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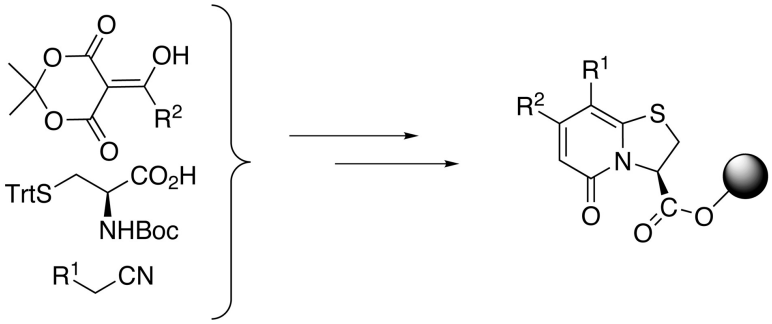

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Design and Parallel Solid-Phase Synthesis of Ring-Fused 2-Pyridinones That Target Pilus Biogenesis in Pathogenic Bacteria

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A new method for the solid-phase synthesis of enantiomerically enriched highly substituted ring-fused 2-pyridinones **13** has been developed. The synthesis mediates introduction of substituents at two positions in the 2-pyridinone ring in a diverse manner and is suitable for parallel synthesis. ^{19}F NMR spectroscopy was used as a tool to monitor each of the five steps in the reaction sequence. The optimized conditions thus obtained were then used to prepare a library of 20 2-pyridinones with high yields. The library members were chosen from a statistical multivariate design to ensure diversity and reliable data for structure−activity relationships. Screening of the library against the bacterial periplasmic chaperone PapD was performed using surface plasmon resonance. Three new 2-pyridinones with a higher affinity for the chaperone PapD than the previous best **13**{*10,1*} were found, and important structural features could be deduced.

Introduction

Heterocycles having a 2-pyridinone framework is an extensively studied class of compounds, owing partly to their diverse biological activities. These range from antibacterial[1−3] and antifungal[4] agents to free radical scavengers.[5,6] Ring-fused 2-pyridinones have also attracted attention as lead compounds for the preparation of selective anticancer drugs,[7,8] antiviral agents,[9] angiotensin-converting enzyme (ACE) inhibitors,[10−12] as well as inhibitors of Aβ-peptide aggregation,[13,14] which is believed to play an important role in amyloid formation in Alzheimer's disease. In addition, dihydro- and tetrahydro derivatives of 2-pyridinones have been applied as scaffolds for the construction of constrained amino acids.[15−19] With all these diverse properties in mind, medicinal chemists often incorporate these motifs in the design of novel biologically active molecules.

Ever since the first synthesis of 2-pyridinones, via a ferricyanide-mediated oxidation of pyridinium salts, was reported,[20] many different methods for constructing these heterocycles in solution have appeared in the literature. Some of the more recent reports include intramolecular Dieckmann-like condensations,[21] Michael additions,[22−24] as well as cycloaddition[25−28] and cyclization procedures.[29,30] However, practical procedures for the synthesis of 2-pyridinones on solid support appeared as late as 1999. Linn et al. synthesized 1,3,5-trisubstituted 2-pyridinones in six steps where the 2-pyridinone unit was preprepared in solution in three steps and then introduced at a late stage of the sequence.[31] Groshe et al. reacted immobilized diaryl-substituted enones with 1-(methoxycarbonylmethyl)pyridinium bromide, according to the Krönkhe procedure,[32] to give 4,6-disubstituted 2-pyridinones.[33] The latter procedure has combinatorial potential, although somewhat limited since so far only aryl substituents have been introduced successfully.

Previously, we have reported a new ketene−imine cycloaddition method for the synthesis of substituted, enantiomerically enriched ring-fused 2-pyridinones **4** in solution (Scheme 1).[34] The key intermediates in this reaction are substituted Δ^2-thiazolines **2** and Meldrum's acid derivatives **3**. Δ^2-Thiazolines are easily synthesized from imino ethers **1** and (*R*)-cysteine methyl ester hydrochloride, and Meldrum's acid derivatives are prepared from Meldrum's acid and activated carboxylic acids.[35] Allowing these building blocks to react under mild acidic conditions gave a small set of substituted 2-pyridinones in good yields (63−86%) and with limited racemization (75−97% ee).

This first set of 2-pyridinones had been selected from structure-based design as highly interesting structures targeting periplasmic chaperones in uropathogenic *Escherichia coli*.[36] Chaperones are key proteins essential for the assembly of long hairlike appendages, i.e., pili or fimbriae, with which the bacteria attach to the host via specific receptors present on the cell surface of host tissue.[37,38] Without these extracellular organelles, the bacteria cannot cause infection, and compounds disrupting this process (pilicides) would thus constitute novel antibacterial agents. There are several advantages to using periplasmic chaperones for the development of pilicides. First, they constitute a novel target that is required for pathogenesis.[39] Second, they are highly conserved among many different types of pathogenic bacteria, which cause diseases such as urinary tract infection, diarrhea, pneumonia, and meningitis.[40,41] Third, good structural knowl-

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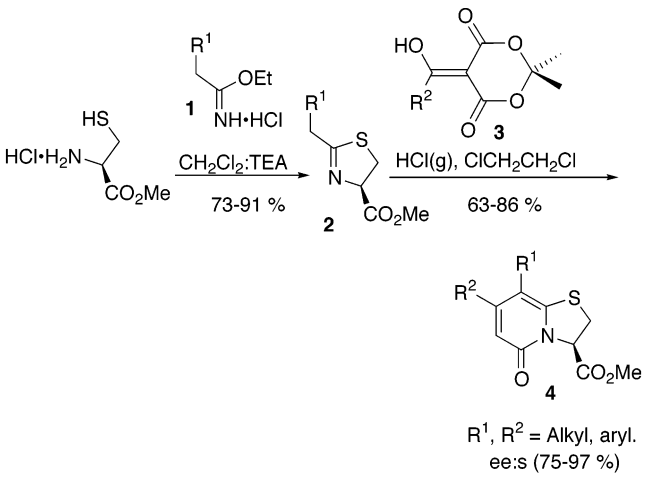
Scheme 1. Solution-Phase Synthesis of Optically Active Ring-Fused 2-Pyridinones **4**[34]



edge of the chaperone-subunit complexes has been obtained by crystallography[42−44] and NMR spectroscopy.[45,46]

