# Solid-Phase Synthesis of 2-Amino-5-sulfanylthiazoles

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**Keywords:** Aromatic substitution / Parallel synthesis / Solid-phase synthesis / Sulfur heterocycles / Thioethers

A solid-phase synthesis that provides easy access to 2-amino-5-sulfanylthiazoles with variable substituents at C-2, C-4, and C-5 has been developed. The key step of this synthesis is a new *C*-sulfanylation of resin-bound 2-aminothiazoles by mixtures of various sulfur-containing building blocks and iodine. The resulting 2-amino-5-sulfanylthiazoles were obtained in high purities and yields after cleavage from the support. This synthesis could also be conducted as a multicomponent reaction, in which treatment of resin-bound thioureas with mixtures of aryl bromomethyl ketones and sulfanylating reagents yielded 2-amino-5-sulfanylthiazoles directly.


## Introduction

2-Aminothiazoles have often found use as drug candidates for the treatment of allergies,[1] arthritis,[2] hypertension,[3] psychoses,[4] osteoporosis,[5] obesity,[6] and bacterial[7] and HIV[8] infections. Several examples of biologically active 2-amino-5-sulfanylthiazoles have also been described; examples include compound **1**,[9] which has an antidiabetic effect, compound **2**,[10,11] which is effective against thrombocytopenia, and the anticancer compound **3**[12] (Figure 1).

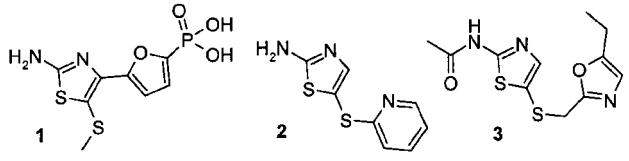
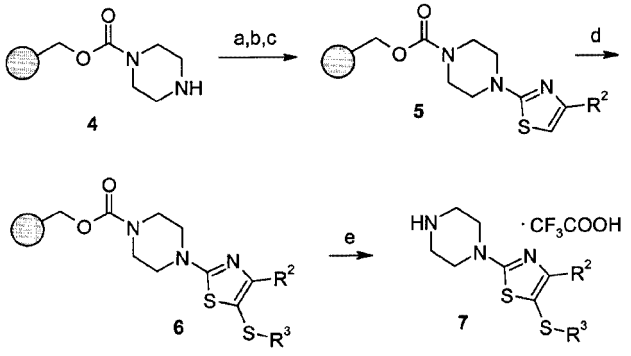


Figure 1. Biologically active 2-amino-5-sulfanylthiazoles

The screening of large libraries of 2-amino-5-sulfanylthiazoles might therefore provide new leads for drug discovery. Parallel solid-phase synthesis is suitable for the automated production of large libraries,[13−16] and we therefore wanted to develop a solid-phase synthesis of 2-amino-5-sulfanylthiazoles, based on commercially available reagents, and providing final products in purities high enough to enable screening without purification.

2-Amino-5-sulfanylthiazoles have previously been synthesized only in solution, either by direct sulfanylation of 2-aminothiazoles at C-5 with aromatic sulfenyl chlorides,[17] or by treatment of 2-amino-5-chlorothiazoles with aromatic thiols in the presence of a base at elevated temperatures.[18,19] We aimed to develop a solid-phase synthesis in which the thiazole moiety would be constructed on the resin to give access to 2-amino-5-sulfanylthiazoles with variable substituents at C-2, C-4, and C-5.

Because only a few sulfenyl halides are commercially available,[20] the generation of electrophilic sulfanylating reagents in situ could be a more practical access to these reagents. Electrophilic sulfanylating reagents can be generated from disulfides by treatment with chlorine, sulfuryl chloride, bromine,[21] or strong Lewis acids,[22,23] but the use of the less electrophilic iodine for this purpose has only rarely been reported.[24,25] To diminish the risk of halogenation instead of sulfanylation[26] or of premature cleavage of the linker by use of the common but highly reactive activating agents mentioned above, we decided to investigate the sul-



Scheme 1. Solid-phase synthesis of sulfanylthiazoles **7**: (a) 9-fluorenylmethyloxycarbonyl isothiocyanate (Fmoc-NCS), DCM, 22 °C, 4 h; (b) piperidine, NMP, 22 °C, 2 × 30 min; (c) $BrCH_2C(O)R^2$, AcOH, NMP, 22 °C, 3 h; (d) $R^3SH/I_2$ (1:2), NMP, 22 °C, 3 h; or $R^3SSR^3/I_2$ (1:1), NMP, 22 °C, 3 h; or $R^3SO_2Cl/PPh_3/I_2$ (1:2:2), NMP, 22 °C, 3 h; (e) trifluoroacetic acid/dichloromethane (TFA/DCM, 1:1, v/v), 22 °C, 30 min

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fanylation at C-5 of resin-bound 2-aminothiazoles with mixtures of thiols or disulfides and iodine.

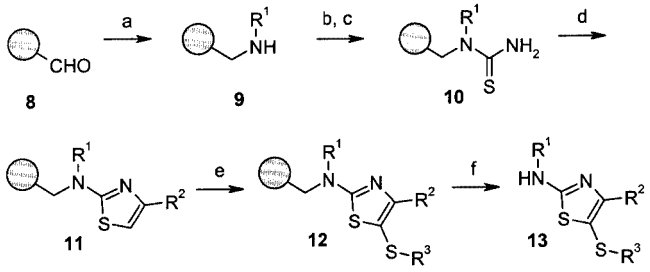
## Results and Discussion

As starting material for this new solid-phase synthesis we chose Wang resin bound piperazine **4** (Scheme 1), because we had previously good experience with this resin.[27] The resin-bound 2-aminothiazoles **5** were synthesized by formation of a resin-bound thiourea and subsequent condensation with various aryl bromomethyl ketones, as described earlier by others.[28]

Sulfanylation of the resin-bound 2-aminothiazoles **5** was initially attempted by treatment with mixtures of thiols and iodine under various conditions. Treatment of thiazoles **5** with mixtures of aromatic thiols and iodine at room temperature in NMP yielded the desired 2-amino-5-sulfanylthiazoles **7** in high purities and yields (Scheme 1, Table 1). When aliphatic thiols were used, however, the sulfanylation did not go to completion even upon addition of various bases that should promote the formation of disulfides.[29] On the other hand, when mixtures of disulfides and iodine were used as sulfanylating reagent, complete conversions were observed both with aliphatic and aromatic disulfides (Scheme 1, Table 1).

