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One-pot synthesis of 2-thioxothiazolidin-4-one, thiazolidine-2,4-dione, 2-iminothiazolidin-4-one based spiro-thiolane and bicyclic chromene-thiolane hybrids *via* Knoevenagel, 1,4-sulfa-Michael and aldol Reactions

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Dedicated to Prof. Sambasivarao Kotha on the occasion of his 65th birthday

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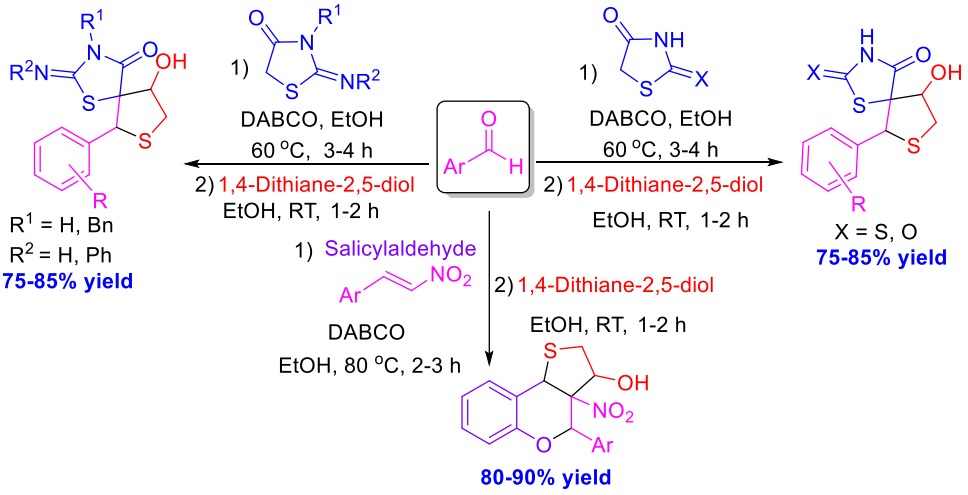
Abstract

A simple and efficient method for the synthesis of new class of 2-thioxothiazolidin-4-one (Rhodanine), thiazolidine-2,4-dione, and 2-iminothiazolidin-4-one based spiro-thiolane hybrids is reported. The title compounds were obtained by the reaction of Knoevenagel adducts of 2-thioxothiazolidin-4-one, thiazolidine-2,4-dione, 2-iminothiazolidin-4-ones and α-mercaptoacetaldehyde in the presence of DABCO (20 mol %) at room temperature. The reaction proceeds *via* 1,4-sulfa-Michael followed by intramolecular aldol reaction to form spiro-thiolane in good to moderate yields. This method was extended for the one-pot synthesis of bicyclic chromene-thiolane hybrids to generate functionalized chromene-tetrahydrothiophene derivatives in good yield.



Keywords: 2-Thioxothiazolidin-4-one, Thiazolidine-2,4-dione, 2-Iminothiazolidin-4-one, α-Mercaptoacetaldehyde, Spiro-thiolane, Chromene-thiolane

Introduction

Structurally analogous five membered heterocyclic molecules 2-thioxothiazolidin-4-one (Rhodanine) (**2**), thiazolidine-2,4-dione (**3**), and 2-iminothiazolidin-4-one (**4**) are considered as privileged class in medicinal chemistry. The 2-thioxothiazolidin-4-one (Rhodanine) skeleton has been used for the preparation of many derivatives with diversified biological applications such as antifungal, antiviral, anticonvulsant, antidiabetic, anticancer and other properties like metallo-β-lactamase inhibitors, dynamin GTPase activity, enoyl reductase InhA, aldose reductase inhibitors, HIV-I integrase inhibitor(Figure 1).[1-4] Rhodanine is also gaining attention in materials chemistry as an alternative to the fullerene based compounds.[5] The derivatives of rhodanine are used for the development of dye-sensitized solar cells (DSSCs),[6,7] organic photovoltaics,[8,9] and semi conducting materials.[10] Thiazolidine-2,4-diones (TZD, 3) are also known for their anti-inflammatory, antioxidant, protein tyrosine phosphatase (PTP1B) inhibitors, thyroid hormone receptor antagonists, anti-prostaglandins, antibacterial, antiviral, and anti-tubercular properties,[1-3] and are common scaffolds in the commercial glitazone class of antidiabetic drugs (Figure 1).[11] The thiazolidine-2,4-dione derivatives are active towards different targets/signalling and metabolic pathways in cancer therapy,[12] as dual glycogen synthase kinase 3β, tau aggregation inhibitors,[13]and for the development of photovoltaics.[14] Similar to rhodanines and TZDs, the 2-iminothiazolidin-4-ones (**4**) the isomeric class in this category) are equally important in medicinal chemistry. The derivatives of 2-iminothiazolidin-4-one are reported for the treatment of auto immune diseases (as S1P1 receptor agonists),[15] cancer (tubulin polymerase inhibitors),[16] antiprotozoan (Trypanosoma cruzi),[17] antimicrobial properties (Figure 1),[18] selective GSK-3β inhibitors,[19] and for selective detection of the copper (II), mercury (II) ions by fluorimetric method.[20] The structural complexity of the molecule is always challenging to synthetic chemists. Often, the incorporation of multiple functional groups in a molecule leads to the development of new properties. In this context, the 2-thioxothiazolidin-4-one (Rhodanine) (**2**), thiazolidine-2,4-dione (**3**), and 2-iminothiazolidin-4-one (**4**) have been used in a multicomponent approach to prepare complex/spiro compounds. Towards this, Knorr and co-workers reported rhodanine-substitued spirooxindole-pyrrolidine derivatives as novel α-amylase inhibitors (Figure 3).[21,22] Narayanan and co-workers used the [3+2]-cycloaddition strategy for the synthesis of thiazolidinedione and rhodanine based dispiropyrrolidines.[23] The resulting compounds were tested for type-2 diabetes (Figure 3).[11,22] Similarly, Zhang *et al*. demonstrated an organocatalytic cascade strategy for the thiazolidinedione-based tricyclic-spiro compounds with anticancer and antifungal properties(Figure 3).[24] Tetrahydrothiophene (THT) is found in natural compounds like coenzyme (biotin),[25,26] salacinol (glucosidase inhibitor),[27] penicillin (Figure 2).[28] They show antiviral, anticancer, anti-platelet, α-glucosidase inhibition, anti-HIV, immunosuppressive and antimicrobial activities.[29]

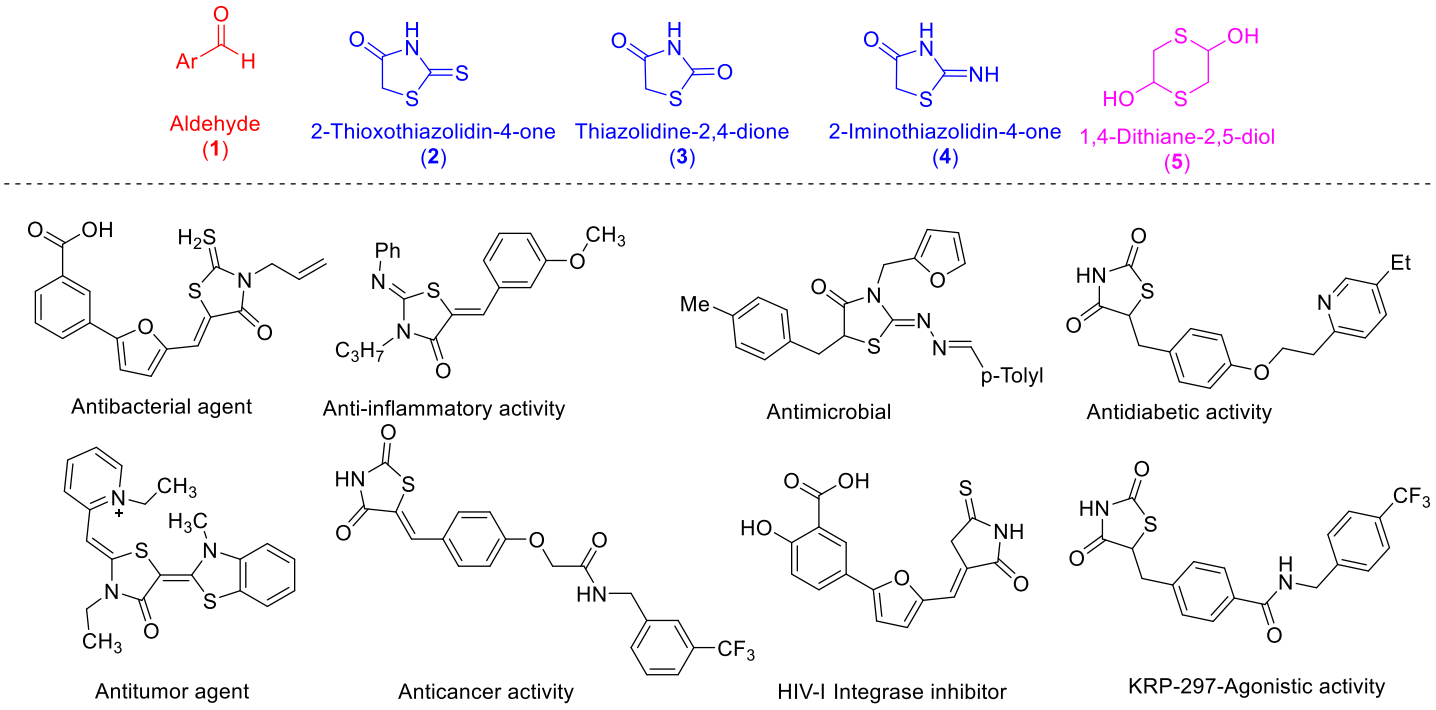


Figure 1. Biologically active derivatives of 2-thioxothiazolidin-4-one (Rhodanine) (**2**), thiazolidine-2,4-dione (**3**), and 2-iminothiazolidin-4-one (**4**).

