Natural Products in Parallel Chemistry—Novel 5-Lipoxygenase Inhibitors from BIOS-Based Libraries Starting from α-Santonin

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Recently, we developed a concept known as *biology-oriented synthesis (BIOS)*, which targets the design and synthesis of small- to medium-sized compound libraries on the basis of genuine natural product templates to provide screening compounds with high biological relevance. We herein describe the parallel solution phase synthesis of two BIOS-based libraries starting from α-santonin (**1**). Modification of the sesquiterpene lactone **1** by introduction of a thiazole moiety followed by a *Lewis-acid*-mediated lactone opening yielded a first library of natural product analogues. An acid-mediated dienone–phenol rearrangement of **1** and a subsequent etherification/amidation sequence led to a second natural product-based library. After application of a fingerprint-based virtual screening on these compounds, the biological screening of 23 selected library members against 5-lipoxygenase resulted in the discovery of four potent novel inhibitors of this enzyme.

Introduction

The mismatch between chemical and biological structure space has been discussed as a major reason for the decline in drug approvals.

In recent years, several attempts were made to exploit natural products (NPs) as starting points for the pharmaceutical industry's drug discovery process.[1] A statistical analysis revealed that, for the period between 1981 and 2007, about 40% of all marketed drugs were NPs themselves or could be traced back to NPs.[2] NPs also cover approximately the same area of chemical space as drugs, whereas compounds originating from classical high-throughput synthesis programs only cover a comparably narrow area in this space.[3] According to Waldmann et al., NPs can be regarded as biologically validated structural entities, since they were synthesized by proteins and, therefore, are highly likely to bind to similar motifs again.[4] A consequence of this consideration is the development of a strategy using genuine NP templates for the synthesis of small- to medium-sized combinatorial libraries in order to deliver compounds of higher biological relevance.[5] We refer to synthesis efforts based on this strategy as *biology-oriented synthesis (BIOS)*.[6]

Herein, we report the synthesis of two BIOS-based libraries starting from α-santonin. α-Santonin (**1**) is a common sesquiterpenlactone occurring in different *Artemisia* species, such as *Artemisia santonica*, *Artemisia absinthium*, and *Artemisia maritima*, and it had been used extensively in traditional Indian and Chinese medicine for the treatment of inflammations and nervous complaints and to combat intestinal worms.[7] We have chosen **1** as the starting material for library synthesis due to its favorable arrangement of functional groups and its abundant availability at comparably low costs. Selecting compounds to be synthesized from a virtually generated library is an important issue, and therefore the potential candidates should obey some basic pharmacological guidelines like oral bioavailibility [Lipinski parameters,[8] topological surface area (TPSA), and number of rotable bonds[9]] and the absence of unwanted fragments. On the other hand, the reaction sequence for final library synthesis should be short and applicable to parallel chemistry.

Results and Discussion

Synthesis of a BIOS-Based Library with a Thiazole Scaffold. α-Santonin (**1**) was transferred into α-tetrahydrosantonin (**2**) by modifying a known protocol[10] (Scheme 1). Under the conditions described earlier, varying qualities and quantities of the desired product were observed depending on the catalyst batch used for hydrogenation. A switch to a much cheaper palladium source ($Pd/SrCO_3$ to $Pd/CaCO_3$) and an elevation of the reaction temperature (room temperature to 50 °C) ensured reliable access to lactone **2** in a 100–150 g scale. Ketone **2** was converted into key intermediate **3** with phenyl trimethyl ammonium tribromide (PTAB)[10] and could be isolated on a 20 g scale as a single diastereomer by crystallization.

The introduction of the thiazole unit was achieved by reaction of bromide **3** with thiourea, monosubstituted thioureas, or thioamides. The reaction of bromo ketone **3** with thiourea in pyridine at 80 °C gave the aminothiazole **4**[11] in excellent yield and purity by precipitation with water and subsequent crystallization from EtOH. Aminothiazole **4** was subsequently acylated with carboxylic acids, acid chlorides, and sulfonyl chlorides, yielding the corresponding amides and sulfonamides **5**{*1–12*}. The substituted aminothiazoles and thiazoles **5**{*13–26*}[12] were prepared starting from bromide **3**; however, in some cases, precipitation was not successful. In this situation, an extractive workup was

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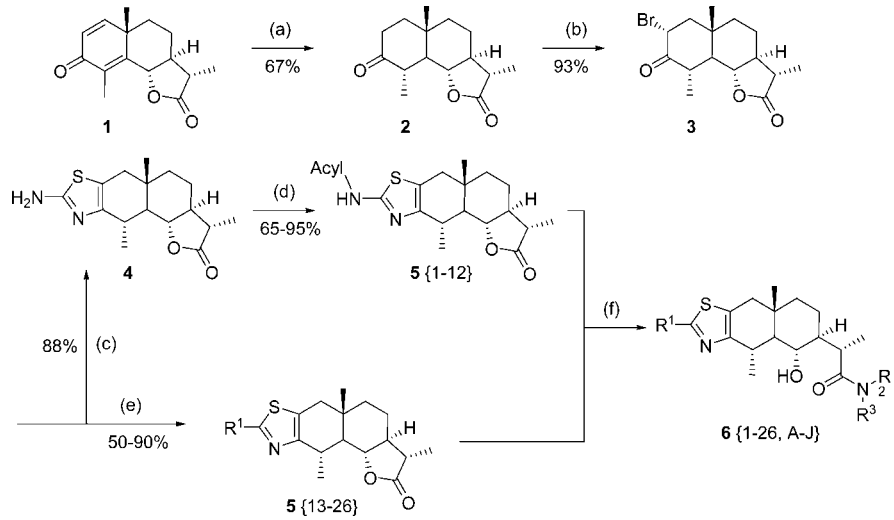
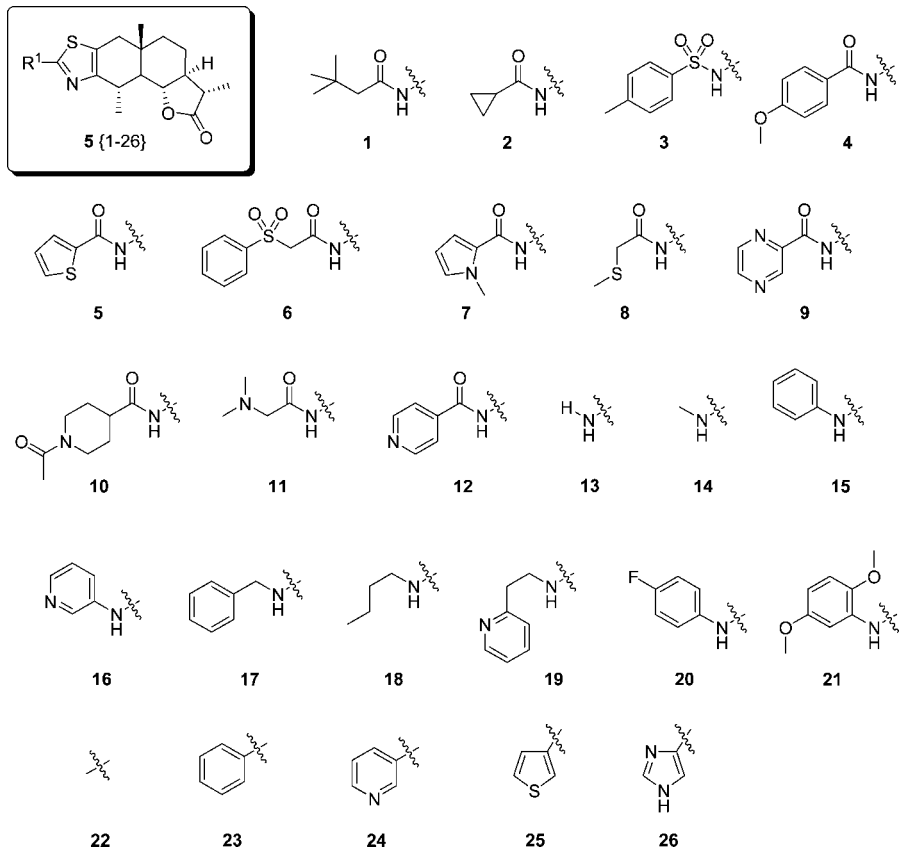
Scheme 1. Synthetic Route for the Santonin-Based Library Containing a Thiazole Unit[a]



[a] Reagents and conditions: (a) (i) $Pd/CaCO_3$, AcOEt, H_2 (1 atm), 50 °C; (ii) EtOH, $HClO_4$, reflux. (b) PTAB, THF, –5 °C. (c) Thiourea, pyridine, 80 °C. (d) Acid chloride or sulfonyl chloride, pyridine, DMAP, rt or carboxylic acid, EDCI, DMAP, Hünig's base, CH_2Cl_2, rt. (e) Substituted thioureas or thioamides, pyridine, 80 °C. (f) Amine, $AlCl_3$, $ClCH_2CH_2Cl$, rt.

