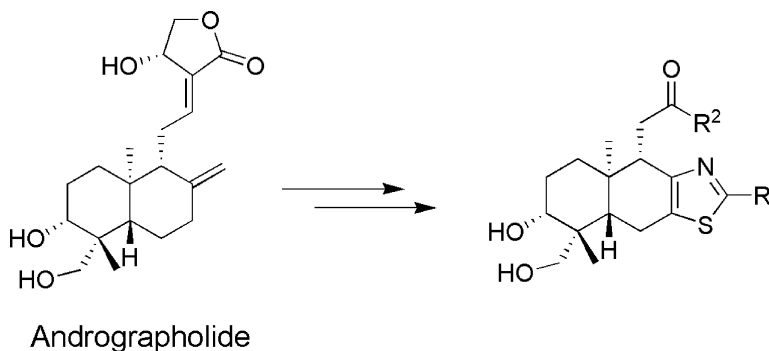


Natural Products in Combinatorial Chemistry: An Andrographolide-Based Library

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Natural Products in Combinatorial Chemistry: An Andrographolide-Based Library

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The generation of a natural-product-based library starting from andrographolide is described. Utilizing andrographolide itself in parallel solution-phase synthesis leads to a 360-membered library. The initial transformation of the starting material via ozonolysis is followed by the conversion into a suitable template by introduction of a thiazole moiety. Subsequent decoration at two points of diversity yields the desired natural product derivatives. The selection of actually synthesized compounds is based on a virtually generated library and the assessment of its members with respect to physicochemical parameters, thus ensuring pharmacological relevance of the compounds.

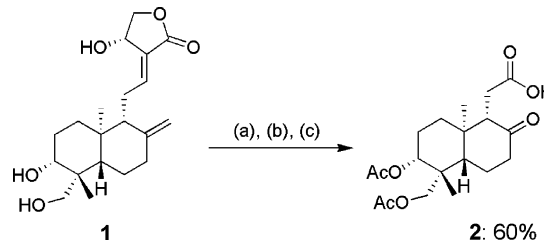
Introduction

Natural products (NPs) represent an enormous source of structural diversity, although, due to their complexity and the experiences in the early years of HTS when mainly substance mixtures were used for screening, NPs were increasingly neglected in the lead-finding process by the pharmaceutical industry. However, in recent years, different approaches led to the conclusion that NP-derived compounds can be extremely valuable for the lead-finding process. A statistical analysis of the available drug index showed that for the period between 1981 and 2002, up to 38% of all new chemical entities could be traced back to NPs.¹ In addition, it was shown that NPs can be regarded as biologically validated structural entities, since they were synthesized by proteins and, therefore, are highly likely to bind to similar folds again.² It was also pointed out that compounds originating from combinatorial chemistry cover a well-defined area in diversity space as compared to NPs, which cover a much larger space. Drugs and natural products have approximately the same coverage of this space.³ With these arguments in mind, we have set up a program for using NPs as scaffolds for the generation of pharmacologically relevant libraries.

In recent years, several attempts were made to exploit the potential of NPs as valuable starting points for the pharmacological discovery process. The field is covered by several excellent review articles.⁴ The two main approaches which are normally used are combinatorial total synthesis and design and synthesis of compounds based on structural motifs. Classes of NPs covered by these explorations are carbohydrates, steroids, fatty acid derivatives, polyketides, peptides, terpenoids, flavonoids, or alkaloids. Our approach consists of the use of NPs themselves as starting points and their transformation into different templates, which are finally converted into libraries by concluding decoration steps.

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Scheme 1. Conversion of Andrographolide **1** to Key Intermediate **2** via Ozonolysis

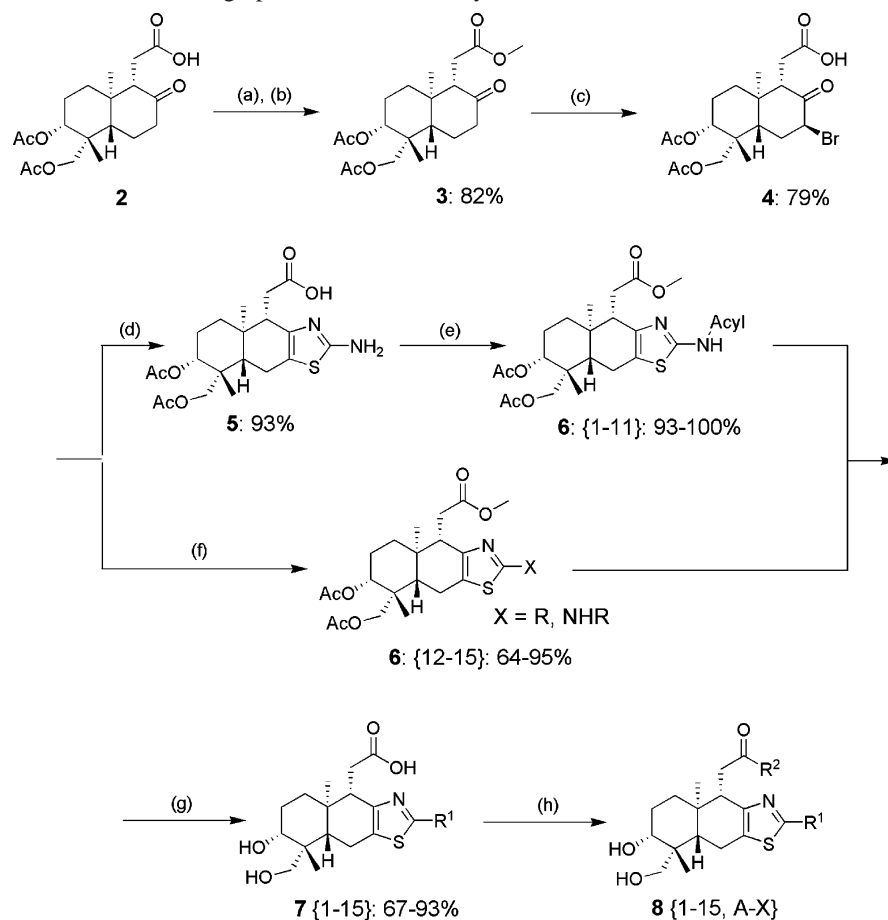


Reagents and conditions: (a) acetic anhydride, pyridine, rt; (b) O₃, CH₂Cl₂/pyridine, -78 °C; (c) H₂O₂.

