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ULTRASOUND-MEDIATED THREE-COMPONENT REACTION "ON-WATER" PROTOCOL FOR THE SYNTHESIS OF NOVEL MONO- AND BIS-1,3-THIAZIN-4-ONE DERIVATIVES

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Abstract – Green synthetic and catalyst-free strategy towards the synthesis of novel mono- and bis-1,3-thiazin-4-one scaffolds through a one pot, reaction of carbon disulfide, monoacetylenic esters and amines under ultrasonication has been reported. The merits of this protocol comprise no need for tedious workup steps and afforded the desired products in excellent yields make this synthetic protocol more efficient and worthy of further attentiveness. Moreover, the method exhibited excellent score in a number of green metrics.

INTRODUCTION

Increasing attention about the environment has forced chemists to create sustainable and unprecedented chemical procedures through the principles of "green chemistry" and "atom economy".[1] As a result, new synthetic protocols that are operationally simple, step-economical, high yielding, and compatible with green solvents are of essentially important. Due to the unparalleled properties of water, much attention has been received for designing of synthetically applicable watery reactions. These water-based reactions are recently classified as "on water" or "in water".[2] In the "on water" type, reactants form a heterogeneous mixture in water which leads to increase of the reaction rate and easiness of product isolation. This rate enhancement may be due to the hydrogen bonds formation at the organic/water interface. While in case of "in water" reaction, only small hydrophobic aggregates are formed which are perfectly surrounded by water clusters with lateral hydrogen bonds.[3] Multi-component reactions (MCRs), which are robust tools in organic chemistry, are the best choice for attaining ideal green synthetic procedures.[4,5] Combination of the MCRs and on-water chemistry concepts has been utilized for only little type of organic reactions[6,7] therefore; it may be of general benefit to broaden the scope of on-water-based MCRs. 1,3-Thiazines are a privileged heterocycles that exhibit innate pharmacological activities such as antifungal, anti-HIV, antipsoriatic, antimicrobial activities and the applications in synthetic materials.[8-13] In literature, there are many reports for the preparation of 1,3-thiazines.[14,15] The most common synthetic methods to access 1,3-thiazine scaffolds involve condensation reaction of aminobenzyl chloride or chalcones with thioamides or thioureas.[16-20] Also, malonic acid, potassium thiocyanate and acid anhydrides are used as a building block for the construction of the 1,3-thiazine ring.[21] Recently, Sharma and his coworkers reported the synthesis of 1,3-thiazine hybrids from amines, dialkyl acetylenedicarboxylates and isothiocyanates under microwave irradiation.[22] Generally, most of these protocols suffer from one or more obstacles, like poor yields, poisonous reagents, long reaction times, tedious work-up, and limited substrate scope. However, to the best of our knowledge, bis-1,3-thiazin-4-one derivatives have never been included in the reported strategies. Ultrasonic-assisted organic synthesis is a robust methodology that is vastly being used in green chemistry.[23] The formation, growth and the sudden collapse of gaseous microbubbles in the liquid phase, due to the cavitation phenomenon, create locally high pressure and temperature that can increase the reaction rate and led to the formation of pure product in higher yields.[24] Motivated by the aforementioned findings and in a continuation of our interest in the preparation of a wide range of mono- and bis-heterocyclic systems using diverse green chemistry techniques,[25,26] we report herein the first on-water-based MCRs synthesis of mono- and bis-1,3-thiazin-4-ones without any catalyst under ultrasonic irradiation (Figure 1). Moreover, the scope and limitations of the reaction are also studied.

RESULTS AND DISCUSSION

In an endeavor to develop a catalyst-free multicomponent reaction for the synthesis of 1,3-thiazin-4-one (**3a**), we commenced our studies with the commercially available starting materials methyl acetylenecarboxylate **1a** (1 mmol) with cyclohexylamine **2a** (1 mmol) and carbon disulfide (1 mmol) as model reactants (Table 1). To commence with, we evaluated the one pot reaction comprising the above reactants in water at 25 ^{o}C. In the outset of the reaction, the reactants formed an emulsion in water, from which a yellow product isolated in low yield (Table 1, entry 1). Increases in both time and temperature have no valuable influence on the reaction yield and instead numerous spots were present on the TLC at high temperature (Table 1, entries 2 & 3), probably due to the co-existence of two highly reactive species; methyl acetylenecarboxylate and cyclohexylamine. Upon examining the role of solvents for anticipating further increase in the yield, a series of solvents other than water, such as ethanol (EtOH), dichloromethane (DCM), and acetonitrile (MeCN) were screened in the present protocol (Table 1, entries 4-6). Unexpectedly, none could provide satisfactory yields of the desired product (**3a**) and thus, amongst the tested solvents, water emerged out as the best solvent for this reaction (Table 1, entries 1 & 2).

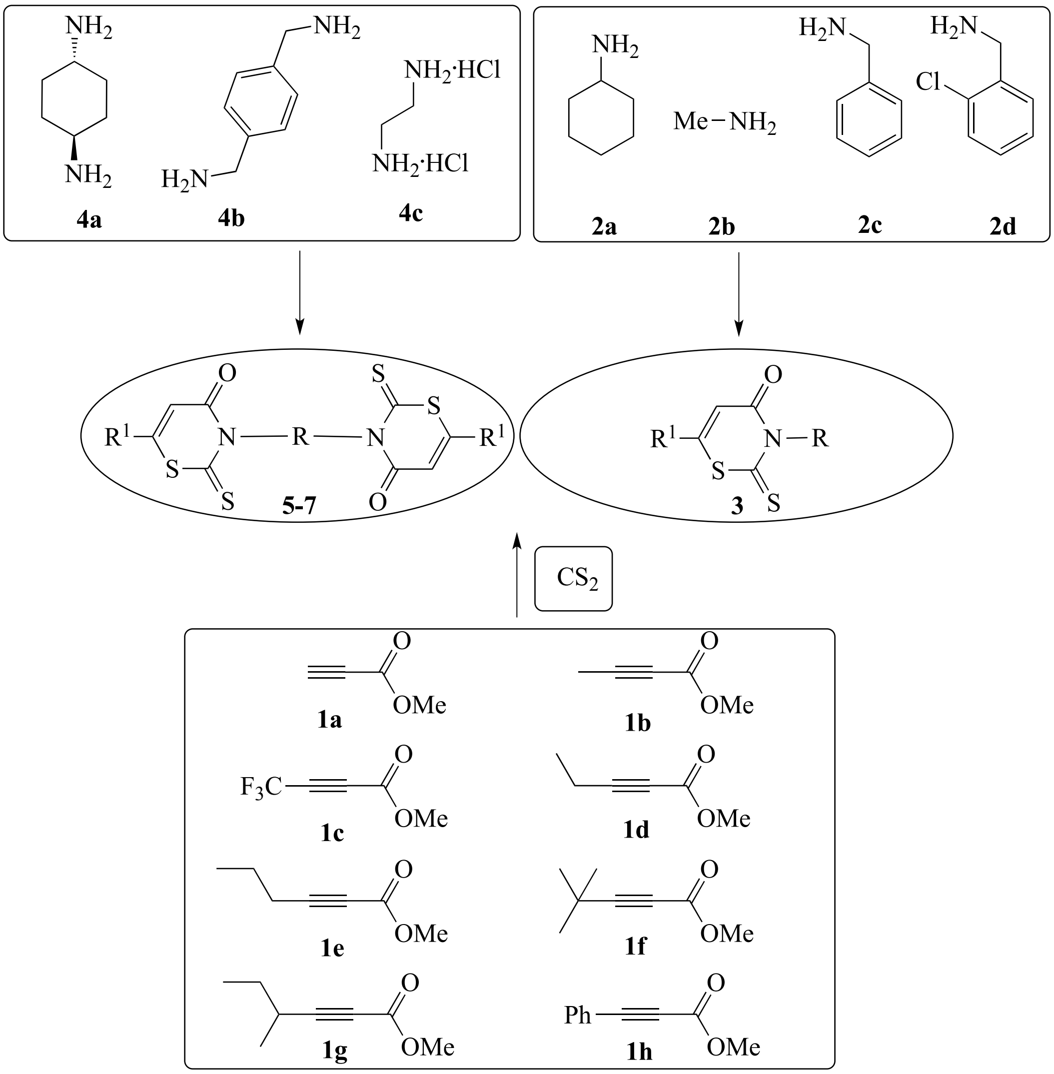
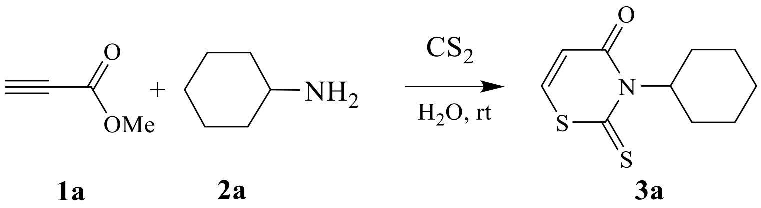


