Synthesis and Quantitative Structure–Activity Relationships of Dequalinium Analogues as K^+ Channel Blockers: Investigation into the Role of the Substituent at Position 4 of the Quinoline Ring

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Dequalinium (**4**) is a potent and selective blocker of small conductance Ca^{2+}-activated K^+ channels, an important but relatively little studied class. The 4-NH_2 group of dequalinium has been shown to contribute significantly to blocking potency. In this study, we have investigated further the role of the 4-NH_2 group. Replacement of this group by other substituents (R^4) and quantitative structure–activity relationship (QSAR) analysis on the resultant analogues have yielded a correlation between blocking potency and σ_R for R^4 for seven of the compounds. The application of calculated electronic indices enabled the extension of the QSAR to compounds for which the appropriate σ_R values are not available, allowing all 13 analogues of this series to be included in the correlations. Analysis using electronic indices obtained from AM1 MO calculations on model compounds revealed that the blocking potency correlates with the partial charge on the ring N atom, E_{LUMO}, and E_{HOMO}. The E_{HOMO} correlation is qualitatively inconsistent as the HOMO is not the same orbital in all compounds. The E_{LUMO} correlation [pEMR = 1.19(±0.21)E_{LUMO} + 5.41(±1.05), n = 13, r = 0.86, s = 0.274] suggests that the higher the E_{LUMO} the more potent is the analogue. This is inconsistent with simple charge transfer from the channel to the blocker and may refer to other processes which are important for the strength of the drug–K^+ channel interaction such as the desolvation of the compounds.

Introduction

There has been an increasing interest in compounds that modulate K^+ ion channels as potential therapeutic agents.[1,2] K^+ channels comprise the most diverse family of ion channels so far described.[3] Despite the large number of K^+ channel subtypes, medicinal chemistry research in this field has centered around a few K^+ channel classes, leaving many of them relatively little studied. Compounds which act as selective modulators of the less well-studied K^+ channel types are important for the elucidation of the physiological and pathophysiological roles of these channels and may lead to the discovery of novel therapeutically useful agents.

Small conductance Ca^{2+}-activated K^+ (SK_{Ca}) channels form a physiologically important class for which few modulators are available and of which the structure is not known.[4,5] SK_{Ca} channels are present in intestinal smooth muscle where their activation mediates the inhibitory action of α_1-adrenergic, neurotensin, and ATP receptors.[6–8] In many neurones, including those of the sympathetic ganglia,[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] In hepatocytes, SK_{Ca} channels mediate adrenaline-evoked hyperkalemia,[13,14] and in brown fat cells, opening of SK_{Ca} channels contributes to the mobilization of intracellular Ca^{2+}.[15]

Apamin, a highly specific and potent blocker of the SK_{Ca} channel, has been used as a pharmacological tool in studies on the involvement of this channel subtype in pathophysiological conditions. Thus, SK_{Ca} channels have been implicated in myotonic muscular dystrophy, since the binding site for apamin is expressed in muscles of patients with this disease, while it is completely absent in normal human muscle.[16,17] It has also been demonstrated recently that injection of apamin into muscle of patients with myotonic dystrophy produced a reduction in basal muscle electrical activity and suppressed significantly myotonic discharges, supporting the hypothesis that SK_{Ca} channels play a role in the genesis of myotonia.[18]

In addition, apamin has been shown to inhibit the stimulatory effects of EtOH on Ca^{2+}-dependent efflux of ^{86}Rb from synaptosomes and to shorten EtOH narcosis[19] suggesting a role of SK_{Ca} channels in alcohol intoxication. Thus, there may be clinical uses for selective blockers of the SK_{Ca} channel.

Existing SK_{Ca} modulators can be categorized into natural peptidic toxins and small organic molecules. Of the first class, apamin[20–22] (an 18-amino acid peptide isolated from the venom of the honey bee *Apis mellifera*) and leiurotoxin I[23] (also called scyllatoxin, a 31-amino acid peptide isolated from the venom of the scorpion *Leiurus quinquestriatus hebraeus*) have been shown (by radioligand-binding studies) to bind to SK_{Ca} channels. Using electrophysiological techniques, they have also been shown to block SK_{Ca} channels potently ($IC_{50} \approx 1$ nM for apamin, $IC_{50} \approx 6$ nM for leiurotoxin I) and selectively. A third toxin, PO5[24] (a 31-amino acid peptide isolated from the venom of the scorpion *Androctonus mauretanicus mauretanicus*), has also been shown to be a high-affinity ligand for the SK_{Ca} channel. Some effort to elucidate the pharmacophore of apamin has been undertaken.[25–29] It is interesting to note that an endogenous ligand with apamin-like activity has been

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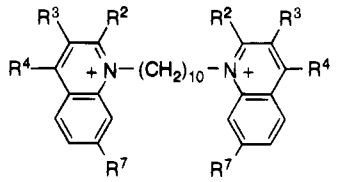
Table 1. Structures and Biological Results for the Compounds



compd	R^2	R^3	R^4	R^7	$IC_{50} \pm SD$ (μM)	$EMR^a \pm SD$	n^b
1	H	H	$NHCH_2Ph$	H	0.52 ± 0.07	0.7 ± 0.3	7
2	H	H	$NHCH_2Ph$	NH_2	0.5 ± 0.15	0.9 ± 0.5	8
3	$CH_2CH_2-CH_2CH_2$		NH_2	H	1.0 ± 0.2	0.9 ± 0.7^c	5
dequalinium (**4**)	CH_3	H	NH_2	H	0.74 ± 0.05	1	18
5	H	H	Y[d]	H	0.6 ± 0.09	1.0 ± 0.6	3
6	H	H	NH_2	H	1.4 ± 0.3	1.3 ± 0.5	4
7	H	H	$N(CH_3)_2$	H	1.4 ± 0.3	1.4 ± 0.6	3
8	H	H	$N(CH_3)Ph$	H	1.4 ± 0.7	1.7 ± 0.8	6
9	H	H	NHPh	H	2.4 ± 0.5	3.4 ± 1.8	8
10	H	H	$NHCOCH_3$	H	4.5 ± 0.3	5.5 ± 1.0	3
11	H	H	OPh	H	2.7 ± 1.6	6.5 ± 1.9	5
12	H	H	H	H	21 ± 5	15 ± 7.9^c	4
13	H	H	CH_3	H	14.5 ± 3.8	26 ± 14	3
14a	H	H	O^-	H	$\gg 10$	$\gg 10$	

[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 Neurones tested. [c] Data from ref 38.

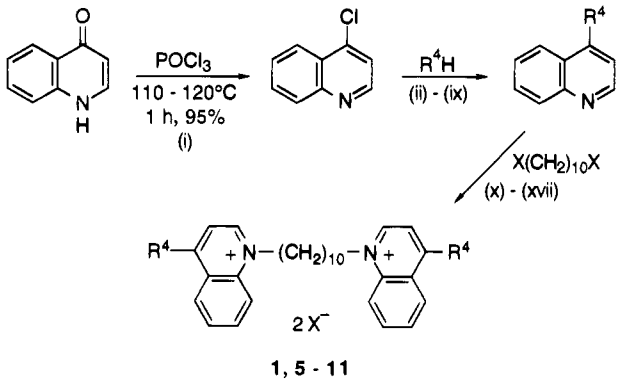
isolated from pig brain,[30] adding to the evidence for a physiological role of the SK_{Ca} channel in the central nervous system (CNS). The distribution of the receptor of apamin in rat brain has been studied using autoradiographic techniques.[31] Furthermore, an endogenous equivalent of scyllatoxin has been characterized in pheochromocytoma cells.[32]

Some synthetic organic molecules which block SK_{Ca} channels effectively have also been described. These include bis-quaternary neuromuscular blockers[33,34,9] such as atracurium ($IC_{50} = 4.5\ \mu M$), tubocurarine ($IC_{50} = 7.5\ \mu M$), and pancuronium ($IC_{50} = 6.8\ \mu M$). Furthermore, dequalinium (**4**; Table 1), a bis-quinolinium compound, has been shown to be a potent and selective nonpeptidic blocker of the SK_{Ca} channel[35,36] ($IC_{50} = 1\ \mu M$). We have initiated studies toward identifying the pharmacophore of dequalinium for SK_{Ca} channel blockade.[37-39] Structure–activity analysis of dequalinium analogues can aid the design of more potent blockers and may also yield structural information on the SK_{Ca} channel. Thus, the role of the quinolinium groups of dequalinium has been examined, and the possibilities that this molecule binds to an anionic or aromatic site on the SK_{Ca} channel have been discussed.[38] It has also been shown that simultaneous removal of the 2-Me and 4-NH_2 groups of dequalinium to give **12** (Table 1) results in 1 order of magnitude drop in potency.[38] Furthermore, it has been suggested[39] that the role of the NH_2 group is electronic, via delocalization of the positive charge. In the present work the role of the substituent at position 4 of the quinoline is further investigated in order to elucidate the nature of its contribution to SK_{Ca} channel blockade. This is done by replacing the NH_2 group of dequalinium with substituents having different electronic properties. Thus, analogues **1**, **3**, and **6**–**13** (Table 1) were selected for this study.

