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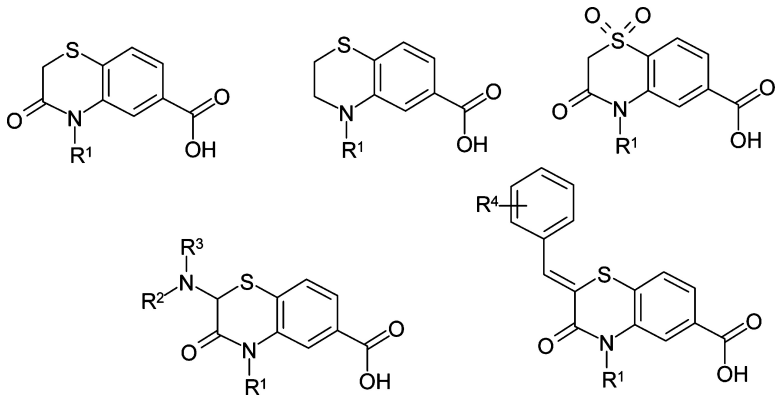

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# Liquid-Phase Parallel Synthesis of Combinatorial Libraries of Substituted 6-Carbamoyl-3,4-dihydro-2*H*-benzo[1,4]thiazines

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In this work, we explored several original combinatorial derivatization patterns for the 3,4-dihydro-2*H*-1,4-benzothiazine scaffold. The synthesis begins with commercially available 4-chloro- and 4-fluoro-3-nitrobenzoates and employs a sequence of moderate and high-yielding reactions that display a relatively high substituent tolerance. Simple manual techniques for parallel reactions were coupled with easy workup and purification procedures to give high-purity final products. The developed approach was easily adaptable for parallel synthesis of more than 2600 novel 2*H*-benzo[1,4]thiazine-6-carboxylic acid amides, which were efficiently prepared in a semiautomatic fashion using special CombiSyn synthesizers.

## Introduction

There is ample precedence documenting the potential of differently substituted 4*H*-benzo[1,4]thiazin-3-ones for biological and therapeutic activity. The Crossfire Beilstein database cites more than 400 small-molecule modulators of activity of different protein biotargets, which contain this fragment in their structure. For example, these compounds were reported as calcium channel blockers,[1] phosphodiesterase 7 inhibitors,[2] 5-$HT_3$ antagonists,[3] anticataract agents,[4] dopamine $D_4$,[5] $Na^+/H^+$ exchange inhibitors,[6] coagulation factor Xa inhibitors,[7] and matrix metalloproteinase inhibitors,[8] to name just a few. According to these numerous examples, 4*H*-benzo[1,4]thiazin-3-one fragment can be considered as a typical "privileged" substructure.[9−11] The ability of molecules containing such substructures to bind to multiple target proteins is generally determined by 3D spatial parameters of the privileged core moiety, which recognizes some conserved binding sites on the protein surfaces. At the same time, the nature of substituents around the core scaffold substantially influences the target specificity of a compound, affects the protein−ligand binding affinity, and significantly influences the pharmacokinetic and metabolic properties.[12] On the basis of these considerations, combinatorial exploration of molecular diversity around the known privileged heterocyclic scaffolds holds great promise in the discovery of promising drug candidates with activity against novel drugable biological targets. From this point of view, variously substituted derivatives of 4*H*-benzo[1,4]thiazine heterocycle represent promising synthetic targets. In this work, our particular attention was paid to derivatives of 2*H*-benzo[1,4]-thiazine-6-carboxylic acid.

One of the first reports on the synthesis of 4*H*-3-oxobenzo-[1,4]thiazin-6-carboxylic acid **III** was a patent publication by Wuppertal-Elberfeld in 1951[13] (Scheme 1). According to this approach, this compound was synthesized by S-alkylation of mercaptoacetate with 3-nitro-4-chlorobenzoic acid **I**, followed by reduction of the nitro group of (phenylthio)acetic acid **II** and intramolecular cyclization of the resulting aniline intermediate. A similar strategy was used with minor modifications for assembly of 4*H*-benzo[1,4]-thiazin-3-one heterocycle in carboxylates **VI**, which were used as precursors in the synthesis of biologically active guanidines.[6] Carboxamide **IX** was obtained using the reaction of polymer-bound mercaptoaniline **VII** with ethyl bromoacetate, followed by mild hydrolytic cleavage of the resulting intermediate **VIII** from the solid support.[14] To the best of our knowledge, compound **IX** is the only amide derivative of 4*H*-3-oxobenzo[1,4]thiazin-6-carboxylic acid reported to date.

In this work, we explored several original combinatorial derivatization patterns for the 3,4-dihydro-2*H*-1,4-benzothiazine scaffold. Specifically, we synthesized five combinatorial series depicted in Figure 1, starting from simple initial reagents. These carboxylic acids were then used as useful building blocks for the synthesis of combinatorial libraries of the corresponding amides.

## Results and Discussion

**Synthesis of Benzo[1,4]thiazine-6-carboxylate Building Blocks.** Our synthetic approach to assembly of the key benzo[1,4]thiazine-6-carboxylic acids shown in Figure 1 used for the synthesis of final carboxamide libraries is depicted in Schemes 2−4.

For the synthesis of acid **4**, we used a modification of approaches by Wuppertal-Elberfeld[12] and Yamamoto[6] (Scheme 2). Commercially available 3-nitro-4-fluorobenzoic acid **1**

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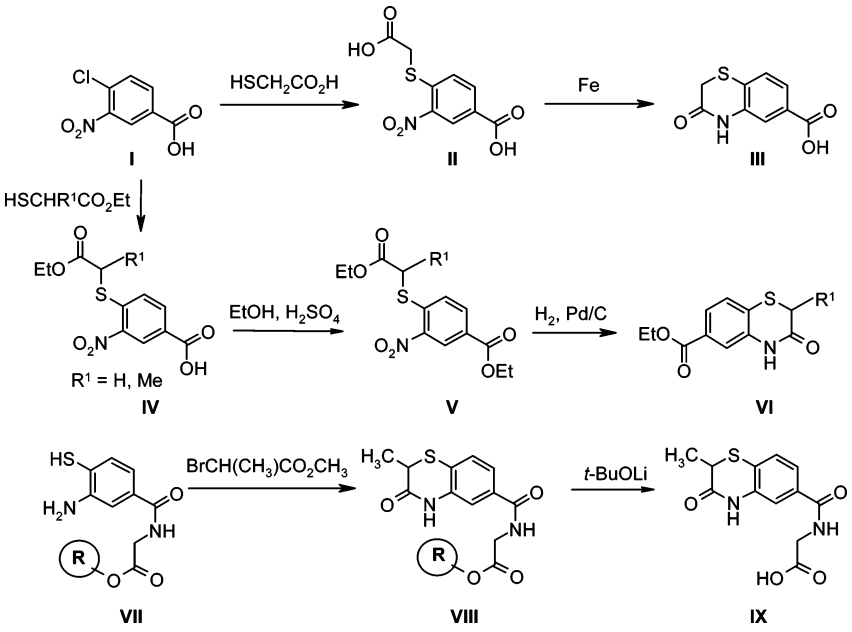
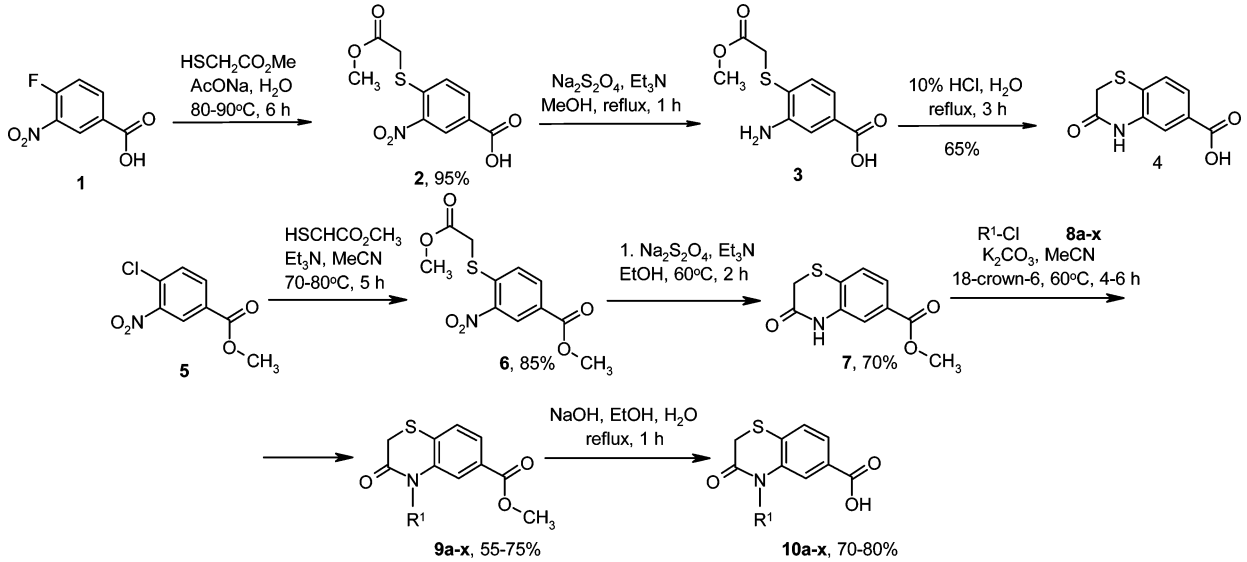
**Scheme 1.** Reported Synthetic Approaches to 4*H*-3-Oxobenzo[1,4]thiazin-6-carboxylic Acids and Their Derivatives[13]




