Pergamon

Tetrahedron 54 (1998) 7955–7976

TETRAHEDRON

Synthesis of Novel Polyazadipyridinocyclophane Scaffolds and Their Application for the Generation of Libraries

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Received 25 March 1998; revised 24 April 1998; accepted 27 April 1998

Abstract: Six novel, asymmetric, 19- to 26-membered polyazadipyridinocyclophane scaffolds **1-6** have been synthesized in high yields by an efficient cyclization of ditosylate **39** with the appropriate six fully protected triamines **40-45**, followed by removing the 2-nitrobenzenesulfonyl protecting groups. Intermediate **39** was synthesized by the Mitsunobu reaction of 2-nitrobenzenesulfonamide (**37**) with 2,6-pyridinedimethanol (**36**), and a subsequent tosylation of the resulted diol **38**. The fully protected asymmetric triamines **41** and **43** were prepared from the corresponding commercially available triamines **52** and **53**. A new synthetic route was developed for the synthesis of the protected asymmetric triamines **44** and **45**. All reactions were carried out at room temperature in high yields. The reaction of *t*-Boc-protected scaffold **1**, having three reactive sites, with nine benzylic bromides and bromoacetonitrile, using a solution phase simultaneous addition of functionalities combinatorial strategy, gave *t*-Boc-protected library **7** containing 1000 compounds. Deprotection of library **7** generated the intermediate library **8** with one reactive site. Subsequent reactions at the unsubstituted position of **8** with various functionalities by four types of reactions gave sixteen final libraries **9-24**. Libraries **7-24** have different functionalities at the fixed position, and each of them contains 1000 compounds. The reaction of scaffold **2**, having four reactive sites without protecting groups, with six sets of polar functionalities afforded eleven diverse libraries **25-35** containing 625 compounds in each library. Totally, twenty-nine libraries containing 24875 compounds were obtained. Eight libraries exhibited antibacterial activity against *Escherichia coli imp*$^-$ and *Streptococcus pyogenes* with the MIC's of 2 to 10-50 μM. Seven libraries disrupted HIV-1 tat/TAR protein-RNA interactions with IC_{50}'s as low as 0.08 μM.

INTRODUCTION

Combinatorial synthesis of chemical libraries has become an important tool for drug discovery and lead optimization.[1] The vast majority of oligomeric[2] and small molecule[3] libraries have been generated by solid phase or liquid phase approaches.[4] Solution phase combinatorial approach has recently begun to attract attention as an alternative for the generation of parallel single compound libraries,[5] indexed libraries,[6] and complex libraries.[7] Solid supports have been successfully used for the purification of single compounds and complex libraries generated by solution phase approaches.[8] As a complementary approach to solid phase chemistry, a simultaneous addition of functionalities in solution approach has been developed using chemically modifying pre-formed asymmetric scaffolds.[9-11] Series of polyazacyclophane[9,10] and linear[11] libraries have been generated, and some unique antibacterial compounds were identified. This solution phase combinatorial approach allows for a rapid and continual change in the scaffolds and functionalities by traditional organic synthesis and, thus, allows the generation of diverse libraries. Because a wide range of organic reactions can be used by this convenient method, one can easily introduce some desired information into scaffolds and libraries, and subsequently, one can rapidly modify libraries according to biological results.

0040-4020/98/$19.00
PII: S0040-4020(98)00441-4

A scaffold is a chemical framework which dictates the general shape of the molecules in the library. Examples include linear peptides or oligonucleotides, 1,4-benzodiazepines, purines, polyazacyclophanes, and others. In the solution phase simultaneous addition of functionalities approach, compounds with more than one reactive position can be used as scaffolds. For example, Rebek and co-workers[7b-e] used *tetra*-carboxylic acid chloride substituted xanthene and cubane as scaffolds to prepare amide libraries by simultaneously adding a mixture of amino acids, and then employed a reverse iterative deconvolution procedure to find active compounds. One obvious disadvantage is that these scaffolds are symmetric which reduces the complexity of the libraries. We choose asymmetric polyazacyclophanes, which are conformationally constrained, as scaffolds

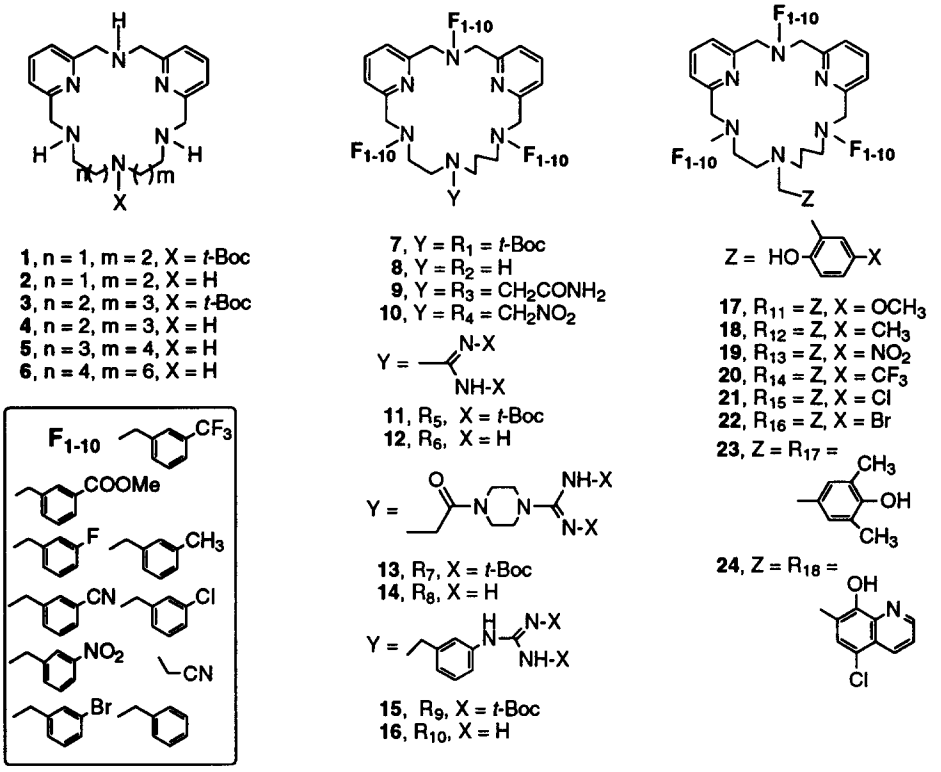


Figure 1. Structures of New Scaffolds **1-6** and libraries **7-24** with different functionalities

for combinatorialization. Utilization of flexible molecules such as linear polyamines in a library will search a greater structure space and, thus, will be more likely to provide an initial activity but with low affinity for the target molecules. More conformationally constrained molecule libraries may not as often exhibit activity as flexible molecule libraries but, when they do, there is a potential for the final compounds to exhibit significantly greater activity.[12] Polyazacyclophane scaffolds can be synthesized conveniently. Libraries based on these scaffolds can be made with conformational constraints in different levels and with different molecular weights by changing the ring size and shape of the scaffolds. Also, the number of compounds in a library can be easily

changed by simply changing the number of reactive positions or functionalities. Utilizing the fix last approach, one position is protected in the combinatorialization process. Deprotection and further reaction on the unreacted position convert the library to different libraries and increase the diversity.[10] In our efforts, we have synthesized libraries based on polyazapyridinocyclophanes.[9,10,13] Some of these libraries demonstrated potent antimicrobial activities and provided useful information to guide our future studies. For example, the libraries generated from the more rigid scaffold triazapyridino-13-crown-4 exhibited more potent activities than those based on the more flexible scaffold triazapyridino-15-crown-4.[13]

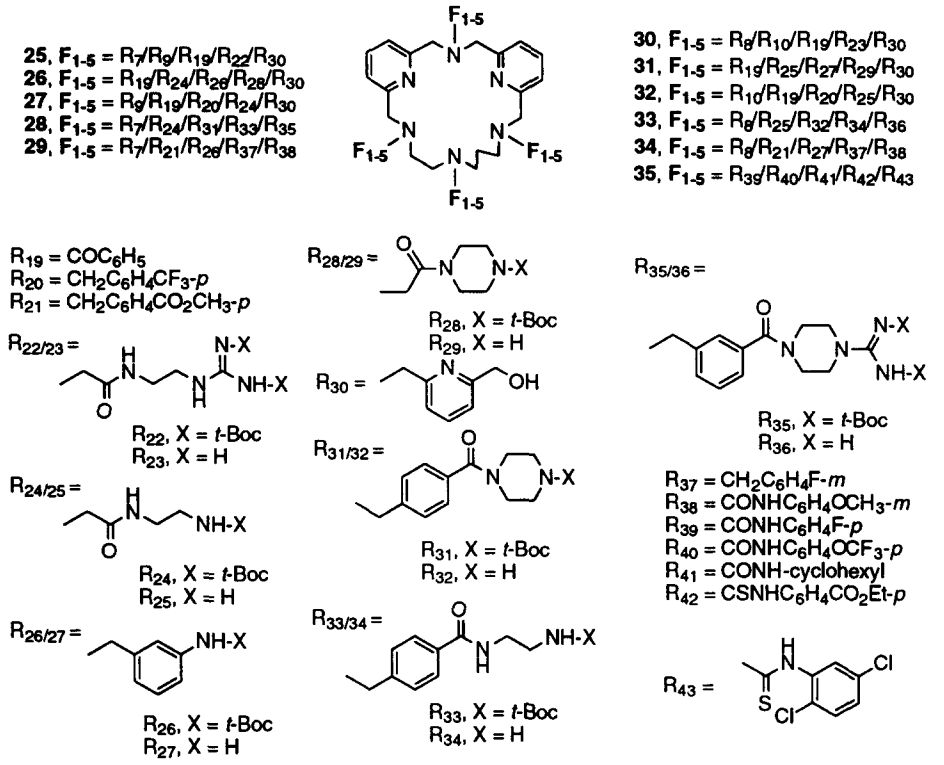


Figure 2. Polar Libraries **25-35** and Functionalities.