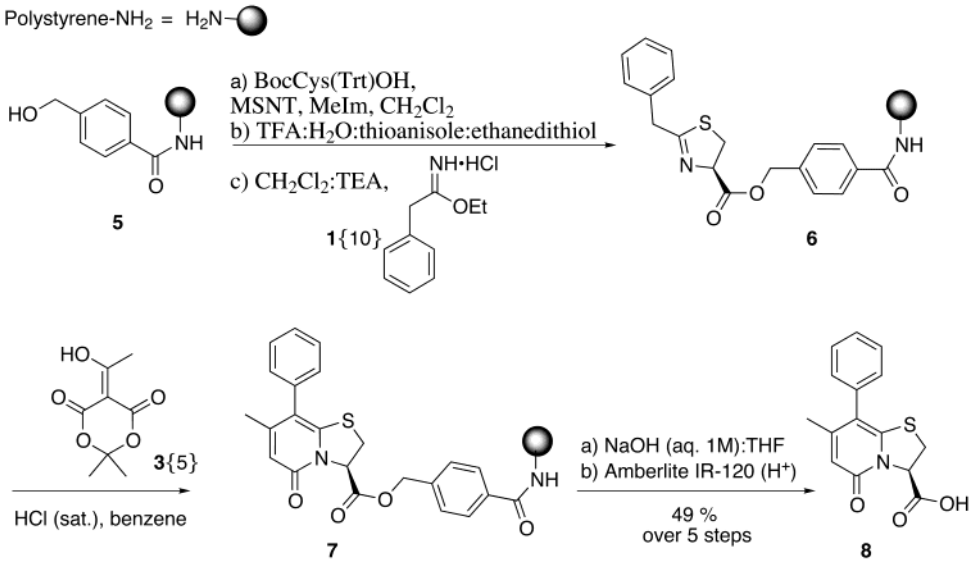
In the initial study we got very promising results showing that the molecular modeling and the affinity predictions using VALIDATE[47] gave a ranking of the pilicides, which also proved to be reliable in the following biological evaluation.[36] With the promising results of ring-fused 2-pyridinones being chaperone inhibitors, we wanted to get more structure−activity data, which could be obtained from a designed library. Also bearing in mind the general interest in these heterocycles and the fact that no synthesis of ring-fused 2-pyridinones on solid phase had previously been reported, we decided to develop a parallel solid-phase synthesis of ring-fused 2-pyridinones based upon our previous synthesis in solution. This article describes the design, solid-phase synthesis, and surface plasmon resonance screening against binding to the periplasmic chaperone PapD (found in uropathogenic *Escherichia Coli*, which is the main cause of urinary tract infections).

Results and Discussion

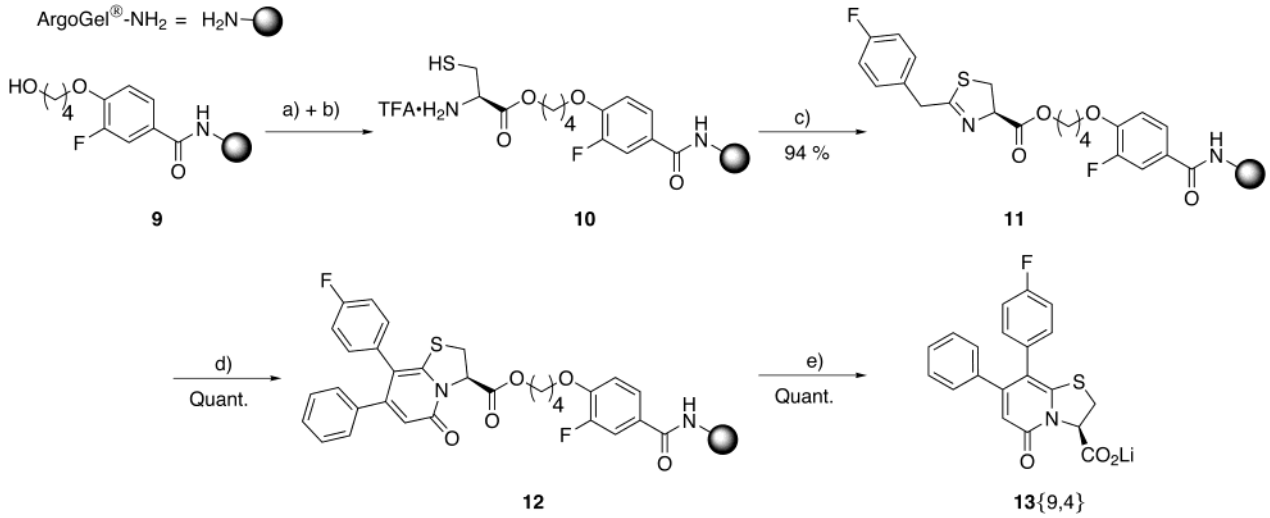
Strategy and Optimization of the Solid-Phase Synthesis. In the previously reported cycloaddition method in solution (Scheme 1),[34] all the steps except the final saponification of the methyl ester were neutral or acidic. Therefore, we decided to use a resin and a linker compatible with acidic conditions, which could be cleaved in the last saponification step. Our approach was to attach an *N*-Boc and *S*-trityl protected cysteine to a polystyrene resin equipped with a HMBA-AM linker **5**, followed by a simultaneous acidic removal of the protecting groups (Scheme 2). Then the key intermediate Δ^2-thiazoline **6** could be constructed by the addition of the imino ether **1**{*10*} using the same conditions as in solution. Thereafter, the solid-phase bound ring-fused 2-pyridinone **7** was synthesized by adding Meldrum's acid derivative **3**{*5*} followed by an HCl presaturated solvent.

With this strategy, crude 2-pyridinone **8** was prepared in a 49% overall yield. Moreover, the purity was higher than 80% according to HPLC. Although encouraging, this was still a 2-pyridinone substituted with relatively unhindered side chains and the conditions to cleave the product from the resin were relatively harsh (1 M aqueous NaOH), constituting a potential risk for racemization. To be able to optimize the synthesis, we desired a solid support with better swelling properties than polystyrene. This was mainly based on the ability to monitor each step in the sequence by gel-phase NMR spectroscopy, where polystyrene solid supports are known to give broad and poorly resolved NMR spectra.[48,49] Therefore, ArgoGel equipped with the fluorine-containing linker **9** was chosen (Scheme 3). This combination fulfilled the monitoring task, since **9** had previously been used successfully to monitor solid-phase reactions with ^{19}F NMR spectroscopy.[50−52] In addition, cleavage of product from this linker could also be performed under somewhat milder conditions (0.1 M aqueous LiOH).[52] The 2-pyridinone **13**{*9,4*} (Scheme 3) was then chosen for the optimization because its substituents were sterically demanding and unflexible. Thus, conditions used for the synthesis of **13**{*9,4*} would also allow preparation of less hindered 2-pyridinones in the library. Moreover, the fluorine substituent in **13**{*9,4*} was introduced already with the imino ether **1**{*9*}, allowing also the optimization of the intermediate Δ^2-thiazoline **11**. Hence, Boc-Cys(Trt)-COOH was coupled to the resin containing the

Scheme 2. Initial Solid-Phase Synthesis



Scheme 3. Optimization of the Solid-Phase Synthesis[a]



[a] (a) BocCys(Trt)OH (4 equiv), MSNT (4 equiv), methylimidazole (2 equiv), CH_2Cl_2 (2 mL), 13 h, the coupling was repeated once for 3 h; (b) TFA/H_2O/thioanisole/ethanedithiol 104:6:6:3 (3 mL), 3.5 h; (c) imino ether **1**{*9*} (3 equiv), TEA, CH_2Cl_2, 0 °C → room temp, 10 h, the coupling was repeated once; (d) Meldrum's acid derivative **3**{*4*} (4 equiv), half HCl(g) saturated CH_2ClCH_2Cl (3 mL), 4 → 64 °C, 10 h, the coupling was repeated once for 3.5 h; (e) 1 M aqueous LiOH/THF 3:1, 3 h. Yields are based on integrals from gel-phase ^{19}F NMR spectra recorded in $CDCl_3$.

