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Substituted Diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecanes as Stable Caged Proton Sponges

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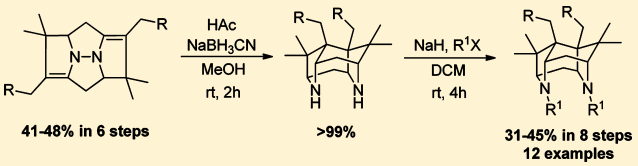
Supporting Information

ABSTRACT: Herein, we report a molecular framework design differing significantly from the traditional topology of proton sponges. We developed a synthetic approach to the preparation of caged secondary amines by acid-catalyzed rearrangement of fused tetracyclic heterocycles synthesized by intramolecular criss-cross cycloaddition. Alkylation of amines led to air nonsensitive diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecanes (DTDs) with rare alicyclic scaffolding in high overall yields. Their pK_{BH}+ values were determined by transprotonation experiments as well as their sensitivity toward nucleophiles, acids and bases. Crystal structures of free base and monoprotonated form are discussed.



INTRODUCTION

Superbasic compounds have attracted a great deal of attention in organic chemistry.[1] This useful group includes amidines[2] (DBN, DBU), guanidines[3] (TMG, TMGN), Schwesinger's[4] phosphazenes (P1−P7), Verkade's proazaphosphatranes,[5] proton sponges (PS),[6] etc. The considerable basicity of these compounds is mainly due to effective resonance stabilization of protonated forms. However, the PS concept differs significantly from all the other bases. In general, PS are organic diamines with unusually high basicity, in which protonation can result in the loss of a lone pair/lone pair repulsion and leads to the formation of an intramolecularly hydrogen-bonded monoprotonated ion.[7] They remain the focus of much current research[8] and are also the subject of much interest among theoretical chemists.[9]

In 1968, Alder et al.[6a] challenged our classical view of acid−base properties with their discovery of the very first PS, 1,8-bis(dimethylamino)naphthalene (DMAN) **1**, which showed a level of basicity about 10 million times higher than similar organic amines. However, significantly higher basicity was achieved by the combination of highly basic guanidine (TMGN) **2**[3] or Schwesinger's phosphazene (HMPN) **3**[10] with Alder's 1,8-disubstituted naphthalene spacer (Figure 1). The latter is currently the most basic representative of this class of PS.

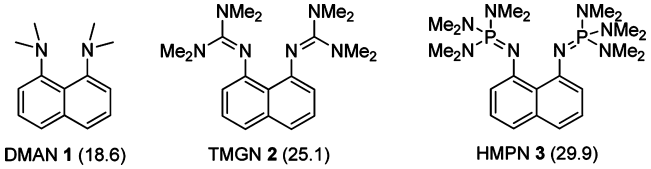


Figure 1. Naphthalene proton sponges (pK_{BH}+ in MeCN).

Further extension of the PS concept has led to the design of a variety of molecular frameworks which differ from the classical naphthalene PS. For instance, Toom[11] found superbasic properties for bispidines (3,7-diazabicyclo[3.3.1]nonanes) **4** and **5** (Figure 2). Structurally related tetraazatricyclooctanes **6**

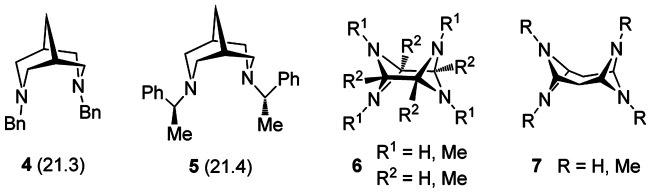


Figure 2. Examples of alicyclic proton sponges (pK_{BH}+ in MeCN).

and tetraazatricyclodecanes **7** designed by Estrada[12] were predicted to have pK_{BH}+ values in water larger by 5−11 units than DMAN **1**.

Our synthetic approach, consisting of several steps, starts with the preparation of allenyl aldehydes **8** and their symmetrical allenyl azines **9**. These compounds undergo intramolecular criss−cross cycloaddition in dry boiling xylene forming stable tetracyclic heterocycles **10** (Scheme 1).[13] Investigation of their chemical properties showed interesting behavior. In the presence of alkyl halide or a reducing agent ($NaBH_3CN$) in an acidic environment they undergo a rearrangement to caged compounds **11** or **12**, respectively.[14,15] These new heterocycles are composed of two five-membered and two six-membered rings (Scheme 2). The reaction mechanism can be explained by the formation of quaternary ammonium salt in the first step followed by polarized N−N bond cleavage and subsequent rearrangement leading to the creation of a new C−C bond.[14]

We have already published the preparation of substituted diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecanes (DTD) **13**.[15] Later,

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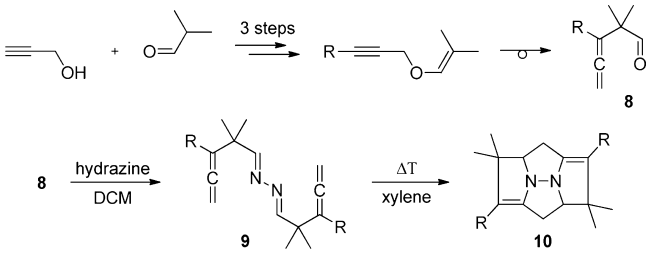
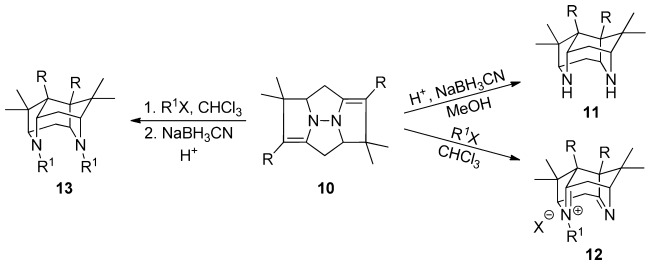
Scheme 1. Preparation of Criss-Cross Cycloadducts 10



Scheme 2. Transformations of Criss-Cross Cycloadducts 10

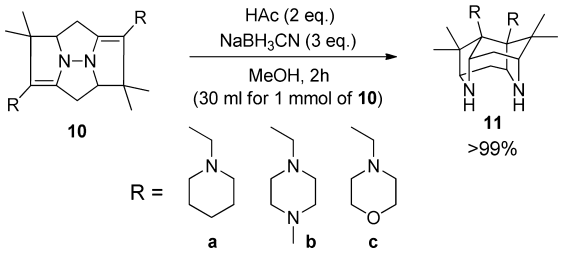


we discovered that these alicyclic fully saturated caged bidentate tertiary amines can serve as a new type of PS with a rare and rigid framework. Our assumption was proven when transprotonation experiments in acetonitrile showed approximate pK_{BH}+ values ranging between 20 and 21 units (R = phenyl, R^1 = benzyl).[15] Because only two examples of **13** were prepared, and in nonstandard conditions, we decided to improve the procedure and prepare a series of similar compounds with differing substitutions at basic nitrogen centers and then to determine their pK_{BH}+ values.

RESULTS AND DISCUSSION

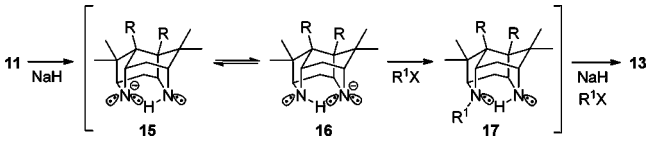
Our recent idea for the preparation of PS **13** is based on the application of compounds **11** in contrast to our previous published procedure (Scheme 2).[15] Because heterocycles **11** are prepared as hydrochlorides,[14] we propose here a new more suitable synthetic protocol for direct free base preparation. The optimized conditions are shown in Scheme 3, where

Scheme 3. Acid-Promoted Rearrangement of 10 to Amines 11



compounds **11** are isolated as pure colorless caged secondary amines in excellent yields. For our study, we selected amine **11c** with morpholinomethyl moiety and several *para*-substituted benzyl bromides, allyl bromide and methyl iodide (R^1X) as the model compounds. This amine **11c** was synthesized in 6 steps with 34% overall yield and, therefore, can be easily prepared even in multigram-scale. We believe that the reaction mechanism for PS **13** synthesis includes two steps (Scheme 4). At first, deprotonation of amine **11c** by NaH produces

Scheme 4. Pathway of DTDs 13 Synthesis



negatively charged species **15** and **16**, which establish a relatively stable equilibrium pair. Although in the presence of an alkylating agent we immediately isolate the final product **13**, we suppose formation of the intermediate **17**, which has never been observed.

Sponges **13**, prepared this way (Table 1), crystallize in minutes from acetone (although kept in a freezer overnight) in very good to excellent yields as colorless, light yellow (**13k**) or orange (**13d**) solids. They are nonsensitive to air and stable in solution for several weeks. We noticed their very good solubility in chloroform in the form of free base but their insolubility in acetonitrile. For the protonated forms **14** the situation is exactly opposite. This behavior is useful when crystallography measurements are necessary for the structure support, because after the deprotonation of **14** in CH_3CN solution, the free bases **13** crystallize as monocrystalline solids suitable for X-ray analysis.