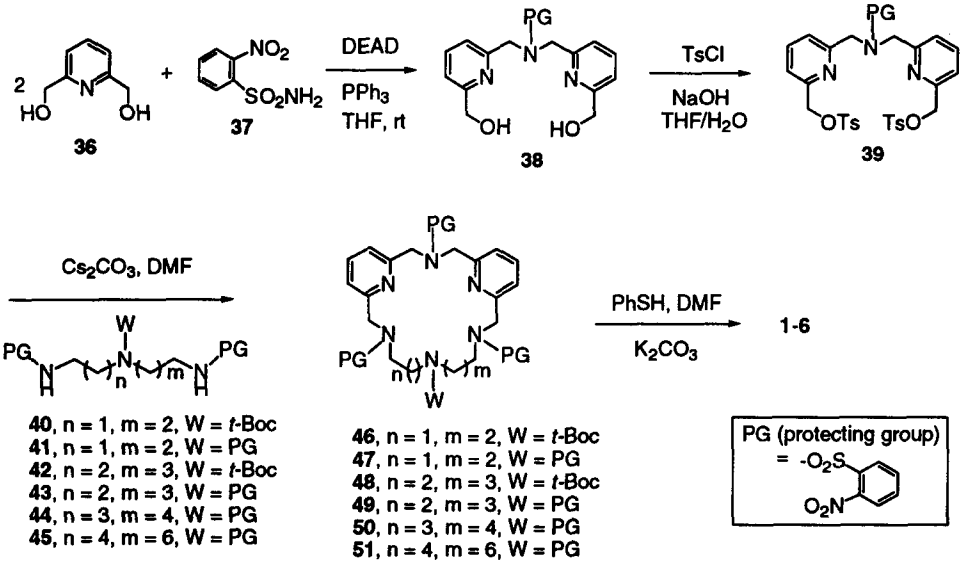
In our continuing effort to design and synthesize new scaffolds and libraries with desired information, we have synthesized six new polyazadipyridinocyclophane scaffolds **1-6** (Figure 1) with two pyridine moieties in the 19- to 26-membered polyazacyclophane rings. Herein, we wish to report the synthesis of these new scaffolds and twenty nine libraries **7-35** with several different types of functionalities based on the 19-membered macrocyclic scaffolds **1** and **2** (Figures 1 and 2), as well as the preliminary biological results in antibacterial and disruption of protein-RNA (HIV-1 tat/TAR) interaction assays. The syntheses of further libraries based on these new scaffolds and the deconvolution of current active libraries by a HPLC fractionation process will be reported in due course.

RESULTS AND DISCUSSION

Syntheses of New Scaffolds.

New asymmetric scaffolds **1-6** (Figure 1) were synthesized as shown in Scheme 1. Three equiv of 2,6-pyridinedimethanol (**36**) was reacted with 2-nitrobenzenesulfonamide (**37**) under the Mitsunobu reaction conditions affording dipyridine compound **38**, which was further reacted with tosyl chloride to generate the corresponding ditosylate **39** in 89% yield. In this procedure, an excess amount of **36** was used to increase the possibility for the formation of the expected product **38** and to decrease the formation of by-products. 2-Nitrobenzenesulfonamide (**37**) was used for the first time in the Mitsunobu reaction to make disubstituted compounds. This procedure has significant advantages over the reported procedures[14,15] for the preparation of the similar compounds. Cyclization of ditosylate **39** with triprotected asymmetric triamines **40** and **41** was accomplished in the presence of anhydrous Cs_2CO_3 as the weak base with the Cs^+ cation serving as a cyclization template. The corresponding fully protected 19-membered macrocycles **46** and **47** were obtained in 77% and 95% yields, respectively. In order to study the ring size effects on the biological activity of polyazacyclophane scaffolds, the 21-membered macrocyclic compounds **48** and **49**, as well as the 23- and 26-membered macrocyclic compounds **50** and **51** were also synthesized under the similar conditions by the

Scheme 1.

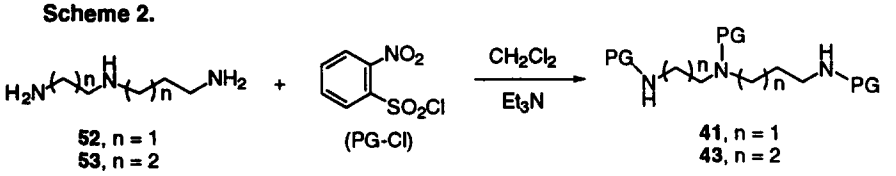


cyclization of ditosylate **39** with the corresponding triprotected asymmetric triamines **42-45**. The yields for the cyclization step generally decreased with an increase of the ring size. Compounds **47**, **49**, **50**, and **51**, having 19-, 21-, 23-, and 26-membered ring systems, were obtained in 95%, 74%, 54%, and 40% yields, respectively. Subsequently, all 2-nitrobenzenesulfonyl protecting groups on the resulting polyazacyclophanes **46-51** were removed with thiophenol in the presence of K_2CO_3 in DMF. The corresponding desired scaffolds **1-6** with 19- to 26-membered ring systems were obtained in high yields. Three nitrogenous reactive sites of the

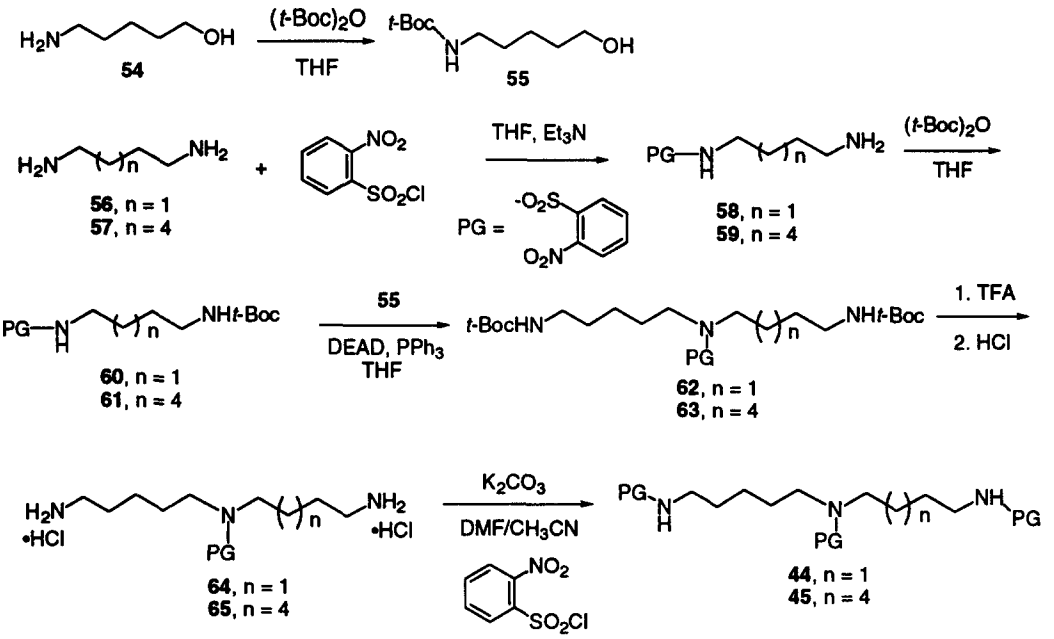
mono-*t*-Boc-protected scaffolds **1** and **3** can be used for combinatorialization, while all four reactive sites of the unprotected scaffolds **2** and **4-6** can be used for library generation.

The orthogonally protected asymmetric triamines **40** and **42** were prepared according to our reported procedure.[9,10] The tris(2-nitrobenzenesulfonyl)-protected compounds **41** and **43** were prepared by the reaction of 2-nitrobenzenesulfonyl chloride with commercially available *N*-(2-aminoethyl)-1,3-propanediamine (**52**) and spermidine (**53**), respectively, in the yields of 87% and 75% (Scheme 2). The corresponding asymmetric

Scheme 2.



Scheme 3.



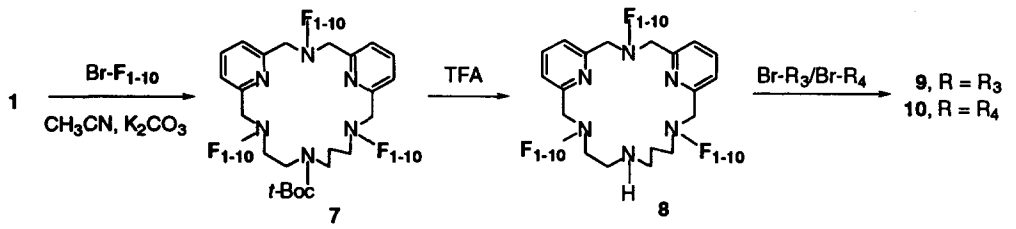
triamines for the 23- and 26-membered macrocyclic scaffolds **5** and **6** are not commercially available. Therefore, a new synthetic route, as shown in Scheme 3, was explored for the synthesis of the corresponding triprotected triamines **44** and **45**. The reaction of 2-nitrobenzenesulfonyl chloride with excess amounts of diamines **56** and **57** gave the corresponding monoprotected diamines **58** and **59** in 73% and 68% yields. Compounds **58** and **59** were then treated with di-*tert*-butyl dicarbonate to give the orthogonally protected diamines **60** and **61** in over 90% yields. The *t*-Boc-protected aminopentyl alcohol (**55**), prepared from the corresponding amino pentanol (**54**), was selectively reacted with the sulfonamide group of compounds **60** and **61** under the Mitsunobu reaction conditions affording triprotected triamines **62** and **63** in 93% and 70% yields,

respectively. The *t*-Boc groups of **62** and **63** were selectively removed by trifluoroacetic acid (TFA) to provide monoprotected triamines **64** and **65** in over 90% yields. Compounds **64** and **65** were then reacted with 2-nitrobenzenesulfonyl chloride giving the desired triprotected asymmetric triamines **44** and **45** in 71% and 77% yields. This procedure affords a very convenient and efficient approach for the synthesis of various linear polyamines. A reported procedure for the synthesis of linear polyamines, starting from benzyl amine, required high temperatures and long reaction times in some steps.[16,17] All reactions in the procedure described above were completed within several hours at room temperature. This procedure is also useful for the preparation of general linear symmetric and asymmetric polyamines with more than two nitrogen atoms in the chain. For example, compounds **44** and **45** can be further reacted with **55** or other similar compounds under the Mitsunobu reaction conditions to form new polyamines with more nitrogen atoms in the molecules. For the synthesis of symmetric polyamines, fewer reaction steps are required. Intermediates **62** and **63** have two different protecting groups. These intermediates are useful for their direct cyclization with dielectrophiles to make macrocyclic compounds as reported by Krakowiak and Bradshaw.[18] We did not thoroughly explore the cyclization of compounds **62** and **63** with ditosylate **39**. New compounds **1-6**, **38**, **39**, **41**, **43-51**, **55**, and **58-65** were characterized by ^{1}H and ^{13}C NMR, high resolution (FAB) mass spectroscopic, and combustion analyses.