Chart 1. Array of Residues Representing the First Center of Diversity for Thiazole **5**



performed to isolate the desired compounds. Purification of the crude products by crystallization or flash chromatography gave the thiazole derivatives **5**{*1–26*} (Chart 1). The yields were varying from 50 to 90%, and in general, the less reactive thioamides gave lower yields under the applied reaction conditions. The amount of thiazoles isolated after purification was satisfying for all investigated cases, and therefore no further optimization of the reaction conditions was performed.

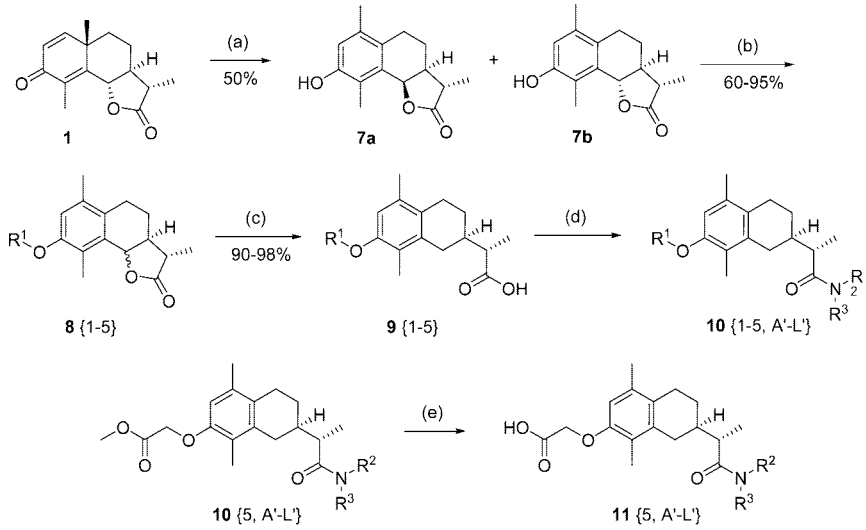
Finally, all thiazole derivatives of type **5** were exposed to an $AlCl_3$-mediated lactone opening using different amines (Chart 2) in dichloroethane, generating a BIOS-based library of the corresponding hydroxy amides **6**{*1–26*,*A–J*}. In order to assure a clean product formation in a short reaction time under mild conditions, the corresponding amines and the Lewis acid had to be used in large excesses (20 equiv of amine and 5 equiv of $AlCl_3$ at room temperature). Under these reaction conditions, full consumption of the starting material to a single product was observed within 30 to 60 min according to thin-layer chromatography (TLC). The mixtures were hydrolized with 2 M aqueous NaOH and subsequently extracted with ethyl acetate. A pH value of at

Table 1. Purity (%) of Final Library Members with a Thiazole Moiety Detected by LC at 215 nm

	A	B	C	D	E	F	G	H	I	J
6{*1*}	100.0	95.5	98.1	97.4	95.1	100.0	97.5	100.0	100.0	*a*
6{*2*}	90.9	65.7	83.6	91.7	96.5	*a*	90.8	55.6	91.8	95.1
6{*3*}	96.8	69.7	91.4	100.0	83.4	100.0	100.0	100.0	92.7	92.1
6{*4*}	96.8	*a*	92.5	93.0	88.3	94.0	100.0	96.6	88.5	30.5
6{*5*}	97.4	100.0	100.0	100.0	98.6	100.0	100.0	100.0	85.4	88.8
6{*6*}	84.6	*a*	85.1	84.0	78.7	86.3	100.0	81.0	80.5	100.0
6{*7*}	97.9	46.8	91.4	86.9	78.0	97.4	98.9	97.0	100.0	93.1
6{*8*}	98.9	100.0	89.5	91.0	100.0	100.0	97.5	97.7	83.9	100.0
6{*9*}	98.9	56.7	93.6	89.7	94.1	86.5	97.5	89.2	98.6	93.0
6{*10*}	41.7	100.0	96.2	61.5	45.6	86.2	100.0	66.1	90.3	99.9
6{*11*}	100.0	38.0	91.5	100.0	90.9	85.6	100.0	66.4	79.9	100.0
6{*12*}	96.0	66.6	39.5	100.0	80.1	85.5	100.0	73.6	86.2	78.5
6{*13*}	*a*	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
6{*14*}	100.0	98.9	98.6	96.8	*a*	100.0	100.0	*a*	92.2	*a*
6{*15*}	100.0	*a*	*a*	*a*	*a*	*a*	*a*	100.0	100.0	100.0
6{*16*}	100.0	95.5	89.8	74.2	93.6	100.0	100.0	*a*	69.5	88.6
6{*17*}	95.7	93.1	88.8	99.8	88.1	26.8	89.2	*a*	91.5	*a*
6{*18*}	92.4	95.6	87.5	65.9	91.1	99.0	100.0	*a*	56.5	93.6
6{*19*}	99.3	99.9	90.5	97.0	98.2	100.0	100.0	97.0	99.7	96.8
6{*20*}	93.7	99.6	94.5	100.0	93.0	100.0	41.0	*a*	98.8	69.8
6{*21*}	97.3	98.7	78.1	100.0	72.6	88.7	78.0	*a*	95.1	92.7
6{*22*}	100.0	98.9	*a*	95.3	92.9	100.0	100.0	100.0	*a*	95.0
6{*23*}	91.2	100.0	*a*	89.5	100.0	89.7	96.7	100.0	*a*	89.2
6{*24*}	99.0	97.4	94.5	99.0	95.8	99.7	99.6	96.8	98.0	97.7
6{*25*}	94.7	98.8	*a*	81.9	*a*	94.3	97.1	93.8	*a*	95.9
6{*26*}	39.9	61.7	90.6	99.8	89.9	94.9	99.5	95.6	*a*	72.7

[a] No product observed.

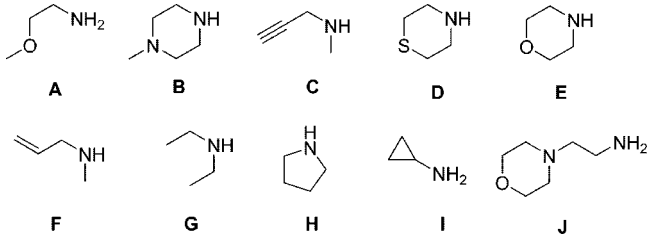
Scheme 2. Synthetic Route for the Santonin-Based Library Containing a Tetrahydronaphthalene Unit[a]



[a] Reagents and conditions: (a) HCOOH, 100 °C, then water; (b) alkylating agent, acetone or butanone, K_2CO_3, NaI*, reflux; (c) 10–15 mol % $Pd(OH)_2$/C, MeOH, H_2 (1 atm), rt; (d) amine, EDCI, DMAP, Hünig's base, CH_2Cl_2, rt; (e) MeOH, aq NaOH, rt. * denotes only used for the preparation of **8**{*3–4*}.

least 11 was crucial in order to redissolve the temporary observed Al–O precipitate and assure phase separation. The organic extracts were washed with water to remove, or at least reduce, the excess of amine present in the organic layer. Attempts to remove the remaining amines by using polymer-supported scavenger resins like PS-*p*TsOH or washing the organic layer with diluted aqueous HCl failed due to reformation of the starting lactone. After isolation, the identity and purity of each final library member was determined by liquid chromatography (LC) methods. The purities of crude products are summarized in Table 1. Compounds with a purity below 85% (see below) were purified by reverse-phase high-performance liquid chromatograph (RP-HPLC).

