Articles

Synthesis and Quantitative Structure−Activity Relationship of a Novel Series of Small Conductance Ca^{2+}-Activated K^+ Channel Blockers Related to Dequalinium

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Received July 19, 1995[⊗]

The synthesis, pharmacological testing, and quantitative structure−activity relationship studies of a novel series of bisquinolinium small conductance Ca^{2+}-activated K^+ channel blockers (**23**) related to dequalinium are described. In this series, two quinolinium rings are linked via the 4-position to an α,ω-diamino alkylene chain and the ring N atom is quaternized with a methyl or benzyl group. The exocyclic N atom can be replaced by O, S, or CH_2 but with some loss of potency. The quinoline groups do not have to be quaternized for blocking activity, as long as they are basic enough to be protonated at the site of action. For the quaternary compounds, there is considerable steric tolerance for the group R attached to the ring N atom of the quinoline; a benzyl group gave the optimum potency in this series. Moreover, and in contrast to previously reported results for dequalinium analogues, there is no correlation of activity with N^1 charge or E_{HOMO}. On the other hand, a good correlation was obtained between the blocking potency of the compounds and E_{LUMO} [pEMR = 1.16(±0.26)E_{LUMO} + 5.33(±1.29) (n = 11, r = 0.83, s = 0.243)]. It has been possible to combine this equation with the previously reported E_{LUMO} correlation for a series of dequalinium analogues to include all the compounds of both series [pEMR = 1.17(±0.15)E_{LUMO} + 5.33(±0.76) (n = 24, r = 0.85, s = 0.249)]. A possible physical meaning for the E_{LUMO} correlation based upon the principle of maximum hardness is discussed.

Introduction

Small conductance Ca^{2+}-activated K^+ (SK_{Ca}) channels comprise an important but relatively little studied subtype.[1,2] These channels are present in a variety of cell types, and their physiological role is known in some cases including intestinal smooth muscle,[3−5] hepatocytes,[6,7] and brown fat cells.[8] In sympathetic neurons,[9,10] opening of SK_{Ca} channels mediates a long hyperpolarization following the action potential (AHP) which is important for spike frequency adaptation.[11,12]

Three natural peptidic toxins, apamin,[13−15] leiurotoxin I[16] (scyllatoxin), and PO5,[17] are known to block SK_{Ca} channels with potencies in the low nanomolar range. In particular, apamin has been an invaluable tool for the study of SK_{Ca} channels; using this as a probe, a role of the SK_{Ca} channel in the genesis of myotonia has been suggested, since the binding site for apamin is expressed in muscles of myotonic muscular dystrophy patients, while it is completely absent in normal human muscle.[18,19] In addition, injection of apamin into muscle of myotonic patients significantly suppressed myotonic discharges.[20] There is also some evidence for the involvement of SK_{Ca} channels in EtOH intoxication.[21] Thus, there may be therapeutic possibilities for selective SK_{Ca} channel blockers.

Apamin contains two arginine residues at positions 13 and 14, the charged guanidinium groups of which are important for SK_{Ca} channel blockade, although, alone, they cannot account for the potency of apamin.[22] The bis-charged pharmacophore of this peptide has prompted testing of other compounds bearing two positively charged N atoms. Thus, the neuromuscular blockers[9,23,24] atracurium, tubocurarine, and pancuronium (Chart 1) were found to be effective SK_{Ca} channel blockers, having potencies in the low micromolar range. The significantly lower potencies of these bis-charged compounds compared with apamin add to the suggestion that the interaction of apamin with the SK_{Ca} channel involves not only Arg_{13} and Arg_{14} but also other amino acids.

Furthermore, dequalinium (**22**, $R^2 = CH_3$, $R^3 = H$, $R^4 = NH_2$, $R^7 = H$; Chart 1) has been shown to be a potent and selective blocker of the SK_{Ca} channel[25,26] ($IC_{50} = 1\ \mu M$). Studies have been undertaken to identify the pharmacophore of dequalinium for SK_{Ca} channel blockade.[27] Replacements for the quinolinium groups of this molecule have been investigated, and the possibilities that the molecules of the general structure **22** bind to an anionic or aromatic site on the channel have been discussed.[28] Moreover, it has been suggested that the role of the NH_2 group of dequalinium is electronic, probably via delocalization of the positive charge.[29] Quantitative structure−activity relationship (QSAR) analysis on analogues of the general structure **22** has revealed that the blocking potency correlates well with the partial charge on the ring N atom (obtained from AM1 semiempirical molecular orbital calculations) and

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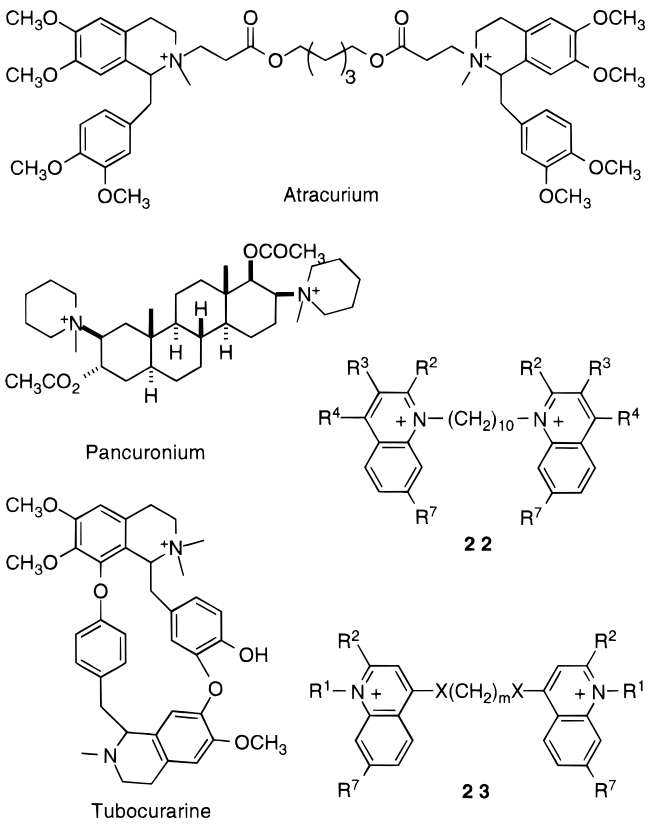
[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1995.

0022-2623/96/1839-0359$12.00/0

Chart 1



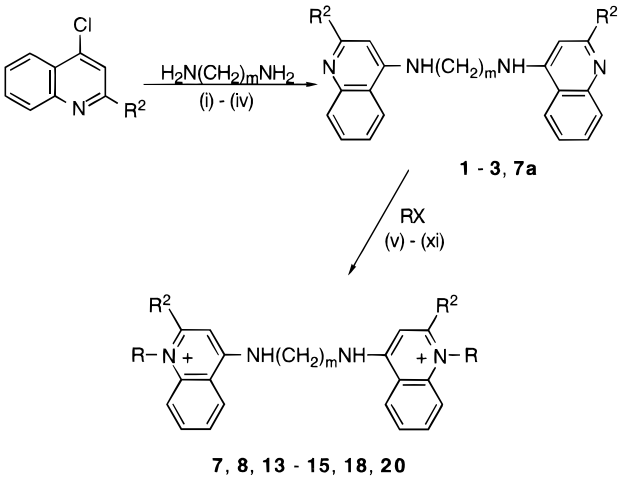
with the energy of the lowest unoccupied molecular orbital (E_{LUMO}).[30]

Since the contribution of substituent R^4 to activity was found to be electronic in nature, it seemed possible that analogues in which the quinolinium groups in dequalinium are inverted might also be active, i.e., linking the rings via the exocyclic N atoms. This has afforded another opportunity to investigate electronic effects, and a second series of analogues having the structure **23** has been synthesized in which the roles of the heteroatom X and the group R^1 attached to the ring N atom have been investigated. Correlations have also been sought between the blocking potency of the analogues and electronic indices, and the results have been compared with those from structures **22**. Furthermore, in this series it has also been possible to address the question of the need for the quinoline groups to possess a quaternized ring N atom. Such an examination was not possible in the structures **22**, which are necessarily quaternary derivatives.

Chemistry

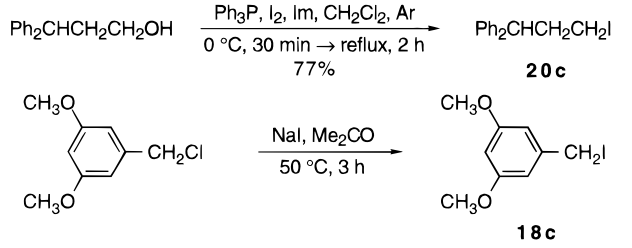
Scheme 1 shows the synthesis of compounds **1**−**3**, **7a**, **7**, **8**, **13**−**15**, **18**, and **20**. Either 4-chloroquinoline or 4-chloroquinaldine was treated with the necessary diamine to provide compounds **1**−**3** and **7a**. These analogues have been previously synthesized using PhOH as the solvent[31,32] which has been suggested to facilitate the reaction,[33] but we found it more convenient to use an alcoholic solvent. Quaternization of the ring N atom of **1**−**3** and **7a** with the appropriate halide yielded compounds **7**, **8**, **13**−**15**, **18**, and **20**. Note that for **1** and **2**, each bearing a Me group at position 2 of the quinoline, high temperatures and longer reaction times were required for the quaternization step. The ring N

Scheme 1[a]



[a] Methods: (i) **1**, $m = 10$, $R^2 = CH_3$, *n*-pentanol, reflux, 30 h; (ii) **2**, $m = 12$, $R^2 = CH_3$, as for **1**; (iii) **3**, $m = 10$, $R^2 = H$, *n*-butanol, reflux, 96 h; (iv) **7a**, $m = 8$, $R^2 = H$, *n*-butanol, reflux, 78 h; (v) **7**, $m = 8$, $R^2 = H$, R = CH_3, X = I, MEK, reflux, 2 h; (vi) **8**, $m = 10$, $R^2 = H$, R = CH_3, X = I, as for **7**; (vii) **13**, $m = 10$, $R^2 = H$, R = Bn, X = Br, MEK, reflux, 24 h; (viii) **14**, $m = 10$, $R^2 = CH_3$, R = Bn, X = Br, $PhNO_2$, 100−120 °C, 96 h → 120−140 °C, 12 h; (ix) **15**, $m = 12$, $R^2 = CH_3$, R = Bn, X = Br, $(iBu)_2CO$, reflux, 24 h; (x) **18**, $m = 10$, $R^2 = CH_3$, R = 3,5-di$MeOC_6H_3CH_2$, X = I, $PhNO_2$, Ar, reflux, 100−120 °C, 144 h; (xi) **20**, $m = 10$, $R^2 = CH_3$, R = $Ph_2CHCH_2CH_2$, X = I, 4-methylpentan-2-ol, reflux, Ar, 120 h.

