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# Solid-Phase Syntheses of Heterocycles Containing the 2-Aminothiophenol Moiety[1]

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Efficient and general procedures have been developed for the solid-phase preparation of substituted benzothiazoles (**1**), 3,4-dihydro-1,4-benzothiazines (**2**), 3,4-dihydro-1,4-benzothiazine-1,1-dioxides (**3**), 3,4-dihydro-3-oxo-1,4-benzothiazines (**4**), and 3,4-dihydro-3-oxo-1,4-benzothiazine-1,1-dioxides (**5**). All five classes of compounds were prepared from a common intermediate, resin-bound 2-amino-4-carboxythiophenol, in a minimal number of steps. This intermediate was generated by (i) coupling 4-fluoro-3-nitrobenzoic acid onto Wang resin, or onto an amino acid bound to the resin, (ii) substitution of the aryl fluoride with a protected thiol, (iii) reduction of the nitro group, and (iv) removal of sulfur protection. Reaction with the appropriate substrates and reagents to effect cyclization gave the substituted core structures, which were modified further to introduce additional point(s) of diversity. Following cleavages from the solid support, the compounds were obtained in high initial purities and good isolated yields after purification.

## Introduction

Combinatorial chemistry is now well established as a powerful technique for the generation of vast numbers of compounds in minimal time.[2] The focus of combinatorial synthesis is currently shifting from the initial arena of the synthesis of linear oligomers (e.g., peptides, oligonucleotides) to the construction of small molecule libraries, particularly those containing heterocyclic entries. This trend follows the belief that biological oligomers are inherently limited as potential therapeutic agents, whereas small molecules are more likely candidates for development into pharmaceuticals.[2c,2f] Hence, the exploration and optimization of new solid-phase chemistries for the preparation of small molecule libraries is well warranted.

Benzothiazoles (**1**), 3,4-dihydro-1,4-benzothiazines (**2**), 3,4-dihydro-1,4-benzothiazine-1,1-dioxides (**3**), 3,4-dihydro-3-oxo-1,4-benzothiazines (**4**), and 3,4-dihydro-3-oxo-1,4-benzothiazine-1,1-dioxides (**5**) (Figure 1) are five structurally related classes of molecules that exhibit a broad spectrum of biological activities, including anticancer, antibacterial, antiinflammatory, ataractic, and antirheumatic.[3] These compounds (**1**−**5**) are attractive targets for library development because their structures contain multiple positions for facile derivatization and/or modification. Although a myriad of solution-phase routes to **1**−**5** have been reported, solid-phase routes are yet to be described. We envisioned preparing all five classes of compounds from one common intermediate, resin-bound 2-amino-4-carboxythiophenol, via cyclization to form the core structure, followed by the introduction of points of diversity. We report here novel, efficient, solid-phase routes to attain the title compounds.
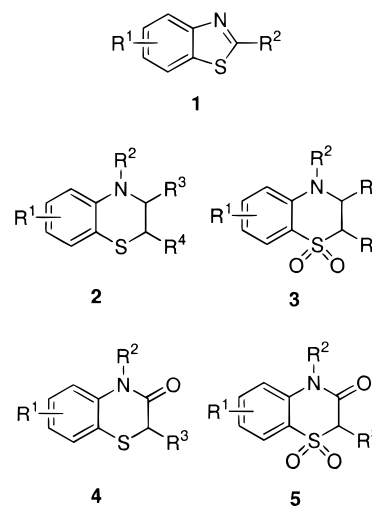


**Figure 1.**

## Results and Discussion

**Preparation of Resin-Bound 2-Amino-4-carboxythiophenol.** The starting point for syntheses was the hydroxymethyl group of Wang resin or the α-amino group of an amino acid bound to Wang resin. 4-Fluoro-3-nitrobenzoic acid (4 equiv) was anchored to the supports as mediated by *N,N′*-diisopropylcarbodiimide (DIPCDI) (4 equiv) and 4-(dimethylamino)-pyridine (DMAP) (1 equiv) in DMF (Scheme 1).[4] Next, nucleophilic aromatic substitution of the aryl fluoride by triphenylmethyl mercaptan (Trt-SH) (5 equiv) in DMF, in the presence of *N,N*-diisopropylethylamine (DIEA) (10 equiv), yielded intermediate **6**.[5] Other procedures (e.g., CH$_3$-COSH−DIEA in DMF, followed by treatment with piperidine−DMF) were investigated for sulfur introduction, but resulted in multicomponent mixtures and were not pursued further. Subsequent reduction of the aromatic nitro group in **6** with 2 M SnCl$_2$ in DMF[6] gave the aniline intermediate,

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**Scheme 1.** Preparation of Resin-Bound 2-Amino-4-carboxythiophenol[a]
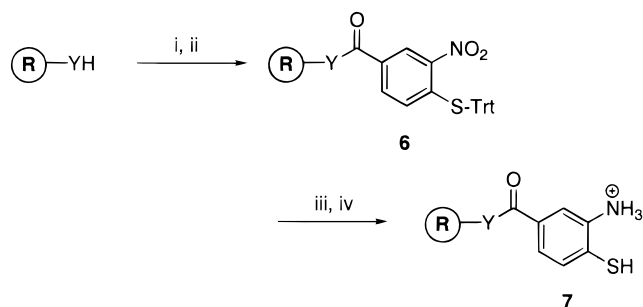


(R) = polystyrene

Y= Wang or Wang-CO-CH(R)-NH-

[a] Reagents and conditions: (i) 4-Fluoro-3-nitrobenzoic acid (4 equiv), DIPCDI (4 equiv), DMAP (1 equiv), DMF, 4 h; (ii) Trt-SH (5 equiv), DIEA (10 equiv), DMF, 24 h; (iii) 2 M SnCl$_2$ in DMF, 24 h; (iv) TFA−TES−CH$_2$Cl$_2$ (2:5:93, 3 × 1 min).

**Scheme 2.** Preparation of Benzothiazoles[a]
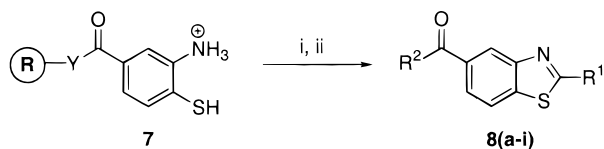


[a] Reagents and conditions: (i) R$^1$CHO (4 equiv), DDQ (1 equiv), CH$_2$Cl$_2$, 24 h; (ii) TFA−H$_2$O (19:1), 1 h.

which was treated briefly with TFA−triethylsilane (TES)−CH$_2$Cl$_2$ (2:5:93) to unmask the thiol and provide resin-bound 2-amino-4-carboxythiophenol (**7**). The use of 2% TFA was essential, because higher acid concentrations caused substantial loss of substrate from the resin, and lower concentrations led to incomplete deprotections or required extended time.

**Preparation of Benzothiazoles.** Freshly prepared **7** was converted to a series of benzothiazoles by a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-mediated oxidative cyclocondensation with aldehydes (Scheme 2).[7] Thus, treatment of **7** with aldehydes (4 equiv) and DDQ (1 equiv)[8] in CH$_2$Cl$_2$ gave the resin-bound benzothiazoles, which were cleaved from the resin with TFA−H$_2$O (19:1) to provide **8a−i** (Table 1). Purities of the cleaved materials, as determined by HPLC analysis with monitoring at 220 nm, ranged from 75 to 94%, and the isolated yields (following purification over silica gel), calculated based on the substitution level of the starting resin, were between 60 and 72%. The cyclocondensation-oxidation procedure was efficient using aromatic (**8a−e, 8g**), electron-rich aromatic (**8b**), electron-deficient aromatic (**8c, 8e**), and aliphatic (**8f, 8h**) aldehydes. The inclusion of an amino acid at R$^2$ position (**8i**) did not hinder benzothiazole formation, with the purity and yield being similar to other entries. An alternate route to benzothiazoles that did not use DDQ was also investigated; this procedure may be useful when introducing DDQ-sensitive moieties.[9] The resin-bound substrate (**7**) was heated to 80 °C with an aldehyde (10 equiv) in DMF−HOAc (99:1), and cleavage from the resin provided the free benzothiazole. The purities and yields of this route were generally the same as the DDQ-mediated route when using aromatic

**Table 1.** Benzothiazoles **8a−i**



| Entry | R$^1$ | R$^2$ | Initial Purity[1] (%) | Yield[2] (%) |
|---|---|---|---|---|
| a | phenyl | -OH | 92 | 72 |
| b | 4-OMe-phenyl | -OH | 75 | 65 |
| c | 4-Cl-phenyl | -OH | 87 | 65 |
| d | naphthyl | -OH | 90 | 67 |
| e | 4-NO$_2$-phenyl | -OH | 80 | 64 |
| f | cyclohexyl | -OH | 94 | 70 |
| g | thienyl | -OH | 91 | 70 |
| h | heptyl | -OH | 91 | 71 |
| i | phenyl | -NHCH$_2$COOH | 90 | 60 |

[1] Determined by HPLC using relative peak areas with monitoring at 220 nm. [2] Isolated yields; calculated using the substitution level of the starting resin.

**Scheme 3.** Preparation of 3,4-Dihydro-1,4-benzothiazines[a]
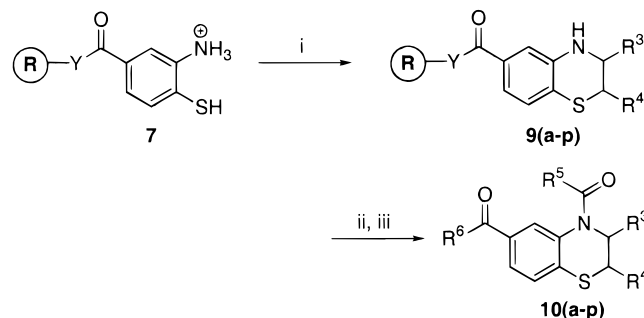


[a] Reagents and conditions: (i) α-Halo ketone (5 equiv), NaCNBH$_3$ (5 equiv), DMF−HOAc (99:1), 24 h; (ii) (a) TMS-Cl (20 equiv), DIEA (60 equiv), CH$_2$Cl$_2$, 80 °C, 1 h; (b) R$^5$COCl (40 equiv), CH$_2$Cl$_2$, 80 °C, 24 h; (iii) TFA−TES (19:1), 1 h.

aldehydes, but were significantly lower with aldehydes containing an α-hydrogen.