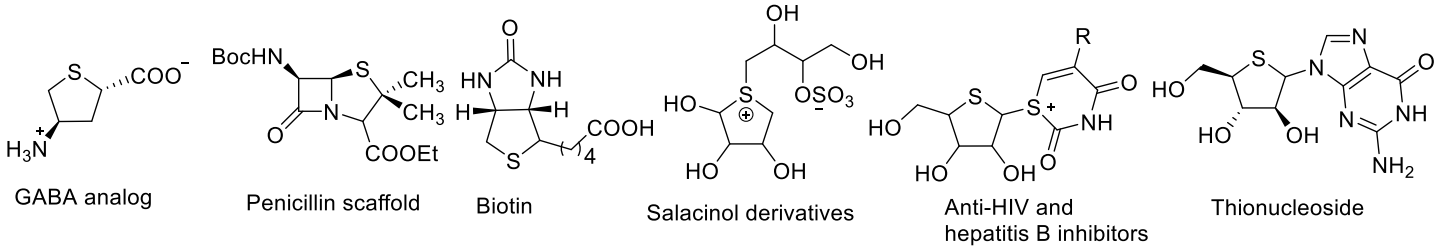


Figure 2. Natural and biologically active tetrahydrothiophene derivatives.

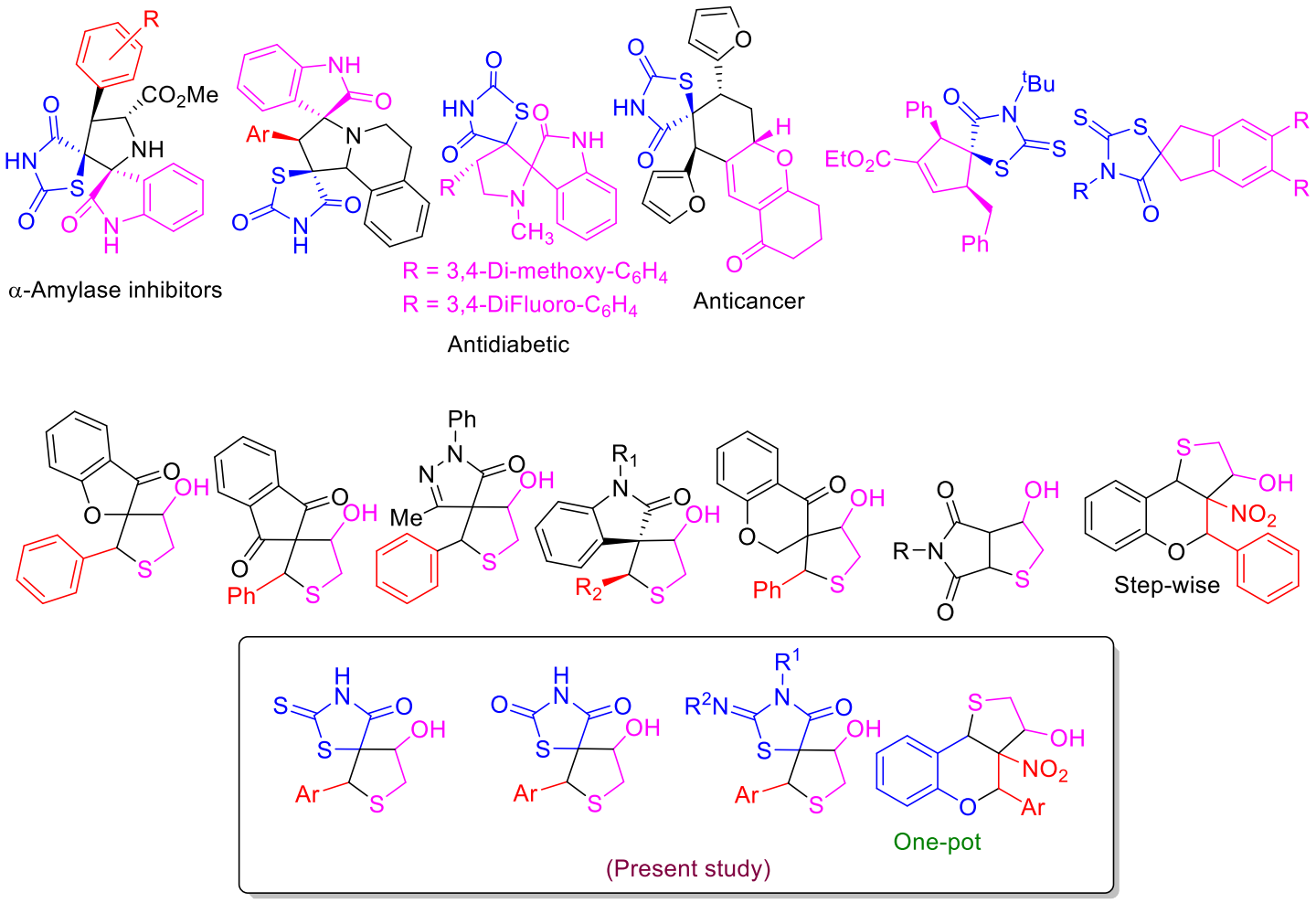


Figure 3. Examples of spiro- and bicyclic thiolanes and new hybrid molecules (present study).

Limited synthetic approaches are known in the literature for the construction of tetrahydrothiophene derivatives. In 1992, Effenberger *et al*.[30] used 1,4-dithiane-2,5-diol (**5**; dimer of α-mercaptoacetaldehyde/2-sulfanylacetaldehyde) for the synthesis of substituted tetrahydrothiophenes by the action of α-mercaptoacetaldehyde and dihydroxyacetone phosphate by rabbit muscle aldolase (RAMA) as a catalyst. The bi-functionality of 1,4-dithiane-2,5-diol (**5**) [electrophile (-CHO) and nucleophile (-SH)] was used for the preparation of thiophenes by Gewald and co-workers.[31] In this regard, the Belleau[32] and Spino[33] groups used 1,4-dithiane-2,5-diol (**5**) to prepare cyclic thia derivatives *via* Michael type addition and intramolecular aldol reaction, which were then used to generate dienes. In 2006, Pollini and co-workers explored the bifunctional nature of 1,4-dithiane-2,5-diol (**5**) (-CHO as electrophile and –SH as nucleophile) for the tandem Michael–Henry or Michael–Michael reactions resulting in 3,4-disubstituted tetrahydrothiophenes.[34] Following these inventions, the application of 1,4-dithiane-2,5-diol (**5**)[35-37] was extended for enantioselective tandem, [3+3]/[3+2]-cycloaddition[38,39] reactions in the presence of organocatalysts (chiral squaramide)[40] lead to (*E*)-2-benzylidenebenzofuran-3(*2H)*-ones,[41] 2-arylidene-1,3-indandiones.[42-44] Similarly, 1,4-dithiane-2,5-diol (**5**) was used for the synthesis of 3-nitro-2-substituted, spiro[pyrazolone-4,3'-tetrahydrothiophenes], spiro-tetrahydrothiophene-indan-1,3-diones using catalytic amount of DDQ,[45] DIPEA[46] and squaramide respectively.[47]

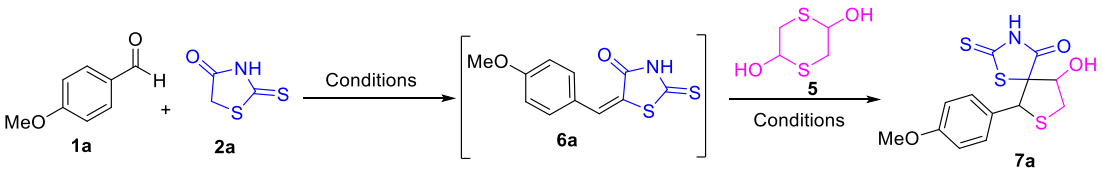
The derivatives of bicyclic pyrrolidone and thiophenes were synthesized *via* [3+2]-cycloaddition[48] reaction of maleimide and 1,4-dithiane-2,5-diol (5) with excellent diastereoselectivity.[49] Similar to these reports, the

use of Lewis acid ($BF_3.OEt_2$),[50] NEt_3[33] DBU,[51] quinine-derived squaramides[52] to generate complex tetrahydrothiophenes is known. Our group also engaged in the synthesis of isoxazole-thiolane derivatives *via* the 1,6-Michael or direct vinylogous reaction of substituted isoxazole with 1,4-dithiane-2,5-diol (**5**)[53] under catalyst-free conditions using the "on water" concept.[53,54]

Results and Discussion

From the above discussion, the thiazolidine-2,4-dione, 2-thioxothiazolidin-4-one, 2-iminothiazolidin-4-ones, tetrahydrothiophenes are important in medicinal chemistry and biology. Also, the above discussion indicates that the spiro-derivatives of the above compounds are also equally important in biology. Considering the medicinal importance of thiazolidine-2,4-dione, 2-thioxothiazolidin-4-one, 2-iminothiazolidin-4-ones, tetrahydrothiophenes and with our experience in the thiolane chemistry, we envisaged the synthesis of thiolane-hybrids (spiro compounds) of these compounds *via* C-S bond formations (sulfa 1,4-Michael addition and aldol reaction as key steps).

