Synthesis and Structure−Activity Relationship Studies of CD4 Down-Modulating Cyclotriazadisulfonamide (CADA) Analogues

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HIV attachment via the CD4 receptor is an important target for developing novel approaches to HIV chemotherapy. Cyclotriazadisulfonamide (CADA) inhibits HIV at submicromolar levels by specifically down-modulating cell-surface and intracellular CD4. An effective five-step synthesis of CADA in 30% overall yield is reported. This synthesis has also been modified to produce more than 50 analogues. Many tail-group analogues have been made by removing the benzyl tail of CADA and replacing it with various alkyl, acyl, alkoxycarbonyl and aminocarbonyl substituents. A series of sidearm analogues, including two unsymmetrical compounds, have also been prepared by modifying the CADA synthesis, replacing the toluenesulfonyl sidearms with other sulfonyl groups. Testing 30 of these compounds in MT-4 cells shows a wide range of CD4 down-modulation potency, which correlates with ability to inhibit HIV-1. Three-dimensional quantitative structure−activity relationship (3D-QSAR) models were constructed using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) approaches. The X-ray crystal structures of four compounds, including CADA, show the same major conformation of the central 12-membered ring. The solid-state structure of CADA was energy minimized and used to generate the remaining 29 structures, which were similarly minimized and aligned to produce the 3D-QSAR models. Both models indicate that steric bulk of the tail group, and, to a lesser extent, the sidearms mainly determine CD4 down-modulation potency in this series of compounds.

Introduction

The CD4 glycoprotein, a major functional cell surface molecule, is predominantly expressed on T-lymphocytes, an important helper T-cell subset.[1] It is also present on the membranes of several other immune cell types such as macrophages/monocytes, dendritic, and Langerhans cells. Various in vitro and in vivo studies have implicated CD4 in several steps of physiological T-cell activation.[2,3] Because of the central role of $CD4^+$ T cells as regulators of immune function, they are believed to play an important part in the pathogenesis of a variety of immunologically based diseases (e.g. asthma, rheumatoid arthritis, and diabetes), and anti-CD4 monoclonal antibodies have been explored as a therapeutic approach for these diseases.[4−8] CD4 is also the main receptor enabling infection by the human immunodeficiency virus (HIV),[9,10] so it is receiving attention as an important target for therapeutic intervention. Viral entry inhibitors are actively being pursued as novel anti-HIV agents,[11−13] including anti-CD4 antibodies[14,15] and chemokine receptor antagonists.[16,17] Multiple domains of CD4 are involved in the viral entry process;[18] therefore, down-regulation of the complete CD4 receptor[19,20] may be considered a more effective method for CD4 blocking in the treatment of HIV infections. Antisense oligonucleotides have been demonstrated to partially reduce lymphocyte surface CD4 expression.[21]

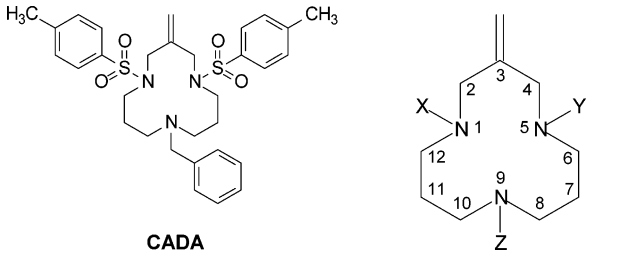

Figure 1. Molecular structure of cyclotriazadisulfonamide (CADA = 9-benzyl-3-methylene-1,5-di-*p*-toluenesulfonyl-1,5,9-triazacyclododecane) and general formula of sidearm (X,Y) and tail (Z) analogues, with ring numbering scheme.

However, treatment of the cells with the small molecule cyclotriazadisulfonamide (CADA, Figure 1) results in more profound CD4 down-modulation.[22]

CADA has been found to specifically decrease the amounts of cell-surface and intracellular CD4 by almost 90% in MT-4 cells, without altering the expression of any other cellular receptor examined, including HIV coreceptors.[22] Similar reduction of CD4 expression was observed in other T-cell lines (i.e., SupT1, MOLT-4, CEM, and Jurkat), in freshly isolated blood lymphocytes and monocytes, in monocytic cell lines (i.e., THP-1 and U937) and in CD4 transfected cells (i.e., U87, A2.01 and C3.2).[19,20] Time course experiments revealed that CD4 down-modulation by CADA differs in its mechanism of action from aurintricarboxylic acid, which binds to CD4, and phorbol myristate acetate, which activates protein kinase C.[22] CD4 mRNA levels are not affected by CADA, suggesting that CD4 expression is not inhibited at a transcriptional level. Despite its superficial structural resemblance to bicyclams,[16,23] CADA does not inhibit HIV replication by simply binding to a cell surface

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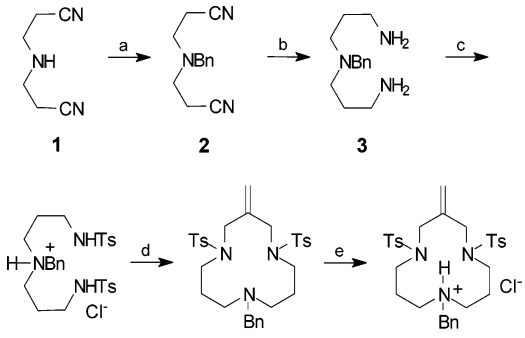
Scheme 1[a]



[a] Reagents and conditions: (a) BnCl, NaI, Na_2CO_3, CH_3CN (83%); (b) H_2, Ni, NaOH, EtOH (72%); (c) TsCl, NaOH, CH_2Cl_2, H_2O (89%); (d) 3-chloro-2-chloromethyl-1-propene, NaH, DMF, 100 °C (54%); (e) HCl, H_2O, CH_2Cl_2 (100%).

receptor or coreceptor and preventing the interaction of gp120 with the receptors. Recently, it was found that the anti-HIV effect of CADA is synergistic with those of antiviral drugs operating by diverse mechanisms, including inhibitors of HIV reverse transcriptase, protease and attachment/entry.[24]

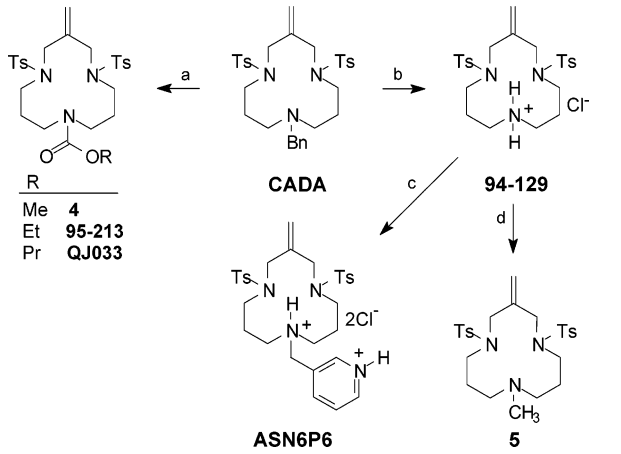
The specific molecular target of CADA remains unknown, and studies have been initiated to map its structure−activity relationships.[25] In a series of more than 25 CADA analogues, anti-HIV potency was directly correlated with CD4 down-modulation ability.[25] Most of the analogues prepared to date have various sidearms (X and Y) or tail groups (Z, cf. Figure 1). Several "headgroup" analogues have also been synthesized in which the exocyclic C═C bond is removed or replaced by a polar group, but these compounds generally show decreased potency.[25] Here we detail the synthesis of CADA and a wide range of sidearm and tail analogues, as well as the X-ray crystal conformations of four of these compounds. These analogues were designed to determine how varying the physicochemical characteristics of sidearm and tail groups affects CD4 down-modulating potency in cell culture assays. These results have been used, in turn, to develop 3D QSAR models for predicting potencies of novel CADA analogues.

Results and Discussion

Synthesis. CADA was first prepared as an intermediate in the attempted synthesis of a bicyclic triamine.[26] The current synthesis (Scheme 1) follows the same plan, involving Atkins−Richman macrocyclization of a bis(tosylamide) dianion with a dihalide,[27,28] though most steps have been increased in scale and improved in yield. The starting material, bis(2-cyanoethyl)-amine (**1**) is now obtained in 84% yield by reaction of acrylonitrile with ammonia. Benzylation in acetonitrile gives bis(cyanoethyl)benzylamine (**2**) in 83% yield. Catalytic hydrogenation over Raney nickel[26] gives triamine **3**, which is tosylated by the Schotten−Bauman method using aqueous base. Bis-(tosylamide) **94**−**127** is readily purified via its crystalline hydrochloride, which is deprotonated in situ in the next step.

Macrocyclization (step d) is best conducted with very slow (30 h) addition of the dichloride to the bis(tosylamide) dianion derived from **94**−**127**, to avoid the formation of side products that are difficult to remove from CADA. Hence, the procedure given here is smaller in scale than that published previously,[26] but 9 g of pure product is reliably obtained per batch. CADA can be quantitatively converted to the hydrochloride salt (**94**−**128**), which has better solubility than the free base in polar solvents. The 5-step synthesis shown in Scheme 1 (ca. 30% overall) is an effective method for production of CADA as an intermediate for synthesis of tail analogues. This route also serves as a model for preparation of sidearm analogues, as described subsequently.

Scheme 2[a]



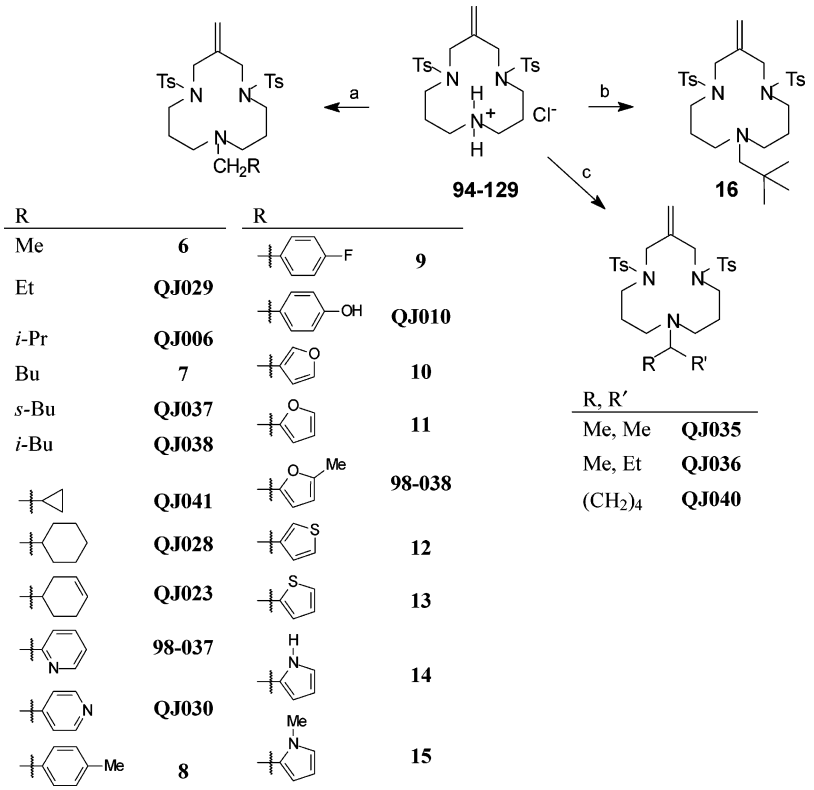
[a] Reagents and conditions: (a) methyl, ethyl or propyl chloroformate, 1,2-dichloroethane, reflux (76−83%); (b) 1-chloroethyl chloroformate, 1,2-dichloroethane, reflux; methanol, reflux (86%); (c) 3-chloromethylpyridine hydrochloride, triethylamine, DMF; HCl (15%); (d) formic acid, formaldehyde, NaOH, H_2O (58%).

Methyl, ethyl, and isopropyl carbamate tail analogues (**4**, **95**−**213**, and **QJ033**, respectively), were prepared in high yield by reaction of CADA with the corresponding chloroformate in refluxing 1,2-dichloroethane (Scheme 2). As reported previously,[26] reaction of CADA with α-chloroethyl chloroformate (ACE-Cl)[29,30] under the same conditions, followed by cleavage of the intermediate carbamate in hot methanol, results in complete removal of the tail group. Hydrochloride salt **94**−**129** is isolated in high yield from reactions starting with several grams of CADA per batch. An alternate procedure involving cleavage of ethyl carbamates with boron triiodide *N*,*N*-diethylaniline complex in hot toluene[31] was also investigated. Low solubilities of intermediate **95**−**213** and the cleavage product in the reaction medium, as well as losses suffered during purification, resulted in a 34% yield of **94**−**129** from this reaction. Debenzylation of CADA by the ACE-Cl method is the preferred route to this key intermediate.

Prior to determining that reductive alkylation of **94**−**129** is the best route to *N*-alkyl tail analogues, direct alkylation with 3-picolyl chloride was investigated. Reaction of **94**−**129** free base with 3-chloromethylpyridine hydrochloride and triethylamine in DMF resulted in partial conversion and isolation of dihydrochloride **ASN6P6** in low yield. Use of stronger bases or higher temperature gave decomposition or polymerization of 3-picolyl chloride. The *N*-methyl analogue **5** was prepared directly from HCl salt **94**−**129** in fair yield by Eschweiler−Clarke methylation[32] (Scheme 2).

The most versatile method used for synthesis of tail analogues is reductive alkylation by reaction of secondary amine hydrochloride **94**−**129** with various aldehydes or ketones and sodium cyanoborohydride (Scheme 3). These reactions were conducted in methanol at room temperature for periods of 1−3 days. The yields of crude products were generally excellent. Those reported for the 25 tail analogues in Scheme 3 (see also Experimental Section) are for analytically pure samples. The reaction did not go to completion if the free base corresponding to **94**−**129** was used. Higher yields from the hydrochloride salt are consistent with the knowledge that iminium salts are reduced rapidly at pH 6−7, while reduction of aldehydes or ketones is negligible

Scheme 3[a]



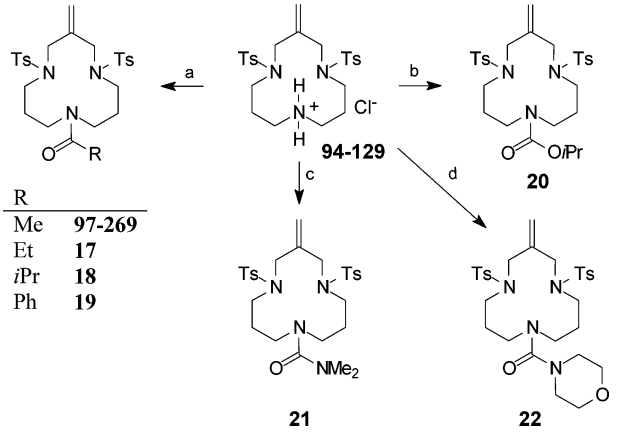
[a] Reagents and conditions: (a) RCHO, $NaBH_3CN$, MeOH (25−89%); (b) pivaldehyde, $NaBH_3CN$, $ZnCl_2$, MeOH (12%); (c) RCOR′, $NaBH_3CN$, $ZnCl_2$, MeOH (62−75%).

at this pH.[33] Reaction times for ketones were far longer than for aldehydes, and zinc chloride was required to activate the ketone carbonyl group[34] to produce **QJ035**, **QJ036**, and **QJ040**. However, the reaction of pivaldehyde to produce **16** was very slow, even in the presence of zinc chloride. In the case of this sterically hindered aldehyde, a mixture of starting material and product was obtained, and **16** was isolated in low yield by chromatography.

As complements of the primary alkyl carbamates prepared directly by reaction of chloroformates with CADA (Scheme 2), other carbonyl group tail analogues were synthesized from intermediate hydrochloride salt **94**−**129**. Reaction with various acyl chlorides, isopropyl chloroformate, or carbamoyl chlorides in the presence of triethylamine gave **97**−**269** and analogues **17**-**22**, generally in good yields, as shown in Scheme 4.

The synthetic route to CADA (Scheme 1) was applied to several sidearm analogues, as shown in Scheme 5. One analogue, bis(methanesulfonamide) **MFS105**, lacks benzene rings in the sidearms. It was prepared in good yield by Atkins-Richman cyclization of hydrochloride salt **23**, reflecting similar properties of methanesulfonamide and arenesulfonamide anions. Attempts to apply this cyclization method to carboxamide sidearm analogues have failed, so far. Seven arenesulfonamide analogues having different steric and electronic characteristics were prepared by macrocyclization of the corresponding dianions. An eighth, bis(*p*-aminobenzenesulfonamide) **MFSPB1**, was synthesized by reduction of bis(*p*-nosylamide) **AS114**. The bis(arenesulfonamide) intermediates (**24**-**30**) were prepared from triamine **3** by Schotten−Bauman sulfonylation, using brine to decrease the solubility of the arenesulfonyl chloride in the aqueous layer, as in CADA synthesis. Most of the disulfonamides are oils and were purified via crystalline HCl salts, though the bis(*p*-bromobenzenesulfonamide) free base **25** was

Scheme 4[a]

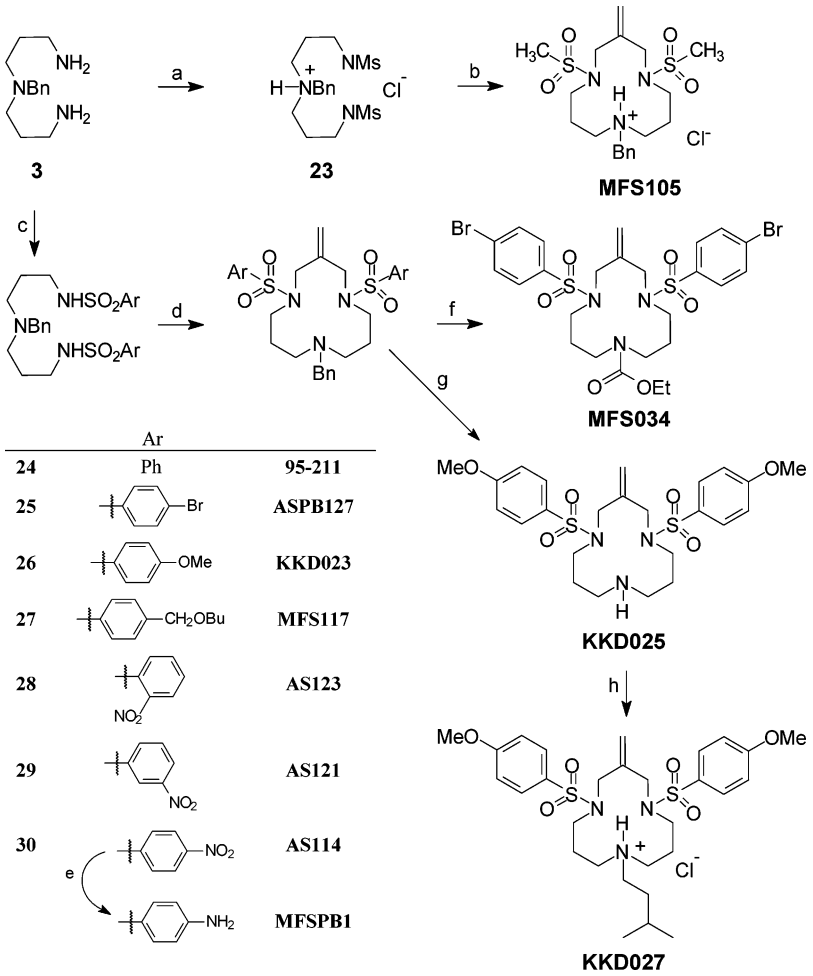


[a] Reagents and conditions: (a) RCOCl, Et_3N, $CHCl_3$ (42−77%); (b) *i*PrOCOCl, Et_3N, $CHCl_3$ (69%); (c) Me_2NCOCl, Et_3N, $CHCl_3$ (64%); (d) 4-morpholinecarbonyl chloride, Et_3N, $CHCl_3$ (74%).

obtained as a crystalline solid. Macrocyclization yields for these arenesulfonamide analogues were comparable to those obtained for CADA.

Conversion of bis(*p*-bromobenzenesulfonamide) **ASPB127** to other sidearm analogues was briefly investigated, but the corresponding bis(aryllithium) and bis(Grignard) reagents were not formed in reasonable yield. One attempt involving treatment of **ASPB127** with *tert*-butyllithium and trapping of the putative dianion with ethyl chloroformate resulted in fortuitous synthesis of carbamate tail analogue **MFS034**. After discovering the CD4 down-modulating potencies of **KKD023** and 3-methylbutyl tail analogue of CADA, **QJ038**,[25] combination of these features appeared attractive. Debenzylation of **KKD023** proceeded in similar yield as cleavage of CADA (cf. Scheme 2), and

Scheme 5[a]



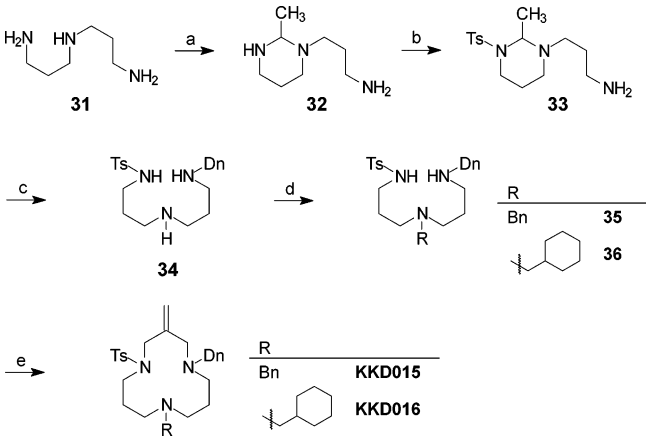
[a] Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2; HCl, Et_2O (64%); (b) NaH, 3-chloro-2-chloromethyl-1-propene, DMF; HCl, CH_2Cl_2, Et_2O (21%); (c) $ArSO_2Cl$, Et_2O or CH_2Cl_2, NaOH, H_2O (82−98%); (d) NaH, 3-chloro-2-chloromethyl-1-propene, DMF (12−85%); (e) $NaBH_4$, $Cu(OAc)_2$, EtOH (55%); (f) EtOCOCl, THF (38%); (g) 1-chloroethyl chloroformate, 1,2-dichloroethane; MeOH, reflux (83%); (h) 1-bromo-3-methylbutane, Na_2CO_3, NaI, CH_3CN, reflux (58%).

alkylation of intermediate secondary amine **KKD025** gave **KKD027** in moderate yield.

Unsymmetrical analogues having two different sidearms are also of interest for testing as CD4 down-modulating agents. Adaptation of the CADA synthesis (Scheme 1) to unsymmetrical analogues requires monofunctionalization of triamine **3**, which is difficult to achieve selectively. Hence, desymmetrization of triamine **31**, an inexpensive starting material, was explored via cyclic aminal **32** (Scheme 6). Unsymmetrical analogues incorporating the fluorescent 5-(dimethylamino)-1-naphthalenesulfonyl (dansyl) group were the initial targets.

Condensation of **31** with acetaldehyde was carried out in the manner described for spermidine and propane-1,3-diamines.[35] The resulting hexahydropyrimidine (**32**) bears primary, secondary, and tertiary nitrogen atoms. Prior work indicated that the secondary nitrogen would react with electrophilic reagents,[36] though quaternization of the tertiary nitrogen (with subsequent reaction) or functionalization of the less nucleophilic primary nitrogen could compete. Reaction of **32** with tosyl chloride under Schotten−Bauman conditions (diethyl ether, aq NaOH), or in CH_2Cl_2 with triethylamine as the base, gave complex mixtures of products. A mixture of THF and aq NaOH cleanly gave a monotosylated product, identified as **33** on the basis of its NMR and IR spectra. Dansylation of the primary nitrogen and ring opening gave **34**, which was converted to the *N*-benzyl (**35**) and *N*-cyclohexylmethyl (**36**) derivatives. These unsymmetrical

Scheme 6[a]



[a] Reagents and conditions: (a) MeCHO, $CHCl_3$, 3 °C (83%); (b) TsCl, NaOH, THF, H_2O (35%); (c) DnCl, Na_2CO_3, NaOH, CH_2Cl_2, H_2O (50%); (d) BnCl or $BrCH_2Cy$, Na_2CO_3, NaI, MeCN (19−50%); (e) NaH, 3-chloro-2-chloromethyl-1-propene, DMF (27−35%); Cy = cyclohexyl, Dn = 5-(dimethylamino)-1-naphthalenesulfonyl.

triamines underwent Atkins−Richman macrocyclization to produce the corresponding CADA analogues, **KKD015** and **KKD016**.

