Highly *cis*-Diastereoselective Synthesis of Coumarin-Based 2,3-Disubstituted Dihydrobenzothiazines by Organocatalysis

by **Mehdi Khoobi**[a])[b]), **Ali Ramazani***[a]), **Alireza Foroumadi**[b]), **Saeed Emami**[c]), **Farnaz Jafarpour**[d]), **Amir Mahyari**[a]), **Katarzyna Ślepokura**[e]), **Tadeusz Lis**[e]), and **Abbas Shafiee***[b])

[a]) Chemistry Department, Zanjan University, P.O. Box 45195-313, Zanjan, Iran (phone: +98 241 5152572; fax: +98 241 5152477; e-mail: aliramazani@yahoo.com)

[b]) Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 14176, Iran (phone: +98 66406757; fax: +98 66461178; e-mail: ashafiee@ams.ac.ir)

[c]) Department of Medicinal Chemistry and Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran

[d]) School of Chemistry, College of Science, University of Tehran, P.O. Box 14155-6455 Tehran, Iran

[e]) Faculty of Chemistry, University of Wrocław, 14 Joliot-Curie St., PL-50-383 Wrocław

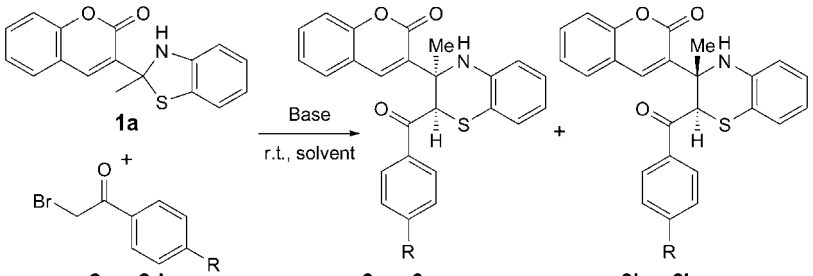
An efficient and organocatalyzed asymmetric reaction of phenacyl halides with coumarin-based dihydrobenzothiazoles was developed to afford *cis*-2,3-disubstituted 3,4-dihydro-2*H*-benzothiazines. This method provides a one-step and highly diastereoselective route to a wide variety of coumarin-based 3,4-dihydro-2*H*-benzothiazines using the cheap and commercially available *Cinchona* alkaloid quinine hydrochloride.

Introduction. – In the field of N,S-heterocycles, benzothiazine derivatives have attracted great interest as they exhibit diverse biological and pharmacological activities [1]. They also have been reported as key intermediates in the synthesis of red-hair pigment pheomelanins [2]. Furthermore, great efforts have been focused on the synthesis of thiazoles and fused thiazoles containing coumarins with antimicrobial and anti-inflammatory activities [3]. However, no catalytic asymmetric synthesis of these interesting structures has been reported to date. Accordingly, the development of a highly efficient and stereoselective methodology seems necessary. In the past few years, organocatalysis has emerged as an important tool for stereoselective formation of C,C and carbon, heteroatom bonds [4]. In this regard, *Cinchona* alkaloids have attracted great interest as they provide non-covalent activation of the reacting partners in several asymmetric transformations and lead to generally highly stereochemically controlled reactions [5]. Here, we report the diastereoselective synthesis of coumarin-based dihydrobenzothiazines *via* ring expansion of dihydrobenzothiazoles assisted by organocatalysis with *Cinchona* alkaloids. This protocol is based on an extension of a method reported by *Mashraqui* and *Kellogg* [6] and takes the advantage of highly diastereoselective construction of dihydrobenzothiazines, which bear substituted benzoyl and coumarin motifs, utilizing readily available *Cinchona* alkaloids.

Results and Discussion. – The starting dihydrobenzothiazoles **1a**–**1d** were easily prepared in excellent yields by the standard protocol recently developed in our

laboratory [7]. First, we examined the reaction of dihydrobenzothiazole **1a** with different phenacyl bromides **2a**–**2d** under various basic conditions at room temperature in order to evaluate their efficiency and diastereoselectivity (*Table 1*).

Table 1. *Screening of the Reaction Conditions for the Preparation of Coumarin-Based 2,3-Disubstituted 3,4-Dihydro-2*H*-benzothiazines*



2a – **2d** **3a** – **6a** (*cis*) **3b** – **6b** (*trans*)