**Preparation of 3,4-Dihydro-1,4-benzothiazines and 3,4-Dihydro-1,4-benzothiazine-1,1-dioxides.** Freshly prepared **7** was converted to a series of 3,4-dihydro-1,4-benzothiazines by a one-pot substitution-reductive cyclization[10] with α-bromo ketones and subsequent acylation of N4 by acid chlorides. The core structures were generated by addition of α-bromo ketones (5 equiv) in DMF−HOAc (99:1), together with NaCNBH$_3$ (5 equiv), to the resin (**7**) and agitating at 25 °C (Scheme 3).[11] The resulting intermediates (**9**) were reacted initially with trimethylsilyl chloride (TMS-Cl) (20 equiv) and DIEA (60 equiv) in CH$_2$Cl$_2$ at 80 °C in a sealed tube. Acid chlorides (40 equiv) were then added, and heating at 80 °C was continued.[12] The substituted 3,4-dihydro-1,4-benzothiazines were cleaved from the resin with TFA−TES (19:1) to give **10a−p** (Scheme 3). Alternatively, after acylation, representative resins were oxidized to 3,4-dihydro-1,4-

**Scheme 4.** Preparation of
3,4-Dihydro-1,4-benzothiazine-1,1-dioxides[a]
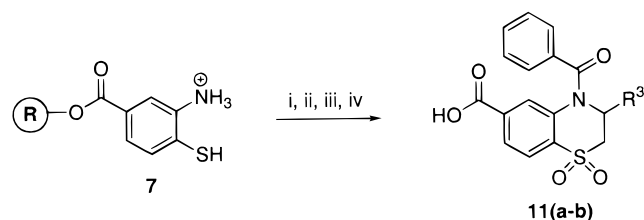


[a] Reagents and conditions: (i) α-Halo ketone (5 equiv), NaCNBH$_3$ (5 equiv), DMF−HOAc (99:1), 24 h; (ii) (a) TMS-Cl (20 equiv), DIEA (60 equiv), CH$_2$Cl$_2$, 80 °C, 1 h; (b) PhCOCl (40 equiv), CH$_2$Cl$_2$, 80 °C, 24 h; (iii) *m*CPBA (16 equiv), CH$_2$Cl$_2$, 6 h; (iv) TFA−TES (19:1), 1 h. **11a**, R$^3$ = phenyl; 95% initial purity, 55% yield. **11b**, R$^3$ = ethyl; 89% initial purity, 52% yield.

benzothiazine-1,1-dioxides with 3-chloroperoxybenzoic acid (*m*CPBA) (16 equiv)[13] in CH$_2$Cl$_2$ and then liberated from the resin with TFA−TES (19:1) to give **11a−b** (Scheme 4). The substitution-reductive cyclizations and acylations proceeded efficiently with a range of α-bromo ketones [aromatic (**10a−e**), electron-rich aromatic (**10b**, **10e**), electron-deficient aromatic (**10c,d**), and aliphatic (**10f**)] and acid chlorides [aromatic (**10a**, **10l−p**), electron-rich aromatic (**10n**), electron-deficient aromatic (**10o,p**), heterocyclic aromatic (**10l,m**), and aliphatic (**10k**)] giving high initial purities (65−96%) and isolated yields (40−70%) (Table 2). As expected, the procedure was also efficient with glycine at R$^6$ (**10g**) (Table 2). The purity and yield of **10h**, substituted on C2 and C3, were somewhat lower than other entries. This can be attributed to a low-yielding acylation, because the precursor (**10j**) was formed in high yield and purity. Also, the isolated yields and initial purities of the 3,4-dihydro-1,4-benzo-thiazine-1,1-dioxides (**11a,b**) were very similar to the parent compounds (**10a**, **10f**), indicating that oxidation was nearly quantitative with aryl or alkyl substituents at R$^3$ (Scheme 4).

The diastereomeric mixtures resulting from cyclization to **10i** and **10j** were characterized by evaluating the coupling constants between the protons on C2 and C3 and comparing to predictions based on the Karplus equation.[14] The syn isomers (syn, $J \sim 3$ Hz; anti, $J \sim 8$ Hz) were the major isomers observed: a 10:1 (syn:anti) ratio for **10i** and a 30:1 ratio for **10j**. The high selectivity for the syn isomers is most likely governed by the location of the C2 substituents, which direct the hydride attack to the opposite face of the planar intermediates.

The substitution-reductive cyclization method was also performed with 1,3-dichloroacetone (in place of a mono-halo ketone) to give resin-bound 3-chloromethyl-3,4-dihydro-1,4-benzothiazine (**12**) (Scheme 5). This intermediate contains a methylene chloride unit on C3; this can be modified easily by nucleophilic substitution. As a representative reaction, resin-bound **12** was reacted with aromatic thiols (50 equiv) in DMF, in the presence of DIEA (50 equiv) at 80 °C in a sealed tube. Following acylation with benzoyl chloride, using conditions described above, and cleavage from the resin with TFA−TES (19:1), **13a,b** were obtained in high initial purities (∼90%) and isolated yields (∼50%) (Scheme 5).

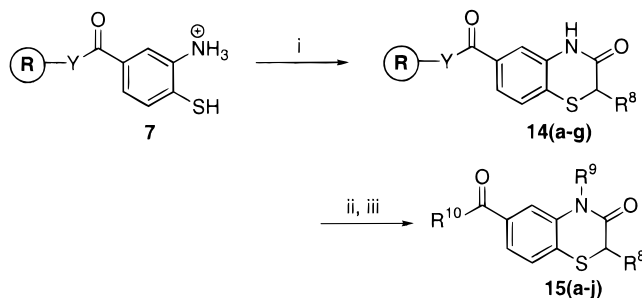**Table 2.** 3,4-Dihydro-1,4-benzothiazines **10a−p**



| Entry | R$^3$ | R$^4$ | R$^5$ | R$^6$ | Initial Purity[1] (%) | Yield[2] (%) |
|---|---|---|---|---|---|---|
| a | phenyl | –H | phenyl | –OH | 96 | 70 |
| b | –OMe phenyl | –H | phenyl | –OH | 90 | 70 |
| c | –Cl phenyl | –H | phenyl | –OH | 91 | 51 |
| d | NO$_2$ phenyl | –H | phenyl | –OH | 80 | 51 |
| e | –Ph phenyl | –H | phenyl | –OH | 93 | 54 |
| f | (alkyl) | –H | phenyl | –OH | 87 | 68 |
| g | phenyl | –H | phenyl | –N(H)CH$_2$C(O)OH | 89 | 63 |
| h | phenyl | phenyl | phenyl | –OH | 65 | 40 |
| i | phenyl | –CH$_3$ | no acylation | –OH | 95 | 59 |
| j | phenyl | phenyl | no acylation | –OH | 92 | 58 |
| k | phenyl | –H | cyclopropyl | –OH | 95 | 56 |
| l | phenyl | –H | thienyl | –OH | 92 | 62 |
| m | phenyl | –H | furyl | –OH | 89 | 55 |
| n | phenyl | –H | –OMe phenyl | –OH | 92 | 69 |
| o | phenyl | –H | –F phenyl | –OH | 92 | 61 |
| p | phenyl | –H | –CN phenyl | –OH | 89 | 59 |

[1] Determined by HPLC using relative peak areas with monitoring at 220 nm. [2] Isolated yields; calculated using the substitution level of the starting resin.

**Scheme 5.** Preparation of 4-Acyl-3-(methanethiol-*S*-aryl)-3,4-dihydro-1,4-benzothiazines[a]
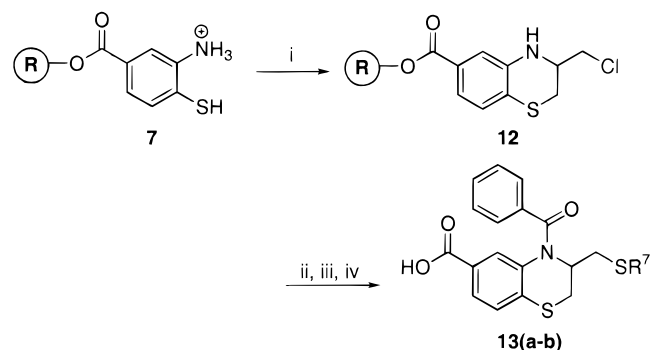


[a] Reagents and conditions: (i) 1,3-dichloroacetone (5 equiv), NaCNBH$_3$ (5 equiv), DMF−HOAc (99:1), 24 h; (ii) Ar-SH (50 equiv), DIEA (50 equiv), DMF, 80 °C, 24 h; (iii) (a) TMS-Cl (20 equiv), DIEA (60 equiv), CH$_2$Cl$_2$, 80 °C, 1 h; (b) PhCOCl (40 equiv), CH$_2$Cl$_2$, 80 °C, 24 h; (iv) TFA−TES (19:1), 1 h. **13a**, R$^7$ = phenyl; 88% initial purity, 50% yield. **13b**, R$^7$ = 4-chlorophenyl; 90% initial purity, 51% yield.