**Scheme 2.** Synthesis of 3-Oxo-3,4-dihydro-2*H*-benzo[1,4]thiazine-6-carboxylic Acids[a]




[a] $R^1$ = Me (**a**), Et (**b**), $CH_2CH{=}CH_2$ (**c**), $CH_2CONH_2$ (**d**), $CH_2CONHCOCH_3$ (**e**), $CH_2CN$ (**f**), $R_n$-$C_6H_4CH_2$. (**g**−**x**): $R_n$ = H (**g**), 2-Me (**h**), 2-F (**i**), 2-Cl (**j**), 3-Me (**k**), 3-F (**l**), 3-Cl (**m**), 4-Me (**n**), 4-F (**o**), 4-Cl (**p**), 2,5-di-Me (**q**), 3-Me-6-MeO (**r**), 2-Cl-4-Me (**s**), 2-Cl-4-F (**t**), 2-Cl-6-F (**u**), 3-Cl-2-Me (**v**), 3-Cl-4-Me (**w**), 4-Br-6-F (**x**).

was reacted with methyl mercaptoacetate in the presence of sodium acetate in water at 80−90 °C to give the corresponding thionitrobenzoate **2** (Scheme 1). Reduction of **2** with sodium dithionite in the presence of $Et_3N$ in methanol furnished the corresponding amino derivative **3**, which underwent intramolecular cyclization upon the treatment with aqueous HCl to afford the desired acid **4** in 60% overall yield from **1**.

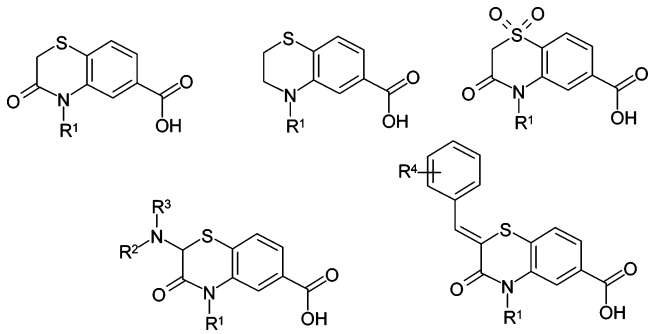
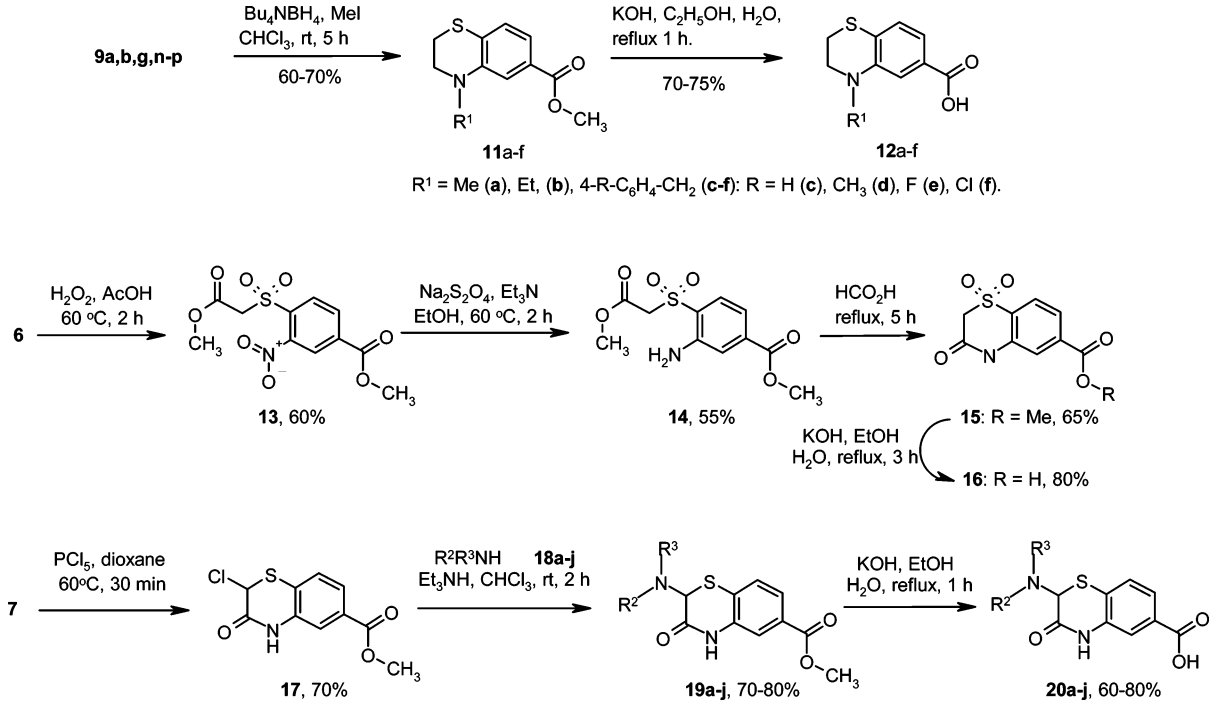


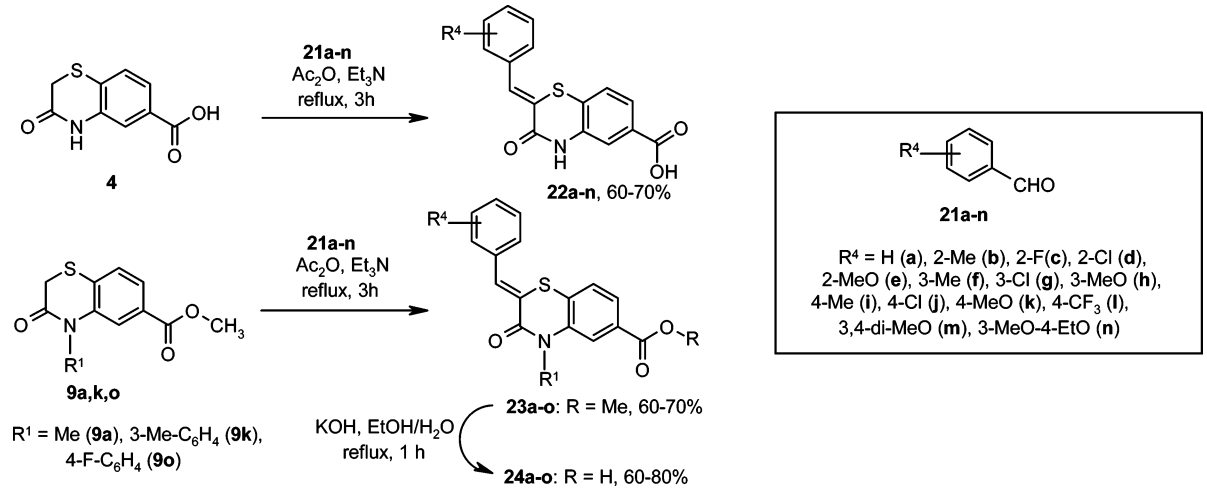
**Figure 1.** 6-Carboxylate derivatives of 3,4-dihydro-2*H*-1,4-benzothiazine heterocycle synthesized in this work.

Methyl ester **7** was obtained from commercially available methyl 3-nitro-4-chlorobenzoate **5** using the similar synthetic approach with insignificant modifications in the experimental protocol. Chloride **5** was reacted with methyl mercaptoacetate in the presence of $Et_3N$ in acetonitrile at 70−80 °C, and thionitrobenzoate **6** was reduced with sodium dithionite in the presence of $Et_3N$ in ethanol. The resulting amino derivative underwent spontaneous in situ intramolecular cyclization to afford the desired ester **7** in 70% yield. To incorporate an additional element of diversity to the obtained scaffold, we studied the alkylation at the N4 atom. Methyl

**Scheme 3.** Synthesis of Benzo[1,4]thiazine-6-carboxylic Acids with a Modified Thiomorpholin-3-one Ring




**Scheme 4.** Synthesis of Substituted 2-Benzylidene-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazine-6-carboxylic Acids



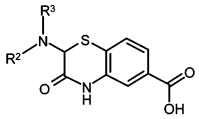

ester **7** was treated with different alkyl chlorides **8a**−**x**. The conditions that provided the best overall results in this reaction, in terms of both yield and purity of the N4-alkylated products, were 1.1 equiv of alkylating agent in acetonitrile in the presence of 1.5 equiv of $K_2CO_3$ and a catalytic amount of 18-crown-6 at 60 °C. The desired N4-alkylated products **9a**−**x** were obtained in 55−75% yield. Esters **9a**−**x** were then readily hydrolyzed under relatively mild alkali hydrolysis conditions (1.2 molar equiv of NaOH in a water/MeOH (1:1) mixture, 60 °C) to afford the corresponding acids **10a**−**x** in 70−80% yield. The described approach to N4-alkylated benzo[1,4]thiazine-6-carboxylic acids **10a**−**x** was found to be well-reproducible and adaptable to a parallel synthesis format.