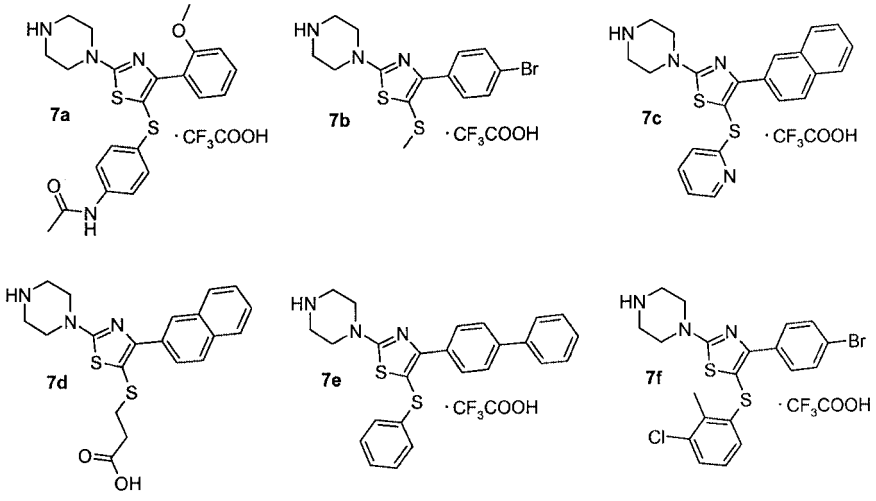
The sulfanylation with mixtures of aromatic thiols or disulfides and iodine was robust and reproducible, and the reaction proceeded equally well in the presence of small amounts of acetic acid or tertiary amines, at temperatures ranging between room temperature and 60 °C. Thiols or disulfides with various functional groups, such as carboxy, pyridyl, or hydroxy groups, could also be used without the need for any protective groups.

Because of the large number of commercially available sulfonyl chlorides,[30] their use as electrophilic sulfanylating intermediates was also investigated. It has previously been reported that aromatic sulfonyl chlorides (but not aliphatic ones) can be converted into the corresponding thiols by treatment with triphenylphosphane and iodine,[31] probably through intermediate formation of sulfenyl chlorides or disulfides. We found that the addition of a mixture of aromatic




Scheme 2. Solid-phase synthesis of sulfanylthiazoles **13**: (a) $R^1NH_2$, $NaBH_3CN$, AcOH, $H_2O$, NMP, 22 °C, 4 h; (b) Fmoc-NCS, DCM, 22 °C, 4 h; (c) piperidine, NMP, 22 °C, 2 × 30 min; (d) $BrCH_2C(O)R^2$, AcOH, NMP, 22 °C, 3 h; (e) $R^3SH/I_2$ (1:2), NMP, 22 °C, 3 h; or $R^3SSR^3/I_2$ (1:1), NMP, 22 °C, 3 h; or $R^3SO_2Cl/PPh_3/I_2$ (1:2:2), NMP, 22 °C, 3 h; (f) TFA/DCM/$Et_3SiH$ (60:35:5, v/v/v), 22 °C, 1 h

Table 1. Purities and yields of thiazoles **7** as obtained after cleavage from the resin; compound **7a** was synthesized from an aromatic thiol; compounds **7b**−**7e** were synthesized from disulfides; compound **7f** was synthesized from an aromatic sulfonyl chloride/triphenylphosphane

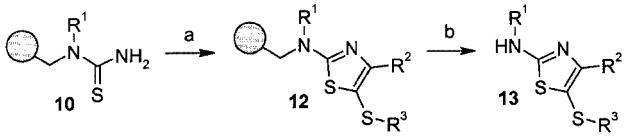



| Compound | LC-MS $[M + H]^+$ | Purity[a] | Yield[b] |
|---|---|---|---|
| **7a** | 441 | 86% | 0.72 mmol |
| **7b** | 372 | 93% | 0.60 mmol |
| **7c** | 405 | 94% | 0.80 mmol |
| **7d** | 400 | 96% | 0.65 mmol |
| **7e** | 430 | 97% | 0.79 mmol |
| **7f** | 482 | 96% | 0.81 mmol |

[a] Determined by HPLC (210 nm). [b] Amount of product obtained per gram of starting Wang resin, as determined by $^1H$ NMR.

sulfonyl chlorides and triphenylphosphane in *N*-methyl-2-pyrrolidinone (NMP) to a mixture of resin-bound 2-aminothiazoles **5** with iodine in the same solvent resulted in the clean formation of 2-amino-5-sulfanylthiazoles **7** (Scheme 1, Table 1). With aliphatic sulfonyl chlorides, however, only nonsulfanylated aminothiazoles were obtained.

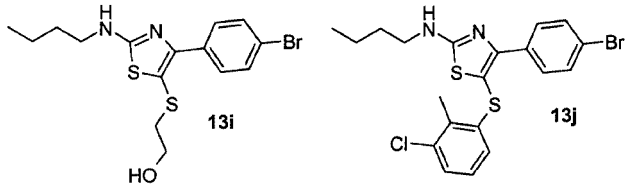
With the aim of preparing 2-amino-5-sulfanylthiazoles with variable primary monoamine substituents at C-2, the use of a formyl-functionalized resin was investigated. The solid-phase synthesis of 2-aminothiazoles on ArgoGel-MB-CHO resin had been reported earlier, but cleavage from this resin required rather harsh conditions (95% TFA, 50 °C, 4 h).[28] Therefore, the more acid-sensitive 2-(3,5-dimethoxy-4-formylphenoxy)ethyl polystyrene resin **8** was tested (Scheme 2).[13] Resin **8** was reductively aminated by a one-step procedure,[32] and the resulting secondary amines **9** were converted into 2-aminothiazoles **11** via thioureas **10**




Scheme 3. Multi-component reaction for direct conversion of thioureas **10** into sulfanylthiazoles **12**: (a) $BrCH_2C(O)R^2/R^3SH/I_2$ (1:2:4), NMP, 22 °C, 3 h; or $BrCH_2C(O)R^2/R^3SSR^3/I_2$ (1:2:2), NMP, 22 °C, 3 h; or $BrCH_2C(O)R^2/R^3SO_2Cl/PPh_3/I_2$ (1:2:4:4), NMP, 22 °C, 3 h; (b) see Scheme 2

by the same procedure as used for resin **4**. The sulfanylation of intermediates **11** was conducted as described above, and subsequent cleavage (60% TFA, 22 °C, 1 h) yielded the desired 2-amino-5-sulfanylthiazoles **13** in similar purities as

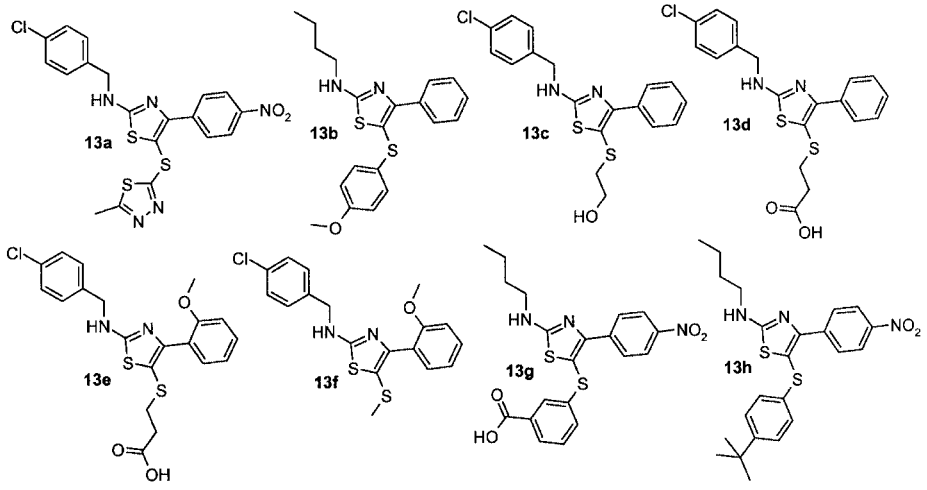
Table 3. Purities and yields of thiazoles **13** synthesized by multi-component reaction: **13a** and **13b** were synthesized from aryl bromomethyl ketones/aromatic thiols; **13f** and **13i** were synthesized from aryl bromomethyl ketones/disulfides; **13h** and **13j** were synthesized from aryl bromomethyl ketones/aromatic sulfonyl chlorides/triphenylphosphane




| Compound | LC-MS [M + H]$^+$ | Purity[a] | Yield[b] |
|---|---|---|---|
| **13a** | 476 | 86% | 0.27 mmol |
| **13b** | 371 | 78% | 0.18 mmol |
| **13f** | 377 | 85% | 0.28 mmol |
| **13h** | 442 | 82% | 0.18 mmol |
| **13i** | 389 | 81% | 0.14 mmol |
| **13j** | 469 | 91% | 0.22 mmol |

[a] See corresponding footnote in Table 1. [b] See corresponding footnote in Table 1.

