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Parallel Solid-Phase Syntheses of 1,3,4-Thiadiazolium-2-Aminides

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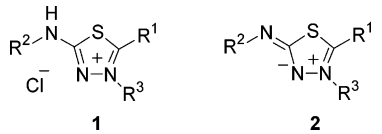
An efficient and advantageous solid-phase strategy has been developed to synthesize 1,3,4-thiadiazolium-2-aminides. The title compounds were prepared in parallel fashion according to the following compact route: (i) anchoring of aromatic aldehydes to the solid support; (ii) solution preparation of 1,4-disubstituted thiosemicarbazides from hydrazines plus isothiocyanates; (iii) trimethylsilyl chloride-promoted cyclization between the resin-bound aldehydes and 1,4-disubstituted thiosemicarbazides; and (iv) removal of the products from the solid support by acid treatment. The products (17 made in all) were cleaved with high initial purities (90−98%) and obtained in generally good isolated yields (53−94%, with one exception).

Introduction

Combinatorial chemistry serves as a powerful tool in drug discovery by allowing the rapid synthesis and biological screening of a large pool of potential candidates in an efficient, cost-effective manner.[1−10] The approach was originally used to prepare peptide libraries[1,11−20] and was later generalized to libraries of small (often heterocyclic) organic molecules,[21−30] whose pharmacokinetic properties make them attractive potential therapeutic agents. In addition to their biological properties, heterocycles are logical targets for library syntheses because they can be prepared in relatively few steps and they offer the potential to incorporate a wide degree of structural diversity.[28]

Derivatives of 1,3,4-thiadiazoles are known antibacterial[31−36] and antifungal[33,35−40] agents. Among these are the 1,3,4-thiadiazolium-2-aminides (Figure 1), which are known to possess sedative,[41] antimicrobial,[42,43] and antitumor properties.[44] These compounds have been synthesized in solution either by reacting *N*-thioacylhydrazines with arylisocyanide dichlorides,[45] by condensation of acid chlorides with 1,4-diphenylthiosemicarbazide,[46,47] or by condensation of monoacylhydrazines with isothiocyanates.[48]

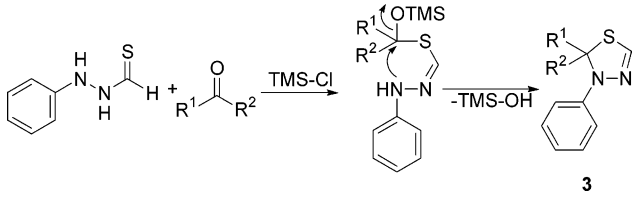
1,3,4-Thiadiazoles have been prepared by the reaction of *N*′-phenylthioformohydrazide with aldehydes and ketones in the presence of trimethylsilyl chloride (TMS-Cl) to prepare substituted 2,3-dihydro-3-phenyl-1,3,4-thiadiazoles (**3**) (Scheme 1).[49,50] In this two-step reaction, formation of the *O*-trimethylsilyl phenylhydrazonomethylmonothioacetal intermediate is followed by intramolecular cyclization to give the final heterocycle.



1 **2**

Figure 1. Structures of 1,3,4-thiadiazolium-2-aminides: hydrochloride salt (**1**) and free base (**2**).

Scheme 1. Preparation of Substituted 2,3-Dihydro-3-phenyl-1,3,4-thiadiazoles.



3

In conjunction with our interest in the combinatorial preparation of sulfur-containing heterocycles,[51] we envisaged that the chemistry described by Scheme 1 could be extended and applied to the solid-phase synthesis of substituted 1,3,4-thiadiazoles. We provide here a detailed account of the synthesis of 1,3,4-thiadiazolium-2-aminides (**1**) in parallel library fashion.