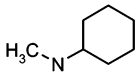
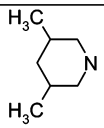
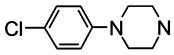
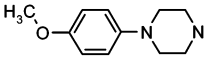
At this synthetic stage, we explored the possibility of selective reduction of the thiazinone ring of the obtained heterocyclic scaffold (Scheme 3). Reaction of several selected esters **9a**,**b**,**g**,**n**−**p** with tetrabutylammonium borohydride and methyl iodide in chloroform at room temperature furnished the corresponding 4-substituted 3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylates **11a**−**f**, which were not described in the literature. The latter ones were then smoothly hydrolyzed under mild alkali conditions to afford the desired acids **12a**−**f** (yield 70−75%).

Scheme 3 also depicts the synthetic approach to 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic acid 1,1-dioxide **16**. Compound **6** was treated with hydrogen peroxide in acetic acid at 60 °C to give the corresponding sulfonate **13**. Reduction of **13** with sodium dithionite in the presence of $Et_3N$ in ethanol yielded the corresponding amino derivative **14**. A solution of **14** in formic acid was heated at reflux for 5 h to afford 1,4-benzothiazine 1,1-dioxide **15** in good yield. Mild alkali hydrolysis of **15** gave the desired acid **16**, which was also not described in the literature.

We next explored the possibility of incorporation of an additional element of diversity at position 2 of the 3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazine heterocycle. We have found that the methylene fragment of compound **7** can be

**Table 1.** Structures and Yields of 2-Amino-substituted 3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid **20a**−**j**

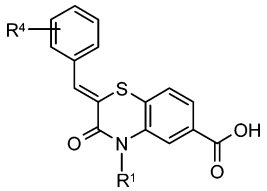


| compound | $R^2R^3N$ | yield, % |
|---|---|---|
| **20a** | $Pr_2N$ | 75 |
| **20b** | *i*-$Pr_2N$ | 70 |
| **20c** |  | 73 |
| **20d** |  | 80 |
| **20e** |  | 77 |
| **20f** |  | 73 |
| **20g** |  | 72 |
| **20h** |  | 76 |
| **20i** |  | 60 |
| **20j** |  | 68 |

chlorinated by reaction with phosphorus pentachloride in dioxane at 60 °C to smoothly afford chloride **17** (Scheme 3). The chlorination proceeded regioselectively and without indication of major side reactions. Similar approaches with the use of thionyl chloride as the chlorinating reagent were reported.[15] Compound **17** has been smoothly converted into the corresponding amine derivatives **19a**−**j** upon reaction with a series of secondary amines **18a**−**j** in chloroform at room temperature (yield 70−80%). The reaction was successful only with secondary aliphatic amines with a pronounced nucleophilic character. Substituted anilines and their heterocyclic analogues were inactive under the described conditions, whereas the aliphatic primary amines gave unwanted dialkylation products. Mild alkali hydrolysis of **19a**−**j** in an EtOH−water solvent mixture smoothly led to the corresponding acids **20a**−**j** (Table 1).

In our attempts to utilize the reactivity of C−H bonds of the methylene fragment in condensation reactions with reactive carbonyl species, we have found that various 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazines could be readily converted to the corresponding 2-benzylidene derivatives. Thus, acid **4** was smoothly converted into the corresponding structures **22a**−**n** upon reaction with 1.8 molar equiv of aromatic aldehyde **21a**−**n** in the presence of $Et_3N$ in acetic anhydride (yield 60−70%). In an analogous manner, three selected esters **9a**,**k**,**o** were reacted with aromatic aldehydes

**Table 2.** Structures and Yields of 2-Benzylidene-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazine-6-carboxylic Acids **24a**−**o**



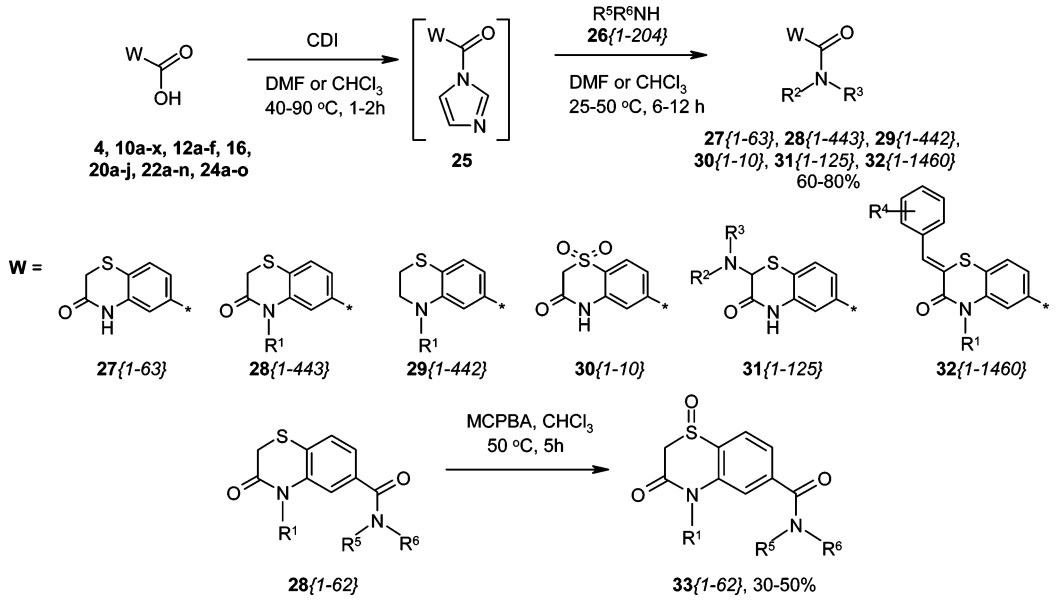
| compound | $R^1$ | $R^4$ | yield from **9a**,**k**,**o**, % |
|---|---|---|---|
| 24a | Me | H | 55 |
| 24b | Me | 2-Me | 50 |
| 24c | Me | 2-F | 52 |
| 24d | Me | 2-Cl | 48 |
| 24e | Me | 2-MeO | 54 |
| 24f | Me | 3-Me | 49 |
| 24g | Me | 3-Cl | 50 |
| 24h | Me | 3-MeO | 58 |
| 24i | Me | 4-Me | 54 |
| 24j | Me | 4-$CF_3$ | 48 |
| 24k | Me | 4-MeO | 51 |
| 24l | Me | 3,4-di-MeO | 44 |
| 24m | Me | 3-MeO-4-EtO | 42 |
| 24n | 3-Me-$C_6H_4$−$CH_2$ | H | 40 |
| 24o | 4-F−$C_6H_4$−$CH_2$ | H | 35 |

**21a**−**n** to afford 2-benzylidene derivatives **23a**−**o**. Similar approaches to 2-benzylidene-3-oxo-3,4-dihydro-2*H*-benzo-[1,4]thiazines were described in a series of previous publications.[15] Products **22a**−**n** and **23a**−**o** were obtained in good yields (60−80%), regardless of the aldehyde $R^4$-substituents' nature, and they were of good chemical and geometrical purity as judged by their $^1$H NMR spectra. On the basis of the chemical shift of the vinyl proton, all the obtained products were assigned the *Z* stereochemistry. The observed $\delta$ value for each of the synthesized compounds ($\delta$ 7.75−7.85 ppm) is in good agreement with the predicted and observed values for the *Z* isomer in a series of structurally related 2-alkylidene-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazines.[15] Esters **23a**−**o** were hydrolyzed under mild alkali conditions to afford the desired acids **24a**−**o** (yield 60−80%). Structures and yields of **24a**−**o** from **9a**,**k**,**o** are shown in Table 2.

The final carboxylic acids **4**, **10a**−**x**, **12a**−**f**, **16**, **20a**−**j**, **22a**−**n**, and **24a**−**o** are stable crystalline compounds which were characterized by LC/MS and $^1$H NMR spectroscopy. The spectral data gave satisfactory results consistent with the suggested molecular structures.

**Synthesis of Combinatorial Libraries.** The obtained acids were used for the synthesis of large combinatorial libraries of the corresponding quinoxaline-6-carboxamides (Scheme 5). Amides **27**{*1*−*63*}, 28{*1*−*443*}, **29**{*1*−*442*}, **30**{*1*−*10*}, **31**{*1*−*125*}, and **32**{*1*−*1460*} were obtained by the reaction of acids **4**, **10a**−**x**, **16**, **20a**−**j**, **12a**−**f**, **22a**−**n**, and **24a**−**o** with primary and secondary amines via CDI-mediated (CDI, *N*,*N*′-carbonyldiimidazole) activation of the carboxylate group. The reactive imidazolide intermediates **25** were obtained upon the treatment of initial acids with CDI in dimethylformamide or chloroform and used in reaction with amines **26**{*1*−*204*} without purification. We evaluated a total of 204 aliphatic and aromatic amines, such as substituted anilines and benzylamines, heteroarylamines,

**Scheme 5.** Parallel Liquid-Phase Synthesis of Combinatorial Libraries of Substituted 3,4-Dihydro-2*H*-1,4-benzothiazine-6-carboxamides




cyclic and acyclic aliphatic amines, and oxygen- and nitrogen-containing compounds. Representative examples of amines used in these reactions are depicted in Figure 2. Unhindered aliphatic amines consistently underwent rapid conversion into the desired products and provided the highest yield and purity of amides in the described transformations. Sterically hindered alkylamines, anilines, and their heterocyclic analogues reacted more slowly and required elevated temperature and increased time for the complete conversion of the initial reactants. Structures of all amines explored in this work are given in the Supporting Information.