Chemistry

The SK_{Ca} channel-blocking action of compounds **3** and **12** has been reported previously.[38] Analogue **13** was synthesized according to the literature.[40] Analogues **1** and **5**–**11** were synthesized via Scheme 1. For the

Scheme 1[a]

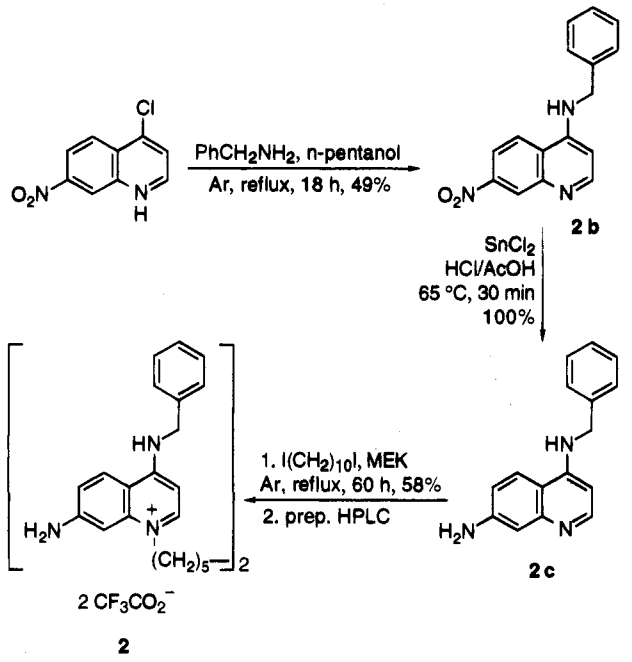


[a] Methods: (i) ref 74; (ii) $R^4 = NHCH_2Ph$, ref 73; (iii) $R^4 = (2,4,6\text{-triMeO})C_6H_2CH_2NH$, 2,4,6-trimethoxybenzylamine·HCl, DBU, dry DMSO, Ar, 120 °C, 30 h, 52%; (iv) $R^4 = NH_2$, ref 74; (v) $R^4 = N(CH_3)_2$, ref 75; (vi) $R^4 = N(CH_3)Ph$, $PhNHCH_3$, glacial AcOH, Ar, reflux, 3 h, 51%; (vii) $R^4 = NHPh$, ref 76; (viii) $R^4 = NHCOCH_3$, ref 77; (ix) $R^4 = OPh$, ref 78; (x) **1**, X = I, 4-methylpentan-2-ol, reflux, 48 h, 56%; (xi) **5**, X = Br, MEK, reflux, 240 h, 47%; (xii) **6**, X = I, 4-methylpentan-2-ol, reflux, 2.5 h, 59%; (xiii) **7**, X = I, 4-methylpentan-2-ol, reflux, 22 h, 17%; (xiv) **8**, X = I, MEK, Ar, reflux, 168 h, 47%; (xv) **9**, X = I, MEK, Ar, reflux, 96 h, 82%; (xvi) **10**, X = I, 4-methylpentan-2-ol, N_2, reflux, 30 h, 71%; (xvii) **11**, X = I, MEK, reflux, 96 h, 16%.

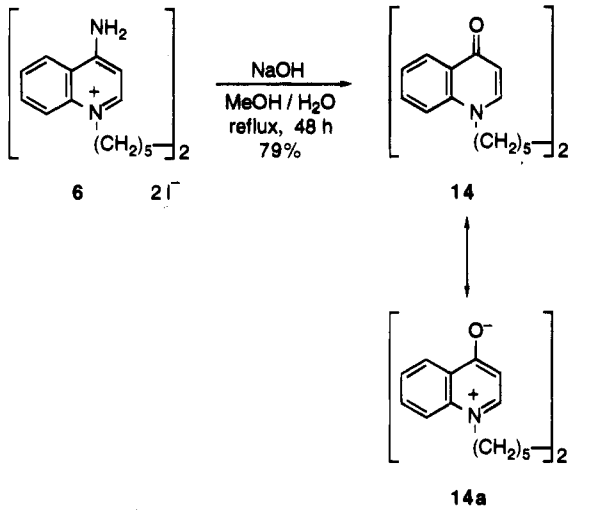
preparation of compound **2**, featuring an NH_2 group at position 7, the chlorine atom of 4-chloro-7-nitroquinoline (synthesized as previously reported[41]) was displaced by benzylamine to give **2b** (Scheme 2), the NO_2 group of which was reduced with $SnCl_2$ in AcOH/HCl to give the 7-NH_2 intermediate **2c**. Quaternization of **2c** with $I(CH_2)_{10}I$ yielded the final product **2** which was purified by reverse phase preparative HPLC since conventional purification methods failed to give an analytically pure sample for biological testing. HPLC was carried out using a Lichrosorb RP SELECT B 7 μM column and a MeOH/H_2O mixture containing 0.1% TFA as eluent. Compound **2** was isolated as the ditrifluoroacetate salt. Finally, analogue **14** was synthesized via alkaline hydrolysis of the NH_2 group of **6**, as shown in Scheme 3.

It should be noted that all the substituents (R^4) in

Scheme 2



Scheme 3[a]



[a] 14a is a resonance structure of compound 14.

Table 1 are electron releasing or neutral; their selection was determined by synthetic accessibility. Quinolines with electron-withdrawing groups at position 4 are very weak nucleophiles, and the alkylation of the ring N in the final quaternization step of the synthesis becomes problematic. Furthermore, the 2-Me group of the quinoline was omitted from all the compounds since it sterically hinders the ring N making it difficult for the latter to undergo alkylation. This is especially important for those compounds possessing a weak electron-releasing group at position 4, since such a group does not sufficiently enhance the nucleophilicity of the N. Moreover, we were unable to obtain an analogue with a MeO group at position 4, since the reaction of 4-methoxyquinoline with 1,10-diiododecane yielded compound **14**.

Pharmacology

The SK_{Ca}-blocking action of the compounds was assessed from their ability to inhibit the after hyperpolarization (AHP) in cultured rat sympathetic neurones as described previously.[36] 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. 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.[36] As most of the compounds tested in the present work have a similar bis-cationic structure to dequalinium, an action on Ca^{2+} 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}) channels at the concentrations tested.

Results

Structures and biological results for the compounds considered in this study are given in Table 1. The 2-Me group of dequalinium makes only a very small contribution to blocking potency, whereas the 4-NH_2 group contributes substantially.[39] The NH_2 group is an excellent potential H-bond donor since its hydrogens are acidic. This results from the participation of the NH_2 group in the delocalization of the ring charge through resonance and, hence, the presence of a fractional positive charge on this group. Clearly, however, H-bond donation from the NH_2 group to the channel does not take place since the dimethylamino analogue **7** is equipotent with the NH_2 compound **6**. The NH_2 group is unlikely to act as an H-bond acceptor either, as its lone pair of electrons is involved in the delocalization of the ring charge and is thus not readily available for H-bonding.

