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Discovery of Novel Pyridinopolyamines with Potent Antimicrobial Activity: Deconvolution of Mixtures Synthesized by Solution-Phase Combinatorial Chemistry

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A 1638-member pyridinopolyamine library, consisting of 13 sublibraries of 126 members prepared by a solution-phase approach, was completely deconvoluted from orthogonally protected intermediates by a combination of iterative and positional scanning procedures. Antibacterial assays against *Streptococcus pyogenes* and *Escherichia coli imp*$^-$ and a *Candida albicans* yeast specificity assay were employed to follow the activity of sublibraries. Screening of the 13 sublibraries, which were prepared by a synthetic method that places the differentiating functionality in a selected position A (secondary amine), at the end of the synthesis (fix last), provided several first-round actives. Subsequently, six single pyridinopolyamines (**2**−**7**) were prepared where the first-round winner, a hydrogen atom, is in the first deconvoluted position and the remaining three positions contained the same functionalities. The range of antibacterial and yeast activities of these single compounds suggested that a more active and selective compound may be discovered by completely deconvoluting the first-round active sublibraries. Pyridinopolyamine positions B (secondary benzylamine) and C (primary benzylamine) were then sequentially positionally scanned with a set of six meta-substituted benzyl functionalities to generate two sets of second/third-round sublibraries, containing 21 or 36 compounds in each sublibrary, respectively. High-throughput screening yielded sublibraries **15**, **18**, and **21** with MICs of 1−5 μM against *S. pyogenes* and *E. coli imp*$^-$. Using rounds 1 and 2/3 screening data, two sets of single compounds (**22**−**27**) and (**28**−**32**) with the combination of *m*-(trifluoromethyl)-benzyl group at position C and *m*-(trifluoromethyl)benzyl or *m*-methylbenzyl group at position B with position D (primary benzylamine) fixed were synthesized in the fourth round deconvolution. Subsequently, broader screening of deconvoluted compounds against a tier II panel of wild-type bacteria identified eight compounds (**5**, **7**, **27**, and **29**−**32**) with approximately 100-fold greater selectivity for Gram-positive than Gram-negative bacteria. Thus, *S. pyogenes*, *S. pyogenes* (wild-type), *Streptomyces aureus*, and *Enterococcus faecalis* were inhibited at MICs of 1−12 μM, whereas MICs for *E. coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, and *Pseudomonas aeruginosa* were >100 μM. These eight compounds were not active (>100 μM) against fungus *C. albicans*.

Introduction

Solution-phase synthesis of chemical libraries[1−6] is emerging as an attractive alternative to solid-phase techniques[7−9] for lead generation and lead discovery. In this regard, we have recently described a method to prepare combinatorial libraries by adding a mixture of functionalities to a single scaffold in solution.[10−12] In this approach, the selection and synthesis of a scaffold where the functionality that differentiates each pool (sublibrary) is placed last in the synthetic scheme (fix last concept)[11] are important. This procedure greatly reduces the required chemistry by diverging at the end of a synthetic sequence rather than early in the scheme and thus repeating the same synthetic sequence for each functionality. A fix last combinatorial method facilitates the use of an iterative deconvolution process to find the active materials. In addition, each fixed position, on deprotection, provides a reactive site to place not only a functionality from the functionality set used to combinatorialize the scaffold but also other functionalities in this position. In this case, the functionality is positionally biased in that it is not placed in all of the combinatorial sites. This is accomplished in the present work by an orthogonal protection scheme allowing the fix last position to remain blocked during the simultaneous addition of functional groups.

Various iterative deconvolution strategies[13] have been described for identifying active compounds from mixtures of chemicals. Recursive,[14] mutational SURF,[15] orthogonal,[16] bogus coin,[17] and positional scanning[18] have been used to identify lead compounds from peptides and oligonucleotide libraries prepared from solid support. These deconvolution strategies were used for selecting the active compounds from oligomeric and small-molecule libraries based only on solid-phase techniques. Rebek and co-workers[19] employing a subtractive (or reverse) iterative deconvolution procedure identified lead compounds from a library based on solution-phase chemistry by sequentially subtracting building blocks/functionalities (amino acids). A systematic deconvolution of a solution-phase mixture has not been reported.

We have reported the synthesis a 1638-member novel pyridinopolyamine library, consisting of 13 sublibraries

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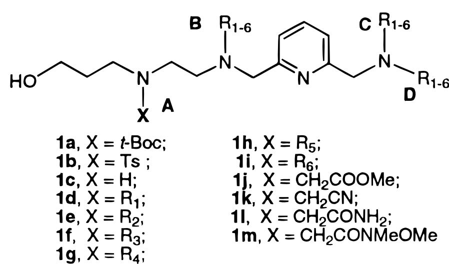
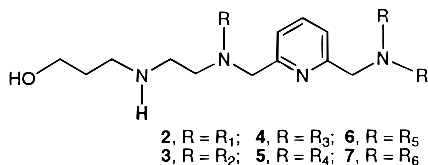
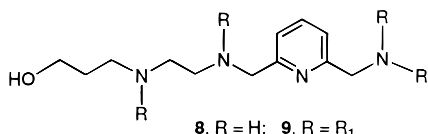
Chart 1. First-Round Iterative Sublibraries **1a**−**m** and Single Compounds **2**−**9**







Functionalities

$R_1 = CH_2Ph$	$R_4 = CH_2C_6H_4NO_2$-*m*
$R_2 = CH_2C_6H_4F$-*m*	$R_5 = CH_2C_6H_4COOCH_3$-*m*
$R_3 = CH_2C_6H_4CH_3$-*m*	$R_6 = CH_2C_6H_4CF_3$-*m*

(**1a**−**m**) of 126 members (Chart 1), by the solution-phase simultaneous addition of functionalities (SPSAF) approach.[12] The 13 sublibraries are differentiated by the functional groups selected to be placed in the chosen fixed position A (see Chart 1 to identify combinatorial positions). Six of the sublibraries (**1d**−**i**) were derived from placing each functionality of the six-member set, used to combinatorialize the three open positions, in position A. The remaining sublibraries were derived from functionalities having similar reactivity for the nucleophilic scaffolds as the functionality set but positionally biased by being only placed at the fixed position A. The complexity of the libraries depends on the number of reactive sites on the scaffold, how many reactive functionalities are simultaneously added, and the symmetry of the scaffold. In the present research, combinatorializing six functionalities over three sites provides the sublibraries of 126 members rather than the expected 216 (6^3) members. This reflects the 2-fold symmetry found in the primary amine.[20] The 13 sublibraries, differentiated by the functional group in the selected fixed position A, were examined for antibacterial activity by two indicator assays against *Streptococcus pyogenes* and *Escherichia coli imp*$^-$ and a *Candida albicans* yeast specificity assay. A hydrogen atom or a benzyl group in the A position of the scaffold were clear winners (**1c**,**d**, respectively) in the first round. Sublibraries **1k**−**m** were also active (Table 1). Subsequently, six single compounds (**2**−**7**, Chart 1) with a hydrogen in position A and uniform functionalities in the remaining B−D positions, a tetrabenzyl derivative (**9**, benzyls in positions A−D), and the unsubstituted scaffold **8** were synthesized. The comparison of the screening results of these single, pure compounds (Table 2) suggested that a more active and selective antibacterial compound may

Table 1. MIC[a] Data (μM) for First-Round Sublibraries (**1a**−**m**) in Growth Inhibition Assays

library number	complexity	*S. pyogenes*	*E. coli imp*$^-$	*C. albicans*
1a	126	>100	>100	
1b	126	>100	>100	
1c	126	1−5	1−5	5−25
1d	126	1−5	1−5	5−25
1e	126	>100	>100	
1f	126	>100	>100	
1g	126	>100	>100	
1h	126	>100	>100	
1i	126	>100	>100	
1j	126	>100	>100	
1k	126	5−12	5−25	25−50
1l	126	12−25	5−25	>100
1m	126	5−12	5−25	25−100

[a] The MIC (minimum inhibitory concentration) value is given as a range of sublibrary concentrations (total concentration of compounds in the sublibrary). After 24 h, the complete inhibition of growth was observed at the higher concentration of the given MIC, and the growth was observed at the lower concentration.

be discovered from the active sublibraries. In this report, we describe a strategy involving iterative and positional scanning to completely deconvolute these active sublibraries. The SPSAF approach[10−12] was used to generate all sublibraries during the deconvolution.

Deconvolution Strategy

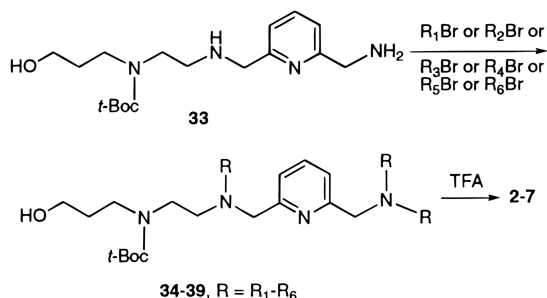
The design and synthesis of the pyridinopolyamine scaffold **1** and its combinatorialization with a set of meta-substituted benzyl bromide functionalities has been reported.[12] The resulting 13 sublibraries of 126 members, prepared by a fix last synthesis method, are suitable for iterative deconvolution. The position A of pyridinopolyamine **1** (Chart 1) was selected as the site to place the differentiating functionalities (fix last) for a first-round iterative deconvolution process. The MIC results of these sublibraries (Table 1) indicated that sublibrary **1c** (hydrogen atom) and sublibrary **1d** (benzyl group) were clear winners. It is interesting to note that the active sublibrary **1c** was obtained by positionally biasing a hydrogen atom at that position. We initially chose meta-substituted benzylic bromides as functionalities to develop the SPSAF process. This allowed diverse functionalities to be placed into the libraries while minimizing the group's ability to affect the reactivity of the benzylic bromides. However, we were uncertain whether this initial functionality set would possess significant differentiating diversity. Therefore, on discovering the low-micromolar activity of sublibraries **1c**,**d**, we first elected to prepare and screen the six single, pure analogues **2**−**7** (Scheme 1), which have the same functionality in positions B−D and a hydrogen atom in position A, and a single compound **9** having benzyl groups in positions A−D. Our reasoning was that if the functional groups in the meta-position of the benzyls did not present sufficient differentiating diversity, then the single compounds would exhibit an activity similar to the 126-member mixture **1c** or **1d**. From Table 2 we see that the first series of single compounds **2**−**7** had an 8-fold range (2.5−20 μM) in *E. coli imp*$^-$ whereas mixture **1c** had 1−5 μM; a 4-fold range (2.5−10 μM) was seen in **2**−**7** compared to 1−5 μM for the mixture in *S. pyogenes* and a greater than 17-fold range (6−100 μM) in the single compounds

Table 2. Activity of Single Compounds **2**−**9** in Growth Inhibition Assays (MIC, μM)[a]

compd number	*E. coli imp*−	*S. pyogenes*	*S. pyogenes* (wt)	*S. aureus*	*E. faecalis*	*E. coli*	*K. pneumoniae*	*P. vulgaris*	*P. aeruginosa*	*C. albicans*
2	5−10	2.5−5	3−6	12−25	6−12	6−12	25−50	25−50	25−50	25−50
3	2.5−5	2.5−5	3−6	6−12	12−25	6−12				25−50
4	2.5−5	2.5−5	3−6	3−6	3−6	3−6	>100	>100	>100	6−12
5	5−10	2.5−5	6−12	6−12	>100	>100	>100	>100	>100	>100
6	10−20	5−10	6−12	12−25	>100	12−25				25−50
7	2.5−5	2.5−5	6−12	3−6	>100	>100	>100	>100	>100	>100
8	>100	>100								>100
9	5−25	5−25								1−5

[a] See footnote a to Table 1 except for single compounds.