The reaction workup was straightforward and compatible with the high-throughput operation mode. The reaction mixtures (solvent $CHCl_3$ or $CH_2Cl_2$) were successively washed in the reaction vials with water and aqueous solutions of $NaHCO_3$ and HCl. Then the organic layers were removed from the vials, filtered, and evaporated to dryness in vacuo. The obtained crude residues were triturated with diethyl ether, and the precipitated crystals were collected and dried to afford the desired products in 60−80% yield. According to LC/MS data, the purity of the obtained compounds was >95% and usually approached 98%. If necessary, the products could be recrystallized from methanol or ethanol.

Additional complexity to the obtained 3,4-dihydro-2*H*-1,4-benzothiazine scaffolds can be introduced via oxidation of the S-1 atom. Thus, a series of selected 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamides **28**{*1*−*62*} were converted into the corresponding sulfoxides **33**{*1*−*62*} upon the reaction with *m*-chloroperbenzoic acid (MCPBA) in $CHCl_3$ at 50 °C.

The resulting combinatorial libraries **27**{*1*−*63*}, **28**{*1*−*443*}, **29**{*1*−*442*}, **30**{*1*−*10*}, **31**{*1*−*125*}, 32{*1*−*1460*}, and **33**{*1*−*62*} include more than 2600 novel 3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamides. For illustration, Figure 3 contains structures of representative compounds from these combinatorial series.

All the synthesized carboxamides were characterized by $^1$H NMR and LC/MS analysis. The $^1$H NMR spectra and LC/MS mass spectral data were consistent with the suggested molecular structures. The characteristic signals from protons of the 3,4-dihydro-2*H*-1,4-benzothiazine ring can be used for identification of the corresponding structures. For instance, the aromatic protons H-5, H-7, and H-8 are usually clearly observed as *abx*-system in the range of $\delta$ 7.70−8.00 ppm with the spin−spin coupling constants $J = 7.6-8.0$ Hz for the doublets. The methylene protons of acids **6** and **10a**−**x** and the corresponding amides **27**{*1*−*63*} and **28**{*1*−*443*} can be observed as singlets at 3.3−3.7 ppm. The protons from two methylene groups of the thiomorpholine ring in acids **12a**−**f** and carboxamides **29**{*1*−*442*} give two narrow multiplets at 3.0−3.2 and 3.5−3.6 ppm. The vinyl protons of the benzylidene compounds **22a**−**n**, **24a**−**o**, and **32**{*1*−*1460*} have resonances at 7.75−7.85 ppm.

## Conclusion

An efficient synthetic route was developed for the combinatorial synthesis of 3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide libraries in solution. In all of the reactions investigated, the corresponding libraries were generated with low levels of impurities using simple workup and purification procedures. Of note, along the whole reaction sequence, the chromatographic purification techniques were omitted. The developed method uses readily available starting materials in moderate- and high-yielding reactions that display a relatively high substituent tolerance and, therefore, is ideally suited for rapid synthesis of diverse libraries. Product yields varied according to reactant structures, but in most cases, the desired products were obtained in good yields. To demonstrate the convenience and generality of the developed method, more than 2600 variously substituted benzothiazine-6-carboxamides were synthesized in 2005 in our laboratories. Biological evaluation of the synthesized compounds is currently in progress.

## Experimental Section

**General Information.** Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel

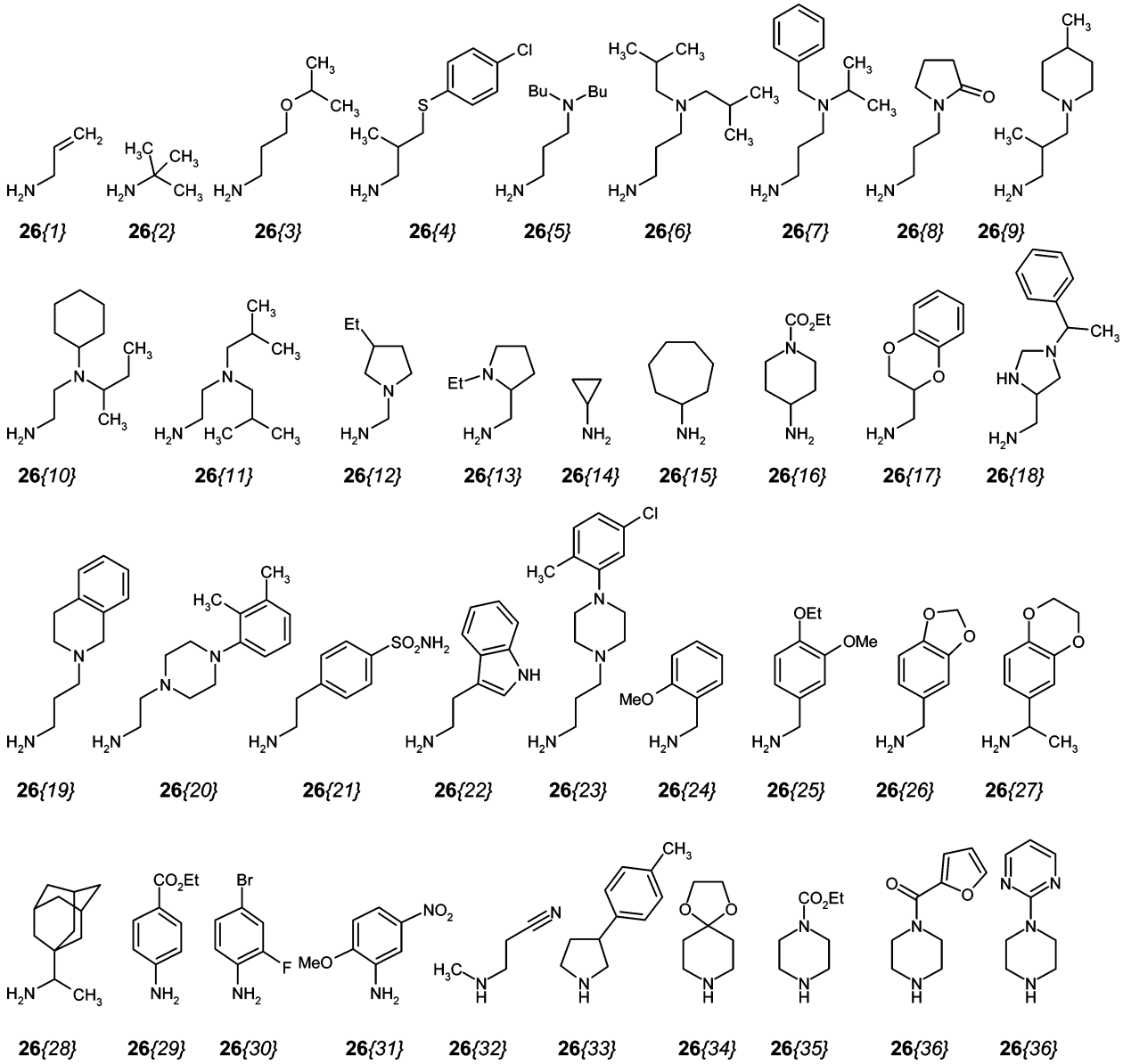



**Figure 2.** Representative examples of amines **26**{*1*−*204*} used for the synthesis of combinatorial libraries.

(Merck, Kieselgel 60 F-254). $^1$H NMR spectra were recorded on a Bruker AMX-400 or Varian spectrometer in DMSO-$d_6$ using TMS as an internal standard chemical shifts in parts per million). LC/MS spectra were recorded with a PE SCIEX API 150EX liquid chromatograph equipped with a UV detector ($\lambda_{max}$ 215 and 254 nm) and using a $C_{18}$ column (100 × 4 mm). Elution started with water and ended with acetonitrile/water (95:5, v/v) and used a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min. According to LC/MS data, all the synthesized compounds have purity >95%. All solvents and reagents were obtained from commercial sources and used without purification. Amines shown in Figure 2 were purchased from Acros Organics, Aldrich, or ChemDiv. The parallel liquid-phase reactions, all the workup, isolation, purification, and analytic procedures were carried out using a proprietary technology platform, which includes all the equipment required for parallel synthesis of large combinatorial libraries.[17] In particular, all parallel reactions were performed using a laboratory synthesizer, CombiSyn-012-3000.

**4-[(2-Methoxy-2-oxoethyl)thio]-3-nitrobenzoic Acid 2.** A solution of 3-nitro-4-fluorobenzoic acid **1** (185 g, 1 mol), methyl mercaptoacetate (116.6 g, 1.1 mol), and sodium acetate (90.2 g, 1.1 mol) in water (500 mL) was stirred at 80−90 °C for 6 h. The reaction mixture was slowly cooled to 10 °C at stirring. The formed precipitate was filtered off, washed with water (5 × 100 mL), and dried in vacuo to afford 257.5 g (95%) of acid **2**, which was used at the next step without further purification (LC/MS *m*/*z* 271.251 00 (M + 1)).

