Pergamon

Tetrahedron 54 (1998) 3999–4012

TETRAHEDRON

Solution Phase Combinatorial Chemistry. Discovery of 13- and 15-Membered Polyazapyridinocyclophane Libraries with Antibacterial Activity

Haoyun An, Tingmin Wang, Venkatraman Mohan, Richard H. Griffey, and P. Dan Cook*

Department of Medicinal Chemistry, Isis Pharmaceuticals, Inc.,
2292 Faraday Avenue, Carlsbad, California 92008, USA

Abstract: A solution phase simultaneous addition of functionalities (SPSAF) combinatorial approach was utilized to synthesize 40 polyazacyclophane libraries (total complexity of 4275). Eighteen different functionality sets, utilizing 42 functionalities, were designed to disrupt RNA-protein interactions. Guanidine functionality sets with a greater potential to form positive charges provided the most active libraries. Differences in antibacterial activity are clearly related to different ring sizes with the more rigid 13-membered scaffold affording more active libraries compared with libraries from the 15-membered scaffold. Molecular modeling established a significant difference in the shapes of 13- and 15-membered pyridinophanes. Several libraries exhibited potent antibacterial activity.

INTRODUCTION

Combinatorial synthesis of chemical libraries is undergoing rapid examination as a tool to enhance drug research and development.[1] While it appears obvious that combinatorial chemistry strategies offer the potential to enhance drug development by shortening the time to optimize a new lead by structure-activity relationship studies, it is often less appreciated that the greatest value of combinatorial chemistry strategies lies in its potential to enhance discovery of novel leads or pharmacophores. Early chemical libraries were prepared as large mixtures generated by solid phase approaches.[2] More recently, parallel synthesis of single compounds, still utilizing solid phase chemistry, has been the major approach; this approach is particularly amenable to lead optimization. Solution phase combinatorial approaches have only recently become of interest.[3-6] We have recently reported a process to prepare chemical libraries by adding a mixture of functionalities to a single scaffold with several reactive sites in solution.[7-9] This process has been labeled SPSAF (solution phase simultaneous addition of functionalities). The approach was designed with an initial focus on lead discovery by incorporating the advantages of the greater diversity obtainable in large mixtures, the opportunity to more rapidly prepare libraries with different scaffolds (shapes), and iterative deconvolution and fractionation processes to reduce the complexity of the libraries. In this approach, we have utilized novel, unsymmetrical polyazaphane scaffolds (not based on known pharmacophores) to enhance our chances of discovering novel pharmacophores, which may provide novel antibacterial modes of action. Furthermore, as the scaffold (or footprint) of a combinatorial library is the major factor in structure-space searches, we have been interested in a chemical process that would allow rapid synthesis of various scaffolds. In this regard, a variety of polyazaphanes with different ring sizes could rapidly be prepared by simply changing the precursor linear polyamine (Figure 1). Changing the ring size of polyazacyclophanes would significantly change footprints or shapes of the cyclic structures. *t*-Boc protected unsymmetrical 13- and 15-membered polyazacyclophanes **1** and **2**

0040-4020/98/$19.00
PII: S0040-4020(98)00131-8

(Scheme 1) have been synthesized by this approach; the 15-membered polyazaphane scaffold was utilized in our initial studies to develop the SPSAF approach.[7-8] In that work, we elected to utilize *meta*-substituted benzyl bromides as reactive functionalities to combinatorialize the nucleophilic secondary amine sites on the scaffold. A series of high-purity, first round libraries were generated from the 15-membered polyazaphane scaffold **2** by employing the SPSAF approach. Several of these libraries exhibited antibacterial activity against bacteria *S. pyogenes* and *E. coli imp*$^-$ with minimum inhibitory concentrations (MICs) in the range of 2.5-20 μM.

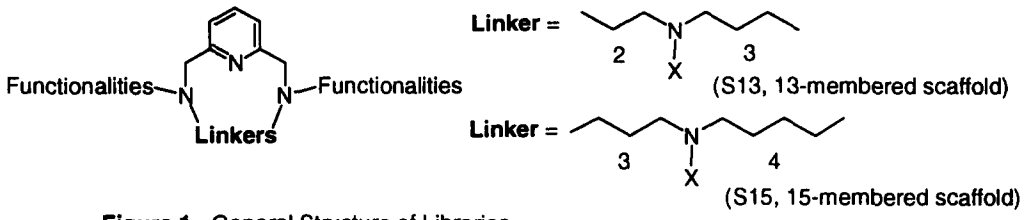


Figure 1. General Structure of Libraries

In the present report, we describe the generation of several series of 40 libraries **Ia,b-IXa,b** and **X-XVII** (total 4275 compounds) (Table 1) with a range of diversity and complexity from the 13- and 15-membered polyazaphane scaffolds **1-3** (Scheme 1). Two or three sites on the polyazaphanes were combinatorialized simultaneously. The functionalities range from the development set of *meta*-substituted benzyls to very complex polar groups which may have a propensity to target RNA motifs. Eighteen different sets of functionalities (Figure 2) were utilized to combinatorialize the 13- and 15-membered polyazaphanes. All of the libraries and sub-libraries were screened for antibacterial activity. In this manner, a direct comparison of the effect of ring size on antibacterial activity could be assessed. Molecular modeling of library members from the 13- and 15-membered scaffolds was accomplished to ascertain that ring size changes, indeed, do significantly alter their shapes and thus biological activity.

RESULTS AND DISCUSSION

Three types of libraries were prepared from the *t*-Boc protected scaffolds **1-2** and the unprotected scaffold **3**. In the first case, libraries **Ia** (13-membered scaffold) and **Ib**[8] (15-membered scaffold) were prepared by simultaneously combinatorializing the benzylic secondary amines of scaffolds **1** and **2** with a set of 10 *meta*-substituted benzyl bromides (functionality set **A**). The *t*-Boc protecting group was removed by trifluoroacetic acid (TFA) to give intermediate libraries. According to the "fix last" method, these libraries were divided into six portions, which were then separately reacted with the corresponding bromide derivatives from functionality set **B** to afford the final sublibraries **Ia** and **Ib**. The functionality placed in the last position structurally differentiates the various sublibraries and also should be responsible for any biological differences among the sublibraries. Thus, 8 new sublibraries **Ia**, each having 100 (10^2) compounds, were prepared. The functional groups in set **A** (Figure 2) were primarily selected to facilitate the development of the SPSAF approach. Several sublibraries generated from this development work demonstrated antibacterial activity and are available for second round screening according to an iterative deconvolution process. The polar libraries **IIa,b-IXa,b** were prepared by combinatorializing the benzylic secondary nitrogens of scaffolds **1** and **2** with more diverse, polar functionalities (functionality sets **C-J**) while the remaining secondary nitrogen was

Scheme 1.