X-ray Structures. Solid-state structures of drugs can provide indirect information about preferred conformation and flexibility

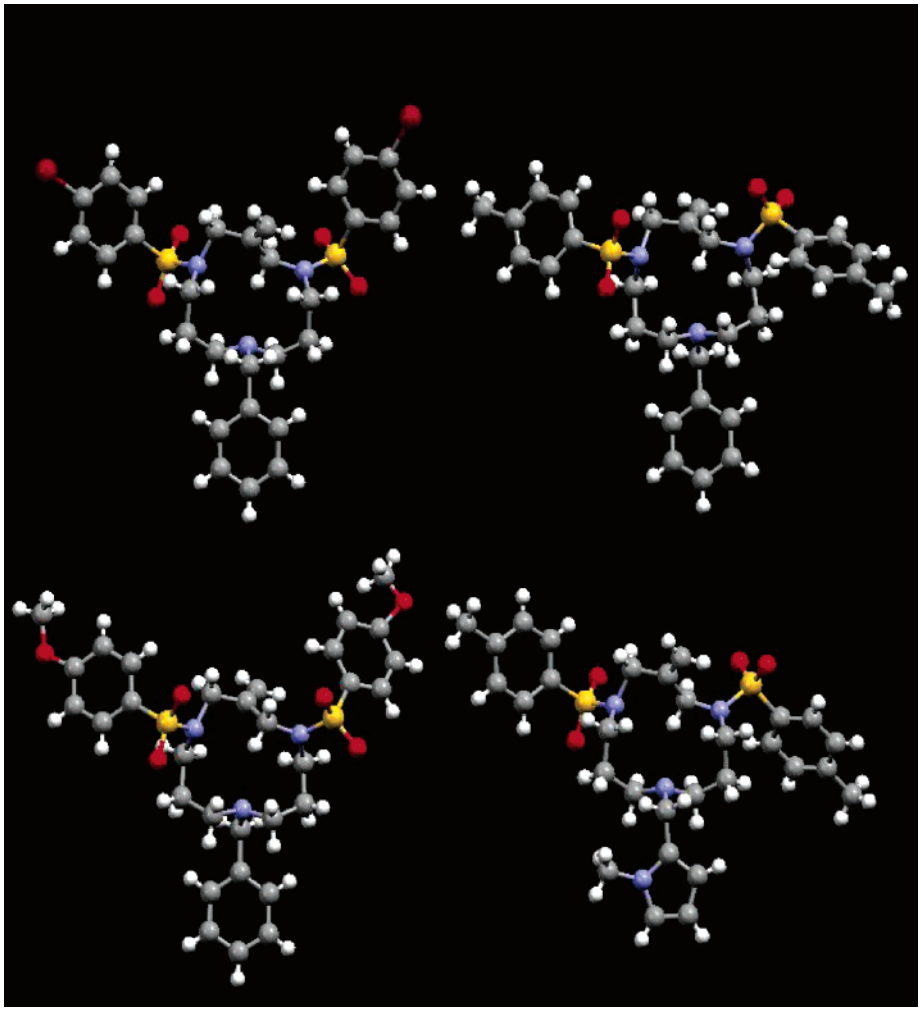


Figure 2. Solid state conformations of **ASPB127** (upper left), CADA (upper right), **KKD023** (lower left), and **15** (lower right). Color code: carbon, gray; hydrogen, white; nitrogen, blue; oxygen, light red; sulfur, yellow; bromine, dark red. See Supporting Information for crystallographic details.

and can be used as templates for modeling quantitative structure−activity relationships (QSAR), especially when the mechanism of action is unknown. The crystal structures of four compounds (**ASPB127**, CADA, **KKD023**, and **15**) were determined by X-ray diffraction analysis, and their solid state conformations are displayed in Figure 2. Each of these analogues crystallized in the free base form, so the tertiary nitrogen atom shown at the bottom of each diagram in Figure 2 is unprotonated. The central, 12-membered ring adopts the same overall conformation in each structure. This is clear from inspection of the diagrams in Figure 2 and by comparison of the torsions (dihedral angles) about each of the 12 bonds in the ring. These torsions, listed in Table 1, display some minor variations, but each corresponding bond for all four molecules lies in the same energy well. Most of the ring atoms are sp^3 hybridized, producing 3-fold rotational potentials for each of these bonds in the central ring. The same combination of torsions is observed in the solid state structures of all four analogues, suggesting that this is a low energy conformation. The tail group at the bottom of each diagram and the two arenesulfonamide sidearms are expected to be more flexible than the central ring. The tail group has approximately the same orientation in each case, as well as one of the two arenesulfonamide sidearms. The other sidearm, shown on the right side of each diagram, has one orientation in two structures and a different orientation in the other two. Overall, these compounds show a high degree of conformational homology, which should facilitate their alignment for modeling three-dimensional quantitative structure−activity relationships (3D-QSAR).

Table 1. Ring Torsional Angles for X-ray Structures of **ASPB127**, CADA, **KKD023**, and **15**[a]

ring atoms	**ASPB127**	CADA[b]	**KKD023**[b]	**15**
N1−C2−C3−C4	57.2(12)	48.6(3)	53.1(7)	49.4(3)
C2−C3−C4−N5	−176.9(9)	−175.0(2)	−173.9(5)	−174.0(2)
C3−C4−N5−C6	64.3(13)	69.0(3)	62.2(7)	68.2(3)
C4−N5−C6−C7	87.3(12)	89.8(3)	91.2(6)	90.2(3)
N5−C6−C7−C8	−62.6(12)	−62.3(3)	−63.9(7)	−62.2(3)
C6−C7−C8−N9	−50.4(13)	−49.3(3)	−49.2(8)	−54.0(4)
C7−C8−N9−C10	164.7(9)	163.9(2)	166.3(5)	162.8(2)
C8−N9−C10−C11	−166.0(8)	−164.1(2)	−166.0(5)	−160.9(2)
N9−C10−C11−C12	55.7(12)	56.8(3)	55.1(7)	59.2(3)
C10−C11−C12−N1	55.3(12)	56.7(3)	56.1(7)	57.2(3)
C11−C12−N1−C2	−152.6(9)	−154.6(2)	−152.5(5)	−155.6(2)
C12−N1−C2−C3	72.5(11)	74.0(3)	74.8(6)	73.1(3)

[a] Angles in degrees; see Supporting Information for crystallographic data; see Figure 2 for numbering scheme; errors shown in parentheses. [b] Torsional angles multiplied by −1.

Structure−Activity Relationships. The CD4 down-modulation potencies of most CADA compounds described in this publication have been reported previously.[25] They appear in Table 2 as IC_{50} values (concentration producing 50% decrease of CD4 on surfaces of MT-4 cells) and as pIC_{50} values (−log IC_{50}). The CD4 down-modulation potencies of **KKD015**, **KKD016**, **KKD023**, **KKD025**, **KKD027**, and **MFS034** are also reported in Table 2. Activity data is not listed for the remaining

Table 2. Experimental and CoMFA Predicted CD4 Down-Modulation Activities of CADA Compounds in MT-4 Cells

compound[a]	IC_{50} (exptl)[b]	pIC_{50} (exptl)[c]	pIC_{50} (pred)[d]	residual[e]
95−211	>15[f]	4.82	4.91	−0.09
95−213	11.1 ± 0.7	4.95	5.14	−0.19
97−269	>75[f]	4.12	4.18	−0.06
98−035	10.3 ± 3.3	4.99	5.21	−0.22
98−037	>75[f]	4.12	4.83	−0.71
AS112	>15[f]	4.82	4.52	0.30
ASN6P6	5.4 ± 1.4	5.27	5.30	−0.03
ASPB127	1.8 ± 0.3	5.74	5.23	0.51
CADA	0.80 ± 0.35	6.10	5.27	0.83
KKD015	1.3 ± 0.3	5.89	5.81	0.08
KKD016	0.61 ± 0.05	6.21	6.73	−0.52
KKD023	0.22 ± 0.06	6.66	6.12	0.54
KKD025	5.3 ± 1.2	5.28	5.43	−0.15
KKD027	0.29 ± 0.12	6.54	6.67	−0.13
MFS034	12.4 ± 3.5	4.91	5.06	−0.15
MFS105	>75[f]	4.12	3.96	0.16
MFS117	>15[f]	4.82	4.85	−0.03
MFSPB1	>15[f]	4.82	5.14	−0.32
QJ023	0.57 ± 0.27	6.24	6.17	0.07
QJ027	7.9 ± 1.6	5.10	5.41	−0.31
QJ028	0.34 ± 0.06	6.47	6.24	0.23
QJ029	4.1 ± 0.8	5.39	5.11	0.28
QJ030	5.5 ± 2.1	5.26	5.42	−0.16
QJ033	2.1 ± 0.3	5.68	5.48	0.20
QJ035	11.0 ± 1.5	4.96	5.02	−0.06
QJ036	3.0 ± 1.6	5.52	5.37	0.15
QJ037	0.98 ± 0.16	6.01	5.89	0.12
QJ038	0.67 ± 0.09	6.17	5.97	0.20
QJ040	8.3 ± 1.2	5.08	5.40	−0.32
QJ041	6.6 ± 2.9	5.18	5.39	−0.21

[a] Compounds **KKD015**, **KKD016**, **KKD023**, **KKD025**, **KKD027**, and **MFS034** were used in the free base or salt forms, as described in the Experimental Section; data for the remaining compounds are from ref 25. [b] IC_{50} (μM) for CD4 down-modulation was the concentration of the compound required for 50% inhibition of cell surface CD4 expression in MT-4 cells, determined exactly as described in ref 25. [c] $pIC_{50} = -\log IC_{50}$. [d] pIC_{50} predicted by CoMFA QSAR model derived from all 30 compounds in this table (see Experimental Section). [e] pIC_{50} (pred) − pIC_{50} (exptl). [f] Minimum IC_{50} estimated from upper limit of concentration used in CD4 down-modulation assay.

compounds described here because they were not tested or they gave ambiguous testing results. In seven cases listed in Table 2, no CD4 down-modulation activity was observed. Toxicities of these compounds prevented reliable testing at concentrations above either 15 μM (**95−211**, **AS112**, **MFS117**, and **MFSPB1**) or 75 μM (**97−269**, **98−037**, and **MFS105**). IC_{50} values for these "inactive" compounds are given in Table 2 as >15 or >75 μM, respectively, to indicate that these are lower limits.

Anti-HIV activities and toxicities are not listed in Table 2, but these data have been reported for 24 of the 30 compounds.[25] Antiviral potencies (IC_{50}) for NL4.3 infection and cytotoxicities (CC_{50}), determined for MT-4 cells exactly as described previously,[25] are as follows for five of the remaining six compounds (IC_{50}/CC_{50}, μM): **KKD015**, 9.5 ± 1.0/>75; **KKD016**, 1.8 ± 0.3/49 ± 25; **KKD023**, 0.62 ± 0.21/26 ± 1; **KKD025**, 6.3 ± 0.6/43 ± 13; **KKD027**, 0.63 ± 0.05/53 ± 29. The anti-HIV potency of **MFS034** was not measured, though its cytotoxicity (CC_{50}) was found to be 29 ± 4 μM. As observed previously for CADA compounds,[25] the anti-HIV potencies of these additional analogues directly correlate with their CD4 down-modulation abilities. This correlation is displayed in Figure 3 for the 30 compounds listed in Table 2.

Three-dimensional quantitative structure−activity relationship (3D-QSAR) modeling was performed to provide a tool for future selection of target compounds for synthesis. When the structure of the molecular target for drug binding is unknown, comparative molecular field analysis (CoMFA) can be used to correlate

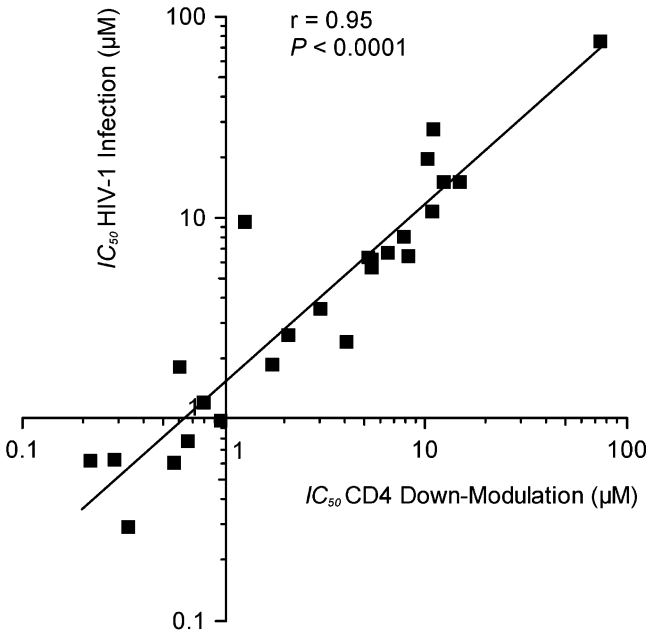


Figure 3. Correlation between anti-HIV-1 (NL4.3) activity and CD4 expression/down-modulation in MT-4 cells by 30 different CADA compounds listed in Table 2 (nonparametric Spearman rank correlation; the probability P indicates significance at the 0.05 level). For each analogue, the anti-HIV activity (IC_{50} value) was plotted against the CD4 down-modulating capability (IC_{50} value calculated from the mean fluorescence intensity of MT-4 cells labeled with the FITC-conjugated anti-CD4 mAb).[25]

steric and electrostatic properties according to Lennard−Jones and Coulomb potentials.[37] We examined hydrophobic potentials using Hansch parameters separately. Hydrophobic potential was insufficient to be the sole predictor of biological activity. Energy minimized structures of all 30 compounds listed in Table 2 were aligned by means of a template based on the X-ray crystal structure of CADA (cf. Figure 2). A CoMFA model was calculated by the partial least squares (PLS) method and validated by the standard "leave-one-out" approach. The pIC_{50} values calculated by this model and residuals (differences between experimental and calculated values) shown in Table 2 have strong statistical significance ($r^2 = 0.80$, $P < 0.001$) and internal predictive ability ($q^2 = 0.41$). Potencies of all 30 compounds are predicted well by the model, which gives calculated IC_{50} values within 10-fold of the experimental values. Steric and electrostatic contour maps generated from this CoMFA model are shown in Figure 4. The steric and electrostatic contributions to this model are 59% and 41%, respectively. As shown in Figure 4, increased steric bulk in the tail region clearly enhances drug potency. In contrast, the strongest electrostatic correlations involve the macrocyclic ring and the sidearms. The effect of using estimated values for the seven "inactive" compounds was examined by recalculating the CoMFA model, leaving out these seven values (15 or 75 μM). This improved the correlation ($r^2 = 0.87$, $P < 0.001$) and predictive ability ($q^2 = 0.50$) of the model for the remaining 23 compounds, but it predicted 4−50-fold greater potencies for the seven "inactives," relative to experimental estimates. This indicates that without these "inactive" compounds, the CoMFA model lacks the diversity of compounds needed to be useful for predictions. Current efforts are aimed at testing further compounds and further refining the model.

A second 3D-QSAR analysis, CoMSIA (comparative molecular similarity indices analysis), was also performed on the 30 compounds listed in Table 2. CoMSIA correlates activity

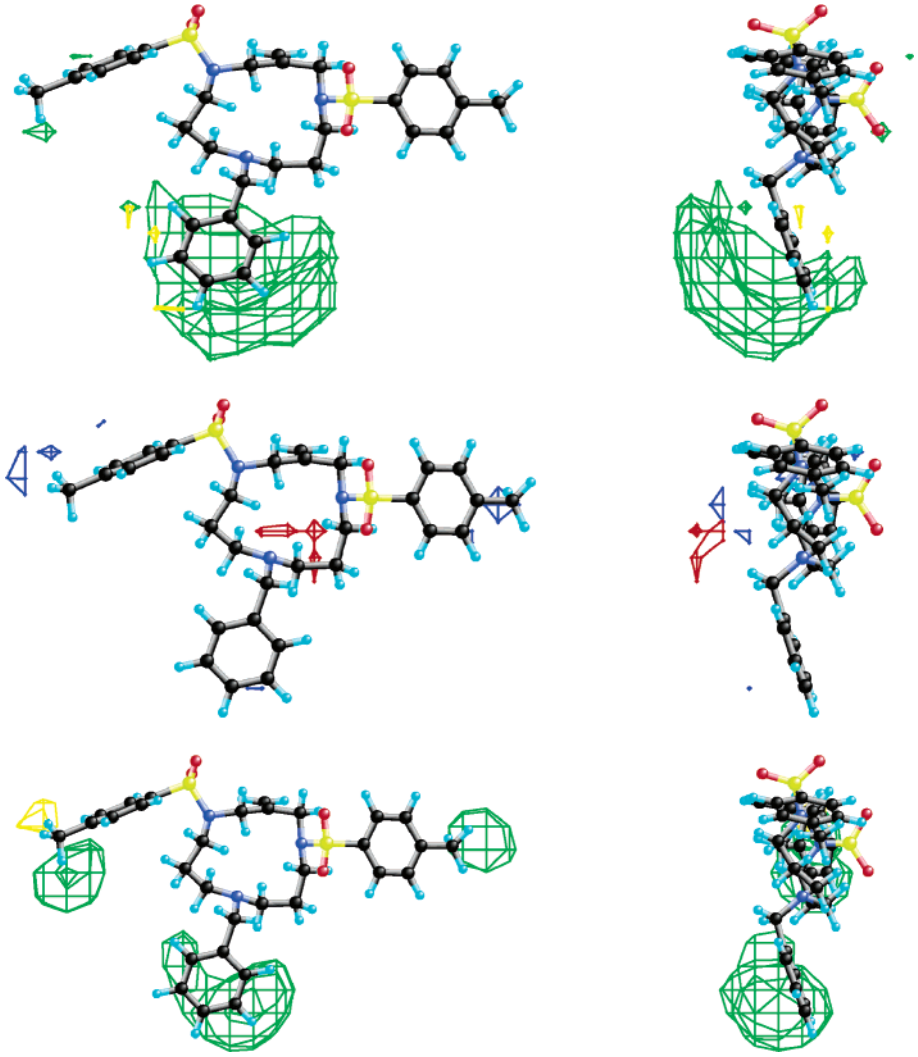


Figure 4. 3-D QSAR contour maps shown for CADA (perpendicular views): CoMFA steric (top) and electrostatic (center), and CoMSIA steric (bottom). Plots contoured at 1/3 of maximum field value, showing only most important correlating points. Top and bottom: mesh in green shows areas correlating increasing steric bulk with increasing potency (greater pIC_{50} value); mesh in yellow shows areas correlating decreasing steric bulk with increasing potency. Center: mesh in red shows areas correlating increasing positive charge with increasing potency; mesh in blue shows areas correlating increasing negative charge with increasing potency.

data with hydrogen bonding and hydrophobicity, in addition to the steric and electrostatic indices included in CoMFA.[38−40] A PLS analysis of each CoMSIA index was run independently of the other indices (i.e. hydrophobic alone, steric alone, etc.), and the same settings were used as in the CoMFA PLS. The results of the CoMSIA and CoMFA analyses agree with respect to steric effects. A correlation between CD4 down-modulation and hydrogen bonding (acceptor and donor), electrostatics, and hydrophobics could not be found (i.e., $q^2 < 0.3$). A correlation was found for sterics, and the PLS analysis returned a $q^2 = 0.44$ and an $r^2 = 0.75$. This agrees with the CoMFA result that changes in steric bulk are the most strongly correlated with changes in pIC_{50} value. The correlation of the change in sterics with pIC_{50} is shown in Figure 4. Both CoMFA and CoMSIA show a strong correlation with increasing steric bulk in the tail region; however, the CoMSIA also has correlation with changes in steric bulk in the sidearm regions. These 3D-QSAR analyses show that changes in substituent size mainly determine changes in CD4 down-modulation potency in CADA compounds. This finding does not diminish the importance of hydrogen bonding, hydrophobicity, and electrostatics in determining efficacy. It indicates that variations of these properties individually prove to be poor predictors of potency. For example, all compounds examined vary in their physicochemical properties. The correlation between changes in hydrogen bonding and efficacy may be obscured by other correlations. In contrast, the effect of changing steric bulk is so strong that other factors do not obscure the correlation between steric bulk and potency.

Summary and Conclusions

Effective approaches have been developed for the synthesis of cyclotriazadisulfonamide (CADA) and more than 50 analogues. Most of these are symmetrical compounds bearing two identical arenedisulfonamide sidearms, but an alternate approach has been used to produce two unsymmetrical analogues (**KKD015** and **KKD016**). Thirty tested compounds show a wide range of CD4 down-modulation potencies, which correlate with their abilities to inhibit HIV-1 infection in MT-4 cells. Computational three-dimensional quantitative structure−activity relationship (3D-QSAR) studies based on conformations observed in the X-ray crystal structures of four of the compounds have produced models that can be used to design analogues for future synthesis. These models show steric bulk of the tail group and, to a lesser extent, the sidearms to be the main determinant of CD4 down-modulation potency.

Experimental Section

General Methods. All reactions were performed under an atmosphere of dry nitrogen. Reagents and solvents purchased from Aldrich Chemical Co., Acros Organics, or Fisher Scientific were of ACS reagent grade or better and were used without purification, unless indicated otherwise. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, and butanol was distilled from sodium. Dichloromethane and 1,2-dichloroethane were distilled from P_2O_5. Anhydrous dimethylformamide (DMF) was purchased from Aldrich in Sure-Seal bottles or distilled from calcium hydride in vacuo. Methanol was distilled from CaH_2 or Mg/I_2. Melting points are uncorrected. All NMR chemical shifts (δ) are reported in ppm units relative to internal standard or solvent resonances, as follows: ^{1}H, ($CDCl_3$) TMS = 0.00, DMSO-d_6 = 2.50; ^{13}C, $CDCl_3$ = 77.23, DMSO-d_6 = 39.7. Infrared spectra were recorded on a Nicolet Protégé 460 FTIR spectrometer, and the frequencies were reported as cm^{-1}. Fast atom bombardment (FAB) mass spectra were obtained on a Finnigan SSQ 710 mass spectrometer with Cs cations. Electron impact mass spectra (3 kV) were acquired on a Finnigan MAT FSQ710 (analytical electrospray source) mass spectrometer. MALDI mass spectra were acquired on a Bruker Profex TOF mass spectrometer. Elemental analysis was performed by NuMega Resonance Labs, Inc.

Bis(2-cyanoethyl)amine (1). To a flask equipped with an addition funnel, a dry ice/acetone-cooled Dewar condenser, thermometer, and nitrogen inlet was added 354 g (6.7 mol) of acrylonitrile. The flask was heated in an 80 °C oil bath, and 208 mL (3.2 mol) of concentrated aqueous ammonia was added dropwise to the vigorously stirred reaction mixture over a period of 2 h. The reaction mixture was stirred without external heating for 30 min, then at 70−75 °C for an additional 30 min. Excess acrylonitrile and most of the water were removed by rotary evaporation, and the residue was dried to constant weight under vacuum (0.5 mm). A solution of the crude product in 500 mL of CH_2Cl_2 was dried over $MgSO_4$ for 16 h. Filtration, evaporation and drying (0.5 mm) gave 330 g (84%) of **1** as a pale yellow oil which was sufficiently pure by ^{1}H NMR spectroscopy[26] to be used in the next step.

Bis(2-cyanoethyl)benzylamine (2). A mixture of 183 g (1.48 mol) of **1**, 450 mL of acetonitrile, 3.75 g (25 mmol) of sodium iodide, 78.4 g (0.74 mol) of sodium carbonate, and 187 g (1.48 mol) of benzyl chloride was stirred mechanically and heated at reflux under nitrogen for 5 h. The cooled reaction mixture was filtered, and the solids were washed with 550 mL of acetonitrile. The combined filtrates were concentrated by rotary evaporation to a thick, deep yellow-orange liquid. A solution of the residue in 350 mL of CH_2Cl_2 was stirred vigorously for 5 min with 124 mL of saturated aqueous $Na_2S_2O_3$. The layers were separated, and the organic layer was washed with saturated aqueous NaCl (2 × 150 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 90 mL). The combined CH_2Cl_2 solutions were dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was dried (0.5 mm), yielding 262 g (83%) of **2** as a yellow oil, which was pure by ^{1}H NMR spectroscopy.[26]

Bis(3-aminopropyl)benzylamine (3). A mixture of 262 g (1.23 mol) of **2**, 47.2 g of a 50% aq slurry of Raney nickel, and 544 mL of a 1.4 M solution of NaOH in 95% ethanol was placed in a 2 L, heavy walled, glass bottle and hydrogenated with shaking in a Parr apparatus at 20−30 psi for 48 h. The catalyst was removed by filtration (**caution**: flammable solid) and washed with 150 mL of 95% ethanol. The combined filtrates were concentrated by rotary evaporation. A solution of the residue in 400 mL of diethyl ether was dried over Na_2SO_4, filtered and concentrated by rotary evaporation to give 241 g (89%) of a pale yellow, clear oil. Vacuum distillation of a 430 g sample provided 349 g (81%) of **3** as a colorless oil, bp 145−147 °C, 0.2 mm (lit.[26] 151−155 °C, 0.5 mm). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5 H, Ph), 3.49 (s, 2 H, CH_2Ph), 2.65 (t, J = 7 Hz, 4 H, H3), 2.42 (t, J = 7 Hz, 4 H, H1), 1.56 (quint., J = 7 Hz, 4 H, H2), 1.26 (s, 4 H, NH). The previously reported ^{1}H NMR data are believed to be in error.[26]

***N,N′*-Bis(*p*-toluenesulfonyl)bis(3-aminopropyl)benzylamine Hydrochloride (94−127).** A solution of 16 g (71 mmol) of triamine **3**, 80 mL of 2 N aq NaOH, and 150 mL of saturated aqueous NaCl was added dropwise over 5 h to a stirred solution of 28 g (0.15 mol) of *p*-toluenesulfonyl chloride and 120 mL of ether, then the reaction mixture was stirred for 12 h at room temperature. The mixture was poured into a separatory funnel, and three layers were observed. The upper two layers were poured into a flask and stirred with 80 mL of 2 N aq HCl and 100 mL of saturated aqueous NaCl for 1 h. The mixture was filtered, and the solid was washed with 3 × 100 mL of distilled water, followed by 3 × 100 mL of ether, then dried (0.5 mm), yielding 35.8 g (89%) of **94−127** as a white solid, mp 124−126 °C (lit.[26] 150−152 °C; 160−161 °C after drying at 78 °C, 1 mm).

