Synthesis of 6-Membered-Ring Fused Thiazine-Dicarboxylates and Thiazole-Pyrimidines via One-Pot Three-Component Reactions

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Abstract: A facile and efficient one-pot three-component reaction method for the synthesis of thiazine-dicarboxylates is reported. Reaction of an isocyanide and dialkyl acetylenedicarboxylate with 2-amino-4H-1,3-thiazin-4-one derivatives containing both an acidic proton and an internal nucleophile gave the products in good yields of 76–85%. The reactivity of dialkyl acetylenedicarboxylates was further tested in the synthesis of thiazole-pyrimidines where a two-component reaction of 2-aminothiazole with dialkyl acetylenedicarboxylates was successfully converted to a more efficient three-component reaction of a thiourea, α-haloketone and dialkyl acetylenedicarboxylate (DMAD/DEtAD) to give thiazole-pyrimidines in good yields of 70–91%.

Keywords: multicomponent reaction; isocyanides; dialkyl acetylenedicarboxylates; thiourea; α-haloketone; thiazine; thiazole-pyrimidines

1. Introduction

Multicomponent reactions (MCRs) are one-pot reactions that comprise at least three reactants [1–3]. Some of the well-known MCRs include the classic Ugi four-component reaction [4] (U-4CR), the Passerini three-component reaction [5] (P-3CR), the Biginelli three-component reaction [6] (B-3CR) and the Hantzsch three-component reaction [7] (H-3CR). The history and discovery of MCRs can be traced back to Strecker’s [8] multicomponent reaction (S-3CR), which was reported in 1850, and three decades on, the Hantzsch reaction for preparing dihydropyridines (DHP) was reported [7]. The Biginelli 3-CR was reported in 1891, whereas Mannich [9] reported his eponymous MCR in 1912. The first isocyanide-based MCRs were reported in 1921 and 1959 by Passerini [5] and Ugi [10], respectively. MCRs represent one of the most convenient synthetic approaches in chemistry, with the main advantages being a reduction in the number of sequential reaction steps required and often better yields [11,12]. The Passerini and Ugi reactions have gained a great deal of attention since the early 1990s [13,14]. The versatility of these reactions relies on the dual reactivity of the isocyanide carbon atom, leading to the formation of diverse and complex products [15,16].

The first reaction of isocyanides 1 with electron deficient alkynes such as DMAD 2 to give zwitterions 3 (Scheme 1) was reported by Winterfeldt and co-workers [17]. This zwitterion adduct 3 can readily undergo cycloaddition reactions with various third components, generating a range of heterocyclic scaffolds of interest [18]. Previously, our group reported the reaction of zwitterion adduct 3 and different five-membered rings, for example, 4, containing both an acidic proton and internal nucleophile, to give products 5 incorporating all three reaction components (Scheme 1). Depending on the nature of the five-membered
ring, in certain cases such as for thiol 6, we observed that there was competition between the three-component reaction (to give 7) and the two-component reaction (to give 8). For the latter, DMAD 2 reacts directly with the five-membered ring, as shown in Scheme 1 for 1H-1,2,4-triazole-5-thiol 6, to give methyl 7-oxo-7H-[1,2,4]triazolo[5,1-b][1,3]thiazine-5-carboxylate 8 [19]. We found that the most successful three-component reactions involved five-membered rings containing more acidic protons.

In this work, we set out to investigate alternative rings to act as the third component substrate in these reactions and selected the acidic six-membered ring 2-amino-4H-1,3-thiazin-4-one derivatives 9, with predicted pKₐ values in the range of −1.80 to −2.21. Thiazines are bioactive scaffolds with a wide range of pharmacological activities, such as antimicrobial [20,21], anti-inflammatory [22], anticancer [23], antitubercular [24] and antiviral [25] activities. Another aim of this work was the further investigation of the two-component reactions between various five-membered rings and DMAD to prepare compounds such as 8 and their analogues. Of particular interest to us were the thiazole-pyrimidine derivatives, which display interesting biological activity. Compounds derived from thiazolopyrimidines are known to exhibit antioxidant and antitumor activities [26]. Derivatives containing a thiazole-pyrimidine moiety as part of a more complex structure were shown to possess activity against Mycobacterium tuberculosis [27], while thiazolopyrimidine containing compounds ritanserin [28] and setoperone [29] have been used in the study of psychiatric disorders.

We initially investigated the direct reactivity of dialkyl acetylenedicarboxylate towards 2-aminothiazoles for the preparation of thiazole-pyrimidine derivatives and subsequently converted this two-component reaction into a one-pot, three-component reaction of dialkyl acetylenedicarboxylate with thiourea and an α-haloketone for the formation of thiazolepyrimidines. Here we present a facile and efficient one-pot, three-component reaction method for the synthesis of novel dihydropyrimido-thiazine-6,7-dicarboxylates from an isocyanide, dialkyl acetylenedicarboxylate and 2-amino-4H-1,3-thiazin-4-one derivatives; and the synthesis of 5H-thiazolo[3,2-a]pyrimidine-7-carboxylates from thiourea, an α-haloketone and dialkyl acetylenedicarboxylates.

2. Results and Discussion

2.1. Synthesis of 4-Oxo-4,6-Dihydropyrimido[2,1-b][1,3]Thiazine-6,7-Dicarboxylates by Three-Component Reaction

The six-membered rings 9a–e, which were selected for use in these three-component reactions, are shown in Figure 1. To the best of our knowledge, none of these compounds has previously been tested in reaction with acetylenedicarboxylates 2 and isocyanides 1. In addition, compounds 9c and 9d have not been previously reported. The initial reaction of 2-amino-4H-1,3-thiazin-4-one 9a [30] with isocyanide 1a and acetylene dicarboxylates 2a–b
resulted in products 10a–b (Table 1). This success encouraged us to further test the reaction of 2-amino-6-methyl-4H,1,3-thiazin-4-one 9b [31], 2-amino-6-ethyl-4H,1,3-thiazin-4-one 9c, 2-amino-6-propyl-4H,1,3-thiazin-4-one 9d and 2-amino-6-phenyl-4H,1,3-thiazin-4-one 9e [31] with the zwitterion adduct formed by the reaction of aliphatic isocyanides 1a–c and acetylenedicarboxylates 2a–b. Generally, the reactions were carried out by the addition of isocyanide 1 to acetylenedicarboxylate 2 at 0 °C under inert conditions, as shown in Table 1, followed by slow introduction of compound 9a–e as a solution in dry dichloromethane to the reaction mixture at room temperature. After purification, novel products 10a–u were obtained in good yields (Table 1). When selected reactions were tested using the green solvents ethanol and isopropanol instead of dichloromethane, low yields of thiazine compounds 10 were obtained. When acetone was employed as a solvent for the synthesis of thiazine compounds 10a–u, using starting materials 9a–e, average yields were obtained. Nonetheless, acetone can be considered as an alternative greener solvent to afford thiazine compounds 10a–u using a three-component reaction. Compound 10o gave the highest yield in acetone of 58%, while the lowest yield obtained was for 10g, at 41%.

Figure 1. Six-membered rings 9a–e chosen for the three-component reaction.

Table 1. Isolated yields of products 10a–u from the reaction of isocyanides 1, dialkyl acetylenedicarboxylates 2 and thiazines 9 at room temperature.

| Compound | R^1 | R^2 | R^3 | Yield % (Time) |
|----------|-----|-----|-----|----------------|
| 10a      | t-Bu| CH_3| H   | 81 (6 h)       |
| 10b      | t-Bu| CH_3| H   | 85 (6 h)       |
| 10c      | t-Bu| CH_3| CH_3| 82 (6 h)       |
| 10d      | t-Bu| CH_3CH_2| CH_3| 83 (6 h)       |
| 10e      | 1,1,3,3-tetramethylbutyl| CH_3| CH_3| 76 (6 h)       |
| 10f      | 1,1,3,3-tetramethylbutyl| CH_3CH_2| CH_3| 77 (6 h)       |
| 10g      | cyclohexyl| CH_3| CH_3| 84 (12 h)      |
| 10h      | cyclohexyl| CH_3CH_2| CH_3| 85 (12 h)      |
| 10i      | t-Bu| CH_3| CH_3CH_2| 84 (6 h) |
| 10j      | t-Bu| CH_3CH_2| CH_3CH_2| 79 (6 h) |
| 10k      | 1,1,3,3-tetramethylbutyl| CH_3| CH_3CH_2| 81 (6 h) |
| 10l      | 1,1,3,3-tetramethylbutyl| CH_3CH_2| CH_3CH_2| 81 (6 h) |
| 10m      | t-Bu| CH_3| CH_3CH_2| 84 (6 h) |
| 10n      | t-Bu| CH_3CH_2| CH_3CH_2| 85 (6 h) |
| 10o      | 1,1,3,3-tetramethylbutyl| CH_3| CH_3CH_2| 79 (6 h) |
| 10p      | 1,1,3,3-tetramethylbutyl| CH_3CH_2| CH_3CH_2| 79 (6 h) |
| 10q      | t-Bu| CH_3| C_6H_5| 77 (6 h) |
| 10r      | t-Bu| CH_3CH_2| C_6H_5| 80 (6 h) |
| 10s      | 1,1,3,3-tetramethylbutyl| CH_3| C_6H_5| 76 (6 h) |
| 10t      | 1,1,3,3-tetramethylbutyl| CH_3CH_2| C_6H_5| 83 (6 h) |
| 10u      | cyclohexyl| CH_3| C_6H_5| 79 (12 h) |
Based on our previous results, we believe the very good yields obtained for 10a–u were due to the presence of an acidic proton on the 2-amino-4H-1,3-thiazin-4-one derivatives 9a–e which enables the reaction with the zwitterion adduct to occur readily in dichloromethane. The highest yields obtained were 85% for 10b, 10h and 10n and the lowest yield was 76% for 10h. Based on the isolated yields it is clear that the 2-amino-4H-1,3-thiazin-4-one derivatives 9a–e were completely inert towards direct reaction with either dialkyl acetylenedicarboxylates 2 or alkyl isocyanides 1, while they demonstrated very high reactivity towards the zwitterion adduct. Although we have not definitively established the mechanism for the formation of 10, a plausible mechanism for this reaction is proposed (after Esmaeili and co-workers [32]) and shown in Scheme 2. Zwitterion adduct 3 deprotonates 9, followed by 1,4-nucleophilic attack on the nitrilium ion A. The resulting ketenimine intermediate B cyclizes to afford compound 10.