Andrographolide is a diterpene lactone that can be isolated from *Andrographis paniculata*, a plant that is used in traditional Chinese and Indian medicine. More recent studies revealed a range of biological activities, such as antiinflammatory antibiotic,⁵ antiplatelet aggregation,⁶ or antiviral.⁷ Andrographolide was chosen as a template for the generation of a combinatorial library due to a favorable arrangement of functional groups and its abundant availability. Since the aim was the generation of a pharmacological relevant library, it was of vital importance to obtain a library design that fulfills basic needs, such as oral bioavailability (Lipinski parameters,⁸ TPSA, and number of rotatable bonds⁹) and the absence of unwanted fragments.¹⁰ Furthermore, the synthesis should be short and amendable to parallel synthesis in solution phase.

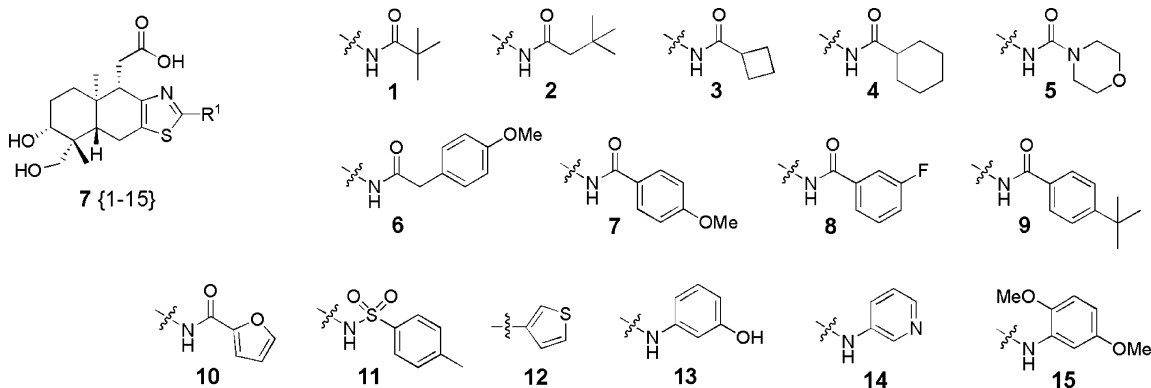
Results and Discussion

Scaffold Synthesis. Andrographolide **1** was subjected to acetylation and degradation via ozonolysis, followed by an oxidative workup (Scheme 1). The three-step procedure was accomplished according to literature procedures and carried out in batches of 50 g, generating **2** in overall yields of ~57%.¹¹ It should be mentioned that the degradation product **2** can be used as the starting point for the generation of several different libraries. Further synthetic work is in progress.

Scheme 2. Synthetic Route for the Andrographolide-Based Library^a

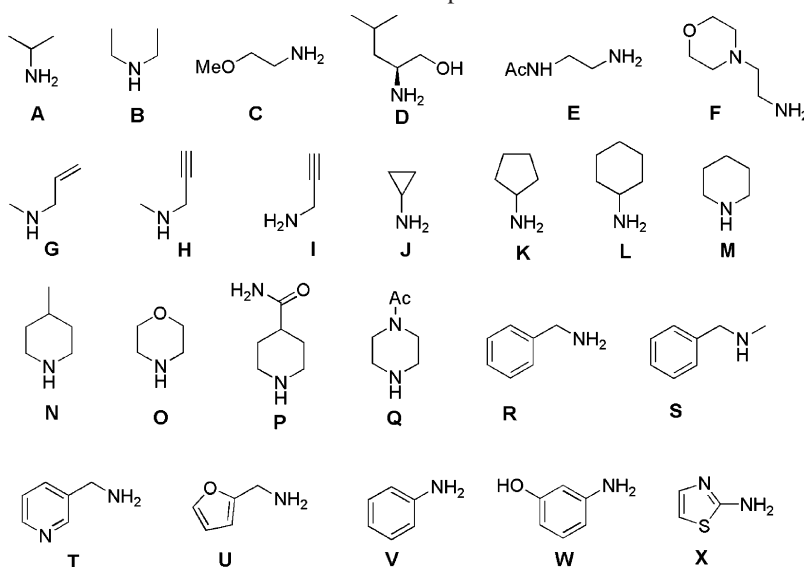
^a Reagents and conditions: (a) dimethoxypropane, HCl; (b) acetic anhydride, pyridine; (c) PTAB, THF; (d) thiourea, pyridine, 80 °C; (e) acid chloride or sulfonyl chloride, pyridine; (f) substituted thiourea or thioamide, pyridine or butanol, reflux; (g) NaOH, THF/MeOH; (h) amine, Mukaiyama's reagent, DMAP, Hünig's base, CH₂Cl₂.

Chart 1. Array of Compounds Generated in the First Diversification Step



Template Synthesis. The degradation product 2 was converted into the methylester 3 via a two-step procedure. First, the methylester moiety was introduced by reaction with dimethoxypropane/HCl,¹² followed by reacetylation using acetic anhydride. Attempts to achieve the same result using diazomethane or SOCl₂/MeOH followed by reacetylation resulted in far lower yields. Bromination in the α -position of the ketone was achieved using PTAB in THF,¹³ yielding mainly the β -isomer of 4, which could easily be isolated and purified in good yields via crystallization. The bromide was then subjected to thiazole formation using thiourea, several substituted thioureas, and some thioamides.¹⁴ Thiourea was

found to be the best thiazole-forming reagent, since the reaction proceeded easily with pyridine as solvent at 80 °C within 2 h, yielding the resulting aminothiazole 5 in sufficient purity to be used in the following steps. Subsequent acylation of the amino functionality worked well for acyl chlorides. It turned out that in each case, aqueous workup gave the desired products 6{1-10} in sufficient purity for the following steps. Acylation using sulfonyl chlorides tended to result in mixtures of mono- and bisulfonylated products. Even when only 1 equiv of the sulfonylating agent was used, the presence of the bisacylated product was detected along with mono-acylated and unreacted starting material. Separation using