Results and Discussion

The general approach used to synthesize the title compounds is illustrated in Scheme 2. Cyclization between a resin-bound aldehyde and a 1,4-disubstituted thiosemicarbazide was accomplished in the presence of TMS-Cl, and the resulting five-membered ring was then cleaved from the solid support. The simple condensation product **4** was expected by analogy to the literature synthesis of substituted 2,3-dihydro-3-phenyl-1,3,4-thiadiazoles (Scheme 1). However, a solution model, in which 1,4-diphenylthiosemicarbazide was reacted with 2-naphthaldehyde and TMS-Cl, established that the highly stabilized, mesoionic[41,52−54]

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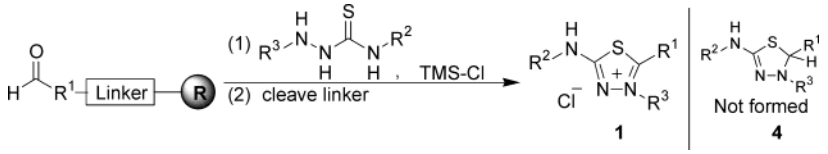
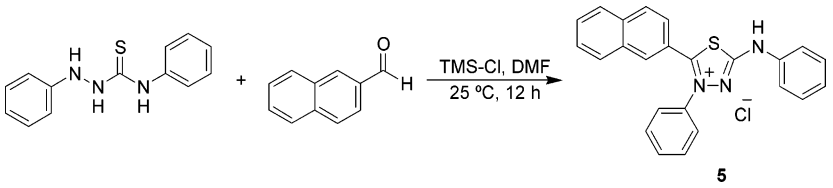
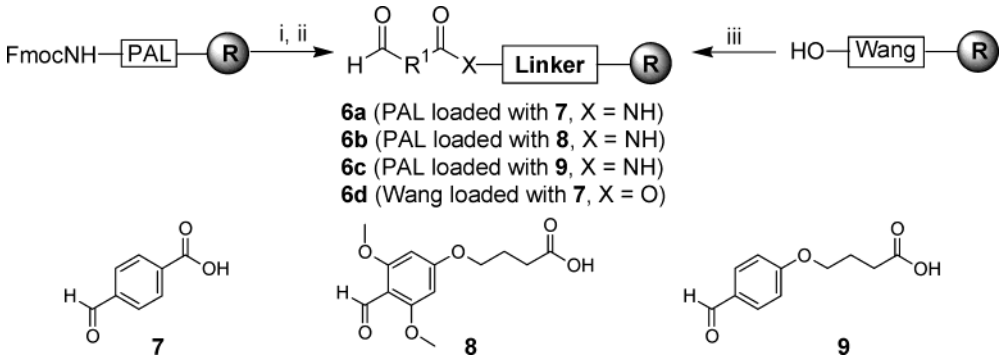
Scheme 2. General Approach to Prepare Title Compounds



Scheme 3. Solution Synthesis of 5-(2-Naphthyl)-4-phenyl-1,3,4-thiadiazolium-2-phenylamine Chloride

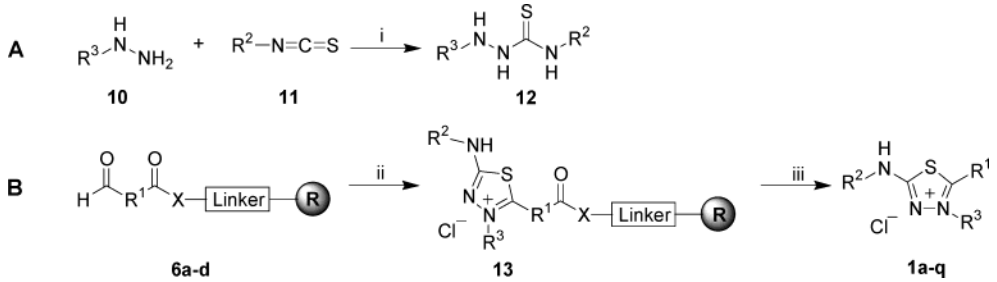


Scheme 4. Loading of Aldehydes to Solid Supports[a]



[a] Reagents and conditions: (i) piperidine−DMF (1:4), 3 × 1 min, 3 × 5 min, 25 °C; (ii) aldehyde (**7**, **8**, or **9**) (4 equiv), HATU (4 equiv), DIEA (8 equiv), DMF, 1 h, 25 °C; (iii) **7** (5 equiv), DIPCDI (5 equiv), DMAP (1 equiv), DMF, 1 h, 25 °C.