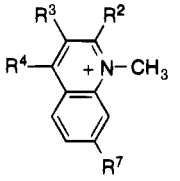
The SK_{Ca} channel-blocking potency of the compounds does not correlate with the lipophilicity of R^4:

$$\text{pEMR} = 0.063(\pm 0.225)\Sigma f - 0.60(\pm 0.23)$$

$$n = 9,\ r = 0.11,\ s = 0.555$$

where pEMR = -log(EMR) (for the definition of EMR see Pharmacology), Σf is the sum of the Rekker hydrophobic fragmental constants[42] for R^4 (data not shown), n is the number of compounds (compounds **1** and **6**–**13**

Table 2. Partial Charges and Frontier Orbital Energies for Model Compounds Used for Correlation Eqs 2–11



					charge				
compd[a]	R^2	R^3	R^4	R^7	C^4	N^1	E_{HOMO}[b]	E_{LUMO}[b]	pEMR[c]
1a	H	H	$NHCH_2Ph$	H	0.262	−0.262	−12.30	−4.693	0.15
2a	H	H	$NHCH_2Ph$	NH_2	0.274	−0.277	−11.97	−4.341	0.05
3a	$-(CH_2)_4-$		NH_2	H	0.267	−0.257	−12.50	−4.743	0.05
4a	CH_3	H	NH_2	H	0.270	−0.254	−12.75	−4.847	0.00
5a	H	H	Y[d]	H	0.260	−0.272	−11.45	−4.347	0.00
6a	H	H	NH_2	H	0.269	−0.255	−12.84	−4.952	−0.11
7a	H	H	$N(CH_3)_2$	H	0.265	−0.261	−12.46	−4.810	−0.15
8a	H	H	$N(CH_3)Ph$	H	0.272	−0.267	−12.25	−4.652	−0.26
9a	H	H	NHPh	H	0.270	−0.261	−12.41	−4.735	−0.53
10a	H	H	$NHCOCH_3$	H	0.263	−0.237	−12.93	−5.148	−0.74
11a	H	H	OPh	H	0.257	−0.228	−12.72	−5.058	−0.81
12a	H	H	H	H	−0.039	−0.183	−13.54	−5.564	−1.18
13a	H	H	CH_3	H	0.083	−0.195	−13.39	−5.456	−1.41

[a] Model compound numbers correspond to the compound numbers of Table 1. [b] in eV. [c] The -log(EMR) of the corresponding bis-quinolinium compound of Table 1 is given for simplicity. For the definition of EMR, see footnote a of Table 1. [d] Y = (2,4,6-triMeO)$C_6H_2CH_2NH$.

are included, in which only R^4 changes), r is the correlation coefficient, s is the standard deviation, and the numbers in brackets are standard errors of estimate.

There is only a poor correlation between pEMR and the size of R^4:

$$\text{pEMR} = 0.007(\pm 0.004)V - 1.01(\pm 0.31)$$

$$n = 9, r = 0.54, s = 0.471$$

where V is the volume (in Å^3) of R^4 (calculated using Macromodel;[43] data not shown).

On the other hand, activity is increased with increasing electron-releasing power of R^4. This can be quantified[39] using the electronic parameter σ_R[44] for R^4 groups, which provides an estimate for the resonance effect of R^4 (eq 1). Note that σ_R values for the substituent R^4 of compounds **1** and **8** are not available.

$$\text{pEMR} = -1.25(\pm 0.26)\sigma_R - 1.33(\pm 0.16) \quad (1)$$

$$n = 7, r = -0.90,$$
$$s = 0.228 \text{ (significance at } \alpha < 0.01)$$

Following these findings, a substituent of higher electron-releasing effect than the NH_2 or NMe_2 groups was sought. However, these are virtually the most electron-releasing *neutral* subtituents known.[45–47] Nevertheless, negatively charged substituents, such as the $-O^-$ group, can exert a greater electron-releasing effect. It was therefore decided to incorporate the $-O^-$ group at position 4 of the quinoline to give structure **14a** (Scheme 3) which is however only a resonance form of the *N*-alkylbis(1*H*)quinolone **14**. This was synthesized but was found to be devoid of K^+ channel-blocking activity. Compound **14** does not have a net positive charge unlike the other analogues of this series. Any fractional positive charges in the quinolone ring result from the contribution of resonance structure **14a** to the hybrid. Therefore, one may draw the inference that for SK_{Ca} blockade it seems to be important to maintain a net positive charge in the quinoline nucleus.

Although the use of conventional electronic parameters (such as σ_R) in quantitative structure–activity relationships (QSAR) can provide initial guidance and useful insight into determinant factors, it is also associated with some limitations. These arise because values for the parameters are available for only a relatively small number of substituents (e.g., values for the electronic parameters for the benzyl and *N*-methylanilino groups are not available) and from the need for multiparameter correlations when more than one substituent is being considered. The latter raises the demand on the number of compounds to be included in the QSAR in order to provide statistically meaningful correlations. Taking these limitations into account and to seek a more appropriate electronic descriptor, molecular orbital (MO) calculations were performed. To simplify the computational problem, the calculations were performed on model compounds consisting of only one of the two substituted quinolinium groups and in which the 10-methylene chain was replaced by a methyl group. This is a reasonable approximation since the two quinolinium rings are sufficiently well separated as to not interact electronically. The replacement of the 10-methylene chain by a methyl group introduces some errors which arise from the different inductive and hyperconjugation effects of a higher alkyl group. However, since these are likely to be similar for all the compounds, the results of the calculations should be comparable. The calculations were performed at the semiempirical level using the AM1 Hamiltonian.[48] The structures of the model compounds are given in Table 2.

The newer PM3 Hamiltonian[49,50] was not used as the partial charge on the ring N calculated with this method was positive. This was in contrast to results from MNDO,[51] AM1, and *ab initio* (3-21G level) calculations, which indicated that the ring N atom carries a negative partial charge (data not shown). The partial charges

on the ring N atom and the carbon atom at position 4 (C^4, to which R^4 is attached) of the quinoline are shown in Table 2.

As can be seen from eq 2 there is only a moderate correlation between pEMR and the partial charge on C^4 of the quinoline, whereas there is a much better correlation between pEMR and the partial charge on the ring N (N^1) atom of the quinoline (eq 3).

$$\text{pEMR} = 3.82(\pm 1.13)(C^4 \text{ charge}) - 1.30(\pm 0.27) \quad (2)$$

$n = 11, r = 0.75, s = 0.366$ (significance at $\alpha < 0.01$)

$$\text{pEMR} = -16.24(\pm 2.80)(N^1 \text{ charge}) - 4.38(\pm 0.68) \quad (3)$$

$n = 11, r = -0.89,$
$s = 0.253$ (significance at $\alpha < 0.001$)

Eq 3 shows that the more negative the partial charge on N^1 the more potent is the compound. The influence of the variation of N^1 charge on the blocking potency of the analogues is in agreement with the σ_R correlation discussed above. The more electron releasing R^4 is, the more electron density is fed into the ring and the more positive charge is withdrawn from it. As a result, the negative charge on N^1 is increased, and so is potency.

Furthermore, in addition to its effect on charge distribution, the electronic influence of R^4 alters MO energies. The energies of the frontier orbitals for the model compounds are shown in Table 2. The blocking potency of the analogues correlates well with the energy of the lowest unoccupied molecular orbital (E_{LUMO}) (eq 4, the correlation being as good as the one with N^1 charge), while the correlation with the energy of the highest occupied molecular orbital (E_{HOMO}) is less good (eq 5).

$$\text{pEMR} = 1.49(\pm 0.27)E_{LUMO} + 6.94(\pm 1.33) \quad (4)$$

$n = 11, r = 0.88,$
$s = 0.262$ (significance at $\alpha < 0.001$)

$$\text{pEMR} = 0.98(\pm 0.25)E_{HOMO} + 12.04(\pm 3.20) \quad (5)$$

$n = 11, r = 0.79,$
$s = 0.336$ (significance at $\alpha < 0.005$)

The validity of the above-mentioned correlations was assessed by synthesizing two additional compounds. MO calculations suggested that the frontier MO energies can be raised in two ways: (i) by introducing electron-releasing substituents at positions 2, 5, and/or 7 of the quinoline (positions in which the substituent would be in direct conjugation with N^1) and/or (ii) by introducing electron-releasing substituents at positions 2, 4, and/or 6 of the Ph ring of analogue **1**. Hence, a representative compound of each type was synthesized.

Compound **1** was selected for structural modification since this is the most potent in this series. An NH_2 group was selected as the electron-releasing substituent for the example of type i. Molecular modeling suggested that an NH_2 group at position 5 would not increase MO energies as much as one at position 2 or 7 because the 5-NH_2 group rotates out of the plane of the ring to avoid severe steric interactions with the NH at the peri (**4**) position. Furthermore, the introduction of the NH_2 group is synthetically more feasible for position 7 than for position 2. Hence, the 7-amino analogue **2** was selected. An example of type ii was investigated by introducing methoxy groups at positions 2, 4, and 6 of the Ph ring of compound **1** to give the trimethoxy analogue **5**.