Chart 2. Selection of Amines for the Lactone Opening



Synthesis of a BIOS-Based Library Containing a Tetrahydronaphthalene Unit. The initial step for the preparation of compounds with a tetrahydronaphthalene core structure was an acid-mediated dienone–phenol rearrangement of α-santonin **1** (Scheme 2). Heating the natural product

Chart 3. Array of Residues Representing the First Center of Diversity for Tetrahydronaphthalene **9**

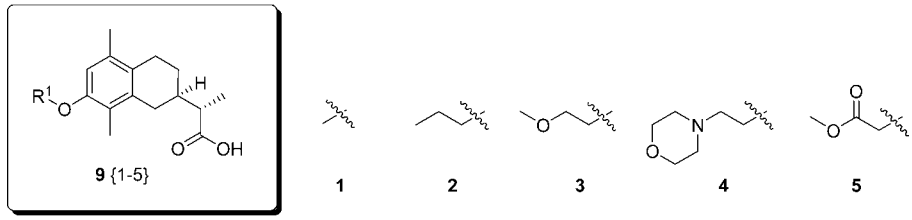


Chart 4. Selection of Amines for the Amidation Chemistry

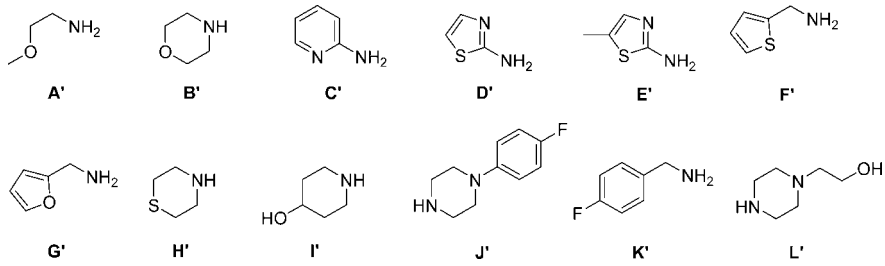


Table 2. Purity (%) of Final Library Members with a Tetrahydronaphthalene Moiety Detected by LC at 215 nm

	A′	B′	C′	D′	E′	F′	G′	H′	I′	J′	K′	L′
10{*1*}	80.0	100.0	95.2	100.0	*a*	85.0	98.9	100.0	93.7	97.0	88.9	100.0
10{*2*}	100.0	100.0	98.7	100.0	97.2	100.0	98.5	97.6	100.0	85.8	93.1	62.8
10{*3*}	52.7	58.1	90.2	96.2	98.2	87.6	100.0	97.8	82.0	80.9	100.0	53.1
10{*4*}	92.3	100.0	88.6	100.0	95.6	93.7	100.0	100.0	61.1	87.3	89.1	48.6
10{*5*}	n.d.	n.d.	n.d.	*a*	56.2	n.d.	n.d.	n.d.	n.d.	*a*	n.d.	n.d.
11{*5*}	96.7	83.8	96.4	*a*	85.8	47.4	99.0	90.9	96.1	*a*	96.3	92.3

[a] No product observed. n.d., not detected. Esters **10**{*5*} were directly cleaved to acids **11**{*5*}. Purities were determined for these compounds.

in formic acid for 8 h followed by the addition of water[13] gave tetrahydronaphthalenes **7a** and **7b** that crystallized from the mixture over night.

The first crop of crystals consists exclusively of diastereomer **7a**. Further addition of water resulted in the precipitation of additional material that turned out to be a mixture of epimeric lactones **7a** and **7b** in varying amounts and ratios. Lactones **7a** and **7b** could be isolated in ~50% total yield collecting both crops of material. Converting a mixture of the lactones **7a** and **7b** with an excess of K_2CO_3 and an alkylating agent in refluxing acetone gave a mixture of the diastereomeric tetrahydronaphthalene ethers **8**{*1*}, **8**{*2*}, and **8**{*5*}. In order to obtain the tetrahydronaphthalene ethers **8**{*3*}and **8**{*4*}, a switch of solvent from acetone to butanone and the addition of 1 equiv NaI was necessary. Purification of the crude products by flash chromatography yielded a diastereomeric mixture of the tetrahydronaphthalene ethers **8**{*1–5*}, whose subsequent catalytic hydrogenation [$Pd(OH)_2$/C] gave the corresponding carboxylic acids **9**{*1–5*} in a diastereomerically pure form. The carboxylic acids **9**{*1–5*} (Chart 3) were used for the final amidation step without further purification.

The coupling of the carboxylic acids **9**{*1–5*} to the corresponding amides **10**{*1–5*,*A′–L′*} was performed using the amines shown in Chart 4 with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and Hünig's base in dichloromethane (DCM) at room temperature. The amides **10**{*5*,*A′–L′*}were subsequently converted to the free carboxylic acids **11**{*5*,*A′–L′*} using aqueous NaOH in MeOH.

After synthesis, the purity and identity of each library member was determined by LC methods. The purities of the crude library members are summarized in Table 2. Compounds that failed to give purities over 85% were submitted to RP-HPLC.

Selection of Compounds for Library Synthesis. One of the main objectives for library production was compliance with some physicochemical parameters related to bioavailability (number of H-bond donors and acceptors, molecular weight, clogP values,[8] number of rotable bonds, and TPSA values[9]) in order to assure general pharmacological relevance. Virtual generation of a 2000-member library (1600 for the thiazole scaffold and 400 for the tetrahydronaphthalene)[14] along with subsequent calculation of the parameters mentioned above[15] and an analysis of the results was performed to find the optimal residues for decoration. Compounds with a molecular weight up to 600 Da were accepted due to the restricted diversity of decoration residues. As shown in Chart 5, the library is compliant in all categories according to commonly accepted guidelines.[8,9]

Performing a feasibility study and assessment of the results led us to the final choice of residues for decoration. The residues used for the thiazole library are shown in Charts 1 and 2. After the first diversification (→ **5**{*1–26*}), about half of the compounds resulted from acylation of the aminothiazole **4**, the other half from the conversion of bromide **3** with substituted thioamides or thioureas, respectively (Chart 1). For the subsequent lactone opening, representing the second point of diversity, the 10 amines shown in Chart 2 gave the best results. The use of anilines and heteroaromatic amines for library synthesis was abandoned due to the formation of complex product mixtures. Also amines with free hydroxy groups were not suitable for the lactone-opening conditions

Chart 5. Calculated Physicochemical Parameters of the Final Library Members

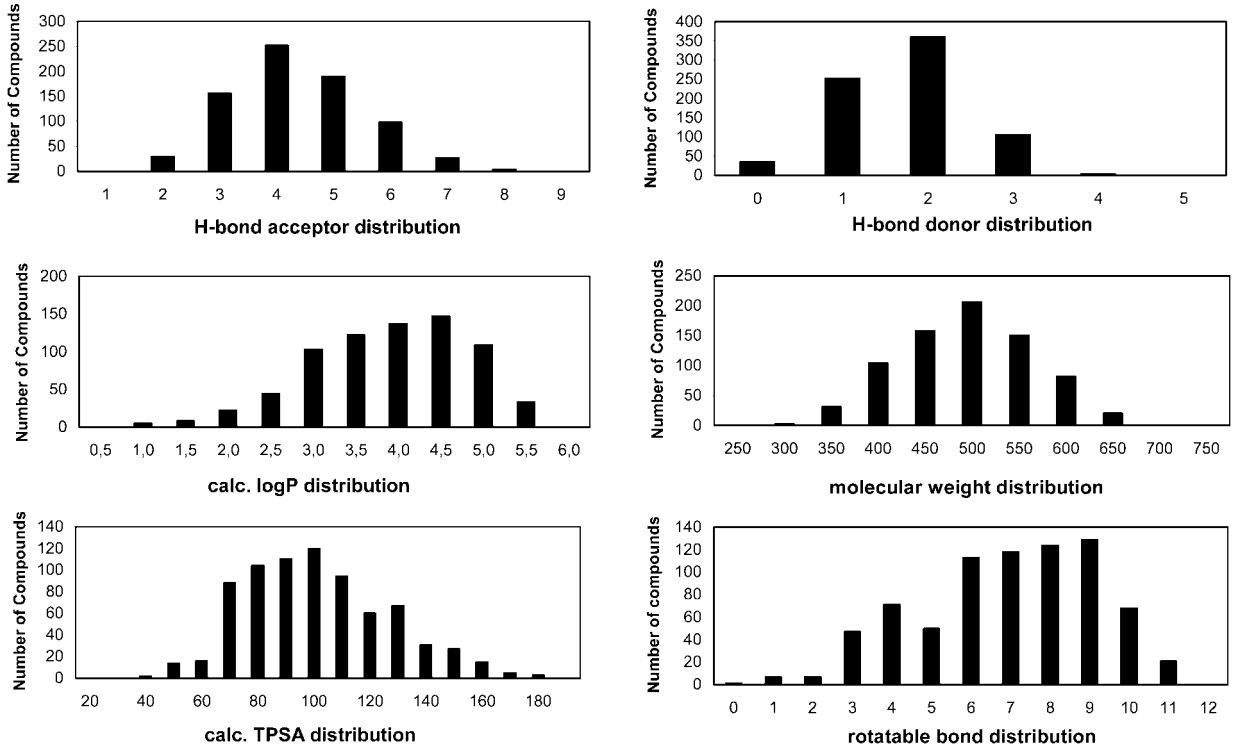
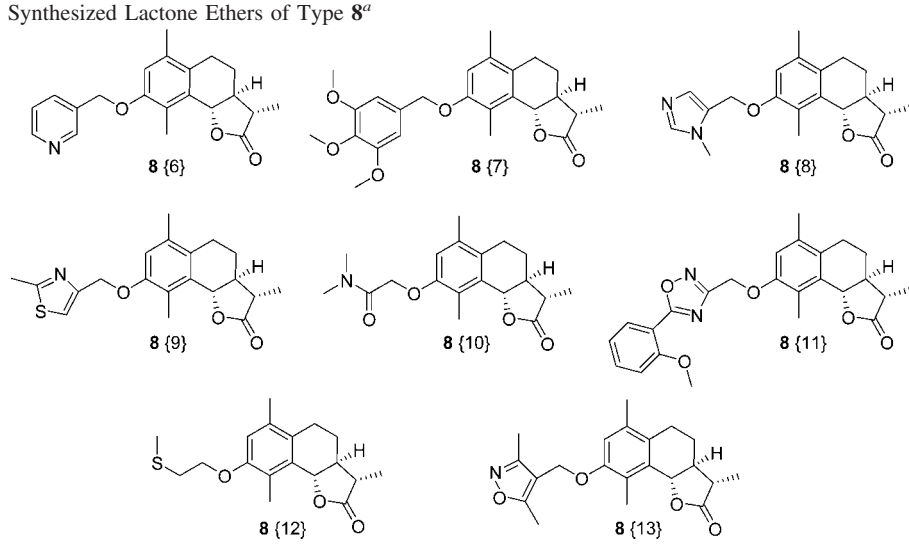