**3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid 4.** Acid **2** (257.5 g, 0.95 mol) was added portionwise to a stirred mixture of sodium dithionite (696 g, 4 mol) and $Et_3N$ (404 g, 561.1 mL, 4 mol) in EtOH (1500 mL). The mixture was heated at reflux under vigorous stirring for 1 h and then filtered without cooling. The obtained solution was evaporated in vacuo to dryness, the crude residue was dissolved in $CHCl_3$ (500 mL), and the solution was washed with water (3 × 100 mL) and 5% aqueous HCl (3 × 300 mL). LC/MS *m*/*z* 210 (M + 1). To the obtained solution of

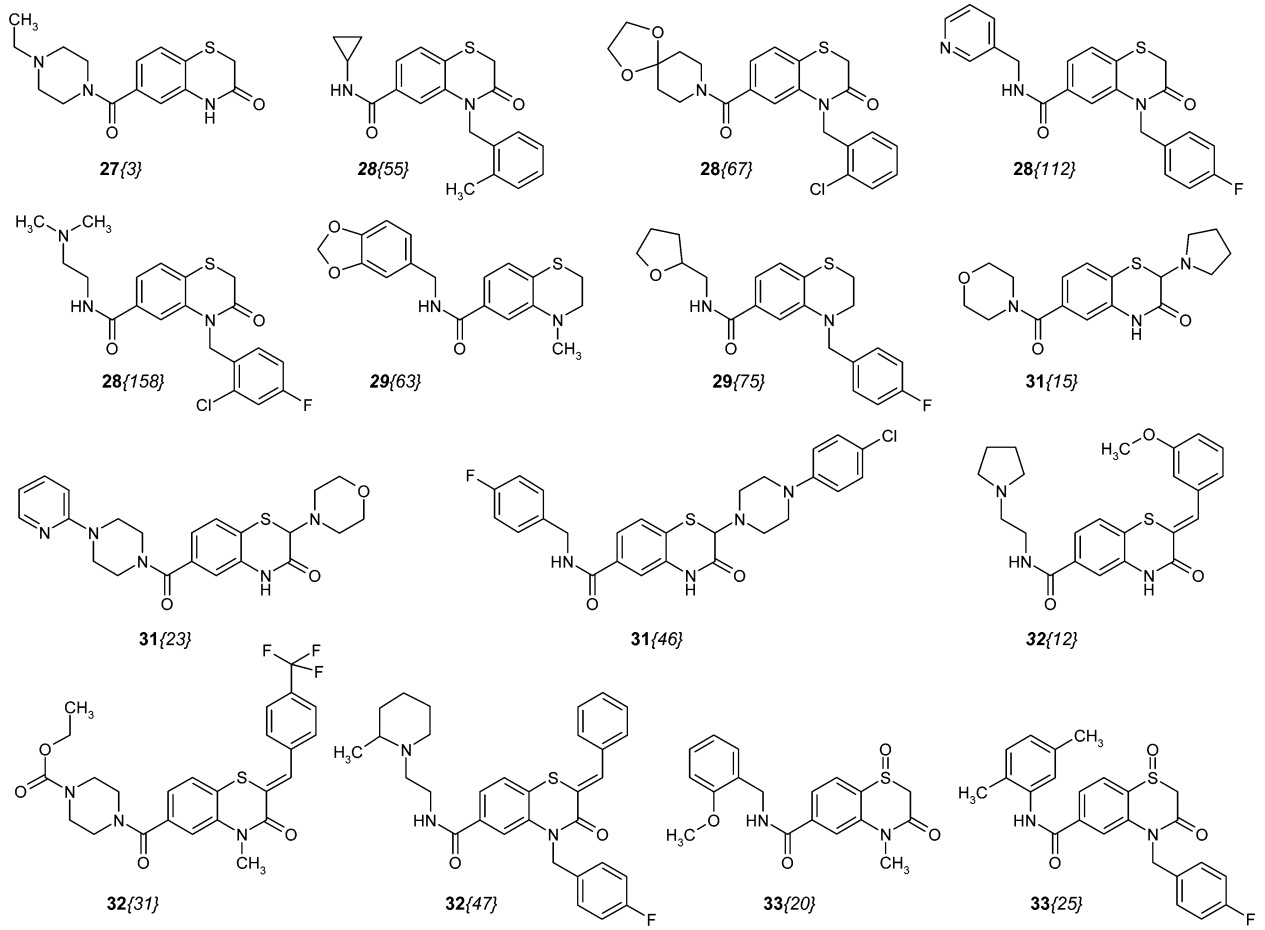



**Figure 3.** Representative examples of compounds from combinatorial libraries of substituted 3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamides.

3-amino-4-[(2-methoxy-2-oxoethyl)thio]benzoic acid **3** (LC/MS *m*/*z* 241.26120 (M + 1)) in $CHCl_3$ was added 10% aqueous HCl (500 mL), and the resulting mixture was vigorously stirred at reflux for 3 h. The organic layer was separated, washed with water (3 × 100 mL) and a 3% aqueous solution of $Na_2CO_3$ (3 × 100 mL), dried over $MgSO_4$, and evaporated in vacuo to dryness to yield 129 g (65% from **1**) of acid **4**. $^1$H NMR $\delta$ (ppm): 3.35 (s, 2H), 7.27 (d, $J$ = 8.4 Hz, 1H), 7.51 (d, $J$ = 8.4 Hz, 1H), 7.57 (s, 1H), 10.68 (s, 1H); LC/MS *m*/*z* 210 (M + 1).

**Methyl 4-[(2-methoxy-2-oxoethyl)thio]-3-nitrobenzoate 6.** A solution of methyl 3-nitro-4-chlorobenzoate **5** (65.1 g, 0.3 mol), methyl mercaptoacetate (35 g, 0.33 mol), and $Et_3N$ (111.1 g, 154.3 mL, 1.1 mol) in MeCN (600 mL) was stirred at 70−80 °C for 5 h. The reaction mixture was evaporated in vacuo to dryness, and the crude residue was dissolved in $CHCl_3$ (400 mL). The solution was washed thoroughly with 5% aqueous HCl and then with water. The organic layer was dried over $Na_2SO_4$ and evaporated in vacuo. The obtained residue was recrystallized from ether to afford 81.3 g (85%) of the title compound **6** (LC/MS *m*/*z* 286 (M + 1)).

**Methyl 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylate 7.** Sodium dithionite (60.9 g, 0.35 mol) was added portionwise to a stirred solution of nitrobenzoate **6** (28.7 g, 0.1 mol) and $Et_3N$ (70.7 g, 98.19 mL, 0.7 mol) in EtOH (300 mL). The temperature of the reaction mixture was kept below 60 °C upon the addition. The reaction mixture was stirred at 60 °C for 2 h, then cooled to room temperature, and the solvent was evaporated in vacuo. The crude residue was dissolved in $CHCl_3$ (200 mL), and the solution was washed thoroughly with water, dried over $Na_2SO_4$, and evaporated in vacuo. The obtained residue was recrystallized from ether−hexane (9:1) to afford 16.7 g (70%) of carboxylate **7** (LC/MS *m*/*z* 256 (M + 1)).

**General Procedure for the Preparation of 4-Substituted Methyl 3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylates 9a−x.** A mixture of carboxylate **7** (44.6 g, 0.2 mol), alkyl chloride **8a−x** (0.2 mol), $K_2CO_3$ (41.4 g, 0.3 mol), and 18-crown-6 (2.1 g, 0.008 mol) in MeCN (400 mL) was stirred at 60 °C for 4−6 h. The resulting mixture was filtered, and the filtrate was evaporated in vacuo to dryness. The crude residue was dissolved in $CHCl_3$ (300 mL), and the solution was washed successively with 5% aqueous KCl (200 mL) and water (2 × 200 mL), dried over $Na_2SO_4$, and evaporated in vacuo. The obtained residue was recrystallized from ether to afford the title compounds in 55−75% yield.

**General Procedure for the Preparation of 4-Substituted 3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acids 10a−x.** A solution of ester **9a−x** (0.1 mol) and NaOH (4.8 g, 0.12 mol) in a mixture of water (250 mL) and EtOH (250 mL) was stirred at 60 °C for 3 h. The reaction mixture was cooled to room temperature and evaporated to half of the initial volume. The obtained solution was filtered and then acidified with 10% HCl until pH 3 was reached. The formed precipitate was filtered off and recrystallized from EtOH−water (7:3) to afford acids **10a−x** in 70−80% yield.

Representative Analytical Data for Compounds **10a**−**x**.

**4-Methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic acid 10a.** Yield 70%; $^1$H NMR $\delta$ (ppm): 3.43 (s, 2H), 3.44 (s, 3H), 7.39 (d, $J$ = 8.2 Hz, 1H), 7.6 (d, $J$ = 8.2 Hz, 1H), 7.69 (s, 1H); LC/MS $m/z$ 224 (M + 1).

**4-(2-Chlorobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic acid 10j.** Yield 73%; $^1$H NMR $\delta$ (ppm): 3.61 (s, 2H), 5.23 (s, 2H), 7.02 (d, $J$ = 6.8 Hz, 1H), 7.14−7.28 (m, 2H), 7.35−7.48 (m, 3H), 7.58 (d, $J$ = 8.4 Hz, 1H); LC/MS $m/z$ 334 (M + 1).

**4-(3-Methylbenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid 10k.** Yield 80%; $^1$H NMR $\delta$ (ppm): 2.33 (s, 3H), 3.56 (s, 2H), 5.18 (s, 2H), 6.93−7.04 (m, 3H), 7.14 (t, $J_a$ = 6.9 Hz, $J_b$ = 7.7 Hz, 1H), 7.38 (d, $J$ = 8.3 Hz, 1H), 7.57 (d, $J$ = 8.3 Hz, 1H), 7.67 (s, 1H); LC/MS $m/z$ 314 (M + 1).

