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-4*H*-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 1*H*-1,2,4-triazole-5-thiol **6**, to give methyl 7-oxo-7*H*-[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.
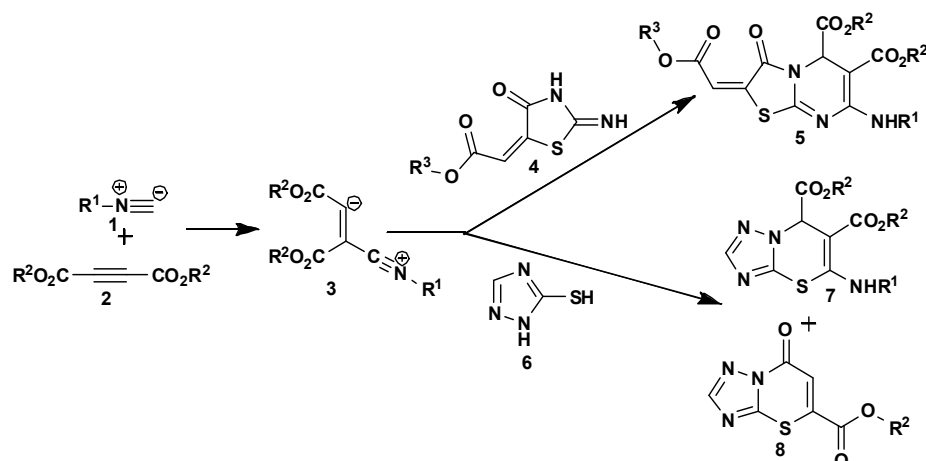
Scheme 1. Our previous work showing synthesis of pyrimidine derivatives and their analogues.

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-4*H*-1,3-thiazin-4-one derivatives **9**, with predicted pK_a 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 thiazole-pyrimidines. 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-4*H*-1,3-thiazin-4-one derivatives; and the synthesis of 5*H*-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-4*H*-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-4*H*-1,3-thiazin-4-one **9b** [31], 2-amino-6-ethyl-4*H*-1,3-thiazin-4-one **9c**, 2-amino-6-propyl-4*H*-1,3-thiazin-4-one **9d** and 2-amino-6-phenyl-4*H*-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%.
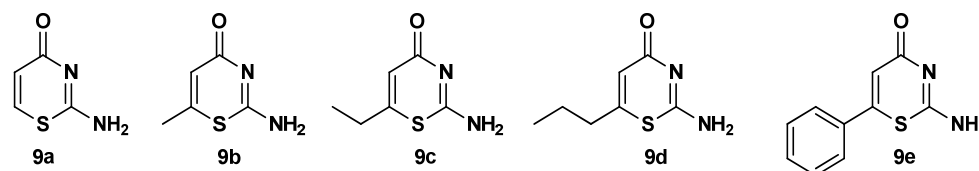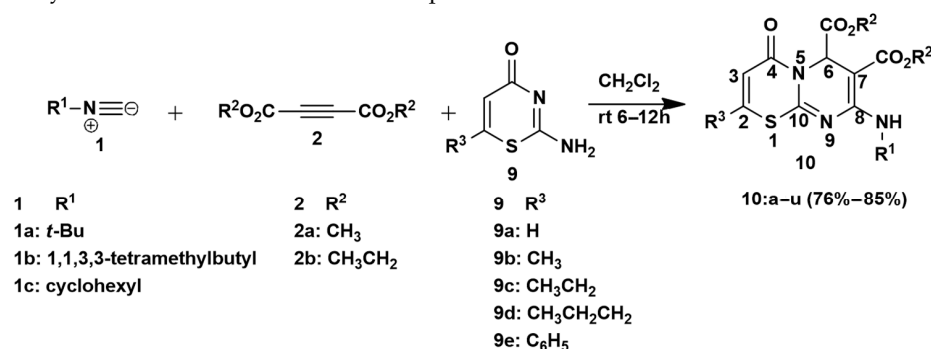

Figure 1. Six-membered rings **9a–e** chosen for the three-component reaction.

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	$CH_3CH_2CH_2$	84 (6 h)
10n	*t*-Bu	CH_3CH_2	$CH_3CH_2CH_2$	85 (6 h)
10o	1,1,3,3-tetramethylbutyl	CH_3	$CH_3CH_2CH_2$	79 (6 h)
10p	1,1,3,3-tetramethylbutyl	CH_3CH_2	$CH_3CH_2CH_2$	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-4*H*-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-4*H*-1,3-thiazin-4-one derivatives **9** 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**.
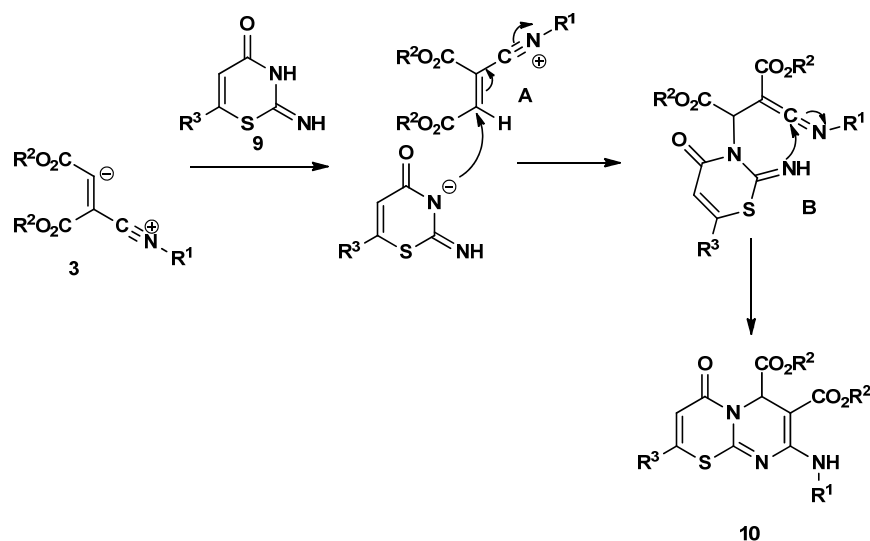

**Scheme 2.** Proposed reaction mechanism for the formation of **10**.

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-7*H*-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-7*H*-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.

Previous work
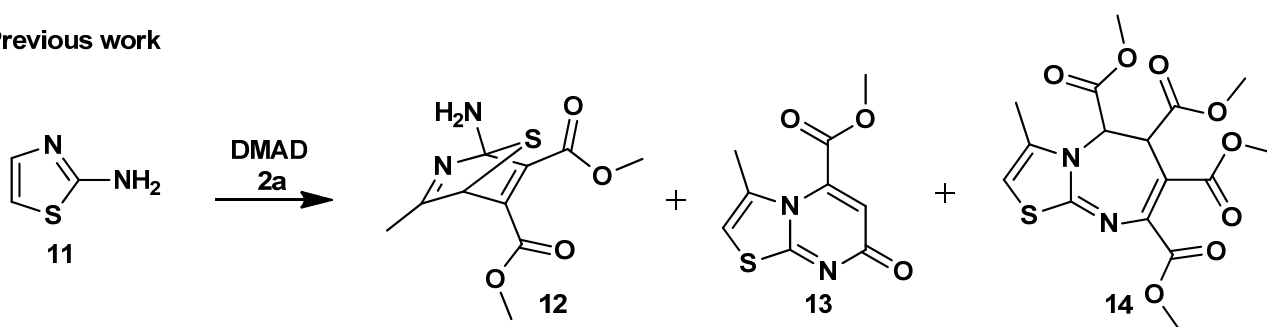
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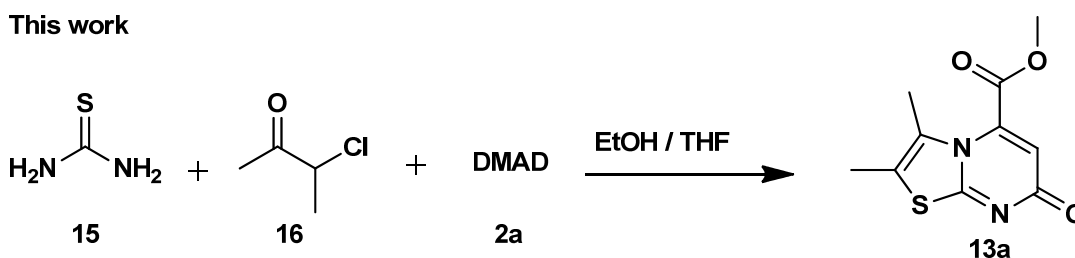
Scheme 3. Synthesis of thiazole-pyrimidines **13**.