Analogues **2** and **5** were found to have EMR values of 0.9 and 1, respectively (Table 1). Note that the predicted EMR value for analogues **2** and **5** is 0.34 on the basis of eq 4 (E_{LUMO} correlation). Furthermore, eq 5 (E_{HOMO} correlation) predicts EMR values of 0.49 and 0.15 for **2** and **5**, respectively. On the other hand, eq 3 predicts an EMR of 0.76 for compound **2** and 0.92 for compound **5**, well within experimental error of the activities measured on the neurone assay. In fact, inclusion of **2** and **5** in the correlation with N^1 charge results in slightly improved statistics (eq 6, Figure 1), while inclusion of **2** and **5** in the correlation with E_{LUMO} (eq 7, Figure 2) or E_{HOMO} (eq 8, Figure 3) results in slightly worse statistics.

$$\text{pEMR} = -15.93(\pm 2.30)(N^1 \text{ charge}) - 4.31(\pm 0.57) \quad (6)$$

$n = 13, r = -0.90,$
$s = 0.230$ (significance at $\alpha < 0.001$)

$$\text{pEMR} = 1.19(\pm 0.21)E_{LUMO} + 5.41(\pm 1.05) \quad (7)$$

$n = 13, r = 0.86,$
$s = 0.274$ (significance at $\alpha < 0.001$)

$$\text{pEMR} = 0.69(\pm 0.18)E_{HOMO} + 8.35(\pm 2.28) \quad (8)$$

$n = 13, r = 0.76,$
$s = 0.349$ (significance at $\alpha < 0.005$)

Note that it is difficult to investigate which of the three factors, N^1 charge, E_{HOMO}, or E_{LUMO}, determines the blocking potency of the analogues since they appear not to be independent variables, being highly correlated:

$$N^1 \text{ charge} = -0.075(\pm 0.007)E_{LUMO} - 0.61(\pm 0.04) \quad (9)$$

$n = 13, r = -0.95,$
$s = 0.009$ (significance $\alpha < 0.001$)

$$E_{HOMO} = 1.45(\pm 0.12)E_{LUMO} - 5.49(\pm 0.6) \quad (10)$$

$n = 13, r = 0.96,$
$s = 0.157$ (significance at $\alpha < 0.001$)

$$N^1 \text{ charge} = -0.046(\pm 0.008)E_{HOMO} - 0.82(\pm 0.1) \quad (11)$$

$n = 13, r = -0.88,$
$s = 0.015$ (significance at $\alpha < 0.001$)

Discussion

It is appropriate to attempt to obtain insight into the physical meaning of the above-mentioned correlations of pEMR with N^1 charge, E_{HOMO}, and E_{LUMO}. This may suggest which of the three electronic parameters is more consistent to use. Such information can help in the validation of the correlations.

The physical meaning of the correlation with N^1 charge is not clear at this stage. On the other hand,

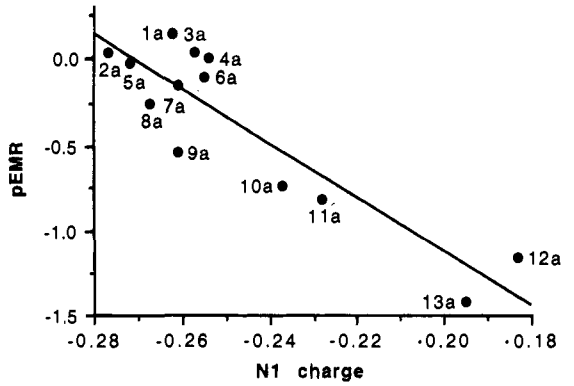


Figure 1. Plot of pEMR vs N^1 charge for the model compounds of Table 2, showing the least squares-fitted regression line.

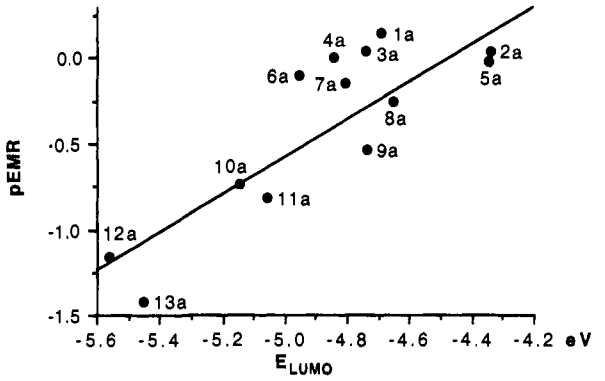


Figure 2. Plot of pEMR vs E_{LUMO} for the model compounds of Table 2, showing the least squares-fitted regression line.

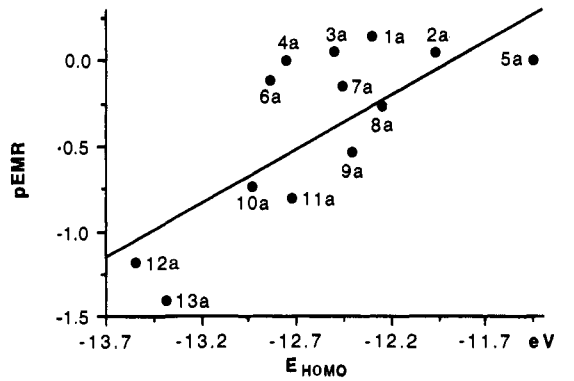


Figure 3. Plot of pEMR vs E_{HOMO} for the model compounds of Table 2, showing the least squares-fitted regression line.

there exist certain differences in the HOMOs and LUMOs of the compounds, which may be valuable in assessing the consistency of the correlations with E_{HOMO} and E_{LUMO}. Thus, in all compounds of Table 2 the LUMO is a π orbital localized on the quinolinium ring, with major contributions from N^1 and carbon atoms C^2, C^4, C^5, C^7, and C^{8a} (Figure 4). In contrast, the HOMO is a π orbital not localised on the quinolinium ring for all the analogues. In particular, for compounds **8a** and **9a** there are considerable contributions to the HOMO from the Ph ring of R^4, while in analogues **1a**, **5a**, and **11a** the HOMO is a π orbital with contributions only from the aryl ring of R^4 (Figure 5). As a result, correlations that use E_{HOMO} are qualitatively inconsistent. Furthermore, the E_{HOMO} 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*. Thus, it is difficult to attribute a physical meaning to the E_{HOMO} correlation.

The E_{LUMO} correlation also suggests that the higher the energy of the LUMO the more potent the compound is. If the contribution of the LUMO is assumed to be at the level of the interaction of the compound with the channel, then the possibility of the formation of a charge transfer interaction with the latter has to be considered in which the HOMO of the channel ($HOMO_{ch}$) would interact with the LUMO of the compound ($LUMO_{compd}$). For efficient stabilization energy to result from such an interaction, the geometry of the $HOMO_{ch}$ and the $LUMO_{compd}$ must exhibit complementary features.[52] If this requirement is satisfied, then the stability of the electron donor–acceptor (EDA) complex depends on the $E_{LUMO} - E_{HOMO}$ difference. The smaller the energy gap the stronger the interaction.[53] It is presumed that the compounds act at the same site and therefore interact with the same $HOMO_{ch}$. The energy of the latter must be lower than the energy of the $LUMO_{compd}$ since the opposite would result in complete electron transfer from the $HOMO_{ch}$ to the $LUMO_{compd}$ and the compound would be reduced.[54] Hence, the $E_{LUMO} - E_{HOMO}$ gap of the drug–ion channel complex would be modified by the E_{LUMO} of the compound since E_{HOMOch} is constant. This in turn means that lower E_{LUMO} values would lead to a smaller $E_{LUMO} - E_{HOMO}$ gap and to a stronger interaction. This is in contrast to the experimental observations suggesting a stronger interaction for compounds with higher E_{LUMO}. As a result, this particular mode of interaction seems unlikely. To the best of our knowledge, this is the first example of activity increasing with higher E_{LUMO} values. E_{LUMO} as an electronic index in QSAR has been employed in the case of mutagenic compounds,[55–58] toxins,[53] opiates,[59] anti-inflammatory agents,[60,61] neuroleptics,[62] antibacterials,[63,64] cardiotoxic compounds,[65] antitumor agents,[66] antifungals,[67] anxiolytics,[68] radiosensitizing compounds,[69] and psychotomimetics.[70] However, in all these cases, potency is associated with a low-lying LUMO, and the explanation given has always been charge transfer or electron transfer from the receptor or enzyme to the compound.

