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Efficient synthesis of N-substituted 1,3-thiazin-2-ones containing sulfonamide

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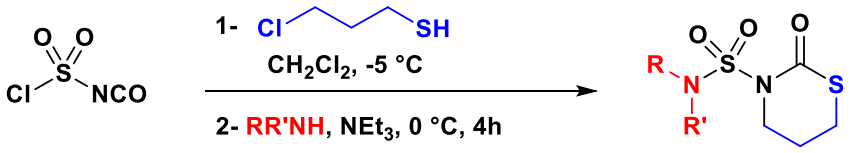
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Abstract

Thiazinones containing sulfonamides are experiencing increased interest due to their importance in the design and development of new molecules of potential pharmaceutical interest. The synthesis of a series of new *N*-substituted *2H*-1,3-thiazin-2-ones containing sulfonamide is described. The compounds were synthesized in good yields in a one-pot reaction starting from commercially available chlorosulfonyl isocyanate (CSI), 3-chloro-1-propanethiol, and various primary and secondary aliphatic, aromatic or heteroaromatic amines. The structure of one of these compounds was established by X-ray crystallography. The compounds are being evaluated for their biological activity.



20 examples: rapid, efficient, inexpensive

Keywords: chlorosulfonyl isocyanate; sulfonamide; thiazin-2-one.

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Introduction

The synthesis of thiazinones and sulfonamides have attracted increased interest due to their wide use in the design and preparation of novel synthetic antibiotics. Sulfur is a ubiquitous element for life with a broad presence in natural products and medicines.[1-7] One class of such sulfur-containing molecules contains 1,3-thiazines and the related thiazinones, heterocycles containing four carbons, one nitrogen, and one sulfur atom (Scheme 1). The synthesis of thiazin-2-ones has not been explored much, probably due to the lack of a good general method to synthesize them. To the best of our knowledge, only three methods for the preparation of 1,3-thiazin-2-ones have been reported so far.[8-10] But the versatility of the thiazine skeleton, in addition to its relative chemical simplicity, makes these chemicals amongst the most promising sources of bioactive compounds. For example, the thiazine-fused β-lactam Cefaclor belongs to the class of β-lactam antibiotics used for the treatment of bacterial infections.[11] The BTZ043 is used to kill *Mycobacterium tuberculosis*.[12] The thiazin-4-one-containing chlormezanone is a commercial drug used as an anxiolytic and a muscle relaxant.[13]

The sulfonamide group, moreover, is considered as a pharmacophore (that part of a molecular structure responsible for recognition and interaction with biological receptors), which is present in many biologically active molecules, particularly antimicrobial agents.[14] It was shown that sulfonamide moieties can enhance largely the activity of antibacterial agents, especially against both Gram-positive and Gram-negative bacteria.[15] In addition, the sulfonamide derivatives constitute an important class of drugs, with several types of pharmacological agents possessing antibacterial,[16] antitumor,[17] anticarbonic anhydrase,[18] anticonvulsant[19] or protease inhibitory activity[20], among others. Some representative examples of bioactive molecules containing 1,3-thiazine cores or sulfonamide motif, and their various pharmacological properties, are shown in Figure 1.

