# Synthesis of Functionalized 1,3-Thiazine Libraries Combining Solid-Phase Synthesis and Post-Cleavage Modification Methods

**Gernot A. Strohmeier,[a] Willibald Haas,[a, b] and C. Oliver Kappe*[a]**

**Abstract:** The solid-phase synthesis of diverse sets of 1,3-thiazine-5-carboxylates on Wang resin is described. Acetoacetylation, followed by Knoevenagel condensation and an acid-promoted ring-closure reaction with thioureas furnished polymer-bound 1,3-thiazines. As an alternative to transesterification, a de-novo synthesis of β-keto esters, starting from polymer-bound malonic acid through reaction with acyl imidazoles, was applied to increase the diversity. To reduce contamination, an on-bead purification of resin-bound 1,3-thiazines that makes use of differences in the reactivity of ester bonds toward alkoxides is reported. A final four-step post-cleavage modification of thiazine-5-carboxylates, derived by TFA cleavage from the Wang linker, leads to esters or amides. Twenty 1,3-thiazines were obtained in yields of up to 61% over either 9 or 13 steps.

**Keywords:** combinatorial chemistry · heterocycles · solid-phase synthesis · synthetic methods · thiazines

## Introduction

Organic chemistry has extended itself over the last decade by an important facet, as indicated by the massive increase of publications describing applications of polymeric supports in synthesis .[1] This vivid demonstration of its impact on the chemical community is highlighted by the fact that only few other changes in synthetic methodology have shown such growing passion or had such a significant influence on the way synthetic chemistry is performed today. The advantages associated with this methodology are mainly devoted to four factors.

1) The ease of synthetic manipulation by having only three main steps: addition of reagents, filtering, and washing the resin. This allows for automation.
2) The omission of purification, except for a washing step after each manipulation. Only the final product after cleavage requires purification.
3) Large excess of reagents can be used to drive reactions to completion.
4) As a result of this straightforward concept, reactions are easy to run in parallel mode.

In order to make full use of these benefits, some issues have to be addressed, including the choice of solid support and the mode of attachment and cleavage of molecules from the resin.[2] It is evident that the selection of the linker system has great impact on the chemistry being performed and, therefore, must be carefully considered when planning a synthetic strategy. The more flexible an anchor system is, the more goals can be attained; that is, to produce several defined products upon release, or to affect partial release for monitoring reactions and for use in deconvolution methods. Apart from the diverse applications of linkers, they are often just connections between molecules and the polymeric supports during the course of synthesis. In continuation of our interest in the solid-phase organic synthesis of *N*-heterocycles,[3] we report herein a strategy for the preparation of 1,3-thiazine libraries (Scheme 1).

The particular scaffolds described here are 2-amino-1,3-thiazine-5-carboxylates **12**, which possess close structural similarity to privileged structures[4] of the dihydropyrimidone (DHPM) type.[5] In contrast to this last class of heterocycles,[5] 2-amino-1,3-thiazine-5-carboxylates of type **12** have hitherto rarely been described in the literature. Furthermore, there appears to be very little published information on both synthetic methods and biological-activity data.[6] In addition to our recently developed solution-phase strategy toward this promising heterocyclic system,[7] we present a solid-phase approach that allows for the synthesis of highly diverse libraries of thiazines **12** (Scheme 1) by addressing all

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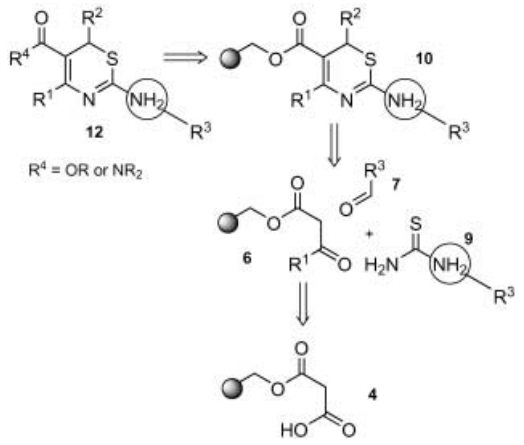


Scheme 1. Synthetic strategy towards 1,3-thiazine-5-carboxylates: a combined solid-phase process and subsequent post-cleavage modification.

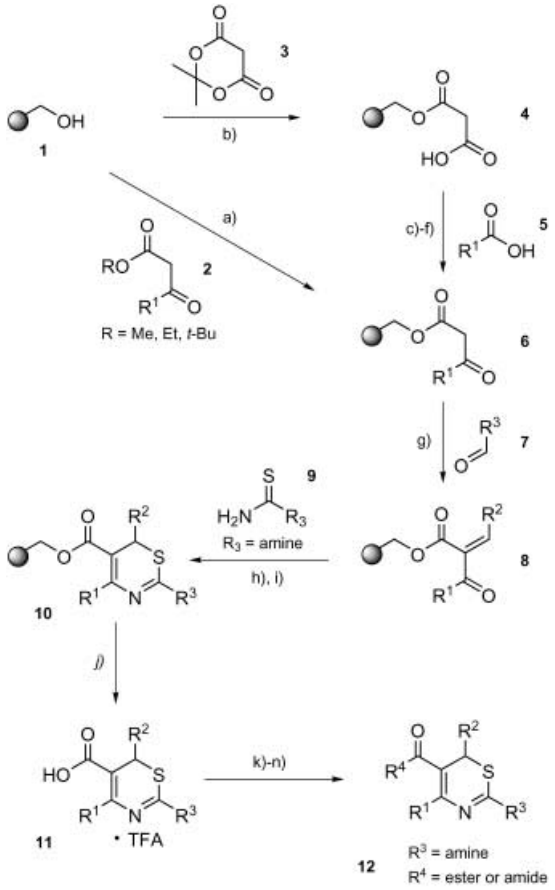
four possible diversity points ($R^1$–$R^4$) around the heterocyclic core.