So far, the contribution of the LUMO to the SK_{Ca} channel-blocking activity of the compounds has been assumed to be at the level of the drug–K^+ channel interaction. Nevertheless, the possibility of the LUMO being involved at a level other than the compound–K^+ channel complex has to be considered. In this case, the LUMO correlation may be implying that an EDA interaction takes place at a site which is remote from the channel and that this interaction reduces the efficiency of the K^+ channel blockade either by reducing the available concentration of the compound or by increasing the free energy change of the binding process. The free energy (ΔG) change of the drug (D)–K^+ channel (K) complex formation is given by:

$$\Delta G = \Delta G_{DK} - (\Delta G_D + \Delta G_K)$$

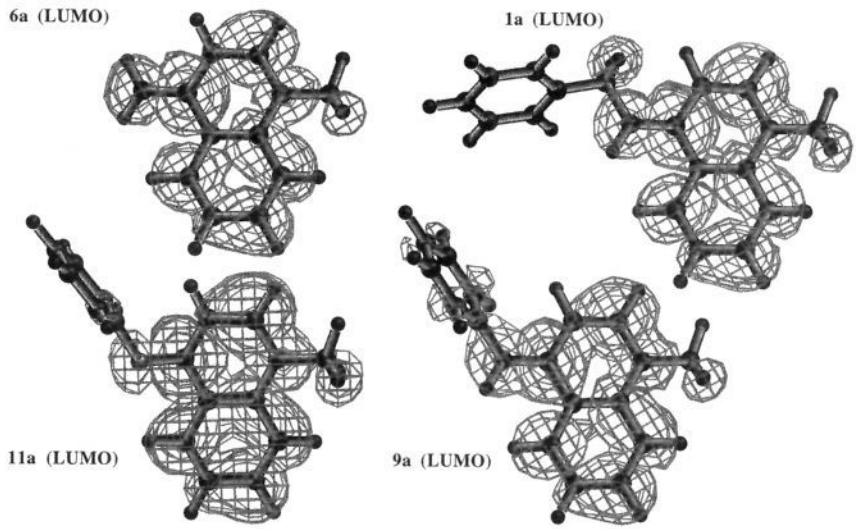


Figure 4. LUMO contour plots for representative model compounds of Table 2. The LUMO contours of the rest of the analogues of Table 2 are similar to those shown. The molecules are drawn to match the general structure of Table 2. Contours were drawn in SYBYL 6.03 at the PSI² mode, at the 0.0009 e/Å³ level.

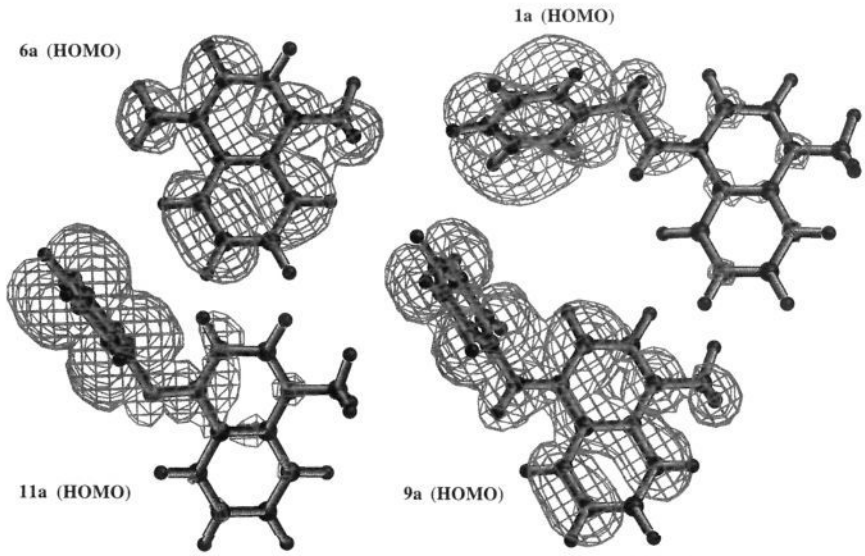


Figure 5. HOMO contour plots for representative model compounds of Table 2. The different contributions to the HOMO in different molecules is exemplified using **1a**, **6a**, **9a**, and **11a**. The molecules are drawn to match the general structure of Table 2. Contours were drawn in SYBYL 6.03 at the PSI² mode, at the 0.0009 e/Å³ level.

where ΔG_{DK} is the energy of the drug−K^+ channel complex, ΔG_D is the energy of the uncomplexed drug, and ΔG_K is the energy of the uncomplexed channel.

For the drug−ion channel interaction to take place, the drug molecule would have to desolvate (wholly or partly), and the same possibly applies to the binding site as well. Therefore, ΔG_D includes the solvation energy of the molecule which is adverse to the binding process because the better the solvation of the drug the more negative is ΔG_D and ΔG becomes more positive. EDA forces contribute substantially to solvent solute interactions,[71,72] and if it is assumed that in the case of the quinolinium compounds the latter act as electron acceptors with the solvent (H_2O) molecules acting as electron donors, then increasing the E_{LUMO} of the molecule would result in its weaker solvation; thus, the interaction with the channel would become stronger. The hypothesis that a higher E_{LUMO} value is an indicator of weaker solvation of the compound therefore offers a possible physical meaning for the E_{LUMO} correlation.

Conclusion

In summary, it appears that the size or lipophilicity of R^4 is not critical for SK_{Ca} channel blockade. Furthermore, there is considerable steric tolerance in the direction of R^4 since substituents ranging from H to (2,4,6-trimethoxybenzyl)amino can be accommodated. The influence of R^4 has been suggested to be electronic, probably via delocalization of the positive charge, since for the seven compounds for which σ_R values are available a correlation was obtained between pEMR and σ_R of R^4.[39] The more electron releasing is R^4, the more potent is the compound. The use of electronic indices obtained from MO calculations enables the extension of the QSAR to include all compounds of this series ($n = 13$). Thus, correlations have been obtained between pEMR and N^1 charge or E_{LUMO} of the compounds. The correlation with N^1 charge is slightly better, but it is difficult to assign a physical meaning to it. On the other hand, while the relationship with E_{LUMO} implies that

the blocker acts as an electron acceptor, this is unlikely to be in its complex with the channel but may be related to other processes such as the desolvation of the compounds.

Experimental Section

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 relative to 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 by Dr. M. Mruzek. Electron impact (EI) mass spectrometry was performed at 70 MeV. 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. Elemental analyses were determined by A.A.T. Stones, University College London.

1,1′-(Decane-1,10-diyl)bis[4-(*N*-benzylamino)quinolinium] Diiodide (1). 4-(*N*-Benzylamino)quinoline[73] (0.2 g, 0.85 mmol) and 1,10-diiododecane (0.17 g, 0.43 mmol) were dissolved in 4-methylpentan-2-ol (30 mL), and the solution was heated under reflux for 48 h. The solvent was removed in vacuo to yield a dark solid which was recrystallized from EtOH to yield the product. More product (light brown crystals) was obtained from the filtrate after removal of the EtOH in vacuo and dissolution of the residue in the minimum amount of EtOH (0.145 g, 56%): mp 237–238.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24 (m, 12 H, CH_2), 1.75 (m, 4 H, CH_2), 4.51 (t, J = 7.2 Hz, 4 H, N^+-CH_2), 4.81 (d, J = 5.4 Hz, 4 H, NH-CH_2), 6.86 (d, J = 7.6 Hz, 2 H, quinoline-H_3), 7.36 (m, 10 H, Ph), 7.81 (t, J = 7.8 Hz, 2 H, quinoline-H_6 or -H_7), 8.04 (t, J = 7.5 Hz, 2 H, quinoline-H_7 or -H_6), 8.17, (d, J = 8.5 Hz, 2 H, quinoline-H_5 or -H_8), 8.62 (m, 4 H, quinoline-H_8 or -H_5 and -H_2), 9.90 (t_{br}, 2 H, NH); HPLC column K, A:B = 32.5:67.5, major peak at 6.76 min representing 96.3 of the absorption at 215 nm. Anal. ($C_{42}H_{48}N_4I_2$) H, N; C: calcd, 58.48; found, 58.02.