Scheme 5. (A) Solution Synthesis of 1,4-Disubstituted Thiosemicarbazides; (B) Solid-Phase Synthesis of 1,3,4-Thiadiazolium-2-aminides from Resin-Bound Aromatic Aldehydes[a]

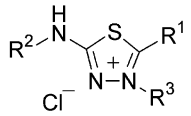


[a] Reagents and conditions: (i) dioxane, 60 °C, 2 h; (ii) **12** (unpurified, direct from part A; nominally 5 equiv), TMS-Cl (5 equiv), dioxane−THF (2:1), 60 °C, 2 h; (iii) TFA−H_2O (19:1), 25 °C, 2 × 1 h.

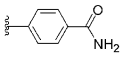
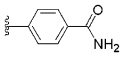
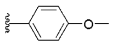
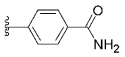
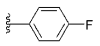
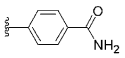
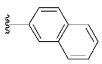
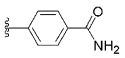
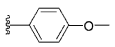
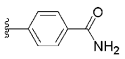
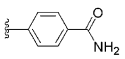
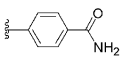
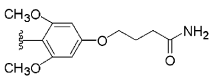
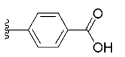
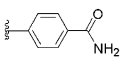
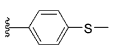
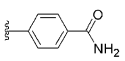
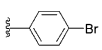
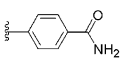
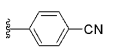
compound **5** was formed (Scheme 3). We speculate that in both the solution and solid-phase cases, proton loss and aromatization provide the driving force to form **1** rather than **4**.

The first step of the parallel synthesis was preparation of resin-bound aldehydes. Loading of diverse aromatic aldehydes **7**−**9** (4 equiv) onto PAL-PEG-PS was mediated by *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridine-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU) (4 equiv) plus *N*,*N*-diisopropylethylamine (DIEA) (8 equiv) in DMF, giving aldehyde resins **6a**−**c** (Scheme 4). In addition, resin **6d** was prepared by anchoring **7** (5 equiv) to *p*-alkoxybenzyl alcohol (Wang) resin using *N*,*N*′-diisopropylcarbodiimide (DIPCDI) (5 equiv) plus 4-(dimethylamino)pyridine (DMAP) (1 equiv) in DMF (Scheme 4). Next, 1,4-disubstituted thiosemicarbazides (**12**) were prepared separately in solution by reacting substituted isothiocyanates (**10**) (15 equiv with respect to resin loading) with hydrazines (**11**) (5 equiv with respect to resin loading) in dioxane (usually; in a few experiments, DMF was used with little difference in purities) at 60 °C for 1 h (Scheme 5, part A). Nine isothiocyanates and six hydrazines were used to prepare 13 examples of **12**. The crude reaction solutions containing **12** were added directly to the appropriate resin-bound aldehydes (**6a**−**d**) plus TMS-Cl (5 equiv) in THF. The ensuing cyclization reactions proceeded for 2 h at 60 °C, providing the resin-bound cyclic intermediates **13** (Scheme 5, part B, step ii). Resins were cleaved with trifluoroacetic acid (TFA)−H_2O (19:1) (Scheme 5, part B, step iii), the filtrates and washes were collected and concentrated, and the residues were purified by flash chromatography to provide the title compounds **1a**−**q** (Table 1). These were analyzed by HPLC (monitoring at 220 nm), mass spectrometry, and ^{1}H NMR (see Figure 2 for repre-

Table 1. 1,3,4-Thiadiazolium-2-aminides (**1a**−**q**)



1

Entry	R^1	R^2	R^3	Initial Purity[a] (%)	Yield[b] (%)
a				92 (89)	74
b				94 (92)	72
c				92 (93)	93
d				97 (96)	81
e				93 (94)	57
f				94 (94)	58
g				92	70
h				92 (91)	74
i				91 (95)	65
j				92	64
k				94	77
l				91	53
m				90	94
n				98 (98)	69
o				91 (91)	86
p				95	62
q				91	38

[a] Determined by HPLC using relative peak areas with monitoring at 220 nm. The number in parentheses is the purity when using DMF in place of dioxane. [b] Isolated yields; calculated using the substitution level of the starting resin.

sentative example, **1h**). Isolated yields were good (53−94%) with one exception (38%, for **1q**), and the initial purities were high (90−98%). Electron-rich aromatic, electron-deficient aromatic, and aliphatic substituents were tolerated in both the hydrazine and isothiocyanate components.

