QSAR & Combinatorial Science QCS

Selective Polymer-Assisted Product Sequestration for the Generation of Combinatorial Libraries of 1,3-Thiazines

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Keywords: Combinatorial Chemistry, Heterocycles, Molecular Recognition, Polymer-bound Reagents, Scavenger Resins

Received: November 16, 2004; Accepted: December 20, 2004

Abstract

Combinatorial approaches for the solution-phase synthesis of diverse 1,3-thiazine-5-carboxylate libraries are described. Knoevenagel condensation of β-ketoesters and aldehydes utilizing a polymer-supported catalyst furnished the anticipated enones, which were subsequently reacted with thioureas to generate 1,3-thiazine heterocycles among various by-products. In the key step, the 1,3-thiazines were selectively sequestered by a polymer-bound sulfonic acid. Subsequent base-induced release from the polymer (catch and release) produced 24 1,3-thiazine products in yields up to 79%, good to excellent purities and in high diversity. In contrast to the polymer-bound acid-mediated reaction, this method tolerates more complex building blocks. Furthermore, polymer-assisted methods for *N*2-derivatization were performed, including reactions with activated carboxylic acids, sulfonyl chlorides and isocyanates.

1 Introduction

High-throughput synthesis, combinatorial chemistry and modern screening methods are among the most important technologies applied in current lead finding and lead optimization processes. The range of applications has continuously expanded over the years, delivering impressive results in medicinal chemistry, material sciences and catalyst discovery [1, 2]. To date, combinatorial methods aiming at the synthesis of small organic molecules are frequently based on two strategies: solid-phase synthesis (SPOS) and solution-phase synthesis aided by scavenger resins and polymer-bound reagents. Solid-phase synthesis allows driving reactions to completion by the action of a large excess of reagents. Despite this enormous advantage, some of the chemistry might be incompatible with the supports, reactions generally proceed slower, and the optimization of many transformations is aggravated by the need to apply on-bead methods for reaction monitoring. Some of these disadvantages can be overcome by the application of solution-phase synthesis aided by scavenger resins and polymer-bound reagents [2–5]. At the stage of the reaction itself, solution-phase methods are often more flexible, especially if they are run in a homogenous phase. The presence of the desired molecules in solution allows for simple analysis by classical methods. Purification strategies are simple if polymer-bound reagents are used, but become more difficult in case of application of scavengers and catch-and-release techniques.

In the context of developing high-throughput synthetic methods for the synthesis of novel heterocycles, we have recently become interested in the generation of 1,3-thiazine libraries utilizing both solution-phase [6] and solid-phase methods [7]. The particular scaffolds of interest are 2-amino-1,3-thiazine-5-carboxylates of type **A**, which possess close structural similarity to privileged cores of the dihydropyrimidine (DHPM) type **B** (Figure 1) [8]. In contrast to the latter class of heterocycles, where more than 10000 entries can be found in the Chemical Abstracts database [9], 2-amino-1,3-thiazine-5-carboxylates of type **B** were hitherto rarely described in the literature and there appears to be very little published information on both, synthetic methods as well as biological activity data [10, 11].

In a recent communication, we reported a solution-phase protocol incorporating a unique polymer-supported acid-mediated ring closure and subsequent selective product capture as key step to obtain a library of diverse 1,3-

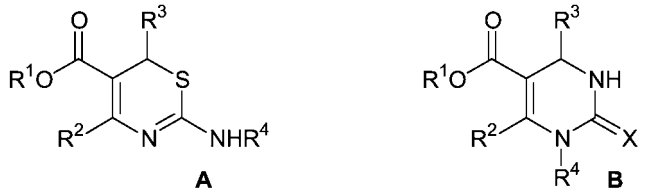
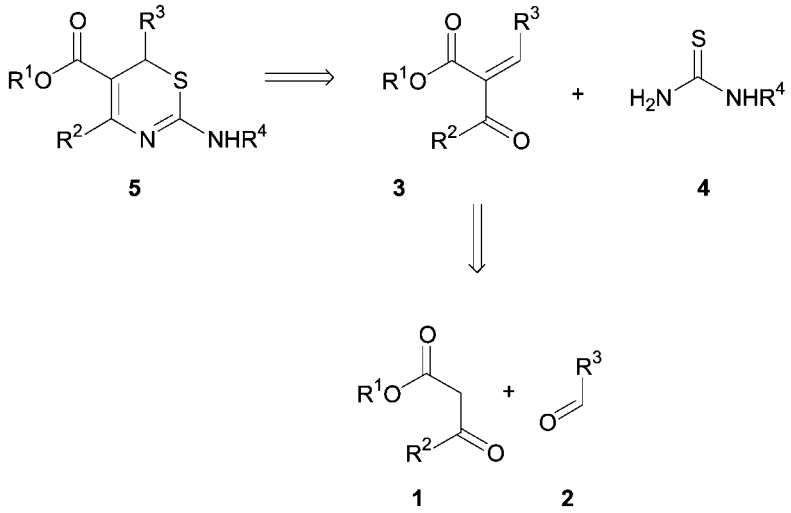


Figure 1. Comparison of 1,3-thiazines **A** and isomeric (X = S) dihydropyrimidines **B.**

 DOI: 10.1002/qsar.200410150



Scheme 1. Synthetic strategy toward 1,3-thiazine-5-carboxylates.

thiazine-5-carboxylates in parallel mode [6]. Yields and purities of the library members were typically good to excellent. Nonetheless, the application of a polymer-bound acid caused problems if unreactive or sterically crowded starting materials were used, in addition to the fact that binding of the basic products on the resin continuously lowered the effective acid concentration, thus leading to a slow-down of the reaction. Therefore, we envisaged a modification of this strategy in order to access building block combinations and therefore target structures not being accessible by our previous strategy [6]. While dihydropyrimidines (Figure 1) are readily available via one-pot Biginelli multicomponent condensation of β-ketoesters **1**, aldehydes **2**, and (thio)ureas **4** [12], the desired isomeric 1,3-thiazines **5** have to be generated by step-wise assembly of the same building blocks (Scheme 1) [6, 7].

2 Results

2.1 General Strategy

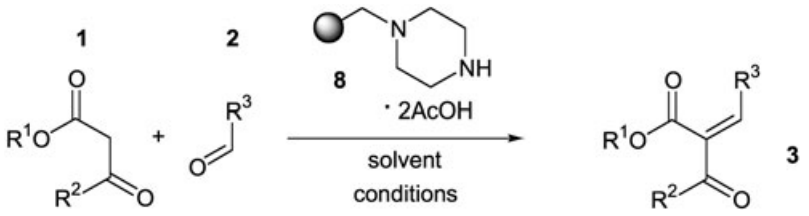
We envisaged increasing the diversity in the target scaffold **5** at position 4 (R^2) by a synthesis of β-ketoesters **1**, overcoming the restrictions derived from the limited commercial availability of these building blocks [13]. A subsequent Knoevenagel condensation with aldehydes **2** with the aid of a polymer-bound catalyst should lead to enones **3** [6], which are converted into 1,3-thiazine-5-carboxylates **5** by acid-mediated ring closure with various thioureas **4** (Scheme 1). Purification of the desired final products should be accomplished by selective sequestration with the aid of polymer-supported sulfonic acid. Since this catch-and-release concept would ideally be applied after three synthetic steps with little or no purification throughout the sequence, we hoped to utilize the idea of a strong molecular recognition of the basic 1,3-thiazines by the resin-bound sulfonic acid [6]. Furthermore, polymer-assisted methods to derivatize products **5**, including acylation, sulfonylation and urea formation, should give rise to second-generation libraries, which meet the requirements of combinatorial chemistry in terms of diversity, purity of products and ease to run in parallel mode.

2.2 Knoevenagel Condensation Utilizing a Polymer-Supported Catalyst

The Knoevenagel condensation between β-ketoesters **1** and aldehydes **2** was investigated under a variety of conditions (Table 1). Particular attention has been given to the usage of a polymer-supported base, since this would allow rapid product purification (see below). Based on a literature precedent [14–16] a polymer-supported piperazine was employed in our studies. As can be seen from Table 1, Knoevenagel condensations with soluble catalysts are slightly faster. On the other hand, the polymer-supported catalyst equivalent binds catalyst-derived by-products and therefore greatly simplifies product separation. The side-product **8c** (Scheme 2) arises from the reaction of polymer-bound piperazinocrotonate **8b** (from reaction of **8** with β-ketoester **1**) and the enone formed by Knoevenagel condensation [17]. Since this side-reaction is slow, one can assume that the overall catalytic efficiency of **8** is not dramatically lowered. Apart from the easy removal of the catalyst itself, the polymer-supported catalyst method also removes the basic 1-amino-1,3-cyclohexadiene by-products formed by known catalyst-derived side-reactions (Scheme 2). Importantly, these *basic* by-products must be removed so they do not interfere with the subsequent thiazine catch-and-release strategy (see below).

