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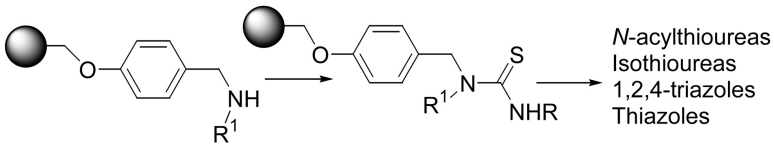

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Solid Phase Synthesis and Application of Trisubstituted Thioureas

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Resin-bound amines **1a**−**e** condense with isothiocyanates to give thiourea resins **2a**−**i**. Resins **2a**−**g** subsequently react with iodomethane followed by cleavage affording *S*-methyl isothioureas **4a**−**g,** and resins **2a**−**b**,**h**−**i** react with acyl chlorides to afford N-acylated thioureas **6a**−**d**. *N*-Acylthioureas **8a**−**f** (R^2 = H) were prepared directly from resin-bound amines **1a**−**d** with acyl isothiocyanates. *N*-Acylthioureas **8a**−**d**,**f** (R^2 = H) were used for the preparation of *S*-methyl-*N*-acylisothioureas **10a**−**e**. Alkylation was performed using methyl iodide. Resin-bound *S*-methyl-*N*-acylisothioureas **10a**,**b**,**d** are converted by an action of hydrazines into 3-amino-1,2,4-triazoles **13a**−**d**. Condensation of resins **8a**−**e** (R^2 = H) with 2-bromoacetophenones in the presence of TEA affords thiazoles **15a**−**e**. All transformations proceeded in high yields and gave products of good purities.

Introduction

The growing application of combinatorial organic synthesis on solid phase supports[1] is reflected in the rapidly increasing range of reaction types and strategies utilized. Interest in solid-phase synthesis continues to increase the scope of preparative methods for producing libraries of small organic molecules.[2]

Thioureas are useful compounds as precursors for the synthesis of different classes of acyclic and heterocyclic compounds[3] as well as are highly biologically active compounds themselves.[4] Recently, solid-phase synthesis of thioureas was applied to the preparation of oligomeric compounds that could be relevant to peptide secondary structures,[5] thiohydantoins,[6] 2-aminothiazoles,[7] and 3-thio-1,2,4-triazoles.[8] Several papers have described the preparation of thioureas on solid support with subsequent conversion into guanidines.[9] Known approaches to the solid-phase synthesis of thioureas include (i) thiourea or a protected thiourea loading on resin,[9b] coupling (ii) solid supported isothiocyanate with amines[7a] or (iii) resin-bound amines with isothiocyanate as a reagent in the solution,[5b,6b,9a] and (iv) displacement of a leaving group from reagents containing, for example, a thiocarbonylimidazole moiety.[10] We herein report an investigation on the preparation of trisubstituted thioureas on solid support, their functionalization, and application for the synthesis of 1,2,4-triazole and thiazole derivatives.

Results and Discussion

We examined the conversion of Wang-resin-linked amines **1a**−**e** into thioureas using isothiocyanates because of the ease of cleavage from this support with trifluoroacetic acid (TFA). Resin-bound amines **1a**−**e** were obtained in a classic three-step procedure[11] involving the conversion of Wang resin into the brominated resin; subsequent nucleophilic substitution with 4-hydroxybenzaldehyde in the presence of potassium *tert*-butoxide; and last, a standard reductive amination protocol in the presence of an amine and sodium triacetoxyborohydride (Scheme 1).

To establish a general protocol for the preparation of thioureas **2a**−**i**, we have investigated the reaction of benzyl-substituted amino resin **1a** with benzyl isothiocyanate in different conditions varying solvents (THF, DCM), catalysts (DIEA), reaction times (1−24 h), and concentrations of benzyl isothiocyanate.

According to the ^{1}H NMR spectra of the cleaved materials, quantitative conversion of the starting amine, **1a**, was observed in all conditions used. However, cleaved thiourea, **3a**, appears in the NMR spectra as a very complicated mixture of rotomers, which can be observed in different proportions, depending on the temperature. To characterize the influence of a substituent R^1 in the amines and R^2 in isothiocyanates on the formation of thioureas, we used condition **A** and prepared a trial library of thioureas **3a**−**i** using a set of five various amines, two aromatic isothiocyanates (for thioureas **3e**,**f**,**g**), *n*-butyl isothiocyanate (for thiourea **3i**) and benzyl isothiocyanate (for thioureas **3a**−**d**,**h**). For analytical purposes, we additionally purified compound **3a**−**e**,**g**−**h** by flash column chromatography.

For most combinations of the substituents used (R^1 = Bu, 4-MeO−Bn, $C_6H_4(CH_2)_2$, 4-MeO−$C_6H_4(CH_2)_2$, 4-MeO−Ph; R^2 = Bn, 4-MeO−C_6H_4, Bu) the corresponding thioureas **3** were obtained in good yields and with high purities (Table 1). Nevertheless, desired thiourea **3c** was obtained in low yield, probably due to decomposition during column chromatography. In contrast, compound **3f** gave good ^{1}H NMR and ^{13}C NMR spectra at room temperature, and all signals were assigned according to the desired structure **3f** without purification. Thiourea **3h** was obtained without the 4-hydrobenzyl group and had a different cleavage point in comparison to other the thiourea resins.

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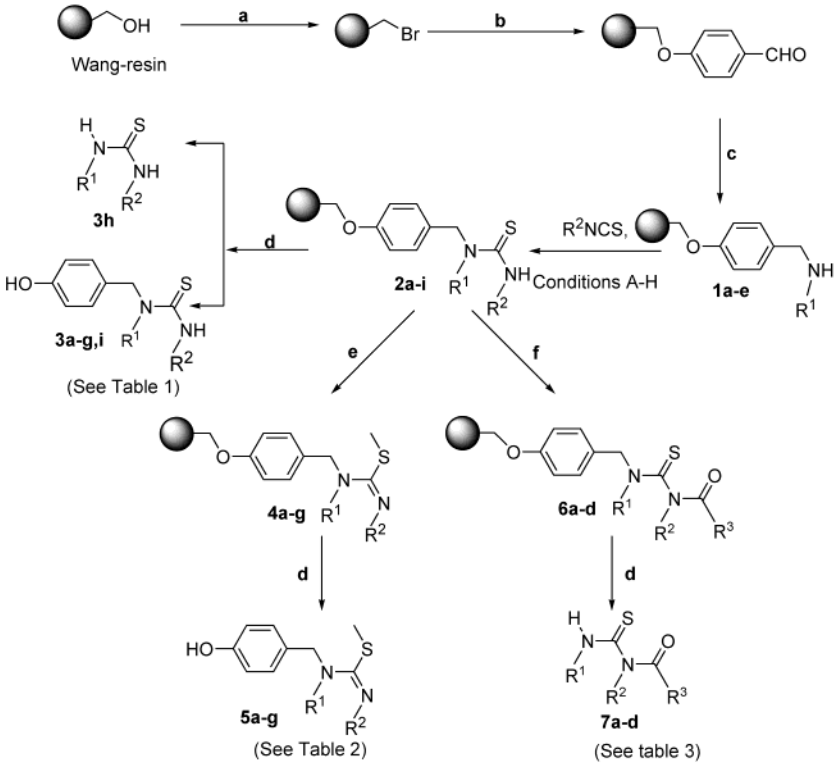
Scheme 1



(a) Ph_3PBr_2, CH_2Cl_2, rt, 4h; (b) *p*-hydroxybenzaldehyde, *t*-BuOK, 55 °C, 16 h; (c) R^1NH_2, $NaBH(AcO)_3$, rt, 24 h; (d) 20% TFA in DCM or 95% TFA in H_2O, rt, 30 min; (e) CH_3I or CH_3I with *t*-BuOK, DMF, rt, 24 h; (f) acyl chloride, TEA, THF, rt, 24 h. A: THF, BnNCS 10 equiv (0.25 mmol/mL), 24 h. B: THF, BnNCS 10 equiv (0.25 mmol/mL), DIEA 10 equiv, 24 h. C−G: DCM, BnNCS 10 equiv (0.25 mmol/mL), 1 h (C), 2 h (D), 3 h (E), 4 h (F), 5 h (G). H: DCM, BnNCS 2.5 equiv (0.8 mmol/mL), 1 h.

