Multistep Solid-Phase Synthesis of an Antibiotic and Receptor Tyrosine Kinase Inhibitors Using the Traceless Phenylhydrazide Linker

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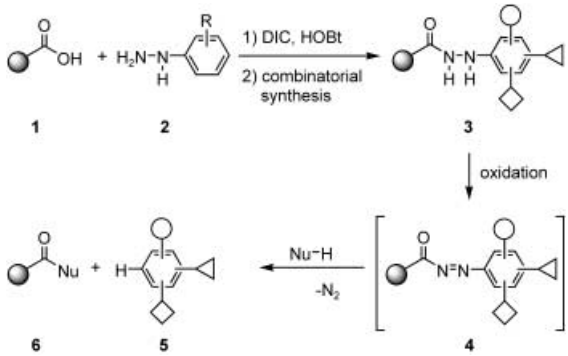
Abstract: The hydrazide group is an oxidatively cleavable traceless linker for solid-phase chemistry. This linker technology was used to develop a multistep solid-phase synthesis of an antibiotic that is active against *Mycobacterium tuberculosis*. Furthermore, we describe an efficient method for the traceless synthesis of 2-aminothiazoles that display dual inhibitory activity against the receptor tyrosine kinases VEGFR-2 and Tie-2. The synthesis method proceeds through 9 steps on the solid phase and should give access to a much larger library of 2-aminothiazoles, from which a new class of anti-angiogenesis drugs may be developed.

Keywords: combinatorial chemistry · inhibitors · phenylhydrazides · solid-phase synthesis · traceless linker

Introduction

The combinatorial and parallel synthesis of compound libraries on polymeric supports is at the heart of research in modern bioorganic and medicinal chemistry. Paramount to success in this field is the development of powerful and efficient solutions to several prevailing problems, in particular: i) The proper choice of the molecular scaffolds onto which different functional groups are grafted in the process of combinatorial synthesis. The generation of large libraries alone is not sufficient, the underlying basic structure of the individual library members must be biologically relevant. ii) The development of reliable multistep sequences on the polymeric support including widely differing types of transformations. The chemistry must be adapted to the particular biologically active compound class; the structure of the targets should not be chosen on the basis of the available chemistry. iii) The use of linker groups that guarantee release of the target compounds from the solid support under the mildest conditions. Ideally, a linker should release the products while forming a C–H bond in place of the resin attachment, thus leaving behind no trace of a solid-phase synthesis ("traceless linker").[1] Herein we describe the use of the traceless hydrazide linker[2, 3] for the multistep synthesis of potentially biologically active compounds. The linker proves to be stable in various synthetic transformations and allows the release of different heterocycles in excellent overall yields and with high purities (Scheme 1).



Scheme 1. Principle of the oxidative cleavage of the hydrazide linker.

Results and Discussion

Synthesis of an antibiotic incorporating a biphenyl structure: For the proper choice of suitable biologically relevant molecular scaffolds, the principle of identifying "privileged

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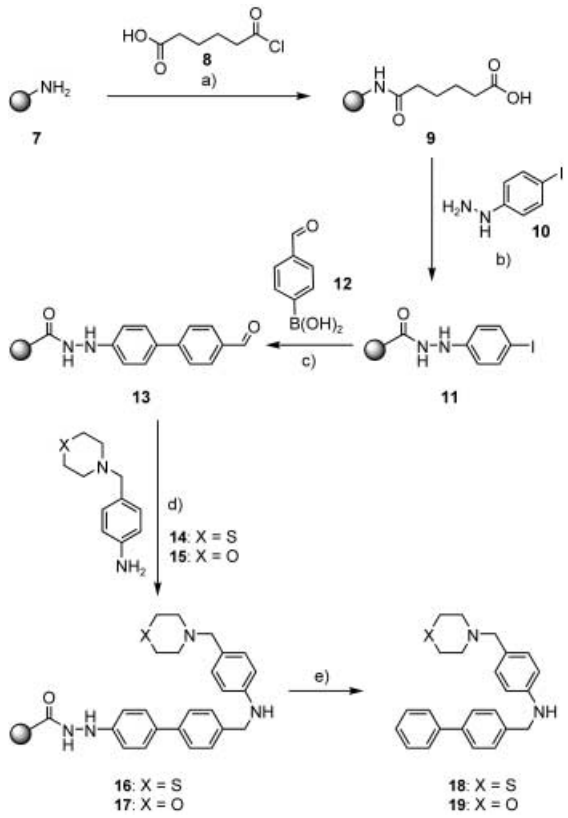
structures",[4] that is compound classes that facilitate interactions with various proteins, provides a strong and powerful guideline. Biphenyls are found in various pharmacologically active compounds, for example, in vitronectin receptor antagonists,[5] angiotensin receptor antagonists,[6] inhibitors of transthyretin-mediated amyloid fibril formation,[7] and novel antibacterial agents.[8] In addition, the biphenyl unit has been proposed as a general scaffold for the combinatorial generation of new drug candidates.[9] In order to prove that the traceless phenylhydrazide linker can be employed efficiently for the synthesis of biologically and pharmacologically relevant compounds, biphenyl derivative **18** and its morpholine analogue **19** were synthesized (Scheme 2). Compound **18** is a representative member of a recently discovered, new class of antibiotics that are active against *Mycobacterium tuberculosis* (the bacterium that causes tuberculosis) and against atypical mycobacteria.[8]

To execute the synthesis, amino-functionalized polystyrene **7** was acylated with adipic acid dichloride (**8**) to yield the corresponding carboxy-functionalized resin **9** after hydrolysis. (Scheme 2).[3, 10] The stable acid-functionalized resin **9** was used for the attachment of *p*-iodophenylhydrazine (**10**) by



Scheme 2. Traceless solid-phase synthesis of antibiotic **18** and its derivative **19** employing a traceless hydrazide linker. a) 20 equiv adipic dichloride (**8**), pyridine, CH_2Cl_2, RT, 18 h, then aqueous work-up; b) 3 equiv *p*-iodophenylhydrazine (**10**), 3 equiv DIC, 3 equiv HOBt, 3 equiv NEt_3, CH_2Cl_2, RT, 18 h; c) 8 equiv *p*-formylphenylboronic acid (**12**), 18 equiv K_2CO_3, 10 equiv *N*,*N*-diisopropyl-*N*-ethylamine, 0.2 equiv $[Pd(OAc)_2]$, dioxane/water 6:1, 95 °C, 24 h; d) 15 equiv aniline **14** or **15**, 10 equiv Na_2SO_4, 10 equiv $NaBH(OAc)_3$, HOAc, RT, 2 h, ultrasound; e) 0.5 equiv $[Cu(OAc)_2]$, pyridine, methanol, O_2, RT, 2 h. DIC = *N*,*N*-diisopropylcarbodiimide, HOBt = 1-hydroxybenzotriazole.

