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Multicomponent reaction for first synthesis of 2,2-dialkyl- and 2-alkyl-2-aralkyl-5,6-diaryl-2*H*-1,3-thiazines as scaffolds for various 3,4-dihydro-2*H*-1,3-thiazine derivatives†

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A two-step sequence for the synthesis of various 3,4-dihydro-2*H*-1,3-thiazines is presented. In the first step, 2*H*-1,3-thiazines were prepared by a new multicomponent reaction (MCR). Starting from β-chlorovinyl aldehydes, this MCR offers an efficient and facile access to 2,2-dialkyl- and 2-alkyl-2-aralkyl-5,6-diaryl-2*H*-1,3-thiazines. The potential of these products in subsequent reactions was verified by the conversion to 3,4-dihydro-2*H*-1,3-thiazine-containing bisamides, β-lactams, and methoxy amides.

Introduction

Heterocyclic compounds containing sulfur and nitrogen are omnipresent in natural products and play a vital role in pharmaceutical applications and materials science.[1] Consequently, there is an ongoing interest in drug discovery and other fields of application of organic chemistry in the development of efficient synthesis routes to new and relevant heterocyclic scaffolds containing sulfur and nitrogen.[2]

Well-known through the famous and widely applied penicillins, the substructure of 1,3-thiazolidine is one of the most important heterocyclic skeleton.[3,4] 2,5-Dihydro-1,3-thiazole, one of the iminic unsaturated forms of the 1,3-thiazolidine, can also be found in several natural products and applicable compounds.[5] Additionally, the use of them as scaffolds in the synthesis of derivatives of 1,3-thiazolidines is prevalent.[6] The preparation of 2,5-dihydro-1,3-thiazoles can be realized by a four-component reaction (4-CR) known as ASINGER reaction, using an α-chloro aldehyde, a second carbonyl compound, ammonia and sodium hydrosulfide.[6b–d,7] In addition the ASINGER reaction provided the basis for the synthesis of several further heterocyclic structures.[8] Combining a multicomponent reaction (MCR) employed to synthesize relatively complex heterocyclic scaffolds with a subsequent post-transformation has been abundantly highlighted as an advantageous method for the synthesis of heterocyclic compounds. This synthesis strategy is characterized by a high diversity.[9]

1,4-Thiazine, an unsaturated six-membered ring containing sulfur and nitrogen, and its hydrogenated structures dihydro-1,4-thiazine and tetrahydro-1,4-thiazine (thiomorpholine) are another well explored heterocycles. They can be found as substructures in natural products extracted from plants like seaweeds[10] and in pharmaceuticals used as antipsychotic[11], soporific[12], analgesic[13], anticonvulsants[14], and antimycobacterial[15] drugs or as TACE inhibitor[16]. In contrast to them, 1,3-thiazines and compounds containing the dihydro-1,3-thiazine and tetrahydro-1,3-thiazine substructure are not sufficiently investigated. Most notably the iminic 2,2,5,6-tetrasubstituted 2*H*-1,3-thiazines and the derived forms of it, *i.e.* 2,2,5,6-tetrasubstituted 3,4-dihydro-2*H*-1,3-thiazines, are interesting substructures and building blocks in the synthesis of novel potentially beneficial compounds.

Ceftazidime[17], one of the dihydro-1,3-thiazine based structural analogues of penicillins utilized as antibacterial agent, and xylazine[18], a widely used drug in veterinary medicine, are two of the few examples of known compounds containing a dihydro-1,3-thiazine substructure.

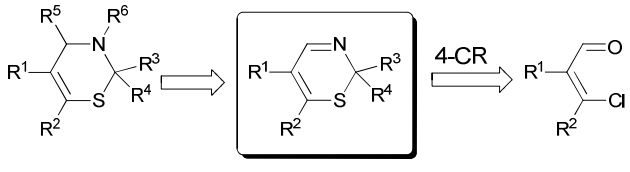


Fig. 1 Retrosynthetic consideration of the target structures.

Main reasons for the lack of known beneficial dihydro-1,3-thiazine-containing compounds lies in the fact that only a few synthesis routes to 1,3-thiazines and the different types of dihydro-1,3-thiazine, first of all 3,4-dihydro-2*H*-1,3-thiazine, containing structures are developed.[19] As a consequence, we developed a MCR for the synthesis of 2,2-dialkyl- and 2-alkyl-2-aralkyl-5,6-diaryl-2*H*-1,3-thiazines (**2**), which were not accessible yet. According to the method mentioned above, theses cyclic imines serve as scaffolds for the preparation of several 3,4-dihydro-2*H*-1,3-thiazines (**5**–**7**) (Fig. 1).

In consideration of our experience[6b–d,7] in the synthesis of 2,5-dihydro-1,3-thiazoles, we envisioned that the formation of 2*H*-1,3-thiazines **2** could be realized on the lines of the ASINGER reaction by modifying the structure of the chloro aldehyde.

Results and discussion

Synthesis of the substrates

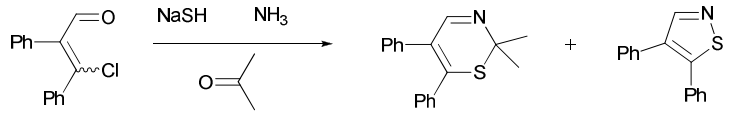
To obtain 2*H*-1,3-thiazines **2** via a procedure analogous to the ASINGER reaction β-chlorovinyl aldehydes instead of α-chloro aldehydes have to be converted with a second carbonyl compound, ammonia and sodium hydrosulfide. β-Chlorovinyl aldehydes are easily accessible by treatment of α-methylene ketones with DMF and $POCl_3$.[20] We were able to synthesize (*E*)-, (*Z*)-, (*EZ*)-2-chloro-2,3-diphenylacrylaldehyde[21] (**1a**), (*EZ*)-3-chloro-3-(4-chlorophenyl)-2-phenylacrylaldehyde[22] (**1b**), (*E*)-3-chloro-2,3-bis(4-methoxyphenyl)acrylaldehyde[23] (**1d**), 2-chloro-1-cyclopentene-1-carboxaldehyde[24] (**1e**), and the previously unknown (*EZ*)-3-chloro-3-(4-hydroxyphenyl)-2-phenylacrylaldehyde (**1c**) and (*E*)-, (*EZ*)-3-chloro-2,3-bis(4-nitrophenyl)acrylaldehyde (**1f**).

Screening of reaction conditions

In an initial attempt to synthesize the 2*H*-1,3-thiazines **2**, we selected (*Z*)-**1a** and acetone as model substrates to probe the reaction conditions (Table 1). In a first experiment, we adopted our standard reaction conditions[6b–d] used in ASINGER reactions, but no 2*H*-1,3-thiazines **2a** was formed. A change of the solvent to the polar protic methanol resulted in a formation of the intended product 2*H*-1,3-thiazine **2a** (Table 1, entry 1). But the known isothiazole **3a** was formed simultaneously. Starting from β-chlorovinyl aldehydes, the preparation of isothiazoles is usually realized by treatment of the aldehydes with ammonium cyanide.[25] The observed formation of isothiazole **3a** is likely to proceeds via a hitherto unknown oxidation of the respective β-mercaptovinyl imine.

To improve the efficiency of the reaction, we examined classical conditions of the ASINGER reaction based on α-chloro aldehydes.[26] Stirring of the β-chlorovinyl aldehyde and NaSH in methanol before addition of all the other reactants and the usage of gaseous ammonia led to a better ratio **2a**:**3a** (Table 1, entry 2). However, according to ^{1}H NMR of the crude product the quantity of other byproducts was likewise increased. Due to the expectable low yield the isolation of the products was consciously abandoned. The use of DMF as solvent did not led to the formation of the desired products **2a** or **3a**. Upon combining the pre-reaction time (aldehyde and NaSH) in methanol and the use of an aqueous ammonia solution (Table 1, entry 3) the yield of **2a** was slightly increased, but the ratio **2a**:**3a** was as unsatisfying as in the first successful experiment (Table 1, entry 1). According to the observation that the slower addition of ammonia by using the gaseous one compared to the all-at-once addition of an aqueous ammonia solution had led to

Table 1 Optimization of the multicomponent reaction to prepare 2*H*-1,3-thiazine **2a**

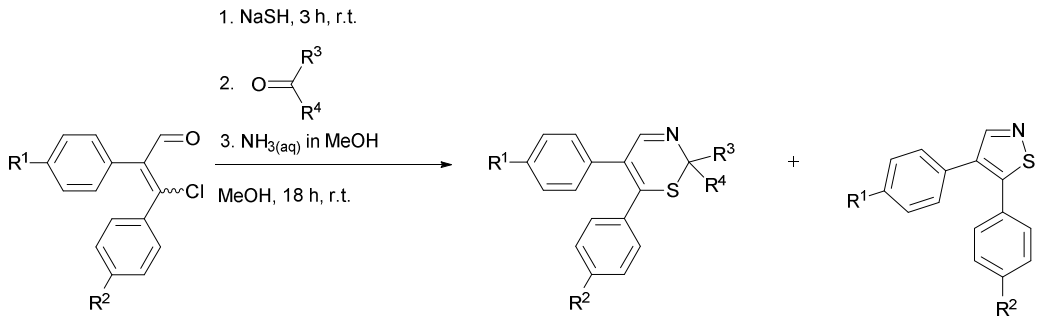


1a **2a** **3a**

Entry	Solvent	**1a**	1a:NaSH:acetone:NH_3	Method[a]	Addition of ammonia	Ratio[b] **2a**:**3a**	Yield [%][c]	
							2a	**3a**
1	MeOH	(*Z*)	1:1.5:2:2	A	aq	63:37	30	29
2	MeOH	(*Z*)	1:1.5:1.5	B, 2 h, r.t.	g, 4 h	75:25	-[f]	-[e]
3	MeOH	(*Z*)	1:1.5:1.5:2	B, 3 h, r.t.	aq	66:34	36	-[e]
4	MeOH	(*Z*)	1:1.5:1.5:2	B, 3 h, 60 °C	aq	-:-	-[d]	-[d]
5	MeOH	(*Z*)	1:1.5:1.5:2	B, 3 h, r.t.	aq, in MeOH, 1 h	77:23	49	-[e]
6	MeOH	(*EZ*)	1:1.5:1.5:2	B, 3 h, r.t.	aq, in MeOH, 1 h	81:19	48	-[e]
7	MeOH	(*EZ*)	1:1.5:1.5:2	B, 4 h, r.t.	aq, in MeOH, 1 h	82:18	46	-[e]
8	MeOH	(*EZ*)	1:1.5:2:2	B, 3 h, r.t.	aq, in MeOH, 1 h	81:19	57	-[e]
9	MeOH	(*EZ*)	1:1.5:3:2	B, 3 h, r.t.	aq, in MeOH, 1 h	80:20	63	14

[a] (i) Method A: NaSH, NH_3 in solvent, then acetone and **1a** at 0 °C, then 18 h at r.t.. (ii) Method B: **1a** and NaSH at given conditions, then acetone, then ammonia at once unless specified otherwise, then 18 h r.t.. [b] Ratio according to ^{1}H NMR of the crude product. [c] All yields are isolated yields. [d] No product was formed. [e] The isolation of the byproduct was consciously abandoned. [f] Due to the excessive presence of undefined byproducts according to the ^{1}H NMR of the crude product the isolation of the thiazine was consciously abandoned.

Table 2 Preparation of 2*H*-1,3-thiazines **2** and isothiazoles **3**



1a-d,f **2a-p** **3a-e**

Entry	aldehyde	R^1	R^2	R^3	R^4	Ratio[a] **2**:**3**	Yield [%][b]	
1	(*EZ*)-**1a**	H	H	Me	Me	79:21	**2a**: 63	**3a**: 14
2	(*EZ*)-**1a**	H	H	–$(CH_2)_5$–		95:05	**2b**: 58	**3a**: 3
3	(*EZ*)-**1a**	H	H	–$(CH_2)_2S(CH_2)_2$–		96:04	**2c**: 66	**3a**: -[c]
4	(*EZ*)-**1a**	H	H	Me	Ph	-[d]	-	-
5	(*EZ*)-**1a**	H	H	Me	CF_3	-[d]	-	-
6	(*EZ*)-**1a**	H	H	H	*i*Bu	98:02	**2d**: 56	**3a**: -[c]
7	(*EZ*)-**1a**	H	H	H	CH_2CH_2Ph	95:05	**2e**: 59	**3a**: -[c]
8	(*EZ*)-**1a**	H	H	H	$CH_2CH_2N(H)Cbz$	86:14	**2f**: 47	**3a**: -[c]
9	(*EZ*)-**1b**	H	Cl	–$(CH_2)_5$–		97:03	**2g**: 72	**3b**: 3
10	(*EZ*)-**1c**	H	OH	H	CH_2CH_2Ph	94:04	**2h**: 77	**3c**: 4
11	(*E*)-**1d**	OCH_3	OCH_3	Me	Me	86:14	**2i**: 79	**3d**: 11
12	(*E*)-**1d**	OCH_3	OCH_3	–$(CH_2)_5$–		97:03	**2j**: 79	**3d**: 3
13	(*E*)-**1d**	OCH_3	OCH_3	–$(CH_2)_2N(CH_3)(CH_2)_2$–		99:01	**2k**: 90	**3d**: -[c]
14	(*E*)-**1d**	OCH_3	OCH_3	Me	CH_2(4-OMe-Ph)	98:02	**2l**: 83	**3d**: -[c]
15	(*E*)-**1d**	OCH_3	OCH_3	Me	CH_2CH_2(4-OH-Ph)	94:06	**2m**: 88	**3d**: -[c]
16	(*E*)-**1d**	OCH_3	OCH_3	Me	CH_2CH_2COOEt	83:17	**2n**: 72	**3d**: -[c]
17	(*E*)-**1d**	OCH_3	OCH_3	H	*i*Bu	97:03	**2o**: 70	**3d**: -[c]
18	(*E*)-**1f**	NO_2	NO_2	–$(CH_2)_5$–		82:18	**2p**: 17	**3e**: 3

[a] Ratio according to ^{1}H NMR of the crude product. [b] All yields are isolated yields. [c] The isolation of the byproduct was consciously abandoned. [d] No products (**2** or **3**) were formed.

an increased formation of the thiazine **2a** in comparison to the isothiazole **3a**, we next added a more diluted solution of aqueous ammonia to the reaction mixture within one hour. Under these conditions the product was obtained in a comparative higher yield and a good ratio **2a**:**3a** (49 %, Table 1, Entry 5).