Figure 1. Pictorial overview of the present work

To the best of our knowledge, the use of ultrasound irradiation to prepare 1,3-thiazin-4-ones has not been explored to date. In order to diminish the reaction time and to ameliorate the reaction yield, we therefore focused on the use of ultrasound irradiation for accelerating the preparation of the 1,3-thiazin-4-one derivative, **3a**. To accomplish this, we used the above model reactants with the same molar ratio under ultrasonic irradiation in water at room temperature. Surprisingly, within 10 min of stirring a yellow solid was separated out from the reaction mixture in 90% yield (Table 1, entry 7) which was confirmed as 1,3-thiazin-4-one derivative (**3a**). There was about 38% increase in yield when using the ultrasonic

Table 1. Optimization of the reaction conditions for the synthesis of 1,3-thiazin-4-one (**3a**)



Entry	Solvent	Method	Temperature (ºC)	Time (min)	Yield (%)
1	H_2O	conventional	rt	120	43
2	H_2O	conventional	rt	180	52
3	H_2O	conventional	70	120	28
4	EtOH	conventional	rt	180	16
5	DCM	conventional	rt	120	trace
6	MeCN	conventional	rt	120	trace
7	H_2O	US	rt	10	90[a]
8	H_2O	US	rt	5	87[a]
9	H_2O	US	70	10	33[a]
10	-	US	rt	10	9
11	H_2O	US	rt	10	85[b]

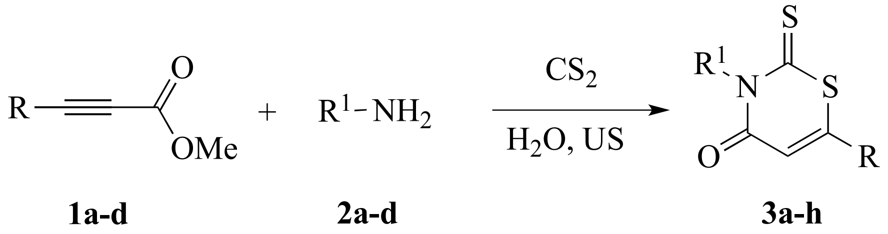
[a] isolated yield at 25 kHz, [b] isolated yield at 40 kHz.

irradiation. In a further reaction, the irradiation time was diminished to 5 min, which reduced the yield of **3a** to 87% (Table 1, entry 8). Moreover, no improvement was observed and the reaction yield was diminished on carrying out the above reaction at high temperature (Table 1, entry 9). To this end, we performed the model reaction in organic solvents such as EtOH, DCM and MeCN under ultrasound irradiation and found that none of them could effectively mediate the preparation of desired product (**3a**). Moreover, we also performed the congruent solvent-free reaction, which generate unresolved and complex product profile (Table 1, entry 10). The results of these experiments indicated that the model reaction related to the on-water class.[27] The unrivaled chemistry of the phenomenon of on-water is such that for each four water molecules there is one molecule at the organic-aqueous interface has hydroxyl group that acts as catalytic site for the reaction. These hydroxyl groups can act as both acceptors and hydrogen-bond donors, and therefore they are participated in trans-phase hydrogen bonding with the transition state, which minimizes the reaction activation energy.[28,29] Also, the current model reaction was performed using different ultrasound frequencies. When the frequency of the ultrasound was 25 kHz, the reaction furnished the required product (**3a**) in 90% yield at ambient temperature (Table 1, entry 7).

Whilst applying 40 kHz, there was little change in the reaction yield (85% in the same time, Table 1, entry 11). It is clear that there is a perfect frequency for efficient preparation of 1,3-thiazin-4-ones in the frequency of 25 kHz. It is also worth noting that this reaction has generated the required product without any catalyst. This may be due to ultrasound irradiation effect which has been reported to supersede catalysis under particular conditions.[26] The amelioration in the results may be due to the cavitations phenomenon, which is grown by decreasing the ambient pressure under ultrasound irradiation. The collapse of cavities resulted in special medium for the reactions. The gases generated in the cavity are pressed, creating intensive heat that rises liquid temperature and generates a topical hot spot which speed up the reaction. Furthermore; the reaction yield was further got better at 25 kHz may be due to the fact that lower ultrasonic frequencies generate larger cavitation bubbles than higher frequencies. Thence, under the final optimized conditions, the reaction achieved completion in 10 min using equimolar amount of cyclohexylamine and the other two substrates, carbon disulfide and methyl acetylenecarboxylate (Table 1, entry 7). At the end of the reaction it is worth noting that, a yellow precipitate was formed, which by a normal filtration and washing with chilled ethanol, gave the desired product (**3a**) in high purity. The simplicity of the workup made this protocol conductive for automation, practicable, and easy for creating libraries of new compounds. Hence, under the optimized reaction conditions, we reacted carbon disulfide (1 mmol), monoacetylenic esters **1a-d** (1 mmol), and mono-amines **2a-f** (1 mmol) in water under ultrasound irradiation at room temperature for 10 min to afford the required products **3a-h** in excellent yields. Having successfully accomplished an optimized strategy for this unprecedented one-pot protocol, we extended the method on diamines (**4a-c**) and interestingly, it worked equally well and yielded the bis-1,3-thiazin-4-ones **5-7** in excellent yields (Scheme 2).

With the optimal conditions in hand, we next evaluated the limitations and the scope of the multicomponent reaction with respect to amines and monoacetylenic esters (Figure 1). In all examples, the reaction proceeded well and furnished the required products (**3** and **5-7**) in good to excellent yields. As for amines, we noticed that the reaction worked evenly well with all the mono or diamines and afforded the desired products in good yields. It was observed that diamines provided better yields of the products in comparison to mono-amines.

Next, impact of diverse monoacetylenic ester moieties was investigated. Impressively, the reaction was suitable for both electron donating groups, e.g. methyl (**3e**, **3f**, **5b**, **6b**, **7b**), ethyl (**5d**, **6d**, **7d**), *n*-propyl (**5e**, **6e**, **7e**), *sec*-butyl (**5g**, **6g**, **7g**), *t*-butyl (**5f**, **6f**, **7f**) as well as electron withdrawing groups, e.g. phenyl (**3h**, **5h**, **6h**, **7h**), and trifluoromethyl (**3g**, **5c**, **6c**, **7c**) on the acetylenic counterpart, although the products in the latter series were obtained in moderate yields. However, the reaction yield decreased slightly for sterically crowded *t*-butyl derivatives (**5f**, **6f**, **7f**) which might be possibly due to steric reasons.



