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Facile access to γ-aminothiols from 1,3-thiazines via a microwave-assisted three-component reaction

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ABSTRACT

A new efficient and general synthetic methodology to access γ-aminothiols was investigated and developed. 1,3-Thiazines were used as convenient precursors and were prepared by a fast microwave-assisted three-component reaction (3CR) of thioamides, aldehydes, and alkenes. The transformation of thiazines into aminothiols was achieved via a thiazinium salt hydrolysis, in three very facile steps.

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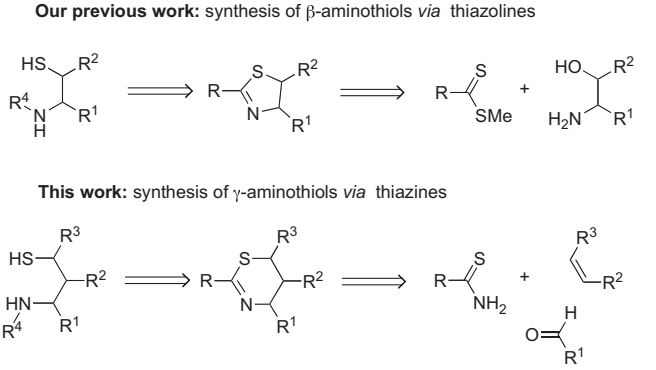
1. Introduction

γ-Aminothiols[1] are much less studied compared to their β-analogues,[2] due to the lack of general methods for their preparation,[3] mainly using little available 1,3-aminoalcohols as precursors. Recent results that we obtained in the preparation of primary and secondary β-aminothiols from thiazolines, via aminoalcohols thioacylation,[4] prompted us to extend the methodology to γ-aminothiols (Scheme 1). Thus, we envisaged the use of 1,3-thiazines as convenient and versatile precursors of γ-aminothiols. Among the various methods developed for the synthesis of 1,3-thiazines,[5] the hetero-Diels–Alder (HDA) reaction involving a thiaazadiene represents a straightforward route.[6] A few examples consist in a three-component reaction (3CR).[7–9] For our purpose this appeared as a versatile methodology, which would enable the access to a large variety of structures (Scheme 1).

Herein, we report an easy and general synthetic methodology of γ-aminothiols from 1,3-thiazines, via a three-component reaction involving a thioamide, an aldehyde, and an alkene, and using simple reagents. Moreover, a very fast and efficient procedure for the 3CR using microwave activation is described and the scope and limitations of the reaction are established.



Scheme 1. Synthetic methodologies for β- and γ-aminothiols preparation.

2. Results and discussion

2.1. Synthesis of 1,3-thiazines

This three-component HDA reaction consists in the in situ condensation of the aminothiocarbonyl partner with an aldehyde to give an *N*-thioacyl imine heterodiene,[6,10] which then reacts with an alkene affording a 1,3-thiazine cycloadduct. This reaction can be promoted by a Lewis acid or a Brønsted acid. We started our study by a screening of the reaction conditions applied to the 3CR

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involving thiobenzamide, benzaldehyde, and 1-hexene. The nature of the catalyst [PTSA, TFA, $BF_3{\cdot}OEt_2$, $Cu(OTf)_2$], the presence of a water-adsorbent agent ($MgSO_4$ or molecular sieves), the solvent (chloroform, dichloromethane, dichloroethane, toluene), the temperature (room temperature to 100 °C), and the reaction stoichiometry were varied. Finally, the best result (98% yield) was obtained for a ratio of aldehyde/thioamide/alkene of 1:1.2:1.2, with 2 equiv of $BF_3{\cdot}OEt_2$, in dichloromethane, at 50 °C, in the presence of $MgSO_4$. The main disadvantage of the reaction was a too long reaction time (5 days for a total conversion). As the use of microwave irradiation was shown to be efficient in this type of reaction, we attempted the use of this type of activation. With the same reagents, after the reaction optimization, we found that in 1,2-dichloroethane, under 40 W irradiation (150 °C), the conversion was total after only 10 min, and the isolated yield was excellent (Scheme 2, Table 1, entry 1).

The [4+2] cycloaddition of *N*-thioacyliminium dienes is known to be regioselective,[6a] however the *endo*/*exo* selectivity of the HDA can vary with the substrate structure. In this first example, thiazine **4a** was obtained in a 1:1 *endo*/*exo* (**A**/**B**) ratio. Nevertheless, it was possible to easily separate the diastereomers by column chromatography on silica gel. Keeping the same protocol (see experimental procedure A), we examined the scope and limitations of this reaction. First, the alkene partner was varied (Table 1, entries 1–8). The formation of the styrene adduct **4b** was highly *endo*-selective[7] (**A**/**B**: 1:0.2) and the product was isolated in a good yield of 94% (Table 1, entry 2). Thiazine **4c** (Table 1, entry 3) represents an interesting case, as the presence of the alkyl bromide enables the introduction of other functional groups. When 4-pentenoic acid was used as the alkene, we were surprised to obtain cleanly the 1,3-thiazine as the ethyl ester derivative **4d** (Table 1, entry 4). This could be explained by the formation of the Meerwein's alkylating reagent ($Et_3O^+BF_4^-$) from $BF_3{\cdot}OEt_2$.[11] As expected, by using $BF_3{\cdot}THF$ as the catalyst, we could preserve the carboxylic acid function in product **4e** (Table 1, entry 5). However, the yield was lower due to the competing formation of the γ-valerolactone as a product of intramolecular hydrocarboxylation.[11]

Then, cyclic *cis*-alkenes (i.e., cyclohexene, cyclooctene, and norbornene) were employed. A mixture of *endo* and *exo* diastereoisomers was obtained for thiazines **4f** and **4g**, in a 1:1.6 and 1:1.3 ratio, respectively (Table 1, entries 6 and 7). In both cases, it was also possible to isolate each stereoisomer after separation by column chromatography. An X-ray structure was obtained for **4f-B** (Fig. 1), which confirmed the relative stereochemistry deducted from the NMR analysis.

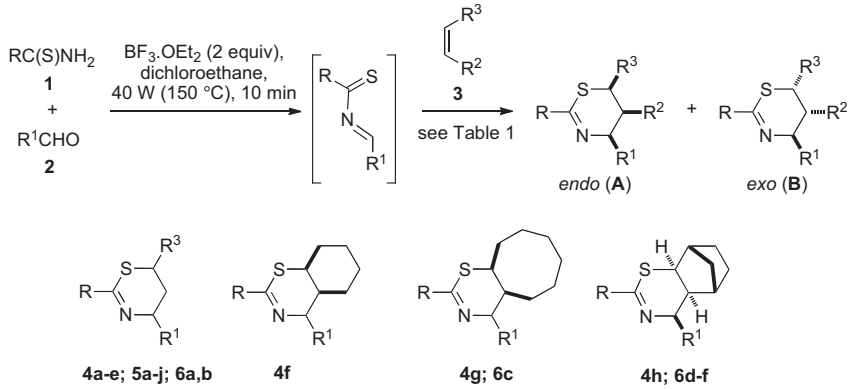
The HDA reaction with norbornene (Table 1, entry 8) can potentially lead to four possible diastereomers: two arising from the *endo* or *exo* facial addition to one or another face of the dienophile and two from the *endo* or *exo* attack related to the [4+2] cycloaddition. The strong preference of norbornene to react via the *exo*-face, together with a high *exo* selectivity of this cycloaddition, led to a single diastereomer **4h-B** with *exo*–*exo* selectivity (Scheme 3).[12] The relative stereochemistry of **4h-B** was unambiguously assigned by X-ray crystallography (Scheme 3 and Supplementary data).

