Bis-Quinolinium Cyclophanes: 8,14-Diaza-1,7(1,4)-diquinolinacyclotetradecaphane (UCL 1848), a Highly Potent and Selective, Nonpeptidic Blocker of the Apamin-Sensitive Ca^{2+}-Activated K^+ Channel

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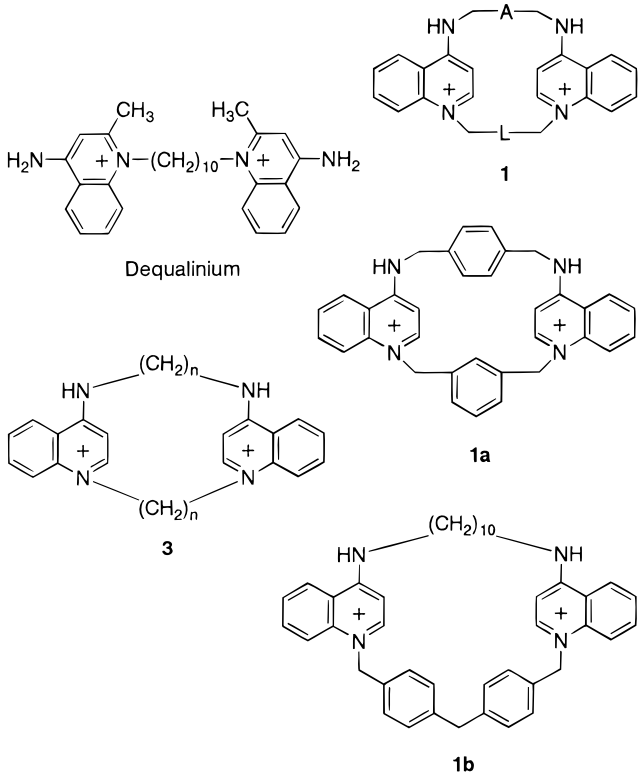
Introduction. Small conductance Ca^{2+}-activated K^+ (SK_{Ca}) channels comprise an important subclass of K^+ channels.[1−4] They occur in many types of cells, both excitable and inexcitable, and have a variety of physiological roles.[1,5−9] Functional, binding, and structural data have suggested the existence of subtypes of the SK_{Ca} channel.[10−13] In accordance with these observations, three SK_{Ca} channel subunits have been identified by DNA cloning: namely SK1, SK2, and SK3.[14,15]

Though apamin, a peptidic toxin from bee venom, potently and selectively blocks SK_{Ca} channels and has been invaluable in their study,[16−18] there is considerable interest in the discovery of nonpeptidic blockers of the SK_{Ca} channel. Such compounds, in addition to being useful pharmacological tools, may have important therapeutic applications. For example, blockade of SK_{Ca} channels gives rise to an increase in gastrointestinal motility,[19] and SK_{Ca} channels are involved in the endothelium-dependent hyperpolarizing factor (EDHF)-mediated relaxation of blood vessels.[6] Repetitive muscle contraction in myotonic muscular dystrophy results from the aberrant expression of SK_{Ca} channels and can be prevented by intramuscular injection of apamin.[20−22] In the central nervous system, a slow after-hyperpolarization (AHP) mediated by SK_{Ca} channels is responsible for the rhythmic firing of subthalamic neurons which are important for the control of movement.[23] SK_{Ca} channels are also thought to play a part in memory and learning,[24,25] sleep disorders,[26] and the effects of chronic ethanol intoxication.[27]

Dequalinium (Chart 1) has been shown to be a relatively potent and selective SK_{Ca} channel blocker.[28,29] We have undertaken a systematic exploration of the stereoelectronic requirements for SK_{Ca} channel blockade in several series of dequalinium analogues[30−37] and have developed bis-quinolinium cyclophanes of the general type **1**, some of which are potent blockers of the SK_{Ca} channel.[38−40] In particular, compound **1a** (UCL 1684, Chart 1) is as effective as apamin in inhibiting the Ca^{2+}-activated K^+ currents in cultured rat superior cervical neurons[39,40] and rat chromaffin cells.[41]

Chart 1



Furthermore, cyclophane **1b** (UCL 1530, Chart 1) shows selectivity for neuronal over hepatocyte SK_{Ca} channels, which adds to the evidence for the existence of SK_{Ca} channel subtypes in different tissues.[13,42] Such selective compounds should prove to be valuable pharmacological tools, not least in establishing which of the subunits identified by cloning are expressed in the SK_{Ca} channels of different cells.

