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Reactions of 1,2-diaza-1,3-dienes with thiol derivatives: a versatile construction of nitrogen/sulfur containing heterocycles

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ABSTRACT

The synthesis of substituted 2,3-dihydro-1,4-thiazines, fused cycloalkyl-1,4-thiazines, 1,4-benzothiazines and fused cycloalkyl-1,4-benzothiazines by 1,4-addition of 1,2-aminothiols to 1,2-diaza-1,3-dienes bearing carboxylate, carboxamide, or phosphorylated groups and subsequent internal heterocyclization is described. The reaction of carboxylated 1,2-diaza-1,3-butadienes with 2-(butylamino)ethanethiol affords 1,4-thiazinan-3-ones. The solid-phase reaction of polymer-bound 1,2-diaza-1,3-butadienes with 1,2-aminothiols produces 2,3-dihydro-1,4-thiazines and 1,4-benzothiazines.

1. Introduction

Nitrogen-containing heterocycles are undoubtedly one of the most important targets in organic chemistry. They are widely distributed in natural products and in pharmaceutical agents, and numerous studies for their chemistry and synthesis have been reported.[1] Consequently new reactions, in which nitrogen-containing heterocycles can be prepared in a chemo- and stereoselective way, will be broadly applicable for endeavours in natural product synthesis and medicinal chemistry. The 1,4-thiazine ring system is important in organic chemistry because it constitutes the skeleton of natural products such as the two cytotoxic terpene quinones, conicaquinones A and B,[2a] xanthiazone[2b] and xanthisidе,[2c] and it is known to play an important role in pigments and dyestuffs.[3] In addition, 1,4-thiazine derivatives also exhibit potential biological activities. Among these, 1,4-thiazine-3-carboxylic acid derivatives are well known for their antibacterial activity,[4a] aroyldihydro-1,4-thiazines are effective antiinflammatories,[4b] and some bicyclic thiazines are attracting the increasing interest in medicinal chemistry due to their hepatoprotective,[4c] calcium antagonistic,[4d] vasopressin receptor antagonistic[4e] and anticancer activities.[4f,g] Similarly, there is a wide precedence documenting the potential of their benzo derivatives, 1,4-benzothiazines and their analogues, for biological and therapeutic activity. For example, these compounds were reported as calcium channel blockers,[5a–c] Na/H exchange inhibitors,[5d] antifungal,[5e,f] antibacterial,[5f] antimicrobial[5g] and antihypertensive[5h,i] agents, to name just a few. Furthermore, it is known that the presence of phosphorus substituents could regulate important biological functions,[6] and the introduction of organophosphorus functionalities in simple synthons may afford useful substrates for the preparation of biologically active compounds. In this context, carboxylated 1,2-diaza-1,3-butadienes[7] have been widely used for the preparation of heterocyclic compounds,[8] while phosphorylated 1,2-diaza-1,3-butadienes have been used for the preparation of α-aminophosphonates,[9] pyridazines,[10] pyrazines and quinoxalines.[8d] As part of our ongoing research programs on the preparation of three,[11] five[12] and six[13] membered nitrogen-containing heterocycles, as well as the synthesis of new amino phosphorus derivatives,[9,14] here we report the behaviour of thiol derivatives **I** towards 1,2-diaza-1,3-dienes **II**. The obtained hydrazones **III** provide flexible access to different classes of nitrogen/sulfur containing heterocycles by means of controlled regioselective cyclizations (Chart 1). The presence of different functional groups in many positions of these heterocycles merits especial emphasis since such compounds are, in turn, potential starting materials for further interesting structural modifications, making them suitable for more complex heterocyclic systems.

In this work, we also investigated the use of polymer-bound 1,2-diaza-1,3-butadienes as building blocks for the facile solid-phase preparation of thiazine and benzothiazine derivatives.

2. Results and discussion

4-Phosphinyl and 4-phosphonyl-1,2-diaza-1,3-butadienes[15] **1a**,**b** (R^1=P(O)Ph_2, P(O)$(OEt)_2$; R^2=OEt), easily reacted with 2-mercaptoethylamine hydrochloride **2a** (R^3=H, Y=NH_3Cl) in

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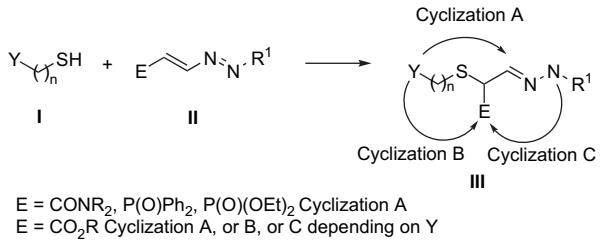
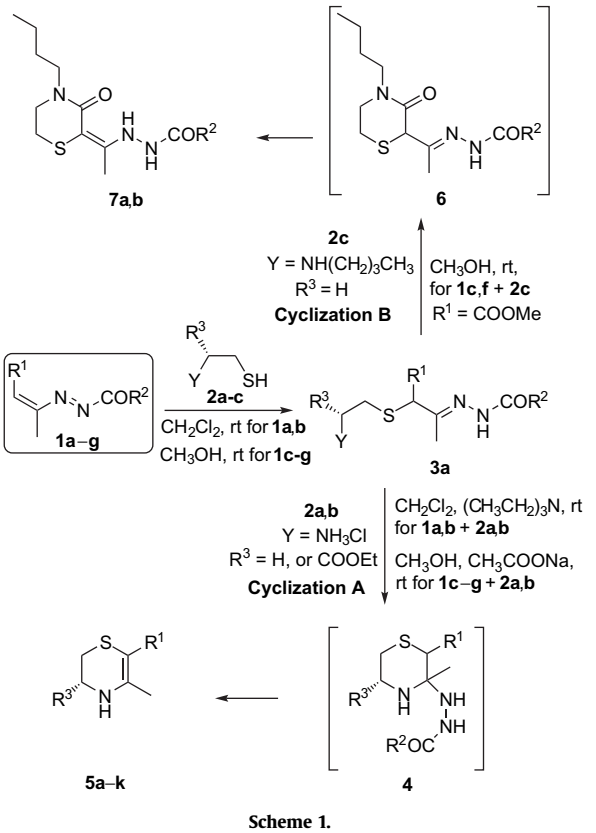


Chart 1. Synthesis and regioselective cyclizations of functionalized thiohydrazones **III**.

dichloromethane (DCM) at room temperature in the presence of triethylamine to give 5-methyl-3,4-dihydro-2*H*-1,4-thiazine-2-phosphine oxides **5a** and -2-phosphonates **5b** (Cyclization A, Chart 1, Scheme 1, Table 1). Similarly, the synthesis of 3,4-dihydro-2*H*-1,4-thiazine containing ester or amide groups **5c**–**e** was achieved by reaction of 1,2-diaza-1,3-butadienes **1c**–**e** (R^1=CO_2Me, CO_2Et, $CONMe_2$; R^2=NH_2) and **1f** (R^1=CO_2Me, R^2=O*t*-Bu) with the same **2a** in methanol (MeOH) at room temperature in the presence of sodium acetate. This process was extended to the preparation of optically active 3-ethyl-(3*R*)-3,4-dihydro-2*H*-1,4-thiazine-3,6-dicarboxylate **5f**–**k** (Scheme 1, Table 1) by using chiral aminothiol derivative like L-cysteine ethyl ester hydrochloride **2b** (R^3=CO_2Et, Y=NH_3Cl). This reaction proceeds by means of preliminary sulfur-nucleophilic attack of the 2-aminoethanothiols **2** on the terminal carbon atom of the 1,2-diaza-1,3-butadiene system **1** to lead the hydrazone 1,4-adducts (Michael type) **3** as evidenced by the disappearance of typical red colour of the 1,2-diaza-1,3-butadienes **1**. At this time a stoichiometric amount of triethylamine in the case of **1a**,**b** or of sodium acetate in the case of **1c**–**g** was added to the crude to obtain the free amino moiety, that gives a subsequent internal nucleophilic attack at the carbon of the hydrazono group with formation of the thiomorpholine intermediates **4**. Then, a spontaneous loss of a hydrazinecarboxylate residue affords thiazines **5a**–**k** (Scheme 1). The structure of compounds **5** was confirmed by NOE experiments (DPFGSE–NOE sequence).[16] For example, irradiation of the methyl signal of compound **5h** in DMSO-d_6 at 2.27 ppm enhances the NH signal at 7.28 ppm and vice versa. This evidence suggests the proximity of these two groups, which is in good agreement with the proposed mechanism. The mercapto group demonstrated better nucleophilicity than the amino moiety. In fact, the same products **5** were obtained when the thiolamines hydrochloride **2a**,**b** were treated with the appropriate base before the reaction with 1,2-diaza-1,3-butadienes **1**. The overall yields of **5** are not influenced from the sequence of base addition.



Scheme 1.

1,4-Thiazines substituted with phosphorus containing functional groups have received scarce attention and only one example of 1,4-thiazine derivatives with a phosphonate group at the position 2 of the heterocyclic system has been described.[17] To the best of our knowledge, this strategy describes the first example of 1,4-thiazine derivatives with a phosphine oxide group as well as the first example of optically active phosphorylated [R^1=$P(O)Ph_2$, $P(O)(OEt)_2$] 1,4-thiazine derivatives. Hydrazone 1,4-adduct intermediate **3a** was isolated when 2-(butylamino)ethanethiol **2c** (R^3=H, Y=NHBu) was added to 1,2-diaza-1,3-butadiene **1e** (R^1=$CONMe_2$, R^2=NH_2) in MeOH at room temperature (Scheme 1, Table 1). Surprisingly, the reaction between **2c** and 1,2-diaza-1,3-butadienes **1c**,**f** (R^1=CO_2Me, R^2=NH_2, O*t*-Bu) containing an ester group in position 4 of the heterodiene system furnished new and interesting 2-[1-(4-butyl-3-oxo-1,4-thiazinan-2-yliden)ethyl]-1-hydrazinecarboxylates **7a**,**b** (Cyclization B, Chart 1). Also in this case, the first step of the mechanism involves the nucleophilic attack of the sulfur to the terminal carbon atom of the diene **1** with the formation of the hydrazones **3**. The subsequent intramolecular nucleophilic attack of the nitrogen at the ester function with loss of an alcohol molecule produces intermediates **6** that tautomerize to give the final 1,4-thiazinan-3-ones **7a**,**b** (Scheme 1, Table 1). The different regioselectivity observed in the cyclization can be ascribed to the presence of a bulky group onto the nitrogen atom. Hydrazone **3a** (R^1=$CONMe_2$) is not prone to cyclization reaction to yield **7**, probably because the amido moiety is less activated towards the nucleophilic attack with respect to the ester function. The methodology for the preparation of 2-substituted 1,4-thiazines **5** can also be applied to the synthesis of their benzo derivatives, when functionalized 2-aminothiophenols **8a**–**c** were used. Thus, Michael addition of **8a**–**c** to phosphorylated 1,2-diaza-1,3-butadienes **1a**,**b** in DCM or to carboxylated 1,2-diaza-1,3-butadienes **1c**,**d**,**h**,**i** in MeOH at room temperature was also investigated. The nucleophilic attack of the mercapto group of compounds **8** at the terminal carbon atom of the heterodiene system followed by cyclization and spontaneous elimination of hydrazine residue leads to 2-substituted-1,4-benzothiazines **9a**–**j** in good yields (Scheme 2, Table 2). Also the structure of compounds **9** was confirmed by NOE experiments (DPFGSE–NOE sequence).[16] In this case, irradiation of the methyl signal of compound **9d** at 2.17 ppm enhances the NH signal at 8.65 ppm and vice versa. Unfortunately, all attempts to obtain 1,4-thiazines **5a**–**k** or 1,4-benzothiazines **9a**–**j** in good yields with the same procedure failed because of the different electronic effects by the substituents. For this reason, we used the most suitable reaction conditions depending on the nature of the substrate.