In conclusion, the solid-phase syntheses of 1,3,4-thiadiazolium-2-aminides has been described. Products were generated in high purity and prepared in a concise two-step procedure from resin-bound aldehydes plus crude solutions of 1,4-disubstituted thiosemicarbazides. Diversity within the library was generated from aldehydes, hydrazines, and

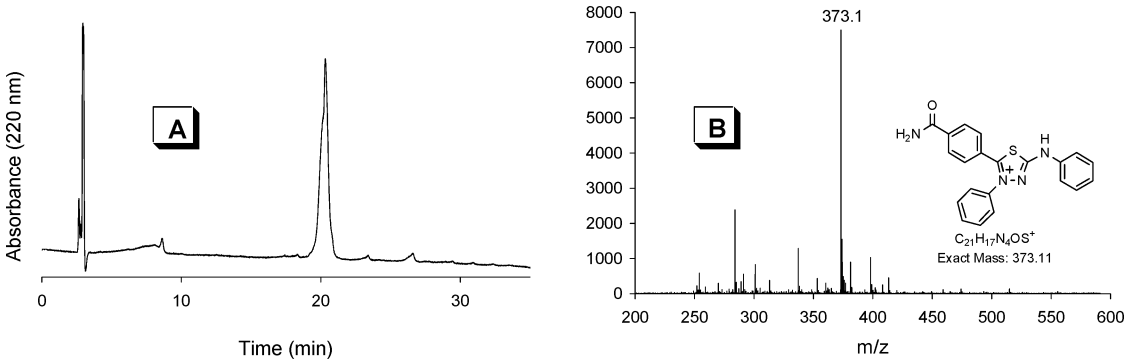


Figure 2. (A) Analytical HPLC of crude product **1h** (Table 1) (a linear gradient of 0.1% aqueous TFA and 0.1% TFA in CH_3CN was run at 1.0 mL/min flow rate from 9:1 to 5:5 over 30 min, then 0:10 over the next 10 min); (B) ESI-MS of purified **1h**.

isothiocyanates. We envision that this simple methodology would be easily amenable to automation for the preparation of a split/pool or parallel combinatorial library of 1,3,4-thiadiazolium-2-aminides to look for more potent analogues.

Experimental Section

General Procedures. Materials, solvents, instrumentation, and general methods were essentially as described in previous publications from our laboratory.[51,55,56] All transformations and washes were at 25 °C, unless indicated otherwise. Room temperature polymer-supported reactions were carried out using plastic syringes (3-, 5-, and 10-mL) fitted with polypropylene frits, whereas heated polymer-supported reactions were performed in 16 × 100-mm glass culture tubes with Teflon-lined caps and shaken on an EStem Electrothermal Reacto-Station RS 6000 orbital shaker, followed by transfer to a fritted plastic syringe for washing. PAL-PEG-PS resin and 4-formyl-(3,5-dimethoxyphenoxy)butyric acid was obtained from PE Biosystems (Framingham, MA), and Wang resin and HATU were obtained from Advanced ChemTech (Louisville, KY). All solvents were reagent grade from Aldrich (Milwaukee, WI). CH_2Cl_2 was freshly distilled from anhydrous calcium hydride. Hydrazine and isothiocyanate diversity elements were obtained from Aldrich (Milwaukee, WI) and Lancaster (Windham, NH). All hydrazines were used in the free base form (those obtained as hydrochloride salts were washed with 10% aqueous $NaHCO_3$ and extracted into Et_2O). ^1H NMR spectra were obtained at ambient temperature on Varian VI 500 or Varian VI 300 spectrophotometers. Chemical ionization mass spectrometry (CIMS) was performed on a Perkin-Elmer Sciex API III triple quadrupole mass spectrometer equipped with an ionspray interface, fast atom bombardment mass spectroscopy (FABMS) was performed on a VG7070E-HF mass spectrometer, and electrospray ionization mass spectroscopy (ESI-MS) was performed on a Bruker Biotof II. Analytical HPLC was performed using a Vydac C_{18} reversed-phase column (0.46 × 25-cm) on a Beckman instrument configured with two 112 pumps and a 165 variable wavelength detector set at 220 and 280 nm. Linear gradients of 0.1% aqueous TFA and 0.1% TFA in CH_3CN were run at 1.0 mL/min flow rate from 9:1 to 5:5 over 30 min, then to 0:10 over the next 10 min.