## Results and Discussion

**Strategy development**: It appeared to us that the ester functionality in the 5-position of thiazines **10** would serve as an excellent anchor position to devise a solid-phase synthesis strategy. This would initially require the attachment of a β-keto ester to the solid support (**1**→**6**) (Scheme 2).[8–11] Subsequently, a Knoevenagel condensation with aldehydes **7** would furnish polymer-bound enones of type **8**,[9,11–13] which could be cyclized to thiazines **10** by means of acid-catalyzed ring closure with thiourea building blocks **9**, in accordance with our solution-phase studies.[7] For both the β-keto ester attachment (**1**→**6**) and the subsequent Knoevenagel condensation (**6**→**8**), we have recently reported efficient protocols employing microwave-assisted solid-phase synthesis.[11] In order to address the 4-position of thiazines **10** by a diversity-generating concept, we envisioned carrying out a β-keto ester synthesis on the solid phase using activated carboxylic acids to acylate polymer-bound malonic acid **4**. In the final step, the polymer-bound products should be released from the support and transformed to carboxylic esters or amides of thiazines **12**. Altogether, the high flexibility embedded in the concept should lead to multifunctionalized thiazines **12** as promising screening candidates.[14]

**Reaction optimization**: The sequence began with the attachment of a β-keto ester moiety to the standard polystyrene Wang resin **1** (1.0 mmol $g^{-1}$) by transesterification of a suitable precursor (**1**+**2**→**6**, Scheme 2). This process requires high temperatures (140 °C) in order to obtain complete conversion in a short time frame. Although reactive *tert*-butyl esters allowed for significantly faster conversions, the reaction conditions were adjusted so that any β-keto ester **2** (mainly ethyl or methyl esters) would undergo complete coupling to the resin (140 °C, 90 min).[11,15]

The limited access to diverse γ-substituted β-keto esters from commercial sources additionally prompted us to develop a de-novo solid-phase synthesis of the β-keto building block. Though there was no precedent in the literature, it required only few optimization experiments to develop a successful protocol. The first step consisted of the attachment of malonic acid to Wang resin **1** by using Meldrum's acid **3** at 60 °C in THF under an argon atmosphere.[13] Higher temperatures gave rise to side reactions that led to undesirable polymer-bound byproducts. Having obtained the resin-bound malonic acid **4**, we continued with neutralization of the acid and subsequent formation of the intermediate magnesium salt by simple treatment with excess $MgCl_2$. Following the solution protocol from Masamune and co-workers,[16] carboxylic acids **5** were activated as imidazoles by using *N*,*N*′-carbonyl diimidazole (CDI) and then added to the polymer-bound magnesium malonate.[17] After agitation for 18 h and subsequent work up with diluted hydrochloric acid



Scheme 2. Solid-phase synthesis of thiazines **12**. a) 5 equiv **2**, cat. DMAP, dichlorobenzene, 140 °C, 90 min, open-vessel conditions; b) 4 equiv **3**, dry THF, argon, 60 °C, 18 h; c) 2 equiv TEA, THF, RT, 15 min; d) 5 equiv $MgCl_2$, DMF/THF 1:1, RT, 2 h; e) 4 equiv **5**, 4 equiv CDI, DMF, RT, 2 h, then add to resin, RT, 18 h; f) 0.5 M HCl/DMF 1:2, RT, 10 min; g) 5 equiv **7**, 30 mol% piperidinium acetate, dichlorobenzene/chlorobenzene 1:1, 115 °C, 3 h; h) 5 equiv **9**, 2 equiv 0.75 M HCl in EtOH (3 equiv for basic aldehydes), THF/EtOH 2:1, 65 °C, 18 h; i) 30 mol% KOH, THF/MeOH 4:1, 55 °C, 6 h, then 5% AcOH in THF/water 1:1; j) TFA/dichloromethane 1:2, RT, 1 h; k) 2 equiv TFAA, DCM, RT, 1 h; l) 1.5 equiv $(COCl)_2$, dichloromethane/THF 1:1, cat. DMF, RT, 2 h; m) 2 equiv appropriate alcohol or amine, 1.5 equiv pyridine, RT, 5 h; n) conc. $NH_3$/MeOH 1:1, RT, 3 h. DMAP = 4-dimethylaminopyridine, TEA = triethylamine, CDI = *N*,*N*′-carbonyl diimidazole, TFAA = trifluoroacetic acid anhydride.

in DMF, the corresponding resin-bound β-keto esters **6** were obtained (conversion >95% as judged by weight gain, on-bead FT-IR spectroscopy and analysis of cleaved products).