In a second series of experiments, the electronic nature and position of the substituents on the aromatic aldehyde were varied (Table 1, entries 9–18). Whatever the aldehyde was used, a mixture of *endo* (**A**) and *exo* (**B**) adducts was obtained (ratios varying from 1:1 to 1:0.5). Total conversions were obtained in all the cases, yields were good to excellent and, in the most of the cases, the two diastereomers were separated by column chromatography on silica gel. The heteroaromatic aldehyde, 3-thiophenyl aldehyde, led to the expected thiazine **5j** (entry 18). Finally, the thioamide partner was also changed. The 3CRs of thioacetamide and benzaldehyde with six different alkenes led to the expected thiazines **6a**–**f** (entries 19–24). The **A**/**B** ratios and the yields were similar to those

Table 1
Synthesis of 1,3-thiazines **4**–**6**

Entry	Product	R	R^1	R^2	R^3	Ratio **A**/**B**[a]	Yields[b] (%) **A**; **B**
1	**4a**	Ph	Ph	H	n-C_4H_9	1:1	47; 49
2	**4b**	Ph	Ph	H	Ph	1:0.2	82; 12
3	**4c**	Ph	Ph	H	$(CH_2)_2Br$	1:1.6	32; 62
4[c]	**4d**	Ph	Ph	H	$(CH_2)_2CO_2Et$	1:1	20; 28
5[d]	**4e**	Ph	Ph	H	$(CH_2)_2CO_2H$	1:1	28; 21
6	**4f**	Ph	Ph	$(CH_2)_4$		1:1.6	26; 50
7	**4g**	Ph	Ph	$(CH_2)_6$		1:1.3	20; 52
8	**4h**	Ph	Ph	$[CHCH_2]_2(CH_2)$		0:1	0; 78
9	**5a**	Ph	4-Me–C_6H_4	H	n-C_4H_9	1:0.9	52; 46
10	**5b**	Ph	4-Cl–C_6H_4	H	n-C_4H_9	1:1	38; 37
11	**5c**	Ph	4-Br–C_6H_4	H	n-C_4H_9	1:1	32; 19
12	**5d**	Ph	4-NO_2–C_6H_4	H	n-C_4H_9	1:0.9	53; 45
13	**5e**	Ph	2-MeO–C_6H_4	H	n-C_4H_9	1:1.5	82[e]
14	**5f**	Ph	3-HO–C_6H_4	H	n-C_4H_9	1:1.1	70[e]
15	**5g**	Ph	3-Br–C_6H_4	H	n-C_4H_9	1:1	54[e]
16	**5h**	Ph	3-NO_2–C_6H_4	H	n-C_4H_9	1:1	69[e]
17	**5i**	Ph	1-Naphthyl	H	n-C_4H_9	1:1.3	30; 55
18	**5j**	Ph	3-Thienyl	H	n-C_4H_9	1:1	38; 49
19	**6a**	Me	Ph	H	n-C_4H_9	1:1.4	34; 57
20	**6b**	Me	Ph	H	Ph	1:0.2	75; 16
21	**6c**	Me	Ph	$(CH_2)_6$		1:1	50; 50
22	**6d**	Me	Ph	$[CHCH_2]_2(CH_2)$		0:1	0; 100
23	**6e**	Me	1-Naphthyl	$[CHCH_2]_2(CH_2)$		0.3:1	23; 76
24	**6f**	Me	4-Cl-C_6H_4	$[CHCH_2]_2(CH_2)$		0.1:1	0; 50

[a] Measured by ^1H NMR in the crude mixture.
[b] Isolated yields of each A (*endo*) and B (*exo*) adducts.
[c] R^3=CO_2H in the alkene; R^3=CO_2Et in the product.
[d] R^3=CO_2H is preserved in the product by using $BF_3{\cdot}THF$ instead $BF_3{\cdot}OEt_2$.
[e] Inseparable mixture of diastereomers.



Scheme 2. Synthesis of 1,3-thiazines **4**–**6**.

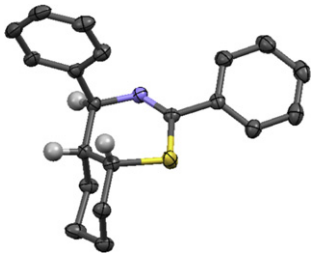
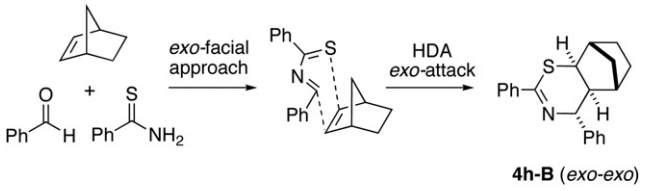
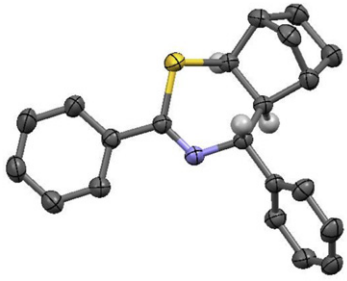


Fig. 1. X-ray crystallographic structures of thiazines **4f-B**.





Scheme 3. Reaction of thiobenzamide, benzaldehyde, and norbornene; formation of adduct **4h-B** and its X-ray crystal structure.

obtained previously. The relative cis spatial arrangement between the phenyl and the cyclooctyl substituents of **6c-A** has been demonstrated by X-ray diffraction (Fig. 2). With norbornene, the *exo-exo* adducts **6e**,**f** were formed again preferentially (see X-ray structure of **6f-B** in Fig. 2). Some limitations of this 3CR were, however, revealed from the study. The expected thiazines were not obtained with the following components: methylenecyclohexane, ethyl vinyl ether, and ethyl acrylate[13] (as alkenes), or isopropylaldehyde, pivalaldehyde, and ethyl glyoxalate (as aldehydes).