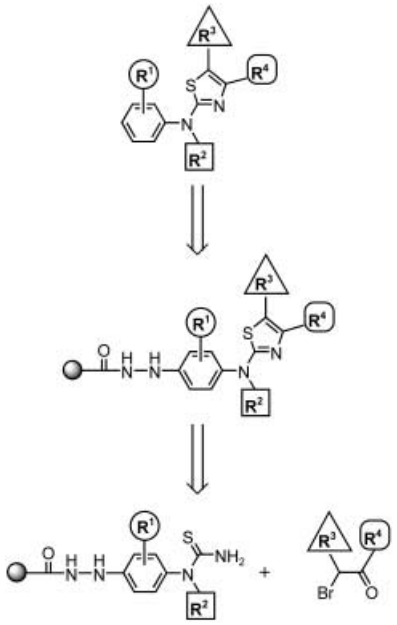
activation with *N*,*N*-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt). The iodophenylhydrazide **11** was treated with *p*-formylphenylboronic acid (**12**) to give rise to the polymer-bound biphenylaldehyde **13**.[3] Initial attempts with potassium phosphate as the base and $[Pd(PPh_3)_4]$ as a palladium source in DMF/water (6:1) yielded only traces of the product. Subsequent fine tuning of the conditions resulted in quantitative conversion of the iodophenylhydrazide **11** with 0.2 equiv $[Pd(OAc)_2]$, 18 equiv potassium carbonate, 8 equiv *N*,*N*-diisopropyl-*N*-ethylamine and 8 equiv *p*-formylphenylboronic acid (**12**).[11] The resulting biphenyl aldehyde **13** was then subjected to reductive amination with thiomorpholine derivative **14**[8] and the morpholine derivative **15**[12] to yield polymer-bound secondary amines **16** and **17**. Initial attempts employing sodium cyanoborohydride in methanol at room temperature[13] yielded the desired product in high yield, but with poor purities. This problem was solved by utilizing the conditions developed by Ley et al.[14] The polymer-bound aldehyde **13** was completely consumed in the presence of sodium trisacetoxyborohydride in CH_2Cl_2/HOAc 10:1 and sodium sulfate to scavenge the released water at room temperature for 2 h with ultrasound.[4] Finally, the traceless hydrazide linker was cleaved oxidatively by treatment with 0.5 equiv of $[Cu(OAc)_2]$ in methanol and pyridine. The desired biphenyl antibiotic **18** and its derivative **19** were obtained in an overall yield of 37 and 31 %, respectively after simple extraction with aqueous $NaHCO_3$ (2 %) and subsequent evaporation of the organic solvent in > 95 % purity.

Synthesis of a 2-aminothiazole library—Identification of Tie-2 inhibitors: A recently emerging compound class that may belong to the category of privileged structures are 2-aminothiazoles. This structural framework has found application in drug development for the treatment of allergies,[15] hypertension,[16] inflammation,[17] schizophrenia,[18] bacterial[19] and HIV infections,[20] and very recently for the treatment of pain,[21] as fibrinogen receptor antagonists with antithrombotic activity,[22] as new inhibitors of bacterial DNA gyrase B[23] and in the development of cyclin-dependent kinase inhibitors.[24]

In the light of these important and probably even more widespread applications, the development of efficient methods for the solid-phase synthesis of 2-aminothiazoles[25] is of great importance for medicinal, bioorganic and combinatorial chemistry.

For the solid-phase synthesis of the 2-aminothiazole nucleus it was planned to employ the Hantzsch synthesis as the key step, that is, the treatment of polymer-bound *N*-monosubstituted and *N*,*N*-disubstituted thioureas with α-bromoketones (Scheme 3). We intended to generate the intermediary thioureas from polymer-bound anilines by treatment with an *N*-protected isothiocyanate. The *para*-position to the aniline amino group was chosen as the attachment point for the traceless hydrazide linker.

Starting from amino-functionalized polystyrene **7** (1.3 mmol g^{-1}) the corresponding carboxy-functionalized resin **9** was prepared. An adipic acid monoamide was formed with adipic methyl ester (**20**) followed by basic saponification of the ester group to yield the carboxy-resin with substantially



Scheme 3. Plan for the traceless solid-phase synthesis of the 2-aminothiazoles **31**.

higher loading levels owing to the prevention of crosslinking of the resin (Scheme 4).[3, 10] Subsequently, the carboxy-functionalized resin **9** was treated with 4-nitrophenylhydrazines **21** to yield the corresponding polymer-bound nitrophenylhydrazides **22**.

Prior to the planned reduction of the nitrobenzene groups to the anilines, the two hydrazide nitrogens of **22** were acylated with Fmoc-Cl. This precaution was taken since we intended to generate the required thiourea intermediates from the corresponding anilines by treatment with Fmoc-isothiocyanate **26** (see below). Under these conditions, the unprotected hydrazides are also acylated resulting in the formation of undesired sideproducts. The acylation with Fmoc-Cl proceeded only in poor yield with dioxane and aqueous $NaHCO_3$ or methylene chloride/triethylamine with 10 equiv Fmoc-Cl. The double acylated hydrazide was smoothly prepared in the solvent system methylene chloride/pyridine (20:1). A double acylation of the hydrazide was achieved under these conditions, thus leaving the amide group of the resin spacer unattached. This was proven by reacting Fmoc-Cl with a polymer-bound nitrophenylhydrazide employing an acid-functionalized support with an ether linkage instead of the amide in resin **9**.[3, 10]

After successful introduction of the Fmoc groups, the reduction of the nitro group to the amino function was investigated. Initial attempts employing $Na_2S_2O_4$ in ethanol at reflux temperature[26a] yielded only traces of product. In the presence of $CrCl_2$ in DMF at room temperature,[26b] $\approx 80\%$ conversion could be observed and application of $SnCl_2$ in NMP[26c] resulted in a conversion of $>90\%$ (determined by GC-MS). Finally, polymer-fixed anilines **23** were formed quantitatively if DMF was employed as the solvent.[26d,e]

The use of polymer-bound anilines **23** in the subsequent synthesis sequence leads to the formation of *N*-monosubstituted 2-aminothiazoles. *N*-functionalization of the amines **23** by means of reductive amination was investigated in order to obtain access to *N*,*N*-disubstituted heterocycles as well. Although this type of transformation is well-established in solid-phase synthesis, its application to anilines **23** turned out to be unexpectedly difficult. Thus, treatment of polymer-bound aniline **23** (R = H) with 10 equiv of 4-bromobenzaldehyde, tetramethylorthoformate, and 10 equiv $NaBH(OAc)_3$[27a] resulted in imine formation, but not reduction to the *N*-substituted amine. Employment of DMF/AcOH 100:1 as the solvent[27b] and 2 equiv of the aldehyde gave 60% reduction product, but 40% of the imine remained. Further fine tuning of the solvent led to $\approx 70\%$ *N*-alkylated amine in THF/AcOH/H_2O 100:1:1[27c] and finally to quantitative conversion if 10 equiv of aldehyde and $NaCNBH_3$ were employed in THF/AcOH 100:1 as solvent. However, under these conditions, formation of the tertiary amine as a result of double reductive alkylation was also observed. This problem was finally overcome by separating the imine formation from the reduction step. Firstly, the polymer-bound aniline **23** was converted into the Schiffs base and the surplus aldehyde **24** was then separated by washing with THF. Then the imine was reduced by treatment with $NaCNBH_3$ in THF/AcOH 100:1. These reaction conditions proved to be efficient for a variety of aromatic and aliphatic aldehydes (see below).