9-Benzyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (CADA**)**. NaH (4.0 g, 0.1 mol, 60% w/w slurry in mineral oil) was washed with hexane under nitrogen. A solution of 18.0 g (32 mmol) of **94−127** in 650 mL of anhydrous DMF was added, and the mixture was stirred at room temperature for 1 h. The resulting cloudy solution was stirred at 80−85 °C under nitrogen as a solution of 4.0 g (32 mmol) of 3-chloro-2-chloromethyl-1-propene in 20 mL of anhydrous DMF was added over 30 h by means of a syringe pump, then the reaction mixture was stirred at 80−85 °C for 20 h. The solvent was completely removed by vacuum distillation at 40 °C (10 mm). A solution of residue in 300 mL of $CHCl_3$ was washed with water (3 × 150 mL) and saturated aqueous NaCl (3 × 150 mL), then dried over Na_2SO_4. Filtration, concentration by rotary evaporation, and by drying under vacuum gave 16.9 g (91%) of crude product as a beige solid. Recrystallization from hot EtOAc gave 9.0 g (54%) of CADA as a white solid (mp 160−164 °C, lit.[26] 156−158 °C), giving identical spectroscopic data to that reported.[26] Prior to recrystallization, less soluble side products can be precipitated by adding hexane to a solution of the crude product in hot toluene.[26] CADA·HCl. A solution of 2.0 g (3.4 mmol) of pure CADA in 20 mL of chloroform was vigorously stirred with 4 mL of 2 N aq HCl and 4 mL of saturated aqueous NaCl for 1 h, over which period CADA·HCl gradually precipitated. The mixture was transferred to a separatory funnel with the aid of 10 mL of chloroform. The cloudy organic layer was separated and heated to boiling. Ethanol was added slowly to the boiling solution, which became clear. Addition of ethanol was continued to maintain a constant, total volume, until the boiling solution became cloudy again. The mixture was cooled to room temperature, and the precipitated white solid was collected by suction filtration and dried at 65−100 °C (0.4 mm, 12 h) to remove chloroform, yielding 2.15 g (100%) of CADA·HCl, mp 210−212 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.0 (br, 1 H, NH^+), 7.67 (m, 6 H, *o*-Ts, *o*-Bn), 7.45 (m, 7 H, *m*-Ts, *m*,*p*-Bn), 5.36 (s, 2 H, C=CH_2), 4.31 (d, J = 5.1 Hz, 2 H, CH_2Ph), 3.65 (s, 4 H, H2, H4), 3.13 (m, 8 H, H6, H8, H10, H12), 2.40 (s, 6 H, CH_3), 1.91 (m, 4 H, H7, H11). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.5 (br, 1 H, NH^+), 7.76 (m, 2 H, *o*-Bn), 7.60 (d, J = 7.9 Hz, 4 H, *o*-Ts), 7.44 (m, 3 H, *m*,*p*-Bn), 7.34 (d, J = 7.9 Hz, 4 H, *m*-Ts), 5.35 (s, 2 H, C=CH_2), 4.11 (d, J = 4 Hz, 2 H, CH_2Ph), 3.72 (d, J = 15 Hz, 2 H, H2, H4), 3.67 (d, J = 15 Hz, 2 H, H2, H4), 3.38, 3.12 (m, 8 H, H6, H8, H10, H12), 2.43 (s, 6 H, CH_3), 2.29, 1.96 (m, 4 H, CH_2, H7, H11). ^{13}C NMR (75 MHz, DMSO-d_6) δ 143.8, 141.6, 134.0, 131.0, 130.3, 130.0, 129.4, 128.8, 127.3, 118.6, 57.2, 51.9, 48.1, 46.3, 21.1, 20.1. IR (KBr) 3029 (w), 2972 (w), 2923 (w), 2864 (w), 2446 (br), 2396 (br), 1465 (m), 1345 (s), 1162 (s), 1119 (m), 1089 (m). UV (CH_3OH): λ_{max} (logϵ), 230 (4.4). Anal. Calcd for $C_{31}H_{39}N_3S_2O_4$·HCl: C, 60.23; H, 6.52; N, 6.80; S, 10.37; Cl, 5.73. Found: C, 60.19; H, 6.55; N, 6.87; S, 10.35; Cl, 5.70.

9-Methoxycarbonyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (4). A solution of 0.49 g (0.84 mmol) of CADA and 0.1 mL (0.12 g, 1.3 mmol) of methyl chloroformate in 25 mL of 1,2-dichloroethane was stirred and heated under reflux for 16 h. The reaction mixture was cooled to room temperature and concentrated by rotary evaporation, and the residue was recrystallized (EtOAc) to give 0.35 g (76%) of **4** as white crystals, mp 159−160 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8

Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.23 (s, 2 H, C=CH_2), 3.86 (s, 4 H, H2, H4), 3.63 (s, 3 H, OCH_3), 3.33 (t, J = 6 Hz, 4 H, H6, H12), 3.12 (m, 4 H, H8, H10), 2.45 (s, 6 H, $ArCH_3$), 1.85 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 143.9, 139.9, 130.1, 127.4, 117.2, 52.8, 51.9, 46.0, 45.4, 28.1, 21.7. IR (KBr) 2956 (m), 1702 (s), 1597 (m), 1481 (s), 1405 (s), 1346 (s), 1226 (s), 1159 (s), 1122 (s), 1094 (s), 1021 (s), 907 (s), 817 (s), 777 (s), 725 (s), 658 (s). MS (FAB) *m*/*z* 550.2 (MH^+). Anal. Calcd for $C_{26}H_{35}N_3O_6S_2$: C, 56.81; H, 6.42; N, 7.64. Found: C, 56.83; H, 6.47; N, 7.65.

9-Ethoxycarbonyl-3-methylene-1,5-bis-(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (95−213). A solution of 8.20 g (14.1 mmol) of CADA and 1.7 mL (18 mmol) of ethyl chloroformate in 1,2-dichloroethane was stirred and heated under reflux for 5 h. Concentration by rotary evaporation gave an oily residue which was crystallized from 60 mL of 2:3 (v/v) ethyl acetate/hexane. Filtration, washing with 3 × 30 mL of cold 2:3 (v/v) ethyl acetate/hexane, and drying at 78 °C (0.9 mm, 19 h) gave 6.63 g (83%) of **95−213** as a white solid, mp 125−126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 4 H, *o*-Ts), 7.33 (d, J = 8.3 Hz, 4 H, *m*-Ts), 5.21 (s, 2 H, C=CH_2), 4.07 (q, J = 7 Hz, 2 H, OCH_2Me), 3.85 (s, 4 H, H2, H4), 3.33 (t, J = 6.4 Hz, 4 H, H8, H10), 3.11 (m, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 1.85 (m, 4 H, H7, H11), 1.21 (t, J = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 143.6, 139.4 135.7, 129.8, 127.2, 116.9, 61.2, 51.4, 45.5, 45.2, 28.0, 21.4, 14.7. IR (KBr) 2990 (w), 2948 (w), 1688 (s), 1598 (w), 1485 (m), 1424 (m), 1343 (s), 1230 (s), 1154 (s), 1093 (s), 1027 (m), 903 (m), 818 (m), 788 (m). UV (CH_3OH): λ_{max} (logϵ), 232 (4.4). MS (FAB) *m*/*z* 564 ($M + H^+$, 100). Anal. Calcd for $C_{27}H_{37}N_3S_2O_6$: C, 57.53; H, 6.62; N, 7.45; S, 11.37. Found: C, 57.36; H, 6.54; N, 7.73; S, 11.74.

9-Propyloxycarbonyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ033). A solution of 0.48 g (0.83 mmol) of CADA and 0.15 mL (0.16 g, 1.3 mmol) of propyl chloroformate in 50 mL of 1,2-dichloroethane was stirred and heated under reflux for 18 h. The reaction mixture was cooled to room temperature and concentrated by rotary evaporation, and the residue was chromatographed on silica, eluting with dichloromethane/ethyl acetate (9:1, v/v), then with ethyl acetate/hexane (6:4, v/v). The resulting 0.41 g of colorless oil was recrystallized from methanol to yield 0.34 g (80%) of **QJ033** as white crystals, mp 134−135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.21 (s, 2 H, C=CH_2), 3.96 (t, J = 7 Hz, 2 H, OCH_2), 3.85 (s, 4 H, H2, H4), 3.33 (t, J = 6 Hz, 4 H, H6, H12), 3.11 (m, 4 H, H8, H10), 2.44 (s, 6 H, $ArCH_3$), 1.85 (m, 4 H, H7, H11), 1.59 (m, 2 H, $CH_2CH_2CH_3$), 0.91 (t, J = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (75 MHz, CDCl3) δ 157.4, 143.8, 139.9, 136.2, 130.1, 127.5, 117.2, 67.3, 51.9, 45.9, 45.5, 28.4, 22.6, 21.7, 10.7. IR (KBr) 3063 (w), 3028 (w), 2969 (m), 1686 (s), 1597 (m), 1481 (m), 1423 (s), 1341 (s), 1163 (s), 1092 (s), 943 (m), 748 (m). MS (FAB) *m*/*z* 578.2 (MH^+). Anal. Calcd for $C_{26}H_{35}N_3O_6S_2$: C, 58.21; H, 6.80; N, 7.27. Found: C, 58.24; H, 6.73; N, 7.37.

3-Methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane Hydrochloride (94−129).[26] A solution of 8.32 g (14.3 mmol) of CADA and 1.7 mL (2.25 g, 15.8 mmol) of 1-chloroethyl chloroformate in 50 mL of 1,2-dichloroethane was stirred and heated under reflux for 1.5 h, cooled to room temperature, then concentrated by rotary evaporation. A solution of the residue in 70 mL of methanol was stirred and heated under reflux overnight, then cooled to room temperature. Filtration, concentration by rotary evaporation, and recrystallization of the residue from ethyl acetate/ethanol gave 6.50 g (86%) of HCl salt **94−129** as a white solid, mp 188−189 °C (lit.[26] 185−186 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 2 H, NH^+), 7.65 (d, J = 8 Hz, 4 H, *o*-Ts), 7.35 (d, J = 8 Hz, 4 H, *m*-Ts), 5.41 (s, 2 H, C=CH_2), 3.76 (s, 4 H, H2, H4), 3.24 (bs, 8 H, H6, H8, H10, H12), 2.44 (s, 6 H, $ArCH_3$), 2.11 (bs, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 139.6, 134.5, 129.8, 127.3, 119.6, 52.3, 47.1, 40.4, 22.5, 21.3. IR (KBr) 3621 (b), 3439 (b), 3086 (w), 2954 (m), 2490 (b), 2361 (b), 1597 (m), 1449 (s), 1339 (s), 1159 (s), 1090 (s), 887 (m).

9-(3-Pyridylmethyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (ASN6P6). A solution of 0.70 g (1.3 mmol) of **94−129** in 10 mL of $CHCl_3$ was stirred vigorously with 3 mL of 1 N NaOH and 10 mL of saturated aqueous NaCl for 1 h. The organic layer was dried ($MgSO_4$) and concentrated by rotary evaporation, and the residue was dried (1 mm) giving 0.60 g (92%) of **94−129** free base as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 7.8 Hz, 4 H, *o*-Ts), 7.31 (d, J = 7.8 Hz, 4 H, *m*-Ts), 5.02 (s, 2 H, C=CH_2), 3.79 (s, 4 H, H2, H4), 3.18 (t, J = 6 Hz, 4 H, H6, H12), 2.60 (t, J = 6 Hz, 4 H, H8, H10), 2.43 (s, 6 H, $ArCH_3$), 1.64 (quint., J = 6 Hz, 4 H, H7, H11), 0.37 (br, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 138.3, 135.7, 129.7, 127.4, 115.3, 51.8, 44.4, 43.2, 27.9, 21.4. IR (KBr) 3330 (w), 3030 (w), 2947 (m), 2854 (m), 2819 (m), 1598 (m), 1450 (m), 1333 (s), 1160 (s), 1091 (m), 915 (m), 815 (m), 733 (m), 688 (m), 657 (m). A solution of 0.56 g (1.14 mmol) of **94−129** free base and 0.23 g (2.27 mmol) of triethylamine in 8 mL of anhydrous DMF was stirred for 18 h at room temperature, then the solvents were removed under vacuum (1 mm) at 25−27 °C. A solution of the residue in 20 mL of $CHCl_3$ was washed with 5 mL of 1 N aq NaOH and 15 mL of saturated aqueous NaCl solution. The combined aqueous layers were extracted with 10 mL of $CHCl_3$. The combined organic solutions were dried ($MgSO_4$), concentrated by rotary evaporation, and the residue was purified by silica gel flash column chromatography, eluting with 69:23:8 (v/v/v) chloroform/ethyl acetate/triethylamine. A solution of the resulting mixture of **94−129** free base and **ASN6P6** in 10 mL of chloroform and 2.5 mL of 1 N HCl in ether was stirred for 1 h at room temperature under N_2. The solvents were removed by rotary evaporation, and the residue was dissolved in 15 mL of acetone. Ethyl acetate (40 mL) was layered on top of the solution, causing a precipitate to form overnight at room temperature. The precipitate was collected by filtration, and the precipitation procedure was repeated, giving 110 mg (15%) of **ASN6P6** that was 99% pure by hplc, mp 176−178 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.5 (br, 1 H, NH^+), 9.01 (s, 1 H, 2-Py), 8.82 (d, J = 5 Hz, 1 H, 6-Py), 8.53 (d, J = 8 Hz, 1 H, 4-Py), 7.81 (t, J = 6 Hz, 1 H, 5-Py), 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.46 (d, J = 8 Hz, 4 H, *m*-Ts), 5.36 (s, 2 H, C=CH_2), 4.46 (s, 2 H, CH_2Ph), 3.67 (s, 4 H, H2, H4), 3.13 (m, 8 H, H6, H8, H10, H12), 2.41 (s, 6 H, $ArCH_3$), 1.90 (m, 4 H, H7, H14). ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.6, 145.0, 143.9, 141.6, 134.1, 130.1, 128.9, 127.3, 125.9, 118.6, 53.6, 51.8, 48.0, 46.6, 21.0, 20.2. IR (KBr) 3052 (w), 2956 (w), 2452 (br, w), 1560 (w), 1462 (m), 1339 (s), 1161 (s), 1090 (m). UV (CH_3OH): λ_{max} (logϵ), 230 (4.4), 260 (3.6). MS (FAB) *m*/*z* 583 (MH^+, 100).

9-Methyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (5). A mixture of 143 mg (0.27 mmol) of **94−129**, 4.0 mL (4.3 g, 53 mmol) of 37% aq formaldehyde, and 5.0 mL (6.1 g, 0.13 mol) of formic acid was stirred at room temperature for 24 h. The pH of the mixture was adjusted to at least 13 with 25% aq NaOH, then the mixture was extracted with CH_2Cl_2 (5 × 5 mL). The combined extracts were washed with 1 N aq NaOH (4 × 10 mL), water (2 × 10 mL), and saturated aqueous NaCl (10 mL), then dried (Na_2SO_4). Concentration by rotary evaporation and drying in vacuo gave 96 mg (64%) of a yellow oil. Recrystallization from chloroform/hexane gave 87 mg (58%) of **5** as a white crystalline solid, mp 134−135.5 °C. ^{1}H NMR (75 MHz $CDCl_3$) δ 7.68 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 4.98 (s, 2 H, C=CH_2), 3.83 (s, 4 H, H2, H4), 3.11 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.33 (t, J = 6 Hz, 4 H, H8, H10), 1.98 (s, 3 H, NCH_3), 1.70 (m, 4 H, H7, H11). ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.9, 143.6, 138.7, 136.2, 129.9, 127.6, 115.3, 53.6, 52.1, 43.5, 40.9, 25.9, 21.6. IR (KBr) 2954 (w), 2802 (w), 1593 (w), 1449 (m), 1329 (s), 1166 (s), 1099 (s), 924 (m), 909 (m), 811 (m), 735 (m), 688 (s), 551 (s). MS (FAB) *m*/*z* 506 (MH^+). Anal. Calcd for $C_{25}H_{35}N_3O_4S_2 \cdot 0.4\ CHCl_3$: C, 55.12; H, 6.45; N, 7.59. Found: C, 55.18; H, 6.50; N, 7.31.

9-Ethyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (6). A solution of 0.47 g (0.89 mmol) of **94−129**, 1 mL (0.79 g, 18 mmol) of acetaldehyde, and 0.18 g (2.9 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred at

room temperature for 40 h, then the solvent was removed by rotary evaporation. A solution of the residue in 20 mL of dichloromethane was washed with water (3 × 10 mL) and saturated aqueous NaCl (10 mL), then dried (Na_2SO_4), concentrated by rotary evaporation, and the residue was dried in vacuo. The crude product was dissolved in 2 mL of dichloromethane, and 10 mL of a 1 N solution of HCl in diethyl ether was added, producing a yellow precipitate. The mixture was sonicated and filtered. A solution of the solid in 20 mL of dichloromethane was stirred with 10 mL of 1 N aq NaOH for 2 h. The organic layer was washed with water (2 × 10 mL), saturated aq NaCl (2 × 10 mL), and dried (Na_2SO_4). Concentration by rotary evaporation and drying in vacuo gave 0.45 g (98%) of a colorless oil. Purification by radial chromatography on silica gel, eluting with ethyl acetate/hexane/triethylamine (35:65:5, v/v/v), yielded 0.25 g (54%) of **6** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.11 (s, 2 H, C=CH_2), 3.81 (s, 4 H, H2, H4), 3.13 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.38 (t, J = 5 Hz, 4 H, H8, H10), 1.66 (m, 6 H, H7, H11, NCH_2Me), 0.85 (t, J = 6 Hz, 3 H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.6, 136.2, 130.0, 127.5, 116.2, 51.6, 50.2, 46.8, 44.3, 25.2, 21.7, 11.1. MS (FAB) *m*/*z* 520 (MH^+). **6**·HCl. A solution of 30 mL of 0.33 N HCl in diethyl ether was added to a solution of 0.25 g (0.48 mmol) of **6** in 2 mL of ethyl acetate, producing a white precipitate. The mixture was sonicated and filtered, yielding 0.22 g (43%) of a white solid. Recrystallization from dichloromethane/diethyl ether gave 0.17 g (35%) of **6**·HCl as white crystals, mp 188−193 °C. IR (KBr) 3421 (bw), 2978 (m), 2944 (m), 2605 (s), 2498 (s), 1597 (w), 1476 (s), 1398 (s), 1336 (s), 1161 (s), 1037 (s), 903 (w), 807 (m), 737 (m), 690 (m), 656 (m), 587 (m), 548 (s). Anal. Calcd for $C_{26}H_{37}N_3O_4S_2$·HCl·1.75 H_2O: C, 54.07; H, 6.97; N, 7.01. Found: C, 54.13; H, 7.32; N, 7.07.

9-Propyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ029). A solution of 0.49 g (0.93 mmol) of **94**−**129**, 0.41 mL (0.33 g, 5.7 mmol) of propionaldehyde, and 0.18 g (2.9 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred at room temperature for 40 h, then the solvent was removed by rotary evaporation. A solution of the residue in 20 mL of dichloromethane was washed with water (3 × 10 mL) and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was dried in vacuo to give 0.47 g (94%) of crude product. Column chromatography on silica gel, eluting with ethyl acetate/hexane/triethylamine (35:65:5, v/v/v), gave **QJ029** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.14 (s, 2 H, C=CH_2), 3.80 (s, 4 H, H2, H4), 3.14 (t, J = 7 Hz, 4 H, H6, H12), 2.44 (s, 6 H, H16), 2.33 (t, J = 5 Hz, 4 H, H8, H10), 2.18 (t, J = 6 Hz, 2 H, NCH_2Et), 1.63 (m, 4 H, H7, H11), 1.28 (m, 2 H, NCH_2CH_2Me), 0.77 (t, J = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.6, 136.2, 130.0, 127.6, 116.4, 56.2, 51.4, 50.1, 44.1, 25.3, 21.7, 20.0, 12.1. **QJ029**·HCl. A solution of 30 mL of 0.33 N HCl in diethyl ether was added to a solution of 0.47 g (0.85 mmol) of **QJ029** in 2 mL of ethyl acetate, producing a white precipitate. The mixture was sonicated and filtered. The white solid was washed with water, dried and recrystallized from dichloromethane/diethyl ether to give 0.41 g (77%) of **QJ029**·HCl as white crystals, mp 204−205 °C. IR (KBr) 3405 (bm), 3067 (w), 2978 (m), 2878 (m), 2403 (bm), 1596 (m), 1455 (m), 1341 (s), 1261 (m), 1164 (s), 1090 (s), 943 (s), 896 (m), 815 (m), 726 (s), 687 (s). MS (3 kV) *m*/*z* 548.1 (M − Cl). Anal. Calcd for $C_{27}H_{39}N_3O_4S_2$·HCl·0.75 H_2O: C, 55.56; H, 7.17; N, 7.20. Found: C, 55.72; H, 7.35; N, 7.24.

9-Isobutyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ006). A solution of 0.30 g (0.53 mmol) of **94**−**129**, 0.26 mL (0.21 g, 2.9 mmol) of isobutyraldehyde, and 62 mg (1.0 mmol) of sodium cyanoborohydride in 20 mL of methanol was stirred at room temperature for 24 h. After workup as described for **QJ029**, 0.24 g (78%) of crude product was obtained as a yellow oil. Sequential recrystallization from methanol, followed by chloroform/hexane gave 0.17 g (48%) of white crystalline **QJ006**, mp. 127−127.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.19 (s, 2 H, C=CH_2), 3.80 (s, 4 H, H2, H4), 3.15 (t, J = 7 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.27 (t, J = 5 Hz, 4 H, H8, H10), 1.92 (d, J = 7 Hz, 2 H, NCH_2iPr), 1.61 (m, 5 H, H7, H11, $CHMe_2$), 0.75 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.3, 136.1, 130.0, 127.6, 116.9, 64.1, 51.2, 50.7, 44.5, 26.6, 24.8, 21.7, 21.2. IR (KBr) 2952 (m), 2801 (m), 1598 (m), 1458 (m), 1332 (s), 1162 (s), 1091 (s), 1038 (m), 935 (m), 816 (s), 743 (m), 718 (m), 708 (m), 689 (s), 550 (s). MS (FAB) *m*/*z* 548 (MH^+). Anal. Calcd for $C_{28}H_{41}N_3O_4S_2$: C, 61.40; H, 7.54; N, 7.67. Found: C, 61.62; H, 7.32; N, 7.63. **QJ006**·HCl. A solution of 0.49 g (0.93 mmol) of **94**−**129**, 0.52 mL (0.41 g, 5.7 mmol) of isobutyraldehyde, and 0.18 g (2.9 mmol) of sodium cyanoborohydride in 25 mL methanol was stirred at room temperature for 40 h. The reaction mixture was worked up as described for **QJ029**, and the crude product was purified via radial chromatography on silica gel, eluting with dichloromethane/ethyl acetate/triethylamine (95:5:5, v/v/v) to give 0.48 g (95%) of **QJ006** as a colorless oil. A solution of 30 mL of 0.33 N HCl in diethyl ether was added to a solution of 0.48 g (0.84 mmol) of **QJ006**, producing a white precipitate. The mixture was sonicated and filtered. The white solid was dried in vacuo at 60 °C for 3 days to give 0.43 g (78%) of **QJ006**·HCl, mp 146−147 °C. IR (KBr) 2967 (m), 2424 (b), 1598 (m), 1457 (m), 1339 (s), 1162 (s), 1110 (s), 1090 (s), 899 (m), 816 (s), 737 (s), 688 (s), 658 (s), 590 (s), 550 (s). Anal. Calcd for $C_{28}H_{41}N_3O_4S_2$·HCl: C, 57.56; H, 7.25; N, 7.19. Found: C, 57.31; H, 7.26; N, 7.20.

9-Butyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (7). A solution of 0.48 g (0.91 mmol) of **94**−**129**, 0.85 mL (0.68 g, 9.5 mmol) of butyraldehyde and 0.18 g (2.9 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred at room temperature for 40 h. The reaction mixture was worked up as described as described for **QJ029**. **7**·HCl. A solution of 30 mL of 0.33 N HCl in diethyl ether was added to a solution of 0.93 g (1.70 mmol) of crude **7** in 2 mL of ethyl acetate, producing a white precipitate. The mixture was sonicated and filtered. Radial chromatography of the residue on silica gel, eluting with dichloromethane, then dichloromethane/methanol (95:5, v/v) gave 0.33 g (62%) of **7**·HCl as a white powder, mp 131−132 °C. IR (KBr) 3417 (bw), 2960 (m), 2874 (w), 2442 (b), 1597 (m), 1453 (m), 1338 (s), 1160 (s), 1108 (s), 1090 (s), 1020 (m), 900 (m), 817 (s), 724 (s), 688 (s), 656 (s), 585 (s), 548 (s). MS (3 kV) *m*/*z* 548.1 (MH^+). Anal. Calcd for $C_{28}H_{41}N_3O_4S_2$·HCl·H_2O: C, 55.84; H, 7.36; N, 6.98. Found: C, 56.14; H, 7.45; N, 7.01. **NMR Sample**. A solution of 20 mg of **7**·HCl in 5 mL of dichloromethane was stirred with 3 mL of 1 N aq NaOH at room temperature for 1 h. The organic layer was washed with water (2 × 5 mL) and saturated aqueous NaCl (2 × 5 mL), then dried (Na_2SO_4). Concentration by rotary evaporation and drying in vacuo gave a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.14 (s, 2 H, C=CH_2), 3.80 (s, 4 H, H2, H4), 3.14 (t, J = 7 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.33 (t, J = 6 Hz, 4 H, H8, H10), 2.21 (t, J = 7 Hz, 2 H, NCH_2Pr), 1.61 (m, 4 H, H7, H11), 1.21 (m, 4 H, $NCH_2CH_2CH_2Me$), 0.84 (t, J = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.4, 136.0, 130.0, 127.5, 116.4, 53.7, 51.4, 49.9, 44.3, 28.9, 25.1, 21.7, 20.9, 14.2.