To achieve our goal and based on our previous results in catalyst-free reactions, we started the investigation using 4-methoxy benzaldehyde (**1a**) (1.0 mmol) and 2,4-thioxothiazolidinone (rhodanine) (**2**) (1.0 mmol) without catalyst in EtOH, water, and CH_3CN at 80 ^oC for 5 h, but the formation of intermediate (**6a**) was not observed. Later, the same reaction was performed in the presence of TEA (10 mol %) to give an intermediate (**6a**), which was subsequently treated with 1,4-dithiane-2-5-diol (**5**) (1.0 mmol) at RT for 6 h to give the desired product (**7a**) with yields of 65%, 58%, and 50%, respectively (Scheme 1 ; Table 1, Entry 1 to 3). Encouraged by these results and to improve the yield, many experiments were conducted by varying the base, solvent, and reaction time. All the results are summarized in Table 1. Among the screened conditions, DABCO in EtOH was found to be the best suitable condition for obtaining the desired product with a good yield (up to 85%) (Table 1, Entry 18). Having optimized reaction condition, different aldehydes (**1b**-**1h**) were treated with 2,4-thioxothiazolidinone (rhodanine) (**2**) (1.0 mmol) in EtOH at 80 ^oC (first step) to generate the intermediates (*in situ*), and 1,4-dithiane-2-5-diol (**5**) (1.0 mmol) were added at RT to give the spiro thioxothiazolidinone-thiolane hybrids (**7b**-**7h**) in moderate to good yields (75-90%). All the newly synthesized compounds are characterized by using ^1H NMR, ^{13}C NMR, and mass spectral techniques. For instance, spectral data of compound **7a**, the -$\underline{CH_3}$ protons of OMe group found at 3.8 δ ppm the $\underline{CH_2}$- protons of thiolane ring appeared at 2.59, and 2.89 δ ppm along with N-H peak in amide group, and alcohol proton observed at 12.68 and 5.13 δ ppm in ^1H NMR. Also, in ^{13}C NMR spectrum, the S-C=S bond in thiolane ring, C=O (carbonyl group) of amide are found 199 and 178 δ ppm respectively. In the FT-IR spectrum, the C=S stretching frequency of thiolane ring attributed at 1510 cm^{-1}, and the stretching frequency of -OH, and C=O groups in amide was identified at 3410, and 1603 cm^{-1}, respectively.



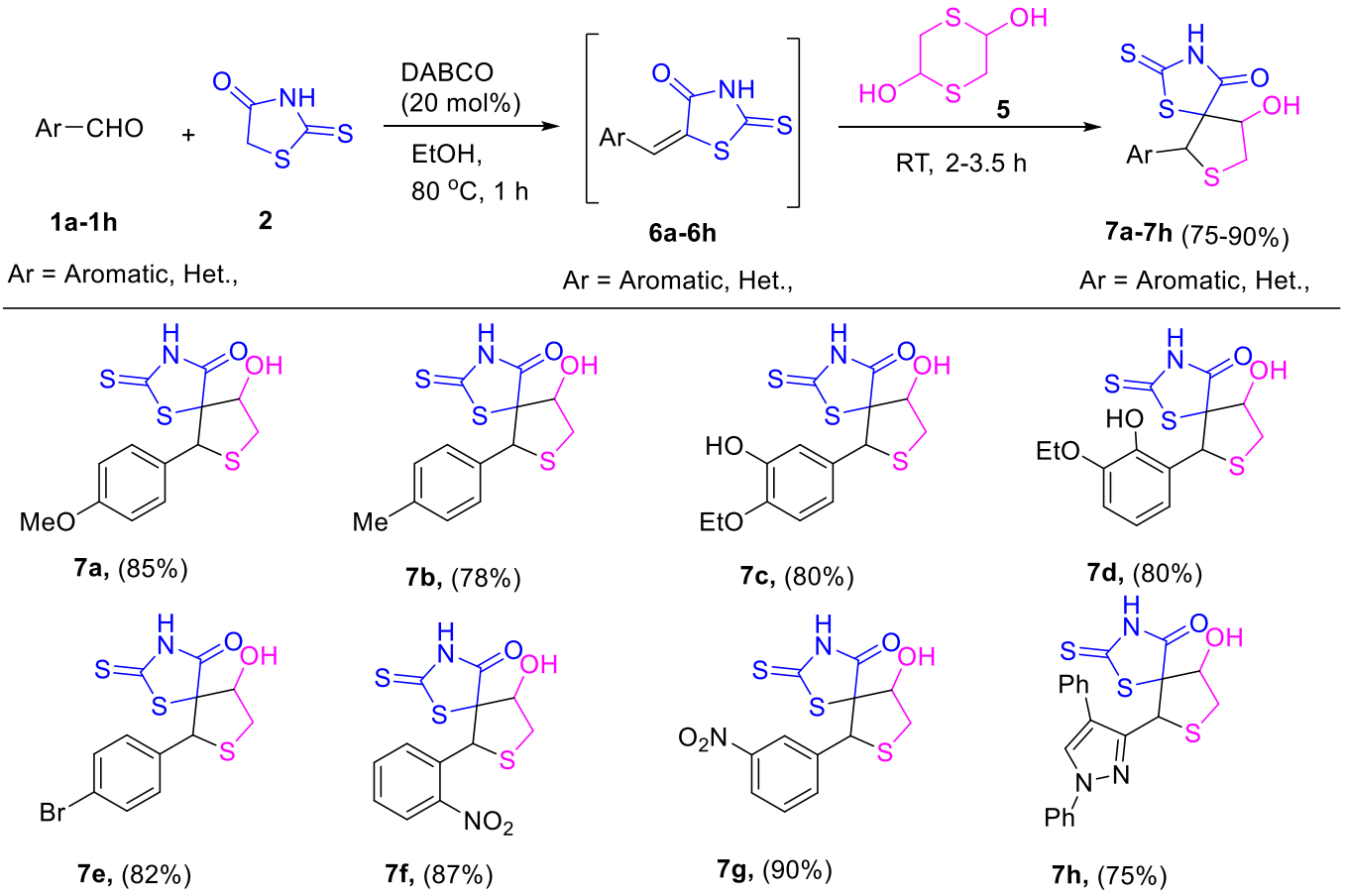
Conditions: 1) TEA (10 mol%), EtOH, 80 °C, 1 h, then 1, RT, 6 h, 65%
2) TEA (10 mol%), Water, 80 °C, 1 h, then 1, RT, 6 h, 58%
3) TEA (10 mol%), MeCN, 80 °C, 1 h, then 1, RT, 6 h, 50%

Scheme 1. Initial attempts for synthesis of 2,4-thioxothiazolidinone-thiolane hybrid **7a**.

Table 1. Optimization of Conditions[a]

Entry	Base	Solvent/Temp (°C)	Time (h) 1st Step	Time (h) 2nd Step (RT)	Yield[c] (%)
1	TEA (10 mol %)	EtOH/80 °C	1	6	65
2	TEA (10 mol %)	Water/80 °C	1	6	58
3	TEA (10 mol %)	CH_3CN /80 °C	1	6	50
4	DABCO (10 mol %)	EtOH/80 °C	1	2	78
5	DABCO (10 mol %)	Water/80 °C	1	7	65
6	DABCO (10 mol %)	DMF/80 °C	1	3	60
7	DABCO (10 mol %)	DMSO/80 °C	1	5	68
8	DABCO (10 mol %)	$CHCl_3$/65 °C	1	5	70
9	DEA (10 mol %)	EtOH/80 °C	1	5	50
10	Piperidine (10 mol %)	EtOH/80 °C	1	5	50
11	DIPEA (10 mol %)	EtOH/80 °C	1	5	55
12	DBU (10mol %)	EtOH/80 °C	1	5	50
13	DMAP (10mol %)	EtOH/80 °C	1	5	50
14	NaOH (10mol %)	EtOH/80 °C	1	5	40
15	KOH (10mol %)	EtOH/80 °C	1	5	15
16	K_2CO_3 (10mol %)	EtOH/80 °C	1	5	Traces
17	Cs_2CO_3 (10mol %)	EtOH/80 °C	1	5	15
18	DABCO (20 mol %)	EtOH/80 °C	1	2	85