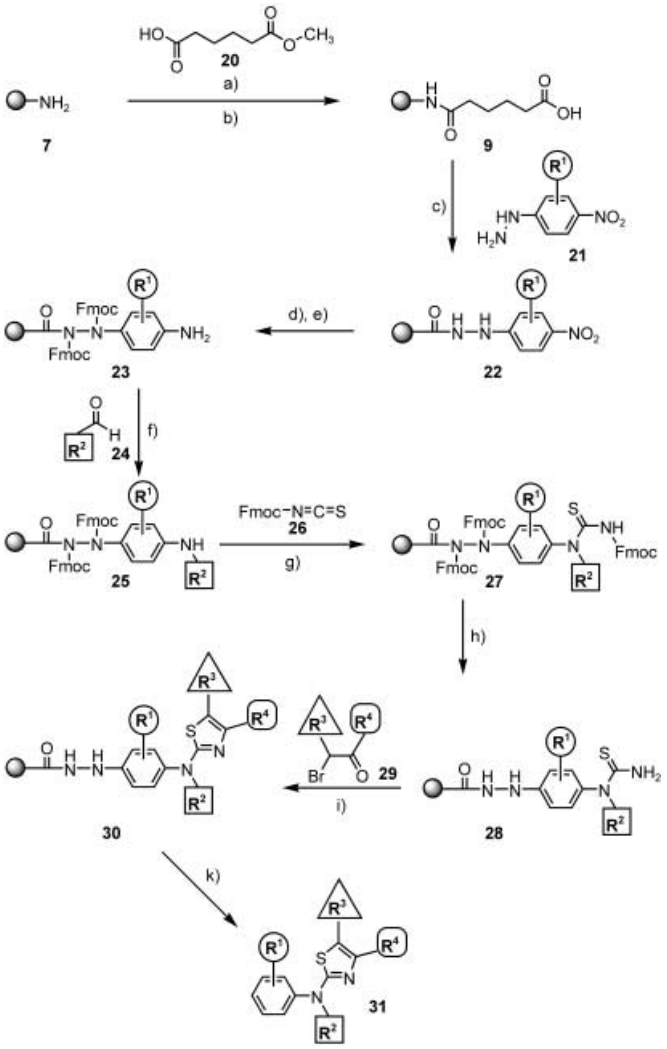
Conversion of anilines **25** to the corresponding thioureas **28** was achieved efficiently by treatment with fluorenylmethoxycarbonyl isothiocyanate (Fmoc-NCS, **26**)[25b] and subsequent removal of all three Fmoc groups present in intermediate **27** by treatment with piperidine in DMF. In the acylation step, the presence of pyridine is probably required to partially deprotonate the amine. A ninhydrin test indicated that conversion to the thioureas **28** is quantitative. The removal of all three Fmoc groups from fully masked resin **27** is not a problem with regard to the subsequent steps of the synthesis. On the one hand, model reactions indicated that the polymer-bound hydrazides do not react with α-bromoketones **29** under the conditions of the Hantzsch synthesis (see below). On the other hand, the possible *N*-alkylation products would no longer be amenable to the oxidative traceless-cleavage process.

With the polymer-bound thioureas **28** in hand, the Hantzsch thiazole synthesis on the polymeric support was investigated. Gratifyingly, the desired 2-aminothiazoles **30** were formed smoothly upon two successive treatments with 0.1M solutions of different α-bromocarbonyl compounds **29** in dioxane (Scheme 4).

Finally, the target compounds **31** were released from the solid support by treatment with a catalytic amount of $[Cu(OAc)_2]$ in *n*-propylamine and purging with O_2 to reoxidize the Cu^+ formed by the oxidation of the linker group.

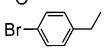
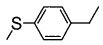
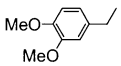
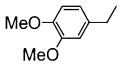
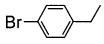
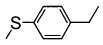
The copper salt was readily and efficiently separated from the products by treatment of the reaction mixture with 10 equiv of a copper-chelating polyamine resin (Advanced Chemtech) or by simple filtration through a silica gel column for solid-phase extraction.[3] In both cases, examination of the crude reaction products by means of atomic absorption spectroscopy indicated that $>99.9\%$ of the copper had been removed.

A total of 23 differently substituted 2-aminothiazoles were synthesized according to this procedure. The results of the



Scheme 4. Traceless solid-phase synthesis of 2-aminothiazoles **31**. a) 3 equiv adipic monomethyl ester (**20V**, 3 equiv DIC, 3 equiv HOBt, 3 equiv NEt_3, CH_2Cl_2, RT, 18 h ; b) THF/1% LiOH 1:1, RT, 24 h; c) 3 equiv nitrophenylhydrazine (**21**), 3 equiv DIC, 3 equiv HOBt, 3 equiv NEt_3, CH_2Cl_2, RT, 18 h; d) 10 equiv Fmoc-Cl, pyridine, CH_2Cl_2, 15 h; e) 2 M $SnCl_2 \times 2H_2O$, DMF, RT, 18 h; f) 10 equiv aldehyde **24**, THF, HOAc, RT, 1 h, wash, then 10 equiv $NaCNBH_3$, THF/HOAc, RT, 15 h; g) 3 equiv Fmoc-NCS **26**, CH_2Cl_2, pyridine, RT, 15 h; h) DMF/piperidine 4:1, RT, 2 × 5 min; i) 0.1 M solution of **29** in dioxane, RT, 2 × 3 h; k) 0.5 equiv $[Cu(OAc)_2]$, *n*-propylamine, O_2, RT, 2 h, then solid-phase extraction.

Table 1. Results of the traceless solid-phase synthesis of 2-aminothiazoles **14**.

	R^1	R^2	R^3	R^4	Overall yield [%]	Purity [%]
31/1	H	H	H		69	96
31/2	H	H	H		49	99
31/3	H	H			34	86
31/4	*m*-CN	H			19	99
31/5	*m*-CN	H	H		29	89
31/6	H		H		28	99
31/7	H				31	92
31/8	H		H		38	99
31/9	H		H		25	92
31/10	H		H		42	99
31/11	H		H		20	86
31/12	H				30	87
31/13	H		H		47	81
31/14	H		H		35	84
31/15	H				19	98
31/16	H		H		24	99
31/17	H				35	86
31/18	H		H		20	82
31/19	H		H		33	85
31/20	H				35	81
31/21	H				28	93
31/22	H		H		42	82
31/23	H		H		31	84

syntheses are summarized in Table 1. The data demonstrate that the 2-aminothiazoles are obtained in nine-step syntheses (*N*-monosubstituted) and 10-step syntheses (*N*,*N*-disubstituted) in very high overall yields (19–69%, average yield per step 86–95%). The synthesis is tolerant of substantial variation in the structure of the substituents, that is, different aromatic, heteroaromatic, and aliphatic groups can be efficiently introduced. The synthesis sequence proceeds so cleanly that the compounds are obtained after cleavage of the traceless linkers in excellent purity (81–99%) without any further separation and purification steps. In any case, they are pure enough to be employed directly for further purposes, for example, biological testing. Of particular interest is the mildness of the conditions required for the completely selective cleavage of the traceless hydrazide linker. In the presence of catalytic amounts of the copper salt employed, even oxidation-sensitive functional groups, such as furans, thiophenes, and sulfides, are not attacked at all.

From the different biological and pharmacological activities of compounds with the 2-aminothiazole scaffold, we were particularly intrigued by the ability of certain 2-aminothiazole derivatives to inhibit cyclin-dependent kinases (Cdks, see above).[24] These serine/threonine kinases drive and control cell cycle progression and have essential roles in cell

proliferation.[28a, 29a] At least two Cdk inhibitors are undergoing human clinical trials to suppress tumor growth.[28, 29] Given the relevance of these proteins, we investigated the 2-aminothiazoles as possible inhibitors of Cdk-2 and Cdk-4. However, none of the compounds showed appreciable inhibitory activity, which indicates that the individual decoration of the 2-aminothiazole nucleus is paramount to achieve biological activity in the compound class.

In the light of the high similarity among the structure of the ATP-binding domains of protein kinases[28, 29] and the notion that this evolutionary conservatism of Nature can be employed as guiding principle for the development of compound libraries,[30] the library was screened for possible inhibitors against receptor tyrosine kinases, which were selected to cover a wide spectrum of biological activities.