Scheme 1



against *C. albicans* compared to 5−25 μM for **1c**. When comparing the activity of single compounds **2**−**7** against wild-type *E. coli*, we see a greater than 33-fold range (3−100 μM) within the groups, and **2**−**7** exhibited a greater than 17-fold range (6−100 μM) within the groups against *C. albicans*. Furthermore, the screening results indicated that the tetrabenzyl-substituted compound **9** was 5 times less active than the parent sublibrary **1d** against *S. pyogenes* and *E. coli imp*− (Table 1), and compound **9** also strongly inhibited *C. albicans* with MICs of 1−5 μM whereas **1d** was 5-fold less active. The parent pyridinoamine scaffold **8** (Chart 1) also did not exhibit antibacterial or antifungal activities (Table 1) which indicated aromatic substituents were required for activity. These data indicated that a significant differentiating structure−activity relationship is presented by the functionalities in the meta-position of the six benzyls and that more active and specific antibacterial compounds may be found by completely deconvoluting sublibraries **1c**,**d**. We elected to deconvolute sublibrary **1c** (hydrogen in position A) rather than sublibrary **1d** (benzyl in position A) because of its potentially greater antimicrobial selectivity (Table 2). Subsequently, activity of two indicator antibacterial assays and a fungus *C. albicans* specificity assay was used to guide the deconvolution of sublibrary **1c**. Orthogonally protected intermediates are required, for both the deconvolution and scale-up of the selected compounds, and their synthesis is described in the next section.

Having position A fixed with a hydrogen atom, as determined by iterative deconvolution, we next elected to determine the optimal functionality residing in positions B and C by positional scanning of positions B−D. Positions B and D were combinatorialized with the six meta-substituted functionalities (Chart 2), while position C was fixed with each of the functionalities to provide six sublibraries (**10**−**15**) of 36 members (Table 3, Scheme 2). In this "second"-round deconvolution, a $CH_2C_6H_4CF_3$-*m* group in the C position was a clear winner (library **15**, Table 3). In a "third" round,

Chart 2. Second-Round Sublibraries **10**−**21** and Single Compounds **22**−**32**, **8**, and **9**

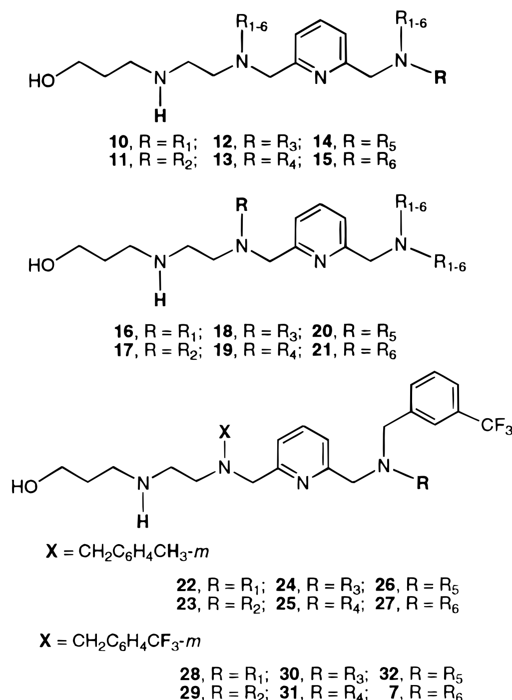


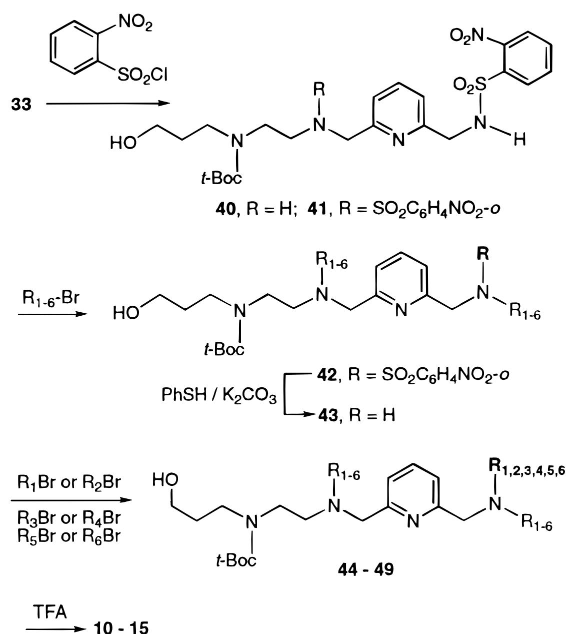
Table 3. MIC Data (μM) for the Positional Scanning 2/3-Round Sublibraries **10**−**21**[a]

library number	complexity	*S. pyogenes*	*E. coli imp*−
10	36	1−5	5−25
11	36	5−25	5−25
12	36	1−5	5−25
13	36	5−25	5−25
14	36	5−25	5−25
15	36	1−5	1−5
16	21	1−5	5−25
17	21	1−5	5−25
18	21	1−5	1−5
19	21	1−5	5−25
20	21	1−5	5−25
21	21	1−5	1−5

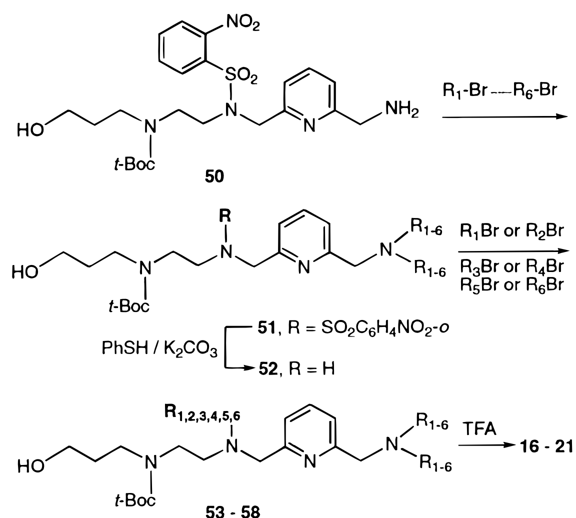
[a] See footnote a to Table 1.

positional scanning positions C and D while fixing B provided six 21-member[20] sublibraries (**16**−**21**) (Table 3, Scheme 3). Table 3 indicates two winners: **18** ($CH_2C_6H_4CH_3$-*m*) and **21** ($CH_2C_6H_4CF_3$-*m*) in position B. Thus, from these three rounds of deconvolution, two series of compounds have emerged, both having a hydrogen in position A, $CH_2C_6H_4CF_3$-*m* in position C, and either $CH_2C_6H_4CF_3$-*m* or $CH_2C_6H_4CH_3$-*m* in position B. To determine the functional group in the final position D, and thus the structure of the most active compounds, the six functionalities were placed in each

Scheme 2



Scheme 3



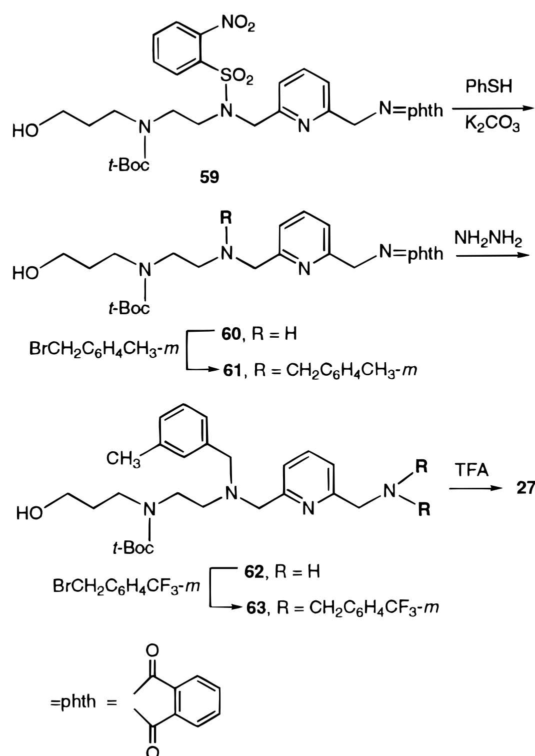
of the two series of compounds to provide two series of six single compounds (**22**−**27** and **28**−**32** and **7**) (Chart 2, Schemes 4−6). Single compounds **22**−**32** and **7** resulting from complete deconvolution were screened against a tier II panel of bacteria consisting of *S. pyogenes*, *S. pyogenes* (wild-type), *Streptococcus aureus*, *Enterococcus faecalis*, *E. coli imp*$^-$, *Klebsiella pneumoniae*, *Proteus vulgaris,* and *Pseudomonas aeruginosa* and fungus *C. albicans* for an indication of specificity.

Deconvolution Chemistry

Fixing the First Position, A. The synthesis of the 13 sublibraries **1a**−**m** (Chart 1) has been described.[12]

Fixing Position C. The deconvolution for the fixing position C originates from the mono-*t*-Boc-protected scaffold **33**[12] (Scheme 2). Compound **33** was treated with 1 equiv of 2-nitrobenzenesulfonyl chloride to provide orthogonally bisprotected product **40** and triprotected compound **41** in 58% and 15% yields, respectively. The secondary amine positions B and D of **40** were combinatorialized with six functionalities (Chart 1) by

Scheme 4

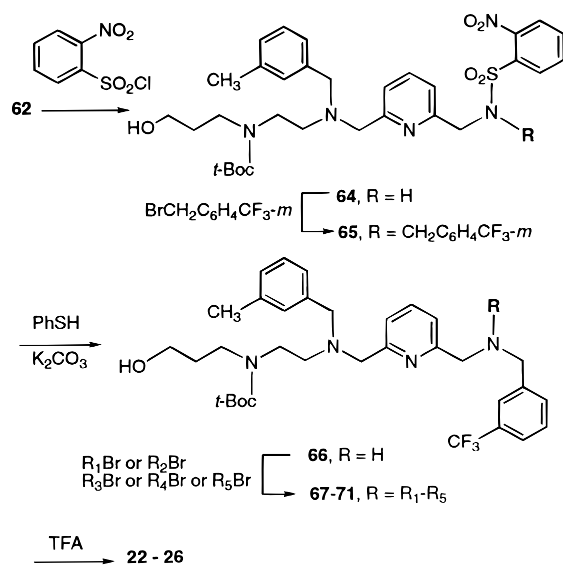


the SPSAF approach[10,11] to generate sublibraries **42** containing 36 compounds (6^2). The 2-nitrobenzenesulfonyl protecting group was then selectively removed by thiophenol in the presence of K_2CO_3 under mild conditions.[10−12,21] The resulting sublibrary **43** was divided into six portions which were then each separately reacted with the six benzylic bromides to give sublibraries **44**−**49** with six different groups on position C. The *t*-Boc protecting group of these sublibraries was removed by trifluoroacetic acid (TFA) to afford six final sublibraries (**10**−**15**) with 6 different groups on position C, a H group on position A, and B and D positions combinatorialized.