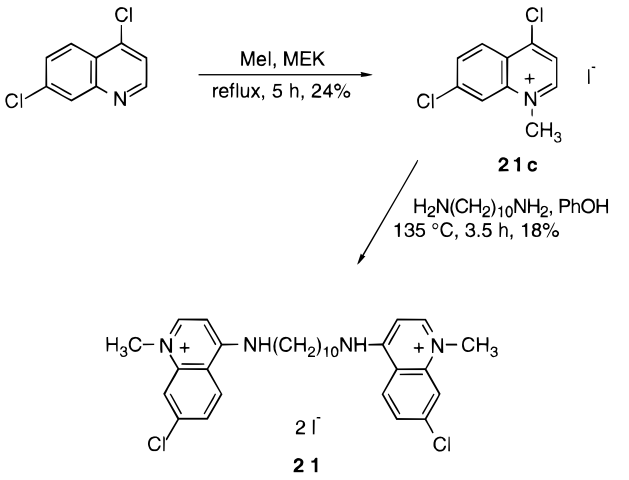
Scheme 2



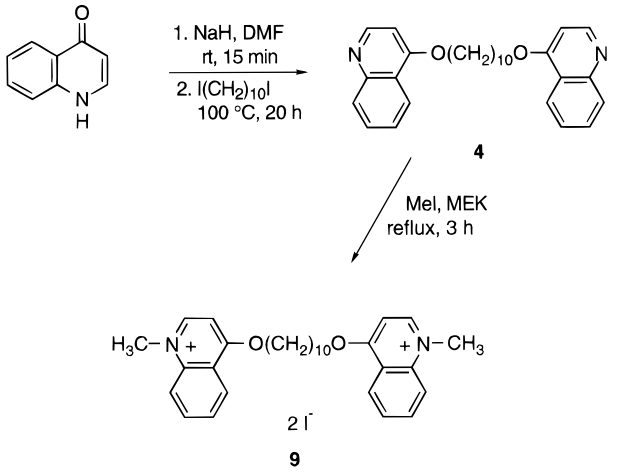
atom of these compounds is substantially hindered by the Me group as well as the peri-H atom (at position 8). Thus, **3** could be benzylated in MEK at reflux (80 °C) in 24 h to give **13**, while for the benzylation of **1**, $PhNO_2$ was used as the solvent and the reaction proceeded at 100−140 °C for 108 h. In all cases, alkylation of the ring N atom of **1** and **2** yielded a mixture of mono- and bisquaternary products which could be separated only by reverse phase preparative HPLC. Despite considerable efforts to find reaction conditions to obtain exclusively the bisquaternary products, this did not prove to be possible. The monoquaternary compounds **16**, **17**, and **19** (Table 2) were obtained through HPLC separation from their bisquaternary analogues **14**, **15**, and **18**, respectively. Of various solvents tested, $PhNO_2$ was found to give the best results. The iodides **18c** and **20c**, required for the synthesis of **18** and **20**, respectively, were obtained as detailed in Scheme 2. Compound **21** can also be synthesized through Scheme 1, but we were unable to obtain an analytically pure sample through this route. Instead, the procedure shown in Scheme 3 was used to provide pure **21** but in low yield.

The oxo analogues **4** and **9** were prepared via Scheme 4. Alkaline hydrolysis of 1,1′-decane-1,10-diylbis-[isothiouronium] dihydrochloride[45] yielded the dianion of the corresponding dithiol which was not isolated but reacted *in situ* with 4-chloroquinoline to afford **5** (Scheme 5). Methylation of the latter gave **10**. Analogues **6** and

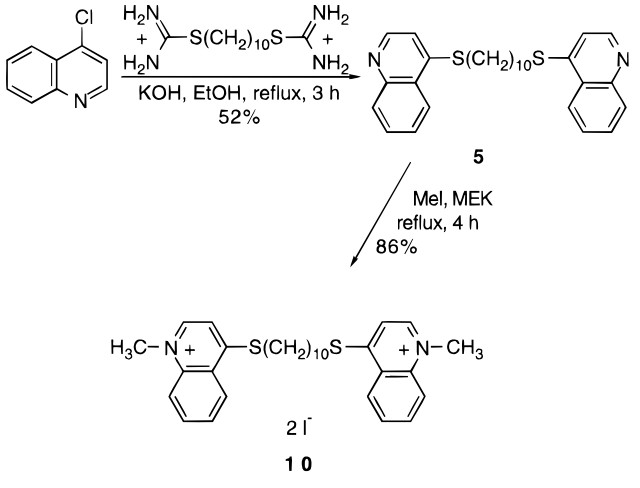
Scheme 3



Scheme 4



Scheme 5



12a were synthesized via alkylation of the anion of lepidine with the appropriate dihalide (Scheme 6), and methylation yielded **11** and **12**, respectively.

Pharmacology

The SK_{Ca}-blocking action of the compounds was assessed from their ability to inhibit the after hyperpolarization (AHP) in cultured rat sympathetic neurons[26] (see the Experimental Section). Briefly, each compound was tested at two to four concentrations on at least three cells. Between one and three compounds were examined at a time, and in each such series of experiments, dequalinium was also included as a reference compound. The Hill equation was fitted to the data to obtain estimates of the IC_{50}. However, because there was some variation in the potency of dequalinium during the course of the study, equieffective molar ratios (EMR; relative to dequalinium) were also obtained by simultaneous nonlinear least-squares fitting of the data with the Hill equation. These are also listed in Tables 1 and 2, and it is these values which have been used for the comparison between compounds. It should be noted that the compounds were applied in a continuously flowing solution to isolated cells, so that differences in depletion as a consequence of variation in lipophilicity are unlikely to have been a complicating factor.

Although relatively simple, this assay relies on Ca^{2+} influx during the action potential to activate the SK_{Ca} channels, and the potency of any compound interfering with this influx may be overestimated. Dequalinium itself is a highly selective blocker of the SK_{Ca} channel, with no detectable effect on Ca^{2+} current even at the relatively high concentration of 10 μM.[26] As most of the compounds tested in the present work have a similar bis-cationic structure to dequalinium, an action on Ca^{2+}

Scheme 6

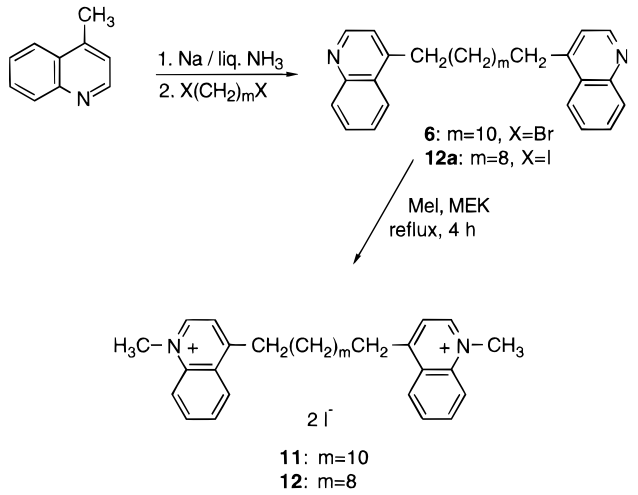
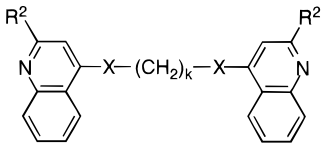


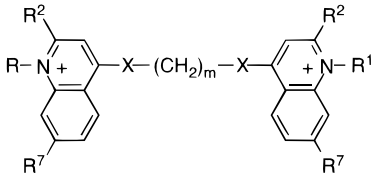
Table 1. Structures and Biological Results for the Nonquaternary Compounds



compd	k	X	R^2	$IC_{50} \pm$ SD (μM)	EMR[a] $\pm$ SD	n[b]
1	10	NH	CH_3	2.5 ± 0.5	3.6 ± 1.2	4
2	12	NH	CH_3	3.8 ± 0.3	7.1 ± 2.8	6
3	10	NH	H	4.4 ± 1.1	3.5 ± 1.2	3
4	10	O	H	18 ± 7.0	16 ± 21	3
5	10	S	H	>10[c]	>10[c]	4
6	10	CH_2	H	≫10[d]	≫10[d]	4

[a] Equieffective molar ratio: the ratio of the concentrations of the test compound and that of dequalinium that cause 50% inhibition of the AHP, as determined in the same experiment. The IC_{50} value for dequalinium in these experiments was 0.87 ± 0.07 μM (n = 8). [b] Number of neurons tested. [c] Insufficient activity up to this concentration to determine IC_{50}. [d] No activity up to this concentration.

Table 2. Structures[a] and Biological Results for the Quaternary Compounds



compd	*m*	X	R	R^1	R^2	R^7	$IC_{50} \pm SD$ (μM)	EMR[b] ± SD	*n*[c]
7	8	NH	CH_3	CH_3	H	H	2.7 ± 0.25	3.1 ± 1.4	3
8	10	NH	CH_3	CH_3	H	H	2.1 ± 0.2	1.9 ± 1.0	4
9	10	O	CH_3	CH_3	H	H	6.8 ± 1.7	7.2 ± 3.4	7
10	10	S	CH_3	CH_3	H	H	3.7 ± 0.6	6.2 ± 1.7	3
11	10	CH_2	CH_3	CH_3	H	H	3.9 ± 0.5	5.9 ± 3.9	3
12	8	CH_2	CH_3	CH_3	H	H	40 ± 39	26 ± 9.8	3
13	10	NH	$PhCH_2$	$PhCH_2$	H	H	0.7 ± 0.1	1.0 ± 0.4	7
14	10	NH	$PhCH_2$	$PhCH_2$	CH_3	H	0.4 ± 0.05	0.6 ± 0.3	7
15	12	NH	$PhCH_2$	$PhCH_2$	CH_3	H	2.4 ± 0.08	4.0 ± 2.0	3
16	10	NH	$PhCH_2$	H	CH_3	H	1.3 ± 1.2	2.4 ± 0.5	3
17	12	NH	$PhCH_2$	H	CH_3	H	4.4 ± 0.6	8.0 ± 5.9	4
18	10	NH	3,5-di$MeOC_6H_3CH_3$	3,5-di$MeOC_6H_3CH_3$	CH_3	H	1.7 ± 0.3	2.1 ± 0.9	4
19	10	NH	3,5-di$MeOC_6H_3CH_3$	H	CH_3	H	0.75 ± 0.05	1.2 ± 0.8	5
20	10	NH	$Ph_2CHCH_2CH_2$	$Ph_2CHCH_2CH_2$	CH_3	H	4.3 ± 1.3	6.2 ± 3.2	6
21	10	NH	CH_3	CH_3	H	Cl	1.3 ± 0.18	1.5 ± 0.6	4

[a] Compounds **7**−**12** and **21** were analyzed and tested as the diiodides, **13** as the dibromide, and **14**−**20** as the bistrifluoroacetates. [b] For the definition of EMR, see footnote a of Table 1. [c] Number of neurons tested.

channels seems unlikely. Nevertheless, because of the indirectness of the assay, test concentrations of more than 10−30 μM were generally avoided. None of the compounds tested produced obvious broadening of the action potential, suggesting that, like dequalinium, they block neither voltage-gated nor the large conductance calcium-activated (BK_{Ca}) K^+ channels at the concentrations tested.