Noteworthy, the reaction could be performed by using a (*EZ*)-mixture of **1a** without a significant decrease of yield (Table 1, entry 6). Due to the formation of a small amount of (*Z*)-**1**, if at all, compared to (*E*)-**1** by converting the respective ketone and the complex isolation of (*Z*)-**1**, the feasibility of using both isomers simplifies the synthesis of the thiazines **2** tremendously. In addition, the efficiency of the synthesis route to the 2*H*-1,3-thiazines **2** starting from the ketone is increased. Finally, by raising the molar equivalents of acetone to 3.0 relative to the aldehyde, the yield of isolated **2a** was improved to 63 % (Table 1, entry 9).

Reaction scope

With these optimized conditions (Table 1, entry 9), we next studied the influence of the substituents at the aldehydes **1** and the second carbonyl compound on the formation of the products **2**.

The results are summarized in Table 2. Thus, we expanded the scope of the second carbonyl compound. Cyclic ketones such as cyclohexanone (Table 2, entries 2, 9, 12, and 18) as well as aldehydes like isopentanal (Table 2, entries 6 and 17) or 3-phenylpropanal (Table 2, entries 7 and 10) were all feasible substrates in the reaction. Although the yield of the 2*H*-1,3-thiazines **2b** and **2d** were slightly lower, we were pleased to find that in both cases the ratio **2**:**3** was enhanced. Aromatic ketones such as acetophenone cannot be converted to the desired product **2** (Table 2, entry 4). Carbonyl compounds containing aromatic groups in α- or β-position, however, are usable substrates for the synthesis of thiazines **2** (Table 2, entries 6, 7, 8, 10, 14, and 15). Moreover, the reaction tolerates several functional groups on the carbonyl compound, such as sulfide (Table 2, entry 3), ether (Table 2, entry 14), ester (Table 2, entry 16) and hydroxy (Table 2, entry 15) groups. Although the yield was a little lower compared to other carbonyl compounds, it is noteworthy that even the use of a substrate bearing a carbamate moiety led to the formation of the perspective product **2** (Table 2, entry 8). Conversion of an amine to thiazine **2k** (Table 2, entry 13) revealed the best ratio **2**:**3** (99:01) and the highest yield (90 %).

Besides model substrate **1a**, other β-chlorovinyl aldehydes were examined likewise. Both substrates with electron-donating (Table 2, entries 9–17) and electron-withdrawing (Table 2, entry 18) groups in *para*-position afforded the target 2*H*-1,3-thiazines **2**. Comparison of the reactions forming products **2b**, **2g**, **2j**, and **2p** (Table 2, entries 2, 9, 12, and 18) as well as products **2e** and **2h** (Table 2, entries 7 and 10) shows that the electron-richer the β-chlorovinyl aldehydes **1**, the better the ratio **2**:**3** and as a consequence thereof the yield of the desired product **2**. By use of the electron-rich aldehyde **1d** the desired 2*H*-1,3-thiazines (**2i**–**o**) are obtained in good to very good yields.

The formation of 2*H*-1,3-thiazines **2** is limited to 2,3-diaryl-β-chlorovinyl aldehydes **1**. Under identical reaction conditions β-chlorovinyl aldehyde **1e** is converted to 1-Chloro-2-(dimethoxymethyl)cyclopent-1-ene (**4**).[27] Even a change of the solvent (acetonitrile, DMF, 1,4-dioxane) did not lead to the desired 2*H*-1,3-thiazine **2**.

Nevertheless, the depicted results documented that the novel MCR (Table 2) allows the preparation of various 2*H*-1,3-thiazines **2** in moderate to excellent yields starting from readily accessible substrates. The synthesis of 2,2-dialkyl- and 2-alkyl-2-aralkyl-5,6-diaryl-2*H*-1,3-thiazines is reported for the first time.

Derivatization

As mentioned in the introduction, the 2*H*-1,3-thiazines **2** can serve as precursor in subsequent reactions to gain sundry 3,4-dihydro-2*H*-1,3-thiazines.

To investigate the reactivity of the synthesized 2*H*-1,3-thiazines **2**, we examined several subsequent reactions, which are typical for imines, i.e. UGI-3CR[28], STAUDINGER reaction[29], and addition of acyl chloride[6b,c] (Scheme 1). By treatment of the imine with an isocyanide and an acid, the UGI-3CR enables the preparation of bisamides.[28] Starting from 2*H*-1,3-thiazines **2**, the bisamides **5** were obtained in all cases with moderate yields.

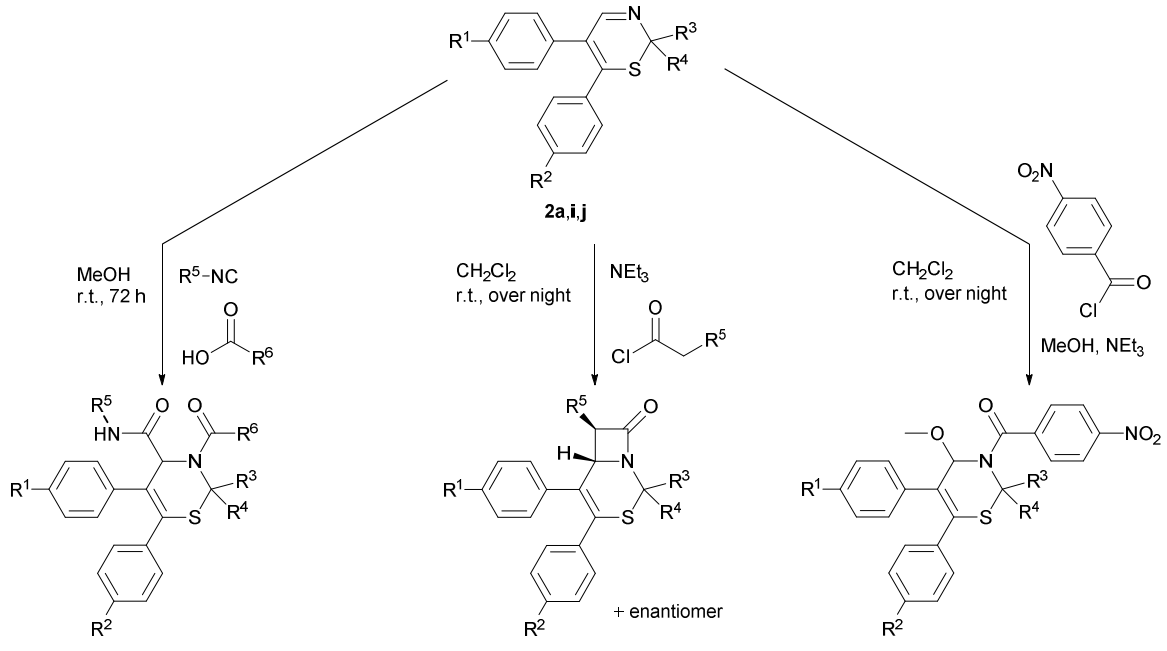
By means of the STAUDINGER reaction, imines could be converted to β-lactams.[29] The 2*H*-1,3-thiazines **2** were therefore treated with triethylamine and an acyl chloride. The desired β-lactams **6** were obtained in moderate to good yields. As expected, the ^{1}H NMR of the crude product revealed the formation of only one racemic diastereomer. We were able to obtain single crystals of **6b** to verify the proposed structure of the β-lactams **6** and as a consequence thereof the constitution of the 2*H*-1,3-thiazines **2** by X-ray crystal structure analysis (Fig. 2) in addition to NMR, IR, and mass analysis. Furthermore, the relative configuration between the two stereocenters was determined. Analogously, the relative configuration of the β-lactams **6a** and **6c** were appointed congruent to the configuration documented by the X-ray crystal structure of **6b**. The foundation for this conclusion by analogy was the comparison of the coupling constants between the protons at the stereocenters of **6a-c**. Coupling constants of all three β-lactams **6**, situated between 1.5 and 1.8 Hz, are in the same range and are characteristic[30] for *trans* β-lactams.

Treatment of imines with acyl chlorides led to the formation of chloro amides. Substitution of the chloride with methanol affords methoxy amides.[6b,c]

Using alkyl acyl chloride like pivaloyl chloride to convert the 2*H*-1,3-thiazines **2** no reaction was observed. However, treatment of 2*H*-1,3-thiazines **2** with more reactive 4-nitrobenzoyl chloride led to the attainment of desired methoxy amides **7**. Starting from **2a,** the methoxy amide **7a** was obtained with 59 % yield. The use of 2*H*-1,3-thiazine (**2i**) bearing electron-donating groups results expectably in an appreciable higher yield (82 %).

Thus, several compounds containing the 3,4-dihydro-2*H*-1,3-thiazine substructures in addition to another biological active structure (i.e. β-lactam) could be formed based on the synthesized 2*H*-1,3-thiazines **2**.

These examples underline the feasibility to create a plenty of 3,4-dihydro-2*H*-1,3-thiazines-containing compounds starting from 2*H*-1,3-thiazines **2** by using diverse subsequent reactions.



5	R^1, R^2	R^3, R^4	R^5	R^6	Yield [%]
a	H	CH_3	Cy	CH_2Br	20
b	H	CH_3	4-Cl-C_6H_4	Bn	43
c	H	CH_3	Bn	Ph	31

6	R^1, R^2	R^3, R^4	R^5	Yield [%]
a	H	CH_3	Ph	49
b	H	CH_3	OCH_3	74
c	OCH_3	$-(CH_2)_5-$	OCH_3	64

7	R^1, R^2	R^3, R^4	Yield [%]
a	H	CH_3	59
b	OCH_3	CH_3	82

Scheme 1 Subsequent reactions to various 3,4-dihydro-2*H*-1,3-thiazine derivatives: bisamides **5**, β-lactams **6**, methoxy amides **7**.

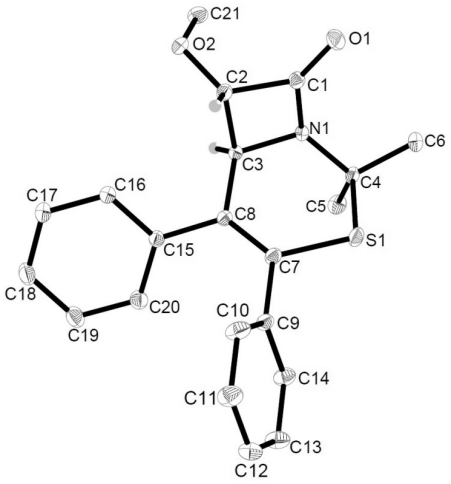


Figure 2 X-ray crystal structure of the racemic β-lactam **6b** (only one enantiomer is shown).[31] The atom numbering does not follow IUPAC nomenclature.

Conclusions

Starting from readily accessible β-chlorovinyl aldehydes, we developed a two-step sequence to synthesize various 3,4-dihydro-2*H*-1,3-thiazines. First, 2*H*-1,3-thiazines were generated by a new four-component-reaction. Characterized by easily accessible substrates, mild conditions, high yields and the toleration of many functional groups this MCR allows the previously unknown preparation of various 2,2-dialkyl- and 2-alkyl-2-aralkyl-5,6-diaryl-2*H*-1,3-thiazines. The shown potential of these 2*H*-1,3-thiazines in subsequent reactions opens the access to 3,4-dihydro-2*H*-1,3-thiazines. In line with this fact several bisamides, β-lactams and methoxy amides with a *S*,*N*-heterocyclic ring were synthesized. Exploiting the developed MCR and following the new two-step synthesis route, it is possible to prepare a great number of products with high diversity, which could be useful in pharmaceutical research.