Chart 2. Set of Amines Selected for the Second Diversification Step**Table 1.** Purity (%) of Final Library Members Detected by LC at 215 nm

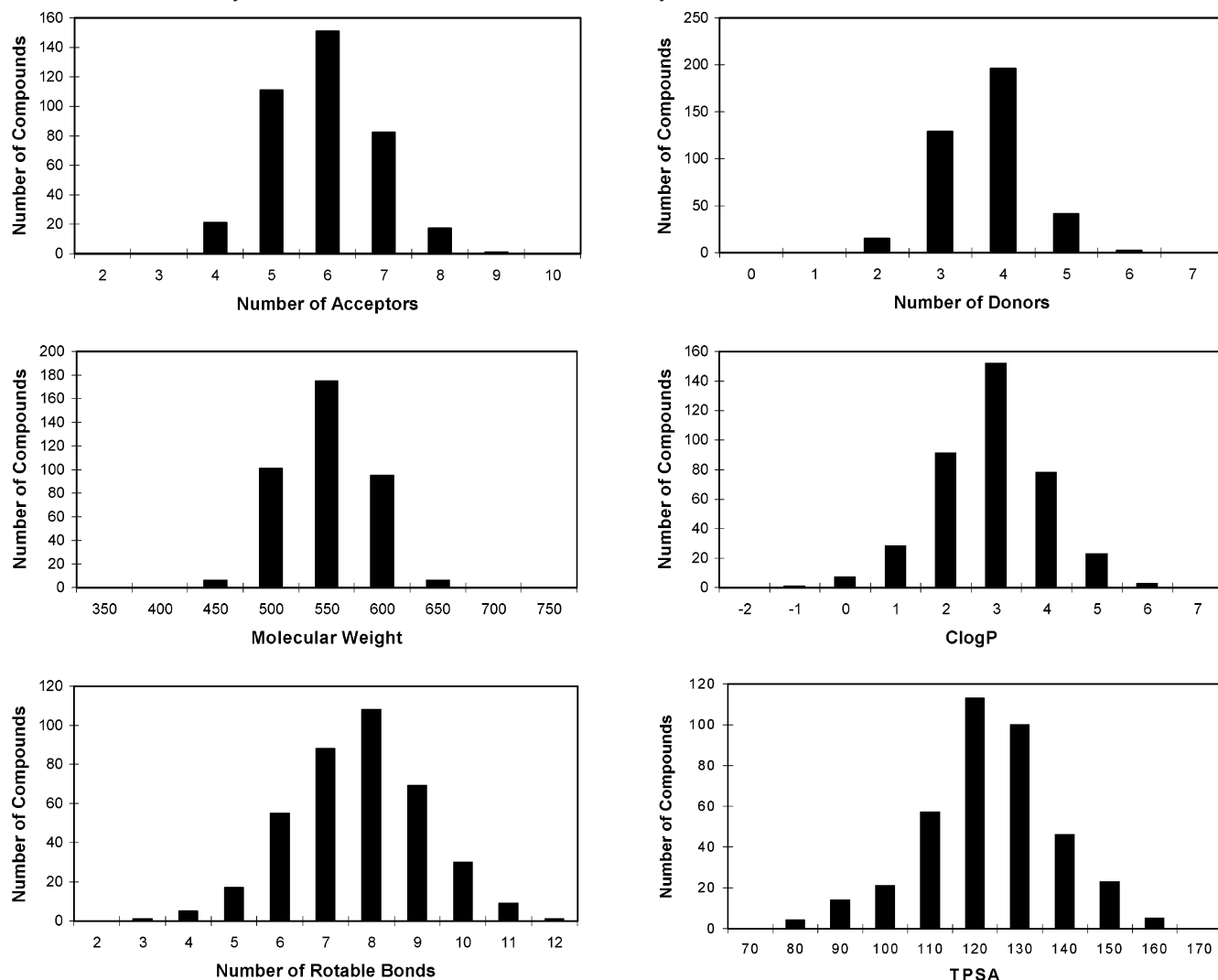
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
A	90.8	80.3	92.8	98.7	94.7	<i>a</i>	91.5	80.8	95.2	93.9	<i>a</i>	100	75.9	90	100
B	50.5	97.8	90.5	<i>a</i>	90.9	<i>a</i>	88.9	82.9	77.3	97.6	100	100	37.4	77.5	100
C	92.3	100	92.5	98.5	98.2	<i>a</i>	89.1	79.8	74	96.5	100	87	89	97.9	100
D	93.1	90.7	<i>a</i>	<i>a</i>	<i>a</i>	<i>a</i>	88.5	83.1	<i>a</i>	93.6	<i>a</i>	<i>a</i>	86.2	73.8	<i>a</i>
E	<i>a</i>	100	96.7	<i>a</i>	70	100	100	100	100	60.7	40.9	71.4	75	71.8	100
F	100	100	100	100	54.1	52.3	100	100	100	100	55.2	56.6	68.9	97.2	100
G	91.4	75.8	90.1	95.5	85.1	63.9	86.6	85.2	86.6	97.3	100	96.7	73.3	84.3	100
H	89.3	97.2	92.2	<i>a</i>	79.9	86.3	87.7	81.6	85.2	96.7	100	97.1	76.1	96.4	100
I	89.7	97	<i>a</i>	100	88.8	<i>a</i>	82.5	80.7	88	94	100	100	66.8	93.1	<i>a</i>
J	91.5	97.5	93.6	98.8	97.2	93.5	95.8	81.3	75.3	96	100	100	80.7	90.7	100
K	90.9	97.8	94.5	95.9	91.8	58	88.3	76.3	75.5	97.9	100	100	93	97.6	100
L	92.5	95.7	93.9	<i>a</i>	<i>a</i>	<i>a</i>	<i>a</i>	85.1	84.8	100	100	<i>a</i>	91.9	66	100
M	89.9	91.8	92.5	94.8	<i>a</i>	<i>a</i>	90.9	78.9	92.2	94.8	100	<i>a</i>	<i>a</i>	70.5	<i>a</i>
N	93.6	96.3	91	<i>a</i>	85.2	40.3	96.4	92.9	82.2	98.9	38.9	97.4	<i>a</i>	67.6	<i>a</i>
O	99.5	98.5	86.6	98.2	97.8	<i>a</i>	90	84.3	85.2	96.8	97.3	100	88	95.4	<i>a</i>
P	<i>a</i>	82.3	<i>a</i>	100	<i>a</i>	92.8	91	<i>a</i>	32	92.3	<i>a</i>	<i>a</i>	76.6	79.9	<i>a</i>
Q	96.7	87	98	99.3	89.7	90.5	85.8	97	<i>a</i>	<i>a</i>	98.1	100	89.9	99.8	<i>a</i>
R	97.3	100	96.4	95.2	93.9	64.2	91.6	91.9	82.2	95.2	59.5	59.5	<i>a</i>	76.4	<i>a</i>
S	95.6	92.1	96.1	85.2	85.2	81.6	92.1	<i>a</i>	<i>a</i>	97.5	<i>a</i>	<i>a</i>	69.5	62.4	100
T	94.5	100	95.4	97.9	56	83.4	100	100	73.5	100	34.3	100	100	<i>a</i>	<i>a</i>
U	90.3	100	90.7	<i>a</i>	89.2	69	90.4	89	90.9	94.5	100	98.7	89	89.6	100
V	96.6	95	94.6	<i>a</i>	<i>a</i>	43.9	79	85.9	83.1	97.4	<i>a</i>	98.3	100	67	50.7
W	89.6	86.5	79.4	74.6	<i>a</i>	69.5	73.1	48	38.5	73.2	<i>a</i>	98.7	67.4	76.9	100
X	91.6	87.4	93.5	86.2	<i>a</i>	<i>a</i>	59.4	84.8	94.1	92.8	<i>a</i>	100	78.7	<i>a</i>	<i>a</i>