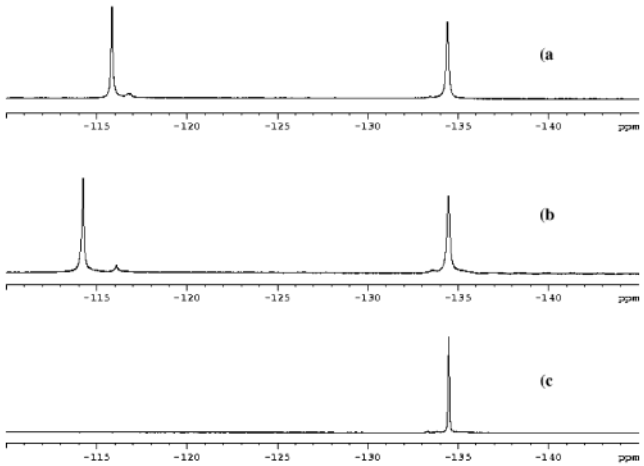


Figure 1. (a) ^{19}F NMR spectra of resin-bound Δ^2-thiazoline **11**. (b) 2-Pyridinone **12** and (c) linker after cleavage.

fluorinated linker with MSNT and methylimidazole.[53] Acidic removal of the protecting groups using TFA/H_2O (52:3) containing ethanedithiol and thioanisole gave **10**. By treatment of the unprotected amino acid with an excess of imino ether **1**{*9*} (3 equiv) in CH_2Cl_2/TEA (99.2:0.8), Δ^2-thiazoline **11** was formed.

The ^{19}F NMR spectrum of this reaction step displayed a new distinct fluorine resonance at δ −115.8 ppm (Figure 1). By comparison of the integral of the new peak with the integral of the peak at −134.4 ppm, which corresponds to the signal for the fluorine atom in the linker, the yield of **11** could be estimated to be 75%. Repeating the coupling under identical conditions raised the yield to 94% (Figure 1a). In solution, 1,2-dichloroethane was shown to be superior to benzene as a solvent in the 2-pyridinone-forming step.[34] Unfortunately, heating the reaction mixture to 64 °C for 10 h and using a solution of 1,2-dichloroethane presaturated with HCl(g) and 6 equiv of Meldrum's acid derivative **3**{*4*} were unsatisfactory in the solid-phase synthesis. ^{19}F NMR spectroscopy showed splitting of the signal from the linker, and a prolonged reaction time was needed in the following cleavage of the product, indicating also that the solid support was affected under these conditions. To overcome this problem, a half-saturated HCl(g) solution of 1,2-dichloroethane and 4 equiv of Meldrum's acid derivative **3**{*4*} was used instead. This time, a distinct fluorine peak appeared at δ −114.3 ppm corresponding to 2-pyridinone **12** and the linker gave a uniform fluorine signal at δ −133.4 ppm (Figure 1b). Repeating the coupling for 3.5 h at 64 °C furnished 2-pyridinone **12** in quantitative yield according to ^{19}F NMR spectroscopy. ^{19}F NMR spectroscopy could also be used to monitor the remaining cleavage step, and complete cleavage was achieved by treatment with LiOH (aqueous, 0.1 M) for 3 h (Figure 1c). This gave the 2-pyridinone **13**{*9,4*}, as its Li salt, in a total isolated yield of 93% over five steps, which agrees very well with the yield that had been estimated from the ^{19}F NMR spectrum (94%).

Library Design and Parallel Synthesis. Our library goals were twofold. We wanted to investigate the scope and limitation of the new synthetic method and get more structure−activity data for 2-pyridinones as chaperone inhibitors. A set of imino ethers **1**{*1*−*12*} (Figure 2), which introduce diversity at position R^1, and Meldrum's acid derivatives **3**{*1*−*7*} (Figure 3) generating diversity at position R^2 were synthesized. These building blocks are stable for months in the freezer, which is convenient for synthesis of future libraries.

We aimed at synthesizing a library using a semiautomatic Quest 210 parallel synthesizer equipped with 20 reaction vessels. Twenty 2-pyridinones would thus cover approximately one-fourth of the library, and by use of a statistical multivariate design to choose which 2-pyridinones to synthesize, reliable data for structure−activity relationships would be obtained.[54] Hence, 28 descriptors were calculated for the 84 different 2-pyridinones that could be generated from the set of building blocks, and then a principal component analysis, PCA, was performed. As can be seen in the PCA-score plot (Figure 4), the 20 chosen 2-pyridinones well cover the chemical space, resulting in a diverse library.

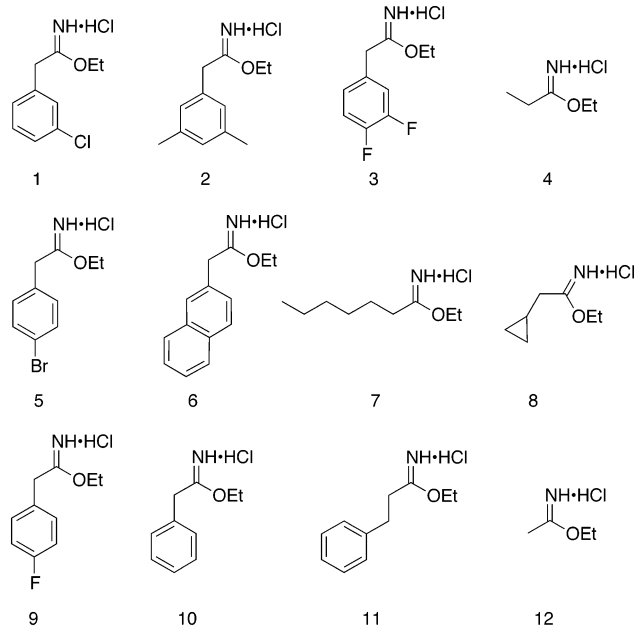


Figure 2. Imino ethers **1**{*1*−*12*} for library synthesis.

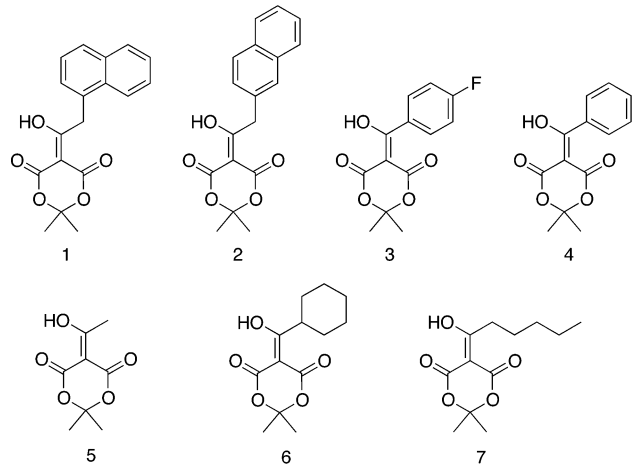


Figure 3. Meldrum's acid derivatives **3**{*1*−*7*} for library synthesis.