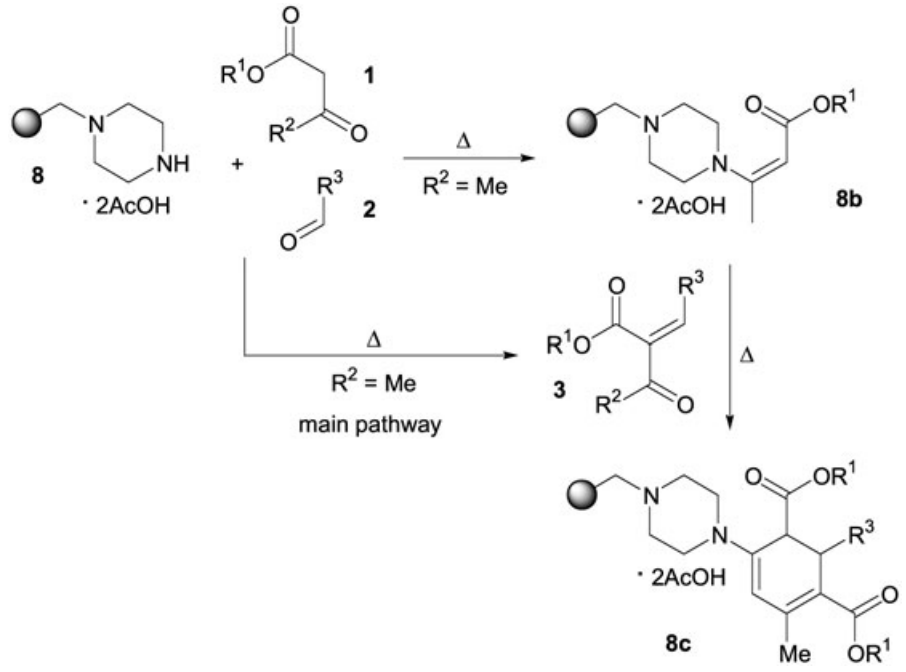
In general, neutralized amines are more efficient in the Knoevenagel condensation (see entries 1–6, Table 1). Mo-

Table 1. Optimization of Knoevenagel condensation (1 equiv β-ketoester **1**, 1 equiv aldehyde **2**, resin-bound piperazine **8** or other catalyst as mentioned).

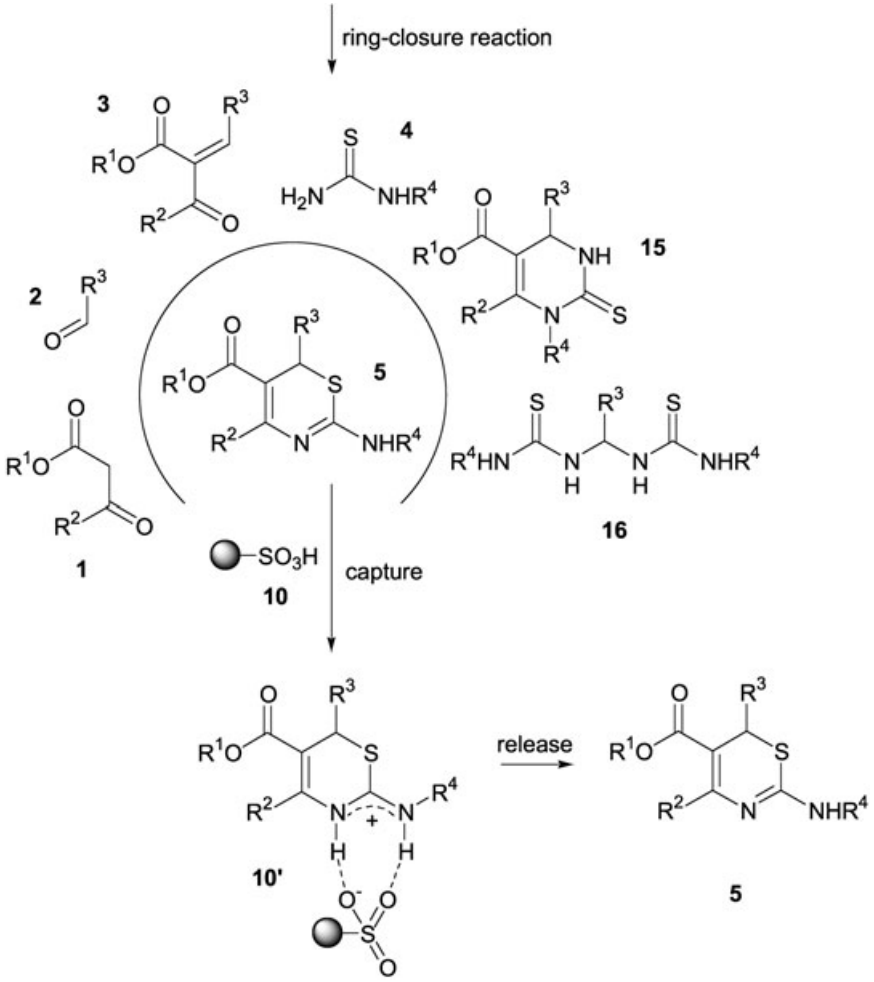


Entry	R^1	R^2	R^3	Solvent	T [°C]	T [h]	cat. [mol-%]	conditions	conv.[a] [%]
1	Et	Me	Ph	toluene	125	2	5[b]	closed, TMOF[c]	34
2	Et	Me	Ph	toluene	125	2	5	closed, TMOF	46
3	Et	Me	Ph	toluene	110	10	5	closed, TMOF	61
4	Et	Me	Ph	toluene	110	10	5	closed, MS 4 Å[d]	74
5	Et	Me	Ph	anisole	130	3	10	closed, MS 4 Å	64
6	Et	Me	Ph	anisole	130	3	10	closed, MS 3 Å[e]	76
7	Et	Me	Ph	anisole	130	2.2	10	open	84
8	Et	Me	Ph	PhCOOEt	130	2.2	10	open	84
9	Et	Me	Ph	nitrobenzene	130	2.2	10	open	81
10	Et	Me	Ph	chlorobenzene	120	1	10	MW, open[f]	89
11	Et	Me	Ph	chlorobenzene	110	3	5[g]	closed, MS 4 Å	74
12	Et	Me	Ph	chlorobenzene	110	3	5[h]	closed, MS 4 Å	78
13	Et	Me	2-NO_2-(Ph)	toluene	110	10	10	closed, TMOF	47
14	Et	Me	2-NO_2-(Ph)	toluene	110	10	10	closed, MS 4 Å	73
15	Et	Me	2-NO_2-(Ph)	chlorobenzene	120	2.5	10	open	60
16	Et	Me	2-NO_2-(Ph)	chlorobenzene	120	4	10	open	76
17	Et	Me	2,3-Cl-(Ph)	chlorobenzene	120	4	10	open	91
18	Et	Me	2-CF_3-(Ph)	toluene	110	10	5	closed, MS 4 Å	54
19	Et	Me	2-CF_3-(Ph)	chlorobenzene	120	1	10	MW, open	77
20	Et	Me	2-CF_3-(Ph)	chlorobenzene	110	14	10	open	86
21	Et	Ph	Ph	chlorobenzene	120	1	10	MW, open	87

[a] Conversion determinated by RP-HPLC at 254 nm. [b] **8** as free base [14–16]. [c] 2 equiv trimethylorthoformate (TMOF). [d] MS 4 Å: Aldrich Cat. No. 23366–8, molecular sieves 4 Å, powder < 5 μm. [e] MS 3 Å: Aldrich Cat. No. 20858–2, molecular sieves 3 Å, pearls 8–12 mesh. [f] MW: microwave irradiation, Milestone Microsynth. [g] Piperidine instead of **8.** [h] Piperidine acetate instead of **8.**



Scheme 2. Formation of catalyst-derived 1-amino-1,3-cyclohexadiene by-product **8c.**



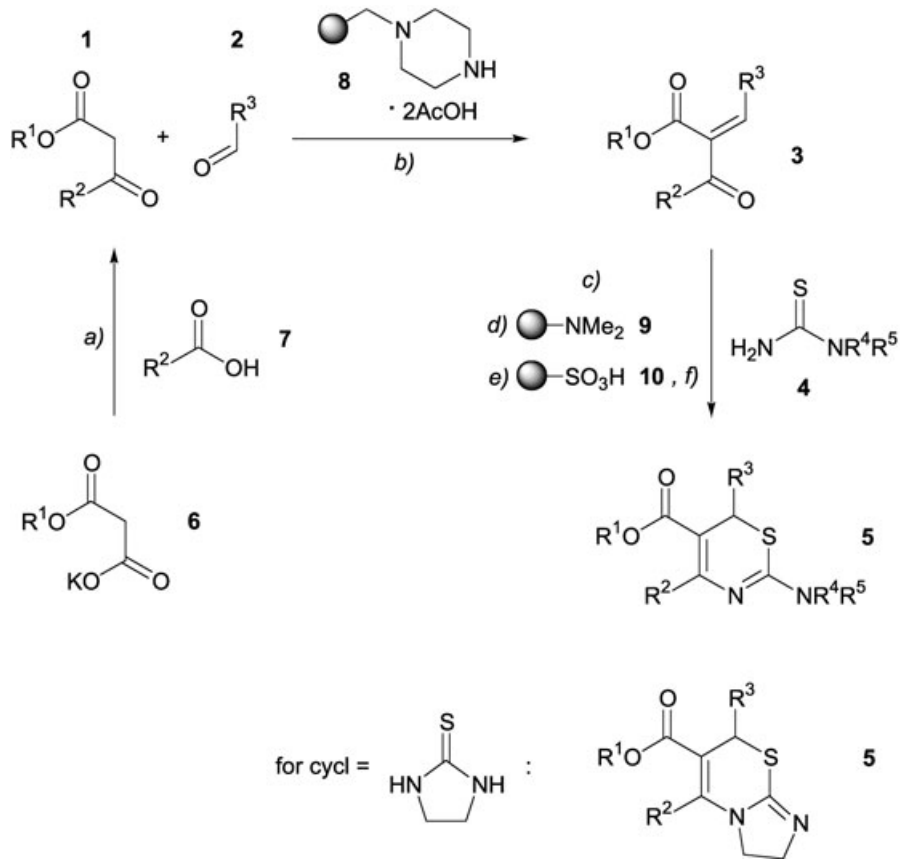
Scheme 3. Schematic overview of the selective sequestration of products 5 from the complex reaction mixture.