Table 1. Preparation of Thioureas **3a**−**h**

compd **3**	R^1	R^2	yield %	HPLC purity %
3a	*n*-C_4H_9	$PhCH_2$	69	95
3b	$PhCH_2CH_2$	$PhCH_2$	60	68
3c	4-CH_3O−$C_6H_4CH_2CH_2$	$PhCH_2$	51	79
3d	4-CH_3O−C_6H_4	$PhCH_2$	68	97
3e	4-CH_3O−$C_6H_4CH_2CH_2$	Ph	60	96
3f	4-CH_3O−C_6H_4	Ph	90	89
3g	4-CH_3O−C_6H_4	4-CH_3O−C_6H_4	89	65
3h	CH_3O−$C_6H_4CH_2$	$PhCH_2$	83	61
3i	$PhCH_2CH_2$	*n*-C_4H_9	95	63

Table 2. Preparation of *S*-Methyl Isothioureas **5a**−**g**

compd **5**	R^1	R^2	yield %	^{1}H NMR purity %
5a	*n*-C_4H_9	$PhCH_2$	95	100
5b	$PhCH_2CH_2$	$PhCH_2$	97	99
5c	4-CH_3O−$C_6H_4CH_2CH_2$	$PhCH_2$	97	99
5d	4-CH_3O−C_6H_4	$PhCH_2$	99	95
5e	4-CH_3O−$C_6H_4CH_2CH_2$	Ph	100	98
5f	4-CH_3O−C_6H_4	Ph	99	97
5g	4-CH_3O−C_6H_4	4-CH_3O−C_6H_4	100	94

Thioureas **2a**−**g** were used for the preparation of resins *S*-methyl isothioureas **4a**−**g**. *S*-Methyl isothioureas **5a**−**g** were obtained in 95−100% yields after the cleavage from resins **4a**−**g** using 20% TFA in DCM. For the alkylation of thioureas **2a**−**d,** methyl iodide was used. Conversion of thioureas **2e**−**g** to **4e**−**g** required the presence of a base (*t*-BuOK). *S*-Methyl isothioureas **5a**−**g** were analyzed by NMR, which showed high purities of cleaved isothioureas (Table 2). However, *S*-methyl isothioureas **5a**−**g** decomposed during analysis by HPLC on HPLC column under the conditions used.

Table 3. Preparation of *N*-Acyl Thioureas **7a**−**d**

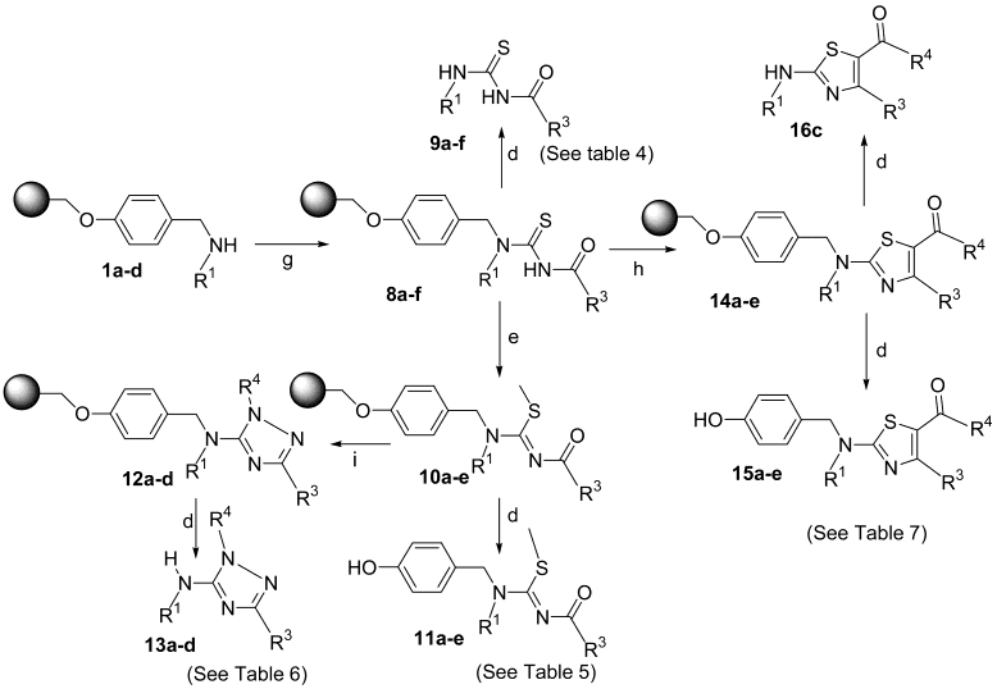
compd **7**	R^1	R^2	R^3	yield %	HPLC purity %
7a	*n*-C_4H_9	$PhCH_2$	Ph	75	90
7b	$PhCH_2CH_2$	$PhCH_2$	$(CH_3)_2CH$	80	96
7c	4-$CH_3OC_6H_4CH_2$	$PhCH_2$	$(CH_3)_2CH$	81	74
7d	$PhCH_2CH_2$	*n*-C_4H_9	$(CH_3)_2CH$	87	96

Acylation of thioureas **2a**,**b**,**h**−**i** with acyl chlorides in the presence of base affords N-acylated thioureas **6a**−**d** with an additional point of diversity for the thiourea library. The NMR spectra of cleaved materials gave N-acylated thioureas **7a**−**d** in 75−87% isolated yields after additional purification by flash column chromatography. The cleavage point for N-acylated thioureas **6** is different from thioureas **2** and *S*-methyl isothioureas **4**, perhaps because of the strong electron-withdrawing properties of the acyl group. The varying concentration of trifluoroacetic acid (20, 50, 95%) did not influence the cleavage point (Scheme 1, Table 3).

N-Acyl thioureas **8a**−**f** (R^2 = H) were prepared directly from resin-bound amines **1a**−**d** in the reaction with acyl isothiocyanates in the presence of triethylamine (Scheme 2, Table 4).

Compounds **9a**−**f** were obtained in 60−83% isolated yields and were characterized by both ^{1}H and ^{13}C NMR. Compounds **9d**,**e** were additionally confirmed by microanalysis. We have investigated the cleavage time of resin **8b**.

