# Synthesis, Molecular Modeling, and Pharmacological Testing of Bis-Quinolinium Cyclophanes: Potent, Non-Peptidic Blockers of the Apamin-Sensitive $Ca^{2+}$-Activated $K^+$ Channel

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*Received May 21, 1999*

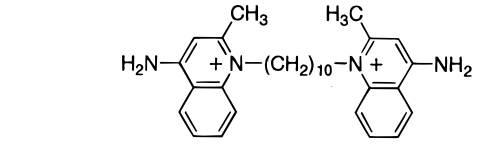
The synthesis and pharmacological testing of two series of novel bis-quinolinium cyclophanes as blockers of the apamin-sensitive $Ca^{2+}$-activated $K^+$ ($SK_{Ca}$) channel are presented. In these cyclophanes the two 4-aminoquinolinium groups are joined at the ring N atoms (linker L) and at the exocyclic N atoms (linker A). In those cases where A and L contain two or more aromatic rings each, the activity of the compound is not critically dependent upon the nature of the linkers. When A and L each have only one benzene ring, the blocking potency changes dramatically with simple structural variations in the linkers. One of these smaller cyclophanes having A = benzene-1,4-diylbis(methylene) and L = benzene-1,3-diylbis(methylene) (**3j**, 6,10-diaza-1,5(1,4)-diquinolina-3(1,3),8(1,4)-dibenzenacyclodecaphanedium tritrifluoroacetate, UCL 1684) has an $IC_{50}$ of 3 nM and is the most potent non-peptidic $SK_{Ca}$ channel blocker described to date. Conformational analysis on the smaller cyclophanes using molecular modeling techniques suggests that the differences in the blocking potencies of the compounds may be attributable to their different conformational preferences.

## Introduction

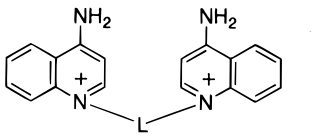
Ion channels selective for $K^+$ form a large family with members differing in their gating characteristics and conductance.[1] By controlling the movement of $K^+$ ions through the membrane they participate in a variety of physiological and pathophysiological processes, thus being, in many cases, suitable targets for therapeutic intervention.[2]

The small conductance $Ca^{2+}$-activated $K^+$ ($SK_{Ca}$) channel is found in many cell types, in some cases its physiological role is known,[3a−f] and it has been suggested that there may exist endogenous modulators of $SK_{Ca}$ channels.[3f−h] Research on $SK_{Ca}$ channels has been hampered substantially by the lack of readily accessible, potent, and selective blockers. The currently available blockers include natural peptidic toxins such as apamin,[4] leiurotoxin I (scyllatoxin),[5] PO5,[6] PO1[7] and Ts K,[8] of which apamin has been an invaluable pharmacological tool. However, the use of such peptides is associated with many problems, arising from their limited availability and cost. Furthermore, the use of peptides as therapeutic agents has many pharmacokinetic drawbacks. Clearly, there is a need for the discovery of potent and selective, non-peptidic $SK_{Ca}$ channel blockers.

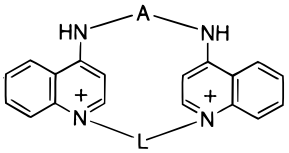
**Chart 1**




Dequalinium




**1**




**2**: A = $(CH_2)_{10}$
**3**: A = aromatic rings

There is scope for the use of such blockers in various disease states. Thus, the receptor for apamin is expressed in muscles of patients with myotonic muscular dystrophy, while it is absent in normal human muscle.[9] Local injection of apamin into muscles of patients with this disease has been shown to reduce basal muscle electrical activity and suppress myotonic discharges.[10] Selective $SK_{Ca}$ channel blockade may also have beneficial effects in dismotilities of the gastrointestinal tract (P. M. Dunn and D. H. Jenkinson, unpublished results), disorders of memory,[11] narcolepsy,[12] and alcohol intoxication.[13]

Research on non-peptidic $SK_{Ca}$ channel blockers has identified dequalinium (Chart 1) as a relatively potent and selective blocker of the $SK_{Ca}$ channel in rat sympathetic neurons.[14] The pharmacophore of dequalinium

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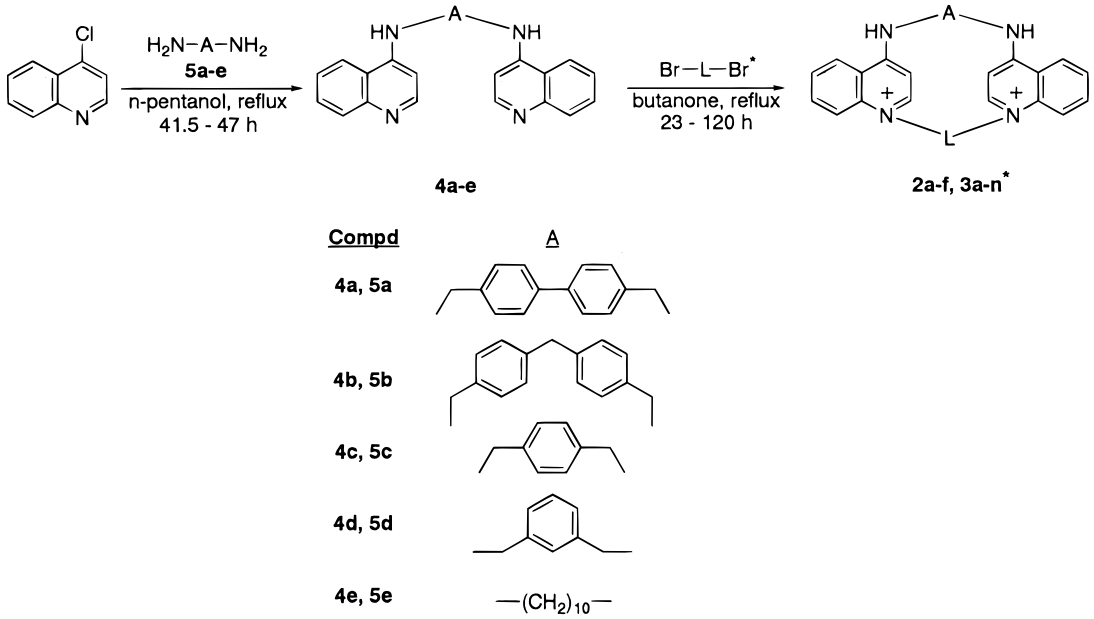
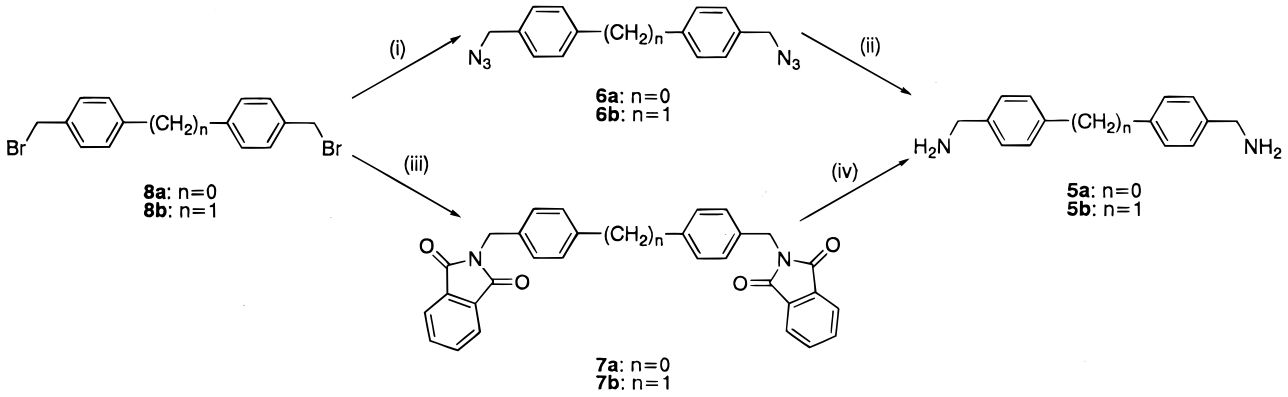
10.1021/jm9902537 CCC: $19.00 
Published on Web 12/28/1999

**Scheme 1**




*For the synthesis of **3g** $I(CH_2)_{10}I$ was used.

**Scheme 2**[a]




[a] (i) $NaN_3$, DMF, 90 °C, 17 h; **6a**: 97%; **6b**: 95%; (ii) $LiAlH_4$, THF, reflux, 1 h; **5a**: 93%; **5b**: 87%; (iii) potassium phthalimide, DMF, 90 °C, 40 min; **7a**: 87%; **7b**: 88%; (iv) $H_2NNH_2 \cdot H_2O$, DMSO, 120 °C, 1.5 h; **5a**: 58%; **5b**: 35%.

for $SK_{Ca}$ channel blockade has been investigated via synthesis of several series of analogues.[15] We have demonstrated that substitution of large groups L containing aromatic rings (general structure **1**, Chart 1) for the 10-methylene chain of dequalinium is well-tolerated.[15g] Furthermore, we have reported in preliminary communications that the exocyclic N atoms of series **1** can be linked via a 10-methylene chain to provide cyclophanes of the general structure **2**[15i] (Chart 1) and that this 10-methylene chain can be replaced with groups containing aromatic moieties to give series **3**[15j] (Chart 1). In the present study, we report the synthesis and pharmacological testing of several cyclophanes belonging to series **2** and **3**, as blockers of the $SK_{Ca}$ channel in rat sympathetic neurons. We also use molecular modeling techniques in an attempt to rationalize the structure–activity trends observed among the cyclophanes.

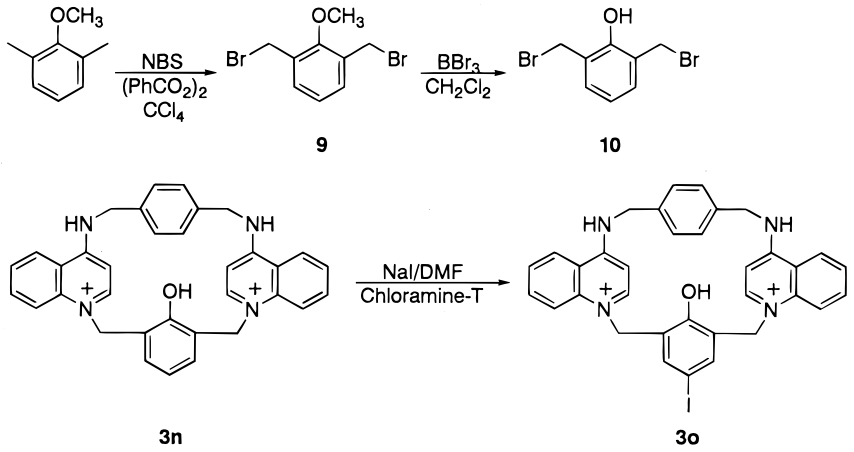
## Chemistry

The cyclophanes **2a**–**f** and **3a**–**n** (Table 1) were synthesized according to Scheme 1. The diquinolines **4a**–**d** are novel, and we have previously reported the synthesis of **4e**.[15e] The conversion of the diquinolines **4a**–**e** to the desired cyclophanes was carried out under high-dilution conditions (1–2 mM).

The preparations of the necessary dibromides 2,7-bis(bromomethyl)fluorene,[16] 3,3′-bis(bromomethyl)biphenyl,[17a] 4,4′-bis(bromomethyl)biphenyl[17b,c] (**8a**, Scheme 2), bis[*p*-(bromomethyl)diphenyl]methane[18] (**8b**, Scheme 2), bis-*p*-(bromomethyl)bibenzyl,[18] 2,6-bis[4-(bromomethyl)-phenyl]pyridine,[19] and *(Z)*-4,4′-bis(bromomethyl)stilbene[15g] have been described previously. In the synthesis of **3g**, the use of $I(CH_2)_{10}I$ was found to be advantageous over $Br(CH_2)_{10}Br$ in terms of cleanness of the reaction. The requisite diamines **5a**,**b** have been reported[20] but were prepared via the two alternative routes, shown in Scheme 2. Higher overall yields were obtained through the diazide route. The diamines **5c**–**e** are commercially available.