5-(2-Naphthyl)-4-phenyl-1,3,4-thiadiazolium-2-phenylamine Chloride (5). To a solution of 1,4-diphenylthiosemicarbazide (**2**) (60 mg, 0.26 mmol) in DMF (1 mL) was added TMS-Cl (98 μL, 0.78 mmol), followed by 2-naphthaldehyde (**3**) (100 mg, 0.62 mmol). The mixture was stirred for 12 h at 25 °C, giving a precipitate which was collected by filtration, washed with toluene, and dried in vacuo, providing the title compound as a yellow solid (70 mg, 72%). R_f 0.28 (CH_2Cl_2−MeOH, 9:1); HPLC t_R 18.5 min; ^1H NMR ($CDCl_3$, 300 MHz) δ 12.90 (s, 1H), 8.15 (d, J = 1.2 Hz, 1H), 7.83 (t, J = 9.2 Hz, 2H), 7.76 (d, J = 8.7 Hz, 1H), 7.50−7.70 (m, 9H), 7.19 (dd, J_1 = 1.8 Hz, J_2 = 8.7 Hz, 1H), 7.15 (t, J = 8.0 Hz, 2H), 6.97 (t, J = 7.5 Hz, 1H). CIMS calcd for $C_{24}H_{18}N_3S$ 380.1, found 380.1 $[M]^+$.

Anal. Calcd for $C_{24}H_{18}ClN_3S$ (415.94): C, 69.30; H, 4.36; Cl, 8.52; N, 10.10; S, 7.71. Found: C, 68.87; H, 4.33; Cl, 8.88; N, 10.06; S, 7.66.

General Procedure for Loading of Aldehyde Diversity Elements to PAL Resin (6a−c). Fmoc-PAL-PEG-PS resin (1.0 g, 0.6 mmol/g, as per manufacturer specifications) was washed with DMF (2 × 2 min) and CH_2Cl_2 (2 × 2 min) and then treated with piperidine−DMF (1:4, 3 × 1 min, 3 × 5 min), followed by washings with DMF (10 × 0.5 min). Next, the aldehyde (4 equiv) plus HATU (4 equiv) were combined in DMF (4 mL), and DIEA (8 equiv) was added. After 1-min preactivation, this solution was added to the resin for a 1.5-h coupling reaction, at the conclusion of which the resin was washed with DMF (5 × 0.5 min) and CH_2Cl_2 (5 × 0.5 min).

Wang Resin-Bound 4-Formyl-carboxybenzene (6d). Wang resin (0.50 g, 0.80 mmol/g) was swollen in a minimal amount of DMF, and 4-formylbenzoic acid (300 mg, 2 mmol) in DMF (2 mL), DIPCDI (0.31 mL, 2 mmol), and DMAP (40 mg, 0.40 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_2Cl_2 (3 × 1 min).

General Procedure for Preparation of 1,4-Disubstituted Thiosemicarbazides (12). The hydrazine (5 equiv, relative to resin used in cyclization step), and isothiocyanate (15 equiv, relative to resin used in cyclization step) were reacted in dioxane (2 mL) for 1 h at 60 °C. The crude product was used, without purification, directly in the following cyclization procedure.

General Procedure for the Preparation of 1,3,4-Thiadiazolium-2-aminides (1a−q). The procedure that follows was carried out using 80 mg of resin as described, on three separate occasions. Subsequently, the three resins were pooled, to total 240 mg, and the entire pooled resins were cleaved to determine the final yields. The resin-bound aldehyde (80 mg, 0.6 mmol/g for **6a**−**6c**; 80 mg, 0.8 mmol/g for **6d**) was swollen in THF (1 mL), and TMS-Cl (5 equiv) was added. Subsequently, the appropriate dioxane solution containing 1,4-disubstituted thiosemicarbazide, prepared as described above, was transferred to the resin, and the reaction proceeded for 2 h at 60 °C. The resin was then washed with THF (5 × 0.5 min), DMF (10 × 0.5 min), and CH_2Cl_2 (5 × 0.5 min) and cleaved with TFA−H_2O (19:1) (2 mL, 2 × 1 h). The filtrates from the cleavage reaction were collected, combined with TFA washes (3 × 1 mL) of the resin, and evaporated under a stream of N_2. The crude residue was redissolved and purified over silica gel with $CHCl_3$−MeOH−HOAc (95:5:0.5).