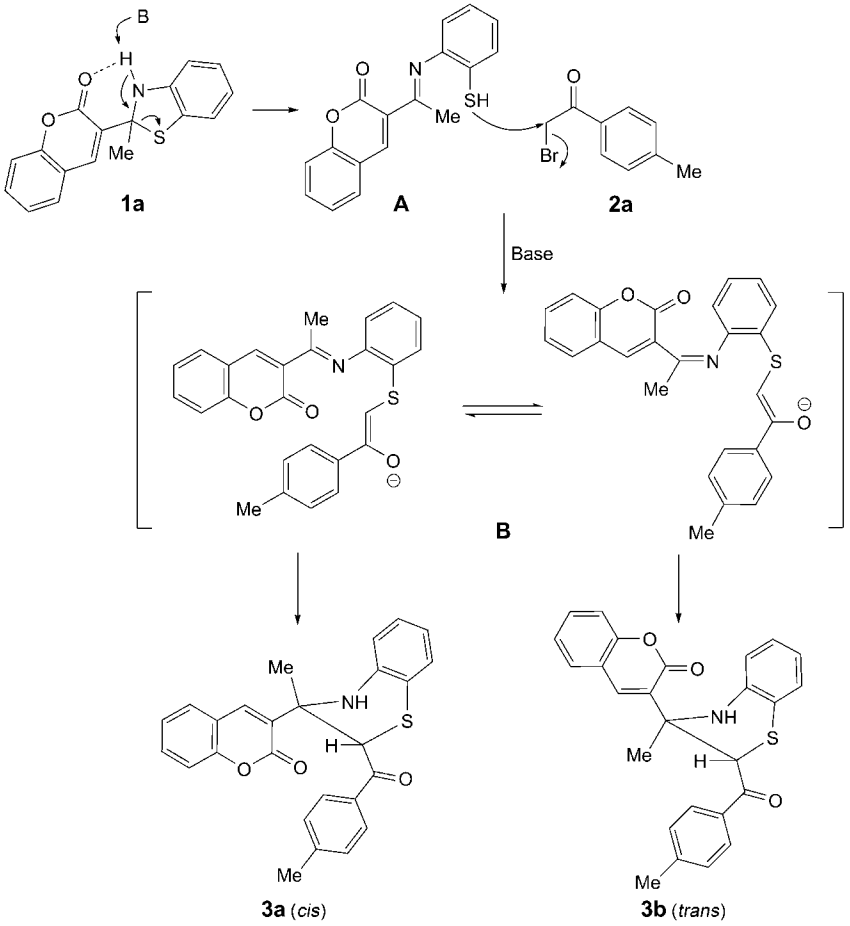
Entry	R	Base	Solvent	Time [h]	Yield[a]) [%]	*cis*/*trans* Ratio[b])
1	Me (**2a**)	K_2CO_3 (1.5 equiv.)	Acetone	12	60	31 : 69
2	Me (**2a**)	K_2CO_3 (1.5 equiv.)	$CHCl_3$	12	74	46 : 54
3	Me (**2a**)	KOH (1 equiv.)	EtOH	5	71	33 : 67
4	Me (**2a**)	KOH (1 equiv.)	$CHCl_3$	6	74	48 : 52
5	Me (**2a**)	DBU[c])	$CHCl_3$	5	80	48 : 52
6	Me (**2a**)	DABCO[d])	$CHCl_3$	7	78	45 : 52
7	Me (**2a**)	KF (10 equiv.)	$CHCl_3$	6	90	50 : 50
8	Me (**2a**)	KF/Al_2O_3[e]) (0.7 g)	$CHCl_3$	4	96	50 : 50
9	NO_2 (**2b**)	KF/Al_2O_3 (0.7 g)	$CHCl_3$	4	92	43 : 57
10	Br (**2c**)	KF/Al_2O_3 (0.7 g)	$CHCl_3$	5	94	50 : 50
11	MeO (**2d**)	KF/Al_2O_3 (0.7 g)	$CHCl_3$	5	90	46 : 54
12	Me (**2a**)	KF/Al_2O_3 (0.7 g)	CH_2Cl_2	4	94	48 : 52
13	Me (**2a**)	KF/Al_2O_3 (0.7 g)	EtOH	7	75	44 : 65
14	Me (**2a**)	KF/Al_2O_3 (0.7 g)	MeCN	5	90	86 : 14
16	Me (**2a**)	KF/Al_2O_3 (0.7 g)	DMF	4	90	20 : 80
17	Me (**2a**)	KF/Al_2O_3 (0.7 g)	NMP[f])	6	86	44 : 56

[a]) Yields of the isolated products. [b]) Diastereoisomer ratios determined by NMR analysis. [c]) 1,8-Diazabicyclo[5.4.0]undec-7-ene. [d]) 1,4-Diazabicyclo[2.2.2]octane. [e]) KF/Al_2O_3 was prepared according to the reported procedure in which the content of KF is *ca.* 40% (*m*/*m*) [8]. [f]) 1-Methylpyrrolidin-2-one.

The results revealed that the corresponding dihydrobenzothiazine derivatives **3**–**6** could be conveniently prepared in the presence of KF/Al_2O_3 in excellent yields, but the products were obtained as mixtures of *cis*/*trans* diastereoisomers. According to the work of *Mashraqui* and *Kelogg* [6], we propose a mechanism for this reaction as depicted in the *Scheme*.

It seems that the reaction is initiated by generation of intermediate **A**, which is produced by ring opening of dihydrobenzothiazole **1a** under basic condition. In the next step, the nucleophilic attack of the formed thiol to 'soft' center of phenacyl bromide **2a**, followed by enolate formation results in intermediate **B**. This is an important intermediate to produce two stereogenic centers. Finally, an interamolecular

Scheme. *Proposed Reaction Mechanism Leading to 3,4-Dihydro-2*H*-1,4-benzothiazine Consisting of Two Diastereoisomers*



Mannich-type reaction results in *cis*/*trans* adducts of **3** by means of a 6-*endo*-trig C–C bond-forming reaction.

In the previous report published by *Mashraqui* and *Kellogg*, it has been mentioned that the *trans*-isomer of 2,3-disubstituted-3,4-dihydro-2*H*-1,4-benzothiazine was the major product, with a lower chemical shift of H–C(2) of the benzothiazine ring with respect to the *cis*-isomer in the ^{1}H-NMR spectrum [6]. By comparing a set of ^{1}H-NMR spectra, it was found that the diastereoisomer ratio (dr) of *cis*/*trans*-dihydrobenzothiazines can be determined by the integration of the benzothiazine H–C(2) signal as an internal probe. For example, the *trans*-isomer **3b** is readily identified, because the H–C(2) absorbs at 5.67 ppm, *i.e.*, it is shielded with respect to 6.00 ppm for the *cis*-isomer **3a** (*Fig. 1*).

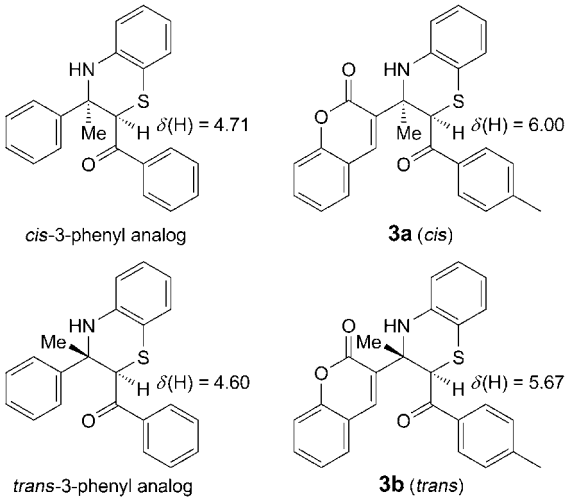


Fig. 1. *The comparison of H–C(2) chemical shifts in* cis- *and* trans-*isomers.* The selected ^{1}H-NMR data of 3-Ph analogs was reported by *Mashraqui* and *Kellogg* [6].

As shown in *Table 1*, the *cis*-diastereoisomer **3a** was the major product in MeCN as solvent (*Table 1*, *Entry 14*), but, in CH_2Cl_2, $CHCl_3$, and NMP (1-methylpyrrolidin-2-one), diastereoselectivity decreased (*Table 1*, *Entries 8*, *12*, and *17*). Also, DMF and EtOH converted diastereoselectivity in favor of the *trans*-diastereoisomer (*Table 1*, *Entries 16* and *13*). In addition, the results revealed that the type of base and variation of the phenacyl bromide do not significantly affect the diastereoselectivity (*Table 1*).