**4-(4-Fluorobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic acid 10o.** Yield 76%; $^1$H NMR $\delta$ (ppm): 3.57 (s, 2H), 5.23 (s, 2H), 7.01 (t, $J$ = 7.7 Hz, 2H), 7.25 (q, $J$ = 7.8 Hz, 2H), 7.4 (d, $J$ = 8.0 Hz, 1H), 7.57 (d, $J$ = 8.0 Hz, 1H), 7.67 (s, 1H); LC/MS $m/z$ 318 (M + 1).

**4-(2-Chloro-4-fluorobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid 10t.** Yield 72%; $^1$H NMR $\delta$ (ppm): 3.64 (s, 2H), 5.2 (s, 2H), 6.95−7.05 (m, 1H), 7.07−7.12 (m, 1H), 7.27 (d, $J$ = 7.4 Hz, 1H), 7.38−7.48 (m, 2H), 7.6 (d, $J$ = 8.3 Hz, 1H); LC/MS $m/z$ 352 (M + 1).

**General Procedure for the Preparation of Methyl 3,4-Dihydro-2*H*-1,4-benzothiazine-6-carboxylates 11a−f.** A solution of MeI (170.4 g, 1.2 mol) in $CHCl_3$ (150 mL) was added dropwise to a stirred mixture of ester **9a**,**b**,**g**,**n**−**p** (1 mol) and $Bu_4NBH_4$ (308.4 g, 1.2 mol) in $CHCl_3$ (500 mL). Upon the addition, the temperature of the reaction mixture was kept below 15 °C. The reaction mixture was stirred at room temperature for 5 h and then poured into water (500 mL). The organic layer was separated and dried over $Na_2SO_4$, the solvent was evaporated in vacuo, and the obtained viscous oil was dissolved in ethyl acetate (500 mL). The solution was filtered and evaporated in vacuo to dryness, and the crude residue was recrystallized from ether to afford the title carboxylates **11a**−**f** as white crystalline products in 60−70% yield.

**General Procedure for the Preparation of 3,4-Dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acids 12a−f.** Acids **12a**−**f** were prepared by alkali hydrolysis of esters **11a**−**f** using the same procedure that was described for acids **10a**−**x**. The title compounds were obtained in 70−75% yields.

**Representative Analytical Data for Compounds 12a−f. 4-Methyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid 12a.** Yield 71%; $^1$H NMR $\delta$ (ppm): 3.0 (s, 3H), 3.1−3.15 (m, 2H), 3.53−3.58 (m, 2H), 6.96 (d, $J$ = 8.2 Hz, 1H), 7.18 (d, $J$ = 8.2 Hz, 1H), 7.21 (s, 1H); LC/MS $m/z$ 210 (M + 1).

**4-(4-Chlorobenzyl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid 12c.** Yield 75%; $^1$H NMR $\delta$ (ppm): 3.08−3.13 (m, 2H), 3.62−3.69 (m, 2H), 4.56 (s, 2H), 7.0 (d, $J$ = 8.1 Hz, 1H), 7.18 (d, $J$ = 8.1 Hz, 1H), 7.2 (s, 1H), 7.27, 7.31 (d + d, $J$ = 8.7 Hz, 4H); LC/MS $m/z$ 314 (M + 1).

**Methyl 4-[(2-Methoxy-2-oxoethyl)sulfonyl]-3-nitrobenzoate 13.** $H_2O_2$ (0.35 mol, 40 mL of 30% solution) was slowly added to a stirred solution of nitrobenzoate **6** (28.5 g, 0.1 mol) in AcOH (100 mL). The reaction mixture was stirred at 60 °C for 2 h and then cooled to room temperature. Water (10 mL) was added, and the formed precipitate was filtered off, washed thoroughly with water, and dried at 50−60 °C to afford 19.0 g (60%) of ester **13** (LC/MS $m/z$ 318 (M + 1)).

**Methyl 4-[(2-Methoxy-2-oxoethyl)sulfonyl]-3-aminobenzoate 14.** Sodium dithionite (36.5 g, 0.21 mol) was added portionwise to a stirred solution of nitrobenzoate **13** (19.0 g, 0.06 mol) and $Et_3N$ (42.4 g, 59 mL, 0.42 mol) in EtOH (180 mL). The reaction mixture was stirred at 60 °C for 2 h, then cooled to room temperature, and the solvent was evaporated in vacuo. The crude residue was dissolved in water (100 mL), and the solution was acidified with 5% HCl until pH 3 was reached. The formed precipitate was filtered off and dried in vacuo to afford 9.5 g of aminobenzoate **14** (LC/MS $m/z$ 288 (M + 1)).

**Methyl 3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylate 1,1-dioxide 15.** A solution of aminobenzoate **14** (9.5 g, 0.1 mol) in formic acid (50 mL) was heated at reflux for 5 h. The reaction mixture was allowed to cool to room temperature, and the formed precipitate was filtered off, washed thoroughly with water, and dried at 50 °C to yield 5.5 g (65%) of the title compound **15**. Yield 65%; $^1$H NMR $\delta$ (ppm): 3.91 (s, 3H), 4.85 (s, 2H), 7.78−7.84 (m, 2H), 7.94 (d, $J$ = 8.2 Hz, 1H), 11.45 (s, 1H); LC/MS $m/z$ 256 (M + 1).

**3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid 1,1-Dioxide 16.** Ester **15** (5.5 g, 0.2 mol) was added to a stirred solution of NaOH (1.6 g, 0.04 mol) in a mixture of water (85 mL) and EtOH (85 mL). The reaction mixture was stirred at 60 °C for 3 h, then cooled to room temperature and evaporated to half of the initial volume. The obtained solution was filtered and then acidified with 10% HCl until pH 3 was reached. The formed precipitate was filtered off and dried in vacuo to afford 3.7 g of acid **16**. Yield 80%; $^1$H NMR $\delta$ (ppm): 4.82 (s, 2H), 7.79 (d, $J$ = 8.9 Hz, 1H), 7.81 (s, 1H), 7.94 (d, $J$ = 8.9 Hz, 1H), 11.39 (s, 1H); LC/MS $m/z$ 242 (M + 1).

**Methyl 2-Chloro-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylate 17.** Ester **7** (11.2 g, 0.05 mol) was added to a solution of $PCl_5$ (11.4 g, 0.055 mol) in dioxane (100 mL). The reaction mixture was stirred at 60 °C for 30 min, then slowly cooled to 15 °C and stirred at this temperature for an additional 30 min. The formed precipitate was filtered off, washed thoroughly with ether, and dried to afford 9.0 g (70%) of chloride **17** (LC/MS $m/z$ 258 (M + 1)).

**General Procedure for the Preparation of 2-Amino-Substituted Methyl 3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylates 19a−j.** A solution of chloride **17** (12.9 g, 0.05 mol), secondary amine **18a**−**j** (0.055 mol), and $Et_3N$ (5.1 g, 7 mL, 0.05 mol) in $CHCl_3$ (150 mL) was stirred at room temperature for 2 h. The reaction mixture was washed with water (2 × 50 mL), and the organic layer was dried over $Na_2SO_4$ and evaporated in vacuo. The obtained crude

residue was recrystallized from ether to yield the title compound **19a**−**j** in 70−80% yield.

**Representative Analytical Data for Compounds 19a**−**j. Methyl 2-Morpholin-4-yl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylate 19h.** Yield 72%; $^1$H NMR $\delta$ (ppm): 2.32−2.42 (m, 2H), 2.58−2.67 (m, 2H), 3.47−3.58 (m, 4H), 4.6 (s, 1H), 7.33 (d, $J$ = 7.9 Hz, 1H), 7.52 (d, $J$ = 7.9 Hz, 1H), 7.58 (s, 1H), 10.91 (s, 1H); LC/MS *m*/*z* 309 (M + 1).

**Methyl 2-[Cyclohexyl(methyl)amino]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylate 19c.** Yield 76%; $^1$H NMR $\delta$ (ppm): 0.98−1.34 (m, 5H), 1.55 (d, $J$ = 12.8 Hz 1H), 1.67−1.9 (m, 4H), 2.18 (s, 3H), 2.48−2.58 (m, 1H), 3.85 (s, 3H), 4.86 (s, 1H), 7.26 (d, $J$ = 7.8 Hz, 1H), 7.47 (d, $J$ = 7.8 Hz, 1H), 7.54 (s, 1H), 10.73 (s, 1H); LC/MS *m*/*z* 335 (M + 1).

**General Procedure for the Preparation of 2-Amino-substituted 3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acids 20a**−**j.** Acids **20a**−**j** were prepared by alkali hydrolysis of esters **19a**−**j** using the same procedure that was described for acids **10a**−**x**. The title compounds were obtained in 60−80% yields. Analytical data for a representative compound, 3-oxo-2-pyrrolidin-1-yl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic acid **20d**: Yield 80%; $^1$H NMR $\delta$ (ppm): 1.68 (br. s, 4H), 2.47 (q, $J$ = 10.8 Hz, 2H), 2.71 (q, $J$ = 10.8 Hz, 2H), 4.7 (s, 1H), 7.25 (d, $J$ = 8.0 Hz, 1H), 7.48 (d, $J$ = 8.0 Hz, 1H), 7.53 (s, 1H), 10.72 (s, 1H); LC/MS *m*/*z* 279 (M + 1).