With the optimized reaction conditions in hand, a library of the chosen ring-fused 2-pyridinones **13** was synthesized in parallel using a semiautomatic Quest 210 synthesizer. To make the method more attractive, considering both cost and efficiency, commercially available ArgoGel-OH was used directly instead of preparing and attaching the fluorinated linker prior to library synthesis. Although there was no fluorine linker this time, ^{19}F NMR spectroscopy could still be useful for monitoring the progress of the library by using ^{19}F NMR spectroscopy on the substances that contained a fluorine atom. Indeed, ^{19}F NMR spectra of the resin-bound 2-pyridinones showed single fluorine signals, indicating that the synthesis had been successful. This turned out to be representative of the whole library. After cleavage and concentration, the resulting 2-pyridinones were obtained in total yields ranging from 75% to 99% based on the initial loading of the resin (Table 1). The purity was higher than 90% as determined by HPLC, and no further purification was performed. Taking into account that the isolated material may also contain LiOH (maximum 0.6 equiv), the yield may be marginally lower (3−7%). Only two of the 2-pyridinones had yields below 80% (Table 1), and they were either substituted with two sterically demanding R groups **13**{*6,2*} (entry 1) or contained a combination of steric hindrance and flexibility **13**{*7,1*} (entry 2). The majority of the library members were synthesized in more than 90% total yield. Also, the cyclopropyl-substituted 2-pyridinones could withstand the reaction conditions, and they were successfully prepared in 85%, 97%, and 93% yield (entries 10, 13, and 14, respectively) using this method.

In the reaction sequence, several of the steps can potentially cause some epimerization. First, repeated MSNT/methylimidazole mediated coupling of protected cysteine to the solid support is known to lead to as much as 40% of the D-isomer if the amount of methylimidazole reaches 2 equiv.[53] Second, both in the formation of the Δ^2-thiazoline and in the synthesis of the 2-pyridinone in solution, some epimerization had previously been observed.[34] Since we knew that the enantiomeric ratio (er) for the methyl esters of the 2-pyridinones could be established by a chiral-phase HPLC ((S,S) Whelk-O 1 column),[34] we prepared the corresponding methyl esters of four of the 2-pyridinones **13**{*10,1*}, **13**{*8,1*}, **13**{*5,5*}, and **13**{*4,5*} by treating them with TMS-diazomethane.[55] These 2-pyridinones were chosen to represent different substitution patterns, thus giving representative information of the limitations of the method for providing enantiomerically enriched material. Fortunately, although not as good as in the synthesis in solution, the methyl esters of **13**{*10,1*}, **13**{*8,1*}, **13**{*5,5*}, and **13**{*4,5*} showed an er of 8:2, 8:2, 8:2, and 7:3, respectively, which we considered to be high enough to ensure a reliable biological evaluation.

Biological Evaluation. Previously we saw a good correlation between chaperone binding affinity and the ability of pilicides to interfere with the formation of complexes between chaperone and pilus proteins.[36] To investigate the chaperone binding properties of the 2-pyridinone library, we used surface plasmon resonance[56] on a Biacore 3000 instrument, which is well suited to effectively screen a library of this size. Thus, the periplasmic chaperone PapD, isolated from uropathogenic *Escherichia coli*, was immobilized on a dextrane-coated sensor chip. Thereafter, the compounds were injected over the sensor chip in triplicate and in random order and binding was observed in real time. To allow comparison of the binding of the 2-pyridinones to PapD, the response from the Biacore 3000 instrument (determined as response units, RU) was corrected for the differences in molecular weight between the ligands. Normalized responses were then calculated using 2-pyridinone **13**{*10,1*} as reference because this was the most potent pilicide in the initial study.[36] Since the 2-pyridinones in the first study were tested as protonated carboxylic acids and not as their Li salts,[36] we prepared the corresponding carboxylic acids of the whole library as described for 2-pyridinone **8**. The Biacore results of these carboxylic acids (data not shown) were in agreement with the data from the Li carboxylates seen in Table 1, showing that an additional protonation step is unnecessary.

The screening confirmed that large substituents are necessary in both the R^1 and R^2 positions of the 2-pyridinone in order to get good binding to the chaperone (entries 1−7 and 12). This is also in agreement with the calculated PCA where all the best binders end up in the first quadrant (Figure 4).

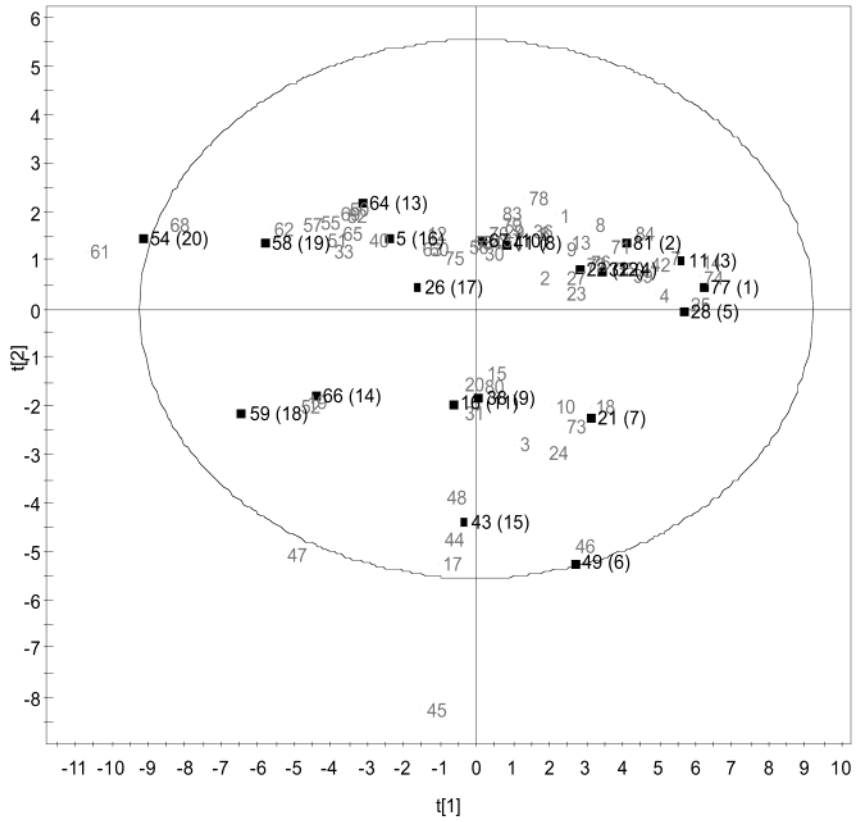
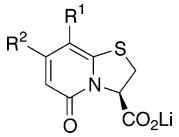


Figure 4. Score scatter plot with the selected 20 2-pyridinones (in black) and the others in gray. Number in parentheses corresponds to the entry number in Table 1. **t**[1] and **t**[2] are the first two score vectors in the principal component analysis describing 78% of the variance.

Table 1. Library Members, Isolated Yields, and Normalized Surface Plasmon Resonance Data



entry	**13**	R^1	R^2	yield[a] (%)	normalized response for PapD[b] (%)
1	{6,2}	1-naphthyl	CH_2−2-naphthyl	78	139
2	{7,1}	*n*-pentyl	CH_2−1-naphthyl	75	75
3	{2,1}	3,5-dimethyl-Ph	CH_2−1-naphthyl	90	127
4	{10,1}	Ph	CH_2−1-naphthyl	97	100
5	{5,2}	4-Br−Ph	CH_2−2-naphthyl	93	127
6	{3,2}	3,4-difluoro-Ph	CH_2−2-naphthyl	91	95
7	{9,2}	4-F−Ph	CH_2−2-naphthyl	98	77
8	{11,6}	CH_2−Ph	cyclohexyl	90	30
9	{11,3}	CH_2−Ph	4-F−Ph	85	23
10	{8,1}	cyclopropyl	CH_2−1-naphthyl	85	51
11	{9,4}	4-F−Ph	Ph	93	23
12	{5,7}	4-Br−Ph	*n*-pentyl	94	72
13	{8,7}	cyclopropyl	*n*-pentyl	97	12
14	{8,3}	cyclopropyl	4-F−Ph	93	11
15	{3,7}	3,4-difluoro-Ph	*n*-pentyl	98	35
16	{1,5}	3-Cl−Ph	Me	89	14
17	{5,5}	4-Br−Ph	Me	87	6
18	{12,3}	H	4-F−Ph	80	9
19	{12,4}	H	Ph	95	5
20	{4,5}	Me	Me	99	5

[a] Yields of the crude products based on initial loading of the resin. [b] Determined by surface plasmon resonance at a fixed pilicide concentration (30 μM) using a Biacore 3000 instrument. The normalized responses were calculated using pilicide **13**{*10,1*} (entry 4) as standard (100% normalized response).