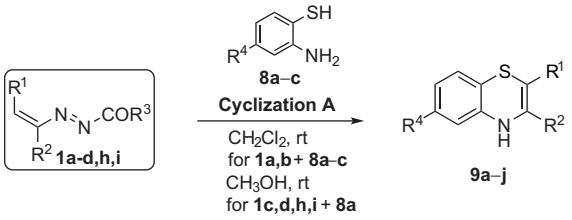
We have also studied the reaction of 1,2-diaza-1,3-butadienes **1a**,**c** with 2-mercaptoethanol **2d** at room temperature, in DCM in the case of **1a**, or in MeOH for **1c** to tentatively obtain 2,3-dihydro-1,4-oxathiine **10** (Scheme 3).

Unfortunately, the expected intramolecular nucleophilic attack of the oxygen derived from **2d** did not occur and only hydrazones **3b**,**c** were recovered. The subsequent addition of catalytic sodium

Table 1
Yields of hydrazone **3a**, 3,4-dihydro-2*H*-1,4-thiazines **5a–k** and 1,4-thiazinan-3-ones **7a,b**

1	R^1	R^2	2	R^3	Y	3	Yield[a] (%)	5	Yield[a] (%)	7	Yield[a] (%)
1a	$POPh_2$	OEt	**2a**	H	NH_3Cl			**5a**	87		
1b	$PO(OEt)_2$	OEt	**2a**	H	NH_3Cl			**5b**	90		
1c	CO_2Me	NH_2	**2a**	H	NH_3Cl			**5c**	74		
1d	CO_2Et	NH_2	**2a**	H	NH_3Cl			**5d**	63		
1e	$CONMe_2$	NH_2	**2a**	H	NH_3Cl			**5e**	82		
1f	CO_2Me	O*t*-Bu	**2a**	H	NH_3Cl			**5c**	65		
1a	$POPh_2$	OEt	**2b**	CO_2Et	NH_3Cl			**5f**	83		
1b	$PO(OEt)_2$	OEt	**2b**	CO_2Et	NH_3Cl			**5g**	89		
1c	CO_2Me	NH_2	**2b**	CO_2Et	NH_3Cl			**5h**	77		
1d	CO_2Et	NH_2	**2b**	CO_2Et	NH_3Cl			**5i**	93		
1e	$CONMe_2$	NH_2	**2b**	CO_2Et	NH_3Cl			**5j**	76		
1g	CO_2t-Bu	NH_2	**2b**	CO_2Et	NH_3Cl			**5k**	87		
1c	CO_2Me	NH_2	**2c**	H	NHBu					**7a**	96
1e	$CONMe_2$	NH_2	**2c**	H	NHBu	**3a**	94				
1f	CO_2Me	O*t*-Bu	**2c**	H	NHBu					**7b**	94

[a] Yield of isolated purified compounds based on 1,2-diaza-1,3-butadienes **1**.



Scheme 2.

hydride at room temperature in MeOH to **3c** (R^1=CO_2Me) promotes the internal nucleophilic attack of the hydrazonic nitrogen to the ester function (Cyclization C, Chart 1) with consequent loss of an alcohol molecule producing substituted pyrazolone intermediate **11**. This latter gives 4-[(2-hydroxyethyl)sulfanyl]-5-methyl-2,3-dihydro-1*H*-3-pyrazolone **12a**, by spontaneous hydrolysis of the ureidic bond (Scheme 3, Table 2). Also in these conditions, no formation of oxathiine **10** was detected. This fact is probably due to the lower nucleophilicity of the oxygen with respect to the nitrogen.

Considering the mild and simple conditions required from these reactions in the liquid phase, we have also investigated this synthetic methodology in solid phase. Polymer-bound 1,2-diaza-1,3-butadienes **14a,b** prepared from polymer-bound *p*-toluenesulfonyl hydrazide **13**[18] were allowed to stand at room temperature in methanol–tetrahydrofuran (THF) (1:1) with 5 equiv of 2-mercaptoethylamine hydrochloride **2a** or L-cysteine ethyl ester hydrochloride **2b**. After 10 min, the resin was washed and then treated with 2 equiv of sodium acetate in MeOH/THF (1:1) at room temperature obtaining 3,4-dihydro-2*H*-1,4-thiazines **5c,d,h,i** directly in solution with a satisfactory degree of purity (Scheme 4, Table 3).

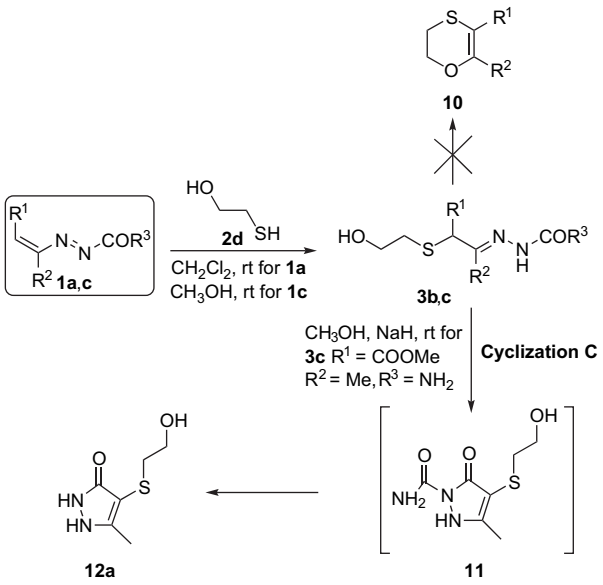
Similarly, polymer-bound 1,2-diaza-1,3-butadienes **14a,b** readily reacted with 5 equiv of 2-aminothiophenol **8a**, at room temperature, in MeOH/THF (1:1) affording directly 2-substituted-1,4-benzothiazines **9c,d** (Scheme 4, Table 3). The overall yields referred to the multistep-process of the solid-phase reactions are comparable with the corresponding ones obtained in solution. To improve the scope of this synthetic methodology, the reaction of 2-mercaptoethylamine hydrochloride **2a** and 2-aminothiophenol **8a** with cycloalkenyl-1-diazenes **15a–d**[19] in MeOH was performed (Scheme 5). The treatment of **15b,c** with **2a** under the usual reaction conditions provides interesting fused cycloalkyl-1,4-thiazine derivatives like ethyl-2,3,5,6,7,8-hexahydro-8a*H*-1,4-benzothiazine-8a-carboxylate **17a** (*n*=2) or methyl-3,5,6,7,8,9-hexahydrocyclohepta[*b*][1,4]thiazine-9a(2*H*)-carboxylate **17b** (*n*=3) in good yields (Scheme 5, Table 4). In the case of reaction between **15a,c,d** and **8a** we achieved attractive fused cycloalkyl-1,4-benzothiazine derivatives like ethyl-1,2,3,3a-tetrahydrobenzo[*b*]cyclopenta[*e*][1,4]thiazine-3a-carboxylate **18a** (*n*=1), or methyl-5a,6,7,8,9,10-hexahydrobenzo[*b*]cyclohepta[*e*][1,4]-thiazine-5a-carboxylate **18b** (*n*=3), or ethyl-6,7,8,9,10,11-hexahydro-5a*H*-benzo[*b*]cycloocta[*e*][1,4]thiazine-5a-carboxylate **18c** (*n*=4) in good yields (Scheme 5, Table 4). This behaviour proves that this easy procedure can be successfully employed for further synthetic applications in the construction of interesting polyfused heterorings.

Then, we extended our investigation to the additions of 2-mercaptobenzimidazole **19a**, and 1*H*-1,2,3-triazole-3-thiol **19b** on 1,2-diaza-1,3-butadiene **1d** at room temperature in MeOH (Scheme 6). The nucleophilic attack of the mercapto moiety of the compounds **19a,b** at the terminal carbon of the heterodiene system of 1,2-diaza-1,3-butadiene **1d** led to hydrazone 1,4-adducts **20a**, **23a**, isolated by chromatography on silica in excellent yields. The subsequent addition of catalytic sodium hydride to a solution of **20a** or

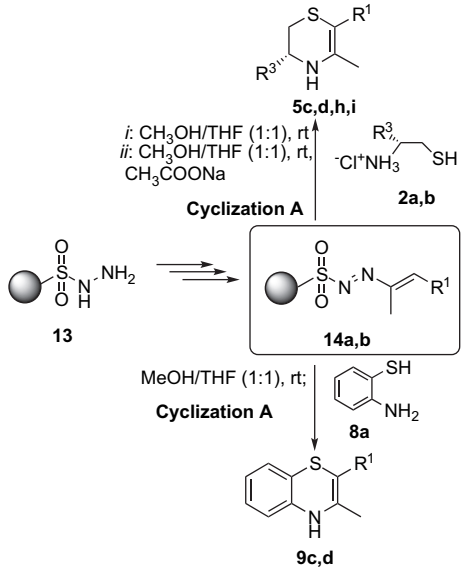
Table 2
Yields of hydrazones **3b,c**, 1,4-benzothiazines **9a–j** and 4-[(2-hydroxyethyl)sulfanyl]-5-methyl-2,3-dihydro-1*H*-3-pyrazolone **12a**

1	R^1	R^2	R^3	2	3	Yield[a] (%)	8	R^4	9	Yield[a] (%)	12	Yield[a] (%)	Yield[b] (%)
1a	$POPh_2$	Me	OEt				**8a**	H	**9a**	77			
1b	$PO(OEt)_2$	Me	OEt				**8a**	H	**9b**	74			
1c	CO_2Me	Me	NH_2				**8a**	H	**9c**	62			
1d	CO_2Et	Me	NH_2				**8a**	H	**9d**	78			
1h	CO_2Bn	Me	NH_2				**8a**	H	**9e**	74			
1i	CO_2Me	Et	NH_2				**8a**	H	**9f**	65			
1a	$POPh_2$	Me	OEt				**8b**	Cl	**9g**	89			
1b	$PO(OEt)_2$	Me	OEt				**8b**	Cl	**9h**	91			
1a	$POPh_2$	Me	OEt				**8c**	CF_3	**9i**	86			
1b	$PO(OEt)_2$	Me	OEt				**8c**	CF_3	**9j**	88			
1a	$POPh_2$	Me	OEt	**2d**	**3b**	97							
1c	CO_2Me	Me	NH_2	**2d**	**3c**	89					**12a**	58	75

[a] Yield of isolated purified compounds based on 1,2-diaza-1,3-butadienes **1**.
[b] Yield of isolated purified compound based on hydrazone **3c**.