Chart 6. Additionally Synthesized Lactone Ethers of Type **8**[a]



[a] Only one diastereomer depicted.

due to reaction with the *Lewis acid* and were therefore not further considered for library preparation.

Compared to the thiazole library, the library with the tetrahydronaphthalene contains less compounds. This is mainly due to the restricted availability of lactone ethers **8** compatible with the reaction conditions for the synthesis of amidation precursor **9** (Chart 3). Although the eight additional lactone ethers **8**{*6–13*} could be synthesized successfully (Chart 6), only compounds **8**{*1–5*} yielded the desired amidation precursors **9**{*1–5*} after catalytic hydrogenation and could therefore be considered for library preparation. Attempts to synthesize the carboxylic acids **9**{*6–13*} under these conditions were not successful.[16] The application of modified reduction procedures to prepare **9**{*6–13*}, such as ionic or *Lindlar* hydrogenation, failed as well.

Nevertheless, the five residues shown in Chart 3 represent in our view a reasonable degree of diversity for this library, as acidic, basic, neutral, polar, and nonpolar compounds are accessible. The amines used for the second diversification step of this library are depicted in Chart 4. Due to the applied amidation conditions using EDCI in the presence of Hünig's base, less nucleophilic heteroaromatic amines and hydroxy amines could be coupled to the desired amides without any problems.

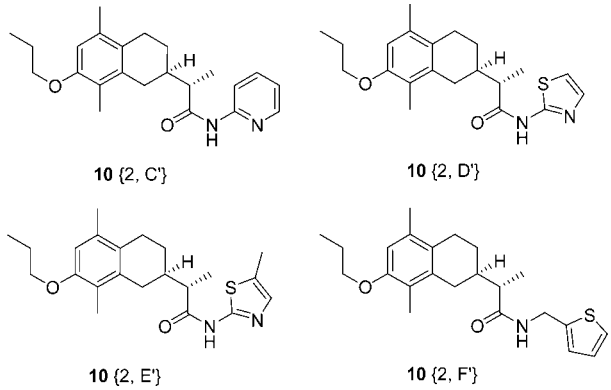
After synthesis, the purity and identity of each library member was determined by LC methods. Compounds with

Table 3. Determination of IC_{50} Values for the Most Potent 5-LO Inhibitors

compound	IC_{50}/intact PMNL[a] [μM]	IC_{50}/partially purified 5-LO [μM]
10{2,C'}	0.9 ± 1	6 ± 3
10{2,D'}	0.8 ± 2	1 ± 10
10{2,E'}	1 ± 1	0.8 ± 2
10{2,F'}	8 ± 2	3 ± 3
quercetin[b]	3 ± 2	n.d.

[a] Polymorphonuclear leucocytes. [b] Reference compound.

Chart 7. Structures of the Most Potent 5-LO Inhibitors



a purity below 85% (ELS detection and UV 215 nm) or yields over 100% (impurities caused by reagent residues for the thiazole and remaining byproducts from the amide coupling for the tetrahydronaphalene library) were purified by RP-HPLC.

Biological Validation of the α-Santonin-Based Libraries. Recently, 5-lipoxygenase (5-LO) has increasingly gained attention as a drug target due to association of its pathway with diseases like atheroclerosis, cancer, osteoporosis, and inflammatory complaints.[17] A-64077 (Zileuton), the only marketed 5-LO inhibitor so far, is used for the treatment of asthma in the U.S.; however, some unfavorable properties of this compound have been seen as an encouragement for the development of better therapeutic agents in this field.[18]

For the discovery of new 5-lipoxygenase inhibitors by means of our BIOS approach,[6] the structures of more than 9000 compounds were submitted to a ligand-based virtual screening cascade.[19,20] This iterative campaign yielded 23 hit compounds from the two santonin-based libraries described above.[20] These compounds were tested *in vitro*[21] against 5-LO product formation, yielding four potent inhibitors with IC_{50} values in low to submicromolar concentrations (Table 3).

The structures of the four most potent inhibitors are shown in Chart 7. They all exhibit a core structure of type **10** bearing a nonpolar propyloxy substituent attached to the aromatic ring and an aromatic heterocyclic amide located in the side chain. Substitution of the propyl ether by a methyl or dimethylaminoethyl group abolished the efficacy, indicating that a lipophilic and bulky residue in this position is required for potent 5-LO inhibition. Modification of the amide moiety by using aliphatic amines or amines prolonging the amide linker by only a single methylene group also results in a loss of potency, suggesting that heterocyclic amines might be a good starting point for a further improvement of inhibition properties.

The substituted tetrahydronaphthalene core structure of the four hit compounds has not been associated with 5-LO inhibition before and, thus, represents a novel inhibitor class for this enzyme.

Conclusion

We described herein the synthesis of two BIOS-based libraries starting from α-santonin. The library members exhibit two centers of diversity and are easily accessible in a short and efficient way (four to five steps for the thiazole library and four steps for the tetrahydronaphthalene library) using parallel solution-phase chemistry. Intermediates **2**, **3**, **4**, and **7** can be synthesized on a large scale and isolated in pure form by crystallization. With the utilization of a late-stage diversification design, purification efforts are kept at a minimum level. The analysis of physicochemical parameters ensured the general pharmacological relevance of the described libraries.

After virtual screening, 23 selected library members were tested against 5-lipoxygenase product formation, resulting in the discovery of four promising agents with substantial inhibition properties. All four compounds exhibit a tetrahydronaphthalene core structure that has not been associated with 5-LO inhibition before. Applying our BIOS approach for library design and synthesis in combination with the use of modern virtual screening tools led to the discovery of a novel inhibitor class of 5-lipoxygenase. This result can be seen as an example for the biological relevance of natural-product-based compound collections and the potential of the corresponding library members for hit and lead structure generation.

Experimental Section

α-Santonin (purity ≥ 98%) was purchased from Sinochem Ningbo Imp. Exp. Co., Ltd. Commercial reagents were used without prior purification. Analytical thin-layer chromatography was performed on F254 silica gel plates from Merck. Flash chromatography was performed using silica gel 60 from Fluka (230–400 mesh). ^{1}H-NMR and ^{13}C-NMR were recorded using $CDCl_3$ or d_6-DMSO (unless otherwise stated) at 500/400 and 125/100 MHz, respectively, on a Bruker Avance 500/400 spectrometer. Proton and carbon chemical shifts are reported in parts per million using $CHCl_3$ or DMSO as an internal standard. All coupling constants are given in hertz. Liquid chromatography/mass spectrometry (LC/MS) spectra were obtained with a PE SCIEX AP 150 instrument equipped with a UV (215 nm) and an evaporative light scattering (ELS) detector. A linear gradient was used starting with a 5 mM ammoniumformiate buffer containing 0.1% formic acid, ending with a MeOH/ACN/ammoniumformiate buffer containing 0.1% formic acid (0.5:0.5:1, v/v/v) at a flow rate of 0.1 mL/min. Physicochemical parameters (number of acceptors, donors, and rotable bonds; MW; ClogP; TPSA) were calculated with ChemOffice 8.0 for Excel from CambridgeSoft Corporation. Detailed experimental data for the compounds prepared according to the procedures given below are available in the Supporting Information.