**Preparation of 3,4-Dihydro-3-oxo-1,4-benzothiazines and 3,4-Dihydro-3-oxo-1,4-benzothiazine-1,1-dioxides.**

**Scheme 6.** Preparation of
3,4-Dihydro-3-oxo-1,4-benzothiazines[a]



[a] Reagents and conditions: (i) α-bromo methyl ester (5 equiv), DIEA (5 equiv), DMF, 80 °C, 24 h; (ii) (a) LiO*t*Bu (5 equiv), THF, 30 min; (b) RBr, RI, or RCOCl (40 equiv), THF, 24 h; (iii) TFA−TES (19:1), 1 h.
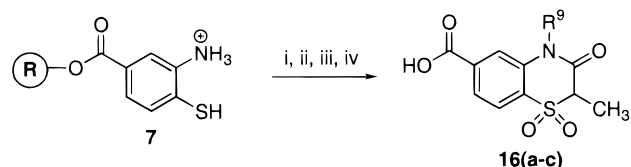
**Table 3.** 3,4-Dihydro-3-oxo-1,4-benzothiazines **14a−g**
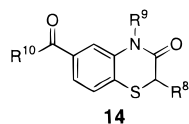


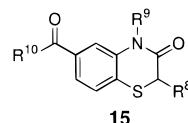| Entry | R[8] | R[9] | R[10] | Initial Purity[1] (%) | Yield[2] (%) |
|---|---|---|---|---|---|
| a | -H | -H | -OH | 92 | 52 |
| b | -CH₃ | -H | -OH | 96 | 67 |
| c | (propyl) | -H | -OH | 92 | 69 |
| d | (phenyl) | -H | -OH | 93 | 55 |
| e | (benzyl-OCF₃) | -H | -OH | 91 | 57 |
| f | -CH₃, -CH₃ | -H | -OH | 84 | 44 |
| g | -CH₃ | -H | -N(H)CH₂C(O)OH | 90 | 55 |

[1] Determined by HPLC using relative peak areas with monitoring at 220 nm. [2] Isolated yields; calculated using the substitution level of the starting resin.

Freshly prepared **7** was converted to a series of 3,4-dihydro-3-oxo-1,4-benzothiazines by a substitution-cyclization with α-bromo methyl esters, followed by alkylation or acylation of the anilide nitrogen (N4) with various electrophiles. The core structures were generated by addition to the resin (**7**) of α-bromo methyl esters (5 equiv) in DMF, together with DIEA (5 equiv), and heating to 80 °C (Scheme 6).[15] The substitution-cyclizations were very efficient with a variety of substituents at C2, even dimethyl, giving high initial purities (84−96%) and isolated yields (44−69%) (Table 3). Alkylation of **7** with α-bromo acids, followed by DIPCDI cyclization, also gave the 3,4-dihydro-3-oxo-1,4-benzothiazine cores. However, purities and yields of this route were 5−10% lower than the route described earlier in this paragraph.[16]

Under an inert atmosphere, the resin-bound 3,4-dihydro-3-oxo-1,4-benzothiazines (**14**) were treated with LiO*t*-Bu (5 equiv)[17] in THF and washed with THF. Next, alkyl bromides, alkyl iodides, or acid chlorides[18] (40 equiv) were added, in THF solution, and the mixture was agitated (Scheme 6). The substituted 3,4-dihydro-3-oxo-1,4-benzothiazines were then

**Scheme 7.** Preparation of
3,4-Dihydro-3-oxo-1,4-benzothiazine-1,1-dioxides[a]



[a] (i) methyl 2-bromopropionate (5 equiv), DIEA (5 equiv), DMF, 80 °C, 24 h; (ii) (a) LiO*t*Bu (5 equiv), THF, 30 min; (b) RI, or RBr (40 equiv), THF, 24 h; (iii) *m*CPBA (16 equiv), CH₂Cl₂, 6 h; (iv) TFA−TES (95:5), 1 h. **16a**, R[9] = H; 91% initial purity, 50% yield. **16b**, R[9] = methyl; 91% initial purity, 51% yield. **16c**, R[9] = 4-fluorobenzyl; 91% initial purity, 48% yield.

**Table 4.** 3,4-Dihydro-3-oxo-1,4-benzothiazines **15a−j**



| Entry | R[8] | R[9] | R[10] | Initial Purity[1] (%) | Yield[2] (%) |
|---|---|---|---|---|---|
| a | -H | -CH₃ | -OH | 92 | 63 |
| b | -CH₃ | -CH₃ | -OH | 94 | 61 |
| c | (propyl) | -CH₃ | -OH | 88 | 65 |
| d | (benzyl-OCF₃) | -CH₃ | -OH | 86 | 55 |
| e | -CH₃, -CH₃ | -CH₃ | -OH | 84 | 51 |
| f | -CH₃ | (allyl) | -OH | 90 | 71 |
| g | -CH₃ | (benzyl) | -OH | 85 | 70 |
| h | -CH₃ | (benzyl-F) | -OH | 90 | 60 |
| i | -CH₃ | (benzoyl) | -OH | 87 | 63 |
| j | -CH₃ | (thienoyl) | -OH | 83 | 59 |

[1] Determined by HPLC using relative peak areas with monitoring at 220 nm. [2] Isolated yields; calculated using the substitution level of the starting resin.

cleaved from the resin with TFA−TES (19:1) to provide **15a−j**. Alternatively, following alkylation, representative resins were oxidized to 3,4-dihydro-3-oxo-1,4-benzothiazine-1,1-dioxides with *m*CPBA (16 equiv) in CH₂Cl₂, and liberated from the resin with TFA−TES (19:1) to give **16a−c** (Scheme 7). The alkylations and acylations were efficient with a range of alkyl halides (benzyl, methyl, and allyl) and aromatic acid chlorides, giving initial purities and isolated yields ranging from 83 to 94% and 50 to 70%, respectively (Table 4). Also, the isolated yields and initial purities of the 3,4-dihydro-3-oxo-1,4-benzothiazine-1,1-dioxides (**16a−c**) were very similar to the parent compounds (**14b**, **15b**, **15h**), indicating that oxidation was nearly quantitative (Scheme 7). Diversity was also introduced onto N4 via a reductive amination of an aldehyde onto the thioether intermediate

generated from the alkylation of **7** with an α-bromo acid.[19] Following reductive amination, the intermediate was cyclized to the 3,4-dihydro-3-oxo-1,4-benzothiazine with DIPCDI. The deprotonation-alkylation route is preferred over the reductive amination route for the introduction of diversity onto N4 because yields were far superior; in addition, imide functionalities can be obtained only by the former route.

**Characterization.** Initial and final purities for each compound were determined by reversed-phase analytical HPLC with monitoring at 220 nm, and final purities were also checked by TLC. Purified compounds were characterized by $^1$H NMR and electrospray ionization mass spectrometry (ESIMS). In most cases, [M + H]$^+$ or [M + Na]$^+$ and [M − H]$^-$ were observed by ESIMS. However, for some 3,4-dihydro-3-oxo-1,4-benzothiazines and 3,4-dihydro-3-oxo-1,4-benzothiazine-1,1-dioxides, only [M − H]$^-$ was observed; fast atom bombardment mass spectrometry (FABMS) and chemical ionization mass spectrometry (CIMS) on these compounds gave inconsistent results.

### Conclusions

We have described herein efficient, solid-phase syntheses of benzothiazoles, 3,4-dihydro-1,4-benzothiazines, 3,4-dihydro-1,4-benzothiazine-1,1-dioxides, 3,4-dihydro-3-oxo-1,4-benzothiazines, and 3,4-dihydro-3-oxo-1,4-benzothiazine-1,1-dioxides. All of the compounds were prepared in two to four steps, using commercially available reagents, from a common starting material, resin-bound 2-amino-4-carboxythiophenol. Isolated yields of these compounds were good, and the initial purities were very high, providing essentially a single component by HPLC analysis in most cases. Also, the reactions are general, thus allowing introduction of a variety of substituents, e.g., aromatic, electron-rich aromatic, electron-deficient aromatic, and aliphatic, at different positions of the compounds. We believe that these chemistries will find application in other systems and provide the basis for preparation of large libraries of these compounds.

### Experimental Section

**Resin-Bound 2-Amino-4-carboxythiophenol (7).** In a 20 mL syringe, Wang resin (1.0 g, 0.80 mmol/g)[20] was swollen in a minimal amount of DMF, and 4-fluoro-3-nitrobenzoic acid (592 mg, 3.2 mmol) in DMF (2 mL), DIPCDI (0.501 mL, 3.2 mmol), and DMAP (98 mg, 0.80 mmol) in DMF (0.5 mL) were added sequentially to the resin. The resulting mixture was reacted for 4 h and then washed consecutively with DMF (3 × 1 min), MeOH (3 × 1 min), and CH$_2$Cl$_2$ (3 × 1 min). Next, Trt-SH (1.11 g, 4.0 mmol) was dissolved in DMF (3 mL), DIEA (1.83 mL, 8.0 mmol) was added, and the solution was added to the resin. After 24 h reaction, the resin was washed with DMF (3 × 1 min) and CH$_2$Cl$_2$ (3 × 1 min) and dried under vacuum to give **6**, which was stable for storage under ambient conditions for months. As needed, a resin portion (42 mg, 0.025 mmol)[21] was swollen in a minimal amount of DMF and reduced with 2 M SnCl$_2$ in DMF (3 mL) for 24 h. The resin was then washed with DMF (3 × 1 min), MeOH (3 × 1 min), and CH$_2$Cl$_2$ (3 × 1 min). Next, the resin was treated with TFA−TES−CH$_2$Cl$_2$ (2:5:93, 3 × 1 min) and washed with CH$_2$Cl$_2$ (3 ×

1 min) to provide the title resin, which was immediately carried forward to the preparations of **8**−**16**.