Scheme 3.



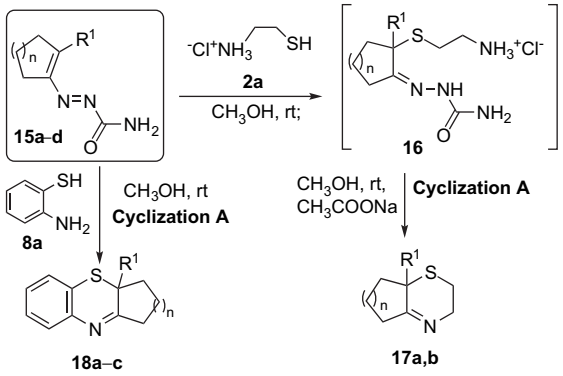
Scheme 4.

23a (R^1=CO_2Et) in MeOH at room temperature promotes the internal nucleophilic attack of the hydrazonic nitrogen to the ester function producing 4-(1*H*-benzo[*d*]imidazol-2-ylsulfanyl)-5-methyl-2,3-dihydro-1*H*-3-pyrazolone **22a** or 5-methyl-4-(1*H*-1,2,4-triazol-3-ylsulfanyl)-2,3-dihydro-1*H*-3-pyrazolone **25a**, respectively

Table 3
Overall yields of 3,4-dihydro-2*H*-1,4-thiazines **5c**,**d**,**h**,**i** and 1,4-benzothiazines **9c**,**d** obtained in solid phase

14	R^1	2	R^3	5	Yield[a] (%)	Purity (%)	8	9	Yield[a] (%)
14a	CO_2Me	**2a**	H	**5c**	14	96			
14b	CO_2Et	**2a**	H	**5d**	16	94			
14a	CO_2Me	**2b**	CO_2Et	**5h**	31	95			
14b	CO_2Et	**2b**	CO_2Et	**5i**	47	98			
14a	CO_2Me						**8a**	**9c**	23
14b	CO_2Et						**8a**	**9d**	28

[a] Yield of isolated purified compounds based on polymer-bound *p*-toluenesulfonyl hydrazide **13**.



Scheme 5.

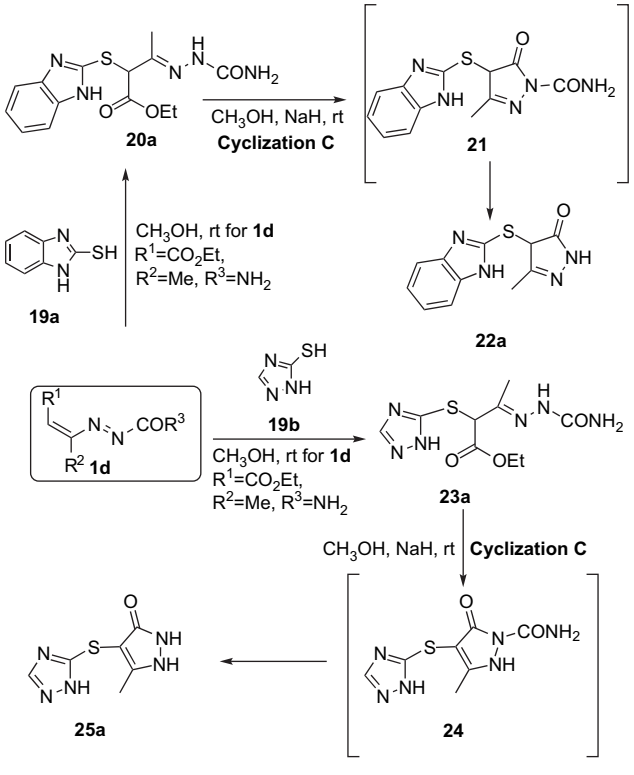
Table 4
Yields of fused cycloalkyl-1,4-thiazines **17a**,**b**, and fused cycloalkyl-1,4-benzothiazines **18a**–**c**

15	R^1	*n*	2	17	Yield[a] (%)	8	18	Yield[a] (%)
15b	CO_2Et	2	**2a**	**17a**	95			
15c	CO_2Me	3	**2a**	**17b**	67			
15a	CO_2Et	1				**8a**	**18a**	59
15c	CO_2Me	3				**8a**	**18b**	87
15d	CO_2Et	4				**8a**	**18c**	76

[a] Yield of isolated purified compounds based on cycloalkenyl-1-diazenes **15**.

(Scheme 6, Table 5), in a similar way to that described for **12a** (Cyclization C, Chart 1).

In this case, the ring closure process leading to the formation of 1,4-thiazines (Cyclization A) does not occur, probably because the aromaticity of mercaptobenzimidazole **19a**, and 1*H*-1,2,3-triazole-3-thiol **19b** makes the nitrogen a weak nucleophile.



Scheme 6.

Table 5
Yields of fused 4-substituted hydrazones **20a**, **23a** and 4-substituted pyrazol-3-ones **22a**, **25a**

1	R^1	R^2	R^3	19	20	Yield[a] (%)	22	Yield[a] (%)	Yield[b] (%)	23	Yield[a] (%)	25	Yield[a] (%)	Yield[c] (%)
1d	CO_2Et	Me	NH_2	**19a**	**20a**	93	**22a**	89	97					
1d	CO_2Et	Me	NH_2	**19b**						**23a**	95	**25a**	92	98

[a] Yield of isolated purified compounds based on 1,2-diaza-1,3-butadienes **1**.
[b] Yield of isolated purified **22a** based on hydrazone **20a**.
[c] Yield of isolated purified **25a** based on hydrazone **23a**.

3. Conclusion

The present investigation demonstrates that the reactions of 1,2-diaza-1,3-dienes and thiol derivatives provide straightforward access to different classes of sulfur containing compounds. As a matter of fact in the whole the syntheses realized indicate that 1,2-diaza-1,3-butadienes **1** or cycloalkenyl-1-diazenes **15** can react with different sulfur nucleophiles showing varied reactivity: (1) with aliphatic **2a**,**b** and aromatic **8**, 1,2-aminothiols 3,4-dihydro-2*H*-1,4-thiazines **5**, fused cycloalkyl-1,4-thiazine **17**, 1,4-benzothiazines **9** and fused cycloalkyl-1,4-benzothiazine **18** can be obtained (Cyclization A); (2) with 2-(butylamino)ethanethiol **2c**, 1,4-thiazinan-3-ones **7** can be prepared (Cyclization B); (3) with 2-mercaptoethanol **2d**, or 2-mercaptobenzimidazole **19a**, or 1*H*-1,2,3-triazole-3-thiol **19b**, new substituted sulfanyl-2,3-dihydro-1*H*-3-pyrazolones **12**, **22**, **25** can be achieved (Cyclization C). The strategy previously described in the point (1) has also been used for the preparation of optically active functionalized 1,4-thiazines with amide, esters, phosphine oxide or phosphonate as substituents. These heterocycles may be important synthons in organic synthesis,[3] organocatalysis[20] and for the preparation of biologically active compounds of interest in medicinal chemistry.[2–5] These synthetic methodologies proceed under mild conditions, using easily available starting materials and furnish interesting new products without complicated work-up procedures. These aspects have allowed us to obtain many cyclic compounds such as 3,4-dihydro-2*H*-1,4-thiazines **5** and 1,4-benzothiazines **9** by means of solid-phase reactions too.

4. Experimental

4.1. General

2-Mercaptoethylamine hydrochloride, L-cysteine ethyl ester hydrochloride, 2-(butylamino)ethanethiol, 2-aminothiophenol, 2-amino 4-chlorothiophenol, 2-amino 4-(trifluoromethyl)-thiophenol, 2-mercaptobenzimidazole, 1*H*-1,2,3-triazole-3-thiol, 3-mercapto-2-butanone and Amberlyst 15H were commercial materials and were used without further purification. Solvents were purchased and used without further purification with the exception of THF, which was distilled over sodium hydroxide. Melting points were determined on in open capillary tubes and are uncorrected. IR–FT spectra were obtained as Nujol mulls, as solids in KBr or as neat oils in NaCl. Mass spectra (MS) were made by electron impact (EI) at an ionizing voltage of 70 eV or by chemical ionization (CI). HRMS were recorded on an MAT95S mass spectrometer. ^{1}H (300, 400 MHz), ^{13}C (75, 100 MHz) and ^{31}P NMR (120, 160 MHz) spectra were recorded on a 300 MHz or 400 MHz spectrometers, respectively, in $CDCl_3$ or in DMSO-d_6, as specified below. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. All coupling constants (J) values are given in hertz. Chemical shifts (δ_C) are reported in parts per million (ppm), relative to $CDCl_3$ or DMSO-d_6, as internal standard in a broad band decoupled mode; the multiplicities were obtained using 135° and 90° DEPT experiments to aid in assignment (CH_3=methyl, CH_2=methylene, CH=methine, C=quaternary). The abbreviations used are as follows: s, singlet; d, doublet; dd, double-doublet; t, triplet; q, quartet; ept, eptet; m, multiplet; br, broad. All the NH and NH_2 exchanged with D_2O. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35–70 μ for column chromatography. All new compounds showed satisfactory elemental analysis (C ±0.35; H ±0.30; N ±0.30). The nomenclature was generated using ACD/IUPAC Name (version 3.50, 5 Apr. 1998), Advanced Chemistry Development Inc., Toronto, ON (Canada).

4.2. General procedure for the synthesis of 3,4-dihydro-2*H*-1,4-thiazines 5a–k and fused cycloalkyl-1,4-thiazines 17a,b

To an ice-cooled solution of 1,2-diaza-1,3-butadienes **1a**,**b** as a mixture of *E*/*Z* isomers (1.0 mmol) and triethylamine (139 μL, 1 mmol) in dichloromethane (5 mL), the corresponding 2-mercaptoethylamine hydrochloride **2a** (1 mmol) or L-cysteine ethyl ester hydrochloride **2b** (1 mmol) was added. The reaction was allowed to stir at room temperature for 30 min. The solvent was removed by rotary evaporation and the residue was stirred with diethyl ether and then it was filtered through a sintered glass vacuum filtration funnel. The solid was washed with ether and the filtrate was concentrated to dryness in vacuum. The crude products were purified by crystallization or by flash-column chromatography (silica gel, AcOEt) to afford 1,4-thiazines **5a**,**b**,**f**,**g** derived from phosphine oxides and phosphonates. To obtain 2-carboxylated 3,4-dihydro-2*H*-1,4-thiazines **5c–e**,**h–k** or fused cycloalkyl-1,4-thiazines **17a**,**b**, a stoichiometric amount of 1,2-diaza-1,3-butadienes **1c–g** (1 mmol) as a mixture of *E*/*Z* isomers[21] or cycloalkenyl-1-diazenes **15b**,**c**[19] was added to a solution of 2-mercaptoethylamine hydrochloride **2a** (1 mmol) or L-cysteine ethyl ester hydrochloride **2b** (1 mmol) in MeOH (20 mL). The reaction was allowed to stand at room temperature for 10 min until complete disappearance of the reagents (monitored by TLC). Sodium acetate (1 mmol) was then added to the mixture and the solution was allowed to stand at room temperature in MeOH under magnetic stirring for 8–14 h. The solvent was removed under reduced pressure, the crude was dissolved in ethyl acetate and washed with a saturated solution of Na_2CO_3 (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The final products **5c–e**,**h–k**, **17a**,**b** were purified by chromatography on silica (elution mixture: ethyl acetate, cyclohexane).