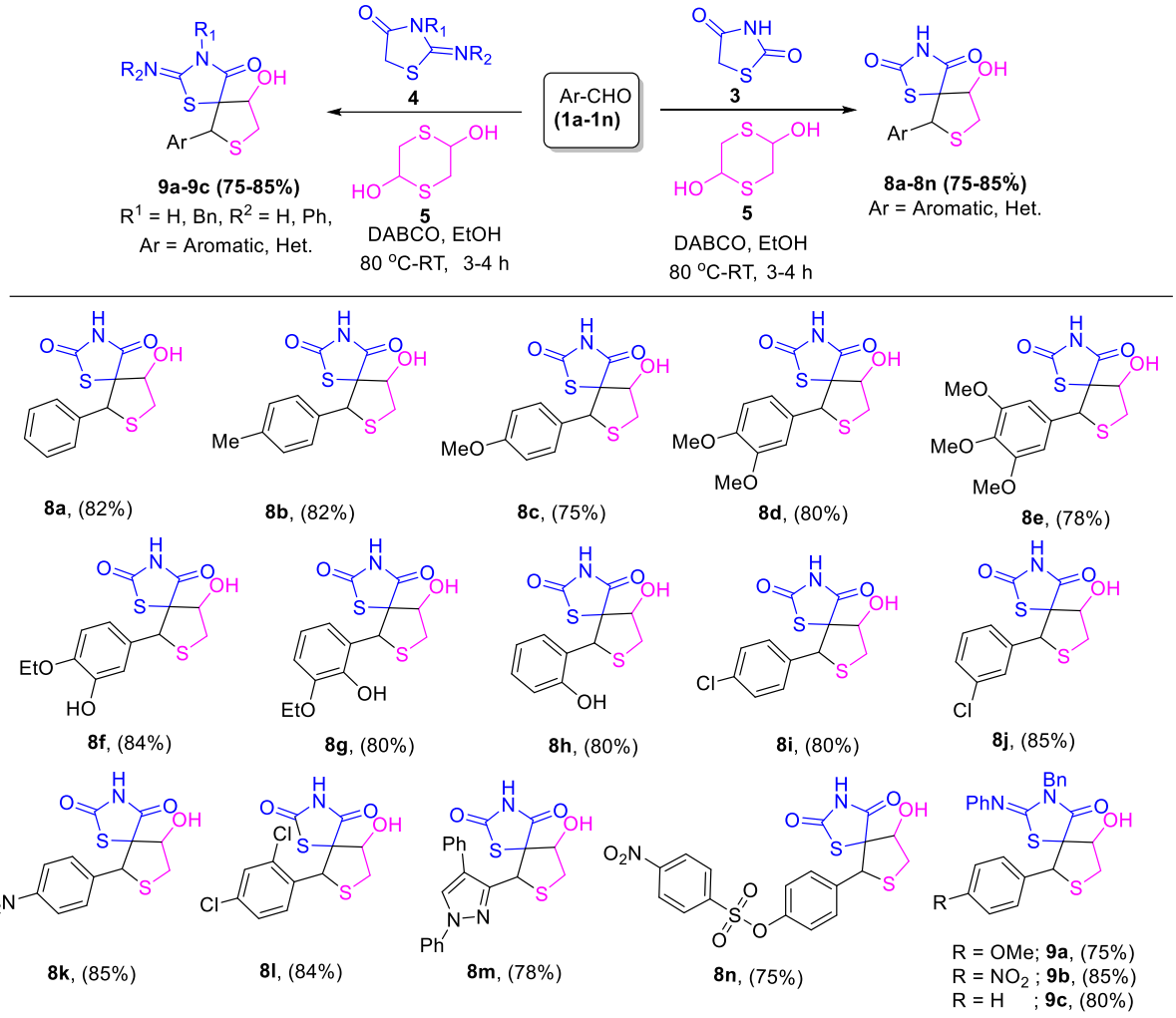
[a]All reactions were carried out using aldehyde (**1a**, 1.0 mmol), thiazolidine-2,4-dione (**2**, 1.0 mmol), and 1,4-dithiane-2,5-diol (**5**, 1.0 mmol), catalyst (10 mol %) in the specified solvent (5.0 mL) at the specified temperature (1st step at 80 °C and 2nd step at RT) and total reaction time 3 h. [b]Isolated yields after purification (for both steps).



[a]Reagents and condition: (**1a**-**1h**) (1.0 mmol) **2** (1.0 mmol), **5** (1.0 mmol) DABCO (20 mol %), EtOH (5 mL) at 80 °C for 1 h then RT up to 2-3 h.

Scheme 2. Synthesis of 2,4-thioxothiazolidinone-thiolane hybrids (**7a**-**7h**) *via* 1,4-Micheal addition followed by intramolecular aldol reaction.

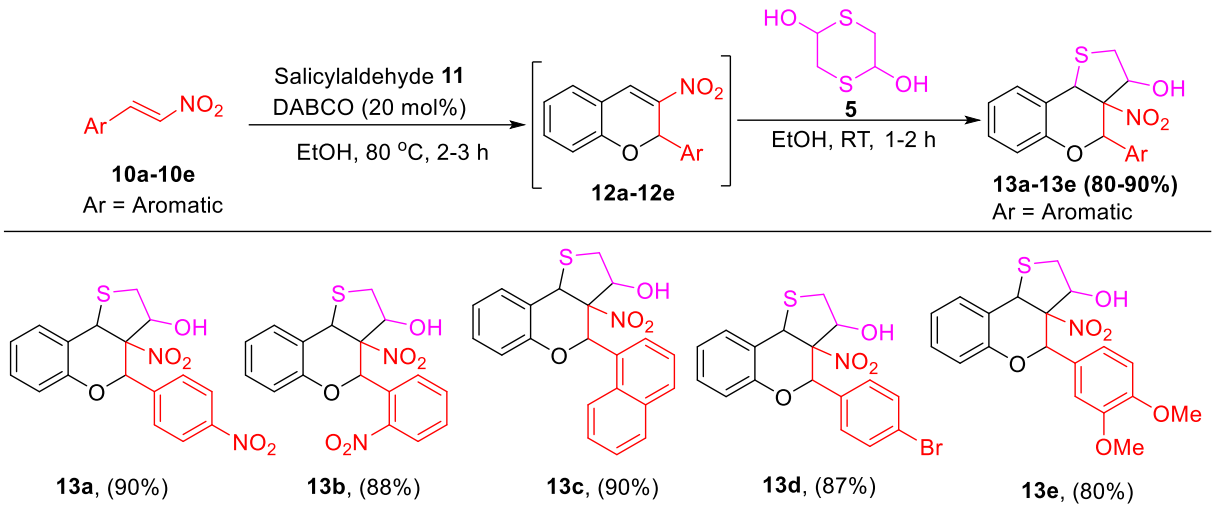
Based on the above results and considering the biological importance of the derivatives of 2,4-thiazolidinedione (**3**) and 2-imino-4-thiazolidinedione (**4**), the synthetic strategy was extended for the synthesis of a new class of thiolane derivatives (**8a**–**8n**)/(**9a**-**9c**) based on (**3**)/ (**4**). Thus, 2,4-thiazolidinedione (**3**)/2-imino-4-thiazolidinedione (**4**) were treated with various aromatic, heteroaromatic aldehydes (**1a**-**1n**) in the presence of DABCO (20 mol %) in EtOH at 80 °C to give the intermediate unsaturated systems (*in situ*), and the intermediates were then treated with 1,4-dithiane-2,5-diol (**5**) at RT to provide the desired products (**8a**–**8n**)/(**9a**-**9c**) with good yields (75–85%) (Scheme 3). All these three reactions proceed *via* sulfa-1,4-Michael addition followed by intramolecular aldol reaction in a one-pot approach. It is noteworthy to mention that the aldehydes containing electron-withdrawing groups (e.g., –NO_2) provide better yields (up to 85%) compared to the substrates containing electron-donating groups.



Reagent and conditions: **3**/**4** (1.0 mmol), **1a**-**1n** (1.0 mmol), 5 (1.0 mmol) DABCO (20 mol %), EtOH 5 mL and stirred at 80 °C for 1 h and RT for 3-4 h.

Scheme 3. Substrate scope of 2,4-thiazolidinediones and 2-imino-4-thiazolidinedione thiolanes (**8a**-**8n** and **9a**-**9c**).

The bicyclic chromenes are important, but limited reports are available in the literature for the bicyclic-fused thiolane derivatives. As an application of dithiane diol (**5**), recently Korotaev and co-workers[55] developed a stereo selective strategy for tetrahydro-*4H*-thieno [*3, 2-c*] chromen-3-ols. To investigate the complexity of the above reaction and substrate scope, various β-nitrostyrenes (**10a-10e**) were treated with salicylaldehyde (**11**) in EtOH at 80 °C for 2-3 h in the presence of DABCO (20 mol %) to give 3-nitro-[*2H*]-chromenes (**12a-12e**) (*in situ*). These 3-nitro-[*2H*]-chromenes (**12a-12e**) were reacted for 1-2 h at room temperature with 1,4-dithiane-2,5-diol (α-mercaptaldehyde) (**5**) to give substituted 3-nitro-[*2H*]-chromene-thiolanes derivatives (**13a-13e**) with good to excellent yields (80-90%). This reaction proceeds *via* 1,4-aza-Michael addition followed by intramolecular Aldol reaction as shown in Scheme 4.



Reagent and condition: **10a**-**10e** (1.0 mmol), **11** (1.0 mmol), 5 (1.0 mmol), DABCO (20 mol %), EtOH 5 mL and stirred at 80 °C for 2-3 h, then at RT for 1-2 h (2nd step).

Scheme 4. Synthesis of 3-nitro-chromene-[*2H*]-thiolane hybrids (**13a**-**13e**).

Proposed reaction mechanism:

Based on the experimental observations and literature reports,[48,49, 56] a mechanism is proposed as shown in Figure 4. The cleavage of 1,4-dithiane-2,5-diol into mercaptaldehyde, Michael addition followed by intramolecular aldol reaction of the mercaptaldehyde with α, β–unsaturated system has been studied well in organic synthesis.[57] The unsaturated system (**I**) (Knoevenagel condensation product) is formed from the reaction of aldehyde (**1**) and 2,4-thiazolidinedione (**2**) in the presence of DABCO which is further reacted with α-mercaptoacetaldehyde *via* sulfa 1,4-Michael addition (**II**) and intramolecular aldol reaction (**III**) to give the expected cyclic spiro-thiophene compound **7a**.