Scheme 2. Proposed reaction mechanism for the formation of 10.

2.2. Synthesis of 5H-Thiazolo[3,2-a]Pyrimidine-7-Carboxylates Using Two-Component and Three-Component Reactions

We went on to investigate the direct reaction of various five-membered ring substrates with electron deficient alkynes (DMAD/DEtAD). This study was started when we noticed the presence of co-products resulting from direct reaction of DMAD with some of the five-membered rings when we were attempting three-component reactions including an isocyanide [19]. Crank and co-workers [33] previously reported the reaction of 4-methylthiazol-2-amine 11 with DMAD 2 to afford Diels–Alder adduct 12, methyl 3-methyl-7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate 13 and product 14, resulting from reaction with two moles of DMAD (Scheme 3). Acheson and Wallis [34] also reported the direct reaction of 2-aminothiazole 11 and DMAD 2 using methanol under reflux to obtain methyl 7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate 13. Thiazolopyrimidines can be obtained using two component reactions, under various conditions, starting from 2-aminothiazole derivatives and Michael acceptors, such as vinyl trichloromethylketones [35], ethyl acetoacetate [36], bis(2,4,6-trichlorophenyl) malonate [37], diethylmalonate, ethyl cyanoacetate, cyanoacetamide, ketonitriles and DMAD [38]. Our first approach was to react DMAD 2a and pre-prepared five-membered ring substrates 11 directly to obtain fused 5-membered ring thiazole-pyrimidines 13. However, the moderate yields achieved using this approach led us to optimize the preparation as a one-pot, three-component reaction from thiourea 15, α-haloketones 16 and DMAD or DEtAD. To the best of our knowledge, this is the first report of such a one-pot preparation.
Initially, in order to achieve thiazole-pyrimidines 13, we prepared 5-membered ring substrates 11a–g [39–42] (Figure 2) to react with DMAD 2a. The reactions were carried out by treating 11c and 11e–g with 2a under ethanol reflux conditions to obtain 13a–d (Method A). Repetition of these reactions using DEtAD 2b afforded 13e–i, whilst di-tert-butyl acetylenedicarboxylate (DTAD) 2c and substrate 11a gave rise to 13j (Table 2). Despite the disappointing yields, the success of this reaction led us to extend it to the use of alternative five-membered ring reactants 17 [43], 18 [44] and 5 [45], with these substrates giving rise to compounds 19a–b, 20 and 8, respectively, in good yields.

![Scheme 3. Synthesis of thiazole-pyrimidines 13.](image)

**Figure 2.** Five membered-ring substrates chosen for the reactions.
Using Method A, low-to-average yields were obtained for most of the products 13. The highest yield from this set of compounds was for 13g with 79% yield and 13f with 71%. However, when using substrates 11d–g with phenyl groups at R\(^1\) the yields dropped slightly due to the weakly activating phenyl ring and the deactivating groups on the phenyl ring (such as fluorine and chlorine) for both DMAD and DEtAD reactions. The presence of fluorine and chlorine at the para-position of substrates 11f and 11g resulted in a slight drop in yield for compounds 13c, 13d, 13h and 13i compared to 13b, with a methyl substituent at the para-position. The reaction of dialkyl acetylenedicarboxylate 2c and substrate 11a gave a 70% yield of product 13j. When substrate 17 was treated with dialkyl acetylenedicarboxylates 2a–b the reaction gave 82% and 80% yield of 19a and 19b, respectively. Substrates 5 and 18 were also treated with DEtAD 2b and gave rise to compounds 8 and 20 in good yields of 88% and 82%, respectively. When comparing the reactivity of the substrates it is evident that substrates 5, 17 and 18 were more reactive towards 2a–b than 11 under these conditions, giving consistently better yields.
The disappointing yields obtained from the direct reaction of substrates 11a–h with dialkyl acetylenedicarboxylates 2a–b prompted us to apply a second approach via a 3-CR to give product 13 (Method B). The reactions were carried out by initially mixing thiourea 15 with α-haloketone 16, followed by introduction of dialkyl acetylenedicarboxylate 2 in a 1:1 ratio of ethanol and THF at room temperature, after which the reactions were heated to ethanol reflux temperature for at least 12 h. This gave rise to products 13a–d in improved yields compared to the first approach (Table 3). The reactions were repeated using DETAD 2b and gave rise to products 13e–i as expected. Room temperature reactions resulted in incomplete reactions, with recovery of some of the starting materials, even after 48 h. The three-component reaction (3-CR) was thus found to be suitable for the synthesis of products 13a–i, which were isolated in good yields of 70–91%, based on the nature of the functional groups in the reactants 16a–e and 2a–b, as shown in Table 3. The highest yields for this set of compounds, using DMAD 2a, was 82% for 13a. The percentage yields of compounds 13b–d were found to be slightly lower when compared to 13a. Even starting materials substituted with fluorine or chlorine at the para-position (16c and 16d) gave very good yields of product. Yields increased when using DETAD 2b rather than DMAD 2a.

Table 3. Isolated yields of 13a–i from one-pot, three-component reaction.

| Compound | X     | R¹   | R²   | R³   | Yield (%) | Time (h) |
|----------|-------|------|------|------|-----------|----------|
| 13a      | Cl    | CH₃  | CH₃  | CH₃  | 82        | 12       |
| 13b      | Br    | Ph-CH₃ | CH₃  | CH₃  | 71        | 6        |
| 13c      | Cl    | Ph-F | CH₃  | CH₃  | 70        | 6        |
| 13d      | Br    | Ph-Cl | H    | CH₃  | 71        | 12       |
| 13e      | Cl    | H    | H    | CH₃CH₂ | 83        | 12       |
| 13f      | Cl    | CH₃  | H    | CH₃CH₂ | 91        | 12       |
| 13g      | Cl    | CH₃  | CH₃  | CH₃CH₂ | 86        | 12       |
| 13h      | Cl    | Ph-F | H    | CH₃CH₂ | 86        | 6        |
| 13i      | Br    | Ph-Cl | H    | CH₃CH₂ | 84        | 6        |

Scheme 4 shows the proposed mechanism for the formation of compound 13 (see Acheson and Wallis [34]). The reaction proceeds by initial nucleophilic attack of the ring-nitrogen of substrate 11 on the α,β-unsaturated ester of DMAD forming an intermediate which undergoes internal cyclisation through nucleophilic attack of the side-chain nitrogen on the ester carbonyl carbon, followed by the loss of methanol, to afford product 13.

Scheme 4. Proposed reaction mechanism for the formation of compounds 13a–j.
The structures of the synthesized compounds were confirmed by mass spectrometry, NMR spectroscopy and FTIR spectroscopy (Supplementary Materials). Explicit confirmation for the structures of 13a, 13b, 13d and 8 was obtained from single-crystal X-ray analysis (Figure 3).

These compounds were prepared as part of our ongoing efforts towards identifying novel heterocycles with biological activity [46–48]. Compounds showing cytotoxicity values of >200 µM in MT-4 cells were evaluated for activity in an HIV assay (see Supplementary Materials). Unfortunately, these compounds were not found to be active as antiviral agents. However, due to the relatively high cytotoxicity values seen for some of the compounds, the possibility of their application as anticancer agents is being further investigated.