3a, R = H, R^1 = cyclohexyl
b, R = H, R^1 = Me[30]
c, R = H, R^1 = benzyl
d, R = H, R^1 = CH_2-C_6H_4-*o*-Cl
e, R = Me, R^1 = Me
f, R = Me, R^1 = cyclohexyl
g, R = CF_3, R^1 = cyclohexyl
h, R = C_6H_5, R^1 = cyclohexyl[31]

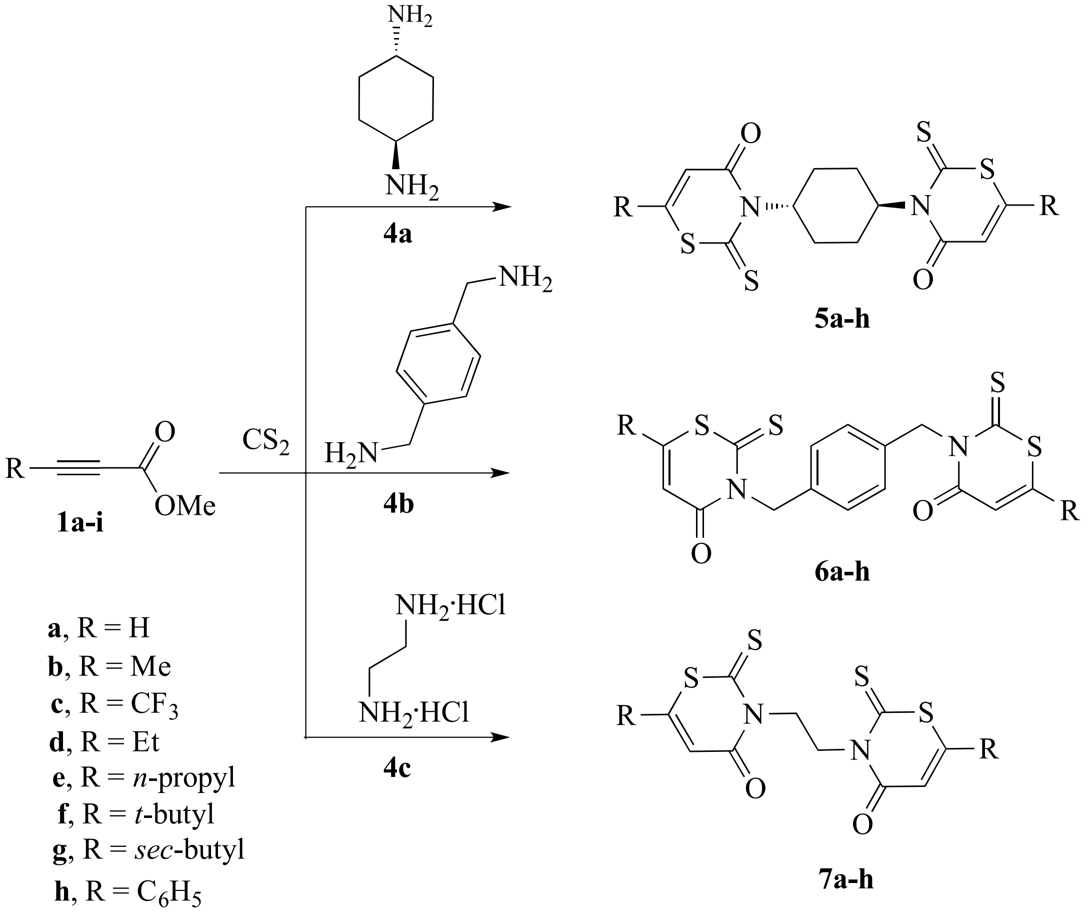
Scheme 1. Synthesis of 2-thioxo-1,3-thiazin-4-ones **3a**-**h**

Expectedly, the reaction failed to deliver the desired product with aromatic amines, owing to the poor nucleophilicity of aromatic amines.

As the trifluoromethyl group is a very important substituent in medicinal chemistry and consider as building blocks in the synthesis of variety types natural products,[32] a diverse of trifluoromethyl-substituted mono- and bis-1,3-thiazin-4-ones, for example, **3g** (83%), **5c** (85%), **6c** (81%), and **7c** (78%), were successfully synthesized.

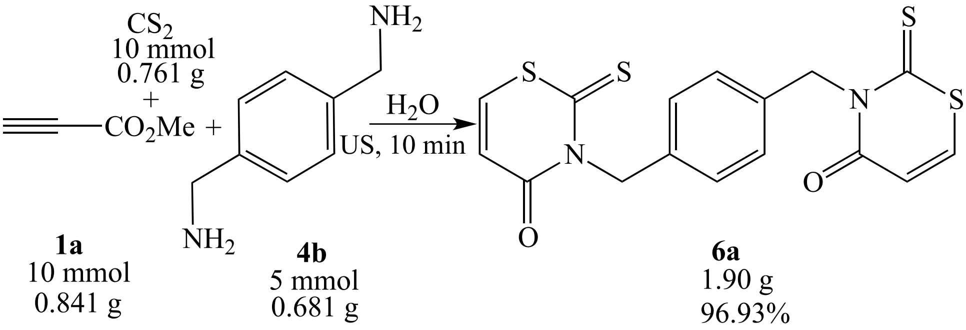
The structure of the newly synthesized derivatives was confirmed by IR, NMR spectroscopy, high-resolution mass spectrometry (HRMS) and elemental analyses. For example, ^{1}H NMR spectrum of derivative **5a** exhibited three multiplet signals recognized as arising from cyclohexyl moiety at δ 1.41, 2.05 and 4.30 ppm. One doublet at 6.23 (2H, J = 10.4 Hz), and one doublet of doublet at 8.54 (2H, J = 10.4, 0.9 Hz) is attributed to thiazine moiety protons. The decoupled ^{13}C NMR spectrum of derivative **5a** exhibited 6 distinct signals, which were in harmonization with the suggested structure. The HRMS spectra of compounds **5-7** revealed that they contained two moles of thiazine moieties per one mole of diamines. For example, the mass spectrum of **5a** displayed the molecular ion (M + H) at m/z 371.0015. The IR spectra of synthesized derivatives exhibited absorption bands due to the carbonyl groups at 1690-1660 cm^{-1} range and the C=S groups around 1230 cm^{-1}.

To conclude the analysis of our multicomponent protocol, a group of green metrics[33,34] have been applied comprising carbon efficiency (CE), Sheldon environmental process mass intensity (PMI), reaction mass efficiency (RME), impact factor (*E*-factor), and atomic economy (AE) for the process. Thence, the preparation of **6a** was conducted on multigram scale (5 mmol) under the optimal conditions, which in turn afforded 1.90 g of pure **6a** in 96.93% yield (Table 2). The current methodology scored a valuable



Scheme 2. Synthesis of bis-1,3-thiazin-4-ones **5**-**7**

Table 2. Calculated green metrics for the scaled-up synthesis of 3-(4-((4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)methyl)benzyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (**6a**)