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.
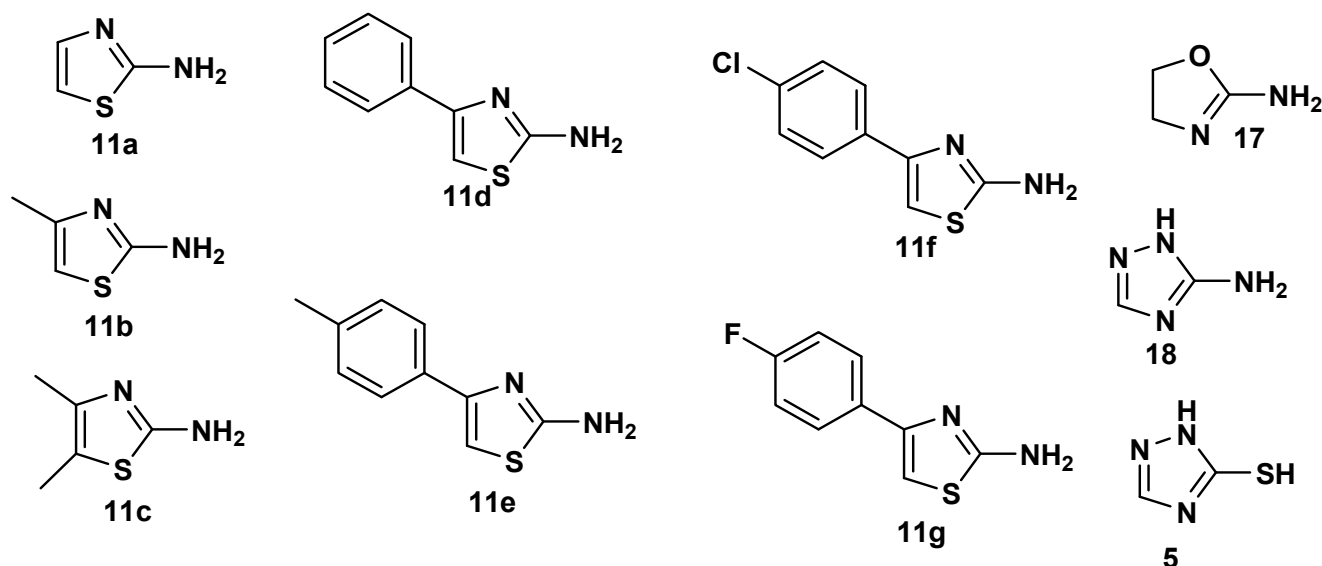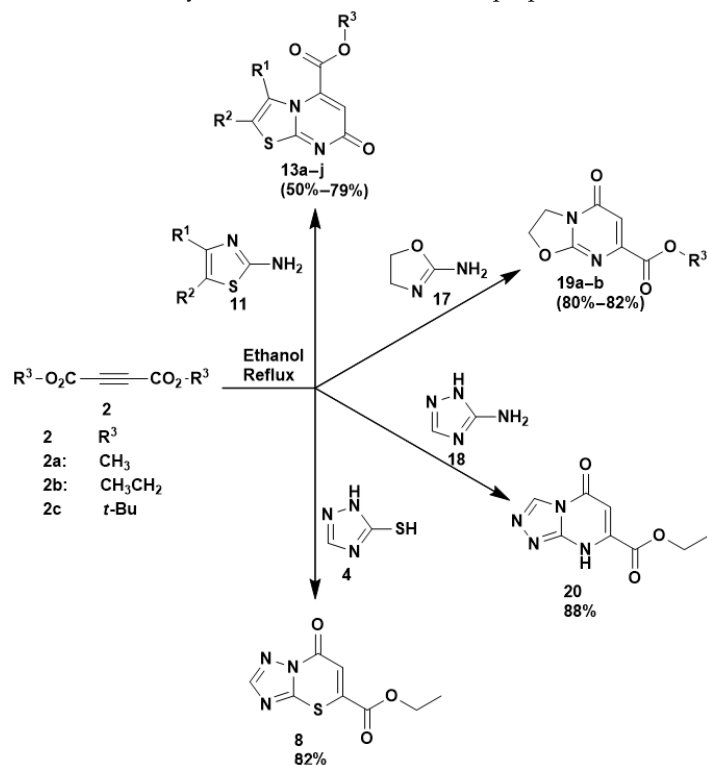

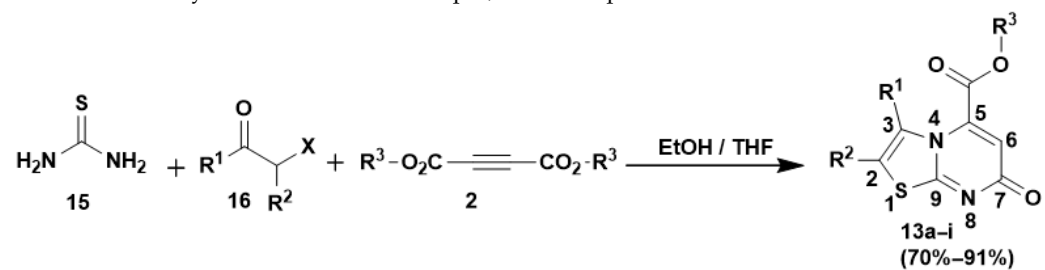**Figure 2.** Five membered-ring substrates chosen for the reactions.

Table 2. Isolated yields and reaction times for preparation of **8**, **13a–j**, **19a–b** and **20**.

Compound	R^1	R^2	R^3	Yield	Time (h)
13a	CH_3	CH_3	CH_3	67	12
13b	Ph-CH_3	H	CH_3	58	6
13c	Ph-F	H	CH_3	48	6
13d	Ph-Cl	H	CH_3	50	6
13e	H	H	CH_3CH_2	69	12
13f	CH_3	H	CH_3CH_2	71	12
13g	CH_3	CH_3	CH_3CH_2	79	12
13h	Ph-F	H	CH_3CH_2	51	6
13i	Ph-Cl	H	CH_3CH_2	52	6
13j	H	H	*t*-Bu	70	12
19a			CH_3	82	12
19b			CH_3CH_2	80	12
20			CH_3CH_2	88	12
8			CH_3CH_2	82	12

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	R^1	R^2	R^3	Yield (%)	Time (h)
13a	Cl	CH_3	CH_3	CH_3	82	12
13b	Br	Ph-CH_3	CH_3	CH_3	71	6
13c	Cl	Ph-F	CH_3	CH_3	70	6
13d	Br	Ph-Cl	H	CH_3	71	12
13e	Cl	H	H	CH_3CH_2	83	12
13f	Cl	CH_3	H	CH_3CH_2	91	12
13g	Cl	CH_3	CH_3	CH_3CH_2	86	12
13h	Cl	Ph-F	H	CH_3CH_2	86	6
13i	Br	Ph-Cl	H	CH_3CH_2	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**.
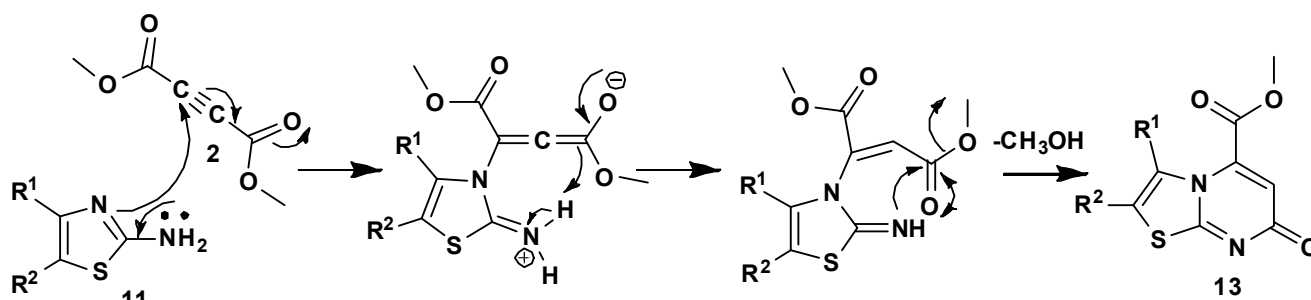
Scheme 4. Proposed reaction mechanism for the formation of compounds **13a–j**.