To this end, epidermal growth factor receptor (EGFR; ErbB-1), ErbB-2, insulin-like growth factor 1 receptor (IGF1R), fibroblast growth factor receptor 1 (FGFR1), vascular endothelial growth factor receptors 2 and 3 (VEGFR-2 and -3) and Tie-2 were chosen. ErbB-2 (also named Her-2/Neu) is over-expressed in approximately 30% of all primary breast, ovary, and stomach cancers. The EGFR, has been implicated in human tumorigenesis, for example, of glioblastoma as well as in numerous tumors of epithelial origin, including breast and oesophageal tumors.[31] The insulin-like growth factor 1 receptor affects cell mitogenesis, survival, transformation, and insulin-like activities by the binding of its ligands, IGF1 and IGF2. This receptor influences postnatal growth physiology, and its activity has been associated with malignant disorders, such as breast cancer.[32]

VEGFR-2 and -3 and Tie-2 are involved in angiogenesis, the development of new blood vessels from pre-existing ones, in particular in tumors (see below). Similarly members of the FGF family, in particular, acidic FGF (FGF1) and basic FGF (FGF2), are potent inducers of angiogenesis.[33]

The library of the 2-aminothiazoles did not contain any inhibitor of EGFR, ErbB-2 and IGF1R which warranted further investigation. Remarkably, however, six compounds turned out to be inhibitors of Tie-2 and five compounds inhibited VEGFR-2 (Table 2). In addition, a potent inhibitor of the FGFR-1 and two inhibitors of VEGFR-3 were identified. Of particular importance is the finding that the 2-aminothiazoles display dual selectivity for VEGFR-2 and Tie-2, and in part also for VEGFR-3, namely, three prime regulators of angiogenesis and lymphoangiogenesis.

Angiogenesis is central to wound repair, inflammation, and embryonic development. Furthermore, aberrant angiogenesis is considered to be a key step in tumor growth, spread, and metastasis.[34] Vascular development depends on the endothelium-specific vascular endothelial growth factor receptors 1–3 (VEGFR1-3) and the Tie-2 receptor.[35] All these receptors have been implicated in tumor angiogenesis[36] and antagonization of Tie-2, VEGFR-2, or VEGF-D (a ligand of VEGFR-3) inhibits tumor growth and tumor metastasis in vivo.[36d, 37] The development of low molecular-weight inhibitors of these receptor tyrosine kinases is among the most promising approaches to the development of new, alternative antitumor drugs, and several inhibitors of VEGFR-2 are in clinical trials.[38] The combination of VEGFR-2 inhibitors with Tie-2 antagonists should potentiate their anti-angiogenic effects.[36c] Furthermore, inhibitors of VEGFR-3 would suppress the metastasis of lymphogenic tumors. To date, however, only a few cases of small-molecule inhibitors of the Tie-2 and VEGFR-3 receptors have been reported.[39]

Table 2. Inhibition of different receptor tyrosine kinases by 2-aminothiazoles.

Compound	IC_{50} for receptor tyrosine kinase [μM][a]						
	VEGFR-2	VEGFR-3	Tie-2	IGF1R	EGFR	ErbB2	FGFR1
31/1	–	–	21	–	–	–	–
31/2	–	–	13	–	–	–	–
31/7	7.4	44	9.8	–	–	–	8.6
31/8	31	–	4.8	–	–	–	–
31/14	12	41	–	–	–	–	–
31/20	86	–	28	–	–	–	–
31/23	63	–	31	–	–	–	–

[a] To assay the inhibitory activity, the kinase-catalyzed phosphorylation of poly(Glu-Tyr) in the presence of varying concentrations of inhibitor was determined. The kinases were employed as fusion proteins of glutathione-*S*-transferase (GST) and the respective kinase domain. The relative amount of phosphorylated substrate was quantified by means of an anti-phosphotyrosine enzyme-linked immunosorbent assay (ELISA), which employed an anti-phosphotyrosine antibody conjugated to horseradish peroxidase (POD). The bound antibody was detected by the light emission after addition of a chemiluminescence substrate for POD.

Conclusion

We have demonstrated that the traceless phenylhydrazide linker can be successfully employed in the multistep synthesis of compound libraries to yield biologically and pharmacologically relevant compounds. Thus, a representative member of a recently discovered new class of antibiotics that are active against *Mycobacterium tuberculosis* and atypical mycobacteria, and its morpholine-derivative were synthesized. Furthermore, an efficient method for the multistep traceless synthesis of 2-aminothiazoles that display dual specifity against the receptor tyrosine kinases VEGFR-2 and Tie-2 was developed. The synthesis method should rapidly give access to a much larger library of 2-aminothiazoles from which dual-selective VEGFR-2 and Tie-2 inhibitors with enhanced biological potency may be identified that could be developed into a new class of anti-angiogenesis drugs. These compounds are obtained readily and efficiently in high overall yields and with high purity after simple extraction and filtration steps.

Experimental Section

General procedures: ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC250, DRX400 or DRX500 spectrometers. HPLC were measured on an Agilent 1100 Series equipped with a C18PPN column (Macherey & Nagel). GC-MS were measured on a Agilent 6890 Series gas chromatograph connected to a Agilent 5973 Series mass spectrometer. All HPLC was performed with a flow rate of 1 mL min^{-1} and a gradient which changed from H_2O/acetonitrile/formic acid 90:10:0.1 (*v*/*v*/*v*) to H_2O/acetonitrile/formic acid 10:90:0.1 (*v*/*v*/*v*) within 30 min. High-resolution mass spectra (HRMS) were measured on a Finnigan MAT 8200 spectrometer. IR spectra were measured on Bruker IFS 88 or Bruker Vector 22

spectrometers with a diffuse reflectance head A527 from Spectra Tech. UV spectra were measured on a Perkin–Elmer Cary 50 spectrometer.

Materials: TLC was performed on Merck silica gel 60F_{254} aluminum sheets. Silica gel (40–60 μm) was used for flash chromatography. The resins were purchased from Rapp Polymere, Advanced Chemtech and Argonaut Technologies. All reactions were performed under an argon atmosphere with freshly distilled, and dried solvents. All solvents were distilled using standard procedures. Commercial reagents were used without further purification.

General procedure for the oxidative cleavage of the phenylhydrazide linker with [Cu(OAc)$_2$] and *n*-propylamine (Method A): The resin was suspended in a solution of 0.5 equiv of [Cu(OAc)$_2$] in *n*-propylamine (5 mM) and was shaken at room temperature for 2 h with oxygen bubbling through the mixture. The solvent was removed under reduced pressure and the work-up was performed with one of the following procedures: i) diethyl ether and 2% $NaHCO_3$ were added to the residue and, after phase separation, the organic layer was dried over $MgSO_4$. The solvent was removed and the residue was dried in vacuo. ii) The residue was suspended in methylene chloride (50 mL g^{-1} resin) and tris-(2-aminoethyl)amino resin (5 equiv, Novabiochem, 200–400 mesh) was added. The mixture was shaken for 1 h at room temperature and then filtered. The filtrate was evaporated and dried in vacuo. iii) The residue was suspended in cyclohexane/ethyl acetate (10:1) or methylene chloride/cyclohexane (5:1), filtered through a SPE-cartridge (SiO_2) and washed 3× with cyclohexane/ethyl acetate (1:1) or methylene chloride. The filtrate was evaporated and dried in vacuo.

General procedure for the oxidative cleavage of the phenylhydrazide linker with [Cu(OAc)$_2$], methanol and pyridine (Method B): The resin was suspended in a solution of 0.5 equiv [Cu(OAc)$_2$] (5 mM) and pyridine (100 mM) in methanol and was shaken at room temperature for 2 h with oxygen bubbling through the mixture. If polystyrene resins were used, the same volume of THF was added. The solvent was removed under reduced pressure and the work-up was performed by means of one of the procedures described above.

Polystyrene-bound *p*-iodophenylhydrazide (11): *N*,*N*-Diisopropylcarbodiimide (42 μL, 0.27 mmol), 1-hydroxybenzotriazole (41 mg, 0.27 mmol), triethylamine (38 μL, 0.27 mmol), and *p*-iodophenylhydrazine (**10**, 63 mg, 0.27 mmol) were added to a suspension of resin **9**[3, 10] (500 mg, 0.09 mmol) in methylene chloride (10 mL) and the mixture was shaken at room temperature for 18 h, and then filtered. The resin was washed with methylene chloride, THF, THF/1N HCl (1:1), THF, methanol, methylene chloride, and cyclohexane (2× each), and dried to constant weight in vacuo to yield the yellow resin **11** (502 mg). IR (KBr): $\tilde{\nu}$ = 3290 (NH), 1661 (C=O) cm^{-1}.