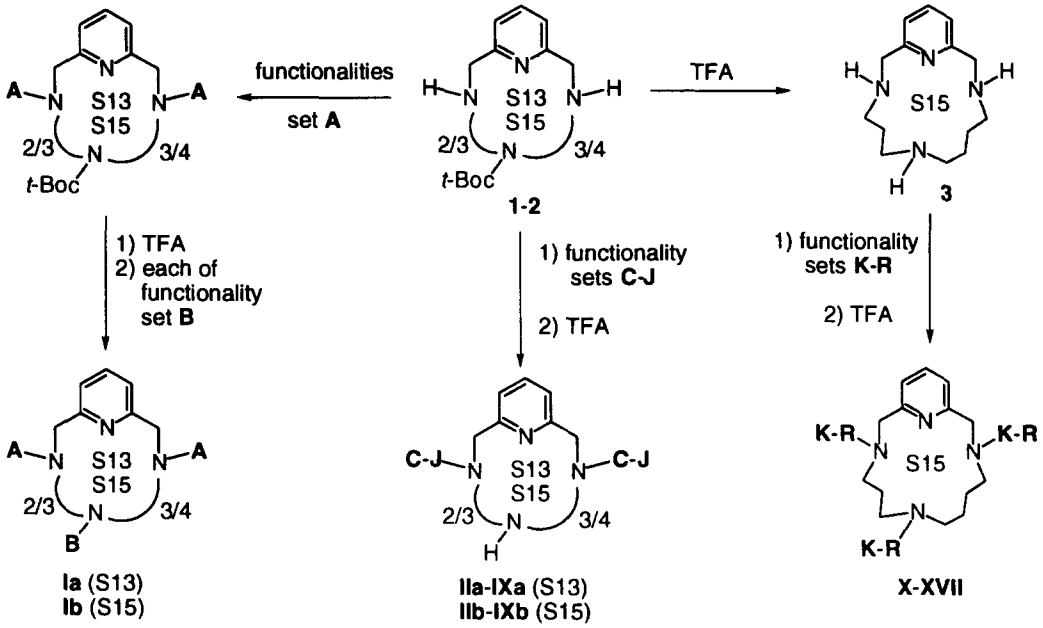


Table 1. The First Round Diverse Combinatorial Libraries

Library number	Scaffold	Functionality Set (functionality #)	X	Complexity	Sublibrary
Ia	S13	A (10)	B	100	8
Ib	S15	A (10)	B	100	8
IIa,b	S13 / S15	C (5)	H	25	2
IIIa,b	S13 / S15	D (5)	H	25	2
IVa,b	S13 / S15	E (6)	H	36	2
Va,b	S13 / S15	F (8)	H	64	2
VIa,b	S13 / S15	G (5)	H	25	2
VIIa,b	S13 / S15	H (6)	H	36	2
VIIIa,b	S13 / S15	I (6)	H	36	2
IXa,b	S13 / S15	J (6)	H	36	2
X	S15	K (6)		216	1
XI	S15	L (6)		216	1
XII	S15	M (7)		343	1
XIII	S15	N (7)		343	1
XIV	S15	O (7)		343	1
XV	S15	P (6)		216	1
XVI	S15	Q (6)		216	1
XVII	S15	R (6)		216	1

protected by a *t*-Boc group. The final libraries for antibacterial screening were obtained by removing the *t*-Boc on the scaffolds and functionalities with TFA and conversion into their hydrochloride salts. In this series, libraries with low complexity (5^2, 6^2 and 8^2) were generated for initial antibacterial studies. In the final group of libraries, all three positions of the completely unprotected scaffold **3** were simultaneously combinatorialized

with diverse functionality sets **K-R** to provide libraries **X-XVII** with complexities of 216 (6^3) and 343 (7^3). These libraries were not divided into sublibraries with fixed positions for an iterative deconvolution process and will be fractionated into smaller samples with one to ten compounds by a HPLC process.[10]

The polar functionalities selected for libraries **IIa,b-IXa,b** and **X-XVII** were based on their commercial availability or synthetic accessibility and whether they possess functional groups that may bind to RNA. The electrophilic functionalities used in this work are activated as benzyl halides, α-halo-acetamides, anhydrides, and electron deficient heterocycles. They have reasonably similar reactivity and are used in a slight excess over total nucleophilic sites on the scaffolds. The corresponding bromide derivatives were used for most functionalities. Chloride derivatives R_{24}-Cl and R_{32}-Cl, and 1,3-propanesulfone were used for functionalities R_{24}, R_{32}, and R_{20} because they have similar reactivity to bromide derivatives as tested. Libraries **VIa,b** and **XIII** were prepared from the corresponding chloride functionalities by heating the reaction mixture at 50-60 °C overnight. We were also interested in several novel functionalities; these were synthesized as described. Bis-*t*-Boc-protected guanyl piperazine **11** was prepared by the reaction of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea **10** with excess piperazine (Scheme 2). However, the same guanyl group could not be introduced onto aniline amino group of compound **5** by the guanylating agent **10**. *N,N'*-bis(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (**4**),[11] a much more reactive guanylating agent, was used for the preparation of guanidine compound **6** in 91% yield. Bromination of **6** with *N*-bromosuccinimide (NBS) in the presence of PPh_3 afforded the corresponding bromide **7**. The guanidine compound **11** was reacted with bromoacetyl bromide, chloroacetyl chloride, 3-(chloromethyl)benzoyl chloride, and 4-(chloromethyl)benzoyl chloride to afford the corresponding guanidine bromide or chloride derivatives **12**, **13**, **14** and **15**, respectively, in excellent yields. *t*-Boc-protected piperazine derivatives **17**, **18**, and **19** were synthesized by the reaction of 1-(*tert*-butoxycarbonyl)piperazine **16**[12] with bromoacetyl bromide, chloroacetyl chloride, and 4-(chloromethyl)benzoyl chloride. Compounds **20** (for R_{18}) and **23** (for R_{42}) were synthesized by the reaction of mono-*t*-Boc-protected ethylenediamine[13] with chloroacetyl chloride and 4-(chloromethyl)benzoyl chloride, respectively. The 1-(*tert*-butoxycarbonyl)-2-(chloromethyl)benzimidazole (**21**) (for R_{29}) was prepared from its corresponding chloride. New compounds **6**, **7**, **11-15**, **18-21** and **23** were characterized by NMR, mass spectroscopic, and combustion analyses. Compounds **17**,[14] **8**[15] and **9**[15] were prepared by modified procedures and were fully characterized. In several cases the desired functionalities in the resulting libraries were obtained by a library from library approach in that reactive functional groups in one library were chemically converted to desired functional groups in the final library. For example, libraries **VIIIa,b** and **IXa,b** with carboxylic acid and acyl guanidine groups in functionality sets **I** and **J** were derived from libraries **VIIa,b** with ester functionality set **H**. Similarly, libraries **XVI** and **XVII** with acid and guanidine functionality sets **Q** and **R** were obtained from library **XV** with ester functionality set **P**. Therefore, ester groups of sets **H** and **P** were hydrolyzed with NaOH to give the corresponding libraries with carboxylic acid sets **I** and **Q**, and also reacted with excess guanidine to afford libraries with acyl guanidine sets **J** and **R**, respectively. Most of the polar functional groups were protected by *t*-Boc groups for the combinatorialization process and the final libraries were obtained by the deprotection of original libraries with TFA.

Our objective in this particular combinatorial chemistry project is to selectively disrupt RNA protein interactions essential for bacterial growth. In this regard, out of 42 different functionalities attached to 13- and 15-membered scaffolds, a number are of a polar nature and are expected to interact with RNA-protein

Functionality set A:

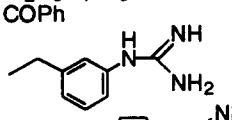
$R_1 = CH_2Ph$
$R_2 = CH_2C_6H_4CH_3$-*m*
$R_3 = CH_2C_6H_4F$-*m*
$R_4 = CH_2C_6H_4CN$-*m*
$R_5 = CH_2CH{=}CHPh$
$R_6 = CH_2C_6H_4NO_2$-*m*
$R_7 = CH_2C_6H_4Cl$-*m*
$R_8 = CH_2C_6H_4COOCH_3$-*m*
$R_9 = CH_2C_6H_4CF_3$-m
$R_{10} = CH_2C_6H_4Br$-*m*

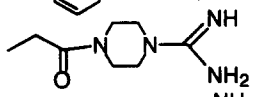
Functionality set B:

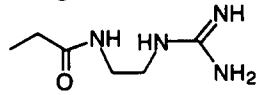
t-Boc, H, R_1, R_2, R_3, R_4, R_5
$R_{11} = CH_2CONH_2$