Table 2. Purities and yields of thiazoles **13** as obtained after cleavage from the resin; compounds **13a** and **13b** were synthesized from aromatic thiols; compounds **13c**−**13f** were synthesized from disulfides; compounds **13g** and **13h** were synthesized from aromatic sulfonyl chlorides




| Compound | LC-MS [M + H]$^+$ | Purity[a] | Yield[b] |
|---|---|---|---|
| **13a** | 476 | 93% | 0.27 mmol |
| **13b** | 371 | 80% | 0.15 mmol |
| **13c** | 377 | 84% | 0.24 mmol |
| **13d** | 405 | 85% | 0.12 mmol |
| **13e** | 435 | 86% | 0.22 mmol |
| **13f** | 377 | 85% | 0.20 mmol |
| **13g** | 430 | 92% | 0.23 mmol |
| **13h** | 442 | 91% | 0.14 mmol |

[a] See corresponding footnote in Table 1. [b] See corresponding footnote in Table 1.

for products **7**, but in lower quantities (Table 2). The lower quantities were caused by a lower initial loading of the formyl resin than on Wang resin. Sulfanylation could also be conducted in this case by treatment with mixtures of aromatic thiols, disulfides, or aromatic sulfonyl chlorides/triphenylphosphane with iodine.

In order to reduce the total number of steps of this synthesis, and thereby improve its efficiency, the possibility of the conversion of resin-bound thioureas **10** into 2-amino-5-sulfanylthiazoles **12** in a one-pot, multi-component reaction was explored. Because both the halogeno ketone and the sulfanylating reagent are electrophiles, we reasoned that thiazole formation and sulfanylation might proceed in a one-pot fashion. This turned out to be the case. Treatment of thioureas **10** with a mixture of aryl bromomethyl ketones and sulfanylating reagents, followed by cleavage from the support, cleanly yielded products **13** (Scheme 3, Table 3). This one-pot procedure requires less solvent and time than the two-step variant, which makes this synthesis even more suitable for automation.

Because the final products of this synthesis were intended for screening without purification, the purities of the crude products were important. As shown in the preceding tables, this requirement was fulfilled. To illustrate the high purity of the crude products further, the $^1$H NMR spectra of both crude and purified thiazole **13f** are shown in Figure 2.

### Mechanistic Considerations

As described in the introduction, direct sulfanylation of 2-aminothiazoles at C-5 can be achieved by treatment with aromatic sulfenyl chlorides,[17] and it is generally assumed that these and related reactions are electrophilic aromatic substitutions.[33,34] We therefore believe that the sulfanylation of resin-bound 2-aminothiazoles at C-5 as described above also proceeds through electrophilic attack at the thiazole (Scheme 4).

No sulfanylation occurred when the resin-bound 2-aminothiazoles **11** were treated with disulfides in the absence of iodine, and it is therefore assumed that the electrophilic sulfanylating intermediates generated in situ must be

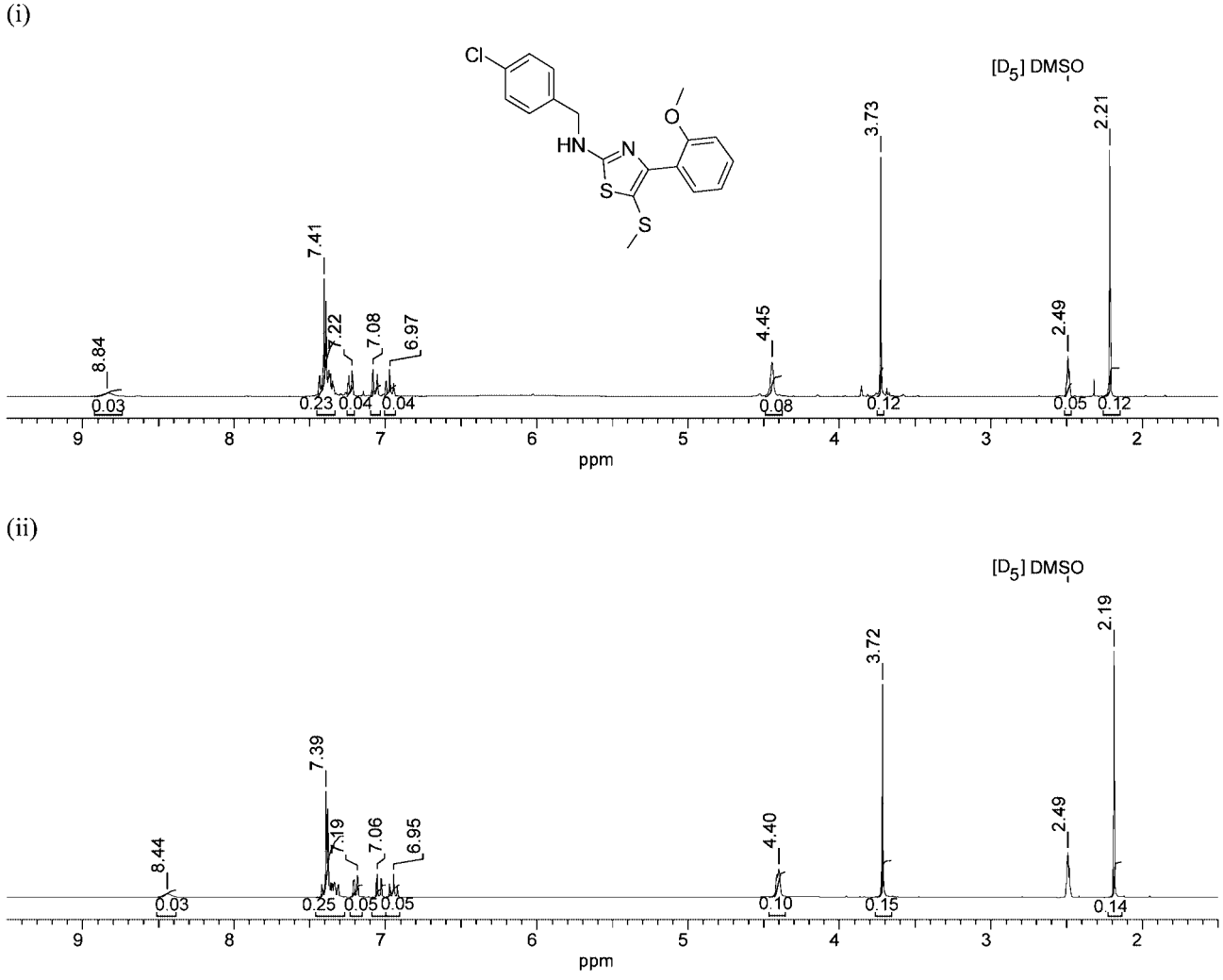
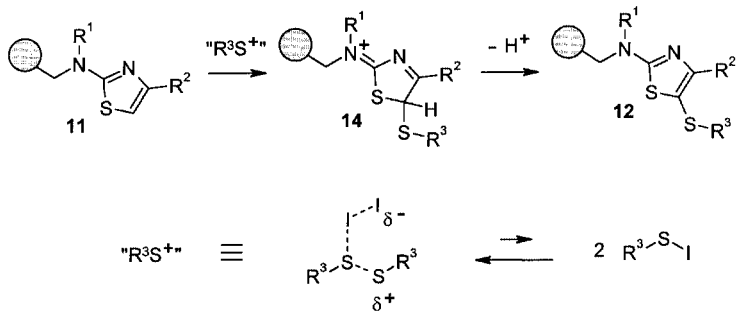