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).
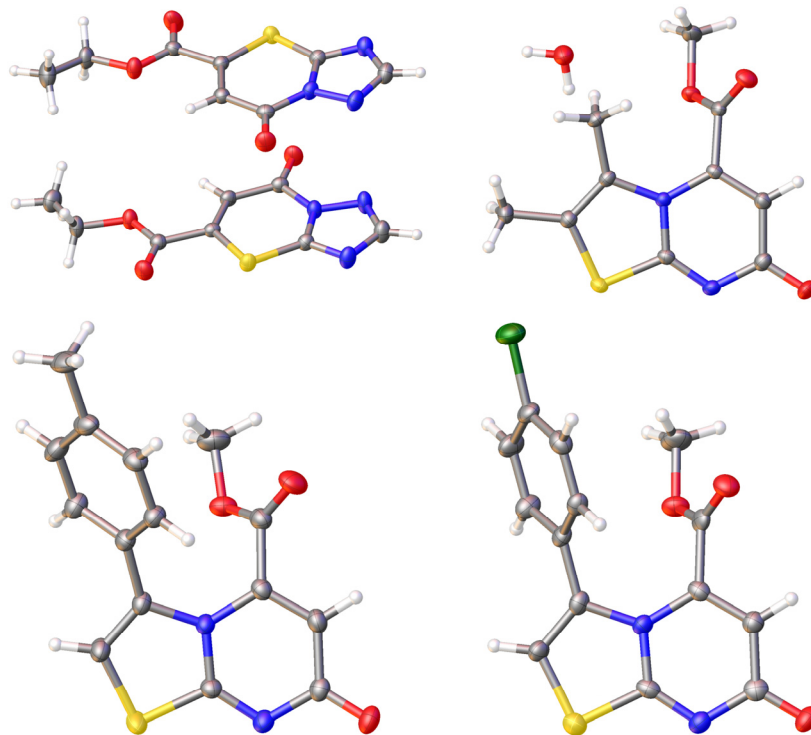

Figure 3. Single-crystal X-ray structure (ORTEP diagrams) of **8** (**top left**), **13a** (**top right**), **13b** (**bottom left**) and **13d** (**bottom right**). Carbon atoms are shown as gray spheres, nitrogen atoms as blue spheres, oxygen atoms as red spheres, sulfur atoms as yellow spheres, chlorine atoms as green spheres and hydrogen atoms as white spheres.

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 (CDCl$_3$) and 2.50 (DMSO-d_6) for ^{1}H NMR; 77.16 (CDCl$_3$) 40.45 (DMSO-d_6) for ^{13}C 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 (v/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 CH_2Cl_2 (2.5 mL) was slowly added to DMAD (**2a**) or DEtAD (**2b**) in dry CH_2Cl_2 (5 mL) at 0 °C, under inert argon, and the solution was allowed to stir for 0.5 h. Then 2-amino-4*H*-1,3-thiazin-4-one derivatives **9a–e** in dry CH_2Cl_2 (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-4*H*-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, **R**$_f$: 0.5, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) 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, OCH$_3$), 3.71 (3H, s, OCH$_3$), 1.42 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) 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 (OCH$_3$), 51.1 (OCH$_3$), 50.8(C(CH$_3$)$_3$), 30.9 (C(CH$_3$)$_3$); FTIR ν$_{max}$/cm^{-1}: 2982, 2913, 1728, 1690, 1648, 1600, 1533, 1472, 1431; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{15}$H$_{20}$N$_3$O$_5$S$^+$ 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-4*H*-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, R$_f$: 0.6, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) 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), 4.31–4.11 (4H, m, 2 × CH$_2$), 1.43 (9H, s, C(CH$_3$)$_3$), 1.33 (3H, t, *J* = 7.2 Hz, CH$_3$), 1.26 (3H, t, *J* = 7.2 Hz, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) 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-CH$_2$), 59.3 (O-CH$_2$), 52.6 (C-6),) 51.3(C(CH$_3$)$_3$, 30.9 (C(CH$_3$)$_3$, 14.9(CH$_3$), 14.2 (CH$_3$); FTIR ν$_{max}$/cm^{-1}: 3067, 2983, 2864, 1728, 1690, 1647, 1599, 1534, 1431; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{17}$H$_{24}$N$_3$O$_5$S$^+$ 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-4*H*-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, **R**$_f$: 0.5, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) 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-CH$_3$), 3.61 (3H, s, O-CH$_3$), 2.17 (Ar-CH$_3$), 1.33 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) 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 (OCH$_3$), 51.0 (OCH$_3$), 50.8 (C(CH$_3$)$_3$), 30.8 (C(CH$_3$)$_3$) 22.1 (Ar-CH$_3$); FTIR ν$_{max}$/cm^{-1}: 2992, 2963, 2902, 1734, 1648, 1682, 1653, 1602, 1525; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{16}$H$_{22}$N$_3$O$_5$S$^+$ 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-4*H*-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, **R**$_f$: 0.6, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.72 (1H, br s, NH), 6.28 (2H, 2 × s, Ar-CH and H-6), 4.27–4.06 (4H, m, 2 × CH$_2$), 2.22 (3H, Ar-CH$_3$), 1.39 (9H, s, C(CH$_3$)$_3$), 1.29 (3H, t, *J* = 7.2 Hz, CH$_3$), 1.22 (3H, t, *J* = 7.2 Hz, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) 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-CH$_2$), 59.2 (O-CH$_2$), 52.6 (C-6), 51.3 (N-C(CH$_3$)$_3$), 30.9 (C(CH$_3$)$_3$, 22.1

(Ar-CH$_3$), 14.9 (CH$_3$), 14.2 (CH$_3$); FTIR ν$_{max}$/cm^{-1}: 3285, 2975, 2890, 1735, 1690, 1643, 1600, 1535, 14377; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{18}$H$_{26}$N$_3$O$_5$S$^+$ 396.1588 found 396.1597.

Dimethyl 2-methyl-4-oxo-8-((2,4,4-trimethylpentan-2-yl)amino)-4,6-dihydropyrimido [2,1-b][1,3]thiazine-6,7-dicarboxylate (**10e**); 2-Amino-6-methyl-4H-1,3-thiazin-4-one (**9b**) (0.25 g, 1.76 mmol), 1,1,3,3-tetramethylbutyl isocyanide (**1b**) (0.25 g, 1.76 mmol) and dimethyl acetylenedicarboxylate (**2a**) (0.25 g, 1.76 mmol). Physical characteristics: yellow solid; Yield: 0.56 g, 76%; Mp: 114–116 °C, R$_f$: 0.6, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.74 (1H, br s, NH), 6.34 and 6.33 (2H, 2 × s, Ar-CH and H-6), 3.76 (3H, s, OCH$_3$), 3.69 (3H, s, OCH$_3$), 2.27 (3H, Ar-CH$_3$), 1.83 (CH$_2$), 1.48 and 1.46 (6H, 2 × s, 2CH$_3$), 0.97 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.1 (C=O), 168.5 (C=O), 161.3 (C=O), 157.6 (C-10), 155.4 (C-8), 149.8, (C-2), 116.1 (C-3), 72.0 (C-7), 56.2 (C(CH$_3$)$_3$), 53.3 (CH$_2$), 52.9 (C-6), 51.1 (OCH$_3$), 50.8 (OCH$_3$), 31.7 (C(CH$_2$)$_2$), 31.8 (C(CH$_3$)$_3$), 31.6 (CH$_3$), 31.5 (CH$_3$), 22.1 (Ar-CH$_3$); FTIR ν$_{max}$/cm^{-1}: 3285, 2951, 2899, 1739, 1687, 1649, 1599, 1535, 1442; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{20}$H$_{30}$N$_3$O$_5$S$^+$ 424.1901 found 424.1906.

Diethyl 2-methyl-4-oxo-8-((2,4,4-trimethylpentan-2-yl)amino)-4,6-dihydropyrimido[2,1-b][1,3] thiazine-6,7-dicarboxylate (**10f**); 2-amino-6-methyl-4*H*-1,3-thiazin-4-one (**9b**) (0.25 g, 1.76 mmol), 1,1,3,3-tetramethylbutyl isocyanide (**1b**) (0.25 g, 1.76 mmol) and dimethyl acetylenedicarboxylate (**2a**) (0.25 g, 1.76 mmol). Physical characteristics: yellow solid; Yield: 0.61 g, 77%; Mp: 112–114 °C, R$_f$: 0.7, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.73 (1H, br s, NH), 6.29 (2H, 2 × s, Ar-CH, H-6), 4.26–4.01 (4H, m, 2 × CH$_2$O) 2.23 (3H, s, Ar-CH$_3$), 1.80 (2H, q, *J* = 14.4 Hz, CH$_2$), 1.44 and 1.42 (6H, 2 × s, 2 × CH$_3$), 1.31 (3H, t, *J* = 6.8 Hz, CH$_3$), 1.21 (3H, t, *J* = 7.2 Hz, CH$_3$), 0.94 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.7 (C=O), 168.2 (C=O), 161.4 (C=O), 157.4 (C-10), 155.3 (C-8), 149.6 (C-2), 116.1 (C-3), 72.3 (C-7), 61.8 (O-CH$_2$), 59.1 (O-CH$_2$), 56.2 (C-(CH$_3$)$_3$), 53.1 (CH$_2$), 51.3 (C-6), 31.6 (C-(CH$_3$)$_3$), 22.1 (Ar-CH$_3$), 14.9 (CH$_3$CH$_2$), 14.2 (CH$_3$CH$_2$); FTIR ν$_{max}$/cm^{-1}: 3285, 2975, 2890, 1735, 1690, 1643, 1600, 1535, 1477; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{22}$H$_{34}$N$_3$O$_5$S$^+$ 452.2214 found 452.2223.