*4.2.1. 5-Methyl-3,4-dihydro-2H-1,4-thiazin-6-yl(diphenyl)phosphine oxide **5a***

Compound **5a** (274 mg, 87%) was obtained as a colourless solid as described in the general procedure: mp 74–75 °C; IR (KBr) ν_{max} 3255, 3041, 1722, 1546, 1434, 1167, 1113 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.05 (s, 3H), 2.64–2.68 (m, 2H), 3.57–3.60 (m, 2H), 7.43–7.72 (m, 10H); ^{13}C NMR (75 MHz, CD_3OD) δ 21.8 (d, $^3J_{PC}$=4.0 Hz), 25.6 (d, $^3J_{PC}$=4.5 Hz), 45.8, 75.7 (d, $^1J_{PC}$=130.0 Hz), 129.5, 129.6, 132.8, 132.9, 133.0, 133.1, 134.8 (d, $^1J_{PC}$=109.3 Hz), 152.1 (d, $^2J_{PC}$=15.5 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 34.2; MS (EI) *m*/*z* (%) 315 (M^+, 100), 314 (M^+-1, 65), 238 (5), 201 (24), 114 (8), 77 (10); Calcd for $C_{17}H_{18}NOPS$ [M^+] 315.0847. Found [M^+] 315.0853.

4.2.2. Diethyl-(5-methyl-3,4-dihydro-2H-1,4-thiazin-6-yl)phosphonate ***5b***

Compound **5b** (225 mg, 90%) was obtained as a colourless oil as described in the general procedure: IR (film) ν_{max} 3413, 1623, 1469, 1250, 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25–1.31 (m, 6H), 2.05 (d, 3H, $^4J_{PH}$=1.6 Hz), 2.63–2.69 (m, 1H), 2.95–2.99 (m, 1H), 3.33–3.40 (1H, m), 3.61–3.68 (m, 1H), 4.04–4.25 (4H, m), 8.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 16.2, 16.4, 34.9, 53.7 (d, $^4J_{PC}$=4.4 Hz), 61.3, 61.4, 61.8, 63.9, 64.0, 64.4, 64.4, 80.1 (d, $^1J_{PC}$=191.9 Hz), 148.3 (d, $^2J_{PC}$=23.0 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 18.7; MS (CI) *m*/*z* (%) 252 (M^++1, 2), 218 (10), 216 (100), 170 (95), 114 (10), 83 (15); Calcd for $C_9H_{18}NO_3PS$ [M^+] 251.0757. Found [M^+] 251.0768.

4.2.3. Methyl-5-methyl-3,4-dihydro-2H-1,4-thiazine-6-carboxylate ***5c***

Compound **5c** (128 mg, 74% starting from **1c**; 112 mg, 65% starting from **1f**; 24 mg, 14% starting from **14a**) was obtained as a colourless powder as described in the general procedure: mp 66–68 °C; IR (Nujol) ν_{max} 3278, 1753, 1690, 1569 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.80–2.83 (m, 2H), 3.60–3.63 (m, 2H), 3.69 (s, 3H), 4.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (CH_3), 23.8 (CH_2), 44.3 (CH_2), 51.1 (CH_2), 84.7 (C), 149.6 (C), 166.5 (C); MS: *m*/*z* (%) 173 (M^+, 100). Anal. Calcd for $C_7H_{11}NO_2S$: C, 48.54; H, 6.40; N, 8.09. Found: C, 48.60; H, 6.37; N, 8.42.

4.2.4. Ethyl-5-methyl-3,4-dihydro-2H-1,4-thiazine-6-carboxylate ***5d***

Compound **5d** (118 mg, 63% starting from **1d**; 30 mg, 16% starting from **14b**) was obtained as a yellow powder as described in the general procedure: mp 58–60 °C; IR (Nujol) ν_{max} 3310, 1768, 1702, 1578 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, 3H, ^3J=7.2 Hz), 2.33 (s, 3H), 2.81–2.84 (m, 2H), 3.60–3.64 (m, 2H), 4.16 (q, 2H, ^3J=7.2 Hz), 4.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (CH_3), 23.3 (CH_3), 24.2 (CH_2), 44.5 (CH_2), 60.1 (CH_2), 85.5 (C), 149.5 (C), 166.4 (C); MS: *m*/*z* (%) 187 (M^+, 100), 149 (23), 125 (17), 111 (25), 97 (38), 83 (39), 69 (62), 57 (100). Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48. Found: C, 51.26; H, 6.97; N, 7.52.

4.2.5. N6,N6,5-Trimethyl-3,4-dihydro-2H-1,4-thiazine-6-carboxamide ***5e***

Compound **5e** (152 mg, 82%) was obtained as a yellow powder as described in the general procedure: mp 76–78 °C; IR (Nujol) ν_{max} 3324, 1772, 1732, 1564 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.69 (s, 3H), 2.68–2.72 (m, 2H), 2.86 (s, 6H), 3.32–3.41 (m, 2H), 5.53 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.0 (CH_3), 23.4 (CH_2), 28.1 (CH_3), 36.3 (CH_3), 43.0 (CH_2), 85.5 (C), 136.1 (C), 169.1 (C); MS: *m*/*z* (%) 186 (M^+, 93), 141 (71), 114 (100), 82 (16), 68 (37), 83 (39), 69 (62), 57 (100). Anal. Calcd for $C_8H_{14}N_2OS$: C, 51.59; H, 7.58; N, 15.04. Found: C, 51.49; H, 7.62; N, 15.12.

4.2.6. Ethyl-(3R)-6-8-diphenylphosphoryl-5-methyl-3,4-dihydro-2H-1,4-thiazine-3-carboxylate ***5f***

Compound **5f** (321 mg, 83%) was obtained as a yellow oil as described in the general procedure: IR (neat) ν_{max} 3244, 3047, 1738, 1540, 1439, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, 3H, *J*=7.2 Hz), 2.14 (t, 3H, $^4J_{PH}$=1.0 Hz), 2.66 (ddd, 1H, $^2J_{HH}$=12.4 Hz, $^3J_{HH}$=7.2 Hz, $^4J_{PH}$=1.7 Hz), 2.87 (dt, 1H, $^2J_{HH}$=12.4 Hz, *J*=3.0 Hz), 4.14 (q, 2H, *J*=7.2 Hz), 4.21 (dd, 1H, *J*=7.2 Hz, *J*=3.0 Hz), 5.32 (d, 1H, $^3J_{HH}$=3.0 Hz), 7.31–7.72 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 21.6 (d, $^3J_{PC}$=5.0 Hz), 27.1 (d, $^3J_{PC}$=4.5 Hz), 55.5, 62.1, 80.1 (d, $^1J_{PC}$=123.4 Hz), 127.9, 128.0, 128.2, 128.3, 128.3, 128.4, 128.5, 130.7, 131.3, 131.4, 131.5, 131.7, 131.7, 131.8, 133.5 (d, $^1J_{PC}$=109.3 Hz), 133.7 (d, $^1J_{PC}$=107.8 Hz), 148.3 (d, $^2J_{PC}$=15.1 Hz), 170.1; ^{31}P NMR (120 MHz, $CDCl_3$) δ 29.3; MS (EI) *m*/*z* (%) 387 (M^+, 100), 314 (40), 207 (50), 185 (15), 112 (20), 77 (22); Calcd for $C_{20}H_{22}NO_3PS$ [M^+] 387.1058. Found [M^+-CO_2Et] 314.0775; $[\alpha]_D^{20}$ −7.01 (*c* 0.50, CH_2Cl_2).

4.2.7. Ethyl-(3R)-6-(diethoxyphosphoryl)-5-methyl-3,4-dihydro-2H-1,4-thiazine-3-carboxylate ***5g***

Compound **5g** (287 mg, 89%) was obtained as a colourless oil as described in the general procedure: IR (neat) ν_{max} 3266, 2983, 1744, 1247, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23–1.34 (m, 9H), 2.03 (d, 3H, $^4J_{PH}$=1.9 Hz), 2.69–2.74 (m, 1H$_{anti}$), 3.26–3.30 (m, 1H$_{syn}$), 4.14–4.24 (m, 6H), 4.33–4.39 (m, 1H), 4.60 (dd, 1H, $^3J_{HH}$=11.0 Hz, $^3J_{HH}$=11.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.4, 14.6, 16.6 (d, $^3J_{PC}$=5.5 Hz), 37.4, 61.5, 62.0, 64.2 (d, $^2J_{PC}$=8.1 Hz), 64.6 (d, $^2J_{PC}$=6.9 Hz), 66.6, 79.6 (d, $^1J_{PC}$=192.8 Hz), 146.6, 170.3; ^{31}P NMR (120 MHz, $CDCl_3$) δ 17.8; MS (CI) *m*/*z* (%) 324 (M^++1, 10), 288 (95), 242 (100), 83 (10); Calcd for $C_{12}H_{22}NO_5PS$ [M^+] 323.0956. Found [M^+] 323.0960; $[\alpha]_D^{20}$ −6.67 (*c* 0.50, CH_2Cl_2).

4.2.8. 3-Ethyl-6-methyl-(3R)-5-methyl-3,4-dihydro-2H-1,4-thiazine-3,6-dicarboxylate ***5h***

Compound **5h** (188 mg, 77%) was obtained as a yellow oil as described in the general procedure; IR (Nujol) ν_{max} 3324, 1772, 1732, 1564 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.18 (t, 3H, ^3J=7.2 Hz), 2.27 (s, 3H), 2.71 (dd, 1H, ^2J=12.8 Hz, ^3J=2.4 Hz), 2.99–3.07 (m, 1H), 3.52 (s, 3H), 4.08–4.18 (m, 2H), 4.47–4.52 (m, 1H), 7.28 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.6 (CH_3), 26.1 (CH_2), 51.1 (CH), 55.4 (CH_3), 62.2 (CH_2), 86.0 (C), 148.4 (C), 166.2 (C), 169.8 (C); MS: *m*/*z* (%) 245 (M^+, 54), 214 (33), 201 (100), 185 (69), 172 (42), 157 (16), 141 (100), 113 (51), 82 (13). Anal. Calcd for $C_{10}H_{15}NO_4S$: C, 51.59; H, 7.58; N, 15.04. Found: C, 51.49; H, 7.62; N, 15.12.