Polystyrene-bound biphenylaldehyde (13): To a suspension of **11** (400 mg, 0.08 mmol) in dioxane (1.5 mL) and water (0.25 mL), were added *p*-formylphenylboronic acid **12** (88 mg, 0.6 mmol), potassium carbonate (182 mg, 1.3 mmol), and *N*,*N*-diisopropyl-*N*-ethylamine and the mixture was degassed by ultrasonication. Palladium(II) acetate (4 mg, 16 μmol) was added and the mixture was heated to 95 °C for 24 h, and then filtered. The resin was washed with DMF, water, ethanol, ethyl acetate and methylene chloride (3× each), and dried to constant weight in vacuo to yield the black resin **13** (502 mg). IR (SiO_2): $\tilde{\nu}$ = 3307 (NH), 2851 (CHO), 1680 (C=O) cm^{-1}.

Polystyrene-bound tetracyclic thiomorpholine (16): To a suspension of polymer-bound biphenylaldehyde **13** (300 mg, 0.06 mmol) in methylene chloride (5 mL) and acetic acid (0.5 mL), were added sodium sulfate (85 mg, 0.6 mmol), sodium triacetoxyborohydride (127 mg, 0.6 mmol), and 4-thiomorpholinomethyl aniline **14**[8] (188 mg, 0.9 mmol). The mixture was ultrasonicated for 2 h, and then filtered. The resin was washed with DMF, isopropanol, water, DMF, methanol, and methylene chloride (3× each), and dried to constant weight in vacuo to yield the black resin **16** (303 mg). IR (SiO_2): $\tilde{\nu}$ = 3255 (NH), 1669 (C=O) cm^{-1}.

4′-Biphenylmethyl-(4-thiomorpholin-4-ylmethyl-phenyl)amine (18): According to Method **B** for the oxidative cleavage of the hydrazide linker, resin **16** (179 mg, 21 μmol) was treated with [Cu(OAc)$_2$] and pyridine in methanol followed by extractive workup to yield a yellowish oil (2.9 mg, 8 μmol, 37%), HPLC: 97% pure (260 nm). R_f = 0.12 (cyclohexane/ethyl acetate 10:1); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.63–7.54 (m, 4H, arom. CH), 7.47–7.39 (m, 5H, arom. CH), 7.12 (d, ^3J(H,H) = 9.1 Hz, 2H, arom. CH), 6.63 (d, ^3J(H,H) = 9.1 Hz, 2H, arom. CH), 4.38 (s, 2H, Ph-Ph-CH_2-NH-), 3.42 (s, 2H, Ph-Ph-CH_2-NH-Ph-CH_2-thiomorpholine), 2.67 (s, 8H, thiomorpholine-CH_2).; GC-MS (70 eV, EI): *m*/*z* (%): 374 (44) [*M*]$^+$, 272 (100), 167 (97), 106 (25); HRMS: calcd for: 374.1817; found: 374.1839. The spectroscopic data are in agreement with reported values.[8]

Polystyrene-bound tetracyclic morpholine (17): To a suspension of polymer-bound biphenylaldehyde **13** (200 mg, 0.04 mmol) in methylene chloride (4 mL) and acetic acid (0.4 mL), were added sodium sulfate (57 mg, 0.4 mmol), sodium triacetoxyborohydride (85 mg, 0.4 mmol), and 4-morpholinomethyl aniline (**15**,[12] 115 mg, 0.6 mmol). The mixture was ultrasonicated for 2 h and then filtered. The resin was washed with DMF, isopropanol, water, DMF, methanol, and methylene chloride (3× each), and dried to constant weight in vacuo to yield the black resin **17** (199 mg). IR (SiO_2): $\tilde{\nu}$ = 3301 (NH), 1667 (C=O) cm^{-1}.

4′-biphenylmethyl-(4-morpholin-4-ylmethyl-phenyl)-amine 819): According to Method B for the oxidative cleavage of the hydrazide linker **16** (195 mg, 23 μmol) was treated with [Cu(OAc)$_2$] and pyridine in methanol followed by extractive workup to yield a yellowish oil (2.5 mg, 7 μmol, 31%). R_f = 0.12 (cyclohexane/ethyl acetate 10:1); HPLC: 94% pure (260 nm); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.64–7.55 (m, 4H, arom. CH), 7.49–7.40 (m, 5H, arom. CH), 7.14 (d, ^3J(H,H) = 8.8 Hz, 2H, arom. CH), 6.65 (d, ^3J(H,H) = 8.8 Hz, 2H, arom. CH), 4.40 (s, 2H, Ph-Ph-CH_2-NH-), 3.81–3.58 (m, 6H, Ph-Ph-CH_2-NH-Ph-CH_2-morpholine, 2× CH_2-O), 2.55 (b, 4H, 2× CH_2-N); GC-MS (70 eV, EI): *m*/*z* (%): 358 (15) [*M*]$^+$, 281 (11), 270 (89), 207 (50), 135 (18), 90 (18), 44 (24), 28 (100); HRMS: 358.2051 (calcd: 358.2045).

Polystyrene-bound *p*-nitrophenylhydrazide (22a): *N*,*N*-Diisopropylcarbodiimide (2.55 mL, 16.5 mmol), 1-hydroxybenzotriazole (2.52 g, 16.5 mmol), triethylamine (2.31 mL, 16.5 mmol), and *p*-nitrophenylhydrazine (**21a**, 2.52 g, 16.5 mmol) were added to a suspension of resin **9**[3, 10] (5 g, 5.5 mmol) in methylene chloride (150 mL). The mixture was shaken at room temperature for 18 h and then filtered. The resin was washed with methylene chloride, THF, THF/1N HCl (1:1), THF, methanol, methylene chloride, and cyclohexane (2× each), and dried to constant weight in vacuo to yield the yellow resin **22a** (6.15 g). IR (KBr): $\tilde{\nu}$ = 3269 (NH), 1677 (C=O), 1351 (NO_2) cm^{-1}.

Polystyrene-bound 2-cyano-4-nitrophenylhydrazide (22b): *N*,*N*-Diisopropylcarbodiimide (2.55 mL, 16.5 mmol), 1-hydroxybenzotriazole (2.52 g, 16.5 mmol), triethylamine (2.31 mL, 16.5 mmol), and 2-cyano-4-nitrophenylhydrazine (**21b**, 2.93 g, 16.5 mmol) were added to a suspension of resin **9**[3, 10] (5 g, 5.5 mmol) in methylene chloride (150 mL). The mixture was shaken at room temperature for 18 h and then filtered. The resin was washed with methylene chloride, THF, THF/1N HCl (1:1), THF, methanol, methylene chloride, and cyclohexane (2× each), and dried to constant weight in vacuo to yield the yellow resin **22b** (6.15 g). IR (KBr): $\tilde{\nu}$ = 3269 (NH), 1677 (C=O), 1351 (NO_2) cm^{-1}.

Polystyrene-bound Fmoc-protected *p*-aminophenylhydrazide (23a): Fmoc-Cl (11.55 g, 46 mmol) was added to a suspension of **22a** (5 g, 4.6 mmol) in methylene chloride/pyridine (10:1, 200 mL). The mixture was shaken for 15 h at room temperature and then filtered. The resin was washed with methylene chloride, THF, methanol, methylene chloride, and cyclohexane (two× each), and dried to constant weight in vacuo to yield a yellow resin (6.85 g). IR (KBr): $\tilde{\nu}$ = 3308 (NH), 1759 (C=O), 1668 (C=O), 1350 (NO_2) cm^{-1}. Fmoc-loading: 0.57 mmol g^{-1} (84% starting from amino polystyrene). A suspension of the resin prepared above (6 g, 3.42 mmol) in 2M $SnCl_2 \times 2H_2O$ in DMF (130 mL) was shaken for 18 h at room temperature and then filtered. The resin was washed with DMF, THF, THF/water (1:1), THF, methanol, methylene chloride, and cyclohexane (2× each), and dried to constant weight in vacuo to yield the off-white resin **23a** (5.79 g). IR (KBr): $\tilde{\nu}$ = 3355 (NH), 1752 (C=O), 1671 (C=O) cm^{-1}. Fmoc-loading: 0.56 mmol g^{-1} (83% starting from amino polystyrene).