Functionality set C:

$R_9 = CH_2C_6H_4CF_3$-*m*
$R_{12} = COPh$

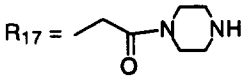
$R_{13} =$ 

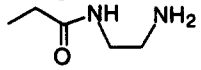
$R_{14} =$ 

$R_{15} =$ 

Functionality set D:

R_3, R_{12}
$R_{16} = CH_2C_6H_4NH_2$-*m*

$R_{17} =$ 

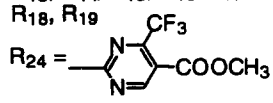
$R_{18} =$ 

Functionality set E:

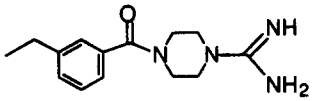
$R_{12} = COPh$
$R_{19} = CH_2COOH$
$R_{20} = CH_2CH_2CH_2SO_3H$
$R_{21} = CH_2C_6H_4COOH$-*p*
$R_{22} = CH_2C_6H_4CH_2COOH$-*p*
$R_{23} = CH_2C_6H_4CN$-*p*

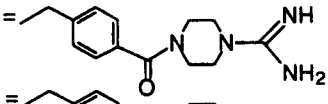
Functionalities set F:

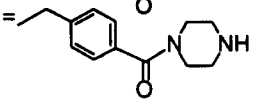
R_{13}, R_{14}, R_{15}, R_{16}, R_{17}
R_{18}, R_{19}

$R_{24} =$ 

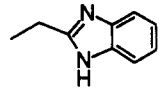
Functionality set G:

$R_{25} =$ 

$R_{26} =$ 

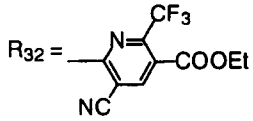
$R_{27} =$ 

$R_{28} = CH_2P(O)(OEt)_2$

$R_{29} =$ 

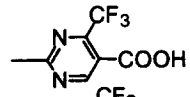
Functionality set H:

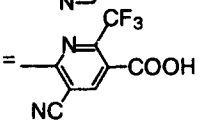
R_1, R_{12}, R_{24}
$R_{30} = CH_2COOCH_3$
$R_{31} = CH_2C_6H_4COOCH_3$-*p*

$R_{32} =$ 

Functionality set I:

R_1, R_{12}, R_{19}, R_{21}

$R_{33} =$ 

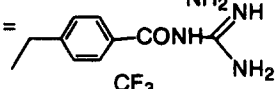
$R_{34} =$ 

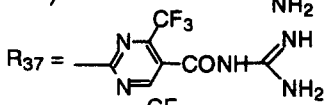
Functionality set R:

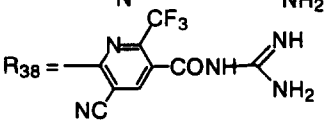
R_{11}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}

Functionality set J:

R_1, R_{12}
$R_{35} = CH_2CONH$ 

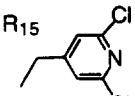
$R_{36} =$ 

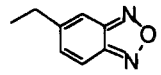
$R_{37} =$ 

$R_{38} =$ 

Functionality set K:

R_{12}, R_{13}, R_{14}, R_{15}

$R_{39} =$ 

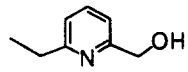
$R_{40} =$ 

Functionality set L:

R_{12}, R_{16}, R_{17}, R_{18}, R_{39}, R_{40}

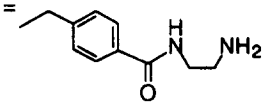
Functionality set M:

R_9, R_{12}, R_{13}, R_{14}, R_{17}, R_{19}

$R_{41} =$ 

Functionality set N:

R_{25}, R_{26}, R_{18}, R_{27}, R_{28}, R_{29}

$R_{42} =$ 

Functionality set O:

R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{19}

Functionality set P:

R_{11}, R_{24}, R_{30}, R_{31}, R_{32}, R_{39}

Functionality set Q:

R_{11}, R_{19}, R_{21}, R_{33}, R_{34}, R_{39}

Figure 2. Functionality Sets A - R for Libraries

complexes. These include nine types of guanidine functionalities (R_{13}, R_{14}, R_{15}, R_{25}, R_{26}, R_{35}, R_{36}, R_{37}, and R_{38}), five types of amine functionalities (R_{16}, R_{17}, R_{18}, R_{27}, and R_{42}), six types of anionic functionalities (R_{19}, R_{20}, R_{21}, R_{22}, R_{33}, and R_{34}), six esters (R_8, R_{24}, R_{28}, R_{30}, R_{31}, and R_{32}). Furthermore, 31 functionalities had an aromatic or a hetero-aromatic ring, and 13 functionalities had an amide moiety. In devising the specific functionalities sets, as an initial approach, we were primarily interested in displaying only one informationally rich functional group in the set, but in several structurally different environments. For example, three or four types of guanidines are displayed in functionality sets **C**, **F**, **J**, **K**, **O**, and **R**; four types of acids are displayed in sets **E**, **I**, and **Q**; three types of amines are contained in sets **D**, **F**, and **L**; and three types of esters in sets **H** and **P**. Each of the functionality sets contained at least one non-polar aromatic ring or one functionality that would reduce the number of cationic charges. Acylation of secondary amines with anhydrides provided an amide which is not protonated, whereas alkylations with halo-benzyls and acetamides provided protonable tertiary amines. Reduction of the cationic charge of the libraries was also achieved by using halo-substituted heterocycles R_{24}, R_{32}, R_{33}, R_{34}, R_{37}, and R_{38} which on alkylation provided non-protonable hetero-aromatic amines. Functionalities R_{33}, R_{34}, R_{37}, and R_{38} are of particular interest as they do not provide protonable sites on the scaffold yet provided negative or positive charges on the outer periphery of the molecules. Thus, a typical library consists of three to four functionalities of similar type but structurally different with non-polar aromatic, acyl, and polar functionalities to control the overall charge. In the second step for evaluating functionality sets, libraries were designed to contain several informationally rich functionalities; guanidines / amines in sets **F**, **G**, and **N**, guanidines / an amine / a hydroxyl in set **M**, and guanidines / amines / an acid in set **O** are examples of mixed different functionality sets with high diversity. In this manner, the libraries would possess a range of pKas (charges), lipophilicities, and complexities (25 to 343

Scheme 2.

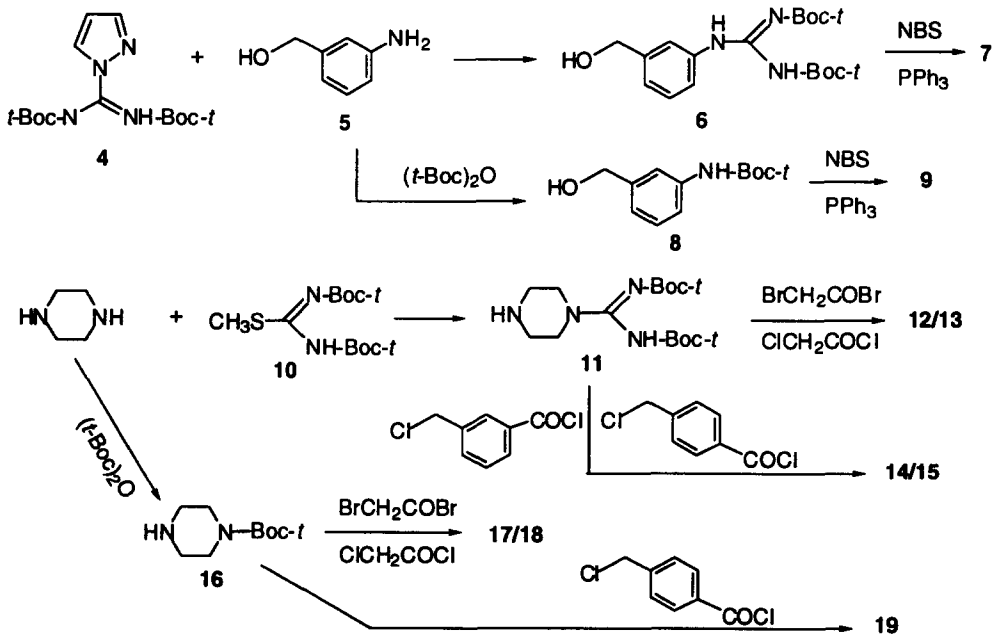


Table 2. Activities of the First Round Libraries in Growth Inhibition Assays[a]