A comparison between a flexible aliphatic *n*-pentyl R^2 substituent (entry 2) and rigid aromatic R^2 substituents (entries 3−7) indicates that the latter substitutents are preferred. One can also observe that 2-pyridinones having a flexible aliphatic substituent can still result in a good binder (entries 2 and 12). To summarize, one could conclude that

three 2-pyridinones in the designed library (entries 1, 3, and 5) had higher affinity for PapD than the previously best pilicide **13**{*10,1*} (entry 4). In addition, four more had affinity almost similar to the affinitiy of **13**{*10,1*} (entries 2, 6, 7, and 12). The most potent 2-pyridinone was **13**{*6,2*} (entry 1), which had a normalized response almost 40% higher than pilicide **13**{*10,1*} (entry 4).

The specificity of the binding affinity was investigated by injecting a selection of 2-pyridinones over nontarget proteins such as protein A, Streptavidine, and an antimyoglobin monoclonal antibody (data not shown). For 2-pyridinones showing high affinity for PapD, some minor binding to the nontarget proteins could be observed. In addition, reference compounds not expected to bind specifically to chaperones were also injected over PapD and nontarget proteins. These control compounds did not show any affinity for PapD.

Conclusions

A new solid-phase method for the synthesis of ring-fused enantiomerically enriched 2-pyridinones has been developed. The new method proved to be suitable for library synthesis, and a small library, selected with statistical multivariate design, was prepared using a semiautomatic Quest 210 synthesizer. Thus, the 2-pyridinones **13** could be obtained in excellent yields and purities throughout the whole library. Also the optical purity proved to be high enough to ensure reliable biological testing. A screen of the 2-pyridinone library for chaperone binding activity using a surface plasmon resonance technique gave seven new 2-pyridinones with almost equal or better affinity than the previous best. Some important structure−activity data could also be deduced clearly showing that two fairly large substituents have to be present at the 2-pyridinone backbone to get a high chaperone affinity. Therefore, future libraries will be prepared to fine-tune these findings, aiming at improved pilicides as novel antibacterial agents targeting pilus biogenesis.

Experimental Section

General. All reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. 1,2-Dichloroethane and CH_2Cl_2 were distilled from calcium hydride immediately before use. Solid-phase synthesis was performed on ArgoGel-NH_2 resin (151 μm, loading capacity of 0.38 mmol/g), on ArgoGel-OH resin (172 μm, loading capacity of 0.40 mmol/g), or on HMBA-AM resin (loading capacity of 1.16 mmol/g) using a semiautomatic Quest 210 synthesizer, which agitates the resin by moving the magnetic stirring bar vertically in the reactor with an external magnet. The ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DRX-400 for solutions in DMSO-d_6 (residual DMSO-d_5 (δ_H 2.50 ppm) as internal standard) at 298 K, unless otherwise stated. Proton-decoupled gel-phase ^{19}F NMR spectra were recorded with a Bruker DRX-400 spectrometer for resin suspensions in $CDCl_3$ ($CFCl_3$ (δ_F 0.00 ppm) as internal standard) at 298 K. Two peaks appear in the spectra around 0.00 ppm; one resonance originates from $CFCl_3$ inside the polymer, and the other resonance originates from $CFCl_3$ outside the polymer. The peak with the highest shift was used as an internal standard. High-resolution mass spectra were recorded on a VG ZabSpec spectrometer with positive FAB and with glycerol and PEG400 in the matrix. In the matrix, the lithium carboxylates of **13** were converted into their corresponding free carboxylic acids. Analytical HPLC were performed on a Beckman System Gold HPLC, using a Kromasil C-8 column (250 mm × 4.6 mm, 5 μm, 100 Å) with a flow rate of 1.5 mL/min, detection at 214 nm, and the following eluent systems: A, 0.1% CF_3CO_2H in H_2O; B, 0.1% CF_3CO_2H in MeCN. Analysis of the enantiomeric ratio was performed using the HPLC equipped with a (S,S) Whelk-O 1 column from Chrom Tech AB with a flow rate of 1.0 mL/min, detection at 254 nm with hexane/dichloromethane/2-propanol 48:48:4 as the mobile phase for the 2-pyridinones (see Supporting Information for details regarding retention times).

(3*R*)-7-Methyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo-[3,2-*a*]pyridine-3-carboxylic Acid (8). Methylimidazole (2 equiv) was added to a solution of Boc-Cys(Trt)-CO_2H (4 equiv) in CH_2Cl_2 (2 mL). This solution was then transferred to MSNT (4 equiv), and this solution was then added to the resin **5** (1 equiv). After agitation for 13 h, the resin was washed with CH_2Cl_2, DMF, and CH_2Cl_2 (5 × 3 mL each). To the resin was added a solution of TFA/H_2O/thioanisole/ethanedithiol 104:6:6:3 (3 mL), and the mixture was agitated for 3.5 h before being washed with CH_2Cl_2, EtOH, DMF, and CH_2Cl_2 (5 × 3 mL each). The resin was swelled in CH_2Cl_2 (4 mL). Triethylamine (0.5 equiv) was added, and the mixture was agitated for 30 min before being washed out. Then the imino ether **1**{*10*} (1.3 equiv) was added neat and to this mixture were added CH_2Cl_2 (4 mL) and triethylamine (0.25 equiv). After agitation overnight, the resin was washed with CH_2Cl_2 (5 × 3 mL) and the coupling was repeated for 6 h. Neat Meldrum's acid derivative **3**{*5*} (1.5 equiv) was added to resin **6**, and benzene saturated with HCl(g) (4 mL) was added at 4 °C. After agitation for 20 min, the mixture was heated to 60 °C, and the mixture was further agitated overnight. The resin was washed with CH_2Cl_2 (5 × 3 mL), and the coupling was repeated twice. Resin **7** was washed with CH_2Cl_2, DMF, CH_2Cl_2, and THF (5 × 3 mL each) and then swelled in THF (1.0 mL). Thereafter, 1 M aqueous NaOH (3.0 mL, 5.2 equiv) was added and the mixture was agitated for 1 h. The resin was washed with MeOH and CH_2Cl_2 (4 × 3 mL each), and the cleavage procedure was repeated once. To the combined cleavage filtrate was added Amberlite IR-120 (H^+). After the mixture was stirred for 5 min, the Amberlite was removed by filtration and the filtrate was concentrated. The residue was lyophilized from AcOH to give **8** (49%) as a solid. ^{1}H NMR: δ 7.33−7.51 (m, 3H), 7.17−7.32 (b, 2H), 6.11 (s, 1H), 5.49 (d, J = 9.15 Hz, 1H), 3.79 (dd, J = 11.80, 9.15 Hz, 1H), 3.46 (d, J = 11.80 Hz, 1H), 1.90 (s, 3H). HRMS (EI+) calcd for (M) $C_{15}H_{13}NO_3S$: 287.0616. Observed: 287.0615.