2,6-Bis(bromomethyl)anisole[17d] (**9**) required for the synthesis of **3m** was prepared via NBS bromination of 2,6-dimethylanisole (Scheme 3). Compound **9** was demethylated with $BBr_3$ to 2,6-bis(bromomethyl)phenol[17e,f]

**Scheme 3**




(**10**, Scheme 3) which was used in the synthesis of **3n**. The latter was converted into **3o** by iodination using NaI/Chloramine-T in DMF, as shown in Scheme 3.

## Biological Testing

The $SK_{Ca}$ blocking action of the compounds was assessed from their ability to inhibit the after-hyperpolarization (AHP) in cultured rat superior cervical ganglion (SCG) neurons as described previously.[14b] Briefly, individual cells were impaled with an intracellular microelectrode which was used both to elicit and to record action potentials. During a successful run, the impaled cell was exposed to several concentrations of one or more of the compounds under test and also of dequalinium which was used as a reference agent. The new compounds were examined in batches of up to 4, and each was tested at 2−4 concentrations on at least 3 cells; 3−4 concentrations of dequalinium were applied. When 3 or more concentrations of a compound had been tested, as was usual, the Hill equation was fitted to obtain an estimate of the $IC_{50}$. However, because there was some "apparent" variation in the potency of dequalinium during the course of the study, equieffective molar concentration ratios (EMR relative to dequalinium) were also determined by simultaneous nonlinear least-squares fitting of the data obtained with each compound, taken together with the values observed with dequalinium in that set of assays. As before, the Hill equation was used to fit the data: a common Hill coefficient was assumed. The EMR values are also listed in Table 1, and it is these values that have been used for the comparison between compounds.

## Results and Discussion

The structures and biological results for the "noncyclic" analogues **1** as well as the cyclophanes of general structures **2** and **3** are shown in Table 1. To aid the structure−activity analysis, the compounds in Table 1 are grouped according to the linker L. It is evident that linking the exocyclic N atoms of analogues **1** with a 10-methylene chain to provide the respective cyclophanes **2** is well-tolerated and, in some cases, results in a small increase in potency (cf. **1a**−**2a**, **1b**−**2b**, **1c**−**2c**, **1d**−**2d**, **1e**−**2e**, **1f**−**2f**). Cyclophanes **2** seem to be quite tolerant to the nature of linker L, and the maximum variation in potency is only approximately 5-fold (cf. compounds **2c**,**e**). Moreover, exchanging the positions of the alkylene chain and the biphenyl moiety of **2f** to give **3g** did not alter the activity.

The transition from the potentially flexible cyclophanes **2** to the more rigid cyclophanes **3** results either in retention or in a small decrease of potency (cf. **2b**−**3a**−**3b**, **2c**−**3c**, **2d**−**3d**, **2f**−**3e**−**3f**). In series **3**, the maximum difference in the activity of the biphenyl analogues **3b**,**c**,**f** is 5−6-fold, and that of the diphenylmethane analogues **3a**,**d**,**e**,**h** is 5-fold. In two cases where L was kept constant and A was varied, the "linear" biphenyl cyclophanes **3b**,**f** showed slightly reduced activity in comparison with the "bent" diphenylmethane analogues **3a**,**e,** respectively. This is reminiscent of the small drop in activity which was observed when the alkylene chain of dequalinium was rigidified via introduction of two (linear) triple bonds.[15b]

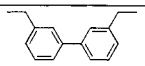
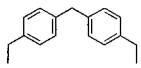
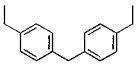
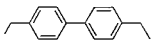
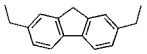
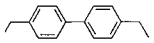
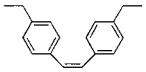
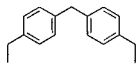
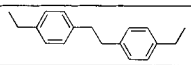
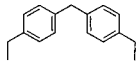
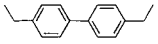
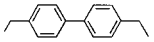
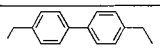
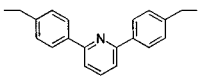
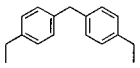
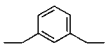
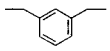
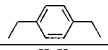
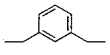
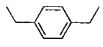
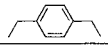
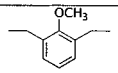
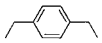
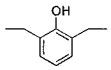
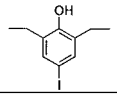
Overall, the compounds of Table 1 in which A and/or L is a large group having two or three aromatic rings show little dependence of potency on the nature and properties of the linkers A and L. This is despite the substantial structural variation in A and L and despite the fact that the compounds belong to three different series (**1**, **2,** and **3**).

The structure−activity trends change dramatically, however, in the case of the smaller cyclophanes **3i**−**o**. Here, linking the exocyclic N atoms of molecules **1h**,**i** with a benzene-1,3-diylbis(methylene) group to give cyclophanes **3i**,**k,** respectively, leads to an approximately 1 order of magnitude increase in activity. Furthermore, when the exocyclic N atoms of **1h**,**i** are joined via a benzene-1,4-diylbis(methylene) group to give cyclophanes **3j**,**l,** respectively, an increase in activity of 2 orders of magnitude is observed.

Within series **3**, the blocking potency of the compound seems to be critically dependent upon the nature of A when L contains a *meta*-disubstituted benzene ring (cf. compounds **3i**,**j**) and less so, when L possesses a *para*-disubstituted benzene ring (cf. compounds **3k**,**l**). Thus, a single change in the substitution pattern of the benzene ring in A from *meta* (**3i**) to *para* (**3j**) leads to a 22-fold increase in potency. On the other hand, a smaller dependence of activity on the substitution pattern of the benzene ring in L is observed (cf. compound pairs **3i**−**3k** and **3j**−**3l**).

That the activity of compounds **3i**−**l** is so sensitive to the pattern of the substitution of the benzene rings in A and L suggests that drug size or shape may be critical

**Table 1.** Structures and Biological Results for the Compounds

| Compd | A | L | $IC_{50}$ ± SD (nM) | EMR[a] ± SD | | n[b] |
|---|---|---|---|---|---|---|
| Deq. | | | 650 ± 40 | 1 | | 89 |
| **1a** | H, H |  | 290 ± 70[c] | 0.55 | ± 0.3[c] | 6 |
| **2a** | $-(CH_2)_{10}-$ | | 110 ± 50 | 0.28 | ± 0.07 | 3 |
| **1b** | H, H | | 450 ± 150[c] | 0.39 | ± 0.12[c] | 4 |
| **2b**[d] | $-(CH_2)_{10}-$ | | 80 ± 20 | 0.16 | ± 0.1 | 9 |
| **3a** |  |  | 260 ± 40 | 0.31 | ± 0.24 | 5 |
| **3b** |  | | 280 ± 10 | 0.80 | ± 0.21 | 8 |
| **1c** | H, H | | 310 ± 40[c] | 0.33 | ± 0.1[c] | 4 |
| **2c** | $-(CH_2)_{10}-$ |  | 90 ± 50 | 0.11 | ± 0.06 | 7 |
| **3c** |  | | 120 ± 40 | 0.15 | ± 0.05 | 4 |
| **1d** | H, H | | 190 ± 30[c] | 0.24 | ± 0.08[c] | 6 |
| **2d** | $-(CH_2)_{10}-$ |  | 150 ± 20 | 0.29 | ± 0.06 | 3 |
| **3d** |  | | 250 ± 90 | 1.1 | ± 0.4 | 4 |
| **1e** | H, H |  | 410 ± 120[c] | 0.71 | ± 0.19[c] | 4 |
| **2e** | $-(CH_2)_{10}-$ | | 180 ± 30 | 0.57 | ± 0.16 | 3 |
| **1f** | H, H | | 380 ± 40[c] | 0.40 | ± 0.1[c] | 3 |
| **2f** | $-(CH_2)_{10}-$ | | 170 ± 50 | 0.26 | ± 0.07 | 7 |
| **3e** |  |  | 150 ± 10 | 0.26 | ± 0.12 | 3 |
| **3f** |  | | 430 ± 60 | 0.89 | ± 0.25 | 4 |
| **3g** |  | $-(CH_2)_{10}-$ | 210 ± 20 | 0.25 | ± 0.06 | 4 |
| **1g** | H, H |  | 360 ± 20[c] | 0.59 | ± 0.34[c] | 4 |
| **3h** |  | | 380 ± 130 | 0.88 | ± 0.4 | 5 |
| **1h** | H, H | | 800 ± 70[c] | 1.32 | ± 0.33[c] | 5 |
| **3i** |  |  | 130 ± 10 | 0.22 | ± 0.04 | 4 |
| **3j**[e] |  | | 3 ± 1 | 0.01 | ± 0.001 | 4 |
| **1i** | H, H | | 2800 ± 250[c] | 3.7 | ± 1.4[c] | 4 |
| **3k** |  |  | 70 ± 40 | 0.18 | ± 0.04 | 5 |
| **3l** |  | | 28 ± 3 | 0.05 | ± 0.01 | 5 |
| **3m** | |  | 25 ± 8 | 0.019 | ± 0.005 | 3 |
| **3n** |  |  | 60 ± 4 | 0.14 | ± 0.02 | 4 |
| **3o** | |  | 100 ± 10 | 0.16 | ± 0.04 | 4 |

[a] Equieffective molar ratio: the ratio of the concentrations of the test compound and dequalinium that cause 50% inhibition of the AHP, as determined in the same experiment. [b] Number of neurons tested. [c] Data from ref 15g. [d] UCL 1530. [e] UCL 1684.

to the interaction of the cyclophane with the binding site. To investigate this hypothesis we used molecular modeling techniques to investigate the conformational behavior and to identify low-energy conformations for **3i**−**l**. The conformational searches for the 4 molecules were performed using the XEDYNIN and XEDMININ routines in the XED/COSMIC package[21] as described in the Experimental Section. All distinct conformers generated were optimized using AM1[22] and then subjected to single-point ab initio (6-31G*) calculations using GAMESS.[23]

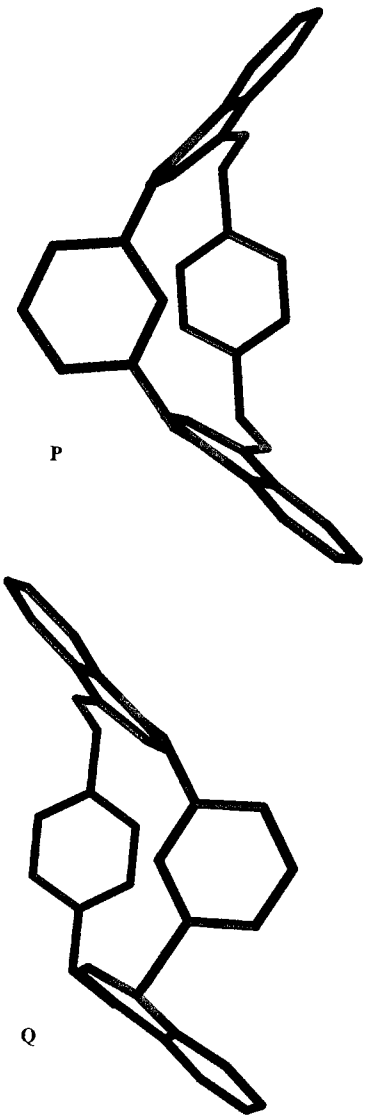



**Figure 1.** "*Cis*" (synperiplanar, P) and "*trans*" (antiperiplanar, Q) conformations of compound **3j**, calculated using AM1.

The resultant conformers can be broadly divided into two groups: those in which the relative orientation of the quinolinium groups is "*cis*" (synperiplanar, structure P in Figure 1) and those in which the relative orientation is "*trans*" (antiperiplanar, structure Q in Figure 1).

The heats of formation for the lowest-energy conformations of **3i**−**l**, calculated at the semiempirical (AM1) or ab initio (6-31G*) level, are given in Table 2. The rank order of energies calculated by the two methods is similar in most cases, but the ab initio method yields larger energy differences.