(6*R*,11*S*)-3-Oxoeudesmano-13,6-lactone (**2**),[10] (2*R*,6*R*,11*S*)-2-bromo-3-oxoeudesmano-13,6-lactone (**3**),[10] (6*R*,11*S*)-[2′-amino-thiazol-(2,3-d)]eudesmano-13,6-lactone (**4**),[11] and (6*S*,7*S*,11*R*)-3-hydroxy-1,4,11-trimethyl-6,7,8,9-tetrahydronaphtho[6,7-b]furan-12(11H)-one (**7a**)[13] could be prepared according to conditions as reported earlier.

5{*1–5*}. To a solution of 612 mg (2 mmol) of aminothiazole **4** in pyridine (6 mL) and dry DCM (12 mL), 1.25 equiv (3.75 mmol) of the corresponding acid chloride or sulfonyl chloride as well as a few crystals of DMAP were added. The solution was stirred at room temperature until TLC showed complete consumption of the starting material (check every 30 min). If conversion was not complete after 60 min, an additional amount of 0.25 equiv of acylating agent was added and stirring was continued. After complete conversion, DCM (50 mL) was added, and the solution was washed with 2 M HCl (50 mL, pH 1). The aqueous phase was extracted twice with DCM, and the combined organic phases were washed with brine. After drying (Na_2SO_4), the solution was concentrated under reduced pressure, and the residue was purified by chromatography. The desired products were isolated as colorless to light brown solids.

5{*6–12*}. To a solution of 612 mg (2 mmol) of aminothiazole **4** in dry DCM (20 mL) were added 4 mmol of the carboxylic acid, 6 mmol of EDCI, and a few crystals of DMAP at room temperature. The solution was adjusted to pH 9–10 by adding Hüning's base and stirred at room temperature until TLC indicated complete conversion. The mixture was diluted with DCM (30 mL), and 2 M HCl (50 mL) was added. The aqueous phase was extracted three times with DCM, and the combined organic phases were washed with water and brine. After drying over Na_2SO_4, the organic phase was concentrated under reduced pressure, and the residue was purified by chromatography. The desired products were isolated as colorless to light brown solids.

In the case of basic acylating agents (for example, nicotinic acid derivatives), water was added for hydrolysis instead of HCl.

4 and 5{*14–26*}. To a solution of 988 mg (3 mmol) of bromo-tetrahydrosantonin **3** in pyridine (3 mL) was added 3.75 mmol of the corresponding thioamide or thiourea derivative, and the mixture was heated at 80 °C for 150 min. The conversion was checked by TLC or LCMS. After complete conversion, the solution was poured into water (25 mL). The resulting solid was collected and recrystallized from ethanol. In the cases where no solid was formed, the solution was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over Na_2SO_4. These crude products were purified by flash chromatography. The desired products were isolated as colorless to light brown solids.

6{*1–26,A–J*}. To a mixture of the corresponding thiazole derivative **5**{*1–26*} (0.2 mmol) were added 5 equiv of $AlCl_3$ in dry 1,2-dichloroethane (5 mL) and 20 equiv of amine, and the solution was stirred at room temperature. After conversion was completed (usually after 30 min), a 2 M NaOH solution (approximately 5 mL, pH value must be basic!) was added and the organic phase was separated. The aqueous phase was extracted three times with ethyl acetate, and the organic phases were combined. The combined extracts were washed with brine and dried over Na_2SO_4. After concentration, the residue was purified by RP-semipreparative HPLC if required. The hydroxy amides were isolated as colorless to amber-colored solids or oils.

9{*1–5*}. To a mixture of 738 mg of tetrahydronaphthalene **7** (both epimers; 3 mmol) in 50 mL of solvent (acetone for **8**{*1*}, **8**{*2*}, and **8**{*5*} and butanone for **8**{*3*} and **8**{*4*}), were added 2.48 g (18 mmol) of K_2CO_3 and 6 mmol of the corresponding alkylating agent, and the mixture was refluxed until TLC showed complete conversion of the starting material.[22] The mixture was hydrolyzed with water and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography. The obtained mixtures of epimeric tetrahydronaphthalene ethers **8**{*1–5*} were dissolved in MeOH (100 mL) and charged with 250 mg of $Pd(OH)_2$/C (20% w/w). The black suspension was stirred under an atmosphere of hydrogen (1 atm) until TLC had shown complete consumption of the starting material (usually overnight). The mixture was filtered through a pad of celite and concentrated, yielding the desired acids **9**{*1–5*} as colorless foams or solids that were used without further purification for the next reaction.

10{*1–5,A′–L′*}. To a solution of the carboxylic acid **9**{*1–5*} (0.2 mmol) in dry DCM (3 mL) were added 2 equiv of the corresponding amine, 3 equiv of EDCI, and a few crystals DMAP, and the pH was adjusted to 10 by adding DIEA (Hünig's base). After complete conversion, 2 M HCl was added (in the case of basic products, water was used for hydrolysis instead of HCl), and the mixture was extracted with DCM. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration led to the crude amides **10**{*1–5,A′–L′*} that were purified by RP-semipreparative HPLC if required.

11{*5,A′–L′*}. The methyl esters **10**{*5,A′–L′*} were dissolved in MeOH (3 mL), and a 2 M NaOH solution (1 mL) was added. After stirring over night at room temperature, the mixture was diluted with water and extracted once with ethyl acetate. The aqueous phase was acidified with 2 M HCl (2.5 mL) and extracted with ethyl acetate. The combined organic extracts were washed with water and brine and dried over Na_2SO_4. Removal of the solvent yielded the carboxylic acids **11**{*5,A′–L′*} as amber-colored solids or oils.

6{*1,B*}. Yield: 77.1 mg (76%); $C_{27}H_{44}N_4O_3S$. LC/MS: *m*/*z* 487 $(M+1-18)^+$, 505 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$): δ 0.78 (s, 3H), 1.07 (s, 9H), 1.12 (d, 3H, J = 9.0 Hz), 1.31–1.48 (m, 3H), 1.52 (d, 3H, J = 8.5 Hz), 1.56–1.72 (m, 4H), 1.78–1.92 (m, 2H), 2.25 (d, 2H, J = 3.0 Hz), 2.31 (s, 3H), 2.33−2.61 (m, 7H), 2.66 (m, 1H), 3.00 (m, 1H), 3.45 (Ψq, 1H, J = 10.5 Hz), 3.60 (m, 3H), 3.68–3.77 (m, 1H), 8.90 (br s, 1H). ^{13}C–NMR ($CDCl_3$): δ 11.6, 18.0, 23.0, 29.7, 31.5, 35.0, 35.6, 36.8, 38.9, 39.9, 41.6, 45.3, 45.8, 47.5, 49.5, 54.8, 55.0, 55.3, 74.4, 120.3, 148.5, 155.6, 170.4, 176.1.

6{*1,G*}. Yield: 86.1 mg (90%); $C_{26}H_{43}N_3O_3S$. LC/MS: *m*/*z* 478 $(M+1)^+$, 500 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 0.77 (s, 3H), 1.05 (s, 9H), 1.11 (t, 3H, J = 7.5 Hz), 1.14 (d, 3H, J = 7.0 Hz), 1.21 (t, 3H, J = 7.5 Hz), 1.30–1.45 (m, 3H),

1.52 (d, 3H, $J = 6.5$ Hz), 1.57 (m, 1H), 1.65–1.78 (m, 3H), 1.87 (m, 1H), 2.14 (d, 1H, $J = 6.5$ Hz), 2.23 (d, 1H, $J = 12.5$ Hz), 2.28 (d, 1H, $J = 12.5$ Hz), 2.36 (d, 1H, $J = 16.0$ Hz), 2.49 (d, 1H, $J = 16.0$ Hz), 2.66 (m, 1H), 2.80 (m, 1H), 3.24–3.34 (m, 2H), 3.40 (Ψq, 1H, $J = 9.5$ Hz), 3.44–3.55 (m, 2H), 9.31 (br s, 1H). ^{13}C-NMR ($CDCl_3$): δ 13.4, 15.0, 16.4, 18.6, 23.5, 24.5, 30.1, 31.8, 35.3, 37.0, 38.6, 39.3, 40.5, 40.9, 48.9, 50.6, 55.5, 120.7, 133.9, 149.1, 169.3, 177.2.