Results and Discussion

From Tables 1 and 2 it can be seen that extension of the aliphatic chain from 10 to 12 methylene groups results in some loss of potency (cf. compounds **1** and **2**, **14** and **15**, **16** and **17**), and the same is true for reduction of the number of methylene groups from 10 to 8 (cf. compounds **7** and **8**, **11** and **12**). Nevertheless, the dependence of activity on the length of the chain is not striking. A methyl group at position 2 of the quinoline hardly makes any contribution [cf. R^2 = H or CH_3 in compounds **1**−**3** (Table 1) and **13** and **14** (Table 2)], and this is consistent with results previously reported on dequalinium analogues.[29]

It is also evident from Table 2 that NH, O, S, and CH_2 groups can be tolerated as heteroatoms X (compounds **8**−**11**, respectively). The most potent is the nitrogen analogue **8**, with the other three compounds (**9**−**11**) having similar potencies to each other and being 3 times less potent than **8**.

A charged heterocycle, preferably a quinolinium group, appears to be an important feature of the pharmacophore of the SK_{Ca} channel blockers for potent blockade of this channel.[28] There is evidence that the heterocycle does not have to be quaternized, as long as it is basic enough to be protonated, and hence charged, at physiological pH.[28] The results of this study are consistent with this model. Thus, of the four nonquaternary compounds (**3**−**6**; Table 1) tested, the NH (**3**) and O (**4**) analogues were active (**3** being more potent than **4**), and the S compound **5** showed some activity at 10 μM but insufficient to determine an IC_{50} value, while the CH_2 analogue **6** was inactive. The results for these

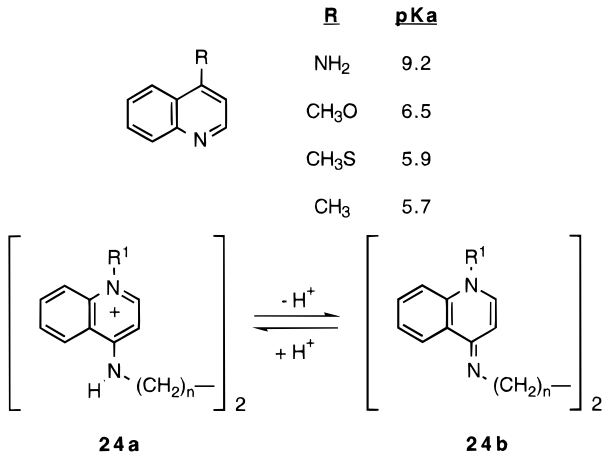
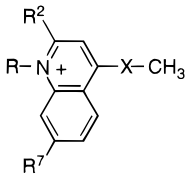


Figure 1. pK_a values[35] for 4-substituted quinolines and deprotonation of 1-alkyl-4-(alkylamino)quinolinium compounds.

compounds could be accounted for by the pK_a values of their quinoline groups. The pK_a values for four analogously substituted quinolines are given in Figure 1.[35] It can be hypothesized that the quinoline groups of **5** and **6** are not sufficiently basic to be protonated to a significant extent at the site of action. Although the pH at the site of action is not known, this is a reasonable hypothesis to explain the inactivity of **5** and **6**, particularly since their quaternary analogues **10** and **11** (Table 2), respectively, are active and equipotent with the quaternary O compound **9**. Proton dissociation in quaternary aminoquinolinium compounds having the general formula **24a** (Figure 1) can, of course, give the neutral imino bases **24b**. However, it does appear to be most likely that the active species is the cation since we have previously shown that the dimethylamino compound **22**, $R^2 = R^3 = R^7$ = H, $R^4 = NMe_2$ (Chart 1), which cannot undergo proton dissociation, is equipotent with the corresponding amino analogue (**22**, $R^2 = R^3 = R^7$ = H, $R^4 = NH_2$).[29]

Quaternization of the ring nitrogen of the quinoline with a CH_3 group increases activity by 2-fold, as can be seen from compound pairs **8** and **3** and **9** and **4**. A

Table 3. Partial Charges and Frontier Orbital Energies for Model Compounds, Used for Correlation Eqs 1−6



					charge				
compd[a]	X	R	R^2	R^7	C^4	N^1	E_{HOMO}[b]	E_{LUMO}[b]	pEMR[c]
1a	NH	H	CH_3	H	0.266	−0.333	−12.74	−4.840	−0.56
3a	NH	H	H	H	0.271	−0.333	−12.82	−4.940	−0.54
4a	O	H	H	H	0.265	−0.302	−13.31	−5.329	−1.20
5a	S	H	H	H	−0.116	−0.286	−12.99	−5.551	<−1
6a	CH_2	H	H	H	0.096	−0.271	−13.50	−5.543	≪−1
8a	NH	CH_3	H	H	0.268	−0.258	−12.64	−4.846	−0.28
9a	O	CH_3	H	H	0.257	−0.225	−13.15	−5.207	−0.86
10a	S	CH_3	H	H	−0.121	−0.208	−12.84	−5.424	−0.79
11a	CH_2	CH_3	H	H	0.087	−0.195	−13.36	−5.406	−0.77
13a	NH	$PhCH_2$	H	H	0.260	−0.248	−12.37	−4.716	0.00
14a	NH	$PhCH_2$	CH_3	H	0.261	−0.249	−12.29	−4.638	0.22
18a	NH	3,5-di$MeOC_6H_3CH_2$	CH_3	H	0.260	−0.245	−11.43	−4.637	−0.32
20a	NH	$Ph_2CHCH_2CH_2$	CH_3	H	0.260	−0.244	−11.43	−4.600	−0.79
21a	NH	CH_3	H	Cl	0.270	−0.260	−12.76	−4.968	−0.18

[a] Model compound numbers correspond to the compound numbers of Tables 1 and 2. [b] In eV. [c] The −log(EMR) of the corresponding bisquinolinium compound of Table 1 or 2 is given for simplicity. For the definition of EMR, see footenote a of Table 1.

further 2-fold increase in potency is achieved if the CH_3 group on the ring N (**8**) is replaced by the larger and more lipophilic benzyl group (**13**, **14**). Thus, there seems to be considerable steric tolerance in the direction of the group R (and R^1) attached to the ring N atom of the quinoline. However, the increase in potency is probably too small to be attributed to the lipophilicity of the benzyl group. Introduction of two MeO groups in each of the phenyl rings of **14** reduced activity (**18**) and so did replacement of the benzyl group of **14** with the considerably bulkier diphenylpropyl group (**20**). Furthermore, nonsymmetrical analogues, having one quaternary and one nonquaternary quinoline, are either approximately equipotent (**19** and **18**) or slightly less potent (**16** and **14**, **17** and **15**) than their symmetrical counterparts. Finally, introduction of a Cl atom at position 7 of the quinoline groups of **8** to give compound **21** had no effect on the blocking potency of the analogue.

We reported that the SK_{Ca} channel-blocking potency of dequalinium analogues of the general structure **22** (Chart 1) correlates well with three electronic descriptors obtained from AM1 MO calculations.[30] These are the partial charge on the ring N atom of the quinolinium group (N^1 charge), the E_{HOMO}, and the E_{LUMO}. Respective correlations were sought for the present series of blockers. Hence, semiempirical MO calculations were performed on the compounds of this study. For consistency, the calculations were done on only the compounds of Table 2 which are symmetrical and have a 10-methylene chain. Furthermore, as before,[30] the calculations were not performed on the whole molecule but on model compounds consisting of one substituted quinolinium group in which the 10-methylene chain was replaced by a methyl. These simplifications were necessary to increase the computational speed of the calculations and should not invalidate the comparability of the results, since any errors introduced are expected to be similar for all the compounds. The MOPAC MO package and the AM1 Hamiltonian[34] were used for the calculations.

The structures of the model compounds and the results of the calculations are given in Table 3. There is no correlation of pEMR with either the partial charge on the C atom at position 4 of the quinoline (eq 1) or the partial charge on the ring N atom of the quinoline (eq 2). The fact that the pEMR of the analogues of Table 2 do not correlate with the N^1 charges is in stark contrast to the good correlation of pEMR with N^1 charge previously found for the compounds represented by **22**, although we commented at the time that it was difficult to assign a physical meaning to this correlation.[30] Moreover, there appears to be no correlation with the energy of the highest occupied molecular orbital (E_{HOMO}, eq 3), and the correlation with the energy of the lowest unoccupied molecular orbital (E_{LUMO}) is only a moderate one (eq 4).

$$\text{pEMR} = 1.03(\pm 1.04)\text{C}^4 \text{ charge} - 0.73(\pm 0.26) \quad (1)$$

$$n = 12,\ r = 0.30,\ s = 0.408$$

$$\text{pEMR} = 0.19(\pm 2.93)\text{N}^1 \text{ charge} - 0.46(\pm 0.77) \quad (2)$$

$$n = 12,\ r = 0.02,\ s = 0.428$$

$$\text{pEMR} = 0.26(\pm 0.19)E_{HOMO} + 2.71(\pm 2.35) \quad (3)$$

$$n = 12,\ r = 0.40,\ s = 0.392$$

$$\text{pEMR} = 0.89(\pm 0.31)E_{LUMO} + 3.93(\pm 1.55) \quad (4)$$

$$n = 12,\ r = 0.67,\ s = 0.316 \text{ (significance at } \alpha < 0.02)$$

With respect to the E_{LUMO} correlation, there appears to be a major outlier, and this is compound **20a** (Figure 2). This compound is much less active than predicted by the equation. The ring nitrogen of the quinoline has been alkylated with the bulky diphenylpropyl group; hence, it is possible that this group interferes sterically in the interaction of the compound with the channel. On this basis, **20a** can be excluded from the correlation which then improves substantially (eq 5). Equation 5 is of comparable quality to the reported[30] E_{LUMO} cor-

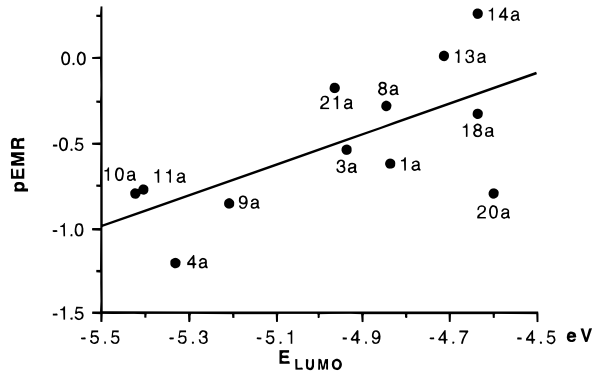


Figure 2. Plot of pEMR vs E_{LUMO} for the model compounds of Table 3, showing the least-squares-fitted regression line.