For the most potent cyclophane **3j**, three conformers were identified, two being "*cis*" and the third being "*trans*". Both calculation methods suggest that the most stable conformation is the "*cis*". The energy difference between the "*cis*" and "*trans*" conformations is not large, and the "*trans*" conformation could be populated to some extent at body temperature. However, the spatial orientation of the two quinolinium groups in the two conformers is considerably different (Figure 1). Thus, it could be hypothesized that only one of the two

**Table 2.** Conformations and Energies for the Cyclophanes

| Compd[1] | Conformation[2] | $\Delta H_f$ (AM1)[3] | $\Delta\Delta H_f$ (AM1)[4] | E (6-31G*)[5] | $\Delta E$ (6-31G*)[6] | EMR |
|---|---|---|---|---|---|---|
| **3j_(1)** | C | 492.6 | 0.0 | -954924.7 | 0.0 | |
| **3j_(2)** | T | 493.2 | 0.6 | -954923.4 | 1.3 | 0.01 |
| **3j_(3)** | C | 494.0 | 1.4 | -954921.6 | 3.1 | |
| **3l_(1)** | C | 494.9 | 0.0 | -954921.6 | 0.0 | 0.05 |
| **3l_(2)** | T | 495.0 | 0.1 | -954920.5 | 1.1 | |
| **3k_(1)** | T | 497.4 | 0.9 | -954918.9 | 0.0 | |
| **3k_(2)** | C | 596.5 | 0.0 | -954918.1 | 0.8 | 0.18 |
| **3k_(3)** | T | 498.0 | 1.5 | -954917.2 | 1.7 | |
| **3k_(4)** | T | 498.5 | 2.0 | -954916.3 | 2.6 | |
| **3i_(1)** | C | 494.5 | 1.0 | -954924.0 | 0.0 | |
| **3i_(2)** | T | 496.5 | 3.0 | -954923.2 | 0.8 | |
| **3i_(3)** | T | 494.3 | 0.8 | -954922.6 | 1.4 | |
| **3i_(4)** | T | 496.5 | 3.0 | -954922.3 | 1.7 | |
| **3i_(5)** | T | 495.6 | 2.1 | -954922.2 | 1.8 | |
| **3i_(6)** | C | 493.5 | 0.0 | -954922.0 | 2.0 | |
| **3i_(7)** | C | 495.8 | 2.3 | -954921.9 | 2.1 | 0.22 |
| **3i_(8)** | T | 494.4 | 0.9 | -954921.2 | 2.8 | |
| **3i_(9)** | C | 494.5 | 1.0 | -954921.1 | 2.9 | |
| **3i_(10)** | C | 495.7 | 2.2 | -954920.2 | 3.8 | |
| **3i_(11)** | T | 496.1 | 2.6 | -954919.9 | 4.1 | |
| **3i_(12)** | C | 497.7 | 4.2 | -954917.6 | 6.4 | |
| **3i_(13)** | T | 497.8 | 4.3 | -954914.9 | 9.1 | |
| **3m_(1)** | T | 455.2 | 0.4 | -1026348.4 | 0.0 | |
| **3m_(2)** | C | 454.8 | 0.0 | -1026348.1 | 0.3 | 0.019 |
| **3m_(3)** | C | 456.6 | 1.8 | -1026346.4 | 2.0 | |
| **3m_(4)** | C | 461.6 | 6.8 | -1026341.2 | 7.2 | |
| **3n_(1)** | T | 448.7 | 0.0 | -1001875.2 | 0.0 | |
| **3n_(2)** | C | 449.2 | 0.5 | -1001873.7 | 1.5 | 0.14 |
| **3n_(3)** | C | 449.9 | 1.2 | -1001873.7 | 1.5 | |
| **3o_(1)** | T | 467.5 | 0.0 | — | — | |
| **3o_(2)** | T | 467.5 | 0.0 | — | — | |
| **3o_(3)** | C | 468.1 | 0.6 | — | — | 0.16 |
| **3o_(4)** | C | 468.8 | 1.3 | — | — | |
| **3o_(5)** | C | 472.2 | 4.7 | — | — | |
| **3o_(6)** | T | 475.7 | 8.2 | — | — | |

[1] The number in parentheses identifies the conformer. [2] C, "*cis*" (synperiplanar); T, "*trans*" (antiperiplanar). [3] Heat of formation of the conformer (in kcal/mol) calculated at the AM1 level. [4] $\Delta H_{f(\text{conformer})} - \Delta H_{f(\text{global minimum conformer})}$. [5] Energy of the molecule (in kcal/mol) calculated at the 6-31G* level. Since this basis set does not have parameters for the I atom, the calculations were not performed for **3o**. [6] $E_{\text{conformer}} - E_{\text{global minimum conformer}}$.

conformers is the "active" one, and it is reasonable to assume that this "active" conformation is the most stable one, i.e., the "*cis*".

Only two conformers were identified for compound **3l**. The ab initio results favor the "*cis*" conformation, which is similar to the "*cis*" conformation of **3j** (structure S in Figure 2).

The two calculation methods give contradictory results for the two less potent cyclophanes, **3k**,**i**. Thus, the AM1 results suggest that both molecules prefer a "*cis*" conformation, while at the ab initio level, a "*trans*" conformation and a "*cis*" conformation are favored for **3k**,**i,** respectively. The two "*cis*" global minimum energy conformers suggested by AM1 are similar to the "*cis*" conformation of **3j** in terms of the spatial orientation of the two quinolinium groups (structure R in Figure 2). Hence, it seems that the results obtained by the ab initio methodology fit better the working hypothesis, since **3k**,**i** would have to pay an energy penalty of 0.8 and 2 kcal/mol, respectively, to adopt the "active" ("*cis*") conformation, which might explain their lower potency.

Nevertheless, the potency of a compound is also a function of the population of the "active" conformation in the biological test environment. To a first approximation, neglecting entropy changes, the calculated internal energies can be equated with free energies. Then, the calculated energy differences in Table 2 are related to the relative population of the conformers via: $\Delta E = -RT \ln(n_1/n_2)$, where $R$ is the gas constant, $T$ is the temperature in K, and $n_1$, $n_2$ are the number of molecules in conformations 1 and 2, respectively. At body temperature (37 °C), the ratio of the populations

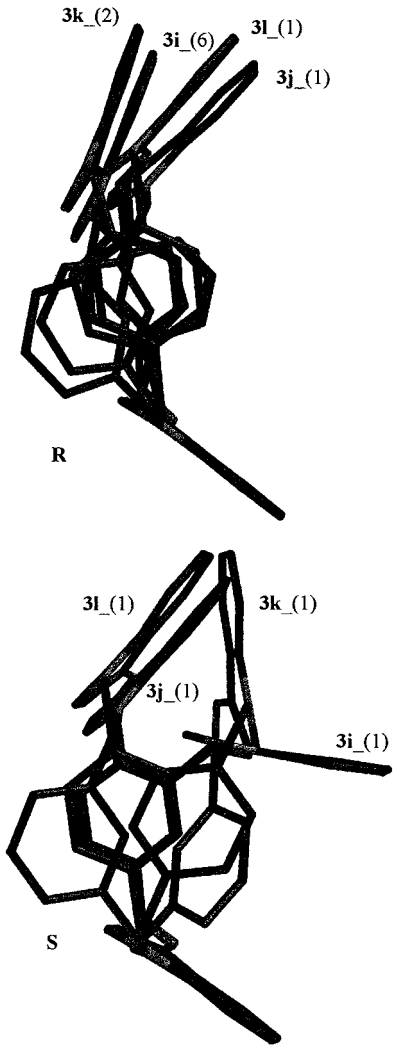



**Figure 2.** Superimposition of the lowest-energy conformer of compounds **3i**−**l** (Table 2), calculated using AM1 (*R*) or 6-31G* (*S*). Only the atoms of one quinolinium ring of each molecule have been superimposed, to show the difference in the spatial orientation of the second quinolinium ring. Hydrogen atoms have been omitted for clarity.

of the "*cis*" [**3j_**(1)] and "*trans*" [**3j_**(2)] conformers of **3j** is calculated to be $n_{cis}/n_{trans} = 8.3$. Similarly, the ratio for **3l** is calculated to be $n_{cis}/n_{trans} = 6$. Thus, the population of the "*cis*" conformer is suggested to be higher for the more potent cyclophane **3j**. Furthermore, the calculated number of distinct conformers which could exist at body temperature is small (2) for the most potent cyclophane **3j** and much greater (9) for the least potent cyclophane **3i**. If the calculated relative rigidity of **3j** is reflected in solution, then it would be another factor to account for the potency of this molecule.

The above analysis of the molecular modeling results offers a challenge: Analogues of compound **3j** which would show a stronger preference for the "*cis*" conformation would be expected to be much more potent blockers of the $SK_{Ca}$ channel.

Compound **3j** (UCL 1684), being 100-fold more potent than dequalinium and having an $IC_{50}$ of 3 nM, is the first example of a small, synthetic, non-peptidic molecule to show a level of activity similar to that of the 18-amino acid peptide, apamin ($IC_{50} = 1$ nM[4]). Having discovered this nanomolar blocker (**3j**), we performed studies toward the synthesis of a radioligand for the

$SK_{Ca}$ channel. Given the low density of expression of the $SK_{Ca}$ channel,[24] $^{125}I$ was selected as the radioactive element for its high specific activity. Furthermore, $^{125}I$ can be easily introduced at the very last step of a synthetic sequence, provided that a suitable functionality exists in the molecule, thus minimizing the handling of radioactive materials.

An iodine atom can be conveniently introduced under mild conditions to a suitably activated aromatic ring. Given the deactivated nature of the quinolinium groups of **3j**, the benzene rings of linker A or L would be more appropriate to accommodate the I atom. More specifically, the *meta*-disubstituted benzene ring of L, activated by an OH group "*ortho*" to both methylene groups (compound **3n**, Table 1), would ensure the introduction of only one I atom, "*para*" to the OH group to give cyclophane **3o**.

However, the introduction of substituents to the linker L of compound **3j** may alter the conformational profile of the molecule. To investigate this possibility, conformational analysis has been performed on the target compound **3o**, as well as on the intermediates **3m**,**n** (Table 1) and the results are shown in Table 2. Unfortunately, the lack of parameters for the I atom in the 6-31G* basis set prevented the calculation of conformational energies for this compound at the ab initio level. The results of the calculations point to almost equistable "*cis*" and "*trans*" conformations for **3m**, while **3n** seems to show some preference for the "*trans*" conformation, and this also appears to be the case for **3o**.

Thus, the synthesis of the model compound **3o** was undertaken, and the compound was found to be much less potent than **3j**. The loss in activity does not seem to be associated with the large I atom, since the hydroxy analogue of **3j** (compound **3n**) shows reduced activity and is equipotent with the hydroxyiodo cyclophane **3o**. Moreover, compound **3m**, the methoxy analogue of **3n**, is almost as potent as **3j**. Although the conformational behavior of **3n**,**o** might be responsible for their reduced potency, it should not be overlooked that some physicochemical characteristics associated with the OH group (such as increased solvation and/or H-bond acidity) might be the cause for the reduced activity of the OH analogues. It is pertinent to recall that we have previously suggested that the desolvation energy of quinolinium $SK_{Ca}$ channel blockers may be an important factor controlling the strength of the drug−ion channel interaction:[15d] the stronger the solvation, the weaker the binding of the blocker to the channel.

In view of the functional[25] and structural evidence (based on cloning studies[26]) for the existence of $SK_{Ca}$ channel subtypes in different tissues, the selectivity of the blocking action of the new compounds becomes an important issue. In this respect, the cyclophanes we have described may well provide useful lead compounds for the development of selective $SK_{Ca}$ channel blockers since we have already shown that **2b** (UCL 1530) is much more active at neuronal (rat SCG) than hepatocyte $SK_{Ca}$ channels.[27] In the course of that work, it was demonstrated that UCL 1530 had no effect on the voltage-activated $Ca^{2+}$ currents in rat SCG cells even when applied at 1 $\mu$M, more than 10 times greater than the $IC_{50}$ for $SK_{Ca}$ inhibition. Moreover, in the present work **2b** caused no significant change in the amplitude or time course of the action potential of SCG neurons. The other compounds tested were also inactive in this regard, including the very potent **3j** (UCL 1684). This suggests that these cyclophanes, certainly when tested at concentrations that inhibit $SK_{Ca}$ channels, do not affect the other kinds of channels (e.g., for sodium) that are involved in the generation of the action potential. Further evidence for the selectivity of **3j** comes from the observation (M. Malik-Hall, C. R. Ganellin, D. Galanakis, and D. H. Jenkinson, unpublished findings) that even when applied at a concentration of 10 $\mu$M (more than 1000 times greater than the $IC_{50}$ for block of the $SK_{Ca}$ channels in SCG neurons (present work) and in rat chromaffin cells[28]), **3j** causes little if any inhibition of the $Ca^{2+}$-activated $K^+$ permeability present in mammalian red cells and mediated by intermediate conductance ($IK_{Ca}$) channels. Clearly the cyclophane derivatives that we have described have considerable selectivity, making them useful pharmacological tools for the further investigation of $Ca^{2+}$-activated $K^+$ channels.