3. Materials and Methods
3.1. Chemical Synthesis
3.1.1. General Information
All commercially available reagents were supplied by Sigma Aldrich (Schnelldorf, Germany) and used without further purification. Dry solvents were used directly from an LC-Tech SP-1 Solvent Purification System (LC Technology Solutions Inc., Seabrook, TX, USA) stored under argon. All solvents used for chromatographic purposes were supplied by RadChem (Johannesburg, South Africa) and were used without further distillation. NMR spectra were recorded at 298 K on a 400 MHz Bruker Avance Spectrometer (Bruker BioSpin, Rheinstetten, Germany). Chemical shifts are reported in ppm and are referenced internally to residual solvent resonances [7.26 (CDCl₃) and 2.50 (DMSO-d₆) for ¹H NMR; 77.16 (CDCl₃) 40.45 (DMSO-d₆) for ¹³C NMR]. For mass spectrometry (LC–MS/MS), high-resolution mass spectra were obtained. Fourier infrared spectra (FTIR) were recorded by
using a Perkin Elmer FTIR Spectrometer Spectrum Two (Perkin Elmer, Midrand, South Africa). All signals are reported on the wavenumber scale (ν/cm⁻¹).

3.1.2. General Synthesis of 4-Oxo-4,6-Dihydropyrimido[2,1-b][1,3]Thiazine-6,7-Dicarboxylate Derivatives (10a–u)

In a round-bottomed flask equipped with a magnetic stirrer, isocyanide derivative (1a–c) in dry CH₂Cl₂ (2.5 mL) was slowly added to DMAD (2a) or DETAD (2b) in dry CH₂Cl₂ (5 mL) at 0 °C, under inert argon, and the solution was allowed to stir for 0.5 h. Then 2-amino-4H-1,3-thiazin-4-one derivatives 9a–e in dry CH₂Cl₂ (2.5 mL) were slowly added to the solution and stirred at room temperature under argon for 6–24 h. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography, using hexane-ethyl acetate as eluent to afford the products.

**Dimethyl 8-(tert-butylamino)-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate** (10a); 2-amino-4H-1,3-thiazin-4-one (9a) (0.25 g, 1.95 mmol), tert-butyl isocyanide (1a) (0.16 g, 1.95 mmol) and dimethyl acetylenedicarboxylate (2a) (0.28 g, 1.95 mmol). Physical characteristics: yellow solid; Yield: 0.55 g, 81%; Mp: 145–147 °C, Rf: 0.5, hexane/ethyl acetate (90%/10%); ¹H NMR (400 MHz, CDCl₃) δ 8.73 (1H, br s, NH), 7.36 (1H, d, J = 10.8 Hz, Ar-CH), 6.51 (1H, d, J = 10.4 Hz, Ar-CH), 6.35 (1H, s, CH), 3.75 (3H, s, OCH₃), 3.71 (3H, s, OCH₃), 1.42 (9H, s, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 170.9 (C=O), 168.4 (C=O), 160.7 (C=O), 157.5 (C-10), 154.9 (C-8), 136.8 (C-3), 118.2 (Ar-CH), 72.3 (C-7), 52.9 (C-6), 52.7 (OCH₃), 51.1 (OCH₃), 50.8(C(CH₃)₃), 30.9 (C(CH₃)₃); FTIR ν_max/cm⁻¹: 2982, 2913, 1728, 1690, 1648, 1600, 1533, 1472, 1431; HRMS (ESI–TOF) m/z: [M + H]^+ calculated for C₁₅H₂₀N₃O₅S^+ 354.1118 found 354.1113.

**Diethyl 8-(tert-butylamino)-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate** (10b); 2-amino-4H-1,3-thiazin-4-one (9a) (0.25 g, 1.95 mmol), tert-butyl isocyanide (1a) (0.16 g, 1.95 mmol) and diethyl acetylenedicarboxylate (2b) (0.33 g, 1.95 mmol). Physical characteristics: yellow solid; Yield: 0.63 g, 85%; Mp: 143–145 °C, Rf: 0.6, hexane/ethyl acetate (90%/10%); ¹H NMR (400 MHz, CDCl₃) δ 8.75 (1H, br s, NH), 7.34 (1H, d, J = 10.8 Hz, Ar-CH), 6.51 (1H, d, J = 10.4 Hz, Ar-CH), 6.34 (1H, s, CH), 3.40–4.11 (4H, m, 2 × CH₂), 1.43 (9H, s, C(CH₃)₃), 1.33 (3H, t, J = 7.2 Hz, CH₃), 1.26 (3H, t, J = 7.2 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 170.6 (C=O), 168.1 (C=O), 160.8 (C=O), 157.3 (C-10), 154.8 (C-8), 136.7 (C-3), 118.2 (Ar-CH), 72.5 (C-7), 61.9 (O-CH₂), 59.3 (O-CH₂), 52.6 (C-6), 51.3(C(CH₃)₃), 30.9 (C(CH₃)₃), 14.9(CH₃), 14.2 (CH₃); FTIR ν_max/cm⁻¹: 3067, 2983, 2864, 1728, 1690, 1647, 1599, 1534, 1431; HRMS (ESI–TOF) m/z: [M + H]^+ calculated for C₁₇H₂₃N₃O₅S^+ 382.1431 found 382.1439.

**Dimethyl 8-(tert-butylamino)-2-methyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate** (10c); 2-amino-6-methyl-4H-1,3-thiazin-4-one (9b) (0.25 g, 1.76 mmol), tert-butyl isocyanide (1a) (0.15 g, 1.76 mmol) and dimethyl acetylenedicarboxylate (2a) (0.25 g, 1.76 mmol). Physical characteristics: yellow solid; Yield: 0.53 g, 82%; Mp: 149–151 °C, Rf: 0.5, hexane/ethyl acetate (90%/10%); ¹H NMR (400 MHz, CDCl₃) δ 8.63 (1H, br s, NH), 6.24 and 6.23 (2H, 2 × s, Ar-CH and H-6), 3.66 (3H, s, O-CH₃), 3.61 (3H, s, O-CH₃), 2.17 (Ar-CH₃), 1.35 (9H, s, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 171.1 (C=O), 168.5 (C=O), 161.2 (C=O), 157.8 (C-10), 155.3 (C-8), 149.7 (C-2), 116.1 (C-3), 72.1 (C-7), 52.9 (C-6), 52.6 (OCH₃), 51.0 (OCH₃), 50.8 (C(CH₃)₃), 30.8 (C(CH₃)₃) 22.1 (Ar-CH₃); FTIR ν_max/cm⁻¹: 2992, 2963, 2902, 1734, 1648, 1682, 1653, 1602, 1525; HRMS (ESI–TOF) m/z: [M + H]^+ calculated for C₁₇H₂₃N₃O₅S^+ 368.1275 found 368.1279.

**Diethyl 8-(tert-butylamino)-2-methyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate** (10d); 2-amino-6-methyl-4H-1,3-thiazin-4-one (9b) (0.25 g, 1.76 mmol), tert-butyl isocyanide (1a) (0.15 g, 1.76 mmol) and diethyl acetylenedicarboxylate (2b) (0.30 g, 1.76 mmol). Physical characteristics: yellow solid; Yield: 0.57 g, 83%; Mp: 135–137 °C, Rf: 0.6, hexane/ethyl acetate (90%/10%); ¹H NMR (400 MHz, CDCl₃) δ 8.72 (1H, br s, NH), 6.28 (2H, 2 × s, Ar-CH and H-6), 4.27–4.06 (4H, m, 2 × CH₂), 2.22 (3H, Ar-CH₃), 1.39 (9H, s, C(CH₃)₃), 1.29 (3H, t, J = 7.2 Hz, CH₃), 1.22 (3H, t, J = 7.2 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 170.7 (C=O), 168.2 (C=O), 161.4 (C=O), 157.7 (C-10), 155.2 (C-8), 149.7 (C-2), 116.1 (C-3), 72.4 (C-7), 61.8 (O-CH₂), 59.2 (O-CH₂), 52.6 (C-6), 51.3 (N-C(CH₃)₃), 30.9 (C(CH₃)₃), 22.1
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(10g), 2-amino-6-methyl-4H-1,3-thiazin-4-one (9b) (0.25 g, 1.76 mmol), cyclohexyl isocyanide (1c) (0.19 g, 1.76 mmol) and dimethyl acetylenedicarboxylate (2a) (0.25 g, 1.76 mmol). Physical characteristics: yellow solid; Yield: 0.69 g, 84%; Mp: 148–150 °C, Rf: 0.42, hexane/ethyl acetate (90:10%); 1H NMR (400 MHz, CDCl3) δ 8.73 (1H, br s, NH), 6.29 (2H, 2 × s, Ar-CH, H-6), 4.26–4.01 (4H, m, 2 × CH2O), 2.23 (3H, s, Ar-CH3), 1.80 (2H, q, J = 14.4 Hz, CH2), 1.44 and 1.42 (6H, 2 × s, 2 × CH3), 1.31 (3H, t, J = 6.8 Hz, CH3), 1.21 (3H, t, J = 7.2 Hz, CH3), 0.94 (9H, s, C(CH3)3); 13C NMR (100 MHz, CDCl3) δ 171.0 (C=O), 168.2 (C=O), 161.4 (C=O), 157.4 (C-10), 155.4 (C-8), 149.8 (C-2), 116.1 (C-3), 56.2 (C(CH3)3), 53.3 (CH2), 52.9 (C-6), 51.1 (OCH3), 50.8 (OCH3), 31.7 (C(CH2)2), 31.8 (C(CH3)3), 31.6 (CH3), 31.5 (CH3), 22.1 (Ar-CH3); FTIR νmax/cm−1: 3285, 2951, 2899, 1739, 1687, 1599, 1535, 1442; HRMS (ESI–TOF) m/z: [M + H]+ calculated for C22H30N3O5S2 452.2214 found 452.2223.