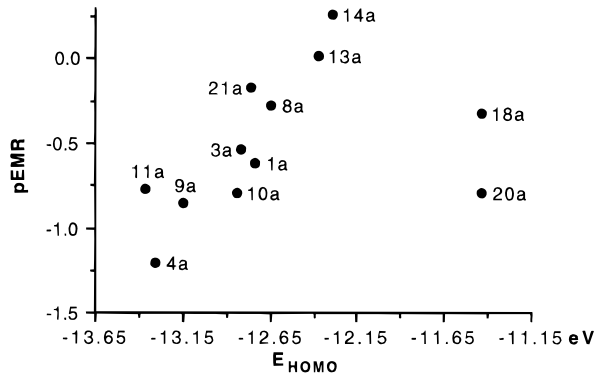


Figure 3. Plot of pEMR vs E_{HOMO} for the model compounds of Table 3, showing the least-squares-fitted regression line.

relation for structures **22**.

$$\text{pEMR} = 1.16(\pm 0.26)E_{LUMO} + 5.33(\pm 1.29) \quad (5)$$

$n = 11$, $r = 0.83$, $s = 0.243$

(significance at $\alpha < 0.005$)

On the other hand, two compounds, **18a** and **20a**, are outliers in the E_{HOMO} correlation (Figure 3). Although **20a** can be excluded on the same basis as above, there appears to be no well-justified reason for excluding **18a**. We have already noted[30] that the E_{HOMO} correlation for the series represented by structure **22** is qualitatively inconsistent, since the E_{HOMO} does not refer to the same orbital in all analogues. This is also the case for the model compounds of Table 3. Whereas in analogues **1a**, **3a**−**6a**, and **8a**−**11a** the HOMO is a π orbital localized on the quinolinium ring, in analogues **13a**, **14a**, **18a**, and **20a** there are contributions to the HOMO only from the benzene ring(s) (Figure 4). Thus, it is also inconsistent to use the E_{HOMO} for the present series of blockers. On the other hand, the LUMO of all the model compounds of Table 2 is localized on the quinolinium part of the molecule (Figure 5). In addition to consistency problems, the physical meaning of a correlation with E_{HOMO} is not clear since such a correlation suggests that the higher the energy of the HOMO the more potent the compound is. If the contribution of the HOMO is assumed to be at the level of the interaction of the compound with the channel, then a charge transfer interaction with the latter is implied in which the compound has the role of the electron *donor*. This is in disagreement with fundamental chemical concepts since it is hard to see how these compounds could act as electron *donors* when they are electron *deficient*.

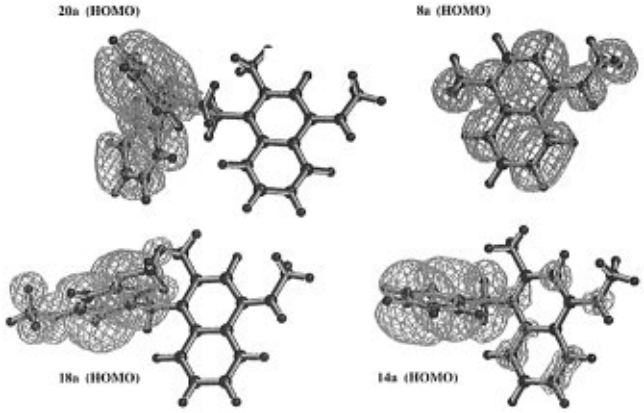


Figure 4. HOMO contour plots for representative model compounds of Table 3. The HOMO is not localized on the quinolinium part of the molecule in all compounds as exemplified using **8a**, **14a**, **18a**, and **20a**. The molecules are drawn to match the general structure of Table 3. Contours were drawn in SYBYL 6.03 at the PSI^2 mode, at the 0.0009 e/Å^3 level.

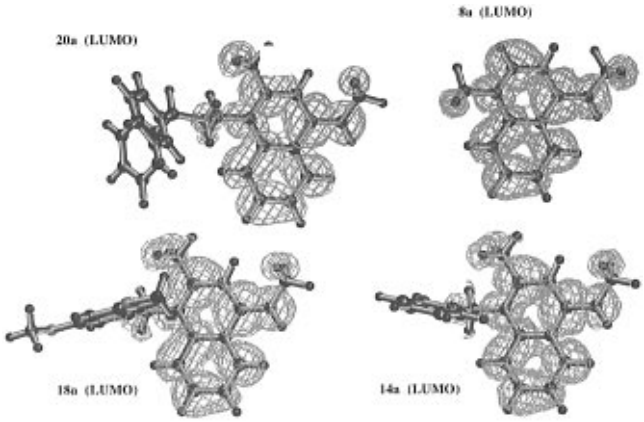


Figure 5. LUMO contour plots for representative model compounds **8a**, **14a**, **18a**, and **20a** of Table 3. The LUMO is localized on the quinolinium part of the molecule in all analogues of Table 3. The molecules are drawn to match the general structure of Table 3. Contours were drawn in SYBYL 6.03 at the PSI^2 mode, at the 0.0009 e/Å^3 level.

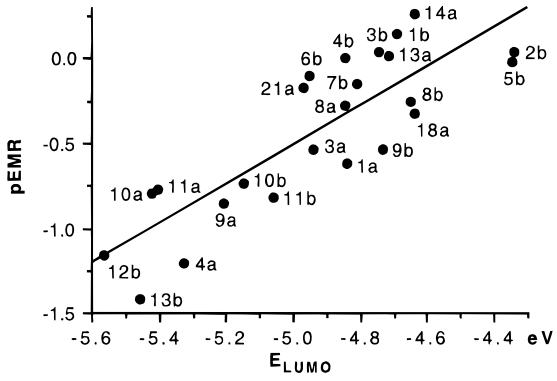
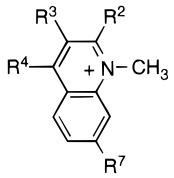


Figure 6. Plot of pEMR vs E_{LUMO} for the model compounds of Tables 3 and 4, showing the least-squares-fitted regression line.

It therefore seems that E_{LUMO} is the best electronic parameter to use both for the series represented by structure **22** and for the compounds of Tables 1 and 2. The E_{LUMO} correlations for both these series can be combined to a single correlation of pEMR with E_{LUMO} (eq 6, Figure 6) of similar quality to eq 5. This includes the model compounds of Table 2 (except the inactive nonquaternary **5a** and **6a** and the bulky **20a**) and the

Table 4. Partial Charges and E_{LUMO} Values for Model Compounds Corresponding to Structure **22**, Used for Correlation Eq 6[a]



compd	R^2	R^3	R^4	R^7	E_{LUMO}[b]	pEMR[c]
1b	H	H	$PhCH_2NH$	H	−4.693	0.15
2b	H	H	$PhCH_2NH$	NH_2	−4.341	0.05
3b	$-(CH_2)_4-$		NH_2	H	−4.743	0.05
4b	CH_3	H	NH_2	H	−4.847	0.00
5b	H	H	2,4,6-triMeO$C_6H_2CH_2NH$	H	−4.347	0.00
6b	H	H	NH_2	H	−4.952	−0.11
7b	H	H	$(CH_3)_2N$	H	−4.810	−0.15
8b	H	H	$Ph(CH_3)N$	H	−4.652	−0.26
9b	H	H	PhNH	H	−4.735	−0.53
10b	H	H	CH_3CONH	H	−5.148	−0.74
11b	H	H	PhO	H	−5.058	−0.81
12b	H	H	H	H	−5.564	−1.18
13b	H	H	CH_3	H	−5.456	−1.41

[a] Data obtained from ref 30. [b] In eV. [c] The −log(EMR) of the corresponding bisquinolinium compound of ref 30 is given for simplicity. For the definition of EMR, see footnote a of Table 1.

model compounds of Table 4 (from ref 29).

$$\text{pEMR} = 1.17(\pm 0.15)E_{LUMO} + 5.33(\pm 0.76) \quad (6)$$

$n = 24$, $r = 0.85$, $s = 0.249$

(significance at $\alpha < 0.001$)

Previously we suggested[30] that the E_{LUMO} correlation is inconsistent with an electron donor−acceptor (EDA) interaction of the channel with the compounds, since activity is increased with increasing E_{LUMO}. We proposed that the E_{LUMO} correlation may be related to processes other than the drug−ion channel itself, such as the solvation of the compounds; the higher the E_{LUMO}, the weaker is the solvation of the blocker and the stronger becomes the interaction with the channel. An alternative explanation for the physical meaning of the E_{LUMO} correlation may be provided by the principle of maximum hardness initially suggested by Pearson[36,37] and described mathematically by Parr using statistical mechanics and density functional theory.[38] Briefly, the hardness of a chemical system (a chemical system being an atom, an ion, a radical, a molecule, or several molecules in a state of interaction[37]) can be defined as one-half the energy gap between the LUMO and the HOMO. The larger the gap, the harder the system and the more stable it is. There appears to be a general trend in nature for chemical systems to adjust themselves so as to maximize the HOMO−LUMO gap and thereby minimize their energy and become more stable.[36−38]

In order to apply this principle to the interaction of the quinolinium compounds with the channel, one must assume that the compounds bind to an anionic site. This assumption is reasonable since, as has been discussed above, the positive charge on the quinoline rings is an essential feature for blocking activity and since all K^+ channel subtypes that have been cloned so far have negatively charged amino acids in the sequence of the putative pore-forming region of the protein.[39−43] These negatively charged amino acids are believed to facilitate energetically the conduction of the positively charged K^+ ions.[44] The alteration of the frontier orbital energies

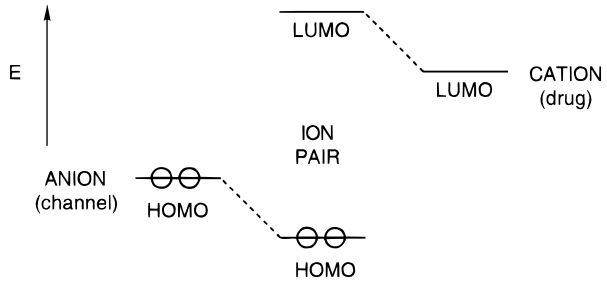


Figure 7. Frontier orbital energy changes on formation of an ion pair.

in the formation of an ion pair is shown in Figure 7.[37] As the cation (compound) approaches the anion (binding site), the potential of the anion raises the E_{LUMO} of the compound and the potential of the cation lowers the E_{HOMO} of the binding site. Since in the quinolinium compounds the E_{LUMO} is progressively increased, the $E_{LUMO}-E_{HOMO}$ gap of the ion pair (drug−K^+ channel complex) is also increased, and the latter becomes more stable. To the best of our knowledge this hypothesis represents the first attempt to apply the principle of maximum hardness to structure−activity relationships in the field of pharmacology.

Conclusion

The synthesis and pharmacological testing of a novel series of SK_{Ca} channel blockers have been described. It has been shown that linking of the two quinolinium groups from the exocyclic N atom rather than the ring N atom (as in dequalinium) is tolerated. The exocyclic N atom can be replaced with O, S. or the CH_2 group but with some loss of potency. The O, S, and CH_2 analogues have similar potencies to each other. Furthermore, it appears that the quinoline groups of the blockers do not have to be quaternized, as long as they are basic enough to be protonated at the site of action. For quaternary compounds, there is considerable steric tolerance for the group R attached to the ring N atom of the quinoline; a benzyl group gave the optimum potency in this series.