4-(3-Phenyl-5-benzylamino-[1,3,4]thiadiazol-2-yl)-benzylamide Chloride (1a). Prepared as described above from resin **6a**, using phenylhydrazine (24 μL, 0.24 mmol), benzyl isothiocyanate (96 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as an orange solid (32.9 mg, 59%). HPLC t_R 20.4 min (92%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.55 (s, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.82 (t, J = 8.9 Hz, 2H), 7.07−7.57 (m, 12H), 1.78 (s, 2H). ESI-MS calcd for $C_{22}H_{19}N_4OS$ 387.1, found 387.0 $[M]^+$.

4-(5-(4-Methoxyphenylamino)-3-phenyl-[1,3,4]thiadiazol-2-yl)benzylamide Chloride (1b). Prepared as described above from resin **6a**, using phenylhydrazine (24 μL, 0.24 mmol), 4-methoxyphenyl isothiocyanate (100 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a yellow solid (49.5 mg, 85%). HPLC t_R 19.6 min (94%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.65 (s, 1H), 8.13 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 1H), 7.46−7.73 (m, 6H), 7.32 (d, J = 7.32 Hz, 1H), 7.13 (d, J = 9.3 Hz, 1H), 7.03 (d, J = 9.3 Hz, 2H), 6.95 (d, J = 9.0 Hz, 1H), 3.75 (s, 3H). FABMS calcd for $C_{22}H_{19}N_4O_2S$ 403.1, found 403.1 $[M]^+$.

4-(5-(4-Fluorophenylamino)-3-phenyl-[1,3,4]thiadiazol-2-yl)benzylamide Chloride (1c). Prepared as described above from resin **6a**, using phenylhydrazine (24 μL, 0.24 mmol), 4-fluorophenyl isothiocyanate (0.110 g, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a yellow solid (33.1 mg, 59%). HPLC t_R 20.9 min (92%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.63 (s, 1H), 8.14 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.55−7.69 (m, 10H), 7.31 (t, J = 8.9 Hz, 2H). ESI-MS calcd for $C_{21}H_{16}FN_4OS$ 391.1, found 391.1 $[M]^+$.

4-(5-(Naphthalen-1-ylamino)-3-phenyl-[1,3,4]thiadiazol-2-yl)benzylamide Chloride (1d). Prepared as described above from resin **6a**, using phenylhydrazine (24 μL, 0.24 mmol), 1-naphthyl isothiocyanate (0.134 g, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as an orange solid (49.1 mg, 81%). HPLC t_R 23.0 min (97%); ^{1}H NMR (CD_3OD, 300 MHz) δ 8.18 (d, J = 7.5 Hz, 1H), 7.99−8.06 (m, 2H), 7.92 (t, J = 8.0 Hz, 4H), 7.52−7.69 (m, 11H). ESI-MS calcd for $C_{25}H_{19}N_4OS$ 423.1, found 423.2 $[M]^+$.

4-(3-(4-Methoxyphenyl)-5-phenylamino-[1,3,4]thiadiazol-2-yl)benzylamide Chloride (1e). Prepared as described above from resin **6a**, using 4-methoxyphenylhydrazine (0.032 g, 0.24 mmol), phenyl isothiocyanate (86 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a brown solid (52.3 mg, 90%). HPLC t_R 21.4 min (93%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.13 (s, 1H), 7.87 (d, J = 7.8 Hz, 2H), 7.29−7.73 (m, 9H), 7.01−7.07 (m, 3H), 3.79 (s, 3H). ESI-MS calcd for $C_{22}H_{19}N_4O_2S$ 403.1, found 403.1 $[M]^+$.

4-(3-(4-Fluorophenyl)-5-phenylamino-[1,3,4]thiadiazol-2-yl)benzylamide Chloride (1f). Prepared as described above from resin **6a**, using 4-fluorophenylhydrazine (0.030 g, 0.24 mmol), phenyl isothiocyanate (86 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a yellow solid (40.1 mg, 71%). HPLC t_R 21.0 min (94%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.61 (s, 1H), 8.15 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.74−7.79 (m, 2H), 7.65 (s, 1H), 7.58 (t, J = 9 Hz, 4H), 7.43−7.49 (m, 4H), 7.18 (t, J = 7.4 Hz, 1H). ESI-MS calcd for $C_{21}H_{16}FN_4OS$ 391.1, found 391.3 $[M]^+$.