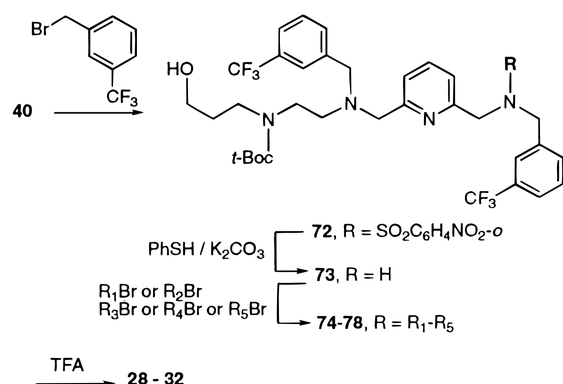
Fixing Position B. Orthogonally bisprotected compound **50**[12] (Scheme 3) was obtained by selective deprotection of the orthogonally protected compound **59** (Scheme 4) with hydrazine.[12] Identical positions C and D of compound **50** were combinatorialized with the six functionalities to give sublibrary **51**. This sublibrary only contains 21 compounds[20] because of the C_2 symmetry of the primary amino group. Similar to sublibrary **42** described above, sublibrary **51** was selectively deprotected with thiophenol. The resulted sublibrary **52** was divided and then separately reacted with the six benzylic bromides. The resulting six sublibraries (**53**−**58**) were treated with TFA, affording six final sublibraries (**16**−**21**) with six different groups on position B, a H on position A, and C and D positions combinatorialized.

Fixing Position D: First Series of Single Compounds. Synthesis of single compounds **22**−**27** started from the orthogonally protected compound **59** (Scheme 4).[12] The 2-nitrobenzenesulfonyl protecting group of **59** was first selectively removed by thiophenol to give compound **60**. The reaction of **60** with α-bromo-*m*-xylene gave compound **61**, which was selectively deprotected with hydrazine to give compound **62**. The

Scheme 5



Scheme 6



primary amino group of **62** was then reacted with 2 equiv of α′-bromo-α,α,α-trifluoro-*m*-xylene. The resulting compound **63** was treated with TFA to afford compound **27** with *m*-(trifluoromethyl)benzyl groups on positions C and D. Compound **62** with a primary amino group was further protected with 2-nitrobenzenesulfonyl group to give compound **64** (Scheme 5). The reaction of **64** with α′-bromo-α,α,α-trifluoro-*m*-xylene gave compound **65** with one *m*-(trifluoromethyl)benzyl group attached on position C. Compound **65** was selectively deprotected with thiophenol to afford compound **66**, which was separately reacted with five benzylic bromides (R_{1-5}Br). The resulting compounds **67**−**71** were treated with TFA to remove *t*-Boc group, giving final single compounds **22**−**26**.

Fixing Position D: Second Series of Single Compounds. Synthesis of compounds **28**−**32** was relatively easy because two *m*-(trifluoromethyl)benzyl groups can be attached onto positions B and C at the same time (Schemes 2 and 6). The bisprotected compound **40** (Scheme 2) was reacted with α′-bromo-α,α,α-trifluoro-*m*-xylene to give compound **72** containing two *m*-(trifluoromethyl)benzyl groups on positions B and C. Compound **72** was then selectively deprotected with thiophenol. The resulted compound **73** was then separately reacted with five benzylic bromides (R_{1-5}Br). Thus obtained compounds **74**−**78** were treated with TFA to afford five final compounds (**28**−**32**) with five different groups on one position D, two *m*-(trifluoromethyl)benzyl groups on positions B and C, and hydrogen (H) on position A. Compound **7** with three *m*-(trifluoromethyl)benzyl groups was synthesized by another route (Scheme 1). All final and intermediate sublibraries were purified by chromatographic techniques, flash chromatography, or preparative thin-layer chromatography (TLC) and confirmed by electrospray mass spectroscopy as indicated previously.[10−12] Final single compounds were characterized by their spectroscopic and combustion analyses.

Conclusions

The value of this deconvolution process may be assessed by comparing the activity and selectivity of the single compounds **22**−**32** and **7** derived from the process with the original 126-member active sublibrary **1c** with those of the single, uniformly modified compounds **2**−**7**. The single compounds **2**−**7** and **22**−**32** were screened against a tier II panel of bacteria consisting of *S. pyogenes*, *S. pyogenes* (wild-type), *S. aureus*, *E. faecalis*, *E. coli imp*⁻, *E. coli* (wild-type), *K. pneumoniae*, *P. vulgaris*, and *P. aeruginosa* and the fungus *C. albicans* as an indication of specificity. When comparing compounds **22**−**32** (Table 4) derived from deconvolution to compounds **2**−**7** (Table 3) derived from single compound synthesis (excluding **7** as it is derived from both processes), we note that the **22**−**32** series has a much more potent activity and greater selectivity for Gram-positive bacteria compared to series **2**−**7**, which identifies compounds with Gram-negative or Gram-positive activity or both activities, and compounds with various levels of yeast activity. In comparing deconvoluted series **7** and **22**−**32** with the original active sublibrary **1c** of 126 members, only the indicator antibacterial assays against *E. coli imp*⁻ and *S. pyogenes* and fungus *C. albicans* are considered, as the mixture was not examined in the tier II panel. In this comparison, we note that the antibacterial activity of **1c** and series **7** and **22**−**32** is very similar; however, the selectivity as determined by the yeast *C. albicans* is very different. Sublibrary **1c** has potent yeast activity, whereas **27**−**32** and **7** from the deconvoluted series are not active against *C. albicans*; a selectivity of greater than 20-fold is observed. Deconvoluted compounds **22**−**26** exhibit yeast activity with a MIC of less than 12.5 μM. We contend from these comparisons that the complete deconvolution of the 1638-member library via active sublibrary **1c** was of considerable value. When considering the differential activities within the deconvoluted series **7** and **22**−**32** (Table 4), it is clearly evident that the deconvolution process has allowed the selection of a series of tribenzylpyridinopolyamines with potent Gram-positive activity (MICs typically in the range of 3−6 μM). The series has a 20-fold greater selectivity for the Gram-positive bacteria than the Gram-negative bacteria in that the typical Gram-negative MICs are greater than 100 μM. Deconvoluted series **22**−**27** differs from series **28**−**32** and **7** by possessing a *m*-methylbenzyl functionality in the B position, whereas **28**−**32** and **7** have a *m*-(trifluoromethyl)benzyl in the B position. This difference has an interesting effect on yeast as the first series exhibits activity (with the exception of **27**) and the second series is not active (>100 μM). Closer examination of the series indicates that

Table 4. Activity of Single Compounds **22**−**32** from the Last Round (4th) Screening (MIC, μM)[a]

compd number	*E. coli imp*⁻	*S. pyogenes*	*S. pyogenes* (wt)	*S. aureus*	*E. faecalis*	*E. coli*	*K. pneumoniae*	*P. vulgaris*	*P. aeruginosa*	*C. albicans*
22	1−5	1−5	3−6	3−6	3−6	12−25	6−12	>100	>100	<12.5
23	1−5	1−5	3−6	3−6	3−6	>100	12−25	>100	>100	<12.5
24	5−25	1−5	3−6	3−6	3−6	>100	6−12	>100	>100	<12.5
25	2−25	1−5	3−6	3−6	3−6	>100	>100	>100	>100	25−50
26	5−25	1−5	3−6	6−12	3−6	>100	>100	>100	>100	<12.5
27	5−25	1−5	3−6	6−12	3−6	>100	>100	>100	>100	>100
28	1−3	1−3	6−12	12−25	6−12	>100	25−50	>100	>100	>100
29	3−6	3−6	3−6	6−12	3−6	>100	>100	>100	>100	>100
30	1−3	1−3	3−6	6−12	3−6	>100	50−100	>100	>100	>100
31	3−6	1−3	3−6	3−6	3−6	>100	>100	>100	>100	>100
32	3−6	1−3	3−6	6−12	3−6	>100	>100	>100	>100	>100
7	2.5−5	2.5−5	6−12	3−6	6−12	>100	>100	>100	>100	>100

[a] See footnote a to Table 1 except for single compounds.

yeast activity can be eliminated if two or three *m*-(trifluoromethyl)benzyl groups reside in positions B−D (**22**−**32** and **7**). The antibacterial and yeast screening of deconvoluted compounds **22**−**32** and **7** suggests that the activity of pyridinopolyamine scaffold **1** requires a tribenzyl substitution pattern, as sublibraries, obtained by the deprotection of sublibraries **43** (Scheme 2) and **52** (Scheme 3), having only two aromatic substituents were not active (data not shown). Having a hydrogen atom in position A is essential for antibacterial activity as all sublibraries and single compounds with a *t*-Boc group at position A were not active (data not shown). An exception to this is active sublibrary **1d** which has a benzyl functionality in position A. In fact, the tetrabenzyl-substituted compound **9** displayed the greatest yeast activity of all compounds screened. The parent pyridinopolyamine **8** (Chart 1) did not exhibit antimicrobial or antifungal activities (Table 2).

In conclusion, we have deconvoluted a 1638-member meta-substituted benzyl pyridinopolyamine library synthesized by solution-phase chemistry. The deconvolution of a selected active sublibrary was accomplished by a combination of iterative and positional scanning procedures from orthogonally protected intermediates. Eight compounds exhibit potent, highly selective activity for Gram-positive bacteria over Gram-negative bacteria and very high specificity for bacteria compared with the fungus *C. albicans*. These results indicate that functional groups in the meta-positions of the benzyl functionality set do indeed provide sufficient differentiating diversity to allow biological activities to be separated and identified from a library by iterative and positional scanning deconvolution processes. In addition, the value of positional biasing in the fixed position has been demonstrated. Several of these compounds are undergoing evaluation in animals.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra for all compounds were recorded at 199.975 MHz. Chemical shifts are expressed relative to the added tetramethylsilane. High-resolution (FAB) positive ion mass spectra were recorded on a VG ZAB-VSE double-focusing high-resolution mass spectrometer equipped with a cesium ion gun. Combustion analyses were performed by M-H-W Laboratories, Phoenix, AZ. 3-[[2-[[[6-(Aminomethyl)-2-pyridinyl]methyl]amino]ethyl](*tert*-butoxycarbonyl)amino]-1-propanol (**33**), 3-[[2-[[(2-nitrophenyl)sulfonyl][[6-(aminomethyl)-2-pyridinyl]methyl]amino]ethyl](*tert*-butoxycarbonyl)amino]-1-propanol (**50**), 3-[[2-[[(2-nitrophenyl)sulfonyl][[6-(phthalimidomethyl)-2-pyridinyl]methyl]amino]ethyl](*tert*-butoxycarbonyl)amino]-1-propanol (**59**), and compounds **8** and **9** were synthesized according to our reported procedure.[12] Other starting materials were purchased from Aldrich and TCI America Chemical Companies.

General Procedure for the Preparation of Compounds 34−39. A mixture of compound **33**[12] (339 mg, 1.0 mmol), anhydrous K_2CO_3 (2.50 g, 18 mol), and the corresponding benzylic bromide derivative (3.6 mmol, 3.6 equiv) in 40 mL of anhydrous CH_3CN was stirred at room temperature overnight. The reaction mixture was concentrated to dryness under reduced pressure. The residue was treated with H_2O−$CHCl_3$, the organic phase was separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column. The gradient elution with 3:1 to 1:4 hexanes−EtOAc afforded compounds **34**−**39**.

Compound 34: colorless oil; yield 401 mg (67%); silica gel TLC R_f 0.56 (2:1 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.40−1.60 (m, 2H), 2.75 (t, 2H, *J* = 7.0 Hz), 3.18−3.37 (m, 4H), 3.42−3.55 (m, 2H), 3.62 (s, 4H), 3.67 (s, 2H), 3.74 (s, 2H), 3.78 (s, 2H), 7.18−7.58 (m, 17H), 7.68 (t, 1H, *J* = 7.6 Hz); MS (FAB) *m*/*z* 741 (M + Cs)$^+$; HRMS (FAB) *m*/*z* 609.381 (M + H)$^+$ ($C_{38}H_{49}N_4O_3$ requires 609.380). Anal. ($C_{38}H_{48}N_4O_3$) C, H, N.