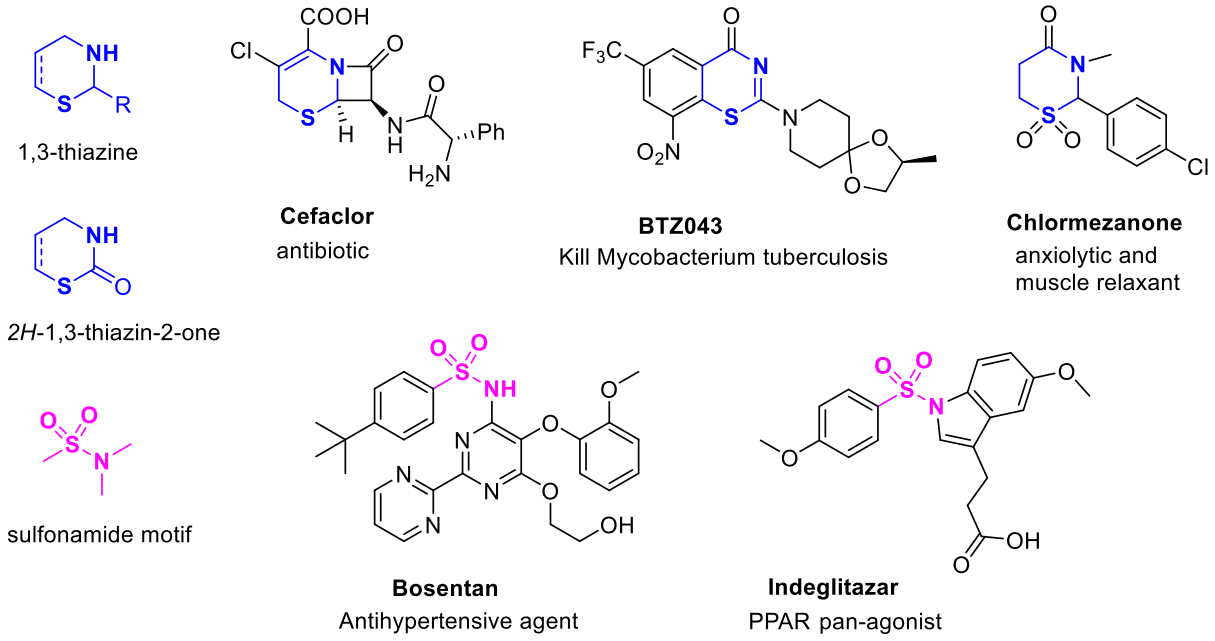


Figure 1: Some examples of bioactive molecules containing 1,3-thiazine cores or the sulfonamide moiety.

Results and Discussion

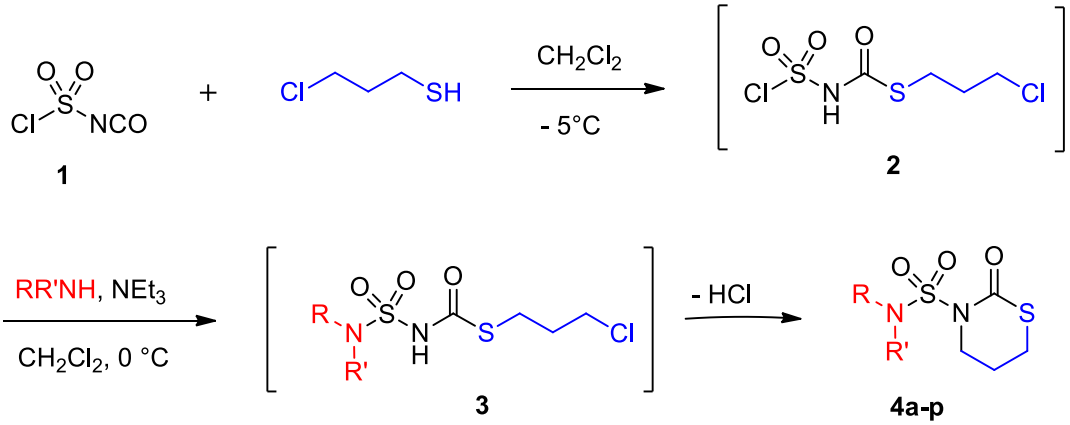
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Modifications of the thiazine moiety displayed valuable biological activities, and these modifications can be utilized to develop potentially active agents in the future. It would be interesting to combine both thiazine and sulfonamide to obtain a new class of heterocycles containing two heteroatoms.

The synthesis of *N*-substituted perhydro-1,3-oxazin-2-ones containing *N*-phenylsulfonamides has been previously reported.[21] In connection with our ongoing interest in the synthesis of sulfonamides and heterocyclic derivatives, we wish to report the extension of the method for the preparation of a series of new N-substituted 2H-1,3-thiazin-2-ones containing sulfonamide. To the best of our knowledge, there is no synthesis of such compounds previously reported in the literature.

Chlorosulfonylisocyanate (CSI) **1** was used as a starting material for the synthesis of some *N*-substituted 2*H*-1,3-thiazin-2-ones **4** (Scheme 1). Indeed, CSI is a versatile reagent in organic synthesis with great interest in heterocyclic chemistry.[22] It has been established in previous literature that CSI is a suitable reagent for allowing the introduction of a sulfonamide moiety in biomolecules.[23] CSI is also the reagent of choice for the preparation of 1,3-thiazin-2-ones containing sulfonamide. In this case, CSI contains the required sulfonyl group and the nitrogen, which is necessary for the formation of thiazin-2-ones.

The synthesis was carried out in a one-pot reaction by sequential addition of 3-chloro-1-propanethiol and a series of primary or secondary amines to chlorosulfonylisocyanate **1** (Scheme 1). Our procedure consists of addition of an equimolar amount of 3-chloro-1-propanethiol dissolved in anhydrous dichloromethane to CSI at -5 °C under nitrogen atmosphere. In fact, the reaction was spontaneous, and gave readily the corresponding N-chlorosulfonylcarbamate intermediates **2**. The latter were further subjected to the action of a primary or secondary amine in the presence of two equivalent amounts of triethylamine at 0 °C to produce the corresponding linear *N*-sulfamoylcarbamate intermediates **3**, which cyclized *in situ*, providing the target N-heterocyclic 6-membered ring as shown in **4(a-p)**. This intramolecular cyclization was reported in the case of 1,3-oxazin-2-ones by Dewinter et al.[24] These compounds were formed by spontaneous cyclization related to the excellent leaving-group character of Cl. No cyclization is observed related to the sulfamide moiety. This is probably linked to the rotational barrier level around the sulfamido group.[25,26]



Scheme 1: synthesis of N-substituted 2*H*-1,3-thiazin-2-ones **4a-p**.