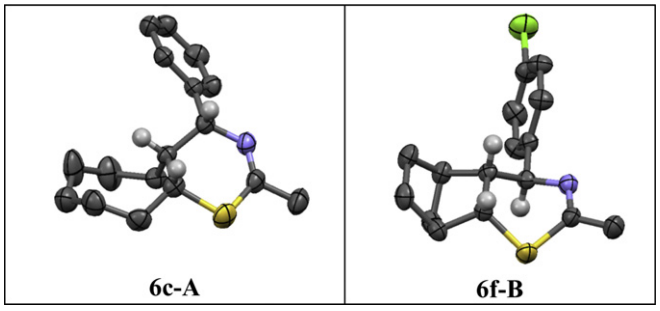
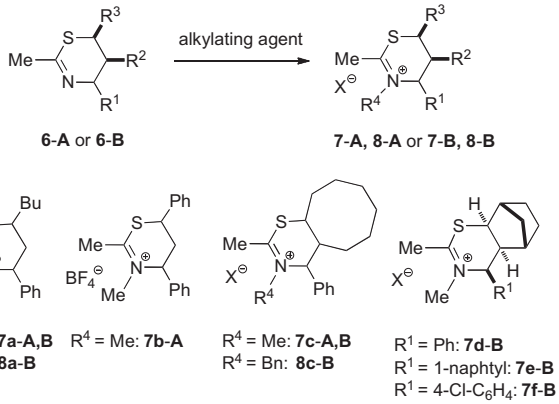


Fig. 2. X-ray crystallographic structures of thiazines **6c-A** and **6f-B**.

2.2. Synthesis of γ-aminothiols

In the second part of our study we attempted the transformation of 1,3-thiazines or their *N*-alkyl thiazinium salts into primary or secondary γ-aminothiols, respectively. Two methods were envisaged: a one-step hydrolysis under acidic conditions, or a two-step hydrolysis via the heterocycle ring-opening, then deprotection of the resulting amide or thioester. When 2-phenyl thiazine **4a** was placed in an aqueous solution of HCl 6 N and maintained under reflux for 7 days, only the thiazinium hydrochloride was recovered. The next experiments were carried out in 2-methyl thiazines series, as their hydrolysis[14] was expected to be easier than that of the 2-phenyl derivatives, by analogy with our previous studies on 2-thiazolines.[4] However, the acidic hydrolysis of **6a** also failed. Then, thiazines **6** were *N*-methylated or benzylated to obtain thiazinium salts **7** or **8**, respectively (Table 2; see experimental procedures B1 and B2). Surprisingly, the N-benzylation of **6**(**a**–**c**)-**A** and **6d-B** failed, probably for steric reasons (Table 2, entries 3, 6, 9, and 12). In the all other cases the desired products were obtained in high yields and did not need purification before their involvement in the next step.

Table 2
Synthesis of 1,3-thiazinium salts **7** and **8**

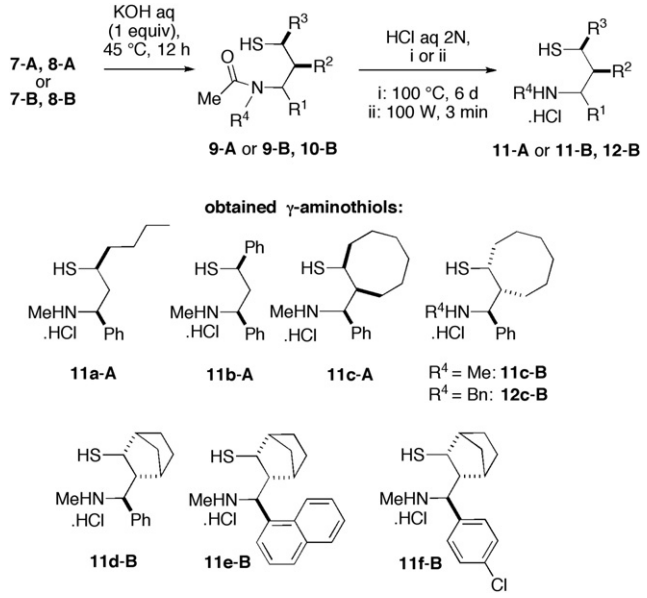


Entry	Thiazine	R^4	X	Thiazinium salt	Yield (%)
1	**6a-A**	Me	BF_4	**7a-A**	95
2	**6a-B**	Me	BF_4	**7a-B**	100
3	**6a-A**	Bn	Br	**8a-A**	—
4	**6a-B**	Bn	Br	**8a-B**	100
5	**6b-A**	Me	BF_4	**7b-A**	82
6	**6b-A**	Bn	Br	**8b-A**	—
7	**6c-A**	Me	BF_4	**7c-A**	97
8	**6c-B**	Me	BF_4	**7c-B**	83
9	**6c-A**	Bn	Br	**8c-A**	—
10	**6c-B**	Bn	Br	**8c-B**	91
11	**6d-B**	Me	BF_4	**7d-B**	95
12	**6d-B**	Bn	Br	**8d-B**	—
13	**6e-B**	Me	BF_4	**7e-B**	65
14	**6f-B**	Me	$MeSO_4$	**7f-B**	90

When thiazinium salt **7a** was placed in an aqueous solution of HCl 6 N and maintained under reflux for 7 days, only the starting material was recovered. Finally, we attempted the two-step hydrolysis. The thiazinium salts **7** or **8** were placed in an aqueous solution containing 1 equiv of potassium hydroxide, at 45 °C (Table 3; see experimental procedure C). In all cases we observed the totally selective C–S cleavage (vs the C–N cleavage),[14a] leading to 3-sulfanyl acetamides **9** or **10**, respectively. Total conversions and moderate to excellent isolated yields (between 47 and 99%) were obtained. Two rotamers were observed by NMR spectroscopy for these products, due to the presence of the tertiary acetamide function (see Supplementary data).

The last step consisted in the treatment of the resulting amides with aqueous HCl, to afford the secondary γ-aminothiols. On the other hand, the deprotection of a tertiary acetamide is not a trivial reaction.[15] Moreover, in our case, the presence of the thiol function

Table 3
Hydrolysis of thiazinium salts: access to aminothiols **11** and **12**



Entry	Thiazinium salt	Sulfanyl amide	Yield[a] (%)	Aminothiol	Yield[a] (%)
1	**7a-A**	**9a-A**	96	**11a-A**	74[c]
2	**7a-B**	**9a-B**	90	**11a-B**	—[b]
3	**8a-B**	**10a-B**	99	**12a-B**	—[b]
4[c]	**7b-A**	**9b-A**	73	**11b-A**	70[d]
5[d]	**7c-A**	**9c-A**	80	**11c-A**	72[d]
6	**7c-B**	**9c-B**	99	**11c-B**	77[d]
7	**8c-B**	**10c-B**	65	**12c-B**	54[d]
8	**7d-B**	**9d-B**	99	**11d-B**	99[c] or[d]
9	**7e-B**	**9e-B**	54	**11e-B**	90[d]
10	**7f-B**	**9f-B**	47	**11f-B**	86[d]

[a] Isolated yields.
[b] Not obtained.
[c] Thermal conditions (i).
[d] MW conditions (ii).

increases the difficulty, as the oxidation in disulfide should be avoided. Acetamide **9a-A** was heated at 100 °C in a 2 N aqueous solution of HCl (see experimental procedure D1) and was totally converted, after 6 days, into the desired aminothiol **11a-A**, isolated in 74% yield as its hydrochloride (Table 3, entry 1). Under the same reaction conditions, **9a-B** and **10a-B** remained unchanged (entries 2 and 3),[16] whereas the norbornene derivative **9d-B** afforded quantitatively the expected product in 24 h (entry 8). To accelerate the hydrolysis, we attempted the same reaction under microwave irradiation.[17] In this case, the formation of **11d-B** was complete after only 3 min, again with an excellent yield. Excepted for the amides derived from thiazine **6a** (entries 1–3), the microwave-activated deacetylation was successfully applied also for other examples, affording the desired secondary γ-aminothiols (entries 4–7 and 9, 10; see experimental procedure D2).