Synthesis of Libraries.

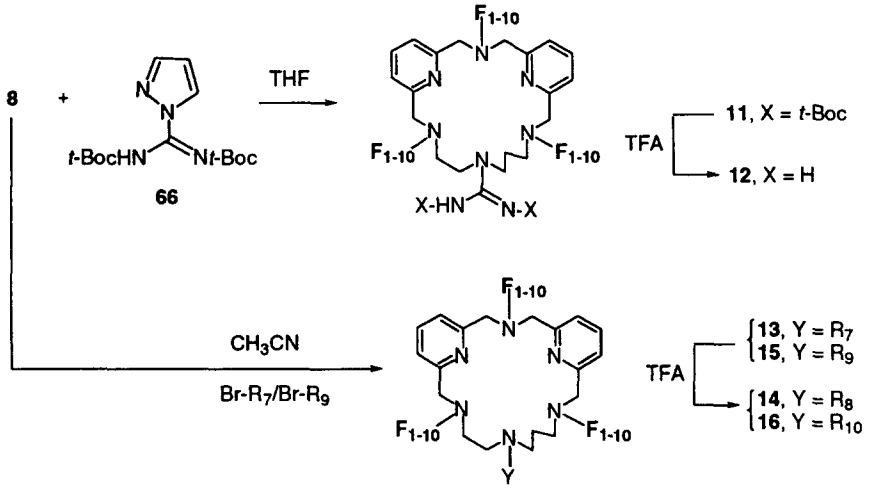
When we developed the solution phase combinatorial approach, *meta*-substituted benzylic bromides were utilized as a set of reactive functionalities to combinatorialize the nucleophilic secondary amine scaffolds. These functionalities have similar reactivity, therefore, all expected compounds could be found in the library. The mass spectrum of a representative library, containing 100 compounds, showed all expected molecular ion peaks, and the abundance pattern of the mass spectrum was consistent with that from a computer simulation.[10] In the present work, nine benzylic bromides and bromoacetonitrile were used as a set of reactive functionalities for the preparation of libraries **7-24** (Schemes 4-6). Three available reactive sites of the mono-*t*-Boc-protected, 19-membered macrocyclic scaffold **1** were combinatorialized with the selected set of functionalities (Br-$\mathbf{F_{1\text{-}10}}$, see Figure 1 for structural details) in the presence of K_2CO_3 in acetonitrile to give the *t*-Boc-protected library **7** containing 1000 compounds (10^3) (Scheme 4). Deprotection of **7** by TFA gave the intermediate library **8** with one reactive site available. Further reaction of **8** with bromoacetamide (BrR_3) and bromonitromethane (BrR_4) gave the corresponding libraries **9** and **10**, respectively. Most of the functionalities in this set are aromatic fragments. Introduction of these fragments into the macrocyclic framework may increase the rigidity of the resulted compounds and improve their preorganization.[19]

Scheme 4.

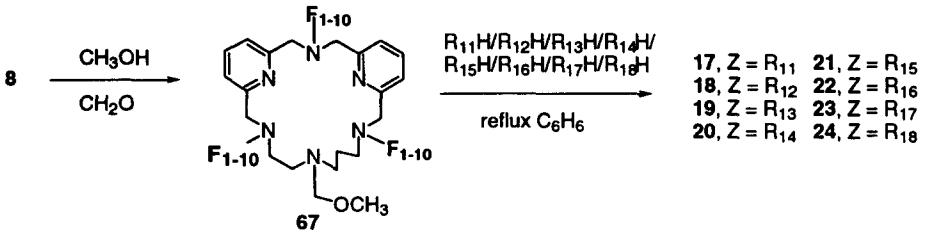


Disruption of protein-RNA interactions represents a new frontier for drug discovery. Functional groups including guanidines, amidines, amides, alcohols, phenols, and amines have potential to bind RNA.[20] In order to prepare libraries that could bind RNA and also exhibit biological activities so that we could further study the mechanism of drug action, we synthesized fourteen libraries **11-24** (Figure 1) with various guanidine and phenol groups at the fixed position as shown in Schemes 5 and 6. *N,N'*-Bis(*tert*-butoxycarbonyl)-1*H*-pyrazol-1-carboxamidine (**66**) was reported as a very effective guanylating reagent.[21] The intermediate library **8** was reacted with the guanylating agent **66** at the refluxing temperature of THF affording the *t*-Boc-protected library **11**. Removing the *t*-Boc protecting groups of library **11** by TFA gave the polar library **12** with guanidine group at the fixed position (Scheme 5). Guanidine functionalities R_8 and R_{10} (Figure 1) were also introduced to the fixed position of library **8**. Reaction of guanidine derivatives[13] BrR_7 and BrR_9 with library **8** at room temperature in the presence of K_2CO_3 gave libraries **13** and **15**, which afforded the corresponding final guanidine libraries **14** and **16**, respectively, after removing the *t*-Boc protecting groups by TFA.

Scheme 5.



Scheme 6.



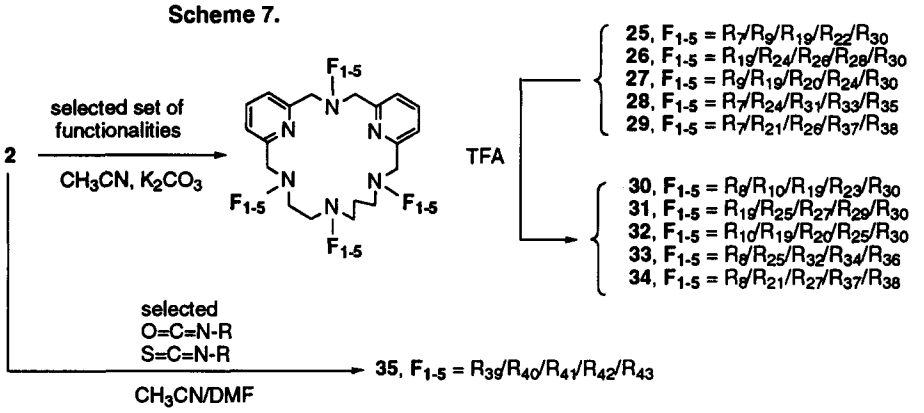
The most direct way to synthesize the phenol-containing macrocycles is the alkylation of macrocycles by halomethyl substituted phenols; however, many of these compounds are not commercially available, and the

protection of phenolic hydroxyl group is required.[22] The modified Mannich reaction[23] provides a convenient way to introducing phenol groups into macrocyclic compounds without protection and deprotection steps. We successfully utilized this method to introduce various phenolic groups into new polyazadipyridinocyclophane libraries (Scheme 6).

Library **8** was reacted with formaldehyde and methanol to give intermediate library **67**, which was further reacted with various phenolic compounds ($R_{11}H$-$R_{18}H$) (Figure 1) in refluxing benzene to give phenolic libraries **17-24**. Intermediate library **67** was used directly for the next step without purification considering its instability to normal workup and purification procedures. Libraries **7-11**, **13**, **15**, and **17-24** were purified by flash chromatography except guanidine libraries **12**, **14**, and **16** because of their high polarity. All libraries **7-24**, each containing 1000 compounds, were confirmed by their electrospray ionization (ESI) mass spectra.

Libraries **7-24** described above have the same set of groups at the three combinatorialized positions and various functionalities at one fixed position. Although the screening results has indicated some of these libraries with biological activity (see below), increasing library diversity would give a greater opportunity for better biological results. In order to increase the overall diversity, adjust the polarity and lipophilicity of libraries, and search for more potent biological activity, a variety of polar functionalities together with benzyl groups were introduced onto all four positions of the 19-membered macrocyclic scaffold **2** (Scheme 7). Six

Scheme 7.



sets of functionalities (see Figures 1 and 2) for libraries **25-29** and **35** were determined to have similar reactivities by preparing and analyzing small libraries as described previously.[10] Scaffold **2** was separately reacted with each of the five sets of selected functionalities to gave five different *t*-Boc-protected intermediate libraries **25-29**. Libraries **25-27** and **29** were obtained under the normal conditions at room temperature, however, library **28** was obtained by stirring the reaction mixture at 50-60 °C for 24 h as the corresponding chloride functionalities are less reactive compared with the bromide functionalities. The *t*-Boc protecting groups of libraries **25-29** were removed by TFA affording the corresponding five final polar libraries **30-34** with high diversity. Scaffold **2** was also reacted with five isocyanates and isothiocyanates at room temperature resulting in the urea/thiourea library **35**. Each of libraries **25-35** contains 625 compounds (5^4). Libraries **25-29** and **35** were purified by flash or preparative thin layer chromatography, while the polar libraries **30-34** with different

guanidine and amino groups were isolated as their hydrochloride salts without further chromatographic purification.

Biological Evaluation.