Experimental

General Methods

Synthetic procedures, performed under argon atmosphere, were performed on a vacuum line using standard Schlenk techniques. Preparative column chromatography was carried out using GRACE SiO_2 (0.035–0.070 mm, type KG 60). TLC was performed on MACHERY-NAGEL SiO_2 F254 plates on aluminum sheets. Melting points were obtained on a melting point apparatus of LABORATORY DEVICES and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a BRUKER AM 300 (measuring frequency: ^{1}H NMR = 300.1 MHz), a BRUKER AMX R 500 (measuring frequency: ^{1}H NMR = 500.1 MHz, ^{13}C NMR = 125.8 MHz) or a BRUKER Avance III 500 (measuring frequency: ^{1}H NMR = 499.9 MHz, ^{13}C NMR = 125.7 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 solution. Chemical shifts are referenced to the residual peaks of the solvent [$CDCl_3$: 7.26 ppm (^{1}H NMR), 77.16 ppm (^{13}C NMR); DMSO-d_6: 2.50 ppm (^{1}H NMR), 39.53 ppm (^{13}C NMR)][32]. Assignments of the signals were supported by measurements applying DEPT and COSY techniques. Mass spectra were obtained on a WATERS Q-TOF Premier (ESI) and a Finnigan MAT 95 (EI) spectrometer. The IR spectra were recorded with a BRUKER Tensor 27 spectrometer equipped with a "Golden Gate" diamond-ATR (attenuated total reflection) unit. Elemental analyses were performed with a Eurovector EA3000.

(*E*)-, (*Z*)-, (*EZ*)-2-Chloro-2,3-diphenylacrylaldehyde[21] (**1a**), (*EZ*)-3-chloro-3-(4-chlorophenyl)-2-phenylacrylaldehyde[22] (**1b**), (*E*)-3-chloro-2,3-bis(4-methoxyphenyl)acrylaldehyde[21] (**1d**), 2-chloro-1-cyclopentene-1-carboxaldehyde[23] (**1e**), and 1,2-bis(4-nitrophenyl)ethan-1-one[33] were prepared according to published procedures. CH_2Cl_2 was refluxed with CaH and freshly distilled prior to use. MeOH was refluxed with Mg and freshly distilled prior to use. Et_3N was dried over molecular sieves (3 Å) and freshly distilled prior to use.

(*EZ*)-3-Chloro-3-(4-hydroxyphenyl)-2-phenylacrylaldehyde (1c): Under argon atmosphere, $POCl_3$ (8.670 g, 56.55 mmol) and DMF (4.133 g, 56.55 mmol), dissolved in 15 mL anhydrous CH_2Cl_2, were cooled down to 0–5 °C. 1-(4-Hydroxyphenyl)-2-phenylethan-1-one (4.000 g, 18.85 mmol) was added dropwise. After stirring for 40 h at r.t., the reaction mixture was brought to pH 7 by addition of saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 x 150 mL). The combined organic phases were washed with a saturated aqueous NaCl solution (2 x 150 mL), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both isomers in a ratio of 76:24 ((*E*)-**1c**:(*Z*)-**1c**). Column chromatography (*n*-hexane/EtOAc, 5:1; R_f = 0.06) afforded the desired (*EZ*)-β-chlorovinyl aldehyde (*EZ*)-**1c** as a mixture of both isomers (3.507 mg, 72 %; (*E*)-/(*Z*)-Isomer 75:25) as a yellow solid, mp 160–161 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3392, 3063, 2892, 1648, 1602, 1576, 1507, 1489, 1433, 1373, 1271, 1232, 1212, 1173, 1083, 902, 828, 766, 707, 635 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 5.26 (1 H, br s, OH^Z), 5.71 (1 H, br s, OH^E), 6.61–6.64 [2 H, m, 2 *m*-$CH_{Ar}(CCl)^Z$], 6.90–6.93 [2 H, m, 2 *m*-$CH_{Ar}(CCl)^E$], 7.00–7.01 [2 H, m, 2 *m*-$CH_{Ar}(CCHO)^Z$], 7.17–7.20 [2 H, m, 2 *o*-$CH_{Ar}(CCl)^Z$], 7.25–7.30 [5 H, m, 2 *m*-$CH_{Ar}(CCHO)^E$, 2 *o*-$CH_{Ar}(CCHO)^Z$, *p*-$CH_{Ar}(CCHO)^Z$], 7.38–7.41 [1 H, m, *p*-$CH_{Ar}(CCHO)^E$], 7.44–7.49 [4 H, m, 2 *o*-$CH_{Ar}(CCHO)^E$, 2 *o*-$CH_{Ar}(CCl)^E$], 9.67 (1 H, s, CHO^E), 10.57 (1 H, s, CHO^Z) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 115.10 [2 *m*-$CH_{Ar}(CCl)^Z$], 115.68 [2 *m*-$CH_{Ar}(CCl)^E$], 128.09 [*p*-$CH_{Ar}(CCHO)^Z$], 128.16 ($C_{Ar}CCl^E$), 128.43 [2 *o*-$CH_{Ar}(CCHO)^E$], 128.51, 128.53 [2 *o*-$CH_{Ar}(CCHO)^Z$, *p*-$CH_{Ar}(CCHO)^E$], 129.67 ($C_{Ar}CCl^Z$), 129.98 [2 *m*-$CH_{Ar}(CCHO)^E$], 130.76 [2 *m*-$CH_{Ar}(CCHO)^Z$], 132.00 [2 *o*-$CH_{Ar}(CCl)^Z$], 132.56 [2 *o*-$CH_{Ar}(CCl)^E$], 134.32 ($C_{Ar}CCHO^Z$), 134.35 ($C_{Ar}CCHO^E$), 136.60 ($CCHO^Z$), 140.13 ($CCHO^E$), 155.99 (CCl^E), 156.02 (CCl^Z), 157.30 ($C_{Ar}OH^Z$), 158.54 ($C_{Ar}OH^E$), 190.53 (CHO^E), 191.84 (CHO^Z) ppm; MS (ESI): m/z 281.1 ($M+Na^+$, 100%); HRMS (ESI): Found 281.0342; Calc. for $C_{15}H_{11}NaO_2Cl$ $[M+Na]^+$ 281.0345.

(*E*)-3-Chloro-2,3-bis(4-nitrophenyl)acrylaldehyde and (*EZ*)-3-chloro-2,3-bis(4-nitrophenyl)acrylaldehyde (1f): Under argon atmosphere, 1,2-bis(4-nitrophenyl)ethan-1-one (4.500 g, 15.72 mmol) and DMF (2.298 g, 31.44 mmol), dissolved in 9 mL anhydrous CH_2Cl_2, were cooled down to 0–5 °C. $POCl_3$ (4.821 g, 31.44 mmol) was added dropwise. After stirring for 20 h at 45 °C, the reaction mixture was brought to pH 7 by addition of saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 x 90 mL). The combined organic phases were washed with a saturated aqueous NaCl solution (2 x 90 mL), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both isomers

in a ratio of 59:41 ((*E*)-**1f**:(*Z*)-**1f**). Column chromatography (*n*-hexane/EtOAc, 7:3; (*E*)-**1f**, R_f = 0.44; (*Z*)-**1f**, R_f = 0.43) afforded the desired (*E*)-β-chlorovinyl aldehyde (*E*)-**1f** (406 mg, 8 %) as a yellow solid, mp 232 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3107, 3071, 1685, 1601, 1510, 1408, 1343, 1295, 1220, 857, 849, 812, 727, 695 cm^{-1}; ^1H NMR (500.1 MHz, DMSO-d_6): δ 7.65–7.68 [2 H, m, 2 *o*-CH_{Ar}(C)], 8.04–8.07 [2 H, m, 2 *o*-CH_{Ar}(C)], 8.34–8.36 [2 H, m, 2 *m*-CH_{Ar}(C)], 8.40–8.43 [2 H, m, 2 *m*-CH_{Ar}(C)], 9.50 (1 H, s, CHO) ppm; ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 123.31, 123.90 [4 *m*-CH_{Ar}(C)], 131.38, 131.59 [4 *o*-CH_{Ar}(C)], 139.86 (*C*CHO), 140.55, 140.82 (2 CC_{Ar}), 147.36, 148.67 (2 NC_{Ar}), 150.85 (CCl), 188.04 (CHO) ppm; MS (EI, 70 eV): m/z 231.7 (M^+, 20%); HRMS (EI): Found 332.0196; Calc. for $C_{15}H_9ClN_2O_5$ $[M+H]^+$ 332.0195. The (*Z*)-β-chlorovinyl aldehyde (*Z*)-**1e** was obtained as a mixture of both isomers (576 mg, 11 %; (*E*)-/(*Z*)-Isomer 74:26) as a yellow solid; ^1H NMR (500.1 MHz, $CDCl_3$): δ 7.16–7.18 [m, 2 H, 2 *o*-CH_{Ar}(C)], 7.43–7.44 [m, 2 H, 2 *o*-CH_{Ar}(C)], 8.11–8.13 [m, 4 H, 4 *m*-CH_{Ar}(C)], 10.58 (s, 1 H, CHO) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 123.82, 123.93 [4 *m*-CH_{Ar}(C)], 130.57, 131.75 [4 *o*-CH_{Ar}(C)], 137.56 (*C*CHO), 139.49, 142.60 (2 CC_{Ar}), 147.83, 148.57 (2 NC_{Ar}), 148.95 (CCl), 188.79 (CHO) ppm.

General Procedure (GP A)

The respective β-chlorovinyl aldehyde (1.0 equiv.) was dissolved in MeOH (5 mL per mmol β-chlorovinyl aldehyde). $NaSH{\cdot}H_2O$ (1.5 equiv.) was added and the solution was stirred for 3 h at r.t.. After addition of the respective carbonyl compound (3.0 equiv.), a mixture of aqueous ammonia solution (2.0 equiv., 25 %) and MeOH (5 mL per mmol β-chlorovinyl aldehyde) was added dropwise within 1 h. After stirring overnight at r.t., the reaction mixture was poured into water (10 mL per mmol β-chlorovinyl aldehyde) and extracted with CH_2Cl_2 (3 x 10 mL per mmol β-chlorovinyl aldehyde). The combined organic phases were dried ($MgSO_4$), the solvent was removed on a rotary evaporator and the crude product was purified by column chromatography on silica gel or by recrystallization.

2,2-Dimethyl-5,6-diphenyl-2*H*-1,3-thiazine (2a) and 4,5-diphenylisothiazole[34] (3a): Following **GP A**, aldehyde (*EZ*)-**1a** (485 mg, 2.00 mmol), $NaSH{\cdot}H_2O$ (222 mg, 3.00 mmol), acetone (348 mg, 6.00 mmol) and 25 % aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ^1H NMR spectroscopy revealed the formation of both title compounds in a ratio of 79:21 (**2a**:**3a**). Column chromatography (*n*-hexane/EtOAc, 7:3; thiazine **2a**, R_f = 0.43; isothiazole **3a** R_f = 0.34) afforded the desired thiazine **2a** (352 mg, 63 %) as a greenish-yellow solid, mp 70 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3076, 3057, 3019, 2970, 2928, 1622, 1599, 1531, 1484, 1459, 1442, 1361, 1196, 1175, 875, 767, 756, 695, 665 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.72 [6 H, s, $C(CH_3)_2$], 7.11–7.13 (2 H, m, 2 CH_{Ar}), 7.16–7.26 (8 H, m, 8 CH_{Ar}), 8.01 (1 H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 28.99 [$C(CH_3)_2$], 63.59 [$C(CH_3)_2$], 126.46 (CH*C*=C), 126.94 (*p*-CH_{Ar}), 128.19, 128.66, 128.84 (4 *m*-CH_{Ar}, 2 *o*-CH_{Ar}), 129.10 (*p*-CH_{Ar}), 130.67 (2 *o*-CH_{Ar}), 136.67 (C_{Ar}CS), 137.39 (C_{Ar}CCH), 143.98 (CHC=*C*), 158.22 (C=N) ppm; MS (ESI): m/z 280.2 ($M+H^+$, 100%); HRMS (ESI): Found 280.1152; Calc. for $C_{18}H_{18}NS$ $[M+H]^+$ 280.1160. The isothiazole[34] **3a** (66 mg, 14 %) was obtained as a brown oil; ^1H NMR (500.1 MHz, $CDCl_3$): δ 7.31–7.33 (10 H, m, 10 CH_{Ar}), 8.52 (1 H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 128.75, 128.79, 128.95, 128.97 (4 *o*-CH_{Ar}, 4 *m*-CH_{Ar}), 129.06 (2 *p*-CH_{Ar}), 130.55 (CH*C*=C), 132.87, 135.65 (C_{Ar}), 159.18 (C=N), 161.57 (CHC=*C*) ppm.