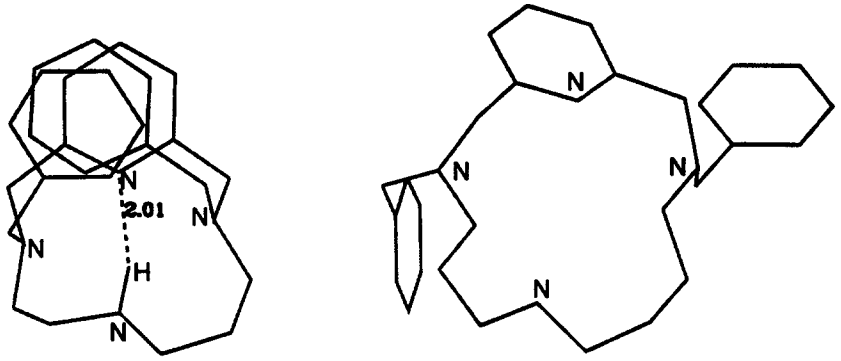
	Ia (S13)		**Ib** (S15)	
X	*S. pyogenes*	*E. coli*	*S. pyogenes*	*E. coli*
Boc	>100	>100	>100	>100
H	5-25	5-25	5-10	10-20
R_1	1-5	5-25	>100	>100
R_2	5-25	1-5	>100	>100
R_3	5-25	5-25	>100	>100
R_4	5-25	5-25	5-10	5-10
R_5	1-5	1-5	2.5-5	<2.5
R_{11}	>100	>100	>100	>100

[a] The MIC (minimum inhibitory concentration, μM) value is given as a range of library concentration (total concentration of compounds in library). 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.

Members / library with 2 to 3 sites and 5 to 7 functionalities) which would lend themselves to HPLC fractionation procedures[10] as well as potentially disrupting RNA-protein interactions.

Libraries **Ia** (S13) and **Ib** (S15), combinatorialized with the *meta*-substituted benzyl functionality set **A**, have members of the functionality set **B** placed in the fixed position. They were screened against *S. pyogenes* and *E. coli imp*$^-$ in bacterial anti-growth assays, and their MIC data are listed in Table 2. Thus, eight sublibraries **Ia** from 13-membered scaffold **1** were directly compared with the corresponding eight sublibraries **Ib** from 15-membered scaffold **2**. The libraries **Ia** from 13-membered scaffold, containing 100 compounds in each subset, exhibited potent activity in the MIC range of 1 to 25 μM in the two bacterial assays for all sublibraries except the *t*-Boc and the acetamide (R_{11}) libraries. Much less activity was seen in the corresponding libraries from the 15-membered scaffold. For example, the sublibraries from 13-membered scaffold with benzyl (R_1) *meta*-methyl benzyl (R_2) and *meta*-fluorobenzyl (R_3) at the fixed position exhibited MICs of 1-25 μM in two assays, whereas the libraries for the corresponding 15-membered scaffold exhibited a MIC of >100 μM. Clearly, the ring size had an effect on the biological activity, with the libraries from the more rigid 13-membered scaffold having greater activity. In the screening of polar libraries, only libraries **IIa** and **IIb** (functionality set **C** displaying three types of guanidines) had activity of 95% inhibition at 20 μM) for *S. pyogenes* and *E. coli imp-* with both ring systems. Library **VIa** from the 13-membered scaffold with two guanidines and an amine exhibited 95% inhibition at 20 μM in both assays, whereas the corresponding libraries **VIb** from the 15-membered scaffold were not active at 100 μM. On the other hand, libraries **X**, **XII** and **XIII**, in which three sites of the 15-membered scaffold **3** were combinatorialized with guanidines and amines, exhibited over 95% inhibition at 20 μM for both tested assays. Libraries with functionality sets primarily displaying acid groups (**IVa,b**, **VIIIa,b**, and **XV** from scaffolds **1-3**) and amines (**IIIb** and **XI** from scaffolds **2** and **3**) were not active. An interesting comparison is that libraries **IXa,b** with functionality set **J**, containing four acylguanidines, is inactive, whereas the most active libraries **IIa,b** with functionality set **C** has three guanidines. Another difference in these sets is that the inactive set **J** has three functionalities that remove positive charge from libraries whereas the active **C** set has only one, the benzoyl R_{12}; thus, libraries from set **C** will have a more cationic nature and this may be essential for antibacterial activity. A crude rank order of activity among the functionality sets is guanidines > guanidines~amines > amines > acids, and the order of

activity for similar libraries from the different scaffolds is 13-membered > 15-membered. The different activity of libraries from 13- and 15-membered scaffolds may be due to the overall shape differences and the conformational preference. Figure 3 depicts the molecular modeling results for the minimum energy conformers of bis-benzyl substituted S13 and S15 compounds. The observed intramolecular hydrogen bond in S13 compound (indicated by the dashed line) orients the three aromatic groups to the most favored stacked conformation. The possibility of such an intramolecular H-bond formation on the larger ring S15 is ruled out; thus, an unstacked conformation of the aromatic groups results.



S13 S15

Figure 3. Minimum Energy Conformers of S13 and S15 compounds

Screening at lower concentrations and deconvolution of active libraries by a HPLC fractionation method are in progress.[10] Furthermore, the polar libraries are being screened in a series of biochemical RNA-protein assays to investigate the correlation of the inhibition of bacteria with the disruption of bacterial RNA-protein interactions.

In conclusion, we have combinatorialized 13- and 15-membered pyridinocyclophane scaffolds **1-3** with 18 selected functionality sets derived from 42 different functionalities. This afforded 40 libraries with a total complexity of 4275 compounds. A solution phase simultaneous addition of functionalities (SPSAF) approach was utilized to synthesize the libraries. The functionality sets were designed to display primarily a polar functional groups in several structural environments, along with several less informationally rich groups to control the cationic nature and complexity of the libraries. Guanidine functionality sets having a greater potential for positive charges provided the most active libraries. Differences in antibacterial activity could clearly be related to the different ring sizes. When directly comparing the antibacterial activity of the two ring sizes, only one library out of 16, had the same activity in both rings. Molecular modeling results indicated that 13- and 15-membered pyridinophanes exhibit significantly different shapes. Several libraries exhibited potent antibacterial activity.

EXPERIMENTAL

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 199.975 MHz. Deuteriochloroform was used as solvent with the added tetramethylsilane as an internal standard. High-resolution (FAB) positive ion mass spectra were recorded on a VG ZAB-BSE double focusing high resolution mass spectrometer

equipped with a cesium ion gun. Polyazacyclophane scaffolds **1-3** were synthesized according to our reported procedures.[7,8] Compounds **16**,[12] *N,N'*-bis(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (**4**),[11] and mono-(*tert*-butoxycarbonyl)ethylenediamine[13] were prepared based on literature procedures. The antimicrobial and antifungal assays were performed against *Streptococcus pyogenes* ATCC 14289 and *Escherichia coli imp*⁻ in microtiter plate format as described elsewhere.[8,9] All the computations were performed on an Indigo2 machine using the MSI molecular modeling software. The initial structures of S13 and S15 compounds have been model-built. Quenched molecular dynamics calculations using the DISCOVER module of the software were performed to explore the conformational space and identify low energy conformations. The CFF91 force field was employed in the present study. A distance dependent dielectric constant used in the calculations mimics the effect of explicit solvent.