lecular sieves are more effective water scavengers than trimethylorthoformate, thus leading to higher yields of enone. In contrast to closed vessel conditions, which require such water scavengers, open systems allow for the azeotropic removal of water formed during the reaction. Since we found generally good yields using open vessel conditions, also when applying less reactive building blocks, we decided to apply the following conditions for the library production: 10 mol-% catalyst **8** (diacetate form), chlorobenzene, 115 °C, 5 h, open vessel conditions (cf. entry 17, Table 1). The crude enones (mixture of *E/Z* isomers) were directly used in the subsequent ring-closure reaction after filtration from the catalyst.

2.3 Thiazine Ring Closure – General Considerations

Having optimized the synthetic strategy toward enones **3**, we next turned our attention to the subsequent ring-closure reaction and purification concept for the desired thiazines **5.** Since Knoevenagel condensations generally did not reach completion, we envisaged a polymer-assisted method for the purification of enones. Disappointingly, none of the methods presented in literature proved to be successful [18, 19]. Scavenger resins with amine functionalities, e.g., polymer-bound ethylenediamine, frequently used for sequestration of aldehydes, led to complete decomposition of enones **3.** Since no other powerful alternative seemed to be available, we had to subject non-purified Knoevenagel products, which contain varying amounts of unreacted aldehydes and β-ketosters, to the subsequent synthetic step.

Considering the fact that the thiazine ring-closure reaction is performed under acidic conditions, we assumed that enones **3** would react in a well-defined manner with thioureas, whereas the impurities would likely undergo two- or three-component reactions to generate by-products with fairly different properties. Aldehydes **2**, β-ketoester **1** and thiourea **4** possibly would react via Biginelli condensation to non-basic dihydropyrimidinethiones **15** [12], or be transformed to bisureides **16** [20] (Scheme 3). With the assumption that no basic building blocks are introduced into the protocol (i.e., aldehydes bearing amino functionalities),



Scheme 4. a) (i) 1 equiv CDI, 1 equiv **7**, THF, RT, 3 h; (ii) 1 equiv **6**, 1.2 equiv $MgCl_2$, MeCN, RT, 3 h; then add (i) to (ii), RT, 14 h; b) 1 equiv β-ketoester, 1.1 equiv aldehyde, 10 mol-% **8**, chlorobenzene, 115 °C, 5 h; c) 2.2 equiv **5**, 3 equiv 4 M HCl in dioxane, abs. ethanol, 80 °C, 8 h; d) 6 equiv **9**; e) 1.5 equiv **10**; f) wash step, then MeOH/TEA 3:1. CDI = *N,N*'-carbonyl diimidazole, TEA = triethylamine.

there would be only one basic structure present in the mixture after the ring-closure event, namely the desired 2-amino-1,3-thiazine products **5**, whereas all the contaminants displayed in Scheme 3 are non-basic in nature. Following neutralization of the acid by basic ion-exchange resin, thiazines **5** could be selectively captured applying molecular recognition (**10'**) by a suitable counterpart, which comprises a strong acid functionality (i.e., sulfonic acid resin **10**) [21]. Release from the polymeric support is conducted by displacement with the significantly stronger base triethylamine.

2.4 Thiazine Library Generation

The synthetic sequence starts with preparation of non-commercial β-ketoesters **1** via acylation of magnesium salts of malonic acid monoesters **6** (Scheme 4) [22]. Acyl donors such as acyl imidazoles used herein do not require complex preparations, simple stirring of a 1:1 mixture of the carboxylic acid **7** and *N,N*'-carbonyl diimidazole (CDI) for 3 h at room temperature suffices. Magnesium malonates are conveniently prepared by transmetallation of potassium salts of malonic acid monoesters by excess $MgCl_2$ [22]. The straightforward transformation of an acid into a β-ketoester, in addition to the simple liquid-liquid extraction work-up, makes this a highly valuable strategy for β-ketoester synthesis.

Having suitable β-ketoesters **1** in hand, prepared either by the method described above or from commercial sources, the sequence continues with a Knoevenagel condensation using aldehydes **2** (10% excess) in chlorobenzene at 115 °C under open-vessel conditions to facilitate the removal of water formed during the reaction (see above). A slight excess of aldehyde was considered the best compromise between optimal yields in this transformation and minimal side effects in the subsequent ring-closure reactions. Polymer-bound piperazine (1.1 mmol g^{-1}, Novabiochem) as diacetate **8** acts as efficient catalyst for this condensation (see also Table 1). Apart from the elegant application of a supported catalyst, impurities contained in enones **3** are kept at a minimum, because most of them are ultimately filtered off together with the catalyst (see Scheme 2).

In contrast to our previously described method [6], here ring closure with thioureas **4** to the desired thiazines **5** was performed with an excess of the thiourea building block

and *hydrochloric acid* instead of a polymer-supported acid. Polar/protic ethanol was found to be the best solvent for this transformation, thus allowing reaction temperature and time to be kept in a range where only little side-reactions occur. Reaction times for reactive enones are around 2–4 h, but in order to achieve good results in other combinations of building blocks, the reaction times were generally set to 8 h. Solvent residues from the previous reaction step (i.e., chlorobenzene) are well tolerated. After performing the ring closure, capture of excess acid and liberation of the free thiazine base **5** was carried out with the polymer-supported tertiary amine Amberlyst-A21. Having removed all acidic species by filtration, selective capture of the desired thiazines **5** was then affected by addition of a small excess of polymer-bound sulfonic acid **10** (DOWEX 50X2, 4.8 mmol g^{-1}), leading to a tight binding of the basic amidine functionality in the product to the sulfonic acid [23]. All other molecules (Scheme 3), including solvents, reagents, starting materials and by-products *do not bind to the resin-bound acid* and are subsequently washed off. Moreover, simple ion-exchange resins with very high loading and, importantly, low cross-linking are used [24], thus making the concept relatively inexpensive. Release of thiazines **5** is initiated by treatment with triethylamine. Final passage through a short plug of silica delivers high purity products, which can be subjected to further transformations.

The strategy described above was used to prepare a set of 24 thiazines, which was intended to show general trends representative of substituent effects on the efficiency of the synthetic method (Table 2). Yields of typically more than 30% and the good purity of all products reveal the successful application of the synthesis/purification concept, in particular the selective sequestration of the thiazines **5.** Aromatic aldehydes, e.g., with electron-donating and -withdrawing substituents, including *ortho* substitution, are all well tolerated. Only in the case of *N*-phenylthioureas did we observe a significantly lower purity of products. Most notably, in contrast to the method using a polymer-supported acid as mediator for the ring closure (denoted as one-resin strategy) [6], aromatic β-ketoesters (position 4 of thiazines, R^2) can also be employed. Product **5/14** can be considered as an "isomer" to the dihydropyrimidone monastrol, which is a specific inhibitor of the mitotic kinesin Eg5 motor protein and therefore a lead structure for the development of novel anticancer drugs [8a]. A comparison with samples prepared by the one-resin strategy (entries **5/6**, **17**, **19** and **24**) [6] further emphasizes the efficiency of the new concept.

Apparently, performing the critical ring-closure step (**3**+**4**→**5**) in homogeneous solution is advantageous, although somewhat more effort is required to obtain pure products at the end. Entry 24 of Table 2 can be considered as a worst-case scenario with a yield of 44% by the new two-resin strategy, and 2% for the one-resin strategy.

Table 2. Solution-phase synthesis of 1,3-thiazines.