2,3-Diphenyl-1-thia-5-azaspiro[5.5]undeca-2,4-diene (2b) and 4,5-diphenylisothiazole[34] (3a): Following **GP A**, aldehyde (*EZ*)-**1a** (485 mg, 2.00 mmol), $NaSH{\cdot}H_2O$ (222 mg, 3.00 mmol), cyclohexanone (589 mg, 6.00 mmol) and 25 % aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ^1H NMR spectroscopy revealed the formation of both title compounds in a ratio of 95:05 (**2b**:**3a**). Column chromatography (*n*-hexane/EtOAc, 9:1; thiazine **2b**, R_f = 0.29; isothiazole **3a**, R_f = 0.16) afforded the desired thiazine **2b** (368 mg, 58 %) as a yellow solid, mp 116 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3078, 3060, 3025, 2926, 2855, 1623, 1600, 1539, 1485, 1459, 1445, 757, 716, 694, 662 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.43–1.51 (1 H, m, $CH_{2,Cy}$), 1.67–1.72 (1 H, m, $CH_{2,Cy}$), 1.76–1.80 (4 H, m, 3 $CH_{2,Cy}$), 1.97–2.03 (2 H, m, 2 $CH_{2,Cy}$), 2.12–2.16 (2 H, m, 2 $CH_{2,Cy}$), 7.11–7.12 (2 H, m, 2 CH_{Ar}), 7.16–7.26 (8 H, m, 8 CH_{Ar}), 8.06 (1 H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 22.24, 25.85, 37.28 (5 $CH_{2,Cy}$), 67.99 [*C*$(CH_2)_2$], 126.87 (*p*-CH_{Ar}), 126.91 (CH*C*=C), 128.14, 128.63, 128.79 (4 *m*-CH_{Ar}, 2 *o*-CH_{Ar}), 129.03 (*p*-CH_{Ar}), 130.84 (2 *o*-CH_{Ar}), 136.84 (C_{Ar}CS), 137.42 (C_{Ar}CCH), 143.11 (CHC=*C*), 158.10 (C=N) ppm; MS (ESI): m/z 320.3 ($M+H^+$, 100%); HRMS (ESI): Found 320.1468; Calc. for $C_{21}H_{22}NS$ $[M+H]^+$ 320.1473. The isothiazole[34] **3a** (14 mg, 3 %) was obtained as a brown oil.

2,3-Diphenyl-1,9-dithia-5-azaspiro[5.5]undeca-2,4-diene (2c) and 4,5-diphenylisothiazole[34] (3a): Following **GP A**, aldehyde (*EZ*)-**1a** (485 mg, 2.00 mmol), $NaSH{\cdot}H_2O$ (222 mg, 3.00 mmol), tetrahydro-4*H*-thiopyran-4-one (697 mg, 6.00 mmol) and 25 % aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ^1H NMR spectroscopy revealed the formation of both title compounds in a ratio of 96:04 (**2c**:**3a**). Recrystallization from MeOH/*n*-hexane afforded the desired thiazine **2c** (445 mg, 66 %) as a yellow solid, mp 123–124 °C; IR (ATR) $\tilde{\nu}$ 3059, 3014, 2938, 2906, 1621, 1574, 1533, 1482, 1442, 1425, 1414, 1271, 1237, 1195, 1094, 1037, 920, 876, 816, 760, 691, 662 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ 2.39–2.41 [4 H, m, $C(CH_2)_2$], 2.87–2.97 [4 H, m, $S(CH_2)_2$], 7.10–7.13 (2 H, m, 2 CH_{Ar}), 7.18–7.25 (8 H, m, 8 CH_{Ar}), 8.09 (1 H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 24.35 [$S(CH_2)_2$], 38.28 [$C(CH_2)_2$], 66.75 [$C(CH_2)_2$], 126.86 (CH*C*=C), 127.09 (*p*-CH_{Ar}), 128.26, 128.74 (6 CH_{Ar}), 129.30 (*p*-CH_{Ar}), 130.80 (2 CH_{Ar}), 136.36 (C_{Ar}CS), 137.01 (C_{Ar}CCH), 142.29 (CHC=*C*), 158.45 (C=N) ppm; MS (ESI): m/z 338.0 ($M+H^+$, 100%); HRMS (ESI): Found 338.1037; Calc. for $C_{20}H_{20}NS_2$ $[M+H]^+$ 338.1037. The isolation of the isothiazole[34] **3a** was consciously abandoned.

(*RS*)-2-Isobutyl-5,6-diphenyl-2*H*-1,3-thiazine (2d) and 4,5-diphenylisothiazole[34] (3a): Following **GP A**, aldehyde (*EZ*)-**1a** (485 mg, 2.00 mmol), $NaSH{\cdot}H_2O$ (222 mg, 3.00 mmol), isopentanal (517 mg, 6.00 mmol) and 25 % aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ^1H NMR spectroscopy revealed the formation of both title compounds in a ratio of 98:02 (**2d**:**3a**). Column chromatography (*n*-hexane/EtOAc, 9:1; thiazine **2d,** R_f = 0.29) afforded the desired thiazine **2c** (345 mg, 56 %) as an orange oil; IR (ATR) $\tilde{\nu}$ 3057, 3025, 2955, 2930, 1683, 1598, 1525, 1484, 1466, 1444, 1367, 1197, 1172, 759, 694, 664 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.04 [6 H, d, ^3J = 6.5 Hz, $CH(CH_3)_2$],

1.86–1.92, 2.01–2.07 (2 H, 2 m, CH_2), 2.09–2.14 [1 H, m, C*H*$(CH_3)_2$], 4.73 (1 H, ddd, ^3J = 7.1 Hz, ^3J = 7.1 Hz, ^4J = 1.9 Hz, SCH), 7.13–7.28 (10 H, m, 10 CH_{Ar}), 8.12 (1 H, d, ^4J = 1.9 Hz, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 22.26, 22.81 [CH(*C*$H_3)_2$], 25.12 [*C*H$(CH_3)_2$], 43.87 (CH_2), 60.47 (SCH), 126.99 (*p*-CH_{Ar}), 128.17 (2 CH_{Ar}), 128.64 (CH*C*=C), 128.65, 128.77 (4 CH_{Ar}), 129.23 (*p*-CH_{Ar}), 131.04 (2 *o*-CH_{Ar}), 136.36 (C_{Ar}CS), 137.06 (C_{Ar}CCH), 145.75 (CHC=*C*), 160.28 (C=N) ppm; MS (ESI): m/z 308.2 ($M+H^+$, 100%); HRMS (ESI): Found 308.1465; Calc. for $C_{20}H_{22}NS$ $[M+H]^+$ 308.1473. The isolation of the isothiazole[34] **3a** was consciously abandoned.

(*RS*)-2-Phenethyl-5,6-diphenyl-2*H*-1,3-thiazine (2e) and 4,5-diphenylisothiazole[34] (3a): Following **GP A**, aldehyde (*EZ*)-**1a** (485 mg, 2.00 mmol), $NaSH{\cdot}H_2O$ (222 mg, 3.00 mmol), 3-phenylpropanal (805 mg, 6.00 mmol) and 25 % aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 95:05 (**2e**:**3a**). Recrystallization from MeOH/*n*-hexane afforded the desired thiazine **2e** (421 mg, 59 %) as a yellow solid, mp 91–92 °C; IR (ATR) $\tilde{\nu}$ 3050, 3029, 2994, 2917, 2859, 1607, 1511, 1480, 1450, 1441, 1281, 1154, 1095, 1026, 883, 768, 745, 699 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.34–2.49 (2 H, m, CHC*H*$_2$), 2.96–3.05 (2 H, m, C_{Ar}C*H*$_2$), 4.71 (1 H, ddd, ^3J = 6.5 Hz, ^3J = 6.5 Hz, ^4J = 1.8 Hz, SCH), 7.14–7.35 (15 H, m, 15 CH_{Ar}), 8.16 (1 H, d, ^4J = 1.8 Hz, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 32.23 (CH*C*H$_2$), 36.30 (C_{Ar}*C*H$_2$), 61.41 (SCH), 126.19, 127.03 (2 *p*-CH_{Ar}), 128.20 (2 CH_{Ar}), 128.62 (CH*C*=C), 128.64, 128.67, 128.74, 128.78 (8 CH_{Ar}), 129.28 (*p*-CH_{Ar}), 131.03 (2 CH_{Ar}), 136.32 (C_{Ar}CS), 137.01 (C_{Ar}CCH), 141.34 (C_{Ar}CH$_2$), 145.49 (CHC=*C*), 160.45 (C=N) ppm; MS (ESI): m/z 356.1 ($M+H^+$, 100%); HRMS (ESI): Found 356.1462; Calc. for $C_{24}H_{22}NOS$ $[M+H]^+$ 356.1473. The isolation of the isothiazole[34] **3a** was consciously abandoned.

(*RS*)-2-{2-[(Benzyloxycarbonyl)amino]ethyl}-5,6-diphenyl-2*H*-1,3-thiazine (2f) and 4,5-diphenylisothiazole[34] (3a): Following **GP A**, aldehyde (*EZ*)-**1a** (243 mg, 1.00 mmol), $NaSH{\cdot}H_2O$ (111 mg, 1.50 mmol), 3-[(benzyloxycarbonyl)amino]propanal (622 mg, 3.00 mmol) and 25 % aqueous ammonia solution (136 mg, 2.00 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 86:14 (**2f**:**3a**). Column chromatography (*n*-hexane/acetone/toluene, 4:3:3; thiazine **2f**, R_f = 0.43) afforded the desired thiazine **2f** (201 mg, 47 %) as a yellow oil; IR (ATR) $\tilde{\nu}$ 3326, 3265, 3059, 3032, 2941, 1700, 1599, 1512, 1443, 1244, 1136, 1027, 759, 694 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.26–2.36 (2 H, m, CHC*H*$_2$), 3.52–3.59, 3.60–3.67 (2 H, 2 m, NC*H*$_2$), 4.76 (1 H, ddd, ^3J = 6.7 Hz, ^3J = 6.7 Hz, ^4J = 1.4 Hz, SCH), 5.14 (2 H, s, $C_{Ar}CH_2$), 5.66 (1 H, dd, ^3J = 5.3 Hz, ^3J = 5.3 Hz, NH), 7.13–7.40 (15 H, m, 15 CH_{Ar}), 8.13 (1 H, d, ^4J = 1.4 Hz, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 34.24 (CH*C*H$_2$), 38.51 (NCH$_2$), 60.40 (SCH), 66.71 (C_{Ar}*C*H$_2$), 127.06, 128.14, 128.18, 128.22 (5 CH_{Ar}, CH*C*=C), 128.57, 128.66, 128.69, 129.37, 131.01 (10 CH_{Ar}), 135.94 (C_{Ar}CS), 136.71 (C_{Ar}CCH, C_{Ar}CH$_2$), 146.03 (CHC=*C*), 156.51 (C=O), 160.75 (C=N) ppm; MS (ESI): m/z 429.2 ($M+H^+$, 100%); HRMS (ESI): Found 429.1626; Calc. for $C_{26}H_{24}N_2O_2S$ $[M+H]^+$ 429.1637. The isolation of the isothiazole[34] **3a** was consciously abandoned.

2-(4-Chlorophenyl)-3-phenyl-1-thia-5-azaspiro[5.5]undeca-2,4-diene (2g) and 5-(4-chlorophenyl)-4-diphenylisothiazole (3b): Following **GP A**, aldehyde (*EZ*)-**1b** (275 mg, 0.99 mmol), $NaSH{\cdot}H_2O$ (110 mg, 1.49 mmol), acetone (172 mg, 2.97 mmol) and 25 % aqueous ammonia solution (135 mg, 1.98 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 97:03 (**2g**:**3b**). Column chromatography (*n*-hexane/MTBE, 9:1; thiazine **2g**, R_f = 0.13) afforded the desired thiazine **2g** (223 mg, 72 %) as a yellow solid, mp 101 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 2932, 2894, 2855, 1672, 1619, 1595, 1586, 1532, 1480, 1443, 1369, 1266, 1244, 1087, 1055, 1014, 884, 830, 821, 765, 737 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.42–1.50 (1 H, m, $CH_{2,Cy}$), 1.66–1.72 (1 H, m, $CH_{2,Cy}$), 1.74–1.79 (4 H, m, 2 $CH_{2,Cy}$), 1.96–2.01 (2 H, m, 2 $CH_{2,Cy}$), 2.09–2.13 (2 H, m, 2 $CH_{2,Cy}$), 7.09–7.11 (2 H, m, CH_{Ar}), 7.15–7.25 (7 H, m, CH_{Ar}), 8.04 (1H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 22.23, 25.81, 37.28 (5 $CH_{2,Cy}$), 68.17 [*C*$(CH_2)_2$], 127.12 (*p*-CH_{Ar}), 127.19 (CH*C*=C), 128.46, 128.73, 128.83, 132.14 (4 *o*-CH_{Ar}, 4 *m*-CH_{Ar}), 135.07, 135.36 (C_{Ar}CS, C_{Ar}Cl), 137.06 (C_{Ar}CCH), 141.66 (CHC=*C*), 157.99 (C=N) ppm; MS (ESI): m/z 354.1 ($M+H^+$, 100%); HRMS (ESI): Found 354.1075, Calc. for $C_{21}H_{21}ClNS$ $[M+H]^+$ 354.1083. The isothiazole **3b** was further purified by a second column chromatography (*n*-hexane/CH_2Cl_2/toluene/EtOH, 6:2:1:1; R_f = 0.62). The isothiazole was obtained (8 mg, 3 %) as a colorless solid, mp 115 °C; IR (ATR) $\tilde{\nu}$ 3082, 3060, 3036, 3029, 2959, 1594, 1576, 1495, 1481, 1397, 1261, 1208, 1089, 1015, 894, 825, 793, 758, 736, 700, 629, 542 cm^{-1}; ^{1}H NMR (499.9 MHz, $CDCl_3$): δ 7.25–7.38 (9 H, m, 9 CH_{Ar}), 8.51 (1 H, s, NCH) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 128.02 [*p*-*C*H$_{Ar}$(C)], 129.00, 129.04 (4 CH_{Ar}), 129.18 (CH*C*=C), 129.33, 130.09 (4 CH_{Ar}), 132.67 (C_{Ar}CS), 135.31 (C_{Ar}Cl), 136.12 (C_{Ar}CCH), 159.33 (C=N), 160.24 (CHC=*C*) ppm; MS (ESI): m/z 272.1 ($M+H^+$, 100%); HRMS (ESI): Found 272.0302, Calc. for $C_{15}H_{11}ClNS$ $[M+H]^+$ 272.0301.