3-[*N,N'*-Bis(*tert*-butoxycarbonyl)guanidino]benzyl Alcohol (6). A solution of 3-aminobenzyl alcohol (**5**) (2.0 g, 16.2 mmol) and *N,N'*-bis(*tert*-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (**4**)[11] (4.53 g, 14.6 mmol) in 30 mL of dry THF was stirred at rt for 2 days. The solvent was evaporated, and the residue was dissolved in $CHCl_3$. The solution was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column. Elution with 200:1 CH_2Cl_2-MeOH and then 4:1 hexanes-EtOAc gave 4.95 g (91%) of product **6** as a white solid, mp 73-75 °C; silica gel TLC R_f 0.34 (2:1 hexanes-EtOAc); ^{1}H NMR δ 1.51 (s, 9H), 1.54 (s, 9H), 4.68 (s, 2H), 7.12 (d, 1H, J = 7.8 Hz), 7.30 (br, 1H, ex.D_2O), 7.34 (t, 1H, J = 7.8 Hz), 7.58 (d, 2H, J = 7.8 Hz), 10.36 (s, 1H), 11.61 (s, 1H); ^{13}C NMR δ 25.5, 27.9, 28.2, 28.6, 64.0, 79.6, 83.6, 120.6, 120.9, 121.0, 123.2, 123.5, 128.6, 128.9, 136.4, 142.3, 153.2, 153.7, 163.3; HRMS (FAB) *m/z* 366.201 $(M + H)^+$ ($C_{18}H_{28}N_4O_5$ requires 366.202).

3-[*N,N'*-Bis(*tert*-butoxycarbonyl)guanidino]benzyl Bromide (7). To a solution of **6** (1.45 g, 3.97 mmol) in 15 mL of CH_2Cl_2 were added *N*-bromosuccinimide (NBS) (0.78 g, 4.4 mmol) and PPh_3 (1.25 g, 4.76 mmol). The resulting solution was stirred at rt for 2 h, and the solvent was evaporated. The residue was purified by flash chromatography on a silica gel column. Elution with 50:1 hexanes-EtOAc gave 1.21 g (72%) of product **7** as a white foam; silica gel TLC R_f 0.54 (5:1 hexanes-EtOAc); ^{1}H NMR δ 1.51 (s, 9H), 1.54 (s, 9H), 4.47 (s, 2H), 7.14 (d, 1H, J = 7.6 Hz), 7.32 (t, 1H, J = 7.8 Hz), 7.58-7.64 (m, 2H), 10.37 (s, 1H), 11.63 (s, 1H); HRMS (FAB) *m/z* 428.117 $(M + H)^+$ ($C_{18}H_{27}BrN_3O_4$ requires 428.118). Anal. Calcd for $C_{18}H_{26}BrN_3O_4$: C, 50.57; H, 6.14; N, 9.84. Found: C, 50.55; H, 6.12; N, 9.99.

3-[(*tert*-Butoxycarbonyl)amino]benzyl Alcohol (8). A solution of 3-aminobenzyl alcohol (**5**) (0.62 g, 5.0 mmol), di-*tert*-butyl dicarbonate (1.09 g, 5.0 mmol) and triethylamine (1.50 g, 15.0 mmol) in 20 mL of dry THF was stirred at rt for two days. The solvent was evaporated under vacuum, and the residue was dissolved in a mixture of $CHCl_3$ and H_2O. 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 200:1 CH_2Cl_2-MeOH gave 0.88 g (79%) of product **8** as a colorless oil (lit:[14] yellow oil with ^{1}H NMR only); silica gel TLC R_f 0.43 (10:1 CH_2Cl_2-MeOH); ^{1}H NMR δ 1.48 (s, 9H), 3.69 (t, 1H, J = 5.0 Hz, ex D_2O), 4.49 (d, 2H, J = 5.4 Hz), 6.92 (d, 1H, J = 7.0 Hz), 7.10-7.26 (m, 4H); ^{13}C NMR δ 28.3, 64.6, 80.5, 117.1, 117.5, 121.3, 128.9, 138.6, 142.0, 153.3; HRMS (FAB) *m/z* 223.129 $(M + H)^+$ ($C_{12}H_{18}NO_3$ requires 223.128). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.54; H, 7.68; N, 6.28. Found: C, 64.31; H, 7.59; N, 6.37.

3-[(*tert*-Butoxycarbonyl)amino]benzyl Bromide (9). Compound **9** was prepared as described

above for **7** from **8** (8.25 g, 37 mmol), PPh_3 (11.64 g, 44.4 mmol), and NBS (7.24 g, 41 mmol) in 145 mL of CH_2Cl_2. Flash chromatographic purification on a silica gel column using 50:1 hexanes-EtOAc as an eluent afforded 6.80 g (65%) of product **9** as a white solid, mp 121-122 °C (lit:[15] mp 120.5-121 °C with ^1H NMR); silica gel TLC R_f 0.52 (5:1 hexanes-EtOAc); ^1H NMR δ 1.52 (s, 9H), 4.42 (s, 2H), 6.77 (s, 1H), 7.04-7.07 (m, 1H), 7.20-7.25 (m, 2H), 7.51(s, 1H); ^{13}C NMR δ 28.4, 33.5, 80.8, 118.9, 123.9, 129.7, 138.7, 152.8; HRMS (FAB) *m/z* 308.027 $(M + Na)^+$ ($C_{12}H_{16}BrNO_2Na$ requires 308.026). Anal. Calcd for $C_{12}H_{16}BrNO_2$: C, 50.52; H, 5.66; N, 4.91. Found: C, 50.30; H, 5.49; N, 4.74.

1-[*N,N'*-Bis(*tert*-butoxycarbonyl)]guanylpiperazine (11). A mixture of piperazine (34.46 g, 0.40 mol) and 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (**10**) (29.0 g, 0.1 mol) in 260 mL of DMF was stirred at 50-60 °C for 2 h. The solvent was evaporated to dryness, and the residue was dissolved in 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 using 1:2 hexanes-EtOAc and then 1:1 EtOAc-MeOH as eluents to afford 27.2 g (83%) of product **11** as a white solid, mp 135-136 °C; silica gel TLC R_f 0.34 (100% MeOH); ^1H NMR δ 1.42 (s, 18H), 2.78-2.91 (m, 4H), 3.40-3.66 (m, 4H); HRMS (FAB) *m/z* 329.218 $(M + H)^+$ ($C_{15}H_{29}N_4O_4$ requires 329.218). Anal. Calcd for $C_{15}H_{28}N_4O_4$: C, 54.86; H, 8.58; N, 17.06. Found: C, 54.87; H, 8.48; N, 17.20.

1-(Bromoacetyl)-4-[*N,N'*-bis(*tert*-butoxycarbonyl)]guanylpiperazine (12). A solution of bromoacetyl bromide (2.06 g, 10.2 mmol) in 20 mL of THF was added dropwise to a stirred solution of **11** (3.28 g, 10.0 mmol) and diisopropylethyl amine (2.1 mL, 1.56 g, 12.0 mmol) in 50 mL of THF at -30 °C. The cooling bath was removed, and the reaction mixture was stirred at rt for 1.5 h. After the solvent was evaporated, the residue was dissolved in chloroform. This solution was washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column. Elution with 5:1, 2:1, and then 1:1 hexanes-EtOAc afforded 3.5 g (78%) of product **12** as a white solid, mp >220 °C; silica gel TLC R_f 0.45 (1:2 hexanes-EtOAc); ^1H NMR δ 1.46 (s, 18H), 3.48-3.75 (m, 8H), 3.85 (s, 2H), 10.26 (br, 1H); HRMS (FAB) *m/z* 449.141 $(M + H)^+$ ($C_{17}H_{30}BrN_4O_5$ requires 449.140). Anal. Calcd for $C_{17}H_{29}BrN_4O_5$: C, 45.44; H, 6.49; N, 12.46. Found: C,45.54; H, 6.25; N, 12.66.