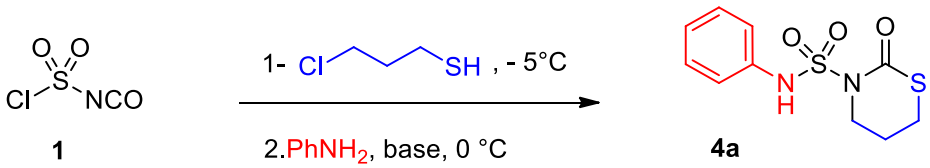
Optimization of the reaction conditions

We first chose aniline as a primary amine. The product was isolated in a 56% yield and was characterized as 3-[*N*-phenyl)sulfamoyl]2*H*-1,3-thiazin-2-one **4a** from its spectral data. The reaction conditions were then optimized to obtain a better yield of the desired product (Table 1) and to develop a general method for the

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synthesis of 2H-1,3-thiazin-2-ones, which are important building blocks for the synthesis of some natural and biologically active compounds.

Table 1: Optimization of the reaction conditions



Entry	Base	Equiv of base	Solvent	Time (in hour)	yield (%)[a]
1	NEt_3	2	CH_2Cl_2	4	56
2	NEt_3	2	CH_2Cl_2	6	54
3	NEt_3	3	CH_2Cl_2	4	73
4	NEt_3	3	CH_2Cl_2	6	66
5[b]	**NEt_3**	**4**	**CH_2Cl_2**	**4**	**92**
6	NEt_3	4	CH_2Cl_2	6	75
7	NEt_3	2	acetone	4	49
8	NEt_3	4	acetone	4	71
9	NEt_3	4	acetone	6	67
10	pyridine	2	CH_2Cl_2	4	50
11	pyridine	3	CH_2Cl_2	4	62
12	pyridine	4	CH_2Cl_2	4	67
13	pyridine	4	CH_2Cl_2	6	60
14	pyridine	2	acetone	4	37
15	pyridine	4	acetone	4	45
16	pyridine	4	acetone	6	42
17	pyridine	2	DMF	4	47
18	pyridine	4	DMF	4	56
19	pyridine	4	DMF	6	53
20	pyridine	2	CH_3CN	4	55
21	pyridine	4	CH_3CN	4	64
22	pyridine	4	CH_3CN	6	61

[a] Isolated yield of **4a**.

[b] Optimized reaction conditions.

From the optimization of the reaction conditions, it was evident that by increasing the base amount to 4 equiv, the yield of **4a** increased and reached 92% (entry 5). Furthermore, when the reaction time was reduced to 4 h, the yield of **4a** increased in all cases, however, further decreases in the reaction time lowered the yield of **4a**, probably due to the incomplete conversion of the starting material. We should also note that the best yield of **4a** was obtained with NEt_3 as the base. A variety of solvents such as CH_2Cl_2, acetone, DMF, and CH_3CN

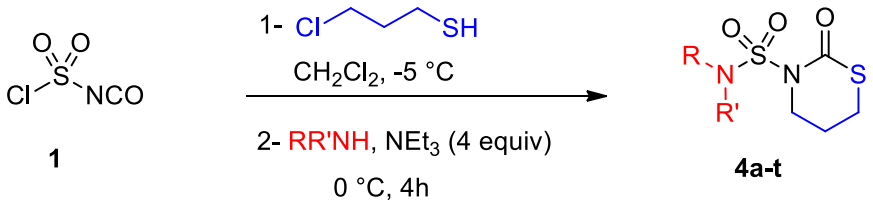
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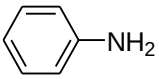
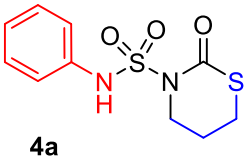
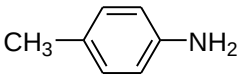
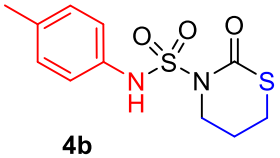
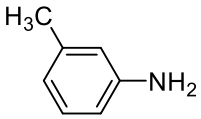
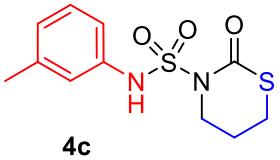
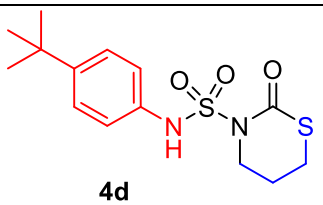
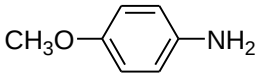
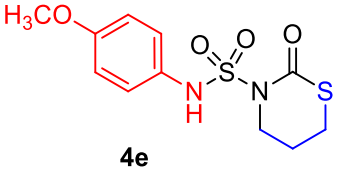
have been tested for this reaction. No solvents were found to be as effective as CH_2Cl_2, which gave 92% of the desired product and, generally speaking, higher yields for all of the compounds. So, from the above table, we observe that 4 equiv of NEt_3 in CH_2Cl_2 at 0 °C for 4 h afforded the optimum yield of **4a**.