At the stage at which the polymer-bound β-keto esters **6** were obtained, the synthesis continued with a standard Knoevenagel condensation with aldehydes **7**, catalyzed by piperidinium acetate.[11] The application of open-vessel conditions and a suitable mixture of solvents (dichlorobenzene/chlorobenzene 1:1) in the Knoevenagel condensation step enabled us to run the reactions at high temperature to ensure short reaction times and, moreover, to avoid the use of water-trapping agents such as trimethylorthoformate (TMOF).[11] In contrast to most of the steps before, the ring-closure reaction (**8**→**10**) required significantly more effort to transfer from solution to solid-phase conditions. After challenging optimization experiments we discovered that the reaction is best performed in a mixture of THF (to allow for the swelling of the resin) and absolute ethanol, the best solvent under conventional solution conditions.[18] Similar to standard solution protocols, hydrochloric acid was found to be the best catalyst for the ring-closure reaction on the solid support. It has to be noted that the acid-labile Wang linker survived the procedure without any undesired cleavage of product. Higher reaction temperatures than the reported 65°C, or other acids, for example, methane sulfonic acid, produced inferior results and jeopardized the success of the cyclization step. On-bead FT-IR monitoring and analysis of the cleaved thiazine acids **11** revealed that the conversion to thiazines reached (more or less) completion for most of the building blocks tested. However, to improve the quality of thiazines **10** bound to the polymer, we developed an on-bead purification method to eliminate unconverted intermediates from the support before entering the cleavage step.[10] After some experimentation we found that enones **8** or β-keto esters **6** were by far more susceptible to transesterification under these conditions (30 mol% KOH in THF/MeOH 4:1) than thiazines **10**. Having purified the products **10** on-bead, subsequent cleavage under standard conditions (TFA in dichloromethane) afforded thiazine acids **11** as trifluoroacetates. In order to increase the diversity of the final library compounds, we decided to apply a post-cleavage modification of the acid functionality in **11** to yield carboxylic esters or amides **12**. At first this strategy appeared to be rather complicated, but after all attempts to apply nucleophile-cleavable linkers instead of the Wang resin had failed (i.e., **10**+nucleophile→**12**),[19] it remained the only possibility to access C5-functionalized thiazines **12**. The key issue on the route towards the most suitable procedure for derivatization of amino acids **11** was to find an activation method for the carboxylate that was mild enough to avoid decomposition of the presumably sensitive intermediates and, on the other hand, offered high reactivity towards various nucleophiles. A prerequisite for the activation step was to protect the primary or secondary amino functionalities (2-position, $R^3$) of thiazines **11**. This problem was solved by acylation with trifluoroacetic acid anhydride (TFAA). After some experimentation it was demonstrated that oxalyl chloride was the best reagent to activate the carboxylic acid function of thiazines **11**. Following an evaporation step, treatment of the crude acid chloride with the desired nucleophile (alcohol or amine) in the presence of dry pyridine, cleavage of the trifluoroacetamide protection (if necessary) with aqueous ammonia, and final chromatographic purification provided thiazines **12**.

**Library synthesis and diversity**: The solid-phase strategy described above was used to prepare a set of 20 thiazines with diversity at all four conceivable positions ($R^1$–$R^4$). This data set should enable the discovery of general trends of substituent effects on the efficiency of the method; this, in turn, should aid in the prediction of the accessibility of other derivatives. Yields were typically in the range of 30–60% for the 9 (or 13) step synthesis, with very few exceptions for which the yields were below 30% (Table 1). In contrast to the solution-phase strategy that employed polymer-bound sulfonic acid,[7] even aldehydes **7** bearing electron-withdrawing substituents (-$CF_3$, -$NO_2$) in the 2-position of the aromatic system reacted smoothly. These results clearly demonstrate the advantages of solid-phase synthesis, that is, the use of large excesses of reagents to drive reactions to completion. Unlike with our solution-phase approach,[7] inherently basic building blocks were also compatible with the

Table 1. Solid-phase synthesis of 1,3-thiazines **12**.

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield [%][a] | Purity [%][b] |
|---|---|---|---|---|---|---|
| **12a** | Me | styryl | $NH_2$ | EtO | 15 | 80 |
| **12b** | Me | 2-Cl-Ph | $NH_2$ | EtO | 24 | >98 |
| **12c** | Me | 2-Cl-Ph | piperidine | *n*-PrO | 44 | 85 |
| **12d** | Me | 2-$CF_3$-Ph | $NH_2$ | EtO | 31 | 89 |
| **12e** | Me | 2-$CF_3$-Ph | $NH_2$ | $C_6H_{12}NH$ | 37 | 95 |
| **12f** | Me | 2-$NO_2$-Ph | $NH_2$ | EtO | 33 | 86 |
| **12g** | Et | $C_5H_{11}$ | NHPh | $C_6H_{12}O$ | 7 | 95 |
| **12h** | *n*-Pr | 3-Cl-Ph | 2,4,6-Me-Ph-NH | *i*-PrO | 36 | >98 |
| **12i** | Me | 3-pyridyl | $NH_2$ | EtO | 32 | 95 |
| **12j** | Me | 3,4-F-Ph | $NH_2$ | *n*-PrO | 26 | 90 |
| **12k** | Me | 3,4-F-Ph | $NH_2$ | *i*-PrO | 27 | 88 |
| **12l** | Me | 4-Me-Ph | $NH_2$ | *n*-BuO | 44 | 95 |
| **12m** | Et | 4-Me-Ph | $NH_2$ | (2-EtO)-EtO | 10 | 98 |
| **12n** | Me | 4-Me-Ph | $NH_2$ | 3-Me-BuO | 61 | 97 |
| **12o** | Ph | 4-Me-Ph | $NH_2$ | *n*-BuO | 30 | 95 |
| **12p** | Me | 4-$NMe_2$-Ph | $NH_2$ | EtO | 52 | 80 |
| **12q**[c] | $C_6H_{11}$-$CH_2$ | 2-Cl-Ph | $NH_2$ | 3-Me-BuO | 48 | >98 |
| **12r**[c] | 4-CN-Ph | 3-Me-Ph | $NH_2$ | *n*-BuO | 26 | 90 |
| **12s**[c] | 3-$NO_2$-Ph | 4-Me-Ph | $NH_2$ | *i*-PrO | 10 | 75 |
| **12t**[c] | 2-Cl-6-F-Bn | 4-Me-Ph | $NH_2$ | MeO | 30 | 85 |

[a] Overall yield over 9 (entries **12a**–**12p**) or 13 steps (entries **12q**–**12t**) based on initial loading of resin **1**. [b] By LC-MS at 215 nm. [c] By means of de-novo β-keto ester synthesis on solid-phase (steps b–f).

solid-phase strategy, as demonstrated by the use of basic aldehydes **7** (entries **12i** and **12p**). The de-novo synthesis of β-keto esters on solid phases fitted perfectly into the sequence. Although this additional feature enlarged the strategy by four steps, the yields of final thiazine products **12** were comparable. Especially for **12q** ($R^1$ = cyclohexyl) we observed excellent yields and purities, which indicated again that γ-alkyl-substituted β-keto esters serve as excellent building blocks for the assembly of thiazines **12**.