## Conclusion

The synthesis and pharmacological testing of novel bis-quinolinium cyclophanes as blockers of the $SK_{Ca}$ channel have been described. In the large cyclophanes **2a**−**f** and **3a**−**h** structural modifications in linkers A and L do not affect potency to a significant extent. In contrast, the activities of the smaller cyclophanes **3i**−**o** are very sensitive to alterations in A and L. Compound **3j** is the most potent non-peptidic blocker reported to date, showing activity in the low nanomolar range. Molecular modeling studies suggest that the variation in the potencies of the small cyclophanes **3i**−**l** may be accounted for by the different spatial orientation of the quinolinium groups. Furthermore, **3j** can exist in "*cis*" or "*trans*" conformations, and analogues of **3j** constrained to adopt either the "*cis*" or "*trans*" conformation may be useful in identifying the cyclophane pharmacophore and are likely to be even more potent $SK_{Ca}$ channel blockers.

## Experimental Section

**Chemistry**. Melting points (mp) were obtained on an Electrothermal melting point apparatus or on a Kofler apparatus equipped with a microscope RCH and are uncorrected. Infrared (IR) spectra were run either on a Perkin-Elmer 1600 FT-IR spectrometer or on a Nicolet 205 FT-IR spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-200 (200 MHz) or VXR-400 (400 MHz) spectrometer, and chemical shifts (ppm) are reported relative to the solvent peak. Signals are designated as follows: s, singlet; $s_{br}$, broad singlet; d, doublet; dd, doublet of doublets; ddd, double double doublet; t, triplet; pt, pseudotriplet; q, quadruplet; m, multiplet. Mass spectra were run on a VG ZAB SE or VG 7070H spectrometer. Analytical high-performance liquid chromatography (HPLC) was performed on a Shimadzu HPLC apparatus with an UV detector set at 254 nm and a Kromasil C18 5-$\mu$m column. Solvent mixtures of A = $H_2O$ + 0.1% TFA and B = MeOH + 0.1% TFA were used. The flow rate was 1 mL/min. For preparative HPLC a Gilson apparatus was used with a Shimadzu UV−Vis detector, a HP3396A Hewlet-Packard integrater, and a Kromasil 100 C18 10-$\mu$m column with a length of 250 mm and an i.d. of 20 mm. The solvent mixtures were as above, and the flow rate was 15 mL/min. Dry tetrahydrofuran (THF) was obtained by distillation from Na/benzophenone ketyl under $N_2$. Elemental combustion analyses were within ±0.4% of theoretical values. Many of the

compounds, particularly the salts, were unavoidably analyzed as solvates, owing to their tendency to retain solvent (particularly TFA after running a preparative HPLC) under nondestructive drying conditions. The compounds gave accurate mass spectra, having the correct isotope abundance and no extraneous peaks. Analytical thin-layer chromatography (TLC) was done on Merck silica gel F-254 plates. For normal column chromatography Merck silica gel 60 was used with a particle size 0.063−0.200 mm (70−230 mesh ASTM). For flash chromatography Merck silica gel 60 was used with a particle size 0.040−0.063 mm (230−400 mesh ASTM). The compounds have been named according to IUPAC Recommendations 1998.[29]

**General Procedure for the Preparation of 4,4′-Bis(azidomethyl)biphenyl (6a) and 4,4′-Bis(azidomethyl)diphenylmethane (6b)**. $NaN_3$ (2 equiv) was added to a solution of either 4,4′-bis(bromomethyl)biphenyl[17b,c] (**8a**) or 4,4′-bis(bromomethyl)diphenylmethane[18] (**8b**) in dry DMF. The solution was heated for 17 h at 90 °C and then concentrated in vacuo to yield a mixture which was treated with $CHCl_3$. The solid (NaBr) was filtered off and the extract concentrated in vacuo to yield the product which was purified by flash chromatography.

**4,4′-Bis(azidomethyl)biphenyl (6a)**. Purified by flash chromatography [$Et_2O$:petroleum ether = 2:13] and isolated as a white solid (97%): mp 73−74 °C; IR (KBr disk) $\nu_{max}$ 2911, 2096, 1437 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (d, $J$ = 7.8 Hz, 4 H, biphenyl), 7.39 (d, $J$ = 7.9 Hz, 4 H, biphenyl), 4.38 (s, 4 H, $N_3$-$CH_2$-$C_6H_4$); MS (EI) $[M]^+$ 264, fragments at $m/z$ 265, 236, 222, 208, 194, 180, 166, 152; HPLC (A:B = 1:9) major peak at 5.16 min representing 100% of the absorption. Anal. ($C_{14}H_{12}N_6$) C, H, N.

**4,4′-Bis(azidomethyl)diphenylmethane (6b)**. Purified by flash chromatography ($Et_2O$:petroleum ether = 1:3) and isolated as an oil (4.49 g, 95%): IR (KBr disk) $\nu_{max}$ 2918, 2092, 1439 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.5 Hz, 4 H, $C_6H_4$-$CH_2$-$C_6H_4$), 7.18 (d, $J$ = 8.2 Hz, 4 H, $C_6H_4$-$CH_2$-$C_6H_4$), 4.29 (s, 4 H, $N_3$-$CH_2$-$C_6H_4$), 3.98 (s, 2 H, $C_6H_4$-$CH_2$-$C_6H_4$); MS (FAB, MNOBA matrix) $[M]^+$ 278, fragments at $m/z$ 279, 264, 250, 237, 194, 180, 166; HPLC (A:B = 12:88) major peak at 6.54 min representing 100% of the absorption. Anal. ($C_{15}H_{14}N_6$) C, H, N.

**General Procedure for the Preparation of 4,4′-Bis(aminomethyl)biphenyl (5a) from 6a and 4,4′-Bis(aminomethyl)diphenylmethane (5b) from 6b**. A solution of **6a** or **6b** in dry THF was added dropwise with stirring to a suspension of $LiAlH_4$ (3.5 molar excess) in dry THF held at room temperature under an argon atomosphere. When the addition was complete, the mixture was boiled under reflux for 1 h, and then the excess of $LiAlH_4$ was decompozed by addition of a saturated aqueous solution of $Na_2SO_4$. The THF layer was dried ($Na_2SO_4$) and concentrated to give a white powder.

**4,4′-Bis(aminomethyl)biphenyl (5a)**. Recrystallized from toluene (93%): mp 143−145 °C (lit.[20b] mp 144−145 °C); IR (KBr disk) $\nu_{max}$ 3268, 3108, 2912, 1587, 794 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (d, $J$ = 8 Hz, 4 H, biphenyl), 7.37 (d, $J$ = 8 Hz, 4 H, biphenyl), 3.90 (s, 4 H, $NH_2$-$CH_2$-$C_6H_4$), 1.55 ($s_{br}$, 4 H, $NH_2$); MS (EI) $[M]^+$ 212, fragments at $m/z$ 213, 211, 196, 182, 166, 30; HPLC (A:B = 7:3) major peak at 3.92 min representing 99.9% of the absorption.

**4,4′-Bis(aminomethyl)diphenylmethane (5b)**. Recrystallized from cyclohexane (87%): mp 86−88 °C (lit.[20b] mp 90 °C); IR (KBr disk) $\nu_{max}$ 3343, 3020, 2912, 1582, 805 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.8 Hz, 4 H, $C_6H_4$-$CH_2$-$C_6H_4$), 7.13 (d, $J$ = 8.8 Hz, 4 H, $C_6H_4$-$CH_2$-$C_6H_4$), 3.93 (s, 2 H, $C_6H_4$-$CH_2$-$C_6H_4$), 3.81 (s, 4 H, $NH_2$-$CH_2$-$C_6H_4$), 1.52 ($s_{br}$, 4 H, $NH_2$); MS (EI) $[M]^+$ 226, fragments at $m/z$ 225, 210, 196, 166, 106; HPLC (A:B = 7:3) major peak at 6.98 min representing 100% of the absorption.

**General Procedure for the Preparation of 4,4′-Bis(phthalimidomethyl)biphenyl (7a) and 4,4′-Bis(phthalimidomethyl)diphenylmethane (7b)**. A mixture of 0.4 g of either 4,4′-bis(bromomethyl)biphenyl[17b,c] (**8a**) or 4,4′-bis(bromomethyl)diphenylmethane[18] (**8b**) and potassium phthalimide (2.2 molar excess) in anhydrous DMF (10 mL) was heated at 90 °C for 40 min. The cooled reaction mixture was diluted with $CHCl_3$ (30 mL) and poured into $H_2O$ (120 mL). The organic layer was separated and the aqueous phase was extracted with $CHCl_3$ (2 × 40 mL). The combined organic extracts were washed with cold 0.1 N NaOH (40 mL) and $H_2O$ (40 mL) and dried ($MgSO_4$). The $CHCl_3$ was removed in vacuo to the point of incipient crystallization. The immediate addition of $Et_2O$ induced a rapid crystallization.

**4,4′-Bis(phthalimidomethyl)biphenyl (7a)**. The ether-washed product weighed 0.456 g (86.6%, as white crystals): mp 293−295 °C; IR (KBr disk) $\nu_{max}$ 3026, 2930, 1762, 1714, 1492, 1460, 1423, 1391, 841, 788 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.84−7.67 (m, 8 H, phthaloyl moiety), 7.46 (s, 8 H, biphenyl moiety), 4.85 (s, 4 H, N-$CH_2$-$C_6H_4$); MS (EI) $[M]^+$ 472, fragments at $m/z$ 325, 178, 165; HPLC (A:B = 15:85) major peak at 7.39 min representing 99.1% of the absorption. Anal. ($C_{30}H_{20}N_2O_4 \cdot 0.3H_2O$) C, H, N.

**4,4′-Bis(phthalimidomethyl)diphenylmethane (7b)**. The ether-washed product weighed 1.23 g (88%) as white crystals: mp 271−272 °C; IR (KBr disk) $\nu_{max}$ 3026, 2930, 1767, 1714, 1508, 1460, 1428, 1386, 799 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.81−7.65 (m, 8 H, phthaloyl moiety), 7.30 (d, $J$ = 8.1 Hz, 4 H, $C_6H_4$-$CH_2$-$C_6H_4$), 7.10 (d, $J$ = 8.1 Hz, 4 H, $C_6H_4$-$CH_2$-$C_6H_4$), 4.76 (s, 4 H, N-$CH_2$-$C_6H_4$), 3.86 (s, 2 H, $C_6H_4$-$CH_2$-$C_6H_4$); MS (EI) $[M]^+$ 486, fragments at $m/z$ 339, 236, 192, 179, 165; HPLC (A:B = 1:9) major peak at 5.44 min representing 100% of the absorption. Anal. ($C_{31}H_{22}N_2O_4 \cdot 0.5H_2O$) C, H, N.

**4,4′-Bis(aminomethyl)biphenyl (5a) from 7a**. A mixture of 1 g (2.12 mmol) of **7a**, 0.55 mL of hydrazine monohydrate 98%, and DMSO (100 mL) was heated at 120 °C for 1.5 h. The DMSO was removed by concentration under reduced pressure. 6 N HCl (100 mL) was added to the residue and the mixture was heated under reflux for 1 h. After cooling to 0 °C, crystalline phthalhydrazine was removed by filtration (A, 0.706 g). The filtrate was then concentrated to dryness. It was then washed with ether (100 mL) and filtered and B (0.320 g) was obtained. A was treated with MeOH (150 mL), filtered, and concentrated to yield C (0.630 g). The mixture B + C was dissolved in MeOH, filtered, and treated with aqueous KOH (10%, 50 mL); after 21 h at room temperature, water (100 mL) was added and the product extracted into $CHCl_3$ (2 × 100 mL) which was dried ($MgSO_4$), filtered, and concentrated to yield the desired product (0.26 g, 58%) as white crystals.