Synthesis of a series of new *N*-substituted 2*H*-1,3-thiazin-2-ones

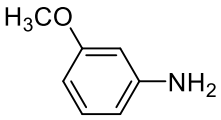
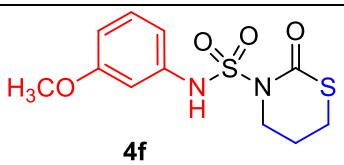
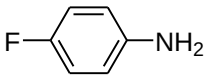
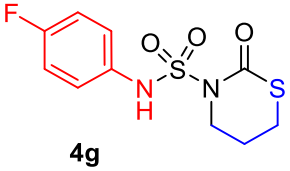
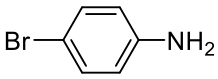
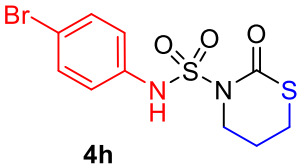
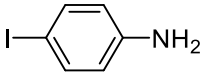
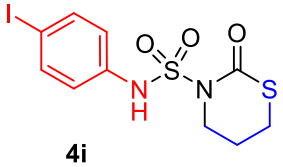
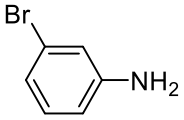
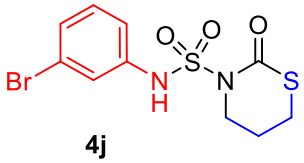
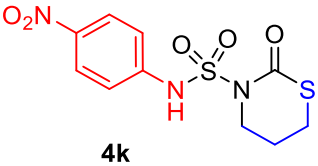
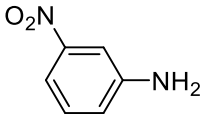
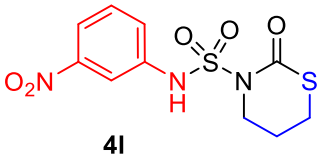
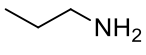
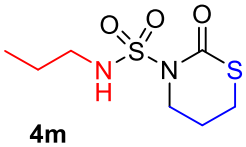
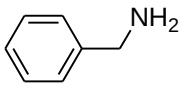
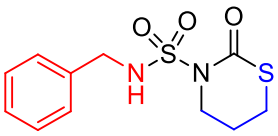
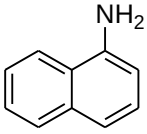
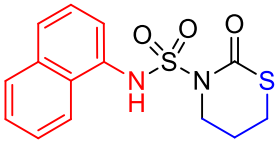
Having the optimized conditions in hand, and encouraged by the results, different primary and secondary aliphatic, aromatic and heteroaromatic amines were investigated to give the desired N-substituted 2*H*-1,3-thiazin-2-ones **4a-t** in good-to-excellent yields (68-92%), as reported in Table 2.

Table 2: Synthesized products **4a-t**

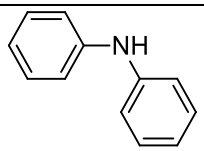
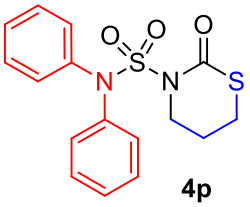
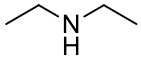
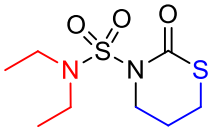
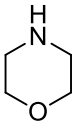
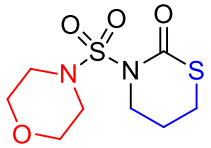
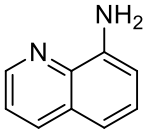
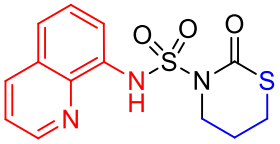
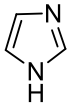
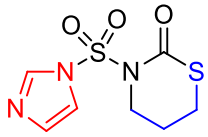


Entry	Amines RR'NH	Products	Yield*
1		 **4a**	92%
2		 **4b**	86%
3		 **4c**	83%
4		 **4d**	75%
5		 **4e**	79%

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6		 **4f**	74%
7		 **4g**	72%
8		 **4h**	77%
9		 **4i**	82%
10		 **4j**	74%
11		 **4k**	79%
12		 **4l**	78%
13		 **4m**	80%
14		 **4n**	68%
15		 **4o**	83%

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16		 **4p**	89%
17		 **4q**	92%
18		 **4r**	85%
19		 **4s**	78%
20		 **4t**	84%

* Yields are given for isolated products.