3. Conclusion

In summary, we developed a first general method to synthesize γ-aminothiols by using 1,3-thiazines as convenient precursors. These latter were prepared by a fast and efficient microwave-assisted three-component reaction (3CR) involving a thioamide, an alkene, and an aldehyde. The transformation of thiazines into aminothiols needs three facile steps via a thiazinium salt hydrolysis, under simple basic (KOH aqueous) and acidic conditions (HCl aqueous). The last step, which consisted in the often difficult deacetylation of a tertiary amide, was achieved by a fast acid hydrolysis under microwave irradiation. By varying the partners in the 3CR, the present methodology enables the access to a wide variety of 1,3-thiazines and γ-aminothiols structures, which are still underexplored compounds with a high potential for synthetic and biological applications.

4. Experimental

4.1. General

All reagents were purchased from Acros Organics, Sigma Aldrich, or Fluka and were used without further purification. Solvents were used in RPE grade without further purification. Anhydrous solvents were obtained from a PURESOLV SPS400 apparatus developed by Innovative Technology Inc.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 MHz or a Bruker DRX 500 MHz spectrometer. Samples were dissolved in an appropriate deuterated solvent ($CDCl_3$, acetone-d_6, D_2O). The chemical shifts (δ) are expressed in parts per million relative to internal tetramethylsilane for ^{1}H and ^{13}C nucleus, and coupling constants are indicated in hertz. Abbreviations for signal coupling are as follows: s=singlet; d=doublet; dd=doublet of doublets; t=triplet; q=quartet; quin=quintet; m=multiplet; br=broad signal. To assign the signals to the different proton and carbon atoms, as well as the relative stereochemistry of the cycloadducts, additional 2D NMR experiments (COSY, HSQC, HMBC) and NOESY experiments were performed. Mass spectra were obtained on a GC/MS Saturn 2000 spectrometer. High-resolution mass spectra (HRMS) were performed on Q-TOF Micro WATERS by electrospray ionisation (ESI). Infrared (IR) spectra were recorded with a Perkin Elmer 16 PC FT-IR ATR spectrometer, using the pure product (oil or solid). Thin layer chromatography (TLC) was run on pre-coated aluminium plates of silica gel 60 F-254 (Merck). Flash chromatography was performed on silica gel column (Merck silica gel, 40–63 μm) using air pressure. Microwave irradiation was carried out with microwave oven Discover® LabMate System from CEM, using 10-mL pressurized vials.

4.2. Procedure (A): synthesis of thiazines 4, 5, and 6

To a stirred solution of thioamide (1.2 equiv, 1.2 mmol), aldehyde (1 equiv, 1 mmol), and alkene (1.2 equiv, 1.2 mmol) in dichloroethane (0.5 mL) at room temperature is added dropwise $BF_3{\cdot}OEt_2$ (2 equiv, 2 mmol, 0.25 mL). The solution was placed in a 10 mL sealed vial equipped with a stirring bar and irradiated in the microwave oven for 10 min under 40 W (150 °C). The experiments were performed without a water scavenger. The reaction mixture was cooled to room temperature, then treated with a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (15 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by flash chromatography on silica gel (cyclohexane/AcOEt). The relative stereochemistry of cycloadducts **A** and **B** was assigned by NMR using NOESY experiments and also by X-ray analysis for **4f-B**, **4h-B**, **6c-A**, and **6f-B**.

Spectroscopic data and NMR spectra for compounds **4** and **5**, and NMR spectra for compounds **6** are given in Supplementary data.

*4.2.1. 6-Butyl-5,6-dihydro-2-methyl-4-phenyl-4H-1,3-thiazine (**6a**).* Compound **6a** was obtained from thioacetamide, benzaldehyde, and hexene according to the general procedure A, in 91% yield, as a separable mixture of two diastereoisomers **A** and **B** (ratio 1:1.4).

Aspect: brown oil; R_f A (98:2 cyclohexane/AcOEt): 0.47, R_f B (98:2 cyclohexane/AcOEt): 0.36.

*4.2.1.1. Compound **6a-A**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.29 (m, 4H, Ar), 7.27–7.22 (m, 1H, Ar), 4.40–4.36 (m, 1H, H-4), 3.50 (dddd, J=16.6, 7.7, 6.0, 3.7 Hz, 1H, H-6), 2.22 (d, J=1.96 Hz, 3H, CH_3), 2.21–2.17 (m, 1H, H-5), 1.55–1.46 (m, 2H, H-7), 1.40–1.30 (m, 4H, H-8 and H-9), 1.29–1.25 (m, 1H, H-5), 0.90 (t, J=7.1 Hz, 3H, H-10). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 158.9 (C-2), 145.1, 128.5, 126.8, 126.7, 62.7 (C-4), 41.7 (C-6), 36.6 (C-5), 36.3 (C-7), 28.2 (C-8), 27.9 (CH_3), 22.4 (C-9), 13.8 (C-10). HRMS (ESI, m/z) calcd for $[C_{15}H_{22}NS]^+$: 248.1473; found: 248.1479. IR (cm^{-1}) 2956, 2928, 1633 (C=N), 1542, 1451, 1132, 758, 698 (C–S).

*4.2.1.2. Compound **6a-B**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.22 (m, 2H, Ar), 7.16–7.09 (m, 3H, Ar), 4.81 (t, J=4.8 Hz, 1H, H-4), 2.93–2.87 (m, 1H, H-6), 2.17 (d, J=1.2 Hz, 3H, CH_3), 1.85–1.79 (m, 1H, H-5), 1.74–1.68 (m, 1H, H-5), 1.53–1.48 (m, 2H, H-7), 1.28–1.15 (m, 4H, H-8 and H-9), 0.78 (t, J=6.8 Hz, 3H, H-10). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.0 (C-2), 143.0, 128.2, 126.63, 126.61, 58.6 (C-4), 37.1 (C-6), 36.5 (C-7), 33.4 (C-5), 28.2 (C-8), 28.0 (CH_3), 22.3 (C-9), 13.8 (C-10). HRMS (ESI, m/z) calcd for $[C_{15}H_{22}NS]^+$: 248.1473; found: 248.1482. IR (cm^{-1}) 2928, 1633 (C=N), 1544, 1450, 1134, 752, 728, 698 (C–S).