Dimethyl 8-(cyclohexylamino)-2-methyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (**10g**); 2-amino-6-methyl-4*H*-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, R$_f$: 0.42, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.52 (1H, br s, NH), 6.29 (2H, 2 × s, Ar-CH, H-6), 3.90 (1H, s N-CH), 3.72 (3H, s, OCH$_3$), 3.67 (3H, s, OCH$_3$), 2.23 (CH$_3$, s, Ar-CH$_3$), 1.93–1.70 (5H, m, cyclohexyl) 1.67–1.32 (5H, m, cyclohexyl); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.1 (C=O), 168.3 (C=O), 161.2 (C=O), 159.1 (C-10), 154.2 (C-8), 149.6 (C-2), 116.0 (C-3), 71.5 (C-7), 52.9 (O-CH$_3$), 51.2 (C-6), 50.7 (O-CH$_3$), 49.6 (CH-NH), 34.3 (CH$_2$, cyclohexyl), 33.7 (CH$_2$, cyclohexyl), 25.7 (CH$_2$, cyclohexyl), 24.8 (CH$_2$, cyclohexyl), 24.7 (CH$_2$, cyclohexyl), 22.1 (Ar-CH$_3$). FTIR ν$_{max}$/cm^{-1}: 3285, 2946, 2858, 1762, 1730, 1692, 1653, 1618, 1590, 1525, 1445; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{18}$H$_{24}$N$_3$O$_5$S$^+$ 394.1431 found 394.1433.

Diethyl 8-(cyclohexylamino)-2-methyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (**10h**); 2-amino-6-methyl-4*H*-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, **R**$_f$: 0.50, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.55 (1H, br s, NH), 6.28 (2H, 2 × s, Ar-CH, H-6), 4.27–4.09 (4H, m, 2 × CH$_2$), 3.92 (1H, s, CH), 2.23 (3H, s, Ar-CH$_3$), 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, CH$_3$), 1.28 (3H, s, *J* = 6.8 Hz, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) 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-CH$_2$), 59.1 (O-CH$_2$), 51.4 (C-6), 49.6 (CH), 34.3(CH$_2$, cyclohexyl), 33.7 (CH$_2$, cyclohexyl), 25.7 (CH$_2$, cyclohexyl), 24.8 (CH$_2$, cyclohexyl), 24.7 (CH$_2$, cyclohexyl), 22.1 (Ar-CH$_3$), 14.9 (CH$_2$CH$_3$), 14.1 (CH$_2$CH$_3$); FTIR ν$_{max}$/cm^{-1}: 2992,

2945, 2867, 1735, 1689, 1648, 1588, 1540, 1440; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{20}$H$_{28}$N$_3$O$_5$S$^+$ 422.1744 found 422.1712.

Dimethyl 8-(tert-butylamino)-2-ethyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicar boxylate (**10i**); 2-amino-6-ethyl-4*H*-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: 0.51 g, 84%; Mp: 135–137 °C, R$_f$: 0.48, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.70 (1H, br s, NH), 6.31 (2H, 2 × s, Ar-CH, H-6), 3.73 (3H, s, OCH$_3$), 3.68 (3H, s, OCH$_3$), 2.50 (2H, q, *J* = 7.2 Hz, Ar-CH$_2$), 1.40 (9H, s, C(CH$_3$)$_3$), 1.28 (3H, t, *J* = 7.6 Hz, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.2 (C=O), 168.5 (C=O), 161.5 (C=O), 157.9 (C-10), 155.8 (C-8), 155.3 (C-2), 114.4 (C-3), 72.1 (C-7), 52.9 (OCH$_3$), 52.6 (C-(CH$_3$)$_3$), 51.2 (C-6), 50.8 (OCH$_3$), 30.8 (C(CH$_3$)$_3$), 29.4 (CH$_2$CH$_3$), 12.5 (CH$_2$CH$_3$); FTIR ν$_{max}$/cm^{-1}: 3273, 2967, 2876, 1739, 1674, 1644, 1616, 1591, 1531, 1438; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{17}$H$_{24}$N$_3$O$_5$S$^+$ 382.1430 found 382.1427.

Diethyl 8-(tert-butylamino)-2-ethyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarbo xylate (**10j**); 2-amino-6-ethyl-4*H*-1,3-thiazin-4-one (**9c**) (0.25 g, 1.60 mmol), *tert*-butyl iso-cyanide (**1a**) (0.13 g, 1.60 mmol) and diethyl acetylenedicarboxylate (**2b**) (0.27 g, 1.60 mmol). Physical characteristics: yellow solid; Yield: 0.52 g, 79%; Mp: 94–96 °C, R$_f$: 0.6, hex-ane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) 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 × CH$_2$), 2.50 (2H, q, *J* = 7.6 Hz, Ar-CH$_2$), 1.40 (9H, s, C(CH$_3$)$_3$), 1.29–1.26 (6H, m, 2 × CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.7 (C=O), 168.2 (C=O), 161.6 (C=O), 157.8 (C-10), 155.7 (C-8), 155.2 (C-2), 114.4 (C-3), 72.31 (C-7), 61.8 (O-CH$_2$), 59.2 (O-CH$_2$), 52.5 (C(CH$_3$)$_3$), 51.4 (C-6), 30.9 (C(CH$_3$)$_3$, 29.3 (Ar-CH$_2$), 14.9 (CH$_3$), 14.2 (CH$_3$), 12.5 (CH$_3$); FTIR ν$_{max}$/cm^{-1}: 3285, 2975, 2890, 1735, 1690, 1643, 1600, 1535, 14377; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{19}$H$_{28}$N$_3$O$_5$S$^+$ 410.1744 found 410.1749.

Dimethyl 8-((2,4-dimethylpentan-2-yl)amino)-2-ethyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3] thiazine-6,7-dicarboxylate (**10k**); 2-amino-6-ethyl-4*H*-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 acetylenedicar-boxylate (**2a**) (0.23 g, 1.60 mmol). Physical characteristics: yellow paste; Yield: 0.57 g, 81%, R$_f$: 0.5, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.64 (1H, br s, NH), 6.25 and 6.24 (2H, 2 × s, Ar-CH, H-6), 3.66 (3H, s, OCH$_3$), 3.59 (3H, s, OCH$_3$), 2.44 (2H, q, *J* = 7.6 Hz, Ar-CH$_2$), 1.73 (CH$_2$), 1.38 and 1.36 (6H, 2 × s, 2 × CH$_3$), 1.21 (3H, t, *J* = 7.2 Hz, CH$_3$CH$_2$), 0.87 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) 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(CH$_3$)$_3$), 53.3 (CH$_2$), 52.8 (OCH$_3$), 51.1 (C-6), 50.7 (OCH$_3$), 31.8 (C(CH$_3$)$_3$), 31.7, 31.6 (2 × CH$_3$) 29.3 (Ar-CH$_2$), 12.4 (CH$_3$); FTIR ν$_{max}$/cm^{-1}: 3285, 2950, 2902, 1780, 1738, 1687, 1649, 1598, 1532; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{21}$H$_{32}$N$_3$O$_5$S$^+$ 438.2057 found 438.2021.