Compound 35: colorless oil; yield 445 mg (67%); silica gel TLC R_f 0.59 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.45−1.65 (m, 2H), 2.64 (t, 2H, *J* = 7.0 Hz), 3.15−3.38 (m, 4H), 3.40−3.55 (m, 2H), 3.60 (s, 4H), 3.64 (s, 2H), 3.71 (s, 2H), 3.76 (s, 2H), 6.85−6.99 (m, 3H), 7.05−7.50 (m, 11H), 7.68 (t, 1H, *J* = 7.6 Hz); MS (FAB) *m*/*z* 663 (M + H)$^+$; HRMS (FAB) *m*/*z* 795.251 (M + Cs)$^+$ ($C_{38}H_{45}N_4O_3F_3Cs$ requires 795.250). Anal. ($C_{38}H_{45}N_4O_3F_3$) C, H, N.

Compound 36: colorless oil; yield 388 mg (60%); silica gel TLC R_f 0.59 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.40−1.60 (m, 2H), 2.33 (s, 9H), 2.62 (t, 2H, *J* = 7.0 Hz), 3.15−3.35 (m, 4H), 3.40−3.50 (m, 2H), 3.57 (s, 4H), 3.62 (s, 2H), 3.71 (s, 2H), 3.75 (s, 2H), 6.98−7.09 (m, 3H), 7.10−7.28 (m, 9H), 7.35 (d, 1H, *J* = 7.7 Hz), 7.50 (d, 1H, *J* = 7.7 Hz), 7.66 (t, 1H, *J* = 7.6 Hz); HRMS (FAB) *m*/*z* 783.326 (M + Cs)$^+$ ($C_{41}H_{54}N_4O_3Cs$ requires 783.325). Anal. ($C_{41}H_{54}N_4O_3$) C, H, N.

Compound 37: colorless oil; yield 525 mg (71%); silica gel TLC R_f 0.38 (1:4 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.50−1.65 (m, 2H), 2.68 (t, 2H, *J* = 7.0 Hz), 3.20−3.38 (m, 4H), 3.40−3.55 (m, 2H), 3.75 (s, 8H), 3.81 (s, 2H), 7.31−7.40 (m, 2H), 7.49 (t, 3H, *J* = 7.8 Hz), 7.70 (t, 4H, *J* = 9.0 Hz), 8.01−8.14 (m, 3H), 8.26 (d, 3H, *J* = 8.0 Hz); MS (FAB) *m*/*z* 744 (M + H)$^+$; HRMS (FAB) *m*/*z* 876.236 (M + Cs)$^+$ ($C_{38}H_{45}N_7O_9Cs$ requires 876.233). Anal. ($C_{38}H_{45}N_7O_9$) C, H, N.

Compound 38: colorless oil; yield 610 mg (78%); silica gel TLC R_f 0.39 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9H), 1.45−1.60 (m, 2H), 2.63 (t, 2H, *J* = 7.0 Hz), 3.14−3.35 (m, 4H), 3.38−3.54 (m, 2H), 3.63 (s, 4H), 3.67 (s, 2H), 3.70 (s, 2H), 3.75 (s, 2H), 3.89 (s, 9H), 7.30−7.70 (m, 9H), 7.88 (d, 3H, *J* = 7.7 Hz), 8.01 (d, 3H, *J* = 8.6 Hz); MS (FAB) *m*/*z* 784 (M +

H)$^+$; HRMS (FAB) *m/z* 915.298 (M + Cs)$^+$ ($C_{44}H_{54}N_4O_9Cs$ requires 915.294). Anal. ($C_{44}H_{54}N_4O_9 \cdot {}^1/_2H_2O$) C, H, N.

Compound 39: colorless oil; yield 487 mg (60%); silica gel TLC R_f 0.28 (1:1 hexanes–EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9H), 1.50–1.62 (m, 2H), 2.64 (t, 2H, J = 7.0 Hz), 3.13–3.38 (m, 4H), 3.40–3.55 (m, 2H), 3.67 (s, 4H), 3.70 (s, 2H), 3.72 (s, 2H), 3.77 (s, 2H), 7.30–7.70 (m, 15H); MS (FAB) *m/z* 813 (M + H)$^+$; HRMS (FAB) *m/z* 945.243 (M + Cs)$^+$ ($C_{41}H_{45}N_4O_3F_9Cs$ requires 945.240). Anal. ($C_{41}H_{45}N_4O_3F_9$) C, H, N.

General Procedure for the Preparation of Compounds 2–7. TFA (8 mL) was added to a solution of the corresponding compounds **34**–**39** (0.6 mmol) in 2 mL of $CHCl_3$ at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and washed with aqueous Na_2CO_3 solution. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on a silica gel column. Elution with 100% MeOH and then 100:1 or 50:1 MeOH–30% NH_4OH afforded the corresponding products **2**–**7**.

Compound 2: colorless oil; yield 274 mg (87%); silica gel TLC R_f 0.44 (100:1 MeOH–30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.51–1.66 (m, 2H), 2.55–2.70 (m, 6H), 3.56–3.63 (m, 6H), 3.65–3.80 (m, 6H), 7.15–7.45 (m, 16H), 7.51 (d, 1H, J = 7.2 Hz), 7.66 (t, 1H, J = 7.6 Hz); MS (FAB) *m/z* 641 (M + Cs)$^+$; HRMS (FAB) *m/z* 509.329 (M + H)$^+$ ($C_{33}H_{41}N_4O$ requires 509.328). Anal. ($C_{33}H_{40}N_4O$) C, H, N.

Compound 3: colorless oil; yield 320 mg (95%); silica gel TLC R_f 0.54 (100:1 MeOH–30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.56–1.70 (m, 2H), 2.58–2.78 (m, 6H), 3.55–3.64 (m, 6H), 3.66–3.85 (m, 6H), 6.82–6.98 (m, 3H), 7.00–7.35 (m, 10H), 7.45 (d, 1H, J = 7.3 Hz), 7.67 (t, 1H, J = 7.6 Hz); MS (FAB) *m/z* 563 (M + H)$^+$; HRMS (FAB) *m/z* 695.196 (M + Cs)$^+$ ($C_{33}H_{37}N_4OF_3Cs$ requires 695.197). Anal. ($C_{33}H_{37}N_4OF_3 \cdot {}^1/_2H_2O$) C, H, N.

Compound 4: colorless oil; yield 270 mg (86%); silica gel TLC R_f 0.46 (100:1 MeOH–30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.57–1.70 (m, 2H), 2.35 (s, 3H), 2.37 (s, 6H), 2.60–2.72 (m, 6H), 3.56–3.65 (m, 6H), 3.72–3.82 (m, 6H), 3.95 (br, 1H), 7.00–7.30 (m, 12H), 7.33 (d, 1H, J = 7.3 Hz), 7.54 (d, 1H, J = 7.3 Hz), 7.69 (t, 1H, J = 7.6 Hz); MS (FAB) *m/z* 551 (M + H)$^+$; HRMS (FAB) *m/z* 683.274 (M + Cs)$^+$ ($C_{36}H_{46}N_4OCs$ requires 683.272). Anal. ($C_{36}H_{46}N_4O$) C, H, N.

Compound 5: colorless oil; yield 383 mg (91%); silica gel TLC R_f 0.22 (100:1 MeOH–30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.57–1.71 (m, 2H), 2.65–2.80 (m, 6H), 3.50–3.85 (m, 12H), 7.27–7.52 (m, 5H), 7.60–7.78 (m, 4H), 8.05 (t, 3H, J = 7.6 Hz), 8.23 (d, 3H, J = 11.4 Hz); HRMS (FAB) *m/z* 776.179 (M + Cs)$^+$ ($C_{33}H_{37}N_7O_7Cs$ requires 776.180). Anal. ($C_{33}H_{37}N_7O_7$) C, H, N.

Compound 6: colorless oil; yield 463 mg (92%); silica gel TLC R_f 0.45 (100:1 MeOH–30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.52–1.68 (m, 2H), 2.55–2.70 (m, 6H), 3.55–3.80 (m, 12H), 3.86 (s, 3H), 3.88 (s, 6H), 7.27–7.69 (m, 9H), 7.82–8.05 (m, 6H); MS (FAB) *m/z* 815 (M + Cs)$^+$; HRMS (FAB) *m/z* 683.344 (M + H)$^+$ ($C_{39}H_{47}N_4O_7$ requires 683.344). Anal. ($C_{39}H_{46}N_4O_7 \cdot H_2O$) C, H, N.

Compound 7: colorless oil; yield 326 mg (82%); silica gel TLC R_f 0.42 (100:1 MeOH–30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.56–1.70 (m, 2H), 2.62–2.75 (m, 6H), 3.60–3.84 (m, 12H), 7.22–7.70 (m, 15H); MS (FAB) *m/z* 713 (M + H). Anal. ($C_{36}H_{37}N_4OF_9$) C, H, N.

Preparation of Compounds 40 and 41. A solution of 2-nitrobenzenesulfonyl chloride (1.80 g, 8.1 mmol, 1.0 equiv) in 50 mL of $CHCl_3$ was added dropwise to a stirred solution of compound **33**[12] (2.76 g, 8.1 mmol) and diisopropylethylamine (1.40 mL, 1.04 g, 8.0 mmol) in 60 mL of $CHCl_3$ at 0 °C. The resulting reaction mixture was stirred at 0 °C for 40 min and diluted with 200 mL of $CHCl_3$. After being washed twice with aqueous Na_2CO_3 solution and once with brine, the organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on a silica gel column. Elution with 1:0, 15:1, and then 5:1 EtOAc–MeOH afforded mono- and disubstituted products **40** and **41**.

Compound 40: pale-yellow oil; yield 2.47 g (58%); silica gel TLC R_f 0.45 (1:1 EtOAc–MeOH); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.60–1.80 (m, 2H), 2.75–2.88 (m, 2H), 3.25–3.45 (m, 4H), 3.48–3.62 (m, 2H), 3.80 (s, 2H), 4.39 (s, 2H), 7.11 (t, 2H, J = 6.8 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.62–7.72 (m, 2H), 7.80–7.90 (m, 1H), 8.06–8.16 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.4, 30.05, 47.2, 47.9, 54.1, 58.6, 80.0, 120.2, 121.2, 125.2, 130.9, 132.6, 133.5, 137.4, 147.9, 154.1; MS (FAB) *m/z* 524 (M + H)$^+$; HRMS (FAB) *m/z* 656.118 (M + Cs)$^+$ ($C_{23}H_{33}N_5SO_7Cs$ requires 656.115).

Compound 41: white foam; yield 0.86 g (15%); silica gel TLC R_f 0.50 (100% EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 1.45–1.70 (m, 2H), 3.09–3.26 (m, 4H), 3.40–3.60 (m, 4H), 4.32 (s, 1H), 4.35 (s, 1H), 4.55 (s, 2H), 6.65 (br, 1H, NH), 7.05–7.25 (m, 2H), 7.50–8.10 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 28.3, 30.4, 43.1, 45.2, 46.7, 47.8, 53.1, 58.4, 80.7, 120.9, 121.3, 124.3, 125.3, 130.7, 131.9, 132.7, 133.2, 133.8, 137.8, 147.9, 154.5, 155.6; HRMS (FAB) *m/z* 841.096 (M + Cs)$^+$ ($C_{29}H_{36}N_6S_2O_{11}Cs$ requires 841.093).