*4.2.2. 5,6-Dihydro-2-methyl-4,6-diphenyl-4H-1,3-thiazine (**6b**).* Compound **6b** was obtained from thioacetamide, benzaldehyde, and styrene according to the general procedure A, in 91% yield, as a separable mixture of two diastereoisomers **A** and **B** (ratio 1:0.2).

Aspect: orange oil; R_f A (98:2 cyclohexane/AcOEt): 0.29, R_f B (98:2 cyclohexane/AcOEt): 0.22.

*4.2.2.1. Compound **6b-A**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.23 (m, 8H, Ar), 7.22–7.15 (m, 2H, Ar), 4.58 (dd, J=12.4, 3.4 Hz, 1H, H-4), 4.56–4.52 (m, 1H, H-6), 2.32 (dt, J=13.8, 3.5 Hz, 1H, H-5), 2.20 (d, J=2.0 Hz, 3H, CH_3), 1.78–1.69 (m, 1H, H-5). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 158.9 (C-2), 144.6, 140.5, 128.8, 128.5, 127.9, 127.4, 126.9, 126.6, 62.9 (C-4), 45.7 (C-6), 36.9 (C-5), 27.8 (CH_3). HRMS (ESI, m/z) calcd for $[C_{17}H_{18}NS]^+$: 268.1160; found: 268.1165. IR (cm^{-1}) 1630, 1607 (C=N), 1493, 1454, 1250, 1128, 761, 746, 694 (C–S).

*4.2.2.2. Compound **6b-B**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.23 (m, 8H, Ar), 7.19–7.17 (m, 2H, Ar), 5.06 (t, J=4.2 Hz, 1H, H-4), 4.13 (dd, J=7.3 Hz, J=6.3 Hz, 1H, H-6), 2.34 (d, J=1.2 Hz, 3H, CH_3), 2.18 (d, J=4.6 Hz, 1H, H-5), 2.16 (dd, J=4.9, 1.6 Hz, 1H, H-5). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 159.0 (C-2), 142.4, 140.9, 128.6, 128.4, 127.6, 127.5, 126.9, 126.6, 58.8 (C-4), 40.6 (C-6), 34.2 (C-5), 27.8 (CH_3). HRMS (ESI, m/z) calcd for $[C_{17}H_{18}NS]^+$: 268.1160; found: 268.1171. IR (cm^{-1}) 1632 (C=N), 1492, 1450, 1128, 760, 731, 695 (C–S).

*4.2.3. 5,6-Dihydro-2-methyl-4-phenyl-4H-cycloocta[5,6-e]-1,3-thiazine (**6c**).* Compound **6c** was obtained from thioacetamide, benzaldehyde, and cyclooctene according to the general procedure A, in 99% yield, as a separable mixture of two diastereoisomers A and B (ratio 1:1).

Aspect: orange oil; R_f A (98:2 cyclohexane/AcOEt): 0.53, R_f B (98:2 cyclohexane/AcOEt): 0.36.

*4.2.3.1. Compound **6c-A**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.46 (m, 2H, Ar), 7.38–7.34 (m, 2H, Ar), 7.26–7.21 (m, 1H, Ar), 4.45 (s, 1H, H-4), 3.86 (m, 1H, H-6), 2.41–2.37 (m, 1H, H-5), 2.23 (d, J=2.0 Hz, 3H, CH_3), 1.79–1.71 (m, 4H, CH_2), 1.57–1.55 (m, 4H, CH_2), 1.34–1.24 (m, 2H, CH_2), 1.22–1.16 (m, 1H, CH_2), 0.86–0.78 (m, 1H, CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 160.4 (C-2), 143.5, 128.0, 127.2, 126.2, 66.1 (C-4), 47.8 (C-6), 36.6 (C-5), 30.4, 28.6, 27.6 (CH_3), 27.8, 24.6, 24.5, 19.9. HRMS (ESI, m/z) calcd for $[C_{17}H_{24}NS]^+$: 274.1629; found: 274.1630. IR (cm^{-1}) 2914, 1628 (C=N), 1466, 1449, 1129, 769, 735, 712 (C–S).

*4.2.3.2. Compound **6c-B**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.31 (m, 2H, Ar), 7.27–7.22 (m, 1H, Ar), 7.15–7.13 (m, 2H, Ar), 4.99 (d, J=3.3 Hz, 1H, H-4), 3.16–3.11 (m, 1H, H-6), 2.28 (d, J=0.7 Hz, 3H, CH_3), 2.16–2.11 (m, 1H, H-5), 1.84–1.76 (m, 1H, CH_2), 1.71–1.55 (m, 9H, CH_2), 1.48–1.46 (m, 1H, CH_2), 1.38–1.33 (m, 1H, CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 160.1 (C-2), 142.2, 128.3, 126.7, 126.6, 68.2 (C-4), 39.1 (C-6), 36.3 (C-5), 30.3, 28.2, 28.0, 27.7 (CH_3), 27.4, 25.0, 23.6. HRMS (ESI, m/z) calcd for $[C_{17}H_{24}NS]^+$: 274.1629; found: 274.1628. IR (cm^{-1}) 2919, 1629 (C=N), 1448, 1134, 729, 697 (C–S).

*4.2.4. 5,6-Dihydro-2-methyl-4-phenyl-4H-norbornano[5,6-e]-1,3-thiazine (**6d**).* Compound **6d** was obtained from thioacetamide, benzaldehyde, and norbornene according to the general procedure A, in 99% yield, as a separable mixture of two diastereoisomers A and B (ratio 1:0.2).

Aspect: yellow crystals; R_f (98:2 cyclohexane/AcOEt): 0.49.

*4.2.4.1. Compound **6d-B**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J=4.4 Hz, 4H, Ar), 7.31–7.28 (m, 1H, Ar), 3.64 (dq, J=10.8, 2.0 Hz 1H, H-4), 3.06 (dd, J=8.0, 1.1 Hz 1H, H-6), 2.29 (d, J=2.0 Hz, 3H, CH_3), 2.26 (d, J=4.0 Hz, 1H, H-7), 2.20 (dt, J=10.4, 1.7 Hz, 1H, H-11), 2.07 (d, J=3.7 Hz, 1H, H-10), 1.82 (dd, J=10.1, 8.7 Hz, 1H, H-5), 1.66–1.57 (m, 1H, H-8), 1.53–1.45 (m, 1H, H-9), 1.31–1.24 (m, 1H, H-8), 1.21 (dt, J=10.4, 1.3 Hz, 1H, H-11), 1.16–1.09 (m, 1H, H-9). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.1 (C-2), 144.2, 128.4, 128.3, 126.9, 68.6 (C-4), 53.9 (C-5), 48.8 (C-6), 43.9 (C-7), 40.6 (C-10), 33.8 (C-11), 29.8 (C-9), 29.3 (C-8), 29.2 (CH_3). HRMS (ESI, m/z) calcd for $[C_{16}H_{20}NS]^+$: 258.1316; found: 258.1337. IR (cm^{-1}) 2955, 1614 (C=N), 1451, 1135, 1118, 751, 731, 698 (C–S). Anal. Calcd: C, 74.66; H, 7.44; N, 5.44; S, 12.46. Found: C, 74.84; H, 7.29; N, 5.51; S, 12.08.