9-(2-Methylbutyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ037). A solution of 0.19 g (0.36 mmol) of **94**−**129**, 0.25 mL (197 mg, 2.3 mmol) of 2-methylbutyraldehyde, and 78 mg (1.2 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred at room temperature for 24 h. The reaction mixture was worked up as described for **QJ029**. Chromatography on silica gel, eluting with ethyl acetate/hexane/triethylamine (30:60:5, v/v/v), gave 0.18 g (90%) of a colorless oil. **QJ037**·HCl. A solution of 25 mL of 0.2 N HCl in diethyl ether was added to a solution of 0.18 g (0.32 mmol) of crude **QJ037** in 2 mL of ethyl acetate, producing a white precipitate. The mixture was sonicated and filtered. The white solid was dried in vacuo (60 °C, 3 d) to give 0.15 g (64%) of **QJ037**·HCl, mp 129−130 °C. IR (KBr) 2964 (m), 2877 (w), 2610 (w), 1597 (m), 1457 (m), 1337 (s), 1161 (s), 1111 (m), 1090 (m), 896 (m), 817 (s), 737 (m), 689 (s), 656 (s),

587 (s), 551 (s). MS (3 kV) *m*/*z* 562 (M − Cl). Anal. Calcd for $C_{29}H_{43}N_3O_4S_2$·HCl·H_2O: C, 56.52; H, 7.52; N, 6.82. Found: C, 56.61; H, 7.35; N, 6.80. **NMR Sample**. A solution of 20 mg of **QJ037**·HCl in 5 mL of dichloromethane was stirred with 3 mL of 1 N aqueous NaOH at room temperature for 1 h. The organic layer was washed with water (2 × 5 mL) and saturated aqueous NaCl (2 × 5 mL), dried (Na_2SO_4), then concentrated by rotary evaporation. Drying in vacuo gave a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.19 (s, 2 H, C=CH_2), 3.87 (d, J = 16 Hz, 2 H, H2, H4), 3.73 (d, J = 16 Hz, 2 H, H2, H4), 3.15 (m, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.24 (m, 4 H, H8, H10), 1.95 (m, 2 H, $NCH_2$2-Bu), 1.61 (m, 4 H, H7, H11), 1.31 (m, 2 H, CHCH_2Me), 0.81 (m, 1 H, C$H$$CH_3$), 0.74 (t, J = 7 Hz, 3 H, CH_2CH_3), 0.74 (d, J = 6 Hz, 3 H, CHCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 138.1, 135.8, 130.0, 127.5, 116.9, 62.2, 51.1, 50.5, 44.4, 33.0, 27.8, 24.6, 21.7, 18.1, 11.5.

9-(3-Methylbutyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ038). A solution of 0.19 g (0.36 mmol) of **94**−**129**, 0.25 mL (0.20 g, 2.3 mmol) of isovaleraldehyde and 72 mg (1.1 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred at room temperature for 24 h. The reaction mixture was worked up as described for **QJ029**. Column chromatography on silica gel, eluting with ethyl acetate/hexane/ triethylamine (30:60:5, v/v/v), gave 0.21 g (98%) of a colorless oil. **QJ038**·HCl. A solution of 30 mL of 0.3 N HCl in diethyl ether was added to a solution of 0.21 g (0.37 mmol) of crude **QJ038** in 2 mL of ethyl acetate, producing a white precipitate. The residue was dried in vacuo (60 °C, 3 d) to give 0.20 g (87%) of **QJ038**·HCl as a white solid, mp 137−138 °C. IR (KBr) 2957 (m), 2498 (b), 1597 (m), 1453 (s), 1337 (s), 1161 (s), 1113 (s), 1090 (s), 1019 (m), 816 (s), 736 (m), 725 (m), 689 (s), 656 (s), 586 (s), 589 (s). MS (3 kV) *m*/*z* 562 (M − Cl). Anal. Calcd for $C_{29}H_{43}N_3O_4S_2$·HCl·H_2O: C, 56.52; H, 7.52; N, 6.82. Found: C, 56.43; H, 7.64; N, 6.85. **NMR Sample**. A solution of 15 mg of **QJ038**·HCl in 5 mL of dichloromethane was stirred with 3 mL of 1 N aq NaOH at room temperature for 1 h. The organic layer was washed with water (2 × 5 mL) and saturated aqueous NaCl (2 × 5 mL), dried (Na_2SO_4), then concentrated by rotary evaporation. Drying in vacuo gave a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.13 (s, 2 H, C=CH_2), 3.80 (s, 4 H, H2, H4), 3.14 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.33 (t, J = 5 Hz, 4 H, H8, H10), 2.24 (t, J = 8 Hz, 2 H, NCH_2*i*Bu), 1.63 (m, 4 H, H7, H11), 1.46 (m, 1 H, $CHMe_2$), 1.15 (m, 2 H, CH_2*i*Pr), 0.81 (d, J = 7 Hz, 6 H, CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.6, 136.2, 129.9, 127.6, 116.3, 52.0, 51.5, 50.1, 44.4, 35.7, 26.5, 25.3, 22.9, 21.7, 14.4.

9-Cyclopropylmethyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ041). A solution of 0.20 g (0.37 mmol) of **94**−**129**, 0.20 mL (188 mg, 2.7 mmol) of cyclopropanecarboxaldehyde, and 77 mg (1.2 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred at room temperature for 24 h. The reaction mixture was worked up as described for **QJ029**. **QJ041**·HCl. A solution of 25 mL of 0.2 N HCl in diethyl ether was added to a solution of 0.23 g (0.41 mmol) of crude **QJ041** in 2 mL of ethyl acetate, producing a white precipitate. The mixture was sonicated and filtered. The residue was dried in vacuo (60 °C, 3 d) to give 0.20 g (89%) of **QJ041**·HCl, as a white solid, mp 134−135 °C. IR (KBr) 2950 (w), 2581 (w), 2360 (m), 2341 (m), 1597 (m), 1455 (m), 1338 (s), 1161 (s), 1091 (m), 1018 (w), 900 (w), 816 (m), 737 (m), 689 (s), 656 (s), 584 (s), 549 (s). MS (3 kV) *m*/*z* 546 (M − Cl). Anal. Calcd for $C_{28}H_{39}N_3O_4S_2$·HCl·H_2O: C, 56.03; H, 7.05; N, 7.00. Found: C, 56.41; H, 6.84; N, 6.94. **NMR Sample**. A solution of 20 mg of **QJ041**·HCl in 5 mL of dichloromethane was stirred with 3 mL of 1 N aq NaOH at room temperature for 1 h. The organic layer was washed with water (2 × 5 mL) and saturated aqueous NaCl (2 × 5 mL), dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was dried in vacuo to give **QJ041** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.12 (s, 2 H, C=CH_2), 3.81 (s, 4 H, H2, H4), 3.16 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (s, 10 H, H8, H10, $ArCH_3$), 2.14 (d, J = 7 Hz, 2 H, CH_2cyloPr), 1.64 (t, J = 6 Hz, 4 H, H7, H11), 0.69 (m, 1 H, 1-cycloPr), 0.41 (m, 2 H, 2-cycloPr), −0.04 (m, 2 H, 2-cycloPr). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.6, 136.1, 130.0, 128.1, 116.3, 58.6, 51.5, 49.9, 44.4, 25.3, 21.7, 8.4, 4.1.

9-Cyclohexylmethyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ028). A solution of 0.47 g (0.89 mmol) of **94**−**129**, 0.70 mL (0.65 mg, 5.8 mmol) of cyclohexanecarboxaldehyde, and 0.18 g (2.9 mmol) of sodium cyanoborohydride in 20 mL of methanol was stirred at room temperature for 24 h. The reaction mixture was worked up as described for **QJ029**. **QJ028**·HCl salt. A solution of 30 mL of 0.33 N HCl in diethyl ether was added to a solution of 0.93 g (1.87 mmol) of crude **QJ028** (prepared as described above) in 2 mL of ethyl acetate, producing a white precipitate, which was collected by filtration. Recrystallization from dichloromethane/ether gave 0.33 g (59%) of **QJ028**·HCl as white crystals, mp 138.5−140 °C. IR (KBr) 2928 (w), 2855 (w), 2360 (w), 1597 (w), 1449 (m), 1339 (m), 1160 (m), 1091 (m), 900 (w), 816 (m), 726 (s), 686 (s), 584 (s), 548 (s). MS (3 kV) *m*/*z* 588 (M − Cl). Anal. Calcd for $C_{31}H_{45}N_3O_4S_2$·HCl·H_2O: C, 57.97; H, 7.53; N, 6.54. Found: C, 58.32; H, 7.67; N, 6.66. **NMR Sample of QJ028**. A solution of 15 mg of **QJ028**·HCl in 5 mL of dichloromethane was stirred with 3 mL of a 1 N aq NaOH at room temperature for 1 h. The organic layer was washed with water (2 × 5 mL) and saturated aqueous NaCl (2 × 5 mL), then dried (Na_2SO_4), and concentrated by rotary evaporation. The residue was dried in vacuo to give a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.18 (s, 2 H, C=CH_2), 3.80 (s, 4 H, H2, H4), 3.15 (t, J = 7 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.26 (t, J = 6 Hz, 4 H, H8, H10), 1.96 (d, J = 6 Hz, 2 H, NCH_2Cy), 1.60 (m, 9 H, H7, H11, Cy), 1.14 (m, 4 H, Cy), 0.68 (m, 2 H, Cy). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.4 136.1, 130.0, 127.6, 116.7, 62.5, 51.2, 50.7, 44.5, 36.2, 32.2, 27.0, 26.3, 24.9, 21.7.

9-(3-Cyclohexenylmethyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclo-dodecane (QJ023). A solution of 0.49 g (0.93 mmol) of **94**−**129**, 0.67 mL (0.63 g, 5.7 mmol) of 3-cyclohexene-1-carboxaldehyde, and 0.18 g (2.9 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred at room temperature for 40 h. The reaction mixture was worked up as described for **QJ029**. **QJ023**·HCl. A solution of 30 mL of 0.33 N HCl in diethyl ether was added to a solution of 0.94 g (1.9 mmol) of **QJ023** in 2 mL of ethyl acetate, producing a white precipitate. Chromatography on silica gel, eluting with dichloromethane/methanol (95:5, v/v) followed by recrystallization from dichloromethane/diethyl ether, gave 0.50 g (86%) of white crystalline **QJ023**·HCl, mp 148−149 °C. ^{13}C NMR (75 MHz, $CDCl_3$S) δ 144.5, 141.7, 130.3, 127.8, 127.7, 127.2, 124.9, 119.6, 60.7, 53.0, 48.8, 47.8, 30.7, 30.1, 27.5, 24.4, 21.7, 20.5. IR (KBr) 2921 (m), 1597 (m), 1456 (s), 1344 (s), 1160 (s), 1091 (s), 1019 (m), 928 (m), 898 (m), 817 (m), 737 (m), 657 (s), 585 (s), 547 (s). MS (3 kV) *m*/*z* 586 (M − Cl). Anal. Calcd for $C_{31}H_{43}N_3O_4S_2$·HCl·H_2O: C, 58.15; H, 7.24; N, 6.56. Found: C, 58.54; H, 7.36; N, 6.56. **NMR Sample**. A solution of 15 mg of **QJ023**·HCl in 5 mL of dichloromethane was stirred with 3 mL of 1 N aq NaOH at room temperature for 1 h. The organic layer was washed with water (2 × 5 mL) and saturated aqueous NaCl (2 × 5 mL), dried (Na_2SO_4), and concentrated by rotary evaporation. Drying in vacuo gave a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.59 (m, 2 H, C=CH), 5.19 (s, 2 H, C=CH_2), 3.81 (s, 4 H, H2, H4), 3.15 (t, J = 7 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.30 (m, 3 H, H8, H10, NCH_2CH), 2.06 (d, J = 6 Hz, 2 H, NCH_2Cy), 2.05 (m, 2 H, H8, H10), 1.60 (m, 8 H, H7, H11, CH_2C=CCH_2), 1.06 (m, 2 H, $CHCH_2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 138.5, 136.1, 130.0, 127.6, 127.4, 126.4, 116.7, 61.6, 51.2, 50.7, 44.5, 32.0, 30.6, 27.4, 24.9, 24.8, 21.7.

9-(2-Pyridylmethyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (98−037). A solution of 0.49 g (0.93 mmol) of **94**−**129**, 0.54 mL (0.61 g, 5.7 mmol) of 2-pyridinecarboxaldehyde, and 0.15 g (2.4 mmol) of sodium cyanoborohydride

in 25 mL of methanol was stirred at room temperature for 40 h. The resulting white precipitate was removed by filtration, then washed with cold methanol, followed by water. Recrystallization from methanol/chloroform gave 0.32 g (59%) of **98**−**037** as white crystals, mp 202.5−203 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 3 Hz, 1 H, 6-Py), 7.66 (d, J = 8 Hz, 4 H, *o*-Ts), 7.60 (m, 1 H, 4-Py), 7.31 (d, J = 8 Hz, 4 H, *m*-Ts), 7.21 (d, J = 8 Hz, 1 H, 3-Py), 7.13 (m, 1 H, 5-Py), 5.22 (s, 2 H, C=CH_2), 3.85 (s, 4 H, H2, H4), 3.58 (s, 2 H, CH_2Py), 3.14 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (bm, 10 H, $ArCH_3$, H8, H10), 1.67 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 149.3, 143.6, 139.1, 136.3, 136.2, 130.0, 127.6, 123.1, 122.1, 116.2, 61.1, 51.5, 50.3, 44.5, 25.1, 21.7. IR (KBr) 2949 (w), 2838 (w), 1597 (m), 1145 (m), 1329 (s), 1164 (s), 1091 (s), 1038 (m), 930 (s), 910 (m), 822 (s), 744 (s), 689 (s), 555 (s). MS (3 kV) m/z 583 (MH^+). Anal. Calcd for $C_{30}H_{38}N_4O_4S_2$: C, 61.83; H, 6.57; N, 9.61. Found: C, 61.63; H, 6.65; N, 9.53.

9-(4-Pyridylmethyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ030). A solution of 0.49 g (0.93 mmol) of **94**−**129**, 0.55 mL (0.61 g, 5.7 mmol) of 4-pyridinecarboxaldehyde, and 0.15 g (2.4 mmol) sodium cyanoborohydride in 25 mL of methanol was stirred at room temperature for 24 h. The reaction mixture was worked up as described for **QJ029**. Column chromatography on silica gel, eluting with chloroform/ethyl acetate/triethylamine (90:5:5, v/v/v), yielded 0.26 g (48%) of **QJ030** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 5 Hz, 2 H, 2-Py), 7.66 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 7.10 (d, J = 5 Hz, 2 H, 3-Py), 5.24 (s, 2 H, C=CH_2), 3.86 (s, 4 H, H2, H4), 3.42 (s, 2 H, CH_2Py), 3.14 (t, J = 7 Hz, 4 H, H6, H12), 2.44 (s, 4 H, $ArCH_3$), 2.39 (t, J = 5 Hz, 4 H, H8, H10), 1.67 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 149.4, 144.2, 139.4, 136.3, 130.5, 127.9, 124.3, 116.9, 59.3, 51.7, 50.5, 44.8, 25.2, 22.2. MS (FAB) m/z 583 (MH^+). **QJ030**·HCl. A solution of 30 mL of 0.3 N HCl in diethyl ether was added to a solution of 0.26 g (0.45 mmol) of **QJ030** in 2 mL of ethyl acetate, producing a white precipitate. The mixture was sonicated and filtered. The white solid was dried in vacuo (60 °C, 3 days) to give 0.22 g (38%) of white crystalline **QJ030**·HCl, mp 162−163 °C. IR (KBr) 3424 (bm), 3059 (w), 2924 (w), 2578 (bm), 1641 (m), 1598 (m), 1450 (m), 1337 (s), 1161 (s), 1090 (s), 901 (w), 805 (s), 727 (m), 688 (s), 656 (s), 559 (s). MS (3 kV) m/z 583 (M − Cl). Anal. Calcd for $C_{30}H_{38}N_4O_4S_2$·HCl·1.5 H_2O: C, 52.78; H, 6.35; N, 8.21. Found: C, 52.61; H, 6.42; N, 8.04.

9-(*p*-Methylbenzyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (8). A solution of 0.15 g (0.28 mmol) of **94**−**129**, 0.15 mL (153 mg, 1.3 mmol) of 4-methylbenzaldehyde, and 28 mg (0.44 mmol) of sodium cyanoborohydride in 20 mL of methanol was stirred at room temperature for 40 h. The reaction mixture was worked up as described for **QJ029**, yielding 86 mg (60%) of a white solid. Two recrystallizations from chloroform/diethyl ether followed by one recrystallization from ethyl acetate/hexane gave 64 mg (45%) of **8** as white crystals, mp 260−261 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8 Hz, 4 H, *o*-Ts), 7.31 (d, J = 8 Hz, 4 H, *m*-Ts), 7.05 (m, 2 H, *o*-Bn), 7.01 (m, 2 H, *m*-Bn), 5.22 (s, 2 H, C=CH_2), 3.82 (s, 4 H, H2, H4), 3.33 (s, 2 H, CH_2Ar), 3.11 (t, J = 6 Hz, 4 H, H6, H12), 2.43 (s, 6 H, SO_2ArCH_3), 2.33 (t, J = 6 Hz, 4 H, H8, H10), 2.30 (s, 3 H, CH_2ArCH_3), 1.63 (m, 4H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 138.4 (2C), 136.3, 136.1, 135.8, 129.6, 128.7, 128.6, 127.2, 58.6, 51.0, 49.5, 44.0, 24.5, 21.3, 20.9. IR (KBr) 2949 (m), 2918 (m), 2819 (m), 1597 (m), 1445 (m), 1330 (s), 1157 (s), 1092 (m), 927 (m), 897 (m), 743 (m), 688 (s), 551 (s). MS (FAB) m/z 596 (MH^+), 618 (MNa^+). Anal. Calcd for $C_{32}H_{41}N_3O_4S_2$·0.25($CH_3CO_2C_2H_5$): C, 64.15; H, 7.01; N, 6.80. Found: C, 64.04; H, 7.16; N, 7.15.

9-(*p*-Fluorobenzyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (9). A solution of 0.11 g (0.21 mmol) of **94**−**129**, 0.25 mL (0.28 g, 2.3 mmol) of 4-fluorobenzaldehyde and 43 mg (0.68 mmol) of sodium cyanoborohydride in 20 mL of methanol was stirred at room temperature for 24 h. The reaction mixture was worked up as described for **QJ029**, yielding 0.12 g (95%) of crude product. Two recrystallizations from ethyl acetate gave 43 mg (34%) of **9** as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8 Hz, 4 H, *o*-Ts), 7.31 (d, J = 8 Hz, 4 H, *m*-Ts), 7.11 (m, 2 H, *m*-FBn), 6.94 (m, 2 H, *o*-FBn), 5.21 (s, 2 H, C=CH_2), 3.84 (s, 4 H, H2, H4), 3.36 (s, 2 H, CH_2Ar), 3.11 (t, J = 7 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.35 (t, J = 5 Hz, 4 H, H8, H10), 1.65 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 138.9, 136.0, 135.3, 130.4, 130.0, 127.5, 116.4, 115.4, 115.1, 58.7, 51.4, 49.8, 44.4, 24.9, 21.7. MS (FAB) m/z 600 (MH^+). Anal. Calcd for $C_{31}H_{38}FN_3O_4S_2$: C, 62.08; H, 6.39; N, 7.01. Found: C, 61.94; H, 6.44; N, 6.90.

9-(*p*-Hydroxybenzyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ010). A solution of 0.11 g (0.21 mmol) of **94**−**129**, 0.25 g (2.0 mmol) of 4-hydroxybenzaldehyde, and 43 mg (0.68 mmol) of sodium cyanoborohydride in 20 mL of methanol was stirred at room temperature for 24 h. The reaction mixture was worked up as described for **QJ029**. Three recrystallizations from chloroform/hexane gave 75 mg (60%) of **QJ010** as white crystals, mp 175−176 °C. ^{1}H NMR (300 MHz, CDCl3) δ 7.66 (d, J = 8 Hz, 4 H, *o*-Ts), 7.31 (d, J = 8 Hz, 4 H, *m*-Ts), 7.00 (d, J = 8 Hz, 2 H, *o*-OHBn), 6.71 (d, J = 8 Hz, 2 H, *m*-OHBn), 5.21 (s, 2 H, C=CH_2), 4.66 (bs, 1 H, OH), 3.83 (s, 4 H, H2, H4), 3.31 (s, 2 H, CH_2Ar), 3.10 (t, J = 7 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.33 (t, J = 5 Hz, 4 H, H8, H10), 1.64 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 143.7, 138.6, 135.8, 131.6, 130.3, 130.0, 127.5, 116.5, 115.2, 58.5, 51.3, 49.6, 44.3, 24.7, 21.8. IR (KBr) 3454 (bm), 2949 (w), 1614 (m), 1597 (m), 1541 (m), 1443 (m), 1321 (s), 1156 (s), 1090 (s), 923 (m), 742 (m), 551 (s). MS (FAB) m/z 598 (MH^+). Anal. Calcd for $C_{31}H_{39}N_3O_5S_2$: C, 62.29; H, 6.58; N, 7.03; S, 10.73. Found: C, 61.99; H, 6.84; N, 6.92l; S, 11.11.

9-(3-Furylmethyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (10). A solution of 0.11 g (0.20 mmol) of **94**−**129,** 0.15 mL (0.16 g, 1.7 mmol) of 3-furaldehyde, and 39 mg (0.63 mmol) of sodium cyanoborohydride in 20 mL of methanol was stirred at room temperature for 20 h, producing a pale yellow precipitate. Filtration and recrystallization from chloroform/hexane gave 78 mg (68%) of **10** as white crystals, mp 139.5−140.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 7.31 (s, 1 H, 2-furyl), 7.21 (bs, 1 H, 5-furyl), 6.17 (bs, 1 H, 4-furyl), 5.17 (s, 2 H, C=CH_2), 3.82 (s, 4 H, H2, H4), 3.27 (s, 2 H, CH_2Ar), 3.12 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.35 (m, 4 H, H8, H10), 1.66 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 143.3, 140.7, 138.9, 136.2, 130.0, 127.6, 122.2, 116.2, 111.3, 51.5, 49.7, 48.4, 44.2, 25.1, 21.7. IR (KBr) 2930 (w), 2822 (w), 1589 (m), 1441 (m), 1336 (s), 1169 (s), 1083 (s), 1037 (m), 877 (m), 819 (s), 730 (s). MS (FAB) m/z 572 (MH^+). Anal. Calcd for $C_{29}H_{37}N_3O_5S_2$: C, 60.92; H, 6.52; N, 7.35. Found: C, 60.53; H, 6.49; N, 7.09.

9-Furfuryl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (11). A solution of 0.11 g (0.20 mmol) of **94**−**129**, 0.15 mL (0.17 g, 1.8 mmol) of 2-furaldehyde, and 63 mg (0.68 mol) of sodium cyanoborohydride in 20 mL of methanol was stirred at room temperature for 20 h, producing a pale yellow precipitate, which was collected by filtration and recrystallized from ethyl acetate, yielding 66 mg (58%) of **11** as white crystals, mp 162−162.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.31 (d, J = 8 Hz, 4 H, *m*-Ts), 7.29 (d, J = 1 Hz, 1 H, 5-furyl), 6.26 (dd, J = 3 Hz, 1 Hz, 1 H, 4-furyl), 6.04 (d, J = 3 Hz, 1 H, 3-furyl), 5.09 (s, 2 H, C=CH_2), 3.82 (s, 4 H, H2, H4), 3.44 (s, 2 H, CH_2Ar), 3.12 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.42 (t, J = 6 Hz, 4 H, H8, H10), 1.69 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 143.6, 142.0, 138.5, 136.1, 130.0, 127.6, 116.0, 110.3, 108.3, 51.7, 49.9, 49.5, 43.9, 25.4, 21.7. IR (KBr) 2952 (w), 2835 (w), 1598 (m), 1446 (m), 1331 (s), 1163 (s), 1092 (s), 929 (s), 910 (m), 818 (s), 743 (s), 689 (s). MS (FAB) m/z 572 (MH^+). Anal. Calcd for $C_{29}H_{37}N_3O_5S_2$: C, 60.92; H, 6.52; N, 7.35. Found: C, 60.83; H, 6.90; N, 7.62.

9-(5-Methylfurfuryl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (98−**038).** A solution of 0.49 mg (0.93 mmol) of **94**−**129**, 0.57 mL (0.63 g, 6.2 mmol) of 5-methylfurfural, and 0.17 g (2.7 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred at room temperature for 40 h, producing a

pale yellow precipitate. Filtration and recrystallization from methanol/chloroform gave 0.32 g (59%) of **98**−**038** as white crystals, mp 204−205 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.90 (s, 1 H, furyl), 5.83 (s, 1 H, furyl), 5.10 (s, 2 H, C=CH_2), 3.82 (s, 4 H, H2, H4), 3.38 (s, 2 H, CH_2Ar), 3.12 (t, J = 5 Hz, 4 H, H6, H12), 2.44 (m, 10 H, H8, H10, SO_2ArCH_3), 2.20 (s, 3 H, furylCH_3), 1.69 (m, 4 H, H7, H11). ^{13}C NMR (300 MHz, $CDCl_3$) δ 151.1, 150.4, 143.1, 138.2, 135.8, 129.5, 127.2, 115.6, 108.7, 105.7, 51.5, 49.6, 49.2, 43.6, 24.9, 21.3, 13.3. IR (KBr) 2955 (w), 2834 (w), 1598 (w), 1445 (w), 1331 (m), 1164 (s), 1116 (m), 1092 (m), 930 (m), 912 (m), 821 (m), 743 (m), 688 (s), 551 (s). MS (FAB) *m*/*z* 586 (MH^+). Anal. Calcd for $C_{30}H_{39}N_3O_5S_2$: C, 61.51; H, 6.71; N, 7.17. Found: C, 61.13; H, 6.77; N, 7.07.