4-(3-(2,5-Dimethylphenyl)-5-phenylamino-[1,3,4]thiadiazol-2-yl)benzylamide Chloride (1g). Prepared as described above from resin **6a**, using 2,5-dimethylphenylhydrazine (0.032 g, 0.24 mmol), phenyl isothiocyanate (86 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a yellow solid (39.7 mg, 69%). HPLC t_R 23.6 min (92%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.19 (s, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.66 (s, 1H), 7.52−7.57 (m, 5H), 7.43 (t, J = 7.7 Hz, 2H), 7.36 (s, 2H), 7.15 (t, J = 7.1 Hz, 1H), 2.28 (s, 3H), 2.15 (s, 3H). ESI-MS calcd for $C_{23}H_{21}N_4OS$ 401.1, found 401.1 $[M]^+$.

4-(3-Phenyl-5-phenylamino-[1,3,4]thiadiazol-2-yl)-benzylamide Chloride (1h). Prepared as described above from resin **6a**, using phenylhydrazine (24 μL, 0.24 mmol), phenyl isothiocyanate (86 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a yellow solid (41.1 mg, 76%). HPLC t_R 19.7 min (92%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.54 (s, 1H), 8.13 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.55−7.69 (m, 10H), 7.45 (t, J = 7.8 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H). FABMS calcd for $C_{21}H_{17}N_4OS$ 373.1, found 373.3 $[M]^+$.

4-(3,5-Dimethoxy-4-(3-phenyl-5-phenylamino-[1,3,4]-thiadiazol-2-yl)phenoxy]butyramide Chloride (1i). Prepared as described above from resin **6b**, using phenylhydrazine (24 μL, 0.24 mmol), phenylisothiocyanate (86 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a brown solid (45.0 mg, 65%). HPLC t_R 25.7 min (91%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.20 (s, 1H), 7.60 (d, J = 12.0 Hz, 1H), 7.38−7.46 (m, 5H), 7.28 (t, J = 13.0 Hz, 2H), 7.12 (m, 2H), 6.93 (t, J = 12.0 Hz, 2H), 6.79 (m, 2H), 6.21 (s, 2H), 3.97 (t, J = 7.2 Hz, 2H), 3.63 (s, 3H), 2.18 (t, J = 7.2 Hz, 2H), 1.89 (s, 3H), 1.84−1.89 (m, 2H). ESI-MS calcd for $C_{26}H_{27}N_4O_4S$ 491.2, found 491.2 $[M]^+$.

4-(3-Phenyl-5-phenylamino-[1,3,4]thiadiazol-2-yl)benzoic Acid Chloride (1j). Prepared as described above from

resin **6d**, using phenylhydrazine (24 μL, 0.24 mmol), phenyl isothiocyanate (86 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a brown solid (39.4 mg, 73%). HPLC t_R 22.5 min (92%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.62 (s, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.54−7.68 (m, 9H), 7.46 (t, J = 7.95 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H). ESI-MS calcd for $C_{21}H_{16}N_3O_2S$ 374.1, found 374.1 $[M]^+$.

4-(5-(4-Methylsulfanylphenylamino)-3-phenyl-[1,3,4]-thiadiazol-2-yl)benzylamide Chloride (1k). Prepared as described above from resin **6a**, using phenylhydrazine (24 μL, 0.24 mmol), 4-methylthiophenyl isothiocyanate (0.130 g, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as an orange solid (42.0 mg, 70%). HPLC t_R 23.1 min (94%); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.93 (dt, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 2H), 7.57−7.65 (m, 9H), 7.50 (dt, J_1 = 9.3 Hz, J_2 = 2.4 Hz, 2H), 7.02 (dt, J_1 = 9.0 Hz, J_2 = 2.3 Hz, 2H), 3.81 (s, 3H). ESI-MS calcd for $C_{22}H_{19}N_4OS_2$ 419.1, found 419.1 $[M]^+$.