1-(Chloroacetyl)-4-[*N,N'*-bis(*tert*-butoxycarbonyl)]guanylpiperazine (13). A solution of chloroacetyl chloride (1.77 g, 15.6 mmol) in 20 mL of anhydrous THF was added to a stirred solution of **11** (4.93 g, 15.0 mmol) and diisopropylethyl amine (3.2 mL, 2.34 g, 18 mmol) in 80 mL of THF at 0 °C. The resulted reaction mixture was allowed to warm to rt and stirred for 2 h. The solvent was evaporated, and the residue was dissolved in chloroform. The chloroform solution was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column. Elution with 5:1, 2:1, and then 1:1 hexanes-EtOAc afforded 5.76 g (95%) of product **13** as a white solid, mp 138-139 °C; silica gel TLC R_f 0.48 (1:2 hexanes-EtOAc); ^1H NMR δ 1.38 (s, 18H), 3.40-3.66 (m, 8H), 4.00 (s, 2H), 10.00 (br, 1H); HRMS (FAB) *m/z* 537.086 $(M + Cs)^+$ ($C_{17}H_{29}ClN_4O_5Cs$ requires 537.088). Anal. Calcd for $C_{17}H_{29}ClN_4O_5$: C, 50.43; H, 7.21; N, 13.83. Found: C, 50.56; H, 7.12; N, 14.00.

1-[3-(Chloromethyl)benzoyl]-4-[*N,N'*-bis(*tert*-butoxycarbonyl)]guanylpiperazine (14). Compound **14** was prepared as described above for **13** from **11** (3.28 g, 10.0 mmol), 3-(chloromethyl)benzoyl chloride (1.94 g, 10.26 mmol), and diisopropylethyl amine (2.1 mL, 1.56 g, 12.0 mmol) in 70 mL of THF. Flash chromatographic purification afforded 4.33 g (90%) of product **14** as a white

foam; silica gel TLC R_f 0.42 (1:1 hexanes-EtOAc); ^{1}H NMR δ 1.37 (s, 18H), 3.28-3.85 (m, 8H), 4.48 (s, 2H), 7.20-7.40 (m, 4H), 10.10 (s, 1H); MS (FAB) *m/z* 503 (M + Na)$^+$; HRMS (FAB) *m/z* 481.222 (M + H)$^+$ ($C_{23}H_{34}ClN_4O_5$ requires 481.221). Anal. Calcd for $C_{23}H_{33}ClN_4O_5$: C, 57.43; H, 6.90; N, 11.64. Found: C, 57.33; H, 6.72; N, 11.86.

1-[4-(Chloromethyl)benzoyl]-4-[*N,N'*-bis(*tert*-butoxycarbonyl)]guanylpiperazine (15). Compound **15** was prepared as described above for **13** from **11** (6.56 g, 20.0 mmol), 4-(chloromethyl)benzoyl chloride (3.88 g, 20.0 mmol), and diisopropylethyl amine (4.2 mL, 3.1 g, 24.0 mmol) in 150 mL of THF. Flash chromatographic purification afforded 9.5 g (98%) of product **15** as a white foam; silica gel TLC R_f 0.38 (1:1 hexanes-EtOAc); ^{1}H NMR δ 1.36 (s, 18H), 3.25-3.80 (m, 8H), 4.48 (s, 2H), 7.25-7.37 (m, 4H), 10.05 (br, 1H); MS (FAB) *m/z* 503 (M + Na)$^+$; HRMS (FAB) *m/z* 481.220 (M + H)$^+$ ($C_{23}H_{34}ClN_4O_5$ requires 481.221). Anal. Calcd for $C_{23}H_{33}ClN_4O_5$: C, 57.43; H, 6.90; N, 11.64. Found: C, 57.30; H, 7.08; N, 11.40.

1-(Bromoacetyl)-4-(*tert*-butoxycarbonyl)piperazine (17). Compound **17** was prepared as described above for compound **13** from **16**[12] (23.0 g, 123 mmol), bromoacetyl bromide (25.0 g, 123 mmol), and diisopropylethyl amine (21 mL, 15.6 g, 120 mmol) in 240 mL of CH_2Cl_2. Flash chromatographic purification afforded 25.0 g (66%) of product **17** as pale yellow crystals, mp 98-99 °C (lit:[14] brown oil with ^{1}H NMR only); silica gel TLC R_f 0.34 (1:1 hexanes-EtOAc); ^{1}H NMR δ 1.37 (s, 9H), 3.30-3.56 (m, 8H), 3.80 (s, 2H); ^{13}C NMR δ 25.8, 28.2, 28.5, 41.9, 43.2, 46.5, 80.3, 154.4, 165.4; MS (FAB) *m/z* 331 (M + Na)$^+$; HRMS (FAB) *m/z* 307.066 (M + H)$^+$ ($C_{11}H_{20}BrN_2O_3$ requires 307.065). Anal. Calcd for $C_{11}H_{19}BrN_2O_3$: C, 43.01; H, 6.22; N, 9.12. Found: C, 43.24; H, 6.22; N, 9.37.

1-(Chloroacetyl)-4-(*tert*-butoxycarbonyl)piperazine (18). Compound **18** was prepared as described above for **13** from **16**[12] (9.32 g, 50.0 mmol), chloroacetyl chloride (5.67 g, 50.2 mmol), and diisopropylethyl amine (10.5 mL, 7.79 g, 60.0 mmol) in 200 mL of THF. Flash chromatographic purification afforded 12.14 g (92%) of product **18** as a white solid, mp 95-96 °C; silica gel TLC R_f 0.50 (1:2 hexanes-EtOAc); ^{1}H NMR δ 1.39 (s, 9H), 3.30-3.56 (m, 8H), 4.02 (s, 2H); ^{13}C NMR δ 28.3, 40.8, 41.9, 43.1, 43.4, 46.1, 80.4, 154.4, 165.3; MS (FAB) *m/z* 263 (M + H)$^+$; HRMS (FAB) *m/z* 285.098 (M + Na)$^+$ ($C_{11}H_{19}ClN_2O_3Na$ requires 285.098). Anal. Calcd for $C_{11}H_{19}ClN_2O_3$: C, 50.29; H, 7.28; N, 10.66. Found: C, 50.10; H, 7.21; N, 10.90.

1-(*tert*-Butoxycarbonyl)-4-[4-(bromomethyl)benzoyl]piperazine (19). Compound **19** was prepared as described above for **13** from **16**[12] (3.82 g, 20.5 mmol), 4-(chloromethyl)benzoyl chloride (3.88 g, 20 mmol), and diisopropylethyl amine (3.92 mL, 2.91 g, 22.5 mmol) in 60 mL of THF. Flash chromatographic purification afforded 6.40 g (94%) of product **19** as a white solid, mp 147-148 °C; silica gel TLC R_f 0.45 (1:1 hexanes-EtOAc); ^{1}H NMR δ 1.44 (s, 9H), 3.25-3.70 (m, 8H), 4.57 (s, 2H), 7.30-7.48 (m, 4H); MS (FAB) *m/z* 361 (M + Na)$^+$; HRMS (FAB) *m/z* 339.146 (M + H)$^+$ ($C_{17}H_{24}ClN_2O_3$ requires 339.147). Anal. Calcd for $C_{17}H_{23}ClN_2O_3$: C, 60.26; H, 6.83; N, 8.26. Found: C, 60.10; H, 6.88; N, 7.99.