Diethyl 8-((2,4-dimethylpentan-2-yl)amino)-2-ethyl-4-oxo-4,6-dihydropyrimido[2,1-b][1,3]thi azine-6,7-dicarboxylate (**10l**); 2-amino-6-ethyl-4*H*-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 acetylenedicarboxy-late (**2b**) (0.27 g, 1.60 mmol). Physical characteristics: yellow solid; Yield: 0.61 g, 81%; Mp: 98–100 °C, R$_f$: 0.6, hexane-ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) 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 × CH$_2$O), 2.50 (2H, q, *J* = 7.2 Hz, Ar-CH$_2$), 1.80 (2H, q, *J* = 14.8 Hz, CH$_2$), 1.45 and 1.42 (6H, 2 × s, (CH$_3$)$_2$-C), 1.31–1.25 (6H, m, 2 × OCH$_2$CH$_3$), 1.21 (3H, s, *J* = 7.2 Hz, ArCH$_2$CH$_3$), 0.94 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.7 (C=O), 168.2 (C=O), 161.6 (C=O), 157.6 (C-10), 155.7 (C-8), 155.3 (C-2), 114.4 (C-3), 72.2 (C-7), 61.8 (O-CH$_2$), 59.1 (O-CH$_2$), 56.1 (C(CH$_3$)$_3$), 53.3 (Ar-CH$_2$), 51.4 (C-6), 31.7 (C(CH$_3$)$_2$), 29.3 (C-(CH$_3$)$_3$), 29.3 (CH$_2$), 14.9 (CH$_3$), 14.2 (CH$_3$), 12.5 (CH$_3$); FTIR ν$_{max}$/cm^{-1}: 3270, 2973, 2913, 1737, 1688, 1646, 1600, 1535, 1432; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ Calculated for C$_{23}$H$_{36}$N$_3$O$_5$S$^+$ 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-4*H*-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%, R$_f$: 0.5, hexane/ethyl

acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.72 (1H, br s, NH), 6.32 (2H, s, Ar-CH, H-6), 3.74 (3H, s, OCH$_3$), 3.69 (3H, s, OCH$_3$), 2.46 (2H, t, *J* = 7.6 Hz, Ar-CH$_2$), 1.71 (2H, sextet, *J* = 7.6 Hz, CH$_2$), 1.42 (9H, s, C(CH$_3$)$_3$), 1.03 (3H, t, *J* = 7.2 Hz, CH$_3$CH$_2$); ^{13}C 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$_2$), 21.6 (CH$_3$CH$_2$) 13.4 (CH$_3$); FTIR ν_{max}/cm^{-1}: 3282, 2960, 2916, 1739, 1685, 1647, 1597, 1567, 1531, 1441; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{18}$H$_{26}$N$_3$O$_5$S$^+$ 396.1588 found 396.1545.

Diethyl 8-(tert-butylamino)-4-oxo-2-propyl-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (**10n**); 2-amino-6-propyl-4*H*-1,3-thiazin-4-one (**9d**) (0.25 g, 1.47 mmol), *tert*-butyl isocyanide (**1a**) (0.12 g, 1.47 mmol) and diethyl acetylenedicarboxylate (**2b**) (0.25 g, 1.60 mmol). Physical characteristics: yellow paste; Yield: 0.53 g, 85%, R$_f$: 0.56, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.74 (1H, br s, NH), 6.30 (2H, s, Ar-CH, H-6), 4.29–4.13 (4H, m, 2 × CH$_2$), 2.46 (2H, t, *J* = 7.6 Hz, Ar-CH$_2$), 1.71 (2H, sextet, *J* = 7.2 Hz, CH$_2$), 1.42 (9H, s, C(CH$_3$)$_3$), 1.34–1.32 (6H, m, 2 × CH$_3$), 1.32 (3H, t, *J* = 7.2 Hz, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.7 (C=O), 168.2 (C=O), 161.5 (C=O), 157.8 (C-10), 155.2 (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$_2$), 30.8 (C(CH$_3$)$_3$, 21.6 (CH$_3$CH$_2$), 14.9, 14.1 and 13.4 (3 × CH$_3$); FTIR ν_{max}/cm^{-1}: 3285, 2975, 2910, 2870, 1737, 1687, 1646, 1600, 1535, 1432; HRMS (ESI–TOF) *m/z*: [M+H]$^+$ calculated for C$_{20}$H$_{30}$N$_3$O$_5$S$^+$ 424.1901 found 424.1873.

Dimethyl 4-oxo-2-propyl-8-((2,4,4-trimethylpentan-2-yl)amino)-4,6-dihydropyrimido [2,1-b][1,3]thiazine-6,7-dicarboxylate (**10o**); 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%, R$_f$: 0.5, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.64 (1H, br s, NH), 6.24 (2H, 2 × 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$_2$), 1.73 (2H, s, C-CH$_2$), 1.64 (2H, sextet, *J* = 7.2 Hz, CH$_3$CH$_2$), 1.38 and 1.36 (6H, 2 × s, 2 × CH$_3$), 0.94 (3H, *J* = 7.2 Hz, CH$_3$), 0.87 (9H, s, C(CH$_3$)$_3$); ^{13}C 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), 154.4 (C-2), 115.1 (C-3), 71.9 (C-7), 56.2 (C(CH$_3$)$_3$), 53.3 (Ar-CH$_2$), 52.8 (OCH$_3$), 51.1 (C-6), 50.7 (OCH$_3$), 37.9 (C-CH$_2$), 31.8 (C(CH$_3$)$_3$), 31.7, 31.6 (2 × CH$_3$) 21.6 (CH$_3$CH$_2$), 13.4 (CH$_2$CH$_3$); FTIR ν_{max}/cm^{-1}: 3279, 2951, 2873, 1739, 1686, 1648, 1598, 1598, 1532, 1442; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{22}$H$_{34}$N$_3$O$_5$S$^+$ 452.2214 found 452.2190.

Diethyl 4-oxo-2-propyl-8-((2,4,4-trimethylpentan-2-yl)amino)-4,6-dihydropyrimido[2,1-b][1,3] thiazine-6,7-dicarboxylate (**10p**); 2-amino-6-propyl-4*H*-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 diethyl acetylenedicarboxylate (**2b**) (0.25 g, 1.60 mmol). Physical characteristics: yellow paste; Yield: 0.55 g, 79%, R$_f$: 0.6, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.75 (1H, br s, NH), 6.30 (2H, 2 × s, Ar-CH, H-6), 4.29–4.09 (4H, m, 2 × CH$_2$CH$_3$), 2.46 (2H, t, *J* = 7.2 Hz, Ar-CH$_2$), 1.85–1.69 (2 × 2H, m, 2 x CH$_2$), 1.46 and 1.44 (6H, 2 × s, (CH$_3$)$_2$-C), 1.33 and 1.21 (6H, 2 × s, 2 × CH$_3$), 1.31 (3H, t, *J* = 6.8 Hz, CH$_3$), 1.22 (3H, t, *J* = 7.2 Hz, CH$_3$), 1.03 (3H, t, *J* = 7.2 Hz, CH$_3$), 0.96 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.7 (C=O), 168.1(C=O), 161.5 (C=O), 157.6 (C-10), 155.3 (C-8), 154.3 (C-2), 115.1 (C-3), 72.1 (C-7), 61.7 (O-CH$_2$), 59.1 (O-CH$_2$), 56.1 (C(CH$_3$)$_3$), 53.2 (O-CH$_2$), 51.3 (C-6), 37.9 (Ar-CH$_2$), 31.6 (C(CH$_3$)$_3$), 21.6 (CH$_3$CH$_2$), 14.9 (CH$_3$), 14.1 (CH$_3$), 13.4 (CH$_3$); FTIR ν_{max}/cm^{-1}: 3285, 2957, 2910, 2870, 1737, 1687, 1646, 1600, 1535, 1432; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{24}$H$_{38}$N$_3$O$_5$S$^+$ 480.2527 found 480.2526.

Dimethyl 8-(tert-butylamino)-4-oxo-2-phenyl-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (**10q**); 2-amino-6-phenyl-4*H*-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 (**2a**) (0.17 g, 1.22 mmol). Physical characteristics: yellow solid; Yield: 0.40 g, 77%; Mp: 99–101 °C, R$_f$: 0.58, hexane/ethyl acetate (90%:10%); ^{1}H 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$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.1 (C=O), 168.5 (C=O),

161.8 (C=O), 157.7 (C-10), 155.1 (C-8), 150.9 (C-2), 133.9 (Ar-C), 132.0 (Ar-C), 129.6 (Ar-CH), 126.6 (Ar-CH), 126.5 (Ar-CH), 113.9 (C-3), 72.1 (C-7), 53.0 (C-6), 52.7 (OCH$_3$), 51.3 (OCH$_3$), 50.9 (C(CH$_3$)$_3$), 30.9 (C(CH$_3$)$_3$); FTIR ν_{max}/cm^{-1}: 2977, 2841, 1735, 1683, 1582, 1448, 1370; HRMS (ESI–TOF) *m/z*: [M + H]+ calculated for C$_{21}$H$_{24}$N$_3$O$_5$S$^+$ 430.1431 found 430.1445.