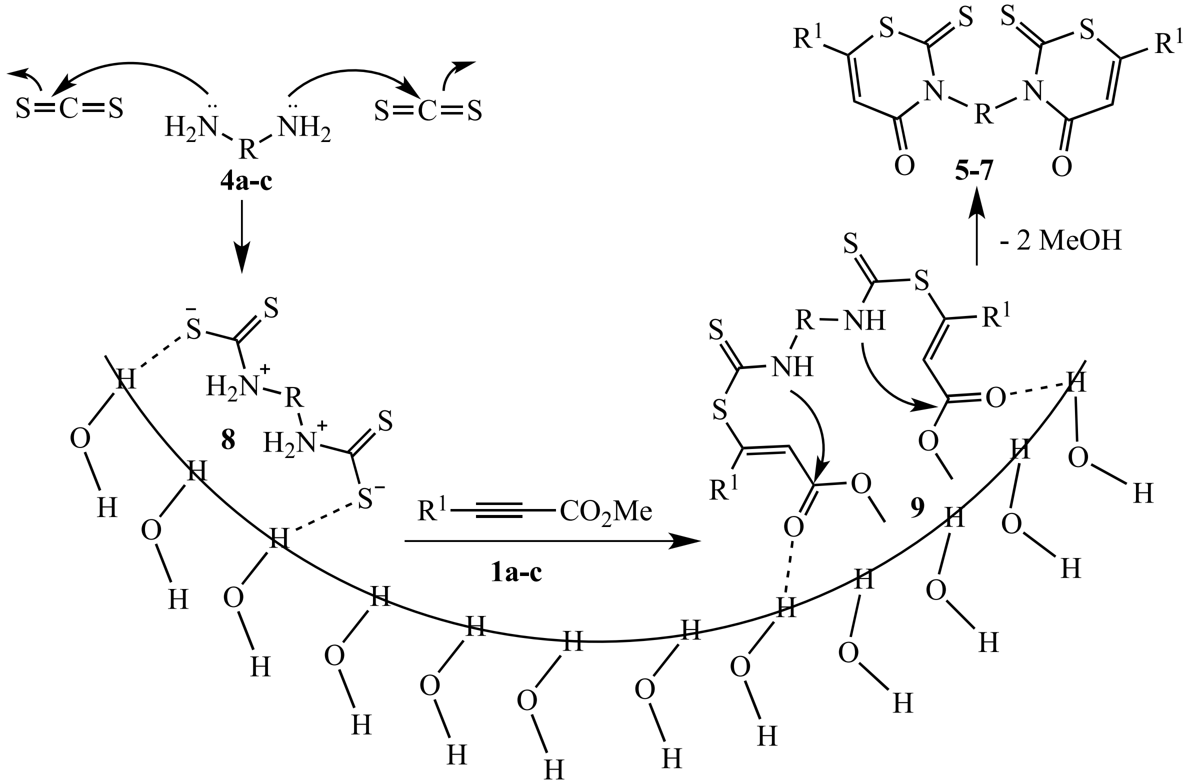


Yield (%)	CE (%)	PMI	RME (%)	*E*-factor[a]	AE (%)
96.93	88.88	1.20	83.22	0.031	85.95

[a] Calculation up to the crude product.

environmental compatibility calculated green metrics such as small *E*-factor (0.031) and high values of AE (85.95%), CE (88.88%), RME (83.22%), and PMI (1.20). This makes the present protocol an ideal green and sustainable process which could have an economical production on a commercial scale.

A tentative mechanistic pathway[25,35] for the synthesis of bis-1,3-thiazin-4-ones (**5-7**) is outlined in Scheme 3. It is conceivable that, nucleophilic attack of the amine nitrogen on carbon disulphide triggered the formation of a zwitter ionic intermediate **8**, which in turn reacted with the acetylenic derivatives to produce **9**. Thereafter, the reactive intermediate **9** underwent ring closure by losing of methanol molecules to afford final isolable derivatives **5-7** (Scheme 3).



Scheme 3. Mechanistic on-water consideration for the synthesis of bis[1,3]thiazin-4-ones **5-7**

CONCLUSIONS

We have reported a straightforward and efficient catalyst-free methodology for the preparation of mono- and bis-1,3-thiazin-4-ones in good to excellent yields under minutes of ultrasound irradiation. Moreover, the protocol is devoid of any monotonous workup or column purification makes it an attractive option to access such mono- and bis-1,3-thiazin-4-ones. Furthermore, the strategy scored acceptable values on the "greenness" report card on employing the green metrics and hence may be of sustainable and procedural utility in the future.

EXPERIMENTAL

Chemicals and instruments

Starting materials were commercially available and were used without further purification. Silica gel G [E-Merck] was used for thin layer chromatography (TLC). ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded at 400, 377 and 100 MHz, respectively. Splitting patterns are designated as singlet (s), doublet (d), triplet (t), doublet of doublet (dd), doublet of triplet (dt), triplet of triplet (tt) quartet (q), broad (br). Splitting patterns that could not be explicated or easily visualized are written as multiplet (m). High resolution mass spectra (HRMS) measurements were recorded on a Bruker Daltonics microTOF spectrometer. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer, using samples prepared as KBr discs. Ultrasonication was done in a SY5200DH-T ultrasound cleaner with an output power of 250 W and a frequency of 25 and 40 kHz. The reaction vial was placed in the maximum energy area in the cleaner. Water was added or removed in order to control the bath temperature.

General procedure for the synthesis of mono and bis-1,3-thiazin-4-ones (3, and 5-7)

Conventional Method:

Amines **2a-d** (2 mmol) or diamines **4a-c** (1 mmol) was slowly added to a magnetically stirred solution of carbon disulfide (2 mmol) and monoacetylenic ester **1a-h** (2 mmol) in water (4 mL) (in case of **2b**, 40% $MeNH_2$ aqueous solution was used, so no need to add water). The resultant solution was stirred for 2 h at room temperature. After completion of the reaction as indicated by TLC (DCM/*n*-heptane or MeOH), the crude material formed was filtered and washed with chilled EtOH (3x5 mL) to afford pure title compounds.

Ultrasound irradiation method:

Amines **2a-d** (2 mmol) or diamines **4a-c** (1 mmol) was slowly added to a magnetically stirred solution of carbon disulfide (2 mmol) and monoacetylenic ester **1a-h** (2 mmol) in water (4 mL) (in case of **2b**, no need to add water). After a pre-stirring of 1 min at rt, the vial was subjected to ultrasound irradiation for 10 min. The completion of the reaction was monitored by TLC. The crude material formed was filtered and washed with chilled EtOH (3x5 mL) to afford pure title compounds.

3-Cyclohexyl-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (3a): Yield 90%; yellow solid; mp 88-90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (dd, J = 10.3, 0.9 Hz, 1H), 6.11 (d, J = 10.4 Hz, 1H), 1.44 (m, 3H, Cyclohexyl), 1.73 (m, 3H, Cyclohexyl), 2.01 (ddd, J = 12.3, 5.2, 2.6 Hz, 2H, Cyclohexyl), 2.39 (tt, J = 12.7, 6.9 Hz, 2H, Cyclohexyl), 5.01 (tt, J = 12.5, 3.6 Hz, 1H, Cyclohexyl). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3 (C=S), 165.1 (C=O), 153.1 (C6), 134.0 (C5), 25.2, 25.8, 27.5, 58.2 (4C, Cyclohexyl). IR (KBr, cm^{-1}): ν_{max} 1687 (C=O), 1223 cm^{-1}. HRMS (EI) for $(M + Na)^{+}$: calcd. 250.0332; found 250.0335. Anal. Calcd for $C_{10}H_{13}NOS_2$: C, 52.83; H, 5.76; N, 6.16. Found: C, 52.76; H, 5.88; N, 6.04.

2,3-Dihydro-3-methyl-2-thioxo-1,3-thiazin-4-one (3b):[30] Yield 92%; yellow solid; mp 77-79 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (dd, J = 10.3, 0.9 Hz, 1H), 6.10 (d, J = 10.4 Hz, 1H), 2.89 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3 (C=S), 165.5 (C=O), 154.2 (C6), 134.3 (C5), 33 (CH_3). IR (KBr, cm^{-1}): ν_{max} 1688 (C=O), 1234 cm^{-1}. HRMS (EI) for (M + Na)$^+$: calcd. 181.9709; found 181.9712. Anal. Calcd for $C_5H_5NOS_2$: C, 37.72; H, 3.17; N, 8.80. Found: C, 37.79; H, 3.04; N, 8.75.