To determine experimental pK_{BH}+ values (pK_a of the conjugated acids) of compounds **13a–k**, transprotonation experiments on **14a–k** with known organic bases were carried out by ^{1}H NMR spectroscopy at 30 °C. Compounds **14** were prepared by the treatment of **13** with equimolar amounts of ammonium perchlorate at 50 °C in dry acetonitrile in quantitative yields. As reference bases, 2-phenyl-1,1,3,3-tetramethylguanidine (PhTMG, pK_{BH}+ (MeCN) = 20.84)[16] and Alder's DMAN[6a] (Figure 1) were used. Each individual measurement was repeated at least three times, including the integration of appropriate signals at different ratios (see Supporting Information). The results showed that the basic nitrogen center is much more influenced by electron-withdrawing substituents than by electron-donating groups, where pK_{BH}+ values are uniform (Table 1). Thus, the basicity value can be very simply modulated within more than 3 orders of magnitude by changing different *para*-substitutions at benzyl bromides. We observed only one exception, namely for product **14k**, where we recorded an unexpected drop in basicity of approximately one-half of an order of magnitude. This anomaly can be explained by the interaction of sulfur atoms of other molecules with caught protons, which probably tends to weaken the intramolecular hydrogen bridge and results in slightly decreased basicity.

Protonation of **13** to **14** is reflected in both ^{1}H and ^{13}C NMR by the small degree of deshielding of their signals with typical broad singlet of NH proton ranging between 12 and 13 ppm (CD_3CN). This moderate downfield shift, similar to bispidines **4** and **5** (Figure 2) compared to δ ~18.6 ppm (CD_3CN) in DMAN and other naphthalene-based proton sponges,[6d] is assigned to the formation of a weaker, unsymmetrical hydrogen bridge. An excess of NH_4ClO_4 never leads to bis-protonated products. With deuterium oxide, we observed the complete exchange of "acidic" hydrogen in **14** for deuterium without any hydrolysis or decomposition, even with the temperature elevated to 75 °C. On the other hand, **13** forms in an excess of D_2O stable hydrates, such as $[\mathbf{13}+D]^+[OD]^-$. This hydration is accompanied by similar deshielding of NMR signals, as was

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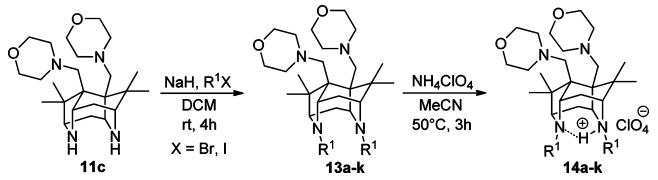
Table 1. Formation of DTDs 13 and Their Conjugated Acids 14 with Determined pK_{BH}+ Values



DTDs **13**/**14**	R^1	yield (**13**) [%]	pK_{BH}+ (**14**) (CD_3CN)
a	Me	89	22.6 ± 0.1
b	allyl	85	22.4 ± 0.1
c	benzyl	91	21.7 ± 0.1
d	*p*-NO_2-benzyl	80	19.0 ± 0.1
e	*p*-CN-benzyl	87	19.4 ± 0.1
f	*p*- CF_3-benzyl	89	20.0 ± 0.1
g	*p*-F-benzyl	87	21.1 ± 0.1
h	*p*-Me-benzyl	81	22.1 ± 0.1
i	*p*-*t*Bu-benzyl	77	22.0 ± 0.1
j	*p*-MeO-benzyl	75	22.2 ± 0.1
k	*p*-MeS-benzyl	79	21.6 ± 0.1

mentioned for protonated forms **14**. Actually, particular signals of DTDs were assigned by 2D NMR experiments (DQF-COSY, HMQC, HMBC). In the presence of trifluoroacetic acid (ca. 5 equiv), **13** afforded only monoprotonated trifluoroacetates **14**, but perchlorates **14** performed species protonated even at morpholine nitrogen atoms. Under very basic conditions ($KOH/D_2O/DMSO$-d_6), we did not observe any decomposition at the cage skeleton, even within a one week period at 75 °C. The nucleophilicity of **13** was tested by the addition of propyl iodide in excess (ca. 10 equiv). While in these conditions the alkylated species were never observed, DTDs were completely converted to the protonated molecules $[\mathbf{13}+H]^+[I]^-$ under decomposition of propyl iodide. Moreover, compounds **13** were absolutely resistant toward very reactive methyl iodide.

The molecular structure of free base **13c** (Figure 3) shows a rather strong deviation from the expected symmetry as a

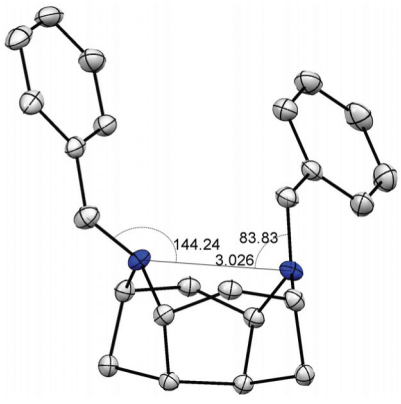


Figure 3. ORTEP representation of **13c** shown at the 50% probability level (upside-down view; hydrogen atoms, methyl and morpholinomethyl groups are omitted for clarity).

consequence of the electronic and steric repulsion between the two lone electron pairs. This repulsion means that the angles defined by two nitrogen atoms and the adjacent benzylic methylene carbon at both sides of the molecule differ significantly one from another (~84 vs ~144°). Moreover, compared to other PS previously discussed,[6c,e] DTDs reveal a large nonbonding distance of 302.6 pm between the nitrogen acceptor atoms, similarly as in molecules of bispidines **4** and **5** (Figure 2).[11]

Before we started focusing on amine **11c** (Scheme 3), we prepared PS **13l** bearing piperidine moiety (R) and benzyl substituents like R^1. In an excess of HCl in acetone solution, the free base **13l** immediately crystallized as its conjugated acid **14l** and was determined by X-ray analysis (Figure 4). It revealed a

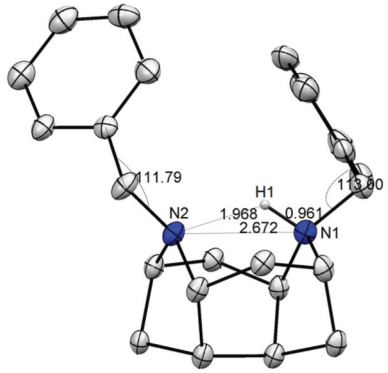


Figure 4. ORTEP representation of **14l** shown at the 30% probability level (upside-down view; hydrogen atoms except for the captured proton including chloride anion, methyl and piperidinomethyl groups are omitted for clarity).

strongly unsymmetrical, nonlinear intramolecular hydrogen bridge (IHB) (N1–H1 ~ 96 pm; N2–H1 ~ 197 pm; N1–H1–N2–128°). Because of the influence of the IHB, the nonbonding distance between the nitrogen atoms N1 and N2 was reduced to 267.2 pm, which was slightly higher than the average value of 258 pm in $DMANH^+$ structures.[6d] At the same time, the deviation mentioned above at **13c** disappeared and angles relaxed substantially toward normal values.

The crystal structure of the product **13e** (Figure 5) with cyano substitution is evidence of the decreased basicity of PS with electron-withdrawing groups. The angles among nitrogen atoms and benzylic methylene carbon at both sides of the molecule are almost the same and the nonbonding distance between the nitrogen atoms ranges between the values belonging to the free base and the protonated sponge. This

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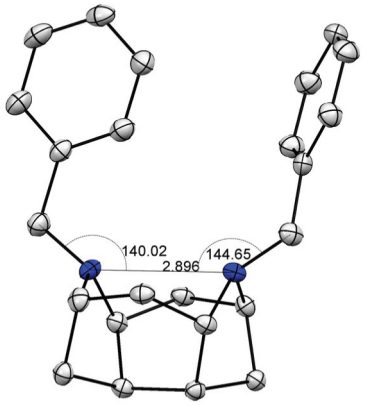

Figure 5. ORTEP representation of **13e** shown at the 50% probability level (upside-down view; hydrogen atoms, methyl, morpholinomethyl and cyano groups are omitted for clarity).

means that the repulsion is suppressed by the electronic influence of cyano groups upon lone pairs. It results in the lower basicity of those types of DTDs **13**.

In our research, we were interested in the synthesis of DTDs with direct connection between the two nitrogen atoms of our skeleton **11** via vicinal dihalogenides shown in Figure 6. From

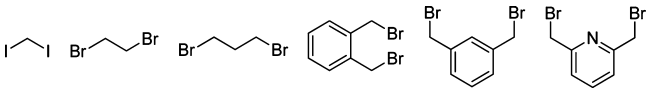

Figure 6. Selected alkyl halides for intramolecular bridge formation.