In series **1**, A and/or L can be alkylene groups or moieties containing one or two aromatic rings. We have attributed[40] the high potency of compound **1a** to the conformational restriction which results from the presence of the rigid benzene rings in A and L and to the ability of the molecule to adopt a low-energy conformation suitable for interaction with the channel.

To explore further the nature of the contribution of the linkers A and L, we have now synthesized a series of bis-alkylene cyclophanes of the general structure **3** (n = 3−10) and have tested them for inhibition of the slow AHP which follows the action potential on rat sympathetic neurons. This AHP is thought to be mediated by SK_{Ca} channels comprised largely or wholly of SK3 subunits.[43]

Chemistry. The cyclophanes **3a**−**g** (Table 1) were synthesized according to Scheme 1. The diquinolines **2a**−**f** were obtained via treatment of 4-chloroquinoline with the necessary α,ω-diaminoalkane in pentanol. The conversion of the diquinolines **2a**−**c** to the desired

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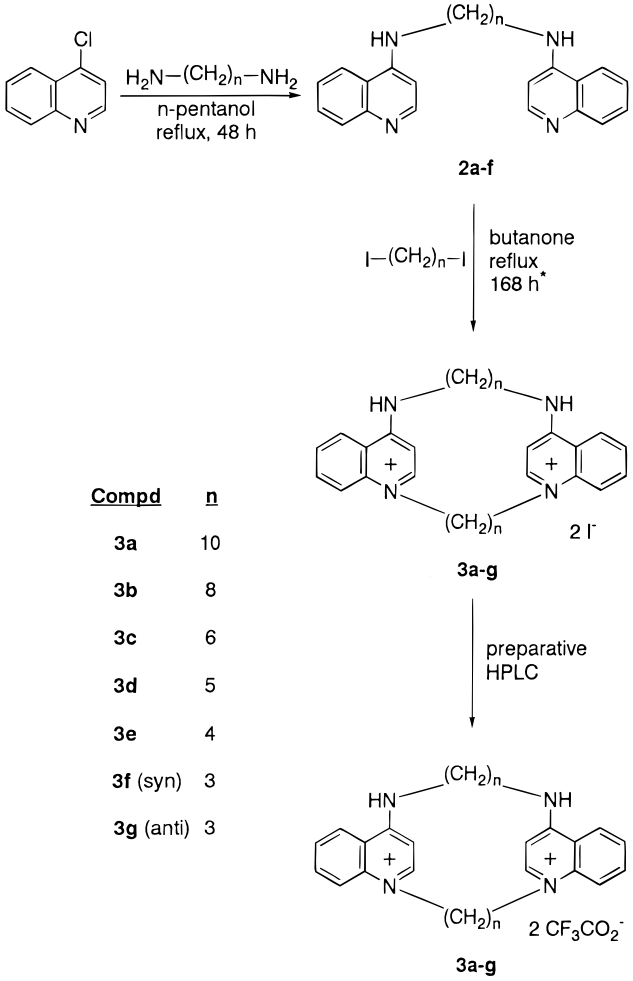
Scheme 1



Compd	n
3a	10
3b	8
3c	6
3d	5
3e	4
3f (syn)	3
3g (anti)	3

* For the synthesis of **3f** and **3g** 4-methyl-2-pentanol was used as the solvent and the reaction time was 192 h.

cyclophanes **3a**−**c** was carried out under high-dilution conditions (2.7−3.2 mM), while more concentrated solutions (4.3−10.5 mM) were necessary to obtain compounds **3d**−**g**. In all cases but one, the synthesis of the cyclophanes involved reaction of the respective diquinoline **2** with the appropriate α,ω-diiodoalkane in butanone for a prolonged period of time (168 h). However, the use of these conditions failed to yield the smaller cyclophanes **3f**,**g**, which necessitated the use of a higher-boiling point solvent (4-methyl-2-pentanol) and longer reaction times (192 h). The final compounds were purified by preparative HPLC[40] (purity > 99.8%) and analyzed as ditrifluoroacetate salts, except for compound **3b** which was purified by crystallization and analyzed as the diiodide salt (purity 99.1% by HPLC).

