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New 2-functionalized 2*H*-3,4-dihydro-1,4-benzothiazin-3-ones and their application in the synthesis of spiro heterocycles

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Abstract—The reaction of 2-chloro-3,4-dihydro-2*H*-1,4-benzothiazin-3-ones **1** with enamines is an efficient synthetic method to produce 2-substituted derivatives. The resulting bifunctional compounds such as **6a**,**b**, **7c**,**d** and **8b** react with hydrazines to furnish the spiro derivatives of *N*-aminopyrrole or 3-pyridazinone depending on the direction of the primary nucleophilic attack and the nature of the nucleophile. Under the reaction conditions, spiro pyridazinones **13** are converted into the 3-pyridazinone-4-carboxylic acid derivatives **9** via the 1,4-thiazine ring opening.

1. Introduction

Many 2*H*-1,4-benzothiazin-3-one derivatives exhibit a broad spectrum of biological activities, so that the purposeful modification of their structure attracts great interest in pharmacology and other related fields.[1] Generally methods for preparing these compounds rely on condensation of 2-aminothiophenols with α,β-unsaturated acids or α-haloacetic acids (or esters).[2] The limited availability of such acids is the major disadvantage of the method. As an alternative method, one can use 2-chloro-2*H*-1,4-benzothiazin-3-ones (**1**), easily accessible starting materials, in the synthesis of various 2-substituted 1,4-benzothiazin-3-ones. Like any α-halogeno sulfides, compounds **1** are distinguished by an extremely easy nucleophilic substitution of the chlorine atom. For instance, they react with alcohols, primary and secondary amines and triethyl phosphite.[3] An efficient synthetic route to 2-aryl-2*H*-1,4-benzothiazin-3-ones (useful as Ca^{2+} antagonists, blood platelet aggregation inhibitors and vascular agents) is offered by the Friedel–Crafts reaction of compounds **1** with aromatics.[4] Recently we have prepared 2-heteroaryl-2*H*-1,4-benzothiazin-3-ones by the reaction of **1** with electron-rich heterocycles.[5] The research work presented here is a part of the program aimed at the development of methods for synthesis of 2-heteroaryl and 2-spiro derivatives of 1,4-benzothiazin-3-one.

The carbethoxy group at the c-2 position in compound **1b** greatly extends its synthetic potential, especially in the molecular design of the various spiro derivatives of 2*H*-1,4-benzothiazin-3-one. It is noteworthy that although spiro heterocycles have been a subject of a large number of publications,[6] only few syntheses of 2*H*-1,4-benzothiazin-3-one spiro derivatives have been reported hitherto.[5,7] For instance, one of the present authors has previously described the synthesis of 1,4-benzothiazin-2-spiro-(2′-aryliminothiazolidin-5′-3-ones) (**2**) by the amine-induced cyclization of isothiocyanates readily obtained from compound **1b**.[7b] As we found in our preceding study on the synthesis of 2-heteroaryl-2*H*-1,4-benzothiazin-3-ones, the reaction between **1b** and 6-aminouracils involves the C-5 atom of the pyrimidine ring and likewise results in the intramolecular spirocyclization to provide spiro[1,4-benzothiazine-2,7′-pyrrolo[3,2-*d*]pyrimidine] (**3**) derivatives (Fig. 1).[5]

A remarkably high reactivity of **1a** and **b** towards electron-rich heterocycles suggests that these compounds can be reacted in a similar manner with other C-nucleophiles to form a new C–C bond. The present work addresses the reaction of compounds **1a** and **b** with enamines **4a**,**b** and **5** as

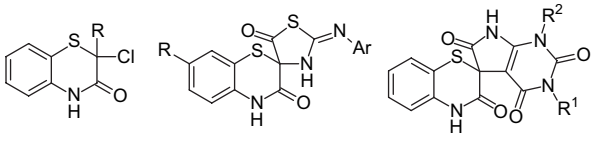

Figure 1.

Keywords: Chloro derivatives; Enamines; Electrophilic substitution; Cyclization; Spiro heterocycles.
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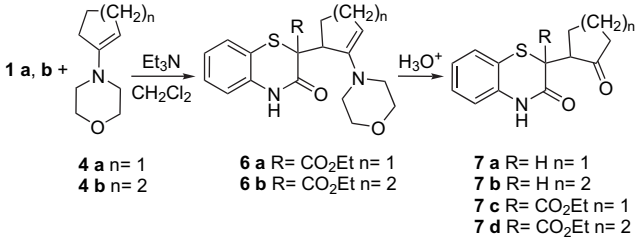
a synthetic entry into 2-functionalized 2*H*-1,4-benzothiazin-3-ones and also describes their further use as starting compounds in the synthesis of 1,4-benzothiazin-3-one spiro derivatives.