NMR measurements we identified reactions only with α,α'-dibromo-*m*-xylene and 2,6-bis(bromomethyl)pyridine under the formation of compounds **18** (Figure 7) and **19** (see

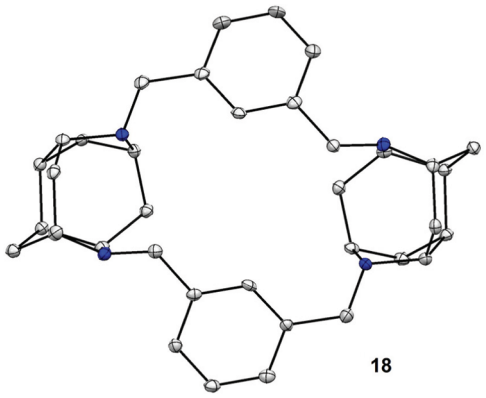

Figure 7. ORTEP representation of dimeric product **18** shown at the 30% probability level (view perpendicular to the phenyl ring planes; hydrogen atoms including methyl and morpholinomethyl groups are omitted for clarity).

Supporting Information). The single carbon atom in diiodomethane is probably not suficient to form a bridge between the two nitrogen atoms. The reactions with 1,2-dibromoethane and 1,3-dibromopropane then afforded unidentified mixtures only.

After successful preparation of the crystal and its subsequent RTG analysis, we identified the formation of an unexpected product with dibromo-*m*-xylene (**18**). Even at conditions of high dilution (≤2 mM), only a dimeric structure **18** (Figure 7) was formed. This product might be considered to be a macrocyclic compound.[17] Actually, this fact appears to be the starting point in the synthesis of these types of compounds, because the design and synthesis of new macrocyclic polyamine ligands are of current interest.[18] The cavity size and shape of a host molecule as well as the number and nature of N-substituents may be tuned to improve the coordination properties and the selectivity for specific guests. We cannot ignore the possible enhanced basicity of such compounds either.

CONCLUSIONS

In summary, we investigated a multistep synthetic pathway to the formation of new caged rigid PS with four fused alicyclic rings in high overall yields. Their $pK_{BH}+$ values depending upon different substitution were determined by NMR measurements of transprotonation reactions. We discovered that the basicity is influenced by electron-withdrawing groups rather than the donating ones. Although DTDs do not exhibit a record basicity, they belong to the rare family of alicyclic PS with a highly stable cage core. Their $pK_{BH}+$ values range between 19 and 22 units. The new products were fully characterized and the structures of the free bases and their protonated forms were investigated by X-ray crystallographic analyses. It was found that monoprotonated DTDs had a strongly unsymmetrical, nonlinear intramolecular hydrogen bridge where the nonbonding distance between nitrogen atoms was reduced from 302.6 to 267.2 pm. Moreover, reactivity under very basic and very acidic conditions revealed the high stability of the cage core, including resistance to bis-protonation. Similarly, testing in reactions with alkylating agents showed resistance to such a reaction. The high stability as well as significantly high basicity of DTDs could be properties leading to applications in many base-catalyzed transformations.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were purchased from commercial suppliers and used as received. Dichloromethane was dried with calcium chloride, distilled from P_2O_5 and stored over dry 3 Å molecular sieves. All reactions were carried out under a dry argon atmosphere. Melting points were determined in open capillaries. ^1H and ^{13}C NMR spectra were recorded at 300.13 MHz (^1H) and 75.47 MHz (^{13}C) with $CDCl_3$ or CD_3CN as solvent. Data are presented as follows: chemical shift (in ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, m = multiplet), coupling constant (J/Hz), integration. Tetramethylsilane (δ 0.00 ppm) or residual protons (δ 7.27 ppm or 1.94 ppm) served as internal standards for ^1H NMR and $CDCl_3$ (δ 77.23 ppm) or CD_3CN (δ 118.7 ppm) for ^{13}C NMR spectra. MS data were obtained at 70 eV in the electron impact mode. Elemental analyses were performed with a CHN apparatus. High-resolution mass spectra (HRMS) were recorded in the positive ESI (CV = 30 V) mode. X-ray diffraction data were collected on a four-circle CCD diffractometer and corrected for Lorentz and polarization effects. The structures were resolved by direct methods and refined by full-matrix least-squares methods using the SHELXTL program package.[19,20] Hydrogen atoms were placed in calculated idealized positions. PhTMG[16] and *p*-methoxybenzyl bromide[21] were prepared according to literature. The numbering of atoms in DTDs is shown in the following structure:

General Procedure for the Rearrangement of 10 to Secondary Amines 11. To the methanolic solution (30 mL) of

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the criss-cross product **10** (1 mmol), glacial acetic acid (2 mmol) was added and, after 10 min of stirring, the slow addition of $NaBH_3CN$ (3 mmol) followed. After 2 h the solvent was removed, 15 mL of 1.0 M aqueous NaOH was added and the mixture was extracted with DCM (3 × 15 mL). The combined extracts were dried over $MgSO_4$, filtered and evaporated to yield a colorless powder **11**. NMR spectra were recorded in $CDCl_3$.

1,6-Bis(pyrrolidin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (11a). Yield 414 mg, >99%. ^{1}H NMR δ 6.40 (bs, 2H, NH), 4.04 (bs, 2H, H3+H8), 3.16 (bs, 2H, H5+H10), 2.55 (d, ^2J = 15.2, 2H, H13+H14), 2.30−2.50 (m, 8H, N−CH_2), 2.28 (d, ^2J = 15.2, 2H, H13+H14), 2.12−2.19 (m, 4H, H4+H9), 1.28−1.58 (m, 12H, 6 × CH_2), 1.22 (s, 6H, CH_3), 1.13 (s, 6H, CH_3). ^{13}C NMR δ 63.2 (C3+C8), 57.6 (N−CH_2), 55.7 (N−CH_2), 55.1 (C5+C10), 53.6 (C2+C7), 49.5 (C1+C6), 31.2 (C4+C9), 27.8 (2 × CH_3), 26.6 (N−CH_2−CH_2), 24.1 (N−CH_2−CH_2−CH_2), 22.2 (2 × CH_3). *m*/*z* (EI) 414 (M^+, 1), 329 (7), 245 (100), 229 (8), 205 (11), 136 (13), 122 (16), 98 (52). HRMS *m*/*z* Calcd. for $C_{26}H_{47}N_4$: 415.3801. Found: 415.3802.

1,6-Bis[(4-methylpiperazin-1-yl)methyl]-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (11b). Yield 444 mg, >99%. ^{1}H NMR δ 3.76 (bs, 2H, NH), 3.69 (d, ^3J = 3.5, 2H, H3+H8), 2.76 (d, ^3J = 2.5, 2H, H5+H10), 2.53 (d, ^2J = 15.0, 2H, H13+H14), 2.26 (d, ^2J = 15.0, 2H, H13+H14), 2.21 (s, 6H, N−CH_3), 2.15−2.60 (m, 16H, N−CH_2-CH_2-N), 2.01 (dd, ^2J = 15.0, ^3J = 3.5, 2H, H4+H9), 1.90 (dd, ^2J = 14.7, ^3J = 2.5, 2H, H4+H9), 1.14 (s, 6H, CH_3), 1.10 (s, 6H, CH_3). ^{13}C NMR δ 63.6 (C3+C8), 56.0 (N−CH_2), 55.8 (N−CH_2), 55.6 (N−CH_2), 53.5 (C5+C10), 53.3 (C2+C7), 49.6 (C1+C6), 46.1 (N−CH_3), 34.3 (C4+C9), 28.5 (2 × CH_3), 22.7 (2 × CH_3). *m*/*z* (EI) 444 (M^+, 1), 356 (6), 344 (6), 245 (100), 229 (8), 220 (8), 136 (10), 113 (28), 100 (15), 83 (25). HRMS *m*/*z* Calcd. for $C_{26}H_{49}N_6$: 445.4019. Found: 445.4004.

1,6-Bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (11c). Yield 418 mg, >99%. ^{1}H NMR δ 6.23 (bs, 2H, NH), 3.88 (bs, 2H, H3+H8), 3.52−3.63 (m, 8H, O−CH_2), 3.01 (bs, 2H, H5+H10), 2.52 (d, ^2J = 15.1, 2H, H13+H14), 2.37−2.52 (m, 8H, N−CH_2), 2.26 (d, ^2J = 15.1, 2H, H13+H14), 2.00 (dd, ^2J = 14.7, ^3J = 4.1, 2H, H4+H9), 1.90 (dd, ^2J = 14.7, ^3J = 2.5, 2H, H4+H9), 1.15 (s, 6H, CH_3), 1.09 (s, 6H, CH_3). ^{13}C NMR δ 67.2 (O−CH_2), 63.0 (C3+C8), 56.6 (N−CH_2), 56.0 (N−CH_2), 54.2 (C5+C10), 53.3 (C2+C7), 49.2 (C1+C6), 32.2 (C4+C9), 27.8 (2 × CH_3), 22.1 (2 × CH_3). *m*/*z* (EI) 418 (M^+, 3), 245 (100), 229 (11), 136 (15), 122 (19), 100 (58), 83 (30). HRMS *m*/*z* Calcd. for $C_{24}H_{43}N_4O_2$: 419.3386. Found: 419.3384.