Libraries **7-24**, each containing 1000 compounds, and diverse polar libraries **30-35**, each containing 625 compounds, were screened against bacteria *Escherichia coli imp*$^-$ and *Streptococcus pyogenes* antigrowth assays. A scintillation proximity assay (SPA) was used to screen these libraries for the identification of libraries or compounds that could be used to disrupt the HIV-1 tat/TAR protein-RNA interaction. Table 1 shows biological results for active libraries. Library **8** with hydrogen (H) at the fixed position showed antibacterial activity against two tested bacteria in the MIC range of 4-20 μM. Libraries **14** and **16** with substituted guanidinyl functionalities at the fixed position exhibited potent activity with the MIC's of 10-20 μM and 2-10 μM, respectively. These three libraries also showed activity in the tat/TAR SPA. The human immunodeficiency virus, HIV-1 mRNA, contains a sequence known as TAR (transactivating responsive). The TAR element forms a stable RNA stem loop structure which binds the HIV-1 tat (trans-activator) protein and mediates increased viral gene expression. Disruption of the natural tat/TAR interaction may inhibit the normal HIV-1 life cycle and provide the opportunity for novel therapeutics in the treatment of AIDS.[24] A high through-put

Table 1. Antibacterial and tat/TAR Activities[a] of Libraries

Library No.	complexity	*E. coli imp*$^-$	*S. pyogenes*	tat/TAR
8	1000	4-20	4-20	<12.5
14	1000	10-20	10-20	10
16	1000	2-10	2-10	20
30	625	10-50	10-50	<10
31	625	10-50	<50	
32	625	2-5	2-5	10
33	625	10-50	10-50	0.08
34	625	10-50	10-50	<10

[a]The MIC (minimum inhibitory concentration, μM) values are 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. Ampicillin and tetracycline were used as antibacterial references. IC_{50} values (μM) were given for tat/TAR activity.

screening assay was developed for the identification of compounds which could be used to disrupt the tat/TAR interaction. The IC_{50} values of libraries **8**, **14**, and **16** in the disruption of tat/TAR protein-RNA interaction assay ranged from 10 to 20 μM. Much less activity was observed for other libraries in this series (libraries **7-24**). These results indicated that the libraries with different functionalities at the fixed position did exhibit the different biological activity. Libraries **17-24** with phenolic groups, *t*-Boc-protected libraries **7**, **11**, **13**, and **15** are not active in bacteria antigrowth and tat/TAR scintillation proximity assays. Library **16** with guanidine benzyl group R_{10} at the fixed position exhibited potent antibacterial activity, however, library **12** with a guanidine type group R_6 (amidine) at the fixed position did not show an activity similar to guanidine libraries

14 and **16**. All final polar libraries **30-34** containing guanidine, amine, alcohol, and amide groups exhibited antibacterial activity against *E. coli imp*$^-$ and *S. pyogenes* with the MIC's of 2 to 50 μM. Libraries **30** and **32-34** showed RNA-protein disrupting activity as indicated by tat/TAR SPA screening results. Library **32** exhibited the most potent antibacterial activity for the two assays with the MIC's of 2-5 μM. Library **33** showed the best activity in tat/TAR SPA with an IC_{50} of 0.08 μM, which represents a strong ability to disrupt HIV-1 tat/TAR protein-RNA interactions.

In conclusion, we have synthesized six novel asymmetric, 19- to 26-membered polyazadipyridinocyclophane scaffolds, and developed an efficient procedure for the synthesis of linear polyamines. Based on two of the six scaffolds, we have prepared twenty-nine combinatorial libraries containing 1000 or 625 compounds in each library with a total complexity of 24875 compounds. Eight libraries **8**, **14**, **16**, and **30-34** exhibited potent antimicrobial activity with the MIC's of low micromolar range against *E. coli imp*$^-$ and *S. pyogenes* in initial bacterial antigrowth assays. The guanidine library **33** demonstrated potent activity in disrupting HIV-1 tat/TAR protein-RNA interaction with an IC_{50} of 80 nM.

EXPERIMENTAL

Proton and carbon NMR spectra were recorded at 199.975 MHz unless otherwise indicated. 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. Compounds **40**,[9,10] **42**,[9,10] **66**,[21] and functionalities[13] BrR_7, BrR_9, BrR_{22}, BrR_{24}, BrR_{26}, BrR_{28}, BrR_{30}, ClR_7, ClR_{24}, ClR_{31}, ClR_{33}, and ClR_{35} were prepared according to reported procedures. Other materials were purchased from Aldrich Chemical Company.

***N,N*-Bis[[6-(hydroxymethyl)pyridin-2-yl]methyl]-2-nitrobenzenesulfonamide (38) (Scheme 1).** A solution of diethyl azodicarboxylate (DEAD) (18.8 g, 0.11 mol) in 100 mL of anhydrous THF was added dropwise to a stirred mixture of 2,6-pyridinedimethanol (**36**) (16.7 g, 0.12 mol, 3 equiv) and PPh_3 (28.3 g, 0.108 mol) in 200 mL of anhydrous THF at rt. The resulting solution was stirred at rt for 30 min. A solution of 2-nitrobenzenesulfonamide (**37**) (8.10 g, 0.040 mol) in 200 mL of anhydrous THF was added dropwise to the above stirred solution very slowly. The resulting solution was stirred at rt overnight. The solvent was evaporated, and the residue was dissolved in $CHCl_3$. The solution was washed with water to remove the excess starting material **36**. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on a silica gel column using 50:1 and 30:1 CH_2Cl_2-MeOH as eluents to give 6.01 g (34%) of compound **38** as a white solid, mp 91-92 °C; ^1H NMR ($CDCl_3$) δ 4.35 (br, 2H, ex D_2O), 4.49 (s, 4H), 4.61 (s, 4H), 7.02 (d, 2H, J = 7.4 Hz), 7.06 (d, 2H, J = 7.4 Hz), 7.43-7.63 (m, 5H), 7.94 (d, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 52.9, 64.0, 119.5, 120.9, 124.3, 130.9, 131.9, 133.5, 133.8, 137.5, 147.7, 154.4, 159.2; HRMS (FAB) *m /z* 577.016 $(M + Cs)^+$ ($C_{20}H_{20}N_4O_6SCs$ requires 577.015). Anal. Calcd for $C_{20}H_{20}N_4O_6S$: C, 54.04; H, 4.54; N, 12.61. Found: C, 54.36; H, 4.70; N, 12.67.

***N,N*-Bis[[6-(*p*-tosyloxymethyl)pyridin-2-yl]methyl]-2-nitrobenzenesulfonamide (39) (Scheme 1).** A solution of tosyl chloride (1.72 g, 9.0 mmol) in 20 mL of THF was added dropwise into a stirred mixture of **38** (1.05 g, 2.25 mmol) and NaOH (0.54 g, 13.5 mmol) in 15 mL of THF and 15 mL of

H_2O at 0 °C. The resulting reaction mixture was stirred at rt for 3 h, and then poured onto a mixture of ice (30 g) and hydrochloric acid solution (37%, 2 mL). The resulting mixture was extracted with $CHCl_3$. The combined organic phase was washed with H_2O, 5% aqueous $NaHCO_3$ solution, and then H_2O. After dried (Na_2SO_4), the organic solution was concentrated. The residue was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 100:1 CH_2Cl_2-MeOH as eluents to give 1.51 g (89%) of ditosylate **39** as a white foam; ^1H NMR ($CDCl_3$) δ 2.45 (s, 6H), 4.62 (s, 4H), 4.90 (s, 4H), 7.18-7.24 (m, 4H), 7.33 (s, 2H), 7.37 (s, 2H), 7.53-7.62 (m, 5H), 7.80 (d, 4H, J = 8.3 Hz), 7.98 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 52.7, 71.5, 120.8, 122.2, 124.0, 127.7, 128.0, 130.0, 131.0, 131.7, 132.8, 133.6, 133.8, 137.7, 145.3, 147.9, 153.2, 155.5; HRMS (FAB) m/z 885.034 $(M + Cs)^+$ ($C_{34}H_{32}N_4O_{10}S_3Cs$ requires 885.033). Anal. Calcd for $C_{34}H_{32}N_4O_{10}S_3$: C, 54.25; H, 4.29; N, 7.45. Found: C, 54.10; H, 4.43; N, 7.49.

3,10,18-Tris(2-nitrobenzenesulfonyl)-6-(*tert*-butoxycarbonyl)-3,6,10,18,24,25-hexaazatricyclo[18.3.1^{1,20}.1^{12,16}]pentacosa-1(24),12(25),13,15,20,22-hexaene (46) (Scheme 1). A mixture of ditosylate **39** (7.0 g, 9.3 mmol), protected triamine **40**[10] (5.75 g, 9.3 mmol), and anhydrous Cs_2CO_3 (12.1 g, 37.2 mmol) in 450 mL of anhydrous DMF was stirred at rt overnight. The solvent was evaporated, 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 200:1 CH_2Cl_2-MeOH as an eluent to give 7.13 g (77%) of product **46** as a white foam; ^1H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.55-1.75 (m, 2H), 3.05 (t, 2H, J = 5.8 Hz), 3.23-3.30 (m, 4H), 3.44-3.48 (m, 2H), 4.41 (s, 2H), 4.55 (s, 2H), 4.71 (s, 2H), 4.73 (s, 2H), 7.17-7.28 (m, 4H), 7.53-8.00 (m, 14 H); HRMS (FAB) m/z 1128.134 $(M + Cs)^+$ ($C_{42}H_{45}N_9O_{14}S_3Cs$ requires 1128.130). Anal. Calcd for $C_{42}H_{45}N_9O_{14}S_3 \cdot 3H_2O$: C, 48.03; H, 4.86; N, 12.01. Found: C, 47.68; H, 4.42; N, 11.90.

3,6,10,18-Tetrakis(2-nitrobenzenesulfonyl)-3,6,10,18,24,25-hexaazatricyclo-[18.3.1^{1,20}.1^{12,16}]pentacosa-1(24),12(25),13,15,20,22-hexaene (47) (Scheme 1). Compound **47** was synthesized as above for **46** from **39** (2.36 g, 3.13 mmol) and **41** (2.10 g, 3.13 mmol) in the presence of Cs_2CO_3 (4.0 g, 12.5 mmol). The crude product was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2, 500:1, and then 300:1 CH_2Cl_2-MeOH as eluents to give 3.21 g (95%) of compound **47** as a yellow foam; ^1H NMR ($CDCl_3$) δ 1.75 (m, 2H), 3.20-3.60 (m, 8H), 4.40 (s, 2H), 4.55 (s, 2H), 4.70 (s, 4H), 7.10-7.25 (m, 4H), 7.50-8.10 (m, 18H); MS (ESI) m/z 1081 $(M + H)^+$ ($C_{43}H_{41}N_{10}O_{16}S_4$ requires 1081). Anal. Calcd for $C_{43}H_{40}N_{10}O_{16}S_4 \cdot 3H_2O$: C, 45.49; H, 4.06; N, 12.35. Found: C, 45.29; H, 4.00; N, 12.15.