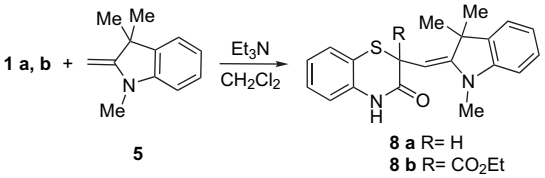
2. Results and discussion

Compounds **1a**,**b** and **4a**,**b** were reacted in methylene chloride at room temperature in the presence of a slight excess of triethylamine (see Scheme 1). Under these conditions, no notable distinctions are observed in the reactivity of the secondary and tertiary chloro derivatives **1a** and **b**, in contrast to the case when they are reacted with electron-rich heterocycles. If morpholinocycloalkenes **4a** and **b** are replaced with their more reactive 1-pyrrolidinyl-substituted counterparts, pronounced resinification of the reaction mixture occurs and the yields of the target products drop. If the reaction is conducted with **1a**, treatment of the resulting reaction mixture with water immediately affords the hydrolysis products, ketones **7a** and **b**, in high yields, since the initially formed enamines are too labile to be isolated. Intermediate enamines **6a** and **b** containing a carbethoxy group proved to be more stable towards hydrolysis and were both isolated as a mixture of two diastereomers. On heating in 10% hydrochloric acid, these compounds are readily hydrolyzed to furnish γ-ketoesters **7c** and **d** in nearly quantitative yields.



Scheme 1.

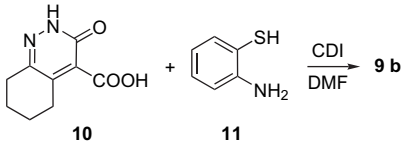
Heterocyclic enamine **5** likewise smoothly reacts with compounds **1a** and **b** under the same conditions to produce monosubstituted indolines **8a** and **b** (see Scheme 2). The readiness and equally good yields of the reaction with **4a** and **b** (70–90%) and **5** (70–75%) are attributable, on the one hand, to the high electrophilic reactivity of reagents **1a** and **b** and, on the other hand, to their sterically hindered reaction centre precluding polysubstitution of the enamines.[8]



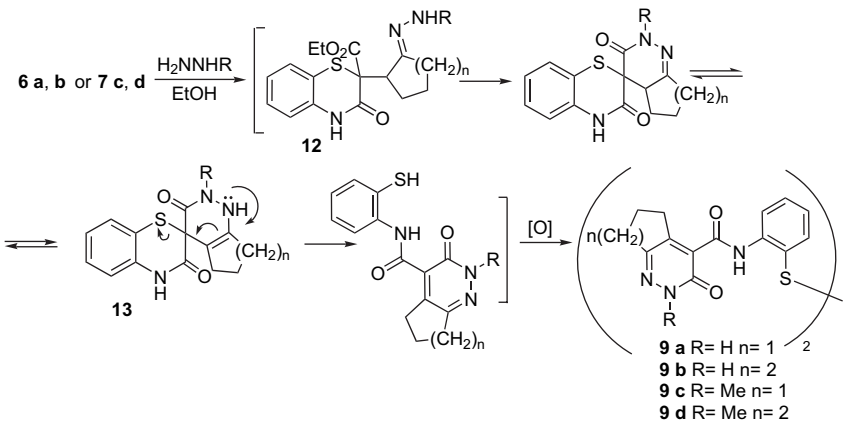
Scheme 2.

The prepared γ-ketoesters **7c** and **d** as well as enamines **6a**,**b** and **8b** are 1,4-biselectrophiles and show promise in the synthesis of 2*H*-1,4-benzothiazin-3-one spiro derivatives. Here we study the reaction of these compounds with the simplest 1,2-bisnucleophiles, hydrazine and methylhydrazine, in an effort to synthesize the 1,4-benzothiazin-3-one-2-spiro-4[1]-3[1]-oxopyridazine derivatives **13**. On boiling **6a** and **b** or **7c** and **d** in ethanol with a slight excess of hydrazine hydrate or methylhydrazine, we isolated, in moderate yields, high-melting yellow solids that was recrystallized from DMF or DMSO (see Scheme 3). The ^{1}H, ^{13}C NMR, IR and mass spectroscopic data led us to infer that the compounds formed were disulfides **9a–d**, 3-pyridazinone-4-carboxylic acid derivatives, rather than the desired spiro systems **13**.

For unequivocal structural determination of compounds **9a–d**, one of them was obtained by alternate synthesis. Following the known procedure,[9] we started from diethyl mesoxalate and cyclohexanone, and thus came, in three stages, to 3-oxo-2,3,5,6,7,8-hexahydro-4-cinnoline carboxylic acid **10** (see Scheme 4). Acylation of *ortho*-aminophenol **11** with acid **10** (CDI, DMF) resulted in a product identical with compound **9b** as judged from the melting point and spectral characteristics.



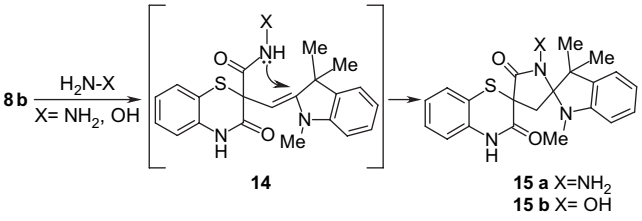
Scheme 4.