General Procedure for the Coupling of the Boc-Cys-(Trt)-CO_2H to the Linker. Methylimidazole (2 equiv) was added to a solution of Boc-Cys(Trt)-CO_2H (4 equiv) in CH_2Cl_2 (2 mL). This solution was then transferred to MSNT (4 equiv), and this solution was then added to the resin (1 equiv). The mixture was agitated for 13 h. The resin was

washed with CH_2Cl_2, DMF, and CH_2Cl_2 (5 × 3 mL each). The coupling was repeated once, but in this case, the mixture was agitated for 3 h. Data for the resin-bound Boc-Cys(Trt)-CO_2H, ^{19}F NMR ($CDCl_3$): δ −134.3 (s, 1F).

General Procedure for the Cleavage of the Protecting Groups. A solution of TFA/H_2O/thioanisole/ethanedithiol 104:6:6:3 (3 mL) was added to the resin, and the mixture was agitated for 3.5 h. The resin was washed with CH_2Cl_2, EtOH, DMF, and CH_2Cl_2 (5 × 3 mL each). Resin **10**, ^{19}F NMR data ($CDCl_3$): δ −75.51 (s, 0.27F), −75.83 (s, 2.76F), −134.47 (s, 1F).

General Procedure for the Synthesis of Resin-Bound Δ^2-Thiazoline. Triethylamine (2.5 mL of a 0.4% solution in CH_2Cl_2) was added to the resin at 4 °C, and the mixture was agitated for 10 min before being filtered. Then the imino ether **1** (3 equiv) was added neat. Triethylamine (2.5 mL of a 0.8% solution in CH_2Cl_2, 1.7 equiv) was added at 4 °C, and after the mixture was agitated overnight, the resin was washed with CH_2Cl_2 (5 × 3 mL) and the coupling was repeated for 8 h. The resin was washed with CH_2Cl_2, EtOH, DMF, and CH_2Cl_2 (5 × 3 mL each). Resin **11**, ^{19}F NMR data ($CDCl_3$): δ −115.84 (s, 0.94F), −134.42 (s, 1F).

General Procedure for the Preparation of the 2-Pyridinone. Neat Meldrum's acid derivative **3** (4 equiv) was added to the resin, and 1,2-dichloroethane half-saturated with HCl(g) (3.5 mL) was added at 4 °C. After agitation for 20 min, the mixture was heated to 64 °C, and the mixture was further agitated for 10 h. The resin was washed with CH_2Cl_2 (5 × 3 mL). The coupling was repeated once, but in this case, the mixture was agitated for 3.5 h. The resin was washed with CH_2Cl_2, EtOH, DMF, CH_2Cl_2, EtOH, AcOH, EtOH, CH_2Cl_2, DMF (5 × 3 mL each), DMF with 5% pyridine (1×), DMF, THF, H_2O, and THF (5 × 3 mL each). Resin **12**, ^{19}F NMR data ($CDCl_3$): δ −114.25 (s, 0.94F), −134.44 (s, 1F).

General Procedure for the Cleavage of the Product from the Linker. The resin was allowed to swell in THF (0.5 mL). Thereafter, 0.1 M aqueous LiOH (1.4 mL, 1.6 equiv) was added, and the mixture was agitated for 3 h. The resin was washed with MeOH and CH_2Cl_2 (4 × 3 mL each), and finally the filtrate was collected and concentrated to give 2-pyridinones **13** as a powder. ^{19}F NMR data on the linker revealed complete cleavage.

Lithium (3*R*)-8-Naphthalen-2-yl-7-naphthalen-2-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*6,2*}). ^1H NMR: δ 7.66−7.97 (m, 7H), 7.65−7.59 (m, 1H), 7.49−7.58 (m, 2H), 7.40−7.47 (m, 2H), 7.32−7.39 (s, 1H), 7.13 (d, J = 8.42 Hz, 1H), 7.08−7.17 (m, 1H), 5.81 (s, 1H), 5.06 (d, J = 8.05 Hz, 1H), 3.70−3.84 (m, 2H), 3.51−3.62 (m, 1H). HRMS (FAB+) calcd for (M + 1) $C_{29}H_{22}NO_3S$: 464.1320. Observed: 464.1341.

Lithium (3*R*)-7-Naphthalen-1-ylmethyl-5-oxo-8-pentyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*7,1*}). ^1H NMR: δ 7.82−8.00 (m, 3H), 7.45−7.55 (m, 3H), 7.27−7.33 (m, 1H), 5.29 (s, 1H), 4.95 (dd, J = 7.80 and 1.74 Hz, 1H), 4.17−4.30 (m, 2H), 3.52−3.63 (m, 2H), 2.28−2.35 (m, 2H), 1.30−1.53 (m, 2H), 1.20−1.27 (m, 4H), 0.78−0.84 (m, 3H). HRMS (FAB+) calcd for (M + 1) $C_{24}H_{26}NO_3S$: 408.1633. Observed: 408.1640.

Lithium (3*R*)-8-(3,5-Dimethylphenyl)-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*2,1*}). ^1H NMR: δ 7.87−7.95 (m, 1H), 7.77−7.85 (m, 1H), 7.64−7.73 (m, 1H), 7.39−7.53 (m, 3H), 7.26−7.30 (m, 1H), 6.92−6.98 (m, 2H), 6.82−6.89 (b, 1H), 5.35 (s, 1H), 5.00 (d, J = 8.32 Hz, 1H), 3.84−4.02 (m, 2H), 3.49−3.54 (m, 1H), 3.42−3.48 (m, 1H), 2.19−2.27 (b, 6H). HRMS (FAB+) calcd for (M + 1) $C_{27}H_{24}NO_3S$: 442.1477. Observed: 442.1520.

Lithium (3*R*)-7-Naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*10,1*}). ^1H NMR: δ 7.87−7.94 (m, 1H), 7.78−7.84 (m, 1H), 7.66−7.73 (m, 1H), 7.24−7.52 (m, 9H), 5.34 (s, 1H), 5.04 (d, J = 8.32 Hz, 1H), 3.86−4.02 (m, 2H), 3.53−3.61 (m, 1H), 3.45−3.52 (m, 1H). HRMS (FAB+) calcd for (M + 1) $C_{25}H_{20}NO_3S$: 414.1164. Observed: 414.1171.

Lithium (3*R*)-8-(4-Bromophenyl)-7-naphthalen-2-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*5,2*}). ^1H NMR: δ 7.81−7.89 (m, 1H), 7.69−7.81 (m, 2H), 7.50−7.61 (b, 2H), 7.41−7.49 (m, 2H), 7.34 (s, 1H), 7.00−7.20 (m, 3H), 5.82 (s, 1H), 5.06 (d, J = 8.05 Hz, 1H), 3.72 (s, 2H), 3.52−3.61 (m, 1H), 3.44−3.50 (m, 1H). HRMS (FAB+) calcd for (M + 1) $C_{25}H_{19}BrNO_3S$: 492.0269. Observed: 492.0179.