^a No product was obtained.

liquid chromatography turned out to be tedious; we therefore decided to use the mixtures for the subsequent reaction and performed the purification on a later stage. The introduction of a urea moiety using isocyanates as acylating agents led to low yields (below 40%) and was consequently not pursued in greater detail. Thiazole formation using substituted thioureas was somehow slower as compared to thiourea itself, but still gave **6**{12–15} in good to acceptable yields after refluxing for 2–4 h in pyridine. In each case, the product quality was sufficient to be directly used in the following reaction steps. The reaction of **4** with thioamides proved to be difficult, because the ring formation turned out to be very slow. This resulted in longer reaction times and increased decomposition of the starting material. Therefore, these products had to be purified by liquid chromatography. In some cases (i.e., thionicotinamide), the use of pyridine as a solvent

did not lead to the formation of the desired product in acceptable yield. Here, the use of butanol as solvent was superior.

The next step of the reaction sequence (**6**{1–15} to **7**{1–15}) consisted of the saponification of the methylester moiety and the acetate groups using 5 N NaOH. Under these conditions, the mixtures derived from the sulfonylation of the aminothiazole **5** were converted to the monosulfonylamides as single products. Since the total conversion from **6**{1–15} to **7**{1–15} consisted of three or four reactions (saponification of two acetyl groups, one methylester, and in some cases, one sulfonyl residue) in one step, monitoring the reaction by TLC turned out to be difficult. Additional reaction control using LC/MS was necessary. The reaction workup consisted of the precipitation of the products by addition of aqueous HCl to yield **7**{1–15} in good yields and excellent purity.

Chart 3. Calculated Physicochemical Parameters of the Final Library Members

Library Synthesis. The final step in the library synthesis consisted of the amidation of the free carboxylic acid. Initial experiments were performed using EDCI as coupling reagent. Under these conditions, the coupling was surprisingly difficult, since it was necessary to use both coupling reagent and amine in large excess (5 equiv EDCI, 10 equiv amine) to ensure complete conversion of the starting material. In some cases, the formation of the N-acylated urea was detected. In addition to this, EDCI failed completely in the coupling of some acids (i.e. **7{1}** and **7{3}**) which prompted us to try 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) as an alternative coupling agent. In this case, the reaction required equally high amounts of coupling reagent and amine, although the reaction proceeded smoothly for all starting materials at room temperature, without the formation of any side products. A preactivation period of 30 min prior to the addition of amine turned out to be crucial for the success of the reaction. After the reaction, the majority of basic reagents were removed by the use of solid supported *p*TosOH, followed by addition of water, which led to product precipitation in about 3/4 of all investigated cases. When no or unsatisfactory precipitation could be achieved, normal extractive workup was performed.

Compound Selection and Final Library Synthesis. One of the main objectives for the production of this library was the compliance to physicochemical parameters related to bioavailability (acc, don, MW, clogP,⁸ nroth, and TPSA⁹). Virtual generation of a 2400-member library (40 times 60), subsequent calculation of the physicochemical values, and assessment of these results with respect to the above-mentioned parameters was used to find the optimal decoration residues. Of particular interest in this respect was the molecular weight, since of the assortment of virtual generated compounds showed that obeying this criterion (MW ≤ 500 Da) would lead to a severe restriction with respect to the decoration residues. We therefore decided to soften this criterion and to shift the acceptable molecular weight to a value of 600 Da.

Assessment of the feasibility study results led us to the selection of residues as shown in Chart 1. For the first point of diversity, 11 out of 15 compounds resulted from the acylation of aminothiazole **5** due to the ease of introduction of highly diverse substituents as well as easy workup and purification methods. The use of substituted thioureas and thioamides led to the formation of the remaining compounds. Due to the use of standard amidation chemistry for the second point of diversity, virtually no restriction existed concerning

the residues, which led to the selection of amines in Chart 2 with, in our view, a reasonable degree of diversity.