**General Procedure for Preparation of Benzothiazoles.** Resin-bound 2-amino thiophenol (**7**) (0.025 mmol), prepared immediately before use, was washed with CH$_2$Cl$_2$ (3 × 1 min) and swollen in a minimal amount of CH$_2$Cl$_2$. Next, a solution of aldehyde (0.1 mmol) in CH$_2$Cl$_2$ (0.5 mL) and then solid DDQ (5.7 mg, 0.025 mmol) were added sequentially to the resin and reacted for 24 h at 25 °C. The resulting resin was washed with CH$_2$Cl$_2$ (3 × 1 min), DMF (3 × 1 min), and CH$_2$Cl$_2$ (3 × 1 min) and cleaved with TFA−H$_2$O (19:1) (2 mL) for 1 h. The filtrate from the cleavage reaction was collected, combined with TFA washes (3 mL) of the resin, and evaporated under a stream of N$_2$. The crude residue was redissolved and purified over silica gel with CHCl$_3$−THF−HOAc (95:5:0.5) to elute compounds **8a**−**h** or with CHCl$_3$−THF−HOAc (6:4:0.5) to elute **8i**.

**2-Phenylbenzothiazole-5-carboxylic Acid (8a).** Prepared as described above, using benzaldehyde (10 μL, 0.1 mmol), to provide a white solid (4.6 mg, 72%) following purification. $^1$H NMR (DMSO-$d_6$) δ 8.52 (d, $J$ = 1.5 Hz, 1H), 8.26 (d, $J$ = 8.4 Hz, 1H), 8.11 (m, 2H), 7.98 (dd, $J$ = 8.4, 1.5 Hz, 1H), 7.58 (m, 3H). ESIMS $m/z$ 256.3 [M + H]$^+$, 254.1 [M − H]$^-$.

**2-(4-Methoxyphenyl)benzothiazole-5-carboxylic Acid (8b).** Prepared as described above, using *p*-anisaldehyde (12 μL, 0.1 mmol), to provide a white solid (4.6 mg, 65%) following purification. $^1$H NMR (acetone-$d_6$) δ 8.60 (dd, $J$ = 1.5, 0.6 Hz, 1H), 8.18 (dd, $J$ = 8.4, 0.6 Hz, 1H), 8.11 (ddd, $J$ = 9.0, 2.4, 2.4 Hz, 2H), 8.06 (dd, $J$ = 8.7, 1.2 Hz, 1H), 7.13 (ddd, $J$ = 9.0, 2.1, 2.1 Hz, 2H), 3.92 (s, 3H). ESIMS $m/z$ 286.3 [M + H]$^+$, 284.1 [M − H]$^-$.

**2-(4-Chlorophenyl)benzothiazole-5-carboxylic Acid (8c).** Prepared as described above, using *p*-chlorobenzaldehyde (14.1 mg, 0.1 mmol), to provide a white solid (4.7 mg, 65%) following purification. $^1$H NMR (acetone-$d_6$) δ 8.66 (dd, $J$ = 1.5, 0.6 Hz, 1H), 8.25 (dd, $J$ = 8.4, 0.6 Hz, 1H), 8.19 (ddd, $J$ = 8.7, 2.1, 2.1 Hz, 2H), 8.12 (dd, $J$ = 8.4, 1.5 Hz, 1H), 7.65 (ddd, $J$ = 8.7, 2.1, 2.1 Hz, 2H). ESIMS $m/z$ 290.3 [M + H]$^+$, 288.1 [M − H]$^-$.

**2-(2-Naphthyl)benzothiazole-5-carboxylic Acid (8d).** Prepared as described above, using 2-naphthaldehyde (15.6 mg, 0.1 mmol), to provide a white solid (5.1 mg, 67%) following purification. $^1$H NMR (DMSO-$d_6$) δ 8.73 (s, 1H), 8.55 (d, $J$ = 1.5 Hz, 1H), 8.30−8.10 (m, 4H), 8.00 (m, 2H), 7.63 (t, $J$ = 4.2 Hz, 2H). ESIMS $m/z$ 306.3 [M + H]$^+$, 304.1 [M − H]$^-$.

**2-(4-Nitrophenyl)benzothiazole-5-carboxylic Acid (8e).** Prepared as described above, using *p*-nitrobenzaldehyde (15.1 mg, 0.1 mmol), to provide a white solid (4.8 mg, 64%) following purification. $^1$H NMR (acetone-$d_6$) δ 8.73 (m, 1H), 8.46 (m, 4H), 8.32 (d, $J$ = 8.1 Hz, 1H), 8.16 (d, $J$ = 8.1 Hz, 1H). ESIMS $m/z$ 301.2 [M + H]$^+$, 299.0 [M − H]$^-$.

**2-Cyclohexylbenzothiazole-5-carboxylic Acid (8f).** Prepared as described above, using cyclohexane carboxaldehyde (12 μL, 0.1 mmol), to provide a white solid (4.6 mg, 70%) following purification. $^1$H NMR (DMSO-$d_6$) δ 8.39 (d, $J$ = 1.5 Hz, 1H), 8.15 (d, $J$ = 8.4 Hz, 1H), 7.92 (dd, $J$ = 8.4,

1.5 Hz, 1H), 3.14 (m, 1H), 2.08 (m, 2H), 1.82−1.18 (m, 9H). ESIMS *m/z* 262.3 [M + H]$^+$, 260.1 [M − H]$^-$.

**2-(3-Thienyl)benzothiazole-5-carboxylic Acid (8g).** Prepared as described above, using 3-thiophene carboxaldehyde (9 *μ*L, 0.1 mmol), to provide a white solid (5.5 mg, 70%) following purification. $^1$H NMR (acetone-$d_6$) δ 8.61 (d, *J* = 1.5 Hz, 1H), 8.33 (dd, *J* = 2.7, 1.2 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.08 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.79 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.72 (dd, *J* = 5.1, 2.7 Hz, 1H). ESIMS *m/z* 262.2 [M + H]$^+$, 260.0 [M − H]$^-$.

**2-*n*-Heptylbenzothiazole-5-carboxylic Acid (8h).** Prepared as described above, using octyl aldehyde (16 *μ*L, 0.1 mmol), to provide a white solid (4.9 mg, 71%) following purification. $^1$H NMR (DMSO-$d_6$) δ 8.38 (d, *J* = 1.2 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.92 (dd, *J* = 8.4, 1.2 Hz, 1H), 3.11 (t, *J* = 7.8 Hz, 2H), 1.78 (pentet, *J* = 7.5 Hz, 2H), 1.28 (m, 8H), 0.83 (t, *J* = 6.6 Hz, 3H). ESIMS *m/z* 278.3 [M + H]$^+$, 276.1 [M − H]$^-$.

***N*-[(2-Phenylbenzothiazol-5-yl)carbonyl]-glycine (8i).** Prepared as described above, using benzaldehyde (10 *μ*L, 0.1 mmol), to provide a white solid (4.7 mg, 60%) following purification. $^1$H NMR (CD$_3$OD) δ 8.52 (dd, *J* = 1.8, 0.6 Hz, 1H), 8.11 (m, 3H), 7.92 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.56 (m, 3H), 4.14 (s, 2H). ESIMS *m/z* 313.2 [M + H]$^+$, 311.1 [M − H]$^-$.

**General Procedure for Preparation of 3,4-Dihydro-1,4-benzothiazines.** Resin-bound 2-aminothiophenol (**7**) (0.025 mmol), prepared immediately before use, was washed with DMF (3 × 1 min) and swollen in a minimal amount of DMF−HOAc (99:1). Next, a solution α-bromo ketone (0.125 mmol) in DMF−HOAc (99:1; 1 mL) and then solid NaCNBH$_3$ (7.8 mg, 0.125 mmol) were added sequentially to the resin. After 24 h reaction at 25 °C, the resulting resin was washed with DMF (3 × 1 min) and CH$_2$Cl$_2$ (3 × 1 min), placed in a Teflon-capped hydrolysis tube, and dried under vacuum. Subsequently, under an inert atmosphere, CH$_2$Cl$_2$ (1 mL), DIEA (0.26 mL, 1.5 mmol), and TMS-Cl (63.0 *μ*L, 0.5 mmol) were added in order to the resin, and the mixture was heated for 1 h at 80 °C. The reaction was then cooled, an acid chloride (1.0 mmol) was added, and heating occurred for 24 h at 80 °C. The resulting resin was washed, cleaved, and worked-up as described in the general procedure for preparation of benzothiazoles, except for using TFA−TES (19:1) as the cleavage reagent. The crude residue was redissolved and purified over silica gel with CHCl$_3$−THF−HOAc (95:5:0.5).

**4-Benzoyl-3-phenyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10a).** Prepared as described above, using phenacyl bromide (24.9 mg, 0.125 mmol) and benzoyl chloride (116 *μ*L, 1.0 mmol), to provide a white solid (6.6 mg, 70%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.55 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.48 (m, 2H), 7.39−7.26 (m, 9H), 7.20 (m, 1H), 6.35 (t, *J* = 5.1 Hz, 1H), 3.94 (dd, *J* = 13.2, 5.7 Hz, 1H), 3.67 (dd, *J* = 13.2, 5.1 Hz, 1H). ESIMS *m/z* 376.1 [M + H]$^+$, 398.0 [M + Na]$^+$, 374.1 [M − H]$^-$.

**4-Benzoyl-3-(4-methoxyphenyl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10b).** Prepared as described above, using 2-bromo-4′-methoxyacetophenone (28.6

mg, 0.125 mmol) and benzoyl chloride (116 *μ*L, 1.0 mmol), to provide a white solid (7.1 mg, 70%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.54 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.40−7.26 (m, 9H), 6.83 (dt, *J* = 6.6, 2.1 Hz, 2H), 6.30 (t, *J* = 5.1 Hz, 1H), 3.92 (dd, *J* = 13.2, 5.1 Hz, 1H), 3.72 (s, 3H), 3.67 (dd, *J* = 13.2, 4.8 Hz, 1H). ESIMS *m/z* 406.0 [M + H]$^+$, 428.1 [M + Na]$^+$, 404.1 [M − H]$^-$.