Diethyl 8-(tert-butylamino)-4-oxo-2-phenyl-4,6-dihydropyrimido[2,1-b][1,3]thiazine-6,7-dicarboxylate (**10r**); 2-amino-6-phenyl-4*H*-1,3-thiazin-4-one (**9e**) (0.25 g, 1.22 mmol), *tert*-butyl isocyanide (**1a**) (0.10 g, 1.22 mmol) diethyl acetylenedicarboxylate (**2b**) (0.21 g, 1.22 mmol). Physical characteristics: yellow solid; Yield: 0.45 g, 80%; Mp: 145–147 °C, R$_f$: 0.5, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.76 (1H, br s, NH), 7.59-7.47 (5H, m, Ar-H), 6.68 (1H, s, Ar-CH), 6.34 (1H, s, H-6), 4.29–4.10 (4H, m, 2 × CH$_2$), 1.43 (9H, s, C(CH$_3$)$_3$), 1.33–1.22 (6H, m, 2 × CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.7 (C=O), 168.2 (C=O), 161.8 (C=O), 157.5 (C-10), 155.2 (C-8), 150.9 (C-2), 133.9 (Ar-C), 131.9 (Ar-C), 129.6 (Ar-C), 126.4 (ArCH), 113.9 (C-3), 72.4 (C-7), 61.9 (O-CH$_2$), 59.2 (O-CH$_2$), 52.6 (C-6),) 51.5 (C(CH$_3$)$_3$), 30.9 (C(CH$_3$)$_3$), 14.9 (CH$_3$), 14.2 (CH$_3$); FTIR ν_{max}/cm^{-1}: 3279, 2976, 2873, 1734, 1676, 1645, 1606, 1535, 1462; HRMS (ESI–TOF) m/z: [M+H]$^+$ calculated for C$_{23}$H$_{28}$N$_3$O$_5$S$^+$ 458.1744 found 458.1744.

Dimethyl 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-4*H*-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.(0.17 g, 1.22 mmol). Physical characteristics: yellow solid; Yield: 0.45 g, 76%; Mp: 162–164 °C, R$_f$: 0.4, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.77 (1H, br s, NH), 7.62–7.49 (5H, m, Ar-H), 6.71 (1H, s, Ar-CH), 6.39 (1H, s, H-6), 3.77 (3H, s, OCH$_3$), 3.71 (3H, s, OCH$_3$) 1.85 (CH$_2$), 1.50 and 1.48 (6H, 2 × s, 2 × CH$_3$), 0.98 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.0 (C=O), 168.4 (C=O), 161.6 (C=O), 157.4 (C-10), 155.4 (C-8), 150.9 (C-2), 133.8(Ar-C), 131.9 (Ar-CH), 129.5 (Ar-CH), 126.4 (Ar-CH), 113.9 (C-3), 71.2 (C-7), 56.2 (C(CH$_3$)$_3$), 53.3 (CH$_2$), 52.9 (C-6), 51.3 and 50.7 (2 × OCH$_3$), 31.8 (C(CH$_3$)$_2$), 31.7 (C(CH$_3$)$_3$), 31.6 (CH$_3$O), 31.5 (CH$_3$O); FTIR ν_{max}/cm^{-1}: 2953, 2878, 1732, 1681, 1651, 1613, 1542, 1450;$^-$HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{25}$H$_{32}$N$_3$O$_5$S$^+$ 486.2057 found 486.2044.

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-4*H*-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**) (0.21 g, 1.22 mmol). Physical characteristics: yellow solid; Yield: 0.52 g, 83%; Mp: 88–90 °C, R$_f$: 0.5, hexane-ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.00 (1H, br s, NH), 7.63–7.50 (5H, m, Ar-H), 6.72 (1H, s, Ar-CH), 6.37 (1H, s, H-6), 4.34–4.11 (4H, m, 2 × O-CH$_2$), 1.87 (2H, q, *J* = 14.8 Hz, CH$_2$), 1.50 and 1.48 (6H, 2 × s, 2 × CH$_3$), 1.34 (3H, t, *J* = 7.2 Hz, CH$_2$CH$_3$), 1.26 (3H, t, *J* = 6.8 Hz, CH$_2$CH$_3$), 0.98 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.7 (C=O), 168.2 (C=O), 161.8 (C=O), 157.31 (C-10), 155.3 (C-8), 150.9 (C-2), 133.9 (Ar-C), 131.9 (Ar-CH), 129.6 (Ar-CH), 126.4 (Ar-CH), 113.9 (C-3), 72.2 (C-7), 61.8 (O-CH$_2$), 59.2 (O-CH$_2$), 56.2 (C(CH$_3$)$_3$), 53.3 (O-CH$_2$), 51.5 (C-6), 31.8 (C(CH$_3$)$_3$), 31.8 (CH$_3$), 31.7 (CH$_3$), 14.9 (CH$_3$), 14.2 (CH$_3$); FTIR ν_{max}/cm^{-1}: 2963, 2925, 2864, 1735, 1671, 1641, 1611, 1535, 1441; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ Calculated for C$_{27}$H$_{36}$N$_3$O$_5$S$^+$ 514.2370 found 514.2350.

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, R$_f$: 0.4, hexane/ethyl acetate (90%:10%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.59 (1H, br s, NH), 7.63–7.51 (5H, m, Ar-H), 6.71 (1H, s, Ar-CH), 6.39 (1H, s, CH-6), 3.99 (1H, s, N-CH), 3.78 (3H, s, OCH$_3$), 3.73 (3H, s, OCH$_3$), 1.99–1.59 (6H, m, cyclohexyl), 1.45–1.24 (4H, m, cyclohexyl); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.1 (C=O), 168.4 (C=O), 161.7 (C=O), 159.0 (C-10), 154.2 (C-8), 150.9 (C-2), 133.9 (Ar-C), 132.0 (Ar-CH), 129.6 (Ar-CH), 126.4 (Ar-CH), 113.8 (C-3), 71.4 (C-7), 52.9 (O-CH$_3$), 51.5 (C-6), 50.8 (O-CH$_3$), 49.7 (CHNH), 34.3 (CH$_2$, cyclohexyl), 33.7 (CH$_2$, cyclohexyl), 25.7 (CH$_2$, cyclohexyl), 24.8 (CH$_2$, cyclohexyl), 24.7 (CH$_2$, cyclohexyl);

FTIR ν_{max}/cm^{-1}: 3282, 2918, 2846, 1740, 1677, 1651, 1604, 1533, 1444; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for $C_{23}H_{26}N_3O_5S^+$ 456.1588 found 456.1592.

3.1.3. Synthesis of Methyl 7-Oxo-7*H*-Thiazolo[3,2-*a*]Pyrimidine-5-Carboxylate Derivatives (**13a–j**). Method B (3-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 (DEtAD) (**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 brown solid; Yield: 0.89 g, 82%; Mp: 165–167 °C; **R$_f$** 0.5, hexane/ethyl acetate (40%:60 %); ^{1}H NMR (400 MHz, DMSO-d6), 6.50 (1H, s, H-6), 3.95 (3H, s, O-CH$_3$), 2.28 (3H, s, CH$_3$), 2.10 (3H, s, CH$_3$); ^{13}C NMR (101 MHz, DMSO-d6) δ 164.9 (C=O), 164.7 (C=O), 161.5 (C-9), 138.9 (C-5), 127.9 (C-2), 116.7 (C-3), 112.1 (C-6), 54.0 (O-CH$_3$), 12.6 (CH$_3$), 11.8 (CH$_3$); FTIR νmax/cm^{-1}: 2993, 1734, 1638, 1608, 1491, 1413; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for $C_{10}H_{11}N_2O_3S^+$ 239.0485, found 239.0486.

Methyl 7-oxo-3-(p-tolyl)-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (**13b**). Thiourea (**15**) (0.19 g, 2.4 mmol), 2-bromo-4-methylacetophenone (**16d**) (0.52 g, 2.4 mmol) and DMAD (**2a**) (0.34 g, 2.4 mmol). Physical properties: orange solid; Yield: 0.51 g, 71%; Mp: 176–178 °C; R$_f$ 0.4, hexane/ethyl acetate (40%:60%); ^{1}H NMR (400 MHz, DMSO-*d$_6$*) 7.35–7.33 (2H, m, ArH), 7.30–7.27 (3H, m, ArH), 6.47 (1H, s, H-6), 3.15 (3H, s, O-CH$_3$), 2.35 (3H, s, CH$_3$); ^{13}C NMR (101 MHz, DMSO-d6) δ 166.8 (C=O), 165.3 (C=O), 160.6 (C-9), 139.4 (C-5), 138.9 (Ar-C), 136.6 (Ar-C), 129.4 (Ar-CH), 127.5 (Ar-C), 127.2 (ArCH), 113.01 (C-6), 108.14 (C-2), 52.8 (O-CH$_3$); FTIR νmax/cm^{-1}: 3041, 1742, 1639, 1587, 1509, 1485, 1416; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for $C_{15}H_{13}N_2O_3S^+$ 301.0641, found 301.0648.