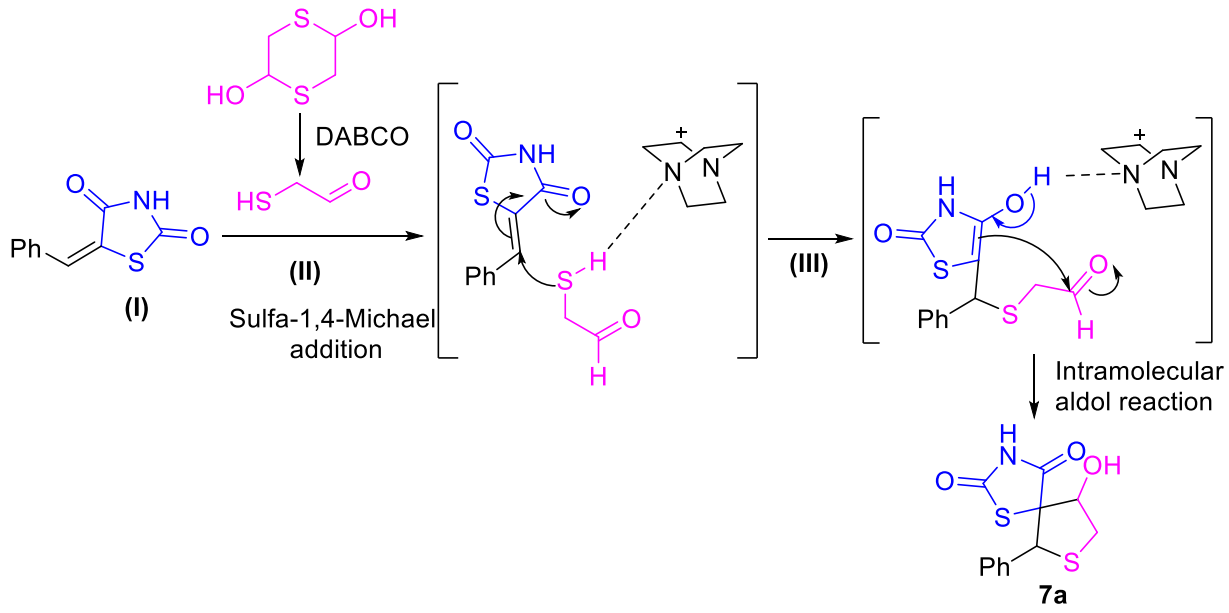


Figure-4. Proposed reaction mechanism of spiro based- 2,4-thioxothiazolidinone-thiolane hybrid **7a**.

Conclusions

In conclusion, we successfully synthesized novel spiro-based 2,4-thioxothiazolidinone, 2,4-thiazolidinedione, substituted 2-imino-4-thiazolidinedione thiolane derivatives using 20 mol % of DABCO as a catalyst with moderate to good yields in one-pot MCR approach. The key steps for the reaction include Knoevenagel condensation followed by 1,4-sulfa-Michael reactions and intramolecular aldol reaction which led to cyclization and formation of a new C-S bond for the construction of thiolane hybrids. Same method was extended for the bicyclic chromene-thiolane hybrids.

Experimental Section

General. All the commercial compounds were bought from Spectrochem, SRL, SD-Fine, and Sigma-Aldrich. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 solvents (reported in δ ppm). The mass spectra were recorded on Shimadzu LCMS-2020 or Agilent 6530 QTOF with a 1290 quaternary UHPLC system. IR spectra were recorded using the Perkin Elmer FT-IR instrument and melting points are recorded using the Stuart melting point apparatus.

General procedure for the synthesis of 2-thioxothiazolidin-4-one-thiolane derivatives (7a-7h). To a solution of aldehydes (**1a**-**1h**) (1.0 mmol) in EtOH (5 mL) was added thioxothiazolidin-4-one (**2**) (1.0 mmol) followed by DABCO (20 mol %). The mixture was heated at 80 ^{o}C for 1 h to form Knoevenagel condensation product (*in situ*) (confirmed on TLC). To this, 1,4-dithiane-2,5-diol (**5**) (1.0 mmol) was added and the mixture was allowed to stir at room temperature for 2 h. After completion of the reaction (on TLC), aq. NH_4Cl solution (5 mL) was added and extracted with EtOAc (2X10mL). The combined organic layers were dried over sodium sulfate. Evaporation of the solvent gave the crude mixture, which was purified by silica gel column chromatography. Elution of the column with hexane-EtOAc mixture gave the desired products (**7a**-**7h**) in moderate to good yields of (75-90%).

General procedure for the synthesis of 2,4-thiazolidine-thiolane derivatives (8a-8n). To a solution of aldehydes (**1a-1n**) (1.0 mmol) in EtOH (5 mL) was added 2,4-thiazolidine (3) (1.0 mmol) followed by DABCO (20 mol %). The mixture was heated at 80 ^{o}C for 1 h to form Knoevenagel condensation product (*in situ*) (confirmed on TLC). To this, 1,4-dithiane-2,5-diol (5) (1.0 mmol) was added and the mixture was allowed to stir at room temperature for 2 h. After completion of the reaction (on TLC), aq. NH_4Cl solution (5 mL) was added and extracted with EtOAc (2X10ml). The combined organic layers were dried over sodium sulfate. Evaporation of the solvent gave the crude mixture, which was purified by silica gel column chromatography. Elution of the column with hexane-EtOAc mixture gave the desired products (**8a-8n**) in moderate to good yields of 75-85%.

General procedure for the synthesis of 2-iminothiazolidin-4-one-thiolane derivatives (9a-9c). To a solution of aldehydes (**1a**-**1c**) (1.0 mmol) in EtOH (5 mL) was added 2-iminothiazolidin-4-one (**4**) (1.0 mmol) followed by DABCO (20 mol %). The mixture was heated at 80 ^{o}C for 1 h to form Knoevenagel condensation product (*in situ*) (confirmed on TLC). To this, 1,4-dithiane-2,5-diol (**5**) (1.0 mmol) was added and the mixture was allowed to stir at room temperature for 2 h. After completion of the reaction (on TLC), aq. NH_4Cl solution (5 mL) was added and extracted with EtOAc (2X10mL). The combined organic layers were dried over sodium sulfate. Evaporation of the solvent gave the crude mixture which was purified by silica gel column chromatography. Elution of the column with hexane-EtOAc mixture gave the desired products (**9a**-**9c**) in moderate to good yields of 75-85%.

General procedures for the synthesis of spiro- 3-nitro-[2*H*]-chromene-thiolane derivatives (13a-13e). To a solution of β-nitro-styrenes (**10a**-**10e**) (1.0 mmol) in EtOH (5 mL) was added 2-hydroxy benzaldehyde (**11**) (1.0 mmol) and DABCO (20 mol %). The mixture was heated at 80 °C for 2-3 h to give 3-nitro 2-phenyl-[*2H*]-chromenes (**12a**-**12e**). To this, 1,4-dithiane-2,5-diol (**5**) (1.0 mmol) was added, and stirring continued at RT for 1-2 h till the completion of the reaction (confirmed by TLC). After completion of the reaction, the mixture was quenched with aq. NH_4Cl (10 mL) and extracted with EtOAc (2X10mL). The combined organic layers were washed with brine, and water and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography. Elution of the column with *n*-hexane-EtOAc mixture gave the desired product **13a**-**13e** in good to excellent yields (80-90%).

9-Hydroxy-6-(4-methoxyphenyl)-4-thioxo-1,7-dithia-3-azaspiro[4.4]nonan-2-one (7a). Pale yellow solid, mp 156–157 °C, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 2.59 (t, *J* 10.4 Hz, 1H) 2.89 (s, 1H), 3.24–3.19 (m, 1H), 3.79 (s, 3H), 4.87 (dd, *J* 10.0, 7.4 Hz, 1H), 5.13 (s, 1H), 6.82 (t, *J* 8.8 Hz, 2H), 7.32 (d, *J* 8.8 Hz, 2H), 12.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 35.5, 45.1, 57.6, 76.1, 85.1, 118.9 ,131.4, 136.3, 146.4, 178.4, 199.2; HRMS (ESI, *m/z*): Calcd. for $C_{13}H_{13}NO_3S_3$ 327.0058, found 328.0134 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 832, 1026, 1223, 1510, 1603, 1715, 2927, 3002, 3202, 3410.

9-Hydroxy-2-thioxo-6-(*p*-tolyl)-1,7-dithia-3-azaspiro[4.4] nonan-4-one (7b). Colorless sticky solid, mp 180–181 °C, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.78 (t, *J* 10.4 Hz, 1H), 3.27 (dd, *J* 10.8, 7.6 Hz, 1H), 4.95–4.90 (m, 1H), 5.13 (s, 1H), 7.05 (d, *J* 8.0 Hz, 2H),7.20 (d, *J* 8.4 Hz, 2H), 9.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1,34.0, 52.1, 79.7, 82.6, 128.9, 129.2,130.2, 139.1, 175.7, 198.0; HRMS (ESI, *m/z*): Calcd. for $C_{13}H_{13}NO_2S_3$ 311.0181, found 312.0173 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 821, 1022, 1210, 1520, 1602, 1710, 2956, 3402, 3520.

6-(4-Ethoxy-3-hydroxyphenyl)-9-hydroxy-2-thioxo-1,7-dithia-3-azaspiro[4.4] nonan-4-one (7c). Pale yellow sticky solid, mp 160–161 °C, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, *J* 6.8 Hz, 1H) ,2.75 (t, *J* 10.0 Hz, 1H), 3.09 (d, *J* 12.0 Hz, 1H),3.30–3.25 (m, 1H), 4.03 (q , *J* 3.6 Hz, 2H), 4.93–4.87 (m, 1H), 5.09 (s, 1H), 5.66 (s, 1H),6.78 (s, 2H),6.92 (s, 1H),9.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 13.5, 41.0, 48.5, 55.2, 65.6, 80.0, 117.2, 128.7, 130.1, 133.5, 138.8, 158.8, 180.1, 189.7; HRMS (ESI, *m/z*): Calcd. for $C_{14}H_{15}NO_4S_3$ 357.0236, found 358.0247 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 800, 1105, 1438, 1515, 1700, 2854, 2932, 3070,3506, 4714.