Polystyrene-bound Fmoc-protected 2-cyano-4-aminophenylhydrazide (23b): Fmoc-Cl (11.3 g, 45 mmol) was added to a suspension of **22b** (5 g, 4.5 mmol) in methylene chloride/pyridine (10:1, 200 mL). The mixture was shaken for 15 h at room temperature and then filtered. The resin was washed with methylene chloride, THF, methanol, methylene chloride, and cyclohexane (two× each), and dried to constant weight in vacuo to yield the yellow resin **23b** (6.80 g). IR (KBr): $\tilde{\nu}$ = 3314 (NH), 1741 (C=O), 1672 (C=O), 1351 (NO_2) cm^{-1}. Fmoc-loading: 0.55 mmol g^{-1} (82% starting from amino polystyrene). A suspension of the resin prepared as described above (6 g, 3.3 mmol) in a 2M solution of $SnCl_2 \cdot 2H_2O$ in DMF (130 mL) was

shaken for 18 h at room temperature and then filtered. The resin was washed with DMF, THF, THF/water (1:1), THF, methanol, methylene chloride, and cyclohexane (2 × each), and dried to constant weight in vacuo to yield the off-white resin **23b** (5.68 g). IR (KBr): $\tilde{\nu} = 3303$ (NH), 1759 (C=O), 1670 (C=O) cm^{-1}. Fmoc-loading: 0.54 mmol g^{-1} (81 % starting from amino polystyrene).

General procedure for the reductive amination of the polymer-bound amines 23 (Procedure A): To a suspension of the polymer-bound aniline **23** in THF/HOAc (100:1, 5 mL/100 mg resin) was added aldehyde **24** (10 equiv). The mixture was shaken for 6 h and then filtered. The resin washed with THF (3 ×), suspended in THF/HOAc (100:1, 5 mL/100 mg resin) and $NaCNBH_3$ (10 equiv) was added. The mixture was shaken for 12 h at room temperature and then filtered. The resin was washed with THF, methanol, methylene chloride, and cyclohexane (2 × each), and dried to constant weight in vacuo.

General procedure for the preparation 2-aminothiazoles 31 (Procedure B): Fmoc-NCS **26**[25b] (5 equiv) was added to a suspension of the polymer-bound aniline **23** or **25** in methylene chloride/pyridine (100:1, 3 mL/100 mg resin). The mixture was shaken for 15 h at room temperature and then filtered. The resin was washed with methylene chloride, THF, methanol, methylene chloride, and cyclohexane (2 × each), and dried to constant weight in vacuo. The resin was shaken with DMF/piperidine (4:1, 3 mL per 100 mg resin, 2 × 5 min) at room temperature, and then filtered. It was then was washed with DMF, THF, methanol, methylene chloride, and cyclohexane (2 × each), and dried to constant weight in vacuo. This polymer-bound thiourea was treated twice with a solution of 2-bromocarbonyl compound in dioxane (0.1 M, 3 mL per 100 mg resin) for 3 h at room temperature, and then filtered. The resin was washed with dioxane, THF, methanol, methylene chloride, and cyclohexane (2 × each), and dried to constant weight in vacuo. The oxidative cleavage of the hydrazide linker was achieved according to Method **A** with $[Cu(OAc)_2]$ in *n*-propylamine followed by work-up with SPE.

2-Aminothiazole 31/1: According to Procedure B, **23a** (168 mg, 94 μmol) was treated with Fmoc-NCS (**26**, 132 mg, 0.47 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-4′-chloroacetophenone in dioxane (0.1 M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/1** (18.6 mg, 65 μmol, 69 % overall yield, i.e., 96 % per step); HPLC: 96 % pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.79$ (d, ^3J(H,H) = 8.8 Hz, 2H, arom. CH), 7.44 – 7.35 (m, 6H, arom. CH), 7.11 (t, ^3J(H,H) = 6.8 Hz, 1H, arom. CH), 6.81 (s, 1H, thiazole-CH); GC-MS (70 eV, EI): *m*/*z* (%): 286 (100) $[M]^+$, 168 (19), 150 (16), 133 (14), 125 (13), 104 (8), 89 (12), 77 (9).

2-Aminothiazole 31/2: According to Procedure B, **23a** (168 mg, 94 μmol) was treated with Fmoc-NCS (**26**, 132 mg, 0.47 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc-groups were removed, and the resin was treated with 2-bromo-2′,5′-dimethoxyacetophenone in dioxane (0.1 M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/2** (14.4 mg, 46 μmol, 49 % overall yield, i.e., 92 % per step); HPLC: 99 % pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.76$ (d, ^4J(H,H) = 3.1 Hz, 1H, arom. CH), 7.44 – 7.24 (m, 4H, arom. CH), 7.08 (t, ^3J(H,H) = 7.0 Hz, 1H, arom. CH), 6.93 – 6.82 (m, 3H, arom. CH, thiazole-CH), 3.92, 3.85 (2s, 6H, $2OCH_3$); GC-MS (70 eV, EI): *m*/*z* (%): 312 (100) $[M]^+$, 281 (16), 265 (15), 194 (18), 179 (26), 161 (37), 149 (14), 136 (11), 77 (13).

2-Aminothiazole 31/3: According to Procedure B, **23a** (168 mg, 94 μmol) was treated with Fmoc-NCS (**26**, 132 mg, 0.47 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc-groups were removed, the resin was treated with 2-bromo-2′-phenyl-acetophenone in dioxane (0.1 M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/3** (10.5 mg, 32 μmol, 34 % overall yield, i.e., 89 % per step); HPLC: 86 % pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.36 – 7.25$, 7.54 – 7.51 (2 M, 15H, arom. CH); GC-MS (70 eV, EI): *m*/*z* (%): 328 (100) $[M]^+$, 251 (6), 210 (10), 178 (17), 165 (4), 150 (17), 121 (6), 104 (8), 77 (8).

2-Aminothiazole 31/4: According to Procedure B, **23b** (170 mg, 92 μmol) was treated with Fmoc-NCS (**26**, 132 mg, 0.47 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2′-phenyl-acetophenone in dioxane (0.1 M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/4** (6.2 mg, 17 μmol, 19 % overall yield, i.e., 84 % per step); HPLC: 99 % pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.92 – 7.21$ (m, 14H, arom. CH); GC-MS (70 eV, EI): *m*/*z* (%): 353 (100) $[M]^+$, 276 (3), 250 (2), 210 (10), 178 (26), 165 (25), 121 (6), 104 (7).

2-Aminothiazole 31/5: According to Procedure B, **23b** (170 mg, 92 μmol) was treated with Fmoc-NCS (**26**, 132 mg, 0.47 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2′,5′-dimethoxyacetophenone in dioxane (0.1 M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/5** (9.0 mg, 27 μmol, 29 % overall yield, i.e., 87 % per step); HPLC: 89 % pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.82$ (d, ^4J(H,H) = 3.2 Hz, 1H, arom. CH), 7.76 (dd, ^3J(H,H) = 8.4, ^3J(H,H) = 3.2 Hz, 2H, arom. CH), 7.41 – 7.23 (m, 2H, arom. CH), 6.93 – 6.82 (m, 3H, arom. CH, thiazole-CH), 3.91, 3.89 (2s, 6H, $2OCH_3$); GC-MS (70 eV, EI): *m*/*z* (%): 337 (100) $[M]^+$, 304 (16), 290 (9), 194 (17), 179 (29), 161 (53), 151 (9), 102 (7).