Figure 2. $^1$H NMR spectra of crude and purified thiazole **13f**: (i) crude **13f** (HPLC purity: 85%); (ii) **13f** purified by preparative HPLC (HPLC purity: 100%)




Scheme 4. Suggested mechanism for the sulfanylation of 2-aminothiazoles **11** by a sulfenium ion equivalent "$R^3S^+$", and possible structure of this electrophilic sulfanylating intermediate

disulfide−iodine complexes or sulfenyl iodides (Scheme 4). Complexes between disulfides and Lewis acids,[22,23,35] Brønsted acids,[36,37] or iodine[24] have been suggested as the reactive electrophilic intermediates in several substitution and addition reactions. Spectrophotometric studies furthermore also indicated the existence of 1:1 charge-transfer complexes between disulfides and iodine in solution.[38] Sulfenyl iodides, on the other hand, could in principle also be the electrophilic reactive species.[24,25,39]

Although we cannot fully exclude a mechanism in which the resin-bound 2-aminothiazoles are first iodinated and then undergo nucleophilic aromatic substitution with a thiol, we consider this mechanism unlikely. In most of our experiments no thiols or only traces of thiols were present in the reaction mixtures. Furthermore, we never observed any 2-amino-5-iodothiazoles as by-products, and it seems unlikely that 2-amino-5-iodothiazoles would undergo smooth nucleophilic aromatic substitution at room temperature in the absence of strong bases (i.e., under the conditions of the title reaction).

## Conclusion

The sulfanylation of resin-bound 2-aminothiazoles at C-5 by electrophilic sulfanylating intermediates generated in situ from mixtures of various sulfur derivatives and iodine has been developed. We believe that this mild method for the generation of electrophilic sulfanylating intermediates from easily available reagents such as thiols, disulfides, and sulfonyl chlorides might in the future find use in a range of other sulfanylation reactions both on solid phase and in solution.

With this reaction, a solid-phase synthesis of 2-amino-5-sulfanylthiazoles with variable substituents at C-2, C-4, and C-5 has been developed. The 2-amino-5-sulfanylthiazoles could be prepared either by sulfanylation of resin-bound 2-aminothiazoles, or by a multi-component reaction in which resin-bound thioureas were treated with mixtures of aryl bromomethyl ketones and various sulfanylating reagents. This synthesis provides a fast and efficient route to highly substituted 2-amino-5-sulfanylthiazoles featuring functional groups important for protein binding such as hydroxy, carboxy, and amido groups, as well as various heterocycles. With this synthesis it should therefore be possible to prepare both libraries for general screening and libraries directed towards specific biological targets.

## Experimental Section

**General:** All reagents were used as purchased. *p*-Benzyloxybenzyl alcohol polystyrene resin (Wang resin) was purchased with a loading capacity of 1.07 mmol/g, and 2-(3,5-dimethoxy-4-formylphenoxy)ethyl polystyrene resin (**8**) was purchased with a loading capacity of approx. 0.4 mmol/g.[40] All reactions were performed in either 60- or 12-mL fritted Teflon reactors fixed on an orbital shaker. Products were cleaved from the resin (150 mg) either by treatment with TFA/DCM (1:1, v/v, 2 mL, 30 min) or with TFA/DCM/$Et_3SiH$ (60:35:5, v/v/v, 2 mL, 1 h). After cleavage, the resin was washed with DCM (1 mL), and the combined filtrates were concentrated and redissolved in acetonitrile (2.5 mL). An aliquot (100 μL) of this solution was used for HPLC-MS analysis; the remaining solution was reconcentrated, stripped with MeOH (2 mL), dried under reduced pressure at 50 °C, and dissolved in 0.6 mL of [$D_6$]DMSO. The amount of product was determined by $^1$H NMR of these samples, using [$D_5$]DMSO as internal standard. All NMR spectra were recorded with a 300-MHz instrument. Purities of all compounds were estimated from integrated peak areas obtained by UV detection (210 nm) during an HPLC-MS experiment. HPLC systems from Merck-Hitachi (Hibar™ RT 250-4, Lichrosorb™ RP 18, 5.0 μm, 4.0 × 250 mm, gradient elution, 20−80% acetonitrile in water over 30 min, 1.0 mL/min, detection at 254 nm) and Waters (Symmetry™, C18, 3.5 μm, 3.0 × 150 mm, gradient elution, 5−90% acetonitrile in water over 15 min, 1.0 mL/min, detection at 214 nm) were used. All products were furthermore characterized by $^{13}$C NMR, $^1$H-$^1$H COSY, and HSQC. The trifluoroacetate ion gave rise to two quadruplets at δ = 159 ppm ($J$ = 35 Hz) and δ = 116 ppm ($J$ = 294 Hz), but these signals have been omitted from the listing of $^{13}$C NMR chemical shifts. Five representative compounds were recrystallized and their molecular formula confirmed by elemental analysis. Four compounds were furthermore purified by preparative HPLC, and their $^1$H NMR spectra were compared with the spectra of the crude products. These compounds were eluted over 11 min with 10−100% acetonitrile in water (both solvents contained 0.01% TFA), and the flow rate was 10 mL/min.

**General Washing Procedure:** The resin was washed with DCM, MeOH, DCM, MeOH, and 2 × DCM (20 mL or 2 mL).

**General Procedure for the Synthesis of 2-Amino-5-sulfanylthiazoles 7 and 13**

**Sulfanylation with Disulfides:** First a solution of iodine (1 mmol) in NMP (1 mL), and then a solution of $R^3SSR^3$ (1 mmol) in NMP (1 mL), were added to resin **5** or **11** (150 mg).

**Sulfanylation with Aromatic Thiols:** First a solution of iodine (2 mmol) in NMP (1 mL), and then a solution of $R^3SH$ (1 mmol) in NMP (1 mL) were added to the same amount of resin as above.

**Sulfanylation with Aromatic Sulfonyl Chlorides/$PPh_3$:** A solution of $R^3SO_2Cl$ (1 mmol) and $PPh_3$ (2 mmol) in NMP (0.8 mL) was stirred at room temperature for 30 min. First, a solution of iodine (2 mmol) in NMP (1 mL), and then a solution of $R^3SO_2Cl/PPh_3$ were added to the same amount of resin as above.