**4-Benzoyl-3-(4-chlorophenyl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10c).** Prepared as described above, using 2-bromo-4′-chloroacetophenone (29.2 mg, 0.125 mmol) and benzoyl chloride (116 *μ*L, 1.0 mmol), to provide a white solid (5.2 mg, 51%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.56 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.53 (br s, 1H), 7.50 (br s, 1H), 7.39−7.27 (m, 9H), 6.34 (t, *J* = 5.1 Hz, 1H), 3.95 (dd, *J* = 13.5, 5.4 Hz, 1H), 3.68 (dd, *J* = 13.5, 5.1 Hz, 1H). ESIMS *m/z* 410.1 [M + H]$^+$, 432.0 [M + Na]$^+$, 408.2 [M − H]$^-$.

**4-Benzoyl-3-(3-nitrophenyl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10d).** Prepared as described above, using 2-bromo-3′-nitroacetophenone (30.5 mg, 0.125 mmol) and benzoyl chloride (116 *μ*L, 1.0 mmol), to provide a white solid (5.4 mg, 51%) following purification. $^1$H NMR (acetone-$d_6$) δ 8.36 (m, 1H), 8.10 (m, 1H), 7.97 (dpent, *J* = 7.8, 0.9 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.40−7.27 (m, 6H), 6.48 (t, *J* = 5.7 Hz, 1H), 4.04 (dd, *J* = 13.5, 5.7 Hz, 1H), 3.77 (dd, *J* = 13.5, 5.4 Hz, 1H). ESIMS *m/z* 421.1 [M + H]$^+$, 443.0 [M + Na]$^+$, 419.1 [M − H]$^-$.

**4-Benzoyl-3-(4-biphenyl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10e).** Prepared as described above, using 2-bromo-4′-phenylacetophenone (34.4 mg, 0.125 mmol) and benzoyl chloride (116 *μ*L, 1.0 mmol), to provide a white solid (6.1 mg, 54%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.62−7.56 (m, 7H), 7.45−7.27 (m, 10H), 6.39 (t, *J* = 5.1 Hz, 1H), 3.97 (dd, *J* = 13.5, 5.7 Hz, 1H), 3.92 (dd, *J* = 13.5, 5.1 Hz, 1H). ESIMS *m/z* 452.1 [M + H]$^+$, 474.1 [M + Na]$^+$, 450.2 [M − H]$^-$.

**4-Benzoyl-3-ethyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10f).** Prepared as described above, using 1-bromo-2-butanone (13 *μ*L, 0.125 mmol) and benzoyl chloride (116 *μ*L, 1.0 mmol), to provide a white solid (5.6 mg, 68%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.61 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.40−7.26 (m, 7H), 5.16 (m, 1H), 3.65 (dd, *J* = 12.6, 5.1 Hz, 1H), 3.20 (dd, *J* = 12.6, 2.7 Hz, 1H), 1.54 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H). ESIMS *m/z* 328.0 [M + H]$^+$, 350.1 [M + Na]$^+$, 326.1 [M − H]$^-$.

***N*-[(4-Benzoyl-3-phenyl-3,4-dihydro-2*H*-1,4-benzothiazin-6-yl)carbonyl]-glycine (10g).** Prepared as described above, using phenacyl bromide (24.9 mg, 0.125 mmol) and benzoyl chloride (116 *μ*L, 1.0 mmol), to provide a white solid (6.8 mg, 63%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.47−7.18 (m, 11H), 7.14 (m, 2H), 6.22 (t, *J* = 5.7 Hz, 1H), 4.40 (AB, *J* = 17.7 Hz, 2H), 3.87 (dd, *J* = 13.2, 5.7 Hz, 1H), 3.46 (dd, *J* = 13.2, 6.0 Hz, 1H). ESIMS *m/z* 431.1 [M − H]$^-$.

**4-Benzoyl-2,3-diphenyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10h).** Prepared as described above, using desyl bromide (34.4 mg, 0.125 mmol) and benzoyl

chloride (116 µL, 1.0 mmol), to provide a white solid (4.5 mg, 40%) following purification. ^{1}H NMR (acetone-$d_6$) δ 7.67 (dd, $J$ = 8.4, 1.8 Hz, 1H), 7.50−7.31 (m, 7H), 7.27 (br s, 5H), 7.19−7.04 (m, 5H), 6.39 (d, $J$ = 4.5 Hz, 1H), 5.58 (d, $J$ = 4.5 Hz, 1H). ESIMS $m/z$ 452.1 [M + H]$^+$, 474.1 [M + Na]$^+$, 450.2 [M − H]$^-$.

**2-Methyl-3-phenyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10i).** Prepared as described above, using 2-bromopropiophenone (19 µL, 0.125 mmol), to provide a white solid (4.2 mg, 59%) following purification. ^{1}H NMR (acetone-$d_6$) δ 7.47 (d, $J$ = 1.5 Hz, 1H), 7.43−7.30 (m, 5H), 7.25 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.07 (d, $J$ = 8.1 Hz, 1H), 5.95 (br s, 1H), 4.94 (t, $J$ = 2.4 Hz, 1H), 3.49 (qd, $J$ = 6.9, 2.7 Hz, 1H), 1.14 (d, $J$ = 6.9 Hz, 3H). ESIMS $m/z$ 284.2 [M + H]$^+$, 284.2 [M − H]$^-$.

**2,3-Diphenyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10j).** Prepared as described above, using desyl bromide (34.4 mg, 0.125 mmol), to provide a white solid (5.0 mg, 58%) following purification. ^{1}H NMR (acetone-$d_6$) δ 7.57 (d, $J$ = 1.8 Hz, 1H), 7.37−7.33 (m, 1H), 7.21−7.09 (m, 7H), 6.97−6.90 (m, 4H), 6.05 (br s, 1H), 5.09 (t, $J$ = 2.7 Hz, 1H), 4.62 (d, $J$ = 2.7 Hz, 1H). ESIMS $m/z$ 348.1 [M + H]$^+$, 346.2 [M − H]$^-$.

**4-(Cyclopropylcarbonyl)-3-phenyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10k).** Prepared as described above, using phenacyl bromide (24.9 mg, 0.125 mmol) and cyclopropanecarbonyl chloride (91 µL, 1.0 mmol), to provide a white solid (4.8 mg, 56%) following purification. ^{1}H NMR (acetone-$d_6$) δ 8.10 (d, $J$ = 1.8 Hz, 1H), 7.68 (dd, $J$ = 8.4, 1.8 Hz, 1H), 7.40−7.15 (m, 6H), 6.37 (t, $J$ = 5.4 Hz, 1H), 3.73 (dd, $J$ = 13.2, 5.7 Hz, 1H), 3.57 (dd, $J$ = 13.2, 5.4 Hz, 1H), 1.88−1.81 (m, 1H), 1.20−1.11 (m, 1H), 1.05−0.86 (m, 2H), 0.79−0.69 (m, 1H). ESIMS $m/z$ 340.1 [M + H]$^+$, 362.1 [M + Na]$^+$, 338.2 [M − H]$^-$.

**3-Phenyl-4-(2-thienylcarbonyl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10l).** Prepared as described above, using phenacyl bromide (24.9 mg, 0.125 mmol) and 2-thiophenecarbonyl chloride (107 µL, 1.0 mmol), to provide a white solid (5.9 mg, 62%) following purification. ^{1}H NMR (acetone-$d_6$) δ 7.67 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.65−7.62 (m, 2H), 7.50−7.46 (m, 2H), 7.39−7.27 (m, 3H), 7.22−7.20 (m, 1H), 6.94−6.90 (m, 2H), 6.35 (t, $J$ = 5.4 Hz, 1H), 3.90 (dd, $J$ = 13.2, 6.3 Hz, 1H), 3.65 (dd, $J$ = 13.2, 5.1 Hz, 1H). ESIMS $m/z$ 382.1 [M + H]$^+$, 404.0 [M + Na]$^+$, 380.1 [M − H]$^-$.

**4-(2-Furoyl)-3-phenyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10m).** Prepared as described above, using phenacyl bromide (24.9 mg, 0.125 mmol) and 2-furoyl chloride (99 µL, 1.0 mmol), to provide a white solid (5.0 mg, 55%) following purification. ^{1}H NMR (acetone-$d_6$) δ 7.67 (dd, $J$ = 8.4, 2.1 Hz, 1H), 7.56−7.46 (m, 4H), 7.35−7.19 (m, 4H), 6.69 (dd, $J$ = 3.6, 0.9 Hz, 1H), 6.48 (dd, $J$ = 3.6, 1.8 Hz, 1H), 6.33 (t, $J$ = 5.4 Hz, 1H), 3.88 (dd, $J$ = 13.2, 5.7 Hz, 1H), 3.67 (dd, $J$ = 13.2, 5.1 Hz, 1H). ESIMS $m/z$ 366.1 [M + H]$^+$, 388.0 [M + Na]$^+$, 364.1 [M − H]$^-$.

**4-(4-Methoxybenzoyl)-3-phenyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10n).** Prepared as de-

scribed above, using phenacyl bromide (24.9 mg, 0.125 mmol) and *p*-anisoyl chloride (170.6 mg, 1.0 mmol), to provide a white solid (7.0 mg, 69%) following purification. ^{1}H NMR (acetone-$d_6$) δ 7.54 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.47 (m, 2H), 7.38−7.16 (m, 7H), 6.83 (dt, $J$ = 9.0, 2.7 Hz, 2H), 6.34 (t, $J$ = 5.1 Hz, 1H), 3.92 (dd, $J$ = 13.2, 5.4 Hz, 1H), 3.77 (s, 3H), 3.71 (dd, $J$ = 13.2, 4.5 Hz, 1H). ESIMS $m/z$ 406.0 [M + H]$^+$, 428.0 [M + Na]$^+$, 404.2 [M − H]$^-$.