**4,4′-Bis(aminomethyl)diphenylmethane (5b) from 7b**. A mixture of 1 g (2.02 mmol) of **7b**, 0.53 mL of hydrazine monohydrate 98%, and DMSO (100 mL) was heated at 120 °C for 1.5 h. The DMSO was removed by concentration under reduced pressure. 2 N HCl (225 mL) was added to the residue and the mixture was stirred overnight at room temperature. Crystalline phthalhydrazine was removed by filtration. The filtrate was concentrated until a precipitate started to appear (40 mL). After filtration a solid was obtained which was dissolved in MeOH, 10% aqueous NaOH (25 mL) was added, and the solution was left for 4 h. A precipitate appeared when the solution was concentrated to 30 mL. The product was extracted into $CHCl_3$ (3 × 20 mL) which was dried ($MgSO_4$), filtered, and concentrated to yield white crystals (0.16 g, 35%).

**2,6-Bis(bromomethyl)anisole**[17d] **(9)**. A mixture of 2,6-dimethylanisole (1.3 g, 14 mmol), *N*-bromosuccinimide (4.9 g, 30 mmol), and dibenzoyl peroxide (0.4 g, 1.3 mmol) in $CCl_4$ was heated under reflux with stirring for 4 h, cooled, and filtered to remove the solid. The solvent was removed in vacuo to give an oil which solidified on cooling. This was recrystallized from hexane/EtOAc to give the product as a pale yellow crystalline solid (1.4 g, 50%): mp 90−91 °C (lit.[17d] mp 75 °C); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.36 (d, $J$ = 7.1 Hz, 2 H, H-3 and H-5), 7.10 (t, $J$ = 7 Hz, 1 H, H-4), 4.56 (s, 4 H, $CH_2Br$), 4.02 (s, 3 H, $OCH_3$); MS (EI) $[M]^+$ 296, fragment at $m/z$ 215.

**2,6-Bis(bromomethyl)phenol**[17e,f] **(10)**. To a stirred solution of **10** (1.23 g, 4.25 mmol) in $CH_2Cl_2$ was added a 1 M solution of $BBr_3$ in $CH_2Cl_2$ (2.15 mL). The mixture was heated under reflux with stirring for 18 h, cooled, and poured into water (100 mL). The organic layer was separated, dried

($MgSO_4$), and concentrated to dryness in vacuo to yield the product (1.1 g, 82%): mp 80−82 °C (lit.[17f] mp 80−82 °C); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.27 (d, $J$ = 8 Hz, 2 H, H-3 and H-5), 6.90 (t, $J$ = 7.9 Hz, 1 H, H-4), 5.61 (s, 1 H, OH), 4.50 (s, 4 H, $CH_2Br$); MS (EI) $[M - H]^+$ 280.

**General Procedure for the Preparation of 4,4′-Bis-[(quinolin-4-yl)aminomethyl]biphenyl Hydrate (4a), 4,4′-Bis[(quinolin-4-yl)aminomethyl]diphenylmethane Dimethanolate (4b), *p*-Bis[(quinolin-4-yl)aminomethyl]benzene (4c), and *m*-Bis[(quinolin-4-yl)aminomethyl]benzene Hydrate (4d)**. 4-Chloroquinoline and the respective diamine **5a**−**d** (0.5 equiv) were dissolved with heating in *n*-pentanol. The solution was heated under reflux for 41.5−47 h. In the course of the reaction a creamy precipitate formed. The solvent was removed in vacuo and the residue was suspended in MeOH; the solution was made alkaline by addition of aqueous NaOH (10%) and the suspension stirred for 3 h. The precipitate was collected by filtration and dried.

**4,4′-Bis[(quinolin-4-yl)aminomethyl]biphenyl Hydrate (4a)**. Recrystallized from MeOH, $CHCl_3$, petroleum ether (creamy crystals, 0.089 g, 29%): mp 250−252 °C dec; IR (KBr disk) $\nu_{max}$ 3265, 3061, 2925, 1533, 870 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.29 (d, $J$ = 5.3 Hz, 2 H, H-2), 8.28 (d, $J$ = 8.4 Hz, 2 H, H-5), 7.91 (t, $J$ = 5.9 Hz, 2 H, NH), 7.76 (dd, $J_1$ = 0.9 Hz, $J_2$ = 8 Hz, 2 H, H-8), 7.61 (dt, $J_1 = J_2$ = 1.3 Hz, 2 H, H-7), 7.58 (d, $J$ = 8.4 Hz, 4 H, biphenyl), 7.45 (dt, $J_1 = J_2$ = 1.3 Hz, 2 H, H-6), 7.44 (d, $J$ = 8.4 Hz, 4 H, biphenyl), 6.35 (d, $J$ = 5.4 Hz, 2 H, H-3), 4.57 (d, $J$ = 5.9 Hz, 2 H, NH-$CH_2$-$C_6H_4$); MS (FAB, MNOBA matrix) $[M + H]^+$ 467, fragments at $m/z$ 336, 322, 180, 145; HPLC (A:B = 1:1) major peak at 5.89 min representing 100% of the absorption. Anal. ($C_{26}H_{22}N_4 \cdot 1.6H_2O$) C, H, N.

**4,4′-Bis[(quinolin-4-yl)aminomethyl]diphenylmethane Dimethanolate (4b)**. Purified by column chromatography (MeOH:$CHCl_3$ = 1:1): mp 116−118 °C dec; IR (KBr disk) $\nu_{max}$ 3257, 3052, 2923, 2836, 1577, 1539, 766 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.3 (d, $J$ = 8.2 Hz, 2 H, H-5), 8.27 (d, $J$ = 5.5 Hz, 2 H, H-2), 7.93 (t, $J$ = 5.9 Hz, 2 H, NH), 7.77 (d, $J$ = 8.2 Hz, 2 H, H-8), 7.62 (dt, $J$ = 1, 7 Hz, $J_2$ = 7.7 Hz, 2 H, H-7), 7.44 (dt, $J_1$ = 1,7 Hz, $J_2$ = 7.7 Hz, 2 H, H-6), 7.28 (d, $J$ = 8 Hz, 4 H, $C_6H_4$-$CH_2$-$C_6H_4$), 7.16 (d, $J$ = 8 Hz, 4 H, $C_6H_4$-$CH_2$-$C_6H_4$), 6.32 (d, $J$ = 5.5 Hz, 2 H, H-3), 4.49 (d, $J$ = 5.8 Hz, 4H, NH-$CH_2$-$C_6H_4$), 3.85 (s, 2 H, $C_6H_4$-$CH_2$-$C_6H_4$); MS (FAB, MNOBA matrix) $[M + H]^+$ 481, fragments at $m/z$ 336, 103, 77; HPLC (A:B = 1:1) major peak at 11.5 min representing 100% of the absorption. Anal. ($C_{33}H_{28}N_4 \cdot 2.3CH_3OH$) C, H, N.

***p*-Bis[(quinolin-4-yl)aminomethyl]benzene (4c)**. Recrystallized from MeOH (creamy crystals, 0.573 g, 62%): mp 278−279 °C dec; IR (KBr disk) $\nu_{max}$ 3224, 3053, 1577, 1542, 879 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.28 (d, $J$ = 5.3 Hz, 2 H, H-2), 8.26 (d, $J$ = 7.6 Hz, 2 H, H-5), 7.89 (t, $J$ = 5.9 Hz, 2 H, NH), 7.76 (dd, $J_1$ = 0.8 Hz, $J_2$ = 8 Hz, 2 H, H-8), 7.60 (dt, $J_1$ = 1.3, $J_2$ = 7 Hz, $J_3$ = 7.6 Hz, 2 H, H-7), 7.43 (dt, $J_1$ = 1.3 Hz, $J_2$ = 7, $J_3$ = 7.6 Hz, 2 H, H-6), 7.33 (s, 4 H, *p*-phenylene moiety), 6.32 (d, $J$ = 5.5 Hz, 2 H, H-3), 4.51 (d, $J$ = 5.9 Hz, 4H, NH-$CH_2$-$C_6H_4$); MS (FAB, MNOBA matrix) $[M + H]^+$ 391, fragments at $m/z$ 246, 145; HPLC (A:B = 6:4) major peak at 7.84 min representing 100% of the absorption. Anal. ($C_{26}H_{22}N_4 \cdot 0.4H_2O$) C, H, N.

***m*-Bis[(quinolin-4-yl)aminomethyl]benzene Hydrate (4d)**. Recrystallized from MeOH (beige crystals, 0.772 g, 77.2%): mp 243−246 °C dec; IR (KBr disk) $\nu_{max}$ 3231, 3072, 2925, 2857, 1533, 757, 695 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.50 (d, $J$ = 5.3 Hz, 2 H, H-2), 7.98 (d, $J$ = 5.7 Hz, 2 H, H-5), 7.72 (d, $J$ = 8.4 Hz, 2 H, H-8), 7.63 (dt, $J_1$ = 1.3 Hz, $J_2$ = 7.7 Hz, 2 H, H-7), 7.43−7.33 (m, 6H, H-6, 2′ 4′, 5′ and 6′), 6.39 (d, $J$ = 5.3 Hz, 2 H, *m*-phenylene moiety), 5.44 ($s_{br}$, 2 H, NH), 4.55 (d, $J$ = 5.3 Hz, 4 H, NH-$CH_2$-$C_6H_4$); MS (FAB, MNOBA matrix) $[M + H]^+$ 391, fragments at $m/z$ 390, 260, 246, 145, 104; HPLC (A:B = 6:4) major peak at 6.81 min representing 98.4% of the absorption. Anal. ($C_{26}H_{22}N_4 \cdot 1.7H_2O$) C, H, N.

**General Procedure for the Preparation of the Cyclophanes 2a−f and 3a−n**. Equimolar amounts of the bisquinoline **4a**−**e** and of the appropriate dibromide Br-L-Br ($I(CH_2)_{10}I$ in the case of **3g**) were dissolved with heating in MEK. The solution was boiled with stirring under reflux for 23−120 h. The product was isolated by filtration and preparative HPLC was carried out. The resultant compound was dissolved in the minimum amount of cold $^i$PrOH and filtered by gravity and the solvent removed in vacuo, to give the product. The experimental details for the synthesis of cyclophanes **2b** and **3j** are given below as representative examples.

**7,18-Diaza-1,6(1,4)-diquinolina-3,4(1,3)-dibenzenacyclooctadecanephanedium Tetratrifluoroacetate Dihydrate (2a)**. Off-white powder: mp 112−114 °C; IR (Nujol mull) $\nu_{max}$ 3183, 1684, 799, 758 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.49 (t, $J$ = 6.1 Hz, 2 H, NH), 8.75 (d, $J$ = 7.6 Hz, 2 H, H-2), 8.55 (d, $J_1$=1 Hz, $J_2$ = 8.6 Hz, 2 H, H-8), 8.36 (d, $J$ = 8.9 Hz, 2 H, H-5), 8.00 (dt, $J_1$ = 0.8 Hz, $J_2$ = 7.9 Hz, $J_3$ = 8 Hz, 2 H, H-6 or H-7), 7.73 (t, $J$ = 7.8 Hz, 2 H, H-7 or H-6), 7.64−7.62 (m, 2 H, biphenyl moiety), 7.53−7.52 (m, 4 H, biphenyl moiety), 7.51 (s, 2 H, biphenyl moiety), 6.91 (d, $J$ = 7.6 Hz, 2 H, H-3), 5.83 (s, 4 H, $N^+$-$CH_2$), 3.56−3.50 (m, 4 H, NH-$CH_2$), 1.62−1.55 (m, 4 H, $CH_2$), 1.30−1.11 (m, 12 H, $CH_2$); MS (FAB, MNOBA + Na matrix) $[M]^+$ 606, fragments at $m/z$ 462, 426; HPLC (A:B = 35:65) major peak at 5.3 min representing 99.6% of the absorption. Anal. ($C_{42}H_{46}N_4^{2+} \cdot 2CF_3COO^- \cdot 2.2CF_3COOH \cdot 2.2H_2O$) C, H, N.