The mixtures were shaken for 3 h at room temperature. Afterwards, the resins were washed with NMP (10 × 2 mL), and then as described in the general washing procedure. Finally, the products were cleaved from the resin either by treatment with TFA/DCM (1:1, v/v, 2 mL) for 30 min (products **7**), or with TFA/DCM/$Et_3SiH$ (60:35:5, v/v/v, 2 mL) for 1 h (products **13**).

**General Procedure for the Synthesis of 2-Amino-5-sulfanylthiazoles 13 by a Multicomponent Reaction:** Resin-bound thiourea **10** (200 mg) was swollen in NMP, and a solution of $BrCH_2C(O)R^2$ (0.5 mmol) in NMP (0.5 mL) was added. The following reagents were then added.

**Disulfides as Sulfanylating Reagents:** A solution of iodine (1 mmol) in NMP (0.5 mL) and a solution of $R^3SSR^3$ (1 mmol) in NMP (1 mL) were added.

**Aromatic Thiols as Sulfanylating Reagents:** A solution of iodine (2 mmol) in NMP (0.5 mL) and a solution of $R^3SH$ (1 mmol) in NMP (1 mL) were added.

**Aromatic Sulfonyl Chlorides/$PPh_3$ as Sulfanylating Reagents:** A solution of iodine (2 mmol) in NMP (0.5 mL) and a premixed solution (30 min) of $R^3SO_2Cl$ (1 mmol) and $PPh_3$ (2 mmol) in NMP (0.8 mL) were added.

The mixtures were shaken for 3 h at room temperature. Afterwards the resins were washed with NMP (10 × 2 mL), and then as described in the general washing procedure. Finally, the products were cleaved from the resins by treatment with TFA/DCM/$Et_3SiH$ (60:35:5, v/v/v, 2 mL) for 1 h.

**4-[5-{[4-(Acetylamino)phenyl]sulfanyl}-4-(2-methoxyphenyl)thiazol-2-yl]piperazin-1-ium Trifluoroacetate (7a):** LC-MS: *m*/*z* = 441 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 9.99 (s, 1 H, NHCO), 9.11 (br. s, 2 H, $NH_2^+$), 7.51 (d, *J* = 8.7 Hz, 2 H), 7.35 (td, *J* = 1.9, *J* = 7.9 Hz, 1 H), 7.24 (dd, *J* = 1.9, *J* = 7.5 Hz, 1 H), 7.09 (d, *J* = 8.7 Hz, 2 H), 7.05 (br. d, *J* = 7.9 Hz, 1 H), 6.95 (td, *J* = 0.8, *J* = 7.3 Hz, 1 H), 3.65 (s, 3 H, MeO), 3.64 (br. s, 4 H, $CH_2$), 3.24 (br. s, 4 H, $CH_2$), 2.00 (s, 3 H, Ac) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 170.13, 168.32 (C-2, CO), 156.98, 154.87 (C-4), 137.91, 130.89, 130.85, 130.03, 127.74, 123.38, 119.89, 119.81, 111.46, 110.88 (C-5), 55.23 (MeO), 44.34, 42.00 ($CH_2$), 23.89 (Ac). Purification of the product obtained from resin **4** (0.13 g) by preparative HPLC gave **7a** (22.6 mg, 0.041 mmol).

**4-[4-(4-Bromophenyl)-5-(methylsulfanyl)thiazol-2-yl]piperazin-1-ium Trifluoroacetate (7b):** See Figure 3. LC-MS: *m*/*z* = 372 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 9.21 (br. s, 2 H, $NH_2^+$), 7.88 (d, *J* = 8.66 Hz, 2 H, 2′′-H), 7.62 (d, *J* = 8.66 Hz, 2 H, 3′′-H), 3.67 (br. s, 4 H, 2′-H), 3.25 (br. s, 4 H, 3′-H), 2.36 (s, 3 H, 2′′′-H) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 168.60 (C-2), 151.20 (C-4), 133.22 (C-1′′), 131.10 (C-3′′), 130.36 (C-2′′), 121.41 (C-4′′), 114.23 (C-5), 44.47 (C-2′), 41.94 (C-3′), 21.75 (C-2′′′).

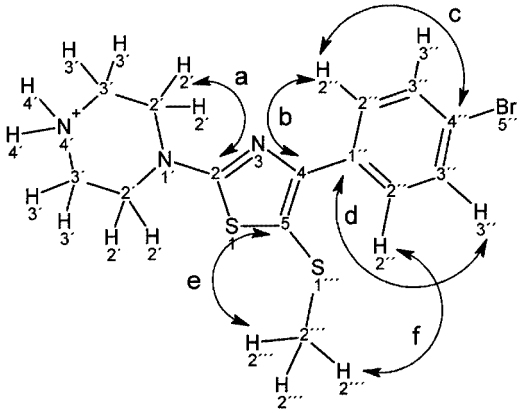



Figure 3. The structure of **7b** was determined by $^1$H NMR, $^{13}$C NMR, $^1$H-$^1$H COSY, HSQC, HMBC, and HMBC- INADEQUATE; the HMBC spectrum showed long-range $^{13}$C-$^1$H coupling between: (a) C-2 and 2′-H, (b) C-4 and 2′′-H, (c) C-4′′ and 2′′-H, (d) C-1′′ and 3′′-H, and (e) C-5 and 2′′′-H, the NOESY spectrum showed an NOE between 2′′′-H and 2′′-H, and the HMBC-INADEQUATE spectrum showed a $^{13}$C-$^{13}$C coupling between C-4 and C-5

**4-{4-(Naphth-2-yl)-5-[(pyridin-2-yl)sulfanyl]thiazol-2-yl}piperazin-1-ium Trifluoroacetate (7c):** LC-MS: *m*/*z* = 405 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 9.25 (br. s, 2 H, $NH_2^+$), 8.48−8.40 (m, 1 H), 8.33 (s, 1 H), 8.01−7.78 (m, 4 H), 7.77−7.67 (m, 1 H), 7.55−7.46 (m, 2 H), 7.23−7.13 (m, 2 H), 3.79 (br. s, 4 H, $CH_2$), 3.31 (br. s, 4 H, $CH_2$) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 170.57 (C-2), 159.81, 156.80 (C-4), 149.81, 137.84, 132.69, 132.39, 131.14, 128.24, 127.88, 127.51 (double intensity), 126.76, 126.49, 126.01, 120.90, 119.92, 104.71 (C-5), 44.46, 42.02 ($CH_2$).

**3-{[4-(Naphth-2-yl)-2-(piperazin-1-yl)thiazol-5-yl]sulfanyl}propionic Acid (7d):** LC-MS: *m*/*z* = 400 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 9.17 (br. s, 2 H, $NH_2^+$), 8.46 (s, 1 H), 8.13−8.07 (m, 1 H), 8.00−7.87 (m, 3 H), 7.57−7.49 (m, 2 H), 3.72 (br. s, 4 H, $CH_2$), 3.28 (br. s, 4 H, $CH_2$), 2.93 (t, *J* = 7.0 Hz, 2 H, $CH_2$), 2.49 (t, *J* = 7.0 Hz, 2 H, $CH_2$) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 172.42, 168.95 (C-2, CO), 153.87 (C-4), 132.56, 132.51, 131.54, 128.36, 127.80, 127.47, 127.39, 126.55, 126.40, 126.34, 111.13 (C-5), 44.47, 42.01, 33.67, 33.44 ($CH_2$). Recrystallization of the product obtained from resin **4** (0.11 g) from MeOH gave **7d** (5.3 mg, 0.013 mmol) as a colorless solid. $C_{20}H_{21}N_3O_2S_2{\cdot}H_2O$ (417.6): calcd. C 57.53, H 5.55, N 10.06; found C 57.80, H 5.80, N 10.20.