General Procedure for the PS 13 Preparation. A mixture of **11** (0.5 mmol) with NaH (1.5 mmol) in dry DCM (25 mL) was stirred 10 min under an argon atmosphere and then alkyl halide (1.5 mmol) was added. After 4 h, 5 M aqueous KOH (25 mL) was added, the organic phase was separated and the aqueous layer extracted with DCM (3 × 15 mL). Combined organic phases were dried over $MgSO_4$, filtered and evaporated to dryness. The crude solid **13** was dissolved in acetone and, after overnight crystallization in a freezer, the colorless, light-yellow (**13k**) or orange (**13d**) crystals were filtered and dried under a high vacuum (~0.1 Torr) for several hours. NMR spectra were recorded in $CDCl_3$.

1,6-Bis(morpholin-1-ylmethyl)-2,2,7,7,11,12-hexamethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (13a). Yield 198 mg, 89%; mp 138.0−138.8 °C. ^{1}H NMR δ 3.62 (t, ^3J = 4.5, 8H, O−CH_2), 3.25 (d, ^3J = 4.8, 2H, H3+H8), 2.59 (s, 6H, N−CH_3), 2.55 (d, ^2J = 14.9, 2H, H13+H14), 2.50 (m, 8H, N−CH_2), 2.40 (bs, 2H, H5+H10), 2.18 (d, ^2J = 14.9, 2H, H13+H14), 1.99 (dm, ^2J = 14.1, 2H, H4+H9), 1.50 (dd, ^2J = 14.1, ^3J = 4.2, 2H, H4+H9), 1.11 (s, 6H, CH_3), 1.06 (s, 6H, CH_3). ^{13}C NMR δ 70.0 (C3+C8), 67.6 (O−CH_2), 58.7 (C5+C10), 56.6 (N−CH_2), 56.6 (N−CH_2), 54.9 (C2+C7), 48.3 (C1+C6), 40.2 (2 × N−CH_3), 29.2 (2 × CH_3), 28.6 (C4+C9), 23.6 (2 × CH_3). *m*/*z* (EI) 446 (M^+, 29), 418 (11), 257 (11), 136 (70), 124 (29), 100 (100), 56 (13). HRMS *m*/*z* Calcd. for $C_{26}H_{47}N_4O_2$: 447.3699. Found: 447.3708.

11,12-*N*,*N*′-Diallyl-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (13b). Yield 212 mg, 85%; mp 164.8−166.3 °C. ^{1}H NMR δ 5.87−6.04 (m, 2H, =CH), 5.17 (d, ^3J = 17.0, 2H, =CH_2), 5.00 (d, ^3J = 9.9, 2H, =CH_2), 3.62 (m, 8H, O−CH_2), 3.42−3.55 (m, 4H, −CH_2), 3.35 (d, ^3J = 4.0, 2H, H3+H8), 2.55 (d, ^2J = 14.8, 2H, H13+H14), 2.40−2.62 (m, 10H, N−CH_2+H5+H10), 2.19 (d, ^2J = 14.8, 2H, H13+H14), 1.85 (dd, ^2J = 14.3, ^3J = 3.1, 2H, H4+H9), 1.49 (dd, ^2J = 14.3, ^3J = 4.0, 2H, H4+H9), 1.10 (s, 6H, CH_3), 1.07 (s, 6H, CH_3). ^{13}C NMR δ 139.5 (N−CH_2−CH=), 114.7 (=CH_2), 67.5 (O−CH_2), 66.5 (C3+C8), 58.2 (C5+C10), 56.6 (N−CH_2−CH=), 56.5 (N−CH_2), 56.4 (N−CH_2), 54.6 (C2+C7), 48.4 (C1+C6), 29.5 (C4+C9), 29.1 (2 × CH_3), 23.6 (2 × CH_3). *m*/*z* (EI) 498 (M^+, 21), 457 (11), 444 (57), 398 (40), 357 (27), 100 (100). HRMS *m*/*z* Calcd. for $C_{30}H_{51}N_4O_2$: 499.4012. Found: 499.4008. Anal. Calcd. for $C_{30}H_{50}N_4O_2$: C, 72.25; H, 10.10; N, 11.23. Found: C, 72.17; H, 10.29; N, 11.46.

11,12-*N*,*N*′-Dibenzyl-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (13c). Yield 272 mg, 91%; mp 163.8−165.0 °C. ^{1}H NMR δ 7.17−7.42 (m, 10H, Ph), 4.09 (d, ^2J = 13.8, 2H, CH_2−Ph), 3.97 (d, ^2J = 13.8, 2H, CH_2−Ph), 3.63 (t, ^3J = 4.5, 8H, O−CH_2), 3.45 (d, ^3J = 3.9, 2H, H3+H8), 2.60 (d, ^2J = 14.9, 2H, H13+H14), 2.36−2.62 (m, 10H, N−CH_2+H5+H10), 2.21 (d, ^2J = 14.9, 2H, H13+H14), 1.80 (dm, ^2J = 13.9, 2H, H4+H9), 1.43 (dd, ^2J = 13.9, ^3J = 3.9, 2H, H4+H9), 1.16 (s, 6H, CH_3), 1.09 (s, 6H, CH_3). ^{13}C NMR δ 142.3 (C, Ph), 129.0 (4 × CH, Ph), 128.2 (4 × CH, Ph), 126.5 (2 × CH, Ph), 67.5 (O−CH_2), 67.0 (C3+C8), 58.4 (C5+C10), 58.2 (CH_2−Ph), 56.6 (N−CH_2), 56.5 (N−CH_2), 54.8 (C2+C7), 48.8 (C1+C6), 30.0 (C4+C9), 29.4 (2 × CH_3), 23.8 (2 × CH_3). *m*/*z* (EI) 598 (M^+, 22), 494 (100), 438 (12), 407 (17), 100 (71). HRMS *m*/*z* Calcd. for $C_{38}H_{55}N_4O_2$: 599.4325. Found: 599.4330. Anal. Calcd. for $C_{38}H_{54}N_4O_2$: C, 76.21; H, 9.09; N, 9.36. Found: C, 75.97; H, 9.16; N, 9.23.

11,12-*N*,*N*′-Bis(4-nitrobenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]-dodecane (13d). Yield 276 mg, 80%; mp 238.4−239.7 °C. ^{1}H NMR δ 8.17 (d, ^3J = 8.2, 4H, Ph), 7.51 (d, ^3J = 8.2, 4H, Ph), 4.21 (d, ^2J = 14.8, 2H, CH_2−Ph), 4.02 (d, ^2J = 14.8, 2H, CH_2−Ph), 3.60−3.68 (m, 8H, O−CH_2), 3.50 (d, ^3J = 3.7, 2H, H3+H8), 2.63 (d, ^2J = 14.9, 2H, H13+H14), 2.43−2.60 (m, 10H, N−CH_2+H5+H10), 2.24 (d, ^2J = 14.9, 2H, H13+H14), 1.77 (dd, ^2J = 14.3, ^3J = 2.2, 2H, H4+H9), 1.54 (dd, ^2J = 14.3, ^3J = 3.7, 2H, H4+H9), 1.18 (s, 6H, CH_3), 1.13 (s, 6H, CH_3). ^{13}C NMR δ 149.9 (C, Ph), 147.1 (C, Ph), 129.4 (CH, Ph), 123.7 (CH, Ph), 67.6 (C3+C8), 67.5 (O−CH_2), 59.0 (C5+C10), 58.3 (CH_2−Ph), 56.5 (N−CH_2), 56.4 (N−CH_2), 54.8 (C2+C7), 49.1 (C1+C6), 30.4 (C4+C9), 29.4 (2 × CH_3), 23.8 (2 × CH_3). *m*/*z* (EI) 688 (M^+, 3), 588 (8), 539 (8), 452 (5), 404 (5), 257 (8), 245 (5), 100 (100), 56 (8). HRMS *m*/*z* Calcd. for $C_{38}H_{53}N_6O_6$: 689.4027. Found: 689.4027. Anal. Calcd. for $C_{38}H_{52}N_6O_6$: C, 66.26; H, 7.61; N, 12.20. Found: C, 65.45; H, 7.38; N, 11.89.

11,12-*N*,*N*′-Bis(4-cyanobenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]-dodecane (13e). Yield 289 mg, 89%; mp 237.2−238.3 °C. ^{1}H NMR δ 7.60 (d, ^3J = 8.1, 4H, Ph), 7.44 (d, ^3J = 8.1, 4H, Ph), 4.14 (d, ^2J = 14.6, 2H, CH_2−Ph), 3.97 (d, ^2J = 14.6, 2H, CH_2−Ph), 3.57−3.70 (m, 8H, O−CH_2), 3.47 (d, ^3J = 4.2, 2H, H3+H8), 2.62 (d, ^2J = 14.9, 2H, H13+H14), 2.40−2.60 (m, 10H, N−CH_2+H5+H10), 2.23 (d, ^2J = 14.9, 2H, H13+H14), 1.74 (dd, ^2J = 14.4, ^3J = 3.2, 2H, H4+H9), 1.51 (dd, ^2J = 14.4, ^3J = 4.2, 2H, H4+H9), 1.17 (s, 6H, CH_3), 1.12 (s, 6H, CH_3). ^{13}C NMR δ 147.8 (C, Ph), 132.2 (CH, Ph), 129.4 (CH, Ph), 119.2 (C≡N), 110.6 (C, Ph), 67.5 (O−CH_2), 67.4 (C3+C8), 58.7 (C5+C10), 58.4 (CH_2−Ph), 56.5 (N−CH_2), 56.4 (N−CH_2), 54.7 (C2+C7), 49.0 (C1+C6), 30.2 (C4+C9), 29.4 (2 × CH_3), 23.7 (2 × CH_3). *m*/*z* (EI) 648 (M^+, 13), 548 (40), 532 (18), 519 (41), 432 (24), 237 (16), 100 (100). HRMS *m*/*z* Calcd. for $C_{40}H_{53}N_6O_2$: 649.4230. Found: 649.4236. Anal. Calcd. for $C_{40}H_{52}N_6O_2$: C, 74.04; H, 8.08; N, 12.95. Found: C, 73.62; H, 8.10; N, 12.79.