General Procedure for the Preparation of Libraries 42 and 51. A solution of benzyl bromide (298 μL, 420 mg, 2.46 mmol), α-bromo-*m*-xylene (346 μL, 455 mg, 2.46 mmol), 3-fluorobenzyl bromide (305 μL, 465 mg, 2.46 mmol), 3-nitrobenzyl bromide (532 mg, 2.46 mmol), methyl 3-(bromomethyl)benzoate (564 mg, 2.46 mmol), and α'-bromo-α,α,α-trifluoro-*m*-xylene (380 μL, 588 mg, 2.46 mmol) (total 14.7 mmol, 2.4 equiv) in 50 mL of anhydrous CH_3CN was added to a stirred mixture of compound **40** or **50**[12] (6.1 mmol) and anhydrous K_2CO_3 (15.8 g, 0.11 mol) in 260 mL of anhydrous CH_3CN at room temperature. The resulting reaction mixture was stirred at room temperature overnight and concentrated to dryness under reduced pressure. After the residue was dissolved in H_2O–$CHCl_3$, the layers were separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column. Elution with 10:1 and then 1:1 hexanes–EtOAc followed by 100% EtOAc afforded library **42** or **51** in 72–86% yields as a light-yellow oil.

General Procedure for the Preparation of Libraries 43 and 52. Thiophenol (544 μL, 584 mg, 5.29 mmol, 1.2 equiv) was added to a stirred mixture of library **42** or **51** (4.4 mmol) and anhydrous K_2CO_3 (2.50 g, 18 mmol) in 50 mL of anhydrous DMF. The reaction mixture was stirred at room temperature for 3 h and worked up as described above for **42** and **51**. Purification by flash chromatography and elution with 1:1 hexanes–EtOAc followed by 5:1 and 2:1 EtOAc–MeOH afforded library **43** or **52** as a light-yellow oil in 82–93% yields.

General Procedure for the Preparation of Libraries 44–49 and 53–58. A mixture of library **43** or **52** (1.0 mmol), anhydrous K_2CO_3 (2.0 g, 14.4 mmol), and the corresponding benzyl bromide derivative (1.2 mmol, 1.2 equiv) was stirred at room temperature overnight. The reaction mixture was worked up as described above for libraries **42** and **51**. Chromatographic purification by using 6:1 and then 1:2 hexanes–EtOAc as eluents afforded library **44**–**49** or **53**–**58** in 75–99% yields.

General Procedure for the Preparation of Libraries 10–15 and 16–21. Trifluoroacetic acid (TFA) (20 mL) was added to a stirred solution of the corresponding *t*-Boc-protected library **44**–**49** or **53**–**58** (0.9 mmol) in 6 mL of $CHCl_3$ at 0 °C. The resulting mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and washed twice with an aqueous Na_2CO_3 solution. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on a silica gel column. Elution with MeOH and then 30:1 or 40:1 MeOH–30% NH_4OH afforded library **10**–**15** or **16**–**21** in 80–95% yields.

Preparation of Compound 60. Thiophenol (2.2 mL, 21.4 mmol, 1.2 equiv) was added to a stirred mixture of compound **59**[12] (11.44 g, 17.5 mmol) and anhydrous K_2CO_3 (7.26 g, 52.5 mmol, 3.0 equiv) in 90 mL of DMF. The reaction mixture was stirred at room temperature for 4 h and the solvent was

removed under vacuum. The residue was dissolved in H_2O and CH_2Cl_2. The separated organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The crude oil was purified by flash chromatography using 8:2 to 10:0 EtOAc–hexanes and then 9:1 to 8:2 EtOAc–MeOH as eluents to give 6.37 g (78%) of product **60** as a pale-yellow oil: silica gel TLC R_f 0.38 (9:1 EtOAc–MeOH); ^{1}H NMR ($CDCl_3$) δ 0.87–0.94 (m, 2H), 1.26–1.39 (m, 2H), 1.43 (s, 9H), 2.04 (br, 1H, NH), 2.73–2.76 (m, 2H), 3.22–3.38 (m, 4H), 3.54 (br, 1H, OH), 3.84 (s, 2H), 5.00 (s, 2H), 7.10–7.16 (m, 2H), 7.59–7.61 (m, 1H), 7.88–7.89 (m, 2H), 7.90–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 10.9, 14.0, 23.0, 23.8, 28.4, 30.4, 38.8, 43.0, 47.9, 54.5, 58.5, 68.2, 80.1, 119.5, 120.9, 123.5, 128.8, 130.9, 132.2, 134.1, 137.2, 155.0, 159.2, 168.13; HRMS (FAB) *m/z* 601.143 (M + Cs)$^+$ ($C_{25}H_{32}N_4O_5$-Cs requires 601.142).

Preparation of Compound 61. A mixture of compound **60** (7.29 g, 15.5 mmol), anhydrous K_2CO_3 (25.8 g, 186.7 mmol, 1.2 equiv), and α-bromo-*m*-xylene (2.52 mL, 18.6 mmol, 1.2 equiv) in 300 mL of anhydrous CH_3CN was stirred at room temperature overnight. The solvent was evaporated, and the residue was dissolved in a mixture of H_2O and CH_2Cl_2. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using 2:8 to 6:4 EtOAc–hexanes as eluents to afford 8.11 g (91%) of product **61** as a colorless oil: silica gel TLC R_f 0.54 (100% EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.37–1.53 (m, 4H), 2.32 (s, 3H), 2.54–2.61 (m, 2H), 3.12–3.27 (m, 4H), 3.40–3.46 (m, 2H), 3.58 (s, 2H), 3.71 (s, 2H), 4.99 (s, 2H), 7.04–7.26 (m, 5H), 7.33–7.36 (m, 1H), 7.57–7.60 (m, 1H), 7.71–7.76 (m, 2H), 7.86–7.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 28.3, 30.5, 42.7, 44.9, 52.0, 58.3, 59.1, 60.0, 80.0, 119.3, 120.4, 123.5, 127.8, 128.2, 129.4, 132.3, 134.1, 137.1, 137.8, 139.1, 154.5, 156.9, 159.8; HRMS (FAB) *m/z* 705.206 (M + Cs)$^+$ ($C_{33}H_{40}N_4O_5Cs$ requires 705.205).

Preparation of Compound 62. Hydrazine (0.10 mL, 1.96 mmol, 3.0 equiv) was added to a stirred solution of compound **61** (0.374 g, 0.65 mmol) in 3.4 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 2 h, and the solvent was removed under vacuum. The residue was dissolved in a mixture of H_2O and CH_2Cl_2. The separated organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was further purified by flash chromatography using 9:1 to 1:1 EtOAc–MeOH as eluents to afford 0.12 g (42%) of product **62** as a colorless oil: silica gel TLC R_f 0.51 (100:1 MeOH–30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.41–1.44 (m, 2H), 1.55–1.56 (m, 2H), 2.34 (s, 3H), 2.62–2.66 (m, 2H), 3.21–3.23 (m, 2H), 3.30–3.32 (m, 2H), 3.46–3.48 (m, 2H), 3.63 (s, 2H), 3.77 (s, 2H), 3.94 (s, 2H), 7.04–7.20 (m, 3H), 7.36–7.38 (m, 1H), 7.61–7.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 10.9, 14.0, 21.4, 22.9, 23.7, 28.2, 30.5, 38.7, 43.0, 44.9, 47.6, 52.1, 58.2, 59.2, 60.5, 68.1, 80.0, 119.4, 120.7, 125.7, 127.8, 128.2, 129.4, 137.02, 137.9, 138.9, 156.8, 159.4, 160.9; HRMS (FAB) *m/z* 465.283 (M + Na)$^+$ ($C_{25}H_{38}N_4O_3Na$ requires 465.284).

Preparation of Compound 63. A mixture of compound **62** (0.40 g, 0.90 mmol), anhydrous K_2CO_3 (1.49 g, 10.8 mmol, 12.0 equiv), and α′-bromo-α,α,α-trifluoro-*m*-xylene (0.47 g, 1.97 mmol, 2.2 equiv) in 30 mL of anhydrous CH_3CN was stirred at room temperature overnight. The solvent was evaporated, and the residue was dissolved in a mixture of H_2O and CH_2Cl_2. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography using 8:2 to 7:3 EtOAc–hexanes as eluents to afford 0.41 g (60%) of product **63** as a colorless oil: silica gel TLC R_f 0.66 (3:7 hexanes–EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H), 1.29–1.55 (m, 4H), 2.32 (s, 3H), 2.58–2.65 (m, 2H), 3.18–3.33 (m, 4H), 3.40–3.52 (m, 2H), 3.60 (s, 2H), 3.66 (s, 4H), 3.72 (s, 2H), 3.75 (s, 2H), 7.04–7.18 (m, 4H), 7.34–7.71 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 10.9, 14.0, 21.4, 23.0, 23.7, 28.2, 28.9, 30.3, 38.7, 42.9, 44.9, 52.2, 58.1, 59.1, 59.8, 60.5, 68.1, 80.1, 120.9, 124.0, 125.4, 125.7, 127.8, 128.2, 128.8, 129.4, 130.9, 132.0, 137.1, 138.9, 140.0, 156.9, 158.3, 159.3; HRMS (FAB) *m/z* 891.269 (M + Cs)$^+$ ($C_{41}H_{48}N_4O_3F_6Cs$ requires 891.268).

Preparation of Compound 64. A solution of 2-nitrobenzenesulfonyl chloride (2.33 g, 10.5 mmol, 1.16 equiv) in 30 mL of CH_2Cl_2 was added dropwise to a stirred solution of **62** (4.0 g, 9.0 mmol) and Et_3N (3.2 g, 3.2 mmol) in 60 mL of CH_2Cl_2 at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h, diluted with 200 mL of $CHCl_3$, and washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on a silica gel column. Elution with 2:1, 1:1, and then 0:1 hexanes–EtOAc afforded 3.60 g (63%) of product **64** as a pale-yellow oil: silica gel TLC R_f 0.41 (1:4 hexanes–EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.40–1.65 (m, 2H), 2.32 (s, 3H), 2.56 (t, 2H, J = 7.0 Hz), 3.10–3.35 (m, 4H), 3.40–3.72 (m, 6H), 4.37 (s, 2H), 6.80–8.05 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 21.4, 28.3, 30.5, 43.1, 44.9, 48.0, 52.3, 58.3, 59.0, 60.1, 80.0, 119.9, 121.5, 125.2, 125.7, 127.9, 128.3, 129.4, 130.8, 132.6, 133.4, 137.2, 137.9, 138.9, 147.8, 153.5, 156.8, 159.7; MS (FAB) *m/z* 760 (M + Cs)$^+$; HRMS (FAB) *m/z* 628.281 (M + H)$^+$ ($C_{31}H_{42}N_5O_7S$ requires 628.280).

Preparation of Compound 65. A mixture of **64** (3.60 g, 5.73 mmol), anhydrous K_2CO_3 (10.0 g, 72 mmol), and α′-bromo-α,α,α-trifluoro-*m*-xylene (1.66 g, 6.9 mmol, 1.2 equiv) in 110 mL of CH_3CN was stirred at room temperature overnight. The reaction mixture was worked up using the same procedure as described above for library **42**. The crude product was purified by flash chromatography on a silica gel column. Elution with 3:1, 1:1, and then 1:2 hexanes–EtOAc afforded 3.60 g (80%) of product **65** as a pale-yellow oil: silica gel TLC R_f 0.45 (1:4 hexanes–EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.45–1.65 (m, 2H), 2.31 (s, 3H), 2.56 (t, 2H, J = 7.0 Hz), 3.10–3.38 (m, 4H), 3.40–3.50 (m, 2H), 3.53 (s, 2H), 3.56 (s, 2H), 4.55 (s, 2H), 4.63 (s, 2H), 6.98–7.60 (m, 14H), 7.94 (d, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 28.2, 30.4, 43.0, 44.9, 51.2, 52.2, 52.6, 58.2, 58.9, 60.2, 80.0, 120.7, 121.4, 124.2, 124.6, 125.0, 125.7, 127.9, 128.2, 129.1, 129.4, 130.9, 131.7, 131.8, 133.7, 136.6, 137.2, 137.9, 138.9, 147.8, 154.5, 156.8, 159.8; MS (FAB) *m/z* 918 (M + Cs)$^+$; HRMS (FAB) *m/z* 786.316 (M + H)$^+$ ($C_{39}H_{47}N_5O_7SF_3$ requires 786.314).