7-Nitro-4-(*N*-benzylamino)quinoline (2b). 7-Nitro-4-chloroquinoline[41] (0.2 g, 0.96 mmol) and benzylamine (0.515 g, 4.8 mmol) were heated under reflux in *n*-pentanol (10 mL) containing *N,N,N′,N′*-tetramethylethylenediamine (0.123 g, 1.06 mmol) under Ar for 18 h. After cooling to room temperature, excess of petroleum ether (40–60 °C) was added, and the solid was collected by filtration. The filtrate was concentrated to dryness in vacuo, and the residue was purified by column chromatography on silica gel using petroleum ether: EtOAc = 1:2. The product (R_f = 0.3) was isolated as a yellow powder (0.13 g, 49%): mp 140–141 °C; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 4.57 (d, J = 5.1 Hz, 2 H, CH_2), 5.50 (s_{br}, 1 H, NH), 6.60 (d, J = 5.4 Hz, 1 H, quinoline-H_3), 7.42 (m, 5 H, Ph), 7.92 (d, J = 9.1 Hz, 1 H, quinoline-H_5), 8.20 (dd, J_1 = 2.4 Hz, J_2 = 9.2 Hz, 1 H, quinoline-H_6), 8.69 (d, J = 5.4 Hz, 1 H, quinoline-H_2), 8.88 (d, J = 2.3 Hz, 1 H, quinoline-H_8); MS (FAB, MNOBA matrix) [M + H]$^+$ 280 fragments at *m/z* 264, 234, 91. Anal. ($C_{16}H_{13}N_3O_2$·1.5H_2O) C, H, N.

7-Amino-4-(*N*-benzylamino)quinoline (2c). To a solution of **2b** (0.1 g, 0.36 mmol) in 1 mL of AcOH at room temperature was added a suspension of $SnCl_2$ (0.296 g, 1.31 mmol) in concentrated HCl (2 mL)/water (0.2 mL), and the mixture was heated at 65 °C for 30 min. The solid dissolved on heating. On cooling to room temperature, a precipitate formed. The reaction mixture was basified with 20% NaOH and extracted with 10 × 15 mL $CHCl_3$. The extracts were combined and dried (Na_2SO_4), and the solvent was removed in vacuo to yield a gum (0.089 g, 100%): ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 3.99 (s_{br}, 2 H, NH_2), 4.51 (d, J = 5.3 Hz, 2 H, CH_2), 5.30 (s_{br}, 1 H, NH), 6.28 (d, J = 5.5 Hz, 1 H, quinoline-H_3), 6.86 (dd, J_1 = 2.3 Hz, J_2 = 8.9 Hz, 1 H, quinoline-H_6), 7.14 (d, J = 2.3 Hz, 1 H, quinoline-H_8), 7.39 (m, 5 H, Ph), 7.59 (d, J = 8.9 Hz, 1 H, quinoline-H_5), 7.41 (d, J = 5.3 Hz, 1 H, quinoline-H_2); MS (FAB, MNOBA matrix) [M + H]$^+$ 250 fragment at *m/z* 144.

1,1′-(Decane-1,10-diyl)bis[7-amino-4-(*N*-benzylamino)quinolinium] Bistrifluoroacetate (2). **2c** (0.08 g, 0.32 mmol) and 1,10-diiododecane (0.063 g, 0.16 mmol) were dissolved in 5 mL of butanone, and the solution was heated under reflux for 60 h under Ar. A gum came out of solution which, after decanting of the solvent, was dried in vacuo to yield a foam (0.083 g, 58%). This was purified by preparative HPLC using a Lichrosorb RP SELECT B 7 μM column and A:B = 35:65. After evaporation of the solvents in vacuo, the residue was dissolved in EtOH and filtered and the solvent removed in vacuo to yield a yellow-brown crystalline material: mp 113–115 °C; IR (KBr disk) ν_{max} 3359, 3200, 2919, 2852, 1685, 1621, 1558 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 1.29 (m, 12 H, CH_2), 1.73 (m, 4 H, CH_2), 4.22 (t, J = 7.1 Hz, 4 H, N^+-CH_2), 4.70 (d, J = 5.9 Hz, 4 H, NH-CH_2), 6.49 (d, J = 7.5 Hz, 2 H, quinoline-H_3), 6.65 (s, 4 H, NH_2), 6.83 (d, J = 1.8 Hz, 2 H, quinoline-H_8), 7.00 (dd, J_1 = 1.7 Hz, J_2 = 9 Hz, 2 H, quinoline-H_6), 7.28 (t, J = 6.6 Hz, 2 H, Ph-H_4′), 7.37 (m, 8 H, Ph), 8.25 (m, 4 H, quinoline-H_2 + -H_5), 9.39 (t, 2 H, NH); MS (FAB, MNOBA matrix) [M − H]$^+$ 637, fragment at *m/z* 311; HPLC column L, A:B = 35:65, major peak at 4.88 min representing 94.8% of the absorption at 215 nm. Anal. ($C_{46}H_{50}F_6N_6O_4$·CF_3CO_2H·1.5CH_3CH_2OH·2H_2O) C, H, N.

4-[*N*-(2,4,6-Trimethoxybenzyl)amino]quinoline (5b). 4-Chloroquinoline[74] (0.7 g, 4.28 mmol), 2,4,6-trimethoxybenzylamine hydrochloride (2 g, 8.56 mmol), and DBU (1.95 g, 12.84 mmol) were dissolved in 15 mL of dry DMSO, and the solution was heated at 120 °C for 30 h under Ar. The solvent was removed by vacuum distillation, and the residue was partitioned between 50 mL of 10% NaOH and 50 mL of $CHCl_3$. The aqueous phase was extracted with another 50 mL of $CHCl_3$. The extracts were combined and dried (Na_2SO_4), and the solvent was removed in vacuo to yield a gum. This was purified by column chromatography on silica gel using EtOAc: MeOH = 10:1. The product (R_f = 0.3) was dissolved in $CHCl_3$ and filtered and the solvent removed in vacuo to yield a creamy solid (0.72 g, 52%): mp 204–205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3 H, OCH_3), 3.85 (s, 6 H, OCH_3), 4.49 (d, J = 5.6 Hz, 2 H, N-CH_2), 5.54 (s_{br}, 1 H, NH), 6.14 (s, 2 H, Ph), 6.71 (d, J = 5.6 Hz, 1 H, quinoline-H_3), 7.37 (t, J = 7.1 Hz, 1 H, quinoline-H_6 or -H_7), 7.58 (t, J = 7 Hz, 1 H, quinoline-H_7 or -H_6), 7.66 (d, J = 8 Hz, 1 H, quinoline-H_5 or -H_8), 7.94 (d, J = 8.1 Hz, 1 H, quinoline-H_8 or -H_5), 8.52 (d, J = 5.6 Hz, 1 H, quinoline-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.0, 55.4, 55.8, 90.6, 99.1, 106.2, 118.9, 119.5, 124.4, 129.0, 129.3, 150.4, 150.5, 159.3, 161.1. Anal. ($C_{19}H_{20}N_2O_3$·0.2$CHCl_3$) C, H, N.

1,1′-(Decane-1,10-diyl)bis[4-[*N*-(2,4,6-trimethoxybenzyl)amino]quinolinium] Dibromide Dihydrate (5). **5b** (0.3 g, 0.92 mmol) and 1,10-dibromodecane (0.139 g, 0.46 mmol) were dissolved in 10 mL of butanone, and the solution was heated under reflux for 240 h. The white precipitate formed was collected by filtration and washed extensively with butanone. This was recrystallized from MeOH:EtOH = 2:1 to give a white solid. This was not sufficiently pure (by HPLC); therefore, it was recrystallized from MeOH to yield pure product (0.207 g, 47%): mp 163–164 °C; IR (KBr disk) ν_{max} 3412, 3199, 3092, 2930, 1611, 1451, 1224, 1200, 1151, 1131 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.19–1.25 (m, 12 H, CH_2), 1.75 (m, 4 H, CH_2), 3.78 (s, 6 H, OCH_3), 3.80 (s, 12 H, OCH_3), 4.47–4.53 (m, 8 H, NH-CH_2 + N^+-CH_2), 6.29 (s, 4 H, Ph), 6.93 (d, J = 7.6 Hz, 2 H, quinoline-H_3), 7.69 (t, J = 7.6 Hz, 2 H, quinoline-H_6 or -H_7), 7.98 (t, J = 7.9 Hz, 2 H, quinoline-H_7 or -H_6), 8.10 (d, J = 8.7 Hz, 2 H, quinoline-H_5 or -H_8), 8.65 (m, 4 H, quinoline -H_8 or -H_5 + -H_2), 9.30 (t_{br}, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.9, 28.6, 28.8, 28.9,

36.8, 53.8, 55.4, 56.0, 90.9, 98.3, 103.2, 117.6, 118.3, 124.3, 126.5, 133.8, 137.3, 146.5, 154.7, 159.3, 161.3; MS (FAB, MNOBA matrix) $[M + {}^{81}Br]^+$ 569, $[M + {}^{79}Br]$ 867, $[M - H]^+$ 787, fragment at *m/z* 607; HPLC column K, A:B = 35:65, major peak at 16.72 min representing 99.5% of the absorption at 215 nm. Anal. ($C_{48}H_{60}N_4O_6Br_2 \cdot 2.6H_2O$) C, H, N.