(*RS*)-6-(4-Hydroxyphenyl)-2-phenethyl-5-phenyl-2*H*-1,3-thiazine (2h) and 5-(4-hydroxyphenyl)-4-phenylisothiazole (3c): Following **GP A**, aldehyde (*EZ*)-**1c** (388 mg, 1.50 mmol), $NaSH{\cdot}H_2O$ (167 mg, 2.25 mmol), 3-phenylpropanal (604 mg, 4.50 mmol) and 25 % aqueous ammonia solution (204 mg, 3.00 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 94:4 (**2h**:**3c**). Column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 6:2:2; thiazine **2h**, R_f = 0.29; isothiazole 3**c**, R_f = 0.47) afforded the desired thiazine **2h** (429 mg, 77 %) as a yellow solid, mp 198–200 °C (decomp.; from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3029, 3990, 2917, 2854, 2661, 1598, 1574, 1495, 1475, 1438, 1289, 1217, 1171, 1090, 958, 840, 767, 744, 700 cm^{-1}; ^{1}H NMR (500.1 MHz, DMSO-d_6): δ 2.19–2.31 (2 H, m, CHC*H*$_2$), 2.89–2.92 (2 H, m, C_{Ar}C*H*$_2$), 4.62 (1 H, ddd, ^3J = 6.4 Hz, ^3J = 6.4 Hz, ^4J = 1.7 Hz, SCH), 6.60–6.62 [2 H, m, 2 *m*-CH_{Ar}(CS)], 7.06–7.08 [2 H, m, 2 *o*-CH_{Ar}(CS)], 7.17–7.32 (10 H, m, 10 CH_{Ar}), 8.13 (1 H, d, ^4J = 1.7 Hz, NCH), 9.86 (1 H, s, OH) ppm; ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 31.53 (CH*C*H$_2$), 35.77 (C_{Ar}*C*H$_2$), 60.97 (SCH), 115.10 [2 *m*-*C*H$_{Ar}$(CS)], 125.94 (*p*-CH_{Ar}), 126.15 (C_{Ar}CS), 126.61 (*p*-CH_{Ar}), 127.12 (CH*C*=C), 128.40, 128.43, 128.47, 128.55 (8 CH_{Ar}), 132.31 [2 *o*-*C*H$_{Ar}$(CS)], 136.99 (C_{Ar}CCH), 141.22 (C_{Ar}CH$_2$), 144.06 (CHC=*C*), 158.61 (C_{Ar}OH), 159.91 (C=N) ppm; MS (ESI): m/z 372.1 ($M+H^+$, 100%); HRMS (ESI): Found 372.1417, Calc. for $C_{24}H_{22}NOS$ $[M+H]^+$ 372.1422. The isothiazole[34] **3c** (15 mg, 4 %) was obtained as a colorless solid, mp 220–221 °C; IR (ATR) $\tilde{\nu}$ 3114, 2801, 2730, 2667, 1612, 1586, 1542, 1510, 1402, 1280, 1209, 1173, 827, 762, 695, 657 cm^{-1}; ^{1}H NMR (499.9 MHz, DMSO-d_6): δ 6.77–6.80 [2 H, m, 2 *o*-

CH_{Ar}(OH)], 7.12–7.15 [2 H, m, 2 *m*-CH_{Ar}(OH)], 7.32–7.39 (5 H, m, 5 CH_{Ar}), 8.63 (1 H, s, NCH), 9.90 (1 H, br s, OH) ppm; ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 115.97 [2 *o*-CH_{Ar}(OH)], 120.28 (C_{Ar}CS), 127.67 [*p*-CH_{Ar}(CCH)], 128.69, 128.78 [2 *o*-CH_{Ar}(CCH), 2 *m*-CH_{Ar}(CCH)], 129.78 [2 *m*-CH_{Ar}(OH)], 132.61 (CH*C*=C), 134.42 (C_{Ar}CCH), 158.50 (C_{Ar}OH), 159.72 (C=N), 161.33 (CHC=*C*) ppm; MS (ESI): m/z 276.0 (M+Na$^+$, 100%); HRMS (ESI): Found 276.0455, Calc. for $C_{15}H_{11}NNaOS$ [M+Na]$^+$ 276.0459.

5,6-Bis(4-methoxyphenyl)-2,2-dimethyl-2*H*-1,3-thiazine (2i) and 4,5-bis(4-methoxyphenyl)isothiazole[25a] (3d): Following **GP A**, aldehyde (*E*)-**1d** (303 mg, 1.00 mmol), NaSH·H_2O (111 mg, 1.50 mmol), acetone (174 mg, 3.00 mmol) and 25 % aqueous ammonia solution (136 mg, 2.00 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 86:14 (**2i**:**3d**). Column chromatography (*n*-hexane/EtOAc, 9:1; thiazine **2i**, R_f = 0.11, isothiazole **3d**, R_f = 0.22) afforded the desired thiazine **2i** (267 mg, 79 %) as an orange oil; IR (ATR) $\tilde{\nu}$ 3031, 2999, 2966, 2929, 2835, 1666, 1621, 1573, 1508, 1495, 1460, 1440, 1291, 1243, 1197, 1172, 828, 805, 787 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.67 [6 H, s, C(CH_3)$_2$], 3.76, 3.76 (6 H, 2 s, 2 OCH_3), 6.70–6.73 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.76–6.79 [2 H, m, 2 *m*-CH_{Ar}(CCH)], 7.03–7.06 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.18–7.21 [2 H, m, 2 *o*-CH_{Ar}(CS)], 7.96 (1 H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 28.96 [C(CH_3)$_2$], 55.34 (2 OCH_3), 63.54 [C(CH_3)$_2$], 113.62 [2 *m*-CH_{Ar}(CS)], 114.24 [2 *m*-CH_{Ar}(CCH)], 125.12 (CH*C*=C), 128.99 (C_{Ar}CS), 129.82 [2 *o*-CH_{Ar}(CCH)], 129.87 (C_{Ar}CCH), 132.12 [2 *o*-CH_{Ar}(CS)], 142.46 (CHC=*C*), 158.51 [*p*-C_{Ar}(CCH)], 158.62 (C=N), 160.15 [*p*-C_{Ar}(CS)] ppm; MS (ESI): m/z 340.2 (M+H$^+$, 100%); HRMS (ESI): Found 340.1368, Calc. for $C_{20}H_{21}NO_2S$ [M+H]$^+$ 340.1371. The isothiazole[25a] **3d** (33 mg, 11 %) was obtained as a yellow oil; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.81, 3.82 (6 H, 2 s, 2 OCH_3), 6.85–6.89 [4 H, m, 4 *m*-CH_{Ar}(C)], 7.22–7.26 [4 H, m, 4 *o*-CH_{Ar}(C)], 8.45 (1 H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 55.34, 55.38 (2 CH_3), 114.29, 114.43 [4 *m*-CH_{Ar}(C)], 123.08, 125.46 (2 C_{Ar}C), 130.03, 130.16 [4 *o*-CH_{Ar}(C], 134.75 (CH*C*=C), 159.18 [*p*-C_{Ar}(C)], 159.33 (C=N), 160.21 (CHC=*C*), 160.67 [*p*-C_{Ar}(C)] ppm.

2,3-Bis(4-methoxyphenyl)-1-thia-5-azaspiro[5.5]undeca-2,4-diene (2j) and 4,5-bis(4-methoxyphenyl)isothiazole[25a] (3d): Following **GP A**, aldehyde (*EZ*)-**1d** (303 mg, 1.00 mmol), NaSH·H_2O (111 mg, 1.50 mmol), cyclohexanone (294 mg, 3.00 mmol) and 25 % aqueous ammonia solution (136 mg, 2.00 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 97:03 (**2j**:**3d**). Column chromatography (*n*-hexane/EtOAc, 7:3; thiazine **2j**, R_f = 0.29, isothiazole **3c**, R_f = 0.65) afforded the desired thiazine **2j** (301 mg, 79 %) as a yellowish-orange solid, mp 162 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3070, 3040, 3024, 2931, 2855, 2835, 1623, 1603, 1571, 1538, 1497, 1459, 1441, 1295, 1256, 1243, 1172, 846, 828, 802, 786 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.41–1.49 (1 H, m, $CH_{2,Cy}$), 1.65–1.70 (1 H, m, $CH_{2,Cy}$), 1.74–1.79 (4 H, m, 3 $CH_{2,Cy}$), 1.93–1.99 (2 H, m, 2 $CH_{2,Cy}$), 2.08–2.12 (2 H, m, 2 $CH_{2,Cy}$), 3.75 (3 H, s, SCPhOCH_3), 3.76 (3 H, s, CHCPhOCH_3), 6.70–6.73 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.75–6.78 [2 H, m, 2 *m*-CH_{Ar}(CCH)], 7.02–7.05 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.19–7.22 [2 H, m, 2 *o*-CH_{Ar}(CS)], 8.02 (1H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 22.27, 25.86, 37.23 (5 $CH_{2,Cy}$), 55.31 (2 OCH_3), 67.93 [C(CH_2)$_2$], 113.55 [2 *m*-CH_{Ar}(CS)], 114.19 [2 *m*-CH_{Ar}(CCH)], 125.51 (CH*C*=C), 129.14 (C_{Ar}CS), 129.75 [2 *o*-CH_{Ar}(CCH)], 129.90 (C_{Ar}CCH), 132.24 [2 *o*-CH_{Ar}(CS)], 141.25 (CHC=*C*), 158.43 [*p*-C_{Ar}(CCH)], 158.46 (C=N), 160.07 [*p*-C_{Ar}(CS)] ppm; MS (ESI): m/z 380.3 (M+H$^+$, 100%); HRMS (ESI): Found 380.1671, Calc. for $C_{23}H_{25}NO_2S$ [M+H]$^+$ 380.1684. The isothiazole[25a] **3d** (9 mg, 3 %) was obtained as a yellow oil.

2,3-Bis(4-methoxyphenyl)-9-methyl-1-thia-5,9-diazaspiro[5.5]undeca-2,4-diene (2k) and 4,5-bis(4-methoxyphenyl)isothiazole[25a] (3d): Following **GP A**, aldehyde (*E*)-**1d** (606 mg, 2.00 mmol), NaSH·H_2O (222 mg, 3.00 mmol), *N*-methylpiperidin-4-on (678 mg, 6.00 mmol) and 25 % aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 99:1 (**2k**:**3d**). Column chromatography (acetone/EtOH, 9:1; thiazine **2k**, R_f = 0.06) afforded the desired thiazine **2k** (705 mg, 90 %) as a yellow solid, mp 125–127 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3001, 2938, 2836, 2792, 2739, 1602, 1509, 1495, 1463, 1440, 1377, 1292, 1244, 1174, 1144, 1030, 881, 826, 729, 540 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.06–2.18 [4 H, m, C(CH_2)$_2$], 2.28 (3 H, s, NCH_3), 2.49–2.54 [2 H, m, N(CH_2)$_2$], 2.62–2.66 [2 H, m, N(CH_2)$_2$], 3.63 (3 H, s, SCPhOCH_3), 3.64 (3 H, s, CHCPhOCH_3), 6.61–6.64 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.66–6.69 [2 H, m, 2 *m*-CH_{Ar}(CCH)], 6.94–6.97 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.11–7.14 [2 H, m, 2 *o*-CH_{Ar}(CS)], 7.98 (1H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 36.71 [C(CH_2)$_2$], 46.04 (NCH_3), 51.37 [S(CH_2)$_2$], 54.99 (2 OCH_3), 64.95 [C(CH_2)$_2$], 113.34 [2 *m*-CH_{Ar}(CS)], 113.98 [2 *m*-CH_{Ar}(CCH)], 125.46 (CH*C*=C), 128.53 (C_{Ar}CS), 129.43 [2 *o*-CH_{Ar}(CCH)], 129.30 (C_{Ar}CCH), 131.99 [2 *o*-CH_{Ar}(CS)], 140.83 (CHC=*C*), 158.24 [*p*-C_{Ar}(CCH)], 158.69 (C=N), 159.91 [*p*-C_{Ar}(CS)] ppm; MS (ESI): m/z 395.2 (M+H$^+$, 100%); HRMS (ESI): Found 395.1782, Calc. for $C_{23}H_{27}N_2O_2S$ [M+H]$^+$ 395.1793. The isolation of the isothiazole[25a] **3d** was consciously abandoned.