Methyl 3-(4-fluorophenyl)-7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (**13c**). Thiourea (**15**) (0.19 g, 2.3 mmol), 2-bromo-4-fluoroacetophenone (**16e**) (0.51 g, 2.3 mmol) and DMAD (**2a**) (0.33 g, 2.3 mmol). Physical properties: yellow solid; Yield: 0.49 g, 70%; Mp: 220–222 °C; R$_f$ 0.5, hexane/ethyl acetate (40%:60%); ^{1}H NMR (400 MHz, DMSO-*d6*) 7.56–7.53 (2H, m, ArH), 7.37–7.34 (3H, m, ArH), 6.49 (1H, s, H-6), 3.23 (3H, s, O-CH$_3$); **^{13}C NMR** (101 MHz, DMSO-*d6*) δ 166.7 (C=O), 165.3 (C=O), 162.6 (d, J_{CF} = 246 Hz, Ar-C), 161.3 (ArC), 160.6 (ArC), 138.7 (Ar-C), 135.4 (ArC), 129.9 (d, J_{CF} = 8.1 Hz, Ar-CH), 126.9 (d, J_{CF} = 3.0 Hz, Ar-C), 115.9 (d, J_{CF} = 22.1 Hz, Ar-CH), 113.1 (C-6), 109.0 (C-2), 52.9 (O-CH$_3$); FTIR νmax/cm^{-1}: 3058, 1742, 1640, 1581, 1489; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for $C_{14}H_{10}FN_2O_3S^+$ 305.0391, found 305.0391.

Methyl 3-(4-chlorophenyl)-7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (**13d**). Thiourea (**15**) (0.16 g, 2.1 mmol), 2-bromo-4-chloroacetophenone (**16f**) (0.50 g, 2.1 mmol) and DMAD (**2a**) (0.30 g, 2.1 mmol). Physical properties: yellow solid; Yield: 0.48 g, 71%; Mp: 200–202 °C; R$_f$ 0.8, hexane/ethyl acetate (40%:60%); ^{1}H NMR (400 MHz, DMSO-*d6*) 7.58 (2H, d, *J* = 8.4 Hz, ArH), 7.50 (2H, d, *J* = 8.4 Hz, ArH), 7.39 (1H, s, H-2), 6.50 (1H, s, H-6), 3.23 (3H, s, O-CH$_3$); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 166.8 (C=O), 165.3 (C=O), 160.6 (C-9), 138.6 (Ar-C), 135.2 (Ar-C), 134.3 (Ar-C), 129.3 (Ar-C), 129.1 (Ar-CH), 129.0 (Ar-CH), 128.7 (Ar-CH), 127.4 (Ar-CH), 113.2 (C-6), 109.5 (C-2), 52.90 (O-CH$_3$); FTIR νmax/cm^{-1}: 3049, 1734, 1633, 1583, 1494, 1481; HRMS (ESI–TOF) m/z: [M+H]$^+$ calculated for $C_{14}H_{10}ClN_2O_3S^+$ 321.0095, found 321.0087.

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; R$_f$ 0.4, hexane/ethyl acetate (40%:60%); ^{1}H NMR (400 MHz, DMSO-*d6*) 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-CH$_2$), 1.34 (3H, t, *J* = 7.2 Hz,

CH$_3$); ^{13}C 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-CH$_2$), 13.7 (CH$_3$); FTIR νmax/cm^{-1}: 3176, 3077, 2978, 1720, 1621, 1557, 1471; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_9$H$_9$N$_2$O$_3$S$^+$ 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 DEtAD (**2b**) (0.92 g, 5.4 mmol); Physical properties: brown solid; Yield: 1.1 g, 86%; Mp: 150–152 °C; R$_f$ 0.5, hexane/ethyl acetate (40%:60%); ^{1}H NMR (400 MHz, DMSO-*d6*) 7.10 (1H, s, H-2), 6.53 (1H, s, H-6), 4.38 (2H, q, *J* = 6.8 Hz, O-CH$_2$), 2.23 (3H, s, CH$_3$) 1.34 (3H, t, *J* = 6.8 Hz, CH$_3$); ^{13}C 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 (CH$_2$), 15.3 (CH$_3$) 13.6 (CH$_3$); FTIR νmax/cm^{-1}: 2973, 1731, 1634, 1493; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{10}$H$_{11}$N$_2$O$_3$S$^+$ 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-butanone (**16c**) (0.50 g, 4.6 mmol) and DEtAD (**2b**) (0.78 g, 4.6 mmol). Physical properties: brown solid; Yield: 0.94 g, 81%; Mp: 153–155 °C; R$_f$ 0.5, hexane/ethyl acetate (40%:60%); ^{1}H NMR (400 MHz, DMSO-*d6*), 6.5 (1H, s, H-6), 4.40 (2H, q, *J* = 5.2 Hz, CH$_2$), 2.28 (3H, s, CH$_3$), 2.12 (3H, s, CH$_3$), 1.33 (3H, t, *J* = 7.6 Hz, CH$_2$CH$_3$); ^{13}C 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-CH$_2$), 13.6, 12.7, (2 × CH$_3$), 11.8 (CH$_2$CH$_3$); FTIR νmax/cm^{-1}: 2988, 1732, 1641, 1489, 1452; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{11}$H$_{13}$N$_2$O$_3$S$^+$ 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-fluoroacetophenone (**16e**) (0.51 g, 2.3 mmol) and DEtAD (**2b**) (0.39 g, 2.3 mmol). Physical properties: yellow solid, Yield 0.63 g, 86%; **Mp:** 180–182 °C; R$_f$ 0.5, hexane/ethyl acetate (40%:60%); ^{1}H NMR (400 MHz, DMSO-*d6*) 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-CH$_2$) 1.04 (3H, t, *J* = 7.2 Hz, CH$_3$); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 166.8 (C=O), 165.4 (C=O), 162.6 (d, *J*$_{CF}$ = 246 Hz, Ar-C), 161.4 (Ar-C), 160.2 (Ar-C), 138.9 (Ar-C), 135.4 (Ar-C), 129.9 (d, *J*$_{CF}$ = 9.1 Hz, Ar-CH), 128.0 (d, *J*$_{CF}$ = 8.1 Hz, Ar-CH), 126.9 (d, *J*$_{CF}$ = 4.0 Hz, Ar-CH), 115.9 (d, *J*$_{CF}$ = 22.2 Hz, Ar-CH) 113.1 (C-6), 109.1 C-2), 62.7 (CH$_2$-O), 13.3 (O-CH$_3$); FTIR νmax/cm^{-1}: 3061, 1733, 1639, 1489; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{15}$H$_{12}$FN$_2$O$_3$S$^+$ 319.0547, found 319.0565.

Ethyl 3-(4-chlorophenyl)-7-oxo-7H-thiazolo[3,2-a]pyrimidine-5-carboxylate (**13i**). Thiourea (**15**) (0.16 g, 2.1 mmol), 2-bromo-4-chloroacetophenone (**16f**) (0.50 g, 2.1 mmol) and DEtAD (**2b**) (0.36 g, 2.1 mmol). Physical properties: yellow solid, Yield: 0.59 g, 84%; Mp: 198–200 °C; R$_f$ 0.9, hexane/ethyl acetate (40%:60%); ^{1}H NMR (400 MHz, DMSO-*d6*) 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-CH$_2$), 1.03 (3H, t, *J* = 6.8, Hz, CH$_3$); ^{13}C 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-CH), 128.9 (Ar-CH), 113.2 (C-6), 109.38 (C-2), 62.7 (CH$_2$-O), 13.2 (CH$_3$); FTIR νmax/cm^{-1}: 3057, 2986, 1733, 1640, 1580, 1501, 1482; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{15}$H$_{12}$ClN$_2$O$_3$S$^+$ 335.0252, found 335.0267.

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

In a round-bottomed flask equipped with a magnetic stirrer bar, DMAD/DEtAD (**2**) was added to the mixture of 2-aminothiazole derivative (**11a–h**) or 2-imino-1,3-oxazolidine (**17**) or 1*H*-1,2,4-triazol-5-amine (**18**) or 1*H*-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 acetylenedicarboxylate (DTAD) (**2c**) (0.45 g, 1.99 mmol); Physical properties: yellow solid; Yield: 0.36 g, 72%; **Mp:** 246–248 °C; R$_f$ 0.5, hexane/ethyl acetate (40%:60%); ^{1}H NMR (400 MHz, DMSO-*d6*) 8.29 (1H, d, *J* = 4.4 Hz, H-2), 7.34 (1H, d,

J = 5.2 Hz, H-3), 6.73 (1H, s, H-6), 1.57 (9H, s, ((CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d6) δ 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 (C(CH$_3$)$_3$), 27.4 ((CH$_3$)$_3$); FTIR νmax/cm^{-1}: 2923, 1729, 1639; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_{11}$H$_{13}$N$_2$O$_3$S$^+$ 253.0641, found 253.0642.