Preparation of Compound 66. Compound **66** was synthesized as described above for libraries **52** and **43** from **65** (3.50 g, 4.45 mmol), thiophenol (0.59 g, 5.35 mmol, 1.2 equiv), and anhydrous K_2CO_3 (3.0 g, 21.7 mmol) in 60 mL of DMF. Flash chromatographic purification by using 100% EtOAc and then 10:1 EtOAc–MeOH as eluents afforded 2.20 g (82%) of product **66** as a pale-yellow oil: silica gel TLC R_f 0.47 (20:1 EtOAc–MeOH); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.50–1.65 (m, 2H), 2.32 (s, 3H), 2.64 (t, 2H, J = 6.8 Hz), 3.15–3.40 (m, 4H), 3.47 (t, 2H, J = 5.5 Hz), 3.63 (s, 2H), 3.78 (s, 2H), 3.88 (s, 4H), 7.00–7.70 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 21.4, 28.3, 30.6, 43.1, 45.0, 52.2, 53.0, 54.3, 58.3, 59.2, 60.5, 80.0, 120.5, 120.9, 123.8, 125.0, 125.8, 127.0, 127.9, 128.2, 128.8, 129.0, 129.5, 130.4, 131.0, 131.6, 137.0, 137.9, 139.1, 141.2, 156.8, 158.5, 159.7; MS (FAB) *m/z* 601 (M + H)$^+$; HRMS (FAB) *m/z* 733.237 (M + Cs)$^+$ ($C_{33}H_{43}N_4O_3F_3Cs$ requires 733.234).

Preparation of Compound 72. Compound **72** was synthesized as described above for libraries **42** from **40** (2.70 g, 5.1 mmol), anhydrous K_2CO_3 (13.0 g, 94.0 mmol), and α′-bromo-α,α,α-trifluoro-*m*-xylene (2.90 g, 12.1 mmol, 2.37 equiv) in 120 mL of CH_3CN. Flash chromatographic purification by using 5:1 and then 1:1 hexanes–EtOAc as eluents afforded 2.59 g (60%) of product **72** as a colorless oil: silica gel TLC R_f 0.55 (1:4 hexanes–EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.45–1.68 (m, 2H), 2.60 (t, 2H, J = 6.8 Hz), 3.10–3.40 (m, 4H), 3.42–3.55 (m, 2H), 3.62 (s, 2H), 3.64 (s, 2H), 4.58 (s, 2H), 4.63 (s, 2H), 7.11 (d, 1H, J = 7.2 Hz), 7.27–7.68 (m, 13H), 7.97 (d, 1H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 28.2, 30.5, 43.1, 45.0, 51.3, 52.3, 52.8, 58.4, 59.7, 60.2, 80.1, 120.9, 121.5, 124.0, 124.2, 124.6, 125.1, 126.5, 126.9, 128.8, 129.1, 130.4, 131.0, 131.6, 133.6, 136.6, 137.3, 140.4, 147.9, 154.8, 156.7, 159.2; MS (FAB) *m/z* 840 (M + H)$^+$; HRMS (FAB) *m/z* 972.187 (M + Cs)$^+$ ($C_{39}H_{43}N_5SO_7F_6Cs$ requires 972.184).

Preparation of Compound 73. Compound **73** was synthesized as described above for libraries **52** and **43** from **72** (2.58 g, 3.0 mmol), thiophenol (0.41 g, 3.6 mmol, 1.2 equiv), and anhydrous K_2CO_3 (2.0 g, 14.0 mmol) in 40 mL of DMF. Flash chromatographic purification by using 20:1 and then 10:1 EtOAc−MeOH as eluents afforded 1.77 g (88%) of product **73** as a colorless oil: silica gel TLC R_f 0.40 (20:1 EtOAc−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9H), 1.45−1.62 (m, 2H), 2.65 (t, 2H, J = 7.0 Hz), 3.10−3.38 (m, 4H), 3.47 (t, 2H, J = 5.0 Hz), 3.71 (s, 2H), 3.77 (s, 2H), 3.89 (s, 4H), 7.16 (d, 1H, J = 7.2 Hz), 7.30−7.68 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 28.2, 30.6, 36.3, 43.3, 45.0, 52.3, 53.0, 54.3, 58.3, 58.6, 60.4, 80.0, 120.6, 120.9, 121.5, 123.8, 124.8, 125.2, 126.9, 128.8, 130.3, 130.9, 131.6, 131.9, 136.9, 140.5, 141.2, 156.6, 158.6, 159.0; MS (FAB) m/z 655 (M + H)$^+$; HRMS (FAB) m/z 787.204 (M + Cs)$^+$ ($C_{33}H_{40}N_4O_3F_6Cs$ requires 787.205).

General Procedure for the Synthesis of Compounds 67−71 and 74−78. A mixture of **66** or **73** (0.60 mmol), anhydrous K_2CO_3 (1.0 g, 7.2 mmol), and the corresponding benzylic bromide derivative (1.3 equiv) in 10 mL of CH_3CN was stirred at room temperature overnight. The solvent was evaporated, and the residue was treated with H_2O−$CHCl_3$. The organic layer was separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column. Gradient elution with 4:1 to 1:1 hexanes−EtOAc afforded the corresponding product **67**−**71** or **74**−**78**.

Compound 67: pale-yellow oil; yield 354 mg (85%); silica gel TLC R_f 0.53 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.45−1.65 (m, 2H), 2.33 (s, 3H), 2.64 (t, 2H, J = 7.0 Hz), 3.18−3.40 (m, 4H), 3.42−3.56 (m, 2H), 3.63 (s, 4H), 3.67 (s, 2H), 3.74 (s, 2H), 3.78 (s, 2H), 7.00−7.72 (m, 16H); MS (FAB) m/z 691 (M + H)$^+$; HRMS (FAB) m/z 823.284 (M + Cs)$^+$ ($C_{40}H_{49}N_4O_3F_3Cs$ requires 823.281).

Compound 68: colorless oil; yield 420 mg (98%); silica gel TLC R_f 0.57 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.45−1.65 (m, 2H), 2.32 (s, 3H), 2.63 (t, 2H, J = 7.0 Hz), 3.17−3.38 (m, 4H), 3.42−3.56 (m, 2H), 3.62 (s, 4H), 3.67 (s, 2H), 3.72 (s, 2H), 3.77 (s, 2H), 6.88−7.74 (m, 15H); MS (FAB) m/z 841 (M + Cs)$^+$; HRMS (FAB) m/z 709.376 (M + H)$^+$ ($C_{40}H_{49}N_4O_3F_4$ requires 709.374).

Compound 69: colorless oil; yield 420 mg (99%); silica gel TLC R_f 0.62 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.48−1.70 (m, 2H), 2.35 (s, 3H), 2.36 (s, 3H), 2.51−2.76 (m, 2H), 3.15−3.45 (m, 4H), 3.47−3.58 (m, 2H), 3.62 (s, 2H), 3.66 (s, 2H), 3.68 (s, 2H), 3.77 (s, 2H), 3.82 (s, 2H), 7.00−7.75 (m, 15H); MS (FAB) m/z 837 (M + Cs)$^+$; HRMS (FAB) m/z 705.402 (M + H)$^+$ ($C_{41}H_{52}N_4O_3F_3$ requires 705.399).

Compound 70: pale-yellow oil; yield 430 mg (97%); silica gel TLC R_f 0.50 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.45−1.65 (m, 2H), 2.32 (s, 3H), 2.63 (t, 2H, J = 6.8 Hz), 3.15−3.38 (m, 4H), 3.40−3.54 (m, 2H), 3.61 (s, 2H), 3.70 (s, 2H), 3.73 (s, 2H), 3.74 (s, 2H), 3.78 (s, 2H), 6.98−7.20 (m, 4H), 7.30−7.75 (m, 9H), 8.08 (d, 1H, J = 8.3 Hz), 8.28 (s, 1H); MS (FAB) m/z 868 (M + Cs)$^+$; HRMS (FAB) m/z 736.371 (M + H)$^+$ ($C_{40}H_{49}N_5O_5F_3$ requires 736.369).

Compound 71: colorless oil; yield 490 mg (99%); silica gel TLC R_f 0.45 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9H), 1.45−1.65 (m, 2H), 2.31 (s, 3H), 2.58−2.72 (m, 2H), 3.15−3.38 (m, 4H), 3.40−3.57 (m, 2H), 3.62 (s, 2H), 3.66 (s, 4H), 3.73 (s, 2H), 3.77 (s, 2H), 3.91 (s, 3H), 6.98−7.20 (m, 4H), 7.32−7.71 (m, 9H), 7.92 (d, 1H, J = 7.7 Hz), 8.07 (s, 1H); MS (FAB) m/z 749 (M + H)$^+$; HRMS (FAB) m/z 881.289 (M + Cs)$^+$ ($C_{42}H_{51}N_4O_5F_3Cs$ requires 881.286).

Compound 74: colorless oil; yield 250 mg (96%); silica gel TLC R_f 0.60 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.45−1.62 (m, 2H), 1.75 (br, 1H), 2.64 (t, 2H, J = 7.0 Hz), 3.15−3.38 (m, 4H), 3.40−3.58 (m, 2H), 3.62 (s, 2H), 3.66 (s, 2H), 3.70 (s, 2H), 3.72 (s, 2H), 3.77 (s, 2H), 7.20−7.70 (m, 16H); MS (FAB) m/z 754 (M + H)$^+$; HRMS (FAB) m/z 877.250 (M + Cs)$^+$ ($C_{40}H_{46}N_4O_3F_6Cs$ requires 877.252).

Compound 75: colorless oil; yield 256 mg (96%); silica gel TLC R_f 0.31 (1:1 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.40−1.60 (m, 2H), 1.74 (br, 1H), 2.64 (t, 2H, J = 7.0 Hz), 3.12−3.38 (m, 4H), 3.40−3.55 (m, 2H), 3.60 (s, 2H), 3.66 (s, 2H), 3.70 (s, 2H), 3.71 (s, 2H), 3.77 (s, 2H), 6.86−6.99 (m, 1H), 7.13 (d, 2H, J = 7.3 Hz), 7.20−7.72 (m, 12H); MS (FAB) m/z 763 (M + H)$^+$; HRMS (FAB) m/z 895.246 (M + Cs)$^+$ ($C_{40}H_{45}N_4O_3F_7Cs$ requires 895.243).

Compound 76: colorless oil; yield 258 mg (97%); silica gel TLC R_f 0.38 (1:1 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.40−1.65 (m, 2H), 1.80 (br, 1H), 2.34 (s, 3H), 2.64 (t, 2H, J = 7.2 Hz), 3.12−3.38 (m, 4H), 3.40−3.52 (m, 2H), 3.58 (s, 2H), 3.65 (s, 2H), 3.70 (s, 2H), 3.72 (s, 2H), 3.77 (s, 2H), 7.00−7.71 (m, 15H); MS (FAB) m/z 891 (M + Cs)$^+$; HRMS (FAB) m/z 759.368 (M + H)$^+$ ($C_{41}H_{49}N_4O_3F_6$ requires 759.370).