6{*1,H*}. Yield: 84.5 mg (89%); $C_{26}H_{41}N_3O_3S$. LC/MS: *m/z* 476 $(M+1)^+$, 498 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 0.78 (s, 3H), 1.06 (s, 9H), 1.14 (d, 3H, $J = 9.0$ Hz), 1.30–1.44 (m, 3H), 1.50 (d, 3H, $J = 8.0$ Hz), 1.58 (d, 1H, $J = 10.0$ Hz), 1.74 (m, 1H), 1.80–2.03 (m, 5H), 2.23 (d, 1H, $J = 16.5$ Hz), 2.27 (d, 1H, $J = 16.5$ Hz), 2.44 (d, 1H, $J = 19.5$ Hz), 2.49 (d, 1H, $J = 19.5$ Hz), 2.61–2.74 (m, 2H), 3.40 (q, 1H, $J = 12.5$ Hz), 3.44–3.54 (m, 2H), 3.55–3.63 (m, 1H), 9.02 (br s, 1H). ^{13}C-NMR ($CDCl_3$): δ 14.0, 18.2, 23.3, 24.4, 26.2, 29.8, 31.6, 34.9, 37.0, 40.1, 40.2, 46.3, 47.0, 47.7, 49.9, 55.3, 60.8, 120.4, 145.1, 148.6, 168.3, 177.2.

6{*4,A*}. Yield: 62.7 mg (61%); $C_{27}H_{37}N_3O_5S$. LC/MS: *m/z* 516 $(M+1)^+$, 538 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 0.70 (s, 3H), 1.11 (d, 3H, $J = 7.0$ Hz), 1.22–1.44 (m, 3H), 1.36 (d, 3H, $J = 6.5$ Hz), 1.48–1.61 (m, 2H), 1.77 (m, 1H), 2.20 (m, 2H), 2.35 (d, 1H, $J = 15.0$ Hz), 2.46 (d, 1H, $J = 15.0$ Hz), 2.54 (m, 1H), 3.22–3.35 (m, 1H), 3.31 (s, 3H), 3.38–3.54 (m, 4H), 3.84 (s, 3H), 6.40 (br s, 1H), 6.93 (d, 2H, $J = 8.5$ Hz), 7.88 (d, 2H, $J = 8.5$ Hz), 11.35 (br s, 1H). ^{13}C-NMR ($CDCl_3$): δ 14.1, 18.5, 23.6, 23.8, 34.7, 37.1, 39.4, 39.6, 40.1, 42.9, 49.2, 55.2, 55.8, 58.9, 71.52, 76.0, 114.3, 120.4, 125.6, 130.1, 149.0, 163.3, 165.2, 170.5, 177.5.

6{*8,G*}. Yield: 85.0 mg (90%); $C_{23}H_{37}N_3O_3S_2$; LC/MS: *m/z* 468 $(M+1)^+$, 490 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 0.77 (s, 3H), 1.11 (t, 3H, $J = 7.0$ Hz), 1.14 (d, 3H, $J = 7.0$ Hz), 1.21 (t, 3H, $J = 7.0$ Hz), 1.30–1.46 (m, 3H), 1.53 (d, 3H, $J = 6.5$ Hz), 1.58 (m, 1H), 1.72 (m, 1H), 1.86 (m, 1H), 2.13 (m, 1H), 2.17 (s, 3H), 2.37 (d, 1H, $J = 15.0$ Hz), 2.50 (d, 1H, $J = 15.0$ Hz), 2.68 (m, 1H), 2.81 (m, 1H), 3.23–3.35 (m, 2H), 3.38 (s, 2H), 3.36–3.54 (m, 3H), 9.92 (br s, 1H). ^{13}C-NMR ($CDCl_3$): δ 13.4, 15.0, 16.2, 16.8, 18.5, 23.6, 24.4, 35.3, 37.1, 38.5, 39.4, 40.5, 40.9, 42.5, 48.9, 55.5, 121.3, 149.7, 154.4, 166.7, 177.2.

6{*9,J*}. Yield: 82.3 mg (76%); $C_{27}H_{38}N_6O_4S$. LC/MS: *m/z* 543 $(M+1)^+$, 525 $(M+1-18)^+$. ^{1}H-NMR ($CDCl_3$): δ 0.78 (s, 3H), 1.16 (d, 3H, $J = 6.5$ Hz), 1.32–1.50 (m, 3H), 1.52–1.67 (m, 2H), 1.56 (d, 3H, $J = 7.0$ Hz), 1.82 (m, 1H), 2.34–2.61 (m, 9H), 2.75 (m, 1H), 3.29–3.43 (m, 3H), 3.70 (br s, 6H), 6.25 (br s, 1H), 8.61 (s, 1H), 8.82 (s, 1H), 9.47 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 14.6, 18.5, 23.5, 35.4, 35.9, 36.0, 37.1, 39.3, 40.3, 43.3, 49.4, 53.7, 55.4, 57.5, 67.2, 76.3, 121.8, 143.3, 145.0, 148.5, 150.2, 153.9, 160.6, 170.5, 177.5.

6{*11,F*}. Yield: 57.2 mg (62%); $C_{24}H_{38}N_4O_3S$. LC/MS: *m/z* 463 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) (mixture of rotamers present, approximate ratio: 45:55): δ 0.77, 0.78 (2s, 3H), 1.12, 1.13 (2d, 3H, $J = 8.5$ Hz), 1.30–1.48 (m, 3H), 1.54 (d, 3H, $J = 8.0$ Hz), 1.58 (m, 1H), 1.70 (m, 1H), 1.76–2.00 (m, 2H), 2.35 (m, 1H), 2.38 (br s, 6H), 2.50 (m, 1H), 2.68 (m, 1H), 2.92 (m, 1H), 2.93, 3.04 (2s, 3H), 3.13 (d, 1H, $J = 21.5$ Hz), 3.19 (d, 1H, $J = 21.5$ Hz), 3.41 (Ψq, 1H, $J = 12.0$ Hz), 3.88, 4.16 (m, 1H), 4.01 (d, 1H, $J = 7.5$ Hz), 5.12–5.26 (m, 2H), 5.78 (m, 1H), 10.29 (br s, 1H).

6{*21,E*}. Yield: 90.3 mg (85%); $C_{28}H_{39}N_3O_5S$. LC/MS: *m/z* 530 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$): δ 0.83 (s, 3H), 1.10 (d, 3H, $J = 7.5$ Hz), 1.30–1.48 (m, 3H), 1.53–1.66 (m, 2H), 1.60 (d, 3H, $J = 9.0$ Hz), 1.76–1.84 (m, 1H), 2.29 (d, 1H, $J = 15.5$ Hz), 2.47 (d, 1H, $J = 15.5$ Hz), 2.70 (m, 1H), 3.03 (m, 1H), 3.41–3.49 (m, 2H), 3.53–3.76 (m, 8H), 3.79 (s, 3H), 3.84 (s, 3H), 6.43 (dd, 1H, $J = 2.0$, 8.5 Hz), 7.77 (d, 1H, $J = 8.5$ Hz), 7.56 (br s, 1H), 7.78 (d, 1H, $J = 2.0$ Hz). ^{13}C-NMR ($CDCl_3$): δ 13.8, 14.5, 18.7, 22.8, 23.3, 35.7, 36.7, 37.2, 39.4, 40.4, 48.2, 55.4, 56.0, 56.7, 60.8, 67.2, 76.7, 103.1, 105.6, 111.1, 115.8, 131.5, 141.7, 150.7, 154.5, 160.5, 176.3.

6{*24,J*}. Yield: 76.5 mg (79%); $C_{27}H_{38}N_4O_3S$. LC/MS: *m/z* 499 $(M+1)^+$, 481 $(M+1-18)^+$. ^{1}H-NMR ($CDCl_3$): δ 0.81 (s, 3H), 1.19 (d, 3H, $J = 9.0$ Hz), 1.36–1.52 (m, 3H), 1.58 (m, 1H), 1.67 (d, 3H, $J = 9.0$ Hz), 1.76–1.88 (m, 2H), 2.40–2.64 (m, 9H), 2.89 (m, 1H), 3.31–3.44 (m, 3H), 3.50 (m, 1H), 3.68–3.73 (m, 4H), 6.15 (br s, 1H), 7.34 (dd, 1H, $J = 6.0$, 10.0 Hz), 8.19 (d, 1H, $J = 10.0$ Hz), 8.59 (d, 1H, $J = 6.0$ Hz), 9.09 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 14.5, 18.6, 23.6, 23.8, 36.0, 37.2, 39.9, 40.3, 43.2, 49.4, 51.1, 53.7, 55.3, 57.4, 67.2, 76.2, 124.0, 128.0, 133.6, 147.8, 150.4, 157.2, 160.9, 170.5, 177.5.