Scheme 3.

Formation of products **9** in the reaction of **7c**,**d** and **6a**,**b** with hydrazine can be accounted for the following reaction pathway: the primary nucleophilic attack on the carbonyl group of the cyclic ketone (in **7c**,**d**) or on the α-enamine carbon atom (in **6a**,**b**) leads to hydrazones **12**, which then cyclize to spiro derivatives **13**. The next stage represents quite an unusual 1,4-thiazine ring opening via the C–S bond cleavage and the formation of the stable 3-pyridazinone system, the latter appearing to be a driving force for the process.

Though the indoline derivative **8b** also reacts smoothly with hydrazine, the reaction proceeds differently than described above. In the first stage, hydrazide **14** is formed (see Scheme 5), which further undergoes the 5-*endo-trig* type cyclization to produce 1-amino-1,3,3-trimethyl-1,3-dihydro-5*H*-dispiro[1,4-benzothiazine-2,4-pyrrolidine-2,2-indole]-3,5(4*H*)-dione **15a** via the intramolecular nucleophilic attack of the amide nitrogen atom on the C-2 atom of the indoline ring. The yield of product **15a** amounts to 88%. Interestingly, the reaction of enamine **8b** with hydroxylamine under analogous conditions provides a mixture of two products, spiro compound **15b** and hydroxamic acid derivative **14** (X=OH); only boiling in ethanol for 8 h brings the cyclization to completion.



Scheme 5.

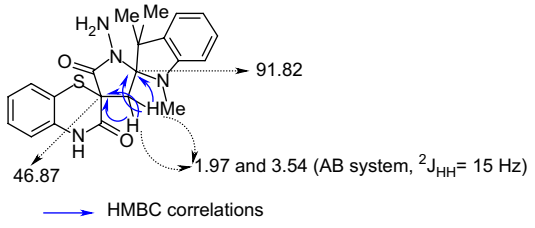


Figure 2.

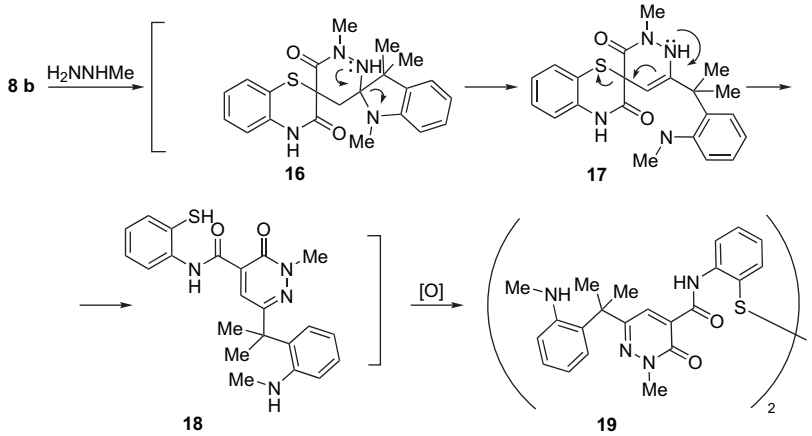
The structural determination of compounds **15a** and **b** was based on the ^{1}H and ^{13}C NMR spectra as well as on the HMQC and HMBC data (see Fig. 2).

It is also noteworthy that the C-acyl derivatives of enamine **5** act as 1,3-biselectrophiles and are known to react with hydrazine and hydroxylamine affording the spiro derivatives of 1,2-azoles such as pyrazole and isoxazole.[10] However, they readily undergo the indoline ring opening, i.e., a despiro conversion, to release pyrazole and isoxazole during the course of the reaction or on the treatment with hydrochloric acid. On the contrary, the bis-spiro system in compounds **15a** and **b** proved unexpectedly stable. For instance, these compounds remain unchanged even after extended heating in DMF. Boiling **15a** in hydrochloric acid results only in hydrochloride formation rather than in the cleavage of the spiro structure.

When methylhydrazine instead of hydrazine was used in the reaction with enamine **8b**, a mixture of products was formed from which the 3-pyridazinone-4-carboxylic acid derivative **19** was isolated in 40% yield (see Scheme 6). Evidently, in this case the primary nucleophilic attack occurs on the carbethoxy group, just as in the reaction of **8b** with hydrazine, and the N-1 atom of methylhydrazine acts as a nucleophile. However, the resulting hydrazide cannot cyclize to *N*-aminopyrrole derivative like **15**. An alternative reaction pathway is therefore realized, which implies that the formation of intermediate spiro pyridazinone **16** is followed by the indoline ring opening and the conversion of intermediate **17** into disulfide **19** (similar to the **6**→**9** conversion described above). The structure of compound **19** is supported by ^{1}H and ^{13}C NMR spectroscopies including the HH COSY experiments.