Lithium (3*R*)-8-(3,4-Difluorophenyl)-7-naphthalen-2-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*3,2*}). ^1H NMR: δ 7.82−7.87 (m, 1H), 7.72−7.80 (m, 2H), 7.35−7.50 (m, 4H), 6.87−7.29 (m, 3H), 5.83 (s, 1H), 5.05 (d, J = 8.32 Hz, 1H), 3.74 (s, 2H), 3.53−3.60 (m, 1H), 3.45−3.50 (m, 1H). ^{19}F NMR: δ −138.8−(−)138.5 (m, 1F), −140.2−(−)139.9 (m, 1F). HRMS (FAB+) calcd for (M + 1) $C_{25}H_{18}F_2NO_3S$: 450.0975. Observed: 450.1054.

Lithium (3*R*)-8-(4-Fluorophenyl)-7-naphthalen-2-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*9,2*}). ^1H NMR: δ 7.81−7.87 (m, 1H), 7.71−7.79 (m, 1H), 7.41−7.49 (m, 2H), 7.36 (b, 1H), 7.08−7.27 (m, 5H), 5.82 (s, 1H), 5.04 (d, J = 8.23 Hz, 1H), 3.71 (s, 2H), 3.50−3.58 (m, 1H), 3.43−3.49 (m, 1H). ^{19}F NMR: δ −114.7 (s, 1F). HRMS (FAB+) calcd for (M + 1) $C_{25}H_{19}FNO_3S$: 432.1081. Observed: 432.1100.

Lithium (3*R*)-8-Benzyl-7-cyclohexyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*11,6*}). ^1H NMR: δ 7.22−7.29 (m, 2H), 7.13−7.20 (m, 3H), 5.87 (s, 1H), 5.05 (d, J = 7.78 Hz, 1H), 3.58−3.78 (m, 3H), 3.53−3.58 (m, 1H), 2.27−2.39 (m, 1H), 1.51−1.72 (m, 3H), 1.29−1.45 (m, 2H), 1.00−1.27 (m, 5H). HRMS (FAB+) calcd for (M + 1) $C_{21}H_{24}NO_3S$: 370.1477. Observed: 370.1386.

Lithium (3*R*)-8-Benzyl-7-(4-fluorophenyl)-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*11,3*}). ^1H NMR: δ 7.07−7.20 (m, 7H), 6.85−6.90 (m, 2H), 5.85 (s, 1H), 5.10 (d, J = 8.05 Hz, 1H), 3.62−3.70 (m, 1H), 3.55−3.61 (m, 3H). ^{19}F NMR: δ −114.5 (s, 1F). HRMS (FAB+) calcd for (M + 1) $C_{21}H_{17}FNO_3S$: 382.0913. Observed: 382.0978.

Lithium (3*R*)-8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*8,1*}). ^1H NMR: δ 7.93−7.99 (m, 1H), 7.83−7.92 (m, 2H), 7.46−7.56 (m, 3H), 7.36 (d, J = 6.95 Hz, 1H),

5.16 (s, 1H), 4.92−4.97 (m, 1H), 4.45 (d, J = 17.29 Hz, 1H), 4.34 (d, J = 17.29 Hz, 1H), 3.47−3.56 (m, 2H), 1.62−1.69 (m, 1H), 0.78−0.96 (m, 2H), 0.56−0.73 (m, 2H). HRMS (FAB+) calcd for (M + 1) $C_{22}H_{20}NO_3S$: 378.1164. Observed: 378.1163.

Lithium (3*R*)-8-(4-Fluorophenyl)-5-oxo-7-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*9,4*}). ^{1}H NMR: δ 7.18−7.26 (m, 3H), 6.92−7.10 (m, 6H), 6.01 (s, 1H), 5.13 (d, J = 8.32 Hz, 1H), 3.56−3.63 (m, 1H), 3.50−3.55 (m, 1H). ^{19}F NMR: δ −115.3 (s, 1F). HRMS (FAB+) calcd for (M + 1) $C_{20}H_{15}FNO_3S$: 368.0757. Observed: 368.0848.

Lithium (3*R*)-8-(4-Bromophenyl)-5-oxo-7-pentyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*5,7*}). ^{1}H NMR: δ 7.62 (d, J = 8.42 Hz, 2H), 7.00−7.31 (m, 2H), 5.94 (s, 1H), 5.06 (d, J = 8.32 Hz, 1H), 3.52−3.59 (m, 1H), 3.44−3.50 (m, 1H), 2.17 (t, J = 7.87 Hz, 2H), 1.19−1.34 (m, 2H), 1.02−1.16 (m, 4H), 0.74 (t, J = 6.91 Hz, 3H). HRMS (FAB+) calcd for (M + 1) $C_{19}H_{21}BrNO_3S$: 422.0426. Observed: 422.0474.

Lithium (3*R*)-8-Cyclopropyl-5-oxo-7-pentyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*8,7*}). ^{1}H NMR: δ 5.80 (s, 1H), 4.94−5.02 (m, 1H), 3.46−3.53 (m, 2H), 2.52−2.67 (m, 1H), 1.45−1.63 (m, 3H), 1.14−1.40 (m, 5H), 0.73−0.97 (m, 5H), 0.39−0.55 (m, 2H). HRMS (FAB+) calcd for (M + 1) $C_{16}H_{22}NO_3S$: 308.1320. Observed: 308.1396.

Lithium (3*R*)-8-Cyclopropyl-7-(4-fluorophenyl)-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*8,3*}). ^{1}H NMR: δ 7.42−7.51 (m, 2H), 7.20−7.30 (m, 2H), 5.84 (s, 1H), 5.04 (dd, J = 7.96 and 1.56 Hz, 1H), 3.53−3.64 (m, 2H), 1.62−1.70 (m, 1H), 0.44−0.58 (m, 2H), −0.08−0.08 (m, 2H). HRMS (FAB+) calcd for (M + 1) $C_{17}H_{15}FNO_3S$: 332.0757. Observed: 332.0761.

Lithium (3*R*)-8-(3,4-Difluorophenyl)-5-oxo-7-pentyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*3,7*}). ^{1}H NMR: δ 7.45−7.55 (m, 1H), 6.94−7.44 (m, 2H), 5.94 (s, 1H), 5.05 (d, J = 8.23 Hz, 1H), 3.44−3.59 (m, 2H), 2.19 (t, J = 7.78 Hz, 2H), 1.20−1.34 (m, 2H), 1.05−1.16 (m, 4H), 0.75 (t, J = 7.04 Hz, 3H). ^{19}F NMR: δ −138.7−(−)138.4 (m, 1F), −140.1 (d, J = 23 Hz, 1F). HRMS (FAB+) calcd for (M + 1) $C_{19}H_{20}F_2NO_3S$: 380.1132. Observed: 380.1151.

Lithium (3*R*)-8-(3-Chlorophenyl)-7-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*1,5*}). ^{1}H NMR: δ 7.39−7.49 (m, 2H), 7.13−7.34 (m, 2H), 5.98 (s, 1H), 5.06 (d, J = 8.32 Hz, 1H), 3.52−3.59 (m, 1H), 3.45−3.50 (m, 1H), 1.89 (s, 3H). HRMS (FAB+) calcd for (M + 1) $C_{15}H_{13}ClNO_3S$: 322.0305. Observed: 322.0362.

