.19; H: 4.31; N: 9.38.

9,9-Dimethyl-6-(pyridin-4-yl)-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5, 7(8H)-dione **(4r).**

White powder; (0.34 g, 89%) mp = 248–250 °C; IR (KBr) ($\upsilon_{max}/cm^{-1}$): 1659, 1598 (2 C=O).$^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 0.91 (3H, s, $CH_3$), 1.05 (3H, s, $CH_3$), 2.07, 2.23 (AB system, 2H, $J_{AB}$ = 16.2 Hz), 2.55 (2H, $S_{br}$, CO–$CH_2$), 3.57 (2H, t, J = 7.2 Hz, S–$CH_2$), 4.41–4.57 (2H, m, N–$CH_2$), 4.86 (1H, s, CH), 7.23 (2H, d, J = 4.8 Hz, ArH), 8.38 (2H, d, J = 4.8 Hz, ArH), 9.32 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.2, 27.0, 29.3, 32.6, 34.2, 40.1, 50.4, 50.9, 95.7, 110.4, 123.6, 143.4, 149.5, 150.7, 154.5, 164.8, 168.1, 194.8 MS: (m/z, %): 380 ($M^+$, 5), 377 (43), 299 (85), 240 (22), 185 (5), 91 (25), 28 (100). Ana. Calcd for $C_{20}H_{20}N_4O_2S$ C: 63.14; H: 5.30; N: 14.73. found C: 63.19; H: 5.41; N: 14.48.

9,9-Dimethyl-6-(thiophen-2-yl)-1,2,6,9,10,11-hexahydro-5*H*-thiazolo[2',3':2,3]pyrimido[4,5-*b*]quinoline-5,7(8H)-dione (**4 s**).

White powder; (0.35 g, 91%) mp = 288–290 °C; IR (KBr) ($\upsilon_{max}/cm^{-1}$): 1657, 1578 (2 C=O).$^1$H NMR (300.13 MHz, DMSO-$d_6$): δ (ppm) 1.02 (3H, s, $CH_3$), 1.07 (3H, s, $CH_3$), 2.15, 2.27 (AB system, 2H, $J_{AB}$ = 16.0 Hz), 2.57 (2H, $S_{br}$, CO–$CH_2$), 3.57 (2H, t, J = 7.2 Hz, S–$CH_2$), 4.41–4.58 (2H, m, N–$CH_2$), 5.19 (1H, s, CH), 6.77–6.78 (1H, m, ArH), 6.82–6.85 (1H, m, ArH), 7.18–7.20 (1H, m, ArH), 9.42 (1H, s, NH). $^{13}$C NMR (75.46 MHz, DMSO-d6): δ (ppm) 26.2, 27.0, 29.3, 32.6, 34.2, 40.1, 50.4, 50.9, 95.7, 110.4, 123.6, 143.4, 149.5, 150.7, 154.5, 164.8, 168.1, 194.8 MS: (m/z, %): 385 ($M^+$, 15), 299 (92), 243 (88), 228 (32), 216 (50), 188 (32), 84 (92), 28 (102). Ana. Calcd for $C_{19}H_{19}N_3O_2S_2$ C: 59.20; H: 4.97; N: 10.90. found C: 59.11; H: 5.01; N: 11.12.

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## Declarations

**Conflict of interest** The authors declare no conflict of interest.

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