3,12,20-Tris(2-nitrobenzenesulfonyl)-7-(*tert*-butoxycarbonyl)-3,7,12,20,26,27-hexaazatricyclo[20.3.1^{1,22}.1^{14,18}]heptacosa-1(26),14(27),15,17,22,24-hexaene (48) (Scheme 1). Compound **48** was synthesized as above for **46** from **39** (9.16 g, 9.51 mmol) and **42**[10] (5.86 g, 9.51 mmol) in the presence of Cs_2CO_3 (12.4 g, 38.0 mmol). The crude product was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 200:1 CH_2Cl_2-MeOH as eluents to give 6.14 g (63%) of compound **48** as a yellow foam; ^1H NMR ($CDCl_3$) δ 1.10-1.45 (m, 13H), 1.45-1.70 (m,

2H), 2.78-2.92 (m, 4H), 3.00-3.35 (m, 4H), 4.27 (s, 2H), 4.35 (s, 2H), 4.70 (s, 4H), 7.01-7.21 (m, 6H), 7.40-7.91 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 25.2, 25.6, 26.9, 28.3, 44.9, 46.1, 46.5, 46.8, 48.1, 52.8, 77.6, 79.4, 121.0, 121.4, 121.6, 122.2, 123.8, 124.2, 125.3, 128.2, 129.0, 130.5, 130.8, 131.6, 131.9, 133.0, 133.7, 133.9, 137.8, 147.8, 148.1, 155.2, 155.6, 155.9, 156.1; HRMS (FAB) *m / z* 1136.166 $(M + Cs)^+$ ($C_{44}H_{49}N_9O_{14}S_3Cs$ requires 1136.161). Anal. Calcd for $C_{44}H_{49}N_9O_{14}S_3$: C, 51.59; H, 4.83; N, 12.32. Found: C, 51.65; H, 5.00; N, 12.24.

3,7,12,20-Tetrakis(2-nitrobenzenesulfonyl)-3,7,12,20,26,27-hexaazatricyclo-[20.3.1^{1,22}.1^{14,18}]heptacosa-1(26),12(27),15,17,22,24-hexaene (49) (Scheme 1). Compound **49** was synthesized as above for **46** from **39** (2.28 g, 3.0 mmol) and **43** (2.12 g, 3.0 mmol) in the presence of Cs_2CO_3 (3.90 g, 12.0 mmol). The crude product was purified by flash chromatography on a silica gel column using 400:1 CH_2Cl_2-MeOH as an eluent to give 2.46 g (74%) of product **49** as a white foam; ^1H NMR ($CDCl_3$) δ 1.25-1.54 (m, 4H), 1.60-1.85 (m, 2H), 2.95-3.35 (m, 8H), 4.32 (s, 2H), 4.39 (s, 2H), 4.74 (s, 4H), 7.12-7.99 (m, 22H); ^{13}C NMR ($CDCl_3$) δ 25.0, 25.5, 26.9, 45.6, 45.9, 47.6, 47.9, 53.0, 53.7, 121.1, 121.5, 121.9, 122.2, 123.9, 124.2, 130.2, 130.4, 130.7, 131.8, 132.1, 132.5, 132.6, 132.8, 133.5, 134.0, 137.9, 147.9, 155.2, 155.6, 155.8; HRMS (FAB) *m / z* 1241.092 $(M + Cs)^+$ ($C_{45}H_{44}N_{10}O_{16}S_4Cs$ requires 1241.087). Anal. Calcd for $C_{45}H_{44}N_{10}O_{16}S_4$: C, 48.72; H, 4.00; N, 12.64. Found: C, 48.64; H, 4.28; N, 12.59.

3,8,14,22-Tetrakis(2-nitrobenzenesulfonyl)-3,8,14,22,28,29-hexaazatricyclo-[22.3.1^{1,24}.1^{16,20}]nonacosa-1(28),16(29),17,19,24,26-hexaene (50) (Scheme 1). Compound **50** was synthesized as above for **46** from **39** (1.52 g, 2.02 mmol) and **44** (1.47 g, 2.02 mmol) in the presence of Cs_2CO_3 (2.63 g, 8.1 mmol). The crude product was purified by flash chromatography on a silica gel column using 2:1, 1:1, and then 1:2 hexanes-EtOAc as eluents to give 1.25 g (54%) of compound **50** as a yellow foam; ^1H NMR ($CDCl_3$) δ 1.00-1.20 (m, 2H), 1.20-1.55 (m, 8H), 3.01-3.10 (m, 4H), 3.17-3.28 (m, 4H), 4.40 (s, 4H), 4.68 (s, 2H), 4.69 (s, 2H), 7.15-7.98 (m, 22H); HRMS (FAB) *m / z* 1269.125 $(M + Cs)^+$ ($C_{47}H_{48}N_{10}O_{16}S_4Cs$ requires 1269.118). Anal. Calcd for $C_{47}H_{48}N_{10}O_{16}S_4$: C, 49.63; H, 4.23; N, 12.32. Found: C, 49.45; H, 4.42; N, 12.06.

3,9,17,25-Tetrakis(2-nitrobenzenesulfonyl)-3,9,17,25,31,32-hexaazatricyclo-[25.3.1^{1,27}.1^{19,23}]dotriaconta-1(31),16(32),17,19,27,29-hexaene (51) (Scheme 1). Compound **51** was synthesized as above for **46** from **39** (1.70 g, 2.26 mmol) and **45** (1.75 g, 2.26 mmol) in the presence of Cs_2CO_3 (3.0 g, 9.3 mmol). The crude product was purified by flash chromatography on a silica gel column using 2:1 hexanes-EtOAc and then 200:1 CH_2Cl_2-MeOH as eluents to give 1.07 g (40%) of compound **51** as a yellow foam; ^1H NMR ($CDCl_3$) δ 1.09-1.42 (m, 16H), 3.05-3.12 (m, 4H), 3.24 (m, 4H), 4.42 (s, 4H), 4.65 (s, 4H), 7.15-7.27 (m, 4H), 7.53-7.68 (m, 14 H), 7.87-7.99 (m, 4H); MS (ESI) *m / z* 1179 $(M + H)^+$ ($C_{50}H_{55}N_{10}O_{16}S_4$ requires 1179). Anal. Calcd for $C_{50}H_{54}N_{10}O_{16}S_4$: C, 50.92; H, 4.62; N, 11.88. Found: C, 50.76; H, 4.84; N, 11.74.

6-(*tert*-Butoxycarbonyl)-3,6,10,18,24,25-hexaazatricyclo[18.3.1^{1,20}.1^{12,16}]-pentacosa-1(24),12(25),13,15,20,22-hexaene (1) (Scheme 1 and Figure 1). Thiophenol (3.3 g, 29.9 mmol) was added to a stirred mixture of compound **46** (7.09 g, 7.13 mmol) and anhydrous K_2CO_3 (13.8 g, 100 mmol) in 160 mL of anhydrous DMF. The resulting mixture was stirred at rt overnight. The solvent was evaporated, 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 20:1 CH_2Cl_2-MeOH and then 30:1 MeOH-30% NH_4OH as eluents to give 3.10 g (99%) of compound **1** as a pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.77-1.86 (m, 2H), 2.64 (t, 2H, J = 5.5 Hz), 2.50-2.70 (br, 3H, ex D_2O), 2.81 (t, 2H, J = 6.2 Hz), 3.27-3.37 (m, 4H), 3.85 (s, 2H), 3.88 (s, 2H), 3.95 (s, 2H), 3.97 (s, 2H), 7.02-7.13 (m, 4H), 7.54-7.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.4, 29.0, 46.4, 46.7, 48.1, 48.3, 54.5, 54.6, 79.2, 120.8, 136.6, 136.7, 155.5, 158.9; HRMS (FAB) m/z 441.296 $(M + H)^+$ ($C_{24}H_{37}N_6O_4$ requires 441.297). Anal. Calcd for $C_{24}H_{36}N_6O_4 \cdot H_2O$: C, 62.84; H, 8.29; N, 18.33. Found: C, 62.70; H, 7.93; N, 18.13.

3,6,10,18,24,25-Hexaazatricyclo[18.3.1^{1,20}.1^{12,16}]pentacosa-1(24),12(25),13,15,20,22-hexaene (2) (Scheme 1 and Figure 1). Compound **2** was synthesized as above for **1** from **47** (3.13 g, 1.50 mmol) and thiophenol (2.84 g, 25.8 mmol) in the presence of K_2CO_3 (11.7 g, 85.0 mmol). The crude product was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 20:1 MeOH-30% NH_4OH as eluents to give 0.76 g (72%) of compound **2** as a pale yellow oil; ^1H NMR (CD_3OD) δ 1.76-1.86 (m, 2H), 2.82-2.90 (m, 8H), 3.92 (s, 2H), 3.95 (s, 2H), 3.97 (s, 2H), 3.99 (s, 2H), 7.23-7.33 (m, 4H), 7.71-7.78 (m, 2H); ^{13}C NMR (CD_3OD) δ 30.6, 49.9, 50.7, 56.5, 123.1, 126.5, 138.7, 139.4, 152.3, 161.3, 161.7, 161.9; HRMS (FAB) m/z 341.244 $(M + H)^+$ ($C_{19}H_{29}N_6$ requires 341.245). Anal. Calcd for $C_{19}H_{28}N_6$: C, 67.01; H, 8.37. Found: C, 66.53; H, 8.33.

7-(*tert*-Butoxycarbonyl)-3,7,12,20,26,27-hexaazatricyclo[20.3.1^{1,22}.1^{14,18}]-heptacosa-1(26),14(27),15,17,22,24-hexaene (3) (Scheme 1 and Figure 1). Compound **3** was synthesized as above for **1** from **48** (5.94 g, 5.81 mmol) and thiophenol (2.69 g, 24.4 mmol) in the presence of K_2CO_3 (10.2 g, 73.8 mmol). The crude product was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 30:1 MeOH-30% NH_4OH as eluents to give 2.66 g (98%) of compound **3** as a pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.33 (s, 9H), 1.36-1.54 (m, 4H), 1.60-1.78 (m, 2H), 2.54-2.61 (m, 4H), 2.95 (s, 3H, ex D_2O), 3.06-3.19 (m, 4H), 3.77 (s, 4H), 3.85 (s, 4H), 6.99-7.09 (m, 4H), 7.44-7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.5, 27.1, 28.4, 29.3, 46.0, 46.8, 48.0, 48.8, 53.4, 54.7, 79.0, 120.8, 136.7, 155.6, 158.6, 158.8, 159.0; HRMS (FAB) m/z 469.328 $(M + H)^+$ ($C_{26}H_{14}N_6O_2$ requires 469.329). Anal. Calcd for $C_{26}H_{40}N_6O_2 \cdot 1/2HCl$: C, 64.12; H, 8.39; N, 17.27. Found: C, 64.26; H, 8.00; N, 17.37.