(*RS*)-2-(4-Methoxybenzyl)-5,6-bis(4-methoxyphenyl)-2-methyl-2*H*-1,3-thiazine (2l) and 4,5-bis(4-methoxyphenyl)isothiazole[25a] (3d): Following **GP A**, aldehyde (*E*)-**1d** (606 mg, 2.00 mmol), NaSH·H_2O (222 mg, 3.00 mmol), 1-(4-methoxyphenyl)propan-2-one (985 mg, 6.00 mmol) and 25 % aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 98:02 (**2l**:**3d**). Column chromatography (*n*-hexane/CH_2Cl_2/EtOAc, 10:4:1; thiazine **2l**, R_f = 0.06) afforded the desired thiazine **2l** (738 mg, 83 %) as an orange solid, mp 136–137 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3036, 3015, 2973, 2955, 2923, 2838, 1604, 1574, 1509, 1498, 1455, 1300, 1293, 1246, 1171, 1113, 1078, 1027, 830, 821, 806, 755 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.67 (3 H, s, CCH_3), 3.08 (1 H, d, ^2J = 13.9 Hz, CH_2), 3.20 (1 H, d, ^2J = 13.8 Hz, CH_2), 3.75, 3.76, 3.78 (9 H, 3 s, 3 OCH_3), 6.69–6.72 (2 H, m, CH_{Ar}), 6.74–6.77 (2 H, m, CH_{Ar}), 6.83–6.86 (2 H, m, CH_{Ar}), 6.93–6.96 (2 H, m, CH_{Ar}), 7.16–7.19 (2 H, m, CH_{Ar}), 7.23–7.26 (2 H, m, CH_{Ar}) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 28.02 (CCH_3), 46.44 (CH_2), 55.27 (3 OCH_3), 67.89 (CCH_3), 113.35, 113.56, 114.07 [6 *o*-CH_{Ar}(O)], 124.83 (CH*C*=C), 128.58, 128.91, 129.87 (3 C_{Ar}C), 129.87, 131.92, 132.12 [6 *m*-CH_{Ar}(O)], 142.02 (CHC=*C*), 158.43, 158.60 [2 C_{Ar}O], 158.78 (C=N), 160.08 [C_{Ar}O] ppm; MS (ESI): m/z 446.0 (M+H$^+$, 100%); HRMS (ESI): Found 446.1779, Calc. for $C_{27}H_{28}NO_3S$ [M+H]$^+$ 446.1790. The isolation of the isothiazole[25a] **3d** was consciously abandoned.

(*RS*)-2-(4-Hydroxyphenethyl)-5,6-bis(4-methoxyphenyl)-2-methyl-2*H*-1,3-thiazine (2m) and 4,5-bis(4-methoxyphenyl)isothiazole[25a] (3d): Following **GP A**, aldehyde (*E*)-**1d** (606 mg, 2.00 mmol), NaSH·H_2O (222 mg, 3.00 mmol), 4-(4-hydroxyphenyl)butan-2-one (985 mg, 6.00 mmol) and 25 % aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 94:6 (**2m**:**3d**). Column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 6:2:2; thiazine **2m**, R_f = 0.26) afforded the desired thiazine **2m** (780 mg, 88 %) as a yellow solid, mp 161–162 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3101, 3004, 2931, 2836, 2679, 2607, 1601, 1510, 1494, 1441, 1372, 1293, 1244, 1173, 1077, 1029, 825 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.71 (CCH_3), 2.15–2.22, 2.27–2.33 [2 H, 2 m, C(CH_3)CH_2], 2.72–2.87 (2 H, m, $C_{Ar}CH_2$), 3.77 (6 H, 2 s, OCH_3), 6.73–6.76 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.77–6.80 [4 H, m, 2 *m*-CH_{Ar}(CCH), 2 *o*-CH_{Ar}(OH)], 7.02–7.07 [4 H, m, 2 *o*-CH_{Ar}(CCH), 2 *m*-CH_{Ar}(OH)], 7.21–7.24 [2 H, m, 2 *o*-CH_{Ar}(CS)], 7.61 (1H, br s, OH), 8.07 (1H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 27.11 (CCH_3), 30.74 ($C_{Ar}CH_2$), 43.89 [C(CH_3)CH_2], 55.35 (2 OCH_3), 67.05 (CCH_3), 113.69 [2 *m*-CH_{Ar}(CS)], 114.13 [2 *m*-CH_{Ar}(CCH)], 115.67 [*o*-CH_{Ar}(OH)], 124.87 (CHC=C), 128.82 (C_{Ar}CS), 129.56 [C_{Ar}CCH, 2 *m*-CH_{Ar}(OH)], 129.85 [2 *o*-CH_{Ar}(CCH)], 132.12 [2 *o*-CH_{Ar}(CS)], 133.31 ($C_{Ar}CH_2$), 143.20 (CHC=*C*), 154.74 (C_{Ar}OH), 158.56 [*p*-C_{Ar}(CCH)], 159.26 (C=N), 160.30 [*p*-C_{Ar}(CS)] ppm; MS (ESI): m/z 446.2 (M+H$^+$, 100%); HRMS (ESI): Found 446.1786, Calc. for $C_{27}H_{28}NO_3S$ [M+H]$^+$ 446.1790. The isolation of the isothiazole[25a] **3d** was consciously abandoned.

(*RS*)-2-(3-Ethoxy-3-oxopropyl)-5,6-bis(4-methoxyphenyl)-2-methyl-2*H*-1,3-thiazine (2n) and 4,5-bis(4-methoxyphenyl)isothiazole[25a] (3d): Following **GP A**, aldehyde (*E*)-**1d** (606 mg, 2.00 mmol), NaSH·H_2O (222 mg, 3.00 mmol), ethyl oxo-pentanoate (865 mg, 6.00 mmol) and 25 % aqueous ammonia solution (272 mg, 4.00 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 83:17 (**2n**:**3d**). Column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 6:2:2; thiazine **2n**, R_f = 0.27) afforded the desired thiazine **2n** (525 mg, 72 %) as an orange oil; IR (ATR) $\tilde{\nu}$ 3032, 2972, 2930, 2836, 1730, 1602, 1509, 1496, 1441, 1374, 1291, 1244, 1173, 1077, 1030, 828, 615 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.24 (3 H, t, ^3J = 7.1 Hz, CH_2CH_3), 1.63 (3 H, s, CCH_3), 2.22–2.28 [1 H, m, C(CH_3)CH_2], 2.31–2.37 [1 H, m, C(CH_3)CH_2], 2.54–2.65 (2 H, m, CH_2C=O], 3.75 (3 H, s, SCPhOCH_3), 3.76 (3 H, s, CHCPhOCH_3), 4.13 (2 H, q, ^3J = 7.1 Hz, CH_2CH$_3$), 6.69–6.72 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.76–6.79 [2 H, m, 2 *m*-CH_{Ar}(CCH)], 7.02–7.05 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.17–7.20 [2 H, m, 2 *o*-CH_{Ar}(CS)], 7.98 (1H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.34 (CH_2CH_3), 27.06 (CCH_3), 30.40 (CH_2C=O), 36.42 (CH_2CH_2C=O), 55.32 (2 OCH_3), 60.57 (CH_2CH_3), 66.53 (CCH_3), 113.62 [2 *m*-CH_{Ar}(CS)], 114.24 [2 *m*-CH_{Ar}(CCH)], 124.76 (CHC=C), 128.91 (C_{Ar}CS), 129.75 (C_{Ar}CCH), 129.84 [2 *o*-CH_{Ar}(CCH)], 132.05 [2 *o*-CH_{Ar}(CS)], 141.95 (CHC=*C*), 158.53 [*p*-C_{Ar}(CCH)], 158.94 (C=N), 160.18 [*p*-C_{Ar}(CS)] ppm; MS (ESI): m/z 426.2 (M+H$^+$, 100%); HRMS (ESI): Found 426.1729, Calc. for $C_{24}H_{28}NO_4S$ [M+H]$^+$ 426.1739. The isolation of the isothiazole[25a] **3d** was consciously abandoned.

(*RS*)-2-Isobutyl-5,6-bis(4-methoxyphenyl)-2*H*-1,3-thiazine (2o) and 4,5-bis(4-methoxyphenyl)isothiazole[25a] (3d): Following **GP A**, aldehyde (*EZ*)-**1d** (303 mg, 1.00 mmol), NaSH·H_2O (111 mg, 1.50 mmol), isopentanal (258 mg, 3.00 mmol) and 25 % aqueous ammonia solution (136 mg, 2.00 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 97:03 (**2o**:**3d**). Column chromatography (*n*-hexane/EtOAc, 9:1; thiazine **2o,** R_f = 0.17) afforded the desired thiazine **2o** (257 mg, 70 %) as an orange oil; IR (ATR) $\tilde{\nu}$ 3036, 3002, 2956, 2935, 2910, 2870, 2838, 1656, 1603, 1575, 1529, 1511, 1496, 1465, 1443, 1294, 1246, 1176, 829, 799 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.02, 1.02 [6 H, 2 d, ^3J = 6.5 Hz, CH(CH_3)$_2$,], 1.84–1.89, 2.00–2.06 (2 H, 2 m, CH_2), 2.07–2.13 [1 H, m, CH(CH_3)$_2$], 3.75 (3 H, s, SCPhOCH_3), 3.76 (3 H, s, CHCPhOCH_3), 4.65 (1 H, ddd, ^3J = 7.2 Hz, ^3J = 7.2 Hz, ^4J = 1.9 Hz, SCH), 6.70–6.73 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.76–6.79 [2 H, m, 2 *m*-CH_{Ar}(CCH)], 7.06–7.09 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.21–7.24 [2 H, m, 2 *o*-CH_{Ar}(CS)] 8.09 (1 H, d, ^4J = 1.9 Hz, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 22.63, 22.80 [CH(CH_3)$_2$], 25.17 [CH(CH_3)$_2$], 43.95 (CH_2), 55.33 (2 OCH_3), 60.52 (SCH), 113.59 [2 *m*-CH_{Ar}(CS)], 114.24 [2 *m*-CH_{Ar}(CCH)], 127.27 [CHC=C], 128.70 (C_{Ar}CS), 129.57 (C_{Ar}CCH), 129.74 [2 *o*-CH_{Ar}(CCH)], 132.54 [2 *o*-CH_{Ar}(CS)], 144.31 [CHC=*C*], 158.54 [*p*-C_{Ar}(CCH)], 160.27 [*p*-C_{Ar}(CS)], 160.71 (C=N) ppm; MS (ESI): m/z 368.3 (M+H$^+$, 100%); HRMS (ESI): Found 368.1678, Calc. for $C_{22}H_{26}NO_2S$ [M+H]$^+$ 368.1684. The isolation of the isothiazole[25a] **3d** was consciously abandoned.

2,3-Bis(4-nitrophenyl)-1-thia-5-azaspiro[5.5]undeca-2,4-diene (2p) and 4,5-bis(4-nitrophenyl)isothiazole (3e): Following **GP A**, aldehyde (*E*)-**1f** (318 mg, 0.96 mmol), NaSH·H_2O (107 mg, 1.44 mmol), cyclohexanone (283 mg, 2.88 mmol) and 25 % aqueous ammonia solution (107 mg, 1.44 mmol) were used. Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of both title compounds in a ratio of 82:18 (**2p**:**3e**). Column chromatography (*n*-hexane/EtOAc, 8:2; thiazine **2p**, R_f = 0.16) afforded the desired thiazine **2p** (65 mg, 17 %) as an orange solid, mp 138 °C; IR (ATR) $\tilde{\nu}$ 3107, 3032, 2921, 2856, 1624, 1594, 1516, 1481, 1451, 1340, 1294, 1252, 1209, 905, 890, 856, 843, 751, 728, 707, 694, 633 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.46–1.52 (1 H, m, $CH_{2,Cy}$), 1.66–1.88 (5 H, m, 3 $CH_{2,Cy}$), 2.01–2.06 (2 H, m, 2 $CH_{2,Cy}$), 2.09–2.13 (2 H, m, 2 $CH_{2,Cy}$), 7.25–7.26 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.38–7.41 [2 H, m, 2 *o*-CH_{Ar}(CS)], 8.04 (1 H, s, NCH), 8.07–8.09 [2 H, m, 2 *m*-CH_{Ar}(CS)], 8.08–8.11 [2 H, m, 2 *m*-CH_{Ar}(CCH)] ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 22.07, 25.59, 37.45 (5 $CH_{2,Cy}$), 68.99 [C_q(CH_2)$_2$], 123.78 [2 *o*-CH_{Ar}(CS)], 124.26 [2 *o*-CH_{Ar}(CCH)], 126.67 (CHC=C), 129.38 [2 *m*-CH_{Ar}(CCH)], 131.70 [2 *m*-CH_{Ar}(CS)], 142.69, 143.36 [2 C_{Ar}C], 144.21 (CHC=*C*), 146.92 [*p*-C_{Ar}(CCH)], 148.22 [*p*-C_{Ar}(CS)], 155.82 (C=N) ppm; MS (ESI): m/z 410.1 (M+H$^+$, 100%); HRMS (ESI): Found 410.1164, Calc. for $C_{21}H_{20}N_3O_4S$ [M+H]$^+$ 410.1160. The isothiazole **3e** was further purified by a second column chromatography (CH_2Cl_2/*n*-hexane/EtOAc, 15:4:1; R_f = 0.71). The isothiazole was obtained (9 mg, 3 %) as a yellow solid, mp 226 °C; IR (ATR) $\tilde{\nu}$ 3113, 3062, 3040, 1595, 1537, 1506, 1479, 1408, 1346, 1314, 1287, 898, 848, 795, 750, 734, 693, 673, 523 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.44–7.48 [4 H, m, 4 *o*-CH_{Ar}(C)], 8.23–8.26 [4 H, m, 4 *m*-CH_{Ar}(C)], 8.61 (1 H, s, NCH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 124.55, 124.68 [4 *m*-CH_{Ar}(C)], 129.83, 129.88 [4 *o*-CH_{Ar}(C)], 135.03 (CHC=C), 136.30, 138.68 (2 C_{Ar}C), 147.69 148.44 (C_{Ar}N), 158.70 (C=N), 160.86 (CHC=*C*) ppm; MS (EI, 70 eV): m/z 326.8 (M$^+$, 20%); HRMS (EI): Found 327.0300, Calc. for $C_{15}H_9N_3O_4S$ [M+H]$^+$ 327.0308.