3-Benzyl-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (3c): Yield 89%; yellow solid; mp 106-108 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (dd, J = 10.3, 0.9 Hz, 1H), 7.31–7.44 (m, 5H, 5CH of Ph), 6.11 (d, J = 10.4 Hz, 1H), 5.31 (s, 2H, CH_2Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2 (C=S), 165.8 (C=O), 154.3 (C6), 134.4 (C of Ph), 134.0 (C5), 128.3 (CH of Ph), 128.6 (2CH of Ph), 128.9 (2CH of Ph), 52.8 (CH_2Ph). IR (KBr, cm^{-1}): ν_{max} 1684 (C=O), 1230 cm^{-1}. HRMS (EI) for (M + Na)$^+$: calcd. 258.0020; found 258.0025. Anal. Calcd for $C_{11}H_9NOS_2$: C, 56.14; H, 3.85; N, 5.95. Found: C, 56.10; H, 3.96; N, 5.83.

3-(2-Chlorobenzyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (3d): Yield 91%; yellow solid; mp 123-125 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (dd, J = 10.3, 0.9 Hz, 1H), 7.42 (d, J = 7.4 Hz, 1H, CH of Ar), 7.22 (d, J = 7.4 Hz, 1H, CH of Ar), 7.21 (t, J = 6.6 Hz, 1H, CH of Ar), 6.98 (t, J = 7.0 Hz, 1H, CH of Ar), 6.13 (d, J = 10.4 Hz, 1H), 5.43 (s, 2H, CH_2Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5 (C=S), 166.0 (C=O), 154.8 (C6), 134.7 (C5), 132.9 (C of Ar), 131.4 (C of Ar), 129.8 (CH of Ar), 129.1 (CH of Ar), 127.1 (CH of Ar), 126.9 (CH of Ar), 52.3 ($ArCH_2$). IR (KBr, cm^{-1}): ν_{max} 1689 (C=O), 1241 cm^{-1}. HRMS (EI) for (M + Na)$^+$: calcd. 291.9630; found 291.9628. Anal. Calcd for $C_{11}H_8ClNOS_2$: C, 48.97; H, 2.99; N, 5.19. Found: C, 49.09; H, 2.85; N, 5.04.

2,3-Dihydro-3,6-dimethyl-2-thioxo-1,3-thiazin-4-one (3e): Yield 94%; yellow solid; mp 89-91 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.17 (s, 1H), 2.90 (s, 3H, CH_3), 1.98 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3 (C=S), 166.2 (C=O), 141.4 (C6), 132.4 (C5), 32.6 (CH_3), 26.9 (CH_3). IR (KBr, cm^{-1}): ν_{max} 1675 (C=O), 1221 cm^{-1}. HRMS (EI) for (M + Na)$^+$: calcd. 195.9861; found 195.9866. Anal. Calcd for $C_6H_7NOS_2$: C, 41.59; H, 4.07; N, 8.08. Found: C, 41.43; H, 4.10; N, 7.96.

3-Cyclohexyl-2,3-dihydro-6-methyl-2-thioxo-1,3-thiazin-4-one (3f): Yield 95%; yellow solid; mp 97-99 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (s, 1H), 5.06 (m, 1H, Cyclohexyl), 2.43 (tt, J = 12.5, 6.7 Hz, 2H, Cyclohexyl), 2.06 (m, 2H, Cyclohexyl), 1.92 (s, 3H, CH_3), 1.77 (m, 3H, Cyclohexyl), 1.43 (m, 3H, Cyclohexyl). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0 (C=S), 165.4 (C=O), 142.4 (C6), 133.7 (C5), 58.3, 27.4, 25.6, 25.1 (4C, Cyclohexyl). IR (KBr, cm^{-1}): ν_{max} 1667 (C=O), 1230 cm^{-1}. HRMS (EI) for (M + H)$^+$: calcd. 242.0670; found 242.0675. Anal. Calcd for $C_{11}H_{15}NOS_2$: C, 54.74; H, 6.26; N, 5.80. Found: C, 54.70; H, 6.31; N, 5.71.

3-Cyclohexyl-6-(trifluoromethyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (3g): Yield 83%; yellow solid; mp 122-124 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (s, 1H), 5.12 (m, 1H, Cyclohexyl), 2.45 (m, 2H, Cyclohexyl), 2.08 (m, 2H, Cyclohexyl), 1.83 (m, 3H, Cyclohexyl), 1.47 (m, 3H, Cyclohexyl). ^{13}C

NMR (100 MHz, $CDCl_3$): δ 195.9 (C=S), 166.7 (C=O), 163.8 (d, J_{CF} = 25.9 Hz, C6), 148.6 (d, J_{CF} = 11.2 Hz, C5), 127.4 (CF_3), 58.7, 27.5, 25.9, 25.6 (4C, Cyclohexyl). ^{19}F NMR (377 MHz, $CDCl_3$); δ = – 62.23. IR (KBr, cm^{-1}): ν_{max} 1675 (C=O), 1238 cm^{-1}. HRMS (EI) for $(M + Na)^+$: calcd. 318.0206; found 318.0210. Anal. Calcd for $C_{11}H_{12}F_3NOS_2$: C, 44.73; H, 4.10; N, 4.74. Found: C, 44.67; H, 4.18; N, 4.77.

3-Cyclohexyl-2,3-dihydro-6-phenyl-2-thioxo-1,3-thiazin-4-one (3h):[31] Yield 87%; yellow solid; mp 138-140 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54-7.41 (m, 5H, 5CH of Ph), 6.86 (s, 1H), 5.10 (m, 1H, Cyclohexyl), 2.47 (m, 2H, Cyclohexyl), 2.06 (m, 2H, Cyclohexyl), 1.82 (m, 3H, Cyclohexyl), 1.49 (m, 3H, Cyclohexyl). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2 (C=S), 166.3 (C=O), 164.3 (C6), 143.5 (C5), 134.8 (C of Ph), 128.7 (*C*H of Ph), 128.2 (2*C*H of Ph), 127.9 (2*C*H of Ph), 58.8, 27.3, 25.4, 25.7 (4C, Cyclohexyl). IR (KBr, cm^{-1}): ν_{max} 1675 (C=O), 1268 cm^{-1}. HRMS (EI) for $(M + Na)^+$: calcd. 326.0646; found 326.0649. Anal. Calcd for $C_{16}H_{17}NOS_2$: C, 63.33; H, 5.65; N, 4.62. Found: C, 63.41; H, 5.60; N, 4.54.

2,3-Dihydro-3-((1r,4r)-4-(4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)cyclohexyl)-2-thioxo-1,3-thiazin-4-one (5a): Yield 89%; yellow solid; mp 222-224 °C; ^1H NMR (400 MHz, DMSO): δ 8.54 (dd, J = 10.4, 0.9 Hz, 2H), 6.23 (d, J = 10.4 Hz, 2H), 4.30 (br, 2H, Cyclohexane), 2.05 (t, J = 12.9 Hz, 4H, Cyclohexane), 1.41 (dt, J = 20.1, 10.1 Hz, 4H, Cyclohexane). ^{13}C NMR (100 MHz, DMSO): δ 192.3 (C=S), 166.3 (C=O), 151.6 (C6), 131.4 (C5), 66.4, 32.9 (Cyclohexane). IR (KBr, cm^{-1}): ν_{max} 1690 (C=O), 1227 cm^{-1}. HRMS (EI) for $(M + H)^+$: calcd. 371.0017; found 371.0015. Anal. Calcd for $C_{14}H_{14}N_2O_2S_4$: C, 45.38; H, 3.81; N, 7.56. Found: C, 45.41; H, 3.99; N, 7.64.