6-(3-Ethoxy-2-hydroxyphenyl)-9-hydroxy-2-thioxo-1,7-dithia-3-azaspiro[4.4]nonan-4-one (7d). Yellow solid, mp 135–136 °C, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ1.34 (t, *J* 6.4 Hz, 3H), 2.76 (t, *J* 10.0 Hz, 1H), 3.12 (t, *J* 8.8 Hz, 1H), 3.99 (d, *J* 6.0 Hz, 2H), 4.76 (t, *J* 8.4 Hz, 1H), 4.99 (s, 1H), 6.68 (s, 2H), 6.86 (s, 1H), 12.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 14.7, 34.0, 52.3, 64.7, 79.4, 82.9, 112.5, 114.3, 122.1, 124.9, 145.5, 146.4, 175.7, 197.8; HRMS (ESI, *m/z*): Calcd. for $C_{14}H_{15}NO_4S_3$ 357.0236, found 358.0252; IR (KBr, thin film, cm^{-1}): ν_{max} 756,1077,1278, 1439, 1515, 1632, 3313, 3490.

6-(4-Bromophenyl)-9-hydroxy-2-thioxo-1,7-dithia-3-azaspiro[4.4] nonan-4-one (7e). Yellow solid, mp 179–180 °C, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 2.86 (t, *J* 10.4 Hz, 1H), 3.21 (t, *J* 9.6 Hz, 1H), 4.90–4.80 (m,1H), 5.13 (s, 1H), 6.36 (s, 1H), 7.29 (d, *J* 7.6 Hz, 2H), 7.47 (d, *J* 8.0 Hz, 2H), 12.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 26.8, 29.0, 52.7, 53.2, 126.6, 132.6, 133.8, 135.0, 176.8, 183.4; HRMS (ESI, *m/z*): Calcd. for $C_{12}H_{10}BrNO_2S_3$ 375.9203, found 377.9112; IR (KBr, thin film, cm^{-1}): ν_{max} 580, 1220, 1420, 1540, 1715, 2985, 3065, 3455.

9-Hydroxy-6-(2-nitrophenyl)-2-thioxo-1,7-dithia-3-azaspiro[4.4] nonan-4-one (7f). Colorless sticky solid, mp 178–179 °C, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ, 2.88 (t, *J* 10.4 Hz, 1H), 3.19 (dd, *J* 10.8, 7.2 Hz, 1H) 3.83 (s, 1H), 4.85 (dd, *J* 10.2, 7.2 Hz, 1H), 5.20 (s, 1H), 7.54–7.49 (m, 2H), 8.08 (d, *J* 7.2 Hz, 2H), 12.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ, 34.0, 51.5, 79.6, 81.7, 123.3, 130.3, 143.3, 147.8, 176.9, 200.7;

HRMS (ESI, *m/z*): Calcd. for $C_{12}H_{10}N_2O_4S_3$ 341.9875, found 342.9860 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 865, 1012, 1540, 1620, 1705, 2986, 3430.

9-Hydroxy-6-(3-nitrophenyl)-2-thioxo-1,7-dithia-3-azaspiro[4.4] nonan-4-one (7g). Colorless solid, mp 140–141 °C, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 2.90 (t, *J* 10.4 Hz, 1H), 3.21(t, *J* 9.2 Hz, 1H), 4.86 (t, *J* 8.4 Hz, 1H), 5.22 (s, 1H), 6.27 (s, 1H), 7.49 (t, *J* 7.6 Hz, 1H), 7.70 (d, *J* 7.2 Hz, 1H), 8.11 (d, *J* 7.6 Hz, 1H), 8.19 (s, 1H), 12.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 32.1, 49.4, 77.4, 79.8, 121.7, 122.0,127.5, 133.53 , 135.2, 145.9, 174.9, 198.6; HRMS (ESI, *m/z*): Calcd. For $C_{14}H_{15}N_2O_4S3$ 341.9875, found 342.9880 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 797, 1227, 1077, 1462, 1524, 1711, 2850, 2920, 3110, 3408.

6-(1,4-Diphenyl-1H-pyrazol-3-yl)-9-hydroxy-4-thioxo-1,7-dithia-3-azaspiro[4.4] nonan-2-one (7h). Colorless solid, mp 201–202 °C, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 2.88 (t, *J* 10.4 Hz, 1H), 3.24–3.19 (m, 1H), 4.80 (dd, *J* 9.6, 7.4 Hz, 1H), 5.24 (s, 1H), 7.33 (t, *J* 7.6 Hz, 1H), 7.50–7.43 (m, 5H), 7.61–7.57 (m, 2H), 7.76–7.74 (m, 2H), 7.79 (s, 1H), 8.48 (s, 1H),12.88 (s, 1H),; ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 31.5, 44.4, 80.7, 80.9, 121.0, 128.8, 130.3, 130.5, 130.7, 131.4, 131.5, 134.3, 141.6, 154.7, 172.7, 176.6, 117.4; HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{17}N_3O_2S_3$ 439.0556, found 440.0562 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 758, 1073, 1198, 1597, 1719, 2925, 3101, 3230, 3397.

9-Hydroxy-6-phenyl-1,7-dithia-3-azaspiro[4.4] nonane-2,4-dione (8a). Colorless solid, mp 205–206 °C, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (t, *J* 10.4 Hz, 1H), 3.28–3.23 (m, 1H), 4.92–4.88 (m, 1H), 5.14 (s, 1H), 7.27–7.19 (m, 5H), 8.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8, 51.5, 79.3, 82.0, 128.7, 130.5, 130.8, 132.1, 135.0, 174.0; HRMS (ESI, *m/z*): Calcd. for $C_{12}H_{11}NO_3S_2$ 281.0253, found 282.0250 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 815,1120, 1220, 1563, 1710, 2975, 3052, 3402.

9-Hydroxy-6-(p-tolyl)-1,7-dithia-3-azaspiro[4.4] nonane-2,4-dione (8b). Colorless solid, mp 196–197 °C, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 2.25 (s, 3H), 2.79 (t, *J* 10.4 Hz, 1H), 3.15 (dd, *J* 10.4, 7.2 Hz, 1H), 4.86–4.80 (m, 1H), 5.13 (s, 1H), 5.55 (s, 1H), 7.02 (d, *J* 8.0 Hz, 2H), 7.27–7.20 (m, 2H), 11.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 21.1, 33.7, 52.0, 79.0, 79.7, 128.8, 129.1, 131.3, 138.3, 170.8, 175.3; HRMS (ESI, *m/z*): Calcd. for $C_{13}H_{13}NO_3S_2$ 295.0410, found 296.0407 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 835,1005, 1210, 1520, 1595, 2966, 3056, 3480.

9-Hydroxy-6-(4-methoxyphenyl)-1,7-dithia-3-azaspiro[4.4]nonane-2,4-dione (8c). Pale yellow solid, mp 185–186 °C, 75% yield. ^{1}H NMR (400 MHz, CDCl3) δ2.82 (t, *J* 10.0 Hz, 1H), 3.39–3.34 (m, 1H), 3.82 (s, 3H), 4.99 (dd, *J* 16.6, 8.4 Hz, 1H), 5.25 (s, 1H), 5.51 (s, 1H), 6.87 (d, *J* 8.4 Hz, 2H), 7.35 (d, *J* 8.0 Hz, 1H), 7.41 (d, *J* 8.0 Hz, 1H), 8.12 (s, 1H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.0, 47.8, 61.0, 71.8, 82.7, 117.2, 124.1, 132.2, 160.2, 168.3, 178.8; HRMS (ESI, *m/z*): Calcd. For $C_{13}H_{13}NO_4S_2$ 311.0359, found 312.0350 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 841, 1177, 1502, 1609, 1687, 2790, 2929, 3469.

6-(3,4-Dimethoxyphenyl)-9-hydroxy-1,7-dithia-3-azaspiro[4.4] nonane-2,4-dione (8d). Pale yellow solid, 80% yield, mp 176–177 °C. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ2.60 (s, 1H) , 2.86 (t, *J* 10.4 Hz, 1H), 3.21 (t, *J* 10.4, 1H), 3.86 (s, 6H), 4.89 (dd, *J* 10.0, 7.4 Hz, 1H), 5.18 (s, 1H), 6.80 (d, *J* 8.0 Hz, 1H), 6.93 (d, *J* 8.0 Hz, 1H), 6.97 (s, 1H), 11.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 33.7, 52.1, 55.8, 55.8, 78.7, 79.8, 110.7, 112.5, 121.7, 126.8, 148.2, 149.0, 170.9, 175.5; HRMS (ESI, *m/z*): Calcd. For $C_{14}H_{15}NO_5S_2$ 341.0392, found 341.0390; IR (KBr, thin film, cm-1): vmax 1022, 1254, 1267, 1514, 1696, 2763, 2934, 3069, 3211, 3417.

6-(3,4,5-Trimethoxyphenyl)-9-hydroxy-1,7-dithia-3-azaspiro[4.4] nonane-2,4-dione (8e). Colorless solid, mp 192–193 °C, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (t, *J* 10.4 Hz, 1H), 3.29 (dd, *J* 10.6, 7.2 Hz, 1H), 3.80 (s, 6H), 3.80 (s, 3H), 4.96–4.94 (m, 1H), 5.14 (s, 1H), 6.69–6.61 (m, 2H), 10.04 (s, 1H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6, 33.8, 52.4, 56.3, 60.8, 79.5, 82.5, 106.3, 129.1, 131.07, 132.4, 138.3, 152.9, 176.2, 198.3,; HRMS (ESI, *m/z*): Calcd. for $C_{14}H_{15}NO_5S_2$ 371.0570, found 372.0560 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 860, 1011, 1198, 1511, 1595, 1720, 2985, 3480.