9-(3-Thienylmethyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (12). A solution of 0.49 g (0.93 mmol) of **94**−**129**, 0.50 mL (0.64 g, 5.7 mmol) of 3-thiophenecarboxaldehyde, and 0.18 g (2.9 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred at room temperature for 40 h. The reaction mixture was worked up as described for **QJ029.** Column chromatography on neutral alumina, eluting with ethyl acetate/hexane/triethylamine (30:60:5, v/v/v), followed by recrystallization from ethyl acetate, gave 0.13 mg (25%) of **12** as white crystals, mp 149−149.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8 Hz, 4 H, *o*-Ts), 7.31 (d, J = 8 Hz, 4 H, *m*-Ts), 7.23 (m, 1 H, 4-thienyl), 7.00 (s, 1 H, 2-thienyl), 6.89 (d, J = 4 Hz, 1 H, 5-thienyl), 5.20 (s, 2 H, C=CH_2), 3.83 (s, 4 H, H2, H4), 3.46 (s, 2 H, CH_2Ar), 3.13 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.40 (m, 4 H, H8, H10), 1.68 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 140.0, 139.0, 136.2, 130.0, 128.4, 127.6, 125.8, 122.6, 116.3, 53.4, 51.5, 49.9, 44.4, 25.0, 21.7. IR (KBr) 2949 (m), 2816 (m), 2360 (m), 2341 (m), 1655 (w), 1598 (m), 1444 (m), 1329 (s), 1162 (s), 1091 (s), 1039 (m), 929 (s), 898 (m), 816 (s), 743 (s), 725 (s), 689 (s), 551 (s). MS (3 kV) *m*/*z* 588 (MH^+). Anal. Calcd for $C_{29}H_{37}N_3O_4S_3 \cdot 0.5H_2O$: C, 58.36; H, 6.42; N, 7.04. Found: C, 58.07; H, 6.28; N, 6.99.

9-(2-Thienylmethyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (13). A solution of 0.47 g (0.89 mmol) of **94**−**129**, 0.55 mL (0.69 g, 5.7 mmol) of 2-thiophenecarboxaldehyde, and 0.18 g (2.9 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred at room temperature for 40 h. The reaction mixture was worked up as described for **QJ029**. Recrystallization from dichloromethane/methanol gave 0.45 g (85%) of **13** as pale yellow crystals, mp 264−265 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.31 (d, J = 7 Hz, 4 H, *m*-Ts), 7.17 (d, J = 4 Hz, 1 H, 5-thienyl), 6.89 (bs, 1 H, 4-thienyl), 6.79 (m, 1 H, 3-thienyl), 5.21 (s, 2 H, C=CH_2), 3.83 (s, 4 H, H2, H4), 3.61 (s, 2 H, CH_2Ar), 3.16 (m, 4 H, H6, H12), 2.44 (bs, 10 H, H8, H10, $ArCH_3$), 1.68 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 142.9, 138.5, 136.3, 130.0, 127.6, 126.4, 125.7, 125.0, 116.7, 53.2, 51.5, 49.8, 44.2, 25.1, 21.7. IR (KBr) 3063 (w), 2946 (w), 2929 (w), 2821 (w), 1598 (m), 1444 (m), 1329 (s), 1154 (s), 1091 (m), 1035 (m), 929 (m), 896 (m), 817 (m), 743 (m), 688 (s), 574 (m). MS (FAB) *m*/*z* 588 (MH^+). Anal. Calcd for $C_{29}H_{37}N_3O_4S_3$: C, 59.26; H, 6.34; N, 7.15. Found: C, 59.50; H, 6.67; N, 7.30.

9-(2-Pyrrylmethyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (14). A solution of 0.50 g (0.94 mmol) of **94**−**129**, 0.54 g (5.6 mmol) of pyrrole-2-carboxyaldehyde, and 0.18 g (2.9 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred for 40 h at room temperature. The reaction mixture was worked up as described for **QJ029**. The HCl salt was formed as described for **6**·HCl. A solution of the resulting dark red solid in 30 mL of CH_2Cl_2 was stirred with 10 mL of 1 N aq NaOH overnight. The mixture was filtered, and the residue was washed with CH_2Cl_2. The combined filtrates were concentrated by rotary evaporation to a brown oil. Column chromatography on silica gel, eluting with AcOEt/CH_2Cl_2/Et_3N (5:93:2, v/v/v), then AcOEt/CH_2Cl_2/Et_3N (10:88:2, v/v/v), yielded 0.47 g (89%) of a brown solid. A solution of the product in ethyl acetate was filtered through neutral alumina, then concentrated by rotary evaporation. Recrystallization from chloroform/hexane gave 0.26 g (48%) of white crystalline **14**, mp 171−171.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (bs, 1 H, NH), 7.66 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 6.69 (m, 1 H, 5-pyrryl), 6.08 (m, 1 H, 3-pyrryl), 5.94 (m, 1 H, 4-pyrryl), 5.22 (s, 2 H, C=CH_2), 3.84 (s, 4 H, H2, H4), 3.44 (s, 2 H, CH_2Ar), 3.12 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.40 (t, J = 6 Hz H8, H10), 1.65 (m, 4 H, H7, H11). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 140.2, 135.8, 130.0, 127.7, 117.8, 116.3, 108.4, 107.8, 52.3, 51.8, 50.2, 45.6, 25.0, 21.9. IR (KBr) 3416 (bm), 2953 (m), 1597 (m), 1445 (m), 1323 (s), 1160 (s), 1092 (s), 1039 (m), 929 (s), 895 (m), 817 (s), 743 (s), 717 (s), 690 (s), 547 (s). MS (3 kV) *m*/*z* 492 ($MH^+ - C_5H_6N$). Anal. Calcd for $C_{29}H_{38}N_4O_4S_2$: C, 61.0; H, 6.7; N, 9.8. Found: C, 60.88; H, 6.88; N, 9.66.

9-[(1-Methyl-2-pyrryl)methyl]-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triaza-cyclododecane (15). A solution of 0.50 g (0.95 mmol) of **94**−**129**, 0.31 mL (0.31 mg, 2.9 mmol) of *N*-methylpyrrole-2-carboxaldehyde, and 0.18 g (2.9 mmol) of sodium cyanoborohydride in 25 mL of methanol was stirred at room temperature for 40 h. The reaction mixture was worked up as described for **QJ029**, obtaining a mixture of starting material and product. Methanol (25 mL), 0.31 mL (0.31 g, 2.9 mmol) of *N*-methylpyrrole-2-carboxyaldehyde, and 0.18 g (2.9 mmol) of sodium cyanoborohydride were added, and the resulting solution was stirred at room temperature for 40 h. The reaction mixture was worked up as described for **QJ029** to give 0.35 g (63%) of crude **15** as a brown solid. Column chromatography on neutral alumina, eluting with ethyl acetate/hexane/triethylamine (30:60:5, v/v/v), followed by recrystallization from chloroform/methanol, gave 0.20 g (36%) of **15** as white crystals, mp 146−146.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.31 (d, J = 8 Hz, 4 H, *m*-Ts), 6.53 (m, 1 H, 5-pyrryl), 5.98 (m, 1 H, 4-pyrryl), 5.91 (m, 1 H, 3-pyrryl), 5.20 (s, 2 H, C=CH_2), 3.84 (s, 4 H, H2, H4), 3.48 (s, 3 H, NCH_3), 3.34 (s, 2 H, CH_2Ar), 3.11 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.35 (t, J = 6 Hz, 4 H, H8,10), 1.56 (m, 4 H, H7, H11). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 139.2, 136.0, 129.9, 129.5, 127.4, 122.6, 116.2, 109.8, 106.6, 52.2, 51.1, 49.6 44.7, 33.8, 24.6, 21.7. IR (KBr) 2939 (m), 2839 (m), 1598 (m), 1494 (m), 1444 (m), 1327 (s), 1172 (s), 1115 (s), 1090 (s), 927 (s), 898 (m), 817 (s), 743 (s), 719 (s), 690 (s), 551 (s). MS (3 kV) *m*/*z* 492 ($MH^+ - C_6H_8N$). Anal. Calcd for $C_{30}H_{40}N_4O_4S_2$: C, 61.62; H, 6.89; N, 9.58. Found: C, 61.99; H, 7.03; N, 9.54.

9-Neopentyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (16). A solution of 0.25 g (0.47 mmol) of **94**−**129**, 0.25 mL (0.20 g, 2.2 mmol) of trimethylacetaldehyde in 12 mL of methanol was stirred for 30 min at room temperature. A solution of 76 mg (1.2 mmol) of sodium cyanoborohydride and 50 mg (0.36 mmol) of zinc chloride in 13 mL of methanol was added over 30 min. The resulting solution was stirred at room temperature for 3 days, then worked up as described for **QJ029**. Column chromatography on silica gel, eluting with ethyl acetate/hexane/triethylamine (30:60:5, v/v/v), gave 55 mg (26%) of **16** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.24 (s, 2 H, C=CH_2), 3.82 (s, 4 H, H2, H4), 3.22 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.34 (t, J = 6 Hz, 4 H, H8, H10), 1.99 (s, 2 H, NCH_2tBu), 1.59 (m, 4 H, H7, H11), 0.77 (s, 9 H, CCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 138.4, 135.9, 130.0, 127.4, 116.9, 68.3, 52.3, 51.0, 44.5, 32.9, 28.9, 25.1, 21.7. **16**·HCl. A solution of 30 mL of 0.33 N HCl in diethyl ether was added to a solution of 55 mg (0.12 mmol) of **16** in 2 mL of ethyl acetate, producing a white precipitate. The mixture was sonicated and filtered. The residue was dried in vacuo (60 °C, 3 d) to give 35 mg (12%) of **16**·HCl, mp 140−142 °C. IR (KBr) 3421 (bm), 2956 (m), 1597 (m), 1457 (m), 1336 (s), 1157 (s), 1090 (m), 1021 (w), 936 (w), 889 (w), 816 (m), 737 (m), 689 (m), 657 (m), 587 (m), 549 (s). MS (FAB) *m*/*z* 562 (M − Cl). Anal. Calcd for $C_{29}H_{43}N_3O_4S_2 \cdot HCl \cdot 1.25\ H_2O$: C, 56.11; H, 7.55; N, 6.77. Found: C, 56.0; H, 7.55; N, 6.77.

9-Isopropyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ035). A solution of 0.25 g (0.47 mmol) of

94−**129**, 0.35 mL (0.28 g, 4.8 mmol) of acetone, 89 mg (1.4 mmol) of sodium cyanoborohydride, and 39 mg (0.24 mmol) of zinc chloride in 25 mL of methanol was stirred at room temperature for 3 d. The reaction mixture was worked up as described for **QJ029** to give 0.21 g (84%) of crude **QJ035**. Column chromatography on silica gel, eluting with ethyl acetate/hexane/triethylamine (30:60:5, v/v/v), gave 0.18 g (72%) of **QJ035** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8 Hz, 4 H, *o*-Ts), 7.33 (d, J = 8 Hz, 4 H, *m*-Ts), 5.20 (s, 2 H, C=CH_2), 3.80 (s, 4 H, H2, H4), 3.14 (t, J = 7 Hz, 4 H, H6, H12), 2.76 (m, 1 H, NCH), 2.44 (s, 6 H, $ArCH_3$), 2.33 (t, J = 5 Hz, 4 H, H8, H10), 1.59 (m, 4 H, H7, H11), 0.84 (d, J = 6.4 Hz, 6 H, NCHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 138.5, 136.1, 130.0, 127.5, 116.8, 51.1, 49.8, 45.4, 44.4, 25.6, 21.7, 21.6, 17.8. **QJ035**·HCl. A solution of 30 mL of 0.33 N HCl in diethyl ether was added to a solution of 0.18 g (0.34 mmol) of the **QJ035** in 2 mL of ethyl acetate, producing a white precipitate. The mixture was sonicated and filtered. The precipitate was dried in vacuo (60 °C, 3 d) to give 0.17 g (62%) of **QJ035**·HCl, mp 137.5−138.5 °C. IR (KBr) 3422 (bm), 2943 (m), 2585 (bm), 1597 (m), 1451 (m), 1335 (s), 1150 (s), 1090 (m), 816 (m), 725 (m), 687 (m), 656 (m), 586 (m), 549 (s). Anal. Calcd for $C_{27}H_{39}N_3O_4S_2$·HCl·H_2O: C, 55.13; H, 7.20; N, 7.14. Found: C, 55.19; H, 7.19; N, 7.14.

9-*sec*-Butyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ036). A solution of 0.19 g (0.37 mmol) of **94**−**129**, 0.34 mL (0.27 g, 3.8 mmol) of 2-butanone, 72 mg (1.1 mmol) of sodium cyanoborohydride, and 30 mg (0.22 mmol) of zinc chloride in 25 mL of methanol was stirred at room temperature for 3 d. The reaction mixture was worked up as described for **QJ029.** Column chromatography on silica gel, eluting with ethyl acetate/hexane/triethylamine (30:60:5, v/v/v) followed by recrystallization from ethyl acetate/hexane, gave 0.15 g (75%) of **QJ036** as white crystals, mp 187−188 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.21 (s, 2 H, C=CH_2), 4.00 (d, J = 16 Hz, 2 H, H2, H4), 3.62 (d, J = 16 Hz, 2 H, H2, H4), 3.15 (m, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 2.40 (m, 4 H, H8, H10), 2.28 (m, 1 H, NCH), 1.57 (m, 4 H, H7, H11), 1.20 (m, 2 H, CH_2CH$_3$), 0.77 (m, 6 H, CH_3CHCH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.8, 136.4, 130.0, 127.6, 116.9, 56.9, 51.2, 45.3, 44.6, 26.6, 25.7, 21.7, 13.7, 12.1. IR (KBr) 2962 (m), 1598 (m), 1458 (m), 1346 (s), 1162 (s), 1091 (m), 921 (m), 744 (m). MS (3 kV) *m*/*z* 548 (MH^+). Anal. Calcd for $C_{28}H_{41}N_3O_4S_2$: C, 61.39; H, 7.54; N, 7.67. Found: C, 61.62; H, 7.59; N, 7.66.

9-Cyclopentyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (QJ040). A solution of 0.20 g (0.37 mmol) of **94**−**129**, 1.0 mL (0.95 g, 11 mmol) of cyclopentanone, and 30 mg (0.22 mmol) of zinc chloride in 12 mL of methanol was stirred for 30 min at room temperature. A solution of 76 mg (1.2 mmol) of sodium cyanoborohydride in 13 mL methanol was added over 30 min. The resulting solution was stirred at room temperature for 24 h. The reaction mixture was worked up as described for **QJ029**. Column chromatography on silica gel, eluting with ethyl acetate/hexane/triethylamine (30:60:5, v/v/v), gave 0.17 g (80%) of **QJ040** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.32 (d, J = 8 Hz, 4 H, *m*-Ts), 5.23 (s, 2 H, C=CH_2), 3.79 (s, 4 H, H2, H4), 3.15 (t, J = 7 Hz, 4 H, H6, H12), 2.92 (m, 1 H, NCH), 2.44 (s, 6 H, $ArCH_3$), 2.40 (m, 4 H, H8, H10), 1.58−1.65 (m, 8 H, H7, H11, cyclopentyl), 1.43 (m, 2 H, cyclopentyl), 1.21 (m, 2 H, cyclopentyl). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 139.1, 136.0, 130.0, 127.5, 117.1, 63.7, 51.3, 47.8, 45.4, 28.5, 25.7, 24.2, 21.7. **QJ040**·HCl. A solution of 30 mL of 0.33 N HCl in diethyl ether was added to a solution of 0.50 g (0.89 mmol) of **QJ040** in 2 mL of ethyl acetate, producing a white precipitate. The mixture was sonicated and filtered. The precipitate was dried in vacuo (60 °C, 3 d) to give 0.15 g (67%) of **QJ040**·HCl, mp 200−201 °C. IR (KBr) 3422 (b), 2954 (m), 2870 (m), 2357 (bs), 1597 (m), 1456 (s), 1340 (s), 1160 (s), 1103 (s), 900 (m), 816 (m), 737 (s), 695 (s), 652 (s), 552 (s). MS (3 kV) *m*/*z* 560 (M − Cl). Anal. Calcd for $C_{29}H_{39}N_3O_4S_2$·HCl·0.75 H_2O: C, 57.12; H, 7.19; N, 6.89. Found: C, 56.91; H, 6.77; N, 6.80.

9-Acetyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (97−**269).** A solution of 0.11 mL (0.29 g, 2.9 mmol) of acetic anhydride in 5 mL of chloroform was added dropwise over 30 min to a stirred solution of 0.15 g (0.19 mmol) of **94**−**129** and 0.25 mL (0.29 g, 2.9 mmol) of triethylamine in 5 mL of chloroform at room temperature. The reaction mixture was heated under reflux for 18 h, then concentrated by rotary evaporation. A solution of the residue in 10 mL of CH_2Cl_2 was washed with 1 N aq HCl (2 × 5 mL), 1 N aq NaOH (5 mL), water (3 × 10 mL), and saturated aqueous NaCl (10 mL), then dried (Na_2SO_4). Concentration by rotary evaporation, drying in vacuo, and recrystallization from diethyl ether/acetone gave 82 mg (54%) of white crystalline **97**−**269**, mp 163 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8 Hz, 2 H, *o*-Ts), 7.66 (d, J = 8 Hz, 2 H, *o*-Ts), 7.34 (d, J = 8 Hz, 4 H, *m*-Ts), 5.31 (s, 2 H, C=CH_2), 3.94 (s, 2 H, H2 or H4), 3.78 (s, 2 H, H4 or H2), 3.41 (m, 4 H, H8, H10), 3.24 (t, J = 6 Hz, 2 H, H6 or H12), 3.10 (t, J = 6 Hz, 2 H, H12 or H6), 2.45 (s, 6 H, $ArCH_3$), 2.03 (s, 3 H, CH_3C=O), 1.89 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 144.0, 140.8, 130.1, 127.5, 117.6, 54.0, 50.9, 48.5, 46.7, 46.2, 43.3, 28.1, 27.4, 22.0, 21.7. IR (KBr) 2950 (w), 2858 (w), 1644 (s), 1597 (m), 1449 (m), 1332 (s), 1162 (s), 1103 (m), 1018 (m), 923 (m), 723 (s), 680 (s), 548 (s). MS (FAB) *m*/*z* 534 (MH^+). Anal. Calcd for $C_{26}H_{35}N_3O_5S_2$: C, 58.51; H, 6.67; N, 7.87; S, 12.01. Found: C, 58.82; H, 6.93; N, 8.11; S, 12.43.

9-Propanoyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (17). A solution of 75 μL (80 mg, 0.86 mmol) of propionyl chloride in 5 mL of chloroform was added dropwise to a solution of 0.15 g (0.28 mmol) of **94**−**129** and 0.24 mL (0.17 g, 1.7 mmol) of triethylamine in 5 mL of chloroform over 30 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h, then concentrated by rotary evaporation. A solution of the residue in 15 mL of methanol was stirred with 5 mL of 1 N aq NaOH for 10 h at room temperature. The reaction mixture was then worked up as described for **97**−**269**. Recrystallization from diethyl ether/dichloromethane gave 0.12 g (77%) of white crystalline **17**, mp 130.5−131.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8 Hz, 4 H, *o*-Ts), 7.66 (d, J = 8 Hz, 4 H, *o*-Ts), 7.33 (d, J = 8 Hz, 4 H, *m*-Ts), 5.31 (s, 2 H, C=CH_2), 3.94, (s, 2 H, H2 or H4), 3.77 (s, 2 H, H4 or H2), 3.40 (m, 4 H, H8, H10), 3.24 (t, J = 6 Hz, 2 H, H6 or H12), 3.10 (t, J = 6 Hz, 2 H, H12 or H6), 2.45 (s, 6 H, $ArCH_3$), 2.26 (q, J = 7 Hz, 2 H, CH_2C=O), 1.90 (m, 4 H, H7, H11), 1.10 (t, J = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 144.0, 140.5, 130.2, 127.5, 117.7, 54.2, 50.4, 48.8, 45.9, 45.6, 43.4, 28.3, 27.0, 26.9, 21.8, 9.7. IR (KBr) 2938 (m), 2872 (m), 1645 (s), 1597 (m), 1448 (m), 1331 (s), 1159 (s), 1104 (s), 1019 (m), 923 (m), 820 (m), 722 (s), 630 (s), 549 (s). MS (FAB) *m*/*z* 548 (MH^+), 570 (MNa^+). Anal. Calcd for $C_{27}H_{37}N_3O_5S_2$: C, 59.21; H, 6.81; N, 7.67; S, 11.71. Found: C, 59.18; H, 7.06; N, 7.99; S, 12.08.

9-Isobutanoyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (18). A solution of 0.10 mL (0.10 g, 0.95 mmol) of isobutyryl chloride in 5 mL of chloroform was added dropwise to a solution of 0.20 g (0.38 mmol) of **94**−**129** and 0.26 mL (0.19 g, 1.9 mmol) of triethylamine in 5 mL of chloroform over 30 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h, then worked up as described for **97**−**269**. Recrystallization from ethanol gave 89 mg (42%) of white crystalline **18**, mp 135−136 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8 Hz, 2 H, *o*-Ts), 7.66 (d, J = 8 Hz, 2 H, *o*-Ts), 7.34 (d, J = 8 Hz, 4 H, *m*-Ts), 5.30 (s, 2 H, C=CH_2), 3.93 (s, 2 H, H2 or H4), 3.78 (s, 2 H, H4 or H2), 3.41 (m, 4 H, H8, H10), 3.23 (t, J = 7 Hz, 2 H, H6 or H12), 3.07 (t, J = 5 Hz, 2 H, H12 or H6), 2.75 (m, 1 H, $CHMe_2$), 2.45 (s, 6 H, $ArCH_3$), 1.89 (m, 4 H, H7, H11), 1.07 (d, J = 7 Hz, 6 H, CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 144.0, 140.6, 130.2, 127.5, 127.3, 117.7, 54.0, 50.5, 48.4, 45.9, 45.7, 43.8, 30.7, 28.5, 27.4, 21.7, 19.9. IR (KBr) 2957 (m), 2870 (m), 1636 (s), 1597 (m), 1449 (m), 1337 (s), 1160 (s), 1101 (s), 921 (m), 819 (M), 743 (m), 720 (m), 680 (s), 659 (m), 549 (s). MS (FAB) *m*/*z* 562 (MH^+). Anal. Calcd for $C_{28}H_{39}N_3O_5S_2$: C, 59.87; H, 7.00; N, 7.48. Found: C, 60.20, H, 7.28, N, 7.59.

9-Benzoyl-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (19). A solution of 0.11 mL (0.13 g, 0.95 mmol) of benzoyl chloride in 5 mL of chloroform was added dropwise to a solution of 0.20 g (0.38 mmol) of **94**−**129** and 0.26 mL (0.19 g, 1.9 mmol) of triethylamine in 5 mL of chloroform over 30 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h, then worked up as described for **97**−**269**. Recrystallization from ethanol/water yielded 0.13 g (60%) of **19** as white crystals, mp. 179.3−179.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8 Hz, 4 H, *o*-Ts), 7.39 (m, 2 H, *o*-Bz), 7.33 (d, J = 8 Hz, 4 H, *m*-Ts), 7.28 (m, 3 H, *m*,*p*-Bz), 5.37 (s, 2 H, C=CH_2), 3.85 (bs, 4 H, H2, H4), 3.46 (bs, 4 H, H8, H10), 3.18 (t, J = 6 Hz, 4 H, H6, H12), 2.44 (s, 6 H, $ArCH_3$), 1.96 (bs, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 144.0, 141.2, 137.1, 135.8, 130.2, 129.6, 128.8, 127.5, 126.7, 117.7, 27.0, 21.7. IR (KBr) 3057 (w), 2978 (m), 2947 (m), 2922 (m), 1633 (s), 1599 (m), 1495 (m), 1344 (s), 1330 (s), 1161 (s), 1102 (s), 946 (m), 896 (m), 786 (s), 754 (m), 708 (s), 656 (s), 550 (s). MS (FAB) *m*/*z* 596 (MH^+), 618 (MNa^+). Anal. Calcd for $C_{31}H_{37}N_3O_5S_2$: C, 62.50; H, 6.26; N, 7.05; S, 10.76. Found: C, 62.29; H, 6.32; N, 7.14; S, 11.10.

9-Isopropoxycarbonyl-3-methylene-1,5-di-*p*-toluenesulfonyl-1,5,9-triazacyclododecane (20). A solution of 2.9 mL (2.9 mmol) of a 1 M toluene solution of isopropyl chloroformate in 10 mL of chloroform was added dropwise to a solution of 0.50 g (0.94 mmol) of **94**−**129** and 0.80 mL (0.58 g, 5.7 mmol) of triethylamine in 10 mL of chloroform over 30 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h, then concentrated by rotary evaporation. Column chromatography on silica gel, eluting with ethyl acetate/hexane (60:40, v/v), and drying in vacuo gave 0.37 g (69%) of **20** as a white solid, mp 83−85 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.33 (d, J = 8 Hz, 4 H, *m*-Ts), 5.19 (s, 2 H, C=CH_2), 4.84 (m, 1 H, $CHMe_2$), 3.84 (s, 4 H, H2, H4), 3.32 (t, J = 6 Hz, 4 H, H6, H12), 3.01 (m, 4 H, H8, H10), 2.42 (s, 6 H, $ArCH_3$), 1.81 (m, 4 H, H7, H11), 1.18 (d, J = 6 Hz, 6 H, $CHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 143.8, 139.7, 136.2, 130.1, 127.5, 117.3, 68.9, 51.8, 51.7, 45.6, 28.7, 22.4, 21.7. IR (KBr) 2979 (m), 2871 (w), 1692 (s), 1598 (m), 1472 (m), 1420 (m), 1339 (s), 1162 (s), 1111 (m), 1093 (m), 1030 (m), 924 (m), 816 (m), 747 (m), 658 (s), 581 (s). MS (FAB) *m*/*z* 578 (MH^+). Anal. Calcd for $C_{28}H_{39}N_3O_6S_2$: C, 58.2; H, 6.8; N, 7.3. Found: C, 58.09; H, 6.86; N, 7.26.