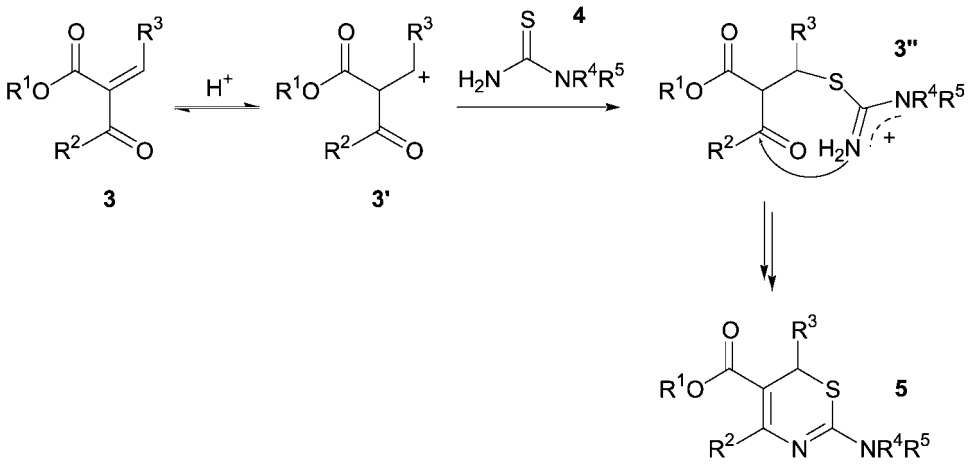
Entry	R^1	R^2	R^3	R^4	Yield[a] [%]	Purity[b] [%]
5/1	Et	Me	Ph	NH_2	77	90
5/2	Et	Me	Ph	NHMe	79	>98
5/3	Et	Me	Ph	NEt_2	56	91
5/4	Et	Me	Ph	cycl[e]	63	97
5/5	Et	Pr	styryl	NH_2	51	83
5/6	Et	Pr	styryl	NHMe	69 (7)[c]	94 (<50)[c]
5/7	Et	Pr	styryl	NEt_2	25	91
5/8	Et	Pr	2-CF_3-Ph	NH_2	51	>98
5/9	Et	Pr	2-CF_3-Ph	NHMe	53	98
5/10	Et	Me	2-NO_2-Ph	NH_2	43	98
5/11	Et	Me	2-NO_2-Ph	NHBn	72	80
5/12	Et	Pr	2,3-Cl-Ph	NHBn	40	84
5/13	Et	Pr	2,3-Cl-Ph	cycl[e]	60	92
5/14	Et	Me	3-OH-Ph	NH_2	51	92
5/15	Et	Me	3-OH-Ph	NHPh	49	78
5/16	Et	Me	3-OH-Ph	cycl[e]	57	90
5/17	Bn	Me	3-NO_2-Ph	NEt_2	36 (15)[c]	88 (<50)[c]
5/18	Bn	Me	3-NO_2-Ph	cycl[e]	33	95
5/19	Et	Ph	4-Me-Ph	NH_2	35 (8)[c]	84 (<50)[c]
5/20	Et	Me	4-Cl-Ph	NH_2	56	>98
5/21	Et	Me	4-Cl-Ph	NHMe	47	>98
5/22[d]	Me	4-F-Ph	pentyl	NH_2	44	92
5/23[d]	Me	4-F-Ph	pentyl	NHMe	36	91
5/24[d]	Me	2-Cl-6-F-Bn	3,4-F-Ph	NH_2	44 (2)[c]	94 (<50)[c]

[a] Over 2 steps based on β-ketoester. [b] By LC-MS at 215 nm. [c] Values in brackets refer to the results obtained by ring closure with polymer-bound sulfonic acid [6]. [d] β-Ketoester 1 prepared via malonic ester route (Scheme 4) prior to Knoevenagel condensation; all other esters are commercially available. [e] Imidazolidine-2-thione, see Scheme 4

Therefore, the two-resin strategy proves to be more flexible for the construction of diverse thiazin libraries **5.**

We assume that the initiation step in the ring closure is a protonation at the nucleophilic α-position of enones **3**, followed by trapping of the thiourea **4** to furnish basic *S*-alkyl-thiouronium intermediate **3″.** Finally the amino group undergoes a nucleophilic attack at the β-ketoester, followed by a dehydration of the hemi-aminal intermediate to yield thiazine **5** (Scheme 5). As an alternative pathway (not shown) one could envision the initial protonation of the thiourea building block **4** leading to a highly nucleophilic thiol intermediate. This active species could undergo conjugate addition to the enone **3** and finally furnish thiazine **5.**

The efficacy of the two-resin purification concept is furthermore illustrated by high-performance liquid chromatography (HPLC) monitoring of the crucial step – the selective sequestration of product **5/14** (Figure 2). The HPLC trace in figure 2a displays all non-basic species which are not able to bind to the acidic ion-exchange resin. Complete disappearance of almost all by-products, starting materials and solvents used throughout the sequence reveals the successful sequestration (Figure 2b).



Scheme 5. Plausible mechanism for the formation of thiazines **5** from enones **3** via acid mediated ring-closure reaction.

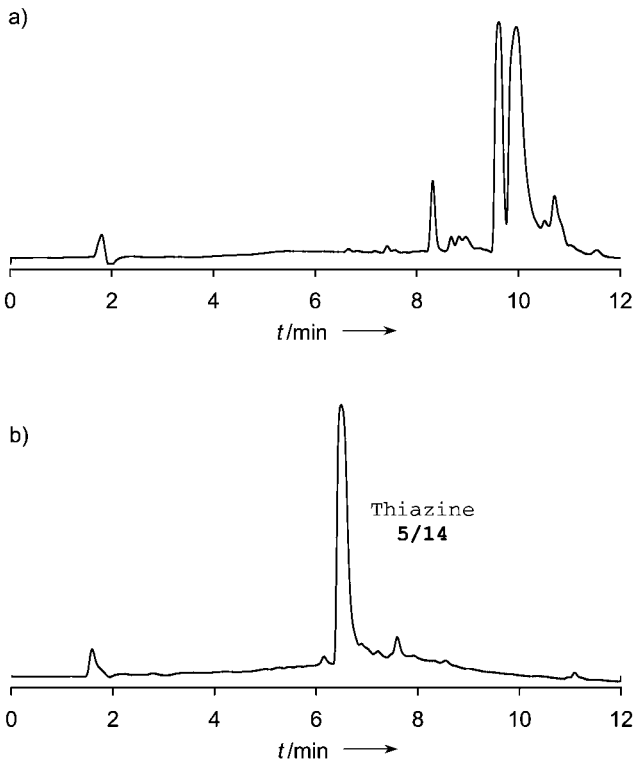


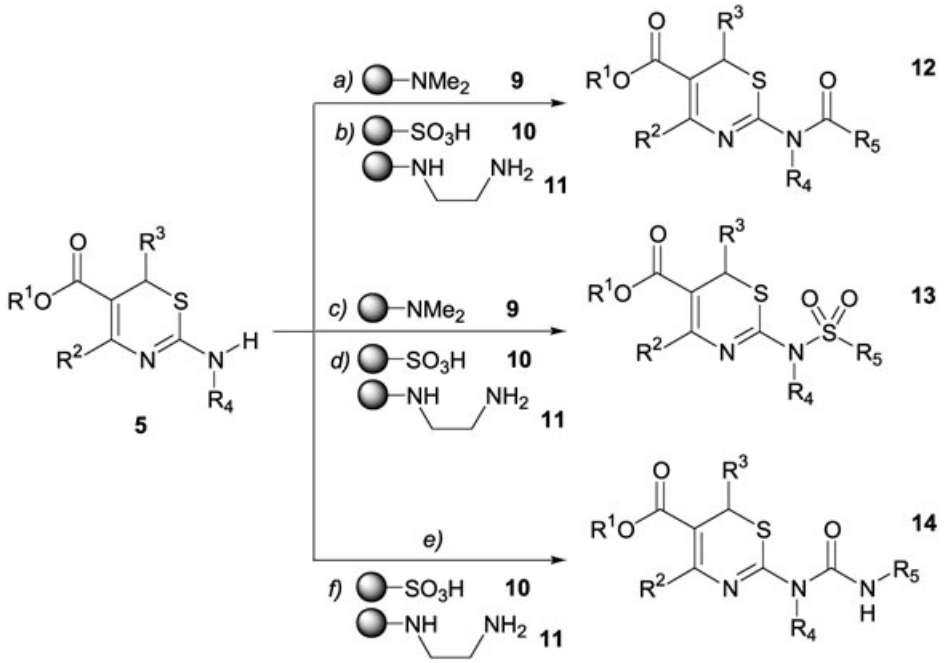
Figure 2. HPLC monitoring of thiazine synthesis. a) substances not bound to polymer-bound sulfonic acid in the selective sequestration step; b) final product **5/14.**

2.5 Scaffold Decoration of Thiazines

To synthesize more diverse analogs of the parent 1,3-thiazine scaffold (i.e., introduce a fifth diversity point) we envisioned a polymer-assisted derivatization of thiazines **5** at the 2-amino position. In our previous communication [6] we demonstrated a method for the selective monoalkylation of amino groups in position 2 using a Mitsunobu strategy. Here, we report on acylations, sulfonylations and urea formations on the amino position, thereby siginificantly increasing the diversity that can be achieved around the thiazine ring (Scheme 6, Figure 3). After some experimentation using conventional solution-phase chemistry, we were pleased to obtain conversion with various acyl donors, sulfonyl chlorides and isocyanates in all of the investigated cases.