*4.2.5. 5,6-Dihydro-2-methyl-4-(naphthalen-1-yl)-4H-norbornano[5,6-e]-1,3-thiazine (**6e**).* Compound **6e** was obtained from thioacetamide, naphthaldehyde, and norbornene according to the general procedure A, in 99% yield, as a separable mixture of two diastereoisomers A and B (ratio 0.3:1). Aspect: brown oil; R_f A (98:2 cyclohexane/AcOEt): 0.60, R_f B (98:2 cyclohexane/AcOEt): 0.54.

*4.2.5.1. Compound **6e-A**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J=8.52 Hz, 1H, Ar), 8.02 (d, J=7.2 Hz, 1H, Ar), 7.92–7.89 (m, 1H, Ar), 7.80 (d, J=8.3 Hz, 1H, Ar), 7.60–7.58 (m, 1H, Ar), 7.55–7.46 (m, 2H, Ar), 4.94 (d, J=1.9 Hz, 1H, H-4), 3.52 (d, J=9.2 Hz, 1H, H-5), 2.52 (dd, J=9.7, 4.2 Hz, 1H, H-7), 2.41–2.38 (m, 4H, CH_3 and H-6), 2.10 (m, 1H, H-10), 1.56–1.47 (m, 2H, H-11 and H-8), 1.23–1.12 (m, 2H, H-9 and H-8), 0.97 (d, J=10.2 Hz, 1H, H-11), 0.81–0.75 (m, 1H, H-9). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.3 (C-2), 138.8, 133.9, 130.3, 129.0, 127.0, 126.9, 125.8, 125.7, 125.1, 122.6, 62.3 (C-4), 50.4 (C-5), 49.8 (C-6), 48.2 (C-7), 37.4 (C-10), 35.3 (C-11), 31.4 (C-9), 29.2 (CH_3), 28.3 (C-8). HRMS (ESI, m/z) calcd for $[C_{20}H_{22}NS]^+$: 308.1473; found: 308.1488. IR (cm^{-1}) 2953, 1616 (C=N), 1133, 782, 771, 731.

*4.2.5.2. Compound **6e-B**.* ^{1}H NMR (400 MHz, acetone-d_6): δ 8.07 (m, 1H, Ar), 7.81–7.79 (m, 1H, Ar), 7.72 (d, J=8.1 Hz, 1H, Ar), 7.48 (dd, J=8.5, 1.8 Hz, 1H, Ar), 7.41–7.33 (m, 3H, Ar), 3.07 (d, J=7.7 Hz, 1H, H-4), 2.23 (dt, J=10.2, 1.8 Hz, 1H, H-11), 2.12–2.10 (m, 4H, CH_3 and H-5), 2.07–2.05 (m, 1H, H-7), 1.91 (quin, J=2.2 Hz, 1H, H-6), 1.78 (d, J=3.3 Hz, 1H, H-8), 1.51–1.42 (m, 1H, H-9), 1.26–1.15 (m, 2H, H-10 and H-8), 1.11 (dt, J=10.3, 1.4 Hz, 1H, H-11), 0.81 (m, 1H, H-9). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.4 (C-2), 133.5, 132.9, 132.0, 128.9, 127.7, 125.8, 125.4, 49.3 (C-4), 44.1 (C-5), 41.2 (C-6), 34.2 (C-7), 30.3 (C-10), 30.0 (C-11), 29.4 (CH_3), 29.2 (C-9), 27.0 (C-8). HRMS (ESI, m/z) calcd for $[C_{20}H_{22}NS]^+$: 308.1473; found: 308.1472. IR (cm^{-1}) 2956, 1614 (C=N), 1135, 801, 771, 735.

*4.2.6. 5,6-Dihydro-4-(4-chlorophenyl)-2-methyl-4H-norbornano [5,6-e]-1,3-thiazine (**6f-B**).* Compound **6f-B** was obtained from thioacetamide, 4-chlorobenzaldehyde, and norbornene according to the general procedure A, in 50% yield. The diastereoisomer (**6f-A**) was observed in the crude mixture but was not isolated.

Aspect: colourless crystals (mp 89 °C); R_f (90:10 cyclohexane/AcOEt): 0.24.

*4.2.6.1. Compound **6f-B**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.23 (m, 4H, Ar), 3.56 (dd, J=10.8, 2.0 Hz, 1H, H-4), 3.00 (dd, J=8.0, 1.1 Hz, 1H, H-6), 2.23 (d, J=2.0 Hz, 3H, CH_3), 2.19 (d, J=3.8 Hz, 1H, H-7), 2.12 (d, J=10.5 Hz, 1H, H-11), 1.98 (d, J=3.8 Hz, 1H, H-10), 1.69 (dd, J=10.2, 8.8 Hz, 1H, H-5), 1.59–1.50 (m, 1H, H-8), 1.46–1.38 (m, 1H, H-9), 1.23–1.18 (m, 1H, H-8), 1.16–1.13 (m, 1H, H-11), 1.07–0.99 (m, 1H, H-9). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.7 (C-2), 142.9, 132.8, 129.8, 128.6, 68.0 (C-4), 54.2 (C-5), 48.9 (C-6), 43.9 (C-7), 40.7 (C-10), 33.9 (C-11), 29.9 (C-9), 29.4 (CH_3), 29.2 (C-8). HRMS (ESI, m/z) calcd for [C16H19NSCl]$^+$: 292.0927; found: 292.0932. IR (cm^{-1}) 2955, 1615 (C=N), 1491, 1137, 1090, 1014, 825, 730.

4.3. Three-step synthesis of aminothiols 11 and 12

*4.3.1. Procedures (B): synthesis of thiazinium salts **7** and **8**. Procedure B1*: To a stirred solution of thiazine (1 equiv, 1 mmol) in dichloroethane (1.7 mL) at room temperature was added trimethyloxonium tetrafluoroborate (1.1 equiv, 1.1 mmol, 0.282 g). The solution was stirred overnight. The reaction mixture was concentrated in vacuo. The crude material was purified by trituration in ether.

Procedure B2: To a stirred solution of thiazine (1 equiv, 1 mmol) in acetonitrile (1.7 mL) at room temperature was added benzyl bromide (1 equiv, 1 mmol, 0.12 mL). The solution was stirred overnight. The reaction mixture was concentrated in vacuo. The crude material was purified by trituration in ether.

Spectroscopic data and NMR spectra for compounds **7a**–**f** and **8a**,**c** are given in Supplementary data.