Dimethyl 8-(cyclohexylamino)-2-methyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarbonyl (10h); 2-amino-6-methyl-4H-1,3-thiazin-4-one (9b) (0.25 g, 1.76 mmol), cyclohexyl isocyanide (1c) (0.19 g, 1.76 mmol) and dimethyl acetylenedicarboxylate (2b) (0.30 g, 1.76 mmol). Physical characteristics: yellow solid; Yield: 0.63 g, 85%; Mp: 170–172 °C, Rf: 0.50, hexane/ethyl acetate (90:10%); 1H NMR (400 MHz, CDCl3) δ 8.55 (1H, br s, NH), 6.28 (2H, 2 × s, Ar-CH, H-6), 4.27–4.09 (4H, m, 2 × CH2O), 3.92 (1H, s, CH), 2.23 (3H, s, Ar-CH3), 1.93–1.69 (4H, m, cyclohexyl), 1.66–1.55 (4H, m, cyclohexyl), 1.41–1.33 (2H, m, cyclohexyl) 1.34 (3H, s, J = 7.2 Hz, CH3), 1.28 (3H, s, J = 6.8 Hz, CH3); 13C NMR (101 MHz, CDCl3) δ 170.7 (C=O), 168.2 (C=O), 161.3 (C=O), 158.9 (C-10), 154.1 (C-8), 149.6 (C-2), 115.9 (C-3), 71.8 (C-7), 61.7 (O-CH2), 59.1 (O-CH2), 51.4 (C-6), 49.6 (CH), 34.3 (CH2, cyclohexyl), 33.7 (CH2, cyclohexyl), 25.7 (CH2, cyclohexyl), 24.8 (CH2, cyclohexyl), 24.7 (CH2, cyclohexyl), 22.1 (Ar-CH3). FTIR νmax/cm−1: 3285, 2946, 2888, 1762, 1730, 1692, 1653, 1618, 1590, 1525, 1445; HRMS (ESI–TOF) m/z: [M + H]+ calculated for C18H15N3O5S2 394.1431 found 394.1433.

Diethyl 8-(cyclohexylamino)-2-methyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarbonyl (10h); 2-amino-6-methyl-4H-1,3-thiazin-4-one (9b) (0.25 g, 1.76 mmol), cyclohexyl isocyanide (1c) (0.19 g, 1.76 mmol) and diethyl acetylenedicarboxylate (2b) (0.30 g, 1.76 mmol). Physical characteristics: yellow solid; Yield: 0.63 g, 85%; Mp: 170–172 °C, Rf: 0.50, hexane/ethyl acetate (90:10%); 1H NMR (400 MHz, CDCl3) δ 8.55 (1H, br s, NH), 6.28 (2H, 2 × s, Ar-CH, H-6), 4.27–4.09 (4H, m, 2 × CH2O), 3.92 (1H, s, CH), 2.23 (3H, s, Ar-CH3), 1.93–1.69 (4H, m, cyclohexyl), 1.66–1.55 (4H, m, cyclohexyl), 1.41–1.33 (2H, m, cyclohexyl) 1.34 (3H, s, J = 7.2 Hz, CH3), 1.28 (3H, s, J = 6.8 Hz, CH3); 13C NMR (101 MHz, CDCl3) δ 170.7 (C=O), 168.2 (C=O), 161.3 (C=O), 158.9 (C-10), 154.1 (C-8), 149.6 (C-2), 115.9 (C-3), 71.8 (C-7), 61.7 (O-CH2), 59.1 (O-CH2), 51.4 (C-6), 49.6 (CH), 34.3 (CH2, cyclohexyl), 33.7 (CH2, cyclohexyl), 25.7 (CH2, cyclohexyl), 24.8 (CH2, cyclohexyl), 24.7 (CH2, cyclohexyl), 22.1 (Ar-CH3), 14.9 (CH2CH3), 14.1 (CH2CH3); FTIR νmax/cm−1: 2992,
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2945, 2867, 1735, 1689, 1648, 1588, 1540, 1440; HRMS (ESI-TOF) m/z: [M + H]+ calculated for C_{92}H_{82}N_{36}O_{36}S_{4} 422.1744 found 422.1712.

Dimethyl 8-(tert-butyldiamino)-2-ethyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (10i); 2-amino-6-ethyl-4H-1,3-thiazin-4-one (9c) (0.25 g, 1.60 mmol), tert-butyl isocyanide (1a) (0.13 g, 1.60 mmol) and dimethyl acetylenedicarboxylate (2a) (0.22 g, 1.60 mmol). Physical characteristics: yellow solid; Yield: 0.52 g, 79%; Mp: 94–96 °C; Rf: 0.6, hexane/ethyl acetate (90:10%); 1H NMR (400 MHz, CDCl3) δ 8.72 (1H, br s, NH), 6.30 and 6.28 (2H, 2 × s, Ar-CH, H-6), 4.27–4.09 (4H, m, 2 × CH2), 2.50 (2H, q, J = 7.6 Hz, Ar-CH2), 1.40 (9H, s, C(CH3)3), 0.77 (3H, s, OCH3), 3.56 (3H, s, OCH3), 2.24, 2.15, 1.89 (2H, q, J = 7.6 Hz, Ar-CH2), 1.73 (CH3), 0.71 (3H, s, OCH3), 0.77 (3H, s, OCH3), 3.56 (3H, s, OCH3), 2.44 (2H, q, J = 7.6 Hz, Ar-CH2), 1.73 (CH3), 1.38 and 1.36 (6H, 2 × s, 2 × CH2), 1.21 (3H, t, J = 7.2 Hz, CH3CH2), 0.87 (9H, s, C(CH3)3); 13C NMR (101 MHz, CDCl3) δ 171.1 (C=O), 168.4 (C=O), 161.4 (C=O), 157.7 (C-10), 155.8 (C-8), 155.4 (C-2), 114.3 (C-3), 71.9 (C-7), 56.2 (C(CH3)3), 53.3 (C(CH3)2), 52.8 (OCH3), 51.1 (C-6), 50.7 (OCH3), 31.8 (C(CH3)3), 31.7, 31.6, 2 (× 2) 29.3 (Ar-CH2), 12.4 (CH3); FTIR νmax/cm⁻¹: 3285, 2975, 2890, 2786, 1739, 1674, 1644, 1616, 1591, 1531, 1438; HRMS (ESI-TOF) m/z: [M + H]+ calculated for C_{92}H_{82}N_{36}O_{36}S_{4} 438.2057 found 438.2038. 

Dimethyl 8-(2,4-dimethylpentan-2-ylamino)-2-ethyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (10k); 2-amino-6-ethyl-4H-1,3-thiazin-4-one (9c) (0.25 g, 1.60 mmol), 1,1,3,3-tetramethylbutyl isocyanide (1b) (0.22 g, 1.76 mmol) and dimethyl acetylenedicarboxylate (2a) (0.23 g, 1.60 mmol). Physical characteristics: yellow paste; Yield: 0.57 g, 81%; Rf: 0.5, hexane/ethyl acetate (90:10%); 1H NMR (400 MHz, CDCl3) δ 8.64 (1H, br s, NH), 6.25 and 6.24 (2H, 2 × s, Ar-CH, H-6), 3.66 (3H, s, OCH3), 3.59 (3H, s, OCH3), 2.44 (2H, q, J = 7.6 Hz, Ar-CH2), 1.73 (CH3), 1.38 and 1.36 (6H, 2 × s, 2 × CH2), 1.21 (3H, t, J = 7.2 Hz, CH3CH2), 0.87 (9H, s, C(CH3)3); 13C NMR (101 MHz, CDCl3) δ 171.1 (C=O), 168.4 (C=O), 161.4 (C=O), 157.7 (C-10), 155.8 (C-8), 155.4 (C-2), 114.3 (C-3), 71.9 (C-7), 56.2 (C(CH3)3), 53.3 (C(CH3)2), 52.8 (OCH3), 51.1 (C-6), 50.7 (OCH3), 31.8 (C(CH3)3), 31.7, 31.6, 2 (× 2) 29.3 (Ar-CH2), 12.4 (CH3); FTIR νmax/cm⁻¹: 3285, 2975, 2890, 2786, 1739, 1674, 1649, 1598, 1532; HRMS (ESI-TOF) m/z: [M + H]+ calculated for C_{92}H_{82}N_{36}O_{36}S_{4} 438.2057 found 438.2038. 