To the best of our knowledge, there has been no report on the asymmetric reaction of dihydrobenzothiazoles and phenacyl bromides *via* an interamolecular *Mannich*-type reaction to give dihydrobenzothiazines. In light of the capacity of *Cinchona* alkaloids and amino acids in various organocatalytic transformations, especially in *Mannich* reactions [9], and the importance of the development of highly diastereoselective organocatalytic approaches, we probed the reaction between dihydrobenzothiazole **1a** and 2-bromo-1-(4-methylphenyl)ethanone (**2a**) in the presence of some of *Cinchona* alkaloids (*Fig. 2*) and amino acids.

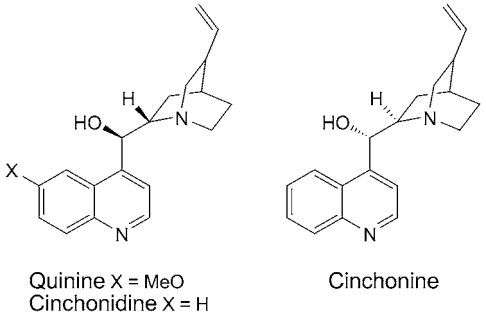
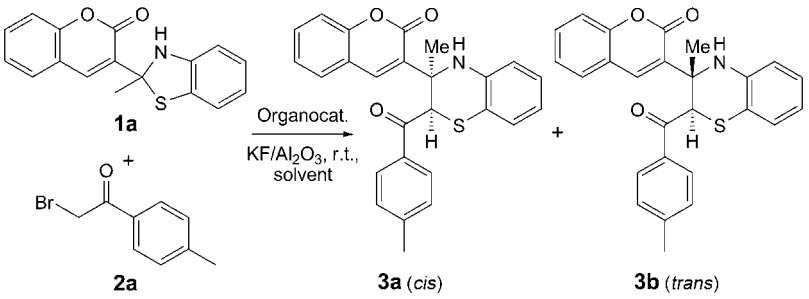


Fig. 2. *The structures of* Cinchona *alkaloids used in our study*

The screening of reactions was performed with some organocatalysts such as natural alkaloids as well as α-amino acids in CH_2Cl_2. While quinine showed slight diastereoselectivity in CH_2Cl_2 (*Table 2*, *Entry 12*), some amino acids gave the desired product in good-to-high diastereoselectivity in favor of the diastereoisomer **3b** (*Table 2*, *Entries 8–11*).

Table 2. *Organocatalyzed Synthesis of Compound* **3**



Entry[a])	Organocatalyst	Solvent	*t* [h]	Yield[b]) [%]	dr[c]) **3a** (*cis*)/**3b** (*trans*)
1	–	CH_2Cl_2	4	94	48 : 52
2	L-Proline	CH_2Cl_2	4	94	34 : 66
3	L-Proline	MeCN	3	95	49 : 51
4	L-Proline	DMF	3	95	43 : 57
5	L-Proline	Toluene	6	74	35 : 65
6	L-Proline	EtOH	10	67	66 : 34
7	*N*-benzyl-L-Proline	CH_2Cl_2	5	88	48 : 52
8	L-Alanine	CH_2Cl_2	12	92	26 : 74
9	L-Methionine	CH_2Cl_2	12	80	20 : 80
10	*N*-Acetyl-L-cysteine	CH_2Cl_2	12	88	17 : 83
11	L-Serine	CH_2Cl_2	12	90	14 : 86
12	Quinine	CH_2Cl_2	3	96	42 : 58
13	Quinine	Toluene	4	84	28 : 72
14	Quinine	EtOH	2	80	88 : 12
15	*t*-Butyl (2*S*)-2-(hydroxymethyl)-pyrrolidine-1-carboxylate	MeCN	2	91	95 : 5
16	*t*-Butyl (2*S*)-2-(hydroxymethyl)-pyrrolidine-1-carboxylate	DMF	3	90	50 : 50
17	Quinine hydrochloride	EtOH	3	78	100 : 0
18	Quinine hydrochloride	MeCN	3	91	67 : 33
19	Cinchonidine	EtOH	2	73	100 : 0
20	Cinchonine	EtOH	2	78	100 : 0

[a]) Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), organocatalyst (10 mol-%), and KF/Al_2O_3 (0.7 g) in solvent (3.0 ml) at r.t. [b]) Yields of isolated products. [c]) Diastereoisomer ratios (dr) determined by ^{1}H-NMR analysis.

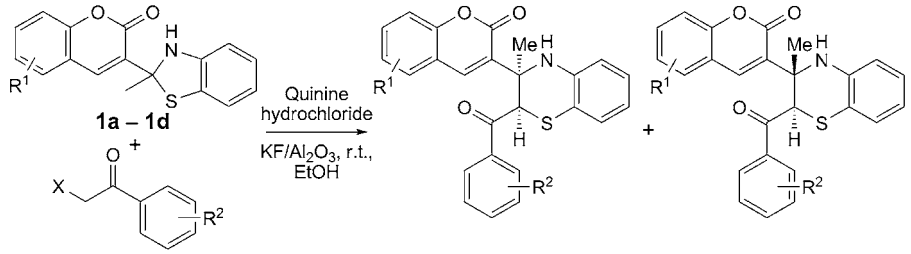
Replacing CH_2Cl_2 with toluene as solvent, led to increased diastereoselectivity for quinine as catalyst in favor of **3b** (*Table 2*, *Entry 13*). Furthermore, the reaction was very sensitive to the nature of the employed solvent, and the diastereoselectivity

changed in favor of **3a**, when EtOH was used as the solvent (*Table 2*, *Entry 14*). It is noteworthy that, in EtOH as the solvent and in the absence of a catalyst, the mixture of two diastereoisomers was obtained in 75% yield with low diastereoselectivity (*Table 1*, *Entry 13*). The *cis*-diastereoselectivity was even improved by using *tert*-butyl (2*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (*Table 2*, *Entry 15*). Most remarkably, natural alkaloids such as quinine hydrochloride, cinchonidine, and cinchonine afforded the desired product as a single *cis*-diastereoisomer in EtOH (*Table 2*, *Entries 17*, *19*, and *20*).

It should be mentioned that the reaction did not run in the presence of quinine (up to 50 mol-%) and in the absence of KF/Al_2O_3 after 12 h at room temperature. In addition, according to the results of other parallel reactions, quinine hydrochloride for the reaction of other phenacyl bromides, **2b** and **2c**, with coumarin **1a** was preferred over cinchonidine and cinchonine. On the whole, we were delighted to see that, under the optimized conditions, the reaction of coumarin **1a** (1.0 mmol), **2a** (1.2 mmol, 1.2 equiv.), quinine hydrochloride (10 mol-%), and KF/Al_2O_3 (0.7 g) in EtOH (3.0 ml) at room temperature for 3 h afforded exclusively the *cis*-diastereoisomer of **3a** in 78% yield (*Table 2*, *Entry 17*).