2-Aminothiazole 31/6: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with furane-2-carbaldehyde (65 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2′,5′-dimethoxyacetophenone in dioxane (0.1 M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/6** (6.4 mg, 16 μmol, 28 % overall yield, i.e., 88 % per step); HPLC: 99 % pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.91$ (d, ^4J(H,H) = 3.2 Hz, 1H, arom. CH), 7.42 – 7.24 (m, 8H, arom. CH), 7.24 (s, 1H, thiazole-CH), 6.90 (d, ^3J(H,H) = 9.0 Hz, 1H, arom. CH), 6.82 (dd, ^3J(H,H) = 9.0, ^4J(H,H) = 3.2 Hz, 1H, arom. CH), 5.21 (s, 2H, benzyl-CH_2), 3.89, 3.86 (2s, 6H, $2OCH_3$); GC-MS (70 eV, EI): *m*/*z* (%): 392 (100) $[M]^+$, 361 (54), 311 (56), 300 (27), 281 (70), 179 (25), 157 (20), 81 (58).

2-Aminothiazole 31/7: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with furane-2-carbaldehyde (65 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2-phenyl-acetophenone in dioxane (0.1 M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/7** (8.6 mg, 21 μmol, 31 % overall yield, i.e., 89 % per step); HPLC: 92 % pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.59 – 7.21$ (m, 16H, arom. CH), 6.40 (d, ^3J(H,H) = 3.2 Hz, 1H, arom. CH), 6.32 (dd, ^3J(H,H) = 3.3, ^4J(H,H) = 1.8 Hz, 1H, arom. CH), 5.29 (s, 2H, benzyl-CH_2); GC-MS (70 eV, EI): *m*/*z* (%): 408 (72) $[M]^+$, 327 (100), 316 (14), 210 (80), 165 (17), 81 (18).

2-Aminothiazole 31/8: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with 4-bromobenzaldehyde (126 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-4′-chloroacetophenone in dioxane (0.1 M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/8** (11.8 mg, 26 μmol, 38 % overall yield, i.e., 91 % per step); HPLC: 99 % pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.79$ (d, ^3J(H,H) = 8.8 Hz, 2H, arom. CH), 7.44 – 7.24 (m, 11H, arom. CH), 6.68 (s, 1H, thiazole-CH), 5.24 (s, 2H, benzyl-CH_2); GC-MS (70 eV, EI): *m*/*z* (%): 456 (70) $[M]^+$, 364 (11), 285 (100), 245 (45), 168 (63), 90 (23), 77 (18).

2-Aminothiazole 31/9: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with cyclohexanecarbaldehyde (76 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-4′-chloroacetophenone in dioxane (0.1 M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/9** (7.5 mg, 20 μmol, 29 % overall yield, i.e., 92 % per step); HPLC: 92 % pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.78$ (d, ^3J(H,H) = 8.8 Hz, 2H, arom. CH), 7.55 – 7.22 (m, 7H, arom. CH), 6.69 (s, 1H, thiazole-CH), 3.92 (b, 2H, cyclohexyl-CH_2), 1.84 – 1.12 (m, 11H, cyclohexane-CH); GC-MS (70 eV, EI): *m*/*z* (%): 384 (15) $[M+H]^+$, 382 (35), 285 (21), 250 (10), 168 (25), 97 (100), 77 (9).

2-Aminothiazole 31/10: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with furane-2-carbaldehyde (65 mg, 0.68 mmol) and $NaCNBH_3$

(43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-4′-chloroacetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/10** (10.5 mg, 29 μmol, 42% overall yield, i.e., 92% per step); HPLC: 99% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.78-7.12$ (m, 10H, arom. CH), 6.67 (s, 1H, thiazole-CH), 6.32–6.19 (m, 2H, arom. CH), 5.20 (s, 2H, benzyl-CH_2); GC-MS (70 eV, EI): *m*/*z* (%): 366 (70) $[M]^+$, 337 (9), 285 (38), 274 (10), 250 (17), 168 (35), 157 (17), 81 (100).

2-Aminothiazole 31/11: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with cyclohexanecarbaldehyde (76 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2′,5′-dimethoxyacetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/11** (5.6 mg, 14 μmol, 20% overall yield, i.e., 85% per step); HPLC: 86% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.85$ (d, ^4J(H,H) = 3.0 Hz, 1H, arom. CH), 7.49–7.29 (m, 5H, arom. CH), 7.14 (s, 1H, thiazole-CH), 6.90 (d, ^3J(H,H) = 8.8 Hz, 1H, arom. CH), 6.82 (dd, ^3J(H,H) = 8.8, ^4J(H,H) = 3.0 Hz, 1H, arom. CH), 3.97 (b, 2H, C_6H_{11}-CH_2), 3.89, 3.85 (2s, 6H, $2OCH_3$), 1.80–1.07 (m, 11H, cyclohexyl-CH); GC-MS (70 eV, EI): *m*/*z* (%): 408 (44) $[M]^+$, 377 (13), 325 (23), 312 (100), 249 (19), 235 (16), 162 (12), 91 (18).

2-Aminothiazole 31/12: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with thiophene-2-carbaldehyde (76 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2-phenyl-acetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/12** (8.7 mg, 20 μmol, 30% overall yield, i.e., 89% per step); HPLC: 87% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.63$ (dd, ^3J(H,H) = 8.0, ^4J(H,H) = 1.8 Hz, 1H, arom. CH), 7.45–7.20 (m, 15H, arom. CH), 7.03 (d, ^3J(H,H) = 3.0 Hz, 1H, arom. CH), 6.93 (dd, ^3J(H,H) = 5, ^4J(H,H) = 3.5 Hz, 1H, arom. CH), 5.46 (s, 2H, benzyl-CH_2); GC-MS (70 eV, EI): *m*/*z* (%): 424 (53) $[M]^+$, 327 (100), 210 (73), 173 (19), 165 (15), 97 (27).

2-Aminothiazole 31/13: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with thiophene-2-carbaldehyde (76 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2′,5′-dimethoxyacetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/13** (13.1 mg, 32 μmol, 47% overall yield, i.e., 93% per step); HPLC: 81% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.02$ (d, ^3J(H,H) = 3.3 Hz, 1H, arom. CH), 7.43–7.12 (m, 7H, arom. CH), 6.97–6.80 (m, 4H, arom. CH, thiazole-CH), 5.37 (s, 2H, benzyl-CH_2), 3.89, 3.86 (2s, 6H, $2OCH_3$); GC-MS (70 eV, EI): *m*/*z* (%): 408 (100) $[M]^+$, 377 (44), 316 (69), 296 (24), 281 (78), 194 (17), 179 (28), 173 (43), 97 (99), 77 (14).

2-Aminothiazole 31/14: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with 4-mercaptobenzaldehyde (103 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-4′-chloroacetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/14** (10.1 mg, 24 μmol, 35% overall yield, i.e., 90% per step); HPLC: 84% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.83$ (d, ^3J(H,H) = 8.8 Hz, 2H, arom. CH), 7.44–7.24 (m, 9H, arom. CH), 7.18 (d, ^3J(H,H) = 8.6 Hz, 2H, arom. CH), 6.61 (s, 1H, thiazole-CH), 5.46 (s, 2H, benzyl-CH_2), 2.46 (s, 3H, SCH_3); GC-MS (70 eV, EI): *m*/*z* (%): 424 (6) $[M]^+$, 422 (13) $[M+H]^+$, 285 (5), 250 (4), 213 (5), 168 (9), 137 (100), 122 (13), 77 (5).