The solid-phase sequence up to the polymer-bound enones **8** was close to ideal for all investigated cases, as confirmed by on-bead FT-IR spectroscopy (see below). One of the main reasons for lower yields obtained at the end was associated with the ring-closure reaction (**8**→**10**). Enones **8** possessing an aromatic substituent as $R^1$ usually failed to give complete conversion, thus making an on-bead purification method essential for the crude resin-bound thiazines **10**. Furthermore, at this stage of the synthesis, thiazines **10** existed as salts (hydrochlorides). This may have had negative effects on the swelling of the resin and therefore affected the diffusion of reagents through the beads. A second reason for the occurrence of lower yields was that undesired decarboxylation of thiazine acids **11** took place at the stage of cleavage and post-cleavage modification. It should be emphasized, however, that this last effect was not general and could not be used to develop a reliable traceless cleavage protocol.

**Reaction monitoring and on-bead purification**: Polymer-bound acetoacetates **6** typically display two characteristic vibrational bands at 1720 and 1743 $cm^{-1}$. After performing the Knoevenagel condensation, only one of these centered vibrational band at 1723 $cm^{-1}$ remains (additional bands at 1700 and 1670 $cm^{-1}$).[11] Thiazines **10** usually exhibit carbonyl bands with weaker intensity relative to acetoacetate and enone (1702 $cm^{-1}$), and a very strong characteristic band at 1544 $cm^{-1}$. Wang resin bands are at 1612, 1602, 1514, 1493 and 1452 $cm^{-1}$ (Figure 1).

Ring-closure reactions on the solid-support proceeded smoothly with enones **8** with a simple alkyl substituent in the 4-position ($R^1$ = Me); this resulted in complete conversion after only 2–6 h at 70 °C (Scheme 3). To ensure full conversion of the thiazine formation during library production with any combination of building blocks, the reaction time was set to 18 h at a temperature of 65 °C. In the case of a phenyl substituent, instead of a methyl substituent at the crucial $R^1$ position, reactions were sluggish and did not reach completion even after 120 h at 80 °C (Figure 2).

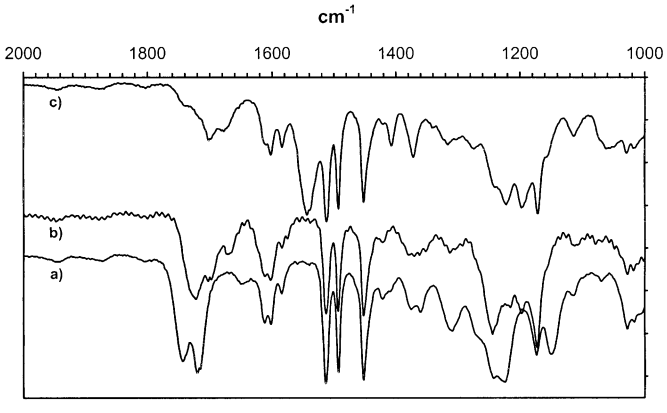
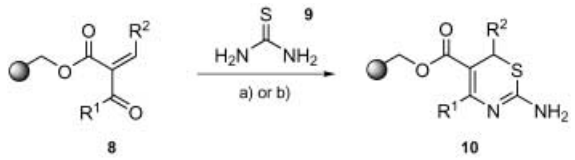



Figure 1. FT-IR analysis of different stages of thiazine synthesis leading to **12/12**. a) Acetoacetylation with ethyl acetoacetate; b) Knoevenagel condensation with p-tolylaldehyde; c) ring-closure reaction with thiourea.




Scheme 3. Kinetic investigations of the ring closure reaction: 5 equiv thiourea **9**, 2 equiv HCl in THF/EtOH 2:1, 200 mg resin per 3 mL solvent, a) 70 °C, b) 80 °C.

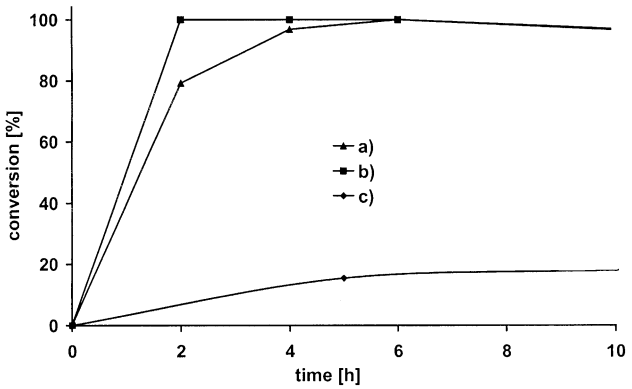
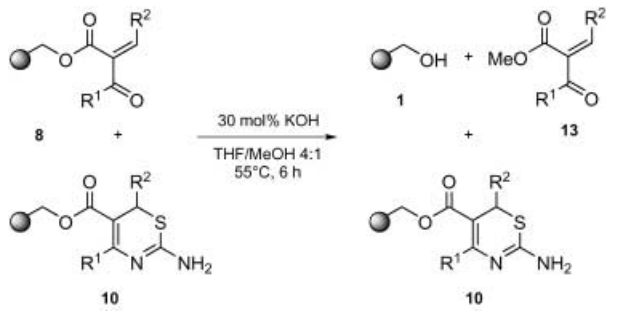



Figure 2. Kinetics of ring-closure reactions on Wang resin (1.0 mmol $g^{-1}$, 1% DVB) in a solvent mixture of THF/ethanol 2:1 and various combinations of building blocks. a) Method A, $R^1$ = Me, $R^2$ = 4-Me-Ph, 70 °C; b) method A, $R^1$ = Me, $R^2$ = 3,4-F-Ph, 70 °C; c) method B, $R^1$ = Ph, $R^2$ = 4-Me-Ph, 80 °C; data points not shown in the figure: *t*[h](conversion[%]): 10.5 h (18%), 23 (25), 48 (31), 120 (35).