Encouraged by these results, we sought to generalize the scope of the reaction by using various substituted coumarins and phenacyl halides (*Table 3*). The results revealed that phenacyl halides bearing both electron-donating and -withdrawing

Table 3. *Scope of Diastereoselective Synthesis of Coumarin-Based 3,4-Dihydro-2*H*-benzothiazines* **3**–**13**



Entry[a])	R^1	R^2	X	Product	*t* [h]	Yield[b]) [%]	dr[c]) *cis*/*trans*
1	H (**1a**)	4-Me (**2a**)	Br	**3**	4	78	100 : 0
2	H (**1a**)	4-NO_2 (**2b**)	Br	**4**	3	78	100 : 0
3	H (**1a**)	4-Br (**2c**)	Br	**5**	6	80	100 : 0
4	H (**1a**)	4-MeO (**2d**)	Br	**6**	6	82	100 : 0
5	H (**1a**)	H (**2e**)	Cl	**7**	8	82	100 : 0
6	H (**1a**)	4-Ph (**2f**)	Br	**8**	5	74	100 : 0
7	H (**1a**)	4-$MeSO_2$ (**2g**)	Br	**9**	3	93	100 : 0
8	8-MeO (**1b**)	4-NO_2 (**2b**)	Br	**10**	4	82	65 : 35
9	6-Br (**1c**)	4-$MeSO_2$ (**2g**)	Br	**11**	6	68	60 : 40
10	H (**1a**)	3-cPentO,4-MeO[d]) (**2h**)	Br	**12**	4	78	20 : 80
11	7-HO (**1d**)	4-$MeSO_2$ (**2g**)	Br	**13**	4	40	100 : 0

[a]) Reaction conditions: Coumarin **1** (1.0 mmol), phenacyl halide **2** (1.2 mmol), quinine hydrochloride (10 mol-%), and KF/Al_2O_3 (0.7 g) in EtOH (3.0 ml) at r.t. [b]) Yields of isolated products. [c]) Diastereoisomer ratios (dr) determined by NMR analysis. [d]) cPentO: Cyclopentyloxy.

groups on the phenyl ring such as Me, MeO, NO_2, halo, and $MeSO_2$ groups were well tolerated under the optimized reaction conditions, and the desired products were obtained in high yields with *cis*-diastereoselectivity (*Table 3*, *Entries 1–7*). However, the reactivity as well as the level of stereoselectivity was influenced by the nature of substituents on the coumarin ring. Coumarins bearing 8-MeO or 6-Br groups showed inferior stereoselectivity (*Table 3*, *Entries 8* and *9*). In addition, to investigate the steric compatibility of this stereoselective reaction, a sterically more hindered phenacyl bromide **2h** was selected, and dihydrobenzothiazine derivative **12** was obtained in 78% yield (*Table 3*, *Entry 10*). In this case, the diastereoselectivity was influenced by the steric hindrance of the substituent on phenacyl bromide, and the diastereoselectivity changed in favor of the isomer **12b**. It should be mentioned that, despite high and versatile diastereoselectivities, no enantioselectivity was observed within the scope of the reaction.

Furthermore, the diastereoselective quinine hydrochloride-catalyzed reaction of dihydrobenzothiazoles to *cis*-dihydrobenzothiazines was also successfully scaled up. We performed a scale-up reaction employing 10.0 mmol of coumarin **1a** and 12.0 mmol of 2-bromo-1-[4-(methylsulfonyl)phenyl]ethanone (**2g**) to give the desired product **9** in 90% yield and 98% de.

The compound **10b** (*trans*-diastereoisomer, *Table 3*, *Entry 8*) with a lower solubility in MeCN could be separated and isolated in pure form as suitable crystals for X-ray crystallography (CCDC-789191M; *Fig. 3*). The ORTEP plot clearly shows that the adjacent C(7)–C(19) (ORTEP numbering) substituents have the *trans*-configuration, which is in agreement with our earlier assigned configuration based on ^{1}H-NMR data. Unfortunately, crystals of the *cis*-diastereoisomer **10a** were unsuitable for structural

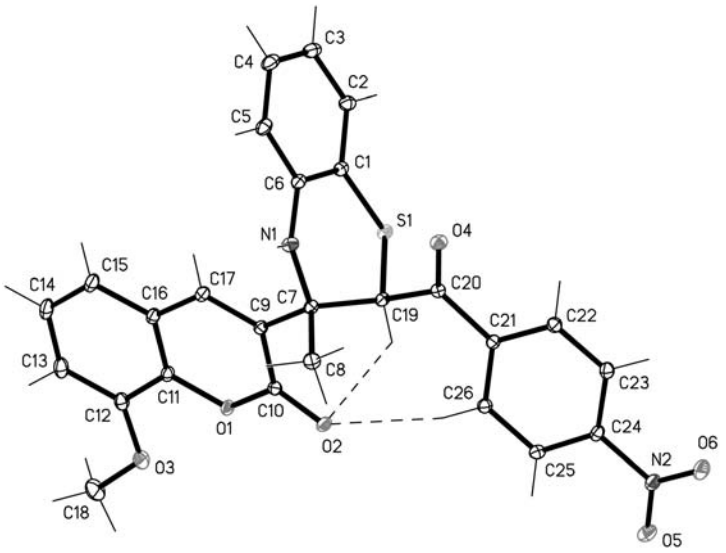


Fig. 3. *Single-crystal X-ray structure of one enantionmer of* **10b** (displacement ellipsoids at 50% probability level). The intramolecular C–H···O contacts are shown with dashed lines.

determination. Nevertheless, on the basis of the greater δ value [6] and X-ray crystal structure of the *trans*-diastereoisomer, our suggestion was unambiguously confirmed.

Based on experimental results, we proposed a model to rationalize the observed quinine-catalyzed *cis*-diastereoselectivity in the preparation of coumarin-based dihydrobenzothiazines (*Fig. 4*). With the key insight into the active conformer of the quinine, the kinetic results are consistent with an acid–base bifunctional catalysis mode [10], and the observed solvent effect indicate that H-bond interactions between the catalyst and the substrates play an important role. Therefore, we propose the transition-state model **C** or **D** to rationalize the stereochemical outcome of this asymmetric intramolecular *Mannich*-type reaction (*Fig. 4*). The enolization of the phenacyl moieties in the intermediates can be catalyzed by KF/Al_2O_3, as well as the tertiary amine group of quinine. Quinine, as a bifunctional catalyst, could coordinate with the imine group of the intermediate through H-bond interaction with the OH group. Chelation of the C=O group of the coumarin moiety with the OH moiety of quinine provides excellent stereocontrol in the reaction (*Fig. 4*; **C**). This chelating may be facilitated by EtOH as protic solvent (*Fig. 4*; **D**). In addition, the electrostatic interactions in the tight-ion pair model of *Corey* [11] between the quaternary ammonium salt and enolate can play an important role for the catalytic process and the *cis* selectivity.