2-Aminothiazole 31/15: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with cyclohexanecarbaldehyde (76 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2-phenyl-acetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/15** (5.5 mg, 13 μmol, 19% overall yield, i.e., 85% per step); HPLC: 98% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.58-7.18$ (m, 15H, arom. CH), 3.99 (br., 2H, cyclohexyl-CH_2), 1.85–1.09 (m, 11H, cyclohexane-CH); GC-MS (70 eV, EI): *m*/*z* (%): 424 (35) $[M]^+$, 341 (19), 328 (100), 251 (12), 210 (20), 178 (14), 165 (12), 91 (12).

2-Aminothiazole 31/16: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with 3,4-dimethoxybenzaldehyde (113 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-4′-chloroacetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/16** (7.1 mg, 16 μmol, 24% overall yield, i.e., 87% per step); HPLC: 99% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.82$ (d, ^3J(H,H) = 8.5 Hz, 2H, arom. CH), 7.50–6.76 (m, 10H, arom. CH), 6.68 (s, 1H, thiazole-CH), 5.19 (s, 2H, benzyl-CH_2), 3.88, 3.87 (2s, 6H, $2OCH_3$); GC-MS (70 eV, EI): *m*/*z* (%): 436 (9) $[M]^+$, 285 (3), 168 (6), 151 (100), 107 (6).

2-Aminothiazole 31/17: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with 3,4-dimethoxybenzaldehyde (113 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2-phenyl-acetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/17** (11.4 mg, 24 μmol, 35% overall yield, i.e., 90% per step); HPLC: 86% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.58$ (dd, ^3J(H,H) = 7.0, ^4J(H,H) = 2.0 Hz, 2H, arom. CH), 7.39–7.20 (m, 11H, arom. CH), 7.00 (d, ^4J(H,H) = 2.0 Hz, 1H, arom. CH), 6.90 (dd, ^3J(H,H) = 8.4, ^4J(H,H) = 1.9 Hz, 2H, arom. CH), 6.78 (d, ^3J(H,H) = 8.0 Hz, 2H, arom. CH), 5.25 (s, 2H, benzyl-CH_2), 3.86, 3.79 (2s, 6H, $2OCH_3$); GC-MS (70 eV, EI): *m*/*z* (%): 478 (19) $[M]^+$, 368 (11), 327 (9), 227 (9), 210 (18), 151 (100), 107(5).

2-Aminothiazole 31/18: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with 4-bromobenzaldehyde (126 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2′,5′-dimethoxyacetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/18** (6.5 mg, 13.5 μmol, 20% overall yield, i.e., 85% per step); HPLC: 82% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.73$ (d, ^4J(H,H) = 3.0 Hz, 1H, arom. CH), 7.44–7.24 (m, 9H, arom. CH), 7.16 (s, 1H, thiazole-CH), 6.90 (d, ^3J(H,H) = 9.0 Hz, 1H, arom. CH), 6.83 (dd, ^3J(H,H) = 9.0, ^4J(H,H) = 3.0 Hz, 1H, arom. CH), 5.32 (s, 2H, benzyl-CH_2), 3.89, 3.83 (2s, 6H, $2OCH_3$); GC-MS (70 eV, EI): *m*/*z* (%): 482 (100), 480 (93) $[M+H]^+$, 449 (14), 390 (19), 311 (100), 281 (95), 194 (26), 171 (40), 90 (25), 77 (17).

2-Aminothiazole 31/19: According to Procedure A,, **23a** (120 mg, 68 μmol) was treated with 4-mercaptobenzaldehyde (103 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2′,5′-dimethoxyacetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/19** (10.1 mg, 22 μmol, 33% overall yield, i.e., 90% per step); HPLC: 85% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.81$ (d, ^4J(H,H) = 3.3 Hz, 1H, arom. CH), 7.35–7.12 (m, 8H, arom. CH), 6.85 (d, ^3J(H,H) = 8.8 Hz, 1H, arom. CH), 6.76 (dd, ^3J(H,H) = 8.8, ^4J(H,H) = 3.3 Hz, 1H, arom. CH), 6.38 (s, 1H, thiazole-CH), 5.19 (s, 2H, benzyl-CH_2), 3.85, 3.79 (2s, 6H, $2OCH_3$), 2.42 (s, 3H, SCH_3); GC-MS (70 eV, EI): *m*/*z* (%): 448 (30) $[M]^+$, 417 (11), 356 (10), 309 (13), 281 (15), 213 (15), 137 (100), 122 (13).

2-Aminothiazole 31/20: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with 4-mercaptobenzaldehyde (103 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/

pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2-phenyl-acetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/20** (11.0 mg, 24 μmol, 35% overall yield, i.e., 90% per step); HPLC: 81% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.60-7.18$ (m, 19H, arom. CH), 5.38 (s, 2H, benzyl-CH_2), 2.47 (s, 3H, SCH_3); GC-MS (70 eV, EI): *m*/*z* (%): 464 (35) $[M]^+$, 372 (17), 327 (25), 210 (38), 165 (10), 137 (100), 122 (12).

2-aminothiazole 31/21: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with 4-bromobenzaldehyde (126 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2-phenyl-acetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/21** (9.5 mg, 19 μmol, 28% overall yield, i.e., 88% per step); HPLC: 93% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.47$ (dd, ^3J(H,H) = 8.2, ^4J(H,H) = 1.8 Hz, 2H, arom. CH), 7.36–7.14 (m, 17H, arom. CH), 5.16 (s, 2H, benzyl-CH_2); GC-MS (70 eV, EI): *m*/*z* (%): 498 (39) $[M]^+$, 496 (38), 404 (24), 327 (97), 210 (100), 178 (15), 165 (21), 90 (11), 77 (10).

2-aminothiazole 31/23: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with 3,4-dimethoxybenzaldehyde (113 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-2′,5′-dimethoxyacetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/22** (13.2 mg, 29 μmol, 42% overall yield, i.e., 92% per step); HPLC: 82% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.91$ (d, ^4J(H,H) = 3.2 Hz, 2H, arom. CH), 7.50–6.76 (m, 9H, arom. CH), 6.68 (s, 1H, thiazole-CH), 5.19 (s, 2H, benzyl-CH_2), 3.88, 3.87, 3.85, 3.77 (4s, 12H, 4 OCH_3); GC-MS (70 eV, EI): *m*/*z* (%): 462 (17) $[M]^+$, 370 (16), 281 (7), 227 (9), 151 (100), 107 (6).

2-Aminothiazole 31/23: According to Procedure A, **23a** (120 mg, 68 μmol) was treated with thiophene-2-carbaldehyde (76 mg, 0.68 mmol) and $NaCNBH_3$ (43 mg, 0.68 mmol). According to Procedure B, this resin was treated with Fmoc-NCS (**26**, 96 mg, 0.34 mmol) in methylene chloride/pyridine (100:1, 5 mL). The Fmoc groups were removed, and the resin was treated with 2-bromo-4′-chloroacetophenone in dioxane (0.1M, 2 × 3 mL) and oxidatively cleaved with $[Cu(OAc)_2]$ in *n*-propylamine to yield the aminothiazole **31/23** (8.1 mg, 21 μmol, 31% overall yield, 89% per step); HPLC: 84% pure (260 nm); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.87$ (d, ^3J(H,H) = 8.6 Hz, 2H, arom. CH), 7.45–7.20 (m, 8H, arom. CH), 7.00 (d, ^3J(H,H) = 3.1 Hz, 1H, arom. CH), 7.92 (dd, ^3J(H,H) = 3.1, ^4J(H,H) = 1.8 Hz, 1H, arom. CH), 6.68 (s, 1H, thiazole-CH), 5.44 (s, 2H, benzyl-CH_2); GC-MS (70 eV, EI): *m*/*z* (%): 384 (15) $[M]^+$, 382 (35) $[M+H]^+$, 285 (21), 250 (10), 168 (25), 97 (100), 77 (9).

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