3,7,12,20,26,27-Hexaazatricyclo[20.3.1^{1,22}.1^{14,18}]heptacosa-1(26),12(27),15,17,22,24-hexaene (4) (Scheme 1 and Figure 1). Compound **4** was synthesized as above for **1** from **49** (2.29 g, 2.0 mmol) and thiophenol (1.23 g, 11.2 mmol) in the presence of K_2CO_3 (4.64 g, 33.6 mmol). The compound was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 10:1

MeOH-30% NH_4OH as eluents to give 0.67 g (91%) of product **4** as a pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.50-1.80 (m, 6H), 2.57-2.85 (m, 8H), 3.85 (s, 4H), 3.94 (s, 2H), 3.95 (s, 2H), 3.90-4.10 (br, 4H, ex D_2O), 7.08 (d, 2H, J = 7.4 Hz), 7.14 (d, 2H, J =7.4 Hz), 7.57 (d, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 26.0, 26.7, 27.0, 47.5, 47.7, 47.9, 48.1, 49.3, 53.8, 54.0, 120.5, 120.7, 136.7, 157.8, 158.1, 158.8; HRMS (FAB) m/z 369.275 $(M + H)^+$ ($C_{21}H_{33}N_6$ requires 369.276). Anal. Calcd for $C_{21}H_{32}N_6 \cdot HCl$: C, 62.37; H, 8.91; N, 20.77. Found: C, 62.86; H, 8.46; N, 19.95.

3,8,14,22,28,29-Hexaazatricyclo[22.3.1^{1,24}.1^{16,20}]nonacosa-1(28),16(29),17,19,24,26-hexaene (5) (Scheme 1 and Figure 1). Compound **5** was synthesized as above for **1** from **50** (1.22 g, 1.06 mmol) and thiophenol (0.61 g, 5.52 mmol) in the presence of K_2CO_3 (2.3 g, 16.5 mmol). After the reaction was completed, the reaction mixture was filtered to remove part of K_2CO_3. The solution was concentrated, and the residue was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 20:1 MeOH-30% NH_4OH as eluents to give 0.37 g (88%) of compound **5** as a pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.27-1.54 (m, 10H), 2.52-2.65 (m, 12H, 4H ex D_2O), 3.85 (s, 4H), 3.95 (s, 4H), 7.08-7.20 (m, 4H), 7.49-7.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.6, 27.4, 27.7, 29.0, 29.6, 48.7, 49.1, 55.0, 77.9, 120.6, 120.7, 136.8, 159.3, 159.5; HRMS (FAB) m/z 397.309 $(M + H)^+$ ($C_{23}H_{37}N_6$ requires 397.308). Anal. Calcd for $C_{23}H_{36}N_6 \cdot H_2O$: C, 66.66; H, 9.17; N, 20.32. Found: C, 66.79; H, 8.96; N, 19.83.

3,9,17,25,31,32-Hexaazatricyclo[25.3.1^{1,27}.1^{19,23}]dotriaconta-1(31),16(32),17,19,27,29-hexaene (6) (Scheme 1 and Figure 1). Compound **6** was synthesized as above for **1** from **51** (1.06 g, 0.899 mmol) and thiophenol (0.52 g, 4.67 mmol) in the presence of K_2CO_3 (1.93 g, 14.0 mmol). After the reaction was completed, the reaction mixture was filtered to remove part of K_2CO_3. The solution was concentrated, and the residue was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2, 5:1 MeOH-CH_2Cl_2, and then 20:1 MeOH-30% NH_4OH as eluents to give 0.19 g (48%) of compound **6** as a pale yellow oil; ^1H NMR (CD_3OD) δ 1.29-1.65 (m, 16H), 2.60-2.76 (m, 8H), 3.91 (s, 4H), 3.95 (s, 4H), 7.29-7.38 (m, 4H), 7.77 (t, 2H, J = 7.7 Hz); ^{13}C NMR (CD_3OD) δ 25.3, 27.3, 27.5, 28.4, 29.4, 29.5, 29.8, 55.1, 122.4, 138.8, 159.6, 160.0; HRMS (FAB) m/z 439.353 $(M + H)^+$ ($C_{26}H_{43}N_6$ requires 439.354). Anal. Calcd for $C_{26}H_{42}N_6 \cdot 1/2HCl$: C, 68.33; H, 9.38; N, 18.40. Found: C, 68.56; H, 9.13; N, 17.98.

***N*^{1},*N*^{3},*N*^{6}-Tris(2-nitrobenzenesulfonyl)-1,6-diamino-3-azahexane (41) (Scheme 2).** A solution of 2-nitrobenzenesulfonyl chloride (69.8 g, 31.5 mmol) in 200 mL of anhydrous CH_2Cl_2 was added dropwise to a stirred solution of *N*-(2-aminoethyl)-1,3-propanediamine (**52**) (11.7 g, 10.0 mmol) and Et_3N (50.5 g, 0.50 mol) at 0 °C. The resulting reaction mixture was stirred at rt overnight. The solvent was evaporated, 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 5% aqueous $NaHCO_3$ solution and then brine. After dried (Na_2SO_4), the organic solution was concentrated. The residue was purified by flash chromatography on a silica gel column using 4:1, 1:1, and then 1:4 hexanes-EtOAc to give 5.84 g (87%) of compound **41** as a yellow solid, mp 140-142 °C; ^1H NMR ($CDCl_3$) δ 1.84-1.95 (m, 4H), 3.17 (t,

2H, J = 6.4 Hz), 3.29 (t, 2H, J = 6.4 Hz), 3.0-3.54 (m, 4H), 5.60-5.71 (m, 2H, ex D_2O), 7.25-7.89 (m, 9H), 8.05-8.13 (m, 3H); HRMS (FAB) m/z 804.963 $(M + Cs)^+$ ($C_{23}H_{24}N_6O_{12}S_3Cs$ requires 804.966). Anal. Calcd for $C_{23}H_{24}N_6O_{12}S_3$: C, 41.07; H, 3.60; N, 12.50. Found: C, 41.30; H, 3.74; N, 12.30.

N^1,N^4,N^8-Tris(2-nitrobenzenesulfonyl)-1,8-diamino-4-azaoctane (43) (Scheme 2). Compound **43** was synthesized as above for **41** from spermidine (**53**) (1.0 g, 7.0 mmol), 2-nitrobenzenesulfonyl chloride (4.65 g, 21.0 mmol), and 8.0 mL of Et_3N. The crude product was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 200:1 CH_2Cl_2-MeOH as eluents to give 3.68 g (75%) of compound **43** as a white foam; ^1H NMR ($CDCl_3$) δ 1.40-1.70 (m, 4H), 1.72-1.83 (m, 2H), 3.05-3.17 (m, 4H), 3.21-3.37 (m, 4H), 5.42 (t, 1H, J = 5.9 Hz, ex D_2O), 5.67 (t, 1H, J = 6.2 Hz, ex D_2O), 7.57-8.11 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 25.2, 26.6, 28.9, 40.9, 43.1, 45.1, 47.5, 124.3, 125.3, 130.6, 130.9, 132.0, 132.9, 133.5, 133.7, 148.0; HRMS (FAB) m/z 833.000 $(M + Cs)^+$ ($C_{25}H_{28}N_6O_{12}S_3Cs$ requires 832.998). Anal. Calcd for $C_{25}H_{28}N_6O_{12}S_3$: C, 42.85; H, 4.03; N, 12.00. Found: C, 42.60; H, 4.24; N, 11.80.

5-(*tert*-Butoxycarbonyl)amino-1-pentanol (55) (Scheme 3). A solution of di-*tert*-butyl dicarbonate (21.8 g, 0.10 mol) in 100 mL of anhydrous THF was added to a solution of 5-amino-1-pentanol (**54**) (10.3 g, 0.10 mol) and Et_3N (30.3 g, 0.30 mol) in 20 mL of anhydrous THF at 0 °C. The resulting solution was stirred at rt overnight. The solvent was evaporated, and the residue was dissolved in $CHCl_3$. The solution was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 20:1 CH_2Cl_2-MeOH as eluents to give 19.3 g (95%) of compound **55** as a pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.39-1.59 (m, 16H, 1H ex D_2O), 3.12 (q, 2H, J = 6.3 Hz), 3.65 (q, 2H, J = 5.5 Hz), 4.55 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 22.9, 28.4, 29.8, 32.1, 40.4, 62.3, 79.0, 156.1; HRMS (FAB) m/z 204.159 $(M + H)^+$ ($C_{10}H_{22}NO_3$ requires 204.160). Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.07; H, 10.42; N, 6.89. Found: C, 58.97; H, 10.29; N, 7.00.

1-(2-Nitrobezenesulfonyl)amino-4-aminobutane (58) (Scheme 3). A solution of 2-nitrobenzenesulfonyl chloride (44.2 g, 0.20 mol) in 200 mL of dry CH_2Cl_2 was added dropwise to a solution of 1,4-butanediamine (**56**) (53.0 g, 0.60 mol, 3 equiv) and 80 mL of Et_3N in 300 mL of anhydrous CH_2Cl_2 at 0 °C. The resulting solution was stirred at rt for 3 h. The solvent was evaporated, 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 2:1 CH_2Cl_2-MeOH as an eluent to give 39.8 g (73%) of compound **58** as a yellow solid, mp 100.5-101.5; ^1H NMR ($CDCl_3$) δ 1.43-1.63 (m, 4H), 2.68 (t, 2H, J = 6.0 Hz), 3.07 (t, 2H, J = 6.4 Hz), 3.12 (br, 3H, ex D_2O), 7.68-7.82 (m, 3H), 8.08-8.12 (m, 1H); HRMS (FAB) m/z 274.086 $(M + H)^+$ ($C_{10}H_{16}N_{13}O_4S$ requires 274.086). Anal. Calcd for $C_{10}H_{15}N_{13}O_4S$: C, 43.94; H, 5.53; N, 15.38. Found: C, 44.16; H, 5.47; N, 15.60.