Both electron-withdrawing and electron-donating substituents on the m- or p-position of the phenyl group were well tolerated. Replacing the phenyl group of the amine with a naphthyl group (Entry 15, **4o**) or an alkyl group (Entries 13 and 17) had little effect on the reaction outcome. The use of benzylamine (Entry 14) led to the corresponding product with a moderate yield of 68%. It is noteworthy to mention that halo substituents such as F (**4g**), Br (**4h** and **4j**), and I (**4i**) remained intact after the reaction, and, therefore, available for further functionalization. Moreover, heteroaromatic amines (Entries 19-20) can also be used, leading to the corresponding thiazine derivatives in good yields.

Identification of all isolated products **4a-t** was accomplished by usual spectroscopic methods. Interesting to note is that all new 2*H*-1,3-thiazin-2-ones **4** are thermally stable compounds, and most of them are crystalline (see Experimental). Compound **4o** was submitted for X-ray crystallographic analysis, which gave the structure shown in Fig. 2.

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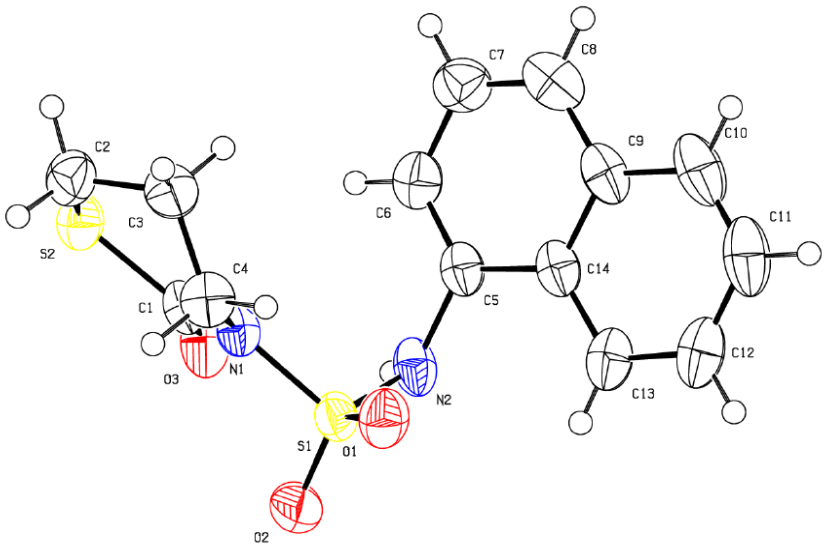


Figure 2: Structure of 2*H*-1,3-thiazin-2-one **4o** from X-ray crystallographic analysis (CDCC: 2046152).

Conclusions

We have described a new class of N-substituted 2*H*-1,3-thiazin-2-ones containing sulfonamide from simple and commercially-available reagents. A key feature of the present method is that the products are synthesized in a single step and are stable, easily isolable and characterized. Other advantages of this protocol are its operational simplicity, short-time reactions, and good-to-excellent yields. Further investigations to evaluate the applicability of this process to a broad range of chiral substrates, synthesizing more complex products, and testing their biological activity are currently in progress in our laboratories and will be reported in due course.

Experimental section

General. All chemicals and solvents were reagent grade and used without purification. Dry EtOH was purchased from Merck and all the amines used were commercially available. Chromatographic purification of products was accomplished using Merck Silica Gel 60 (70−230 or 230−400 mesh). Thin layer chromatography (TLC) was performed on Silica Gel 60 F254 aluminum plates. TLC spots were visualized with UV light or phosphomolybdic acid in EtOH. Melting points were determined on a Büchi 530 apparatus. The ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as a solvent and tetramethylsilane (TMS) as internal reference. ^{13}C NMR and Dept 135 spectra were recorded on on a Bruker 100 MHz spectrometer using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as internal reference. Coupling constants (J values) are given in Hertz (Hz). HRMS spectra were recorded on a Bruker Maxis Impact QTOF Spectrometer. Single-crystal X-ray diffraction of **4o** was selected with SuperNova, Dual, and AtlasS2 diffractometer, using CuKα radiation. The crystal was kept at 295 K during data collection. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimisation.

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General procedure of the reaction (Table 2)

To a stirring solution of chlorosulfonyl isocyanate (CSI) (1 mmol) in dry CH_2Cl_2 (20 mL) at -5 °C and under a nitrogen atmosphere, 3-chloro-1-propanethiol (1 mmol, 1 eq) was slowly added over 5 min. Stirring of the reaction mixture was continued at the same temperature for a minimum of 20 min. The product following the carbamoylation reaction and 4 eq of triethylamine (TEA) were slowly added at 0 °C into a solution containing the amine (1 mmol, 1 eq) in dry CH_2Cl_2 (20 mL). The reaction was followed by TLC and, upon completion (4 hours), the reaction mixture was diluted with aqueous HCl (0.1 N, 40 mL), extracted with CH_2Cl_2 (2x20 mL), and the combined organic layers were washed with brine (25 mL) and dried over $MgSO_4$. After evaporation of the solvent, the product was isolated and appropriately purified.