3. Conclusions

To conclude, the studied reaction between chloro derivatives **1** and enamines appears as an efficient synthetic method to produce 2-substituted 3,4-dihydro-2*H*-1,4-benzothiazin-3-ones. The resulting bifunctional compounds such as **6a**,**b**, **7c**,**d** and **8b** react with hydrazines to furnish the spiro derivatives of *N*-aminopyrrole or 3-pyridazinone depending on the direction of the primary nucleophilic attack and the nature of



Scheme 6.

the nucleophile. Under the reaction conditions, spiro pyridazinones **13** are converted into the 3-pyridazinone-4-carboxylic acid derivatives **9** via the 1,4-thiazine ring opening.

4. Experimental

4.1. General

CH_2Cl_2 and DMF for the reactions were freshly distilled and dried by standard methods. All solvents for the crystallization were used without additional purification. The ^1H and ^{13}C NMR (500 and 125 MHz, respectively) were recorded on a Bruker Avance DRX 500 with DMSO-d_6 as the solvent and TMS as an internal standard. EIMS were recorded on a mass spectrometer MX-1321 using direct sample insertion into the ion source with an ionizing electron accelerating voltage of 70 V and an ionization chamber temperature of 150 °C. LC/MS spectra were recorded using chromatography/mass spectrometric system that consists of high-performance liquid chromatograph 'Agilent 1100 Series' equipped with diode-matrix and mass-selective detector 'Aligent LCMSD SL'. The parameters of chromatography-mass analysis: Column: Zorbax SB-C18, 1.8 μm×4.6 mm× 15 mm. Solvents: A—acetonitrile/water (95:5), 0.1% TFA, B—water (0.1% of TFA). Eluent flow: 3 mL s^{-1}. The volume of injected sample: 1 μL. UV-detectors operate at 215, 254 and 265 nm. Ionization method: chemical ionization under atmospheric pressure (APCI). Ionization mode: simultaneous scanning of positive and negative ions in the mass range of 80–1000 MHz. Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. IR spectra were recorded on a Nexus-470 spectrometer for samples in KBr disks. Melting points (mp) were determined with electrothermal capillary melting point apparatus and are uncorrected.

4.1.1. General procedure for the synthesis of 6a,b, 7a,b and 8a,b. To a stirred solution of the appropriate enamine (5 mmol) and Et_3N (0.72 mL, 5.1 mmol) in anhydrous CH_2Cl_2 (30 mL), **1a** (5 mmol) or **1b** (5 mmol) was added. The reaction mixture was boiled with a reflux condenser for 2 h, cooled and washed with water (2×30 mL). The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The crude product was crystallized from the appropriate solvent.

4.1.1.1. Ethyl 2-(2-morpholin-4-ylcyclopent-2-en-1-yl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-2-carboxylate (6a).[†] Colourless solid, mp 146–147 °C; δ_H ($CDCl_3$) 8.75 (1H, br s), 7.34 (1H, d, *J* 7.2 Hz), 7.12 (1H, t, *J* 8.3 Hz), 7.00 (1H, t, *J* 7.7 Hz), 6.80 (1H, d, *J* 7.8 Hz), 5.00 (1H, s), 4.37–4.29 (1H, m), 4.02–3.93 (2H, m), 3.68–3.56 (4H, m), 2.99–2.93 (2H, m), 2.58–2.11 (6H, m), 0.86 (3H, t, *J* 7.2 Hz); δ_C 167.37, 163.01, 151.51, 136.01, 127.80, 127.12, 123.56, 120.11, 116.96, 109.23, 66.36, 62.65, 61.90, 50.83, 45.58, 29.82, 28.14, 13.77; MS [*m*/*z* (%)]: 388 (M+) (28.20), 237 (61.14), 191 (49.73), 152 (100.00), 151 (59.22); IR (cm^{-1}): 1665, 1738, 2980; Anal. Calcd for $C_{20}H_{24}N_2O_4S$: C 61.84; H 6.23; N 7.21; found C 61.86; H 6.26; N 7.24; yield (solvent): 76% (EtOH).

4.1.1.2. Ethyl 2-(2-morpholin-4-ylcyclohex-2-en-1-yl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-2-carboxylate (6b).[†] Colourless solid, mp 151–152 °C; δ_H 10.61 (1H, s), 7.29 (1H, d, *J* 7.5 Hz), 7.14 (1H, t, *J* 7.7 Hz), 6.98–6.91 (2H, m), 5.23 (1H, s), 4.02–3.95 (2H, m), 3.77 (1H, br s), 3.59–3.49 (2H, m), 3.48–3.38 (2H, m), 2.94 (2H, br s), 2.31 (2H, br s), 2.17–1.93 (2H, m), 1.88–1.68 (2H, m), 1.60–1.37 (2H, m), 0.94 (3H, t, *J* 7.0 Hz); δ_C 167.70, 163.80, 147.52, 136.17, 127.23, 126.87, 122.70, 118.68, 116.10, 114.05, 66.39, 61.64, 60.97, 51.35, 35.56, 26.10, 24.05, 19.57, 13.63; MS [*m*/*z* (%)]: 402 (M+) (6.78), 252 (9.45), 167 (8.00), 166 (100), 41 (4.25); IR (cm^{-1}): 1670, 1710, 2980; Anal. Calcd for $C_{21}H_{26}N_2O_4S$: C 62.66; H 6.51; N 6.96; found C 62.88; H 6.53; N 6.96; yield (solvent): 78% (EtOH).