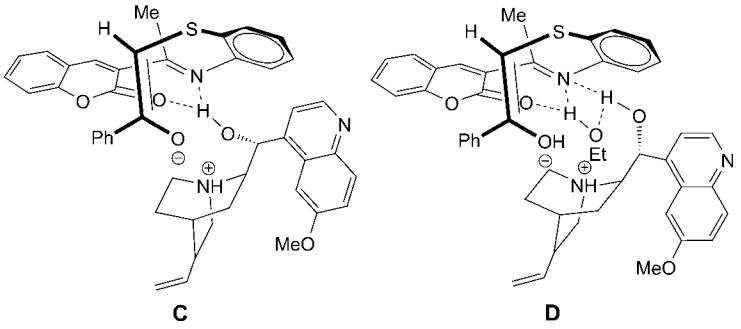


Fig. 4. *Transition-state models for organocatalysis by quinine*

In contrast to the observed *cis*-diastereoselectivity in the catalytic process by quinine, no enantioselectivity was observed in the asymmetric intramolecular *Mannich*-type reaction of the enolate intermediate. The lack of enantioselectivity *via* enolate intermediate was attributed to the free rotation of two pendant groups on the aminothiophenol. The enolate intermediate may adopt two possible conformations that are mirror images to each other (*Fig. 5*). It is obvious from *Fig. 5* that quinine-catalyzed asymmetrization of the enolate intermediate showed no enantioselectivity, and both enantiomers of *cis*-isomer could be formed.

Conclusions. – In summary, we have developed a highly diastereoselective one-step synthesis of *cis*-2,3-disubstituted dihydrobenzothiazines, which contain coumarin scaffolds, and which are not easily accessible by conventional methods. A systematic study on the reaction of different phenacyl halides with coumarin-based dihydroben-

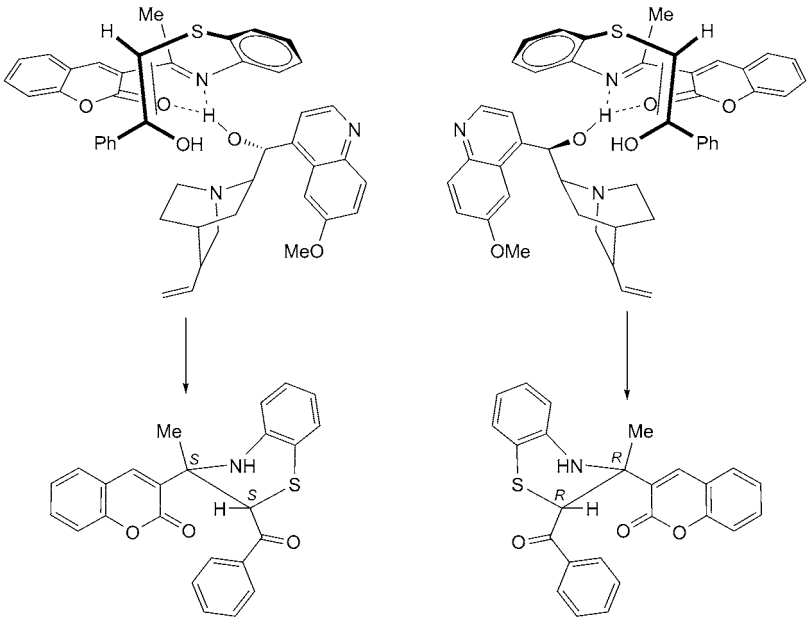


Fig. 5. cis-*Diastereoselectivity in organocatalysis by quinine and the lack of enantioselectivity*

zothiazoles by using commercially available organocatalysts revealed that the desired products could be obtained with high *cis*-diastereoselectivity in high yields, utilizing non-expensive quinine hydrochoride as the catalyst, and in protic rather than aprotic solvents.

Experimental Part

1. *General.* All reagents and catalysts were commercially available and used as received. Compounds **1a**–**1d** were prepared as reported in [7]. Alumina-supported potassium fluoride (KF/Al_2O_3) was prepared as described in [8]. M.p.: *Kofler* hot stage apparatus; uncorrected. IR Spectra: *Nicolet Magna 550-FT* spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Bruker FT-500* spectrometer; TMS as an internal standard. MS: *Finnigan MAT TSQ-70* spectrometer. Elemental analyses: *Perkin-Elmer* model *240-C* apparatus; the results (C, H, N) within $\pm 0.4\%$ of the calculated values.

2. *Typical Procedure for Diastereoselective Synthesis of Coumarin-Based Dihydrobenzothiazines.* A suspension of the coumarin **1a**–**1d** (1.0 mmol), KF/Al_2O_3 (0.7 g), and quinine hydrochloride (10 mol-%) in EtOH (3.0 ml) was stirred at r.t. for 5 min. Then, phenacyl halide **2a**–**2h** (1.2 mmol) was added to the mixture, which was stirred for appropriate time. Progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. Then, AcOEt (5 ml) was added, and the catalyst was filtered and washed with AcOEt (3×5 ml). Removal of the solvent gave a crude mixture, which was purified by column chromatography (CC; hexane/AcOEt 9:1).

*3-[3,4-Dihydro-3-methyl-2-(4-methylbenzoyl)-2*H*-1,4-benzothiazin-3-yl]-2*H*-1-benzopyran-2-one* (**3a**). Yellow solid (330 mg, 78%). *cis*-Isomer. M.p. 203–205°. IR: 3363 (NH), 1716 (C=O). ^{1}H-NMR ($CDCl_3$): 1.77 (*s*, Me of benzothiazine); 2.45 (*s*, *Me*–C_6H_4); 4.52 (br. *s*, NH); 6.00 (*s*, 1 H of benzothiazine); 6.73 (*t*, $J = 7.5$, 1 H); 6.93–6.95 (*m*, 2 H); 7.12 (*t*, $J = 8.0$, 1 H); 7.23 (*t*, $J = 7.5$, 1 H); 7.30 (*d*, $J = 8.0$, 2 H); 7.36 (*d*, $J = 8.0$, 1 H); 7.41 (*d*, $J = 8.0$, 1 H); 7.50 (*t*, $J = 8.0$, 1 H); 7.80 (*s*, 1 H); 7.95 (*d*,

$J = 8.0$, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.6; 24.6; 37.4; 57.6; 112.4; 116.1; 117.0; 119.2; 119.3; 124.3; 126.5; 128.3; 128.4; 128.7; 129.4; 131.3; 131.4; 134.3; 139.6; 140.9; 144.0; 153.2; 161.2; 192.6. EI-MS: 427 (3, M^+), 279 (40), 167 (82), 149 (100), 71 (48), 57 (68), 43 (54). Anal. calc. for $C_{26}H_{21}NO_3S$ (427.51): C 73.04, H 4.95, N 3.28; found: C 72.90, H 4.71, N 3.50.