**4-(4-Fluorobenzoyl)-3-phenyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10o).** Prepared as described above, using phenacyl bromide (24.9 mg, 0.125 mmol) and *p*-fluorobenzoyl chloride (118 µL, 1.0 mmol), to provide a white solid (6.0 mg, 61%) following purification. ^{1}H NMR (acetone-$d_6$) δ 7.60 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.50−7.40 (m, 4H), 7.36−7.15 (m, 5H), 7.11−7.04 (m, 2H), 6.36 (t, $J$ = 5.1 Hz, 1H), 3.96 (dd, $J$ = 13.2, 5.7 Hz, 1H), 3.70 (dd, $J$ = 13.2, 5.1 Hz, 1H). ESIMS $m/z$ 394.0 [M + H]$^+$, 416.0 [M + Na]$^+$, 392.1 [M − H]$^-$.

**4-(4-Cyanobenzoyl)-3-phenyl-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (10p).** Prepared as described above, using phenacyl bromide (24.9 mg, 0.125 mmol) and *p*-cyanobenzoyl chloride (165.6 mg, 1.0 mmol), to provide a white solid (5.9 mg, 59%) following purification. ^{1}H NMR (acetone-$d_6$) δ 7.73 (m, 2H), 7.60−7.48 (m, 5H), 7.39−7.20 (m, 5H), 6.36 (t, $J$ = 5.4 Hz, 1H), 3.98 (dd, $J$ = 13.5, 5.7 Hz, 1H), 3.68 (dd, $J$ = 13.5, 5.4 Hz, 1H). ESIMS $m/z$ 423.1 [M + Na]$^+$, 399.1 [M − H]$^-$.

**General Procedure for Preparation of 4-Acyl-3-(methanethiol-*S*-aryl)-3,4-dihydro-1,4-benzothiazines.** Resin-bound 3-chloromethyl-3,4-dihydro-1,4-benzothiazine (0.025 mmol), prepared using the above procedure for 3,4-dihydro-1,4-benzothiazines but with 1,3-dichloroacetone (15.9 mg, 0.125 mmol) and NaCNBH$_3$ (7.8 mg, 0.125 mmol), was washed with CH$_2$Cl$_2$ (3 × 1 min), placed in a Teflon-capped hydrolysis tube, and dried under vacuum. Under an inert atmosphere, a solution of DIEA (0.22 mL, 1.25 mmol) and an aromatic thiol (1.25 mmol), together in DMF (1.0 mL), were added to the resin. After heating the reaction at 80 °C for 24 h, the resulting resin was washed with DMF (3 × 1 min) and CH$_2$Cl$_2$ (3 × 1 min), placed in a Teflon-capped hydrolysis tube, and dried under vacuum. Subsequently, under an inert atmosphere, CH$_2$Cl$_2$ (1 mL), DIEA (0.26 mL, 1.5 mmol), and TMS-Cl (63 µL, 0.5 mmol) were added in order, and the mixture was heated for 1 h at 80 °C. The reaction was then cooled, benzoyl chloride (116 µL, 1.0 mmol) was added, and heating occurred for 24 h at 80 °C. The resulting resin was washed, cleaved, and worked-up as described in the general procedure for preparation of benzothiazoles, except for using TFA−TES (19:1) as the cleavage reagent. The crude residue was redissolved and purified over silica gel with CHCl$_3$−THF−HOAc (95:5:0.5).

**4-Benzoyl-3-(methanethiol-*S*-phenyl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (13a).** Prepared as described above, using thiophenol (128 µL, 1.25 mmol), to provide a white solid (5.5 mg, 50%) following purification. ^{1}H NMR (acetone-$d_6$) δ 7.64 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.47−7.43 (m, 2H), 7.38−7.22 (m, 10H), 5.35 (m, 1H), 3.68 (dd, $J$ = 12.9, 5.1 Hz, 1H), 3.39 (dd, $J$ = 12.9, 3.6 Hz, 1H),

3.21 (AB, $J = 14.1$ Hz, 1H), 3.18 (AB, $J = 14.1$ Hz, 1H). ESIMS $m/z$ 422.0 [M + H]$^+$, 444.1 [M + Na]$^+$, 420.2 [M − H]$^-$.

**4-Benzoyl-3-(methanethiol-*S*-(4-chlorophenyl)-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic Acid (13b).** Prepared as described above, using *p*-chlorothiophenol (180.8 mg, 1.25 mmol), to provide a white solid (5.8 mg, 51%) following purification. $^1$H NMR (acetone-$d_6$) $\delta$ 7.64 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.47 (ddd, $J = 8.7$, 2.1, 2.1 Hz, 2H), 7.38−7.22 (m, 9H), 5.33 (m, 1H), 3.69 (dd, $J = 12.9$, 5.1 Hz, 1H), 3.37 (dd, $J = 12.9$, 3.9 Hz, 1H), 3.22 (AB, $J = 14.1$ Hz, 1H), 3.20 (AB, $J = 14.1$ Hz, 1H). ESIMS $m/z$ 456.0 [M + H]$^+$, 478.0 [M + Na]$^+$, 454.1 [M − H]$^-$.

**General Procedure for Preparation of 3,4-Dihydro-3-oxo-1,4-benzothiazines.** Resin-bound 2-amino thiophenol (**7**) (0.025 mmol), prepared immediately before use, was washed with CH$_2$Cl$_2$−DIEA (19:1) (3 × 1 min), CH$_2$Cl$_2$ (3 × 1 min), and DMF (3 × 1 min) and swollen in DMF (0.8 mL). Next, DIEA (22 $\mu$L, 0.125 mmol) and an $\alpha$-bromo methyl ester (0.125 mmol) were added sequentially to the resin, and the mixture was heated to 80 °C for 24 h. The resulting resin was washed with DMF (3 × 1 min) and CH$_2$Cl$_2$ (3 × 1 min), and dried under vacuum. Subsequently, under an inert atmosphere, THF (1 mL) and LiO*t*-Bu in THF (1 M) (0.13 mL, 0.125 mmol) were added, in order, and the mixture was agitated for 30 min. The resin was then washed with THF (3 × 0.25 min) under argon pressure, and a solution of an electrophile (alkyl bromide, alkyl iodide, or acid chloride) (1 mmol) in THF (1 mL) was added. The resulting resin was agitated at 25 °C for 24 h, washed with DMF (3 × 1 min) and CH$_2$Cl$_2$ (3 × 1 min), and cleaved with TFA−TES (19:1, 2 mL) for 1 h. The filtrate from the cleavage reaction was collected, combined with TFA washes (3 mL) of the resin, evaporated under a stream of N$_2$, taken up in CH$_3$CN−H$_2$O, and lyophilized. The crude residue was redissolved and purified over silica gel with CHCl$_3$−THF−HOAc (95:5:0.5) to elute compounds **14a**−**f**, **15a**−**j** or with CHCl$_3$−THF−HOAc (6:5:0.5) to elute **14g**.

**3,4-Dihydro-3-oxo-2*H*-1,4-benzothiazine-6-carboxylic Acid (14a).** Prepared as described above, using methyl bromoacetate (12 $\mu$L, 0.125 mmol), to provide a white solid (2.7 mg, 52%) following purification. $^1$H NMR (acetone-$d_6$) $\delta$ 7.73 (d, $J = 1.8$ Hz, 1H), 7.64 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.45 (d, $J = 8.1$ Hz, 1H), 3.52 (s, 2H). ESIMS $m/z$ 208.1 [M − H]$^-$.

**2-Methyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-6-carboxylic Acid (14b).** Prepared as described above, using methyl 2-bromopropionate (14 $\mu$L, 0.125 mmol), to provide a white solid (3.7 mg, 67%) following purification. $^1$H NMR (acetone-$d_6$) $\delta$ 7.74 (d, $J = 1.8$ Hz, 1H), 7.65 (dd, $J = 8.1$, 1.8 Hz, 1H), 7.45 (d, $J = 8.1$ Hz, 1H), 3.68 (q, $J = 6.9$ Hz, 1H), 1.42 (d, $J = 6.9$ Hz, 3H). ESIMS $m/z$ 222.0 [M − H]$^-$.

**2-Ethyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-6-carboxylic Acid (14c).** Prepared as described above, using methyl 2-bromobutyrate (14 $\mu$L, 0.125 mmol), to provide a white solid (4.1 mg, 69%) following purification. $^1$H NMR (acetone-$d_6$) $\delta$ 7.73 (d, $J = 1.5$ Hz, 1H), 7.65 (dd, $J = 8.1$, 1.8 Hz, 1H), 7.46 (d, $J = 8.1$ Hz, 1H), 3.46 (dd, $J = 8.4$,

6.3 Hz, 1H), 1.91 (m, 1H), 1.62 (m, 1H), 1.05 (t, $J = 7.5$ Hz, 3H). ESIMS $m/z$ 236.1 [M − H]$^-$.

**2-Phenyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-6-carboxylic Acid (14d).** Prepared as described above, using methyl $\alpha$-bromophenylacetate (20 $\mu$L, 0.125 mmol), to provide a white solid (3.9 mg, 55%) following purification. $^1$H NMR (acetone-$d_6$) $\delta$ 7.78 (d, $J = 1.5$ Hz, 1H), 7.64 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.42−7.27 (m, 5H), 4.94 (s, 1H). ESIMS $m/z$ 286.1 [M + H]$^+$, 308.1 [M + Na]$^+$, 284.1 [M − H]$^-$.

**2-(4-Trifluoromethoxybenzyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-6-carboxylic Acid (14e).** Prepared as described above, using methyl 2-bromo-3-[4-(trifluoromethoxy)phenyl]-propionate (40.9 mg, 0.125 mmol), to provide a white solid (5.5 mg, 57%) following purification. $^1$H NMR (DMSO-$d_6$) $\delta$ 7.54 (d, $J = 1.8$ Hz, 1H), 7.48 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.37−7.27 (m, 5H), 3.95 (dd, $J = 9.0$, 6.0 Hz, 1H), 3.16 (dd, $J = 14.4$, 6.0 Hz, 1H), 2.79 (dd, $J = 14.4$, 9.0 Hz, 1H). ESIMS $m/z$ 382.1 [M − H]$^-$.

**2,2-Dimethyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-6-carboxylic Acid (14f).** Prepared as described above, using methyl $\alpha$-bromoisobutyrate (16 $\mu$L, 0.125 mmol), to provide a white solid (2.6 mg, 44%) following purification. $^1$H NMR (acetone-$d_6$) $\delta$ 7.76 (d, $J = 1.8$ Hz, 1H), 7.66 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.44 (d, $J = 7.8$ Hz, 1H), 1.43 (s, 6H). ESIMS $m/z$ 236.0 [M − H]$^-$.

***N*-[(2-Methyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazin-6-yl)carbonyl]glycine (14g).** Prepared as described above, using methyl 2-bromopropionate (14 $\mu$L, 0.125 mmol), to provide a white solid (3.9 mg, 55%) following purification. $^1$H NMR (CD$_3$OD) $\delta$ 7.48 (dd, $J = 8.1$, 1.8 Hz, 1H), 7.43 (d, $J = 1.8$ Hz, 1H), 7.39 (d, $J = 8.1$ Hz, 1H), 4.06 (s, 2H), 3.60 (q, $J = 6.9$ Hz, 1H), 1.42 (d, $J = 6.9$ Hz, 3H). ESIMS $m/z$ 281.0 [M + H]$^+$, 303.0 [M + Na]$^+$, 279.1 [M − H]$^-$.

**4-Methyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-6-carboxylic Acid (15a).** Prepared as described above, using methyl bromoacetate (12 $\mu$L, 0.125 mmol) and methyl iodide (62 $\mu$L, 1.0 mmol), to provide a white solid (3.5 mg, 63%) following purification. $^1$H NMR (acetone-$d_6$) $\delta$ 7.79 (d, $J = 1.2$ Hz, 1H), 7.70 (dd, $J = 8.1$, 1.8 Hz, 1H), 7.51 (d, $J = 7.8$ Hz, 1H), 3.53 (s, 2H), 3.47 (s, 3H). ESIMS $m/z$ 222.1 [M − H]$^-$.

**2,4-Dimethyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-6-carboxylic Acid (15b).** Prepared as described above, using methyl 2-bromopropionate (14 $\mu$L, 0.125 mmol) and methyl iodide (62 $\mu$L, 1.0 mmol), to provide a white solid (3.6 mg, 61%) following purification. $^1$H NMR (acetone-$d_6$) $\delta$ 7.79 (d, $J = 1.5$ Hz, 1H), 7.70 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.51 (d, $J = 8.1$ Hz, 1H), 3.64 (q, $J = 7.2$ Hz, 1H), 3.49 (s, 3H), 1.40 (d, $J = 7.2$ Hz, 3H). ESIMS $m/z$ 236.1 [M − H]$^-$.

**2-Ethyl-4-methyl-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-6-carboxylic Acid (15c).** Prepared as described above, using methyl 2-bromobutyrate (14 $\mu$L, 0.125 mmol) and methyl iodide (62 $\mu$L, 1.0 mmol), to provide a white solid (4.1 mg, 65%) following purification. $^1$H NMR (acetone-$d_6$) $\delta$ 7.80 (d, $J = 1.5$ Hz, 1H), 7.70 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 3.94 (m, 4H), 1.94−1.79 (m, 1H), 1.63−1.48 (m, 1H), 1.01 (t, $J = 7.5$ Hz, 3H). ESIMS $m/z$ 250.1 [M − H]$^-$.

**4-Methyl-2-(4-trifluoromethoxybenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-6-carboxylic Acid (15d).** Prepared as described above, using methyl 2-bromo-3-[4-(trifluoromethoxy)phenyl]propionate (40.9 mg, 0.125 mmol) and methyl iodide (62 μL, 1.0 mmol), to provide a white solid (5.5 mg, 55%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.81 (d, $J$ = 1.2 Hz, 1H), 7.71 (dd, $J$ = 8.1, 1.2 Hz, 1H), 7.50 (d, $J$ = 8.1 Hz, 1H), 7.39−7.37 (m, 2H), 7.25 (dd, $J$ = 7.8, 0.9 Hz, 2H), 3.88 (dd, $J$ = 9.0, 6.3 Hz, 1H), 3.52 (s, 3H), 3.28 (dd, $J$ = 14.1, 6.0 Hz, 1H), 2.90 (dd, $J$ = 14.1, 9.0 Hz, 1H). ESIMS $m/z$ 396.2 [M − H]$^-$.

**2,2,4-Trimethyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-6-carboxylic Acid (15e).** Prepared as described above, using methyl α-bromoisobutyrate (16 μL, 0.125 mmol) and methyl iodide (62 μL, 1.0 mmol), to provide a white solid (3.2 mg, 51%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.81 (d, $J$ = 1.5 Hz, 1H), 7.72 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.48 (d, $J$ = 8.1 Hz, 1H), 3.51 (s, 3H), 1.39 (s, 6H). ESIMS $m/z$ 250.2 [M − H]$^-$.

**4-Allyl-2-methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-6-carboxylic Acid (15f).** Prepared as described above, using methyl 2-bromopropionate (14 μL, 0.125 mmol) and allyl iodide (91 μL, 1.0 mmol), to provide a white solid (4.7 mg, 71%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.84 (d, $J$ = 1.5 Hz, 1H), 7.70 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.51 (d, $J$ = 8.1 Hz, 1H), 5.94 (m, 1H), 5.15 (m, 2H), 4.68 (m, 2H), 3.72 (q, $J$ = 6.9 Hz, 1H), 1.43 (d, $J$ = 6.9 Hz, 3H). ESIMS $m/z$ 262.1 [M − H]$^-$.

**4-Benzyl-2-methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-6-carboxylic Acid (15g).** Prepared as described above, using methyl 2-bromopropionate (14 μL, 0.125 mmol) and benzyl bromide (119 μL, 1.0 mmol), to provide a white solid (5.5 mg, 70%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.78 (d, $J$ = 1.5 Hz, 1H), 7.65 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.52 (d, $J$ = 8.1 Hz, 1H), 7.34−7.18 (m, 5H), 5.36 (s, 2H), 3.83 (q, $J$ = 7.2 Hz, 1H), 1.50 (d, $J$ = 7.2 Hz, 3H). ESIMS $m/z$ 336.1 [M + Na]$^+$, 312.1 [M − H]$^-$.

**4-(4-Fluorobenzyl)-2-methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-6-carboxylic Acid (15h).** Prepared as described above, using methyl 2-bromopropionate (14 μL, 0.125 mmol) and *p*-fluorobenzyl bromide (125 μL, 1.0 mmol), to provide a white solid (5.0 mg, 60%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.80 (d, $J$ = 1.5 Hz, 1H), 7.66 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.52 (d, $J$ = 8.1 Hz, 1H), 7.31 (m, 2H), 7.08 (m, 2H), 5.35 (s, 2H), 3.83 (q, $J$ = 6.9 Hz, 1H), 1.49 (d, $J$ = 6.9 Hz, 3H). ESIMS $m/z$ 354.1 [M + Na]$^+$, 330.2 [M − H]$^-$.

**4-Benzoyl-2-methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-6-carboxylic Acid (15i).** Prepared as described above, using methyl 2-bromopropionate (14 μL, 0.125 mmol) and benzoyl chloride (116 μL, 1.0 mmol), to provide a white solid (5.2 mg, 63%) following purification. $^1$H NMR (acetone-$d_6$) δ 8.01−7.96 (m, 2H), 7.79 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.75−7.66 (m, 2H), 7.61−7.54 (m, 2H), 7.51 (d, $J$ = 1.5 Hz, 1H), 4.01 (q, $J$ = 6.9 Hz, 1H), 1.52 (d, $J$ = 6.9 Hz, 3H). ESIMS $m/z$ 350.0 [M + Na]$^+$, 326.1 [M − H]$^-$.

**2-Methyl-4-(2-thienylcarbonyl)-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-6-carboxylic Acid (15j).** Prepared as described above, using methyl 2-bromopropionate (14 μL,

0.125 mmol) and 2-thiophenecarbonyl chloride (107 μL, 1.0 mmol), to provide a white solid (4.9 mg, 59%) following purification. $^1$H NMR (acetone-$d_6$) δ 8.10 (dd, $J$ = 5.1, 1.5 Hz, 1H), 7.81 (d, $J$ = 1.5 Hz, 1H), 7.78 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.64 (d, $J$ = 8.1 Hz, 1H), 7.55 (d, $J$ = 1.5 Hz, 1H), 7.24 (dd, $J$ = 5.1, 3.9 Hz, 1H), 3.97 (q, $J$ = 6.9 Hz, 1H), 1.52 (d, $J$ = 6.9 Hz, 3H). ESIMS $m/z$ 356.0 [M + Na]$^+$, 332.0 [M − H]$^-$.

**General Procedure for Preparation of 1,1-Dioxides.** Either resin-bound 3,4-dihydro-1,4-benzothiazines or 3,4-dihydro-3-oxo-1,4-benzothiazines (0.025 mmol) were washed with CH$_2$Cl$_2$ (3 × 1 min) and swollen in a minimal amount of CH$_2$Cl$_2$. Next, a solution $m$CPBA (69 mg, 0.4 mmol) in CH$_2$Cl$_2$ (1 mL) was added to the resin, and reaction was for 6 h. The resulting resin was washed, cleaved, and worked-up as described in the general procedure for preparation of benzothiazoles, except for using TFA−TES (19:1) as the cleavage reagent. The crude residue was taken up in CH$_3$CN−H$_2$O, lyophilized, and purified over silica gel with CHCl$_3$−THF−HOAc (95:5:0.5).