Compound 77: colorless oil; yield 270 mg (97%); silica gel TLC R_f 0.44 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9H), 1.40−1.65 (m, 2H), 2.66 (t, 2H, J = 6.8 Hz), 3.15−3.38 (m, 4H), 3.40−3.58 (m, 2H), 3.70 (s, 4H), 3.72 (s, 2H), 3.74 (s, 2H), 3.79 (s, 2H), 7.30−7.82 (m, 13H), 8.06 (d, 1H, J = 8.0 Hz), 8.27 (s, 1H); MS (FAB) m/z 790 (M + H)$^+$; HRMS (FAB) m/z 922.239 (M + Cs)$^+$ ($C_{40}H_{45}N_5O_5F_6Cs$ requires 922.238).

Compound 78: colorless oil; yield 275 mg (97%); silica gel TLC R_f 0.46 (2:1 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 9H), 1.40−1.65 (m, 2H), 1.55−1.72 (m, 2H), 3.12−3.38 (m, 4H), 3.40−3.58 (m, 2H), 3.66 (s, 4H), 3.70 (s, 2H), 3.72 (s, 2H), 3.77 (s, 2H), 3.89 (s, 3H), 7.30−7.71 (m, 13H), 7.90 (d, 1H, J = 7.7 Hz), 8.06 (s, 1H); MS (FAB) m/z 803 (M + H)$^+$; HRMS (FAB) m/z 935.260 (M + Cs)$^+$ ($C_{42}H_{48}N_4O_5F_6Cs$ requires 935.258).

General Procedure for the Preparation of Compounds 22−26, 27, and 28−32. Compounds **22**−**26**, **27**, and **28**−**32** were synthesized as described above for **2**−**7** from the corresponding compounds **67**−**71**, **63** (0.5−0.7 mmol), or **74**−**78** (0.3−0.6 mmol) and 8 mL of TFA. The crude product was purified by flash chromatography on a silica gel column using 100% MeOH and then 100:1 MeOH−30% NH_4OH as eluents or by preparative TLC on a silica gel plate using 100:1 MeOH−30% NH_4OH as developing agent to afford the corresponding products **22**−**26**, **27** or **28**−**32**.

Compound 22: colorless oil; yield 222 mg (75%); silica gel TLC R_f 0.34 (100:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.45−1.70 (m, 2H), 2.35 (s, 3H), 2.50−2.75 (m, 6H), 3.45−3.90 (m, 12H), 6.90−7.74 (m, 16H); MS (FAB) m/z 723 (M + Cs)$^+$; HRMS (FAB) m/z 591.332 (M + H)$^+$ ($C_{35}H_{42}N_4OF_3$ requires 591.331). Anal. ($C_{35}H_{41}N_4OF_3\cdot{}^1/_2H_2O$) C, H, N.

Compound 23: colorless oil; yield 301 mg (92%); silica gel TLC R_f 0.45 (100:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.54−1.68 (m, 2H), 2.33 (s, 3H), 2.58−2.72 (m, 6H), 3.62 (s, 2H), 3.63 (s, 2H), 3.68 (s, 2H), 3.75 (s, 4H), 6.86−7.72 (m, 15H); HRMS (FAB) m/z 609.324 (M + H)$^+$ ($C_{35}H_{41}N_4OF_4$ requires 609.321). Anal. ($C_{35}H_{40}N_4OF_4\cdot{}^1/_2H_2O$) C, H, N.

Compound 24: colorless oil; yield 329 mg (91%); silica gel TLC R_f 0.48 (100:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.57−1.75 (m, 2H), 2.36 (s, 3H), 2.38 (s, 3H), 2.58−2.82 (m, 6H), 3.58−3.95 (m, 12H), 7.00−7.80 (m, 15H); MS (FAB) m/z 737 (M + Cs)$^+$; HRMS (FAB) m/z 605.344 (M + H)$^+$ ($C_{36}H_{44}N_4OF_3$ requires 605.346). Anal. ($C_{36}H_{43}N_4OF_3\cdot{}^1/_2H_2O$) C, H, N.

Compound 25: pale-yellow oil; yield 360 mg (97%); silica gel TLC R_f 0.45 (100:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.56−1.71 (m, 2H), 2.31 (s, 3H), 2.58−2.80 (m, 6H), 3.55−3.95 (m, 12H), 4.28 (br, 1H), 6.95−7.75 (m, 13H), 7.98−8.10 (m, 1H), 8.22−8.30 (m, 1H); MS (FAB) m/z 768 (M + Cs)$^+$; HRMS (FAB) m/z 636.317 (M + H)$^+$ ($C_{35}H_{41}N_5O_3F_3$ requires 636.316). Anal. ($C_{35}H_{40}N_5O_3F_3\cdot H_2O$) C, H, N.

Compound 26: light-yellow oil; yield 410 mg (98%); silica gel TLC R_f 0.47 (100:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.55−1.70 (m, 2H), 2.25−2.37 (m, 3H), 2.58−2.75 (m, 6H), 3.55−3.82 (m, 12H), 3.92 (s, 3H), 4.21 (br, 1H), 6.95−7.72 (m, 13H), 7.93 (d, 1H, J = 7.8 Hz), 8.10 (s, 1H); MS (FAB) m/z 781 (M + Cs)$^+$; HRMS (FAB) m/z 649.337 (M + H)$^+$ ($C_{37}H_{44}N_4O_3F_3$ requires 649.336). Anal. ($C_{37}H_{43}N_4O_3F_3\cdot H_2O$) C, H, N.

Compound 27: colorless oil; yield 250 mg (74%); silica gel TLC R_f 0.16 (100:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.25−1.35 (m, 4H), 1.59−1.64 (m, 2H), 2.62−2.68 (m, 6H), 3.48 (s, 1H), 3.58 (s, 2H), 3.67 (s, 4H), 3.70−3.77 (m, 6H), 7.02−7.19 (m, 4H), 7.30−7.71 (m, 11H); HRMS (FAB) m/z 659.312

$(M + H)^+$ ($C_{36}H_{41}N_4OF_6$) requires 659.318). Anal. ($C_{36}H_{40}N_4OF_6$) C, H, N.

Compound 28: colorless oil; yield 163 mg (76%); silica gel TLC R_f 0.40 (100:1 MeOH−30% NH_4OH); ^1H NMR ($CDCl_3$) δ 1.54−1.70 (m, 2H), 2.60−2.74 (m, 6H), 3.60−3.82 (m, 12H), 7.18−7.71 (m, 16H); MS (FAB) m/z 777 $(M + Cs)^+$; HRMS (FAB) m/z 645.304 $(M + H)^+$ ($C_{35}H_{39}N_4OF_6$ requires 645.302). Anal. ($C_{35}H_{38}N_4OF_6 \cdot H_2O$) C, H, N.

Compound 29: colorless oil; yield 198 mg (90%); silica gel TLC R_f 0.40 (100:1 MeOH−30% NH_4OH); ^1H NMR ($CDCl_3$) δ 1.57−1.71 (m, 2H), 2.60−2.76 (m, 6H), 3.56−3.80 (m, 12H), 3.90 (br, 1H), 6.85−6.98 (m, 1H), 7.08−7.77 (m, 14H); MS (FAB) m/z 795 $(M + Cs)^+$; HRMS (FAB) m/z 663.292 $(M + H)^+$ ($C_{35}H_{38}N_4OF_7$ requires 663.293). Anal. ($C_{35}H_{37}N_4OF_7 \cdot H_2O$) C, H, N.

Compound 30: colorless oil; yield 212 mg (96%); silica gel TLC R_f 0.38 (100:1 MeOH−30% NH_4OH); ^1H NMR ($CDCl_3$) δ 1.58−1.72 (m, 2H), 2.35 (s, 3H), 2.62−2.80 (m, 6H), 3.55−3.82 (m, 12H), 4.04 (br, 1H), 7.00−7.11 (m, 1H), 7.15−7.72 (m, 14H); MS (FAB) m/z 791 $(M + Cs)^+$; HRMS (FAB) m/z 659.317 $(M + H)^+$ ($C_{36}H_{41}N_4OF_6$ requires 659.318). Anal. ($C_{36}H_{40}N_4OF_6 \cdot H_2O$) C, H, N.

Compound 31: colorless oil; yield 178 mg (76%); silica gel TLC R_f 0.43 (100:1 MeOH−30% NH_4OH); ^1H NMR ($CDCl_3$) δ 1.58−1.71 (m, 2H), 2.65−2.80 (m, 6H), 3.62−3.82 (m, 12H), 4.35 (br, 1H), 7.25 (d, 1H, $J = 6.2$ Hz), 7.30−7.72 (m, 12H), 8.05 (d, 1H, $J = 8.2$ Hz), 8.26 (s, 1H); MS (FAB) m/z 822 $(M + Cs)^+$; HRMS (FAB) m/z 690.286 $(M + H)^+$ ($C_{35}H_{38}N_5O_3F_6$ requires 690.287).

Compound 32: pale-yellow oil; yield 232 mg (97%); silica gel TLC R_f 0.44 (100:1 MeOH−30% NH_4OH); ^1H NMR ($CDCl_3$) δ 1.58−1.72 (m, 2H), 2.65−2.80 (m, 6H), 3.60−3.80 (m, 12H), 3.79 (br, 1H), 3.89 (s, 3H), 7.19 (d, 1H, $J = 7.3$ Hz), 7.30−7.68 (m, 12H), 7.89 (d, 1H, $J = 7.7$ Hz), 8.06 (s, 1H); MS (FAB) m/z 835 $(M + Cs)^+$; HRMS (FAB) m/z 703.306 $(M + H)^+$ ($C_{37}H_{41}N_4O_3F_6$ requires 703.308).

Antimicrobial and Antifungal Assays. The bacterial and yeast antigrowth assays were performed in microtiter plate format essentially as recommended by the National Committee for Clinical Laboratory Standards.[22] In initial (tier I) screens, the strains *Escherichia coli imp*$^-$,[23] a gift of Spenser Benson (University of Maryland at College Park), and *Streptococcus pyogenes* ATCC 14289 were used. The *E. coli imp*$^-$ strain was grown in LB broth, and the *S. pyogenes* strain was grown in Todd-Hewitt broth. Interesting samples were further evaluated in tier II against the following strains of bacteria or yeast in the indicated media: *S. pyogenes* ATCC 49399 in Todd-Hewitt broth, *Staphylococcus aureus* ATCC 25923 in trypticase soy broth, *Enterococcus faecalis* ATCC 29212 in Todd-Hewitt broth, *E. coli* ATCC 11775 in nutrient broth, *Klebsiella pneumoniae* ATCC 13883 in nutrient broth, *Proteus vulgaris* ATCC 8427 in nutrient broth, *Pseudomonas aeruginosa* ATCC 27853 in nutrient broth, and yeast *Candida albicans* ATCC 10231 in YM broth. The bacteria and yeast were grown at 37 and 22 °C, respectively. The assays were carried out in 150 μL volume in duplicate in 96-well flat-bottom plates. The bacterial or yeast suspension from an overnight culture growth in appropriate medium was added to a solution of compound or library sample in 4% DMSO in water. Final inoculum was approximately 1×10^7 cells/well for bacteria and 1×10^5 cells/well for yeast. The percent growth of the bacteria relative to a well containing no compound or library was determined by measuring absorbance at 595 nm (A_{595}) after 24 h. The growth of the yeast was observed at 48 h by visual inspection. The minimum inhibitory concentration (MIC) was given as a range of single compound or total sublibrary concentration, where the complete inhibition of growth was observed at the higher concentration and cells were viable at the lower concentrations. Both ampicillin and tetracycline were used as antibiotic-positive controls in each screening assay for bacteria *S. pyogenes*, *E. coli imp*$^-$, *S. aureus*, *E. faecalis*, *E. coli*, *K. pneumoniae,* and *P. vulgaris*. Ciprofloxacin was used as an antibiotic-positive control in each screening assay for bacterial *P. aeruginosa*. Amphotoericin B was used as an antifungal-positive control in each screening assay for *C. albicans*.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **31**, **32**, **40**, **41**, and **60**−**78**; ^{13}C NMR spectroscopic data for compounds **34**−**39**, **2**−**7**, **67**−**71**, **74**−**78**, and **22**−**32**; and an ES mass spectrum of sublibrary **16** (57 pages). Ordering information is given on any current masthead page.