**General Procedure for the Preparation of (2Z)-2-Benzylidene-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylates 22a**−**n and 23a**−**o.** A solution of acid **4** or ester **9a**,**k**,**o** (0.3 mol), aldehyde **21a**−**n** (0.55 mol), and $Et_3N$ (64.8 g, 90 mL, 0.64 mol) in $Ac_2O$ (150 mL) was stirred at reflux for 3 h. The reaction mixture was allowed to cool to room temperature, and the formed precipitate was filtered off, washed with ether, and dried to afford acids **22a**−**n** or esters **23a**−**o** in 60−70% yield.

**General Procedure for the Preparation of (2Z)-2-Benzylidene-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acids 24a**−**o.** Acids **24a**−**o** were prepared by alkali hydrolysis of esters **23a**−**o** using the same procedure that was described for acids **10a**−**x**. The title compounds were obtained in 60−80% yields.

**Representative Analytical Data for Compounds 24a**−**o. (2*Z*)-2-(3-Methoxybenzylidene)-4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid 24a.** Yield 66%; $^1$H NMR $\delta$ (ppm): 3.82 (s, 3H), 6.99 (d, $J$ = 8.0 Hz, 1H), 7.16−7.29 (m, 3H), 7.41 (t, $J_a$ = 8.0 Hz, $J_b$ = 7.6 Hz, 1H), 7.49 (d, $J$ = 8.2 Hz, 1H), 7.64 (s, 1H), 7.77 (s, 1H), 11.04 (s, 1H); LC/MS *m*/*z* 328 (M + 1).

**(2*Z*)-4-Methyl-3-oxo-2-[4-(trifluoromethyl)benzylidene]-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid 24k.** Yield 75%; $^1$H NMR $\delta$ (ppm): 3.59 (s, 3H), 7.32 (d, $J$ = 7.9 Hz, 1H), 7.66 (d, $J$ = 7.9 Hz, 1H), 7.7, 7.78 (d + d, $J$ = 8.2 Hz, 4H), 7.73 (s, 1H), 7.85 (s, 1H); LC/MS *m*/*z* 380 (M + 1).

**(2*Z*)-2-Benzylidene-4-(4-fluorobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid 24o.** Yield 61%; $^1$H NMR $\delta$ (ppm): 5.48 (s, 2H), 7.07 (t, $J$ = 8.1 Hz, 2H), 7.27−7.41 (m, 4H), 7.46 (t, $J$ = 8.1 Hz, 2H), 7.56−7.67 (m, 3H), 7.88 (s, 1H); LC/MS *m*/*z* 406 (M + 1).

**General Procedure for the Parallel Synthesis of Substituted 3-Oxo-3,4-dihydro-2*H*-benzo[1,4]thiazine-6-carboxylic Acid Amide Libraries 27{*1*−*63*}, 28{*1*−*443*}, 30{*1*−*10*}, 31{*1*−*125*}, and 32{*1*−*1460*}.** To a stirred solution of acid **4**, **10a**−**x**, **16**, **20a**−**j**, **22a**−**n**, or **24a**−**o** (300 mmol) in dry $CHCl_3$ (150 mL) was added CDI (50 g, 305 mmol), and the mixture was stirred at room temperature for 30 min and then at 40−50 °C until complete dissolution of the solid reactants. The resulting solution was diluted up to 500 mL with dry $CHCl_3$. The resulting stock solution was dispensed to 100 combinatorial vials of the CombiSyn reactors for parallel synthesis (5 mL per vial, ∼3 mmol of the corresponding imidazolide **25**). A solution of the corresponding amine **26**{*1*−*204*} (3.2 mmol) in dry $CHCl_3$ (3 mL) was injected into each vial, and the reaction mixtures were stirred under a moisture-free atmosphere overnight. The reactions with aromatic or heteroaromatic amines required elevated temperature (50 °C). The conversion was monitored by TLC (eluent 5% MeOH in $CH_2Cl_2$). Each reaction mixture was successively washed with cold water (5 mL), 2% $NaHCO_3$ (5 mL), and 2% HCl (5 mL). The remaining solutions were transferred into standard glass vials and evaporated in vacuo to dryness. The obtained residues were triturated with ether (15 mL), and the formed precipitates were filtered off, washed with ether, and dried. If necessary, the products were recrystallized from methanol or ethanol. The title amides were obtained in 60−80% yield.

**Representative Analytical Data for Compounds 27, 28, 31, 32. 6-[(4-Ethylpiperazin-1-yl)carbonyl]-2*H*-1,4-benzothiazin-3(4*H*)-one 27{*3*}.** Yield 70%; $^1$H NMR $\delta$ (ppm): 1.03 (t, 3H), 2.36 (q, 3H), 3.32 (s, 2H), 3.25−3.7 (m, 4H), 6.88 (d, $J$ = 8.5 Hz, 2H), 6.95 (s, 1H), 7.2 (d, $J$ = 8.5 Hz, 1H), 10.62 (s, 1H); LC/MS *m*/*z* 210 (M + 1).

***N*-Cyclopropyl-4-(2-methylbenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide 28{*55*}.** Yield 71%; $^1$H NMR $\delta$ (ppm): 0.55 (br. s., 2H), 0.68 (d, $J$ = 11.4 Hz, 2H), 2.42 (s, 3H), 2.71−2.81 (m, 1H), 3.54 (s, 2H), 5.16 (s, 2H), 6.92 (d, $J$ = 7.1 Hz, 1H), 6.99−7.19 (m, 3H), 7.37 (d, $J$ = 8.0 Hz, 1H); LC/MS *m*/*z* 353 (M + 1).

**4-(2-Chlorobenzyl)-6-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylcarbonyl)-2*H*-1,4-benzothiazin-3(4*H*)-one 28{*67*}.** Yield 65%; $^1$H NMR $\delta$ (ppm): 1.15−1.83 (m, 4H), 3.04−3.7 (m, 4H), 3.6 (s, 2H), 3.89 (s, 4H), 5.23 (s, 2H), 6.88 (s, 1H), 7.02 (d, $J$ = 8.1 Hz, 2H), 7.2 (t, $J$ = 7.8 Hz, 1H), 7.24 (t, $J$ = 7.8 Hz, 1H), 7.41 (d, $J$ = 8.1 Hz, 2H); LC/MS *m*/*z* 459 (M + 1).

**4-(4-Fluorobenzyl)-3-oxo-*N*-(pyridin-3-ylmethyl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide 28{*112*}.** Yield 61%; $^1$H NMR $\delta$ (ppm): 3.49 (s, 2H), 4.47 (d, $J$ = 6.0 Hz, 2H), 5.24 (s, 2H), 6.97 (t, $J$ = 8.2 Hz, 2H), 7.17−7.29 (m, 3H), 7.37 (d, $J$ = 7.7 Hz, 1H), 7.53 (d, $J$ = 7.7 Hz, 1H), 7.64 (d, $J$ = 8.1 Hz, 1H), 7.72 (s, 1H), 8.39 (d, $J$ = 4.8 Hz, 1H), 8.49 (s, 1H), 8.88 (t, $J$ = 8.1 Hz, 1H); LC/MS *m*/*z* 408 (M + 1).

**4-(2-Chloro-4-fluorobenzyl)-*N*-[2-(dimethylamino)ethyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide 28-{*158*}.** Yield 57%; $^1$H NMR $\delta$ (ppm): 2.19 (s, 6H), 2.38 (t,

$J$ = 11.4 Hz, 2H), 3.31 (q, 2H), 3.57 (s, 2H), 5.24 (s, 2H), 6.97 (t, $J$ = 7.8 Hz, 1H), 7.08 (t, $J$ = 7.8 Hz, 1H), 7.21 (d, $J$ = 8.9 Hz, 1H), 7.4 (d, $J$ = 8.0 Hz, 1H), 7.45 (s, 1H), 7.5 (d, $J$ = 8.0 Hz, 1H), 7.99 (t., $J$ = 8.4 Hz, 1H); LC/MS *m*/*z* 422 (M + 1).

**6-(Morpholin-4-ylcarbonyl)-2-pyrrolidin-1-yl-2*H*-1,4-benzothiazin-3(4*H*)-one 31**{***15***}**.** Yield 64%; $^1$H NMR $\delta$ (ppm): 1.71 (br s, 4H), 2.49−2.55 (m, 2H), 2.7−2.79 (m, 2H), 3.5 (br s, 4H), 3.61 (br s, 4H), 4.69 (s, 1H), 6.93 (d, $J$ = 7.8 Hz, 1H), 6.99 (s, 1H), 7.25 (d, $J$ = 7.8 Hz, 1H), 10.72 (s, 1H); LC/MS *m*/*z* 348 (M + 1).

**2-Morpholin-4-yl-6-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]-2*H*-1,4-benzothiazin-3(4*H*)-one 31**{***23***}**.** Yield 59%; $^1$H NMR $\delta$ (ppm): 2.37−2.45 (m, 2H), 2.64−2.73 (m, 2H), 3.48−3.63 (m, 12H), 4.56 (s, 1H), 6.58 (t, $J_a$ = 4.9 Hz, $J_b$ = 5.6 Hz, 1H), 6.69 (d, $J$ = 8.5 Hz, 1H), 6.99 (d, $J$ = 8.2 Hz, 1H), 7.05 (s, 1H), 7.29 (d, $J$ = 8.2 Hz, 1H), 7.43 (t, $J_a$ = 5.6 Hz, $J_b$ = 8.5 Hz, 1H), 8.05 (d, $J$ = 4.9 Hz, 1H), 10.82 (s, 1H); LC/MS *m*/*z* 440 (M + 1).