6{*25,D*}. Yield: 46.6 mg (49%); $C_{24}H_{32}N_2O_2S_3$. LC/MS: *m/z* 477 $(M+1)^+$, 499 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 0.80 (s, 3H), 1.05 (d, 3H, $J = 7.0$ Hz), 1.32–1.49 (m, 3H), 1.56–1.66 (m, 2H), 1.65 (d, 3H, $J = 6.5$ Hz), 1.76–1.85 (m, 1H), 1.95 (m, 1H), 2.47 (d, 1H, $J = 16.0$ Hz), 2.57 (d, 1H, $J = 16.0$ Hz), 262 (m, 3H), 2.70 (m, 1H), 2.88 (m, 1H), 3.01 (m, 1H), 3.43 (m, 1H), 3.80–3.96 (m, 4H), 7.33 (dd, 1H, $J = 3.0$, 5.0 Hz), 7.50 (d, 1H, $J = 5.0$ Hz), 7.75 (br s, 1H). ^{13}C-NMR ($CDCl_3$): δ 13.8, 18.5, 22.7, 23.9, 28.3, 35.8, 36.9, 39.8, 40.3, 45.1, 48.1, 48.8, 55.5, 76.7, 123.1, 126.2, 126.5, 126.7, 136.6, 155.9, 159.8, 176.2.

10{*1,I′*}. Yield: 64.3 mg (93%); $C_{21}H_{31}NO_3$. LC/MS: *m/z* 346 $(M+1)^+$, 368 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 1.20 (d, 3H, $J = 6.4$ Hz), 1.30 (dq, 1H, $J = 5.2$, 11.6 Hz), 1.44–1.58 (m, 2H), 1.68–1.97 (br m, 4H), 1.98–2.08 (br m, 1H), 2.10 (s, 3H), 2.20 (s, 3H), 2.26 (dd, 1H, $J = 11.6$, 16.0 Hz), 2.54 (m, 1H), 2.62–2.76 (m, 2H), 2.83 (m, 1H), 3.12–3.36 (br m, 2H), 3.79 (s, 3H), 3.76–4.00 (br m, 2H), 4.08–4.28 (br m, 1H), 6.60 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 11.2, 15.5, 20.2, 27.2, 28.4, 31.7, 35.3, 37.5, 41.1, 56.1, 67.8, 110.7, 122.3, 122.4, 127.7, 134.3, 136.0, 155.4, 175.0.

10{*1,J′*}. Yield: 81.8 mg (96%); $C_{26}H_{33}FN_2O_2$. LC/MS: *m/z* 425 $(M+1)^+$, 447 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 1.23 (d, 3H, $J = 7.0$ Hz), 1.34 (dq, 1H, $J = 5.2$, 11.6 Hz), 1.87–1.96 (m, 1H), 2.00–2.08 (m, 1H), 2.11 (s, 3H), 2.20 (s, 3H), 2.28 (dd, 1H, $J = 11.5$, 16.5 Hz), 2.55 (m, 1H), 2.63–2.78 (m, 2H), 2.86 (dd, 1H, $J = 3.5$, 16.5 Hz), 3.02–3.16 (m, 4H), 3.80 (s, 3H), 3.66–3.92 (m, 4H), 6.60 (s, 1H), 6.89 (m, 2H), 6.98 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 11.2, 15.4, 20.2, 27.2, 28.4, 31.6, 37.5, 41.0, 42.1, 46.1, 51.0, 51.4, 56.1, 110.7, 116.0, 116.1, 118.8, 118.9, 122.4, 127.6, 134.3, 135.9, 147.9, 155.4, 157.0, 158.9, 175.1.

10{*2,A′*}. Yield: 65.2 mg (94%); $C_{21}H_{33}NO_3$. LC/MS: *m/z* 348 $(M+1)^+$, 370 $(M+23)^+$. ^{1}H-NMR (d_4-MeOH): δ 1.04

(t, 3H, $J = 7.2$ Hz), 1.19 (d, 3H, $J = 6.8$ Hz), 1.30 (dq, 1H, $J = 5.2$, 12.0 Hz), 1.76–1.83 (m, 1H), 1.77 (Ψsep, 2H, $J = 7.6$ Hz), 1.84–1.95 (m, 1H), 2.05 (s, 3H), 2.14 (s, 3H), 2.12–2.28 (m, 2H), 2.45 (m, 1H), 2.68 (m, 1H), 2.81 (dd, 1H, $J = 4.0$, 16.8 Hz), 3.34 (s, 3H), 3.38–3.50 (m, 4H), 3.85 (dt, 2H, $J = 2.8$, 6.4 Hz), 6.56 (s, 1H). ^{13}C-NMR (d_4-MeOH): δ 11.0, 11.1, 15.6, 19.9, 24.0, 27.8, 28.7, 32.7, 38.7, 40.1, 47.6, 58.9, 71.1, 72.1, 112.7, 122.9, 128.1, 134.8, 136.4, 155.8, 179.3.

10{*2,C′*}. Yield: 32.1 mg (43 %); $C_{23}H_{30}N_2O_2$. LC/MS: m/z 367 $(M+1)^+$, 389 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 1.04 (t, 3H, $J = 7.6$ Hz), 1.35 (d, 3H, $J = 6.6$ Hz), 1.44 (dq, 1H, $J = 5.2$, 12.0 Hz), 1.80 (m, 2H), 1.95–2.08 (m, 2H), 2.12 (s, 3H), 2.20 (s, 3H), 2.30 (m, 2H), 2.55 (m, 1H), 2.71 (m, 1H), 2.88 (dd, 1H, $J = 4.0$, 16.7 Hz), 3.88 (ψdt, 2H, $J = 1.5$, 6.6 Hz), 6.59 (s, 1H), 7.04 (dd, 1H, $J = 5.5$, 7.6 Hz), 7.72 (ψdt, 1H, $J = 1.1$, 7.6 Hz), 8.07 (br. s, 1H), 8.28 (m, 2H). ^{13}C-NMR (d_6-DMSO): δ 10.6, 14.8, 19.5, 22.4, 26.1, 27.1, 30.7, 36.9, 45.4, 54.9, 69.4, 111.5, 113.8, 119.3, 121.1, 126.6, 133.3, 135.1, 138.6, 147.2, 151.8, 153.9, 175.5.

10{*2,D′*}. Yield: 64.1 mg (68%); $C_{21}H_{28}N_2O_2S$. LC/MS: *m/z* 373 $(M+1)^+$, 395 $(M+23)^+$. ^{1}H-NMR (d_6-DMSO): δ 0.98 (t, 3H, $J = 7.6$ Hz), 1.19 (d, 3H, $J = 6.8$ Hz), 1.31 (dq, 1H, $J = 5.2$, 12.4 Hz), 1.64–1.78 (m, 3H), 1.82–1.92 (m, 1H), 2.01 (s, 3H), 2.11 (s, 3H), 2.19 (dd, 1H, $J = 10.4$, 16.8 Hz), 2.38 (m, 1H), 2.56–2.69 (m, 2H), 2.77 (dd, 1H, $J = 4.8$, 16.8 Hz), 2.87 (dd, 1H, $J = 4.5$, 16.7 Hz), 3.84 (m, 2H), 7.20 (d, 1H, $J = 3.2$ Hz), 7.47 (d, 1H, $J = 3.2$ Hz), 12.32 (br. s, 1H). ^{13}C-NMR (d_6-DMSO): δ 10.6, 10.7, 14.8, 19.5, 22.4, 26.0, 27.0, 30.8, 36.8, 44.6, 69.4, 111.5, 113.4, 121.1, 126.5, 133.3, 134.9, 137.6, 153.9, 157.9, 174.2.