1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-[*N*-(chloroacetyl)amino]ethane (20). A solution of chloroacetyl chloride (2.82 g, 25 mmol) in 50 mL of dry THF was added dropwise to a solution of mono-(*tert*-butoxycarbonyl)ethylenediamine[13] (4.0 g, 25.0 mmol) and diisopropylethyl amine (3.15 g, 27.5 mmol) in 100 mL of dry THF at -10 °C. The resulting solution was stirred at -10 °C for 30 min, and the solvent was evaporated under vacuum. The residue was dissolved in a mixture of $CHCl_3$ and H_2O. The phases 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 recrystallized from 1:3 EtOAc-hexanes to give 5.47 g (93%) of product **20** as white crystals, mp 111.5-112.0 °C; silica gel TLC R_f 0.60 (10:1 CH_2Cl_2-MeOH); ^1H NMR δ 1.44 (s, 9H), 3.29-3.44 (m, 4H), 4.03 (s, 2H), 4.92 (br, 1H), 7.21 (br, 1H); ^{13}C NMR δ 28.5, 39.7, 41.0, 42.5, 79.7, 156.8, 166.9; HRMS (FAB) *m/z* 237.101 $(M + H)^+$ ($C_9H_{18}ClN_2O_3$ requires 237.100). Anal. Calcd for $C_9H_{17}ClN_2O_3$: C, 45.75; H, 7.26; N, 11.86. Found: C, 46.00; H, 7.32; N, 12.04.

1-(*tert*-Butoxycarbonyl)-2-(chloromethyl)benzimidazole (21). A solution of di-*tert*-butyl dicarbonate (6.6 g, 30.0 mmol) in 50 mL of THF was added slowly to a stirred solution of 2-(chloromethyl)benzimidazole (5.0 g, 30 mmol) and triethylamine (5.0 mL, 36 mmol) in THF (150 mL) at 0 °C. The reaction mixture was stirred at rt overnight. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2-H_2O. The layers were 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 under high vacuum. The residue was purified by flash chromatography on a silica gel column using 3:8 and then 4:6 EtOAc-hexanes to give 1.8 g (25%) of **21** as a pale yellow oil; ^1H NMR δ 1.81 (s, 9 H), 5.05 (s, 2 H), 7.30-7.41 (m, 2 H), 7.70-7.78 (m, 1 H), 7.91-8.00 (m, 1 H). ^{13}C NMR δ 24.0, 39.9, 86.4, 115.5, 120.2, 124.4, 125.9, 133.5, 142.0, 148.0, 150.1; HRMS (FAB) *m/z* 267.090 $(M + H)^+$ ($C_{13}H_{16}N_2O_2Cl$ requires 267.092).

2-(Bromomethyl)-6-(hydroxymethyl)pyridine (22). Compound **22** was prepared by a modified procedure as described above for **7** from 2,6-pyridinedimethanol (4.17g, 30.0 mmol), PPh_3 (5.24 g, 20.0 mmol), and NBS (3.56 g, 20.0 mmol). The spectroscopic property of this white crystalline product was consistent with that reported.[16]

1-[(*tert*-Butoxycarbonyl)amino]-2-[[4-(chloromethyl)benzoyl]amino]ethane (23). Compound **23** was synthesized as above for **19** from mono-(*tert*-butoxycarbonyl)ethylenediamine[13] (4.1 g 25.7 mmol), 4-(chloromethyl)benzoyl chloride (5.0 g, 25.7 mmol) and diisopropylethyl amine (9.96 g, 77.1 mmol). Purification by flash chromatography on a silica gel column gave 7.52 g (93.5%) of product **23** as a white solid, mp 143-144 °C; silica gel TLC R_f 0.50 (10:1 CH_2Cl_2-MeOH); ^1H NMR δ 1.43 (s, 9H), 3.34-3.42 (m, 2H), 3.49-3.56 (m, 2H), 4.58 (s, 2H), 5.19 (br, 1H), 7.38-7.42 (m, 3H), 7.78-7.82 (m, 2H); ^{13}C NMR δ 27.9, 28.2, 28.5, 28.8, 40.0, 42.0, 45.5, 79.9, 127.6, 128.5, 128.76, 134.2, 140.7, 157.6, 167.4; HRMS (FAB) *m/z* 313.133 $(M + H)^+$ ($C_{15}H_{22}ClN_2O_3$ requires 313.131). Anal. Calcd for $C_{15}H_{21}ClN_2O_3$: C, 57.67; H, 6.78; N, 8.97. Found: C, 57.47; H, 6.74; N, 8.93.

Library Ia (B = *t*-Boc). A mixture of benzyl bromide (147 μL, 207 mg, 1.2 mmol), α-bromo-*m*-xylene (169 μL, 222 mg, 1.2 mmol), 3-fluorobenzyl bromide (149 μL, 227 mg, 1.2 mmol), 3-cyanobenzyl bromide (237 mg, 1.2 mmol), cinnamyl bromide (237 mg, 1.2 mmol), 3-chlorobenzyl bromide (163 μL, 248 mg, 1.2 mmol), 3-nitrobenzyl bromide (259 mg, 1.2 mmol), methyl 3-(bromomethyl)benzoate (276 mg, 1.2 mmol), α′-bromo-α,α,α-trifluoro-*m*-xylene (185 μL, 288 mg, 1.2 mmol), and 3-bromobenzyl bromide (300 mg, 1.2 mmol) (total 12 mmol, 2.4 equiv) in 50 mL of anhydrous CH_3CN was added to a stirred mixture of compound **1** (1.60 g, 5.0 mmol) and anhydrous K_2CO_3 (10.0 g, 72 mmol) in 130 mL of CH_3CN. The resulting reaction mixture was stirred at rt overnight and concentrated. The residue was dissolved in a mixture of chloroform-water. 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 using 15:1 hexanes-EtOAc, 100% EtOAc, and then 20:1

EtOAc-MeOH as eluents. The library fractions, monitored by TLC, were collected and concentrated to afford 2.80 g (97%) of library **Ia** (B = *t*-Boc) as a pale yellow oil; MS (ES) *m/z* 501-659 $(M + H)^+$.

Library Ia (B = H). Trifluoroacetic acid (TFA) (35 mL) was added to a stirred solution of library **Ia** (B = *t*-Boc) (2.80 g, 4.87 mmol) in 7 mL of $CHCl_3$ at 0 °C. The resulting reaction mixture was stirred at rt for 3 h and concentrated to remove excess amount of TFA. The residue was dissolved in $CHCl_3$. The solution was washed with aqueous Na_2CO_3 solution, brine, dried (Na_2SO_4), and then concentrated. The residue was purified by flash chromatography on a silica gel column using 100:0, 40:1 and then 5:1 MeOH-30% aqueous NH_3 to afford 2.30 g (88%) of library **Ia** (B = H) as a light yellow oil; silica gel TLC R_f 0.35 (5:1 MeOH-30% aqueous NH_3); ^1H NMR δ 1.65-1.82 (m, 2H), 2.28-2.35 (m, 0.3H), 2.45-2.65 (m, 4H), 2.64-2.96 (m, 4H), 3.40-4.00 (m, 10.3H), 6.20-8.40 (m, 11.3H); MS (ES) *m/z* 401-559 $(M + H)^+$.