**2-[4-(4-Chlorophenyl)piperazin-1-yl]-*N*-(4-fluorobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide 31**{***46***}**.** Yield 73%; $^1$H NMR $\delta$ (ppm): 2.51−2.57 (m, 2H), 2.68−2.78 (m, 2H), 3.07 (br s, 4H), 4.33−4.68 (m, 2H), 4.87 (s, 1H), 6.72, 7.12 (d + d, $J$ = 8.8 Hz, 4H), 7.05 (t, $J$ = 8.4 Hz, 2H), 7.28−7.37 (m, 3H), 7.48 (d, $J$ = 9.1 Hz, 1H), 7.57 (s, 1H), 8.99 (t, $J$ = 8.4 Hz, 1H), 10.97 (s, 1H); LC/MS *m*/*z* 512 (M + 1).

**(2*Z*)-2-(3-Methoxybenzylidene)-3-oxo-*N*-(2-pyrrolidin-1-ylethyl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide 32**{***12***}**.** Yield 58%; $^1$H NMR $\delta$ (ppm): 2.02 (br s, 4H), 2.87−2.98 (m, 2H), 3.29 (t, $J$ = 10.5 Hz, 2H), 3.54−3.72 (m, 4H), 3.79 (s, 3H), 6.89 (d, $J$ = 7.7 Hz, 1H), 7.15 (s, 1H), 7.18 (d, $J$ = 7.3 Hz, 1H), 7.25 (d, $J$ = 7.7 Hz, 1H), 7.34 (t, $J_a$ = 8.2 Hz, $J_b$ = 7.3 Hz, 1H), 7.58 (s, 1H), 7.64 (d, $J$ = 8.2 Hz, 1H), 7.73 (s, 1H), 8.88 (t, $J$ = 8.2 Hz, 1H), 11.2 (s, 1H); LC/MS *m*/*z* 424 (M + 1).

**Ethyl 4-({(2*Z*)-4-Methyl-3-oxo-2-[4-(trifluoromethyl)-benzylidene]-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl}-carbonyl)piperazine-1-carboxylate 32**{***31***}**.** Yield 71%; $^1$H NMR $\delta$ (ppm): 1.24 (t, $J$ = 11.5 Hz, 3H), 3.27−3.7 (m, 8H), 3.54 (s, 3H), 4.07 (q, 2H), 7.11 (d, $J$ = 7.9 Hz, 1H), 7.28 (s, 1H), 7.33 (d, $J$ = 7.9 Hz, 1H), 7.73 (d, $J$ = 7.4 Hz, 2H), 7.79 (d, $J$ = 7.4 Hz, 2H), 7.84 (s, 1H); LC/MS *m*/*z* 520 (M + 1).

**(2*Z*)-2-Benzylidene-4-(4-fluorobenzyl)-*N*-[2-(2-methylpiperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide 32**{***47***}**.** Yield 45%; $^1$H NMR $\delta$ (ppm): 0.99 (d, $J$ = 12.4 Hz, 3H), 1.09−1.29 (m, 2H), 1.33−1.65 (m, 4H), 2.12−2.4 (m, 3H), 2.62−2.82 (m, 2H), 3.14−3.37 (m, 2H), 5.39 (s, 2H), 7.04 (t, $J$ = 8.0 Hz, 2H), 7.24−7.4 (m, 4H), 7.41−7.49 (m, 3H), 7.54 (s, 1H), 7.62 (d, 2H), 7.84 (s, 1H), 8.14 (t, $J$ = 6.8 Hz, 1H); LC/MS *m*/*z* 530 (M + 1).

**General Procedure for the Parallel Synthesis of Library of 3,4-Dihydro-2*H*-benzo[1,4]thiazine-6-carboxamides 29**{***1***−***442***}**.** A solution of acid **12a**−**f** (10 mmol) and CDI (1.78 g, 11 mmol) in DMF (50 mL) was stirred at 90 °C for 1 h under a moisture-free atmosphere, then the reaction mixture was allowed to cool to room temperature. The resulting stock solution was pipetted into 10 vials of the CombiSyn reactor for parallel synthesis (5 mL per vial, ∼1 mmol of the corresponding imidazolide **25**), followed by addition of the corresponding amine **26** (1.2 mmol). The reaction mixtures were stirred at 50 °C for 6 h and then allowed to cool to room temperature. Then they were transferred into standard glass vials and diluted with $CH_2Cl_2$ (20 mL per vial). The resulting solutions were successively washed with equal amounts of 1% aqueous $Na_2CO_3$, water, 1% HCl, and again with water. Then the solutions were dried over $Na_2SO_4$, and the solvent was evaporated in vacuo. The obtained residues were triturated with ether (5 mL), and the formed precipitates were filtered off, washed with ether, and dried. If necessary, the products were recrystallized from ethanol. Amides **29**{*1*−*442*} were obtained in 60−80% yield.

**Representative Analytical Data for Compounds 29. *N*-(1,3-Benzodioxol-5-ylmethyl)-4-methyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide 29**{***63***}**.** Yield 72%; $^1$H NMR $\delta$ (ppm): 3.02 (s, 3H), 3.07−3.14 (m, 2H), 3.51−3.57 (m, 2H), 4.35 (d, $J$ = 5.9 Hz, 2H), 5.93 (s, 2H), 6.71 (d, $J$ = 7.3 Hz, 1H), 6.77 (d, $J$ = 7.3 Hz, 1H), 6.83 (s, 1H), 6.94 (d, $J$ = 7.9 Hz, 1H), 7.1 (d, $J$ = 7.9 Hz, 1H), 7.17 (s, 1H), 8.5 (br s, 1H); LC/MS *m*/*z* 343 (M + 1).

**4-(4-Fluorobenzyl)-*N*-(tetrahydrofuran-2-ylmethyl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide 29**{***75***}**.** Yield 58%; $^1$H NMR $\delta$ (ppm): 1.52−1.64 (m, 1H), 1.77−1.96 (m, 3H), 3.05 (t, $J$ = 9.9 Hz, 2H), 3.18−3.38 (m, 2H), 3.58 (t, $J$ = 10.4 Hz, 2H), 3.63 (q, $J$ = 10.6 Hz, 1H), 3.77 (q, $J$ = 10.6 Hz, 1H), 3.89−3.97 (m, 1H), 4.58 (t, $J$ = 9.6 Hz, 2H), 6.97 (d, $J$ = 7.9 Hz, 1H), 7.0−7.1 (m, 3H), 7.2 (s, 1H), 7.31 (q, $J$ = 7.8 Hz, 2H), 7.96 (t, $J$ = 6.9 Hz, 1H); LC/MS *m*/*z* 387 (M + 1).

**General Procedure for the Parallel Synthesis of Library of 3-Oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide 1-Oxides 33**{***1***−***62***}**.** In each individual reaction unit of the CombiSyn reactor, the corresponding amide **28**{*1*−*62*} (0.2 mmol) was added to a freshly prepared solution of MCPBA (0.43 g, 2.5 mmol) in $CHCl_3$ (5 mL). The reaction mixtures were stirred at 50 °C for 5 h and then cooled to room temperature. The mixtures were filtered from the precipitated *m*-chlorobenzoic acid, diluted with $CHCl_3$ (5 mL), and then washed thoroughly with water and 2% aqueous $Na_2CO_3$. The resulting solutions were dried over $Na_2SO_4$, and the organic solvent was evaporated in vacuo. The obtained residues were triturated with 2-propanol (1 mL), and the formed precipitates were filtered off, washed with ether and dried. If necessary, the products were flash-chromatographed on silica gel (eluent 2% MeOH in $CH_2Cl_2$). Amides **33**{*1*−*62*} were obtained in 30−50% yield.

**Representative Analytical Data for Compounds 33. *N*-(2-Methoxybenzyl)-4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide 1-Oxide 33**{***20***}**.** Yield 37%; $^1$H NMR $\delta$ (ppm): 3.54 (s, 3H), 3.88 (s, 3H), 3.97, 4.09 (d + d, $J$ = 15.2 Hz, 2H), 4.49 (d, $J$ = 5.7 Hz, 2H), 6.82−6.91 (m, 2H), 7.14−7.21 (m, 2H), 7.75 (d, $J$ = 7.7 Hz, 1H), 7.79 (d, $J$ = 7.7 Hz, 1H), 7.85 (s, 1H), 8.84 (t, $J$ = 8.4 Hz, 1H); LC/MS *m*/*z* 359 (M + 1).

***N*-(2,5-Dimethylphenyl)-4-(4-fluorobenzyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide 1-Oxide 33-{*25*}.** Yield 45%; $^1$H NMR $\delta$ (ppm): 2.17 (s, 3H), 2.34 (s, 3H), 4.26 (s, 2H), 5.35, 5.45 (d + d, $J$ = 16.3 Hz, 2H), 6.93 (d, $J$ = 7.6 Hz, 1H), 6.99 (t, $J$ = 7.8 Hz, 2H), 7.09 (d, $J$ = 7.6 Hz, 1H), 7.17 (s, 1H), 7.34−7.42 (m, 2H), 7.77−7.89 (m, 3H), 9.74 (s, 1H); LC/MS *m*/*z* 437 (M + 1).

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**Supporting Information Available.** $^1$H NMR spectra of synthesized compounds from libraries **27**−**33** and structures of amines **26**{*1*−*204*} evaluated in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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