*4.3.2. Procedure (C): thiazinium salts hydrolysis; synthesis of 3-sulfanyl amides **9** and **10**.* A solution of potassium hydroxide (1 mmol, 56 mg) in water (10 mL) was added to the thiazinium salt (1 mmol) and the mixture was stirred overnight at 45 °C. The reaction mixture was concentrated in vacuum, then the crude product was purified by flash chromatography on silica gel (70:30 cyclohexane/AcOEt).

Spectroscopic data and NMR spectra for compounds **9a**–**f** and **10a**,**c** are given in Supplementary data.

*4.3.3. Procedures (D): 3-sulfanyl amides hydrolysis; synthesis of aminothiols **11a**–**f**, **12c**. Procedure D1*: A 2 N aqueous solution of HCl (1.5 mL) was added to the 3-sulfanyl acetamide (0.3 mmol) and the mixture was stirred for 6 days at 100 °C, in a sealed vial. When the reaction was completed (monitored by ^{1}H NMR spectroscopy), water was removed under reduced pressure, then the residue dried by lyophilisation to afford 3-aminothiol hydrochloride.

Procedure D2: A 2 N aqueous solution of HCl (1.5 mL) was added to the 3-sulfanyl acetamide (0.3 mmol) and the mixture was placed in a 10 mL sealed vial equipped with a stirring bar and irradiated in the microwave oven for 3 min, under 100 W (200 °C). The reaction mixture was cooled to room temperature and the water was removed under reduced pressure, then the residue dried by lyophilisation to afford 3-aminothiol hydrochloride.

*4.3.3.1. 1-(Methylamino)-1-phenylheptane-3-thiol hydrochloride (**11a-A**).* Compound **11a-A** was obtained from **9a-A** according to the general procedure (D1), in 74% yield. Aspect: brown solid (mp 201 °C).

*4.3.3.1.1. Compound **11a-A**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.68 (m, 1H, Ar), 7.46–7.34 (m, 4H, Ar), 4.59 (dd, J=8.8, 6.3 Hz 1H, H-3), 2.86–2.79 (m, 1H, H-2), 2.70–2.64 (m, 1H, H-1), 2.48 (s, 3H, NMe), 2.38–2.31 (m, 1H, H-2), 1.50–1.46 (m, 2H, H-4), 1.30–1.11 (m, 5H, H-5, H-6, and SH), 0.79 (t, J=7.3 Hz, 3H, H-7). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 133.7, 129.6, 129.5, 128.7, 61.6 (C-3), 47.2 (C-1), 38.4 (C-2), 33.6 (C-4), 30.7 (NMe), 28.3 (C-5), 22.3 (C-6), 13.8 (C-7). HRMS (ESI, m/z) calcd for [$C_{14}H_{24}NS$]$^+$: 238.1629; found: 238.1625. IR: (cm^{-1}) 2929, 1457, 730, 701 (C–S).

*4.3.3.2. 1,3-Diphenyl-3-methylamino-1-propanethiol hydrochloride (**11b-A**).* Compound **11b-A** was obtained from **9b-A** according to the general procedure (D2), in 70% yield. Aspect: yellow oil.

*4.3.3.2.1. Compound **11b-A**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.50 (m, 1H, Ar), 7.39–7.31 (m, 3H, Ar), 7.18–7.50 (m, 6H, Ar), 4.25–4.20 (m, 1H, H-3), 3.63–3.57 (m, 1H, H-1), 2.97–2.89 (m, 1H, H-2), 2.70–2.63 (m, 1H, H-2), 2.31–2.27 (m, 3H, NMe), 1.82 (d, J=8.1 Hz, 1H, SH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 143.7, 133.2, 129.8, 129.7, 128.8, 128.6, 127.5, 126.7, 63.3 (C-3), 43.2 (C-2), 40.5 (C-1), 30.9 (NMe). HRMS (ESI, m/z) calcd for [$C_{16}H_{20}NS$]$^+$: 258.1316; found: 258.1320. IR: (cm^{-1}) 3384, 2503, 1453, 754, 696 (C–S).

*4.3.3.3. 2-[(1-Methylamino)phenylmethyl]cyclooctane-1-thiol hydrochloride (**11c-A**).* Compound **11c-A** was obtained from **9c-A** according to the general procedure (D2), in 72% yield. Aspect: white solid (mp 232 °C).

*4.3.3.3.1. Compound **11c-A**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.51 (m, 1H, H–Ar), 7.39–7.29 (m, 4H, H–Ar), 3.90 (d, J=10.8 Hz, 1H, H-3), 2.72–2.70 (m, 1H, H-1), 2.38–2.34 (m, 1H, H-2), 2.27 (s, 3H, NMe), 1.86–1.74 (m, 2H, CH_2), 1.68–1.40 (m, 11H, CH_2 and SH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 135.4, 129.4, 129.1, 128.9, 69.8 (C-3), 42.7 (C-2), 42.4 (C-1), 37.0, 32.6 (NMe), 28.3, 27.2, 24.92, 24.9, 24.8. HRMS (ESI, m/z) calcd for [$C_{16}H_{26}NS$]$^+$: 264.1786; found: 264.1794. IR: (cm^{-1}) 2920, 1457, 762, 701 (C–S).

*4.3.3.4. 2-[(1-Methylamino)phenylmethyl]cyclooctane-1-thiol hydrochloride (**11c-B**).* Compound **11c-B** was obtained from **9c-B** according to the general procedure (D2), in 77% yield. Aspect: white solid (mp 199 °C).

*4.3.3.4.1. Compound **11c-B**.* ^{1}H NMR (500 MHz, D_2O): δ 7.39–7.32 (m, 3H, Ar), 7.14–7.12 (m, 2H, Ar), 5.05 (s, 1H, H-3), 3.42 (s, 3H, NMe), 3.30–3.28 (m, 1H, H-1), 2.59–2.56 (m, 1H, H-2), 1.71–1.35 (m, 12H, CH_2 and SH), 1.20–1.16 (m, 1H, CH_2). ^{13}C NMR (125 MHz, D_2O): δ 135.8, 129.4, 129.0, 125.7, 74.2 (C-3), 44.7 (NMe), 42.6 (C-1), 38.6 (C-2), 27.0, 26.8, 26.7, 26.6, 24.4, 23.3. HRMS (ESI, m/z) calcd for [$C_{16}H_{26}NS$]$^+$: 264.1786; found: 264.1788. IR: (cm^{-1}) 2916, 2852, 1603, 1450, 698 (C–S).

*4.3.3.5. 2-[(1-Benzylamino)phenylmethyl]cyclooctane-1-thiol hydrochloride (**12c-B**).* Compound **12c-B** was obtained from 10c-B according to the general procedure (D2), in 54% yield. Aspect: white solid (mp 90 °C).