1-(2-Nitrobezenesulfonyl)amino-7-aminoheptane (59) (Scheme 3). Compound **59** was synthesized as above for **58** from 1,7-diaminoheptane (**57**) (2.60 g, 20.0 mmol, 2 equiv) and 2-

nitrobenzenesulfonyl chloride (2.2 g, 10.0 mmol) in the presence of 4 mL of Et_3N. The product was purified by flash chromatography on a silica gel column using 200:1 CH_2Cl_2-MeOH and then 150:1 MeOH-30% NH_4OH as eluents to give 2.10 g (68%) of compound **59** as a yellow oil; ^1H NMR ($CDCl_3$) δ 1.10-1.40 (m, 10H), 2.51 (t, 2H, J = 6.8 Hz), 2.92 (t, 2H, J = 7.1 Hz), 3.35 (br, 3H, ex D_2O), 7.58-7.66 (m, 3H), 7.95-7.98(m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.3, 26.5, 28.7, 29.4, 32.9, 41.5, 43.4, 124.9, 130.8, 132.6, 133.6, 147.9; HRMS (FAB) m / z 316.133 $(M + H)^+$ ($C_{13}H_{22}N_3O_4S$ requires 316.133). Anal. Calcd for $C_{13}H_{21}N_3O_4S{\cdot}H_2O$: C, 46.82; H, 6.90; N, 12.61. Found: C, 46.74; H, 6.79; N, 12.68.

1-(2-Nitrobezenesulfonyl)amino-4-(*tert*-butoxycarbonyl)aminobutane (60) (Scheme 3). A solution of di-*tert*-butyl dicarbonate (3.63 g, 16.7 mmol) in 15 mL of anhydrous THF was added to a solution of **58** (3.05 g, 11.1 mmol) and Et_3N (3.36 g, 33.3 mmol) in 30 mL of anhydrous THF at 0 °C. The resulting solution was stirred at rt overnight. The solvent was evaporated, and the residue was dissolved in $CHCl_3$. The solution was washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 100:1 CH_2Cl_2-MeOH as eluents to give 4.08 g (99%) of compound **60** as a yellow solid, mp 81-83 °C; ^1H NMR ($CDCl_3$) δ 1.37 (s, 9H), 1.44-1.50 (m, 4H), 3.00-3.07 (m, 4H), 4.73 (br, 1H), 5.52 (br, 1H, ex D_2O), 7.68-7.80 (m, 3H), 8.04-8.08 (m, 1H); HRMS (FAB) m /z 396.121 $(M + Na)^+$ ($C_{15}H_{23}N_3O_6SNa$ requires 396.120). Anal. Calcd for $C_{15}H_{23}N_3O_6S$: C, 48.24; H, 6.21; N, 11.26. Found: C, 48.25; H, 6.05; N, 11.31.

1-(2-Nitrobezenesulfonyl)amino-7-(*tert*-butoxycarbonyl)aminoheptane (61) (Scheme 3). Compound **61** was synthesized as above for **60** from **59** (5.5 g, 17.9 mmol) and di-*tert*-butyl dicarbonate (5.0 g, 23.3 mmol) in the presence of Et_3N (7.06 g, 70 mmol). The product was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 50:1 CH_2Cl_2-MeOH as eluents to give 6.90 g (93%) of compound **61** as a yellow solid, mp 61.5-63 °C; ^1H NMR ($CDCl_3$) δ 1.23-1.53 (m, 19H), 3.00-3.11 (m, 4H), 4.51 (br, 1H), 5.31 (t, 1H, J = 5.7 Hz, ex D_2O), 7.70-7.86 (m, 3H), 8.09-8.13 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.3, 26.5, 28.3, 28.5, 29.4, 29.8, 40.5, 43.8, 78.9, 125.3, 130.9, 132.8, 133.6, 148.0, 156.1; HRMS (FAB) m / z 416.184 $(M + H)^+$ ($C_{18}H_{30}N_3O_6S$ requires 416.185). Anal. Calcd for $C_{18}H_{29}N_3O_6S{\cdot}H_2O$: C, 52.03; H, 7.04; N, 10.12. Found: C, 52.17; H, 6.97; N, 10.25.

N^1,N^{10}-Bis(*tert*-butoxycarbonyl)-N^5-(2-nitrobenzenesulfonyl)-1,10-diamino-5-azadecane (62) (Scheme 3). A solution of DEAD (3.66 g, 21.0 mmol) in 100 mL of anhydrous THF was added dropwise to a solution of **55** (4.27 g, 21.0 mmol), **60** (7.14 g, 19.1 mmol), and PPh_3 (5.52 g, 21.0 mmol) in 200 mL of anhydrous THF at rt. The resulting solution was stirred at rt for 2 h. The solvent was evaporated, and the residue was dissolved in anhydrous diethyl ether. The solution was stood in refrigerator overnight, and then the solid was filtered to remove most of the side products Ph_3PO and EtOCONHNHCOOEt. The filtrate was concentrated, and the residue was purified by flash chromatography on a silica gel column using 2:1 and 1:1 hexanes-EtOAc as eluents to give 9.95 g (93%) of compound **62** as a yellow solid, mp 79.5-81 °C; ^1H NMR ($CDCl_3$) δ 1.20-1.62 (m, 28H), 3.01-3.12 (m, 4H), 3.23-3.31 (m, 4H), 4.58 (br, 2H), 7.57-7.70 (m, 3H), 7.93-8.03 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.66, 25.47, 27.16, 27.77, 28.43, 29.53, 33.93, 40.23, 47.08, 47.29, 79.13, 124.14, 130.58, 131.69, 133.50, 148.02, 156.09;

HRMS (FAB) m/z 691.175 $(M + Cs)^+$ ($C_{25}H_{42}N_4O_8SCs$ requires 691.177). Anal. Calcd for $C_{25}H_{42}N_4O_8S$: C, 53.73; H, 7.58; N, 10.03. Found: C, 54.00; H, 7.67; N, 9.94.

N^1,N^{13}-Bis(*tert*-butoxycarbonyl)-N^6-(2-nitrobenzenesulfonyl)-1,13-diamino-6-azatridecane (63) (Scheme 3). Compound **63** was synthesized as above for compound **62** from **61** (1.21 g, 2.97 mmol), **55** (0.60 g, 2.97 mmol), PPh_3 (0.78 g, 2.97 mmol), and DEAD (0.52 g, 2.97 mmol). The crude product was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 100:1 CH_2Cl_2-MeOH as eluents to give 1.25 g (70%) of compound **63** as a yellow oil; ^1H NMR ($CDCl_3$) δ 1.26-1.58 (m, 34H), 3.02-3.10 (m, 4H), 3.21-3.30 (m, 4H), 4.53 (br, 2H), 7.55-7.70 (m, 3H), 7.97-8.03 (m, 1H); HRMS (FAB) m/z 601.328 $(M + H)^+$ ($C_{28}H_{49}N_4O_8S$ requires 601.327). Anal. Calcd for $C_{28}H_{48}N_4O_8S \cdot H_2O$: C, 55.97; H, 8.06; N, 9.33. Found: C, 55.83; H, 7.88; N, 9.60.

N^5-(2-Nitrobenzenesulfonyl)-1,10-diamino-5-azadecane Dihydrochloride (64) (Scheme 3). A solution of **62** (1.85 g, 3.31 mmol) and TFA (35 mL) in 5 mL of CH_2Cl_2 was stirred at rt for 5 h. The solvent was evaporated, and the residue was dissolved in MeOH-HCl (14%). The resulting solution was evaporated under high vacuum to give 1.20 g (92%) of compound **64** (HCl salt) as a yellow solid, mp 90-91 °C; ^1H NMR (CD_3OD) δ 1.21-1.41 (m, 2H), 1.35-1.71 (m, 8H), 2.61-2.70 (m, 4H), 3.25-3.42 (m, 4H); ^{13}C NMR (CD_3OD) δ 24.9, 27.0, 29.3, 30.0, 32.2, 41.8, 42.0, 48.7, 48.9, 125.5, 131.4, 133.3, 134.3, 135.3, 149.6; HRMS (FAB) m/z 359.174 $(M + H)^+$ ($C_{15}H_{27}N_4O_4S$ requires 359.175). Anal. Calcd for $C_{15}H_{26}N_4O_4S \cdot 2HCl$: C, 41.84; H, 6.56. Found: C, 41.86; H, 6.34.

N^6-(2-Nitrobenzenesulfonyl)-1,13-diamino-6-azatridecane Dihydrochloride (65) (Scheme 3). A solution of **63** (1.15 g, 1.90 mmol) and TFA (20 mL) in 5 mL of CH_2Cl_2 was stirred at rt for 5 h. The solvent was evaporated, and the residue was dissolved in MeOH-HCl (14%). The resulting solution was evaporated under high vacuum to give 0.81 g (90%) of compound **65** (HCl Salt) as a yellow foam; ^1H NMR (DMSO-d_6) δ 1.12-1.21 (m, 8H), 1.35-1.56 (m, 8H), 2.66-2.73 (m, 4H), 3.18-3.26 (m, 4H), 7.82-8.03 (m, 10H, 6H ex D_2O); MS (ESI) m/z 401 $(M + H)^+$ ($C_{18}H_{33}N_4O_4S$ requires 401). Anal. Calcd for $C_{18}H_{32}N_4O_4S \cdot 2HCl$: C, 45.64; H, 7.24; N, 11.84. Found: C, 45.75; H, 7.19; N, 11.59.