4.1.1.3. 2-(2-Oxocyclopentyl)-2*H*-1,4-benzothiazin-3(4*H*)-one (7a). Colourless solid, mp 207–208 °C; δ_H 10.52 (1H, s), 7.25 (1H, d, *J* 7.5 Hz), 7.13 (1H, t, *J* 7.7 Hz), 6.98–6.91 (2H, m), 3.93 (1H, d, *J* 3.9 Hz), 2.52–1.72 (7H, m); δ_C 216.36, 165.49, 137.38, 127.76, 127.61, 123.49, 119.70, 117.55, 47.45, 41.90, 37.61, 25.84, 20.60; MS [*m*/*z* (%)]: 247 (M+) (100.00), 191 (93.80), 164 (24.20), 136 (25.68), 55 (25.50); IR (cm^{-1}): 1680, 1720, 2980; Anal. Calcd for $C_{13}H_{13}NO_2S$: C 63.14; H 5.30; N 5.66; found C 63.16; H 5.31; N 5.68; yield (solvent): 75% (MeOH).

4.1.1.4. 2-(2-Oxocyclohexyl)-2*H*-1,4-benzothiazin-3(4*H*)-one (7b). Colourless solid, mp 168–169 °C; δ_H 10.57 (1H, s), 7.21 (1H, d, *J* 7.2 Hz), 7.10 (1H, t, *J* 7.2 Hz), 6.97–6.75 (2H, m), 3.93 (1H, d, *J* 5.4 Hz), 2.55–2.30 (3H, m), 2.10–1.60 (6H, m); δ_C 209.10, 166.28, 137.21, 127.75, 127.49, 123.47, 119.37, 117.44, 49.49, 41.39, 40.99, 29.68, 27.43, 23.89; MS [*m*/*z* (%)]: 261 (M+) (100.00), 233 (25.21), 136 (30.09), 132 (16.81), 109 (18.63); IR (cm^{-1}): 1670, 1700, 2940; Anal. Calcd for $C_{14}H_{15}NO_2S$: C 64.34; H 5.79; N 5.36; found C 64.32; H 5.78; N 5.35; yield (solvent): 84% ($C_6H_5CH_3$).

4.1.1.5. 2-[(1,3,3-Trimethyl-1,3-dihydro-2*H*-indol-2-ylidene)methyl]-2*H*-1,4-benzothiazin-3(4*H*)-one (8a). Colourless solid, mp 212–213 °C; δ_H 10.52 (1H, s), 7.32 (1H, d, *J* 7.8 Hz), 7.22–6.96 (5H, m), 6.74 (1H, t, *J* 7.5 Hz), 6.64 (1H, d, *J* 8.0 Hz), 4.69 (1H, d, *J* 11 Hz), 4.23 (1H, d, *J* 11 Hz), 2.85 (1H, s), 1.50 (6H, s); δ_C 165.75, 156.79, 145.04, 137.68, 136.91, 127.80, 127.63, 126.82, 122.91, 121.35, 118.68, 118.47, 116.84, 105.49, 85.79, 44.52, 32.00, 29.13, 28.61, 28.05; MS [*m*/*z* (%)]: 336 (M+) (96.91), 184 (100.00), 170 (63.65); IR (cm^{-1}): 1670, 2980; Anal. Calcd for $C_{20}H_{20}N_2OS$: C 71.40; H 5.99; N 8.33; found C 71.37; H 5.96; N 8.32; yield (solvent): 71% (EtOH).

4.1.1.6. Ethyl 3-oxo-2-[(1,3,3-trimethyl-1,3-dihydro-2*H*-indol-2-ylidene)methyl]-3,4-dihydro-2*H*-1,4-benzothiazine-2-carboxylate (8b). Colourless solid, mp 187–188 °C; δ_H 10.82 (1H, s), 7.21–7.02 (5H, m), 6.91 (1H, t, *J* 8.1 Hz), 6.76 (1H, t, *J* 7.1 Hz), 6.64 (1H, d, *J* 7.8 Hz), 4.18 (1H, s), 4.10–4.02 (2H, m), 3.39 (3H, s), 1.20 (3H, s), 1.06 (3H, s), 1.01 (3H, t, *J* 7.2 Hz); δ_C 169.78, 166.86, 158.78, 147.13, 138.13, 137.3, 128.19, 127.90, 123.47,

[†] The compounds were obtained as a mixture of two diastereomers (10:1) and ^1H NMR signals of major diastereomers are given. ^{13}C NMR spectra exhibited signals of only one diastereomer.