References

(1) Sim, M. M.; Ganesan, A. Solution-Phase Synthesis of a Combinatorial Thiohydantoin Library. *J. Org. Chem.* **1997**, *62*, 3230−3235.

(2) (a) Shipps, G. W., Jr.; Spitz, U. P.; Rebek, J., Jr. Solution-Phase Generation of Tetraurea Libraries. *Bioorg. Med. Chem.* **1996**, *4*, 655−657. (b) Carell, T.; Wintner, E. A.; Bashir-Hashemi, A.; Rebek, J., Jr. A Novel Procedure for the Synthesis of Libraries Containing Small Organic Molecules. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2059−2061.

(3) (a) Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. I.; Boger, D. L. Novel Solution Phase Strategy for the Synthesis of Chemical Libraries Containing Small Organic Molecules. *J. Am. Chem. Soc.* **1996**, *118*, 2567−2573. (b) Cheng, S.; Tarby, C. M.; Comer, D. D.; Williams, J. P.; Caporale, L. H.; Mayers, P. L.; Boger, D. L. A Solution-Phase Strategy for the Synthesis of Chemical Libraries Containing Small Organic Molecules: A Universal and Dipeptide Mimetic Template. *Bioorg. Med. Chem.* **1996**, *4*, 727−737. (c) Boger, D. L.; Tarby, C. M.; Myers, P. L.; Caporale, L. H. Generalized Dipeptidomimetic Template: Solution Phase Parallel Synthesis of Combinatorial Libraries. *J. Am. Chem. Soc.* **1996**, *118*, 2109−2110.

(4) (a) McDevitt, J. P.; Lansbury, P. T., Jr. Glycosamino Acids: New Building Blocks for Combinatorial Synthesis. *J. Am. Chem. Soc.* **1996**, *118*, 3818−3828. (b) Pirrung, M. C.; Chen, J. Preparation and Screening against Acetylcholinesterase of a Non-Peptide "Indexed" Combinatorial Library. *J. Am. Chem. Soc.* **1995**, *117*, 1240−1245. (c) Smith, P. W.; Lai, J. Y. Q.; Whittington, A. R.; Cox, B.; Houston, J. G.; Stylli, C. H.; Banks, M. N.; Tiller, P. R. Synthesis and Biological Evaluation of a Library Containing Potentially 1600 Amides/Esters. A Strategy for Rapid Compound Generation and Screening. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2821−2824.

(5) (a) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. Use of Solid Supported Nucleophiles and Electrophiles for the Purification of Non-Peptide Small Molecule Libraries. *Tetrahedron Lett.* **1996**, *37*, 7193−7196. (b) Kaldor, S. W.; Fritz, J. E.; Tang, J.; Mckinney, E. R. Discovery of Antirhinoviral Leads by Screening a Combinatorial Library of Ureas Prepared Using Covalent Scavengers. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3041−3044.

(6) (a) Booth, R. J.; Hodges, J. C. Polymer-supported Quenching Reagents for Parallel Purification. *J. Am. Chem. Soc.* **1997**, *119*, 4882−4886. (b) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. Chemical Library Purification Strategies Based on Principles of Complementary Molecular Reactivity and Molecular Recognition. *J. Am. Chem. Soc.* **1997**, *119*, 4874−4881.

(7) (a) Balkenhohl, F.; von dem Hussche-Hünnefeld, C.; Lansky, A.; Zechel, C. Combinatorial Synthesis of Small Organic Molecules. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337. (b) Lam, K. S.; Lebl, M.; Krchnak, V. The "One-Bead-One-Compound" Combinatorial Library Methodology. *Chem. Rev. (Washington, D.C.)* **1997**, *97*, 411−448.

(8) (a) Pirrung, M. C. Spatially Addressable Combinatorial Libraries. *Chem. Rev. (Washington, D.C.)* **1997**, *97*, 473−488. (b) Ding, Y.; Labbe, J.; Kanie, O.; Hindsgaul, O. Toward Oligosaccharide Libraries: A Study of the Random Galactosylation of Unprotected *N*-Acetylglucosamine. *Bioorg. Med. Chem.* **1996**, *4*, 683−692.

(9) (a) Ellman, J. A. Design, Synthesis, and Evaluation of Small-Molecule Libraries. *Acc. Chem. Res.* **1996**, *29*, 132−143. (b) Thompson, L. A.; Ellman, J. A. Synthesis and Applications of Small Molecule Libraries. *Chem. Rev.* (Washington, D.C.) **1996**, *96*, 555−600. (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. The Current Status of Heterocyclic Combinatorial Libraries. *Chem. Rev. (Washington, D.C.)* **1997**, *97*, 449−472.

(10) An, H.; Cook, P. D. Solution Phase Combinatorial Chemistry I. Synthesis of Polyazacyclophane Scaffolds and Tertiary Amine Libraries. *Tetrahedron Lett.* **1996**, *37*, 7233−7236.

(11) An, H.; Cummins, L. L.; Griffey, R. H.; Bharadwaj, R.; Haly, B. D.; Fraser, A. S.; Wilson-Lingardo, L.; Risen, L. M.; Wyatt, J. R.; Cook, P. D. Solution Phase Combinatorial Chemistry. Discovery of Novel Polyazapyridinophanes with potent Antibacterial Activity by a Solution Phase Simultaneous Addition of Functionalities Approach. *J. Am. Chem. Soc.* **1997**, *119*, 3696−3708.

(12) An, H.; Haly, B. D.; Fraser, A. S.; Guinosso, C. J.; Cook, P. D. Solution Phase Combinatorial Chemistry. Synthesis of Novel Linear Pyridinopolyamine Libraries with Potent Antibacterial Activity. *J. Org. Chem.* **1997**, *62*, 5156−5164.

(13) (a) Blondelle, S. E.; Takahashi, E.; Houghten, R. A.; Perez-Paya, E. Rapid Identification of Compounds with Enhanced Antimicrobial Activity by Using Conformationally Defined Combinatorial Libraries. *Biochem. J.* **1996**, *313*, 141−147. (b) Kurth, M. J.; Randall, L. A. A.; Takenouchi, K. Solid-Phase Combinatorial Synthesis of Polyisoxazolines: A Two-Reaction Iterative Protocol. *J. Org. Chem.* **1996**, *61*, 8755−8761. (c) Look, G. C.; Schullek, J. R.; Holmes, C. P.; Chinn, J. P.; Gordon, E. M.; Gallop, M. A. The Identification of Cyclooxygenase-1 Inhibitors from 4-Thiazolidinone Combinatorial Libraries. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 707−712. (d) Janda, K. D. Tagged versus Untagged Libraries: Methods for the Generation and Screening of Combinatorial Chemical Libraries. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 10779−10785.

(14) (a) Erb, E.; Janda, K. D.; Brenner, S. Recursive Deconvolution of Combinatorial Libraries. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11422−11426. (b) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. Liquid-Phase Combinatorial Synthesis. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419−6423.

(15) (a) Freier, S. M.; Konings, D. A. M.; Wyatt, J. R.; Ecker, D. J. 'Mutational SURF': A Strategy for Improving Lead Compounds Identified from Combinatorial Libraries. *Bioorg. Med. Chem.* **1996**, *4*, 717−725. (b) Konings, D. A. M.; Wyatt, J. R.; Ecker, D. J.; Freier, S. M. Deconvolution of Combinatorial Libraries for Drug Discovery: Theoretical Comparison of Pooling Strategies. *J. Med. Chem.* **1996**, *39*, 2710−2719. (c) Wilson-Lingardo, L.; Davis, P. W.; Ecker, D. J.; Hebert, N.; Acevedo, O.; Sprankle, K.; Brennan, T.; Schwarcz, L.; Freier, S. M.; Wyatt, J. R. Deconvolution of Combinatorial Libraries for Drug Discovery: Experimental Comparison of Pooling Strategies. *J. Med. Chem.* **1996**, *39*, 2720−2726. (d) Freier, S. M.; Konings, D. A. M.; Wyatt, J. R.; Ecker, D. J. Deconvolution of Combinatorial Libraries for Drug Discovery: A Model System. *J. Med. Chem.* **1995**, *38*, 344−352.

(16) Deprez, B.; Williard, X.; Bourel, L.; Coste, H.; Hyafil, F.; Tartar, A. Orthogonal Combinatorial Chemical Libraries. *J. Am. Chem. Soc.* **1995**, *117*, 5405−5406.

(17) Blake, J.; Litzi-Davis, L. Evaluation of Peptide Libraries: An Iterative Strategy To Analyze the Reactivity of Peptide Mixtures with Antibodies. *Bioconjugate Chem.* **1992**, *3*, 510−513.

(18) (a) Pinilla, C.; Appel, J. R.; Blanc, P.; Houghten, R. A. Rapid Identification of High Affinity Peptide Ligands Using Positional Scanning Synthetic Peptide Combinatorial Libraries. *BioTechniques* **1992**, *13*, 901−905. (b) Pinilla, C.; Buencamino, J.; Appel, J. R.; Hopp, T. P.; Houghten, R. A. Mapping the Detailed Specificity of a Calcium-Dependent Monoclonal Antibody Through the Use of Soluble Positional Scanning Combinatorial Libraries: Identification of Potent Calcium-Independent Antigens. *Mol. Diver.* **1995**, *1*, 21−28. (c) Spatola, A. F.; Crozet, Y.; Dewit, D.; Yanagisawa, M. Rediscovering an Endothelin Antagonist (BQ-123): A Self-Deconvoluting Cyclic Pentapeptide Library. *J. Med. Chem.* **1996**, *39*, 3842−3846.

(19) (a) Carell, T.; Wintner, E. A.; Rebek, J., Jr. A Solution-Phase Screening Procedure for the Isolation of Active Compounds form a Library of Molecules. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2061−2064. (b) Carell, T.; Wintner, E. A.; Sutherland, A. J.; Rebek, J., Jr.; Dunayevskiy, Y. M.; Vouros, P. New Promise in Combinatorial Chemistry: Synthesis, Characterization, and Screening of Small-Molecule Libraries in Solution. *Chem. Biol.* **1995**, *2*, 171−183.

(20) A scaffold with n sites and one C_2-symmetric element is combinatorialized with m functionalities to give a library containing $[m^{(n-1)}(m + 1)]/2$ compounds. Here, each of sublibraries **1a**−**m** contains $[6^{(3-1)}(6 + 1)]/2 = 126$ compounds, and each of sublibraries **16**−**21** contains $[6^{(2-1)}(6 + 1)]/2 = 21$ compounds.

(21) Fukuyama, T.; Jow, C. K.; Chung, M. 2- and 4-Nitrobenzenesulfonamides: Exceptionally Versatile Means for Preparation of Secondary Amines and Protection of Amines. *Tetrahedron Lett.* **1995**, *36*, 6373−6374.

(22) National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*; NCCLS Document M7-A3; NCCLS: Villanova, PA, 1993; Vol. 13.

(23) Benson, S. A.; Misra, R.; Sampson, B. A. Identification and Characterization of a New Gene of *Escherichia coli* K-12 Involved in Outer Membrane Permeability. *Genetics* **1989**, *122*, 491−501.

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