Scheme 2



(d) 20% TFA in DCM or 95% TFA in H_2O, rt, 30 min. (e) CH_3I, DMF, rt, 24 h; (g) acyl isothiocyanate, PhH, rt, 24 h; (h) 2-bromoacetophenone, CH_3CN, TEA, reflux, 16−36 h; (i) hydrazine, CH_3CN, reflux, 48 h.

Table 4. Preparation of *N*-Acyl Thioureas **9a**−**f**[a]

compd **9**	R^1	R^3	yield % (HPLC purity %)
9a	*n*-C_4H_9	Ph	83 (100)
9b	$PhCH_2CH_2$	Ph	80 (96)
9c	4-$CH_3O-C_6H_4CH_2$	Ph	65 (95)
9d	4-$CH_3OC_6H_4CH_2CH_2$	4-$CH_3O-C_6H_4$	64
9e	4-$CH_3OC_6H_4CH_2CH_2$	Ph	75
9f	4-$CH_3O-C_6H_4CH_2$	4-$CH_3O-C_6H_4$	60 (79)

[a] R^2 = H.

Table 5. Yields and Purities of Compounds **11a**−**e**

compd **11**	R^1	R^3	yield (%)	HPLC purity (%)
11a	*n*-C_4H_9	Ph	95	94
11b	$PhCH_2CH_2$	Ph	50	81
11c	4-$CH_3OC_6H_4CH_2$	Ph	93	95[a]
11d	4-$CH_3OC_6H_4CH_2CH_2$	4-$CH_3OC_6H_4$	98	89[a]
11e	4-$CH_3OC_6H_4CH_2CH_2$	Ph	96	95[a]

[a] HPLC purity calculated for double peaks in the same compound.

The yields of **9b** were 41 and 65% as times of cleavage were 20 and 40 min, respectively. Longer cleavage times do not increase the amount of cleaved material.

N-Acyl thioureas **8a**−**d**,**f** (R^2 = H) were used for the preparation of *S*-methyl-*N*-acylisothioureas **10a**−**e**. Alkylation was performed using methyl iodide. Cleavage of resins **10a**−**e** showed, according to the NMR spectra, that the desired compounds **11a**−**e** were obtained in almost quantitative yields. However, NMR spectra of cleaved *S*-methyl-*N*-acyl isothioureas **11b**,**d**,**e** appeared as a mixture of rotomers, which can be observed in different proportions, depending on the solvent and temperature used for spectra acquisition. Heating the sample to 70 °C gave satisfactorily resolved ^1H NMR. In contrast, compounds **11a**,**c** give satisfactory ^1H and ^{13}C NMR at room temperature.

Table 6. Yields and Purities of Compounds **13a**−**d**

compd **13**	R^1	R^3	R^4	yield % (HPLC purity %)
13a	*n*-C_4H_9	Ph	H	80 (90)
13b	$PhCH_2CH_2$	Ph	H	69 (90)
13c	*n*-C_4H_9	Ph	Ph	88
13d	4-$CH_3OC_6H_4CH_2CH_2$	4-$CH_3OC_6H_4$	Ph	76 (98)

We attempted the reactions of substituted thiourea resins **6c** (R^2 = $PhCH_2$) and **8a** (R^2 = H) directly with hydrazine monohydrate in solution, as suggested by the literature,[12] varying solvent (THF, PhH, acetonitrile), catalyst (*t*-BuOK), reaction time (24−48h), and reaction temperature (50, 80, 100 °C) to try to prepare 3-amino-1,2,4-triazoles; however, no reaction was observed.

Condensation of resin-bound *S*-methyl-*N*-acylisothioureas **10a**−**b**,**d** with hydrazines in refluxing actonitrile during 24 h gave 3-amino-1,2,4-triazoles **13a**−**d** after the cleavage from resins **12a**−**d**. The cleaved materials were purified by flash column chromatography. 3-Amino-1,2,4-triazoles **13a**−**d** were obtained in good yields (69−88%) and characterized by NMR and HPLC. Compound **13c** was additionally confirmed by microanalysis. The aromatic triazole ring influences the cleavage point, enabling the preparation of compounds **13a**−**d** tracelessly (Scheme 2, Table 6).

Thiazoles **14a**−**e** were prepared from N-acylated thioureas **8a**−**d**,**f** (R^2 = H) in the reaction with 2-bromoacetophenones in refluxing acetonitrile in the presence of base (TEA). After the cleavage, the desired compounds **15a**−**e** were obtained in 62−80% isolated yields and characterized by HPLC and both ^1H and ^{13}C NMR. Compounds **15a**,**b** were additionally

Table 7. Yields and Purities of Thiazoles **15a**−**e** and **16c**

entry	R^1	$R^3 = R^4$	compd **15** yield (purity)	compd **16** yield (purity)
a	*n*-C_4H_9	Ph	80	
b	$PhCH_2CH_2$	Ph	75	
c	4-$CH_3OC_6H_4$	Ph	62 (93)	10 (76)
d	4-$CH_3O-C_6H_4CH_2CH_2$	4-$CH_3OC_6H_4$	73 (87)	
e	4-$CH_3O-C_6H_4CH_2$	4-$CH_3OC_6H_4$	77 (90)	

confirmed by microanalysis. A condensation time of 16 h was used to make the precursors 1**4a**−**e**. The two exceptions were derivatives **15d**,**e**, which required prolonged treatment (36 h). The reaction of resin **8c** with 2-bromoacetophenone gave mainly product **15c** (62%), while byproduct **16c** was obtained in 10% yield because of the possible influence of the aryl substituent in position 1. In all other cases, R^1 is an alkyl substituent.

We tried to obtain only product **16** by using Merrifield resin instead of Wang resin and following the protocol Merrifield resin → thiourea **2** → *N*-acylisothiourea **10** → thiazole **16**. The results obtained were similar to the results with Wang resin **14c** and produced both compound **15c** (65%) and **16c** (5%) independent of the concentration of trifluoroacetic acid (30, 50, 95%) for the cleavage. Moreover, we obtained only product **15e** using 95% TFA for cleaving Merrifield resin. (Scheme 2, Table 7).

Conclusions

In this work, we have developed the general protocols for the preparation of thioureas **2a**−**i**, acyl thioureas **6a**−**d** and **8a**−**f**, *S*-methyl isothioureas **4a**−**g**, and *S*-methyl-*N*-acyl-isothiourea **10a**−**e** libraries in high yields and with good purities. Resin-bound *S*-methyl-*N*-acylisothioureas **10a**,**b**,**d** were used for the preparation of 3-amino-1,2,4-1*H*-triazoles **13a**−**d** in high yields and with high purities. Condensation of resins **8a**−**e** with 2-bromoacetophenones in the presence of TEA affords 2-amino-5-acyl-thiazoles **15a**−**e** in good yields and with good purities.

Experimental Section

General Methods. ^1H, ^{13}CNMR spectra were recorded on a 300 MHz, NMR spectrometer (300 and 75 MHz respectively) using $CDCl_3$, DMSO-d_6 and acetone-d_6 as solvents. Tetrahydrofuran (THF) was distilled under nitrogen immediately before use from sodium/benzophenone. All other reagents and solvents were obtained from commercial sources and were used without purification.