2,3-Dihydro-6-methyl-3-((1r,4r)-4-(6-methyl-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)cyclohexyl)-2-thioxo-1,3-thiazin-4-one (5b): Yield 85%; yellow solid; mp 238-240 °C; ^1H NMR (400 MHz, DMSO): δ 6.33 (s, 2H), 4.24 (br, 2H, Cyclohexane), 2.19 (s, 6H, CH_3), 2.00 (t, J = 12.8 Hz, 4H, Cyclohexane), 1.40 (m, 4H, Cyclohexane). ^{13}C NMR (100 MHz, DMSO): δ 192.8 (C=S), 165.5 (C=O), 141.9 (C6), 132.1 (C5), 65.2, 32.8 (Cyclohexane), 20.8 (CH_3). IR (KBr, cm^{-1}): ν_{max} 1686 (C=O), 1224 (C=S) cm^{-1}. HRMS (EI) for $(M + H)^+$: calcd. 399.0328; found 399.0326. Anal. Calcd for $C_{16}H_{18}N_2O_2S_4$: C, 48.21; H, 4.55; N, 7.03. Found: C, 48.11; H, 4.59; N, 7.11.

6-(Trifluoromethyl)-3-((1r,4r)-4-(6-(trifluoromethyl)-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)cyclohexyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (5c): Yield 85%; yellow solid; mp 265-267 °C; ^1H NMR (400 MHz, DMSO): δ 6.98 (s, 2H), 4.54 (br, 2H, Cyclohexane), 2.10 (t, J = 12.7 Hz, 4H, Cyclohexane), 1.42 (m, 4H, Cyclohexane). ^{13}C NMR (100 MHz, DMSO): δ 193.5 (C=S), 166.4 (C=O), 164.6 (C6), 144.2 (C5), 128.5 (CF_3), 65.5, 32.4 (Cyclohexane). ^{19}F NMR (377 MHz, DMSO); δ = – 60.52. IR (KBr, cm^{-1}): ν_{max} 1689 (C=O), 1232 (C=S) cm^{-1}. HRMS (EI) for $(M)^+$: calcd. 505.9687; found 505.9684. Anal. Calcd for $C_{16}H_{12}F_6N_2O_2S_4$: C, 37.94; H, 2.39; N, 5.53. Found: C, 38.11; H, 2.30; N, 5.63.

6-Ethyl-3-((1r,4r)-4-(6-ethyl-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)cyclohexyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (5d): Yield 97%; yellow solid; mp 206-208 ºC; ^{1}H NMR (400 MHz, DMSO): δ 6.25 (s, 2H), 4.26 (m, 2H, Cyclohexane), 2.34 (q, J = 7.2 Hz, 4H, CH_2CH_3), 2.03 (m, 4H, Cyclohexane), 1.40 (m, 4H, Cyclohexane), 1.11 (t, J = 7.1 Hz, 6H, CH_2CH_3). ^{13}C NMR (100 MHz, DMSO): δ 191.4 (C=S), 166.9 (C=O), 148.1 (C6), 127.6 (C5), 66.2 (Cyclohexane), 38.5 (CH_2), 33.3 (Cyclohexane), 12.3 (CH_3). IR (KBr, cm^{-1}): ν_{max} 1690 (C=O), 1230 (C=S) cm^{-1}. HRMS (EI) for $(M + H)^+$: calcd. 427.0642; found 427.0686. Anal. Calcd for $C_{18}H_{22}N_2O_2S_4$: C, 50.67; H, 5.20; N, 6.57. Found: C, 50.72; H, 5.15; N, 6.52.

2,3-Dihydro-3-((1r,4r)-4-(4-oxo-6-propyl-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)cyclohexyl)-6-propyl-2-thioxo-1,3-thiazin-4-one (5e): Yield 98%; yellow solid; mp 120-122 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.44 (s, 2H), 4.53 (m, 2H, Cyclohexane), 2.12 (m, 4H, Cyclohexane), 2.02 (m, $CH_2CH_2CH_3$), 1.43 (m, 8H, Cyclohexane + $CH_2CH_2CH_3$), 1.03 (m, 6H, $CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8 (C=S), 165.3 (C=O), 145.0 (C6), 127.3 (C5), 66.4 (Cyclohexane), 38.9 (CH_2), 34.1 (Cyclohexane), 22.5 (CH_2), 15.8 (CH_3). IR (KBr, cm^{-1}): ν_{max} 1678 (C=O), 1232 (C=S) cm^{-1}. HRMS (EI) for $(M + H)^+$: calcd. 455.0956; found 455.0950. Anal. Calcd for $C_{20}H_{26}N_2O_2S_4$: C, 52.83; H, 5.76; N, 6.16. Found: C, 52.77; H, 5.90; N, 6.04.

6-*tert*-Butyl-3-((1r,4r)-4-(6-*tert*-butyl-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)cyclohexyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (5f): Yield 81%; yellow solid; mp 214-216 ºC; ^{1}H NMR (400 MHz, DMSO): δ 6.52 (s, 2H), 4.66 (m, 2H, Cyclohexane), 2.23 (m, 4H, Cyclohexane), 1.43 (m, 4H, Cyclohexane), 1.07 (s, 18 H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ 191.3 (C=S), 165.8 (C=O), 146.2 (C6), 127.9 (C5), 66.7 (Cyclohexane), 41.5 (C), 33.8 (Cyclohexane), 27.2 (CH_3). IR (KBr, cm^{-1}): ν_{max} 1669 (C=O), 1238 (C=S) cm^{-1}. HRMS (EI) for $(M + Na)^+$: calcd. 505.1089; found 505.1090. Anal. Calcd for $C_{22}H_{30}N_2O_2S_4$: C, 54.74; H, 6.26; N, 5.80. Found: C, 54.83; H, 6.18; N, 5.77.

6-*sec*-Butyl-3-((1r,4r)-4-(6-*sec*-butyl-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)cyclohexyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (5g): Yield 90%; yellow solid; mp 186-188 ºC; ^{1}H NMR (400 MHz, DMSO): δ 6.63 (s, 2H), 4.65 (m, 2H, Cyclohexane), 2.42 (m, 2H, CH), 2.20 (m, 4H, Cyclohexane), 1.46 (m, 4H, Cyclohexane), 1.39 (m, 4 H, CH_2), 1.11 (m, 12 H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ 192.0 (C=S), 165.3 (C=O), 146.5 (C6), 128.3 (C5), 66.7 (Cyclohexane), 40.1 (CH), 33.5 (Cyclohexane), 28.4 (CH_2), 18.2 (CH_3), 12.1 (CH_3). IR (KBr, cm^{-1}): ν_{max} 1677 (C=O), 1242 (C=S) cm^{-1}. HRMS (EI) for $(M + Na)^+$: calcd. 505.1089; found 505.1092. Anal. Calcd for $C_{22}H_{30}N_2O_2S_4$: C, 54.74; H, 6.26; N, 5.80. Found: C, 54.77; H, 6.21; N, 5.73.

6-Phenyl-3-((1r,4r)-4-(6-phenyl-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)cyclohexyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (5h): Yield 85%; yellow solid; mp 240-242 ºC; ^{1}H NMR (400 MHz, DMSO): δ 7.43 (m, 4H, Ar-H), 7.21 (m, 6H, Ar-H), 6.88 (s, 2H), 4.29 (m, 2H, Cyclohexane), 2.12 (m, 4H, Cyclohexane), 1.40 (m, 4H, Cyclohexane). ^{13}C NMR (100 MHz, DMSO): δ 193.2 (C=S), 166.8 (C=O), 151.0, 131.5, 130.2, 129.4, 127.9, 127.2 (Ar-C), 66.2 (Cyclohexane), 32.6 (Cyclohexane). IR (KBr, cm^{-1}): ν_{max} 1688 (C=O), 1222 (C=S) cm^{-1}. HRMS (EI) for (M + H)$^+$: calcd. 523.0652; found 523.0633. Anal. Calcd for $C_{26}H_{22}N_2O_2S_4$: C, 59.74; H, 4.24; N, 5.36. Found: C, 59.66; H, 4.31; N, 5.20.