4.2.9. Diethyl-(3R)-5-methyl-3,4-dihydro-2H-1,4-thiazine-3,6-dicarboxylate ***5i***

Compound **5i** (239 mg, 93% starting from **1d**; 122 mg, 47% starting from **14b**) was obtained as a yellow oil as described in the general procedure; IR (Nujol) ν_{max} 3352, 1745, 1685, 1579, 1523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25–1.32 (m, 6H), 2.38 (s, 3H), 2.76 (dd, 1H, ^2J=12.4 Hz, ^3J=8.4 Hz), 3.09–3.15 (m, 1H), 4.15 (q, 2H, ^3J=7.2 Hz), 4.19–4.22 (m, 1H), 4.26 (q, 2H, ^3J=7.2 Hz), 4.85 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 14.4 (CH_3), 22.7 (CH_3), 26.3 (CH_2), 55.4 (CH), 60.0 (CH_2), 62.3 (CH_2), 86.6 (C), 147.9 (C), 165.8 (C), 169.9 (C); MS: *m*/*z* (%) 259 (M^+, 75), 231 (8), 214 (20), 186 (100). Anal. Calcd for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.40. Found: C, 51.01; H, 6.60; N, 5.38.

4.2.10. Ethyl-6-[(dimethylamino)carbonyl]-(3R)-5-methyl-3,4-dihydro-2H-1,4-thiazine-3-carboxylate ***5j***

Compound **5j** (196 mg, 76%) was obtained as a yellow oil as described in the general procedure; IR (Nujol) ν_{max} 3298, 1776, 1749, 1541 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.18 (t, 3H, ^3J=7.2 Hz), 1.72 (s, 3H), 2.80 (dd, 1H, ^2J=12.8 Hz, ^3J=3.6 Hz), 2.85 (s, 6H), 3.03 (dd, 1H, ^2J=12.8 Hz, ^3J=4.0 Hz), 4.10 (q, 2H, ^3J=7.2 Hz), 4.38 (m, 1H), 5.90 (d, 1H, ^3J=4.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.1 (CH_3), 18.8 (CH_3), 25.5 (CH_2), 36.1 (CH_3), 53.5 (CH), 60.7 (CH_2), 86.5 (C), 134.7 (C), 168.5 (C), 170.4 (C); MS: *m*/*z* (%) 258 (M^+, 63), 214 (33), 186 (83), 168 (100), 142 (21), 113 (7), 81 (36). Anal. Calcd for $C_{11}H_{18}N_2O_3S$: C, 51.14; H, 7.02; N, 10.84. Found: C, 51.23; H, 6.96; N, 10.71.

4.2.11. 6-(tert-Butyl) 3-ethyl-(3R)-5-methyl-3,4-dihydro-2H-1,4-thiazine-3,6-dicarboxylate ***5k***

Compound **5k** (250 mg, 87%) was obtained as a yellow oil as described in the general procedure; IR (Nujol) ν_{max} 3373, 1745, 1685, 1586, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, 3H, ^3J=7.2 Hz), 1.45 (s, 9H), 2.32 (s, 3H), 2.68–2.75 (m, 1H), 3.06–3.12 (m, 1H), 4.12–4.19 (m, 1H), 4.23 (q, 2H, ^3J=7.2 Hz), 4.75 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.6 (CH_3), 26.5 (CH_2), 28.3 (C), 55.3 (CH), 62.2 (CH_2), 80.0 (C), 88.3 (C), 146.8 (C), 165.3 (C), 170.0 (C); MS: *m*/*z* (%) 287 (M^+, 23), 231 (97), 214 (25), 158 (100), 140 (12),

114 (30), 82 (20), 68 (23). Anal. Calcd for $C_{13}H_{21}NO_4S$: C, 54.33; H, 7.37; N, 4.87. Found: C, 54.40; H, 7.40; N, 4.82.

4.2.12. *Ethyl-2,3,5,6,7,8-hexahydro-8aH-1,4-benzothiazine-8a-carboxylate* ***17a***

Compound **17a** (215 mg, 95%) was obtained as a yellow oil as described in the general procedure; IR (Nujol) ν_{max} 1763, 1710, 1586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, 3H, ^3J=7.2 Hz), 1.35–1.42 (m, 2H), 1.43–1.58 (m, 1H), 1.65–1.71 (m, 1H), 1.74–1.82 (m, 1H), 2.03–2.10 (m, 1H), 2.27–2.32 (m, 2H), 2.53–2.58 (m, 1H), 2.73–2.81 (m, 1H), 3.54–3.62 (m, 1H), 3.85–3.93 (m, 1H), 4.10–4.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_2), 21.3 (CH_2), 23.2 (CH_2), 26.2 (CH_2), 36.8 (CH_2), 46.4 (C), 47.7 (CH_2), 61.3 (CH_2), 162.3 (C), 170.2 (C); MS: *m*/*z* (%) 227 (M^+, 8), 182 (16), 125 (55), 111 (100). Anal. Calcd for $C_{11}H_{17}NO_2S$: C, 58.21; H, 7.54; N, 6.16. Found: C, 58.17; H, 7.60; N, 6.18.

4.2.13. *Methyl-3,5,6,7,8,9-hexahydrocyclohepta[b][1,4]thiazine-9a(2H)-carboxylate* ***17b***

Compound **17b** (152 mg, 67%) was obtained as a yellow oil as described in the general procedure; IR (Nujol) ν_{max}, 1789, 1713, 1516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34–1.63 (m, 4H), 1.66–1.79 (m, 2H), 1.90–2.03 (m, 1H), 2.14–2.21 (m, 1H), 2.28–2.34 (m, 1H), 2.42–2.50 (m, 2H), 3.01–3.09 (m, 1H), 3.75 (s, 3H), 3.88–3.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0 (CH_2), 24.1 (CH_2), 28.7 (CH_2), 30.1 (CH_2), 35.6 (CH_2), 39.5 (CH_2), 48.2 (C), 49.7 (CH_2), 53.0 (CH_3), 168.1 (C), 172.4 (C); MS: *m*/*z* (%) 227 (M^+, 28), 211 (20), 181 (33), 167 (42), 149 (100), 137 (63), 123 (82), 111 (100). Anal. Calcd for $C_{11}H_{17}NO_2S$: C, 58.21; H, 7.54; N, 6.16. Found: C, 58.34; H, 7.46; N, 6.04.

4.3. General procedure for the synthesis of hydrazone 3a and 1,4-thiazinan-3-ones 7a,b

To synthesize **3a** a stoichiometric amount of 2-(butylamino)-ethanethiol **2c** (1 mmol) was added to a solution of 1,2-diaza-1,3-butadiene **1e** (1 mmol) as a mixture of *E*/*Z* isomers in MeOH (20 mL). The reaction was allowed to stand at room temperature for 10 min until complete disappearance of the reagents (monitored by TLC). The solvent was removed under reduced pressure and the product **3a** was purified by chromatography on silica (elution mixture: ethyl acetate, MeOH 90:10). To obtain products **7a**,**b** a stoichiometric amount of 2-(butylamino)ethanethiol **2c** (1 mmol) was added to a solution of 1,2-diaza-1,3-butadienes **1c**,**f** (1 mmol) as a mixture of *E*/*Z* isomers in MeOH (20 mL). The reaction was allowed to stand at room temperature for 0.5–1 h until complete disappearance of the reagents (monitored by TLC). The solvent was removed under reduce pressure and the 1,4-thiazinan-3-ones 7**a**,**b** were purified by chromatography on silica (elution mixture: ethyl acetate, MeOH 90:10).

4.3.1. *2[2-{[2-(Butylamino)ethyl]sulfanyl}-3-(dimethylamino)-1-methyl-3-oxopropylidene]-1-hydrazinecarboxamide* ***3a***

Compound **3a** (299 mg, 94%) was obtained as a colourless powder as described in the general procedure: mp 161–163 °C; IR (Nujol) ν_{max} 3311, 1763, 1712 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, 3H, ^3J=7.2 Hz), 1.18 (t, 3H, ^3J=7.2 Hz), 1.19–1.42 (m, 4H), 1.87 (s, 3H), 2.56–2.92 (m, 4H), 4.02–4.15 (m, 4H), 6.05 (br s, 2H), 9.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.3 (CH_3), 13.9 (CH_3), 14.8 (CH_2), 14.9 (CH_2), 19.7 (CH_2), 29.4 (CH_2), 30.7 (CH_2), 35.4 (CH_3), 36.6 (CH_3), 67.5 (CH), 144.1 (C), 157.0 (C), 169.8 (C); MS: *m*/*z* (%) 318 (M^+, 1), 272 (26), 255 (11), 229 (100), 208 (5), 186 (12), 156 (100), 143 (100), 129 (100), 111 (100). Anal. Calcd for $C_{13}H_{26}N_4O_3S$: C, 49.03; H, 8.23; N, 17.59. Found: C, 48.98; H, 8.22; N, 17.60.

4.3.2. *2-[1-(4-Butyl-3-oxo-1,4-thiazinan-2-yliden)ethyl]-1-hydrazinecarboxamide* ***7a***

Compound **7a** (261 mg, 96%) was obtained as a colourless powder as described in the general procedure: mp 170–171 °C; IR (Nujol) ν_{max} 3311, 1763, 1712 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.90 (t, 3H, ^3J=7.2 Hz), 1.31–1.42 (m, 2H), 1.58–1.65 (m, 2H), 1.99 (s, 3H), 2.56–2.61 (m, 2H), 2.84–2.95 (m, 4H), 6.91 (d, 1H, ^3J=3.2 Hz), 8.73 (d, 1H, ^3J=3.2 Hz), 9.47 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.1 (CH_3), 13.5 (CH_3), 19.3 (CH_3), 27.7 (CH_2), 30.9 (CH_2), 46.2 (CH_2), 46.4 (CH_2), 90.3 (C), 148.8 (C), 153.1 (C), 163.1 (C); MS: *m*/*z* (%) 272 (M^+, 4), 229 (100), 187 (14), 172 (1), 156 (34), 144 (100), 129 (100). Anal. Calcd for $C_{11}H_{20}N_4O_2S$: C, 48.51; H, 7.40; N, 20.57; S, 11.77. Found: C, 48.59; H, 7.42; N, 20.60; S, 11.75.

4.3.3. *tert-Butyl 2-[1-(4-butyl-3-oxo-1,4-thiazinan-2-yliden)ethyl]-1-hydrazinecarboxylate* ***7b***

Compound **7b** (118 mg, 63%) was obtained as a colourless powder as described in the general procedure: mp 130–132 °C; IR (Nujol) ν_{max} 3249, 1766, 1737, 1593 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.90 (t, 3H, ^3J=7.2 Hz), 1.31–1.42 (m, 2H), 1.58–1.65 (m, 2H), 1.99 (s, 3H), 2.56–2.61 (m, 2H), 2.84–2.95 (m, 4H), 6.91 (d, 1H, ^3J=3.2 Hz), 8.73 (d, 1H, ^3J=3.2 Hz), 9.47 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.4 (CH_3), 13.5 (CH_3), 19.4 (CH_3), 27.7 (CH_2), 32.7 (CH_2), 45.0 (CH_2), 45.5 (CH_2), 80.4 (C), 149.1 (C), 153.7 (C), 167.4 (C); MS: *m*/*z* (%) 272 (M^+, 11), 273 (6), 229 (83), 186 (8), 156 (21), 144 (100). Anal. Calcd for $C_{11}H_{20}N_4O_2S$: C, 48.51; H, 7.40; N, 20.57; S, 11.77. Found: C, 48.59; H, 7.42; N, 20.60; S, 11.75.