*3-[3,4-Dihydro-3-methyl-2-(4-methylbenzoyl)-2*H*-1,4-benzothiazin-3-yl]-2*H*-1-benzopyran-2-one* (**3b**). Yellow solid. *trans*-Isomer. IR: 3363 (NH), 3065, 2970, 2934, 1716 (C=O), 1603, 1475, 1448, 1324, 1176, 749. ^{1}H-NMR ($CDCl_3$): 1.87 (*s*, Me of benzothiazine); 2.36 (*s*, *Me*–C_6H_4); 4.60 (*s*, NH); 5.67 (*s*, 1 H of benzothiazine); 6.79 (*t*, $J = 7.2$, 1 H); 6.98 (*d*, $J = 7.9$, 1 H); 7.05 (*d*, $J = 7.7$, 1 H); 7.08 (*t*, $J = 6.8$, 1 H); 7.18 (*d*, $J = 8.0$, 2 H); 7.24–7.26 (*m*, 2 H); 7.47 (*t*, $J = 7.2$, 1 H); 7.52 (*d*, $J = 7.7$, 1 H); 7.73 (*d*, $J = 8.0$, 2 H); 8.17 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.6; 27.5; 43.4; 56.0; 112.5; 114.1; 118.0; 119.2; 119.7; 124.3; 126.4; 128.0; 128.4; 128.9; 129.4; 131.4; 132.0; 133.8; 140.2; 140.9; 143.6; 146.3; 160.2; 192.8. EI-MS: 427 (3, M^+), 279 (40), 167 (82), 149 (100), 71 (48), 57 (68), 43 (54). Anal. calc. for $C_{26}H_{21}NO_3S$ (427.51): C 73.04, H 4.95, N 3.28; found: C 73.15, H 5.21, N 3.02.

*3-[3,4-Dihydro-3-methyl-2-(4-nitrobenzoyl)-2*H*-1,4-benzothiazin-3-yl]-2*H*-1-benzopyran-2-one* (**4a**). Red crystal (357 mg, 78%). *cis*-Isomer. M.p. 214–216°. IR: 3394 (NH), 1693 (C=O), 1518 (NO_2), 1335 (NO_2). ^{1}H-NMR ($CDCl_3$): 1.81 (*s*, Me of benzothiazine); 4.52 (*s*, NH); 6.00 (*s*, 1 H of benzothiazine); 6.74 (*t*, $J = 7.3$, 1 H); 6.90 (*d*, $J = 7.3$, 1 H); 6.95 (*d*, $J = 7.3$, 1 H); 7.15 (*t*, $J = 8.0$, 1 H); 7.26 (*t*, $J = 7.3$, 1 H); 7.36 (*d*, $J = 8.0$, 1 H); 7.42 (*d*, $J = 8.0$, 1 H); 7.52 (*t*, $J = 8.0$, 1 H); 7.80 (*s*, 1 H); 8.13 (*d*, $J = 8.5$, 2 H); 8.31 (*d*, $J = 8.5$, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.4; 38.3; 57.6; 110.9; 116.2; 116.9; 119.0; 119.5; 123.9; 124.5; 127.1; 128.5; 128.6; 129.5; 130.9; 131.7; 139.5; 141.3; 141.4; 150.1; 153.2; 161.3; 190.2. EI-MS: 458 (60, M^+), 440 (13), 334 (100), 308 (90), 294 (45), 274 (63). Anal. calc. for $C_{25}H_{18}N_2O_5S$ (458.49): C 65.49, H 3.96, N 6.11; found: C 65.22, H 3.71, N 6.31.

*3-[2-(4-Bromobenzoyl)-3,4-dihydro-3-methyl-2*H*-1,4-benzothiazin-3-yl]-2*H*-1-benzopyran-2-one* (**5a**). Yellow solid (393 mg, 80%). *cis*-Isomer. M.p. 95–97°. IR: 3386 (NH), 1708 (C=O). ^{1}H-NMR ($CDCl_3$): 1.87 (*s*, Me of benzothiazine); 4.50 (*s*, NH); 5.95 (*s*, 1 H of benzothiazine); 6.73 (*t*, $J = 7.3$, 1 H); 6.91–6.93 (*m*, 2 H); 7.12 (*t*, $J = 7.3$, 1 H); 7.23 (*t*, $J = 7.3$, 1 H); 7.35 (*d*, $J = 8.0$, 1 H); 7.40 (*d*, $J = 8.0$, 1 H); 7.50 (*t*, $J = 8.0$, 1 H); 7.62 (*d*, $J = 8.5$, 2 H); 7.78 (*s*, 1 H); 8.88 (*d*, $J = 8.5$, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.5; 37.5; 55.6; 111.8; 116.1; 116.9; 119.1; 119.4; 124.4; 126.7; 128.3; 128.4; 130.0; 131.1; 131.5; 131.9; 132.0; 135.5; 139.5; 141.1; 153.3; 161.3; 191.6. EI-MS: 493 (31, $[M+2]^+$), 491 (29, M^+), 369 (49), 368 (47), 308 (100), 294 (51), 280 (64), 185 (32), 155 (15), 76 (13). Anal. calc. for $C_{25}H_{18}BrNO_3S$ (492.38): C 60.98, H 3.68, N 2.84; found: C 70.15, H 3.49, N 2.68.