Procedure for the Preparation of the Resin-Bound Aldehyde. Brominated Wang resin was prepared following a described protocol.[11] A solution of 4-hydroxybenzaldehyde (4.58 g, 37.5 mmol) in dry DMA (150 mL) was treated with potassium *tert*-butoxide (4.21 g, 37.5 mmol) under inert atmosphere for 10 min. The solution obtained was added to the brominated resin (2.4 g, 0.87−1.3 mmol/g), and the mixture was heated to 55−60 °C for 16 h. After removal of the solution, the resin was washed consecutively with DMA, THF, THF/H_2O, THF, DCM, MeOH, DCM, MeOH, DCM, and MeOH (2 × 70 mL each) and dried under vacuum for 24 h. The obtained resin was cleaved with 20% TFA solution in DCM for 30 min, and the isolated residue was characterized by ^1H, ^{13}C NMR spectra.

Procedure for the Preparation of Resins 1a−**e.** The resin-bound aldehyde, prepared as described above (0.2 g, loading 0.87−1.3 mmol/g), was placed in dichloroethane (20 mL), and an appropriate amine (l0 equiv) was added into the solvent followed by sodium triacetoxyborohydride (l0 equiv). The reaction mixture was shaken overnight (for ∼12−14 h). After the solution was removed, the resin was washed. The washing sequence was as follows (10 mL of a solvent was used for each 200 mg of a resin): DCE (4×), THF (2×), THF/H_2O:1/1 (2×), THF (2×), THF/ H_2O:1/1 (2×), H_2O (2×), THF (4×), DCM (2×), THF (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×)2, DCM (2×), MeOH (4×). After washing, the resin was dried in a vacuum for 15 h. Cleavage of **1a**−**e** gave amines as their TFA salts.

General Procedure for the Preparation of Resins 2a−**i.** A solution of an appropriate isothiocyanate (l0 equiv) in dry DCM (50 mL) was added to resins **1a**−**e** (5 Tea bag, 1.2 mmol) and shaken at room temperature (rt) overnight. After removal of the solution, the resin **2a**−**i** was washed. The washing sequence was as follows (10 mL of a solvent was used for each 200 mg of a resin): DCM (4×), THF (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (4×). After washing, the resin was dried in a vacuum for 24 h. The obtained resin **2a**−**i** was cleaved with 20% TFA in DCM for 30 min, and the isolated residue was characterized by NMR. Compounds **3a**−**f**, **h** were additionally purified on silica gel with ethyl acetate/hexanes 1:6 as eluent.

***N′*-Benzyl-*N*-butyl-*N*-(4-hydroxybenzyl)thiourea (3a).** Yellow oil, 69%. ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.28−1.39 (m, 2H), 1.59−1.70 (m, 2H), 3.70 (t, J = 7.7 Hz, 2H), 4.79−4.84 (m, 4H), 5.45−5.65 (m, 1H), 6.79 (d, J = 8.4 Hz, 2H), 7.06−7.16 (m, 4H), 7.20−7.32 (m, 3H); ^{13}C NMR δ 13.8, 20.1, 29.5, 50.4, 51.6, 53.7, 115.9, 127.5, 127.6, 127.8, 128.2, 128.7, 137.9, 155.5, 181.6. HPLC: 95%.

***N′*-Benzyl-*N*-(4-hydroxybenzyl)-*N*-phenethylthiourea (3b).** Yellow oil, 60%. ^1H NMR ($CDCl_3$) δ 2.99 (t, J = 7.6 Hz, 2H), 3.99 (t, J = 7.5 Hz, 2H), 4.67 (s, 2H), 4.76 (d, J = 4.7 Hz, 2H), 5.51 (br s, 1H), 6.68−6.78 (m, 3H), 7.00−7.28 (m, 11H). HPLC: 68%.

***N′*-Benzyl-*N*-(4-methoxybenzyl)-*N*-(4-methoxyphenethyl)thiourea (3c).** Yellow oil, 51%. ^1H NMR (acetone-d_6) δ 2.92 (t, J = 7.5 Hz, 2H), 3.75 (s, 3H), 3.90 (t, J = 7.7 Hz, 2H), 4.90−4.96 (m, 4H), 6.78−6.86 (m, 5H), 7.10−7.18 (m, 4H), 7.26−7.29 (m, 4H). HPLC: 79%.

***N′*-Benzyl-*N*-(4-methoxybenzyl)-*N*-(4-methoxyphenyl)-thiourea (3d).** Yellow oil, 97%. ^1H NMR ($CDCl_3$) δ 3.76 (s, 3H), 4.85 (d, J = 5.5 Hz, 2H), 5.42 (s, 2H), 5.58−5.64 (m, 1H), 6.72 (d, J = 8.5 Hz, 2H), 6.79−6.89 (m, 4H), 7.15−7.23 (m, 4H), 7.23−7.33 (m, 4H); ^{13}C NMR δ 49.9, 55.4, 57.9, 115.1, 115.5, 127.2, 127.3, 128.5, 128.6, 129.4, 129.7, 130.3, 138.1, 155.0, 159.4, 182.6. HPLC: 97%.

***N*-(4-Methoxyphenethyl)-*N′*-phenylthiourea (3e).** Colorless oil, 60%. ^1H NMR ($CDCl_3$) δ 2.85 (t, J = 6.8 Hz, 2H), 3.79 (s, 3H), 3.80−3.90 (m, 2H), 5.96 (br s, 1H), 6.81 (d, J

= 8.5 Hz, 2H), 6.94−7.08 (m, 4H), 7.20−7.37 (m, 3H), 7.59 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 33.8, 46.5, 55.3, 114.1, 125.2, 127.3, 129.7, 130.1, 130.3, 135.7, 158.4, 180.5. HPLC: 97%.

***N*-(4-Methoxybenzyl)-*N*-(4-methoxyphenyl)-*N′*-phenylthiourea (3f).** Yellow oil, 90%. ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 5.43 (s, 2H), 6.68−6.74 (m, 2H), 6.84−6.93 (m, 2H), 6.94−7.01 (m, 2H), 7.12−7.20 (m, 3H), 7.24−7.31 (m, 4H); ^{13}C NMR δ 55.5, 57.8, 115.3, 115.6, 126.2, 126.4, 128.6, 129.0, 129.2, 130.3, 132.5, 138.9, 155.0, 159.7, 181.3. HPLC: 89%.

***N*-(4-Methoxybenzyl)-*N*,*N′*-bis(4-methoxyphenyl)thiourea (3g).** Yellow oil, 90%. ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3H), 3.79 (s, 3H), 5.20 (br s, 1H), 5.44 (s, 2H), 6.68−6.74 (m, 2H), 6.80−6.84 (m, 2H), 6.85−6.93 (m, 3H), 6.94−7.00 (m, 2H), 7.14−7.21 (m, 4H); ^{13}C NMR δ 55.4, 55.5, 57.8, 113.8, 115.2, 115.5, 128.0, 129.2, 129.4, 130.3, 132.2, 132.8, 155.2, 157.9, 159.6, 182.4. HPLC: 89%.

***N′*-Benzyl-*N*-(4-hydroxybenzyl)-*N*-(4-methoxybenzyl)thiourea (3h).** Yellow oil, 61%. ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 4.80 (d, J = 4.7 Hz, 2H), 4.89 (br s, 4H), 5.72−5.79 (m, 1H), 6.77 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.99−7.03 (m, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 7.18−7.24 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 30.9, 50.6, 53.7, 55.3, 114.4, 115.9, 127.5 (2), 127.8, 128.4, 128.5, 128.6, 129.0, 137.6, 155.5, 159.3, 182.5. HPLC: 83%.