Since the ring-closure reaction of enones **8**, bearing aromatic substituents in α-position ($R^1$), to give thiazines **10** was very difficult to achieve, and it was assumed that incomplete conversion occurred (Figure 2 and Scheme 3), we aimed at an on-bead purification method to eliminate unconverted intermediates from the support before entering the cleavage step.[10] The main goal was to take advantage of the significantly different susceptibilities of thiazines **10** and enones **8** toward nucleophilic attack by alkoxides. In contrast to thiazine ester bonds, enones were considerably more prone to undergo either base-catalyzed transesterification or another stepwise degradation, for example, retro-Knoevenagel condensation and β-keto ester cleavage, thus resulting in selective cleavage from the support (Scheme 4). After a few optimization experiments, it turned out that 30 mol% potassium hydroxide in a mixture of THF/MeOH (4:1) at 55 °C was the superior cocktail to affect the purification. As long as no drastic conditions (higher temperatures, >2 equiv of strong base) were applied, thiazines **10** remained on the solid phase without any detectable decomposition. Figure 3 shows two selected examples that verify the effect of on-bead purification. Example A ($R^1$ = Me) displays a situation




Scheme 4. On-bead purification of thiazines **10**.

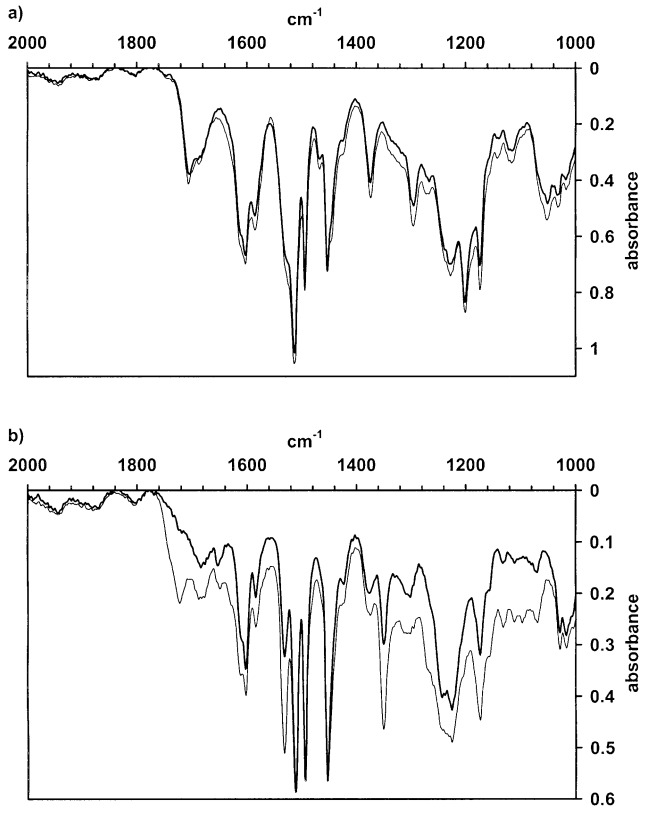



Figure 3. FT-IR monitoring of the on-bead purification. a) $R^1$ = Me, $R^2$ = 4-Me-Ph; b) $R^1$ = Ph, $R^2$ = 3-$NO_2$-Ph. Thin line: before on-bead purification; thick line: after on-bead purification.

of almost complete ring-closure reaction and, therefore, only a small change after removal of the impurities. In contrast, example B ($R^1$ = Ph)—a troublesome case—revealed efficient cleavage of unconverted enone from the resin, thus furnishing pure thiazine on the solid support. On-bead purification simplified the workup at the end of the synthesis. Another important advantage is that application of the on-bead purification could be used to minimize the interference of impurities in on-bead-screening assays.

## Conclusion

In summary, we have developed a solid-phase synthesis strategy for the generation of combinatorial libraries of 2-amino-1,3-thiazine-5-carboxylates supplementing our recently described solution-phase studies. The method addresses all positions on the thiazine scaffold in order to generate maximum diversity. Most notably, we have performed a de-novo synthesis of β-keto esters on a solid support to overcome the restrictions associated with limited substitution patterns of commercially available building blocks. Final post-cleavage derivatization gives rise to esters and amides of thiazines. The solid-phase synthesis is conducted on standard Wang resin, which makes the concept economic and therefore competitive with solution-phase protocols. In contrast to polymer-assisted solution methods, this concept tolerates basic building blocks without the need for major changes.

## Experimental Section

**General**: $^1$H NMR spectra were recorded on a Bruker AMX 360 at 360 MHz in the solvents indicated. Chemical shifts ($\delta$) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. On-bead FTIR spectra were recorded on a Unicam Galaxy Series FTIR 7000 (Mattson Instruments Inc.) using ground resin beads in KBr pellets.[11] Polymer-supported reactions were carried out on an Advanced Chemtech Synthesizer PL4×6 in Teflon frits or in appropriate 10 mL sealed glass vials. 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 and B: acetonitrile + 0.1 % TFA (HPLC solvents of gradient grade quality were purchased from Acros; 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 30 % solution 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.

**Materials**: Wang resin (1.0 mmol g$^{-1}$, Lot and Filling Code 408655/1 64900) was purchased from Fluka. All reactions were performed without a protective gas atmosphere. All solvents were distilled using standard procedures. Commercial reagents were used without further purification.