After synthesis, the purity of each library member was determined by LC at 215 nm; the results are shown in Table 1. The crude yields of the final library compounds were in general <100%. Higher yields (and lower purity) of more polar compounds are a consequence of the workup procedure. Since precipitation (normally leading to very pure substances) is, in most cases, applicable to the less polar part of substances, polar compounds were isolated by extraction and are often associated with lower purity.¹⁵ Compounds with a purity below 85% (UV 215 nm) or a crude yield higher than 100% were purified using RP-HPLC.

One key feature for the usefulness of a library is the compliance to guidelines concerning physicochemical parameters, such as the number of acceptors, donors, or rotatable bonds; molecular weight; C logP; and TPSA.^{8,9} To check this, we calculated these values for the synthesized compounds. As shown in Chart 3, the library gives good to reasonable results in all categories according to commonly accepted rules.^{8,9}

Conclusion

A short synthesis sequence was developed for the synthesis of a pharmacologically relevant library based on the diterpene lactone andrographolide. The first steps of the 6- or 7-step sequence starting from **2** consist of reactions that can easily be done on a large scale. Purification efforts are incorporated at a minimum level by implementing a late-stage diversification design. The analysis of physicochemical parameters demonstrates the pharmacological relevance of the described library. Due to the highly functionalized key intermediate **2**, the development and synthesis of further libraries based on andrographolide are currently under investigation.

Experimental Section

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). ¹H NMR and ¹³C NMR were recorded using DMSO-*d*₆ (unless otherwise stated) at 500 and 125 MHz, respectively, on a Bruker Avance 500 spectrometer. Proton and carbon chemical shifts are reported in parts per million using DMSO as an internal standard. All coupling constants are given in Hertz. LC/MS spectra were obtained with a PE SCIEX AP 150 instrument equipped with a UV (215 nm) and an ELS detector. A linear gradient was used starting with 5 mM ammonium formate buffer containing 0.1% formic acid, ending with MeOH/ACN/ammonium formate buffer containing 0.1% formic acid (0.5:0.5:1, v/v/v) at a flow rate of 0.1 mL/min. Most physicochemical parameters (number of acceptors, donors, and rotatable bonds; MW; C logP) were calculated with ChemOffice for Excel from CambridgeSoft Corporation. TPSA was calculated using MOE (Chemical Computing Group, Montreal, QB, Canada). Library members are coded by the acid (**7**{*I*–*I5*}) and the amine (*A*–*X*). Detailed experimental data for the procedures given below are given in the Supporting Information.

2-((1*S*,4*aS*,5*R*,6*R*,8*aR*)-6-Acetoxy-5-(acetoxymethyl)-5,8*a*-dimethyl-2-oxo-decahydronaphthalen-1-yl)acetic Acid Methyl ester (3**).** A 50-g (13.57 mmol) portion of ketoacid **2** was suspended in 1.7 L of dimethoxypropane, and methanol was added until the solution was clear. A 168-mL portion of concentrated hydrochloric acid was added, and the solution was stirred at room temperature for 12 h. The dark brown solution was concentrated under reduced pressure and coevaporated twice with toluene.

The remaining black oil was dissolved in 1.5 L of a pyridine/acetic anhydride mixture (2:1, v/v) and stirred for 12 h at room temperature. The solvent was evaporated, and the residue was coevaporated twice with toluene, then redissolved in ethyl acetate. The solution was washed with 1 M hydrochloric acid, water, and brine and dried with Na₂SO₄. The solvent was evaporated, and the black oily residue was purified using a short silica column (hexane/ethyl acetate 1:1). Yield: 42.6 g (82%) of **3** as a colorless oil.

2-((1*S*,3*S*,4*aS*,5*R*,6*R*,8*aR*)-6-Acetoxy-5-(acetoxymethyl)-3-bromo-5,8*a*-dimethyl-2-oxo-decahydronaphthalen-1-yl)acetic Acid Methyl ester (4**).** A 15-g (39.22 mmol) portion of the methyl ester **3** was dissolved in 400 mL of THF. After the solution was cooled to –5 °C, a solution of 17.7 g (47.1 mmol, 1.2 equiv) of PTAB in 100 mL of THF was added over a period of 10 min. The mixture was stirred at 0 °C for 12 h, then filtered. Saturated NaHCO₃ solution (100 mL) was added to the filtrate until the pH was 8, then 250 mL of a 1 M Na₂S₂O₃ solution was added, and the solution was extracted three times with CHCl₃. The combined organic phases were concentrated, and the residue was recrystallized from diethyl ether. Yield: 15.02 g (79%) of **4** as white crystals.

2-((4*S*,4*aR*,7*R*,8*R*,8*aS*)-7-Acetoxy-8-(acetoxymethyl)-2-amino-4*a*,8-dimethyl-4,4*a*,5,6,7,8,8*a*,9-octahydronaphtho-[2,3-*d*]thiazol-4-yl)acetic Acid Methyl Ester (5**).** A 12.01-g (26.03 mmol) portion of bromide **4** and 2.97 g (39.05 mmol, 1.5 equiv) of thiourea were dissolved in 65 mL of pyridine, and the solution was heated to 80 °C for 2 h. The solvent was evaporated, the residue was dissolved in CHCl₃, and unreacted thiourea was filtered off. The solution was washed with water and brine, followed by drying with Na₂SO₄ and evaporation of the solvent. The product was used for the following steps without further purification. Yield: 10.6 g (92.8%) of **5** as a slightly yellow amorphous solid.

6{*I*–*II*}. Aminothiazole **4** (2.5 g, 5.7 mmol) was dissolved in 30 mL of CH₂Cl₂. The acylation reagent was added (8.55 mmol, 1.5 equiv), followed by 5 mL of pyridine. Depending on the acylation reagent, the reaction took between 2 and 12 h to go to completion (monitored by TLC). The solvent was evaporated, and the residue was dissolved in ethyl acetate. The organic phase was washed with water and brine and dried over Na₂SO₄. Evaporation of the solvent yields a material that was used in the following steps without further purification.