1,1′-(Decane-1,10-diyl)bis(4-aminoquinolinium) Diiodide (6). A solution of 4-aminoquinoline[74] (0.5 g, 3.5 mmol) and 1,10-diiododecane (0.67 g, 1.7 mmol) in 4-methylpentan-2-ol (50 mL) was heated under reflux for 2.5 h. After cooling to room temperature, the cream solid that had formed was collected and dried (0.43 g, 59%): mp 241–242.5 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.40 (m, 12 H, CH_2), 1.78 (m, 4 H, CH_2), 4.56 (t, J = 7 Hz, 4 H, N^+-CH_2), 6.83 (d, J = 7 Hz, 2 H, quinoline-H_3), 7.78 (t, J = 7 Hz, 2 H, quinoline-H_6 or -H_7), 8.10 (t, J = 6.8 Hz, 2 H, quinoline-H_7 or -H_6), 8.20 (d, J = 8.9 Hz, 2 H, quinoline-H_5 or -H_8), 8.50 (m, 4 H, quinoline-H_8 or -H_5 and -H_2), 9.05 (s_{br}, 4 H, NH_2); HPLC column L, flow rate 0.75 mL/min, C:D = 30:70, major peak at 5.19 min representing 98.8% of the absorption at 254 nm. Anal. ($C_{28}H_{38}N_4I_2$) C, H, N.

1,1′-(Decane-1,10-diyl)bis[4-(*N*,*N*-dimethylamino)quinolinium] Diiodide Hydrate (7). 4-(*N*,*N*-Dimethylamino)-quinoline[75] (0.3 g, 1.74 mmol) was dissolved in 4-methylpentan-2-ol (30 mL) and treated with 1,10-diiododecane (0.34 g, 0.87 mmol) under reflux for 22 h. The solid precipitate was collected by vacuum filtration, washed with EtOAc, and dried. Recrystallization from iPrOH/MeOH gave the product as yellow needles (0.11 g, 17%): mp 194–195 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.39 (m, 12 H, CH_2), 1.92 (quint, J = 6.8 Hz, 4 H, CH_2), 3.51 (s, 12 H, CH_3), 4.56 (t, J = 7.4 Hz, 4 H, N^+-CH_2), 6.95 (d, 2 H, quinoline-H_3), 7.69 (t, 2 H, quinoline-H_6 or -H_7), 7.99 (t, 2 H, quinoline-H_7 or -H_6), 8.06 (d, 2 H, quinoline-H_5 or -H_8), 8.39 (d, 2 H, quinoline-H_8 or -H_5), 8.48 (d, 2 H, quinoline-H_2); HPLC column L, C:D = 33:67, major peak at 5.11 min representing 99.7% of the absorption at 215 nm. Anal. ($C_{32}H_{44}N_4I_2 \cdot H_2O$) C, H, N.

4-(*N*-Phenyl-*N*-methylamino)quinoline (8b). 4-Chloroquinoline[74] (0.77 g, 4.71 mmol) and freshly distilled *N*-methylaniline (0.63 g, 5.88 mmol) were dissolved in 10 mL of glacial AcOH, and the solution was heated under reflux for 3 h under Ar. The solvent was removed in vacuo and the residue basified with concentrated NH_4OH and extracted with 3 × 40 mL of $CHCl_3$. The extracts were combined and dried (Na_2SO_4), and the solvent was removed in vacuo to yield an oil. This was purified by column chromatography on silica gel using EtOAc:petroleum ether = 1:1 until all the *N*-methylaniline had been eluted and then using EtOAc until all the product had been eluted. This was isolated as a yellow oil. This was still impure; therefore, it was converted to the hydrochloride salt using HCl/MeOH. Evaporation of the solvents gave an oil which upon trituration with toluene solidified. This was dissolved in MeOH (10 mL), and Et_2O was added until the solution became slightly cloudy. It was then kept at −20 °C for 2 h. A dark solid precipitated. The supernatant was decanted into another flask, Et_2O was added until the solution became cloudy, and the solution was kept at −20 °C. The resulting yellow crystals of **8b** HCl were collected, washed with Et_2O, and dried (0.65 g, 51%); mp 216–218 °C. Anal. ($C_{16}H_{14}N_2 \cdot HCl \cdot 0.1H_2O$) C, H, N.

The hydrochloride was dissolved in water, basified with concentrated NH_4OH, and extracted with 4 × 20 mL of CH_2Cl_2. The extracts were combined and dried ($MgSO_4$), and the solvent was removed in vacuo to yield **8b** as an oil (0.395 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3 H, CH_3), 7.01 (d, J = 6.7 Hz, 1 H, quinoline-H_3), 7.16 (m, 3 H, Ph), 7.22 (d, J = 8.8 Hz, 1 H, quinoline-H_5 or -H_8), 7.36 (t, J = 7.1 Hz, 1 H, quinoline-H_6 or -H_7), 7.44 (t, J = 7.9 Hz, 2 H, Ph), 7.66 (td, J_1 = 1.3 Hz, J_2 = 6.8 Hz, 1 H, quinoline-H_7 or -H_6), 8.51 (d, J = 8.4 Hz, 1 H, quinoline-H_8 or -H_5), 8.56 (d, J = 6.8 Hz, 1 H, quinoline-H_2).

1,1′-(Decane-1,10-diyl)bis[4-(*N*-phenyl-*N*-methylamino)quinolinium] Diiodide Hydrate (8). **8b** (0.395 g, 1.68 mmol) and 1,10-diiododecane (0.332 g, 0.84 mmol) were dissolved in butanone and heated under reflux for 168 h under Ar. The yellow solid formed was collected by filtration and washed with the solvent. It was recrystallized from a mixture of iPrOH:MeOH = 1:1 to yield yellow crystals (0.34 g, 47%): mp 208–209 °C dec; IR (KBr disk) ν_{max} 3423, 3017, 2920, 2853, 1614, 1557, 1489 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26–1.35 (m, 12 H, CH_2), 1.84 (m, 4 H, CH_2), 3.70 (s, 6 H, CH_3), 4.70 (t, J = 7.3 Hz, 4 H, N^+-CH_2), 7.37 (m, 10 H, Ar), 7.47 (m, 6 H, Ar), 7.89 (t, J = 7.2 Hz, 2 H, quinoline-H_6 or -H_7), 8.22 (d, J = 9 Hz, 2 H, quinoline-H_8), 8.95 (d, J = 7.4 Hz, 2 H, quinoline-H_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.9, 28.6, 28.9, 29.0, 45.0, 54.7, 106.6, 118.8, 119.7, 125.4, 125.8, 127.4, 127.6, 130.5, 133.4, 138.6, 146.7, 147.9, 157.6; MS (FAB, thioglycerol + glycerol + TFA matrix) $[M + I]^+$ 735, $[M - H]^+$ 607, fragments at *m/z* 721, 643, 593, 501, 359, 345, 331, 317, 303, 289, 275, 261, 247, 234, 219; HPLC column K, A:B = 40:60, major peak at 12.15 min representing 100% of the absorption at 215 nm. Anal. ($C_{42}H_{48}N_4I_2 \cdot H_2O$) C, H, N.