6-(4-Ethoxy-3-hydroxyphenyl)-9-hydroxy-1,7-dithia-3-azaspiro[4.4]nonane-2,4-dione (8f). Pale brown solid, mp 155–156 °C, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 1.42 (t, *J* 6.8 Hz, 3H), 2.81 (t, *J* 10.0 Hz, 1H), 3.08 (d, *J* 11.2 Hz, 1H), 3.18 (t, *J* 9.6 Hz, 1H), 4.07 (d, *J* 6.4 Hz, 2H), 4.84 (dd, *J* 17.0, 8.6 Hz, 1H), 5.11 (s, 1H), 6.76 (s, 2H), 6.96 (d, *J* 14.8 Hz, 1H), 11.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 14.9, 33.7, 37.0, 52.2, 64.3, 80.0, 114.2, 115.0, 121.9, 125.3, 146.1, 147.1, 170.9, 175.5; HRMS (ESI, *m/z*): Calcd. for $C_{14}H_{15}NO_5S_2$ 341.0464, found 342.0454 (M+1); IR (KBr, thin film, cm-1): vmax 820,1173, 1518, 1698, 1734, 2753, 2937, 3129, 3403, 3794.

6-(3-Ethoxy-2-hydroxyphenyl)-9-hydroxy-1,7-dithia-3-azaspiro[4.4] nonane-2,4-dione (8g). Yellow sticky solid, mp 181–182 °C, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* 6.8 Hz, 3H), 2.76 (t, *J* 10.4 Hz, 1H), 3.26 (dd, *J* 10.8, 7.6 Hz, 1H), 4.03 (q, *J* 3.2 Hz, 2H), 4.93–4.88 (m, 1H), 5.08 (s, 1H), 5.71 (s, 1H), 6.77 (s, 2H), 6.88 (s, 1H), 9.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 15.8, 30.5, 34.7, 53.3, 65.4, 80.9, 115.0, 115.8, 123.0, 126.4, 147.0, 147.9, 171.9, 176.5,; HRMS (ESI, *m/z*): Calcd. for $C_{14}H_{15}NO_5S_2$ 341.0392, found 342.0460 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 860,1120, 1240, 1590, 1702, 2956, 3086, 3429, 3520.

9-Hydroxy-6-(2-hydroxyphenyl)-1,7-dithia-3-azaspiro[4.4] nonane-2,4-dione (8h). Colorless sticky solid, mp 192–193 °C, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ2.75 (t, *J* 10.0 Hz, 1H), 3.12 (d, *J* 7.6 Hz, 1H), 3.99 (d, *J* 6.8 Hz, 1H), 4.83–4.76 (dd, *J* 10.2, 7.6 Hz, 1H), 5.04 (s, 1H), 6.66 (d, *J* 8.4 Hz, 2H), 7.12 (d, *J* 8.4 Hz, 1H), 7.60 (s, 1H), 11.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 33.0, 50.3, 78.0, 78.1, 122.6, 123.2, 128.4, 134.6, 136.3, 146.9, 169.1, 174.1,; HRMS (ESI, *m/z*): Calcd. for $C_{12}H_{11}NO_4S_2$ 297.0202, found 298.0202 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 834, 1023, 1513, 1610, 1693, 2852, 2924, 3380.

6-(4-Chlorophenyl)-9-hydroxy-1,7-dithia-3-azaspiro[4.4] nonane-2,4-dione (8i). Colorless solid, 80% yield, mp 134–135 °C, ^{1}H NMR (400 MHz, CDCl3) δ 2.77 (t, *J* 10.4 Hz, 1H), 3.03 (d, *J* 12.4 Hz, 1H), 3.31–3.26 (m, 1H), 4.91 (dd, *J* 15.6, 7.6 Hz, 1H), 5.15 (s, 1H), 7.19 (s, 2H), 7.39 (d, *J* 8.4 Hz, 2H), 8.55 (s, 1H); ^{13}C NMR (100 MHz, CDC_3+DMSO-d_6) δ 33.9, 51.6, 79.5, 82.1, 128.3, 130.6, 133.0, 134.3, 177.1, 201.1; HRMS (ESI, *m/z*): Calcd. for $C_{12}H_{10}ClNO_3S_2$ 314.9863, found 315.9803 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 795, 1064, 1588, 1774, 2778, 2951, 3064, 3447, 3401.

6-(3-Chlorophenyl)-9-hydroxy-1,7-dithia-3-azaspiro[4.4] nonane-2,4-dione (8j). Yellow solid, mp 169–170 °C, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (d, *J* 12.4 Hz, 1H), 3.31–3.26 (m, 1H), 4.90 (dd, *J* 10.0, 2.4 Hz, 1H), 5.15 (s, 1H), 7.29 – 7.19 (m, 2H), 7.39 (d, *J* 8.4 Hz, 2H), 8.45 (s, 1H), 2.77 (t, *J* 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 38.5, 56.2, 84.1, 86.9, 127.1, 135.8, 136.0, 136.2, 138.7, 175.3, 180.0; HRMS (ESI, *m/z*): Calcd. for $C_{12}H_{10}NO_3S_2$ 314.9791, found 315.9855 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 835, 1176, 1253, 1608, 1709, 2924, 3077, 3389, 3515.

9-Hydroxy-6-(4-nitrophenyl)-1,7-dithia-3-azaspiro[4.4] nonane-2,4-dione (8k). Colorless solid, mp 202–203 °C, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 2.76 (t, *J* 10.4 Hz, 1H), 2.99 (dd, *J* 11.8, 2.4 Hz, 1H), 3.08 (dd, *J* 10.6, 7.2 Hz, 1H), 4.78–4.72 (m, 1H), 5.15 (s, 1H), 7.51–7.42 (m, 2H), 7.98 (d, *J* 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 29.5, 33.9, 51.4, 79.1, 123.2, 130.4, 142.4, 147.8, 170.0, 175.0; HRMS (ESI, *m/z*): Calcd. for $C_{12}H_{10}N_2O_5S_2$ 326.0104, found 327.0100 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 840, 1190, 1540, 1610, 2985, 3068, 3390.

6-(2,4-Dichlorophenyl)-9-hydroxy-1,7-dithia-3-azaspiro[4.4] nonane-2,4-dione (8l). Colorless solid, mp 171–172 °C, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ2.85 (t, *J* 10.4 Hz, 3H), 3.20 (t, *J* 7.2 Hz, 1H), 4.83 (d, *J* 8.4 Hz, 1H), 4.87 (d, *J* 10.4 Hz, 1H), 5.16 (s, 1H), 7.29 (s, 1H), 7.42 (d, *J* 8.4 Hz, 2H),11.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 27.0, 44.3, 72.4, 74.7, 116.6, 117.0, 122.5, 128.4, 130.1, 140.8, 169.9, 193.6; HRMS (ESI, *m/z*): Calcd. For $C_{12}H_9Cl_2NO_3S_2$ 348.9474, found 349.9412 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 730, 795, 1063, 158, 1558, 1417, 2778, 2951, 3064, 3400, 3446.

6-(1,4-Diphenyl-1H-pyrazol-3-yl)-9-hydroxy-1,7-dithia-3-azaspiro[4.4] nonane-2,4-dione (8m). Yellow solid, mp 195–196 °C, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ2.80 (t, *J* 10.0 Hz, 1H), 3.21-3.17 (m, 1H), 4.75 (dd, *J* 9.6, 7.6 Hz, 1H),5.28 (s, 1H), 7.33 (t, *J* 7.4 Hz, 1H), 7.60–7.42 (m, 7H), 7.84 (d, *J* 8.0 Hz, 2H), 8.61 (s, 1H), 11.93 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$) δ 55.6, 59.3, 72.39, 82.1, 116.7, 121.7, 127.4, 129.6, 131.7, 132.1, 133.0, 134.4, 134.8, 145.0, 149.0, 152.7, 161.7; HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{17}N_3O_3S_2NH$ 437.1050, found 441.0702; IR (KBr, thin film, cm^{-1}): ν_{max} 758, 1073, 1198, 1597, 1719, 2925, 3101, 3230, 3397.

4-(9-Hydroxy-2,4-dioxo-1,7-dithia-3-azaspiro[4.4]nonan-6-yl)phenyl4-nitrobenzene sulfonate (8n). Light brown solid, mp 209–210 °C, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ2.79 (t, *J* 10.4 Hz, 1H), 3.18 (dd, *J* 10.2, 7.2 Hz, 1H), 4.23 (t, *J* 6.4 Hz, 1H), 4.85–4.81 (m, 1H), 5.14 (s, 1H), 6.96 (d, *J* 7.6 Hz, 2H), 7.34 (d, *J* 8.4 Hz, 2H), 7.96 (d, *J* 8.0 Hz, 2H), 8.39 (d, *J* 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 81.1, 31.035.4, 53.1, 123.4, 126.3, 131.6, 132.4, 136.1, 141.4, 150.5, 152.7, 172.0, 176.7; HRMS (ESI, *m/z*): Calcd. for $C_{18}H_{14}N_2O_8S_3$ 481.9912, found 482.9943 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 765, 1056, 1283, 1375, 1432, 1540, 1662, 3322, 3485.