122.21, 120.18, 119.58, 117.06, 107.05, 83.61, 62.73, 55.01, 46.77, 33.85, 30.37, 14.16; MS [*m*/*z* (%)]: 408 (M+) (17.65), 335 (100.00), 158 (21.72); IR (cm^{-1}): 1680, 1740, 2980; Anal. Calcd for $C_{23}H_{24}N_2O_3S$: C 67.62; H 5.92; N 6.86; found C 67.65; H 5.96; N 6.89; yield (solvent): 75% (EtOH).

4.1.2. Procedure for the synthesis of 7c and d. To a stirred solution of HCl (10%, 30 mL) **6a** and **b** (1.8 mmol) was added and heated at 60 °C for 30 min. The precipitate was filtered and recrystallized from EtOH.

4.1.2.1. Ethyl 3-oxo-2-(2-oxocyclopentyl)-3,4-dihydro-2*H*-1,4-benzothiazine-2-carboxylate (7c). Colourless solid, mp 205–206 °C; δ_H 10.86 (1H, s), 7.25 (1H, d, *J* 7.5 Hz), 7.19 (1H, t, *J* 7.8 Hz), 7.02 (1H, d, *J* 8.1 Hz), 6.96 (1H, t, *J* 8.0 Hz), 4.08–3.90 (2H, m), 2.88 (1H, t, *J* 9.5 Hz), 2.45–2.36 (1H, m), 2.30–2.14 (2H, m), 2.08–1.98 (1H, m), 1.92–1.76 (2H, m), 0.95 (3H, t, *J* 7.2 Hz); δ_C 214.91, 168.81, 163.90, 137.64, 128.41, 127.99, 123.73, 117.28, 116.33, 61.97, 55.83, 49.99, 37.76, 26.54, 20.49, 14.09; MS [*m*/*z* (%)]: 319 (M+) (53.97), 247 (34.97), 246 (100.00), 191 (26.89), 55 (41.13); IR (cm^{-1}): 1590, 1680, 1730, 2950; Anal. Calcd for $C_{16}H_{17}NO_4S$: C 60.17; H 5.37; N 4.39; found C 60.15; H 5.35; N 4.37; yield: 91%.

4.1.2.2. Ethyl 3-oxo-2-(2-oxocyclohexyl)-3,4-dihydro-2*H*-1,4-benzothiazine-2-carboxylate (7d). Colourless solid, mp 154–155 °C; δ_H 10.81 (1H, s), 7.16–7.33 (2H, m), 7.03–6.92 (2H, m), 3.99–3.85 (2H, m), 3.14–3.06 (1H, m), 2.38–2.12 (3H, m), 2.11–1.51 (5H, m), 0.86 (3H, t, *J* 6.9 Hz); δ_C 205.98, 167.84, 163.02, 137.13, 127.61, 127.54, 126.93, 123.03, 116.42, 116.38, 61.15, 54.05, 40.79, 30.35, 27.32, 24.57, 23.81, 13.50; MS [*m*/*z* (%)]: 333 (M+) (97.59), 260 (100.00), 243 (26.66), 232 (40.41), 164 (35.87); IR (cm^{-1}): 1590, 1680, 1720, 2990; Anal. Calcd for $C_{17}H_{19}NO_4S$: C 61.24; H 5.74; N 4.20; found C 61.26; H 5.76; N 4.22; yield: 92%.

4.1.3. General procedure for the synthesis of 9a–d, 15a,b and 19. To a solution of **6a** and **b** or **7c** and **d** or **8b** (5 mmol) in EtOH (30 mL), hydrazine hydrate (or methylhydrazine) (1 mL) was added. The mixture was boiled with a reflux condenser for 4 h. The EtOH was evaporated in vacuo and the precipitate was recrystallized from DMF.

4.1.3.1. *N*,*N*′-[Dithiobis(2,1-phenylene)]bis(3-oxo-3,5,6,7-tetrahydro-2*H*-cyclopenta[*c*]pyridazine-4-carboxamide) (9a). Yellow solid, mp 315–317 °C; δ_H 13.36 (1H, s), 12.52 (1H, s), 8.29 (1H, d, *J* 8.1 Hz), 7.32 (1H, t, *J* 8.3 Hz), 7.24 (1H, d, *J* 7.2 Hz), 6.98 (1H, t, *J* 7.4 Hz), 2.91–2.70 (4H, m), 2.15–2.01 (2H, m); δ_C 161.24, 160.56, 155.77, 154.50, 139.78, 135.58, 130.84, 124.42, 124.17, 122.49, 121.39, 32.49, 29.49, 23.35; MS APCI: 573 ($M+H^+$); IR (cm^{-1}): 1635, 1695, 2900, 2985; Anal. Calcd for $C_{28}H_{24}N_6O_4S_2$: C 58.73; H 4.22; N 14.68; found C 58.70; H 4.19; N 14.66; yield: 64%.