1,1′-(Decane-1,10-diyl)bis(4-anilinoquinolinium) Diiodide (9). 4-Anilinoquinoline[76] (0.5 g, 2.27 mmol) and 1,10-diiododecane (0.447 g, 1.13 mmol) were dissolved in 50 mL of MEK, and the solution was heated under reflux for 96 h under Ar. The yellow precipitate formed was collected by filtration, washed with butanone and Et_2O, and dried. This was dispersed in ca. 25 mL of absolute EtOH and heated to boiling, and MeOH was added dropwise until the solution became clear. It was then allowed to concentrate by boiling to ca. 20 mL, cooled to room temperature, and kept at 4 °C overnight. The yellow crystals formed were collected and dried in vacuo at 45 °C over P_2O_5 (0.777 g, 82%): mp 241–243 °C; IR (KBr disk) ν_{max} 3446, 3386, 3159, 3039, 2919, 2845, 1611, 1588, 1545, 1525 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 1.21–1.27 (m, 12 H, CH_2), 1.78 (m, 4 H, CH_2), 4.60 (t, J = 7.3 Hz, 4 H, N^+-CH_2), 6.79 (d, J = 7.3 Hz, 2 H, quinoline-H_3), 7.43–7.49 (m, 6 H, Ph-H_2' + -H_6' + -H_4'), 7.59 (t, J = 7.8 Hz, 4 H, Ph-H_3' + -H_5'), 7.88 (t, J = 7.6 Hz, 2 H, quinoline-H_8 or -H_7), 8.11 (td, J_1 = 1.3 Hz, J_2 = 7.7 Hz, 2 H, quinoline-H_7 or -H_6), 8.25 (d, J = 9 Hz, 2 H, quinoline-H_5 or -H_8), 8.61 (d, J = 7.5 Hz, 2 H, quinoline-H_2), 8.74 (dd, J_1 = 0.9 Hz, J_2 = 8 Hz, 2 H, quinoline-H_8 or -H_5); MS (FAB, MNOBA matrix) $[M - H]^+$ 579, fragments at *m/z* 290, 221, 54; HPLC column L, C:D = 35:65, major peak at 9.25 min representing 99.2% of the absorption at 215 nm. Anal. ($C_{40}H_{44}N_4I_2 \cdot 0.7H_2O$) C, H, N.

1,1′-(Decane-1,10-diyl)bis(4-acetamidoquinolinium) Diiodide Hemihydrate (10). 4-Acetamidoquinoline[77] (0.09 g, 0.48 mmol) and 1,10-diiododecane (0.095 g, 0.24 mmol) were dissolved in 10 mL of 4-methyl-2-pentanol, and the solution was heated under reflux for 30 h under N_2. The yellow solid formed was collected by filtration, washed extensively with the solvent and Et_2O, and dried in vacuo (0.13 g, 71%): mp 202–203 °C; IR (KBr disk) ν_{max} 3426, 3000, 2918, 2839, 1718, 1618, 1601, 1531, 1505, 1408 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 1.25–1.35 (m, 12 H, CH_2), 1.89 (m, 4 H, CH_2), 2.43 (s, overlaps with DMSO signal, $COCH_3$), 4.87 (t, J = 7.4 Hz, 4 H, N^+-CH_2), 8.04 (t, J = 7.9 Hz, 2 H, quinoline-H_6 or -H_7), 8.24 (t, J = 8.1 Hz, 2 H, quinoline-H_7 or -H_6), 8.51 (d, J = 9 Hz, 2 H, quinoline-H_5 or -H_6), 8.70 (d, J = 7 Hz, 2 H, quinoline-H_3), 8.88 (d, J = 8.7 Hz, 2 H, quinoline-H_8 or -H_5), 9.26 (d, J = 7 Hz, 2 H, quinoline-H_2), 11.08 (s, 2 H, NH); MS (FAB, MNOBA matrix) $[M - H]^+$ 511, fragments at *m/z* 469, 427, 325, 283, 269, 256, 241, 227, 213, 200, 187; HPLC column L, C:D = 40:60, major peak at 5.86 min representing 98.2% of the absorption at 215 nm. Anal. ($C_{32}H_{40}N_4O_2I_2 \cdot 0.5H_2O$) C, H, N.

1,1′-(Decane-1,10-diyl)bis(4-phenoxyquinolinium) Diiodide Hydrate (11). 4-Phenoxyquinoline[78] (0.806 g, 3.64 mmol) and 1,10-diiododecane (0.718 g, 1.82 mmol) were dissolved in 40 mL of MEK and heated under reflux for 96 h. On cooling a yellow oil came out of solution. The supernatant was decanted and the oil washed extensively with MEK. On drying in vacuo the oil solidified to a yellow powder (0.24 g, 15.7%): mp 100–102 °C; IR (KBr disk) ν_{max} 3439, 3012, 2919, 2845, 1618, 1571, 1525, 1477, 1461, 1405, 1304, 1194 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 1.23–1.35 (m, 12 H, -CH_2-), 1.87 (m, 4 H, -CH_2-), 4.89 (t, 4 H, N^+-CH_2), 7.06 (d, 2 H, quinoline-H_3), 7.46–7.53 (m, 6 H, Ph), 7.66 (t, 4 H, Ph), 8.06 (t, 2 H, quinoline-H_6 or -H_7), 8.31 (t, 2 H, quinoline-H_7 or H_6), 8.54 (d, 2 H, quinoline-H_5), 8.72 (d, 2 H, quinoline-H_6);

9.21 (d, 2 H, quinoline-H_2); MS (FAB, matrix MNOBA) [M + I]$^+$ 709, [M]$^+$ 582, fragments at *m/z* 505, 488, 360; HPLC column K, A:B = 35:65, major peak at 6.21 min representing 96.2% of the absorption at 215 nm. Anal. ($C_{40}H_{42}N_2O_2I_2 \cdot H_2O$) C, H, N.

1,1′-(Decane-1,10-diyl)bis(4-methylquinolinium) diiodide[40] (13): mp 217–219 °C (lit.[40] mp not given); HPLC column K, A:B = 50:50, major peak at 5.1 min representing 96.6% of the absorption at 254 nm. Anal. ($C_{30}H_{38}N_2I_2$) C, H, N.

1,1′-(Decane-1,10-diyl)bis(4-(1*H*)quinolone) (14). 6 (0.28 g, 0.446 mmol) was dispersed in 10 mL of a 50% solution of NaOH in water, and MeOH was added to help dissolution. The mixture was heated under reflux for 48 h. After cooling to room temperature, it was extracted with 8 × 30 mL of CH_2Cl_2. After drying and evaporation of the solvent, a yellowish solid was obtained. This was recrystallized from CH_2Cl_2/EtOAc to yield a yellowish solid (0.15 g, 79%): mp 155–157 °C; IR (KBr disk) ν_{max} 3439, 3039, 2919, 2845, 1621, 1604, 1581, 1478 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 1.26–1.34 (m, 12 H, CH_2), 1.84 (quint, 4 H, CH_2), 4.11 (t, J = 7.2 Hz, 4 H, N-CH_2), 6.28 (d, J = 7.7 Hz, 2 H, quinoline-H_3), 7.38 (t, J = 7.5 Hz, 2 H, quinoline-H_6 or -H_7), 7.42 (d, J = 8.6 Hz, 2 H, quinoline-H_5 or -H_8), 7.53 (d, J = 7.7 Hz, 2 H, quinoline-H_2), 7.66 (td, J_1 = 1.6 Hz, J_2 = 7.8 Hz, 2 H, quinoline-H_7 or -H_6), 8.47 (dd, J_1 = 1.6 Hz, J_2 = 8.1 Hz, 2 H, quinoline-H_8 or -H_5); MS (EI) [M]$^+$ 428, fragments at *m/z* 284, 270, 256, 242, 228, 214, 200, 186, 172, 158, 145; HPLC column L, C:D = 35:65, major peak at 12.19 min representing 98.7% of the absorption at 215 nm. Anal. ($C_{28}H_{32}N_2O_2 \cdot 0.2H_2O$) C, H, N.

MO Calculations. These were performed on the model compounds of Table 2. The structures were initially built in Sybyl 5.5[79] running on a Silicon Graphics IRIS 4D workstation and then submitted for semiemperical MO calculations using the MOPAC 5.0 MO package and the AM1[48] 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[80] 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. MMOK was used as a keyword in the case of compound **10a**. A Mulliken population analysis was also performed, and the charges obtained were used in the correlation studies.

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