2-(Benzylimino)-9-hydroxy-6-(4-methoxyphenyl)-3-phenyl-1,7-dithia-3-azaspiro[4.4] nonan-4-one (9a). Pale yellow sticky solid, mp 158–159 °C, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ2.66 (t, *J* 10.4 Hz, 1H), 3.29–3.25 (m, 1H), 3.79 (s, 1H), 4.74 (dd, *J* 14.2, 6.8 Hz, 1H), 4.86 (d, *J* 14.4 Hz, 1H), 4.97 (d, *J* 14.0 Hz, 1H), 5.18 (s, 1H), 6.67 (d, *J* 8.4 Hz, 2H), 6.74 (d, *J* 7.6 Hz, 2H), 7.20–7.12 (m, 5H), 7.26–7.25 (m, 3H), 7.32 (t, *J* 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.2, 46.4, 52.2, 55.8, 75.6, 78.3, 120.7, 123.6, 124.5, 125.0, 127.9, 128.4, 128.5, 128.5, 129.1, 129.3, 129.3, 147.6, 147.8, 172.3; HRMS (ESI, *m/z*): Calcd. for $C_{26}H_{24}N_2O_3S_2$ 476.1228, found 477.1296 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 750,1034, 1384, 1637, 2850, 2931, 3412,.

2-(Benzylimino)-9-hydroxy-6-(4-nitrophenyl)-3-phenyl-1,7-dithia-3-azaspiro[4.4]nonan-4-one (9b). Colorless solid, mp 173–174 °C, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 2.73 (t, *J* 9.6 Hz, 1H), 3.13 (t, *J* 8.4 Hz, 1H), 4.01 (d, *J* 6.0 Hz, 1H), 4.79 (d, *J* 14.8 Hz, 1H), 4.93–4.87 (m, 2H), 5.13 (s, 1H), 6.66 (d, *J* 7.6 Hz, 2H), 7.02 (t, *J* 7.6 Hz, 1H), 7.11 (d, *J* 6.8 Hz, 3H), 7.23–7.17 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.2, 47.4, 54.0, 77.3, 79.6, 121.9, 125.8, 128.6, 129.0, 129.1, 129.2, 129.4, 129.6, 130.2, 130.5, 134.7, 136.3, 148.6, 173.6,; HRMS (ESI, *m/z*): Calcd. for $C_{25}H_{21}N_3O_4S_2$ 491.0973, found 492.0952 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 675, 1162, 1520, 1384, 1634, 3346.

3-Benzyl-9-hydroxy-6-phenyl-2-(phenylimino)-1,7-dithia-3-azaspiro[4.4]nonan-4-one (9c). Light brown solid, mp 201–202 °C, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ2.62 (t, *J* 10.4 Hz, 1H), 3.22 (dd, *J* 10.6, 7.2 Hz, 1H), 4.81 (d, *J* 15.6 Hz, 1H), 4.91 (d, *J* 2.8 Hz, 1H), 4.96–4.93 (m, 1H), 5.18 (s, 1H), 6.64 (d, *J* 7.2 Hz, 2H), 7.14–7.05 (m, 6H), 7.24–7.17 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6) δ 30.0, 34.1, 46.3, 53.3,76.7, 121.5, 125.0, 127.8, 128.1, 128.5, 128.8, 129.0, 129.6, 129.8, 134.9, 136.1, 148.4, 152.5, 173.4; HRMS (ESI, *m/z*): Calcd. for $C_{25}H_{22}N_2O_2S_2$ 446.1195, found 447.0905 (M+1); IR (KBr, thin film, cm^{-1}): ν_{max} 652, 1122, 1322, 1542, 1642, 3456,.

3-Nitro-4-(4-nitrophenyl)-3,3a,4,9b-tetrahydro-*2H*-thieno[*3,2-c*]chromen-3-ol (13a). Colorless solid, mp 177–178 °C, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (d, *J* 12.0 Hz, 1H) , 3.53 (d, *J* 10.8 Hz, 1H), 4.75 (s, 1H), 5.36 (s, 1H), 5.56 (s, 1H), 7.02 (d, *J* 8.4 Hz, 1H),7.08 (t, *J* 7.2 Hz, 1H), 7.29 (d, *J* 7.6 Hz, 1H), 7.36 (d, *J* 6.4 Hz, 2H), 7.49 (d, *J* 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.50, 42.97, 75.87, 76.46, 98.56, 117.39, 121.63, 122.58, 127.14, 128.71, 128.81, 129.26, 129.88, 133.66, 152.38,; HRMS (ESI, *m/z*): Calcd. for $C_{18}H_{18}N_2O_6SNH4+$ 392.0911, found 392.0630; IR (KBr, thin film, cm^{-1}): ν_{max} 757, 810, 1111, 1239, 1259, 1554, 1610, 2937,3062, 3425.

3-Nitro-4-(2-nitrophenyl)-3,3a,4,9b-tetrahydro-*2H*-thieno[*3,2-c*]chromen-3-ol (13b). Pale yellow solid, mp 183–184 °C, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (s, 1H), 3.10 (d, *J* 12.0 Hz, 1H), 3.49 (dd, *J* 12.0, 4.0 Hz, 1H), 4.72 (s, 1H), 5.32 (s, 1H), 5.53 (s, 1H), 6.98 (d, *J* 8.4 Hz, 1H), 7.04 (t, *J* 7.6 Hz, 1H), 7.23 (d, *J* 4.4 Hz, 1H), 7.32

(d, *J* 6.0 Hz, 2H), 7.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6+$CDCl_3$) δ 42.77, 46.86, 70.59, 75.55, 114.60, 116.34, 118.53, 121.87, 125.22, 128.23, 128.93, 129.05, 130.15, 130.71, 135.74, 140.60, 157.12; HRMS (ESI, *m/z*): Calcd. for $C_{17}H_{15}N_2O_6S^+$ 375.0645, found 375.0640; IR (KBr, thin film, cm^{-1}): ν_{max} 757, 810, 1111, 1239,1259, 1554, 1610, 2937, 3062, 3425.

4-(Naphthalen-1-yl)-3a-nitro-3,3a,4,9b-tetrahydro-*2H*-thieno[*3,2-c*]chromen-3-ol (13c). Yellow solid, mp 183–184 °C, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (dd, *J* 12.4, 2.4 Hz, 1H), 3.56 (dd, *J* 12.4, 5.2 Hz, 1H), 4.12 (q, *J* 7.2 Hz, 1H), 4.49 (s, 1H), 5.42 (s, 1H), 6.97 (d, *J* 8.0 Hz, 1H), 7.08–7.04 (m, 1H), 7.20–7.28 (m, 1H), 7.23–7.21 (m, 1H), 7.56–7.50 (m, 4H), 7.95 (d, *J* 7.2 Hz, 2H), 8.09 (d, *J* 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.77, 44.26, 60.47, 76.20, 99.35, 117.51, 121.73, 122.61, 125.20, 126.01, 126.68, 126.96, 128.85, 129.06, 129.17, 129.24, 129.53, 130.41, 131.30, 133.74, 152.59; HRMS (ESI, *m/z*): Calcd. for $C_{21}H_{18}NO_4S^+$ 380.0951, found 380.0940; IR (KBr, thin film, cm^{-1}): ν_{max} 783, 1170, 1230, 1547, 1585, 2924, 3046, 3429.

4-(4-Bromophenyl)-3a-nitro-3,3a,4,9b-tetrahydro-*2H*-thieno[*3,2-c*]chromen-3-ol (13d). Colorless solid, mp 186–187 °C, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (dd, *J* 12.2, 1.6 Hz, 1H), 3.45 (dd, *J* 12.2, 4.4 Hz, 1H), 4.69 (s, 1H), 5.32 (s, 1H), 5.50 (s, 1H), 6.97–6.95 (m, 1H), 7.07–7.03 (m, 1H), 7.20 (d, J 8.4 Hz, 2H), 7.24–7.22 (m, 2H), 7.58 (d, *J* 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.47, 42.90, 75.35, 76.42, 98.42, 117.36, 121.47, 122.77, 124.09, 128.76, 128.89, 129.28, 131.89, 132.73, 152.16; HRMS (ESI, *m/z*): Calcd. for $C_{17}H_{16}BrNO_4S^+$ 408.9978, found 408.9970; IR (KBr, thin film, cm^{-1}): ν_{max} 768, 1212, 1264, 1545, 1654, 2957,3414.

4-(3,4-Dimethoxyphenyl)-3a-nitro-3,3a,4,9b-tetrahydro-*2H*-thieno[*3,2-c*]chromen-3-ol (13e). Pale yellow solid, mp 155–156 °C, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 2.93 (d, *J* 11.6 Hz, 1H), 3.72 (s, 3H), 3.46 (dd, *J* 12.0, 3.6 Hz, 1H), 3.77 (s, 3H), 4.47 (d, *J* 2.8 Hz, 1H), 5.26 (s, 1H), 5.45 (s, 1H), 6.76 (t, *J* 6.8 Hz, 2H), 6.88 (d, *J* 8.4 Hz, 3H), 7.22 (d, *J* 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.63, 44.00, 56.15, 56.70, 76.47, 76.76, 99.05, 111.75, 114.43, 121.65, 122.64, 122.93, 124.07, 126.99, 129.57, 143.03, 143.37, 149.08, 161.06,; Mass (ESI, *m/z*): Calcd. for $C_{19}H_{20}NO_6S^+$ 390.1006, found 390.1004; IR (KBr, thin film, cm^{-1}): ν_{max} 766, 1024, 1226, 1257, 1550, 1664, 2937, 3423.

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Supplementary Material

Copies of ^{1}H, ^{13}C NMR and mass spectra of all the compounds are given in the Supplementary Material file associated with this manuscript.

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