**4-[4-(Biphenyl-4-yl)-5-(phenylsulfanyl)thiazol-2-yl]piperazin-1-ium Trifluoroacetate (7e):** LC-MS: *m*/*z* = 430 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 9.34 (br. s, 2 H, $NH_2^+$), 7.99 (d, *J* = 8.3 Hz, 2 H), 7.73−7.64 (m, 4 H), 7.44 (t, *J* = 7.3 Hz, 2 H), 7.39−7.31 (m, 3 H), 7.24−7.17 (m, 3 H), 3.75 (br. s, 4 H, $CH_2$), 3.29 (br. s, 4 H, $CH_2$) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 170.11 (C-2), 156.02 (C-4), 140.21, 139.38, 137.57, 132.66, 129.55, 128.96, 128.92, 127.71, 126.65, 126.40, 126.16, 125.60, 106.01 (C-5), 44.40, 41.95 ($CH_2$). Recrystallization of the product obtained from resin **4** (0.13 g) from acetonitrile gave **7e** (33.8 mg, 0.059 mmol) as a colorless solid. $C_{25}H_{23}N_3S_2{\cdot}C_2HF_3O_2{\cdot}1.5H_2O$

(570.7): calcd. C 56.83, H 4.77, N 7.36; found C 56.61, H 4.52, N 7.55.

**4-{4-(4-Bromophenyl)-5-[(3-chloro-2-methylphenyl)sulfanyl]thiazol-2-yl}piperazin-1-ium Trifluoroacetate (7f):** LC-MS: *m/z* = 482 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 9.35 (br. s, 2 H, NH$_2^+$), 7.77 (d, *J* = 8.7 Hz, 2 H), 7.59 (d, *J* = 8.7 Hz, 2 H), 7.28 (d, *J* = 7.9 Hz, 1 H), 7.17 (t, *J* = 7.7 Hz, 1 H), 6.91 (d, *J* = 7.9 Hz, 1 H), 3.73 (br. s, 4 H, CH$_2$), 3.28 (br. s, 4 H, CH$_2$), 2.34 (s, 3 H, Me) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 170.46 (C-2), 155.77 (C-4), 138.96, 134.27, 132.57, 131.73, 131.26, 130.24, 128.08, 126.67, 123.94, 122.23, 105.42 (C-5), 44.41, 41.91 (CH$_2$), 16.27 (Me).

**2-[(4-Chlorobenzyl)amino]-5-[(5-methyl[1,3,4]thiadiazol-2-yl)sulfanyl]-4-(4-nitrophenyl)thiazole (13a):** LC-MS: *m/z* = 476 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 8.98 (br. t, *J* = 5.7 Hz, 1 H, NH), 8.28 (d, *J* = 9.0 Hz, 2 H), 8.10 (d, *J* = 9.0 Hz, 2 H), 7.44−7.38 (m, 4 H), 4.54 (d, *J* = 5.7 Hz, 2 H, NHC*H*$_2$), 2.60 (s, 3 H, Me) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 170.03, 168.25, 166.75 (thiadiazole, C-2), 154.63 (C-4), 147.17, 139.26, 137.21, 131.85, 129.67, 129.53, 128.44, 123.57, 103.88 (C-5), 46.65 (NHCH$_2$), 15.33 (Me). Recrystallization of the product obtained from resin **10** (0.19 g) from acetonitrile gave **13a** (16.1 mg, 0.034 mmol) as an orange solid. $C_{19}H_{14}ClN_5O_2S_3 \cdot 0.1H_2O$ (477.8): calcd. C 47.76, H 3.00, N 14.66; found C 48.14, H 3.08, N 14.29.

**2-(Butylamino)-5-[(4-methoxyphenyl)sulfanyl]-4-phenylthiazole (13b):** LC-MS: *m/z* = 371 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 8.11 (br. s, 1 H, NH), 7.83 (dd, *J* = 1.7, *J* = 8.1 Hz, 2 H), 7.42−7.30 (m, 3 H), 7.12 (d, *J* = 8.7 Hz, 2 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 3.70 (s, 3 H, OMe), 3.24 (m, 2 H, NHC*H*$_2$), 1.55 (q, *J* = 7.3 Hz, 2 H, CH$_2$), 1.35 (sext, 2 H, *J* = 7.4 Hz, CH$_2$), 0.89 (t, *J* = 7.3 Hz, 3 H, Me) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 169.00 (C-2), 158.10, 154.99 (C-4), 133.99, 132.07, 128.42, 128.08, 127.98, 125.78, 115.13, 104.46 (C-5), 55.20 (OMe), 43.87 (NHCH$_2$), 30.64, 19.56 (CH$_2$), 13.62 (Me).

**2-[(4-Chlorobenzyl)amino]-5-[(2-hydroxyethyl)sulfanyl]-4-phenylthiazole (13c):** LC-MS: *m/z* = 377 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 8.46 (br. s, 1 H, NH), 7.89 (dd, *J* = 1.3 Hz, 2 H, *J* = 8.5 Hz), 7.44−7.30 (m, 7 H), 5.34 (br. s, 1 H, OH), 4.46 (br. s, 2 H, NHC*H*$_2$), 3.46 (t, *J* = 6.8 Hz, 2 H, CH$_2$), 2.74 (t, *J* = 6.8 Hz, 2 H, CH$_2$) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 167.58 (C-2), 152.60 (C-4), 137.91, 134.26, 131.60, 129.39, 128.56, 128.31, 127.91, 127.85, 108.61 (C-5), 59.77 (CH$_2$), 46.52 (NHCH$_2$), 40.48 (CH$_2$). Purification of the product obtained from resin **10** (0.19 g) by preparative HPLC gave **13c** (10.6 mg, 0.028 mmol).

**5-[(2-Carboxyethyl)sulfanyl]-2-[(4-chlorobenzyl)amino]-4-phenylthiazole (13d):** LC-MS: *m/z* = 405 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 8.53 (br. s, 1 H, NH), 7.87 (dd, *J* = 1.5 Hz, 2 H, *J* = 8.3 Hz), 7.43−7.31 (m, 7 H), 4.48 (br. s, 2 H, NHC*H*$_2$), 2.83 (t, *J* = 7.2 Hz, 2 H, CH$_2$), 2.44 (t, *J* = 7.2 Hz, 2 H, CH$_2$) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 172.45 (CO), 167.80 (C-2), 152.94 (C-4), 137.79, 134.02, 131.63, 129.40, 128.59, 128.32, 127.94, 125.73, 107.87 (C-5), 46.77 (NHCH$_2$), 33.66, 33.17 (CH$_2$). Recrystallization of the product obtained from resin **10** (0.20 g) from acetonitrile gave **15d** (7.4 mg, 0.018 mmol) as a colorless solid. $C_{19}H_{17}ClN_2O_2S_2 \cdot 0.3\ H_2O$ (410.3): calcd. C 55.61, H 4.32, N 6.83; found C 55.53, H 4.24, N 6.76.