**General procedure for the synthesis of compounds 11 and 12**: Synthesis of compound **11d** (outlined for the main route leading to compound **12d**). Wang resin **1** (200 mg, 1.0 mmol g$^{-1}$, 200–400 mesh, Fluka) was placed in an Advanced Chemtech Synthesizer PL4×6 frit, swollen in dichlorobenzene (2 mL) and subsequently heated to 140 °C for 1.5 h (open conditions) in the presence of catalytic amounts of DMAP and *tert*-butyl acetoacetate (160 mg, 1.0 mmol, 5 equiv). After cooling, the resin was rinsed several times with toluene, THF, and MeOH. Knoevenagel condensation was initiated by heating the acetoacetylated resin, swollen in dichlorobenzene/chlorobenzene 1:1 (2 mL), with piperidinium acetate (9 mg, 0.06 mmol, 0.3 equiv) and 2-trifluoromethyl-benzaldehyde (170 mg, 1.0 mmol, 5 equiv) at 115 °C for 3 h (open conditions). Subsequent washing was performed with toluene, THF, MeOH, and again with THF. The ring closure was conducted under closed conditions using thiourea (76 mg, 1.0 mmol, 5 equiv) and a mixture of 0.75 M HCl in absolute EtOH (0.53 mL, 0.4 mmol, 2 equiv), absolute EtOH (0.5 mL), and THF (2 mL) at 65 °C over 18 h. The resin was subsequently filtered and washed with 10 % triethylamin in DMF (2×), followed by DMF (2×), MeOH (2×), THF (2×), and MeOH (2×). Subsequently, 78 mM KOH in

methanol (0.75 mL, 0.06 mmol, 0.3 equiv) and THF (3 mL) were added, and the mixture was shaken for a period of 6 h at 55 °C. The resin was then filtered and washed with 5% acetic acid in THF/water 1:1 (2×), THF (2×), MeOH (2×), and finally dichloromethane (2×). Cleavage was conducted affected by adding dichloromethane (1.3 mL) and TFA (0.7 mL) at room temperature for a period of 60 min. Finally the cleavage cocktail was filtered off, the resin washed with 5% TFA in dichloromethane (2×2 mL), and the combined filtrates evaporated to dryness.

**General procedure for post-cleavage modification (outlined for the main route leading to compound 12d)**: Dry dichloromethane (2 mL) and trifluoroacetic anhydride (60 μL, 0.4 mmol, 2 equiv relative to amount of resin used for the synthesis) was added to crude thiazine acid **11d**. After stirring at RT for 1 h the mixture was evaporated to dryness. The residue was then dissolved in THF (1 mL) containing DMF (catalytic amounts), treated with 0.38 M oxalyl chloride in dichloromethane (0.8 mL, 0.3 mmol, 1.5 equiv), and stirred for 2 h at RT. Following evaporation to dryness, the thiazine acid chloride was dissolved in dry THF (2 mL). Pyridine (24 μL, 0.3 mmol, 1.5 equiv) and ethanol (24 μL, 0.4 mmol, 2 equiv) were added to this solution. After 4 h at RT and subsequent evaporation, concentrated aqueous ammonia (1 mL) and methanol (1 mL) were added. After 3 h the solution was evaporated to dryness and the residue purified by flash chromatography on silica gel (eluent: mixtures of ethyl acetate and petroleum ether) yielding 2-amino-4-methyl-6-(2-trifluoromethylphenyl)-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester **12d** (21.6 mg, 31% rel. to original resin loading).

**General procedure for the synthesis of β-keto esters on the solid phase as alternative to transacetoacetylation (outlined for the route leading to compound 12q)**: Malonic acid resin: Wang resin **1** (1.0785 g, 1.0 mmol g$^{-1}$, 200–400 mesh, Fluka) and Meldrum's acid **3** (620 mg, 4.3 mmol, 4 equiv) in dry THF (15 mL) were stirred at 60 °C (exactly!) under argon for 18 h. Finally the resin was filtered, washed with THF, MeOH, THF, MeOH, and dichloromethane, and dried to give malonic acid Wang resin **4** (1.1939 g, >98%). β-Keto ester synthesis: Malonic acid Wang resin **4** (250 mg, 230 μmol) was treated with triethylamine (65 μL, 0.46 mmol, 2 equiv) in THF (3 mL) for 15 min and then washed with THF (3×). Subsequently, dry $MgCl_2$ (110 mg, 5 equiv) and a mixture of DMF/THF 1:1 (2 mL) were added to the neutralized resin, and the mxture was shaken for 2 h. Parallel to this process cyclohexylacetic acid (135 mg, 0.95 mmol, 4 equiv) was activated by the use of *N*,*N*′-carbonyl diimidazole (150 mg, 0.95 mmol, 4 equiv) in DMF (1 mL) over 2 h. Finally, the activated carboxylic acid was added to the mixture containing the resin and shaking was continued for another 18 h at RT. At the end the resin was filtered and treated with 0.5 M HCl/DMF 1:2 (3 mL) over 10 min at RT. Following filtering and washing (2× each of DMF, MeOH, THF, MeOH, dichloromethane), the thiazine synthesis was conducted as described above.

**Kinetics of the ring-closure reaction 8→10**: The appropriate enone resin **8** (200 μmol), thiourea **9** (80 mg, 0.95 mmol, 5 equiv) and a mixture of 0.75 M HCl in absolute EtOH (0.53 mL, 2 equiv), absolute EtOH (0.5 mL), and THF (2 mL) were heated to 70 °C (80 °C for $R^1$=Ph) in a closed vessel under gentle stirring. Resin samples were taken from the mixture, washed with 10% triethylamine in DMF (2×), DMF (2×), MeOH (2×), THF (2×), and MeOH (2×), dried, and analyzed by FT-IR (comparison of bands of enone at 1725 cm$^{-1}$, thiazine at 1700 cm$^{-1}$ and 1544 cm$^{-1}$ as well as Wang resin at 1452 cm$^{-1}$.[11]

**General procedure for on-bead purification**: 78 mM KOH in methanol (0.22 g KOH dissolved in 50 mL methanol, 0.75 mL, 0.3 equiv) and THF (3 mL) were added to polymer-bound thiazine on Wang resin **10** (derived from 200 mg Wang resin **1**), and the mixture was shaken for 6 h at 55 °C. The resin was then filtered and washed with 5% acetic acid in THF/water 1:1 (2×), THF (2×), MeOH (2×), and finally dichloromethane (2×).

**Library compounds (NMR and MS data, for yields and purities, see Table 1)**

**Ethyl ester of 2-amino-4-methyl-6-styryl-6*H*-[1,3]thiazine-5-carboxylic acid (12a)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=1.27 (t, 3H), 2.47 (s, 3H), 4.23 (q, 2H), 4.90 (d, 1H), 6.07 (dd, 1H), 6.42 (dd, 1H), 7.20–7.35 ppm (m, 5H); MS (pos. APCI): *m*/*z*: 303.2 [*M*+1] (*M*=302.11).