3-(4-((4-Oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)methyl)benzyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (6a): Yield 85%; yellow solid; mp196-198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, J = 10.2 Hz, 2H), 7.36 (s, 4H), 6.17 (d, J = 10.2 Hz, 2H), 5.00 (d, J = 3.8 Hz, 4H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0 (C=S), 167.7 (C=O), 153.1, 144.2, 131.4, 128.4 (Ar-C), 62.7 (CH_2). IR (KBr, cm^{-1}): ν_{max} 1674 (C=O), 1245 (C=S) cm^{-1}. HRMS (EI) for (M + H)$^+$: calcd. 392.9861; found 392.9859, for (M + Na)$^+$: calcd. 414.9680; found 414.9678. Anal. Calcd for $C_{16}H_{12}N_2O_2S_4$: C, 48.96; H, 3.08; N, 7.14. Found: C, 48.88; H, 3.17; N, 7.20.

3-(4-((6-Methyl-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)methyl)benzyl)-2,3-dihydro-6-methyl-2-thioxo-1,3-thiazin-4-one (6b): Yield 85%; yellow solid; mp 168-170 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.33 (s, 4H), 6.22 (s, 2H), 4.95 (d, J = 3.6 Hz, 4H, CH_2), 2.21 (s, 6H, CH_3).^{13}C NMR (100 MHz, DMSO): δ 193.6 (C=S), 166.3 (C=O), 150.4, 145.3, 130.2, 128.6 (Ar-C), 62.7 (CH_2), 27.1 (CH_3). IR (KBr, cm^{-1}): ν_{max} 1683 (C=O), 1237 (C=S) cm^{-1}. HRMS (EI) for (M + H)$^+$: calcd. 421.0173; found 421.0170. Anal. Calcd for $C_{18}H_{16}N_2O_2S_4$: C, 51.40; H, 3.83; N, 6.66. Found: C, 51.35; H, 3.96; N, 6.57.

3-(4-((6-(Trifluoromethyl)-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)methyl)benzyl)-6-(trifluoromethyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (6c): Yield 81%; yellow solid; mp 199-201 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.35 (s, 4H), 6.87 (s, 2H), 4.95 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO): δ 193.9 (C=S), 166.6 (C=O), 150.2, 163.5, 144.0, 128.4 (Ar-C), 128.0 (CF_3), 62.4 (CH_2). ^{19}F NMR (377 MHz, DMSO); $\delta = -60.69$. IR (KBr, cm^{-1}): ν_{max} 1688 (C=O), 1241 (C=S) cm^{-1}. HRMS (EI) for (M + H)$^+$: calcd. 528.9609; found 528.9606. Anal. Calcd for $C_{18}H_{10}F_6N_2O_2S_4$: C, 40.90; H, 1.91; N, 5.30. Found: C, 41.02; H, 1.87; N, 5.26.

3-(4-((6-Ethyl-4-oxo-2-thioxo-2H-1,3-thiazin-3(4*H*)-yl)methyl)benzyl)-6-ethyl-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (6d): Yield 88%; yellow solid; mp 155-157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 4H), 6.19 (s, 2H), 4.97 (s, 4H, CH_2), 2.11 (q, J = 7.1 Hz, 4H, CH_2CH_3), 1.17 (t, J = 7.1 Hz, 6H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9 (C=S), 165.7 (C=O), 149.3, 144.0, 131.7, 128.4 (Ar-C), 62.7 (CH_2), 38.2 (CH_2CH_3), 14.7 (CH_2CH_3). IR (KBr, cm^{-1}): ν_{max} 1690 (C=O), 1239 (C=S). HRMS (EI) for (M + H)$^+$: calcd. 449.0484; found 449.0481. Anal. Calcd for $C_{20}H_{20}N_2O_2S_4$: C, 53.54; H, 4.49; N, 6.24. Found: C, 53.66; H, 4.40; N, 6.32.

3-(4-((4-Oxo-6-propyl-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)methyl)benzyl)-2,3-dihydro-6-propyl-2-thioxo-1,3-thiazin-4-one (6e): Yield 94%; yellow solid; mp 177-179 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.32 (s, 4H), 6.21 (s, 2H), 4.95 (s, 4H, CH_2), 2.02 (m, 4H, CH_2), 1.52 (m, 4H, CH_2), 1.03 (m, 6H, CH_3).

^{13}C NMR (100 MHz, DMSO): δ 194.7 (C=S), 166.3 (C=O), 149.1, 144.5, 131.4, 128.2 (Ar-C), 62.9 (*C*H$_2$), 39.8 (*C*H$_2$), 21.6 (*C*H$_2$), 15.3 (*C*H$_3$). IR (KBr, cm^{-1}): ν_{max} 1688 (C=O), 1242 (C=S). HRMS (EI) for (M + Na)$^+$: calcd. 499.0613; found 499.0621. Anal. Calcd for $C_{22}H_{24}N_2O_2S_4$: C, 55.43; H, 5.07; N, 5.88. Found: C, 55.49; H, 5.01; N, 5.69.

3-(4-((6-*tert*-Butyl-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)methyl)benzyl)-6-*tert*-butyl-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (6f): Yield 79%; yellow solid; mp 244-246 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.35 (s, 4H), 6.26 (s, 2H), 4.91 (s, 4H, CH$_2$), 1.19 (s, 18H, CH$_3$). ^{13}C NMR (100 MHz, DMSO): δ 195.2 (C=S), 166.1 (C=O), 149.0, 144.3, 131.0, 128.6 (Ar-C), 62.7 (*C*H$_2$), 41.5 (*C*), 29.4 (*C*H$_3$). IR (KBr, cm^{-1}): ν_{max} 1682 (C=O), 1249 (C=S). HRMS (EI) for (M)$^+$: calcd. 504.1031; found 504.1036. Anal. Calcd for $C_{24}H_{28}N_2O_2S_4$: C, 57.11; H, 5.59; N, 5.55. Found: C, 57.26; H, 5.46; N, 5.42.

3-(4-((6-*sec*-Butyl-4-oxo-2-thioxo-2H-1,3-thiazin-3(4*H*)-yl)methyl)benzyl)-6-*sec*-butyl-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (6g): Yield 92%; yellow solid; mp 220-222 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.33 (s, 4H), 6.22 (s, 2H), 4.94 (s, 4H, CH$_2$), 2.52 (m, 2H, CH), 1.43 (m, 4H, CH$_2$), 1.22 (m, 6H, CH$_3$), 1.01 (m, 6H, CH$_3$). ^{13}C NMR (100 MHz, DMSO): δ 195.6 (C=S), 165.7 (C=O), 149.2, 144.4, 131.4, 128.5 (Ar-C), 62.8 (*C*H$_2$), 40.1 (*C*H), 29.0 (*C*H$_2$), 19.7 (CH$_3$), 13.4 (CH$_3$). IR (KBr, cm^{-1}): ν_{max} 1680 (C=O), 1244 (C=S). HRMS (EI) for (M + H)$^+$: calcd. 505.1109; found 505.1113. Anal. Calcd for $C_{24}H_{28}N_2O_2S_4$: C, 57.11; H, 5.59; N, 5.55. Found: C, 57.19; H, 5.50; N, 5.63.

3-(4-((4-Oxo-6-phenyl-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)methyl)benzyl)-2,3-dihydro-6-phenyl-2-thioxo-1,3-thiazin-4-one (6h): Yield 88%; yellow solid; mp 182-184 °C. ^{1}H NMR (400 MHz, DMSO): δ 7.57 (m, 4H), 7.26 (s, 4H), 7.12 (m, 6H), 6.32 (s, 2H), 4.89 (s, 4H, CH$_2$). ^{13}C NMR (100 MHz, DMSO): δ 192.0 (C=S), 165.7 (C=O), 163.2, 139.1, 131.7, 128.4, 127.4, 127.0, 125.8, 121.2 (Ar-C), 62.7 (*C*H$_2$). IR (KBr, cm^{-1}): ν_{max} 1679 (C=O), 1213 (C=S). HRMS (EI) for (M + H)$^+$: calcd. 545.0487; found 545.0488. Anal. Calcd for $C_{28}H_{20}N_2O_2S_4$: C, 61.74; H, 3.70; N, 5.14. Found: C, 61.68; H, 3.99; N, 5.22.