11,12-*N*,*N*′-Bis(4-(trifluoromethyl)benzyl)-1,6-bis-(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (13f). Yield 327 mg, 89%; mp 228.1−229.5 °C. ^{1}H NMR δ 7.56 (d, $^3J_{H,H}$ = 8.0, 4H, Ph), 7.43 (d, $^3J_{H,H}$ = 8.0, 4H, Ph), 4.14 (d, $^2J_{H,H}$ = 14.3, 2H, CH_2−Ph), 3.97 (d, $^2J_{H,H}$ = 14.3, 2H, CH_2−Ph), 3.61−3.70 (m, 8H, O−CH_2), 3.48 (d,

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$^3J_{H,H}$ = 4.0, 2H, H3+H8), 2.63 (d, $^2J_{H,H}$ = 14.9, 2H, H13+H14), 2.43−2.60 (m, 10H, N−CH_2+H5+H10), 2.23 (d, $^2J_{H,H}$ = 14.9, 2H, H13+H14), 1.77 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 2.4, 2H, H4+H9), 1.51 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 4.0, 2H, H4+H9), 1.18 (s, 6H, CH_3), 1.12 (s, 6H, CH_3). ^{13}C NMR δ 146.4 (C, Ph), 129.1 (q, $^2J_{C,F}$ = 31.8, C, Ph), 129.0 (CH, Ph), 125.3 (q, $^3J_{C,F}$ = 3.7, CH, Ph), 124.6 (q, $^1J_{C,F}$ = 272.0, CF_3), 67.6 (O−CH_2), 67.6 (C3+C8), 58.9 (C5+C10), 58.4 (CH_2−Ph), 56.5 (N−CH_2), 56.5 (N−CH_2), 54.8 (C2+C7), 49.0 (C1+C6), 30.4 (C4+C9), 29.4 (2 × CH_3), 23.8 (2 × CH_3). *m*/*z* (EI) 734 (M^+, 29), 634 (61), 575 (15), 562 (76), 506 (13), 475 (22), 280 (8), 159 (8), 100 (100). HRMS *m*/*z* Calcd. for $C_{40}H_{53}F_6N_4O_2$: 735.4073. Found: 735.4083.

11,12-*N*,*N*′-Bis(4-fluorobenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (13g). Yield 276 mg, 87%; mp 194.2−196.1 °C. ^{1}H NMR δ 7.24−7.35 (m, 4H, Ph), 6.93−7.04 (m, 4H, Ph), 4.04 (d, $^2J_{H,H}$ = 13.7, 2H, CH_2−Ph), 3.90 (d, $^2J_{H,H}$ = 13.7, 2H, CH_2−Ph), 3.59−3.66 (m, 8H, O−CH_2), 3.42 (d, $^3J_{H,H}$ = 4.3, 2H, H3+H8), 2.60 (d, $^2J_{H,H}$ = 15.0, 2H, H13+H14), 2.42−2.60 (m, 10H, N−CH_2+H5+H10), 2.20 (d, $^2J_{H,H}$ = 15.0, 2H, H13+H14), 1.75 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 2.6, 2H, H4+H9), 1.45 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 4.3, 2H, H4+H9), 1.15 (s, 6H, CH_3), 1.09 (s, 6H, CH_3). ^{13}C NMR δ 161.9 (d, $^1J_{C,F}$ = 243.9, C−F), 137.9 (d, $^4J_{C,F}$ = 2.8, C, Ph), 130.3 (d, $^3J_{C,F}$ = 7.8, CH, Ph), 115.0 (d, $^2J_{C,F}$ = 21.0, CH, Ph), 67.6 (O−CH_2), 67.1 (C3+C8), 58.5 (C5+C10), 57.6 (CH_2−Ph), 56.6 (N−CH_2), 56.6 (N−CH_2), 54.8 (C2+C7), 48.9 (C1+C6), 30.2 (C4+C9), 29.4 (2 × CH_3), 23.8 (2 × CH_3). *m*/*z* (EI) 634 (M^+, 10), 534 (43), 512 (74), 425 (18), 100 (100). HRMS *m*/*z* Calcd. for $C_{38}H_{53}F_2N_4O_2$: 635.4137. Found: 635.4137. Anal. Calcd. for $C_{38}H_{52}F_2N_4O_2$: C, 71.89; H, 8.26; N, 8.83. Found: C, 71.66; H, 8.25; N, 8.80.

11,12-*N*,*N*′-Bis(4-methylbenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (13h). Yield 254 mg, 81%; mp 155.1−156.4 °C. ^{1}H NMR δ 7.30 (d, ^3J = 7.8, 4H, Ph), 7.14 (d, ^3J = 7.8, 4H, Ph), 4.08 (d, ^2J = 13.7, 2H, CH_2−Ph), 3.98 (d, ^2J = 13.7, 2H, CH_2−Ph), 3.66 (t, ^3J = 4.3, 8H, O−CH_2), 3.47 (d, ^3J = 4.7, 2H, H3+H8), 2.63 (d, ^2J = 14.8, 2H, H13+H14), 2.45−2.60 (m, 10H, N−CH_2+H5+H10), 2.24 (d, ^2J = 14.8, 2H, H13+H14), 1.83 (dd, ^2J = 14.3, ^3J = 3.5, 2H, H4+H9), 1.45 (dd, ^2J = 14.3, ^3J = 4.7, 2H, H4+H9), 1.19 (s, 6H, CH_3), 1.12 (s, 6H, CH_3). ^{13}C NMR δ 139.2 (C, Ph), 135.9 (C, Ph), 129.0 (CH, Ph), 128.9 (CH, Ph), 67.6 (O−CH_2), 66.8 (C3+C8), 58.4 (C5+C10), 57.9 (CH_2−Ph), 56.7 (N−CH_2), 56.5 (N−CH_2), 54.8 (C2+C7), 48.8 (C1+C6), 30.1 (C4+C9), 29.4 (2 × CH_3), 23.8 (2 × CH_3), 21.3 (Ph−CH_3). *m*/*z* (EI) 626 (M^+, 17), 526 (48), 508 (100), 452 (14), 421 (14), 175 (13), 100 (87). HRMS *m*/*z* Calcd. for $C_{40}H_{59}N_4O_2$: 627.4638. Found: 627.4633.

11,12-*N*,*N*′-Bis(4-*tert*-butylbenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (13i). Yield 274 mg, 77%; mp 178.4−179.6 °C. ^{1}H NMR δ 7.25−7.38 (m, 8H, Ph), 4.07 (d, ^2J = 13.8, 2H, CH_2−Ph), 3.96 (d, ^2J = 13.8, 2H, CH_2−Ph), 3.57−3.72 (m, 8H, O−CH_2), 3.46 (d, ^3J = 2.9, 2H, H3+H8), 2.61 (d, ^2J = 15.0, 2H, H13+H14), 2.43−2.60 (m, 10H, N−CH_2 +H5+H10), 2.23 (d, ^2J = 15.0, 2H, H13+H14), 1.85 (dm, ^2J = 13.4, 2H, H4+H9), 1.45 (dm, ^2J = 13.4, 2H, H4+H9), 1.34 (s, 18H, *t*Bu), 1.18 (s, 6H, CH_3), 1.11 (s, 6H, CH_3). ^{13}C NMR δ 149.3 (C, Ph), 139.3 (C, Ph), 128.7 (CH, Ph), 125.1 (CH, Ph), 67.6 (O−CH_2), 67.0 (C3+C8), 58.6 (C5+C10), 57.8 (CH_2−Ph), 56.7 (N−CH_2), 56.6 (N−CH_2), 54.8 (C2+C7), 48.9 (C1+C6), 34.6 (C, *t*Bu), 31.7 (6 × CH_3, *t*Bu), 30.1 (C4+C9), 29.4 (2 × CH_3), 23.8 (2 × CH_3). *m*/*z* (EI) 710 (M^+, 13), 610 (46), 563 (13), 550 (100), 147 (17), 100 (29). HRMS *m*/*z* Calcd. for $C_{46}H_{71}N_4O_2$: 711.5577. Found: 711.5582. Anal. Calcd. for $C_{46}H_{70}N_4O_2$: C, 77.70; H, 9.92; N, 7.88. Found: C, 77.04; H, 10.03; N, 7.51.