1,3-Thiazin-2-ones (4a). White solid (250.2 mg, 92%). Mp 157-158 °C; ^{1}H NMR (DMSO-d_6) δ 7.28 (m, 5H, Ar-H), 3.55 (t, *J* 6.9 Hz, 2H, CH_2N), 3.08 (t, *J* 6.4 Hz, 2H, CH_2S), 2.06 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 168.8, 138.8, 129.5, 126.9, 119.9, 43.9, 25.2, 24.5; HRMS (EI) for $C_{10}H_{12}N_2O_3S_2$ [M^+] calcd: 272.0289; found: 272.0286.

1,3-Thiazin-2-ones (4b). White solid (245.9 mg, 86%). Mp 131-132 °C; ^{1}H NMR (DMSO-d_6) δ 7.16 (d, *J* 8.2 Hz, 2H, Ar-H), 7.10 (d, *J* 8.2 Hz, 2H, Ar-H), 3.58 (t, *J* 6.3 Hz, 2H, CH_2N), 3.08 (t, *J* 6.4 Hz, 2H,CH_2S), 2.34 (s, 3H, CH_3), 2.10 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 169.9, 134.9, 134.1, 129.9, 121.1, 44.1, 32.6, 26.6, 20.8; HRMS (EI) for $C_{11}H_{14}N_2O_3S_2$ [M^+] calcd: 286.0446; found: 286.0450.

1,3-Thiazin-2-ones (4c). Oil (237.4 mg, 83%). ^{1}H NMR (DMSO-d_6) δ 7.03 (m, 1H, Ar-H), 6.64 (d, *J* 8.2 Hz, 1H, Ar-H), 6.53 (d, *J* 8.2 Hz, 1H, Ar-H), 6.39 (s, 1H, Ar-H), 3.38 (m, 2H,CH_2N), 3.08 (t, *J* 6.4 Hz, 2H,CH_2S), 2.50 (m, 2H, CH_2), 2.29 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 169.6, 139.1, 137.9, 130.2, 126.9, 120.1, 116.8, 44.9, 24.9, 24.6, 21.2; HRMS (EI) for $C_{11}H_{14}N_2O_3S_2$ [M^+] calcd: 286.0446; found: 286.0452.

1,3-Thiazin-2-ones (4d). Yellow oil (246.0 mg, 75%). ^{1}H NMR (DMSO-d_6) δ 7.20 (d, *J* 8.4 Hz, 2H, Ar-H), 7.02 (d, *J* 8.4 Hz, 2H, Ar-H), 6.39 (s, 1H, NH), 3.51 (m, 2H,CH_2N), 2.82 (t, *J* 6.4 Hz, 2H,CH_2S), 2.11 (m, 2H, CH_2), 1.36 (s, 9H, $(CH_3)_3$); ^{13}C NMR (DMSO-d_6) δ 169.8, 150.6, 134.1, 127.1, 124.8, 44.8, 34.3, 31.5, 24.8, 24.5 HRMS (EI) for $C_{11}H_{20}N_2O_3S_2$ [M^+] calcd: 328.0915; found: 328.0921.

1,3-Thiazin-2-ones (4e). White solid (238.6 mg, 79%). Mp 83-84 °C; ^{1}H NMR (DMSO-d_6) δ 10.60 (s, 1H, NH), 7.14 (d, *J* 8.9 Hz, 2H, Ar-H), 6.94 (d, *J* 9.0 Hz, 2H, Ar-H), 3.79 (s, 3H, OCH_3), 3.42 (m, 2H,CH_2N), 3.16 (m, 2H,CH_2S), 2.47 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 172.0, 157.4, 132.2, 125.8, 114.0, 55.5, 43.7, 33.2, 27.5 ; HRMS (EI) for $C_{11}H_{14}N_2O_4S_2$ [M^+] calcd: 302.0395; found: 302.0402.

1,3-Thiazin-2-ones (4f). White solid (223.5 mg, 74%). Mp 115-116 °C; ^{1}H NMR (DMSO-d_6) δ 8.01 (bs, 1H, NH), 7.13 (t, *J* 10.1 Hz, 1H, Ar-H), 6.75 (m, 3H, Ar-H), 3.66 (s, 3H, OCH_3), 3.43 (t, *J* 6.4 Hz, 2H,CH_2N), 2.96 (t, *J* 6.4 Hz, 2H,CH_2S), 2.12 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 166.0, 160.1, 138.8, 130.4, 112.4, 109.7, 106.2, 55.6, 44.1, 32.6, 26.7; HRMS (EI) for $C_{11}H_{14}N_2O_4S_2$ [M^+] calcd: 302.0395; found: 302.0403.

1,3-Thiazin-2-ones (4g). Colourless oil (208.8 mg, 72%); ^{1}H NMR (DMSO-d_6) δ 8.20 (bs, 1H, NH), 7.01 (d, *J* 8.6 Hz, 2H, Ar-H), 6.88 (d, *J* 8.6 Hz, 2H, Ar-H), 3.16 (m, 4H, CH_2N and CH_2S), 2.15 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 168.8, 164.1, 132.8, 120.7, 118.6, 44.9, 31.8, 24.5; HRMS (EI) for $C_{10}H_{11}FN_2O_3S_2$ [M^+] calcd: 290.0195; found: 290.0198.