**Ethyl ester of 2-amino-6-(2-chlorophenyl)-4-methyl-6*H*-[1,3]thiazine-5-carboxylic acid (12b)**: $^1$H NMR (360 MHz, [$D_6$]acetone): $\delta$=1.15 (t, 3H), 2.47 (s, 3H), 2.85 (br, 2H, $NH_2$), 4.05 (q, 2H), 5.70 (s, 1H), 7.03 (dd, 1H), 7.25 (m, 2H), 7.44 ppm (dd, 1H); MS (pos. APCI): *m*/*z*: 311.2 [*M*+1]$^+$ (*M*=310.05).

**Propyl ester of 6-(2-chlorophenyl)-2-cyclohexylamino-4-methyl-6*H*-[1,3]thiazine-5-carboxylic acid (12c)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=0.80 (t, 3H), 1.43 (s, 6H), 1.56 (sextet, 2H), 1.60–1.66 (m, 4H), 2.27 (s, 1H), 2.57 (s, 3H), 3.99 (t, 2H), 4.60 (br, 1H, NH), 5.71 (s, 1H), 6.99 (d, 1H), 7.14 (m, 2H), 7.34 ppm (d, 1H); MS (neg. APCI): *m*/*z* 405.2 [*M*−1]$^+$ (*M*=406.15).

**Ethyl ester of 2-amino-4-methyl-6-(2-trifluoromethylphenyl)-6*H*-[1,3]thiazine-5-carboxylic acid (12d)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=1.03 (t, 3H), 2.43 (s, 3H), 3.95 (q, 2H), 5.51 (s, 1H), 7.15 (d, 1H), 7.45 (t, 1H), 7.60 (t, 1H), 7.71 ppm (d, 1H); MS (neg. APCI): *m*/*z*: 343.2 [*M*−1]$^+$ (*M*=344.08).

**Cyclohexylamide of 2-amino-4-methyl-6-(2-trifluoromethylphenyl)-6*H*-[1,3]thiazine-5-carboxylic acid (12e)**: $^1$H NMR (360 MHz, [$D_6$]DMSO): $\delta$=1.00–1.23 (m, 6H), 1.45–1.58 (m, 4H), 2.13 (s, 3H), 3.45 (m, 1H), 5.23 (s, 1H), 7.31 (d, 1H), 7.47 (t, 1H), 7.65 (t, 1H), 8.03 ppm (d, 1H); MS (pos. APCI): *m*/*z*: 373.3 [*M*+1]$^+$ (*M*=372.11).

**Ethyl ester of 2-amino-4-methyl-6-(2-nitrophenyl)-6*H*-[1,3]thiazine-5-carboxylic acid (12f)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=1.15 (t, 3H), 2.54 (s, 3H), 4.08 (q, 2H), 5.45 (br, 2H, NH), 6.05 (s, 1H), 7.24 (d, 1H), 7.41 (t, 1H), 7.52 (t, 1H), 7.98 ppm (d, 1H); MS (pos. APCI): *m*/*z*: 322.3 [*M*+1]$^+$ (*M*=321.08).

**Cyclohexyl ester of 4-ethyl-6-pentyl-2-phenylamino-6*H*-[1,3]thiazine-5-carboxylic acid (12g)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=0.88 (t, 3H), 1.24 (t, 3H), 1.30–1.64 (m, 14H), 1.72 (m, 2H), 1.88 (m, 2H), 2.67 (sextet, 1H), 2.90 (sextet, 1H), 4.04 (t, 1H), 4.89 (m, 1H), 7.12 (dd, 2H), 7.33 ppm (t, 3H); MS (pos. APCI): *m*/*z*: 415.3 [*M*+1]$^+$ (*M*=414.23).

**Isopropyl ester of 6-(3-chloro-phenyl)-4-propyl-2-(2,4,6-trimethylphenylamino)-6*H*-[1,3]thiazine-5-carboxylic acid (12h)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=0.94 (t, 3H), 1.15 (d, 3H), 1.25 (d, 3H), 1.65 (s, 5H), 2.09 (s, 3H), 2.26 (s, 3H), 2.45 (m, 1H), 2.82 (m, 1H), 5.01 (sep, 1H), 5.11 (s, 1H), 6.79 (s, 1H), 6.85 (s, 1H), 7.11 (d, 1H), 7.19 ppm (m, 3H); MS (pos. APCI): *m*/*z*: 471.3 [*M*+1]$^+$ (*M*=470.18).

**Ethyl ester of 2-amino-4-methyl-6-pyridin-3-yl-6*H*-[1,3]thiazine-5-carboxylic acid (12i)**: $^1$H NMR (360 MHz, [$D_6$]DMSO): $\delta$=1.13 (t, 3H), 2.38 (s, 3H), 4.03 (q, 2H), 5.37 (s, 1H), 7.32 (t, 1H), 7.52 (d, 1H), 7.70 (br, 1H, $NH_2$), 8.39 ppm (s, 2H); MS (pos. APCI): *m*/*z*: 278.2 [*M*+1]$^+$ (*M*=277.09).

**Propyl ester of 2-amino-6-(3,4-difluorophenyl)-4-methyl-6*H*-[1,3]thiazine-5-carboxylic acid (12j)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=0.88 (t, 3H), 1.64 (sextet, 2H), 2.52 (s, 3H), 4.08 (t, 2H), 5.29 (s, 1H), 6.94 (s, 1H), 6.99–7.09 ppm (m, 2H); MS (pos. APCI): *m*/*z*: 327.2 [*M*+1]$^+$ (*M*=326.09).