Diethyl 8-(2,4-dimethylpentan-2-ylamino)-2-ethyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (10l); 2-amino-6-ethyl-4H-1,3-thiazin-4-one (9c) (0.25 g, 1.60 mmol), 1,1,3,3-tetramethylbutyl isocyanide (1b) (0.22 g, 1.60 mmol) and diethyl acetylenedicarboxylate (2b) (0.27 g, 1.60 mmol). Physical characteristics: yellow solid; Yield: 0.61 g, 81%; Mp: 98–100 °C; Rf: 0.6, hexane-ethyl acetate (90:10%); 1H NMR (400 MHz, CDCl3) δ 8.73 (1H, br s, NH), 6.30 and 6.29 (2H, 2 × s, Ar-CH, H-6), 4.26–4.08 (4H, m, 2 × CH2O), 2.50 (2H, q, J = 7.2 Hz, Ar-CH2), 1.80 (2H, q, J = 14.8 Hz, CH2), 1.45 and 1.42 (6H, 2 × s, (CH2)2-C), 1.31–1.25 (6H, m, 2 × OCH2CH3), 1.21 (3H, s, J = 7.2 Hz, ArCH2CH3), 0.94 (9H, s, C(CH3)3); 13C NMR (101 MHz, CDCl3) δ 170.7 (C=O), 168.2 (C=O), 161.6 (C=O), 157.6 (C-10), 157.0 (C-8), 155.3 (C-2), 114.3 (C-3), 71.2 (C-7), 56.2 (C(CH3)3), 53.3 (Ar-CH2), 51.4 (C-6), 31.7 (C(CH3)3), 29.3 (C(CH3)3), 29.3 (CH3), 14.9 (CH3), 14.2 (CH3), 12.5 (CH3); FTIR νmax/cm⁻¹: 3270, 2973, 2913, 1737, 1688, 1646, 1600, 1535, 1432; HRMS (ESI-TOF) m/z: [M + H]+ calculated for C_{92}H_{82}N_{36}O_{36}S_{4} 466.2370 found 466.2333. 

Dimethyl 8-(tert-butylamino)-4-oxo-2-propyl-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (10m); 2-amino-6-propyl-4H-1,3-thiazin-4-one (9d) (0.25 g, 1.47 mmol), tert-butyl isocyanide (1a) (0.12 g, 1.47 mmol) and dimethyl acetylenedicarboxylate (2a) (0.21 g, 1.47 mmol). Physical characteristics: yellow paste; Yield: 0.48 g, 84%; Rf: 0.5, hexane/ethyl
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1.22 mmol). Physical characteristics: yellow solid; Yield: 0.40 g, 77%; Mp: 99–101

1.47 mmol), 1,1,3,3-tetramethylbutyl isocyanide (1b)

1.38 (CH$_2$C$_6$H$_4$), 59.1 (O-CH$_2$), 52.5 (C($CH_3$)$_3$), 51.3 (C-6), 38.0 (Ar-CH$_3$), 30.8 (C($CH_3$)$_3$), 21.6 (CH$_2$C$_6$H$_4$), 14.9, 14.1 and 13.4 (3 × CH$_3$); FTIR ν$_{max}$/cm$^{-1}$: 3285, 2925, 2910, 2870, 1737, 1687, 1646, 1600, 1535, 1432; HRMS (ESI–TOF) m/z: [M+H]$^+$ calculated for C$_{24}$H$_{31}$N$_2$O$_5$S$^+$ 424.1901 found 424.1873.

Diethyl 8-(2-oxo-2-propyl-4H-1,3-thiazin-4-one (1a)

Yield: 0.21 g, 1.47 mmol) and diethyl acetylenedicarboxylate (2b) (0.25 g, 1.60 mmol).

Physical characteristics: yellow paste; Yield: 0.55 g, 79%; Rf: 0.6, hexane/ethyl acetate (90%:10%); 1H NMR (400 MHz, CDCl$_3$) δ 8.75 (1H, br s, NH), 6.33 (2H, s, Ar-CH, H-6), 4.13 (5H, s, OCH$_3$), 3.85 (3H, s, OCH$_3$), 3.59 (3H, s, OCH$_3$), 3.24 (2H, t, $J = 7.2$ Hz, CH$_2$), 1.73 (2H, s, C-CH$_3$), 1.64 (2H, sektet, $J = 7.2$ Hz, CH$_2$C$_6$H$_4$), 1.38 and 1.36 (6H, $2 	imes s$, $2 	imes CH_3$), 0.94 (3H, $s$, CH$_3$), 0.87 (9H, s, C($CH_3$)$_3$); 13C NMR (101 MHz, CDCl$_3$) δ 171.1 (C-O), 168.4 (C-O), 161.3 (C=O), 157.9 (C-10), 155.3 (C-8), 154.4 (C-2), 115.1 (C-3), 72.0 (C-7), 52.9 (OCH$_3$), 52.6 (C($CH_3$)$_3$), 51.1 (C-6), 50.8 (OCH$_3$), 37.9 (C($CH_3$)$_3$), 30.8 (Ar-CH$_3$), 21.6 (CH$_2$C$_6$H$_4$) 13.4 (CH$_3$), FTIR ν$_{max}$/cm$^{-1}$: 3285, 2925, 2910, 2870, 1737, 1687, 1646, 1600, 1535, 1432; HRMS (ESI–TOF) m/z: [M+H]$^+$ calculated for C$_{24}$H$_{31}$N$_2$O$_5$S$^+$ 424.1901 found 424.1873.

Diethyl 4-oxo-2-propyl-8-(2,4,4-trimethylpentan-2-ylamino)-4,6-dihydroxyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (10p)

2-amino-6-propyl-4H-1,3-thiazin-4-one (9d) (0.25 g, 1.47 mmol), 1,1,3,3-tetramethylbutyl isocyanide (1b) (0.21 g, 1.47 mmol) and dimethyl acetylenedicarboxylate (2a) (0.21 g, 1.47 mmol) physical characteristics: yellow paste; Yield: 0.52 g, 79%; Rf: 0.5, hexane/ethyl acetate (90%:10%); 1H NMR (400 MHz, CDCl$_3$) δ 8.64 (1H, br s, NH), 6.24 (2H, $2 	imes s$, Ar-CH, H-6), 3.65 (3H, s, OCH$_3$), 3.59 (3H, s, OCH$_3$), 2.38 (2H, t, $J = 7.6$ Hz, Ar-CH$_3$), 1.73 (2H, s, C-CH$_3$), 1.64 (2H, sektet, $J = 7.2$ Hz, CH$_2$C$_6$H$_4$), 1.38 and 1.36 (6H, $2 	imes s$, $2 	imes CH_3$), 0.94 (3H, $s$, CH$_3$), 0.87 (9H, s, C($CH_3$)$_3$); 13C NMR (101 MHz, CDCl$_3$) δ 171.1 (C-O), 168.4 (C-O), 161.3 (C=O), 157.8 (C-10), 155.4 (C-8), 154.3 (C-2), 115.2 (C-3), 72.3 (C-7), 61.7 (O-CH$_2$), 59.1 (O-CH$_2$), 52.5 (C($CH_3$)$_3$), 51.3 (C-6), 38.0 (Ar-CH$_3$), 30.8 (C($CH_3$)$_3$) 21.6 (CH$_2$C$_6$H$_4$), 14.9, 14.1 and 13.4 (3 × CH$_3$); FTIR ν$_{max}$/cm$^{-1}$: 3285, 2925, 2910, 2870, 1737, 1687, 1646, 1600, 1535, 1432; HRMS (ESI–TOF) m/z: [M+H]$^+$ calculated for C$_{24}$H$_{31}$N$_2$O$_5$S$^+$ 452.2214 found 452.2190.

Dimethyl 8-(2-oxo-2-propyl-4H-1,3-thiazin-4-one (1a)

Yield: 0.10 g, 1.22 mmol and dimethyl acetylenedicarboxylate (2a) (0.17 g, 1.22 mmol). Physical characteristics: yellow solid; Yield: 0.40 g, 77%; Mp: 99–101 °C, Rf: 0.58, hexane/ethyl acetate (90%:10%); 1H NMR (400 MHz, CDCl$_3$) δ 8.74 (1H, br s, NH), 7.59–7.48 (5H, m, Ar-H) 6.69 (1H, s, Ar-CH), 6.36 (1H, s, H-6), 3.75 (3H, s, OCH$_3$), 3.71 (3H, s, OCH$_3$), 1.43 (9H, s, C($CH_3$)$_3$); 13C NMR (101 MHz, CDCl$_3$) δ 171.1 (C=O), 168.5 (C=O), 161.3 (C=O), 157.9 (C=O), 155.3 (C-8), 154.4 (C-2), 115.1 (C-3), 72.0 (C-7), 52.9 (OCH$_3$), 52.6 (C($CH_3$)$_3$), 51.1 (C-6), 50.8 (OCH$_3$), 37.9 (C($CH_3$)$_3$), 30.8 (Ar-CH$_3$), 21.6 (CH$_2$C$_6$H$_4$) 13.4 (CH$_3$), FTIR ν$_{max}$/cm$^{-1}$: 3285, 2925, 2910, 2870, 1737, 1687, 1646, 1600, 1535, 1432; HRMS (ESI–TOF) m/z: [M+H]$^+$ calculated for C$_{18}$H$_{20}$N$_2$O$_5$S$^+$ 396.1588 found 396.1545.
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1.22 mmol). Physical characteristics: yellow solid; Yield: 0.44 g, 79%; Mp: 168–170 °C.