Acylations with acyl chlorides and sulfonylations are similar in terms of their realization. Both transformations utilize polymer-supported amine **9** (Amberlyst A-21) to bind the acid that is formed during the course of the reaction, resin **11** (polymer-supported ethylenediamine) to scavenge excess reagents, and resin **10** (DOWEX 50X2) to remove unreacted thiazines **5** and DMAP (4-dimethylaminopyridine) (Scheme 6) [25, 26] The participation of acyl imidazoles requires higher temperatures and more acid scavenger **11** to remove all imidazole at the end. Urea formation with aromatic isocyanates requires significantly elevated temperatures (80 °C) and strict exclusion of water. The sequestration of excess reagent is straightforward, as described for the other derivatizing reagents. It is important to note that the types of small-scale derivatizations described herein, especially when using isocyanates, are better performed in the presence of active molecular sieves. This simple precaution prevents the undesired hydrolysis of reagents by traces of moisture in the system and therefore from side-products, which cannot be removed by scavengers.

Acylations with acid chlorides and sulfonylations with sulfonyl chlorides generally provided high yields and good purities. Reaction with an acyl imidazole gave only 52% of the desired product, but this mainly resulted from the low reactivity of the complex phenylacetic acid moiety. Despite the incomplete conversion it was still possible to obtain a good purity of product **12/6.** Reactions with isocyanates were the most difficult to achieve because of the low reactivity of building blocks (see **14/2** and **14/3**). Large excess of the isocyanate reagent led to lower purity of prod-



Scheme 6. Polymer-assisted derivatization of 1,3-thiazines **5.** For acyl chlorides: a) 2 equiv R^5COCl, thiazine **5**, cat. DMAP, 6 equiv **9**, powdered MS 4 Å, dichloromethane, RT, 14 h; b) 1 equiv **10**, 1.5 equiv **11**, RT, 4 h. For carboxylic acids via acyl imidazoles: a) 1.43 equiv CDI, 1.5 equiv R^5COOH, acetonitrile, RT, 2 h; then add to **5**, cat. DMAP, acetonitrile, 50 °C, 4 h; b) 5 equiv **10**, 1 equiv **11**, RT, 4 h. c) 2 equiv R^5SO_2Cl, **5**, cat. DMAP, 6 equiv **9**, powdered MS 4 Å, dichloromethane, RT, 14 h; d) 1 equiv **10**, 1.5 equiv **11**, RT, 4 h; e) 2 equiv R^5NCO, **5**, powdered MS 4 Å, dioxane, 80 °C, 6 h; d) 1.5 equiv **10**, 1.5 equiv **11**, RT, 4 h. DMAP = 4-dimethylaminopyridine, CDI = *N*,*N*'-carbonyl diimidazole, MS 4 Å = molecular sieves, 4 Å.

ucts but not to a significantly higher yield. Although it was possible to apply a polymer-assisted strategy for ureas **14**, it should be pointed out, that a final purification by chromatographic methods was necessary.

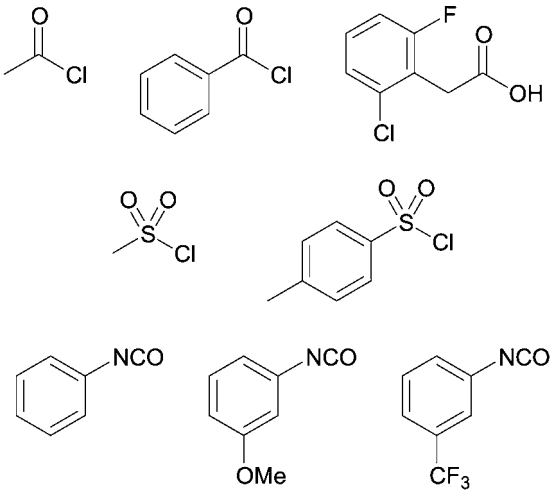


Figure 3. Building blocks for the derivatization of 1,3-thiazines **5.**

3 Conclusion

In summary, we have successfully applied a new strategy to generate combinatorial libraries of 2-amino-1,3-thiazine-5-carboxylates using selective sequestration of the desired product from a complex mixture of substances at the end of a multiple reaction step sequence. The method tolerates a wide range of building blocks as well as incomplete transformations at any stage of the sequence. Inexpensive, readily available ion-exchange resins are utilized in the polymer-assisted processes, which, together with the fact that all transformations were performed only with little excess of reagents, makes the overall strategy very economical and easy to perform. Together with our previously described solution- [6] and solid-phase [7] protocols, the current methods allow the preparation of large libraries of 1,3-thiazine products with at least 5 points of diversity and therefore may lead to the discovery of novel biologically active molecules.

4 Experimental Section

4.1 General Procedures

^{1}H-NMR spectra were recorded on a Bruker AMX 360 or AMX 500 operating at 360 MHz and 500 MHz, respective-

Table 3. Derivatization of thiazines **5** with building blocks displayed in Figure 3.

Entry	R^1	R^2	R^3	R^4	R^5	Yield [%]	Purity[a] [%]
12/1	Et	Me	Ph	H	Ph	98	90
12/2	Et	Me	Ph	Me	Me	97	>98
12/3	Et	Me	Ph	Me	Ph	98	>98
12/4	Et	Pr	styryl	Me	Me	90	88
12/5	Et	Me	2-NO_2-C_6H_4	H	Ph	91	85
12/6	Et	Me	Ph	H	2-Cl-6-F-Bn	52	86
13/1	Et	Me	Ph	H	4-Me-C_6H_4	95	98
13/2	Et	Pr	styryl	Me	Me	80	85[b]
13/3	Et	Ph	4-Me-C_6H_4	H	4-Me-C_6H_4	82	90
13/4	Me	4-F-C_6H_4	pentyl	Me	4-Me-C_6H_4	79	85
14/1	Et	Me	Ph	H	Ph	98	85
14/2	Et	Me	Ph	H	3-MeO-C_6H_4	57	82
14/3	Et	Me	Ph	H	3-CF_3-C_6H_4	45	80

[a] By LC-MS at 215 nm. [b] By ^{1}H NMR spectroscopy.

ly, in the solvents indicated. Chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane (TMS) as the internal standard. The letters s, d, t, q and m are used to indicate singlet, doublet, triplet, quadruplet and multiplet structures, respectively. Polymer-supported reactions were carried out on an Advanced Chemtech Synthesizer in Teflon frits or in appropriate 10 mL sealed glass vials. Merrifield resin (1.7 mmol g^{-1}, Cat. No. 63866, Lot&-Filling Code 390481/1 43599) and DOWEX 50X2 (4.8 mmol g^{-1}, Lot&Filling Code 428749/1 25001) were purchased from Fluka and Amberlyst A-21 (4.8 mmol g^{-1}, Lot. No. BI09308 AU) from Aldrich. Analytical HPLC analysis was performed on a Shimadzu LC-10 system, equipped with LC10-V T(AP) pumps, an autosampler (Sil-10AXL) and a dual-wavelength UV detector set at 215 and 280 nm. Analytical liquid chromatographic separations were carried out on a C18 reversed phase analytical column, LiChrospher 100 RP-18 (E. Merck, 119 × 3 mm, particle size 5 μm) at 25 °C using a mobile phase A: water/acetonitrile 90:10 (v/v) + 0.1% TFA (trifluoroacetic acid) and B: acetonitrile + 0.1% TFA (HPLC solvents were purchased from Acros with gradient grade quality; TFA was of analytical reagent grade, Aldrich) at a flow rate of 0.5 mL min^{-1}. The following gradient was applied: linear increase from solution 30% B to 100% B in 7 min, hold at 100% solution B for 2 min. Analytical LC-MS measurements were carried out on a HP 1100 Series LC/MSD System using a Zorbax Eclipse XDB-C8,150 × 4.6 mm (particle size 5 μm). Mobile phase: A: 0.1% formic acid in water, B: 0.1% formic acid in acetonitrile and C: methanol. Gradient: C constant at 4% (v/v), linear increase from 18 to 78% B in 10 min, hold at 78% B for 4 min, re-equilibration of the column at the initial settings for 6 min; flow rate: 1 mL min^{-1}; UV detection at 220 nm.

4.2 Polymer-Supported Knoevenagel Catalyst ***8***

The commercially available polymer-bound piperazine (1.1 mmol g^{-1}, Novabiochem) was modified by neutralization with excess glacial acetic acid to give the diacetate. After washing with tetrhydrofuran (THF), MeOH and dichloromethane the resin was dried and stored at room temperature (RT).

4.3 Polymer-Supported Dimethylamine ***9***

Commercially available basic ion-exchange resin Amberlyst A-21 (Aldrich, 64 mesh, loading stated as 4.7 meq mL^{-1} resin) was washed prior to use with 5% NaOH, water and methanol to remove impurities and dried afterwards. The completely dry resin was stored under anhydrous conditions at RT.

4.4 Polymer-Supported Sulfonic Acid ***10***

Commercially available ion-exchange resin DOWEX 50X2 (Fluka, 200–400 mesh, 2% DVB (1,4-divinylbenzene), loading stated as 4.8 mmol g^{-1} dry resin) was washed prior to use with 1 M hydrochloric acid, water and methanol to remove impurities and dried afterwards.