In cyclophanes **1** and **3** (Chart 1) synperiplanar or antiperiplanar conformers are possible which arise from the different relative spatial orientation of the two quinolinium groups (Figure 1).[40] When the linkers of the quinolinium groups are short propylene chains (**3f**,**g**) the interconversion of the synperiplanar and antiperiplanar conformers becomes very slow at room temperature and HPLC separation of the conformational isomers **3f**,**g** is possible.

The assignment of the conformers was based on their 1D and 2D (COSY, NOESY) ^{1}H NMR spectra. Thus, H-2 and H-3 in **3g** resonate upfield (7.16 and 5.86 ppm, respectively) compared with **3f** (8.05 and 6.73 ppm, respectively). This is consistent with H-2 and H-3 being above the quinolinium groups in **3g** (Figure 1). The magnitude of the observed upfield shift (≈1.1 ppm) is similar to that observed in the antiperiplanar conformer of the related naphthalene cyclophane **4** (Figure 1).[44]

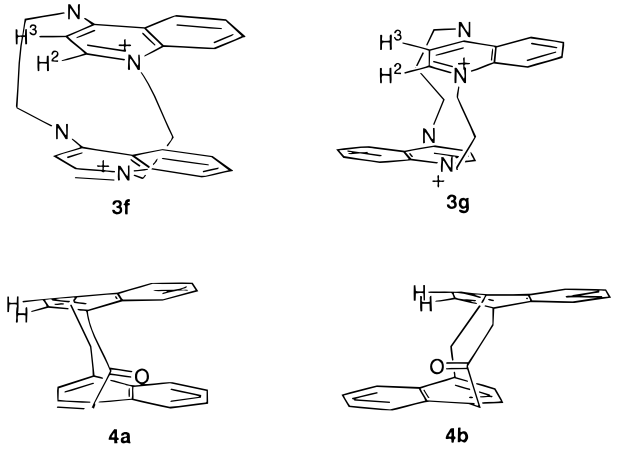


Figure 1. Synperiplanar (**3f**) and antiperiplanar (**3g**) conformers of the propylene diquinolinium cyclophane homologue as well as of the related naphthalene cyclophane **4**. In the antiperiplanar conformers the hydrogen atoms indicated lie above the opposite aromatic ring and hence are shielded and resonate upfield in the ^{1}H NMR spectrum.

Furthermore, the protons of the middle CH_2 groups of the propylene chains in **3f** are diastereotopic and, hence, give rise to four distinct peaks in the ^{1}H NMR spectrum, while, due to their symmetry, the same protons in **3g** are chemical shift equivalent and give rise to two distinct peaks in the ^{1}H NMR spectrum, one for each CH_2 group. All the above suggest that **3f** is the synperiplanar and **3g** is the antiperiplanar conformer.

Biological Testing. The SK_{Ca} blocking action of the compounds was assessed from their ability to inhibit the AHP in cultured rat sympathetic neurons as described previously.[29] Briefly, individual cells were impaled with an intracellular microelectrode which was used both to elicit and to record action potentials. During a successful run, the impaled cell was exposed to several concentrations of one or more of the compounds under test and also of dequalinium which was used as a reference agent. All the compounds were made up as 1−10 mM stock solutions in dimethyl sulfoxide (DMSO) and were thereafter diluted first in water and finally in the physiological bathing fluid. This had the composition (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. It was warmed to 30−31 °C and equilibrated with 95% O_2, 5% CO_2. The final concentration of DMSO was always <0.1%. The new compounds were examined in batches of up to 4 and each was tested at 3−4 concentrations on at least 3 cells. Dequalinium was also applied at 3−4 different concentrations. The Hill equation was fitted to the results to obtain an estimate of the IC_{50}. However, because there was some variation in the potency of dequalinium during the course of the study, equieffective molar concentration ratios (EMR relative to dequalinium) were also determined by simultaneous nonlinear least-squares fitting of the data obtained with each compound, taken together with the values observed with dequalinium in that set of assays. As before, the

Table 1. Compound Structures and Biological Results

compd	n^a	$IC_{50} \pm SD$ (nM)	$EMR^b \pm SD$	m^c
dequalinium		490 ± 50	1	23
1a		3 ± 1	0.01 ± 0.001	4
3a	10	260 ± 5	0.44 ± 0.17	4
3b	8	190 ± 20	0.43 ± 0.17	4
3c	6	60 ± 6	0.1 ± 0.03	4
3d[d]	5	2 ± 0.5[e]	0.003 ± 0.001	4
3e	4	40 ± 5	0.09 ± 0.03	4
3f	3	380 ± 10	0.77 ± 0.25	4
3g	3	130 ± 60	0.27 ± 0.07	6