Diethyl 8-(tert-butyloxycarbonyl)-4-oxo-2-phenyl-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (10r); 2-amino-6-phenyl-4H-1,3-thiazin-4-one (9e) (0.25 g, 1.22 mmol), tert-butyl isocyanide (1a) (0.10 g, 1.22 mmol) and dimethyl acetylenedicarboxylate (2b) (0.21 g, 1.22 mmol). Physical characteristics: yellow solid; Yield: 0.45 g, 76%; Mp: 162–164 °C.

Diethyl 4-oxo-2-phenyl-8-((2,4,4-trimethylpentan-2-yl)amino)-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (10s); 2-amino-6-phenyl-4H-1,3-thiazin-4-one (9e) (0.25 g, 1.22 mmol), 1,1,3,3-tetramethylbutyl isocyanide (1b) (0.17 g, 1.22 mmol) and dimethyl acetylenedicarboxylate (2b) (3.017 g, 1.22 mmol). Physical characteristics: yellow solid; Yield: 0.52 g, 83%; Mp: 88–90 °C.

Diethyl 4-oxo-2-phenyl-8-((2,4,4-trimethylpentan-2-yl)amino)-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (10t); 2-amino-6-phenyl-4H-1,3-thiazin-4-one (9e) (0.25 g, 1.22 mmol). Physical characteristics: yellow solid; Yield: 0.40 g, hexane/ethyl acetate (90%:10%); 1H NMR (400 MHz, CDCl3) δ 8.76 (1H, br s, N-H), 7.63–7.51 (5H, m, Ar-H), 6.68 (1H, s, Ar-CH), 3.73 (3H, s, OCH3), 1.33–1.22 (6H, m, 2 × CH2), 1.26 (3H, t, J = 7.2 Hz, CH2CH3), 1.23 (6H, t, J = 6.8 Hz, CH2CH2CH3), 1.08 (9H, s, C(CH3)3), 1.06 (9H, s, C(CH3)3); 13C NMR (101 MHz, CDCl3) δ 170.7 (C-O), 161.7 (C=O), 159.3 (C-10), 151.2 (C-8), 149.4 (C-2), 133.8 (Ar-C), 131.9 (Ar-C), 129.5 (Ar-C), 126.9 (Ar-C), 126.4 (Ar-C), 113.9 (C-3), 71.2 (C-7), 56.2 (C(CH3)3), 53.3 (CH3), 52.9 (C-6), 51.3 and 50.7 (2 × OCH3), 31.8 (C(CH3)2), 31.7 (C(CH3)2), 31.6 (CH2O), 31.5 (CH2O); FTIR νmax/cm−1: 2953, 2878, 1732, 1681, 1651, 1613, 1542, 1450; HRMS (ESI–TOF) m/z: [M + H]+ calculated for C25H32N3O5S5 486.2057 found 486.2044.

Dimethyl 8-(cyclohexylamino)-4-oxo-2-phenyl-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (10u); 2-amino-6-phenyl-4H-1,3-thiazin-4-one (9e) (0.25 g, 1.22 mmol), cyclohexyl isocyanide (1c) (0.13 g, 1.22 mmol) and dimethyl acetylenedicarboxylate (2a) (0.17 g, 1.22 mmol). Physical characteristics: yellow solid; Yield: 0.44 g, 79%; Mp: 168–170 °C, Rf: 0.4, hexane/ethyl acetate (90%:10%); 1H NMR (400 MHz, CDCl3) δ 8.76 (1H, br s, N-H), 7.63–7.51 (5H, m, Ar-H), 6.71 (1H, s, Ar-CH), 3.71 (3H, s, OCH3), 1.37 (3H, s, OCH3), 1.50 and 1.48 (6H, 2 × s, 2 × CH3), 0.98 (9H, s, C(CH3)3); 13C NMR (101 MHz, CDCl3) δ 170.7 (C-O), 161.7 (C=O), 159.3 (C-10), 151.2 (C-8), 149.4 (C-2), 133.8 (Ar-C), 131.9 (Ar-C), 129.5 (Ar-C), 126.9 (Ar-C), 113.9 (C-3), 71.2 (C-7), 56.2 (C(CH3)3), 53.3 (CH3), 52.9 (C-6), 51.3 and 50.7 (2 × OCH3), 31.8 (C(CH3)2), 31.7 (C(CH3)2), 31.6 (CH2O), 31.5 (CH2O); FTIR νmax/cm−1: 2953, 2878, 1732, 1681, 1651, 1613, 1542, 1450; HRMS (ESI–TOF) m/z: [M + H]+ calculated for C25H32N3O5S5 486.2057 found 486.2044.
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3.1.3. Synthesis of Methyl 7-Oxo-7H-Thiazolo[3,2-a]Pyrimidine-5-Carboxylate Derivatives (13a–j): Method B (S-CR)

In a round-bottomed flask equipped with a magnetic stirrer bar, thiourea (15) was added to a solution of α-haloketone (16) in absolute ethanol (15 mL) and tetrahydrofuran (THF) (15 mL), and the reaction mixture was allowed to stir at room temperature for at least 15 min. After this time, dimethyl acetylenedicarboxylate (DMAD) or diethyl acetylenedicarboxylate (DEAD) (2) was slowly added over at least 10 min, and the reaction mixture was heated at 80 °C for 6–12 h while being monitored by TLC. After completion, the reaction was cooled, and the solvents were removed under reduced pressure to obtain a residue which was washed with cold ethanol and filtered to give a solid product.

**Methyl 2,3-dimethyl-7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (13a).** Thiourea (15) (0.36 g, 4.6 mmol), 3-chloro-2-butanone (16c) (0.50 g, 4.6 mmol) and DMAD (2a) (0.65 g, 4.6 mmol). Physical properties: orange solid; Yield: 0.51 g, 71%; Mp: 176–178 °C.

**Methyl 3-(4-fluorophenyl)-7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (13c).** Thiourea (15) (0.19 g, 2.4 mmol), 2-bromo-4-chloroacetophenone (15a) (0.33 g, 2.3 mmol). Physical properties: yellow solid; Yield: 0.49 g, 70%; Mp: 220–222 °C.

**Methyl 7-oxo-3-(p-tolyl)-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (13d).** Thiourea (15) (0.31 g, 4.1 mmol), chloroacetaldehyde (16a) (0.50 g, 4.1 mmol) and DETAD (2b) (0.69 g, 4.1 mmol). Physical properties: yellow solid; Yield: 0.84 g, 91%; Mp: 180–182 °C; Rf 0.4, hexane/ethyl acetate (40:60); 1H NMR (400 MHz, DMSO-d6) δ 8.30 (1H, d, J = 4.8 Hz, Ar-H), 7.63 (1H, d, J = 4.8 Hz, H-2), 7.36 (1H, d, J = 4.8 Hz, H-3), 6.76 (1H, s, H-6), 4.38 (2H, q, J = 6.8 Hz, O-CH2), 1.34 (3H, t, J = 7.2 Hz, CH3) 13C NMR (101 MHz, DMSO-d6) δ 166.8 (C=O), 165.3 (C=O), 160.6 (C-9), 138.6 (Ar-C), 138.9 (Ar-C), 127.5 (Ar-CH), 127.2 (Ar-CH3), 113.1 (C-6), 109.0 (C-2), 52.9 (O-CH3); FTIR v max/cm−1: 3041, 1742, 1639, 1587, 1509, 1485, 1416; HRMS (ESI–TOF) m/z: [M + H]+ calculated for C13H13N2O2S+ 304.0391, found 304.0391.

**Ethyl 7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (13e).** Thiourea (15) (0.31 g, 4.1 mmol), chloroacetaldehyde (16a) (0.50 g, 4.1 mmol) and DETAD (2b) (0.69 g, 4.1 mmol). Physical properties: yellow solid; Yield: 0.84 g, 91%; Mp: 180–182 °C; Rf 0.4, hexane/ethyl acetate (40:60); 1H NMR (400 MHz, DMSO-d6) δ 8.30 (1H, d, J = 4.8 Hz, H-2), 7.36 (1H, d, J = 4.8 Hz, H-3), 6.76 (1H, s, H-6), 4.38 (2H, q, J = 6.8 Hz, O-CH2), 1.34 (3H, t, J = 7.2 Hz, CH3) 13C NMR (101 MHz, DMSO-d6) δ 166.8 (C=O), 165.3 (C=O), 160.6 (C-9), 138.6 (Ar-C), 138.9 (Ar-C), 127.5 (Ar-CH), 127.2 (Ar-CH3), 113.1 (C-6), 109.0 (C-2), 52.9 (O-CH3); FTIR v max/cm−1: 3041, 1742, 1639, 1587, 1509, 1485, 1416; HRMS (ESI–TOF) m/z: [M + H]+ calculated for C13H13N2O2S+ 304.0391, found 304.0391.