***N′*-Butyl-*N*-(4-hydroxybenzyl)-*N*-phenethylthiourea (3i).** Yellow oil, 95%. ^{1}H NMR ($CDCl_3$) δ 0.80−0.93 (m, 3H), 1.13−1.24 (m, 2H), 1.30−1.41 (m, 2H), 2.80−3.00 (m, 2H), 3.48−3.79 (m, 2H), 3.93−4.07 (m, 2H), 4.75 (s, 2H), 6.33 (br s, 1H), 6.72−6.84 (m, 2H), 7.04−7.16 (m, 2H), 7.20−7.36 (m, 5H). HPLC: 63%. LC/MS: 343.15, [MH^+]; ret. time, 2.79 min.

General Procedure for the Preparation of Resins 4a−g. A solution of iodomethane (0.33 mL, 5.34 mmol, l0 equiv) and potassium *tert*-butoxide (0.60 g, 5.34 mmol, 10 equiv, for resin **2e**−**g**) in dry DMF (20 mL) was added to resin **2a**−**g** (3 Tea-bag, 0.534 mmol), and the mixture was shaken at rt for 24 h. After removal of the solution, the resin was washed. The washing sequence was as follows (10 mL of a solvent was used for each 200 mg of a resin): DMF (4×), THF (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (4×). After washing, the resin was dried under vacuum for 24 h. Cleavage of resins **4a**−**g** with 20% TFA solution in DCM for 30 min gave compounds **5a**−**g**.

***S*-Methyl-*N′*-benzyl-*N*-butyl-*N*-(4-hydroxybenzyl)isothiourea (5a).** Yellow oil, 69%. ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7.2 Hz, 3H), 1.13−1.27 (m, 2H), 1.48−1.58 (m, 2H), 2.34 (s, 3H), 3.53 (t, J = 7.7 Hz, 2H), 4.75 (s, 2H), 4.78 (s, 2H), 6.77 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 7.20−7.32 (m, 5H), 8.37 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 17.4, 19.4, 29.2, 50.9, 52.1, 55.5, 116.3, 123.4, 127.6, 128.2, 128.9, 129.1, 135.9, 157.7, 169.6. HPLC: 95%.

***S*-Methyl-*N′*-benzyl-*N*-(4-hydroxybenzyl)-*N*-phenethylisothiourea (5b).** Yellow oil, 97%. ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 2.83 (t, J = 6.3 Hz, 2H), 3.83 (t, J = 6.2 Hz, 2H), 4.65 (s, 2H), 4.71 (d, J = 4.2 Hz, 2H), 6.79 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 8.1 Hz, 2H), 7.04 (d, J = 6.5 Hz, 2H), 7.14−7.18 (m, 2H), 7.22−7.32 (m, 6H), 9.44 (br s, 1H); ^{13}C NMR (acetone-d_6) δ 17.3, 33.5, 51.0, 53.6, 55.8, 116.3, 124.7, 127.3, 128.1, 128.3, 129.1, 129.5, 130.1, 137.2, 137.7, 158.5, 160.2, 171.5. LC/MS: 391.17, [MH^+]; ret. time, 2.33 min.

***S*-Methyl-*N′*-benzyl-*N*-(4-hydroxybenzyl)-*N*-(4-methoxyphenethyl)isothiourea (5c).** Yellow oil, 97%. ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H), 2.77 (t, J = 6.4 Hz, 2H), 3.74 (s, 3H), 3.79 (t, J = 6.4 Hz, 2H), 4.64 (s, 2H), 4.69 (d, J = 4.9 Hz, 2H), 6.75−6.83 (m, 4H), 6.89−6.99 (m, 4H), 7.07−7.14 (m, 2H), 7.27−7.32 (m, 3H), 9.18 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.1, 32.5, 51.1, 53.4, 55.2, 55.6, 114.4, 116.4, 123.5, 127.6, 128.0, 128.5, 129.0, 129.2, 129.8, 135.1, 157.0, 158.8, 170.6.

***S*-Methyl-*N′*-benzyl-*N*-(4-hydroxybenzyl)-*N*-(4-methoxyphenyl)isothiourea (5d).** Yellow oil, 99%. ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H), 3.78 (s, 3H), 4.63 (s, 2H), 5.06 (s, 2H), 6.72 (d, J = 8.5 Hz, 2H), 6.81−6.91 (m, 4H), 6.97 (d, J = 9.1 Hz, 2H), 7.09−7.15 (m, 2H), 7.27−7.33 (m, 3H), 9.42 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.8, 50.9, 55.5, 59.9, 115.2, 116.1, 124.1, 127.5, 127.8, 128.4, 129.0, 129.8, 134.9, 156.9, 160.0, 160.8, 171.0.

***S*-Methyl-*N*-(4-hydroxybenzyl)-*N*-(4-methoxyphenethyl)-*N′*-phenylisothiourea (5e).** Yellow oil, 100%. ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3H), 2.79 (t, J = 6.3 Hz, 2H), 3.76 (s, 3H), 3.89 (t, J = 6.3 Hz, 2H), 4.79 (s, 2H), 6.78−6.88 (m, 4H), 6.95−7.05 (m, 4H), 7.06−7.13 (m, 2H), 7.20−7.36 (m, 3H), 9.83 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.2, 32.9, 54.2, 55.2, 56.6, 114.4, 116.4, 117.7, 123.1, 123.6, 127.4, 128.2, 129.6, 129.9, 136.7, 157.3, 158.8, 170.8.

***S*-Methyl-*N*-(4-hydroxybenzyl)-*N*-(4-methoxyphenyl)-*N′*-phenylisothiourea (5f).** Yellow oil, 99%. ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3H), 3.76 (s, 3H), 5.11 (s, 2H), 6.73 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 9.1 Hz, 2H), 6.88−6.99 (m, 4H), 7.20−7.30 (m, 3H), 7.31−7.39 (m, 2H), 9.57 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.7, 55.5, 60.2, 115.2, 116.0, 123.6, 124.2, 127.8, 128.0, 129.9, 130.4, 136.5, 156.8, 160.3, 160.8, 171.7.

***S*-Methyl-*N*-(4-hydroxybenzyl)-*N*,*N′*-bis(4-methoxyphenyl)isothiourea (5g).** Yellow oil, 100%. ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 5.10 (s, 2H), 6.73 (d, J = 7.9 Hz, 2H), 6.77−6.87 (m, 4H), 6.90 (d, J = 8.1 Hz, 2H), 6.96 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 9.21 (br s, 1H); ^{13}C NMR (acetone-d_6) δ 16.3, 55.4, 55.7, 59.2, 114.6, 114.8, 115.7, 124.4, 126.0, 128.1, 129.4, 129.9, 132.2, 156.8, 158.2, 159.0, 171.8.