6{*I2*–*I5*}. A 3-g (6.7 mmol) portion of the bromide **4** and 8.05 mmol (1.2 equiv) of the substituted thiourea or thioamide were dissolved in 30 mL of pyridine (in the case of **6**{*I4*}, *n*-BuOH), and the solution was heated to reflux for 2–4 h. The solvent was evaporated, the residue was

dissolved in CHCl_3 , and unreacted thiourea was filtered off. The solution was washed with water and brine, followed by the evaporation of the solvent. In most cases, the compounds were of sufficient quality to be used in the next step without further purification.

7{1–15}. The residue was dissolved in 30 mL of THF, and 10.2 mL of a 5 N NaOH solution was added. In some cases, a phase separation occurred, which made it necessary to add some more methanol. The solution was stirred overnight and acidified to pH 3, after which the organic solvents were evaporated. The precipitate was filtered off, washed with water, and dried in air.

8{1–15}. A solution of the acid **7{1–15}** in methylene chloride was treated with 3 equiv of Mukaiyama's reagent, and the pH of the solution was adjusted to 10–11 using diisopropylethylamine. After 30 min of stirring at room temperature, 10 equiv of the amine was added, and the stirring was continued overnight. A 200-mg portion of polymer-bound *p*-TosOH was added, and the mixture was placed on a shaker for 30 min. The resin was filtered off, and the solvent was evaporated. The residue was dissolved in 1–2 mL of MeOH, and water was added until the precipitation was complete (normally 1.5 mL). The precipitate was filtered off, washed with water, and dried in air.

If no or incomplete precipitation was obtained, methanol was evaporated, and the remaining aqueous phase was extracted three times with ethyl acetate. The collected organic phases were dried over Na_2SO_4 , and the solvent was evaporated.

8{1, O}. 11.25 (s, 1H), 5.09 (d, $J = 4.4$ Hz, 1H), 4.37 (m, 1H), 3.90 (dd, $J = 11.1$ Hz, $J = 7.9$ Hz, 1H), 3.70–3.42 (m, 8H), 3.32–3.08 (m, 2H), 2.87 (dd, $J = 4.5$ Hz, 17.1 Hz, 1H), 3.8–3.65 (m, 3H), 1.75–1.67 (m, 5H), 1.20 (s, 9H), 1.13 (s, 3H), 0.76 (s, 3H); LC/MS: m/z 494 (M + H)⁺.

8{3, V}. 11.6 (s, 1H), 9.96 (s, 1H), 7.62 (d, $J = 7.5$ Hz, 2H), 7.28 (t, $J = 7.7$ Hz, 2H), 7.00 (t, $J = 7.7$ Hz, 1H), 5.1 (d, $J = 4.9$ Hz, 1H), 4.37 (m, 1H), 3.98 (s, 1H), 3.91 (d, $J = 8.0$ Hz, 1H), 3.54 (m, 1H), 3.35 (m, 2H), 3.02 (s, 1H), 2.84–2.65 (m, 4H), 2.20–2.00 (m, 4H), 1.97–1.83 (m, 1H), 1.82–1.76 (m, 3H), 1.70–1.50 (m, 4H), 1.25 (t, $J = 6.1$ Hz, 3H), 1.13 (s, 3H), 0.77 (s, 3H); LC/MS: m/z 498 (M + H)⁺.

8{5, B}. 10.47 (s, br, 1H), 5.11 (s, 1H), 4.38 (m, 2H), 3.90 (d, $J = 9.7$ Hz, 1H), 3.6–3.44 (m, 9H), 3.3 (m, 1H), 3.0–2.6 (m, 3H), 1.75–1.45 (m, 4H), 1.36–1.08 (m, 6H), 1.02 (t, $J = 7.0$ Hz, 3H), 0.77 (s, 3H); LC/MS: m/z 509 (M + H)⁺.

8{5, I}. 10.47 (s, br, 1H), 8.30 (s, br, 1H), 5.09 (d, $J = 5.0$ Hz, 1H), 4.36 (m, 1H), 4.00–3.76 (m, 3H), 3.63–3.4 (m, 10H), 3.33–3.05 (m, 4H), 2.93–2.56 (m, 5H), 2.40–2.10 (m, 3H), 1.77–1.43 (m, 5H), 1.28–1.12 (m, 3H), 1.11 (s, 3H), 0.73 (s, 3H); LC/MS: m/z 491 (M + H)⁺.

8{5, H}. 10.45 (s, br, 1H), 5.09 (d, $J = 4.5$ Hz, 1H), 4.4–4.05 (m, 3H), 3.6–3.38 (m, 9H), 3.28–3.15 (m, 3H), 3.05 (s, 2H), 2.87 (s, 1H), 2.78–2.58 (m, 2H), 1.75–1.55 (m, 5H), 1.23–1.15 (m, 1H), 1.12 (s, 3H), 0.76 (s, 3H); LC/MS: m/z 505 (M + H)⁺.

8{6, S}. 11.86 (d, br, $J = 11.5$ Hz, 1H), 7.3 (m, 8H), 6.90 (t, $J = 7.1$ Hz, 1H), 5.11 (m, 1H), 4.95–4.25 (m, 3H), 3.95–3.45 (m, 12H), 3.34–2.60 (m, 13H), 2.4–2.1 (m, 6H), 1.7–1.45 (m, 5H), 1.13 (s, 3H), 0.76 and 0.62 (2s, 3H); LC/MS: m/z 592 (M + H)⁺.

8{7, H}. 12.1 (d, $J = 6.6$ Hz, 1H), 8.04 (d, $J = 8.5$ Hz, 1H), 7.05 (d, $J = 9.2$ Hz, 1H), 5.12 (d, $J = 5.1$ Hz, 1H), 4.45–3.94 (m, 7H), 3.84 (s, 3H), 3.6–3.55 (m, 1H), 3.33–2.60 (m, 9H), 1.76–1.55 (m, 4H), 1.30–1.20 (m, 2H), 1.15 (s, 3H), 0.79 (s, 3H); LC/MS: m/z 526 (M + H)⁺.