4.4. General procedure for the synthesis of 1,4-benzothiazines 9a–j and fused cycloalkyl-1,4-benzothiazines 18a–c

To an ice-cooled solution of 1,2-diaza-1,3-butadiene **1a**,**b** as a mixture of *E*/*Z* isomers (1.0 mmol) in dichloromethane (5 mL), the corresponding 2-aminothiophenol **8a–c** (1 mmol) was added. The reaction was allowed to stir at room temperature for 30 min. The solvent was removed by rotary evaporation and the residue was stirred with diethyl ether and then it was filtered through a sintered glass vacuum filtration funnel. The solid was washed with ether and the filtrate was concentrated to dryness in vacuum. The crude products were purified by crystallization or by flash-column chromatography (silica gel, AcOEt) to afford 1,4-benzothiazines **9a**,**b**,**g–j** derived from phosphine oxides and phosphonates. To prepare **9c–f** or **18a–c** a stoichiometric amount of 1,2-diaza-1,3-butadienes **1c**,**d**,**h**,**i** (1 mmol) as a mixture of *E*/*Z* isomers or cycloalkenyl-1-diazenes **15a**,**c**,**d** (1 mmol) was added to a solution of 2-aminothiophenol **8a** (1 mmol) in MeOH (20 mL). The reaction was allowed to stand at room temperature for 20–24 h until the disappearance of the reagents (monitored by TLC). Then, the solvent was removed under reduced pressure. The products **9c–f** and **18a–c** were purified by chromatography on silica (elution mixture: ethyl acetate, cyclohexane 50:50).

4.4.1. *3-Methyl-4H-1,4-benzothiazin-2-yl(diphenyl)-phosphine oxide* ***9a***

Compound **9a** (279 mg, 77%) was obtained as a yellow solid as described in the general procedure: mp 209–210 °C; IR (KBr) ν_{max} 3250, 3052, 1616, 1466, 1429, 1162, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (d, 3H, $^4J_{PH}$=1.6 Hz), 6.57 (td, 1H, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=0.8 Hz), 6.60 (br s, 1H), 6.74 (dd, 1H, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=1.2 Hz), 6.79 (td, 1H, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=0.8 Hz), 6.87 (td, 1H, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=1.2 Hz), 7.43–7.54 (m, 6H), 7.78–7.83 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (d, $^3J_{PC}$=2.8 Hz), 86.8 (d, $^1J_{PC}$=115.2 Hz), 114.5, 124.3, 126.5, 126.6, 126.8, 127.0, 127.2, 127.5, 127.7, 127.8, 128.3, 128.4, 128.6, 128.8, 131.5, 131.6, 131.7, 131.8, 131.8, 131.9, 132.2, 133.3, 141.7, 154.6 (d, $^2J_{PC}$=16.9 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 27.3; MS

(EI) *m*/*z* (%) 363 (M^+, 24), 201 (36), 162 (35), 149 (100), 108 (30), 69 (24); Calcd for $C_{21}H_{18}NOPS$ [M^+] 363.0847. Found [M^+] 363.0848.

4.4.2. Diethyl-(3-methyl-4H-1,4-benzothiazin-2-yl)-phosphonate **9b**

Compound **9b** (221 mg, 74%) was obtained as a yellow oil as described in the general procedure: IR (film) ν_{max} 3415, 1621, 1471, 1226, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ data for the enamine: 1.34 (td, 6H, $^3J_{HH}$=7.2 Hz, $^4J_{PH}$=0.4 Hz), 2.31 (d, 3H, $^4J_{PH}$=2.0 Hz), 3.92–4.15 (m, 4H), 6.09 (br s, 1H), 6.51 (d, 1H, $^3J_{HH}$=7.6 Hz), 6.86–6.99 (m, 3H); data for the imine: 1.06 (td, 3H, $^3J_{HH}$=7.2 Hz, $^4J_{PH}$=0.4 Hz), 1.16 (td, 3H, $^3J_{HH}$=7.2 Hz, $^4J_{PH}$=0.4 Hz), 2.48 (d, 3H, $^4J_{PH}$=4.0 Hz), 3.64 (d, 1H, $^2J_{PH}$=20.1 Hz), 3.92–4.15 (m, 4H), 7.10–7.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (d, $^3J_{PC}$=2.2 Hz)$_{minor}$, 16.0 (d, $^3J_{PC}$=3.0 Hz)$_{minor}$, 16.1 (d, $^3J_{PC}$=6.9 Hz)$_{major}$, 19.5 (d, $^3J_{PC}$=1.9 Hz)$_{major}$, 28.4 (d, $^3J_{PC}$=2.7 Hz)$_{minor}$, 34.8 (d, $^1J_{PC}$=143.6 Hz)$_{minor}$, 61.9 (d, $^2J_{PC}$=5.1 Hz)$_{major}$, 63.1 (d, $^2J_{PC}$=7.3 Hz)$_{minor}$, 63.5 (d, $^2J_{PC}$=7.1 Hz)$_{minor}$, 82.6 (d, $^1J_{PC}$=210.3 Hz)$_{major}$, 114.4, 118.4, 118.4, 119.1, 124.3, 126.4, 126.7, 126.8, 127.1, 127.2, 140.9, 142.0 (d, $^4J_{PC}$=2.3 Hz)$_{minor}$, 154.0 (d, $^2J_{PC}$=25.8 Hz)$_{major}$, 156.4 (d, $^2J_{PC}$=1.5 Hz)$_{minor}$; ^{31}P NMR (160 MHz, $CDCl_3$) δ 14.9$_{major}$, 17.5$_{minor}$; MS (EI) *m*/*z* (%) 299 (M^+, 20), 177 (10), 162 (70), 149 (100), 130 (10), 108 (34), 82 (12); Calcd for $C_{13}H_{18}NO_3PS$ [M^+] 299.0745. Found [M^+] 299.0736.

4.4.3. Methyl-3-methyl-4H-1,4-benzothiazine-2-carboxylate **9c**

Compound **9c** (137 mg, 62% starting from **1c**; 51 mg, 23% starting from **14a**) was obtained as a yellow powder as described in the general procedure: mp 136–137 °C; IR (Nujol) ν_{max} 3228, 1786, 1725, 1568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.73 (s, 3H), 5.81 (br s, 1H), 6.41 (d, 1H, ^3J=7.6 Hz), 6.60–6.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 51.6 (CH_3), 83.3 (C), 114.3 (CH), 120.2 (C), 124.8 (CH), 126.6 (CH), 127.0 (CH), 139.0 (CH), 1514 (C), 161.8 (C); MS: *m*/*z* (%) 221 (M^+, 70), 162 (100), 130 (10). Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 61.25; H, 5.01; N, 6.33. Found: C, 61.32; H, 4.99; N, 6.35.

4.4.4. Ethyl-3-methyl-4H-1,4-benzothiazine-2-carboxylate **9d**

Compound **9d** (183 mg, 78% starting from **1d**; 66 mg, 28% starting from **14b**) was obtained as a yellow powder as described in the general procedure: mp 128–130 °C; IR (Nujol) ν_{max} 3316, 1778, 1713, 1561 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.17 (t, 3H, ^3J=7.2 Hz), 2.17 (s, 3H), 4.03 (q, 2H, ^3J=7.2 Hz), 6.59 (d, 1H, ^3J=7.6 Hz), 6.74–6.79 (m, 2H), 6.86–6.90 (m, 1H), 8.65 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.4 (CH_3), 19.8 (CH_3), 59.7 (CH_2), 85.8 (C), 114.6 (CH), 119.4 (C), 124.0 (CH), 125.6 (CH), 126.9 (CH), 139.0 (C), 152.8 (C), 162.8 (C); MS: *m*/*z* (%) 235 (M^+, 88), 207 (19), 190 (10), 162 (100). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.38; H, 5.63; N, 5.90.

4.4.5. Benzyl-3-methyl-4H-1,4-benzothiazine-2-carboxylate **9e**

Compound **9e** (220 mg, 74%) was obtained as a yellow powder as described in the general procedure: mp 152–154 °C; IR (Nujol) ν_{max} 3257, 1792, 1741, 1537 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 5.20 (s, 2H), 5.66 (br s, 1H), 6.39 (d, 1H, ^3J=8.0 Hz), 6.80–6.90 (m, 3H), 7.28–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8 (CH_3), 66.6 (CH_2), 91.1 (C), 114.7 (CH), 120.9 (C), 125.2 (CH), 127.0 (CH), 127.2 (CH), 128.3 (CH), 128.4 (CH), 129.0 (CH), 136.8 (C), 139.3 (C), 152.2 (C), 163.3 (C); MS: *m*/*z* (%) 297 (M^+, 50), 220 (1), 206 (4), 190 (3), 162 (100), 149 (4), 118 (12). Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.53; H, 5.13; N, 4.75.

4.4.6. Methyl-3-ethyl-4H-1,4-benzothiazine-2-carboxylate **9f**

Compound **9f** (153 mg, 65%) was obtained as a yellow powder as described in the general procedure: mp 120–122 °C; IR (Nujol) ν_{max} 3275, 1765, 1735, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, 3H, ^3J=7.2 Hz), 2.71 (q, 2H, ^3J=7.2 Hz), 3.74 (s, 3H), 6.43 (d, 1H, ^3J=7.6 Hz), 6.69 (br s, 1H), 6.82–6.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4 (CH_3), 27.6 (CH_2), 51.8 (CH_3), 89.5 (C), 114.1 (CH), 120.3 (C), 124.8 (CH), 126.8 (CH), 127.2 (CH), 139.4 (CH), 157.6 (C), 163.8 (C); MS: *m*/*z* (%) 235 (M^+, 70), 220 (3), 204 (5), 176 (100), 160 (5), 130 (10). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.36; H, 5.52; N, 5.86.

4.4.7. 6-Chloro-3-methyl-4H-1,4-benzothiazin-2-yl(diphenyl)phosphine oxide **9g**

Compound **9g** (353 mg, 89%) was obtained as a yellow solid as described in the general procedure: mp 147–148 °C (dec); IR (KBr) ν_{max} 3258, 3172, 3052, 1568, 1453, 1168, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (d, 3H, $^4J_{PH}$=0.9 Hz), 6.58 (s, 1H), 6.65 (d, 1H, $^3J_{HH}$=8.1 Hz), 6.68 (br s, 1H), 6.79 (d, 1H, $^3J_{HH}$=8.1 Hz), 7.43–7.56 (m, 6H), 7.76–7.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5 (d, $^3J_{PC}$=3.0 Hz), 87.3 (d, $^1J_{PC}$=111.2 Hz), 114.7, 124.0, 127.2, 128.5, 131.6, 131.7, 131.9, 131.9, 131.9, 133.1, 133.2, 142.9, 154.0 (d, $^2J_{PC}$=16.5 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 27.1; MS (EI) *m*/*z* (%) 397 (M^+, 4), 281 (40), 207 (100), 183 (20), 133 (8); Calcd for $C_{21}H_{17}ClNOPS$ [M^+] 397.0457. Found [M^+] 397.0453.