1,3-Thiazin-2-ones (4h). Colourless oil (269.5 mg, 77%). ^{1}H NMR (DMSO-d_6) δ 7.43 (d, *J* 8.4 Hz, 2H, Ar-H), 6.96 (d, *J* 8.4 Hz, 2H, Ar-H), 3.36 (m, 2H, CH_2N), 3.07 (m, 2H, CH_2S), 2.38 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 169.7, 137.4, 133.5, 122.1, 119.6, 45.3, 32.2, 26.1; HRMS (EI) for $C_{10}H_{11}BrN_2O_3S_2$ [M^+] calcd: 349.9394; found: 349.9399.

1,3-Thiazin-2-ones (4i). White solid (326.4 mg, 82%). Mp 97-98 °C; ^{1}H NMR (DMSO-d_6) δ 8.57 (bs, 1H, NH), 7.46 (d, *J* 8.4 Hz, 2H, Ar-H), 6.94 (d, *J* 8.4 Hz, 2H, Ar-H), 3.58 (m, 2H,CH_2N), 2.64 (m, 2H,CH_2S), 1.86 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 169.7, 141.9, 137.2, 120.7, 83.6, 44.7, 33.7, 27.4; HRMS (EI) for $C_{10}H_{11}IN_2O_3S_2$ [M^+] calcd: 397.9256; found: 397.9262.

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1,3-Thiazin-2-ones (4j). White solid (259.0 mg, 74%). Mp 85-86 °C; ^{1}H NMR (DMSO-d_6) δ 8.48 (bs, 1H, NH), 6.29 (s, 1H, Ar-H), 7.05 (m, 3H, Ar-H), 3.58 (t, *J* 6.5 Hz, 2H,CH_2N), 2.63 (t, *J* 6.5 Hz, 2H, CH_2S), 1.86 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 169.8, 143.7, 130.6, 123.2, 121.7, 120.3, 117.1, 44.7, 33.7, 27.4; HRMS (EI) for $C_{10}H_{11}BrN_2O_3S_2$ [M^+] calcd: 349.9394; found: 349.9401.

1,3-Thiazin-2-ones (4k). White solid (250.0 mg, 79%). Mp 152-153 °C; ^{1}H NMR (DMSO-d_6) δ 7.96 (d, *J* 8.6 Hz, 2H, Ar-H), 7.22 (d, *J* 8.6 Hz, 2H, Ar-H), 3.52 (t, *J* 6.4 Hz, 2H,CH_2N), 2.61 (t, *J* 6.4 Hz, 2H, CH_2S), 1.92 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 169.7, 145.0, 143.2, 127.6, 123.3, 45.1, 28.8, 26.4; HRMS (EI) for $C_{10}H_{11}N_3O_5S_2$ [M^+] calcd: 317.0140; found: 317.0146.

1,3-Thiazin-2-ones (4l). White solid (247.3 mg, 78%). Mp 241-242 °C; ^{1}H NMR (DMSO-d_6) δ 7.84 (s, 1H, Ar-H), 7.18 (m, 3H, Ar-H), 6.92 (bs, 1H, NH), 3.62 (t, *J* 6.4 Hz, 2H,CH_2N), 2.66 (t, *J* 6.4 Hz, 2H,CH_2S), 2.08 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 168.9, 150.7, 143.1, 129.3, 127.5, 120.3, 119.1, 45.8, 29.4, 27.1; HRMS (EI) for $C_{10}H_{11}N_3O_5S_2$ [M^+] calcd: 317.0140; found: 317.0142.

1,3-Thiazin-2-ones (4m). Colourless oil (190.4 mg, 80%); δ ^{1}H NMR (DMSO-d_6) δ 7.92 (bs, 1H, NH), 3.48 (m, 4H,CH_2N), 2.92 (t, *J* 6.4 Hz, 2H,CH_2S), 2.46 (m, 2H, CH_2), 1.83 (m, 2H, C$\underline{H_2}$CH$_3$), 1.26 ((t, *J* 6.4 Hz, 3H, $CH_2C\underline{H_3}$); ^{13}C NMR (DMSO-d_6) δ 168.4, 46.2, 45.3, 29.9, 25.1, 22.3, 14.2; HRMS (EI) for $C_7H_{14}N_2O_3S_2$ [M^+] calcd: 238.0446; found: 238.0452.