4-(3-(4-Bromophenyl)-5-phenylamino-[1,3,4]thiadiazol-2-yl)benzylamide Chloride (1l). Prepared as described above from resin **6a**, using 4-bromophenylhydrazine (0.044 g, 0.24 mmol), phenyl isothiocyanate (86 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a brown solid (36.1 mg, 56%). HPLC t_R 23.8 min (91%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.60 (s, 1H), 7.16−8.15 (m, 15H). ESI-MS calcd for $C_{21}H_{16}BrN_4OS$ 451.0, found 451.1 $[M]^+$.

4-(5-(4-Cyanophenylamino)-3-phenyl-[1,3,4]thiadiazol-2-yl)benzylamide Chloride (1m). Prepared as described above from resin **6a**, using phenylhydrazine (24 μL, 0.24 mmol), 4-cyanophenyl isothiocyanate (86 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a yellow solid (34.5 mg, 60%). HPLC t_R 18.2 min (90%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.92 (s, 1H), 8.06 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.51−7.63 (m, 8H), 7.40 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H). ESI-MS calcd for $C_{22}H_{16}N_5OS$ 398.1, found 398.1 $[M]^+$.

4-(3-Methyl-5-methylamino-[1,3,4]thiadiazol-2-yl)-benzylamide Chloride (1n). Prepared as described above from resin **6a**, using methylhydrazine (12 μL, 0.24 mmol), methyl isothiocyanate (0.052 g, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a beige solid (25.2 mg, 67%). HPLC t_R 15.8 min (98%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.98 (d, J = 4.2 Hz, 1H), 8.04 (t, J = 7.8 Hz, 2H), 7.94 (t, J = 8.1 Hz, 2H), 7.46 (s, 1H), 3.82 (s, 3H), 3.07 (d, J = 4.2 Hz, 3H). ESI-MS calcd for $C_{11}H_{13}N_4OS$ 249.1, found 249.1 $[M]^+$.

4-(3-Methyl-5-phenylamino-[1,3,4]thiadiazol-2-yl)-benzylamide Chloride (1o). Prepared as described above from resin **6a**, using methylhydrazine (12 μL, 0.24 mmol), phenyl isothiocyanate (86 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a yellow solid (23.4 mg, 51%). HPLC t_R 16.2 min (91%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.52 (s, 1H), 7.90−8.13 (m, 3H), 7.74−7.80 (m, 1H), 7.36−7.50 (m, 5H), 7.25 (d, J = 6.6 Hz, 1H), 7.06 (d, J = 6.6 Hz, 1H), 1.91 (s, 3H). ESI-MS calcd for $C_{16}H_{15}N_4OS$ 311.1, found 311.1 $[M]^+$.

4-(3-Phenyl-5-*p*-tolylamino-[1,3,4]thiadiazol-2-yl)benzylamide Chloride (1p). Prepared as described above from resin **6a**, using phenylhydrazine (24 μL, 0.24 mmol), *p*-tolyl isothiocyanate (0.108 g, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a yellow solid (46.1 mg, 83%). HPLC t_R 22.4 min (95%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.96 (s, 1H), 8.13 (s,1H), 7.88 (d, J = 8.4 Hz, 2H), 7.38−7.72 (m, 10H), 7.22 (d, J = 7.8 Hz, 2H), 2.27 (s, 3H). ESI-MS calcd for $C_{22}H_{19}N_4OS$ 387.1, found 387.1 $[M]^+$.

4-[4-(3-Phenyl-5-phenylamino-[1,3,4]thiadiazol-2-yl)-phenoxy]butyramide Chloride (1q). Prepared as described above from resin **6c**, using phenylhydrazine (24 μL, 0.24 mmol), phenyl isothiocyanate (86 μL, 0.72 mmol), and TMS-Cl (30 μL, 0.24 mmol), providing the title compound as a green solid (55.9 mg, 91%). HPLC t_R 23.1 min (91%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.43 (s, 1H), 8.08 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 7.68 (dd, J_1 = 7.5 Hz, J_2 = 2.3 Hz, 2H), 7.52−7.63 (m, 4H), 7.44 (d, J = 7.2 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 7.27 (t, J = 8.6 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 6.91 (s, 1H), 4.01 (t, J = 6.5 Hz, 2H), 2.17 (t, J = 7.1 Hz, 2H), 1.88 (quintet, J = 6.8 Hz, 2H). ESI-MS calcd for $C_{24}H_{23}N_4O_2S$ 431.2, found 431.1 $[M]^+$.

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