9-(*N*,*N*-Dimethylcarbamoyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (21). A solution of 62 μL (72 mg, 0.67 mmol) of *N*,*N*-dimethylcarbamoyl chloride in 5 mL of chloroform was added dropwise to a solution of 0.14 g (0.27 mmol) of **94**−**129** and 0.22 mL (0.16 g, 1.6 mmol) of triethylamine in 5 mL of chloroform over 30 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h, then worked up as described for **97**−**269**. Recrystallization from methanol/chloroform gave 98 mg (64%) of white crystalline **21**, mp 229−230 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8 Hz, 4 H, *o*-Ts), 7.33 (d, J = 8 Hz, 4 H, *m*-Ts), 5.31 (s, 2 H, C=CH_2), 3.84 (s, 4 H, H2, H4), 3.20 (m, 8 H, H6, H8, H10, H12), 2.75 (s, 6 H, NCH_3), 2.44 (s, 6 H, $ArCH_3$), 1.83 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 142.9, 140.2, 134.8, 129.1, 126.5, 116.1, 50.9, 46.4, 43.5, 37.8, 24.9, 20.7. IR (KBr) 3028 (w), 2947 (m), 2899 (m), 1631 (s), 1596 (m), 1495 (s), 1340 (s), 1320 (s), 1157 (s), 1120 (s), 1090 (s), 939 (s), 895 (s), 819 (s), 805 (s), 665 (s), 590 (s), 564 (s). MS (FAB) *m*/*z* 563 (MH^+). Anal. Calcd for $C_{27}H_{38}N_4O_5S$: C, 57.63; H, 6.81; N, 9.96; S, 11.39. Found: C, 57.99; H, 7.16; N, 10.34; S, 11.74.

9-(4-Morpholinocarbonyl)-3-methylene-1,5-bis(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (22). A solution of 70 μL (90 mg, 0.60 mmol) of 4-morpholinecarbonyl chloride in 5 mL of chloroform was added dropwise to a solution of 0.11 g (0.21 mmol) of **94**−**129** and 0.20 mL (0.15 g, 1.4 mmol) of triethylamine in 5 mL of chloroform over 30 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h, then worked up as described for **97**−**269**. Two recrystallizations from methanol/water gave 92 mg (74%) of **22** as white crystals, mp 177.5−178.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8 Hz, 4 H, *o*-Ts), 7.33 (d, J = 8 Hz, 4 H, *m*-Ts), 5.33 (s, 2 H, C=CH_2), 3.82 (s, 4 H, H2, H4), 3.67 (m, 4 H, CH_2O), 3.14−3.27 (m, 12 H, H6, H8, H10, H12, OCH_2CH_2N), 2.45 (s, 6 H, $ArCH_3$), 1.86 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 144.0, 141.4, 135.7, 130.1, 127.5, 117.5, 66.9, 52.1, 47.9, 47.7, 44.6, 26.0, 21.7. IR (KBr) 2977 (w), 2920 (w), 2861 (w), 1645 (s), 1598 (w) 1412 (m), 1340 (s), 1231 (m), 1157 (s), 1118 (s), 1099 (m), 894 (m), 815 (m), 785 (m), 755 (w), 662 (m), 550 (s). MS (FAB) *m*/*z* 605 (MH^+). Anal. Calcd for $C_{29}H_{40}N_4O_6S_2 \cdot 0.25\ H_2O$: C, 57.17; H, 6.70; N, 9.20; S, 10.53. Found: C, 56.49; H, 6.76; N, 9.28; S, 10.85.

***N*,*N*′-Bis(methanesulfonyl)bis(3-aminopropyl)benzylamine Hydrochloride (23).** A solution of 40 mL (59 g, 0.52 mol) of methanesulfonyl chloride in 220 mL of CH_2Cl_2 was stirred in a flask immersed in a 23 °C water bath as a solution of triamine **3** (40 g, 0.18 mol) in 100 mL (78 g, 0.77 mol) of Et_3N was added dropwise over a period of 3 h. Saturated aq NaCl (50 mL) was added within an hour of the start of the addition, and the reaction mixture was stirred for 16 h at room temperature. The organic layer was extracted with 3 × 50 mL of saturated aqueous NaCl. The resulting emulsion was broken by vacuum-filtration. The combined aqueous solutions were extracted with 2 × 70 mL of $CHCl_3$. The combined extracts were dried (Na_2SO_4) and concentrated by rotary evaporation to give a thick, yellowish oil. A solution of 40 g (0.10 mol) of this crude product in 150 mL of $CHCl_3$ was treated with 130 mL of 1 M HCl in ether to give 40 g (97%) of **23**. Recrystallization from hot methanol gave 25 g (64%) of white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.45 (bs, 1 H, NH^+), 7.66 (m, 2 H, *o*-Bn), 7.44 (m, 3 H, *m*,*p*-Bn), 4.04 (d, J = 4.0 Hz, 2 H, CH_2Ph), 3.72 (t, J = 6.2 Hz, 4 H, H1), 3.58 (m, 4 H, H3), 3.39 (s, CH_3), 3.04 (m, 2 H, SO_2NH), 2.19 (m, 4 H, H2). ^{13}C NMR, APT (75 MHz, $CDCl_3$) δ 131.1 (CH), 129.7 (C), 129.2 (CH), 128.6 (CH), 55.6 (CH_2), 48.7 (CH_2), 45.0 (CH_2), 43.1 (CH_3), 23.5 (CH_2).

9-Benzyl-3-methylene-1,5-bis(methanesulfonyl)-1,5,9-triazacyclododecane (MFS105). A mixture of NaH (0.4 g of a 60% (w/w) slurry in mineral oil, 0.24 g NaH, 10 mmol, washed with hexane under nitrogen) and 100 mL of anhydrous DMF was stirred at room temperature as a solution of 1.0 g (2.4 mmol) of hydrochloride salt **23** in 50 mL of anhydrous DMF was added. The resulting mixture was stirred as a solution of 0.6 mL (0.65 g, 5.2 mmol) of 3-chloro-2-chloromethyl-1-propene in 28 mL of anhydrous DMF was added over a period of 14 h by means of a syringe pump. The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was allowed to cool, and the solvent was removed by rotary evaporation using a hot water bath. The resulting solid residue was treated as described for crude CADA, giving 0.85 g (82%) of a solid. Flash chromatography of 0.44 g of this solid yielded 0.11 g (21%) of **MFS105** free base as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H, Bn), 5.37 (s, 2 H, C=CH_2), 3.90 (s, 4 H, H2, H4), 3.46 (s, 2 H, CH_2Ph), 3.32 (t, J = 7.0 Hz, 4 H, H6, H12), 2.85 (s, 6 H, SO_2CH_3), 2.44 (t, J = 6 Hz, 4 H, H8, H10), 1.83 (quint., J = 6 Hz, 4 H, H7, H11). ^{13}C NMR, APT (75 MHz, $CDCl_3$) δ 139.6 (C), 129.2 (CH), 128.5 (CH), 127.3 (CH), 116.2 (CH_2), 60.1 (CH_2), 51.4 (CH_2), 50.4 (CH_2), 45.0 (CH_2), 37.8 (CH_3), 26.2 (CH_2). IR (KBr): 2931, 2805, 1452, 1327, 1150, 964, 794, 729. **HCl Salt.** A solution of 0.10 g (0.23 mmol) of the free base in 5 mL of CH_2Cl_2 and 40 mL of ether was stirred vigorously at 0 °C as a cold solution of 1.0 M HCl in ether was added dropwise. The solvents were removed in vacuo and the residue was washed with 3 × 2 mL of cold ether. The ether was carefully pipetted off and the residue was dried under vacuum for 12−48 h at room temperature, yielding 0.11 g (100%) of **MFS105**·HCl. A sample for microanalysis was dried in vacuo for 3 d at room temperature. MS (FAB) *m*/*z* 430 (M − Cl). Anal. Calcd for $C_{19}H_{31}N_3O_4S_2$ HCl: C, 48.97; H, 6.92, N, 9.02. Found: C, 48.67; H, 6.84, N, 6.84.

***N*,*N*′-Bis(benzenesulfonyl)bis(3-aminopropyl)benzylamine (24).** Reaction of 25.4 g (0.12 mol) of triamine **3** and 40.2 g (0.23 mol) of benzenesulfonyl chloride gave three phases, as described for the synthesis of **94**−**127**. The upper two layers were separated, diluted with $CHCl_3$, and dried ($MgSO_4$). Filtration, concentration by rotary evaporation and drying in vacuo gave 57 g (100%) of free base **24**

as a pale yellow oil. A solution of 60 mL of 2 N aq HCl (60 mL) and 60 mL of saturated aqueous NaCl was stirred vigorously with a solution of 57 g of crude **24** in 150 mL of CH_2Cl_2 for 1 h. The organic layer was separated, washed with saturated aqueous NaCl (3 × 50 mL), and concentrated by rotary evaporation. The residue was dissolved in 200 mL of boiling ethanol, and ethyl acetate (ca. 400 mL) was added to induce precipitation. Vacuum filtration gave 55.9 g (90%) of **24**·HCl as a white solid, mp 135−136 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.0 (br, 1 H, NH^+), 7.89 (t, J = 5.7 Hz, 2 H, SO_2NH), 7.79 (d, J = 7.2 Hz, 4 H, *o*-Ph), 7.59 (m, 8 H, *m*,*p*-Ph, *o*-Bn), 7.41 (m, 3 H, *m*,*p*-Bn), 4.23 (d, J = 4.2 Hz, 2 H, CH_2Ph), 2.93 (m, 4 H, H3), 2.74 (m, 4 H, H1), 1.88 (m, 4 H, H2). ^{13}C NMR (75 MHz, DMSO-d_6) δ 140.3, 132.6, 131.5, 129.8, 129.6, 129.4, 128.9, 126.6, 56.0, 49.4, 40.1, 23.3. IR (KBr) 3242 (br), 3073 (s), 2976 (m), 2855 (m), 2609 (s), 1470 (m), 1446 (s), 1330 (s), 1163 (s), 1092 (s), 740 (s), 689 (s). Anal. Calcd for $C_{25}H_{31}N_3S_2O_4$·HCl: C, 55.80; H, 5.99; N, 7.81; S, 11.92; Cl, 6.59. Found: C, 55.47; H, 6.13; N, 7.63; S, 11.63; Cl, 6.92. A mixture of 6.51 g (12.1 mmol) of **24**·HCL, 40 mL of CH_2Cl_2, 15 mL of 1 N aq NaOH, and 15 mL of saturated aqueous NaCl was stirred vigorously for 30 min. The organic layer was dried ($MgSO_4$), concentrated by rotary evaporation, and dried in vacuo (0.4 mm, 45 °C) for 24 h, yielding 5.96 g (98%) of **24** free base as a thick, colorless oil. TLC (silica): R_f 0.21, 1:1 (v/v) ethyl acetate:hexane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 7 Hz, 4 H, *o*-Ph), 7.51 (m, 6 H, *m*,*p*-Ph), 7.22 (m, 3 H, *m*,*p*-Bn), 7.16 (m, 2 H, *o*-Bn), 5.9 (br, 2 H, NH), 3.40 (s, 2 H, CH_2Ph), 2.92 (t, J = 6.3 Hz, 4 H, H3), 2.38 (t, J = 6.3 Hz, 4 H, H1), 1.62 (quint., J = 6.3 Hz, 4 H, H2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 138.2, 132.4, 129.0, 128.4, 127.2, 126.9, 58.7, 51.8, 42.2, 26.1. IR (NaCl) 3277 (br), 3061 (w), 1446 (s), 1325 (s), 1160 (s), 1093 (s).

***N,N′*-Bis(3-*p*-bromobenzenesulfonyl)bis(3-aminopropyl)benzylamine (25)**. A mixture of 22.0 g (86.1 mmol) of *p*-bromobenzenesulfonyl chloride, 100 mL of CH_2Cl_2, and 100 mL of saturated aqueous NaCl was stirred vigorously as a solution of 9.53 g (43.1 mmol) of triamine **3** in 58 mL of 1.5 N aq NaOH was added over 1.5 h, then the reaction mixture was stirred overnight at room temperature. The organic layer was washed with 50 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was dried in vacuo (1 mm) giving 24.4 g (98%) of **25** as a white solid, mp 57−59 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 9 Hz, 4 H, *o*-Bs), 7.63 (d, J = 9 Hz, 4 H, *m*-Bs), 7.27 (m, 3 H, *m*,*p*-Bn), 7.19 (m, 2 H, *o*-Bn), 6.01 (s, 2 H, SO_2NH), 3.44 (s, 2H, CH_2Ph), 2.95 (t, J = 6.4 Hz, 4 H, H3), 2.45 (t, J = 6.4 Hz, 4 H, H1), 1.95 (quint., J = 6.4 Hz, 4 H, H2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.1, 132.3, 129.0, 128.6, 128.5, 127.4, 58.7, 52.0, 42.3, 26.1. IR (KBr) 3261 (br), 3087 (w), 2944 (w), 2867 (w), 1573 (m), 1469 (m), 1437 (m), 1389 (m), 1329 (s), 1165 (s), 1090 (s), 1068 (s), 1010 (s), 883 (m), 824 (s), 738 (s), 609 (s).

***N,N′*-Bis(*p*-methoxybenzenesulfonyl)bis(3-aminopropyl)benzylamine Hydrochloride (26·HCl).** A solution of 18.7 g (90 mmol) of *p*-methoxybenzenesulfonyl chloride in 40 mL of diethyl ether was stirred rapidly as a cloudy solution of 10 g (45 mmol) of triamine **3**, 55 mL of 2 M aq NaOH, and 100 mL of saturated aqueous NaCl was added slowly over 10 h. The reaction mixture was stirred for 10 h at room temperature, producing three layers. The two upper layers were separated and stirred vigorously with 80 mL of 2 M aq HCl and 100 mL of saturated aqueous NaCl for 5 h. The white precipitate was collected by filtration, washed with water (3 × 20 mL) and diethyl ether (3 × 20 mL), dried in vacuo and recrystallized from chloroform/hexane yielding 24.5 g (91%) of **26**·HCl as a white solid, mp 118−120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 9 Hz, 4 H, *o*-$ArSO_2$), 7.56 (m, 3 H, *m*,*p*-Bn), 7.44 (m, 2 H, *o*-Bn), 6.96 (d, J = 9 Hz, 4 H, *m*-$ArSO_2$), 6.50 (bs, 2 H, SO_2NH), 4.23 (s, 2 H, CH_2Ph), 3.85 (s, 6 H, OCH_3), 3.17 (m, 4 H, H3), 2.98 (m, 4 H, H1), 2.16 (m, 4 H, H2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 138.6, 132.4, 129.5, 129.3, 128.8, 127.6, 114.5, 59.2, 55.8, 52.4, 42.5, 26.6. IR (KBr): 3566 (br), 3330 (br), 3099 (br), 2843 (w), 1596 (s), 1577 (m), 1499 (m), 1324 (s), 1260 (s), 1157 (s), 1093 (m), 1029 (m), 927 (w), 830 (s), 804 (m) 704 (m). Anal. Calcd for $C_{27}H_{35}N_3O_6S_2$·HCl·H_2O: C, 52.63; H, 6.17; N, 6.82. Found: C, 52.46; H, 5.98; N, 6.92. MS (MALDI) *m*/*z* 560 (M-35, 40).

***p*-Butoxymethylbenzenesulfonyl Chloride.** Sodium butoxide was prepared by stirring 4.5 g (0.20 mol) of sodium metal with 70 mL of anhydrous butanol until H_2 gas evolution stopped (**Caution**: flammable gas hazard). By means of a solid addition funnel, 13 g (49 mmol) of 4-bromomethylbenzenesulfonyl chloride[41] was added to the stirred sodium butoxide solution in small portions. The reaction mixture was heated to 80 °C for 4 h and cooled to room temperature, then 50 mL water was added slowly. The organic layer was concentrated by rotary evaporation to give 12 g (100%) of sodium *p*-butoxymethylbenzenesulfonate. A mixture of 13 g of the sodium salt, 120 mL of $CHCl_3$, 45 g (0.38 mol) of thionyl chloride, and 0.5 mL of anhydrous DMF was heated under reflux for 4 h. The solvents were removed by rotary evaporation, and the residue was extracted with $CHCl_3$ (5 × 50 mL). Evaporation of the extract gave 7.25 g (52%) of the product as a dark brown liquid. GC-MS *m*/*z* 190 (M − BuO, 100%), 192 (MH^+ + 2 − BuO, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 2 H, *o*-$ArSO_2$), 7.60 (d, J = 8.4 Hz, 2 H, *m*-$ArSO_2$), 4.62 (s, 2 H, $ArCH_2O$), 3.55 (m, 2 H, OCH_2Pr), 1.64 (m, 2 H, CH_2Et), 1.44 (m, 2 H, CH_2Me), 0.94 (m, 3 H, CH_3). ^{13}C NMR, APT (75 MHz, $CDCl_3$) δ 147.6 (C), 143.1 (C), 128.0 (CH), 127.2 (CH), 71.6 (CH_2), 71.2 (CH_2), 31.9 (CH_2), 19.5 (CH_2), 14.1 (CH_3).

***N,N′*-Bis(*p*-butoxymethylbenzenesulfonyl)bis(3-aminopropyl)benzylamine (27).** A mixture of 2.0 g (7.6 mmol) of *p*-butoxymethylbenzenesulfonyl chloride, 0.9 g (4.1 mmol) of triamine **3**, 30 mL of $CHCl_3$, and 10 mL of 2 M aq NaOH was stirred overnight. The aqueous layer was extracted with $CHCl_3$ (4 × 30 mL), and the combined organic solutions were dried (Na_2SO_4) and concentrated by rotary evaporation. Flash column chromatography (1:1 to 2:1 EtOAc/hexane, 1% Et_3N) of a 4.0 g sample gave 3.18 g (85%) of **27** as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 4 H, *o*-$ArSO_2$), 7.46 (m, 4 H, *m*-$ArSO_2$), 7.24 (m, 3H, *m*,*p*-Bn), 7.19 (m, 2 H, *o*-Bn), 5.88 (bs, 2 H, NH), 4.55 (s, 2 H, $ArCH_2O$), 3.51 (t, J = 6.6 Hz, 4 H, OCH_2Pr), 3.42 (s, 2 H, CH_2Ph), 2.92 (m, 4 H, H1), 2.40 (m, 4 H, H3), 1.62 (m, 8 H, H2, CH_2Et), 1.41 (sext., J = 7.7 Hz, CH_2Me), 0.93 (t, J = 7.3 Hz, 6 H, CH_3). ^{13}C NMR, APT (75 MHz, $CDCl_3$) δ 144.0 (C), 139.0 (C), 138.4 (C), 129.2 (CH), 128.7 (CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 72.8 (CH_2), 71.0 (CH_2), 59.0 (CH_2), 52.2 (CH_2), 42.5 (CH_2), 32.0 (CH_2), 26.4 (CH_2), 19.6 (CH_2), 14.1 (CH_3). FT-IR (NaCl) 3281 (br, s), 3086, 3062, 3028, 2957 (s), 2869 (s), 1600, 1455 (s), 1408, 1328, 1158, 1091, 1018, 963, 816, 773, 683, 633. MS (FAB) *m*/*z* 674 (MH^+).

***N,N′*-Bis(*o*-nitrobenzenesulfonyl)bis(3-aminopropyl)benzylamine (28).** Reaction of 24.3 g (0.11 mol) of triamine **3** and 50.0 g (22 mmol) of *o*-nitrobenzenesulfonyl chloride gave three phases, as described for the synthesis of **94**−**127**. The two upper layers were diluted with $CHCl_3$, separated, and dried ($MgSO_4$). Filtration, concentration by rotary evaporation and drying in vacuo gave crude **28** as a brown tar. A solution of the crude product in 300 mL of $CHCl_3$ was dried ($MgSO_4$) and concentrated by rotary evaporation. The residue was dried (1 mm) to give 59 g (91%) of **28** as a brownish yellow residue. A mixture of this residue, 250 mL of $CHCl_3$, 60 mL of 2 N aq HCl, and 60 mL of saturated aqueous NaCl was stirred vigorously at room temperature for 30 min. The organic layer was concentrated by rotary evaporation. Attempted recrystallization of the residue from acetone/ethyl acetate gave **28**·HCl as an oil, which was dried in vacuo (1 mm). A mixture of this oil, 300 mL of $CHCl_3$, 110 mL of 1 N aq NaOH and 220 mL of saturated aqueous NaCl was shaken for 1 h in a tightly stoppered flask. The organic layer was separated, dried (Na_2SO_4), and concentrated by rotary evaporation to give a sample of **28**·HCl that was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (m, 2 H, SO_2NH), 7.73 (m, 4 H, Ns), 7.70 (m, 4 H, Ns), 7.39 (m, 2 H, *o*-Bn), 7.26 (m, 3 H, *m*,*p*-Bn), 3.87 (s, 2 H, CH_2Ph), 3.11 (m, 4 H, H1), 2.81 (m, 4 H, H3), 1.95 (m, 4 H, H2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 133.5, 133.0, 132.7, 130.6, 130.1, 128.6, 128.4, 124.9, 57.5, 50.5, 41.5, 24.9. IR (NaCl) 3342 (br),

3095 (w), 3028 (w), 2953 (w), 2597 (w), 1539 (s), 1364 (m), 1341 (m), 1165 (s), 1125 (m), 853 (m), 782 (w).

***N,N′*-Bis(*m*-nitrobenzenesulfonyl)bis(3-aminopropyl)benzylamine (29).** A mixture of 25.0 g (0.11 mmol) of *m*-nitrobenzenesulfonyl chloride, 100 mL of CH_2Cl_2, and 120 mL of saturated aqueous NaCl was stirred vigorously as a solution of 12.5 g (57 mmol) of triamine **3** in 80 mL of 1.5 N aq NaOH was added over 2 h, then the reaction mixture was stirred overnight at room temperature. The organic layer was washed with 3 × 50 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated by rotary evaporation. Drying in vacuo (1 mm) gave 33 g (91%) of **29** as an amber oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, J = 2.0 Hz, 2 H, *o*-Ns), 8.43 (dd, J = 8.3, 1.5 Hz, 2 H, *p*-Ns), 8.17 (dd, J = 7.8, 1.0 Hz, 2 H, *o′*-Ns), 7.75 (t, J = 8.3 Hz, 2 H, *m*-Ns), 7.27 (m, 3 H, *m*,*p*-Bn), 7.20 (m, 2 H, *o*-Bn), 6.3 (br, 2 H, SO_2NH), 3.48 (s, 2 H, CH_2Ph), 3.03 (t, J = 6 Hz, 4 H, H3), 2.52 (t, J = 6 Hz, 4 H, H1), 1.95 (quint., J = 6 Hz, 4 H, H2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 142.3, 137.8, 132.6, 130.5, 129.0, 128.5, 127.5, 126.9, 122.1, 58.8, 52.1, 42.4, 26.2. IR (NaCl) 3395 (br), 3088 (w), 3029 (w), 2951 (w), 2872 (w), 2825 (w), 1606 (w), 1534 (s), 1429 (m), 1353 (s), 1168 (s), 1127 (s), 1081 (m), 880 (m), 758 (m), 673 (m), 588 (w).