4.4.8. Diethyl-(6-chloro-3-methyl-4H-1,4-benzothiazin-2-yl)phosphonate **9h**

Compound **9h** (303 mg, 91%) was obtained as a yellow solid as described in the general procedure: mp 129–130 °C (dec); IR (KBr) ν_{max} 1722, 1625, 1568, 1459, 1219, 1020, 963 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33–1.37 (m, 6H), 2.27 (d, 3H, $^4J_{PH}$=2.1 Hz), 4.06–4.14 (m, 4H), 6.73–6.79 (m, 3H), 7.73 (d, 1H, $^4J_{HH}$=4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (d, $^3J_{PC}$=7.0 Hz), 19.2 (d, $^3J_{PC}$=2.6 Hz), 62.1 (d, $^2J_{PC}$=5.5 Hz), 82.2 (d, $^1J_{PC}$=209.8 Hz), 114.7, 116.8 (d, $^3J_{PC}$=3.5 Hz), 123.9, 126.9, 132.7, 142.3 (d, $^4J_{PC}$=1.0 Hz), 154.0 (d, $^2J_{PC}$=25.5 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 14.9; MS (EI) *m*/*z* (%) 333 (M^+, 8), 211 (16), 196 (60), 183 (100), 148 (30), 107 (18), 69 (16); Calcd for $C_{13}H_{17}ClNO_3PS$ [M^+] 333.0355. Found [M^+] 333.0355.

4.4.9. 3-Methyl-6-(trifluoromethyl)-4H-1,4-benzothiazin-2-yl(diphenyl)phosphine oxide **9i**

Compound **9i** (371 mg, 86%) was obtained as a yellow solid as described in the general procedure: mp 159–160 °C (dec); IR (KBr) ν_{max} 3452, 3052, 1739, 1436, 1225, 1128, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.24 (d, 3H, $^4J_{PH}$=1.4 Hz), 6.76 (d, 1H, $^3J_{HH}$=8.0 Hz), 6.88 (br s, 1H), 6.99 (d, 1H, $^3J_{HH}$=8.0 Hz), 7.43–7.47 (m, 6H), 7.51–7.80 (m, 4H), 7.88 (d, 1H, $^4J_{HH}$=2.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4 (d, $^3J_{PC}$=2.9 Hz), 85.0 (d, $^1J_{PC}$=115.9 Hz), 111.2 (q, $^3J_{FC}$=3.6 Hz), 120.7 (q, $^3J_{FC}$=4.0 Hz), 123.2, 123.7 (q, $^1J_{FC}$=270.1 Hz), 126.4, 129.7 (q, $^2J_{FC}$=33.0 Hz), 131.6, 131.7, 131.8, 132.0, 132.0, 132.8, 142.3, 154.7 (d, $^2J_{PC}$=16.6 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 27.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.2; MS (EI) *m*/*z* (%) 431 (M^+, 8), 281 (10), 231 (6), 217 (100), 201 (50), 157 (18), 132 (16), 77 (8); Calcd for $C_{22}H_{17}F_3NOPS$ [M^+] 431.0721. Found [M^+] 431.0731.

4.4.10. Diethyl-[3-methyl-6-(trifluoromethyl)-4H-1,4-benzothiazin-2-yl]phosphonate **9j**

Compound **9j** (323 mg, 88%) was obtained as a yellow solid as described in the general procedure: mp 123–124 °C; IR (KBr) ν_{max} 3275, 1625, 1533, 1465, 1328, 1225, 1117, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32–1.38 (m, 6H), 2.28 (d, 3H, $^4J_{PH}$=1.7 Hz), 4.08–4.16 (m, 4H), 6.91 (br s, 1H), 6.92 (d, 1H, $^3J_{HH}$=8.0 Hz), 7.06 (d, 1H, $^3J_{HH}$=8.0 Hz), 7.85 (d, 1H, $^4J_{HH}$=4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1 (d, $^3J_{PC}$=7.0 Hz), 19.2 (d, $^3J_{PC}$=2.6 Hz), 62.2 (d, $^2J_{PC}$=5.0 Hz), 81.7 (d, $^1J_{PC}$=211.3 Hz), 111.0 (q, $^3J_{FC}$=3.4 Hz), 120.8 (q, $^3J_{FC}$=4.0 Hz), 123.6, 123.8 (q, $^1J_{FC}$=270.4 Hz), 126.4, 129.4 (q, $^2J_{FC}$=32.6 Hz), 141.6 (d, $^4J_{PC}$=1.0 Hz), 154.0 (d, $^2J_{PC}$=25.0 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 14.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.2; MS (EI) *m*/*z* (%) 367 (M^+, 8), 281 (6), 230 (45), 217 (100), 207 (12),

157 (20); Calcd for $C_{14}H_{17}F_3NO_3PS$ [M^+] 367.0619. Found [M^+] 367.0618.

4.4.11. Ethyl-1,2,3,3a-tetrahydrobenzo[b]cyclopenta[e][1,4]-thiazine-3a-carboxylate *18a*

Compound **18a** (154 mg, 59%) was obtained as a yellow powder as described in the general procedure: mp 56–58 °C; IR (Nujol) ν_{max} 3318, 1763, 1743, 1565 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, ^3J=7.2 Hz), 1.95–2.05 (m, 2H), 2.05–2.20 (m, 1H), 2.62–2.70 (m, 1H), 2.80–3.02 (m, 2H), 3.98 (q, 2H, ^3J=7.2 Hz), 7.10 (dt, 1H, ^3J=7.6 Hz, ^4J=1.2 Hz), 7.20 (dt, 1H, ^3J=7.6 Hz, ^4J=1.2 Hz), 7.29 (dd, 1H, ^3J=8.0 Hz, ^5J=1.2 Hz), 7.40 (dd, 1H, ^3J=8.0 Hz, ^5J=1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 21.6 (CH_2), 34.8 (CH_2), 36.8 (CH_2), 48.2 (C), 62.0 (CH_2), 120.5 (C), 126.4 (CH), 126.7 (CH), 127.0 (CH), 127.2 (CH), 142.4 (C), 170.1 (C), 170.8 (C); MS: *m*/*z* (%) 261 (M^+, 20), 231 (6), 217 (9), 202 (13), 188 (100), 173 (20). Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.40; H, 5.80; N, 5.32.

4.4.12. Methyl-5a,6,7,8,9,10-hexahydrobenzo[b]cyclohepta[e][1,4]-thiazine-5a-carboxylate *18b*

Compound **18b** (239 mg, 87%) was obtained as a yellow powder as described in the general procedure: mp 62–64 °C; IR (Nujol) ν_{max} 3324, 1775, 1588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60–1.79 (m, 4H), 1.92–2.05 (m, 2H), 2.15–2.22 (m, 1H), 2.32–2.39 (m, 1H), 2.79–2.85 (m, 1H), 2.90–2.97 (m, 1H), 3.52 (s, 3H), 7.06 (dt, 1H, ^3J=7.6 Hz, ^4J=1.2 Hz), 7.16 (dt, 1H, ^3J=7.6 Hz, ^4J=1.6 Hz), 7.25 (dd, 1H, ^3J=7.6 Hz, ^5J=1.2 Hz), 7.40 (dd, 1H, ^3J=8.0 Hz, ^5J=1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7 (CH_2), 27.3 (CH_2), 30.6 (CH_2), 34.0 (CH_2), 40.3 (CH_2), 52.2 (CH_2), 53.0 (CH_3), 122.6 (C), 126.4 (CH), 126.5 (CH), 126.6 (CH), 127.0 (CH), 141.4 (C), 166.4 (C), 171.6 (C); MS: *m*/*z* (%) 275 (M^+, 15), 261 (5), 250 (8), 230 (130), 216 (100). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 64.43; H, 6.22; N, 5.09. Found: C, 64.48; H, 6.20; N, 5.07.

4.4.13. Ethyl-6,7,8,9,10,11-hexahydro-5aH-benzo[b]cycloocta[e]-[1,4]thiazine-5a-carboxylate *18c*

Compound **18c** (230 mg, 76%) was obtained as a yellow powder as described in the general procedure: mp 57–59 °C; IR (Nujol) ν_{max} 3276, 1736, 1561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, 3H, ^3J=7.2 Hz), 1.41–1.50 (m, 1H), 1.56–1.67 (m, 3H), 1.73–1.90 (m, 4H), 2.09–2.16 (m, 1H), 2.53–2.60 (m, 1H), 2.69–2.76 (m, 1H), 2.81–2.94 (m, 1H), 4.05 (q, 2H, ^3J=7.2 Hz), 7.05–7.09 (m, 1H), 7.13–7.17 (m, 1H), 7.20–7.22 (m, 1H), 7.34–7.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 24.5 (CH_2), 25.0 (CH_2), 26.4 (CH_2), 26.8 (CH_2), 28.4 (CH_2), 31.3 (CH_2), 36.2 (CH_2), 52.3 (CH_2), 62.1 (CH_2), 121.7 (C), 126.3 (CH), 127.0 (CH), 127.6 (CH), 140.7 (C), 167.3 (C), 171.1 (C). MS: *m*/*z* (%) 303 (M^+, 10), 230 (100). Anal. Calcd for $C_{17}H_{21}NO_2S$: C, 67.30; H, 6.98; N, 4.62. Found: C, 64.48; H, 6.20; N, 5.07.