Moreover, and in contrast to previously reported results for dequalinium analogues,[30] there is no cor-

relation of pEMR with N^1 charge. In addition, there is no correlation with E_{HOMO} either, due to the presence of two major outliers, compounds **18a** and **20a**. The E_{HOMO} does not refer to the same orbital in all the compounds, and this is in line with previous results for dequalinium analogues.[30] On the other hand, the E_{LUMO} does refer to the same orbital in all the analogues, and a good correlation has been obtained between the blocking potency of the compounds and E_{LUMO}, provided that **20a** is excluded. The absence of any correlation of pEMR with the N^1 charge of the analogues of this study and the fact that the E_{LUMO} correlates with pEMR both in the present series as well as in a previously reported[30] series of dequalinium analogues suggest that E_{LUMO} is the best electronic parameter to use. Assuming an interaction of the blockers with an anionic site on the channel, molecules with a higher E_{LUMO} would form a harder and, hence, more stable ion pair. This hypothesis, which is based on the principle of maximum hardness, provides a possible physical meaning for the E_{LUMO} correlation.

Experimental Section

(a) Chemistry. Melting points (mp) were obtained on an Electrothermal melting point apparatus and are uncorrected. Infrared (IR) spectra were run on a Perkin-Elmer 983 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 ($CHCl_3$ in $CDCl_3$ at 7.24 ppm and DMSO in DMSO-d_6 at 2.49 ppm) or TMS. Signals are designated as follows: s, singlet; s_{br}, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quadruplet; quint, quintet; m, multiplet. Mass spectra were run on a ZAB SE or VG 7070H spectrometer. Analytical reverse phase high-performance liquid chromatography (HPLC) was performed on either a Gilson or Shimadzu HPLC apparatus with a UV detector at 215 or 254 nm and a Kromasil C18 7 μm (K) or Lichrosorb RP SELECT B 7 μm (L) column. Isocratic elutions using solvent mixtures of A = water + 0.1% TFA and B = MeOH + 0.1% TFA or C = water + 0.5% sodium salt of hexanesulfonic acid + 0.5% orthophosphoric acid and D = MeOH + 0.5% sodium salt of hexanesulfonic acid + 0.5% orthophosphoric acid were performed unless otherwise stated. The ratio of A:B or C:D is indicated for each individual compound. The flow rate was 1 mL/min. For preparative reverse phase HPLC, a Kromasil C18 7 μm column was used, the solvent mixture being the same as the one used for analytical HPLC and the flow rate being 15 mL/min.

General Procedure for the Preparation of 1,10-Bis[*N*-(2-methylquinolin-4-yl)amino]decane[31,32] (1) and 1,12-Bis[*N*-(2-methylquinolin-4-yl)amino]dodecane[31,32] (2). 4-Chloroquinaldine (2 g, 11.26 mmol) and the corresponding diamine (1,8-diaminooctane, 1,10-diaminodecane, or 1,12-diaminododecane; 5.68 mmol) were disolved with heating in *n*-pentanol (30 mL). The solution was heated under reflux for 30 h. On cooling a creamy precipitate formed, which was collected by vacuum filtration and dried under vacuum at 50 °C. This was dissolved in methanol, the solution was made alkaline by addition of NaOH (10% in water), excess of water was added, and the mixture was kept at 4 °C overnight. The precipitate formed was collected by vacuum filtration, washed well with water, and dried under high vacuum over P_2O_5.

1,10-Bis[(2-methylquinolin-4-yl)amino]decane[31,32] (1): 84%; mp 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35, 1.48 (m, 12 H, -CH_2-), 1.75 (quint, 4 H, -CH_2-), 2.61 (s, 6 H, -CH_3), 3.29 (q, 4 H, -CH_2-), 4.93 (s_{br}, 2 H, N-H), 6.32 (s, 2 H, quinoline-H_3), 7.36 (t, 2 H, quinoline-H_6 or -H_7), 7.59 (t, 2 H, quinoline-H_7 or -H_6), 7.67 (d, 2 H, quinoline-H_5), 7.90 (d, 2 H, quinoline-H_8); MS (EI) $[M]^+$ 454, fragments at *m*/*z* 297, 283, 269, 255, 241. Anal. ($C_{30}H_{38}N_4$·0.55MeOH) C, H, N.

1,12-Bis[(2-methylquinolin-4-yl)amino]dodecane[31,32] (2): 79%; for experimental details see compound **1**; mp 153−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31, 1.47 (m, 16 H, -CH_2-), 1.75, (quint, 4 H, -CH_2-), 2.61 (s, 6 H, -CH_3), 3.29 (q, 4 H, -CH_2-), 4.90 (s_{br}, 2 H, N-H), 6.32 (s, 2 H, quinoline-H_3), 7.36 (t, 2 H, quinoline-H_6 or -H_7), 7.59 (t, 2 H, quinoline-H_7 or -H_6), 7.67 (d, 2 H, quinoline-H_4), 7.91 (d, 2 H, quinoline-H_8); MS (FAB, matrix MNOBA + NaI) $[M + H]^+$ 483, fragments at *m*/*z* 325, 311, 297, 283, 269. Anal. ($C_{32}H_{42}N_4$·1.5MeOH) N; C: calcd, 76.39; found, 76.84. H: calcd, 9.19; found, 9.66.

1,10-Bis(*N*-quinolin-4-ylamino)decane (3). A solution of 4-chloroquinoline (0.5 g, 3.1 mmol) and 1,10-diaminodecane (0.26 g, 1.5 mmol) in *n*-butanol (30 mL) was heated under reflux with stirring for 96 h. The solvent was removed in vacuo, and the resulting dark solid was treated with NH_4OH. After the latter had been removed in vacuo, the resulting material was purified by column chromatography using 30% MeOH in EtOAc. This gave a solid material which was recrystallized twice from MeOH to give white needles (0.283 g): mp 170−170.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.4 (m, 14 H, -CH_2-), 1.75 (m, 4 H, -CH_2-), 3.30 (q, 4 H, N-CH_2), 5.15 (t_{br}, 2 H, NH), 6.42 (d, 2 H, quinoline-H_3), 7.40 (t, 2 H, quinoline-H_6 or -H_7), 7.62 (t, 2 H, quinoline-H_7 or -H_6), 7.76 (d, 2 H, quinoline-H_5 or -H_8), 8.00 (d, 2 H, quinoline-H_8 or -H_5), 8.55 (d, 2 H, quinoline-H_2); MS (EI) $[M]^+$ 426, fragments at *m*/*z* 283, 269, 255, 241, 227, 213, 199, 185, 171, 157, 144; HPLC (column L, C:D = 40:60) major peak at 5.26 min representing 99.8% of the absorption at 220 nm. Anal. ($C_{28}H_{36}N_4$) H, N; C: calcd, 78.83; found, 78.26.

4,4′-[Decane-1,10-diylbis(oxy)]bis[quinoline] (4). A solution of 4-hydroxyquinoline (1 g, 5 mmol) in DMF (50 mL) was treated with NaH (0.15 g, 6.25 mmol) with stirring at room temperature for 15 min. 1,10-Diiododecane (0.98 g, 2.5 mmol) in DMF was then added and the solution heated to 100 °C for 20 h. After cooling to room temperature, the DMF was removed in vacuo, and the resulting material was diluted with water and extracted three times with EtOAc. The combined extracts were dried, and the solvent was removed in vacuo to give a colorless oil (1.57 g). This was purified by column chromatography using 7% MeOH and 1% NH_4OH in EtOAc. This gave 0.302 g of product which was recrystallized from EtOAc and petroleum ether (small white needles): mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (m, 12 H, -CH_2-), 1.93 (m, 4 H, -CH_2-), 4.17 (t, J = 6.4 Hz, 4 H, O-CH_2), 6.69 (d, 2 H, quinoline-H_3), 7.49 (t, 2 H, quinoline-H_6 or -H_7), 7.67 (t, 2 H, quinoline-H_7 or -H_6), 8.03 (d, 2 H, quinoline-H_5 or -H_8), 8.20 (d, 2 H, quinoline-H_8 or -H_5), 8.72 (d, 2 H, quinoline-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 28.8, 29.3, 29.4, 68.4, 100.6, 121.5, 121.8, 125.4, 128.9, 129.6, 149.2, 151.4, 161.7; MS (EI) $[M - H]^+$ 427, fragments at *m*/*z* 256, 242, 228, 214, 200, 186, 172, 158, 145, 128; HPLC (column L, H_2O + 0.1% TEA:MeOH + 0.1% TEA = 40:60) major peak at 4.42 min representing 95% of the absorption at 240 nm. Anal. ($C_{28}H_{32}N_2O_2$) H, N; C: calcd, 78.40; found, 77.86.

4,4′-[Decane-1,10-diylbis(thio)]bis[quinoline] (5). 1,1′-Decane-1,10-diylbis[isothiouronium] dihydrochloride[45] (0.788 g, 2.17 mmol), 4-chloroquinoline (0.71 g, 4.34 mmol), and KOH (0.789 g, 14.06 mmol) were dissolved with heating in absolute EtOH (30 mL), and the solution was heated under reflux for 3 h. The white precipitate formed was removed by vacuum filtration while the solution was still warm. The filtrate was concentrated to dryness in vacuo, dispersed in water, and extracted with CH_2Cl_2 (5 × 50 mL). The extracts were combined and dried with K_2CO_3, and the solvent was removed in vacuo to yield a yellow oil. This was dissolved in the minimum amount of EtOAc, excess of petroleum ether was added, and the white solid formed was collected by filtration and washed with EtOAc. This was recrystallized from EtOAc to yield a white hygroscopic powder (0.518 g, 52%): mp 96−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.34 (m, 8 H, -CH_2-), 1.52 (quint, 4 H, -CH_2-), 1.82 (quint, 4 H, -CH_2-), 3.10 (t, 4 H, S-CH_2), 7.17 (d, 2 H, quinoline-H_3), 7.54 (t, 2 H, quinoline-H_6 or -H_7), 7.71 (t, 2 H, quinoline-H_7 or -H_6), 8.06 (d, 2 H, quinoline-H_5), 8.13 (d, 2 H, quinoline-H_8), 8.71 (d, 2 H, quinoline-H_2); MS (FAB, matrix MNOBA) $[M + H]^+$ 461, fragments at *m*/*z* 332, 300, 286, 272, 258, 244, 230, 216, 188, 175, 162, 129; HPLC (column K, A:B = 30:70) major peak at

7.06 min representing 98.2% of the absorption at 215 nm. Anal. ($C_{28}H_{32}N_2S_2 \cdot 0.7H_2O$) C, H, N.