**5-[(2-Carboxyethyl)sulfanyl]-2-[(4-chlorobenzyl)amino]-4-(2-methoxyphenyl)thiazole (13e):** LC-MS: *m/z* = 435 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 8.90 (br. s, 1 H, NH), 7.44−7.35 (m, 5 H), 7.22 (dd, *J* = 1.7 Hz, *J* = 7.4 Hz, 1 H), 7.07 (br. d, *J* = 7.9 Hz, 1 H), 6.97 (td, *J* = 0.9, *J* = 7.4 Hz, 1 H), 4.46 (br. s, 2 H, NHC*H*$_2$), 3.72 (s, 3 H, Me), 2.73 (t, *J* = 7.2 Hz, 2 H, CH$_2$), 2.38 (t, *J* = 7.2 Hz, 2 H, CH$_2$) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 172.54, 168.11 (CO, C-2), 157.06, 156.51 (C-4), 137.07, 131.89, 131.27, 130.19, 129.52, 129.45, 128.40, 119.91, 111.39, 110.27 (C-5), 55.33 (Me), 46.93 (NHCH$_2$), 33.78, 32.38 (CH$_2$).

**2-[4-Chlorobenzyl)amino]-4-(2-methoxyphenyl)-5-(methylsulfanyl)-thiazole (13f):** LC-MS: *m/z* = 377 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 8.84 (br. s, 1 H, NH), 7.45−7.34 (m, 5 H), 7.23 (dd, *J* = 1.9 Hz, *J* = 7.5 Hz, 1 H), 7.07 (br. d, *J* = 7.9 Hz, 1 H), 6.97 (td, *J* = 0.9, *J* = 7.4 Hz, 1 H), 4.45 (br. s, 2 H, NHC*H*$_2$), 3.73 (s, 3 H, OMe), 2.21 (s, 3 H, Me) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 167.80 (C-2), 156.99 (C-4), 137.23, 131.83, 131.11, 130.06, 129.48, 129.43, 128.38, 122.40, 119.93, 112.97 (C-5), 111.45, 55.33 (OMe), 46.87 (NHCH$_2$), 21.07 (Me). Purification of the product obtained from resin **10** (0.16 g) by preparative HPLC gave **13f** (8.3 mg, 0.022 mmol).

**2-(Butylamino)-5-[(3-carboxyphenyl)sulfanyl]-4-(4-nitrophenyl)-thiazole (13g):** LC-MS: *m/z* = 430 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 8.31 (br. s, 1 H, NH), 8.24 (d, *J* = 9.0 Hz, 2 H), 8.10 (d, *J* = 9.0 Hz, 2 H), 7.79−7.66 (m, 2 H), 7.51−7.38 (m, 2 H), 3.29 (br. s, 2 H, NHC*H*$_2$), 1.57 (q, *J* = 7.2 Hz, 2 H, CH$_2$), 1.36 (sext, 2 H, *J* = 7.4 Hz, CH$_2$), 0.90 (t, *J* = 7.3 Hz, 3 H, Me) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 169.69, 166.57 (C-2, CO), 154.07 (C-4), 146.83, 139.95, 138.34, 132.04, 129.83, 129.77, 129.33, 127.02, 125.85, 123.47, 104.87 (C-5), 43.89 (NHCH$_2$), 30.60, 19.58 (CH$_2$), 13.63 (Me).

**2-(Butylamino)-5-[(4-*tert*-butylphenyl)sulfanyl]-4-(4-nitrophenyl)-thiazole (13h):** LC-MS: *m/z* = 442 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 8.24 (d, *J* = 9.0 Hz, 2 H), 8.23 (br. s, 1 H, NH), 8.14 (d, *J* = 9.0 Hz, 2 H), 7.33 (d, *J* = 8.7 Hz, 2 H), 7.09 (d, *J* = 8.7 Hz, 2 H), 3.27 (br. t, *J* = 6.6 Hz, 2 H, NHC*H*$_2$), 1.55 (q, *J* = 7.2 Hz, 2 H, CH$_2$), 1.35 (sext, 2 H, *J* = 7.3 Hz, CH$_2$), 1.20 (s, 9 H, C*Me*$_3$), 0.89 (t, *J* = 7.4 Hz, 3 H, Me) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 169.31 (C-2), 153.18 (C-4), 148.97, 146.67, 140.15, 133.81, 129.32, 126.42, 125.81, 123.38, 106.81 (C-5), 43.85 (NHCH$_2$), 34.15 (*C*Me$_3$), 30.94 (C*Me*$_3$), 30.60, 19.58 (CH$_2$), 13.62 (Me). Purification of the product obtained from resin **10** (0.20 g) by preparative HPLC gave **13h** (12.9 mg, 0.029 mmol).

**4-(4-Bromophenyl)-2-(butylamino)-5-[(2-hydroxyethyl)sulfanyl]-thiazole (13i):** LC-MS: *m/z* = 389 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 8.21 (br. s, 1 H, NH), 7.86 (d, *J* = 8.3 Hz, 2 H), 7.61 (d, *J* = 8.3 Hz, 2 H), 4.97 (br. s, 1 H, OH), 3.47 (t, *J* = 6.8 Hz, 2 H, CH$_2$), 3.24 (t, *J* = 6.8 Hz, 2 H, NHC*H*$_2$), 2.75 (t, *J* = 6.8 Hz, 2 H, CH$_2$), 1.54 (q, *J* = 7.2 Hz, 2 H, CH$_2$), 1.34 (sext, 2 H, *J* = 7.3 Hz, CH$_2$), 0.89 (t, *J* = 7.4 Hz, 3 H, Me) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 167.88 (C-2), 156.72 (C-4), 132.82, 130.92, 130.69, 121.30, 108.68 (C-5), 59.68 (CH$_2$), 43.94 (NHCH$_2$), 40.40, 30.56, 19.53 (CH$_2$), 13.62 (Me).

**4-(4-Bromophenyl)-2-(butylamino)-5-[(3-chloro-2-methylphenyl)-sulfanyl]thiazole (13j):** LC-MS: *m/z* = 469 [M + H$^+$]. $^1$H NMR (300 MHz, [D$_6$]DMSO): δ = 8.25 (br. s, 1 H, NH), 7.72 (d, *J* = 8.7 Hz, 2 H), 7.57 (d, *J* = 8.7 Hz, 2 H), 7.26 (d, *J* = 7.9 Hz, 1 H), 7.18 (t, *J* = 7.9 Hz, 1 H), 6.89 (d, *J* = 7.9 Hz, 1 H), 3.28 (br. s, 2 H, NHC*H*$_2$), 2.33 (s, 3 H, Me), 1.55 (q, *J* = 7.2 Hz, 2 H, CH$_2$), 1.36 (sext, 2 H, *J* = 7.3 Hz, CH$_2$), 0.90 (t, *J* = 7.2 Hz, 3 H, Me) ppm. $^{13}$C NMR (75 MHz, [D$_6$]DMSO): δ = 169.76 (C-2), 155.74 (C-4), 139.62, 134.13, 132.94, 131.27, 131.11, 130.21, 128.02, 126.24, 123.40, 121.82, 101.32 (C-5), 43.86 (NHCH$_2$), 30.59, 19.57 (CH$_2$), 16.10, 13.63 (Me). Recrystallization of the product obtained from resin **10** (0.21 g) from acetonitrile gave **13j** (19.5 mg,

0.042 mmol) as a colorless solid. $C_{20}H_{20}BrClN_2S_2$ (467.9): calcd. C 51.34, H 4.31, N 5.99; found C 51.32, H 4.39, N 5.93.