General Procedure for the Preparation of Resins 6a−d. A solution of an appropriate acyl chloride (5.34 mmol) and triethylamine (0.76 mL, 5.34 mmol) in dry THF (20 mL) was added to resins **2a**−**d** (3 Tea-bag, 0.534 mmol), and the resulting mixture was shaken at rt for 24 h. After removal of the solution, the resin **6a**−**d** was washed. The washing sequence was as follows (10 mL of a solvent was used for each 200 mg of a resin): THF (4×), THF/H_2O (2×), H_2O (2×), THF (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (4×). After washing, the resin was dried in a vacuum for 24 h. The obtained resins **6a**−**d** were cleaved with 20% TFA

in DCM for 30 min, and the isolated residues were purified on silica gel with ethyl acetate/hexanes 1:5 as eluent.

***N*-Benzoyl-*N′*-benzyl-*N*-butyrylthiourea (7a).** White microcrystals, 75%; mp 88−90 °C. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.25−1.37 (m, 2H), 1.50−1.61 (m, 2H), 3.57−3.65 (m, 2H), 5.56 (s, 2H), 7.06−7.15 (m, 2H), 7.20−7.28 (m, 3H), 7.32−7.50 (m, 5H), 10.09 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.1, 29.8, 46.8, 54.2, 126.6, 127.0, 127.2, 128.4, 128.5 (2), 130.9, 137.6, 174.2, 184.3. HPLC: 90%.

***N*-Benzyl-*N*-isobutyryl-*N′*-phenethylthiourea (7b).** White prisms, 80%; mp 81−83 °C. ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 5.5 Hz, 6H), 2.79−2.88 (m, 1H), 3.01 (t, J = 7.3 Hz, 2H), 3.90−3.97 (m, 2H), 5.76 (s, 2H), 7.15 (d, J = 7.3 Hz, 2H), 7.20−7.29 (m, 4H), 7.29−7.37 (m, 4H), 8.23 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.7, 34.1, 35.4, 48.6, 52.0, 125.6, 126.6, 127.2, 128.6, 128.7, 128.8, 137.6, 138.5, 182.9, 185.0. HPLC: 96%.

***N*-Benzyl-*N*-isobutyryl-*N′*-(4-methoxybenzyl)thiourea (7c).** Colorless oil, 81%, ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 6.5 Hz, 6H), 2.80−2.90 (m, 1H), 3.81 (s, 3H), 4.79 (d, J = 4.5 Hz, 2H), 5.80 (s, 2H), 6.90 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 7.2 Hz, 2H), 7.28−7.39 (m, 5H), 11.85 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.7, 35.4, 51.2, 52.1, 55.3, 114.2, 125.6, 127.3, 128.4, 128.8, 129.5, 137.5, 159.2, 183.0, 184.6. HPLC: 74%.

***N*-Butyl-*N*-isobutyryl-*N′*-phenethylthiourea (7d).** Colorless oil, 87%. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.19 (d, J = 6.7 Hz, 6H), 1.31−1.43 (m, 2H), 1.63−1.74 (m, 2H), 2.89−3.01 (m, 3H), 3.83−3.92 (m, 2H), 4.27−4.35 (m, 2H), 7.21−7.24 (m, 1H), 7.24−7.26 (m, 2H), 7.27−7.30 (m, 1H), 7.30−7.32 (m, 1H), 11.69 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.7, 19.9, 32.0, 34.1, 34.9, 48.3, 48.7, 126.5, 128.6, 128.7, 138.6, 182.1, 184.4. HPLC: 96%.

General Procedure for the Preparation of Resins 8a−e. A solution of an appropriate isothiocyanate (5.34 mmol, 10 equiv) and triethylamine (0.76 mL, 5.34 mmol) in dry THF (20 mL) was added to resins **1a**−**e** (3 Tea-bag, 0.534 mmol) and the mixture was shaken at rt for 24 h. After removal of the solution, resins **8a**−**e** were washed. The washing sequence was as follows (10 mL of a solvent was used for each 200 mg of a resin): THF (4×), THF/H_2O (2×), H_2O (2×), THF (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (4×). After washing, the resin was dried in a vacuum for 24 h. The obtained resins **8a**−**e** were cleaved with 20% TFA in DCM for 40 min to give compounds **9a**−**e**, which were purified on silica gel with ethyl acetate/hexanes 1:5 as eluent. Compounds **9a**−**e** were additionally recrystallized from MeOH.

***N*-Benzoyl-*N′*-butylthiourea (9a).** White prisms, 80%; mp 48−50 °C. ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3H), 1.39−1.53 (m, 2H), 1.64−1.77 (m, 2H), 3.66−3.76 (m, 2H), 7.52 (t, J = 7.5 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.84 (d, J = 7.4 Hz, 2H), 8.99 (br s, 1H), 10.73 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.1, 30.2, 45.7, 127.4, 129.1, 131.8, 133.5, 166.8, 179.6. HPLC: 100%.

***N*-Benzoyl-*N′*-phenethylthiourea (9b).** White prisms, 80%; mp 90−92 °C. ^{1}H NMR ($CDCl_3$) δ 3.00−3.07 (m, 2H), 3.93−4.01 (m, 2H), 7.22−7.38 (m, 5H), 7.46−7.56 (m, 2H), 7.58−7.66 (m, 1H), 7.82 (d, J = 7.8 Hz, 2H), 8.98 (br s, 1H), 10.76 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.4, 47.2, 126.8, 127.4, 128.7, 128.8, 129.1, 131.8, 133.5, 138.2, 166.7, 179.9. HPLC: 96%.

***N*-Benzoyl-*N′*-(4-methoxybenzyl)thiourea (9c).** Yellow solid, 65%; mp 96−98 °C. ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.84 (d, J = 5.1 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.51 (t, J = 7.3 Hz, 2H), 7.63 (t, J = 7.1 Hz, 1H), 7.82 (d, J = 7.3 Hz, 2H), 9.04 (br s, 1H), 10.93 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 49.4, 55.3, 114.3, 127.4, 128.2, 129.1, 129.4, 131.7, 133.6, 159.4, 166.8, 179.7. HPLC: 95%.

***N*-(4-Methoxybenzoyl)-*N′*-(4-methoxyphenethyl)thiourea (9d).** White prisms, 64%; mp 140−142 °C. ^{1}H NMR ($CDCl_3$) δ 3.02 (t, J = 7.2 Hz, 2H), 3.85 (s, 3H), 3.91−4.01 (m, 5H), 6.93 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 8.96 (br s, 1H), 10.86 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 33.5, 47.4, 55.2, 55.6, 114.1, 114.4, 123.7, 129.6, 129.7, 130.2, 158.4, 163.8, 166.1, 180.0. Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.31. Found: C, 62.76; H, 5.96; N, 8.02.

***N*-Benzoyl-*N′*-(4-methoxyphenethyl)thiourea (9e).** White prisms, 75%; mp 115−117 °C. ^{1}H NMR ($CDCl_3$) δ 2.97 (t, J = 7.2 Hz, 2H), 3.80 (s, 3H), 3.88−3.97 (m, 2H), 6.88 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.82 (d, J = 7.4 Hz, 2H), 9.02 (br s, 1H), 10.75 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 33.4, 47.4, 55.2, 114.1, 127.4, 129.1, 129.7, 130.1, 131.7, 133.5, 158.3, 166.7, 179.8. Anal. Calcd for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91. Found: C, 64.89; H, 5.85; N, 8.85.