4,4′-Dodecane-1,12-diylbis[quinoline] (6). Na (0.482 g, 20.96 mmol) was dispersed in liquid NH_3 containing a catalytic amount of $Fe(NO_3)_3$ under argon. When the dark blue color of the suspension turned gray, lepidine (3 g, 20.95 mmol) was added and the reaction mixture was stirred for 1 h. 1,10-Dibromodecane (2.075 g, 6.91 mmol) was then gradualy added, and the NH_3 was allowed to evaporate overnight. Water was added to the residue and the aqueous phase extracted with Et_2O. The extracts were combined, dried (Na_2SO_4), and concentrated to dryness in vacuo to yield an oil which contained mainly lepidine and the title compound. The latter was purified by column chromatography and isolated as a yellow oil. This was dissolved in the minimum amount of hot MeOH and placed at −20 °C. White crystals separated which were collected by filtration, washed with cold MeOH, and dried under vacuum (1.275 g, 43.4%): mp 50−51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27−1.36 (m, 12 H, -CH_2-), 1.43 (quint, 4 H, -CH_2-), 1.76 (quint, 4 H, -CH_2-), 3.08 (t, 4 H, Ar-CH_2-), 7.27 (d, 2 H, quinoline-H_3), 7.58 (t, 2 H, quinoline-H_6 or -H_7), 7.73 (t, 2 H, quinoline-H_7 or -H_6), 8.06 (d, 2 H, quinoline-H_5), 8.18 (d, 2 H, quinoline-H_8), 8.80 (d, 2 H, quinoline-H_2); MS (FAB, matrix MNOBA) $[M + H]^+$ 425; HPLC (column K, A:B = 35:65) major peak at 10.16 min representing 97.3% of the absorption at 215 nm. Anal. ($C_{30}H_{36}N_2$) C, H, N.

1,8-Bis(*N*-quinolin-4-yldiamino)octane (7a).[32] A solution of 4-chloroquinoline (0.3 g, 2 mmol) in *n*-butanol (30 mL) was treated with 1,8-diaminooctane (0.18 g, 1 mmol) under reflux with stirring for 78 h. After removal of the solvent in vacuo, the residue was treated with NH_4OH and extracted with $CHCl_3$. Drying (Mg_2SO_4) of the extracts and removal of the $CHCl_3$ afforded a white solid which was purified by column chromatography using 10% MeOH in EtOAc. This gave 0.28 g of product which was recrystallized from a mixture of iPrOH and MeOH to yield pale yellow platelets: MS (FAB, matrix MNOBA) $[M + H]^+$ 399, fragments at *m/z* 270, 255, 241, 213, 199, 185, 171, 157, 144, 129.

1,8-Bis[*N*-(1-methylquinolinium-4-yl)amino]octane Diiodide Hydrate (7). Compound **7a** (89 mg, 0.22 mmol) was dissolved in MEK (20 mL) and treated with MeI (2 mL, 32.15 mmol) under reflux for 2 h. The creamy white precipitate was collected and recrystallized from absolute EtOH to give cream microcrystalline needles (94 mg, 63%): mp 279−281 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.51 (m, 8 H, -CH_2-), 1.86 (quint, 4 H, -CH_2-), 3.64 (t, J = 7.3 Hz, 4 H, NH-CH_2), 4.21 (s, 6 H, CH_3), 6.90 (d, J = 7.4 Hz, 2 H, quinoline-H_3), 7.81 (t, J = 6.4 Hz, 2 H, quinoline-H_6 or -H_7), 8.09 (m, 4 H, quinoline), 8.50 (m, 4 H, quinoline); MS (FAB, matrix MNOBA) $[M + I - H]^+$ 554, $[M - H]^+$ 427, fragments at *m/z* 413, 269, 255, 241, 227, 213, 199, 185, 171, 157, 143; HPLC (column L, C:D = 40:60) major peak at 5.61 min representing 97% of the absorption at 215 nm. Anal. ($C_{28}H_{36}N_4I_2 \cdot 1.5H_2O$) C, H, N, I.

1,10-Bis[*N*-(1-methylquinolinium-4-yl)amino]decane Diiodide (8). 3 (0.2 g, 0.5 mmol) was dissolved in MEK (30 mL) and treated with MeI (1 mL, 16.07 mmol) under reflux for 2 h. After cooling, the solvent was removed in vacuo and the resulting solid was dissolved in hot EtOH, treated with charcoal, and filtered and the filtrate allowed to cool. This gave a creamy powdery solid which was collected, washed with a small amount of iPrOH, and dried (0.162 g, 71%): mp 233−236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (m, 12 H, -CH_2-), 1.69 (quint, 4 H, -CH_2-), 3.54 (t, J = 7.2 Hz, 4 H, NH-CH_2), 4.14 (s, 6 H, N^+-CH_3), 6.90 (d, J = 6.5 Hz, 2 H, quinoline-H_3), 7.80 (t, J = 6.5 Hz, 2 H, quinoline-H_6 or -H_7), 8.08 (m, 4 H, quinoline), 8.59 (m, 4 H, quinoline), 9.23 (s_{br}, 2 H, NH); MS (FAB, matrix MNOBA) $[M + I]^+$ 583, $[M - H]^+$ 455, fragments at *m/z* 441, 313, 297, 283, 269, 255, 242, 227, 213, 199, 185, 171, 143; HPLC (column L, C:D = 20:80) major peak at 3.95 min representing 99.8% of the absorption at 240 nm. Anal. ($C_{30}H_{40}N_4I_2 \cdot H_2O$) C, H, N.

4,4′-[Decane-1,10-diylbis(oxy)]bis[1-methylquinolinium] Diiodide (9). Compound **4** (50 mg, 0.12 mmol) was dissolved in MEK (10 mL) and treated with MeI (1 mL, 16.07 mmol) under reflux for 3 h. After cooling to room temperature, the pale yellow precipitate was collected, washed with MEK, and dried (73 mg, 88%): mp 158−161 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.49−1.63 (m, 12 H, -CH_2-), 2.06 (quint, J = 6.5 Hz, 4 H, -CH_2-), 4.47 (s, 6 H, CH_3), 4.60 (t, J = 6.5 Hz, 4 H, O-CH_2), 7.50 (d, 2 H, quinoline-H_3), 7.90 (t, 2 H, quinoline-H_6 or -H_7), 8.22 (t, 2 H, quinoline-H_7 or -H_6), 8.32 (d, 2 H, quinoline-H_5 or -H_8), 8.55 (d, 2 H, quinoline-H_8 or -H_5), 9.12 (d, 2 H, quinoline-H_2); MS (FAB, matrix MNOBA) $[M + I + H]^+$ 586, $[M]^+$ 458, fragments at *m/z* 444, 427, 298, 284, 270, 256, 242, 229, 214, 200. Anal. ($C_{30}H_{38}N_2O_2I_2$) C, H, N, I.

4,4′-[Decane-1,10-diylbis(thio)]bis[1-methylquinolinium] Diiodide Hydrate (10). Compound **5** (0.124 g, 0.27 mmol) and MeI (2 mL, 32.13 mmol) were dissolved in MEK (20 mL), and the solution was heated under reflux for 4 h under Ar. A yellow precipitate formed which, after cooling to room temperature, was collected by vacuum filtration, washed with MEK, and dried in vacuo (0.172 g, 86%): mp 196−198 °C; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 1.32 (m, 8 H, -CH_2-), 1.51 (quint, 4 H, -CH_2-), 1.79 (quint, 4 H, -CH_2-), 3.46 (t, 4 H, S-CH_2), 4.48 (s, 6 H, N^+-CH_3), 7.96−8.03 (m, 4 H, quinoline), 8.25 (t, 2 H, quinoline-H_7 or -H_6), 8.43 (dd, 4 H, quinoline-H_5 + -H_8), 9.14 (d, 2 H, quinoline-H_2); MS (FAB, matrix MNOBA) $[M - H]^+$ 489, fragments at *m/z* 475, 315, 300, 286, 272, 258, 245, 230, 216, 202, 189, 175, 143; HPLC (column K, A:B = 40:60) major peak at 14.13 min representing 100% of the absorption at 215 nm. Anal. ($C_{30}H_{38}N_2S_2I_2 \cdot H_2O$) C, H, N.

1,1′-Dimethyl-4,4′-dodecane-1,12-diylbis[quinolinium] Diiodide (11). Compound **6** (0.2 g, 0.47 mmol) and MeI (2 mL, 32.13 mmol) were dissolved in MEK (40 mL), and the solution was heated under reflux for 4 h under argon. The reaction mixture was cooled to room temperature and the yellow solid collected by filtration, washed with the solvent, and dried under vacuum (0.284 g, 85%): mp 156−158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (m, 8 H, -CH_2-), 1.32 (m, 4 H, -CH_2-), 1.41 (m, 4 H, -CH_2-), 1.73 (m, 4 H, -CH_2-), 3.34−3.38 (m, Ar-CH_2-, water), 4.57 (s, 6 H, N^+-CH_3), 8.03−8.07 (m, 4 H, quinoline-H_3, -H_6, or -H_7), 8.27 (t, 2 H, quinoline-H_7 or -H_6), 8.49 (d, 2 H, quinoline-H_5), 8.60 (d, 2 H, quinoline-H_8), 9.36 (d, 2 H, quinoline-H_2); MS (FAB, matrix MNOBA + Li + Na) $[M - H]^+$ 453, fragments at *m/z* 438, 412, 170; HPLC (column K, A:B = 35:65) major peak at 5.23 min representing 99.2% of the absorption at 215 nm. Anal. ($C_{32}H_{42}N_2I_2$) C, H, N.

4,4′-Decane-1,10-diylbis[quinoline] (12a). Lepidine (2.762 g, 19.28 mmol), Na (0.52 g, 22.6 mmol), and 1,8-diiodooctane (3.53 g, 9.64 mmol) were reacted in a manner similar to that described under **6**. The product was isolated as a yellow oil which solidified after drying under vacuum to yield a creamy solid (1.28 g, 33.5%): mp 61−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.31−1.45 (m, 12 H, -CH_2-), 1.76 (quint, 4 H, -CH_2-), 3.06 (t, 4 H, Ar-CH_3), 7.23 (d, 2 H, quinoline-H_3), 7.55 (t, 2 H, quinoline-H_6 or -H_7), 7.70 (t, 2 H, quinoline-H_7 or -H_6), 8.04 (d, 2 H, quinoline-H_5), 8.12 (d, 2 H, quinoline-H_8), 8.80 (d, 2 H, quinoline-H_2). Anal. ($C_{28}H_{32}N_2 \cdot 0.3H_2O$) C, H, N.

1,1′-Dimethyl-4,4′-decane-1,10-diylbis[quinolinium] Diiodide (12). Compound **12a** was methylated as described in the preparation of **11** in 88.5% yield: mp 198−200 °C; ^{1}H NMR (400 MHz, DMSO-d_6 + 10 drops of TFA, TMS) δ 1.27−1.44 (m, 12 H, -CH_2-), 1.75 (quint, 4 H, -CH_2-), 3.38 (t, 4 H, Ar-CH_2-), 4.59 (s, 6 H, N^+-CH_3), 8.03−8.08 (m, 4 H, quinoline-H_3, -H_6, or -H_7), 8.27 (t, 2 H, quinoline-H_7 or -H_6), 8.51 (d, 2 H, quinoline-H_5), 8.60 (d, 2 H, quinoline-H_8), 9.38 (d, 2H, quinoline-H_2); MS (FAB, matrix MNOBA + Li + Na) $[(M + I) - H]^+$ 552, $[M]^+$ 426, fragments at *m/z* 412, 282, 268, 254; HPLC (column K, A:B = 50:50) major peak at 13.30 min representing 100% of the absorption at 215 nm. Anal. ($C_{30}H_{38}N_2I_2 \cdot H_2O$) C, H, N.