*3-[3,4-Dihydro-2-(4-methoxybenzoyl)-3-methyl-2*H*-1,4-benzothiazin-3-yl]-2*H*-1-benzopyran-2-one* (**6a**). Yellow solid (363 mg, 82%). *cis*-Isomer. M.p. 195–197°. IR: 3363 (NH), 1712 (C=O). ^{1}H-NMR ($CDCl_3$): 1.76 (*s*, Me of benzothiazine); 3.89 (*s*, MeO); 4.52 (*s*, NH); 5.99 (*s*, 1 H of benzothiazine); 6.73 (*t*, $J = 7.3$, 1 H); 6.94–6.96 (*m*, 4 H); 7.11 (*t*, $J = 7.3$, 1 H); 7.23 (*t*, $J = 7.3$, 1 H); 7.36 (*d*, $J = 8.0$, 1 H); 7.41 (*d*, $J = 7.3$, 1 H); 7.50 (*t*, $J = 7.3$, 1 H); 7.80 (*s*, 1 H); 8.04 (*d*, $J = 8.5$, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.7; 37.1; 55.5; 57.6; 112.6; 113.9; 116.1; 117.0; 119.2; 119.3; 124.3; 126.4; 128.2; 128.4; 129.8; 130.9; 131.4; 139.5; 140.9; 153.2; 161.2; 163.6; 191.9. Anal. calc. for $C_{26}H_{21}NO_4S$ (443.51): C 70.41, H 4.77, N 3.16; found: C 70.28, H 4.91, N 3.36.

*3-(2-Benzoyl-3,4-dihydro-3-methyl-2*H*-1,4-benzothiazin-3-yl)-2*H*-1-benzopyran-2-one* (**7a**). Yellow solid (338 mg, 82%). *cis*-Isomer. M.p. 174–176°. IR: 3409 (NH), 1708 (C=O). ^{1}H-NMR ($CDCl_3$): 1.78 (*s*, Me of benzothiazine); 4.54 (*s*, NH); 6.02 (*s*, 1 H of benzothiazine); 6.72 (*t*, $J = 7.3$, 1 H); 6.92–6.94 (*m*, 2 H); 7.12 (*t*, $J = 7.3$, 1 H); 7.22 (*t*, $J = 7.3$, 1 H); 7.35 (*d*, $J = 7.3$, 1 H); 7.48 (*d*, $J = 7.3$, 1 H); 7.57–7.59 (*m*, 3 H); 7.57 (*t*, $J = 7.3$, 1 H); 7.79 (*s*, 1 H); 8.03 (*d*, $J = 7.5$, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.6; 37.5; 57.6; 112.1; 116.1; 117.0; 119.2; 119.3; 124.4; 126.6; 128.4; 128.5; 128.7; 131.3; 131.4; 133.1; 136.8; 139.6; 141.0; 153.2; 161.2; 192.7. Anal. calc. for $C_{25}H_{19}NO_3S$ (413.49): C 72.62, H 4.63, N 3.39; found: C 72.36, H 4.88, N 3.11.

*3-[2-(1,1′-Biphenyl-4-ylcarbonyl)-3,4-dihydro-3-methyl-2*H*-1,4-benzothiazin-3-yl]-2*H*-1-benzopyran-2-one* (**8a**). Yellow solid (362 mg, 74%). *cis*-Isomer. M.p. 224–226°. IR: 3379 (NH), 3048, 3021, 2976, 2918, 1703 (C=O), 1668, 1600, 1476, 1362, 1163, 760. ^{1}H-NMR ($CDCl_3$): 1.82 (*s*, Me of benzothiazine); 4.14 (br. *s*, NH); 6.08 (*s*, 1 H of benzothiazine); 6.75 (*t*, $J = 7.3$, 1 H); 6.95–6.98 (*m*, 2 H); 7.14 (*t*, $J = 7.3$, 1 H); 7.24 (*t*, $J = 7.3$, 1 H); 7.37 (*d*, $J = 8.0$, 1 H); 7.41–7.43 (*m*, 2 H); 7.49–7.51 (*m*, 3 H); 7.65 (*d*, $J = 7.3$, 2 H); 7.73 (*d*, $J = 8.3$, 2 H); 7.82 (*s*, 1 H); 8.13 (*d*, $J = 8.3$, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.6; 37.5;

57.6; 112.1; 116.1; 117.0; 119.1; 119.3; 124.3; 126.6; 127.2; 127.4; 128.2; 128.4; 128.9; 129.1; 131.3; 131.4; 135.4; 139.6; 139.8; 141.0; 145.7; 153.2; 161.2; 192.3. Anal. calc. for $C_{31}H_{23}NO_3S$ (489.58): C 76.05, H 4.74, N 2.86; found: C 76.23, H 4.39, N 2.53.

*3-{3,4-Dihydro-3-methyl-2-[4-(methylsulfonyl)benzoyl]-2*H-*1,4-benzothiazin-3-yl}-2*H-*1-benzopyran-2-one* (**9a**). Yellow solid (457 mg, 93%). *cis*-Isomer. M.p. 231–233°. IR: 3398 (NH), 1712 (C=O), 1301 (SO_2), 1153 (SO_2). ^{1}H-NMR ($CDCl_3$): 1.81 (*s*, Me of benzothiazine); 3.10 (*s*, $MeSO_2$); 4.53 (*s*, NH); 6.01 (*s*, 1 H of benzothiazine); 6.75 (*t*, *J* = 7.5, 1 H); 6.92 (*d*, *J* = 7.5, 1 H); 6.97 (*d*, *J* = 7.5, 1 H); 7.15 (*t*, *J* = 7.5, 1 H); 7.26 (*t*, *J* = 7.3, 1 H); 7.38 (*d*, *J* = 8.0, 1 H); 7.44 (*d*, *J* = 8.0, 1 H); 7.53 (*t*, *J* = 8.0 Hz, 1 H); 7.81 (*s*, 1 H); 8.07 (*d*, *J* = 8.5, 2 H); 8.17 (*d*, *J* = 8.5, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.4; 38.2; 44.3; 57.6; 110.9; 116.1; 116.9; 119.0; 119.4; 124.5; 127.0; 127.8; 128.4; 128.5; 129.3; 130.9; 131.6; 139.6; 140.8; 141.3; 143.9; 153.2; 161.2; 190.6. EI-MS: 491 (33, M^+), 473 (83), 458 (72), 367 (94), 328 (28), 308 (100), 294 (61), 274 (69), 185 (41), 121 (27). Anal. calc. for $C_{26}H_{21}NO_5S_2$ (491.58): C 63.53, H 4.31, N 2.85; found: C 63.38, H 4.66, N 3.11.