***N,N′*-Bis(*p*-nitrobenzenesulfonyl)bis(3-aminopropyl)benzylamine (30).** Reaction of 22.8 g (0.103 mol) of triamine **3** and 50.1 g (0.203 mol) of *p*-nitrobenzenesulfonyl chloride was conducted as described for the synthesis of **94**−**127**. Upon completion of the addition of **3**, the reaction mixture was stirred at room temperature overnight. The resulting two-phase mixture was decanted from a brown tar-like residue, then the ether layer was recombined with the tar. The aqueous portion was extracted with 50 mL of $CHCl_3$. The combined organic portions were concentrated by rotary evaporation, providing crude **30** as a brown tar. A mixture of crude **30**, 250 mL of $CHCl_3$, 60 mL of 2 N aq HCl, and 60 mL of saturated aqueous NaCl was stirred vigorously for 1 h at room temperature. The organic layer was separated and concentrated by rotary evaporation. A mixture of the residue and 300 mL of acetone was heated to boiling and filtered while hot. Precipitation was induced by adding ethyl acetate to the boiling filtrate. Cooling to room temperature and filtration gave 52.3 g (82%) of **30**·HCl as a yellow solid, mp 200−205 °C (dec). A sample for microanalysis was recrystallized from acetone and dried at 78 °C (0.2 mm, 12 h), giving an off-white solid, mp 232−233 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.9 (br, 1 H, NH^+), 8.41 (d, J = 8.7 Hz, 4 H, *m*-Ns), 8.27 (t, 2 H, SO_2NH), 8.03 (d, J = 8.7 Hz, 4 H, *o*-Ns), 7.58 (m, 3 H, *m*,*p*-Bn), 7.43 (m, 2 H, *o*-Bn), 4.24 (d, 2 H, CH_2Ph), 2.95 (m, 4 H, H3), 2.82 (m, 4 H, H1), 1.89 (m, 4 H, H2). ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.7, 146.0, 131.4, 129.8, 129.5, 128.8, 128.2, 124.6, 56.0, 49.4, 40.1, 23.3. IR (KBr) 3436 (br), 3114 (w), 3074 (w), 2578 (br), 2504 (br), 1530 (s), 1352 (m), 1339 (m), 1307 (m), 1161 (s), 1093 (m), 855 (m), 746 (m), 683 (m), 609 (m). Anal. Calcd for $C_{25}H_{29}N_5S_2O_8$·HCl: C, 47.81; H, 4.81; N, 11.15; S, 10.21; Cl, 5.64. Found: C, 47.78; H, 5.01; N, 11.52; S, 10.07. **Free Base**. A mixture of 10.34 g (16.5 mmol) of **30**·HCl, 70 mL of CH_2Cl_2, 17 mL of 1 N aq NaOH, and 20 mL of saturated aqueous NaCl was stirred vigorously for 3 h. The organic layer was separated and washed with 50 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated by rotary evaporation. Drying under vacuum (0.4 mm, 24 h) gave 9.16 g (94%) of **30** as a thick, golden brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 8.7 Hz, 4 H, *m*-Ns), 7.99 (d, J = 8.7 Hz, 4 H, *o*-Ns), 7.27 (m, 3 H, *m*,*p*-Bn), 7.20 (m, 2 H, *o*-Bn), 6.3 (br, 2 H, SO_2NH), 3.45 (s, 2 H, CH_2Ph), 3.02 (t, J = 6 Hz, 4 H, H3), 2.49 (t, J = 6 Hz, 4 H, H1), 1.73 (quint., J = 6 Hz, 4 H, H2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 145.9, 137.8, 129.1, 128.7, 128.3, 127.6, 124.3, 58.9, 52.2, 45.5, 26.2. IR (NaCl) 3294 (br), 3105 (w), 3031 (w), 2951 (w), 2867 (w), 2828 (w), 1606 (w), 1529 (s), 1349 (s), 1309 (m), 1164 (s), 1093 (m), 911 (w), 854 (m), 736 (m), 685 (m).

9-Benzyl-3-methylene-1,5-bis(benzenesulfonyl)-1,5,9-triazacyclododecane Hydrochloride (95−211·HCl). A solution of 5.78 g (11.5 mmol) of **24** in 220 mL of anhydrous DMF was added slowly with stirring to NaH (0.92 g of a 60% (w/w) slurry in mineral oil, 0.55 g NaH, 23 mmol, washed with hexane under nitrogen). The resulting clear solution was stirred as a solution of 1.44 g (11.5 mmol) of 3-chloro-2-chloromethyl-1-propene in 8 mL of anhydrous DMF was added over 10 h, then the reaction mixture was stirred at room temperature for 24 h. The solvent was removed by rotary evaporation using a hot water bath. A solution of the residue in 50 mL of $CHCl_3$ was washed with water (3 × 30 mL), saturated aqueous NaCl (2 × 30 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. The resulting thick yellow oil was dissolved in 100 mL of 1:1 (v/v) ethyl acetate:hexane and filtered through 16 g of basic alumina (Woelm Act 1, 80−200 mesh), washing the alumina with an additional 50 mL of 1:1 ethyl acetate/hexane. Concentration under vacuum gave 4.93 g (77%) of **95**−**211** as a foam. A mixture of crude **95**−**211**, 30 mL of $CHCl_3$, 10 mL of 2 N aq HCl, and 10 mL of saturated aqueous NaCl was stirred for 30 at room temperature. The organic layer was separated, washed with 20 mL of saturated aqueous NaCl, and concentrated by rotary evaporation. The residue was recrystallized from ethanol/ethyl acetate, followed by acetone/ethyl acetate, giving 3.03 (45%) of **95**−**211**·HCl, mp 135−136 °C. A sample for elemental analysis was dried (24 h, 78 °C, 0.3 mm). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.6 (br, 1 H, NH^+), 7.79 (d, J = 7.8 Hz, 4 H, *o*-Ph), 7.75−7.64 (m, 8 H, *m*,*p*-Ph, *o*-Bn), 7.43 (m, 3 H, *m*,*p*-Bn), 5.37 (s, 2 H, C=CH_2), 4.30 (d, 2 H, CH_2Ph), 3.69 (s, 4 H, H2, H4), 3.09 (m, 8 H, H6, H8, H10, H12), 1.95 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, DMSO-d_6) δ 141.5, 136.9, 133.4, 131.1, 130.4, 129.7, 129.4, 128.8, 127.3, 118.8, 57.1, 51.8, 48.2, 46.3, 20.2. IR (KBr) 3060 (w), 2928 (w), 2873 (w), 2445 (br), 1447 (s), 1335 (s), 1163 (s), 1090 (m), 931 (m), 737 (s), 696 (m). UV (CH_3OH): λ_{max} (logϵ), 224 (4.2). MS (FAB) *m*/*z* 554 (MH^+). Anal. Calcd for $C_{29}H_{35}N_3S_2O_4$·HCl: C, 59.02; H, 6.15; N, 7.12. Found: C, 59.39; H, 6.28; N, 7.21.

9-Benzyl-3-methylene-1,5-bis(*p*-bromobenzenesulfonyl)-1,5,9-triazacyclododecane (ASPB127). A mixture of 59.4 g (0.43 mol) of K_2CO_3, 23.0 g (35 mmol) of **25**, and 900 mL of anhydrous DMF was stirred at 60 °C for 1 h. The reaction mixture was stirred at 60 °C as a solution of 5.0 g (40 mmol) of 3-chloro-2-chloromethyl-1-propene in 10 mL of anhydrous DMF was added over 15 h by means of a syringe pump. The reaction mixture was stirred for 1 h at room temperature, then the solvent was removed by rotary evaporation using a hot water bath. A solution of the residue in 250 mL of chloroform was washed with water (2 × 100 mL), 1 N aq NaOH solution (2 × 100 mL), and saturated aqueous NaCl solution (2 × 100 mL). The solution was dried ($MgSO_4$), filtered and concentrated to dryness by rotary evaporation. The residue was dried in vacuo (0.1 mm), yielding 17.5 g (70%) of crude **ASPB127** as a yellow foam. A 1.60 g sample of crude **ASPB127** was purified by silica gel flash chromatography eluting with 95:5 (v/v) chloroform/ethyl acetate, giving 0.83 g (36%) of **ASPB127** as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 9 Hz, 4 H, *o*-Bs), 7.63 (d, J = 9 Hz, 4 H, *m*-Bs), 7.25−7.21 (m, 3 H, *m*,*p*-Bn), 7.15−7.12 (m, 2 H, *o*-Bn), 5.21 (s, 2 H, C=CH_2), 3.85 (s, 4 H, H2, H4), 3.40 (s, 2 H, CH_2Ph), 3.14 (t, J = 6.8 Hz, 4 H, H6, H12), 2.38 (t, J = 5.9 Hz, 4 H, H8, H10), 1.66 (quint., J = 6 Hz, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 138.1, 137.9, 132.5, 128.79, 128.76, 128.2, 127.7, 127.0, 116.4, 59.2, 51.1, 49.7, 44.2, 24.9. **HCl Salt**. A solution of 0.83 g (1.2 mmol) of **ASPB127** in 10 mL of $CHCl_3$ was stirred with 2 mL of 1 M HCl in ether for 2 h. Ethyl acetate (20 mL) was added, and the resulting mixture was stored at −25 °C overnight. A precipitate was collected by vacuum filtration and washed with 10 mL of hexane, giving 0.84 g (97%) of **ASPB127**·HCl as a white solid, mp 175−176 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.9 (s, 1 H, NH^+), 7.88 (d, J = 8.3 Hz, 4 H, *o*-Bs), 7.73 (d, J = 8.3 Hz, 4 H, *m*-Bs), 7.66 (m, 2 H, *o*-Bn), 7.46 (m, 3 H, *m*,*p*-Bn), 5.36 (s, 2 H, C=CH_2), 4.31 (d, 2 H, CH_2Ph), 3.70 (s, 4 H, H2, H4), 3.16−3.06 (m, 8 H, H6, H8, H10, H12), 1.86 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, DMSO-d_6) δ 141.2, 136.2, 132.7, 131.1, 130.4, 129.4, 128.8, 127.5, 118.9, 57.1, 51.8, 48.0, 46.3, 20.1. IR (KBr) 3085 (w), 2976 (w), 2920 (w), 2380 (br), 1574 (m), 1471 (m), 1349 (s), 1163 (s), 1070 (m), 1008 (m), 899 (m), 746 (s), 607 (s). MS (FAB) *m*/*z* 710 (MH^+, 13), 712 (M+3, 26), 714 (M+5, 16). Anal. Calcd for $C_{29}H_{33}N_3S_2O_4Br_2$·

HCl·$CHCl_3$: C, 41.72; H, 4.09; N, 4.87; S, 7.41. Found: C, 41.78; H, 4.14; N, 5.21; S, 7.73.

9-Benzyl-3-methylene-1,5-bis(4-methoxybenzenesulfonyl)-1,5,9-triazacyclododecane (KKD023). A mixture of NaH (3.0 g of a 60% (w/w) slurry in mineral oil, 1.8 g NaH, 75 mmol, washed with hexane under nitrogen) and 500 mL of anhydrous DMF was stirred at 75 °C as a solution of 15.0 g (25 mmol) of **26**·HCl in 60 mL of anhydrous DMF was added. A solution of 3.0 g (25 mmol) of 3-chloro-2-chloromethyl-1-propene in 60 mL of anhydrous DMF was added dropwise over a period of 36 h by means of a syringe pump, then the reaction mixture was stirred at 60 °C for 12 h. The reaction mixture was allowed to cool to room temperature, then the solvent was removed on a rotary evaporator. A solution of the residue in 200 mL of $CHCl_3$ was washed with water (3 × 150 mL), then concentrated to dryness. Column chromatography on silica gel, eluting with 9:1 CH_2Cl_2/hexane, gave 13.0 g (85%) of **KKD023** as a light yellow solid, mp 158−159 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 9 Hz, 4 H, *o*-$ArSO_2$), 7.25 (m, 3 H, *m*,*p*-Bn), 7.13 (m, 2 H, *o*-Bn), 6.98 (d, J = 9 Hz, 4 H, *m*-$ArSO_2$), 5.23 (s, 2 H, C=CH_2), 3.88 (s, 6 H, OCH_3), 3.83 (s, 4 H, H2, H4), 3.39 (s, 2 H, CH_2Ph), 3.12 (t, J = 7 Hz, 4 H, H6, H12), 2.36 (t, J = 6 Hz, 4 H, H8, H10), 1.65 (quint., J = 6 Hz, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 139.7, 139.2, 131.1, 129.6, 129.1, 128.4, 127.2, 116.3, 114.6, 59.7, 55.9, 51.5, 50.3, 44.5, 25.4. IR (KBr): 3100 (w), 2943 (w), 1595 (s), 1577 (s), 1499 (s), 1444 (m), 1346 (s), 1262 (s), 1158 (s), 1117 (m), 1093 (m), 1023 (m), 936 (m), 831 (m), 719 (m), 688 (m), 558 (s). Anal. Calcd for $C_{31}H_{39}N_3O_6S_2$ $2H_2O$: C, 56.38; H, 6.67 N, 6.46. Found: C, 56.23; H, 6.55; N 6.45. MS (MALDI) *m*/*z* 613 (MH^+).

9-Benzyl-3-methylene-1,5-bis(*p*-butoxymethylbenzenesulfonyl)-1,5,9-triazacyclododecane (MFS117). A mixture of 2.88 g (4.27 mmol) of **27**, 40 mL of anhydrous DMF, and NaH (0.6 g of 60% (w/w) slurry in mineral oil, 0.36 g NaH, 14.5 mmol, washed with hexane under nitrogen) was stirred at room temperature as a solution of 1.0 g (8.0 mmol) of 3-chloromethyl-2-chloro-1-propene in 32 mL of anhydrous DMF was added by means of a syringe pump over a period of 10 h. The reaction mixture was stirred for 12 h at room temperature, then the solvent was removed by rotary evaporation (bath temp. 95 °C), giving 3.56 g of a yellow-brown, viscous oil. Flash column chromatography (1:2 to 1:1 EtOAc/hexane, (v/v)) of a 3.3 g sample gave 1.15 g (35%) of **MFS117** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 4 H, *o*-$ArSO_2$), 7.49 (d, J = 8.1 Hz, 4 H, *m*-$ArSO_2$), 7.23 (m, 3 H, *m*,*p*-Bn), 7.14 (d, J = 7.3 Hz, 2 H, *o*-Bn), 5.22 (s, 2 H, C=CH_2), 4.57 (s, 4 H, $ArCH_2O$), 3.85 (s, 4 H, H2, H4), 3.52 (t, J = 6.6 Hz, 4 H, OCH_2Pr), 3.39 (s, 2 H, CH_2Ph), 3.13 (d, J = 6.2 Hz, 4 H, H8, H10), 2.36 (d, J = 6.0 Hz, 4 H, H6, H12), 1.63 (m, 8 H, H7, H11, CH_2Et), 1.42 (sext., J = 7.7 Hz, 4 H, CH_2Me), 0.91 (t, J = 7.32 Hz, 6 H, CH_3). ^{13}C NMR, APT (75 MHz, $CDCl_3$) δ 144.4 (C), 129.0 (CH), 127.9 (CH), 127.6 (CH), 72.1 (CH_2), 71.1 (CH_2), 59.5 (CH_2), 51.4 (CH_2), 50.1 (CH_2), 44.4 (CH_2), 32.1 (CH_2), 19.7 (CH_2), 14.1 (CH_3). FT-IR (NaCl): 3264 (br, s), 3085, 3028, 2940, 2809, 1675 (s), 1545 (s), 1476, 1374, 1320, 1288, 1163, 1134, 878, 777, 729, 698, 578. Anal. Calcd for $C_{39}H_{55}N_3O_6S_2$·HCl: C, 61.44; H, 7.40; N, 5.51. Found: C, 61.05; H, 7.57; N, 5.47%. MS (FAB) *m*/*z* 726 (MH^+).

9-Benzyl-3-methylene-1,5-bis(*o*-nitrobenzenesulfonyl)-1,5,9-triazacyclododecane (AS123). A solution of 10.5 g (17.7 mmol) of **28** in 450 mL of anhydrous DMF was added slowly with stirring to NaH (1.42 g of a 60% (w/w) dispersion in mineral oil, 0.85 g NaH, 35 mmol, washed with hexane under nitrogen). The resulting brown solution was stirred at 55 °C and a solution of 2.46 g (19.7 mmol) of 3-chloro-2-chloromethyl-1-propene in 20 mL of anhydrous DMF was added over 14 h. The reaction mixture was stirred at room temperature under N_2 for 6 h, then the solvent was removed by rotary evaporation using a 68 °C water bath. A solution of the residue in 100 mL of $CHCl_3$ was washed with water (3 × 25 mL), 50 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated by rotary evaporation. A solution of the oily residue in 30 mL of 95:5 (v/v) chloroform/ethyl acetate, was filtered through 45 g of silica gel (60−200 μm), which was washed with 250 mL of 95:5 (v/v) chloroform/ethyl acetate. The combined filtrates were concentrated to dryness by rotary evaporation. A solution of the residue in 25 mL of ethyl acetate was diluted with 12 mL of hexane, causing a dark oil to separate. The cloudy yellow supernatant solution was decanted and the process was repeated twice. The combined supernatants were concentrated by rotary evaporation, and the residue was dried (1 mm), yielding 6.26 g (55%) of a golden foam. A solution of the crude **AS123** in 30 mL of chloroform was stirred at 0 °C as 15 mL of 1.0 M HCl in ether was added. The supernatant liquid was decanted from the gummy residue, which was triturated with 25 mL of acetone. The resulting precipitate was collected by filtration and recrystallized from $CHCl_3$, giving 3.03 g (25%) of **AS123**·HCl, mp 214−215 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.84 (br, 1 H, NH^+), 8.03 (d, J = 7.8 Hz, 4 H, Ns), 7.93 (t, J = 7.3 Hz, 2 H, Ns), 7.87 (t, J = 7.3 Hz, 2 H, Ns), 7.62 (m, 2 H, *o*-Bn), 7.44 (m, 3 H, *m*,*p*-Bn), 5.35 (s, 2 H, C=CH_2), 4.30 (d, J = 3.9 Hz, 2 H, CH_2Ph), 4.07 (d, J = 17 Hz, 4 H, H2, H4), 3.98 (d, J = 17 Hz, 2 H, H2′, H4′), 3.48 (m, 4 H, H8, H10), 3.07 (m, 4 H, H6, H12), 1.89 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 139.5, 134.9, 132.7. 131.3, 130.5, 130.2, 129.9, 129.4, 128.7, 124.6, 118.5, 57.6, 51.0, 47.1, 20.8. IR (KBr) 3093 (w), 3007 (w), 2952 (w), 2388 (br), 1594 (w), 1545 (s), 1459 (m), 1441 (m), 1361 (s), 1347 (s), 1163 (s), 1128 (s), 1061 (m), 1030 (m), 903 (m), 941 (m), 853 (s), 783 (s), 702 (s). Anal. Calcd for $C_{29}H_{33}N_5S_2O_8$·HCl: C, 51.21; H, 5.04; N, 10.30; S, 9.43. Found: C, 51.27; H, 5.15; N, 10.27; S, 9.66.

9-Benzyl-3-methylene-1,5-bis(*m*-nitrobenzenesulfonyl)-1,5,9-triazacyclododecane (AS121). A solution of 8.16 g (13.8 mmol) of **29** in 320 mL of anhydrous DMF was added slowly with stirring to NaH (1.29 g of a 60% (w/w) dispersion in mineral oil, 0.77 g NaH, 32 mmol, washed with hexane under nitrogen). The resulting brown solution was stirred at 45−50 °C and a solution of 1.90 g (15.2 mmol) of 3-chloro-2-chloromethyl-1-propene in 20 mL of anhydrous DMF was added over 12 h. The reaction mixture was stirred under N_2 for an additional 10 h, then the solvent was removed by rotary evaporation using a 65 °C water bath. A solution of the residue in 100 mL of $CHCl_3$ was washed with water (3 × 25 mL), 50 mL of saturated aqueous NaCl, dried ($MgSO_4$), and concentrated by rotary evaporation. A solution of the resulting thick brown oil in 15 mL of 9:1 (v/v) chloroform/ethyl acetate was filtered through 30 g of flash silica gel, washing with 185 mL of 9:1 (v/v) chloroform/ethyl acetate. The combined filtrates were concentrated by rotary evaporation and dried (1 mm). The residue was recrystallized from acetone, giving 2.26 g (25%) of **AS121** as a pale yellow solid, mp 180−181 °C. The mother liquor was diluted with 30 mL of ethanol and cooled to −25 °C to induce precipitation. Filtration and washing with 10 mL of ethanol gave 1.1 g (12%) of **AS121** as a yellow solid, mp 178−180 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 2 Hz, 2 H, *o*-Ns), 8.46 (d, J = 8.3 Hz, 2 H, *p*-Ns), 8.11 (d, J = 7.8 Hz, 2 H, *o*′-Ns), 7.78 (dd, J = 8.3, 7.8 Hz, 2 H, *m*-Ns), 7.24 (m, 3 H, *m*,*p*-Bn), 7.14 (m, 2 H, *o*-Bn), 5.22 (s, 2 H, C=CH_2), 3.92 (s, 4 H, H2, H4), 3.42 (s, 2 H, CH_2Ph), 3.21 (t, J = 6.6 Hz, 4 H, H6, H12), 2.41 (t, J = 5.4 Hz, 4 H, H8, H10), 1.71 (quint., J = 5.9 Hz, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 141.0, 138.9, 137.6, 132.6, 130.6, 128.8, 128.2, 127.1, 122.4, 116.7, 59.1, 51.1, 49.6, 44.5, 25.1. IR (KBr) 3102 (w), 2993 (w), 2950 (w), 2920 (w), 2859 (w), 2809 (w), 1607 (m), 1530 (s), 1466 (m), 1452 (m), 1354 (s), 1329 (s), 1175 (s), 1167 (s), 1124 (m), 1073 (m), 1040 (m), 941 (s), 880 (s), 798 (s), 736 (m), 720 (s), 685 (s). **AS121**·HCl. A solution of 0.80 g (1.2 mmol) of **AS121** in 15 mL of $CHCl_3$ was diluted slowly with 1.5 mL of 1.0 M HCl in ether. The mixture was stirred for 15 min and stored overnight at room temperature. Filtration and washing with 15 mL of $CHCl_3$ gave a solid that was recrystallized from acetone, giving 0.70 (86%) of **AS121**·HCl as a pale yellow solid, mp 168−170 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.90 (br, 1 H, NH^+), 8.57 (dd, J = 8.3, 1.0 Hz, 2 H, *p*-Ns), 8.45 (s, 2 H, *o*-Ns), 8.25 (d, J = 7.3 Hz, 2 H, *o*′-Ns), 7.97 (dd, J = 8.3, 7.8 Hz, 2 H, *m*-Ns), 7.66 (m, 2 H, *o*-Bn), 7.46 (m, 3 H, *m*,*p*-Bn), 5.40 (s, 2 H, C=CH_2), 4.33 (d, J = 5.4 Hz, 2 H, CH_2Ph), 3.79 (s, 4 H, H2, H4), 3.24−3.10 (m, 8 H, H6, H8, H10, H12), 1.94 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, DMSO-

d_6) δ 148.2, 140.8, 138.6, 133.1, 131.7, 131.1, 130.3, 129.4, 128.8, 127.9, 122.1, 119.0, 57.2, 51.7, 46.3, 20.2. IR (KBr) 3088 (w), 2956 (w), 2871 (w), 2480 (br), 1607 (w), 1532 (s), 1458 (m), 1355 (s), 1175 (s), 1127 (m), 1086 (w), 1002 (w), 931 (m), 908 (m), 879 (s), 748 (s), 717 (s), 674 (s). Anal. Calcd for $C_{29}H_{33}N_5S_2O_8$·HCl: C, 51.21; H, 5.04; N, 10.30; S, 9.43; Cl, 5.21. Found: C, 52.24; H, 5.79; N, 9.15.

9-Benzyl-3-methylene-1,5-bis(*p*-nitrobenzenesulfonyl)-1,5,9-triazacyclododecane (AS114). A solution of 9.16 g (15.5 mmol) of **30** in 275 mL of anhydrous DMF was added slowly with stirring to NaH (1.24 g of a 60% (w/w) dispersion in mineral oil, 0.74 g NaH, 31 mmol, washed with hexane under nitrogen). The resulting brown solution was stirred at room temperature and a solution of 1.94 g (15.5 mmol) of 3-chloro-2-chloromethyl-1-propene in 20 mL of anhydrous DMF was added over 12 h. The reaction mixture was stirred at room temperature for 24 h, then the solvent was removed by rotary evaporation using a hot water bath. A solution of the residue in 75 mL of $CHCl_3$ was washed with water (3 × 25 mL), 50 mL of saturated aqueous NaCl, dried ($MgSO_4$), filtered through 21 g of basic alumina (Woelm Act. 1, 80−200 mesh), washing with 75 mL of $CHCl_3$. The combined filtrates were concentrated by rotary evaporation. A mixture of crude **AS114**, 20 mL of $CHCl_3$, 20 mL of 2 N aq HCl, and 30 mL of saturated aqueous NaCl was shaken vigorously for 20 min, then the organic layer was separated and concentrated by rotary evaporation. The resulting yellow solid was triturated with 40 mL of acetone. The precipitate was collected by filtration, washed with acetone (2 × 10 mL) and water (4 × 25 mL), then dried overnight (1 mm), giving 5.82 g (55%) of **AS114**·HCl as a pale yellow solid, mp 198−200 °C. A mixture of **AS114**·HCl (1.26 g), 20 mL of CH_2Cl_2, 2 mL of 1.5 N aq NaOH, and 10 mL of saturated aqueous NaCl was stirred vigorously for 1 h. The organic layer was washed with 15 mL of saturated aqueous NaCl and dried ($MgSO_4$), then concentrated by rotary evaporation. The residue was purified by silica gel flash chromatography, eluting with 95:5 (v/v) chloroform/ethyl acetate, affording 0.76 g of **AS114** as a pale yellow film. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J = 9 Hz, 4 H, *m*-Ns), 7.98 (d, J = 9 Hz, 4 H, *o*-Ns), 7.27 (m, 3 H, *m*,*p*-Bn), 7.17 (m, 2 H, *o*-Bn), 5.22 (s, 2 H, C=CH_2), 3.93 (s, 4 H, H2, H4), 3.42 (s, 2 H, CH_2, CH_2Ph), 3.20 (t, J = 6 Hz, 4 H, H6, H12), 2.40 (t, J = 6 Hz, 4 H, H8, H10), 1.69 (quint., J = 6 Hz, 4 H, H7, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 144.5, 139.0, 137.6, 128.8, 128.4, 128.2, 127.1, 124.5, 116.6, 59.1, 51.1, 49.6, 44.4, 25.1. IR (KBr) 3105 (w), 3028 (w), 2936 (w), 2864 (w), 2807 (w), 1529 (s), 1458 (w), 1350 (s), 1309 (m), 1164 (s), 1090 (m), 1041 (w), 937 (w), 855 (m), 736 (m), 688 (m). **AS114**·HCl. A solution of 0.70 g (1.2 mmol) of **AS114** in 15 mL of $CHCl_3$ was stirred with 1.5 mL of 1.0 M HCl in ether for 15 min at room temperature, then the mixture was stored overnight at room temperature. A precipitate was collected by filtration, washed with 15 mL of $CHCl_3$, and dissolved in 25 mL of warm DMSO. The solution was stored overnight at room temperature. The resulting precipitate was collected by filtration, washed with 4 × 5 mL of water, and dried for 7 d at room temperature (0.4 mm), yielding 0.50 g of **AS114**·HCl as a white solid, mp 200−202 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.89 (br, 1 H, NH^+), 8.45 (d, J = 8.3 Hz, 4 H, *m*-Ns), 8.08 (d, J = 8.8 Hz, 4 H, *o*-Ns), 7.65 (m, 2 H, *o*-Bn), 7.46 (m, 3 H, *m*,*p*-Bn), 5.41 (s, 2 H, C=CH_2), 4.33 (d, J = 4.9 Hz, 2 H, CH_2Ph), 3.78 (s, 4 H, H2, H4), 3.25−3.07 (m, 8 H, H6, H8, H10, H12), 1.91 (m, 4 H, H7, H11). ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.2, 142.5, 140.5, 131.0, 130.2, 129.5, 129.1, 129.0, 128.8, 124.8, 119.1, 57.3, 51.6, 47.8, 46.5 20.3. IR (KBr) 3106 (w), 3031 (w), 2979 (w), 2940 (w), 2872 (w), 2449 (br), 2404 (br), 1607 (w), 1530 (s), 1478 (m), 1459 (m), 1350 (s), 1313 (m), 1165 (s), 1109 (m), 1089 (m), 1005 (w), 937 (m), 902 (m), 857 (m), 742 (s), 687 (s). MS (FAB) *m*/*z* 644 (MH^+). Anal. Calcd for $C_{29}H_{33}N_5S_2O_8$·HCl: C, 51.21; H, 5.04; N, 10.30. Found: C, 49.20; H, 5.53; N, 8.89.