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[1] [1a] K. D. Hargrave, K. H. Friedrich, J. T. Oliver, *J. Med. Chem.* **1983**, *26*, 1158−1163. [1b] F. Bonifacio, M. Fano, L. Trabella, G. Battigelli, D. Montagna, V. Bernareggi, Valeas S.p.a. Industria Chimica e Farmaceutica, *Patent EP 0261503A1*, **1988**, pp. 1−33.[1c] S. Ohkawa, N. Kanzaki, S. Miwatashi, Takeda Chemical Industries Ltd., *Patent WO 0064894A1*, **2000**, pp. 1−152.
[2] Y. Ozato, N. Tamura, H. Masumori, M. Yamamoto, A. Kojima, F. Nishikaku, Y. Kimura, Sumitomo Pharmaceuticals Company Ltd., *Patent EP 0248399A1*, **1987**, pp. 1−57.
[3] W. C. Patt, H. W. Hamilton, M. D. Taylor, M. J. Ryan, D. G. Tayleo, C. J. C. Conolly, A. M. Doherty, S. R. Klutchko, I. Sircar, B. A. Steinbaugh, B. L. Batley, C. A. Painchaud, S. T. Rapundalo, B. M. Michniewicz, S. C. Olson, *J. Med. Chem.* **1992**, *35*, 2562−2572.
[4] B. W. Caprathe, J. C. Jaen, L. D. Wise, Warner-Lambert Co., *Patent EP 0260642A2*, **1988**, pp. 1−58.
[5] L. Alig, A. Edenhofer, K. Hilpert, T. Weller, F. Hoffmann-La Roche AG, *Patent EP 0928793A1*, **1999**, pp. 1−35.
[6] P. Bühlmayer, Novartis AG, *Patent WO 9962892A1*, **1999**, pp. 1−39.
[7] K. Tsuji, H. Ishikawa, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601−1606.
[8] [8a] S. D. Young, M. W. Embrey, T. E. Fisher, Merck & Co., *Patent WO 9962897A1*, **1999**, pp. 1−156.[8b] T. K. Venkatachalam, E. A. Sudbeck, C. Mao, F. M. Uckun, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 523−528.
[9] Q. Dang, S. R. Kasibhatla, K. R. Reddy, M. D. Erion, M. R. Reddy, A. Agarwal, Metabasis Therapeutics Inc., *Patent WO 0014095A1*, **2000**, pp. 1−338.
[10] Thrombocytopenia is a major side effect of cancer chemotherapy and radiotherapy.
[11] M. Matsuo, T. Ogino, N. Igari, H. Seno, K. Shimomura, Fujisawa Pharmaceutical Co., *Patent EP 0412404A2*, **1991**, pp. 1−43.
[12] K. S. Kim, S. D. Kimball, M. A. Poss, R. N. Misra, D. B. Rawlins, K. Webster, J. T. Hunt, W.-C. Han, Bristol-Myers Squibb Co., *Patent WO 9924416*, **1999**, pp. 1−132.
[13] F. Zaragoza, *Organic Synthesis on Solid Phase*, Wiley-VCH, Weinheim, **2000**.
[14] P. Seneci, *Solid-phase Synthesis and Combinatorial Technologies*, Wiley-Interscience, New York, **2000**.
[15] G. Jung, *Combinatorial Chemistry: Synthesis, Analysis, Screening*, Wiley-VCH, Weinheim, **1999**.
[16] W. Bannwarth, E. Felder, *Combinatorial Chemistry: A Practical Approach*; Wiley-VCH, Weinheim, **2000**.
[17] E. Hoggarth, *J. Chem. Soc.* **1947**, 110−118.
[18] T. Ogino, K. Tsuji, T. Tojo, N. Igari, N. Seki, Y. Sudo, T. Manda, F. Nishigaki, M. Matsuo, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 75−80.
[19] K. Tsuji, T. Ogino, N. Seki, M. Sawada, Y. Sudo, F. Nishigaki, T. Manda, M. Matsuo, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2473−2478.
[20] A search of the Available Chemical Directory database (MDL Information Systems, Inc.) gives only 12 commercially available sulfenyl chlorides or bromides.
[21] E. Kühle, *Synthesis* **1970**, 561−580.
[22] P. F. Ranken, B. G. McKinnie, *J. Org. Chem.* **1989**, *54*, 2985−2988.
[23] D. Delfs, K. Wedemeyer, Farbenfabriken Bayer Aktiengesellschaft, *Patent US 292374*, **1960**, pp. 1−2.
[24] E. Campaigne, B. G. Heaton, *J. Org. Chem.* **1964**, *29*, 2372−2378.
[25] R. L. N. Harris, *Aust. J. Chem.* **1970**, *23*, 1199−1207.
[26] R. T. Wragg, *J. Chem. Soc.* **1964**, 5482−5483.
[27] M. Grimstrup, F. Zaragoza, *Eur. J. Org. Chem.* **2001**, *17*, 3233−3246.
[28] P. C. Kearney, M. Fernandez, J. A. Flygare, *J. Org. Chem.* **1998**, *63*, 196−200.
[29] D. L. deLeeuw, K. W. Musker, J. T. Doi, *J. Org. Chem.* **1982**, *47*, 4860−4864.
[30] A search in the Available Chemical Directory database (MDL Information Systems, Inc.) gives more than 250 commercially available aromatic sulfonyl chlorides.
[31] S. Oae, H. Togo, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3802−3812.
[32] E. G. Brown, J. M. Nuss, *Tetrahedron Lett.* **1997**, *38*, 8457−8460.
[33] R. Taylor, *Electrophilic Aromatic Substitution*, John Wiley & Sons, Chichester, **1990**.
[34] S. Patai, *The Chemistry of the Thiol Group*, John Wiley & Sons, London, **1974**, pp. 230−231.
[35] M. C. Caserio, C. L. Fisher, J. K. Kim, *J. Org. Chem.* **1985**, *50*, 4390−4393.
[36] B. S. Farah, *J. Org. Chem.* **1963**, *28*, 2807−2809.
[37] J. A. Pappas, *J. Am. Chem. Soc.* **1977**, *99*, 2926−2930.
[38] H. Tsubomura, R. P. Lang, *J. Am. Chem. Soc.* **1961**, *83*, 2085−2092.
[39] [39a] K. Goto, M. Holler, R. Okazaki, *Chem. Commun.* **1998**, 1915−1916. [39b] K. Goto, G. Yamamoto, B. Tan, R. Okazaki, *Tetrahedron Lett.* **2001**, *42*, 4875−4877.
[40] The loading was determined by reductive amination followed by acylation and cleavage, and for different batches it varied between 0.32 and 0.48 mmol/g.

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