10{*2,F′*}. Yield: 52.8 mg (68%); $C_{23}H_{31}NO_2S$. LC/MS: *m/z* 386 $(M+1)^+$, 408 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 1.04 (t, 3H, $J = 7.6$ Hz), 1.26 (d, 3H, $J = 7.1$ Hz), 1.35 (dq, 1H, $J = 5.6$, 12.4 Hz), 1.80 (m, 2H), 1.89–2.01 (m, 2H), 2.09 (s, 3H), 2.12 (m, 1H), 2.18 (s, 3H), 2.21 (dd, 1H, $J = 10.8$, 16.8 Hz), 2.53 (m, 1H), 2.70 (m, 1H), 2.82 (dd, 1H, $J = 4.0$, 16.4 Hz), 3.88 (dt, 2H, $J = 3.2$, 6.4 Hz), 4.66 (t, 2H, $J = 5.2$ Hz), 5.83 (br t, 1H, $J = 4.8$ Hz), 6.58 (s, 1H), 6.94–6.98 (m, 2H), 7.23 (d, 1H, $J = 4.8$ Hz). ^{13}C-NMR (d_6-DMSO): δ 10.60, 10.69, 14.97, 19.52, 22.37, 26.12, 26.95, 30.79, 36.70, 37.05, 44.89, 69.37, 111.42, 121.06, 124.93, 125.04, 126.56, 126.67, 133.30, 135.23, 143.15, 153.85, 174.93.

10{*2,H′*}. Yield: 60.1 mg (80%); $C_{22}H_{33}NO_2S$. LC/MS: *m/z* 376 $(M+1)^+$, 398 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 1.04 (t, 3H, $J = 6.0$ Hz), 1.19 (d, 3H, $J = 5.6$ Hz), 1.20–1.36 (m, 2H), 1.80 (Ψsep, 2H, $J = 7.2$ Hz), 2.00–2.10 (m, 1H), 2.08 (s, 3H), 2.20 (s, 3H), 2.30 (dd, 1H, $J = 7.2$, 12.8 Hz), 2.48–2.76 (m, 8H), 3.66–3.88 (m, 3H), 3.88 (t, 2H, $J = 5.2$ Hz), 3.99 (m, 1H), 6.58 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 11.0, 11.2, 15.0, 20.1, 23.2, 25.2, 26.2, 33.1, 37.1, 39.3, 44.8, 48.7, 70.5, 112.0, 122.5, 127.2, 134.1, 135.7, 154.90, 175.2.

10{*3,B′*}. Yield: 44.1 mg (59%). $C_{22}H_{33}NO_4$. LC/MS: *m/z* 376 $(M+1)^+$, 398 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 1.21 (d, 3H, $J = 7.2$ Hz), 1.31 (dq, 1H, $J = 5.6$, 12.0 Hz), 1.90 (m, 1H), 1.98–2.08 (m, 2H), 2.12 (s, 3H), 2.18 (s, 3H), 2.25 (dd, 1H, $J = 11.2$, 16.8 Hz), 2.56 (m, 1H), 2.60–2.71 (m, 2H), 2.82 (dd, 1H, $J = 4.0$, 16.0 Hz), 3.46 (s, 3H), 3.54–3.60 (m, 2H), 3.66–3.72 (m, 5H), 3.75 (t, 2H, $J = 4.8$ Hz), 4.08 (dd, 2H, $J = 4.0$, 6.4 Hz), 6.60 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 11.4, 15.3, 20.2, 27.2, 28.3, 31.6, 37.4, 40.9, 46.7, 59.6, 67.2, 68.8, 71.8, 112.6, 123.1, 128.1, 134.3, 136.0, 154.7, 175.2.

10{*4,G′*}. Yield: 82.1 mg (93%); $C_{26}H_{36}N_2O_4$. LC/MS: *m/z* 441 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$): δ 1.15 (d, 3H, $J = 6.5$ Hz), 1.23 (dq, 1H, $J = 4.0$, 11.5 Hz), 1.78–1.88 (m, 1H), 1.98 (s, 3H), 2.08 (s, 3H), 1.93–2.16 (m, 2H), 2.41 (m, 1H), 2.49 (m, 4H), 2.58 (m, 1H), 2.71 (Ψt, 3H, $J = 5.5$ Hz), 3.63 (m, 4H), 3.98 (m, 2H), 4.38 (t, 2H, $J = 5.0$ Hz), 5.69 (br s, 1H), 6.14 (s, 1H), 6.23 (s, 1H), 6.48 (s, 1H), 7.16 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 11.3, 15.4, 20.2, 27.1, 27.8, 31.7, 36.7, 37.7, 47.6, 54.5, 58.3, 67.2, 67.4, 107.8, 110.8, 112.1, 122.7, 127.9, 134.3, 136.0, 142.5, 151.8, 154.5, 175.9.

10{*4,K′*}. Yield: 83.3 mg (88%); $C_{28}H_{37}FN_2O_3$. LC/MS: *m/z* 469 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$): δ 1.10 (m, 1H), 1.26 (d, 3H, $J = 6.5$ Hz), 1.34 (dq, 1H, $J = 4.5$, 11.5 Hz), 1.56–1.74 (m, 2H), 1.88–2.00 (m, 2H), 2.02–2.08 (m, 1H), 2.07 (s, 3H), 2.09–2.18 (m, 1H), 2.18 (s, 3H), 2.23 (dd, 1H, $J = 11.0$, 16.0 Hz), 2.52 (m, 1H), 2.60 (m, 3H), 2.69 (m, 1H), 2.71 (Ψt, 2H, $J = 5.5$ Hz), 3.73 (m, 3H), 4.07 (m, 2H), 4.44 (d, 2H, $J = 6.0$ Hz), 5.77 (br s, 1H), 6.59 (s, 1H), 7.02 (Ψt, 2H, $J = 8.5$ Hz), 7.26 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 11.3, 15.5, 20.2, 27.1, 27.9, 31.7, 37.7, 43.1, 47.7, 54.5, 58.3, 67.2, 67.4, 105.6, 112.1, 115.9, 116.0, 122.7, 127.9, 129.9, 135.9, 154.6, 159.6, 176.0.

10{*5,E′*}. Yield: 32.1 mg (39%); $C_{22}H_{28}N_2O_4S$. LC/MS: *m/z* 417 $(M+1)^+$, 439 $(M+23)^+$. ^{1}H-NMR ($CDCl_3$): δ 1.36 (d, 3H, $J = 6.5$ Hz), 1.44 (dq, 1H, $J = 5.0$, 11.5 Hz), 1.94 (m, 1H), 2.08–2.20 (m, 1H), 2.10 (s, 3H), 2.17 (s, 3H), 2.34–2.42 (m, 1H), 2.38 (s, 3H), 2.46–2.61 (m, 2H), 2.66 (m, 1H), 2.86 (dd, 1H, $J = 4.0$, 16.5 Hz), 3.80 (s, 3H), 4.61 (s, 2H), 6.47 (s, 1H), 6.90 (s, 1H), 12.35 (br s, 1H). ^{13}C-NMR ($CDCl_3$): δ 11.1, 11.6, 15.1, 19.8, 26.3 (2×), 27.3, 31.1, 37.5, 46.1, 52.1 (2×), 66.3, 111.7, 122.9, 128.4, 132.1, 134.2, 135.5, 153.5, 169.9, 174.2.

11{*5,E′*}. Yield: 26.1 mg (32%); $C_{21}H_{26}N_2O_4S$. LC/MS: *m/z* 403 $(M+1)^+$, 425 $(M+23)^+$. ^{1}H-NMR (d_6-DMSO): δ 1.18 (d, 3H, $J = 8.5$ Hz), 1.30 (dq, 1H, $J = 6.5$, 15.5 Hz), 1.74 (m, 1H), 1.80–1.90 (m, 1H), 2.04 (s, 3H), 2.10 (s, 3H), 2.20 (dd, 1H, $J = 14.0$, 20.5 Hz), 2.33 (s, 3H), 2.34–2.44 (m, 1H), 2.53–2.68 (m, 2H), 2.76 (dd, 1H, $J = 5.0$, 20.5 Hz), 4.59 (s, 2H), 6.54 (s, 1H), 7.13 (s, 1H), 11.97 (br s, 1H). ^{13}C-NMR ($CDCl_3$): δ 11.4, 14.7, 20.1, 21.1, 27.1, 27.6, 31.3, 37.5, 46.9, 66.2, 112.1, 123.0, 127.6, 128.8, 132.5, 134.4, 135.9, 153.5, 160.3, 174.4, 177.4.

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Supporting Information Available. Detailed analytical data for the precursors **5**{*1–26*} and **9**{*1–5*} as well as selected library members, crude yields of final library members, NMR spectra of the above mentioned compounds, and information regarding the assay system. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) For the preparation of **9**{*3*} and **9**{*4*}, 1 equiv of NaI was required to obtain complete conversion.

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