Lithium (3*R*)-8-(4-Bromophenyl)-7-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*5,5*}). ^{1}H NMR: δ 7.56−7.62 (m, 2H), 7.10−7.23 (b, 2H), 5.95 (s, 1H), 5.04 (d, J = 8.23 Hz, 1H), 3.50−3.57 (m, 1H), 3.43−3.48 (m, 1H), 1.86 (s, 3H). HRMS (FAB+) calcd for (M + 1) $C_{15}H_{13}BrNO_3S$: 365.9800. Observed: 365.9780.

Lithium (3*R*)-7-(4-Fluorophenyl)-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*12,3*}). ^{1}H NMR: δ 7.69−7.76 (m, 2H), 7.25−7.32 (m, 2H), 6.45 (d, J = 1.65 Hz, 1H), 6.23 (d, J = 1.65 Hz, 1H), 5.03 (d, J = 8.23 Hz, 1H), 3.64−3.72 (m, 1H), 3.56−3.62 (m, 1H). ^{19}F NMR: δ −113.1 (s, 1F). HRMS (FAB+) calcd for (M + 1) $C_{14}H_{11}FNO_3S$: 292.0444. Observed: 292.0358.

Lithium (3*R*)-5-Oxo-7-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*12,4*}). ^{1}H NMR: δ 7.62−7.68 (m, 2H), 7.40−7.48 (m, 3H), 6.44 (d, J = 1.65 Hz, 1H), 6.22 (d, J = 1.65 Hz, 1H), 5.03 (d, J = 7.96 Hz, 1H), 3.63−3.71 (m, 1H), 3.55−3.61 (m, 1H). HRMS (FAB+) calcd for (M + 1) $C_{14}H_{12}NO_3S$: 274.0538. Observed: 274.0597.

Lithium (3*R*)-7,8-Dimethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate (13{*5,5*}). ^{1}H NMR: δ 5.84 (s, 1H), 4.98 (dd, J = 7.23 and 2.10 Hz, 1H), 3.49−3.57 (m, 2H), 2.04 (s, 3H), 1.87 (s, 3H). HRMS (FAB+) calcd for (M + 1) $C_{10}H_{12}NO_3S$: 226.0538. Observed: 226.0535.

General Procedure for Determination of the Enantiomeric Ratio (er). 13 (15 mmol) was dissolved in MeOH, and Amberlite IR-120 (H^+) was added. After the mixtur was stirred for 5 min, the Amberlite was removed by filtration and the filtrate was concentrated. The residue was dissolved in a solution of MeOH (4 mL) and benzene (14 mL), and TMS-diazomethane in hexane (15 μL 2 M, 30 μmol) was added. After the mixture was stirred for 10 h, an additional amount of TMS-diazomethane in hexane (15 μL, 2 M, 30 μmol) was added and the solution was stirred overnight. AcOH (3 mL) was added, and then the solution was concentrated. The residue was coconcentrated from $CHCl_3$. The remaining residue was dissolved in CH_2Cl_2 (5 mL) and injected into the HPLC.

Methyl (3*R*)-7-Naphthalen-1-ylmethyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate. The enantiomeric ratio was determined to be 8:2, and all spectroscopic data were in agreement with published data.[34]

Methyl (3*R*)-8-Cyclopropyl-7-naphthalen-1-ylmethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate. The enantiomeric ratio was determined to be 8:2. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.84−7.89 (m, 1H), 7.75−7.82 (m, 2H), 7.38−7.49 (m, 3H), 7.26−7.29 (m, 1H), 5.74 (s, 1H), 5.55 (dd, J = 8.51, 2.20 Hz, 1H), 4.49 (d, J = 17.29 Hz, 1H), 4.34 (d, J = 17.29 Hz, 1H), 3.78 (s, 3H), 3.65 (dd, J = 11.71, 8.51 Hz, 1H), 3.49 (dd, J = 11.71, 2.20 Hz, 1H), 1.60−1.69 (m, 1H), 0.86−1.00 (m, 2H), 0.68−0.79 (m, 2H).

Methyl (3*R*)-8-(4-Bromophenyl)-7-methyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate. The enantiomeric ratio was determined to be 8:2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.51 Hz, 2H), 7.12 (d, J = 8.51 Hz, 2H), 6.24 (s, 1H), 5.65 (dd, J = 8.60, 2.38 Hz, 1H), 3.84 (s, 3H), 3.66 (dd, J = 11.80, 8.60 Hz, 1H), 3.47 (dd, J = 11.80, 2.38 Hz, 1H), 1.96 (s, 3H).

Methyl (3*R*)-7,8-Dimethyl-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate. The enantiomeric ratio was determined to be 7:3, and all spectroscopic data were in agreement with published data.[34]

Surface Plasmon Resonance Studies of Binding of Pilicides and Peptides to PapD. The binding of the 2-pyridinones to the chaperone PapD was determined by surface plasmon resonance using a BIACORE 3000 instrument. The chaperone was immobilized on a channel of a

sensor chip CM5 using a standard thiol coupling procedure involving activation of the carboxylic acid moieties of the dextrane surface of the sensor chip with *N*-ethyl-*N*-(dimethylaminopropyl)carbodiimide hydrochloride (EDC) and *N*-hydroxysuccinimide, followed by coupling of cystamine in the presence of dithioerythritol. Native carboxyl groups of PapD were modified with 2-(2-pyridinyldithio)ethylamine hydrochloride (PDEA) in the presence of EDC prior to immobilization. Modified PapD (50 μg/mL in 10 mM NaOAc buffer, pH 5.5) was then reacted with the cystamine-derivatized dextrane surface. This procedure was also employed for coupling of protein A and an antimyoglobin monoclonal antibody, which were used as control nontarget proteins. Immobilization levels of 8000 RU were obtained. Unmodified dextrane in one channel was used as a reference surface.

The 2-pyridinones **13** were diluted to 100 μM in phosphate sample buffer (6.7 mM, pH 6.85), prepared by dissolving $Na_2HPO_4 \cdot 2H_2O$ (9.6 g), KH_2PO_4 (1.7 g), and NaCl (4.1 g) in Millipore H_2O (1000 mL) containing Tween (0.01%) from a 2 mM DMSO stock solution. The 100 μM solutions of 2-pyridinones were further diluted to 30 μM using running buffer (DMSO (25 mL) and sample buffer (475 mL)). The compounds were injected over the sensor chip (flow rate of 30 μL/min at 25 °C) in triplicate and in random order, and binding to immobilized PapD was observed in real time. After injection of each compound, the surface of the sensor chip was regenerated by injection of glycine hydrochloride (10 mM, pH 2.0).

To allow comparison of the binding of the compounds to the chaperone, the response from the Biacore instrument (determined as response units, RU) was corrected for the differences in molecular weight between the ligands. Normalized responses were then calculated using 2-pyridinone **13**{*10,1*} as reference.

Library Design. The 84 2-pyridinones in the library were energy-minimized using the force field MMFF94, and then 28 descriptors (see Supporting Information for details) were calculated with the same force field using the program MOE.[57] The principal component analysis was performed using the program SIMCA-P 9.0.[58] Two components were used that explains 78% of the variation.

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Supporting Information Available. ^{1}H NMR spectra of **8** and **13**, ^{19}F NMR spectra of **10**, **11**, **12**, **13**{*3,2*}, **13**{*9,2*}, **13**{*9,4*}, **13**{*8,3*}, **13**{*3,7*}, and **13**{*12,3*}, HPLC chromoatograms of **13**, and ^{1}H NMR spectra and HPLC chromatograms of compounds determining er. This material is available free of charge via the Internet at http://pubs.acs.org.

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