11,12-*N*,*N*′-Bis(4-methoxybenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (13j). Yield 247 mg, 75%; mp 181.1−181.8 °C. ^{1}H NMR δ 7.30 (d, ^3J = 8.1, 4H, Ph), 6.86 (d, ^3J = 8.1, 4H, Ph), 4.03 (d, ^2J = 13.6, 2H, CH_2−Ph), 3.93 (d, ^2J = 13.6, 2H, CH_2−Ph), 3.82 (s, 6H, OCH_3) 3.62−3.67 (m, 8H, O−CH_2), 3.43 (d, ^3J = 4.1, 2H, H3+H8), 2.60 (d, ^2J = 15.0, 2H, H13+H14), 2.40−2.60 (m, 10H, N−CH_2+H5+H10), 2.21 (d, ^2J = 15.0, 2H, H13+H14), 1.79 (dd, ^2J = 14.0, ^3J = 2.2, 2H, H4+H9), 1.43 (dd, ^2J = 14.0, ^3J = 4.1, 2H, H4+H9), 1.16 (s, 6H, CH_3), 1.09 (s, 6H, CH_3). ^{13}C NMR δ 158.4 (C, Ph), 134.4 (C, Ph), 130.1 (CH, Ph), 113.6 (CH, Ph), 67.6 (O−CH_2), 66.7 (C3+C8), 58.3 (C5+C10), 57.5 (CH_2−Ph), 56.6 (N−CH_2), 56.5 (N−CH_2), 55.5 (OCH_3), 54.8 (C2+C7), 48.8 (C1+C6), 30.1 (C4+C9), 29.4 (2 × CH_3), 23.8 (2 × CH_3). *m*/*z* (EI) 658 (M^+, 13), 558 (45), 537 (17), 524 (100), 468 (15), 437 (9), 121 (57), 100 (41). HRMS *m*/*z* Calcd. for $C_{40}H_{59}N_4O_4$: 659.4536. Found: 659.4547.

11,12-*N*,*N*′-Bis(4-(methylthio)benzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (13k). Yield 273 mg, 79%; mp 140.9−142.3 °C. ^{1}H NMR δ 7.28 (d, ^3J = 8.3, 4H, Ph), 7.21 (d, ^3J = 8.3, 4H, Ph), 4.03 (d, ^2J = 13.9, 2H, CH_2−Ph), 3.91 (d, ^2J = 13.9, 2H, CH_2−Ph), 3.63 (t, ^3J = 4.0, 8H, O−CH_2), 3.42 (d, ^3J = 4.6, 2H, H3+H8), 2.59 (d, ^2J = 15.0, 2H, H13+H14), 2.49 (s, 6H, SCH_3), 2.42−2.60 (m, 10H, N−CH_2+H5+H10), 2.20 (d, ^2J = 15.0, 2H, H13+H14), 1.77 (dd, ^2J = 14.2, ^3J = 3.4, 2H, H4+H9), 1.44 (dd, ^2J = 14.2, ^3J = 4.6, 2H, H4+H9), 1.15 (s, 6H, CH_3), 1.09 (s, 6H, CH_3). ^{13}C NMR δ 139.5 (C, Ph), 136.0 (C, Ph), 129.6 (CH, Ph), 127.0 (CH, Ph), 67.6 (O−CH_2), 67.1 (C3+C8), 58.6 (C5+C10), 58.0 (CH_2−Ph), 56.6 (N−CH_2), 56.6 (N−CH_2), 54.8 (C2+C7), 48.9 (C1+C6), 30.3 (C4+C9), 29.4 (2 × CH_3), 23.8 (2 × CH_3), 16.5 (SCH_3). *m*/*z* (EI) 690 (M^+, 6), 590 (21), 553 (13), 540 (43), 484 (6), 453 (6), 207 (6), 137 (71), 122 (6), 100 (100). HRMS *m*/*z* Calcd. for $C_{40}H_{59}N_4O_2S_2$: 691.4079. Found: 691.4079.

11,12-*N*,*N*′-Dibenzyl-1,6-bis(piperidin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane (13l). Yield 277 mg, 93%; mp 132.8−133.1 °C. ^{1}H NMR δ 7.38−7.44 (m, 4H, Ph), 7.27−7.34 (m, 4H, Ph), 7.18−7.26 (m, 2H, Ph), 4.12 (d, ^2J = 13.9, 2H, CH_2−Ph), 3.99 (d, ^2J = 13.9, 2H, CH_2−Ph), 3.44 (d, ^3J = 5.0, 2H, H3+H8), 2.58 (d, ^2J = 14.9, 2H, H13+H14), 2.46 (bs, 2H, H5+H10), 2.22−2.60 (m, 8H, N−CH_2), 2.17 (d, ^2J = 14.9, 2H, H13+H14), 1.81 (dd, ^2J = 14.4, ^3J = 3.4, 2H, H4+H9), 1.30−1.55 (m, 14H, 6 × CH_2+H4+H9), 1.18 (s, 6H, CH_3), 1.11 (s, 6H, CH_3). ^{13}C NMR δ 142.8 (C, Ph), 129.1 (4 × CH, Ph), 128.2 (4 × CH, Ph), 126.4 (2 × CH, Ph), 67.5 (C3+C8), 58.6 (CH_2−Ph), 58.5 (C5+C10), 57.4 (N−CH_2), 56.5 (N−CH_2), 54.9 (C2+C7), 49.1 (C1+C6), 30.4 (C4+C9), 29.7 (2 × CH_3), 26.9 (4 × CH_2), 24.5 (2 × CH_2), 24.1 (2 × CH_3). *m*/*z* (EI) 594 (M^+, 7), 496 (26), 490 (24), 434 (7), 405 (16), 212 (8), 98 (100), 91 (26). Anal. Calcd. for $C_{40}H_{58}N_4$: C, 80.76; H, 9.83; N, 9.42. Found: C, 75.97; H, 9.65; N, 9.05.

General Procedure for the Protonation of 13 to 14. A mixture of **13** (0.1 mmol) with NH_4ClO_4 (0.1 mmol) in dry CH_3CN (10 mL) was stirred 3 h under an argon atmosphere at 50 °C. The solvent was evaporated and the crude product was washed with chloroform. Drying under high vacuum (~0.1 Torr) for several hours gave the colorless crystalline products **14** in quantitative yields. NMR spectra were recorded in CD_3CN.

1,6-Bis(morpholin-1-ylmethyl)-2,2,7,7,11,12-hexamethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14a). ^{1}H NMR δ 12.59 (bs, 1H, NH), 3.67 (d, ^3J = 4.1, 2H, H3+H8), 3.48−3.62 (m, 8H, O−CH_2), 3.03 (d, ^2J = 3.2, 2H, H5+H10), 2.74 (s, 6H, N−CH_3), 2.63 (d, ^2J = 15.3, 2H, H13+H14), 2.40−2.51 (m, 8H, N−CH_2), 2.36 (d, ^2J = 15.3, 2H, H13+H14), 2.16 (ddd, ^2J = 15.7, ^3J = 4.1, ^3J = 1.8, 2H, H4+H9), 2.04 (dd, ^2J = 15.4, ^3J = 3.2, 2H, H4+H9), 1.20 (s, 6H, CH_3), 1.18 (s, 6H, CH_3). ^{13}C NMR δ 72.5 (C3+C8), 68.1 (O−CH_2), 66.4 (C5+C10), 57.4 (N−CH_2), 56.4 (N−CH_2), 56.0 (C2+C7), 50.3 (C1+C6), 42.4 (2 × N−CH_3), 28.9 (C4+C9), 28.8 (2 × CH_3), 23.5 (2 × CH_3). Anal. Calcd. for $C_{26}H_{47}ClN_4O_6$: C, 57.08; H, 8.66; N, 10.24. Found: C, 57.70; H, 8.85; N, 10.61.

11,12-*N*,*N*′-Diallyl-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14b). ^{1}H NMR δ 13.19 (bs, 1H, NH), 5.85−6.03 (m, 2H, =CH), 5.43 (d, ^3J = 17.1, 2H, =CH_2), 5.36 (d, ^3J = 10.1, 2H, =CH_2), 3.82 (bs, 2H, H3+H8), 3.73 (dd, ^2J = 13.3, ^3J = 5.2, 2H, −CH_2), 3.42−3.65 (m, 10H, −CH_2+O−CH_2), 3.21 (bs, 2H, H5+H10), 2.64 (d, ^2J = 15.4, 2H, H13+H14), 2.35−2.55 (m, 8H, N−CH_2), 2.38 (d, ^2J = 15.4, 2H, H13+H14), 2.15 (dm, ^2J = 15.9, 2H, H4+H9), 2.04 (ddd,

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^2J = 15.9, ^3J = 4.1, ^3J = 1.8, 2H, H4+H9), 1.21 (s, 6H, CH_3), 1.19 (s, 6H, CH_3). ^{13}C NMR 133.8 (N−CH_2-CH═), 122.6 (═CH_2), 69.2 (C3+C8), 68.1 (O−CH_2), 65.4 (C5+C10), 58.2 (N−CH_2−CH═), 57.5 (N−CH_2), 56.4 (N−CH_2), 55.8 (C2+C7), 50.2 (C1+C6), 30.1 (C4+C9), 28.6 (2 × CH_3), 23.5 (2 × CH_3).