8{9, V}. 12.26 (s, 1H), 10.01 (s, 1H), 7.98 (d, $J = 8.3$ Hz, 2H), 7.63 (d, $J = 7.3$ Hz, 2H), 7.52 (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 7.5$ Hz, 2H), 7.02 (t, $J = 6.9$ Hz, 1H), 5.12 (d, $J = 5.1$ Hz, 1H), 4.40 (s, 1H), 3.93 (d, $J = 8.5$ Hz, 1H), 3.57 (m, 1H), 3.2–2.55 (m, 5H), 1.8–1.55 (m, 5H), 1.30 (s, 9H), 1.24 (t, $J = 6.0$ Hz, 3H), 1.15 (s, 3H), 0.82 (s, 3H); LC/MS: m/z 576 (M + H)⁺.

8{9, T}. 12.0 (s, br, 1H), 8.85 (s, 1H), 8.5 (m, 1H), 8.41 (d, $J = 4.7$ Hz, 1H), 8.02 (d, $J = 7.9$ Hz, 2H), 7.71 (d, $J = 7.7$ Hz, 1H), 7.58 (d, $J = 8.6$ Hz, 2H), 7.37 (m, 1H), 5.11 (d, $J = 5.2$ Hz, 1H), 4.5–4.43 (dd, $J = 6.0$ Hz, $J = 15.8$ Hz, 1H), 4.42 (m, 1H), 4.28 (dd, $J = 5.1$ Hz, $J = 13.8$ Hz, 1H), 3.9 (d, $J = 13.0$ Hz, 1H), 3.54 (m, 1H), 3.30–3.23 (m, 1H), 2.97 (m, 1H), 2.85–2.66 (m, 3H), 2.42–2.35 (m, 2H), 1.85–1.47 (m, 4H), 1.32 (s, 9H), 1.31–1.13 (m, 3H), 1.13 (s, 3H), 0.76 (s, 3H); LC/MS: m/z 591 (M + H)⁺.

8{13, F}. 9.72 (s, 1H), 9.24 (s, br, 1H), 7.82 (m, 1H), 7.02 (m, 1H), 6.98 (t, $J = 8.0$ Hz, 1H), 6.90 (m, 1H), 6.28 (d, $J = 7.0$ Hz, 1H), 5.12 (m, 1H), 4.36 (s, br, 1H), 3.91 (d, $J = 10.6$ Hz, 1H), 3.60–3.44 (m, 7H), 3.33–3.21 (m, 1H), 3.18 (s, 1H), 3.08 (m, 1H), 2.86 (s, br, 1H), 2.74–2.55 (m, 4H), 2.42 (m, 1H), 2.38–2.27 (m, 6H), 2.25–2.20 (m, 2H), 1.76–1.55 (m, 5H), 1.34–1.19 (m, 2H), 1.11 (s, 3H), 0.75 (s, 3H); LC/MS: m/z 545 (M + H)⁺.

8{13, W}. 9.85 (s, 1H), 9.70 (s, 1H), 9.20 (m, br, 2H), 7.32 (m, 2H), 7.03 (m, 3H), 6.76 (m, 1H), 6.51 (s, 1H), 6.42 (d, $J = 7.6$ Hz, 1H), 6.32–6.14 (m, 2H), 6.05 (d, $J = 9.5$ Hz, 1H), 5.99 (m, 1H), 5.92 (d, $J = 7.1$ Hz, 1H), 5.14 (m, 1H), 4.88 (s, 1H), 4.38 (s, br, 1H), 3.93 (d, $J = 10.6$ Hz, 1H), 3.53 (m, 2H), 3.16–2.95 (m, 5H), 2.8–2.58 (m, 5H), 2.25–2.15 (m, 1H), 2.10 (s, 1H), 2.05 (s, 1H), 1.88–1.80 (m, 1H), 1.76–1.50 (m, 5H), 1.35–1.2 (m, 2H), 1.14 (s, 3H), 1.1–0.92 (m, 3H), 0.79 (s, 3H); LC/MS: m/z 524 (M + H)⁺.

8{15, A}. 9.17 (s, 1H), 7.92 (d, $J = 2.9$ Hz, 1H), 7.67 (d, $J = 7.5$ Hz, 1H), 6.86 (d, $J = 9.1$ Hz, 1H), 6.40 (dd, $J = 3.1$ Hz, $J = 8.7$ Hz, 1H), 5.15 (d, $J = 4.6$ Hz, 1H), 4.36 (d, $J = 6.5$ Hz, 1H), 3.94–3.80 (m, 2H), 3.77 (s, 3H), 3.65 (s, 3H), 3.64–3.48 (m, 2H), 3.28–3.14 (m, 2H), 2.88 (s, br, 1H), 2.75–2.60 (m, 3H), 2.25–2.13 (m, 2H), 1.75–1.5 (m, 5H), 1.3–1.18 (m, 2H), 1.12 (s, 3H), 1.00 (d, $J = 6.5$ Hz, 1H), 0.95 (d, $J = 6.6$ Hz, 1H), 0.76 (s, 3H); LC/MS: m/z 518 (M + H)⁺.

8{15, C}. 9.17 (s, 1H), 7.92 (m, 2H), 6.87 (d, $J = 8.5$ Hz, 1H), 6.41 (dd, $J = 2.4$ Hz, $J = 8.4$ Hz, 1H), 5.12 (d, $J = 5.0$ Hz, 1H), 4.38 (m, 1H), 3.94 (d, 11.1 Hz, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.53 (m, 1H), 3.33–3.20 (m, 4H), 3.21 (s, 3H), 2.90 (s, br, 1H), 2.77–2.65 (m, 3H), 2.38–2.27 (m,

2H), 1.76–1.55 (m, 5H), 1.33–1.20 (m, 1H), 1.13 (s, 3H), 0.77 (s, 3H); LC/MS: m/z 534 (M + H)⁺.