General Procedure for the Preparation of Libraries Ia (B = R_1-R_5 and R_{11}). A mixture of library **Ia** (B = H) (105 mg, 0.22 mmol), a corresponding bromide (R_1Br or R_5Br or $R_{11}Br$) (0.266 mmol), and K_2CO_3 (0.5 g, 3.6 mmol) in CH_3CN (5 mL) was stirred at rt overnight. After the solvent was evaporated, the residue was dissolved in a mixture of water-chloroform. 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 preparative TLC using 90:1 MeOH-30% aqueous NH_3 as a developing agent to afford **Ia** (B = R_1-R_5 and R_{11}) as colorless to light yellow oil in 80-96% yields.

General Procedure for the Preparation of Libraries IIa-VIIIa, IIb-VIIb and X-XV. A solution containing equal molar amounts of the corresponding bromides (R_nBr), or chloride (R_nCl), or benzoic anhydride, or 1,3-propanesultone (for R_{20}) (total 1.1 equiv per reactive site on scaffolds) in CH_3CN was added to a mixture of the corresponding scaffold **1** or **2** or **3** (1.0 equiv) and K_2CO_3 (5.0 g, 36 mmol) in 20 mL of CH_3CN. The resulting reaction mixture was stirred at rt for 2-4 h (monitored by TLC). For the preparation of libraries **VIa, VIb** and **XIII** by using chloride functionalities, the reaction mixtures were stirred at 50-60 °C overnight. The reaction mixture was worked up and purified as described above for library **Ia** (B = *t*-Boc). The corresponding *t*-Boc-protected libraries, thus obtained as pale yellow oil or light yellow foam in 80-99% yields, were deprotected by TFA as described above for library **Ia** (B = H). After evaporation of the excess TFA, the libraries were dissolved in hydrochloride saturated MeOH. Evaporation of the solvent gave the hydrochloride salts of the corresponding libraries as foams without further purification.

General Procedure for the Preparation of Libraries VIIIa,b (S13 and S15) and XVI (S15). A mixture of library **VIIa** or **VIIb** or **XV** (0.5 mmol), 8 mL of MeOH, 4 mL of concentrated aqueous NaOH solution was stirred at rt for 1 day. Acetic acid (2 mL) was added to destroy the excess NaOH. The mixture was concentrated to dryness under vacuum, and the residue was triturated with MeOH to give the corresponding acid libraries as white foams in 95-98% yields.

General Procedure for the Preparation of Libraries IXa,b (S13 and S15) and XVII (S15). A mixture of guanidine chloride (202 mg, 2.1 mmol) and $NaOCH_3$ (120 mg, 2.1 mmol) in 10 mL of MeOH was stirred at rt for 2 h, and the solvent was evaporated. A mixture of thus obtained neutral guanidine and corresponding library **VIIa** or **VIIb** or **XV** (0.7 mmol) in 10 mL of DMF was stirred at 80 °C for 1 day. The solvent was evaporated, and the residue was triturated with MeOH. The MeOH solution was saturated with HCl (g), and the solution was concentrated to give hydrochloride salt of the corresponding library as white foams in 95-98% yields.

Acknowledgments: The authors thank Jacqueline R. Wyatt, Laura Wilson-Lingardo, and Lisa M. Risen for antibacterial screening of libraries, Andy Kawasaki for the preparation of compounds 1-[*N*-(bromoacetyl)amino]-2-[*N,N'*-bis(*tert*-butoxycarbonyl)guanidinyl]ethane (for R_{15}) and 1-[*N*-(*tert*-butoxycarbonyl)-amino]-2-[*N*-(bromoacetyl)amino]ethane (for R_{18}), Becky D. Haly for the preparation of compound **21** and Guillermo Vasquez for scaling up compound **16**.

REFERENCES

1. Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 2288-2337.
2. (a) Lam, K. S.; Lebl, M.; Krchnak, V. *Chem. Rev.* **1997**, 97, 411-448. (b) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, 97, 449-472. (c) Pirrung, M. C. *Chem. Rev.* **1997**, 97, 473-488. (d) Ellman, J. A. *Acc. Chem. Res.* **1996**, 29, 132-143. (e) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, 96, 555-600.
3. Parallel single compound libraries: (a) Sim, M. M.; Ganesan, A. *J. Org. Chem.* **1997**, 62, 3230-3235. (b) Bailey, N,; Dean, A. W.; Judd, D. B.; Middlemiss, D.; Storer, R.; Watson, S. P. *Bioorg. Med. Chem. Lett.* **1996**, 6, 1409-1414. (c) Cheng, S.; Tarby, C. M.; Comer, D. D.; Williams, J. P.; Caporale, L. H.; Myers, P. L.; Boger, D. L. *Bioorg. Med. Chem.* **1996**, 4, 727-737. (d) Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, 118, 2567-2573. (e) Boger, D. L.; Tarby, C. M.; Myers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996**, 118, 2109-2110.
4. Indexed libraries: (a) Neuville, L.; Zhu, J.-P. *Tetrahedron Lett.* **1997**, 38, 4091-4094. (b) Pirrung, M.; Chen, J. *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. *Bioorg. Med. Chem. Lett.* **1994**, 4, 2821-2824.
5. Complex libraries: (a) McDevitt, J. P.; Lansbury, P. T., Jr. *J. Am. Chem. Soc.* **1996**, 118, 3818-3828. (b) Shipps, G. W., Jr.; Spitz, U. P.; Rebek, J., Jr. *Bioorg. Med. Chem.* **1996**, 4, 655-657. (c) Carell, T.; Wintner, E. A.; Sutherland, A. J.; Rebek, J., Jr.; Dunayevskiy, Y. M.; Vouros, P. *Chem. Biol.* **1995**, 2, 171-183. (d) Carell, T.; Wintner, E. A.; Bashir-Hashemi, A.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 2059-2061. (e) Carell, T.; Wintner, E. A.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 2061-2064.
6. Purification of libraries: (a) Booth, R. J.; Hodges, J. C. *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. *J. Am. Chem. Soc.* **1997**, 119, 4874-4881. (c) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, 37, 7193-7196. (d) Kaldor, S. W.; Fritz, J. E.; Tang, J.; McKinney, E. R. *Bioorg. Med. Chem. Lett.* **1996**, 6, 3041-3044.
7. An, H.; Cook, P. D. *Tetrahedron Lett.* **1996**, 37, 7233-7236.
8. 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. *J. Am. Chem. Soc.* **1997**, 119, 3696-3708.
9. An, H.; Haly, B. D.; Fraser, A. S.; Guinosso, C. J.; Cook, P. D. *J. Org. Chem.* **1997**, 62, 5156-5164.
10. Griffey, R. H.; Gaus, H. J.; Cummins, L. L.; Cook, P. D. *Tetrahedron*, **1998**, 54, 4067-4076.
11. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, 34, 3389-3392.
12. Carpino, L. A.; Mansour, E. M. E.; Cheng, C. H.; Williams, J. R.; MacDonald, R.; Knapczyk, J.; Carman, M.; Lopusinski, A. *J. Org. Chem.* **1983**, 48, 661-665.
13. Demonchaux, P.; Ganellin, C. R.; Dunn, P. M.; Haylett, D. G.; Jenkinson, D. H. *Eur. J. Med. Chem.* **1991**, 26, 915-920.
14. Arimoto, M.; Hayano, T.; Soga, T.; Yoshioka, T.; Tayawa, H.; Furukawa, M. *J. Antibiot.* **1986**, 39, 1243-1256.
15. Brown, F. J.; Bernstein, P. R.; Cronk, L. A.; Dosset, D. L.; Hebbel, K. C.; Maduskuie, T. P., Jr.; Shapiro, H. S.; Vacek, E. P.; Yee, Y. K.; Willard, A. K.; Krell, R. D.; Snyder, D. W. *J. Med. Chem.* **1989**, 32, 807-826.
16. Newcomb, M.; Gokel, G. W.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, 96, 6810-6811.