4.5 Polymer-Supported Ethylenediamine ***11***

Commercially available Merrifield resin (Fluka, 200–400 mesh, 1% DVB, 1.7 mmol g^{-1}), suspended in dioxane (7 mL g^{-1} resin), was treated with ethylenediamine (0.75 g/g resin, 7.5 equiv) and heated at 80 °C for 18 h. After cooling the resin was filtered, washed (dioxane, THF/water 1:1 + 10% triethylamine, THF, MeOH, dichloromethane, MeOH) and dried at 60 °C and 10 mbar. The scavenger resin has a loading of 1.63 mmol g^{-1} (>99% conversion as determined by weight gain). It should be noted that the title resin is commercially available from various suppliers.

4.6 Typical Procedure for the Optimization of the Knoevenagel Condensation (Outlined for Enone Leading to Compound ***5/1****)*

Benzaldehyde (110 mg, 1.04 mmol), ethyl acetoacetate (118 mg, 0.91 mmol), polymer-supported piperidine (as diacetate) (45 mg, 5 mol-%) and molecular sieves (200 mg, Aldrich, 4 Å, Cat. No. 23366-8, powder < 50 μm) were placed in a vial containing toluene (1 mL) and heated at 110 °C for 5 h under closed conditions. After cooling a sample was taken from the mixture, diluted with acetonitrile and analyzed by reversed-phase HPLC. The yield was calculated by comparison with pure enone derived from classical preparation (Knoevenagel condensation, Dean-Stark trap, and purification by distillation). All other attempts were carried out according Table 1.

4.7 *Typical Procedure for the Preparation of β-Ketoesters (Outlined for β-Ketoesters Leading to Compound* ***5/24****)*

2-Chloro-6-fluoro-phenylacetic acid (500 mg, 2.65 mmol) and *N*,*N*′-carbonyl diimidazole (CDI) (470 mg, 2.90 mmol, 1.1 equiv) were placed in dry THF (8 mL) and stirred for 3 h at RT until the liberation of carbon dioxide stopped. At the same time potassium 3-methoxy 3-oxopropanoate (460 mg, 2.95 mmol, 1.11 equiv) and anhydrous magnesium chloride (300 mg, 3.15 mmol, 1.2 equiv) in 15 mL dry acetonitrile were stirred at RT over the same period to affect transmetallation. After adding the activated acid to the slurry of magnesium malonate stirring was continued for another 14 h. Finally 0.5 M hydrochloric acid (100 mL) was added slowly and the mixture was extracted with dichloromethane (3×30 mL). The combined extracts were washed with water (60 mL) containing sodium bicarbonate (200 mg), dried over sodium sulfate and evaporated to dryness yielding 4-(2-chloro-6-fluoro-phenyl)-3-oxo-butyric acid methyl ester **1/24** (590 mg, 91%).

4.8 *Typical Procedure for the Two-Step Synthesis of 1,3-Thiazine-5-carboxylates (Outlined for Compound* ***5/10****)*

2-Nitro-benzaldehyde (75 mg, 0.50 mmol, 1.1 equiv), ethyl acetoacetate (59.3 mg, 0.455 mmol) and polymer-supported piperidine (as diacetate) (45 mg, 10 mol-%) were placed in a vial containing chlorobenzene (0.5 mL) and heated at 115 °C for 5 h under open -essel conditions. After removal of the catalyst by filtration thiourea (75 mg, 0.99 mmol, 2.2 equiv), absolute ethanol (1 mL) and 4 M HCl in dioxane (340 μL, 3 equiv) were added. Then the mixture was heated at 80 °C for 8 h under closed-vessel conditions. After cooling basic ion-exchange resin Amberlyst A-21 (0.58 g, ~6 equiv) was added and agitation was continued for 15 min. Then the basic resin was filtered off and selective capture of the desired product was initiated by addition of strongly acidic ion-exchange resin DOWEX 50X2 (160 mg, 1.5 equiv). After 15 min of shaking the resin was collected by filtration, washed (MeOH, water, MeOH, dichloromethane) and release of the product was accomplished by addition of triethylamine (500 μL) and methanol (1.5 mL). After shaking again for 20 min the cocktail was filtered and the resin washed twice with 10% triethylamine in methanol (1.5 mL). The combined filtrates were evaporated to dryness, re-dissolved in dichloromethane and filtered through a 1-cm plug of silica gel (eluent: ethyl acetate/petrol ether 3:1) yielding 63.5 mg (198 μmol, 43% over two reaction steps, based on β-ketoester as limiting component) of compound **10.**

4.9 *Spectral Data of Library Compounds* ***5*** *(for Yields and Purities, see Table 2)*

2-Amino-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/1**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.24 (t, 3H), 2.52 (s, 3H), 4.16 (q, 2H), 4.30 (b, 2H, NH), 5.35 (s, 1H), 7.19 – 7.26 (m, 5H); MS(pos. APCI) *m*/*z*: 277.3 [M + 1], (M = 276.09).

4-Methyl-2-methylamino-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/2**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.23 (t, 3H), 2.56 (s, 3H), 2.98 (s, 3H), 4.14 (q, 2H), 4.92 (b, 1H, NH), 5.31 (s, 1H), 7.20 – 7.27 (m, 5H); MS(pos. APCI) *m*/*z*: 291.3 [M + 1], (M = 290.11).

2-Diethylamino-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/3**): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (b, 6H), 1.22 (t, 3H), 2.53 (s, 3H), 3.39 (m, 2H), 3.61 (b, 2H), 4.13 (q, 2H), 5.32 (s, 1H), 7.15 – 7.23 (m, 5H); MS(pos. APCI) *m*/*z*: 333.2 [M + 1], (M = 332.16).

5-Methyl-7-phenyl-2,3-dihydro-7*H*-imidazo[2,1-b][1,3]thiazine-6-carboxylic acid ethyl ester (**5/4**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.24 (t, 3H), 2.62 (s, 3H), 3.84 – 3.94 (m, 2H), 3.95 – 4.01 (m, 2H), 4.16 (q, 2H), 5.39 (s, 1H), 7.23 – 7.27 (m, 5H); MS(pos. APCI) *m*/*z*: 303.2 [M + 1], (M = 302.11).

Amino-4-propyl-6-styryl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/5**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.99 (t, 3H), 1.32 (t, 3H), 1.65 (q, 2H), 2.79 (sextet, 2H), 4.22 (q, 2H), 4.87 (d, 1H), 6.08 (dd, 1H), 6.39 (d, 1H), 7.20 – 7.32 (m, 5H); MS(pos. APCI) *m*/*z*: 331.2 [M + 1], (M = 330.14).

2-Methylamino-4-propyl-6-styryl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/6**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.99 (t, 3H), 1.31 (t, 3H), 1.67 (q, 2H), 2.79 (sextet, 2H), 3.06 (s, 3H), 4.21 (q, 2H), 4.85 (d, 1H), 6.07 (dd, 1H), 6.37 (d, 1H), 7.20 – 7.40 (m, 5H); MS(pos. APCI) *m*/*z*: 345.2 [M + 1], (M = 344.16).

2-Diethylamino-4-propyl-6-styryl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/7**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.99 (t, 3H), 1.17 (t, 6H), 1.30 (t, 3H), 1.67 (q, 2H), 2.83 (sextet, 2H), 3.31 (q, 2H), 3.44 (q, 2H), 4.19 (q, 2H), 4.87 (d, 1H), 6.03 (dd, 1H), 6.35 (d, 1H), 7.20 (d, 1H), 7.27 – 7.35 (m, 4H); MS(pos. APCI) *m*/*z*: 387.2 [M + 1], (M = 386.20).

2-Amino-4-propyl-6-(2-trifluoromethyl-phenyl)-6*H*-[1,3]-thiazine-5-carboxylic acid ethyl ester (**5/8**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.03 (t, 3H), 1.16 (t, 3H), 1.71 (sextet, 2H), 2.88 (t, 2H), 4.08 (t, 3H), 5.35 (b, 2H, NH_2), 5.72 (s, 1H), 7.22 (d, 1H), 7.35 (t, 1H), 7.45 (t, 1H), 7.66 (d, 1H); MS(pos. APCI) *m*/*z*: 373.3 [M + 1], (M = 372.11).

2-Methylamino-4-propyl-6-(2-trifluoromethyl-phenyl)-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/9**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.03 (t, 3H), 1.15 (t, 3H), 1.75 (sextet, 2H), 2.93 (t, 2H), 3.00 (s, 3H), 4.07 (t, 3H), 4.69 (b, 1H, NH), 5.69 (s, 1H), 7.20 (d, 1H), 7.32 (t, 1H), 7.42 (t, 1H), 7.64 (d, 1H); MS(pos. APCI) *m*/*z*: 387.2 [M + 1], (M = 386.13).

2-Amino-4-methyl-6-(2-nitro-phenyl)-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/10**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.15 (t, 3H), 2.54 (s, 3H), 4.08 (q, 2H), 5.45 (b, 2H, NH), 6.05 (s, 1H), 7.24 (d, 1H), 7.41 (t, 1H), 7.52 (t, 1H), 7.98 (d, 1H); MS(pos. APCI) *m/z*: 322.3 [M + 1], (M = 321.08).

2-Benzylamino-4-methyl-6-(2-nitro-phenyl)-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/11**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.15 (t, 3H), 2.58 (s, 3H), 4.08 (q, 2H), 4.61 (d, 2H), 6.07 (s, 1H), 7.17 (m, 2H), 7.22 – 7.30 (m, 4H), 7.40 (t, 1H), 7.49 (t, 1H), 7.96 (d, 1H); MS(pos. APCI) *m/z*: 412.3 [M + 1], (M = 411.13).