2,3-Dihydro-3-(2-(4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)ethyl)-2-thioxo-1,3-thiazin-4-one (7a): Yield 88%; yellow solid; mp 144-146 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.33 (dd, J = 10.1, 0.7 Hz, 2H), 6.23 (d, J = 10.2 Hz, 2H), 3.81 (s, 4H, CH$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 192.3 (C=S), 166.9 (C=O), 148.4, 129.4 (Ar-C), 55.8 (*C*H$_2$). IR (KBr, cm^{-1}): ν_{max} 1688 (C=O), 1243 (C=S). HRMS (EI) for (M + H)$^+$: calcd. 316.9545; found 316.9544. Anal. Calcd. for $C_{10}H_8N_2O_2S_4$: C, 37.96; H, 2.55; N, 8.85. Found: C, 38.02; H, 2.48; N, 8.80.

2,3-Dihydro-6-methyl-3-(2-(6-methyl-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)ethyl)-2-thioxo-1,3-thiazin-4-one (7b): Yield 87%; yellow solid; mp 137-139 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.22 (s, 2H), 3.83 (s, 4H, CH$_2$), 2.01 (s, 6H, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 192.0 (C=S), 166.3 (C=O), 149.3, 129.8 (Ar-C), 55.6 (*C*H$_2$), 26.7 (*C*H$_3$). IR (KBr, cm^{-1}): ν_{max} 1680 (C=O), 1231 (C=S). HRMS (EI) for (M

+ H)$^+$: calcd. 344.987; found 344.982. Anal. Calcd for $C_{12}H_{12}N_2O_2S_4$: C, 41.84; H, 3.51; N, 8.13. Found: C, 41.78; H, 3.57; N, 8.10.

6-(Trifluoromethyl)-3-(2-(6-(trifluoromethyl)-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)ethyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (7c): Yield 78%; yellow solid; mp 158-160 °C. ^{1}H NMR (400 MHz, DMSO): δ 6.99 (s, 2H), 3.84 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO): δ 195.3 (C=S), 166.0 (C=O), 164.3 (d, J_{CF} = 25.6 Hz, C6), 148.9 (d, J_{CF} = 11.4 Hz, C5), 128.7 (CF_3), 58.7 (CH_2). ^{19}F NMR (377 MHz, DMSO); δ = – 63.40. IR (KBr, cm^{-1}): ν_{max} 1688 (C=O), 1238 (C=S). HRMS (EI) for (M + H)$^+$: calcd. 452.9291; found 452.9297. Anal. Calcd for $C_{12}H_6F_6N_2O_2S_4$: C, 31.86; H, 1.34; N, 6.19. Found: C, 31.76; H, 1.39; N, 6.12.

6-Ethyl-3-(2-(6-ethyl-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)ethyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (7d): Yield 78%; yellow solid; mp 132-134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 6.21 (s, 2H), 3.87 (s, 4H, CH_2), 2.55 (q, J = 7.2 Hz, 4H, CH_2CH_3), 1.83 (t, J = 7.1 Hz, 6H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4 (C=S), 165.7 (C=O), 148.3, 129.2 (Ar-C), 55.5 (CH_2), 36.7 (CH_2CH_3), 14.3 (CH_2CH_3). IR (KBr, cm^{-1}): ν_{max} 1683 (C=O), 1233 (C=S). HRMS (EI) for (M + H)$^+$: calcd. 373.0171; found 373.0169. Anal. Calcd for $C_{14}H_{16}N_2O_2S_4$: C, 45.13; H, 4.33; N, 7.52. Found: C, 45.22; H, 4.28; N, 7.50.

2,3-Dihydro-3-(2-(4-oxo-6-propyl-2-thioxo-2H-1,3-thiazin-3(4*H*)-yl)ethyl)-6-propyl-2-thioxo-1,3-thiazin-4-one (7e): Yield 90%; yellow solid; mp 161-163 °C. ^{1}H NMR (400 MHz, DMSO): δ 6.26 (s, 2H), 3.80 (s, 4H, CH_2), 2.23 (m, 4H, CH_2), 1.87 (m, 4H, CH_2), 1.08 (m, 6H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ 194.2 (C=S), 166.2 (C=O), 148.6, 127.6, 55.5 (CH_2), 41.0 (CH_2), 21.5 (CH_2), 15.1 (CH_3). IR (KBr, cm^{-1}): ν_{max} 1676 (C=O), 1242 (C=S). HRMS (EI) for (M + H)$^+$: calcd. 401.0481; found 401.0485. Anal. Calcd for $C_{16}H_{20}N_2O_2S_4$: C, 47.97; H, 5.03; N, 6.99. Found: C, 48.22; H, 5.13; N, 6.84.

6-*tert*-Butyl-3-(2-(6-*tert*-butyl-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)ethyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (7f): Yield 81%; yellow solid; mp 226-228 °C. ^{1}H NMR (400 MHz, DMSO): δ 6.31 (s, 2H), 3.86 (s, 4H, CH_2), 1.31 (s, 18H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ 195.0 (C=S), 166.6 (C=O), 149.9, 125.3, 55.3 (CH_2), 41.7 (C), 29.7 (CH_3). IR (KBr, cm^{-1}): ν_{max} 1687 (C=O), 1245 (C=S). HRMS (EI) for (M + Na)$^+$: calcd. 451.0613; found 451.0608. Anal. Calcd for $C_{18}H_{24}N_2O_2S_4$: C, 50.44; H, 5.64; N, 6.54. Found: C, 50.53; H, 5.57; N, 6.59.

6-*sec*-Butyl-3-(2-(6-*sec*-butyl-4-oxo-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)ethyl)-2,3-dihydro-2-thioxo-1,3-thiazin-4-one (7g): Yield 92%; yellow solid; mp 195-197 °C. ^{1}H NMR (400 MHz, DMSO): δ 6.35 (s, 2H), 3.84 (s, 4H, CH_2), 2.68 (m, 2H, CH), 1.94 (m, 4H, CH_2), 1.64 (m, 6H, CH_3), 1.22 (m, 6H, CH_3). ^{13}C NMR (100 MHz, DMSO): δ 195.4 (C=S), 166.2 (C=O), 150.7, 124.2, 55.6 (CH_2), 40.5 (CH), 28.2 (CH_2), 19.5 (CH_3), 14.3 (CH_3). IR (KBr, cm^{-1}): ν_{max} 1680 (C=O), 1249 (C=S). HRMS (EI) for (M + Na)$^+$: calcd. 451.0613; found 451.0611. Anal. Calcd for $C_{18}H_{24}N_2O_2S_4$: C, 50.44; H, 5.64; N, 6.54. Found: C, 50.37; H, 5.72; N, 6.50.

2,3-Dihydro-3-(2-(4-oxo-6-phenyl-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)ethyl)-6-phenyl-2-thioxo-1,3-thiazin-4-one (7h): Yield 89%; yellow solid; mp 180-182 ºC. ^{1}H NMR (400 MHz, DMSO): δ 7.55 (m, 4H), 7.20 (m, 4H), 7.04 (m, 2H), 6.21 (s, 2H), 3.77 (s, 4H, CH_2). ^{13}C NMR (100 MHz, DMSO): δ 191.6 (C=S), 166.1 (C=O), 149.0, 137.7, 129.0, 127.7 (Ar-C), 55.6 (*C*H$_2$). IR (KBr, cm^{-1}): ν_{max} 1679 (C=O), 1225 (C=S). HRMS (EI) for $(M + H)^+$: calcd. 469.0171; found 469.0167. Anal. Calcd for $C_{22}H_{16}N_2O_2S_4$: C, 56.38; H, 3.44; N, 5.98. Found: C, 56.41; H, 3.40; N, 5.77.

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