Isopropyl ester of 2-amino-6-(3,4-difluorophenyl)-4-methyl-6*H*-[1,3]thiazine-5-carboxylic acid (**12k**): $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=1.17 (d, 3H), 1.27 (d, 3H), 2.49 (s, 3H), 4.98 (br, 2H, $NH_2$), 5.05 (sep, 2H), 5.27 (s, 1H), 6.93 (d, 1H), 6.98–7.08 ppm (m, 2H); MS (pos. APCI): *m*/*z*: 327.2 [*M*+1]$^+$ (*M*=326.09).

**Propyl ester of 2-amino-4-methyl-6-*p*-tolyl-6*H*-[1,3]thiazine-5-carboxylic acid (12l)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=0.88 (t, 3H), 1.27 (p, 2H), 1.62 (sextet, 2H), 2.31 (s, 3H), 2.51 (s, 3H), 4.05 (q, 2H), 5.30 (s, 1H), 7.08 ppm (s, 5H); MS (pos. APCI): *m*/*z*: 305.2 [*M*+1]$^+$ (*M*=304.12).

**2-Ethoxyethyl ester of 2-amino-4-ethyl-6-p-tolyl-6*H*-[1,3]thiazine-5-carboxylic acid (12m)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=1.16 (t, 3H), 1.25 (t, 3H), 2.30 (s, 3H), 2.84–2.94 (m, 2H), 3.44 (q, 2H), 3.60 (m, 2H), 4.24 (t, 2H), 5.31 (s, 1H), 7.05–7.10 ppm (t, 4H); MS (neg. APCI): *m*/*z*: 347.2 [*M*−1]$^+$ (*M*=348.15).

**3-Methylbutyl ester of 2-amino-4-methyl-6-*p*-tolyl-6*H*-[1,3]thiazine-5-carboxylic acid (12n)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=0.85 (t, 6H), 1.48 (m, 2H), 1.55 (m, 1H), 2.29 8 s, 3H), 2.49 (s, 3H), 4.10 (t, 2H), 5.18 (br, 2H, $NH_2$), 5.27 (s, 1H), 7.06 ppm (s, 4H); MS (pos. APCI): *m*/*z*: 333.3 [*M*+1]$^+$ (*M*=332.16).

**Butyl ester of 2-amino-4-phenyl-6-*p*-tolyl-6*H*-[1,3]thiazine-5-carboxylic acid (12o)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta$=0.73 (t, 3H), 0.96 (sextet, 2H), 1.15 (p, 2H), 2.33 (s, 3H), 3.82 (t, 2H), 5.38 (s, 1H), 7.12 (d, 2H), 7.21 (d, 2H), 7.36 ppm (br, 5H); MS (pos. APCI): *m*/*z*: 381.3 [*M*+1]$^+$ (*M*=380.16).

**Ethyl ester of 2-amino-6-(4-dimethylaminophenyl)-4-methyl-6*H*-[1,3]thiazine-5-carboxylic acid (12p)**: $^1$H NMR (360 MHz, [D$_6$]DMSO): $\delta = 1.13$ (t, 3H), 2.35 (s, 3H), 2.83 (s, 6H), 4.01 (q, 2H), 5.17 (s, 1H), 6.58 (d, 2H), 6.94 ppm (d, 2H); MS (neg. APCI): $m/z$: 318.3 $[M-1]^+$, ($M$ = 319.14).

**Butyl ester of 2-amino-4-(4-cyanophenyl)-6-*m*-tolyl-6*H*-[1,3]thiazine-5-carboxylic acid (12q)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta = 0.77$ (t, 3H), 1.00 (sextet, 2H), 1.27 (p, 2H), 2.35 (s, 3H), 3.87 (t, 2H), 5.42 (s, 1H), 6.75 (s, 1H), 7.11 (m, 3H), 7.53 (d, 2H), 7.68 ppm (d, 2H); MS (pos. APCI): $m/z$: 406.2 $[M+1]^+$ ($M$ = 405.15).

**3-Methylbutyl ester of 2-amino-6-(2-chlorophenyl)-4-cyclohexylmethyl-6*H*-[1,3]thiazine-5-carboxylic acid (12r)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta = 0.76$ (d, 3H), 0.82 (d, 3H), 1.04–1.13 (m, 2H), 1.15–1.28 (m, 4H), 1.37–1.47 (sextet, 2H), 1.60–1.67 (m, 2H), 1.65–1.73 (m, 4H), 2.58 (q, 1H), 3.18 (q, 1H), 4.06 (t, 2H), 5.50 (br, 2H, $NH_2$), 5.71 (s, 1H), 7.03 (dd, 1H), 7.14–7.19 (m, 2H), 7.38 ppm (dd, 1H); MS (pos. APCI): $m/z$: 435.0 $[M+1]^+$ ($M$ = 434.18).

**Isopropayl ester of 2-amino-4-(3-nitrophenyl)-6-*p*-tolyl-6*H*-[1,3]thiazine-5-carboxylic acid (12s)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta = 0.86$ (d, 3H), 0.93 (d, 3H), 2.34 (s, 3H), 4.80 (sep, 1H), 5.45 (s, 1H), 7.14 (d, 2H), 7.21 (d, 2H), 7.55 (t, 1H), 7.75 (d, 1H), 8.23 (d, 1H), 8.30 ppm (s, 1H); MS (pos. APCI): $m/z$: 412.3 $[M+1]^+$ ($M$ = 411.13).

**Methyl ester of 2-amino-4-(2-chloro-6-fluorobenzyl)-6-*p*-tolyl-6*H*-[1,3]thiazine-5-carboxylic acid (12t)**: $^1$H NMR (360 MHz, $CDCl_3$): $\delta =$ 2.29 (s, 3H), 3.72 (s, 3H), 4.50 (d, 1H), 4.63 (d, 1H), 5.33 (s, 1H), 6.95 (dt, 1H), 7.05 (d, 2H), 7.09 (d, 2H), 7.14 ppm (m, 2H); MS (pos. APCI): $m/z$: 405.2 $[M+1]^+$ ($M$ = 404.08).

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