1,3-Thiazin-2-ones (4n). White solid (194.5 mg, 68%). Mp 147-148 °C; ^{1}H NMR (DMSO-d_6) δ 8.52 (bs, 1H, NH), 7.34 (m, 5H, Ar-H), 4.14 (s, 2H, CH_2-Ar), 3.55 (t, *J* 6.5 Hz, 2H, CH_2N), 2.94 (t, *J* 6.4 Hz, 2H, CH_2S), 1.85 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 168.2, 139.4, 129.1, 126.3, 124.1, 48.5, 45.2, 25.7, 24.9; HRMS (EI) for $C_{11}H_{14}N_2O_3S_2$ [M^+] calcd: 286.0446; found: 286.0449.

1,3-Thiazin-2-ones (4o). White solid (255.6 mg, 83%). Mp 185-186 °C; ^{1}H NMR (DMSO-d_6) δ 10.54 (bs, 1H, NH), 8.24 (m, 1H, Ar-H),), 8.92 (m, 2H, Ar-H), 7.58 (m, 3H, Ar-H),), 7.34 (m, 1H, Ar-H), 3.51 (m, 2H, CH_2N), 2.98 (t, *J* 6.4 Hz, 2H, CH_2S), 1.78 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 165.0, 134.2, 128.9, 128.8, 127.4, 127.2, 127.1, 126.2, 126.3, 122.2, 122.1, 42.4, 28.4, 23.1; HRMS (EI) for $C_{13}H_{12}N_2O_3S_2$ [M^+] calcd: 308.0289; found: 308.0292.

1,3-Thiazin-2-ones (4p). Colourless oil (286.6 mg, 89%); ^{1}H NMR (DMSO-d_6) δ 7.39 (m, 4H, Ar-H), 7.28 (m, 4H, Ar-H),), 7.16 (m, 2H, Ar-H),), 3.46 (m, 2H, CH_2N), 2.94 (m, 2H, CH_2S), 1.86 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 165.9, 139.3, 129.6, 129.1, 126.2, 43.4, 28.9, 24.5; HRMS (EI) for $C_{13}H_{12}N_2O_3S_2$ [M^+] calcd: 322.0446; found: 322.0452.

1,3-Thiazin-2-ones (4q). Colourless oil (231.8 mg, 92%); ^{1}H NMR (DMSO-d_6) δ 3.46 (m, 2H,CH_2N), 3.28 (q, J 6.4 Hz, 2H,C$\underline{H_2}$CH$_3$), 2.93 (t, *J* 6.4 Hz, 2H,CH_2S), 2.48 (m, 2H, CH_2), 1.29 (t, *J* 6.4 Hz, 3H,$CH_2C\underline{H_3}$); ^{13}C NMR (DMSO-d_6) δ 166.4, 45.2, 41.3, 26.9, 26.1, 14.4; HRMS (EI) for $C_8H_{16}N_2O_3S_2$ [M^+] calcd: 252.0602; found: 252.0609.

1,3-Thiazin-2-ones (4r). Colourless oil (226.1 mg, 85%); ^{1}H NMR (DMSO-d_6) δ 3.83 (t, *J* 6.4 Hz, 4H, CH_2O), 3.62 (t, *J* 6.4 Hz, 4H, CH_2N), 3.49 (m, 2H, CH_2N), 3.02 (t, *J* 6.4 Hz, 2H, CH_2S), 2.51 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 166.9, 68.2, 54.2, 46.3, 26.9, 24.2; HRMS (EI) for $C_8H_{14}N_2O_4S_2$ [M^+] calcd: 266.0395; found: 266.0401.

1,3-Thiazin-2-ones (4s). Colourless oil (252.0 mg, 78%); ^{1}H NMR (DMSO-d_6) δ 10.56 (bs, 1H, NH), 8.83 (d, 1H, J 8.6 Hz, Ar-H), 8.42 (d, 1H, *J* 8.4 Hz, Ar-H), 7.64 (m, 3H, Ar-H),), 6.99 (d, 1H, *J* 8.6 Hz, Ar-H), 3.47 (m, 2H, CH_2N), 2.88 (t, *J* 6.4 Hz, 2H, CH_2S), 2.34 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 166.1, 152.3, 148.9, 135.8, 134.6, 131.2, 128.2, 125.7, 121.1, 115.3, 46.4, 28.6, 23.7; HRMS (EI) for $C_{13}H_{13}N_3O_3S_2$ [M^+] calcd: 323.0398; found: 323.0402.

1,3-Thiazin-2-ones (4t). Colourless oil (207.5 mg, 84%); ^{1}H NMR (DMSO-d_6) δ 7.87 (s, 1H, Ar-H), 7.04 (d, 1H, *J* 8.6 Hz, Ar-H), 6.95 (d, 1H, *J* 8.6 Hz, Ar-H), 3.39 (m, 2H, CH_2N), 2.75 (t, *J* 6.4 Hz, 2H, CH_2S), 2.46 (m, 2H, CH_2); ^{13}C NMR (DMSO-d_6) δ 166.4, 135.2, 129.2, 124.3, 46.1, 27.5, 23.9; HRMS (EI) for $C_7H_9N_3O_3S_2$ [M^+] calcd: 247.0085; found: 247.0090.

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