*4.3.3.5.1. Compound **12c-B**.* ^{1}H NMR (500 MHz, D_2O): δ 7.41–7.34 (m, 6H, Ar), 7.25–7.23 (m, 2H, Ar), 7.15–7.13 (m, 2H, Ar), 4.96 (d, J=2.1 Hz, 1H, H-3), 5.37 (d, J=15.3, Hz, 1H, CHPh), 4.50 (d, J=15.3, Hz, 1H, CHPh), 3.35–3.31 (m, 1H, H-1), 2.52–2.51 (m, 1H, H-4), 1.72–1.68 (m, 2H, CH_2), 1.60–1.36 (m, 9H, CH_2 and SH), 1.19–1.12 (m, 1H, CH_2), 1.03–0.99 (m, 1H, CH_2). ^{13}C NMR (125 MHz, D_2O): δ 136.1, 131.3, 129.5, 129.4, 129.3, 129.2, 129.0, 125.8, 70.5 (C-3), 59.1 (CH_2Ph), 43.2 (C-1), 38.2 (C-2), 26.9, 26.9, 26.8, 26.5, 25.1, 23.2. HRMS (ESI, m/z) calcd for [$C_{22}H_{30}NS$]$^+$: 340.2099; found: 340.2106. IR: (cm^{-1}) 2921, 1593, 1578, 1451, 922, 725, 698 (C–S).

*4.3.3.6. 2-[(1-Methylamino)phenylmethyl]bicyclo[2.2.1]heptane-1-thiol hydrochloride (**11d-B**).* Compound **11d-B** was obtained from **9d-B** according to the general procedure (D2), in 99% yield. Aspect: white solid (mp 136 °C).

4.3.3.6.1. Compound ***11d-B***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.49 (m, 5H, Ar), 4.15 (d, J=11.6 Hz, 1H, H-3), 3.21 (d, J=7.7 Hz, 1H, H-1), 2.51 (s, 3H, NMe), 2.47–2.42 (m, 2H, H-2 and H-4), 1.64–1.56 (m, 3H, H-8, H-7 and H-5), 1.35–1.30 (m, 2H, H-5 and H-6), 1.18–1.16 (m, 1H, H-6), 1.06 (d, J=10.6 Hz, 1H, H-8). ^{13}C NMR (100.6 MHz, D_2O): δ 133.6, 129.9, 129.5, 65.9 (C-3), 49.5 (C-2), 48.8 (C-4), 44.9 (C-1), 40.5 (C-7), 32.2 (C-8), 30.3 (NMe), 28.9 (C-6), 27.6 (C-5). HRMS (ESI, m/z) calcd for $[C_{15}H_{22}NS]^+$: 248.1473; found: 248.1476. IR: (cm^{-1}) 2954, 2872, 1573, 1456, 1070, 1135, 1007, 753, 701 (C–S).

*4.3.3.7. 2-[(1-Methylamino)(1-naphthyl)methyl]bicyclo[2.2.1] heptane-1-thiol hydrochloride (**11e-B**).* Compound **11e-B** was obtained from **9e-B** according to the general procedure (D2), in 90% yield. Aspect: brown solid (mp 73 °C).

4.3.3.7.1. Compound ***11e-B***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J=7.6 Hz, 1H, Ar), 7.96 (d, J=8.1 Hz, 1H, Ar), 7.86 (t, J=8.7 Hz, 2H, Ar), 7.64–7.47 (m, 3H, Ar), 5.36–5.31 (m, 1H, H-3), 3.65–3.60 (m, 2H, H-2 and H-1), 2.42 (br, 4H, NMe and H-4), 1.51–1.43 (m, 3H, H-8, H-5, and SH), 1.29–1.13 (m, 4H, H-5, H-7, and H-6), 0.91 (d, J=10.3 Hz, 1H, H-8). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 133.8, 132.7, 130.8, 129.7, 129.5, 127.5, 127.0, 126.6, 126.2, 121.7, 60.2 (C-3), 52.1 (C-2), 47.9 (C-4), 46.6 (C-1), 40.2 (C-7), 34.9 (C-8), 31.4 (NMe), 30.3 (C-6), 27.8 (C-5). HRMS (ESI, m/z) calcd for $[C_{19}H_{24}NS]^+$: 298.1629; found: 298.1623. IR: (cm^{-1}) 2954, 2871, 1574, 1456, 908, 801, 780, 727 (C–S).

*4.3.3.8. 2-[(1-Methylamino)(4-chlorophenyl)methyl]bicyclo[2.2.1] heptane-1-thiol hydrochloride (**11f-B**).* Compound **11f-B** was obtained from **9f-B** according to the general procedure (D2), in 86% yield. Aspect: yellow solid (mp 120 °C).

4.3.3.8.1. Compound ***11f-B***. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.37 (m, 4H, Ar), 4.13 (t, J=10.3 Hz, 1H, H-3), 3.50–3.45 (m, 1H, H-1), 2.47–2.39 (m, 6H, SH, NMe, H-2, and H-4), 1.56–1.47 (m, 2H, H-7 and H-5), 1.33–1.11 (m, 4H, H-5, H-6 and H-8), 0.97 (d, J=10.6 Hz, 1H, H-8). ^{13}C NMR (100.6 MHz, D_2O): δ 135.7, 132.7, 130.8, 129.7, 66.7 (C-3), 50.7 (C-2), 47.9 (C-4), 45.9 (C-1), 40.2 (C-7), 33.9 (C-8), 31.2 (NMe), 29.9 (C-6), 27.9 (C-5). HRMS (ESI, m/z) calcd for $[C_{15}H_{21}NSCl]^+$: 282.1083; found: 282.1086. IR: (cm^{-1}) 2956, 1570, 1492, 1459, 1090, 908, 826, 726 (C–S).

4.4. X-ray crystallographic study

Crystallographic data for compounds **4f-B**, **4h-B**, **6c-A**, and **6f-B** have been deposited at the Cambridge Crystallographic Data Centre: CCDC No 885197 (**4f-B**), CCDC No 885196 (**4h-B**), CCDC No 885198 (**6c-A**), and CCDC No 885199 (**6f-B**). Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (+44 1223 336408; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.08.072.

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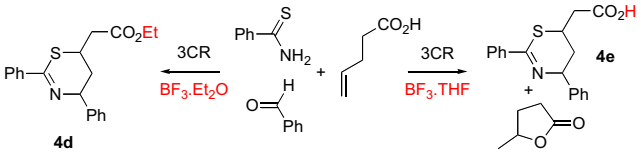

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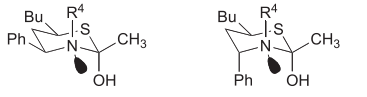
16. It is supposed that the hydrolysis takes place via a heterocyclic form shown below. This could explain the difference of reactivity between the cis and the trans isomers **9a-A** and **9a-B**, as in the case of the latter, the ring-closure would be unfavourable due to the steric hindrance between the axial Ph and OH groups (see Ref. 14b).



from **9a-A** (R^4 = Me) from **9a-B** (R^4 = Me) or **10a-B** (R^4 = Bn)

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