**Ethyl 7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (13f).** Thiourea (15) (0.31 g, 4.1 mmol), chloroacetaldehyde (16a) (0.50 g, 4.1 mmol) and DETAD (2b) (0.69 g, 4.1 mmol). Physical properties: yellow solid; Yield: 0.84 g, 91%; Mp: 180–182 °C; Rf 0.4, hexane/ethyl acetate (40:60); 1H NMR (400 MHz, DMSO-d6) δ 8.30 (1H, d, J = 4.8 Hz, H-2), 7.36 (1H, d, J = 4.8 Hz, H-3), 6.76 (1H, s, H-6), 4.38 (2H, q, J = 6.8 Hz, O-CH2), 1.34 (3H, t, J = 7.2 Hz, CH3)
CH₃); ¹³C NMR (101 MHz, DMSO-d₆) δ 166.8 (C=O), 166.0 (C=O), 160.3 (C-9), 136.6 (C-5), 124.6 (C-2), 114.3 (C-6), 110.0 (C-3), 62.9 (O-CH₂), 13.7 (CH₃); FTIR vmax/cm⁻¹: 3176, 3077, 2978, 1720, 1621, 1557, 1471; HRMS (ESI−TOF) m/z: [M + H]^+ calculated for C₉H₈N₂O₃S^+ 225.0328, found 225.0339.

Ethyl 3-methyl-7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (13f). Thiourea (15) (0.41 g, 5.4 mmol), chloroacetone (16b) (0.5 g, 5.4 mmol) and DETA (2b) (0.92 g, 5.4 mmol); Physical properties: yellow solid; Yield: 0.94 g, 81%; Mp: 180−182 °C; Rf 0.5, hexane/ethyl acetate (40:60%); ¹H NMR (400 MHz, DMSO-d₆) δ 7.10 (1H, s, H-2), 6.53 (1H, s, H-6), 4.38 (2H, q, J = 6.8 Hz, O-CH₂), 2.23 (3H, s, CH₃) 1.34 (3H, t, J = 7.6 Hz, CH₃); ¹³C NMR (101 MHz, DMSO-d₆) δ 166.8 (C=O), 165.0 (C=O), 160.9 (C-9), 139.2 (Ar-C), 132.9 (Ar-C), 111.9 (C-6), 107.1 (C-2), 63.5 (CH₂), 15.3 (CH₃) 13.6 (CH₃); FTIR vmax/cm⁻¹: 2973, 1731, 1634, 1493; HRMS (ESI−TOF) m/z: [M + H]^+ calculated for C₁₀H₁₁N₂O₃S^+ 239.0485, found 239.0497.

Ethyl 2,3-dimethyl-7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (13g). Thiourea (15) (0.36 g, 4.6 mmol), 3-chloro-2-butanoic (16c) (0.50 g, 4.6 mmol) and DETA (2b) (0.78 g, 4.6 mmol). Physical properties: yellow solid; Yield: 0.94 g, 81%; Mp: 153−155 °C; Rf 0.5, hexane/ethyl acetate (40:60%); ¹H NMR (400 MHz, DMSO-d₆) δ 7.15 (1H, s, H-2), 6.53 (1H, s, H-6), 4.45 (2H, q, J = 5.2 Hz, CH₂), 2.28 (3H, s, CH₃) 2.12 (3H, s, CH₃) 1.33 (3H, t, J = 7.6 Hz, CH₂CH₃); ¹³C NMR (101 MHz, DMSO-d₆) δ 165.0 (C=O), 164.7 (C=O), 161.0 (C-9), 139.2 (Ar-C), 127.9 (Ar-C), 116.7 (Ar-C), 112.1 (C-6), 63.5 (O-CH₂), 13.6, 12.7, (2 × CH₃), 11.8 (CH₂CH₃); FTIR vmax/cm⁻¹: 2988, 1732, 1641, 1489, 1452; HRMS (ESI−TOF) m/z: [M + H]^+ calculated for C₁₁H₁₂N₂O₃S^+ 253.0641, found 253.0652.

Ethyl 3-(4-fluorophenyl)-7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (13h). Thiourea (15) (0.19 g, 2.3 mmol), 2-bromo-4-fluorobenzonic (16e) (0.51 g, 2.3 mmol) and DETA (2b) (0.39 g, 2.3 mmol). Physical properties: yellow solid; Yield: 0.63 g, 86%; Mp: 180−182 °C; Rf 0.5, hexane/ethyl acetate (40:60%); ¹H NMR (400 MHz, DMSO-d₆) δ 7.58−7.52 (2H, m, ArH), 7.37−7.27 (3H, m, ArH), 6.49 (1H, s, H-6), 3.61 (2H, q, J = 7.2 Hz, O-CH₂) 1.04 (3H, t, J = 7.2 Hz, CH₃); ¹³C NMR (101 MHz, DMSO-d₆) δ 163.8 (C=O), 164.5 (C=O), 162.6 (C=O), 132.9 (CH₂), 128.9 (CH₂), 120.9 (CH₂), 116.7 (Ar-C), 112.1 (C-6), 63.5 (O-CH₂), 13.6, 12.7, (2 × CH₃), 11.8 (CH₂CH₃); FTIR vmax/cm⁻¹: 2978, 1732, 1641, 1489, 1452; HRMS (ESI−TOF) m/z: [M + H]^+ calculated for C₁₁H₁₂N₂O₃S^+ 253.0641, found 253.0652.

Ethyl 3-(4-fluorophenyl)-7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (13i). Thiourea (15) (0.16 g, 2.1 mmol), 2-bromo-4-nitrobenzon (16f) (0.50 g, 2.1 mmol) and DETA (2b) (0.36 g, 2.1 mmol). Physical properties: yellow solid; Yield: 0.59 g, 84%; Mp: 198−200 °C; Rf 0.9, hexane/ethyl acetate (40:60%); ¹H NMR (400 MHz, DMSO-d₆) δ 7.58 (2H, d, J = 8.4 Hz, Ar-H), 7.51 (2H, d, J = 8.4 Hz, Ar-H), 7.39 (1H, s, H-2), 6.51 (1H, s, H-6), 3.63 (2H, q, J = 7.2 Hz, O-CH₂) 1.03 (3H, t, J = 6.8, Hz, CH₃); ¹³C NMR (101 MHz, DMSO-d₆) δ 166.8 (C=O), 165.3 (C=O), 160.1 (C-9), 138.7 (Ar-C), 135.3 (Ar-CH), 134.3 (Ar-C), 129.4 (Ar-C), 129.1 (Ar-C), 128.9 (Ar-CH), 113.2 (C-6), 109.38 (C-2), 62.7 (CH₂O), 13.2 (CH₃); FTIR vmax/cm⁻¹: 3057, 2986, 1733, 1640, 1580, 1501, 1482; HRMS (ESI−TOF) m/z: [M + H]^+ calculated for C₁₅H₁₃ClN₂O₃S^+ 335.0252, found 335.0267.

3.1.4. Synthesis of Methyl 7-Oxo-7H-Thiazolo[3,2-a]Pyrimidine-5-Carboxylate Derivatives (13), 19a–b, 20 and 5) Method A (2-CR)

In a round-bottomed flask equipped with a magnetic stirrer bar, DMAD/DETA (2) was added to the mixture of 2-aminothiazole derivative (11a–h) or 2-imino-1,3-oxazolidine (17) or 1H-1,2,4-triazol-5-amine (18) or 1H-1,2,4-triazole-5-thiol (5) in ethanol. The reaction mixture was allowed to reflux for 12−15 h while being monitored by TLC. After completion, the reaction was cooled and the solvent was removed under reduced pressure to obtain a residue which was washed with cold ethanol and filtered to give solid product.