*3-[3,4-Dihydro-3-methyl-2-(4-nitrobenzoyl)-2*H-*1,4-benzothiazin-3-yl]-8-methoxy-2*H-*1-benzopyran-2-one* (**10a**). Orange crystals (400 mg, 82%). *cis*-Isomer. M.p. 125–127°. IR: 3401 (NH), 1701 (C=O), 1526 (NO_2), 1351 (NO_2). ^{1}H-NMR ($CDCl_3$): 1.82 (*s*, Me of benzothiazine); 3.99 (*s*, MeO); 4.51 (*s*, NH); 6.01 (*s*, 1 H of benzothiazine); 6.75 (*t*, *J* = 7.3, 1 H); 6.91 (*d*, *J* = 8.0, 1 H); 6.95 (*d*, *J* = 7.3, 1 H); 7.01 (*d*, *J* = 7.3, 1 H); 7.07 (*d*, *J* = 8.0, 1 H); 7.16–7.18 (*m*, 2 H); 7.78 (*s*, 1 H); 8.15 (*d*, *J* = 8.5, 2 H); 8.33 (*d*, *J* = 8.5, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.4; 38.3; 56.3; 57.7; 110.9; 113.4; 116.9; 119.4; 119.7; 119.8; 123.9; 124.3; 127.1; 128.6; 129.5; 131.1; 139.5; 141.3; 141.4; 142.9; 146.9; 150.1; 160.7; 190.2. EI-MS: 488 (29, M^+), 364 (100), 338 (69), 324 (44), 304 (43), 150 (20), 104 (19), 76 (17). Anal. calc. for $C_{26}H_{20}N_2O_6S$ (488.51): C 63.92, H 4.13, N 5.73; found: C 63.79, H 4.34, N 5.48.

*6-Bromo-3-{3,4-dihydro-3-methyl-2-[4-(methylsulfonyl)benzoyl]-2*H-*1,4-benzothiazin-3-yl}-2*H-*1-benzopyran-2-one* (**11a**). Yellow solid (381 mg, 68%). *cis*-Isomer. M.p. 169–171°. IR: 3351 (NH), 1690 (C=O), 1303 (SO_2), 1184 (SO_2). ^{1}H-NMR ($CDCl_3$): 1.80 (*s*, Me of benzothiazine); 3.10 (*s*, $MeSO_2$); 4.52 (*s*, NH); 5.95 (*s*, 1 H of benzothiazine); 6.76 (*t*, *J* = 7.5, 1 H); 6.92 (*d*, *J* = 7.5, 1 H); 6.96 (*d*, *J* = 7.5, 1 H); 7.14–7.17 (*m*, 2 H); 7.60 (*t*, *J* = 7.3, 1 H); 7.73 (*s*, 1 H); 8.07 (*d*, *J* = 8.0, 2 H); 8.15 (*s*, 1 H); 8.16 (*d*, *J* = 8.0, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.4; 38.1; 44.3; 57.8; 110.9; 117.9; 118.5; 119.7; 120.2; 127.2; 127.9; 128.0; 128.6; 129.3; 130.7; 134.3; 139.0; 140.0; 140.3; 140.7; 144.0; 152.0; 160.7; 190.4. Anal. calc. for $C_{26}H_{20}BrNO_5S_2$ (570.47): C 54.74, H 3.53, N 2.46; found: C 54.48, H 3.76, N 2.70.

*3-{2-[3-(Cyclopentyloxy)-4-methoxybenzoyl]-3,4-dihydro-3-methyl-2*H-*1,4-benzothiazin-3-yl}-2*H-*1-benzopyran-2-one* (**12b**). Yellow solid (411 mg, 78%). *trans*-Isomer. M.p. 99–101°. IR: 3378 (NH), 1712 (C=O). ^{1}H-NMR ($CDCl_3$): 1.75–1.82 (*m*, 4 H of cyclopentyl); 1.82–2.06 (*m*, 4 H of cyclopentyl); 1.88 (*s*, Me of benzothiazine); 3.88 (*s*, MeO); 4.60 (*s*, NH); 4.69–4.71 (*m*, CH–O of cyclopentyl); 5.64 (*s*, 1 H of benzothiazine); 6.75 (*t*, *J* = 7.5, 1 H); 6.84 (*d*, *J* = 8.2, 1 H); 6.92–6.94 (*m*, 2 H); 7.07–7.09 (*m*, 2 H); 7.25–7.27 (*m*, 2 H); 7.30 (*s*, 1 H); 7.50–7.52 (*m*, 2 H); 8.14 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.0; 27.7; 32.6; 37.0; 54.4; 56.0; 80.2; 110.4; 113.6; 116.0; 116.7; 118.8; 119.2; 119.8; 122.4; 124.4; 126.4; 127.2; 128.3; 129.1; 130.6; 131.3; 139.9; 140.1; 140.8; 147.6; 161.2; 163.6; 192.0. EI-MS: 527 (28, M^+), 509 (21), 403 (40), 308 (92), 280 (100), 219 (50), 151(95), 41 (37). Anal. calc. for $C_{31}H_{29}NO_5S$ (527.63): C 70.57, H 5.54, N 2.65; found: C 70.33, H 5.62, N 2.37.

*3-{3,4-Dihydro-3-methyl-2-[4-(methylsulfonyl)benzoyl]-2*H-*1,4-benzothiazin-3-yl}-7-hydroxy-2*H-*1-benzopyran-2-one* (**13a**). Yellow solid (153 mg, 30%). *cis*-Isomer. M.p. 154–157°. IR: 3398 (NH), 1708 (C=O), 1312 (SO_2), 1157 (SO_2). ^{1}H-NMR ($CDCl_3$): 1.80 (*s*, Me of benzothiazine); 3.10 (*s*, $MeSO_2$); 4.49 (br. *s*, NH); 5.67 (br. *s*, OH); 5.97 (*s*, 1 H of benzothiazine); 6.73–6.77 (*m*, 2 H); 6.84 (*s*, 1 H); 6.92–6.95 (*m*, 2 H); 7.15 (*t*, *J* = 7.5, 1 H); 7.29 (*d*, *J* = 8.5, 1 H); 7.73 (*s*, 1 H); 8.08 (*d*, *J* = 8.2, 2 H); 8.17 (*d*, *J* = 8.2, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.5; 38.3; 44.3; 57.4; 102.5; 111.0; 113.2; 116.8; 119.3; 127.0; 127.2; 127.5; 127.9; 128.6; 129.3; 129.9; 139.7; 140.9; 141.3; 143.9; 154.9; 159.0; 161.52; 190.7. Anal. calc. for $C_{26}H_{21}NO_6S_2$ (507.58): C 61.52, H 4.17, N 2.76; found: C 61.31, H 4.42, N 2.49.

Supplementary Material. The ^{1}H- and ^{13}C-NMR spectra of the new compounds and the crystal structure data for **10b** are available as supplementary material from the corresponding authors.

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