2-Benzylamino-6-(2,3-dichloro-phenyl)-4-propyl-6*H*-[1,3]-thiazine-5-carboxylic acid ethyl ester (**5/12**): ^{1}H NMR (360 MHz, [D_6]acetone): δ = 0.97 (t, 3H), 1.17 (t, 3H), 1.69 (h, 2H), 2.83 – 2.98 (m, 2H), 4.07 (q, 2H), 4.88 (d, 1H), 4.83 (d, 1H), 5.74 (s, 1H), 6.95 (d, 1H), 7.23 – 7.33 (m, 6H), 7.47 (d, 1H); MS(pos. APCI) *m/z*: 463.3 [M + 1], (M = 462.09).

7-(2,3-Dichloro-phenyl)-5-propyl-2,3-dihydro-7*H*-imidazo[2,1-b][1,3]thiazine-6-carboxylic acid ethyl ester (**5/13**): ^{1}H NMR (360 MHz, [D_6]acetone): δ = 1.08 (t, 3H), 1.15 (t, 3H), 1.73 (m, 2H), 2.97 (m, 2H), 3.80 – 4.20 (m, 6H), 5.79 (s, 1H), 7.09 (d, 1H), 7.24 (t, 1H), 7.47 (d, 1H); MS(pos. APCI) *m/z*: 399.0 [M + 1], (M = 398.06).

2-Amino-6-(3-hydroxy-phenyl)-4-methyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/14**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.26 (t, 3H), 2.19 (s, 1H, OH), 2.51 (s, 3H), 4.18 (q, 2H), 5.34 (s, 1H), 6.66 (s, 1H), 6.72 (dd, 1H), 6.79 (d, 1H), 7.18 (t, 1H); MS(pos. APCI) *m/z*: 293.2 [M + 1], (M = 292.09).

6-(3-Hydroxy-phenyl)-4-methyl-2-phenylamino-6*H*-[1,3]-thiazine-5-carboxylic acid ethyl ester (**5/15**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.24 (t, 3H), 2.47 (s, 3H), 3.05 (s, 1H, OH), 4.16 (q, 2H), 5.27 (s, 1H), 5.40 (s, 1H, NH), 6.67 – 6.72 (t, 2H), 6.78 (d, 1H), 6.96 (d, 1H), 7.04 – 7.15 (m, 3H), 7.28 – 7.34 (m, 2H); MS(pos. APCI) *m/z*: 369.2 [M + 1], (M = 368.12).

7-(3-Hydroxy-phenyl)-5-methyl-2,3-dihydro-7*H*-imidazo[2,1-b][1,3]thiazine-6-carboxylic acid ethyl ester (**5/16**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.23 (t, 3H), 2.58 (s, 3H), 3.85 – 3.95 (m, 4H), 4.14 (q, 2H), 5.31 (s, 1H), 6.67 (d, 2H), 6.75 (s, 1H), 7.06 (t, 1H); MS(pos. APCI) *m/z*: 319.2 [M + 1], (M = 318.10).

2-Diethylamino-4-methyl-6-(3-nitro-phenyl)-6*H*-[1,3]thiazine-5-carboxylic acid benzyl ester (**5/17**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.09 (b, 6H), 2.56 (s, 3H), 3.42 (m, 4H), 5.15 (d, 2H), 5.41 (s, 1H), 7.25 – 7.33 (m, 5H), 7.39 (t, 1H), 7.47 (d, 1H), 8.06 (d, 1H); MS(pos. APCI) *m/z*: 440.2 [M + 1], (M = 439.16).

5-Methyl-7-(3-nitro-phenyl)-2,3-dihydro-7*H*-imidazo-[2,1-b][1,3]thiazine-6-carboxylic acid benzyl ester (**5/18**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.68 (s, 3H), 3.92 – 4.02 (m, 4H), 5.16 (s, 2H), 5.45 (s, 1H), 7.24 – 7.31 (m, 5H), 7.44 (t, 1H), 7.57 (d, 1H), 9.01 (s, 1H), 8.08 (d, 1H); MS(neg. APCI) *m/z*: 408.3 [M-1], (M = 409.11).

2-Amino-4-phenyl-6-p-tolyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/19**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.81 (t, 3H), 2.33 (s, 3H), 3.86 (q, 2H), 5.39 (s, 1H), 5.57 (b, 2H, NH), 7.12 (d, 2H), 7.21 (d, 2H), 7.36 (b, 5H); MS(pos. APCI) *m/z*: 353.2 [M + 1], (M = 352.12).

2-Amino-6-(4-chloro-phenyl)-4-methyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**5/20**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.24 (t, 3H), 2.49 (s, 3H), 4.16 (t, 2H), 5.29 (s, 1H), 5.58 (b, 2H, NH_2), 7.12 (d, 2H), 7.23 (d, 2H); MS(pos. APCI) *m/z*: 311.0 [M + 1], (M = 310.05).

6-(4-Chloro-phenyl)-4-methyl-2-methylamino-6*H*-[1,3]-thiazine-5-carboxylic acid ethyl ester (**5/21**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.23 (t, 3H), 2.55 (s, 3H), 2.99 (s, 3H), 4.15 (t, 2H), 4.75 (b, 1H, NH), 5.27 (s, 1H), 7.11 (d, 2H), 7.21 (d, 2H); MS(pos. APCI) *m/z*: 325.2 [M + 1], (M = 324.07).

2-Amino-4-(4-fluoro-phenyl)-6-pentyl-6*H*-[1,3]thiazine-5-carboxylic acid methyl ester (**5/22**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.90 (t, 3H), 1.30 (m, 4H), 1.49 – 1.71 (m, 4H), 3.51 (s, 3H), 4.14 (t, 1H), 5.48 (b, 1H, NH), 7.03 (d, 2H), 7.27 (d, 2H); MS(pos. APCI) *m/z*: 337.2 [M + 1], (M = 336.13).

4-(4-Fluoro-phenyl)-2-methylamino-6-pentyl-6*H*-[1,3]thiazine-5-carboxylic acid methyl ester (**5/23**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.90 (t, 3H), 1.30 (m, 4H), 1.49 – 1.71 (m, 4H), 3.01 (s, 3H), 3.51 (s, 3H), 4.14 (t, 1H), 5.48 (b, 1H, NH), 7.03 (d, 2H), 7.27 (d, 2H); MS(pos. APCI) *m/z*: 351.2 [M + 1], (M = 350.15).

2-Amino-4-(2-chloro-6-fluoro-benzyl)-6-(3,4-difluoro-phenyl)-6*H*-[1,3]thiazine-5-carboxylic acid methyl ester (**5/24**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 3.77 (s, 3H), 4.46 (d, 1H), 4.67 (d, 1H), 4.97 (b, 2H, NH_2), 5.32 (s, 1H), 6.95 – 7.05 (m, 4H), 7.17 (t, 2H); MS(pos. APCI) *m/z*: 427.0 [M + 1], (M = 426.04).

*4.10 Typical Procedure for N-Acylation Performed with Carboxylic Acid Chlorides (Outlined for Compound **12/1**)*

2-Amino-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester **5/1** (12.3 mg, 44.5 μmol) in 1 mL dry dichloromethane, 4-dimethylamino-pyridine (cat. amounts, ca. 5 mg), dry Amberlyst A-21 (60 mg, ~6 equiv) and molecular sieves (50 mg, Aldrich, 4 Å, Cat. No. 23366 – 8, powder < 50 μm) were placed in a flame-dried vessel and stirred for 30 min. Then benzoyl chloride (10.3 μL, 89 μmol, 2 equiv) was added and stirring continued for 14 h at RT. After that polymer-supported ethylenediamine (40 mg, 1.5 equiv) and DOWEX 50X2 (10 mg, 1 equiv) were added. Stirring was continued for another 4 h. Then the solution was filtered off and the resin washed with dichloromethane (2 × 0.5 mL) and methanol (2 × 0.5 mL). The combined fractions were evaporated to dryness, yielding 2-(*N*-benzoyl-*N*-methyl-amino)-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester **12/1** (16.5 mg, 43.4 μmol, 98%).

*4.11 Typical Procedure for N-Acylation Performed with Acyl Imidazoles (Outlined for Compound **12/6**)*

2-Chloro-6-fluoro-phenylacetic acid (19.2 mg, 101 μmol, 1.5 equiv) and *N*,*N*′-carbonyl diimidazole (15.6 mg, 96 μmol, 1.43 equiv) dissolved in acetonitrile (1 mL) were stirred at room temperature until the liberation of carbon dioxide stopped (approximately 2 h). Then 2-amino-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester **5/1** (18.7 mg, 67.7 μmol) and 4-dimethylamino-pyridine (cat. amounts) were added and stirring was continued for another 4 h at 50 °C. After that polymer-supported ethylenediamine (40 mg, 1 equiv) and DOWEX 50X2 (80 mg, 5 equiv) were added and agitation was continued for another 4 h at RT (removal of acyl imidazole residues, unreacted thiazine, DMAP and imidazole). Finally the solution was filtered off and the resin washed with dichloromethane (2 × 0.5 mL) and methanol (2 × 0.5 mL). The combined fractions were evaporated to dryness, yielding 2-[2-(2-chloro-6-fluoro-phenyl)-acetylamino]-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester **12/6** (15.7 mg, 35.2 μmol, 52%).