N-(tert-butyl)-7-oxo-5H-thiazolo[3,2-a]pyrimidine-5-carboxylate (13j). Thiazol-2-amine (11a) (0.20 g, 1.99 mmol), di-tert-butyl acetylene dicarboxylic acid (DTAD) (2c) (0.45 g, 1.99 mmol); Physical properties: yellow solid; Yield: 0.36 g, 72%; Mp: 246−248 °C; Rf 0.5, hexane/ethyl acetate (40:60%); ¹H NMR (400 MHz, DMSO-d₆) δ 8.29 (1H, d, J = 4.4 Hz, H-2), 7.34 (1H, d,
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\[ J = 5.2 \text{ Hz}, \ H-3, 6.73 (1H, s, H-6), 1.57 (9H, s, (CH}_3)_3; \] ^{13}C NMR (101 MHz, DMSO-d6) \[ \delta \] 
166.8 (C=O), 166.2 (C=O), 159.3 (C-9), 137.4 (C-5), 124.5 (C-2), 114.2 (C-6), 109.9 (C-3), 85.0 (CH(C=O)) 27.4 (\text{CH}_3) \text{); FTIR vmax/cm}^{-1}: 2923, 1729, 1639; HRMS (ESI–TOF) m/z: [M + H]^+ calculated for C_{11}H_{13}N_{2}O_{5}S \text{= 253.0641, found 253.0642.} 

Methyl 5-oxo-3,5-dihydro-2H-oxazolof[3,2-alpyrimidine-7-carboxylate (19a); 2-imino-1,3-oxazolidine (0.51 g, 5.8 mmol) and DzAD (2a) (0.83 g, 5.8 mmol); Physical properties: White solid; Yield: 0.95 g, 82%; Mp: 251–253 °C; Rf 0.5, ethyl acetate (100 %); H NMR (400 MHz, DMSO-d6) 6.37 (1H, s, H-6), 4.67 (2H, t, J = 8.4 Hz, CH2), 4.49 (2H, t, J = 8.4 Hz, CH2), 3.87 (3H, s, O-CH3); ^{13}C NMR (101 MHz, DMSO-d6) \[ \delta \] 
170.4 (C=O) 163.2 (C=O), 161.6 (C-9), 155.7 (C-7), 89.5 (C-6), 61.1 (CH2) \text{); FTIR vmax/cm}^{-1}: 2965, 1732, 1624, 1535, 1476, 1421; HRMS (ESI–TOF) m/z: [M + H]^+ calculated for C_{8}H_{8}N_{2}O_{4}{^+} 197.0577, found 197.0549. 

Ethyl 5-oxo-3,5-dihydro-2H-oxazolof[3,2-alpyrimidine-7-carboxylate (19b); 2-imino-1,3-oxazolidine (0.51 g, 5.8 mmol) and DzAD (2b) (0.98 g, 5.8 mmol). Physical properties: White solid; Yield: 0.98 g, 80%; Mp: 251–253 °C; Rf 0.5, ethyl acetate (100 %); H NMR (400 MHz, DMSO-d6) 6.34 (1H, s, H-6), 4.67 (2H, t, J = 8.2 Hz, CH2), 4.57 (2H, t, J = 8.2 Hz, CH2), 3.62 (2H, t, J = 5.6 Hz, CH2), 1.27 (3H, t, J = 7.2 Hz, CH3); ^{13}C NMR (101 MHz, DMSO-d6) \[ \delta \] 
170.4 (C=O) 163.2 (C=O), 161.6 (C-9), 155.7 (C-7), 89.5 (C-6), 61.1 (CH2), 58.5 (CH2) 13.9 (CH3); FTIR vmax/cm}^{-1}: 3125, 2958, 1639; HRMS (ESI–TOF) m/z: [M + H]^+ calculated for C_{9}H_{7}N_{2}O_{4}{^+} 211.0713, found 211.0708. 

Ethyl 5-oxo-3,5-dihydro-[1,2,4]triazolof[3,5-alpyrimidine-7-carboxylate (20); 1H-1,2,4-triazole-5-amine (0.50 g, 6.0 mmol) and DzAD (2b) (1.02 g, 6.0 mmol). Physical properties: Brown solid; Yield: 1.1 g, 88%; Mp: 185–187 °C; Rf 0.5, ethyl acetate (100 %); H NMR (400 MHz, DMSO-d6) 8.91 (1H, s, H-5), 6.66 (1H, s, H-7), 4.56 (2H, q, J = 6.8 Hz, O-CH2), 1.30 (3H, t, J = 7.2 Hz, CH3); ^{13}C NMR (101 MHz, DMSO-d6) \[ \delta \] 
170.4 (C=O) 163.2 (C=O), 161.6 (C-9), 155.7 (C-7), 89.5 (C-6), 61.1 (CH2), 12.9 (CH3); FTIR vmax/cm}^{-1}: 3150, 3068, 2909, 2731, 1722, 1680, 1610, 1579; HRMS (ESI–TOF) m/z: [M + H]^+ calculated for C_{9}H_{7}N_{2}O_{4}{^+} 209.0669, found 209.0677. 

7-Oxo-7H-[1,2,4]triazolof[5,1-blf[1,3]thiazine-5-carboxylate (5); 1H-1,2,4-triazole-5-thiol (0.50 g, 5.0 mmol) and DzAD (2b) (0.85 g, 5.0 mmol). Physical properties: White solid; Yield: 0.92 g, 82%; Mp: 110–112 °C; Rf 0.9 hexane/ethyl acetate (20%:80 %); H NMR (400 MHz, DMSO-d6) 8.68 (1H, s, H-4), 7.54 (1H, s, H-6), 4.48 (2H, q, J = 7.2 Hz, O-CH2), 1.38 (3H, t, J = 6.8 Hz, CH3); ^{13}C NMR (101 MHz, DMSO-d6) \[ \delta \] 
170.9, (C=O) 162.1 (C=O), 160.8 (C-9), 155.3 (C-7), 153.7 (C-4), 151.56 (C-2), 139.6 (C-7) 122.2 (C-6), 64.1 (CH2), 13.8 (CH3); FTIR vmax/cm}^{-1}: 3123, 3053, 2987, 1698, 1582, 1481; HRMS (ESI–TOF) m/z: [M + H]^+ calculated for C_{8}H_{8}N_{2}O_{4}{^+} 226.0281, found 226.0288. 

3.2. X-ray Crystallography 

Intensity data for 8, 13a, 13b and 13d were collected on a Bruker Apex-II CCD area detector (Bruker AXS, Karlsruhe, Germany) diffractometer with graphite monochromated Mo Kα radiation (50 kV, 30 mA). The collection method involved with the ShelXL [51] refinement package, using least-squares minimization. Non-hydrogen atoms were first refined isotropically, followed by anisotropic refinement by full matrix least-squares calculations based on F^2.
V = 1137.98(8) Å³, Z = 4, T = 173.15 K, μ(MoKα) = 0.290 mm⁻¹, Dcalc = 1.496 g/cm³, 11779 reflections measured (4.04° ≤ 2Θ ≤ 56.70°), 2839 unique (Rint = 0.0356, Rsigma = 0.0325) which were used in all calculations. The final R1 was 0.0359 (I > 2σ(I)) and wR2 was 0.0973 (all data). CCDC 2103714.

Crystal Data for 13b: C₁₅H₁₂N₂O₃S (M =300.33 g/mol): monoclinic, space group C2/c (no. 15), a = 21.5767(7) Å, b = 8.7603(3) Å, c = 14.6735(5) Å, β = 93.5869(11)°, V = 2768.13(16) Å³, Z = 8, T = 173.15 K, μ(MoKα) = 0.245 mm−¹, Dcalc = 1.441 g/cm³, 15439 reflections measured (3.782° ≤ 2Θ ≤ 56.796°), 3474 unique (Rint = 0.0236, Rsigma = 0.0204) which were used in all calculations. The final R1 was 0.0345 (I > 2σ(I)) and wR2 was 0.0887 (all data). CCDC 2103715.

Crystal Data for 13d: C₁₄H₉ClN₂O₃S (M =320.74 g/mol): orthorhombic, space group Pnca (no. 61), a = 15.167(2) Å, b = 8.9457(14) Å, c = 19.944(3) Å, V = 2706.0(7) Å³, Z = 8, T = 173.15 K, μ(MoKα) = 0.447 mm⁻¹, Dcalc = 1.575 g/cm³, 16592 reflections measured (4.084° ≤ 2Θ ≤ 50°), 2381 unique (Rint = 0.1235, Rsigma = 0.1070) which were used in all calculations. The final R1 was 0.0362 (I > 2σ(I)) and wR2 was 0.0696 (all data). CCDC 2103716.

CCDC 2103713-2103716 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (accessed 20 August 2021) (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

4. Conclusions
The synthesis of novel thiazine derivatives was accomplished by using a one-pot, three-component reaction. The facile and convenient reaction of isocyanides and DMAD or DEtAD under inert conditions at 0 °C formed a zwitterion intermediate that further reacted with compounds 9a–e. On the other hand, the synthesis of 5H-thiazolo[3,2-a]pyrimidine-7-carboxylates was successfully accomplished by using two methods, either by two-component or three-component reaction. The one-pot, three-component reaction using thiourea, α-haloketone and dialkyl acetylenedicarboxylate was found to be more effective, achieving improved yields. The 2-aminothiazole derivatives were found to be less reactive towards DMAD and DEtAD as compared to 2-imino-1,3-oxazolidine (17), 1H-1,2,4-triazol-5-amine (18) or 1H-1,2,4-triazole-5-thiol (5) when using the two-component approach.

Supplementary Materials: The supplementary materials including NMR and IR spectra for the reported compounds are available online.

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