11,12-*N*,*N*′-Dibenzyl-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14c). ^1H NMR 11.99 (bs, 1H, NH), 7.37−7.47 (m, 6H, Ph), 7.22−7.30 (m, 4H, Ph), 4.18 (dd, ^2J = 13.1, ^3J = 2.2, 2H, CH_2−Ph), 4.09 (dd, ^2J = 13.1, ^3J = 3.7, 2H, CH_2−Ph), 3.93 (bs, 2H, H3+H8), 3.51−3.67 (m, 8H, O−CH_2), 3.23 (d, ^3J = 3.4, 2H, H5+H10), 2.67 (d, ^2J = 15.4, 2H, H13+H14), 2.35−2.55 (m, 8H, N−CH_2), 2.38 (d, ^2J = 15.4, 2H, H13+H14), 2.02 (dd, ^2J = 15.7, ^3J = 3.8, 2H, H4+H9), 1.63 (dd, ^2J = 15.7, ^3J = 3.4, 2H, H4+H9), 1.29 (s, 6H, CH_3), 1.20 (s, 6H, CH_3). ^{13}C NMR δ 136.1 (C, Ph), 131.2 (4 × CH, Ph), 130.7 (4 × CH, Ph), 130.3 (2 × CH, Ph), 70.0 (C3+C8), 68.1 (O−CH_2), 65.6 (C5+C10), 60.4 (CH_2−Ph), 57.4 (N−CH_2), 56.3 (N−CH_2), 55.7 (C2+C7), 50.4 (C1+C6), 30.9 (C4+C9), 29.0 (2 × CH_3), 23.7 (2 × CH_3). Anal. Calcd. for $C_{38}H_{55}ClN_4O_6$: C, 65.26; H, 7.93; N, 8.01. Found: C, 65.91; H, 7.75; N, 7.83.

11,12-*N*,*N*′-Bis(4-nitrobenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14d). ^1H NMR δ 11.85 (bs, 1H, NH), 8.22 (d, ^3J = 8.6, 4H, Ph), 7.51 (d, ^3J = 8.6, 4H, Ph), 4.32 (d, ^2J = 13.4, ^3J = 2.1, 2H, CH_2−Ph), 4.24 (d, ^2J = 13.4, ^3J = 3.8, 2H, CH_2−Ph), 3.98 (bs, 2H, H3+H8), 3.47−3.68 (m, 8H, O−CH_2), 3.27 (d, ^3J = 2.9, 2H, H5+H10), 2.68 (d, ^2J = 15.4, 2H, H13+H14), 2.35−2.60 (m, 8H, N−CH_2), 2.40 (d, ^2J = 15.4, 2H, H13+H14), 2.10 (dd, ^2J = 16.1, ^3J = 3.8, 2H, H4+H9), 1.74 (dd, ^2J = 16.1, ^3J = 2.9, 2H, H4+H9), 1.29 (s, 6H, CH_3), 1.22 (s, 6H, CH_3). ^{13}C NMR δ 149.7 (C, Ph), 143.2 (C, Ph), 132.3 (CH, Ph), 125.7 (CH, Ph), 70.5 (C3+C8), 68.1 (O−CH_2), 66.4 (C5+C10), 59.6 (CH_2−Ph), 57.4 (N−CH_2), 56.2 (N−CH_2), 55.7 (C2+C7), 50.5 (C1+C6), 31.0 (C4+C9), 28.9 (2 × CH_3), 23.7 (2 × CH_3). Anal. Calcd. for $C_{38}H_{53}ClN_6O_{10}$: C, 57.82; H, 6.77; N, 10.65. Found: C, 57.77; H, 6.79; N, 10.59.

11,12-*N*,*N*′-Bis(4-cyanobenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14e). ^1H NMR δ 11.86 (bs, 1H, NH), 7.81 (d, ^3J = 8.0, 4H, Ph), 7.41 (d, ^3J = 8.0, 4H, Ph), 4.24 (dd, ^2J = 13.3, ^3J = 2.0, 2H, CH_2−Ph), 4.16 (dd, ^2J = 13.3, ^3J = 3.7, 2H, CH_2−Ph), 3.94 (bs, 2H, H3+H8), 3.48−3.67 (m, 8H, O−CH_2), 3.23 (d, ^3J = 3.3, 2H, H5+H10), 2.67 (d, ^2J = 15.4, 2H, H13+H14), 2.37−2.55 (m, 8H, N−CH_2), 2.39 (d, ^2J = 15.4, 2H, H13+H14), 2.06 (dd, ^2J = 16.0, ^3J = 4.2, 2H, H4+H9), 1.69 (dd, ^2J = 16.0, ^3J = 3.3, 2H, H4+H9), 1.28 (s, 6H, CH_3), 1.21 (s, 6H, CH_3). ^{13}C NMR δ 140.9 (C, Ph), 134.3 (CH, Ph), 131.6 (CH, Ph), 119.3 (C≡N), 113.7 (C, Ph), 69.8 (C3+C8), 67.8 (O−CH_2), 65.9 (C5+C10), 59.4 (CH_2−Ph), 57.0 (N−CH_2), 55.9 (N−CH_2), 55.3 (C2+C7), 50.1 (C1+C6), 30.6 (C4+C9), 28.5 (2 × CH_3), 23.4 (2 × CH_3).

11,12-*N*,*N*′-Bis(4-(trifluoromethyl)benzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14f). ^1H NMR δ 11.86 (bs, 1H, NH), 7.72 (d, $^3J_{H,H}$ = 8.0, 4H, Ph), 7.48 (d, $^3J_{H,H}$ = 8.0, 4H, Ph), 4.29 (dd, $^2J_{H,H}$ = 13.2, $^3J_{H,H}$ = 2.0, 2H, CH_2−Ph), 4.21 (dd, $^2J_{H,H}$ = 13.2, $^3J_{H,H}$ = 3.5, 2H, CH_2−Ph), 3.97 (bs, 2H, H3+H8), 3.50−3.68 (m, 8H, O−CH_2), 3.25 (d, $^3J_{H,H}$ = 3.0, 2H, H5+H10), 2.68 (d, $^2J_{H,H}$ = 15.3, 2H, H13+H14), 2.40−2.55 (m, 8H, N−CH_2), 2.40 (d, $^2J_{H,H}$ = 15.3, 2H, H13+H14), 2.07 (dd, $^2J_{H,H}$ = 16.1, $^3J_{H,H}$ = 3.6, 2H, H4+H9), 1.67 (dd, $^2J_{H,H}$ = 16.1, $^3J_{H,H}$ = 3.0, 2H, H4+H9), 1.30 (s, 6H, CH_3), 1.22 (s, 6H, CH_3). ^{13}C NMR δ 140.6 (C, Ph), 132.0 (CH, Ph), 131.7 (q, $^2J_{C,F}$ = 32.6, C, Ph), 127.5 (q, $^3J_{C,F}$ = 3.8, CH, Ph), 125.6 (q, $^1J_{C,F}$ = 271.5, CF_3), 70.4 (C3+C8), 68.1 (O−CH_2), 66.1 (C5+C10), 59.9 (CH_2−Ph), 57.4 (N−CH_2), 56.3 (N−CH_2), 55.8 (C2+C7), 50.4 (C1+C6), 31.0 (C4+C9), 29.0 (2 × CH_3), 23.7 (2 × CH_3). Anal. Calcd. for $C_{40}H_{53}ClF_6N_4O_6$: C, 57.51; H, 6.40; N, 6.71. Found: C, 57.19; H, 6.30; N, 6.96.

11,12-*N*,*N*′-Bis(4-fluorobenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14g). ^1H NMR δ 11.90 (bs, 1H, NH), 7.12−7.35 (m, 8H, Ph), 4.17 (dd, $^2J_{H,H}$ = 13.2, $^3J_{H,H}$ = 2.4, 2H, CH_2−Ph), 4.09 (dd, $^2J_{H,H}$ = 13.2, $^3J_{H,H}$ = 3.8, 2H, CH_2−Ph), 3.92 (bs, 2H, H3+H8), 3.50−3.65 (m, 8H, O−CH_2), 3.24 (d, $^3J_{H,H}$ = 3.2, 2H, H5+H10), 2.67 (d, $^2J_{H,H}$ = 15.4, 2H, H13+H14), 2.35−2.55 (m, 8H, N−CH_2), 2.39 (d, $^2J_{H,H}$ = 15.4, 2H, H13+H14), 2.04 (dd, $^2J_{H,H}$ = 15.9, $^3J_{H,H}$ = 4.0, 2H, H4+H9), 1.65 (dd, $^2J_{H,H}$ = 15.9, $^3J_{H,H}$ = 3.2, 2H, H4+H9), 1.28 (s, 6H, CH_3), 1.21 (s, 6H, CH_3). ^{13}C NMR δ 164.3 (d, $^1J_{C,F}$ = 246.0, C−F), 133.4 (d, $^3J_{C,F}$ = 8.6, CH, Ph), 132.4 (d, $^4J_{C,F}$ = 3.0, C, Ph), 117.5 (d, $^2J_{C,F}$ = 21.9, CH, Ph), 70.0 (C3+C8), 68.1 (O−CH_2), 65.7 (C5+C10), 59.5 (CH_2−Ph), 57.4 (N−CH_2), 56.3 (N−CH_2), 55.8 (C2+C7), 50.4 (C1+C6), 30.9 (C4+C9), 29.0 (2 × CH_3), 23.7 (2 × CH_3).