***N*-(4-Methoxybenzoyl)-*N′*-(4-methoxybenzyl)thiourea (9f).** Yellow oil, 60%. ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.88 (s, 3H), 4.83 (d, J = 5.2 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H), 8.99 (br s, 1H), 10.99 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 49.3, 55.3, 55.6, 114.2, 114.4, 128.3, 129.0, 129.4, 129.6, 159.3, 163.9, 166.2, 179.8. HPLC: 79%.

General Procedure for the Preparation of Resins 10a−d. A solution of iodomethane (0.33 mL, 5.34 mmol) in dry DMF (20 mL) was added to resins **8a**−**d** (3 Tea-bag, 0.534 mmol), and the mixture was shaken at rt for 24 h. After removal of the solution, the resin was washed. The washing sequence was as follows (10 mL of a solvent was used for each 200 mg of a resin): DMF (4×), THF (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (4×). After washing, the resin was dried in a vacuum for 24 h. Cleavage of the resin with 20% TFA solution in DCM for 30 min gave compounds **11a**−**d**. Compound **11b** was purified on silica gel with a mixture of AcOEt/hexanes 1:5 and was additionally recrystallized from MeOH.

***S*-Methyl-*N′*-benzoyl-*N*-butyl-*N*-(4-methoxyphenethyl)-isothiourea (11a).** Colorless oil, 95%. ^{1}H NMR (acetone-d_6) δ 0.89 (t, J = 7.3 Hz, 3H), 1.23−1.40 (m, 2H), 1.60−1.71 (m, 2H), 2.33 (s, 3H), 3.55 (t, J = 7.8 Hz, 2H), 4.82 (s, 2H), 6.84 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.38−7.50 (m, 3H), 8.10 (d, J = 6.7 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 14.1, 16.1, 20.7, 30.3, 50.6, 53.9, 116.4, 127.9,

128.8, 129.2, 129.4, 130.2, 131.8, 158.1, 169.2, 171.9. HPLC: 94%.

***S*-Methyl-*N*′-benzoyl-*N*-(4-hydroxybenzyl)-*N*-phenethylisothiourea (11b).** White needles, 50%; mp 140−143 °C. ^{1}H NMR ($CDCl_3$) δ 2.55−2.70 (m, 3H), 2.80−2.90 (m, 2H), 3.76−3.90 (m, 2H), 4.62−4.80 (m, 2H), 6.76−6.90 (m, 2H), 6.93−7.15 (m, 4H), 7.16−7.37 (m, 3H), 7.43−7.54 (m, 2H), 7.55−7.66 (m, 1H), 8.09 (d, J = 7.5 Hz, 2H), 10.41 (br s, 1H). HPLC: 81%.

***S*-Methyl-*N*′-benzoyl-*N*-(4-hydroxybenzyl)-*N*-(4-methoxybenzyl)isothiourea (11c).** Yellow oil, 93%. ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.80 (s, 3H), 4.71 (s, 2H), 4.74 (s, 2H), 6.81 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 8.11 (d, J = 7.8 Hz, 2H), 8.56 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.2, 53.9, 54.0, 55.3, 114.6, 116.1, 125.0, 125.3, 128.3, 129.3, 129.6, 129.8, 132.4, 134.1, 156.5, 160.0, 167.8, 176.6. HPLC: 95%.

***S*-Methyl-*N*-(4-hydroxybenzyl)-*N*′-(4-methoxybenzoyl)-*N*-(4-methoxyphenethyl)isothiourea (11d).** Colorless oil, 98%. ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3H), 2.80−2.87 (m, 2H), 3.75 (s, 3H), 3.77−3.85 (m, 2H), 3.86 (s, 3H), 4.73 (s, 2H), 6.82 (t, J = 8.7 Hz, 4H), 6.98 (d, J = 7.7 Hz, 4H), 7.10 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 8.7 Hz, 2H), 9.45 (br s, 1H). HPLC: 89%.

***S*-Methyl-*N*′-benzoyl-*N*-(4-hydroxybenzyl)-*N*-(4-methoxyphenethyl)isothiourea (11e).** Yellow oil, 96%. ^{1}H NMR ($CDCl_3$) δ 2.63 (s, 3H), 2.82−2.89 (m, 2H), 3.76 (s, 3H), 3.80−3.85 (m, 2H), 4.74 (s, 2H), 6.83 (t, J = 8.3 Hz, 4H), 6.98 (d, J = 7.9 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 7.48 (t, J = 7.7 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 8.08 (d, J = 7.9 Hz, 2H), 9.39 (br s, 1H). HPLC: 95%.

General Procedure for the Preparation of Resins 12a−d. A solution of an appropriate hydrazine (5.34 mmol, 10 equiv) in dry acetonitrile (20 mL) was added to resins **10a−d** (3 Tea-bag, 0.534 mmol), and the mixture was refluxed for 24 h. After removal of the solution, the resins were washed. The washing sequence was as follows (10 mL of the solvent was used for each 200 mg of a resin): CH_3CN (4×), THF (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (4×). After washing, the resin was dried in a vacuum for 24 h. Cleavage of the resin with TFA gave compounds **13a−d**, which were purified on silica gel with ethyl acetate/hexanes as eluent. Compounds **13c−d** were additionally recrystallized from MeOH.

3-Butylamino-5-phenyl-1*H*-1,2,4-triazole (13a).[13] Yellow oil, 80%. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.3 Hz, 3H), 1.24−1.38 (m, 2H), 1.51−1.62 (m, 2H), 3.22 (t, J = 7.2 Hz, 2H), 7.36−7.49 (m, 3H), 7.83 (d, J = 7.6 Hz, 2H), 8.80 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 19.7, 30.9, 43.3, 124.8, 126.1, 129.2, 131.3, 152.9, 164.1. HPLC: 90%.

3-Phenethylamino-5-phenyl-1*H*-1,2,4-triazole (13b). Yellow oil, 69%, ^{1}H NMR ($CDCl_3$) δ 2.87 (t, J = 6.9 Hz, 2H), 3.47 (t, J = 6.8 Hz, 2H), 6.25 (br s, 1H), 7.11−7.16 (m, 2H), 7.16−7.30 (m, 3H), 7.35−7.44 (m, 3H), 7.82−7.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 35.7, 45.1, 126.2, 126.9, 128.6, 128.7, 128.8, 129.0, 130.6, 138.1, 154.4, 163.7. HPLC: 90%.

3-Butylamino-1,5-diphenyl-1*H*-1,2,4-triazole (13c). White needles, 88%; mp 109−111 °C. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.2 Hz, 3H), 1.39−1.51 (m, 2H), 1.60−1.70 (m, 2H), 3.36 (br s, 2H), 4.18 (br s, 1H), 7.27−7.40 (m, 8H), 7.42−7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.1, 32.1, 43.4, 125.3, 128.1, 128.2, 128.4, 128.8, 129.2, 129.7, 138.4, 152.8, 164.2. Anal. Calcd for $C_{18}H_{20}N_4$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.66; H, 7.27; N, 18.77.