1,10-Bis[*N*-(1-benzylquinolinium-4-yl)amino]decane Dibromide (13). Compound **3** (0.5 g, 1.17 mmol) and benzyl bromide (0.4 g, 2.34 mmol) were dissolved in MEK, and the solution was heated under reflux for 24 h. The white precipitate formed was collected and washed with MeOH (0.46 g, 64%): mp 270−272 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.29 (m, 12 H, CH_2), 1.73 (quint, 4 H, CH_2), 3.53 (t, 4 H, NH-CH_2), 5.72 (s, 4 H, N^+-CH_2), 6.87 (d, 2 H, quinoline-H_3), 7.14 (d, 4 H, Ph), 7.24 (m, 6 H, Ph), 7.60 (ddd, 2 H, quinoline-H_6 or -H_7), 7.78 (ddd, 2 H, quinoline-H_7 or -H_6), 7.87 (d, 2 H, quinoline-

H_5 or -H_8), 8.38 (dd, 2 H, quinoline-H_8 or -H_5), 8.57 (d, 2 H, quinoline-H_2); MS (FAB, matrix MNOBA) $[M]^+$ 608, fragment at *m/z* 517; HPLC (column K, A:B = 33:67) major peak at 7.24 min representing 95.6% of the absorption at 215 nm. Anal. ($C_{42}H_{48}N_4Br_2$) C, H, N.

1,10-Bis[*N*-(1-benzyl-2-methylquinolinium-4-yl)amino]-decane Bis(trifluoroacetate) (14). Compound **1** (0.3 g, 0.66 mmol) was dissolved with heating in previously dried (molecular sieves, 4 Å) nitrobenzene (10 mL), and benzyl bromide (0.288 g, 1.68 mmol) was added. The solution was heated in an oil bath under argon at 100−120 °C for 96 h and then at 120−140 °C for 12 h. More benzyl bromide was added after 48 h (0.144 g, 0.84 mmol) and 72 h (0.144 g, 0.84 mmol). The reaction mixture was cooled to room temperature, excess of ether was added, and a gum came out of solution. The supernatant solution was decanted and the gum washed several times with ether. This consisted mainly of the mono- and bisquaternary products which were separated by reverse phase preparative HPLC. The product was isolated as a green oil which solidified after drying under vacuum: mp 58−60 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31−1.40 (m, 12 H, -CH_2-), 1.71 (quint, 4 H, -CH_2-), 2.73 (s, 6 H, -CH_3), 3.54 (q, 4 H, N-CH_2-), 5.84 (s, 4 H, -CH_2-N^+), 7.05 (d, 6 H, C_3-H, Ph-H_o), 7.29 (t, 2 H, Ph-H_p), 7.35 (t, 4 H, Ph-H_m), 7.69 (t, 4 H, quinoline-H_6 or -H_7), 7.88 (t, 2 H, quinoline-H_7 or -H_6), 7.93 (d, 2 H, quinoline-H_5), 8.56 (d, 2 H, quinoline-H_8), 9.31 (t, 2 H, N-H); MS (FAB, matrix MNOBA) $[M - H]^+$ 635; HPLC (column K, A:B = 35:65) major peak at 19.42 min representing 100% of the absorption at 215 nm. Anal. ($C_{48}H_{52}N_4F_6O_8$·1.2CF_3CO_2H) C, H, N.

1,12-Bis[*N*-(1-benzyl-2-methylquinolinium-4-yl)amino]-dodecane Bis(trifluoroacetate) (15). Compound **2** (0.3g, 0.621 mmol) and benzyl bromide (0.319 g, 1.865 mmol) were dissolved with heating in distilled diisobutyl ketone (10 mL), and the solution was heated under reflux for 24 h. On cooling a dark gum came out of solution which crystallized on standing. This was collected by filtration and dried overnight in vacuo over P_2O_5. It was shown (MS, HPLC) that this was a mixture of three compounds, namely, **36** and the monobenzylated (**37**) and dibenzylated (**38**) products. These were separated by reverse phase preparative HPLC. The compound was isolated as a greenish oil which solidified after thorough drying in vacuo over P_2O_5 (greenish, hygroscopic crystals): mp 133−134 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26−1.41 (m, 16 H, -CH_2-), 1.72 (quint, 4 H, -CH_2-), 2.74 (s, 6 H, -CH_3), 3.55 (q, 4 H, -CH_2-), 5.85 (s, 4 H, Ph-CH_2-N^+), 7.06 (d, s, 6 H, Ph-H_o, quinoline-H_3), 7.30 (t, 2 H, Ph-H_p), 7.36 (t, 4 H, Ph-H_m), 7.69 (t, 2 H, quinoline-H_6 or -H_7), 7.89 (t, 2 H, quinoline-H_7 or -H_6), 7.94 (d, 2 H, quinoline-H_5), 8.57 (d, 2 H, quinoline-H_8), 9.30 (t_{br}, 2 H, N-H); MS (FAB, matrix MNOBA + NaI) $[M]^+$ 664, fragments at *m/z* 547, 482, 431, 415, 401, 387; HPLC (column K, A:B = 35:65) major peak at 27.28 min representing 98.1% of the absorption at 215 nm. Anal. ($C_{50}H_{56}F_6N_4O_4$·2CF_3-COOH·4H_2O) C, H, N [agreed after allowing for the presence of 10.14% of inorganic matter (determined by an ash test)].

1-[*N*-(1-Benzyl-2-methylquinolinium-4-yl)amino]-10-[*N*′-(2-methylquinolinium-4-yl)amino]decane Bis(trifluoroacetate) (16). The preparation is described under **14**. The compound was isolated as a greenish oil which solidified after drying under vacuum: mp 72−74 °C; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 1.30 (m, 12 H, -CH_2-), 1.70 (quint, 4 H, -CH_2-), 2.64 (s, 3 H, -CH_3′), 2.74 (s, 3 H, -CH_3), 2.48 (q, 2 H, N-CH_2-′), 2.55 (q, 2 H, N-CH_2-), 5.85 (s, 2 H, -CH_2-N^+), 6.79 (s, 1 H, quinoline-H_3′), 7.06 (d, 3 H, quinoline-H_3, Ph-H_o), 7.30 (t, 1 H, Ph-H_p), 7.36 (t, 2 H, Ph-H_m), 7.67 (m, 2 H, quinoline-H_6, -H_6′ or quinoline-H_7, -H_7′), 7.83 (d, 1 H, quinoline-H_5′), 7.89 (t, 2 H, quinoline-H_7, -H_7′ or quinoline-H_6, -H_6′), 7.94 (d, 1 H, quinoline-H_5), 8.46 (d, 1 H, quinoline-H_8′), 8.56 (d, 1 H, quinoline-H_8), 9.06 (t, 1 H, N-H′), 9.32 (t, 1 H, N-H); MS (FAB, matrix MNOBA) $[M - H]^+$ 544; HPLC (column K, A:B = 35:65) major peak at 9.52 min representing 96.8% of the absorption at 215 nm. Anal. ($C_{41}H_{46}N_4F_6O_8$·0.5CF_3CO_2H) C, H, N.

1-[*N*-(1-Benzyl-2-methylquinolinium-4-yl)amino]-12-(*N*′-(2-methylquinolinium-4-yl)amino]dodecane Bis(trifluoroacetate) (17). The experimental procedure is described under **15**. The compound was isolated as a greenish oil which solidified after thorough drying in vacuo over P_2O_5 (greenish, hygroscopic crystals): mp 77−79 °C melts, 104−106 °C liquifies; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (m, 16 H, -CH_2-), 1.70 (m, 4 H, -CH_2-), 2.64 (s, 3 H, -CH_3′), 2.74 (s, 3 H, -CH_3), 3.48 (q, 2 H, -CH_2-), 3.52 (q, 2 H, -CH_2-), 5.85 (s, 2 H, Ph-CH_2-N^+), 6.78 (s, 1 H, quinoline-H_3′), 7.06 (d, 3 H, Ph-H_o, quinoline-H_3), 7.32 (t, 1 H, Ph-H_p), 7.36 (t, 2 H, Ph-H_m), 7,67 (ddd, 2 H, quinoline-H_6 or -H_7, quinoline-H_6′ or -H_7′), 7.82−7.95 (m, 4 H, quinoline-H_5, -H_5′, quinoline-H_7 or -H_6, quinoline-H_7′ or -H_6′), 8.46 (d, 1 H, quinoline-H_8′), 8.56 (d, 1 H, quinoline-H_8), 9.03 (t_{br}, 1 H, N-H′), 9.30 (t_{br}, 1 H, N-H); MS (FAB, matrix MNOBA + NaI) $[M + H]^+$ 574, fragment at *m/z* 482; HPLC (column K, A:B = 35:65) major peak at 13.48 min representing 97.5% of the absorption at 215 nm. Anal. ($C_{43}H_{50}F_6N_4O_4$·0.6 CF_3-COOH) C, H, N.

3,5-Dimethoxybenzyl iodide (18c). 3,5-Dimethoxybenzyl chloride (0.5 g, 2.68 mmol) and dry NaI (0.44 g, 2.94 mmol) were dissolved in dry (K_2CO_3) acetone (10 mL), and the solution was heated to 50 °C for 3 h. The solvent was removed in vacuo and the residue treated with CH_2Cl_2 and filtered in order to remove the NaCl formed and the excess of NaI. The filtrate was concentrated to dryness, and the last traces of solvents were removed under vacuum to yield a yellowish solid: mp 84−85 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.77 (s, 6 H, -CH_3), 4.37 (s, 2 H, -CH_2-), 6.31 (m, 1 H, Ph-H_4), 6.51 (d, *J* = 2.25 Hz, 2 H, Ph-H_2, Ph-H_6).

1,10-Bis[*N*-[1-(3,5-dimethoxybenzyl)-2-methylquinolinium-4-yl]amino]decane Bis(trifluoroacetate) (18). Compounds **1** (0.3 g, 0.66 mmol) and **18c** (0.367 g, 1.32 mmol) were dissolved with heating in previously dried (molecular sieves, 4 Å) nitrobenzene (10 mL), and the solution was heated under argon in an oil bath at 100−120 °C for 144 h. The reaction mixture was cooled to room temperature, and dry Et_2O was added until the solution became cloudy. The creamy precipitate formed was collected by filtration, washed three times with EtOH, and dried under vacuum at 60 °C over P_2O_5. The later was a mixture of the mono- and bisquaternary compounds, which were separated by reverse phase preparative HPLC. The product was isolated as a creamy oil which solidified after drying in vacuo: mp 96−98 °C melts, 115−119 °C solidifies, 213−215 °C melts; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30−1.45 (m, 12 H, -CH_2-), 1.71 (quint, 4 H, -CH_2-), 2.72 (s, 6 H, -CH_3), 3.54 (q, overlaps with water signal, N-CH_2-), 3.67 (s, 12 H, O-CH_3), 5.74 (s, 4 H, -CH_2-N^+), 6.14 (d, 4 H, Ph-H_o), 6.44 (t, 2 H, Ph-H_p), 7.04 (s, 2 H, quinoline-H_3), 7.69 (m, 2 H, quinoline-H_6 or -H_7), 7.90 (d, 4 H, quinoline-H_5, -H_7 or quinoline-H_5, -H_6), 8.58 (d, 2 H, quinoline-H_8), 9.30 (t, 2 H, N-H); MS (FAB, matrix glycerol + thioglycerol + TFA) $[M]^+$ 756, fragments at *m/z* 605, 335, 185, 151; HPLC (column K, A:B = 35:65) major peak at 34.83 min representing 99.6% of the absorption at 215 nm. Anal. ($C_{52}H_{60}N_4F_6O_8$·0.5CF_3-CO_2H) C, H, N.