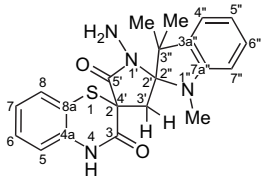
4.1.3.2. *N*,*N*′-[Dithiobis(2,1-phenylene)]bis(3-oxo-2,3,5,6,7,8-hexahydrocinnoline-4-carboxamide) (9b). Yellow solid, mp 282–283 °C; δ_H 13.29 (1H, s), 11.18 (1H, s), 7.75 (1H, d, *J* 7.5 Hz), 7.55 (1H, d, *J* 7.5 Hz), 7.33 (1H, t, *J* 7.7 Hz), 7.16 (1H, t, *J* 7.7 Hz), 2.96 (2H, t, *J* 6 Hz), 2.71 (2H, t, *J* 6.5 Hz), 1.80–1.59 (4H, m); δ_C 162.48, 159.12, 145.85, 144.13, 136.89, 131.68, 129.86, 129.24, 129.03, 125.87, 124.07, 29.24, 26.86, 21.30, 21.07; MS APCI: 601 ($M+H^+$); IR (cm^{-1}): 1630, 1680, 2890, 2955; Anal. Calcd for $C_{30}H_{28}N_6O_4S_2$: C 59.98; H 4.70; N 13.99; found C 59.95; H 4.69; N 13.96; yield: 62%.

4.1.3.3. *N*,*N*′-[Dithiobis(2,1-phenylene)]bis(2-methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-cyclopenta[*c*]pyridazine-4-carboxamide) (9c). Yellow solid, mp 251–252 °C; δ_H (CF_3COOD) 7.99 (1H, d, *J* 7.8 Hz), 7.59 (1H, d, *J* 8.1 Hz), 7.37 (1H, t, *J* 7.5 Hz), 7.21 (1H, t, *J* 7.7 Hz), 4.09 (3H, s), 3.62 (2H, t, *J* 7.5 Hz), 3.16 (2H, t, *J* 7.5 Hz), 2.44–2.32 (2H, m); δ_C (CF_3COOD) 163.25, 160.52, 160.26, 156.63, 137.02, 136.05, 130.93, 128.90, 127.37, 123.96, 122.76, 40.89, 33.23, 29.92, 22.96; MS APCI: 601 ($M+H^+$); IR (cm^{-1}): 1630, 1680, 2950; Anal. Calcd for $C_{30}H_{28}N_6O_4S_2$: C 59.98; H 4.70; N 13.99; found C 59.96; H 4.67; N 13.95; yield: 57%.

4.1.3.4. *N*,*N*′-[Dithiobis(2,1-phenylene)]bis(2-methyl-3-oxo-2,3,5,6,7,8-hexahydrocinnoline-4-carboxamide) (9d). Yellow solid, mp 213–214 °C, δ_H (CF_3COOD) 8.03 (1H, d, *J* 8.1 Hz), 7.55–7.44 (2H, m), 7.27 (1H, t, *J* 8.0 Hz), 4.01 (3H, s), 3.17 (2H, t, *J* 6.0 Hz), 3.04 (2H, t, *J* 6.5 Hz), 2.06–1.91 (4H, m); δ_C (CF_3COOD) 164.41, 159.29, 151.87, 147.26, 135.52, 135.20, 131.14, 129.91, 128.83, 127.87, 124.75, 40.56, 28.74, 27.16, 20.42, 20.25; MS APCI: 601 ($M+H^+$); IR (cm^{-1}): 1630, 1680, 2980; Anal. Calcd for $C_{32}H_{32}N_6O_4S_2$: C 61.13; H 5.13; N 13.37; found C 61.11; H 5.12; N 13.34; yield: 59%.

4.1.4. Procedure for acylation of 2-aminothiophenol (9b). To a stirred solution of **11** (0.50 g, 2.6 mmol) in anhydrous DMF (15 mL), CDI (0.42 g, 2.6 mmol) was added. The mixture was stirred for 30 min and 2-aminothiophenol (0.33 g, 2.6 mmol) was added. The reaction mixture was stirred for 4 h and poured in water (50 mL). The precipitate was filtered and crystallized from DMF (yield 64%).

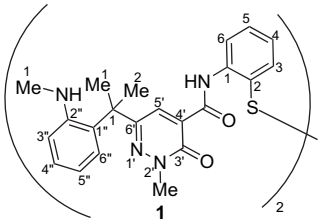
4.1.4.1. 1-Amino-1,3,3-trimethyl-1,3-dihydro-5*H*-dispiro[1,4-benzothiazine-2,4-pyrrolidine-2,2-indole]-3,5(4*H*)-dione (15a).