1-Chloro-2-(dimethoxymethyl)cyclopent-1-ene (4): Following **GP A**, 2-chloro-1-cyclopentene-1-carboxaldehyde (652 mg, 4.99 mmol), $NaSH{\cdot}H_2O$ (555 mg, 7.49 mmol), acetone (869 mg, 14.97 mmol) and 25 % aqueous ammonia solution (680 mg, 9.98 mmol) were used. Column chromatography (*n*-hexane/MTBE/CH_2Cl_2, 6:3:1; R_f = 0.56) afforded the dimethyl acetale **4** instead of the desired thiazine (352 mg, 40 %) as a dark brown oil; IR (ATR) $\tilde{\nu}$ 2956, 2932, 2910, 2857, 2828, 1663, 1443, 1363, 1184, 1111, 1090, 1069, 961, 917, 905 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.92–1.98 (2 H, m, $CH_2CH_2CH_2$), 2.45–2.49 (2 H, m, $CHCCH_2$), 2.59–2.63 (2 H, m, $ClCCH_2$), 3.38 (6 H, s, 2 OCH_3), 5.05 (1 H, s, CH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 20.96 ($CH_2CH_2CH_2$), 29.67 ($CHCCH_2$), 38.39 ($ClCCH_2$), 54.80 (2 OCH_3), 100.83 (CH), 131.05 (CHC=*C*), 134.50 (CH*C*=C) ppm; MS (ESI): m/z 199.1 ($M+Na^+$, 100%); HRMS (ESI): Found 199.0496, Calc. for $C_8H_{13}NNaO_2Cl$ $[M+Na]^+$ 199.0502.

General Procedure (GP B)

The respective imine (1.0 equiv.), dissolved in anhydrous MeOH (2 mL per mmol imine), was treated with the respective isocyanide (1.0 equiv.), dissolved in anhydrous MeOH (2 mL per mmol imine), and the respective acid (1.0 equiv), dissolved in anhydrous MeOH (2 mL per mmol imine). After stirring for 72 h at r.t., the solvent was removed on a rotary evaporator. The crude product was purified by column chromatography on silica gel.

(*RS*)-3-(2-Bromoacetyl)-4-(*N*-cyclohexylcarbamoyl)-2,2-dimethyl-5,6-diphenyl-3,4-dihydro-2*H*-1,3-thiazine (5a): Following **GP B**, 2*H*-1,3-thiazine **2a** (279 mg, 1.00 mmol), bromoacetic acid (139 mg, 1.00 mmol) and isocyanocyclohexane (109 mg, 1.00 mmol) were used. Column chromatography (*n*-hexane/EtOAc, 7:3; R_f = 0.57) afforded the desired bisamide **5a** (105 mg, 20 %) as a colourless solid, mp 75 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3058, 3037, 3021, 2974, 2941, 2931, 2854, 1678, 1651, 1599, 1497, 1462, 1444, 1393, 1377, 1359, 1337, 1205, 1162, 787, 763, 695 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ 1.09–1.28 (3 H, m, 3 $CH_{2,Cy}$), 1.31–1.46 (2 H, m, 2 $CH_{2,Cy}$), 1.55–1.63 (2 H, m, 2 $CH_{2,Cy}$), 1.68–1.70 (1 H, m, $CH_{2,Cy}$), 1.90–1.93 (1 H, m, $CH_{2,Cy}$), 1.97–2.01 (1 H, m, $CH_{2,Cy}$), 1.98, 2.05 [6 H, s, $C(CH_3)_2$], 3.77 (1 H, d, ^2J = 10.9 Hz, C=OCH_2), 3.82–3.91 (1 H, m, CH_{Cy}), 3.95 (1 H, d, ^2J = 10.9 Hz, C=OCH_2), 5.24 (1 H, s, NCHC=O), 6.12 (1 H, d, ^3J = 8.3 Hz, NH), 7.16–7.24 (8 H, m, 8 CH_{Ar}), 7.29–7.31 (2 H, m, 2 CH_{Ar}) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 24.48, 24.66, 25.49 (3 $CH_{2,Cy}$), 26.26, 28.62 [C(*C*$H_3)_2$], 29.44 (C=O*C*H_2), 32.47, 33.02 (2 $CH_{2,Cy}$), 48.83 (NH*C*H_{Cy}), 67.38 (N*C*HC=O), 69.37 [*C*$(CH_3)_2$], 127.77 (*p*-CH_{Ar}), 128.53, 128.60, 128.82 (6 CH_{Ar}), 128.86 (*p*-CH_{Ar}), 129.96 (2 CH_{Ar}), 135.10 (CH*C*=C), 136.83 (C_{Ar}CS), 139.26 (C_{Ar}CCH), 141.04 (CHC=*C*), 166.65 (*C*=OCH_2), 168.03 (*C*=OCH) ppm; MS (ESI): m/z 549.3 ($M+Na^+$, 100%); HRMS (ESI): Found 549.1176, Calc. for $C_{27}H_{31}BrN_2NaO_2S$ $[M+Na]^+$ 549.1187.

(*RS*)-4-(*N*-(4-Chlorophenyl)carbamoyl)-2,2-dimethyl-5,6-diphenyl-3-(2-phenylacetyl)-3,4-dihydro-2*H*-1,3-thiazine (5b): Following **GP B**, 2*H*-1,3-thiazine **2a** (10 mg, 0.07 mmol), phenylacetic acid (10 mg, 0.07 mmol) and *p*-chloroisocyanobenzene (10 mg, 0.07 mmol) were used. Column chromatography (*n*-hexane/EtOAc, 7:3; R_f = 0.44) afforded the desired bisamide **5b** (18 mg, 43 %) as a yellow solid, mp 96 °C; IR (ATR) $\tilde{\nu}$ 3407, 3059, 3027, 2977, 2930, 1693, 1650, 1492, 1444, 1375, 1304, 1163, 1090, 1030, 1013, 826, 757, 721, 693, 627, 579 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ 2.09, 2.16 [6 H, 2 s, $C(CH_3)_2$], 3.78 (2 H, s, CH_2), 5.44 (1 H, s, NCH), 6.98–7.01 (3 H, m, 3 CH_{Ar}), 7.02–7.07 (4 H, m, 4 CH_{Ar}), 7.09–7.15 (3 H, m, 3 CH_{Ar}), 7.18–7.22 (3 H, m, 3 CH_{Ar}), 7.27–7.31 (4 H, m, 4 CH_{Ar}), 7.40–7.42 (2 H, m, 2 $NC_{Ar}CH_{Ar}$), 7.84 (1 H, s, NH) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 26.96, 28.88 [C(*C*$H_3)_2$], 44.36 (CH_2), 67.44 (NCH), 69.47 [*C*$(CH_3)_2$], 121.35 (2 $NC_{Ar}CH_{Ar}$), 127.25, 127.65, 128.17, 128.49, 128.84, 128.92, 128.98, 129.27, 130.08 (17 CH_{Ar}), 134.04 (CH_2C_{Ar}), 135.80 (CH*C*=C), 136.10 (NC_{Ar}), 136.94 (C_{Ar}CS), 139.24 (C_{Ar}CCH), 140.57 (CHC=*C*), 168.05 (CH*C*=O), 171.47 (CH_2C=O) ppm; MS (ESI): m/z 575.0 ($M+Na^+$, 100%); HRMS (ESI): Found 575.1522; Calc. for $C_{33}H_{29}ClN_2NaO_2S$ $[M+Na]^+$ 575.1536.

(*RS*)-3-Benzoyl-4-(*N*-benzylcarbamoyl)-2,2-dimethyl-5,6-diphenyl-3,4-dihydro-2*H*-1,3-thiazine (5c): Following **GP B**, 2*H*-1,3-thiazine **2a** (100 mg, 0.36 mmol), benzoic acid (44 mg, 0.36 mmol) and (isocyanomethyl)benzene (42 mg, 0.36 mmol) were used. Column chromatography (*n*-hexane/EtOAc, 7:3; R_f = 0.35) afforded the desired bisamide **5c** (55 mg, 31 %) as an orange oil; IR (ATR) $\tilde{\nu}$ 3353, 3059, 3028, 2974, 2929, 1718, 1676, 1638, 1600, 1492, 1444, 1377, 1360 ,1298, 1169, 754, 729, 694 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ 2.16, 2.22 [6 H, s, $C(CH_3)_2$], 4.47 (1 H, dd, ^2J = 14.8 Hz, ^3J = 5.2 Hz, CH_2), 4.57 (1 H, dd, ^2J = 14.8 Hz, ^3J = 5.9 Hz, CH_2), 5.29 (1 H, s, NCH), 6.26–6.29 (1 H, m, NH), 6.97–6.98 (2 H, m, 2 CH_{Ar}), 7.05–7.07 (2 H, m, 2 CH_{Ar}), 7.11–7.32 (16 H, m, 16 CH_{Ar}) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 26.76, 29.55 [C(*C*$H_3)_2$], 44.64 (CH_2), 68.87 (CH), 69.39 [*C*$(CH_3)_2$], 125.89 (2 CH_{Ar}), 127.62 (*p*-CH_{Ar}), 127.82, 128.48, 128.49 (6 CH_{Ar}), 128.52 (*p*-CH_{Ar}), 128.56 (2 CH_{Ar}), 128.75 (*p*-CH_{Ar}), 128.79, 128.86 (4 CH_{Ar}), 129.32 (*p*-CH_{Ar}), 130.10 (2 CH_{Ar}), 136.33 (CH*C*=C), 137.06 (C_{Ar}CS), 137.62 (C=OC_{Ar}), 137.93 (CH_2C_{Ar}), 138.97 (C_{Ar}CCH), 140.37 (CHC=*C*), 169.55 (*C*=OCH), 172.08 (*C*=OC_{Ar}) ppm; MS (ESI): m/z 541.1 ($M+Na^+$, 100%); HRMS (ESI): Found 541.1918, Calc. for $C_{33}H_{30}N_2NaO_2S$ $[M+Na]^+$ 541.1926.

General Procedure (GP C)

Under argon atmosphere, the respective 2*H*-1,3-thiazine (1.0 equiv.), dissolved in anhydrous CH_2Cl_2 (5 mL per mmol thiazine), was cooled down to 0–5 °C. After addition of anhydrous Et_3N (2.0 equiv.), the respective acyl chloride (1.0 equiv.), dissolved in anhydrous CH_2Cl_2 (5 mL per mmol thiazine), was added dropwise. After stirring overnight at r.t., the reaction mixture was poured into saturated aqueous NH_4Cl solution (20 mL per mmol thiazine). The layers were separated and the organic phase was washed with water (20 mL per mmol thiazine). The combined aqueous phases were extracted with CH_2Cl_2 (2 x 20 mL per mmol thiazine). The combined organic phases were dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. The crude product was purified by column chromatography on silica gel.

(6*R*,7R)-2,2-Dimethyl-4,5,7-triphenyl-3-thia-1-azabicyclo[4.2.0]oct-4-en-8-one (6a):** Following **GP C**, 2*H*-1,3-thiazine **2a** (138 mg, 0.49 mmol), Et_3N (99 mg, 0.98 mmol) and phenylacetyl chloride (77 mg, 0.49 mmol) were used. Column chromatography ($CHCl_3$/*n*-hexane/toluene/MTBE, 4:3:2:1; R_f = 0.41) afforded the desired β-lactam **6a** (95 mg, 49 %) as a yellow solid, mp 142 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3057, 3027, 3007, 2972, 2934, 1751, 1599, 1494, 1454, 1442, 1155, 1136, 1117, 766, 754, 729, 702, 682 cm^{-1}; ^1H NMR (499.9 MHz, $CDCl_3$): δ 1.83, 2.14 [6 H, 2 s, $C(CH_3)_2$], 4.21–4.22 (1 H, m, CHC_{Ar}), 4.44

(1 H, d, ^3J = 1.8 Hz, NCH), 7.00–7.02 (2 H, m, 2 x CH_{Ar}), 7.04–7.06 [2 H, m, 2 *o*-CH_{Ar}(CH)], 7.11–7.18 (8 H, m, 8 CH_{Ar}), 7.21–7.27 (3 H, m, 3 CH_{Ar}) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 26.28, 29.73 [C(CH_3)$_2$], 58.80 (NCH), 60.66 (CHC_{Ar}), 61.68 [C(CH_3)$_2$], 127.24 (*p*-CH_{Ar}), 127.46 (*o*-$CH_{Ar}CH$), 127.68 (*p*-CH_{Ar}), 127.76 (CH*C*=C), 127.94 (*p*-CH_{Ar}), 128.24, 128.46, 128.90, 129.56, 129.76 (10 CH_{Ar}), 133.66 (CHC=*C*), 134.99 ($C_{Ar}CH$), 138.22, 138.76 (2 C_{Ar}), 166.50 (C=O) ppm; MS (ESI): m/z 398.2 (M+H$^+$, 100%); HRMS (ESI): Found 398.2388; Calc. for $C_{26}H_{24}NOS$ [M+H]$^+$ 398.2394.