**4-Benzoyl-1,1-dioxo-3-phenyl-3,4-dihydro-2H-1,4-benzothiazine-6-carboxylic Acid (11a).** Prepared as described above, starting with resin **10a**, to provide a white solid (5.6 mg, 55%) following purification. $^1$H NMR (acetone-$d_6$) δ 8.02 (d, $J$ = 0.9 Hz, 2H), 7.52 (s, 1H), 7.44−7.23 (m, 10H), 6.27 (t, $J$ = 8.4 Hz, 1H), 4.50 (dd, $J$ = 14.7, 8.1 Hz, 1H), 3.78 (dd, $J$ = 14.7, 9.3 Hz, 1H). ESIMS $m/z$ 408.0 [M + H]$^+$, 430.0 [M + Na]$^+$, 406.1 [M − H]$^-$.

**4-Benzoyl-1,1-dioxo-3-ethyl-3,4-dihydro-2H-1,4-benzothiazine-6-carboxylic Acid (11b).** Prepared as described above, starting with resin **10f**, to provide a white solid (4.7 mg, 52%) following purification. $^1$H NMR (acetone-$d_6$) δ 7.99 (d, $J$ = 0.9 Hz, 2H), 7.47 (t, $J$ = 1.2 Hz, 1H), 7.40−7.25 (m, 6H), 5.26 (m, 1H), 4.24 (dd, $J$ = 14.4, 7.8 Hz, 1H), 3.52 (dd, $J$ = 14.4, 6.3 Hz, 1H), 1.84 (m, 2H), 0.98 (t, $J$ = 7.2 Hz, 3H). ESIMS $m/z$ 382.0 [M + Na]$^+$, 358.0 [M − H]$^-$.

**1,1-Dioxo-2-methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-6-carboxylic Acid (16a).** Prepared as described above, starting with resin **14b**, to provide a white solid (3.2 mg, 50%) following purification. $^1$H NMR (acetone-$d_6$) δ 8.01−7.92 (m, 3H), 4.52 (q, $J$ = 6.9 Hz, 1H), 1.59 (d, $J$ = 6.9 Hz, 3H). ESIMS $m/z$ 254.0 [M − H]$^-$.

**1,1-Dioxo-2,4-dimethyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-6-carboxylic Acid (16b).** Prepared as described above, starting with resin **15b**, to provide a white solid (3.4 mg, 51%) following purification. $^1$H NMR (acetone-$d_6$) δ 8.06 (m, 1H), 8.01 (m, 2H), 4.52 (q, $J$ = 7.2 Hz, 1H), 3.59 (s, 3H), 1.57 (d, $J$ = 6.9 Hz, 3H). ESIMS $m/z$ 268.0 [M − H]$^-$.

**1,1-Dioxo-4-(4-fluorobenzyl)-2-methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-6-carboxylic Acid (16c).** Prepared as described above, starting with resin **15h**, to provide a white solid (4.4 mg, 48%) following purification. $^1$H NMR (acetone-$d_6$) δ 8.03 (d, $J$ = 7.8 Hz, 1H), 8.00 (d, $J$ = 0.9 Hz, 1H), 7.96 (dd, $J$ = 8.1, 1.5 Hz, 1H), 7.40−7.35 (m, 2H), 7.11−7.05 (m, 2H), 5.49 (s, 1H), 4.77 (q, $J$ = 6.9 Hz, 1H), 1.65 (d, $J$ = 6.0 Hz, 3H). ESIMS $m/z$ 362.3 [M − H]$^-$.

**Supporting Information Available.** General procedures, preparation of Wang-glycine resin, alternate experimental procedures for preparation of 2-arylbenzothiazoles and 3,4-dihydro-3-oxo-1,4-benzothiazines cores, and additional ESIMS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Yan, B.; Kumaravel, G. Probing Solid-Phase Reactions by Monitoring the IR Bands of Compounds on a Single "Flattened" Resin Bead. *Tetrahedron* **1996**, *52*, 843−848. For additional examples of nucleophilic aromatic substitution reactions, see: refs 2d, 2h, and 2i.

(6) Meyers, H. V.; Dilley, G. J.; Durgin, T. L.; Powers, T. S.; Winssinger, N. A.; Zhu, H.; Pavia, M. R. Multiple Simultaneous Synthesis of Phenolic Libraries. *Mol. Diversity* **1995**, *1*, 13−20.

(7) A similar reaction has been described for the synthesis of benzimidazoles. See: ref 4b.

(8) The use of excess DDQ resulted in unacceptable levels of side products, as revealed by HPLC analysis.

(9) A solution precedent was reported by: Wallenfels, K.; Gellrich, M.; Kubowitz, F. Über den Mechanismus der Wasserstoffübertragung mit Pyridinnucleotiden, X. Weitere Cozymase-Modelle und ein DPN-Analogon. *Justus Liebigs Ann. Chem.* **1959**, *621*, 137−148.

(10) Alternative stepwise procedures for the generation of the core structures were also investigated: (a) alkylation of **6** with free sulfhydryl (after *S*-trityl removal) by an α-bromo ketone, followed by reduction of the nitro group, and finally reductive amination; and (b) reductive amination of an α-bromo ketone onto *S*-trityl protected **7**, trityl deprotection, and finally treatment with base. These procedures were far inferior to the one-pot method; at most 50% product formed according to HPLC analysis, and in some cases, no product formed.

(11) 3,4-Dihydro-1,4-benzothiazines have been prepared in solution using similar procedures. See: (a) Wilhelm, M.; Schmidt, P. A Study of the Synthesis and Some Reactions of 3-Phenyl-1,4-benzothiazines (1). *J. Heterocycl. Chem.* **1969**, *6*, 635−638. (b) Habermann, J.; Ley, S. V.; Scott, J. S. Clean Six-Step Synthesis of a Piperidino-Thiomorpholine Library Using Polymer-Supported Reagents. *J. Chem. Soc., Perkin Trans. 1.* **1998**, 3127−3130.

(12) Amide bond formation by reactions between amines activated by *N*-silylation [using BSA (*N,O*-bis(trimethylsilyl)acetamide)] and acid fluorides have been described; see: (a) Rajeswari, S.; Jones, R. J.; Cava, M. P. A New Synthesis of Amides from Acyl Fluorides and N-Silylamines. *Tetrahedron Lett.* **1987**, *28*, 5099−5102. (b) Wenschuch, H.; Beyermann, M.; Winter, R.; Bienert, M.; Ionescu, D.; Carpino, L. A. Fmoc Amino Acid Fluorides in Peptide Synthesis − Extension of the Method to Extremely Hindered Amino Acids. *Tetrahedron Lett.* **1996**, *37*, 5483−5486. In our system, amide bond formation was more efficient using TMS-Cl as a silylating agent. Furthermore, we acylate with acid chlorides rather than fluorides.

(13) Mata, E. G. β-Lactams on Solid Support: Mild and Efficient Removal of Penicillin Derivatives from Merrifield Resin using Aluminum Chloride. *Tetrahedron Lett.* **1997**, *38*, 6335−6338.

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(15) 3,4-Dihydro-3-oxo-1,4-benzothiazines have been prepared in solution using similar procedures. See: (a) Funke, A.; Funke, G.; Millet, B. Dérivés de la phényl-2-dihydro-2,3-benzothiazine-1,4. *Bull. Soc. Chim. Fr.* **1961**, 1524−1526. (b) Coutts, R. T.; Peel, H. W.; Smith, E. M. Organic Sulfur Compounds. Part I. Benzothiazine Hydroxamic Acids and Related Compounds. *Can. J. Chem.* **1965**, *43*, 3221−3231. (c) Koós, M. Synthesis and Antimicrobial Activity of Some 2-Alkyl-2*H*-1,4-benzothiazin-3(4*H*)-ones and 2-Alkylbenzo[*d*]imidazolo[2,1-b]-thiazolidin-3-ones. *Monatsh. Chem.* **1994**, *125*, 1011−1016.

(16) Many alternative solution-phase routes to 3,4-dihydro-3-oxo-1,4-benzothiazines have been reported and reviewed in ref 3b.

(17) (a) Dörner, B.; Husar, G. M.; Ostresh, J. M.; Houghten, R. A. The Synthesis of Peptidomimetic Combinatorial Libraries Through Successive Amide Alkylations. *Bioorg. Med. Chem. Lett.* **1996**, *4*, 709−715. (b) Huang, W.; Scarborough, R. M. A New "Traceless" Solid-phase Synthesis Strategy: Synthesis of a Benzimidazole Library. *Tetrahedron Lett.* **1999**, *40*, 2665−2668.

(18) Acid chlorides must be either freshly distilled, or from a newly opened bottle, in order to avoid quenching the anion of the amide with trace acid.

(19) (a) Nefzi, A.; Giulianotti, M.; Houghten, R. A. Solid-Phase Synthesis of 2,4,5-Trisubstituted thiomorpholin-3-ones. *Tetrahedron Lett.* **1998**, *39*, 3671−3674. (b) Schwarz, M. K.; Tumelty, D.; Gallop, M. A. Solid-Phase Synthesis of 3,5-Disubstituted 2,3-Dihydro-1,5-benzothi-azepin-4(5*H*)-ones. *J. Org. Chem.* **1999**, *64*, 4, 2219−2231.

(20) For corresponding experiments using Wang-glycine resin, 1.04 g (0.77 mmol/g, 0.80 mmol) was used.

(21) For corresponding experiments using resin with the substrate bound to glycine, 43.1 mg (0.58 mmol/g, 0.025 mmol) was used.