[a] See Chart 1 or Scheme 1 for generic structure. [b] Equieffective molar ratio: ratio of the concentrations of the test compound and dequalinium that cause 50% inhibition of AHP, as determined in the same experiment. [c] Number of neurons tested. [d] UCL 1848. [e] In more extensive measurements,[47] but omitting the comparison with dequalinium, the IC_{50} was 2.7 ± 0.2 nM (n = 6).

Hill equation was used to fit the data: a common Hill coefficient was assumed. The EMR values are also listed in Table 1, and it is these values that have been used for the comparison between compounds.

Results and Discussion. The cyclophanes **3a**−**g** all blocked the SK_{Ca} channel at submicromolar concentrations (Table 1). The activity of the molecules in the homologous series increased dramatically to a peak as the length of the linkers was reduced from 10 to 5 carbon atoms and then dropped steeply with further shortening of the chain down to 3 carbon atoms. This remarkable dependence on the length of the linker is reminiscent of the activity of bis-alkylammonium compounds as blockers of the nicotinic acetylcholine channel/receptor complex first described by Paton and Zaimis[45] and is in marked contrast to our previous observations on alkylene bis-quinolinium compounds as blockers of the SK_{Ca} channel.[35]

We have previously suggested that the linkers A and L do not interact with the channel in a direct manner but, rather, comprise a scaffold for the two quinolinium groups, controlling both their relative spatial positioning as well as the flexibility of the molecule.[36] In potent compounds such as **1a** (Chart 1), the spacers A and L confer relative conformational rigidity to the molecule, allowing the existence of only a small number of low-energy conformations. In addition, we have proposed that the relative spatial position of the two quinolinium groups in one or more of these low-energy conformers must be favorable for interaction with the channel protein.

The results with the present series **3** support the hypothesis that the linkers A and L do not interact with the channel directly. Thus, the two xylyl linkers of **1a** can be effectively replaced with pentylene groups (compound **3d**) with a slight increase in activity (Table 1). The xylyl and pentylene groups are of almost equal lipophilicity (as indicated by the sums of their Rekker hydrophobic fragmental constants[46] which are respectively 2.696 and 2.595). Therefore, neither the steric bulk nor the aromatic π-system of the benzene rings of the linkers in **1a** seem to be important for SK_{Ca} channel blockade.

Compound **3d** is almost equipotent with apamin in blocking the SK_{Ca} channel in rat sympathetic neurons, having an IC_{50} of 2.7 ± 0.2 nM. Furthermore, like apamin, it is highly selective for the SK_{Ca} channel. Thus at concentrations up to 100 nM it has no effect on the IK_{Ca} channel in rabbit red blood cells, nor on the slow AHP in hippocampal pyramidal neurons.[47] In addition, it is more selective for certain SK_{Ca} subtypes than **1a**. Thus **3d** blocked the cloned SK2 subtype (expressed in HEK293 cells) with an IC_{50} of ∼100 pM as compared with 770 pM for **1a** (unpublished observations by D. C. H. Benton in our laboratory). It also displaced the binding of labeled apamin from guinea-pig hepatocytes with a K_I of 140 ± 10 pM[47] and from SK2 channels in HEK293 cells with a K_I of ∼60 pM (cf. ∼600 pM for **1a**: unpublished observations by D. C. H. Benton and M. Garbarg in our laboratory). Hence this compound should be a useful tool for the study of both native and cloned SK_{Ca} channels.

Conclusion. The synthesis and pharmacological testing of a novel series of bis-quinolinium bis-alkylene cyclophanes as blockers of the SK_{Ca} channel have been described. The biological results of the present series add support to the suggestion that the linkers of the two quinolinium groups do not form direct interactions with the channel protein but, rather, comprise a molecular support for the two quinolinium groups. Thus, the xylyl linkers of **1a**[39,40] (Chart 1), previously the most potent nonpeptidic blocker available, can be replaced with pentylene groups (**3d**) with an increase in selectivity and potency at some subtypes of the SK_{Ca} channel.

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