1-[*N*-[1-(3,5-Dimethoxybenzyl)-2-methylquinolinium-4-yl]amino]-10-[*N*′-(2-methylquinolinium-4-yl)amino]decane Bis(trifluoroacetate) (19). The preparation is described under **18**. The product was isolated as a creamy oil which solidified after drying at high vacuum: mp 77−78 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34−1.38 (m, 12 H, -CH_2-), 1.72 (m, 4 H, -CH_2-), 2.62 (s, 3 H, -CH_3′), 2.72 (s, 3 H, -CH_3′), 3.53 (m, 4 H, N-CH_2-), 3.67 (s, 6 H, O-CH_3), 5.74 (s, 2 H, -CH_2-N^+), 6.15 (s, 2 H, Ph-H_o), 6.44 (s, 1 H, Ph-H_p), 6.78 (s, 1 H, quinoline-H_3′), 7.04 (s, 1 H, quinoline-H_3), 7.64−7.70 (m, 2 H, quinoline-H_6, -H_6′ or quinoline-H_7, -H_7′), 7.81 (d, 1 H, quinoline-H_5′), 7.90 (m, 3 H, quinoline-H_5, -H_7, -H_7′ or quinoline-H_5, -H_6, -H_6′), 8.45 (d, 1 H, quinoline-H_8′), 8.55 (d, 1 H, quinoline-H_8), 9.04 (t, 1 H, N-H′), 9.30 (t, 1 H, N-H); MS (FAB, matrix glycerol + thioglycerol + TFA) $[M]^+$ 605, fragments at *m/z* 455, 185, 171, 151; HPLC (column K, A:B = 35:65) major peak at 14.71 min representing 99.5% of the absorption at 215 nm. Anal. ($C_{41}H_{50}N_4F_6O_8$·0.5CF_3CO_2H) C, H, N.

1,1′-(3-Iodopropylidene)bis[benzene] (20c). To a stirred and cooled to 0 °C solution of 3,3-diphenyl-1-propanol (2.5 g, 11.78 mmol) in dry CH_2Cl_2 were successively added Ph_3P (3.243 g, 12.36 mmol) and iodine (3.048 g, 12.01 mmol). The work was carried out under an atmosphere of argon. The orange solution was stirred for 15 min, and an orange

precipitate formed. Imidazole (1.042 g, 15.31 mmol) was added, the color disappeared, and a white precipitate formed. The reaction mixture was stirred at 0 °C for 30 min and then heated under reflux for 2 h. After cooling to room temperature, the reaction mixture was washed with water (20 mL) and the water layer extracted with CH_2Cl_2 (20 mL). The CH_2Cl_2 extracts were combined, dried with Na_2SO_4, and concentrated to dryness in vacuo to yield a white solid. The iodide was purified by column chromatography (silica gel, petroleum ether 30−40 °C:CH_2Cl_2 = 5:1) and isolated as a white solid (2.910 g, 76.7%): mp 54−55 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.49 (q, 2 H, -CH_2-), 3.02 (t, 2 H, -CH_2-I), 4.04 (t, 1 H, Ph_2-CH), 7.09−7.28 (m, 10 H, Ph); MS (EI) $[M]^+$ 322, fragments at *m*/*z* 245, 168, 167, 155, 141, 127.

1,10-Bis[*N*-[1-(3,3-diphenylprop-1-yl)-2-methylquinolinium-4-yl]amino]decane Bis(trifluoroacetate) (20). Compounds **1** (0.3 g, 0.66 mmol) and **20c** (0.5 g, 1.552 mmol) were dissolved with heating in 4-methylpentan-2-ol (10 mL), and the solution was heated under reflux for 120 h under argon, more iodide being added after 36 h (0.2 g, 0.621 mmol) and 60 h (0.2 g, 0.621 mmol). On cooling, a red solid came out of solution, which was collected by filtration, washed with the solvent, and dried. This was shown (MS, HPLC) to contain mainly the desired product together with some of the monoquaternary compound. Attempts to purify it by crystallization failed; therefore, it was purified by reverse phase preparative HPLC. The product was isolated as a pink oil which was disolved in the minimum amount of cold iPrOH and filtered and the solvent removed in vacuo to yield a pink oil. This solidified after drying in vacuo over P_2O_5 (0.22 g, 30.3%): mp 77−78 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (m, 12 H, -CH_2-), 1.64 (q, 4 H, -CH_2-), 2.56 (m, 10 H, -CH_2-, -CH_3), 3.46 (q, 4 H, NH-CH_2-), 4.29 (t, 6 H, Ph_2CH, -CH_2-N^+), 6.87 (s, 2 H, quinoline-H_3), 7.20 (t, 4 H, Ph-H_p), 7.30 (t, 8 H, Ph-H_m), 7.39 (d, 8 H, Ph-H_o), 7.70 (t, 2 H, quinoline-H_6 or -H_7), 7.93 (t, 2 H, quinoline-H_7 or -H_6), 7.98 (d, 2 H, quinoline-H_5), 8.48 (d, 2 H, quinoline-H_8), 9.10 (t, 2 H, N-H); MS (FAB, matrix glycerol + thioglycerol + TFA) $[M]^+$ 844, fragments at *m*/*z* 649, 422, 380, 365, 200, 185; HPLC (column K, A:B = 25:75) major peak at 18.35 min representing 99.6% of the absorption at 215 nm. Anal. ($C_{64}H_{68}F_6N_4O_4$·0.4HI·0.4CF_3COOH·H_2O) C, H, N, I.

4,7-Dichloro-1-methylquinolinium Iodide (21c). A solution of 4,7-dichloroquinoline (2.53 g, 12.7 mmol) and MeI (1.5 mL, 24.11 mmol) in MEK (20 mL) was stirred and heated under reflux for 5 h. After cooling, the precipitate was collected and purified by column chromatography using MeOH as the eluant. The solid thus obtained was suspended in boiling EtOH, filtered, and washed twice with hot EtOH to yield a yellow powder (1.26 g, 24%): mp 240−242 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.94 (s, 3 H, CH_3), 6.36 (d, J = 7.5 Hz, 1 H, quinoline-H_3), 7.56 (dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz, 1 H, quinoline-H_6), 7.94 (d, J = 1.7 Hz, 1 H, quinoline-H_8), 8.22 (d, J = 8.7 Hz, 1 H, quinoline-H_5), 8.24 (d, J = 7.5 Hz, 1 H, quinoline-H_2); MS (FAB, matrix MNOBA) $[M + I + H - Cl]^+$ 303, $[M + H]^+$ 211, fragment at *m*/*z* 177.

1,10-Bis[*N*-(7-chloro-1-methylquinolinium-4-yl)amino]decane Diiodide Dihydrate (21). Compound **21c** (1 g, 4.7 mmol), 1,10-diaminodecane (0.38 g, 2 mmol), and PhOH (2.3 g) were heated at 135 °C with stirring for 3.5 h. After cooling, the reaction mixture was powdered, poured into EtOAc, filtered, and washed twice with EtOAc. The resulting solid was suspended in boiling EtOH, filtered, and washed with hot EtOH. This procedure was repeated twice to yield a brown-yellow powder (0.175 g, 18%): mp 272−274 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27−1.36 (m, 12 H, -CH_2-), 1.67 (m, 4 H, -CH_2-), 3.44−3.51 (m, 4 H, NH-CH_2), 4.10 (s, 6 H, CH_3), 6.93 (d, J = 7.6 Hz, 2 H, quinoline-H_3), 7.88 (dd, J_1 = 9.0 Hz, J_2 = 1.9 Hz, 2 H, quinoline-H_6), 8.18 (d, J = 1.9 Hz, 2 H, quinoline-H_8), 8.58 (d, J = 9.0 Hz, 2 H, quinoline-H_5), 8.59 (d, J = 7.4 Hz, 2 H, quinoline-H_2), 9.34 (t, J = 5.1 Hz, 2 H, NH); MS (FAB, matrix glycerol + thioglycerol + TFA) $[M + I]^+$ 651, $[M - H]^+$ 523; HPLC (column K, A:B = 40:60) major peak at 10.9 min representing 96.6% of the absorption at 254 nm. Anal. ($C_{30}H_{38}Cl_2N_4I_2$·2.5H_2O) C, N; H: calcd, 5.26; found, 4.79.

(b) Biological Testing. Stock solutions (2 mM) of all compounds were prepared in MeOH. For the free bases **1**−**6**, the solution contained 5 mM HCl. Superior cervical ganglia from 17 day old rats were treated with collagenase and trypsin and then dissociated using a fire-polished pipette. The resultant cell suspension was plated onto laminin-coated plastic dishes and maintained in tissue culture for 3−10 days. Culture dishes were placed on the stage of an inverted microscope and perfused with physiological salt solution of the following composition (in mM): NaCl, 118; KCl, 4.8; $CaCl_2$, 2.5; $MgSO_4$, 1.19; $NaHCO_3$, 25; KH_2PO_4, 1.18; and glucose, 11; warmed to 30 °C and equilibrated with 95% O_2:5% CO_2. Intracellular recordings were made with convetional microelectrodes filled with 1 M KCl (resistance 80−120 MΩ), connected to the headstage of a Neurolog NL 102 amplifier. Action potentials were evoked by injection of 30 ms depolarizing current pulses every 5 s. Data aquisition and analysis were performed on a microcomputer using the pClamp suite of programs (Axon Instruments). Inhibition of the AHP was measured by digitally subtracting records obtained in the presence of blocker from controls and expressing the peak difference as a percentage of the control AHP at the same time point.

(c) MO Calculations. These were performed on the model compounds of Table 2. The structures were initially built in SYBYL 5.5[46] running on a Silicon Graphics IRIS 4D workstation and then submitted for semiempirical MO calculations using the MOPAC 5.0 MO package and the AM1[34] Hamiltonian. The normal self-consistent field (SCF) convergence procedure (default setting) was used, and full geometry optimization of the structures was carried out. Note that reliable energy minimization of the molecules cannot be performed using the Tripos force field[47] since it lacks an sp^2-charged nitrogen atom type which is present in these molecules. The charge on the system was set to 1. A Mulliken population analysis was also performed, and the charges obtained were used in the correlation studies. The MO calculations were performed on the protonated forms of the nonquaternary analogues **1a**−**6a**.

Acknowledgment. This work was supported by the Wellcome Trust (including Fellowships to C.A.D. and P.M.D.). We thank Mr. C. S. Owen and Dr. B. Del Rey Herrero for the synthesis of compounds **13** and **21**, respectively. We are grateful to Drs. J. G. Vinter and J. A. D. Calder for helpful discussions on the MO calculations and to Professor D. H. Jenkinson for helpful discussions on the pharmacology.

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JM950520I