*4.12 Typical Procedure for N-Sulfonylation Performed with Sulfonyl Chlorides (Outlined for Compound **13/1**)*

2-Amino-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester **5/1** (12.3 mg, 44.5 μmol) in 1 mL dry dichloromethane, 4-dimethylamino-pyridine (cat. amounts), dry Amberlyst A-21 (60 mg, ~6 equiv) and molecular sieves (50 mg, Aldrich, 4 Å, Cat. No. 23366–8, powder < 50 μm) were placed in a flame-dried vessel and stirred for 30 min. Then *p*-toluenesulfonyl chloride (17 mg, 89 μmol, 2 equiv) was added and stirring continued for 14 h at RT. After that polymer-supported ethylenediamine (40 mg, 1.5 equiv) and DOWEX 50X2 (10 mg, 1 equiv) were added. Stirring was continued for another 4 h. Then the solution was filtered off and the resin washed with dichloromethane (2 × 0.5 mL) and methanol (2 × 0.5 mL). The combined fractions were evaporated to dryness, yielding 4-methyl-6-phenyl-2-(toluene-4-sulfonylamino)-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester **13/1** (18.2 mg, 42.2 μmol, 95%).

*4.13 Typical Procedure for a Reaction with Isocyanates (Outlined for Compound **14/2**)*

2-Amino-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester **5/1** (25.1 mg, 90.8 μmol) in 1 mL dry dioxane and molecular sieves (70 mg, Aldrich, 4 Å, Cat. No. 23366–8, powder < 50 μm) were placed in a flame-dried vessel and stirred for 30 min. Then 3-methoxy-phenylisocyanate (23.5 μL, 183 μmol, 2 equiv) was added and the mixture heated with stirring at 80 °C for 6 h. After that, polymer-supported ethylenediamine (85 mg, 1.5 equiv) and DOWEX 50X2 (33 mg, 1.5 equiv) were added and agitation was continued for another 4 h. Then the solution was filtered off and the resin washed with ethyl acetate (2 × 0.5 mL) and dichloromethane (2 × 0.5 mL). The combined fractions were evaporated to dryness, yielding 2-[3-(3-methoxy-phenyl)-ureido]-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester **14/2** (22.0 mg, 51.8 μmol, 57%).

*4.14 Spectral Data for Library Compounds **12–14** (for Yields and Purities, see Table 3)*

Benzoylamino-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**12/1**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.27 (t, 3H), 2.60 (s, 3H), 4.22 (q, 2H), 5.32 (s, 1H), 7.29 (m, 4H), 7.40–7.62 (m, 5H), 8.10–8.15 (t, 4H); MS(pos. APCI) *m*/*z*: 381.2 [M + 1], (M = 380.12).

2-(Acetyl-methyl-amino)-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**12/2**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.24 (t, 3H), 2.19 (s, 3H), 2.54 (s, 3H), 3.24 (s, 3H), 4.17 (q, 2H), 5.19 (s, 1H), 7.12 (dd, 2H), 7.20–7.27 (m, 3H); MS(pos. APCI) *m*/*z*: 333.3 [M + 1], (M = 332.12).

2-(Benzoyl-methyl-amino)-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**12/3**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.23 (t, 3H), 2.22 (s, 3H), 3.29 (s, 3H), 4.16 (q, 2H), 5.26 (s, 1H), 7.11 (dd, 2H), 7.24 (t, 3H), 7.35 (t, 2H), 7.43 (m, 3H); MS(pos. APCI) *m*/*z*: 395.2 [M + 1], (M = 394.14).

2-(Acetyl-methyl-amino)-4-propyl-6-styryl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**12/4**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.99 (t, 3H), 1.31 (t, 3H), 1.59 (q, 2H), 2.32 (s, 3H), 2.62 (m, 2H), 3.06 (s, 3H), 4.21 (q, 2H), 4.85 (d, 1H), 6.07 (dd, 1H), 6.35 (d, 1H), 7.24–7.38 (m, 5H); MS(pos. APCI) *m*/*z*: 387.2 [M + 1], (M = 386.17).

2-Benzoylamino-4-methyl-6-(2-nitro-phenyl)-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**12/5**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.14 (t, 3H), 2.65 (s, 3H), 4.09 (q, 2H), 6.03 (s, 1H), 7.38–7.46 (m, 5H), 7.53 (t, 1H), 7.59 (t, 1H), 8.03 (d, 1H), 8.14 (d, 2H); MS(pos. APCI) *m*/*z*: 426.2 [M + 1], (M = 425.10).

2-[2-(2-Chloro-6-fluoro-phenyl)-acetylamino]-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**12/6**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.23 (t, 3H), 2.48 (s, 3H), 3.92 (d, 1H), 3.95 (d, 1H), 4.17 (q, 2H), 5.24 (s, 1H), 6.99 (m ,1H), 7.17–7.31 (m, 7H); MS(pos. APCI) *m*/*z*: 447.3 [M + 1], (M = 446.09).

4-Methyl-6-phenyl-2-(toluene-4-sulfonylamino)-6*H*-[1,3]-thiazine-5-carboxylic acid ethyl ester (**13/1**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.24 (t, 3H), 2.40 (s, 3H), 2.51 (s, 3H), 4.19 (q, 2H), 5.27 (s, 1H), 7.11–7.26 (m, 8H), 7.68 (d, 2H), 9.50 (b, 1H, NH); MS(pos. APCI) *m*/*z*: 431.3 [M + 1], (M = 430.10).

2-(Methanesulfonyl-methyl-amino)-4-propyl-6-styryl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**13/2**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.00 (t, 3H), 1.34 (t, 3H), 1.70 (sex-

tet, 2H), 2.62 (m, 1H), 2.80 (m, 1H), 3.26 (s, 3H), 3.50 (s, 3H), 4.26 (q, 2H), 4.87 (d, 1H), 6.05 (dd, 1H), 6.35 (d, 1H), 7.27 – 7.31 (m, 5H); MS(pos. APCI) *m*/*z*: 423.3 [M + 1], (M = 423.13).

4-Phenyl-2-(toluene-4-sulfonylamino)-6-p-tolyl-6*H*-[1,3]-thiazine-5-carboxylic acid ethyl ester (**13/3**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.87 (t, 3H), 2.35 (s, 3H), 2.43 (s, 3H), 3.94 (q, 2H), 5.30 (s, 1H), 7.10 (d, 2H), 7.21 – 7.27 (m, 5H), 7.34 – 7.48 (m, 4H), 7.67 (s, 1H), 7.77 (t, 2H); MS(pos. APCI) *m*/*z*: 507.2 [M + 1], (M = 506.13).

4-(4-Fluoro-phenyl)-2-[methyl-(toluene-4-sulfonyl)-amino]-6-pentyl-6*H*-[1,3]thiazine-5-carboxylic acid methyl ester (**13/4**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.89 (t, 3H), 1.30 (m, 4H), 1.50 – 1.73 (m, 4H), 2.45 (s, 3H), 3.06 (s, 3H), 3.51 (s, 3H), 4.10 (t, 1H), 7.03 (t, 2H), 7.27 (d, 2H), 7.36 (m, 4H), 7.70 (t, 2H); MS(pos. APCI) *m*/*z*: 505.2 [M + 1], (M = 504.16).

4-Methyl-6-phenyl-2-(3-phenyl-ureido)-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**14/1**): ^{1}H NMR (360 MHz, [D_6]DMSO): δ = 1.15 (t, 3H), 2.50 (s, 3H), 4.08 (q, 2H), 5.32 (s, 1H), 6.97 (t, 1H), 7.22 – 7.32 (m, 7H), 7.45 (d, 1H), 7.54 (d, 1H), 9.49 (s, 1H), 10.75 (s, 1H); MS(pos. APCI) *m*/*z*: 396.3 [M + 1], (M = 395.13).

2-[3-(3-Methoxy-phenyl)-ureido]-4-methyl-6-phenyl-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**14/2**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.25 (t, 3H), 2.54 (s, 3H), 3.79 (s, 3H), 4.20 (q, 2H), 5.31 (s, 1H), 6.63 (dd, 1H), 6.95 (d, 1H), 7.15 – 7.28 (m, 7H); MS(pos. APCI) *m*/*z*: 426.2 [M + 1], (M = 425.14).

4-Methyl-6-phenyl-2-[3-(3-trifluoromethyl-phenyl)-ureido]-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**14/3**): ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.25 (t, 3H), 2.49 (s, 3H), 3.70 (s, 3H), 4.18 (q, 2H), 5.33 (s, 1H), 7.18 – 7.41 (m, 6H), 7.52 (d, 1H), 7.60 (s, 1H), 7.86 (s, 1H); MS(pos. APCI) *m*/*z*: 464.2 [M + 1], (M = 463.12).

Acknowledgement

We are gratefully indebted to BASF AG, Ludwigshafen, Germany, and the Austrian Science Fund (FWF, P-15582) for financial support.

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