(6*R,7*R**)-7-Methoxy-2,2-dimethyl-4,5-diphenyl-3-thia-1-azabicyclo[4.2.0]oct-4-en-8-one (6b)**: Following **GP C**, 2*H*-1,3-thiazine **2a** (200 mg, 0.72 mmol), Et_3N (146 mg, 1.44 mmol) and 2-methoxyacetyl chloride (78 mg, 0.72 mmol) were used. Column chromatography ($CHCl_3$/toluene/*n*-hexane/MTBE, 6:2:1:1; R_f = 0.41) afforded the desired β-lactam **6b** (187 mg, 74 %) as a yellow solid, mp 81 °C (from CH_2Cl_2/*n*-hexane); IR (ATR) $\tilde{\nu}$ 3086, 3058, 3033, 3006, 2970, 2943, 2924, 2841, 1741, 1595, 1586, 1493, 1457, 1440, 1392, 1372, 1324, 1220, 1206, 1131, 1122, 936, 913, 893, 851, 732, 705, 692, 666 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.80, 2.06 [6 H, 2 s, C(CH_3)$_2$], 3.21 (3 H, s, OCH_3), 4.42 (1 H, d, ^3J = 1.5 Hz, NCH), 4.44 (1 H, d, ^3J = 1.5 Hz, C*H*OCH_3), 7.04–7.06 (2 H, m, 2 CH_{Ar}), 7.11–7.19 (8 H, m, 8 CH_{Ar}) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 25.84, 29.14 [C(CH_3)$_2$], 57.67 (OCH_3), 58.63 (NCH), 61.39 [C(CH_3)$_2$], 87.65 ($CHOCH_3$), 125.73 (CH*C*=C), 127.15, 127.91 (2 *p*-CH_{Ar}), 128.15, 128.35, 129.23, 129.54 (8 CH_{Ar}), 134.03 (CHC=*C*), 137.72, 138.49 (2 C_{Ar}), 164.02 (C=O) ppm; MS (ESI): m/z 374.1 (M+Na$^+$, 100%); HRMS (ESI): Found 374.1183, Calc. for $C_{21}H_{21}NNaO_2S$ [M+Na]$^+$ 374.1191.

Crystal structure determination of β-lactam 6b:

Crystal data. $C_{21}H_{21}NO_2S$, M = 351.45, monoclinic, a = 15.9577(7), b = 6.3713(3), c = 17.8868(8) Å, U = 1804.89(14) Å^3, T = 120 K, space group P21/c, Z = 4, 75519 reflection measured, 7935 unique (R_{int} = 0.0291) which were used in all calculations. The final $wR(F_2)$ was 0.1351 (all data).

(6*R,7*R**)-7-Methoxy-4,5-bis(4-methoxyphenyl)-3-thia-1-azaspiro[bicyclo[4.2.0]octane-2,1'-cyclohexan]-4-en-8-one (6c)**: Following **GP C**, 2*H*-1,3-thiazine **2j** (85 mg, 0.22 mmol), Et_3N (45 mg, 0.44 mmol) and 2-methoxyacetyl chloride (24 mg, 0.22 mmol) were used. Column chromatography (CH_2Cl_2/*n*-hexane/toluene/MTBE, 4:3:2:1; R_f = 0.39) afforded the desired β-lactam **6c** (64 mg, 64 %) as a yellow oil; IR (ATR) $\tilde{\nu}$ 2998, 2934, 2855, 2836, 1753, 1604, 1507, 1462, 1442, 1291, 1245, 1219, 1174, 1123, 1031, 1014, 909, 827, 800, 793, 728 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.42–1.48 (1 H, m, $CH_{2,Cy}$), 1.56–1.63 (2 H, m, 2 $CH_{2,Cy}$), 1.68–1.73 (2 H, m, 2 $CH_{2,Cy}$), 1.85–1.94 (2 H, m, 2 $CH_{2,Cy}$), 2.04–2.09 (1 H, m, $CH_{2,Cy}$), 2.25–2.29 (1 H, m, $CH_{2,Cy}$), 2.73–2.77 (1 H, m, $CH_{2,Cy}$), 3.30 (3 H, s, CHOCH_3), 3.73 [3 H, s, CHCPhOCH_3], 3.74 [3 H, s, SCPhOCH_3], 4.30 (1 H, d, ^3J = 1.5 Hz, NCH), 4.44 (1 H, d, ^3J = 1.5 Hz, C*H*OCH_3), 6.68–6.72 [4 H, m, 2 *m*-CH_{Ar}(CS), 2 *m*-CH_{Ar}(CCH)], 6.93–6.96 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.06–7.08 [2 H, m, 2 *o*-CH_{Ar}(CS)] ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 22.64, 22.70, 25.23, 34.44, 36.67 (5 $CH_{2,Cy}$), 55.24, 55.28 (2 $C_{Ar}OCH_3$) 57.59 (CHOCH_3), 58.04 (NCH), 65.69 [C(CH_2)$_2$], 87.63 ($CHOCH_3$), 113.69 [2 *m*-CH_{Ar}(CCH)], 113.83 [2 *m*-CH_{Ar}(CS)], 124.71 (CH*C*=C), 130.39 [C_{Ar}CS, 2 *o*-CH_{Ar}(CCH)], 131.03 [2 *o*-CH_{Ar}(CS)], 131.18 (C_{Ar}CCH), 132.43 (CHC=*C*), 158.39 [*p*-C_{Ar}(CCH)], 159.16 [*p*-C_{Ar}(CS)], 164.81 (C=O) ppm; MS (ESI): m/z 474.1 (M+Na$^+$, 100%); HRMS (ESI): Found 474.1717, Calc. for $C_{26}H_{29}NNaO_4S$ [M+Na]$^+$ 474.1715.

General Procedure (GP D)

Under argon atmosphere, the respective 2*H*-1,3-thiazine (1.0 equiv.), dissolved in anhydrous CH_2Cl_2 (5 mL per mmol thiazine), was cooled down to 0–5 °C. A solution of the respective acyl chloride (1.1 equiv.) in anhydrous CH_2Cl_2 (5 mL per mmol thiazine) was added dropwise. After stirring overnight at r.t., a solution of anhydrous MeOH (3.7 equiv) and anhydrous Et_3N (1.75 equiv.) in anhydrous CH_2Cl_2 (5 mL per mmol thiazine) was added dropwise at 0–5 °C. After stirring overnight at r.t., the reaction mixture was poured into ice-water (20 mL per mmol thiazine). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL per mmol thiazine). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (20 mL per mmol thiazine) and water (20 mL per mmol thiazine) and dried ($MgSO_4$). The solvent was removed on a rotary evaporator and the crude product was purified by column chromatography on silica gel.

(*RS*)-2,2-Dimethyl-5,6-diphenyl-4-methoxy-3-(4-nitrobenzoyl)-2*H*-1,3-thiazin (7a): Following **GP D**, 2*H*-1,3-thiazine **2a** (1.321 g, 4.73 mmol), 4-nitrobenzoyl chloride (798 mg, 5.20 mmol), Et_3N (689 mg, 8.28 mmol) and MeOH (661 mg, 17.50 mmol) were used. Column chromatography (*n*-hexane/diethyl ether/CH_2Cl_2, 7:2:1; R_f = 0.43) afforded the desired methoxy amide **7a** (1.294 g, 59 %) as a yellow solid, mp 107 °C (from CH_2Cl_2/*n*-hexane); Anal. Found: C, 68.12; H, 5.62; N, 6.10; O, 13.62; S, 6.53. Calc. for $C_{26}H_{24}N_2O_4S$: C, 67.81; H, 5.25; N, 6.08; O, 13.90; S, 6.96%; IR (ATR) $\tilde{\nu}$ 3189, 3103, 3078, 3056, 3026, 2975, 2928, 2858, 1661, 1599, 1524, 1498, 1462, 1443, 1389, 1344, 1332, 1197, 1174, 1121, 908, 862, 756, 730, 713, 694 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.17, 2.17 [6 H, 2 s, C(CH_3)$_2$], 3.33 (3 H, s, OCH_3), 5.36 (1 H, s, NCH), 6.93–6.95 (2 H, m, 2 CH_{Ar}), 7.11–7.23 (6 H, m, 6 CH_{Ar}), 7.32–7.34 (2 H, m, 2 CH_{Ar}), 7.42–7.44 [2 H, m, 2 *m*-$CH_{Ar}(NO_2)$], 8.07–8.09 [2 H, m, 2 *o*-$CH_{Ar}(NO_2)$] ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 27.81, 29.48 [C(CH_3)$_2$], 54.97 (OCH_3), 66.43 [C(CH_3)$_2$], 90.27 (NCH), 123.67 [2 *o*-$CH_{Ar}(NO_2)$], 127.50 (*p*-CHAr), 128.18 [2 *m*-$CH_{Ar}(NO_2)$], 128.35 (2 CH_{Ar}), 128.71 (2 CH_{Ar}), 128.73 (*p*-CH_{Ar}), 128.78 (2 CH_{Ar}), 130.19 (2 CH_{Ar}), 132.73 (CH*C*=C), 137.26 (C_{Ar}CS), 138.69 (CHC=*C*), 138.92 (C_{Ar}CCH), 143.01 (C_{Ar}C=O), 148.54 ($C_{Ar}NO_2$), 170.03 (C=O) ppm.

(*RS*)-2,2-Dimethyl-4-methoxy-5,6-bis(4-methoxyphenyl)-3-(4-nitrobenzoyl)-2*H*-1,3-thiazin (7b): Following **GP D**, 2*H*-1,3-thiazine **2i** (1.500 g, 4.42 mmol), 4-nitrobenzoyl chloride (798 mg, 4.86 mmol), Et_3N (689 mg, 7.74 mmol) and MeOH (661 mg, 16.35 mmol) were used. Column chromatography (*n*-hexane/diethyl ether/CH_2Cl_2, 5:3:2; R_f = 0.37) afforded the desired methoxy amide **7b** (1.885 g, 82 %) as a yellow solid, mp 112 °C (from CH_2Cl_2/*n*-hexane); Anal. Found: C, 64.56; H, 5.68; N, 5.36; O, 18.51; S, 5.89. Calc. for $C_{28}H_{28}N_2O_6S$: C, 64.60; H, 5.42; N, 5.38; O, 18.44; S, 6.16%; IR (ATR) $\tilde{\nu}$ 3034, 2933, 2837, 1660, 1602, 1524, 1508, 1462, 1442, 1393, 1345, 1292, 1246, 1174, 1030, 910, 860, 834, 731, 633 cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.13, 2.15 [6 H, 2 s, C(CH_3)$_2$], 3.32 (3 H, s, CHOCH_3), 3.75, 3.77 (6 H, 2 s, 2 $C_{Ar}OCH_3$), 5.29 (1 H, s, NCH), 6.65–6.68 [2 H, m, 2 *m*-CH_{Ar}(CS)], 6.72–6.75 [2 H, m, 2 *m*-CH_{Ar}(CCH)], 6.86–6.89 [2 H, m, 2 *o*-CH_{Ar}(CCH)], 7.26–7.29 [2 H, m, 2 *o*-

$CH_{Ar}(CS)$], 7.45–7.47 [2 H, m, 2 *m*-$CH_{Ar}(NO_2)$], 8.10–8.12 [2 H, m, 2 *o*-$CH_{Ar}(NO_2)$] ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 27.59, 29.28 [$C(CH_3)_2$], 54.83 ($CHOCH_3$), 55.33, 55.34 (2 $C_{Ar}OCH_3$), 66.44 [$C(CH_3)_2$], 90.38 (NCH), 113.81 [2 *m*-CH_{Ar}(CCH)], 114.16 [2 *m*-CH_{Ar}(CS)], 123.65 [2 *o*-$CH_{Ar}(NO_2)$], 128.18 [2 *m*-$CH_{Ar}(NO_2)$], 129.66 (C_{Ar}CCH), 130.03 [2 *o*-CH_{Ar}(CCH)], 130.94 (CH*C*=C), 131.26 (C_{Ar}CS), 131.48 2 *o*-CH_{Ar}(CS)], 137.36 (CHC=*C*), 143.17, 148.51 ($C_{Ar}NO_2$, C_{Ar}C=O) 158.73 [*p*-C_{Ar}(CS)], 159.84 [*p*-C_{Ar}(CCH)], 169.94 (C=O) ppm;.

Notes and references

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