3-(4-Methoxyphenethyl)amino-5-(4-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole (13d). Yellow solid, 76%; mp 154−156 °C. ^{1}H NMR ($CDCl_3$) δ 2.94 (t, J = 7.3 Hz, 2H), 3.56 (t, J = 7.3 Hz, 2H), 3.78 (s, 3H), 3.83 (s, 3H), 6.80−6.91 (m, 4H), 7.18 (d, J = 8.5 Hz 2H), 7.32−7.40 (m, 4H), 7.42−7.49 (m, 3H), 7.60 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.8, 44.7, 55.2, 55.5, 113.9, 114.7, 115.4, 125.5, 129.6, 129.7, 129.8, 130.5, 131.0, 137.1, 149.2, 158.2, 158.6, 162.1. HPLC: 98%.

General Procedure for the Preparation of Resins 14a−e. A solution of an appropriate 2-bromoacetophenone (5.34 mmol, 10 equiv) and triethylamine (1.52 mL, 10.68 mmol, 20 equiv) in dry acetonitrile (30 mL) was added to resins **8a−c** (3 Tea-bag, 0.534 mmol), and the mixture was refluxed overnight. For resins **8d−e**, the mixture needed to be refluxed for 36 h. After removal of the solution, the resin was washed. The washing sequence was as follows (10 mL of a solvent was used for each 200 mg of a resin): CH_3CN (4×), THF (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (2×), DCM (2×), MeOH (4×). After washing, the resin was dried in a vacuum for 24 h. Cleavage of Wang resins **14a−d** with 20% TFA gave compounds **15a−d** and **16c**. For the Merrifield resin **14e**, 95% TFA was used for the cleavage. Compounds **15a−e** were purified by flash column chromatography and additionally recrystallized from MeOH.

2-[*N*-Butyl-*N*-(4-hydroxybenzyl)amino]-4-phenyl-5-benzoyl-1,3-thiazole (15a). Yellow prisms, 80%; mp 177−179 °C. ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.30−1.41 (m, 2H), 1.60−1.73 (m, 2H), 3.43−3.54 (m, 2H), 4.74 (s, 2H), 5.07 (br s, 1H), 6.80 (d, J = 8.5 Hz, 2H), 7.01−7.15 (m, 5H), 7.16−7.24 (m, 3H), 7.27−7.32 (m, 2H), 7.43 (d, J = 7.4 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 13.8, 20.1, 28.7, 50.8, 53.4, 115.6, 122.2, 127.4, 127.5, 127.8, 128.5, 129.1, 129.3, 130.0, 131.1, 135.0, 138.4, 155.6, 160.1, 171.7, 189.0. Anal. Calcd for $C_{54}H_{54}N_4O_5S_2$: C, 71.81; H, 6.03; N, 6.20. Found: C, 72.12; H, 6.28; N, 6.21.

2-[*N*-(4-Hydroxybenzyl)-*N*-phenethylamino]-4-phenyl-5-benzoyl-1,3-thiazole (15b). Yellow prisms, 75%; mp 187−189 °C. ^{1}H NMR ($CDCl_3$) δ 3.04 (t, J = 7.6 Hz, 2H), 3.80 (t, J = 7.6 Hz, 2H), 4.72 (s, 2H), 6.86 (d, J = 8.4 Hz, 2H), 7.06−7.17 (m, 5H), 7.21−7.33 (m, 8H), 7.38 (d, J = 7.0 Hz, 2H), 7.45 (d, J = 7.4 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 33.0, 52.7, 54.2, 115.6, 122.1, 126.6, 127.3, 127.6, 127.8, 128.5, 128.7, 129.0, 129.1, 129.7, 130.2, 131.2, 135.6, 139.0 (2), 157.4, 159.0, 170.9, 187.8. Anal. Calcd for $C_{62}H_{54}N_4O_5S_2$: C, 74.52; H, 5.45; N, 5.61. Found: C, 74.72; H, 5.54; N, 5.52.

2-[*N*-(4-Hydroxybenzyl)-*N*-(4-methoxybenzyl)amino]-4-phenyl-5-benzoyl-1,3-thiazole (15c). Yellow prisms, 62%; mp 180−182 °C. ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 4.61 (s,

2H), 4.65 (s, 2H), 5.73 (br s, 1H), 6.79 (d, $J = 8.3$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2 H), 7.01−7.15 (m, 7H), 7.17−7.25 (m, 3H), 7.32 (d, $J = 6.8$ Hz, 2H), 7.45 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 52.7, 53.0, 55.3, 114.1, 115.7, 116.0, 122.2, 126.8, 127.5, 127.6, 128.7, 128.8, 129.1, 129.4, 130.0, 131.3, 134.7, 138.1, 156.1, 159.3, 160.0, 172.2, 189.1. HPLC: 93%.

2-[*N*-(4-Hydroxybenzyl)-*N*-(4-methoxyphenethyl)amino]-4-(4-methoxyphenyl-5-(4-methoxybenzoyl)-1,3-thiazole (15d). Yellow solid, 73%; mp 184−186 °C. ^{1}H NMR ($CDCl_3$) δ 2.89 (t, $J = 7.5$ Hz, 2H), 3.58−3.66 (m, 2H), 3.72 (s, 3H), 3.74 (s, 3H), 3.77 (s, 3H), 4.54 (s, 2H), 6.04 (br s, 1H), 6.61 (d, $J = 3.1$ Hz, 2H), 6.64 (d, $J = 3.0$ Hz, 2H), 6.77 (d, $J = 8.4$ Hz, 2H), 6.83 (d, $J = 8.5$ Hz, 2H), 7.05−7.13 (m, 4H), 7.33 (d, $J = 8.7$ Hz, 2H), 7.51 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 32.4, 52.7, 54.6, 55.2, 55.3 (2), 113.2, 113.3, 114.3, 115.8, 121.2, 128.0, 128.1, 129.5, 129.8, 130.7, 131.4, 131.5, 131.6, 155.9, 158.3, 158.6, 160.2, 162.5, 170.9, 187.7. HPLC: 87%.

2-[*N*-(4-Hydroxybenzyl)-*N*-(4-methoxybenzyl)amino]-4-(4-methoxyphenyl-5-(4-methoxybenzoyl)-1,3-thiazole (15e). Yellow prisms, 80%; mp 189−191 °C. ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 3.74 (s, 3H), 3.80 (s, 3H), 4.59 (s, 2H), 4.64 (s, 2H), 5.95 (br s, 1H), 6.57−6.68 (m, 4H), 6.79 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 7.12 (d, $J = 8.4$ Hz, 2H), 7.21 (d, $J = 8.6$ Hz, 2H), 7.35 (d, $J = 8.6$ Hz, 2H), 7.52 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 52.6, 52.9, 55.2, 55.3 (2), 113.0, 113.1, 114.1, 115.7, 121.0, 127.1, 127.6, 127.7, 129.4, 129.5, 130.8, 131.5, 131.6, 155.9, 158.6, 159.3, 159.9, 162.3, 171.7, 187.8. HPLC: 89%.

2-[*N*-(4-Methoxybenzyl)amino]-4-phenyl-5-benzoyl-1,3-thiazole (16c). Yellow semi-solid, 10%. ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 4.46 (d, $J = 5.2$ Hz, 2H), 6.94 (d, $J = 8.6$ Hz, 2H), 7.31 (d, $J = 8.5$ Hz, 2H), 7.40−7.49 (m, 3H), 7.50−7.65 (m, 3H), 7.78 (d, $J = 6.8$ Hz, 2H), 8.13 (d, $J = 7.3$ Hz, 2H), 9.98 (br s, 1H). HPLC: 76%.

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