**8,19-Diaza-1,7(1,4)-diquinolina-3,5(1,4)-dibenzenacyclononadecanephanedium Tetratrifluoroacetate Hydrate (2b)**. 1,10-Bis(*N*-quinolin-4-ylamino)decane[15e] (**4e**) (0.2 g, 0.47 mmol) and 4,4′-bis(bromomethyl)diphenylmethane[18] (**8b**) (0.166 g, 0.47 mmol) were dissolved with heating in butanone (50 mL). The solution was boiled with stirring under reflux for 72 h. The solid that had formed was collected by filtration (0.28 g) and was subjected to preparative HPLC. The resultant compound was dissolved in the minimum amount of cold $^i$PrOH and filtered by gravity and the solvent removed in vacuo, to give an off-white powder (0.121 g, 24.5%): mp 181−186 °C; IR (KBr disk) $\nu_{max}$ 3555, 3232, 1684, 827, 765, 721; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.44 (t, 2 H, NH), 8.68 (d, $J$ = 7.3 Hz, 2 H, H-2), 8.51 (d, $J$ = 8.4 Hz, 2 H, H-8), 8.13 (d, $J$ = 9 Hz, 2 H, H-5), 7.92 (t, $J$ = 7.3 Hz, 2 H, H-7 or H-6), 7.69 (t, 2 H, H-7 or H-6), 7.70 (d, $J$ = 8.8 Hz, fluorene moiety), 7.02 (d, $J$ = 7.8 Hz, 2 H, H-6 or H-7), 7.18 (m, 8 H, diphenylmethane moiety), 6.91 (d, $J$ = 7.5 Hz, 2 H, H-3), 5.71 (s, 4 H, $N^+$-$CH_2$), 3.88 (s, 2 H, $C_6H_4$-$CH_2$-$C_6H_4$), 3.54−3.49 (m, 4 H, NH-$CH_2$), 1.59 (m, 4 H, $CH_2$), 1.30−1.22 (m, 12 H, $CH_2$); MS (FAB, MNOBA + Na matrix) $[M - H]^+$ 619, fragments at $m/z$ 426, 194; HPLC (A:B = 4:6) major peak at 11.80 min representing 99.5% of the absorption at 215 nm. Anal. ($C_{43}H_{48}N_4^{2+} \cdot 2CF_3COO^- \cdot 1.5CF_3COOH \cdot 1.5H_2O$) C, H, N.

**6,17-Diaza-1,5(1,4)-diquinolina-3(2,7)-fluorenacycloheptadecanephanedium Tetratrifluoroacetate Dihydrate (2c)**. Off-white powder: mp 214−216 °C; IR (Nujol mull) $\nu_{max}$ 3272, 3207, 1684, 830, 753, 722 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.52 (m, 2 H, NH), 8.71 (d, $J$ = 7.5 Hz, 2 H, H-2), 8.46 (d, $J$ = 7.8 Hz, 2 H, H-8), 8.33 (d, $J$ = 8.8 Hz, 2 H, H-5), 7.96 (t, $J$ = 7.9 Hz, 2 H, H-6 or H-7), 7.90 (d, $J$ = 7.8 Hz, 2 H, fluorene moiety), 7.71−7.67 (m, 2 H, H-7 or H-6), 7.70 (d, $J$ = 8.8 Hz, 2 H, fluorene moiety), 7.02 (d, $J$ = 7.7 Hz, 2 H, H-3), 6.98 (s, 2 H, fluorene moiety), 5.89 (s, 4 H, $N^+$-$CH_2$), 3.61−3.55 (m, 6 H, NH-$CH_2$ and fluorene moiety), 1.57−1.52 (m, 4 H, $CH_2$), 1.26−1.19 (m, 4 H, $CH_2$), 1.17−1.10 (m, 8 H, $CH_2$); MS (FAB, MNOBA + Na matrix) $[M]^+$ 618, fragments at $m/z$ 479, 426; HPLC (A:B = 4:6) major peak at 4.61 min representing 100% of the absorption. Anal. ($C_{43}H_{46}N_4^{2+} \cdot 2CF_3COO^- \cdot 1.9CF_3COOH \cdot 2H_2O$) C, H, N.

**9,20-Diaza-1,8(1,4)-diquinolina-3,6(1,4)-dibenzena-4(*Z*)-enecycloicosaphanedium Tetratrifluoroacetate Dihydrate (2d)**. Off-white powder: mp 184−186 °C; IR (Nujol mull) $\nu_{max}$ 3175, 1684, 722 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.53 (t, $J$ = 6.1 Hz, 2 H, NH), 8.72 (d, $J$ = 7.5 Hz, 2 H, H-2), 8.55 (d, $J$ = 8.5 Hz, 2 H, H-8), 8.02 (t, $J$ = 8.7 Hz, 2 H, H-5), 7.90 (t, $J$ = 6.5 Hz, 2 H, H-7 or H-6), 7.70 (t, $J$ = 6.5 Hz, 2 H, H-6 or H-7), 7.23 (d, $J$ = 8.4 Hz, 4 H, stilbene moiety), 7.18 (d, $J$ = 8.4 Hz, 4 H, stilbene moiety), 6.94 (d, $J$ = 7.6 Hz, 2 H,

H-3), 6.57 (s, 2 H, CH═CH), 5.76 (s, 4 H, $N^+$-*CH*$_2$), 3.56−3.44 (m, 4 H, NH-*CH*$_2$), 1.65 (m, 4 H, $CH_2$), 1.38−1.29 (m, 12 H, $CH_2$); MS (FAB, MNOBA matrix) $[M]^+$ 632, fragments at *m*/*z* 633, 631, 427, 206, 178, 157, 77, 43; HPLC (A:B = 35:65) major peak at 10.3 min representing 99.6% of the absorption. Anal. ($C_{44}H_{48}N_4^{2+}\cdot 2CF_3COO^-\cdot 2.2CF_3COOH\cdot 2.2H_2O$) C, H, N.

**9,20-Diaza-1,8(1,4)-diquinolina-3,6(1,4)-dibenzenacycloicosaphanedium Tritrifluoroacetate Hydrate (2e)**. Off-white powder: mp 202−204 °C; IR (Nujol mull) $\nu_{max}$ 3179, 1685, 825, 765, 722; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.50 (t, $J$ = 5.4 Hz, 2 H, NH), 8.71 (d, $J$ = 7.6 Hz, 2 H, H-2), 8.55 (d, $J$ = 8.5 Hz, 2 H, H-8), 7.86−7.85 (m, 4 H, H-5 and H-6 or H-7), 7.69 (dt, $J_1$ = 1.9 Hz, $J_2$ = 7.6 Hz, 2 H, H-7 or H-6), 7.02−6.95 (m, 10 H, bibenzyl moiety), 5.70 (s, 4 H, $N^+$-*CH*$_2$), 3.60−3.40 (m, 4 H, NH-*CH*$_2$), 2.93 (s, 4 H, $C_6H_4$-*CH*$_2$-*CH*$_2$-$C_6H_4$), 1.67−1.58 (m, 4 H, $CH_2$), 1.39−1.22 (m, 12 H, $CH_2$); HPLC (A:B = 35:65) major peak at 8.15 min representing 100% of the absorption. Anal. ($C_{44}H_{50}N_4^{2+}\cdot 2CF_3COO^-\cdot 1.2CF_3COOH\cdot 1.2H_2O$) C, H, N.

**7,18-Diaza-1,6(1,4)-diquinolina-3,4(1,4)-dibenzenacyclooctadecanephanedium Tritrifluoroacetate Hydrate (2f)**. Off-white powder: mp 280−282 °C; IR (Nujol mull) $\nu_{max}$ 3170, 1684, 800, 758, 722 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.59 (t, 2 H, NH), 8.62 (d, $J$ = 7.3 Hz, 2 H, H-2), 8.61 (d, $J$ = 9.7 Hz, 2 H, H-8), 8.51 (d, $J$ = 8.4 Hz, 2 H, H-5), 8.05 (t, $J$ = 8.7 Hz, 2 H, H-6 or H-7), 7.73 (t, $J$ = 7.7 Hz, 2 H, H-7 or H-6), 7.56 (m, 8 H, biphenyl moiety), 6.91 (d, $J$ = 7.9 Hz, 2 H, H-3), 5.83 (s, 4 H, $N^+$-*CH*$_2$), 3.50−3.42 (m, 4 H, NH-*CH*$_2$), 1.45 (m, 4 H, $CH_2$), 1.22−1.06 (m, 12 H, $CH_2$); MS (FAB, MNOBA matrix) $[M]^+$ 606, fragments at *m*/*z* 605, 180; HPLC (A:B = 4:6) major peak at 5.30 min representing 98.4% of the absorption. Anal. ($C_{42}H_{46}N_4^{2+}\cdot 2CF_3COO^-\cdot 1.4CF_3COOH\cdot 1.4H_2O$) C, H, N.

**8,14-Diaza-1,7(1,4)-diquinolina-3,5,10,12(1,4)-tetrabenzenacyclotetradecaphanedium Tritrifluoroacetate Dihydrate (3a)**. Off-white microcrystalline compound: mp 218−220 °C dec; IR (KBr disk) $\nu_{max}$ 3236, 1685, 832 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.95 (t, $J$ = 5.8 Hz, 2 H, NH), 8.63 (d, $J$ = 7.3 Hz, 2 H, H-5), 8.53 (d, $J$ = 7.6 Hz, 2 H, H-2), 8.11 (d, $J$ = 9 Hz, 2 H, H-8), 7.94 (t, $J$ = 7.5 Hz, 2 H, H-7), 7.71 (t, $J$ = 7.8 Hz, 2 H, H-6), 7.28 (d, $J$ = 8.1 Hz, 4 H, *C*$_6$*H*$_4$-CH$_2$-*C*$_6$*H*$_4$), 7.15 (d, $J$ = 8.1 Hz, 4 H, *C*$_6$*H*$_4$-CH$_2$-*C*$_6$*H*$_4$), 7.14 (s, 8 H, *C*$_6$*H*$_4$-CH$_2$-*C*$_6$*H*$_4$), 6.96 (d, $J$ = 7.7 Hz, 2 H, H-3), 5.71 (s, 4 H, $N^+$-*CH*$_2$), 4.79 (d, $J$ = 5.8 Hz, 4 H, NH-*CH*$_2$), 3.91 (s, 2 H, $C_6H_4$-*CH*$_2$-$C_6H_4$), 3.85 (s, 2 H, $C_6H_4$-*CH*$_2$-$C_6H_4$); MS (FAB, MNOBA matrix) $[M]^+$ 674, fragments at *m*/z 673, 493, 480, 337, 193; HPLC (A:B = 4:6) major peak at 8.21 min representing 100% of the absorption. Anal. ($C_{48}H_{42}N_4^{2+}\cdot 2CF_3COO^-\cdot CF_3COOH\cdot 2.2H_2O$) C, H, N.

**8,13-Diaza-1,7(1,4)-diquinolina-3,5,10,11(1,4)-tetrabenzenacyclotridecaphanedium Tetratrifluoroacetate Heptahydrate (3b)**. Off-white powder: mp > 350 °C; IR (KBr disk) $\nu_{max}$ 3225, 1679, 1339, 805, 762 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.33 (t, $J$ = 6 Hz, 2 H, NH), 8.69 (d, $J$ = 8.4 Hz, 2 H, H-5), 8.64 (d, $J$ = 7.5 Hz, 2 H, H-2), 8.24 (d, $J$ = 9 Hz, 2 H, H-8), 8.02 (pt, $J_1$=7.9 Hz, $J_2$=8.1 Hz, 2 H, H-7), 7.82 (pt, $J_1$=7.6 Hz, $J_2$=7.9 Hz, 2 H, H-6), 7.64 (d, $J$ = 8.3 Hz, 4 H, $C_6H_4$-$C_6H_4$), 7.51 (d, $J$ = 8.3 Hz, 4 H, $C_6H_4$-$C_6H_4$), 7.00 (d, $J$ = 8.6 Hz, 8 H, *C*$_6$*H*$_4$-CH$_2$-*C*$_6$*H*$_4$), 6.65 (d, $J$ = 7.5 Hz, 2 H, H-3), 5.76 (s, 4H, $N^+$-*CH*$_2$), 4.86 (d, $J$ = 5.6 Hz, 4H, NH-*CH*$_2$), 3.87 (s, 2 H, $C_6H_4$-*CH*$_2$-$C_6H_4$); MS (FAB, MNOBA matrix) $[M]^+$ 660, fragments at *m*/*z* 659, 583; HPLC (A:B = 45:55) major peak at 8.54 min representing 100% of the absorption. Anal. ($C_{48}H_{42}N_4^{2+}\cdot 2CF_3COO^-\cdot 2.5CF_3COOH\cdot 7H_2O$) C, H, N.