4.5. General procedure for the synthesis of α-substituted hydrazones 3b,c, 20a, 23a and 4-substituted-5-methyl-2,3-dihydro-1*H*-3-pyrazolones 12a, 22a, 25a

To an ice-cooled solution of 1,2-diaza-1,3-butadiene **1a** as a mixture of *E*/*Z* isomers (1.0 mmol) in dichloromethane (5 mL), 2-mercaptoethanol **2d** (1 mmol) was added. The reaction was allowed to stir at room temperature for 30 min. The solvent was removed by rotary evaporation and the crude product was purified by flash-column chromatography (silica gel, AcOEt) and recrystallized from AcOEt to afford α-substituted hydrazone **3b** derived from phosphine oxide. To obtain α-substituted hydrazones **3c**, **20a**, **23a**, 2-mercaptoethanol **2d** or 2-mercaptobenzimidazole **19a** or 3-mercapto-1,2,4-triazole **19b** (2 mmol) was added to a solution of 1,2-diaza-1,3-butadienes **1c**,**d** (1 mmol) as a mixture of *E*/*Z* isomers in MeOH (20 mL). The reaction mixture was allowed to stand at room temperature under magnetic stirring for 5 h until the complete disappearance of the reagents (monitored by TLC) furnishing methyl-3-[2-(aminocarbonyl)hydrazono]-2-[(2-hydroxyethyl)sulfanyl]butanoate **3c**, or ethyl-3-[2-(aminocarbonyl)hydrazono]-2-(1*H*-benzo[*d*]imidazol-2-ylsulfanyl)butanoate **20a**, or ethyl-3-[2-(aminocarbonyl)hydrazono]-2-(1*H*-1,2,4-triazol-3-ylsulfanyl)butanoate **23a**. Then the solvent was removed under reduced pressure and the crude mixture was purified by chromatography on silica (elution mixture: ethyl acetate) obtaining the pure products **3c**, **20a**, **23a**. To achieve the 4-substituted-5-methyl-2,3-dihydro-1*H*-3-pyrazolones **12a**, **22a**, **25a** a catalytic amount of sodium hydride (0.1 mmol) was added to a solution of the pure hydrazones **3c**, **20a**, **23a** (1 mmol) in MeOH (15 mL) or directly to the crude hydrazones in solution obtained as previously described. The reaction mixture was allowed to stand at room temperature for 48–72 h until the complete disappearance of the starting reagent (monitored by TLC, mixture: ethyl acetate). Pyrazolones **12a**, **22a**, **25a** directly precipitated from the reaction medium and they were collected by filtration as pure products.

4.5.1. Ethyl-2-(diphenylphosphoryl)-2-[(2-hydroxyethyl)sulfanyl]-1-methylethylidene-1-hydrazinecarboxylate *3b*

Compound **3b** (408 mg, 97%) was obtained as a colourless solid as described in the general procedure: mp 125–126 °C; IR (KBr) ν_{max} 3411, 3171, 1725, 1525, 1437, 1230, 1185, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23–1.34 (m, 3H), 2.01 (s, 3H), 2.58–2.76 (m, 2H), 3.57–3.63 (m, 2H), 4.12–4.16 (m, 2H), 4.30 (br s, 1H), 4.64 (d, 1H, $^2J_{PH}$=9.3 Hz), 7.39–7.92 (m, 10H), 8.75 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 14.1, 34.7 (d, $^3J_{PC}$=5.7 Hz), 52.2 (d, $^1J_{PC}$=67.7 Hz), 60.9, 61.2, 128.1, 128.2, 128.3, 128.4, 129.8, 130.3, 130.5, 130.6, 130.8, 130.9, 130.9, 131.0, 131.1, 131.2, 131.4, 131.7, 131.7, 131.8, 131.8, 148.6, 153.8; ^{31}P NMR (120 MHz, $CDCl_3$) δ 29.3; MS (CI) *m*/*z* (%) 421 (M^++1, 100); Calcd for $C_{20}H_{25}N_2O_4PS$ [M^+] 420.1368. Found [M^+] 420.1377.

4.5.2. Methyl-3-[2-(aminocarbonyl)hydrazono]-2-[(2-hydroxyethyl)sulfanyl]butanoate *3c*

Compound **3c** (221 mg, 89%) was obtained as a colourless powder as described in the general procedure: mp 160–162 °C; IR (Nujol) ν_{max} 3308, 1784, 1731, 1598 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.83 (s, 3H), 2.54 (t, 2H, ^3J=6.4 Hz), 3.48 (t, 2H, ^3J=6.4 Hz), 3.65 (s, 3H), 4.44 (s, 1H), 4.85 (s, 1H), 6.28 (br s, 2H), 9.30 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.1 (CH_3), 33.2 (CH_2), 52.6 (CH_3), 54.7 (CH), 60.3 (CH_2), 142.7 (C), 157.0 (C), 169.4 (C); MS: *m*/*z* (%) 249 (M^+, 10), 232 (10), 219 (28), 205 (22), 191 (38), 165 (45), 149 (100). Anal. Calcd for $C_8H_{15}N_3O_4S$: C, 38.55; H, 6.06; N, 16.86. Found: C, 38.42; H, 6.11; N, 16.72.

4.5.3. 4-[(2-Hydroxyethyl)sulfanyl]-5-methyl-2,3-dihydro-1H-3-pyrazolone *12a*

Compound **12a** (101 mg, 58% starting from **1c**, 130 mg, 75% starting from **3e**) was obtained as a colourless powder as described in the general procedure: mp 184–187 °C; IR (Nujol) ν_{max} 3159, 1736, 1606 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.60 (s, 3H), 2.48 (m, 2H), 3.38 (t, 2H, ^3J=6.8 Hz), 4.81 (br s, 1H), 10.16 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.2 (CH_3), 38.0 (CH_2), 60.3 (CH_2), 90.4 (C), 143.5 (C), 162.1 (C); MS: *m*/*z* (%) 174 (M^+, 58), 156 (25), 143 (30), 130 (40), 99 (56), 85 (23), 57 (50), 44 (100). Anal. Calcd for $C_6H_{10}N_2O_2S$: C, 41.37; H, 5.79; N, 16.08. Found: C, 41.31; H, 5.82; N, 16.16.

4.5.4. Ethyl-3-[-2-(aminocarbonyl)hydrazono]-2-(1H-benzo[d]imidazol-2-ylsulfanyl)butanoate *20a*

Compound **20a** (312 mg, 93%) was obtained as a colourless powder as described in the general procedure: mp 198–200 °C; IR (Nujol) ν_{max} 3302, 1789, 1767, 1714, 1516 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.12–1.19 (m, 3H), 1.95 (s, 3H), 4.16 (q, 2H, ^3J=7.2 Hz),

5.45 (s, 1H), 6.30 (br s, 2H), 6.35 (br s, 1H), 7.05–7.14 (m, 2H), 7.38–7.50 (m, 2H), 9.50 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8 (CH_3), 14.3 (CH_3), 56.2 (CH), 61.7 (CH_2), 110.6 (CH), 120.9 (CH), 121.4 (CH), 122.1 (CH), 141.3 (C), 143.4 (C), 147.2 (C), 156.7 (C), 158.2 (C), 167.9 (C); MS: *m*/*z* (%) 335 (M^+, 1), 261 (2), 246 (9), 185 (2), 162 (49), 150 (100). Anal. Calcd for $C_{14}H_{17}N_5O_3S$: C, 50.14; H, 5.11; N, 20.88. Found: C, 50.05; H, 5.04; N, 20.97.

4.5.5. 4-(1H-Benzo[d]imidazol-2-ylsulfanyl)-5-methyl-2,3-dihydro-1H-3-pyrazolone ***22a***

Compound **22a** (219 mg, 89% starting from **1d**; 240 mg, 97% starting from **20a**) was obtained as a colourless powder as described in the general procedure: mp 212–214 °C; IR (Nujol) ν_{max} 3306, 1765, 1723, 1618 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.16 (s, 3H), 7.03–7.07 (m, 2H), 7.30–7.38 (m, 2H), 10.43 (br s, 1H), 11.92 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.6 (CH_3), 79.2 (C), 113.7 (CH), 120.9 (CH), 151.7 (C), 153.0 (C), 153.5 (C), 164.4 (C); MS: *m*/*z* (%) 246 (M^+, 100), 213 (12), 162 (50), 150 (93), 118 (32), 97 (38). Anal. Calcd for $C_{11}H_{10}N_4OS$: C, 53.65; H, 4.09; N, 22.75. Found: C, 53.70; H, 4.04; N, 22.61.

4.5.6. Ethyl-3-[-2-(aminocarbonyl)hydrazono]-2-(1H-1,2,4-triazol-5-ylsulfanyl)butanoate ***23a***

Compound **23a** (272 mg, 95%) was obtained as a colourless powder as described in the general procedure: mp 128–130 °C; IR (Nujol) ν_{max} 3274, 1789, 1765, 1534 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (t, 3H, ^3J=6.8 Hz), 1.91 (s, 3H), 3.16 and 3.17 (2s, 1H), 4.12 (q, 2H, ^3J=6.8 Hz), 5.08 (s, 1H), 6.19 (br s, 2H), 8.95 (s, 1H), 9.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8 (CH_3), 14.1 (CH_3), 56.3 (CH), 61.5 (CH_2), 141.6 (C), 144.9 (CH), 156.7 (C), 158.3 (C), 168.1 (C); MS: *m*/*z* (%) 287 (M^++1, 8), 246 (4), 197 (100), 187 (20), 155 (38), 129 (27), 113 (100). Anal. Calcd for $C_9H_{14}N_6O_3S$: C, 37.76; H, 4.93; N, 29.35. Found: C, 37.65; H, 4.99; N, 29.22.

4.5.7. 5-Methyl-4-(1H-1,2,4-triazol-3-ylsulfanyl)-2,3-dihydro-1H-3-pyrazolone ***25a***

Compound **25a** (181 mg, 92% starting from **1d**; 193 mg, 98% starting from **23a**) was obtained as a colourless powder as described in the general procedure: mp 242–244 °C; IR (Nujol) ν_{max} 3243, 1787, 1723, 1576 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.99 (s, 3H), 4.13 (br s, 1H), 6.96 (s, 1H), 7.80 (br s, 1H), 9.04 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.6 (CH_3), 75.6 (C), 150.0 (C), 153.7 (CH), 165.8 (C). MS: *m*/*z* (%) 197 (M^+, 100), 155 (23), 129 (10), 97 (63), 86 (15). Anal. Calcd for $C_{11}H_{10}N_4OS$: C, 36.54; H, 3.58; N, 35.51. Found: C, 36.70; H, 3.64; N, 35.40.

4.6. General procedure for the synthesis of 3,4-dihydro-2*H*-1,4-thiazines 5c,d,h,i and 1,4-benzothiazines 9c,d in solid phase

To a magnetically stirred solution of N=N-polymer-bound 1,2-diaza-1,3-butadiene **14a**,**b** prepared starting from polymer-bound *p*-toluenesulfonyl hydrazide **13** (1 mmol),[18] the thiolamine **2a**,**b** (5 equiv) was added at room temperature in MeOH/THF (1:1, 10 mL). After 10 min, the solution was filtered and the resin was washed with MeOH, THF, DCM (3×5 mL), and then treated with sodium acetate (2 equiv) in MeOH/THF (1:1, 10 mL). The mixture was allowed to stand at room temperature for 24–28 h under magnetic stirring, obtaining the 3,4-dihydro-2*H*-1,4-thiazines **5c**,**d**,**h**,**i** directly in solution in satisfactory purity. To synthesize compounds **9c**,**d**, 2-aminothiophenol **8a** (5 equiv) in MeOH/THF (1:1, 10 mL) was added to N=N-polymer-bound 1,2-diaza-1,3-butadienes **14a**,**b** prepared starting from polymer-bound *p*-toluenesulfonyl hydrazide (1 mmol). The reaction mixture was allowed to stand at room temperature under magnetic stirring for 6–8 h furnishing directly 1,4-benzothiazines **9c**,**d** in solution. The products **9c**,**d** were purified by chromatography on silica (elution mixture: ethyl acetate, cyclohexane 50:50).

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