Methyl 5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyrimidine-7-carboxylate (**19a**); 2-imino-1,3-oxazolidine (0.51 g, 5.8 mmol) and DMAD (**2a**) (0.83 g, 5.8 mmol); Physical properties: White solid; Yield: 0.95 g, 82%; Mp: 251–253 °C; R$_f$ 0.5, ethyl acetate (100 %); ^{1}H NMR (400 MHz, DMSO-*d6*) 6.37 (1H, s, H-6) 4.67 (2H, t, *J* = 8.4 Hz, CH$_2$), 4.49 (2H, t, *J* = 8.4 Hz, CH$_2$), 3.87 (3H, s, O-CH$_3$); ^{13}C NMR (101 MHz, DMSO-d6) δ 170.9, (C=O) 162.1 (C=O), 160.8 (C-9), 138.1 (C-7), 110.9 (C-6), 66.6 (CH$_2$), 53.5 (O-CH$_3$), 47.03 (CH$_2$); FTIR νmax/cm^{-1}: 2965, 1732, 1624, 1535, 1476, 1421; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_8$H$_9$N$_2$O$_4$$^+$ 197.0557, found 197.0549.

Ethyl 5-oxo-3,5-dihydro-2H-oxazolo[3,2-a]pyrimidine-7-carboxylate (**19b**); 2-imino-1,3-oxazolidine (0.51 g, 5.8 mmol) and DEtAD (**2b**) (0.98 g, 5.8 mmol). Physical properties: White solid: Yield 0.98 g, 80%; Mp: 297–299 °C; R$_f$ 0.5, ethyl acetate (100%); ^{1}H NMR (400 MHz, DMSO-*d6*) 5.64 (1H, s, H-6), 4.27 (2H, q, *J* = 7.2 Hz, O-CH$_2$), 4.04 (2H, t, *J* = 6.0 Hz, CH$_2$), 3.62 (2H, t, *J* = 5.6 Hz, CH$_2$), 1.27 (3H, t, *J* = 7.2 Hz, CH$_3$); ^{13}C NMR (101 MHz, DMSO-*d6*) δ 170.4 (C=O) 163.2 (C=O), 161.6 (C-9), 155.7 (C-7), 89.5 (C-6), 61.1 (CH$_2$), 58.5 (CH$_2$), 48.1 (CH$_2$), 13.8 (CH$_3$); FTIR νmax/cm^{-1}: 3125, 2958, 1700, 1698, 1662, 1642, 1637, 1381; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_9$H$_{11}$N$_2$O$_4$$^+$ 211.0713, found 211.0708.

Ethyl 5-oxo-5,8-dihydro-[1,2,4]triazolo[4,3-a]pyrimidine-7-carboxylate (**20**); 1*H*-1,2,4-triazol-5-amine (0.50 g, 6.0 mmol) and DEtAD (**2b**) (1.02 g, 6.0 mmol). Physical properties: Brown solid: Yield: 1.1 g, 88%; Mp: 185–187 °C; R$_f$ 0.5, ethyl acetate (100 %); ^{1}H NMR (400 MHz, DMSO-*d6*) 8.91 (1H, s, H-5), 6.66 (1H, s, H-7), 4.50 (2H, q, *J* = 6.8 Hz, O-CH$_2$), 1.40 (3H, t, *J* = 7.2 Hz, CH$_3$); ^{13}C NMR (101 MHz, DMSO-d6) δ 160.5 (C=O), 158.9 (C=O), 151.9 (C-5), 134.1 (Ar-C), 132.9 (Ar-C) 112.9 (C-7), 62.5 (CH$_2$), 12.9 (CH$_3$); FTIR νmax/cm^{-1}: 3150, 3068, 2909, 2731, 1722, 1680, 1610, 1579; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_8$H$_9$N$_4$O$_3$$^+$ 209.0669, found 209.0677.

7-Oxo-7H-[1,2,4]triazolo[5,1-b][1,3]thiazine-5-carboxylate (**5**); 1*H*-1,2,4-Triazole-5-thiol (0.50 g, 5.0 mmol) and DEtAD (**2b**) (0.85 g, 5.0 mmol). Physical properties: White solid; Yield: 0.92 g, 82%; Mp: 110–112 °C; R$_f$ 0.9 hexane/ethyl acetate (20%:80%); ^{1}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-CH$_2$), 1.38 (3H, t, *J* = 6.8 Hz, CH$_3$); ^{13}C NMR (101 MHz, DMSO-d6) δ 160.9 (C=O), 155.3 (C=O), 153.7 (C-4), 151.56 (C-2), 139.6 (C-7) 122.2 (C-6), 64.1 (CH$_2$), 13.8 (CH$_3$); FTIR νmax/cm^{-1}: 3123, 3053, 2987, 1698, 1582, 1491; HRMS (ESI–TOF) *m/z*: [M + H]$^+$ calculated for C$_8$H$_8$N$_3$O$_3$S$^+$ 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 ω- and φ-scans of width 0.5° and 1024 × 1024 bit data frames. Using *Olex2* [49], the crystal structures were solved by with the *ShelXT* [50] structure solution program, using Intrinsic Phasing, and refined 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.

Crystal Data for 8: C$_8$H$_7$N$_3$O$_3$S (*M* =225.23 g/mol): triclinic, space group *P*-1 (no. 2), *a* = 8.6289(5) Å, *b* = 9.9003(6) Å, *c* = 11.9343(7) Å, α = 76.618(2)°, β = 72.127(2)°, γ = 89.767(2)°, *V* = 941.51(10) Å^3, *Z* = 4, *T* = 173.15 K, μ(MoKα) = 0.333 mm^{-1}, *Dcalc* = 1.589 g/cm^3, 16,340 reflections measured (3.696° ≤ 2Θ ≤ 56.728°), 4715 unique (R_{int} = 0.0461, R_{sigma} = 0.0464) which were used in all calculations. The final R_1 was 0.0333 (I > 2σ(I)) and wR_2 was 0.0771 (all data). CCDC 2103713.

Crystal Data for 13a: C$_{10}$H$_{12}$N$_2$O$_4$S (*M* =256.28 g/mol): monoclinic, space group *P*2$_1$/*c* (no. 14), *a* = 7.4587(3) Å, *b* = 20.1251(9) Å, *c* = 8.0128(3) Å, β = 108.8923(15)°,

V = 1137.98(8) Å^3, Z = 4, T = 173.15 K, μ(MoKα) = 0.290 mm^{-1}, *Dcalc* = 1.496 g/cm^3, 11779 reflections measured (4.048° ≤ 2Θ ≤ 56.708°), 2839 unique (R_{int} = 0.0356, R$_{sigma}$ = 0.0325) which were used in all calculations. The final R_1 was 0.0359 (I > 2σ(I)) and wR_2 was 0.0973 (all data). CCDC 2103714.

Crystal Data for 13b: C$_{15}$H$_{12}$N$_2$O$_3$S (M =300.33 g/mol): monoclinic, space group *C*2/*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) Å^3, Z = 8, T = 173.15 K, μ(MoKα) = 0.245 mm^{-1}, *Dcalc* = 1.441 g/cm^3, 15439 reflections measured (3.782° ≤ 2Θ ≤ 56.796°), 3474 unique (R_{int} = 0.0236, R$_{sigma}$ = 0.0204) which were used in all calculations. The final R_1 was 0.0345 (I > 2σ(I)) and wR_2 was 0.0887 (all data). CCDC 2103715.

Crystal Data for 13d: C$_{14}$H$_9$ClN$_2$O$_3$S (M =320.74 g/mol): orthorhombic, space group *Pbca* (no. 61), a = 15.167(2) Å, b = 8.9457(14) Å, c = 19.944(3) Å, V = 2706.0(7) Å^3, Z = 8, T = 173.15 K, μ(MoKα) = 0.447 mm^{-1}, *Dcalc* = 1.575 g/cm^3, 16592 reflections measured (4.084° ≤ 2Θ ≤ 50°), 2381 unique (R_{int} = 0.1235, R$_{sigma}$ = 0.1070) which were used in all calculations. The final R_1 was 0.0362 (I > 2σ(I)) and wR_2 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 5*H*-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**), 1*H*-1,2,4-triazol-5-amine (**18**) or 1*H*-1,2,4-triazole-5-thiol (**5**) when using the two-component approach.

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