**6,11-Diaza-1,5(1,4)-diquinolina-3(2,7)-fluorena-8,9(1,4)-dibenzenacycloundecaphanedium Tetratrifluoroacetate Hexahydrate (3c)**. Before performing preparative HPLC, the product was treated with a boiling mixture of EtOH/MeOH and the insoluble material was collected. This was purified by preparative HPLC as detailed above. The compound was isolated as an off-white powder: mp 316−319 °C; IR (KBr disk) $\nu_{max}$ 3214, 1609, 1339, 803, 756 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.28 (t, $J$ = 5.7 Hz, 2 H, NH), 8.73 (d, $J$ = 7.5 Hz, 2 H, H-2), 8.64 (d, $J$ = 9 Hz, 2 H, H-5), 8.40 (d, $J$ = 8.7 Hz, 2 H, H-8), 8.00 (pt, $J_1$ = $J_2$ = 7.6 Hz, 2 H, H-7), 7.79 (d, $J$ = 7.9 Hz, 2 H, fluorene), 7.78 (pt, $J_1$ = 7.9 Hz, $J_2$ = 8.4 Hz, 2 H, H-6), 7.57 (dd, $J_1$ = 1 Hz, $J_2$ = 8 Hz, 2 H, fluorene), 7.53 (d, $J$ = 8.4 Hz, 4 H, $C_6H_4$-$C_6H_4$), 7.45 (d, $J$ = 8.4 Hz, 4 H, $C_6H_4$-$C_6H_4$), 7.02 (d, $J$ = 7.6 Hz, 2 H, H-3), 6.53 (s, 2 H, fluorene), 5.89 (s, 4 H, $N^+$-*CH*$_2$), 4.90 (d, $J$ = 5.7 Hz, 4 H, NH-*CH*$_2$), 3.26 (s, 2 H, fluorene); MS (FAB, MNOBA matrix) $[M]^+$ 658, fragments at *m*/z 657, 467, 192; HPLC (A:B = 1:1) major peak at 7.13 min representing 99.2% of the absorption. Anal. ($C_{47}H_{38}N_4^{2+}\cdot 2CF_3COO^-\cdot 2CF_3COOH\cdot 6.6H_2O$) C, H, N.

**9,15-Diaza-1,8(1,4)-diquinolina-3,6,11,13(1,4)-tetrabenzena-4(*Z*)-enecyclopentadecaphanedium Ditrifluoroacetate Trihydrate (3d)**. Recrystallized from absolute EtOH/$Et_2O$ to give a white powder: mp 267−269 °C dec; IR (KBr disk) $\nu_{max}$ 3214, 1685, 1339, 800, 767 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.10 (t, $J$ = 6 Hz, 2 H, NH), 8.66 (d, $J$ = 8.5 Hz, 2 H, H-5), 8.58 (d, $J$ = 7.4 Hz, 2 H, H-2), 8.10 (d, $J$ = 9 Hz, 2 H, H-8), 7.98 (pt, $J_1$ = 7.8 Hz, $J_2$ = 7.9 Hz, 2 H, H-7), 7.76 (pt, $J_1$ = 7.5 Hz, $J_2$ = 7.9 Hz, 2 H, H-6), 7.31 (d, $J$ = 8.4 Hz, 4 H, *C*$_6$*H*$_4$-CH$_2$-*C*$_6$*H*$_4$), 7.24 (d, $J$ = 8.4 Hz, 4 H, *C*$_6$*H*$_4$-CH═CH-*C*$_6$*H*$_4$), 7.21 (d, $J$ = 8.4 Hz, 4 H, *C*$_6$*H*$_4$-CH$_2$-*C*$_6$*H*$_4$), 7.18 (d, $J$ = 8.4 Hz, 4 H, *C*$_6$*H*$_4$-CH═CH-*C*$_6$*H*$_4$), 6.88 (d, $J$ = 7.6 Hz, 2 H, H-3), 6.58 (s, 2 H, *CH*═*CH*), 5.74 (s, 4 H, $N^+$-*CH*$_2$), 4.79 (d, $J$ = 6 Hz, 4 H, NH-*CH*$_2$), 3.88 (s, 2 H, $C_6H_4$-*CH*$_2$-$C_6H_4$); MS (FAB, MNOBA matrix) $[M]^+$ 686, fragments at *m*/z 685, 349, 206; HPLC (A:B = 35:65) major peak at 8.14 min representing 100% of the absorption. Anal. ($C_{48}H_{42}N_4^{2+}\cdot 2CF_3COO^-\cdot 3.4H_2O$) C, H, N.

**7,13-Diaza-1,6(1,4)-diquinolina-3,4,9,11(1,4)-tetrabenzenacyclotridecaphanedium Tetratrifluoroacetate Dihydrate (3e)**. White microcrystalline compound: mp 224−226 °C dec; IR (KBr disk) $\nu_{max}$ 3257, 1685, 1345, 800, 762 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.95 (t, $J$ = 5.6 Hz, 2 H, NH), 8.62 (d, $J$ = 9.6 Hz, 2 H, H-5), 8.60 (d, $J$ = 8.7 Hz, 2 H, H-2), 8.51 (d, $J$ = 8.4 Hz, 2 H, H-8), 8.06 (pt, $J_1$ = 7.6 Hz, $J_2$ = 7.7 Hz, 2 H, H-7), 7.75 (pt, $J_1$ = 7.6 Hz, $J_2$ = 7.9 Hz, 2 H, H-6), 7.57 (d, $J$ = 8.5 Hz, 4 H, $C_6H_4$-$C_6H_4$), 7.52 (d, $J$ = 8.5 Hz, 4 H, $C_6H_4$-$C_6H_4$), 7.18 (d, $J$ = 8 Hz, 4 H, *C*$_6$*H*$_4$-CH$_2$-*C*$_6$*H*$_4$), 7.07 (d, $J$ = 8 Hz, 4 H, *C*$_6$*H*$_4$-CH$_2$-*C*$_6$*H*$_4$), 7.00 (d, $J$ = 7.8 Hz, 2 H, H-3), 5.82 (s, 4 H, $N^+$-*CH*$_2$), 4.77 (d, $J$ = 5.6 Hz, 4 H, NH-*CH*$_2$), 3.93 (s, 2 H, $C_6H_4$-*CH*$_2$-$C_6H_4$); MS (FAB, MNOBA matrix) $[M]^+$ 660, fragments at *m*/z 659, 480, 180; HPLC (A:B = 45:55) major peak at 8.86 min representing 100% of the absorption. Anal. ($C_{48}H_{42}N_4^{2+}\cdot 2CF_3COO^-\cdot 2CF_3COOH\cdot 2H_2O$) C, H, N.

**7,12-Diaza-1,6(1,4)-diquinolina-3,4,9,10(1,4)-tetrabenzenacyclododecaphanedium Hexatrifluoroacetate Tetrahydrate (3f)**. Off-white powder: mp 190−192 °C; IR (Nujol mull) $\nu_{max}$ 3183, 1652 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.12 (t, 2 H, NH), 8.75 (d, 2 H, H-5 or H-8), 8.61 (d, 2 H, H-2), 8.60 (d, 2 H, H-5 or H-8), 8.13 (t, 2 H, H-6 or H-7), 7.84 (t, 2 H, H-6 or H-7), 7.48 (d, 4 H, biphenyl), 7.42 (d, 8 H, biphenyl), 7.37 (d, 4 H, biphenyl), 6.89 (d, 2 H, H-3), 5.81 (s, 4 H, $N^+$-*CH*$_2$), 4.79 (d, 4 H, NH-*CH*$_2$); MS (FAB, MNOBA matrix) $[M - H]^+$ 645; HPLC (A:B = 50:50) major peak at 7.08 min representing 96% of the absorption. Anal. ($C_{46}H_{38}N_4^{2+}\cdot 2CF_3COO^-\cdot 4CF_3COOH\cdot 4H_2O$) C, H, N.

**2,7-Diaza-1,8(4,1)-diquinolina-4,5(1,4)-dibenzenacyclooctadecaphanedium Trifluoroacetate Hydrate (3g)**. Yellow powder: mp 233−234 °C; IR (Nujol mull) $\nu_{max}$ 3199, 1615 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.35 (t, 2 H, NH), 8.67 (d, 2 H, H-5 or H-8), 8.49 (d, 2 H, H-2), 8.15 (d, 2 H, H-5 or H-8), 8.01 (t, 2 H, H-6 or H-7), 7.80 (t, 2 H, H-6 or H-7), 7.66 (d, 4 H, biphenyl), 7.50 (d, 4 H, biphenyl), 6.57 (d, 2 H, H-3), 4.84 (d, 4 H, NH-*CH*$_2$), 4.48 (t, 4 H, $N^+$-*CH*$_2$), 1.59 (m, 4 H, $CH_2$), 1.10−0.91 (m, 12 H, $CH_2$); MS (FAB, MNOBA matrix) $[M - H]^+$ 605; HPLC (linear gradient from A:B = 45:55 to A:B = 20:80) major peak at 9.88 min representing 99.9% of the absorption. Anal. ($C_{42}H_{46}N_4^{2+}\cdot 2CF_3COO^-\cdot 1.1CF_3COOH\cdot 1.1H_2O$) C, H, N.

**8,14-Diaza-1,7(1,4)-diquinolina-4(2,6)-pyridina-3,5,10,12(1,4)-tetrabenzenacyclotetradecaphanedium Tritrifluoroacetate Dimethanolate Trihydrate (3h)**. Before performing preparative HPLC, the product was treated with boiling EtOH and the insoluble material was collected. This was purified by preparative HPLC as detailed above. The

compound was isolated as an off-white powder: mp 224−226 °C; IR (KBr disk) $\nu_{max}$ 3247, 1614, 1345, 800, 767 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.08 (t, $J$ = 5 Hz, 2 H, NH), 8.87 (d, $J$ = 7.4 Hz, 2 H, H-2), 8.59 (d, $J$ = 8.7 Hz, 2 H, H-5), 8.15 (d, $J$ = 8.4 Hz, 4 H, *bisphenyl*pyridine), 7.96 (s, 3 H, pyridine), 7.90−7.88 (m, 4 H, H-5 and H-7), 7.70 (ddd, $J_1$ = 1.5 Hz, $J_2 = J_3$ = 8.3 Hz, 2 H, H-6), 7.40 (d, $J$ = 8.1 Hz, 4 H, *bisphenyl*pyridine), 7.22 (d, $J$ = 8.1 Hz, 4 H, $C_6H_4$-$CH_2$-$C_6H_4$), 7.20 (d, $J$ = 8.1 Hz, 4 H, $C_6H_4$-$CH_2$-$C_6H_4$), 7.17 (d, $J$ = 7.7 Hz, 2 H, H-3), 5.93 (s, 4 H, $N^+$-$CH_2$), 4.88 (d, $J$ = 5 Hz, 4 H, NH-$CH_2$), 4.03 (s, 2 H, $C_6H_4$-$CH_2$-$C_6H_4$); MS (FAB, MNOBA matrix) $[M]^+$ 737, fragments at *m*/z 636, 594, 257; HPLC (A:B = 4:6) major peak at 7.87 min representing 100% of the absorption. Anal. ($C_{52}H_{43}N_5^{2+}\cdot 3CF_3COO^-\cdot 2CH_3OH\cdot 2.8H_2O$) C, H, N.

**6,10-Diaza-1,5(1,4)-diquinolina-3,8(1,3)-dibenzenacyclodecaphanedium Ditrifluoroacetate Dihydrate (3i)**. White microcrystalline compound: mp 224−226 °C dec; IR (KBr disk) $\nu_{max}$ 3257, 1674, 832, 757, 719 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.19 (t, $J$ = 5.2 Hz, 2 H, *NH*), 8.43 (d, $J$ = 7.5 Hz, 2 H, H-2), 8.33 (dd, $J_1$=0.5 Hz, $J_2$=7.8 Hz, 2 H, H-5), 7.65−7.46 (m, 10 H, H-6, H-7, *m*-phenylene moieties), 7.23 (d, $J$ = 8.9 Hz, 2 H, H-8), 7.08 (s, 1 H, *m*-phenylene moiety), 6.52 (d, $J$ = 7.4 Hz, 2 H, H-3), 5.73, (s, 4 H, $N^+$-$CH_2$), 5.07 (d, $J$ = 0.4 Hz, 1 H, *m*-phenylene moiety), 4.84 (d, $J$ = 5.7 Hz, 4 H, NH-$CH_2$); MS (FAB, MNOBA matrix) $[M]^+$ 494, fragments at *m*/z 493, 391, 247, 104; HPLC (A:B = 6:4) major peak at 5.92 min representing 100% of the absorption. Anal. ($C_{34}H_{30}N_4^{2+}\cdot 2CF_3COO^-\cdot 2.4H_2O$) C, H, N.