11,12-*N*,*N*′-Bis(4-methylbenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14h). ^1H NMR δ 11.94 (bs, 1H, NH), 7.24 (d, ^3J = 7.9, 4H, Ph), 7.15 (d, ^3J = 7.9, 4H, Ph), 4.13 (dd, ^2J = 13.0, ^3J = 2.2, 2H, CH_2−Ph), 4.05 (d, ^2J = 13.0, ^3J = 3.5, 2H, CH_2−Ph), 3.91 (bs, 2H, H3+H8), 3.49−3.66 (m, 8H, O−CH_2), 3.21 (d, $^3J_{H,H}$ = 2.6, 2H, H5+H10), 2.66 (d, ^2J = 15.2, 2H, H13+H14), 2.40−2.54 (m, 8H, N−CH_2), 2.38 (d, ^2J = 15.2, 2H, H13+H14), 2.01 (dd, ^2J = 15.8, ^3J = 3.1, 2H, H4+H9), 1.63 (dd, ^2J = 15.8, ^3J = 2.6, 2H, H4+H9), 1.28 (s, 6H, CH_3), 1.20 (s, 6H, CH_3). ^{13}C NMR δ 140.3 (C, Ph), 133.2 (C, Ph), 131.2 (CH, Ph), 69.9 (C3+C8), 68.1 (O−CH_2), 65.5 (C5+C10), 60.1 (CH_2−Ph), 57.4 (N−CH_2), 56.3 (N−CH_2), 55.7 (C2+C7), 50.3 (C1+C6), 30.9 (C4+C9), 29.0 (2 × CH_3), 23.7 (2 × CH_3), 21.7 (Ph−CH_3). Anal. Calcd. for $C_{40}H_{59}ClN_4O_6$: C, 66.05; H, 8.18; N, 7.70. Found: C, 66.52; H, 8.11; N, 7.46.

11,12-*N*,*N*′-Bis(4-*tert*-butylbenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14i). ^1H NMR δ 12.16 (bs, 1H, NH), 7.46 (d, ^2J = 8.2, 4H, Ph), 7.19 (d, ^2J = 8.2, 4H, Ph), 4.17 (dd, ^2J = 13.1, ^3J = 2.2, 2H, CH_2−Ph), 4.08 (dd, ^2J = 13.1, ^3J = 3.6, 2H, CH_2−Ph), 3.93 (bs, 2H, H3+H8), 3.50−3.67 (m, 8H, O−CH_2), 3.21 (d, ^3J = 3.1, 2H, H5+H10), 2.67 (d, ^2J = 15.4, 2H, H13+H14), 2.35−2.57 (m, 8H, N−CH_2), 2.39 (d, ^2J = 15.4, 2H, H13+H14), 2.02 (dd, ^2J = 15.8, ^3J = 3.6, 2H, H4+H9), 1.67 (dd, ^2J = 15.8, ^3J = 3.1, 2H, H4+H9), 1.34 (s, 18H, *t*Bu), 1.29 (s, 6H, CH_3), 1.21 (s, 6H, CH_3). ^{13}C NMR δ 153.5 (C, Ph), 133.3 (C, Ph), 130.9 (CH, Ph), 127.5 (CH, Ph), 70.0 (C3+C8), 68.2 (O−CH_2), 65.5 (C5+C10), 59.9 (CH_2−Ph), 57.4 (N−CH_2), 56.3 (N−CH_2), 55.7 (C2+C7), 50.4 (C1+C6), 35.8 (C, *t*Bu), 32.0 (6 × CH_3, *t*Bu), 30.7 (C4+C9), 29.0 (2 × CH_3), 23.7 (2 × CH_3). Anal. Calcd. for $C_{46}H_{70}N_4O_2$: C, 68.08; H, 8.82; N, 6.90. Found: C, 68.46; H, 8.77; N, 7.02.

11,12-*N*,*N*′-Bis(4-methoxybenzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14j). ^1H NMR δ 11.88 (bs, 1H, NH), 7.21 (d, ^3J = 8.5, 4H, Ph), 6.94 (d, ^3J = 8.5, 4H, Ph), 4.11 (dd, ^2J = 13.0, ^3J = 2.1, 2H, CH_2−Ph), 4.03 (dd, ^2J = 13.0, ^3J = 3.5, 2H, CH_2−Ph), 3.89 (bs, 2H, H3+H8), 3.82 (s, 6H, OCH_3), 3.50−3.65 (m, 8H, O−CH_2), 3.21 (d, ^3J = 2.8, 2H, H5+H10), 2.66 (d, ^2J = 15.3, 2H, H13+H14), 2.36−2.54 (m, 8H, N−CH_2), 2.37 (d, ^2J = 15.3, 2H, H13+H14), 2.00 (dd, ^2J = 15.7, ^3J = 3.0, 2H, H4+H9), 1.61 (dd, ^2J = 15.7, ^3J = 2.8, 2H, H4+H9), 1.27 (s, 6H, CH_3), 1.19 (s, 6H, CH_3). ^{13}C NMR δ 161.5 (C, Ph), 132.7 (CH, Ph), 128.2 (C, Ph), 115.9 (CH, Ph), 69.8 (C3+C8), 68.1 (O−CH_2), 65.3 (C5+C10), 59.8 (CH_2−Ph), 57.4 (N−CH_2), 56.5 (OCH_3), 56.3 (N−CH_2), 55.7 (C2+C7), 50.3 (C1+C6), 30.9 (C4+C9), 29.0 (2 × CH_3), 23.7 (2 × CH_3). Anal. Calcd. for $C_{40}H_{59}ClN_4O_8$: C, 63.27; H, 7.83; N, 7.38. Found: C, 62.70; H, 8.01; N, 6.99.

11,12-*N*,*N*′-Bis(4-(methylthio)benzyl)-1,6-bis(morpholin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14k). ^1H NMR δ 11.84 (bs, 1H, NH), 7.27 (d, ^3J = 8.4, 4H, Ph), 7.18 (d, ^3J = 8.4, 4H, Ph), 4.13 (dd, ^2J = 13.1, ^3J = 2.6, 2H, CH_2−Ph), 4.06 (dd, ^2J = 13.1, ^3J = 3.6, 2H, CH_2−Ph), 3.91 (bs, 2H, H3+H8), 3.51−3.65 (m, 8H, O−CH_2), 3.22 (d, ^3J = 3.3, 2H, H5+H10), 2.66 (d, ^2J = 15.4, 2H, H13+H14), 2.52 (s, 6H, SCH_3), 2.40−2.55 (m, 8H, N−CH_2), 2.38 (d, ^2J = 15.4, 2H, H13+H14), 2.03 (dd, ^2J = 15.9, ^3J = 3.9, 2H, H4+H9), 1.63 (dd, ^2J = 15.9, ^3J = 3.3, 2H, H4+H9), 1.28 (s, 6H, CH_3), 1.20 (s, 6H, CH_3). ^{13}C NMR δ 141.4 (C, Ph), 132.6 (C, Ph), 131.8 (CH, Ph), 127.8 (CH, Ph), 70.2 (C3+C8), 68.1 (O−CH_2), 65.7 (C5+C10), 60.1 (CH_2−Ph),

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57.4 (N−CH_2), 56.3 (N−CH_2), 55.8 (C2+C7), 50.4 (C1+C6), 31.0 (C4+C9), 29.0 (2 × CH_3), 23.7 (2 × CH_3), 15.8 (SCH_3).

11,12-*N*,*N*′-Dibenzyl-1,6-bis(piperidin-1-ylmethyl)-2,2,7,7-tetramethyl-11,12-diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecane Perchlorate (14l). ^{1}H NMR δ 12.01 (bs, 1H, NH), 7.24−7.46 (m, 10H, Ph), 4.20 (dd, ^2J = 13.0, ^3J = 2.5, 2H, CH_2−Ph), 4.12 (dd, ^2J = 13.0, ^3J = 3.6, 2H, CH_2−Ph), 3.92 (bs, 2H, H3+H8), 3.22 (bs, 2H, H5+H10), 2.30−2.80 (m, 12H, 6 × CH_2), 2.06 (dd, ^2J = 15.7, ^3J = 3.8, 2H, H4+H9), 1.68 (dd, ^2J = 15.7, ^3J = 3.0, 2H, H4+H9), 1.35−1.65 (m, 12H, 6 × CH_2), 1.32 (s, 6H, CH_3), 1.24 (s, 6H, CH_3). ^{13}C NMR δ 136.2 (C, Ph), 131.3 (4 × CH, Ph), 130.7 (4 × CH, Ph), 130.3 (2 × CH, Ph), 70.2 (C3+C8), 65.7 (C5+C10), 60.4 (CH_2−Ph), 58.2 (N−CH_2), 56.4 (C2+C7), 55.9 (N−CH_2), 50.5 (C1+C6), 31.0 (C4+C9), 29.2 (2 × CH_3), 27.6 (4 × CH_2), 25.0 (2 × CH_2), 24.0 (2 × CH_3).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C and 2D NMR spectra, accurate mass measurements, calculation data from transprotonation experiments, and procedures for bridged derivative preparation, hydrolysis and nucleophilicity determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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