Colourless solid, mp 284–285 °C. The signals of ^1H and ^{13}C NMR were assigned on the basis of HMQC and HMBC experiments. δ_H 11.03 (1H, s, NH-4), 7.30 (1H, d, *J* 10.0 Hz, CH-5), 7.18 (1H, t, *J* 5.0 Hz, CH-6), 7.10–6.96 (4H, m), 6.61 (1H, t, *J* 5.0 Hz, CH-5″), 6.42 (1H, d, *J* 10.0 Hz, CH-4″), 4.15 (2H, s, NH_2), 3.54 (1H, d, *J* 15.0 Hz, CH_2-3′), 2.72 (3H, s, 1-NMe), 1.97 (1H, d, *J* 15.0 Hz, CH_2-3′), 1.24 (3H, s, C3″–Me), 1.17 (3H, s, C3″–Me); δ_C 166.94 (CO-5′), 165.09 (CO-3), 150.14 (C-7a″), 137.75 (C-3a″),

137.68 (C-4a), 127.62 (CH-6), 127.30 (CH-5), 127.22 (CH-7″), 123.53 (C-8), 120.51 (C-6″), 118.27 (C-5″), 117.97 (C-8a), 116.97 (CH-7), 105.65 (CH-4″), 91.82 (C-2″), 46.87 (C-2″), 46.71 (C-2), 32.01 (CH_2-3′), 28.75 (1-NCH_3), 28.67 (CH_3-1), 19.50 (CH_3-1); MS [*m*/*z* (%)]: 394 (M+) (33.86), 336 (11.56), 159 (100.00); IR (cm^{-1}): 1590, 1695, 2980, 3158, 3220; Anal. Calcd for $C_{21}H_{22}N_4O_2S$: C 63.94; H 5.62; N 14.20; found C 63.92; H 5.60; N 14.18; yield: 88%.

4.1.4.2. *N*,*N*′-[Dithiobis(2,1-phenylene)]bis(2-methyl-6-{1-methyl-1-[2-(methylamino)phenyl]-ethyl}-3-oxo-2,3-dihydropyridazine-4-carboxamide) (19).



Orange solid, mp 236–237 °C. The signals of ^1H NMR were assigned on the basis of HH COSY experiments. δ_H 12.20 (1H, s, NH), 8.14 (1H, d, *J* 5.0 Hz, CH-6), 7.56 (1H, s, CH-5′), 7.41 (1H, d, *J* 10.0 Hz, CH-3″), 7.29 (1H, d, *J* 5.0 Hz, CH-3), 7.20 (1H, t, *J* 7.5 Hz, CH-5″), 7.07 (1H, t, *J* 7.5 Hz, CH-5), 6.88 (1H, t, *J* 7.5 Hz, CH-4), 6.77 (1H, t, *J* 7.5 Hz, CH-4″), 6.59 (1H, d, *J* 5.0 Hz, CH-6″), 3.84 (1H, d, *J* 5.0 Hz, *NH*Me), 3.70 (3H, s, N*Me*), 2.66 (3H, d, *J* 5.0 Hz, NH*Me*), 1.66 (6H, s, C(*Me*)$_2$); δ_C 159.64, 159.44, 154.10, 147.14, 140.41, 136.75, 132.73, 131.63, 128.96, 128.90, 128.57, 126.81, 125.08; MS APCI: 815 ($M+H^+$); IR (cm^{-1}): 1630, 1690, 2990, 3460; Anal. Calcd for $C_{44}H_{46}N_8O_4S_2$: C 64.84; H 5.69; N 13.75; found C 64.86; H 5.71; N 13.79; yield: 42%.

4.1.5. Procedure for synthesis of 15b. To a stirred suspension of hydroxylamine hydrochloride (0.26 g, 3.75 mmol) in EtOH (30 mL) NaOH (0.12 g, 3.00 mmol) and **8b** (1.02 g, 2.50 mmol) were added. The mixture was boiled with a reflux condenser for 8 h. The EtOH was evaporated in vacuo to dryness and the precipitate was washed with water and recrystallized from DMF.

4.1.5.1. 1′-Hydroxy-1″,3″,3″-trimethyl-1″,3″-dihydro-5′*H*-dispiro[1,4-benzothiazine-2,4′-pyrrolidine-2′,2″-indole]-3,5′(4*H*)-dione (15b).

Colourless solid, mp 282–283 °C; δ_H 11.02 (1H, s), 9.68 (1H, s), 7.25 (1H, d, *J* 7.5 Hz), 7.17 (1H, t, *J* 7.7 Hz), 7.10–6.88 (4H, m), 6.63 (1H, t, *J* 7.1 Hz), 6.42 (1H, d, *J* 8.1 Hz), 3.57 (1H, d, *J* 16.2 Hz), 2.77 (1H, s), 1.95 (1H, d, *J* 16.2 Hz), 1.30 (3H, s), 1.20 (3H, s); δ_C 164.42, 162.83, 149.19, 137.19, 136.95, 127.27, 126.99, 126.75, 123.16, 120.17, 118.16, 117.35, 116.58, 105.57, 90.71, 46.24, 45.13, 30.91, 28.45, 27.03, 19.65; MS [*m*/*z* (%)]: 395 (M+) (36.61), 336 (18.20), 159 (100.00); IR (cm^{-1}): 1590, 1695, 2990, 3080; Anal. Calcd for $C_{21}H_{21}N_3O_3S$: C 63.78; H 5.35; N 10.62; found C 63.77; H 5.33; N 10.57; yield: 65%.

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