9-Ethoxycarbonyl-3-methylenebis(*p*-bromobenzenesulfonyl)-1,5,9-triazacyclododecane (MFS034). A solution of 0.11 g (0.16 mmol) of **ASPB127** in 20 mL of THF was stirred at −78 °C, 1.0 mL of 1.7 M *t*-BuLi in pentane (**caution**: pyrophoric) was added dropwise over a period 5 min, and the reaction mixture was stirred for 20 min at −78 °C. **Note:** *t*-BuLi should not be necessary to form MFS034. Ethyl chloroformate (0.56 g, 5.2 mmol) was added and the reaction mixture was stirred for 2 h. Water (15 mL) was added and the resulting mixture was extracted with $CHCl_3$ (4 × 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to dryness by rotary evaporation. Flash column chromatography (1:2.5 to 1:1.6 (v/v) EtOAc/hexane) gave 26 mg of unreacted **ASPB127** and 41 mg (38%) of **MFS034** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 8 H, Bs), 5.20 (s, 2 H, C=CH_2), 4.50 (s, 4 H, CH_2Ph), 4.07 (q, J = 7.2 Hz, 2 H, OCH_2), 3.87 (s, 4 H, H2, H4), 3.34 (t, J = 6.7 Hz, 4 H, H6, H12 or H8, H10), 3.12 (m, 4 H, H8, H10 or H6, H12), 1.86 (m, 4 H, H7, H11), 1.21 (t, J = 7.2 Hz, 3 H, CH_3). ^{13}C NMR, APT (75 MHz, $CDCl_3$) δ 157.3 (C), 139.0 (C), 138.0 (C), 132.8 (CH_2), 128.9 (CH_2), 128.2 (C), 117.5 (CH_2), 61.6 (CH_2), 45.7 (CH_2), 45.5 (CH_2), 28.4 (CH_2), 14.9 (CH_3). IR (NaCl) 3089, 2980, 2870, 2253 (w), 1772 (w), 1692 (vs), 1571, 1470, 1389, 1342 (vs), 1163 (vs), 1068, 1009, 917, 795, 738 (s), 601. Anal. Calcd for $C_{25}H_{31}Br_2N_3O_6S_2$: C, 43.30; H, 4.51; N, 6.06. Found: C, 43.62; H, 4.49; N, 5.75. MS (FAB) *m*/*z* 694 (M+3).

3-Methylene-1,5-bis(4-methoxybenzenesulfonyl)-1,5,9-triazacyclododecane (KKD025). A mixture of 9.5 g (16 mmol) of **KKD023**, 2.5 g (17.6 mmol) of 1-chloroethyl chloroformate, and 50 mL of 1,2-dichloroethane was stirred and heated under reflux for 2 h, cooled to room temperature, then concentrated to dryness by rotary evaporation. A solution of the residue in 80 mL of methanol was heated under reflux overnight, cooled to room temperature, and filtered. The filtrate was concentrated to dryness by rotary evaporation. A solution of the residue in 60 mL of $CHCl_3$ was stirred with 60 mL of 2 N aq NaOH for 4 h. The $CHCl_3$ layer was dried (Na_2SO_4) and concentrated by rotary evaporation. Column chromatography on silica gel, eluting with 5:95 (v/v) methanol/CH_2Cl_2 gave 6.7 g (83%) of **KKD025** as a white solid, mp 84−86 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 9 Hz, 4 H, *o*-$ArSO_2$), 7.00 (d, J = 9 Hz, 4 H, *m*-$ArSO_2$), 5.04 (s, 2 H, C=CH_2), 3.89 (s, 6 H, OCH_3), 3.79 (s, 4 H, H2, H4), 3.18 (t, J = 6 Hz, 4 H, H6, H12), 2.62 (t, J = 6 Hz, 4 H, H8, H10), 1.65 (m, 5 H, H7, H9, H11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 138.9, 131.0, 129.8, 115.5, 114.6, 55.8, 52.1, 44.8, 43.7, 28.3. IR (KBr): 3340 (br), 3098 (w), 2944 (w), 2840 (w), 1596 (s), 1497 (s), 1461 (m), 1334 (s), 1259 (s), 1157 (s), 1093 (m), 1025 (m), 915 (w), 835 (m), 806 (m), 690 (m), 599 (s). Anal. Calcd for $C_{24}H_{33}N_3O_6S_2$: C, 55.05; H, 6.35; N, 8.02. Found: C, 54.85; H, 6.16; N 7.95. MS (MALDI) *m*/*z* 524 (MH^+).

9-(3-Methylbutyl)-3-methylene-1,5-bis(4-methoxybenzenesulfonyl)-1,5,9-triazacyclododecane (KKD027). A mixture of 0.59 g (1.1 mmol) of **KKD025**, 15 mL of acetonitrile, 0.10 g (0.66 mmol) of NaI, 0.18 g (1.7 mmol) of Na_2CO_3, and 0.22 g (1.7 mmol) of 1-bromo-3-methylbutane was stirred and heated under reflux for 4 h. The reaction mixture was cooled and filtered, washing the solids with 20 mL of acetonitrile. The combined filtrates were concentrated by rotary evaporation. A solution of the resulting thick yellow oil in 15 mL of CH_2Cl_2 was stirred vigorously for 5 min with 10 mL of saturated aqueous $Na_2S_2O_3$. The organic layer was washed with saturated aqueous NaCl (2 × 10 mL). The combined aqueous layers were extracted with CH_2Cl_2. The combined organic solutions were dried (Na_2SO_4) and concentrated by rotary evaporation. Column chromatography on silica gel, eluting with 6:4 (v/v) ethyl acetate/CH_2Cl_2 gave 0.38 g (58%) of **KKD027** free base as a white solid, which was converted to its HCl salt as described for CADA·HCl, mp 133−135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 9 Hz, 4 H, *o*-$ArSO_2$), 6.99 (d, J = 9 Hz, 4 H, *m*-$ArSO_2$), 5.13 (s, 2 H, C=CH_2), 3.88 (s, 6 H, OCH_3), 3.79 (s, 4 H, H2, H4), 3.13 (t, J = 7 Hz, 4 H, H6, H12), 2.33 (t, J = 6 Hz, 4 H, H8, H10), 2.24 (t, J = 7 Hz, 2 H, NCH_2*i*Bu), 1.64 (quint., J = 5 Hz, 4 H, H7, H11), 1.5 (m, 1 H, $CHMe_2$), 1.17 (q, J = 8 Hz, 2 H, CH_2*i*Pr), 0.84 (d, J = 7 Hz, 6 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 138.2, 130.3, 129.4, 128.8, 128.2, 116.1, 114.3, 55.6, 51.6, 51.2, 49.6, 44.0, 35.2, 26.2, 24.8, 22.6. IR (KBr) 3416 (br), 2957 (m), 2871 (w), 2398 (br), 1596 (s), 1577, 1498 (s), 1336 (s), 1306 (s), 1261 (s), 1156 (s), 1112 (m), 1091 (m), 1021 (m), 836 (m), 806

(m), 690 (m), 558 (s). Anal. Calcd for $C_{29}H_{43}N_3O_6S_2 \cdot HCl \cdot 0.5H_2O$: C, 54.48; H, 7.03; N, 6.57. Found: C, 54.14; H, 6.30; N 6.54. MS (MALDI) *m*/*z* 594 (M − Cl).

3-(2-Methyltetrahydropyrimidin-1-yl)propylamine (32). A mixture of 22 g (0.17 mol) of bis(3-aminopropyl)amine and 800 mL of $CHCl_3$ was stirred at 3 °C and 7.4 g (0.17 mol) of acetaldehyde was added dropwise. The reaction mixture was stirred for 5 min at this temperature, then the solvent was removed by rotary evaporation. Drying (0.5 mm) and vacuum distillation (110 mm, 100 °C) gave 22 g (83%) of **32** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.19 (q, $J = 6$ Hz, 1 H, CHMe), 3.08 (m, 2 H, NCH_2), 2.72 (m, 4 H, NCH_2), 2.29 (m, 2 H, NCH_2), 1.63 (quint., $J = 7$ Hz, 4 H, CCH_2C), 1.29 (bs, 3 H, NH, NH_2), 1.23 (d, $J = 6$ Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.4, 51.8, 50.5, 48.1, 45.1, 41.0, 40.7, 34.0, 30.6, 27.2, 20.6. IR (NaCl) 292 (br), 2931 (m), 1576 (s), 1473 (s), 1380 (m), 1315 (m), 1077 (w), 902 (w), 815 (w). MS (FAB) *m*/*z* 158 (MH^+).

3-[2-Methyl-3-(*p*-toluenesulfonyl)tetrahydropyrimidin-1-yl]-propylamine (33). A mixture of 1.14 g (7.3 mmol) of **32** and 25 mL of 1:1:2 (v/v/v) 2 M aq NaOH/THF/water was stirred at 0 °C and a solution of 1.4 g (7.3 mmol) of *p*-toluenesulfonyl chloride in 20 mL of 1:1:2 (v/v/v) 2 aq M NaOH/THF/water was added in one portion. The reaction mixture was stirred overnight at room temperature, then it was saturated with NaCl. The organic layer was dried (Na_2SO_4) and concentrated by rotary evaporation. Drying (0.5 mm) gave 0.8 g (35%) of **33** as a semisolid oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, $J = 8$ Hz, 2 H, *o*-Ts), 7.30 (d, $J = 8$ Hz, 2 H, *m*-Ts), 3.02 (m, 5 H, NCH_2), 2.17 (m, 2 H, NCH_2), 2.43 (s, 3 H, $ArCH_3$), 2.18 (m, 2 H, NCH_2), 1.63 (m, 2 H, CCH_2C), 1.55 (m, 2 H, CCH_2C), 1.23 (bs, 2 H, NH_2), 1.13 (d, $J = 6$ Hz, 3 H, CH_3). IR (KBr) 3285 (s), 3028 (s), 2788 (br), 1605 (s), 1435 (s), 1298 (s), 1159 (s), 913 (s), 715 (s), 561 (s). MS (FAB) *m*/*z* 312 (MH^+).

***N*-(5-Dimethylaminonaphthalene-1-sulfonyl)-*N*′-(*p*-toluenesulfonyl)bis(3-aminopropyl)amine (34).** A mixture of 5.96 g (19.2 mmol) of **33,** 5.17 g (19.2 mmol) of dansyl chloride, 120 mL of CH_2Cl_2, and 120 mL of saturated aqueous Na_2CO_3, was stirred for 18 h at room temperature. Sodium hydroxide (4.0 g, 0.1 mol) was added to the reaction mixture and stirring was continued for 2 h. The organic layer was evaporated to dryness. Two sequential column chromatograms on silica gel, eluting with ethyl acetate, then 1:9 (v/v) methanol/$CHCl_3$ gave 5.0 g (50%) of **34**, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, $J = 8$ Hz, 1 H, 2-Dn), 8.30 (d, $J = 8$ Hz, 1 H, 4-Dn), 8.25 (d, $J = 8$ Hz, 1 H, 8-Dn), 7.75 (d, $J = 8$ Hz, 2 H, *o*-Ts), 7.51 (m, 2 H, 3,7-Dn), 7.29 (d, $J = 8$ Hz, 2 H, *m*-Ts), 7.17 (d, $J = 7$ Hz, 1 H, 6-Dn), 3.00 (m, 4 H, H3), 2.89 (s, 6 H, NCH_3), 2.58 (q, $J = 6$ Hz, 4 H, H1), 2.41 (s, 3 H, $ArCH_3$), 1.62 (m, 5 H, CCH_2C, NH). IR (NaCl) 3294 (m), 2937 (m), 2866 (m), 1573 (m), 1454 (m), 1321 (s), 1158 (s), 1092 (m), 791 (m). MS (FAB) *m*/*z* 519 (MH^+).

***N*-(5-Dimethylaminonaphthalene-1-sulfonyl)-*N*′-(*p*-toluenesulfonyl)bis(3-aminopropyl)benzylamine (35).** A mixture of 2.0 g (3.9 mmol) of **34,** 35 mL of acetonitrile, 0.1 g (0.66 mmol) of sodium iodide, 0.40 g (3.8 mmol) of sodium carbonate, and 0.49 g (3.9 mmol) of benzyl chloride was stirred and heated under reflux for 4 h. The reaction mixture was cooled to room temperature and filtered, washing with 50 mL of acetonitrile. The combined filtrates were concentrated by rotary evaporation. A solution of the resulting viscous oil in 50 mL of CH_2Cl_2 was stirred vigorously for 5 min with 58 mL of saturated aqueous $Na_2S_2O_3$. The organic layer was washed with saturated aqueous NaCl (2 × 70 mL). The combined aqueous layers were extracted with CH_2Cl_2. The combined CH_2Cl_2 solutions were dried ($MgSO_4$) and concentrated by rotary evaporation. Column chromatography on alumina, eluting with ethyl acetate/hexane gave a yellow oil, which gradually solidified upon drying at 65 °C (0.5 mm, 3 d) to give 1.19 g (50%) of **35**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, $J = 8$ Hz, 1 H, 2-Dn), 8.29 (d, $J = 8$ Hz, 1 H, 4-Dn), 8.19 (d, $J = 8$ Hz, 1 H, 8-Dn), 7.67 (d, $J = 8$ Hz, 2 H, *o*-Ts), 7.48 (t, $J = 8$ Hz, 2 H, 3,7-Dn), 7.22 (m, 5 H, *m*-Ts, *m*,*p*-Bn), 7.13 (m, 3 H, 6-Dn, *o*-Bn), 5.99 (bs, 1 H, DnNH), 5.90 (bs, 1 H, TsNH), 3.32 (s, 2 H, CH_2Ph), 2.85 (s, 6 H, NCH_3), 2.85 (m, 4 H, H3), 2.38 (s, 3 H, $ArCH_3$), 2.27 (t, $J = 7$ Hz, 4 H, H1), 1.50 (quint., $J = 6$ Hz, 4 H, H2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 143.3, 138.4, 137.2, 135.2, 130.4, 130.0, 129.8, 129.4, 129.2, 128.6, 128.4, 127.3, 127.2, 123.3, 119.2, 115.3, 58.7, 51.9, 45.5, 42.4, 26.3, 26.0, 21.6. MS (MALDI) *m*/*z* 609 (MH^+). **35**·HCl: IR (KBr) 3374 (w), 3095 (m), 2967 (m), 2464 (br), 1604 (m), 1454 (s), 1325 (m), 1147 (m), 1074 (m), 795 (m), 572 (s). Anal. Calcd for $C_{32}H_{40}N_4O_4S_2 \cdot 2HCl$: C, 56.38; H, 6.21; N, 8.22. Found: C, 55.99; H, 6.32; N, 7.91.

***N*-(5-Dimethylaminonaphthalene-1-sulfonyl)-*N*′-(*p*-toluenesulfonyl)bis(3-aminopropyl)cyclohexylmethylamine (36).** A mixture of 0.25 g (0.41 mmol) of **34**, 50 mL of acetonitrile, 0.1 g (0.66 mmol) of sodium iodide, 0.40 g (3.8 mmol) of sodium carbonate, and 0.38 g (2.1 mmol) of bromomethylcyclohexane was stirred and heated under reflux for 4 h. The reaction mixture was cooled to room temperature and filtered, washing with 50 mL of acetonitrile. The combined filtrates were concentrated by rotary evaporation. A solution of the resulting viscous oil in 50 mL of CH_2Cl_2 was stirred vigorously for 5 min with 58 mL of saturated aqueous $Na_2S_2O_3$. The organic layer was washed with saturated aqueous NaCl (2 × 70 mL). The combined aqueous layers were extracted with CH_2Cl_2. The combined CH_2Cl_2 solutions were dried ($MgSO_4$) and concentrated by rotary evaporation. Column chromatography on alumina, eluting with ethyl acetate/hexane, followed by drying (65 °C, 0.5 mm, 3 d) gave 0.25 g (19%) of **36** as a yellow semisolid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, $J = 9$ Hz, 1 H, 2-Dn), 8.33 (d, $J = 9$ Hz, 1 H, 4-Dn), 8.22 (d, $J = 9$ Hz, 1 H, 8-Dn), 7.71 (d, $J = 8$ Hz, 2 H, *o*-Ts), 7.51 (m, 2 H, 3,7-Dn), 7.28 (d, $J = 8$ Hz, 2 H, *m*-Ts), 7.18 (d, $J = 7$ Hz, 1 H, 6-Dn), 5.81 (bs, 2 H, NH), 2.96 (m, 4 H, H3), 2.88 (s, 6 H, NCH_3), 2.30 (m, 4 H, H1), 2.01 (d, $J = 7$ Hz, 2 H, CH_2), 1.59 (m, 10 H, CH_2), 1.30 (m, 1 H, CH), 1.13 (quint., $J = 7$ Hz, 2 H, H2), 0.77 (quint., $J = 7$ Hz, 2 H, H2′). IR (NaCl) 3264 (br), 2918 (m), 2849 (w), 1664 (w), 1465 (m), 1318 (s), 1155 (s), 1086 (m), 913 (w), 795 (m), 642 (w). MS (MALDI) *m*/*z* 615 (MH^+).

9-Benzyl-1-(5-dimethylaminonaphthalene-1-sulfonyl)-3-methylene-5-(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (KKD015). A solution of 0.5 g (0.8 mmol) of **35** in 5 mL of anhydrous DMF was added to a stirred mixture of NaH (0.13 g of a 60% (w/w) slurry in mineral oil, 78 mg of NaH, 3.3 mmol, washed with hexane under nitrogen) and 40 mL of anhydrous DMF at 75 °C. A solution of 0.13 g (0.93 mmol) of 3-chloro-2-chloromethyl-1-propene in 20 mL of anhydrous DMF was added over 6 h by means of a syringe pump. The reaction mixture was stirred at 60 °C for 12 h, then cooled to room temperature, and the solvent was removed by means of a rotary evaporator. A solution of the residue in 75 mL of $CHCl_3$ was washed with water (3 × 50 mL), then concentrated to dryness by rotary evaporation. Chromatography on silica gel, eluting with 2:3 (v/v) ethyl acetate/hexane and recrystallization from diethyl ether/hexane gave 0.14 g (27%) of **KKD015**, mp 194−195 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, $J = 8$ Hz, 1 H, 2-Dn), 8.27 (d, $J = 8$ Hz, 1 H, 4-Dn), 8.21 (d, $J = 8$ Hz, 1 H, 8-Dn), 7.64 (d, $J = 8$ Hz, 2 H, *o*-Ts), 7.53 (m, 2 H, H6, 3,7-Dn), 7.25 (m, 4 H, *o*,*m*-Bn), 7.19 (m, 2 H, 6-Dn, *p*-Bn), 5.19 (m, 2 H, C=CH_2), 4.13 (s, 2 H, H2), 3.66 (s, 2 H, H4), 3.37 (s, 2 H, CH_2Ph), 3.32 (t, $J = 7$ Hz, 2 H, H12), 2.99 (t, $J = 7$ Hz, 2 H, H6), 2.88 (s, 6 H, NCH_3), 2.44 (s, 3 H, $ArCH_3$), 2.44 (t, $J = 7$ Hz, 2 H, H10), 2.20 (t, $J = 7$ Hz, 2 H, H8), 1.80 (quint., $J = 7$ Hz, 2 H, H11), 1.47 (quint., $J = 7$ Hz, 2 H, H7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 143.7, 139.6, 138.6, 135.1, 134.7, 130.6, 130.3, 129.9, 128.9, 128.3, 127.6, 127.1, 123.3, 119.6, 116.7, 115.4, 59.3, 53.8, 50.4, 49.3, 48.5, 45.6, 45.3, 42.6, 25.9, 24.3, 21.7. IR (KBr) 3067 (w), 2945 (m), 2822 (m), 1577 (m), 1449 (m), 1309 (s), 1164 (s), 1092 (s), 941 (m), 779 (m), 679 (m), 550 (s). Anal. Calcd. for $C_{36}H_{44}N_4O_4S_2$: C, 65.43; H, 6.71; N, 8.45. Found: C, 65.08; H, 6.53; N, 8.43. MS (MALDI) *m*/*z* 661 (MH^+).

9-Cyclohexylmethyl-1-(5-dimethylaminonaphthalene-1-sulfonyl)-3-methylene-5-(*p*-toluenesulfonyl)-1,5,9-triazacyclododecane (KKD016). A solution of 0.25 g (0.41 mmol) of **36** in 5 mL of anhydrous DMF was added to a stirred mixture of NaH (0.06 g of a 60% (w/w) slurry in mineral oil, 36 mg of NaH, 1.6 mmol, washed

with hexane) and 40 mL of anhydrous DMF at 75 °C. A solution of 0.05 g (0.41 mmol) of 3-chloro-2-chloromethyl-1-propene in 20 mL of anhydrous DMF was added over 6 h by means of a syringe pump. The reaction mixture was stirred at 60 °C for 12 h and cooled to room temperature, and the solvent was removed on a rotary evaporator. A solution of the residue in 75 mL of $CHCl_3$ was washed with water (3 × 50 mL) and concentrated to dryness. Chromatography on silica gel, eluting with 3:7 (v/v) ethyl acetate/hexane gave 0.10 g (35%) of **KKD016** as a viscous yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 8 Hz, 1 H, 2-Dn), 8.32 (d, J = 8 Hz, 1 H, 4-Dn), 8.24 (d, J = 8 Hz, 1 H, 8-Dn), 7.63 (d, J = 8 Hz, 2 H, *o*-Ts), 7.53 (m, 2 H, 3,7-Dn), 7.31 (d, J = 8 Hz, 2 H, *m*-Ts), 7.17 (d, J = 7 Hz, 1 H, 6-Dn), 5.12 (m, 2 H, C=CH_2), 4.08 (s, 2 H, H2), 3.62 (s, 2 H, H4), 3.38 (t, J = 7 Hz, 2 H, H12), 2.98 (t, J = 7 Hz, 2 H, H6), 2.88 (s, 6 H, NCH_3), 2.43 (s, 3 H, $ArCH_3$), 2.31 (t, J = 6 Hz, 2 H, H10), 2.16 (t, J = 5 Hz, 2 H, H8), 1.95 (d, J = 9 Hz, 2 H, CH_2Cy), 1.63 (m, 8 H, H7, Cy), 1.13 (m, 3 H, H11, Cy), 0.70 (quint., J = 7 Hz, 2 H, Cy). MS (MALDI) *m*/*z* 666 (M^+, 10). **KKD016**·HCl: IR (KBr) 3419 (br), 2911 (s), 2839 (m), 2359 (br), 1594 (m), 1454 (s), 1309 (s), 1142 (s), 896 (m), 796 (s), 539 (s). Anal. Calcd for $C_{36}H_{50}N_4O_4S_2$·2HCl·3H_2O: C, 54.47; H, 7.31; N, 7.05. Found: C, 54.80; H, 6.89; N, 7.15.

Molecular Modeling. All molecular modeling calculations were performed using the SYBYL program.[42] Energy minimizations were carried out using the Tripos force field,[43] Gasteiger−Hückel charges, and the Powel method, electrostatics included. The X-ray structure of CADA was energy minimized, then modified to produce the data set of 30 structures, each of which was also energy minimized. The structures were aligned with CADA by minimizing the least-squares sum of five deviations, consisting of the three ring nitrogens and two sulfur atoms. Molecular surfaces were mapped using a positively charged sp^3 carbon probe atom. Partial least squares (PLS) analysis[44,45] was used to derive the model, using CoMFA descriptors as independent variables and pIC_{50} as the dependent variable. The leave-one-out method[46] was used for validation with no column filtering. PLS analyses of CoMSIA indices[39,40] were run independently of other indices using the same settings as in the CoMFA PLS. Color coded contour plots in Figure 4 were generated from a CoMFA model produced from all activity data in Table 2 and consist of std*coeff CoMFA steric and electrostatic contour plots generated by SYBYL.

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Supporting Information Available: Numbered thermal ellipsoid plots and X-ray crystallographic data for four compounds, **15**, **ASPB127**, CADA, and **KKD023**. This material is available free of charge via the Internet at http://pub.acs.org.

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