N^1,N^5,N^{10}-Tris(2-nitrobenzenesulfonyl)-1,10-diamino-5-azadecane (44) (Scheme 3). A mixture of **64** (1.30 g, 3.02 mmol) and K_2CO_3 (4.0 g, 28.9 mmol) in 50 mL of DMF and 100 mL of CH_3CN was stirred at rt for 1 h. A solution of 2-nitrobenzenesulfonyl chloride (1.41 g, 6.35 mmol) in 10 mL of acetonitrile was added dropwise to the above solution at 0 °C. The resulting reaction mixture was stirred at rt overnight. The solvent was evaporated, 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 5:1, 2:1, and 1:1 hexanes-EtOAc as eluents to give 1.57 g (71%) of compound **44** as a yellow foam; ^1H NMR ($CDCl_3$) δ 1.15-1.22 (m, 2H), 1.22-1.70 (m, 8H), 2.96-3.05 (m, 4H), 3.11-3.18 (m, 4H), 5.46-5.56 (m, 2H, ex D_2O), 7.55-8.04 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 23.3, 25.2, 26.6, 27.7, 28.9, 43.2, 43.5, 47.1, 47.5, 124.2, 125.3, 130.2, 130.8, 132.1, 133.0, 133.3, 133.9, 147.9; MS (ESI) m/z 751 (M +

Na)$^+$ ($C_{27}H_{32}N_6O_{12}S_3Na$ requires 751). Anal. Calcd for $C_{27}H_{32}N_6O_{12}S_3$: C, 44.51; H, 4.43; N, 11.56. Found: C, 44.38; H, 4.46; N, 11.37.

N^1,N^6,N^{13}-Tris(2-nitrobenzenesulfonyl)-1,13-diamino-6-azatridecane (45) (Scheme 3). Compound **45** was synthesized as above for compound **44** from **65** (7.0 g, 14.8 mmol) and 2-nitrobenzenesulfonyl chloride (6.90 g, 31.1 mmol) in the presence of K_2CO_3 (21.5 g, 155 mmol). The crude product was purified by flash chromatography on a silica gel column using 200:1 CH_2Cl_2-MeOH as an eluent to give 8.81 g (77%) of compound **45** as a yellow oil; ^1H NMR ($CDCl_3$) δ 1.22-1.31 (m, 8H), 1.46-1.56 (m, 8H), 2.96-3.11 (m, 4H), 3.22 (t, 4H, J = 7.8 Hz), 5.20-5.35 (m, 2H, ex D_2O), 7.68-8.15 (m, 12 H); HRMS (FAB) m / z 903.079 (M + Cs)$^+$ ($C_{30}H_{38}N_6O_{12}S_3Cs$ requires 903.076). Anal. Calcd for $C_{30}H_{38}N_6O_{12}S_3 \cdot 5H_2O$: C, 41.84; H, 5.57; N, 9.77. Found: C, 41.53; H, 5.03; N, 9.90.

Preparation of Library 7 (Scheme 4). A solution containing equimolar amounts of selected benzylic bromides and bromoacetonitrile (**BrF$_{1-10}$**) (total 23.25 mmol, 3.3 equiv) in 50 mL of anhydrous acetonitrile was added to a stirred mixture of scaffold **1** (3.10 g, 7.04 mmol) and anhydrous K_2CO_3 (11.7 g, 84.5 mmol) in 150 mL of acetonitrile. The resulting reaction mixture was stirred at rt for one day. The solvent was evaporated, 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 200:1, 100:1, and then 20:1 CH_2Cl_2-MeOH as eluents to give 4.98 g (88%) of library **7** as a pale yellow foam.

Preparation of Library 8 (Scheme 4). A solution of library **7** (4.98 g, 6.22 mmol) and TFA (50 mL) in 15 mL of $CHCl_3$ was stirred at rt overnight. The solvent was evaporated, and the residue was dissolved in H_2O. The aqueous solution was adjusted to pH >8 with aqueous K_2CO_3 solution and then 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 100% MeOH and then 30:1 MeOH-30% NH_4OH as eluents to give 3.98 g (91%) of intermediate library **8** as a pale yellow oil.

General Procedure for the Preparation of Libraries 9, 10, 13, and 15 (Figure 1, Schemes 4 and 5). A mixture of library **8** (0.21 g, 0.30 mmol), the corresponding bromide (BrR_3, BrR_4, BrR_7 or BrR_9) (0.39 mmol, 1.3 equiv), and anhydrous K_2CO_3 (0.60 g, 4.3 mmol) in 10 mL of anhydrous acetonitrile was stirred at rt overnight. The solvent was evaporated, 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 100:1 and 20:1 CH_2Cl_2-MeOH as eluents to give the corresponding library **9**, **10**, **13**, or **15** as a yellow oil in 60-90% yields.

Preparation of Library 11 (Scheme 5). A solution of library **8** (0.28 g, 0.40 mmol) and *N,N'*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazol-1-carboxamidine (**66**)[22] (148 mg, 0.48 mmol, 1.2 equiv) in 10 mL of anhydrous THF was stirred at 60-70 °C for 24 h. The solvent was evaporated, and the residue was dissolved in

$CHCl_3$. The resulting solution was washed with H_2O and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column using 1:0, 100:1, and then 30:1 CH_2Cl_2-MeOH as eluents to give 220 mg (59%) of library **11** as a yellow foam.

General Procedure for the Preparation of Libraries 12, 14, and 16 (Figure 1 and Scheme 5). A solution of the corresponding *t*-Boc-protected library **11**, **13**, or **15** (0.22 mmol) and TFA (2 mL) in 1.5 mL of CH_2Cl_2 was stirred at rt overnight. The solvent and excess TFA were evaporated, and the residue was dissolved in H_2O. The resulting solution was adjusted to pH >8 with aqueous K_2CO_3 solution, and extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated under high vacuum to give a quantitative yield of the corresponding library as a yellow foam.

General Procedure for the Preparation of Libraries 17-24 (Scheme 6). A solution of library **8** (1.0 equiv), formaldehyde (5 equiv), and CH_3OH (3 mL / mmol of library **8**) was stirred at rt overnight. The solvent was evaporated under high vacuum. The resulting intermediate library **67** was dissolved in benzene (2 mL / mmol), and the selected substituted phenol (1.3 equiv) was added to the above solution. The resulting solution was refluxed for 24 h. The solvent was evaporated, and the residue was purified by preparative thin layer chromatography (PLC) or flash chromatography on silica gel to afford the desired libraries **17-24** as pale yellow foams in 50-60% yields.

General Procedure for the Preparation of Libraries 25-29 (Figure 2 and Scheme 7). These libraries were prepared as described above for library **7** from scaffold **2** (1 equiv), a solution containing the corresponding set of selected functionalities (total 4.2 equiv), and anhydrous K_2CO_3 (15 equiv) in 15 mL of anhydrous CH_3CN. The reaction mixture was stirred at rt for 4 h (for library **28**, at 50-60 °C for 24 h). The solvent was evaporated, 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 100% CH_2Cl_2, and then 5:1 to 1:1 CH_2Cl_2-MeOH as eluents to give the corresponding libraries **25-29** as yellow foams in 60-90% yields.

General Procedure for the Preparation of Libraries 30-34 (Figure 2 and Scheme 7). A solution of the corresponding *t*-Boc-protected libraries **25-29** (2 mmol) and TFA (10 mL) in 1 mL of CH_2Cl_2 was stirred at rt for 5 h. The solvent and the excess TFA were evaporated, and the residue was dissolved in CH_3OH-HCl (14%). The resulting solution was evaporated under high vacuum to give quantitative yields of desired libraries **30-34** as hydrochloride salts.

Preparation of Library 35 (Figure 2 and Scheme 7). A solution containing equimolar amounts of cyclohexyl isocyanate, 4-flurophenyl isocyanate, 2,4-dichlorophenyl isothiocyanate, 4-(trifluoromethoxy)-phenyl isocyanate, and 4-(ethyloxycarboxyl)phenyl isothiocyanate (total 4.2 equiv), and scaffold **2** (1.0 equiv) in a mixed solvent of anhydrous DMF (5 mL) and acetonitrile (10 mL) was stirred at rt for 2 h. The solvent was

evaporated, and the residue was purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 and then 5:1 CH_2Cl_2-MeOH as eluents to give 180 mg (62%) of library **35** as a yellow foam.

Antimicrobial Assays. The high through-put antimicrobial assays were performed against bacteria *Streptococcus pyogenes* ATCC 14289 and *Escherichia coli imp*$^-$ in microtiter plate format as described elsewhere.[10,11]

High Through-Put Scintillation Proximity Assay (SPA). For this assay we utilized the peptide ISIS RP-350 which consists of 39 amino acid residues corresponding to positions 48 to 86 of the HIV-1 tat protein. This peptide contains the basic domain of the tat protein and has binding characteristics similar to that of the wild type protein.[25] The peptide was labeled to high specific activity (100 mCi/mL) by conjugation with monoiodinated [^{125}I] Bolton and Hunter reagent at Amersham Life Sciences and purified by reverse phase HPLC on a Vydac C18 column using acetonitrile-water and 0.1% TFA as eluents. ISIS 5832 is a truncated version of the TAR element (residues 16-45) with biotin molecule conjugated to the 3' terminus. It is specifically recognized by tat. The interaction of the ISIS RP-350 peptide with ISIS 5832 was measured using the SPA (scintillation proximity assay) technology. 100 mg of the streptavidin coated SPA beads (Amersham) were incubated for 20 min at room temperature in 50 mL of PRB Buffer (50 mM Tris, pH 8.0, 1.5 mM $MgCl_2$, 50 mM KCl, 10% glycerol, and 0.01% NP-40) with 0.1 mCi of the labeled peptide and 100 nM ISIS 5832 in an opaque 96 well plate. The plate was spun at 1000 rpm for 5 min to settle the SPA beads. The ^{125}I labeled tat peptide bound to the biotinylated TAR oligonucleotide which in turn bound to the streptavidin coated SPA bead. This brought the ^{125}I labeled peptide into the close proximity to the scintillant in the bead, resulting in a quantifiable signal which can be read in the TopCount 96 well scintillation counter. Compounds that interfered the tat/TAR interaction resulted in the ^{125}I labeled tat peptide floating free in buffer where excited electrons were quenched before transferring energy to scintillant in the SPA bead. This was observed as a decrease in signal.

Acknowledgments. The authors thank Drs. Richard H. Griffey, David Ecker, Jacqueline R. Wyatt, Rangarajan Sampath, Larry Blyn, Mrs. Laura Wilson-Lingardo, and Lisa M. Risen for antimicrobial screening of combinatorial libraries.

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