8{15, E}. 9.87 (s, 1H), 7.90 (m, 1H), 7.54 (d, $J = 8.2$ Hz, 1H), 7.22 (d, $J = 7.5$ Hz, 1H), 6.85 (t, $J = 7.7$ Hz, 1H), 5.13 (m, 1H), 4.36 (d, br, 1H), 3.92 (d, $J = 11.0$ Hz, 1H), 3.55–3.50 (m, 1H), 3.33–3.07 (m, 2H), 3.06–2.90 (m, 1H), 2.76–2.58 (m, 1H), 2.43–2.20 (m, 1H), 2.08 (s, 3H), 1.8 (s, 3H), 1.73–1.57 (m, 3H), 1.13 (s, 3H), 0.74 (s, 3H); LC/MS: m/z 561 (M + H)⁺.

8{15, K}. 9.16 (s, 1H), 7.91 (d, $J = 2.9$ Hz, 1H), 7.77 (d, $J = 7.1$ Hz, 1H), 6.87 (d, $J = 8.9$ Hz, 1H), 6.42 (dd, $J = 2.9$ Hz, $J = 8.8$ Hz, 1H), 5.1 (d, $J = 4.6$ Hz, 1H), 4.35 (d, $J = 9.6$ Hz, 1H), 4.06–3.88 (m, 3H), 3.77 (s, 3H), 3.66 (s, 3H), 3.6–3.55 (m, 3H), 3.3–3.15 (m, 3H), 2.91 (s, 1H), 2.75–2.60 (m, 3H), 2.4–2.0 (m, 6H), 1.8–1.4 (m, 12H), 1.35–1.25 (m, 2H), 1.120 (s, 3H), 0.77 (s, 3H); LC/MS: m/z 544 (M + H)⁺.

8{15, G}. 9.132 (s, 1H), 7.86 (s, 1H), 6.85 (dd, $J = 2.4$ Hz, $J = 9.5$ Hz, 1H), 6.40 (d, $J = 8.5$ Hz, 1H), 5.84–5.67 (m, 1H), 5.14–5.05 (m, 3H), 4.37 (m, 1H), 4.33–4.05 (dd, 1H), 3.95–3.89 (m, 2H), 3.77 (s, 3H), 3.66 (s, 3H), 3.6–3.5 (m, 1H), 3.3–3.22 (m, 1H), 3.29 (s, br, 1H), 2.96 and 2.86 (2s, 3H), 2.77–2.58 (m, 3H), 2.38–2.25 (m, 1H), 1.75–1.55 (m, 4H), 1.26–1.18 (m, 1H), 1.13 (s, 3H), 0.74 and 0.74 (2s, 3H); LC/MS: m/z 530 (M + H)⁺.

8{15, H}. 9.16 (s, 1H), 7.83 (m, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 6.41 (m, 1H), 5.12 (d, $J = 4.4$ Hz, 1H), 4.63 and 4.47 (2d, $J = 19.2$ Hz, 1H), 4.37 (m, 1H), 3.93 (dd, $J = 10.4$ Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 3.53 (m, 1H), 3.28–3.15 (m, 2H), 3.06 (s, 3H), 2.8–2.55 (m, 3H), 2.4–2.3 (m, 1H), 1.75–1.55 (m, 5H), 2.25–1.13 (m, 1H), 1.13 (s, 3H), 0.77 (s, 3H); LC/MS: m/z 528 (M + H)⁺.

8{15, I}. 9.17 (s, 1H), 8.24 (t, $J = 5.1$ Hz, 1H), 7.90 (d, $J = 2.8$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 6.40 (dd, $J = 2.5$ Hz, $J = 8.4$ Hz, 1H), 5.12 (d, $J = 4.6$ Hz, 1H), 4.35 (s, br, 1H), 4.05 (dd, $J = 6.0$ Hz, $J = 19.7$ Hz, 1H), 3.92 (d, $J = 10.9$ Hz, 1H), 3.76 (s, 3H), 3.75–3.67 (m, 2H), 3.66 (s, 3H), 3.50 (m, 1H), 3.33–3.12 (m, 3H), 3.06 (s, 1H), 2.91 (s, br, 1H), 2.72–2.56 (m, 3H), 2.37–2.24 (m, 2H), 1.76 (m, 5H), 1.30–1.21 (m, 1H), 1.12 (s, 3H), 0.75 (s, 3H); LC/MS: m/z 514 (M + H)⁺.

8{15, J}. 9.17 (s, 1H), 7.91 (m, 2H), 6.87 (d, $J = 9.0$ Hz, 1H), 6.41 (dd, $J = 2.9$ Hz, $J = 8.9$ Hz, 1H), 5.12 (d, $J = 4.6$ Hz, 1H), 4.35 (s, br, 1H), 3.92 (dd, $J = 2.5$ Hz, $J = 10.6$ Hz, 1H), 3.77 (s, 3H), 3.76–3.67 (m, 1H), 3.66 (s, 3H), 3.55–3.48 (m, 1H), 3.33–3.15 (m, 2H), 2.89 (s, br, 1H), 2.75–2.58 (m, 3H), 2.23–2.17 (m, 1H), 1.73–1.52 (m, 5H), 1.29–1.17 (m, 1H), 1.12 (s, 3H), 0.74 (s, 3H), 0.6–0.52 (m, 2H), 0.38–0.29 (m, 2H); LC/MS: m/z 516 (M + H)⁺.

8{15, O}. 9.14 (s, 1H), 7.84 (d, $J = 2.9$ Hz, 1H), 6.85 (d, $J = 8.8$ Hz, 1H), 6.40 (dd, $J = 3.2$ Hz, $J = 8.6$ Hz, 1H), 5.12 (d, $J = 4.6$ Hz, 1H), 4.37 (s, br, 1H), 3.92 (d, $J = 11.2$ Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 3.66–3.43 (m, 9H), 3.09 (s, br, 1H), 2.76–2.59 (m, 3H), 2.38–2.29 (m, 1H), 1.80–

1.54 (m, 5H), 1.26–1.14 (m, 1H), 1.13 (s, 3H), 0.77 (s, 3H); LC/MS: m/z 546 (M + H)⁺.

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Supporting Information Available. The additional information includes detailed experimental data of intermediates **2–5**, **6{1–15}** and **7{1–15}**, data concerning the reaction conditions required for the final synthetic step for each library member and crude yields for the final library members.

References and Notes

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