**6,10-Diaza-1,5(1,4)-diquinolina-3(1,3),8(1,4)-dibenzenacyclodecaphanedium Tritrifluoroacetate Hydrate (3j)**. *p*-Bis[(quinolin-4-yl)aminomethyl]benzene (**4c**) (0.18 g, 0.046 mmol) and 1,3-bis(bromomethyl)benzene (0.122 g, 0.046 mmol) were dissolved with heating in butanone (25 mL). The solution was boiled with stirring under reflux for 23 h. The solid that had formed was collected by filtration (0.217 g) and was subjected to preparative HPLC. The resultant compound was dissolved in the minimum amount of cold $^i$PrOH and filtered by gravity and the solvent removed in vacuo, to give a white crystalline compound (0.06 g, 29.8%): mp 255−257 °C dec; IR (KBr disk) $\nu_{max}$ 3247, 1688, 832, 761, 717 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.30 (t, $J$ = 5.9 Hz, 2 H, NH), 8.55 (d, $J$ = 7 Hz, 2 H, H-5), 8.54 (d, $J$ = 7.6 Hz, 2 H, H-2), 8.19 (d, $J$ = 8.8 Hz, 2 H, H-8), 7.96 (dd, $J$ = 7.6 Hz, 2 H, H-7), 7.76 (t, $J$ = 8.8 Hz, 2 H, H-6), 7.73 (t, $J$ = 7.9 Hz, 2 H, *m*-phenylene moiety), 7.50 (t, $J$ = 7.8 Hz, 1 H, *m*-phenylene moiety), 7.45 (s, 4 H, *p*-phenylene moiety), 6.88 (s, 1 H, *m*-phenylene moiety), 6.45 (d, $J$ = 7.6 Hz, 2 H, H-3), 5.64 (s, 4 H, $N^+$-$CH_2$), 4.77 (d, $J$ = 5.6 Hz, 4 H, NH-$CH_2$); MS (FAB, MNOBA matrix) $[M - H]^+$ 493, fragments at *m*/z 391, 247, 104, 43; HPLC (A:B = 6:4) major peak at 5.65 min representing 99.5% of the absorption. Anal. ($C_{34}H_{30}N_4^{2+}\cdot 2CF_3COO^-\cdot CF_3COOH\cdot H_2O$) C, H, N.

**6,10-Diaza-1,5(1,4)-diquinolina-8(1,3),3(1,4)-dibenzenacyclodecaphanedium Ditrifluoroacetate Hydrate (3k)**. White powder: mp 234−236 °C dec; IR (KBr disk) $\nu_{max}$ 3236, 1679, 832, 762, 719 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.16 (t, $J$ = 6.1 Hz, 2 H, NH), 8.56 (d, $J$ = 8.9 Hz, 2 H, H-5), 8.53 (d, $J$ = 7.6 Hz, 2 H, H-2), 8.06 (pt, $J_1$ = 7.6 Hz, $J_2$ = 8.4 Hz, 2 H, H-7), 7.78 (pt, $J_1$ = 7.7 Hz, $J_2$ = 7.8 Hz, 2 H, H-6), 7.67 (d, $J$ = 7.6 Hz, 2 H, H-8), 7.43 (s, 4 H, *p*-phenylene moiety), 7.39−7.35 (m, 4 H, *m*-phenylene moiety), 6.57 (d, $J$ = 7.6 Hz, 2 H, H-3), 5.71 (s, 4 H, $N^+$-$CH_2$), 4.67 (d, $J$ = 5.8 Hz, 4H, NH-$CH_2$); MS (FAB, MNOBA matrix) $[M]^+$ 494, fragments at *m*/z 493, 391, 247, 104, 43; HPLC (A:B = 6:4) major peak at 9.93 min representing 98% of the absorption. Anal. ($C_{34}H_{30}N_4^{2+}\cdot 2CF_3COO^-\cdot 1.1H_2O$) C, H, N.

**6,10-Diaza-1,5(1,4)-diquinolina-3,8(1,4)-dibenzenacyclodecaphanedium Tritrifluoroacetate Hydrate (3l)**. White powder: mp 326−328 °C dec; IR (KBr disk) $\nu_{max}$ 3247, 1665, 832 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.21 (t, $J$ = 5.5 Hz, 2 H, NH), 8.70 (d, $J$ = 9 Hz, 2 H, H-5), 8.52 (d, $J$ = 7.6 Hz, 2 H, H-2), 8.28 (d, $J$ = 7.6, 2 H, H-8), 8.08 (pt, $J_1$ = 7.4 Hz, $J_2$ = 8.4 Hz, 2 H, H-7), 7.79 (pt, $J_1$ = 7.4 Hz, $J_2$ = 8.4 Hz, 2 H, H-6), 7.30 (s, 4 H, $C_6H_4$), 7.22 (s, 4 H, $C_6H_4$), 6.66 (d, $J$ = 7.6 Hz, 2 H, H-3), 5.73 (s, 4 H, $N^+$-$CH_2$), 4.68 (d, $J$ = 5.8 Hz, 4 H, NH-$CH_2$); MS (FAB, MNOBA matrix) $[M]^+$ 494, fragments at *m*/z 493, 389, 247, 104; HPLC (A:B = 6:4) major peak at 4.45 min representing 99.97% of the absorption. Anal. ($C_{34}H_{30}N_4^{2+}\cdot 2CF_3COO^-\cdot CF_3COOH\cdot 1.2H_2O$) C, H, N.

**3²-Methoxy-6,10-diaza-1,5(1,4)-diquinolina-3(1,3),8(1,4)-dibenzenacyclodecaphanedium Dibromide Dihydrate (3m)**. The product was isolated by filtration from the reaction mixture and was purified by recrystallization from MeOH to give an off-white crystalline solid: mp 282−285 °C; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.20 ($s_{br}$, 2 H, NH), 8.59 (d, $J$ = 8.8 Hz, 2 H, H-5 or H-8), 8.19 (d, $J$ = 7.5 Hz, 2 H, H-2), 8.05 (t, $J$ = 8 Hz, 2 H, H-6 or H-7), 7.88 (d, $J$ = 7.7 Hz, 2 H, H-5 or H-8), 7.78 (t, $J$ = 7.8 Hz, 2 H, H-6 or H-7), 7.48 (d, 2 H, Ar), 7.37 (s, 4 H, $C_6H_4$), 7.28 (t, $J$ = 7.7 Hz, 1 H, Ar), 6.29 (d, $J$ = 7.5 Hz, 2 H, H-3), 5.70 (s, 4 H, $N^+$-$CH_2$), 4.75 (m, 4 H, NH-$CH_2$), 3.84 (s, 3 H, $OCH_3$); MS (FAB, MNOBA matrix) $[M - H]^+$ 523; HPLC (A:B = 62:38) major peak at 6.96 min representing 94.6% of the absorption. Anal. ($C_{35}H_{32}N_4O^{2+}\cdot 2Br^-\cdot 2H_2O$) C, H, N.

**3²-Hydroxy-6,10-diaza-1,5(1,4)-diquinolina-3(1,3),8(1,4)-dibenzenacyclodecaphanedium Dibromide Methanolate (3n)**. The product was isolated by filtration from the reaction mixture and was purified by recrystallization from MeOH to give a pale yellow crystalline solid: mp 280−282 °C; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.05 (pt, 2 H, NH), 9.43 (s, 1 H, OH), 8.55 (d, $J$ = 8.1 Hz, 2 H, H-5 or H-8), 8.46 (d, $J$ = 8.4 Hz, 2 H, H-8 or H-5), 8.04 (m, 4 H, H-2 and H-6 or H-7), 7.79 (d, $J$ = 8.1 Hz, 2 H, H-6 or H-7), 7.71 (d, $J$ = 7.3 Hz, 2 H, phenol moiety), 7.35 (s, 4 H, $C_6H_4$), 7.08 (t, 1 H, phenol moiety), 6.22 (d, $J$ = 7.7 Hz, 2 H, H-3), 5.63 (s, 4 H, $N^+$-$CH_2$), 4.72 (d, 4 H, NH-$CH_2$); MS (FAB, MNOBA matrix) $[M - H]^+$ 509; HPLC (A:B = 60:40) major peak at 14.5 min representing 97% of the absorption. Anal. ($C_{34}H_{30}N_4O^{2+}\cdot 2Br^-\cdot HBr\cdot CH_3OH$) C, H, N.

**3²-Hydroxy-3⁵-iodo-6,10-diaza-1,5(1,4)-diquinolina-3(1,3),8(1,4)-dibenzenacyclodecaphanedium Diiodide Methanolate Hemihydrate (3o)**. To a solution of **3n** (0.01 g, 0.162 mmol) and NaI (0.0029 g, 0.195 mmol) in DMF at 28 °C was added chloramine-T (0.0055 g, 0.195 mmol). The mixture was stirred at 28 °C for 1 h, then diluted with $H_2O$ (2 mL) and acidified with a 5% solution of HCl in water. The solid which separated was collected by filtration, washed with water (2 mL) and $Na_2S_2O_3$ solution, and dried. This solid was recrystallized from MeOH to give the product as a yellow powder: mp 260 °C; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.86 (s, 1 H, OH), 8.93 (d, $J$ = 8 Hz, 2 H, H-2), 8.46 (m, 4 H, H-5 and H-8), 8.01 (d, $J$ = 2 Hz, 2 H, H-6 or H-7), 7.73 (d, $J$ = 2 Hz, 2 H, H-6 or H-7), 7.54 (s, 2 H, phenol moiety), 7.34 ($s_{br}$, 6 H, $C_6H_4$ and NH), 6.20 (d, $J$ = 2 Hz, 2 H, H-3), 5.27 (s, 4 H, $N^+$-$CH_2$), 4.69 (d, 4 H, NH-$CH_2$); MS (FAB, MNOBA matrix) $[M]^+$ 635, fragment at *m*/*z* 391; HPLC (A:B = 60:40) major peak at 28.8 min representing 94% of the absorption. Anal. ($C_{34}H_{29}IN_4O^{2+}\cdot 2I^-\cdot CH_3OH\cdot 0.5H_2O$) C, H; N: calcd, 6.01; found, 5.60.

**Molecular Modeling**. The conformational search for each molecule involved exploration of the conformational space using torsional dynamics, employing the XEDYNIN module of XED/COSMIC[21] running on a Silicon Graphics $O^2$ workstation, with charges from an ab initio 6-31G* calculation. The temperature of the run was 1000 °C, the length was 400 ps, and the collection interval was 2 ps; i.e., 200 structures were stored from each run. The dynamics run was performed three times with a dielectric constant of 1, 4, or 78.5 to attenuate the influence of the electrostatics which, in vacuo, might restrict the conformational preferences of the molecule. Each set of 200 structures was minimized using the XEDMININ module of XED with a dielectric constant of 1, 4, or 78.5. All structures resulting from the minimizations were placed in one file and filtered for duplicate conformers. All unique conformers were fully minimized at the AM1 level using GAMESS,[23] and duplicate conformers were again discarded. The unique conformers obtained from this procedure were subjected to 6-31G* single-point calculations (GAMESS) to calculate the energy of the conformer at the ab initio level.

**Acknowledgment.** This work was partially supported by the Wellcome Trust including fellowships to

D.G. and P.M.D. The award of a grant from the Spanish DGICYT to J.C.R. is acknowledged. We are grateful to Dr. J. G. Vinter for his advice on the XED/COSMIC molecular modeling system, to Mr. A. A. T. Stones for the elemental combustion analyses, and to Dr. M. Mruzek and Mr. S. Corker for running the mass spectra.

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JM9902537