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Novel Openers of Ca^{2+}-Dependent Large-Conductance Potassium Channels: Symmetrical Pharmacophore and Electrophysiological Evaluation of Bisphenols

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Abstract—Electrophysiological evaluation of symmetrical analogues of the known maxi-K opener NS-004 (**1**) led to the discovery of bisphenols **2a**, **3a** and **4a** as openers of cloned maxi-K channels expressed in oocytes.

The benzimidazolone derivative NS-004 (**1**)[1] was the first among many known openers[2,3] of Ca^{2+}-dependent, large conductance potassium channels (also called maxi-K or BK channels).[4] We have previously reported a pharmacophore model that was applied successfully to identify effective maxi-K openers.[5] In this paper we present the concept of a symmetrical pharmacophore for maxi-K openers by exploring pseudo-symmetrical analogues of NS-004 (**1**). This work culminated in the discovery of novel maxi-K openers through electrophysiological evaluation of bisphenols.

We propose here a symmetrical pharmacophore model for maxi-K channel openers. The phenolic OH has been suggested to be essential for the maxi-K opening properties of the benzimidazolone derivative **1** and its homologues.[3a] Since the weakly acidic amide NH is a known bioisostere of a phenolic OH,[6] NS-004 is intrinsically pseudo-symmetrical in terms of its two H-bond donor sites. One could use the classical bioisosteric approach to replace the amide with a phenolic OH, as shown in the case of maxi-K opener flavonoids.[5] Using a phenolic OH to replace the amide and exploring the pseudo symmetrical elements of NS-004, various bisphenols were predicted to be maxi-K openers. Moreover, we speculated that a full C_s or C_2 symmetrization, as shown in Figure 1, would result in simple molecules with maxi-K opening activities.

To investigate the concept of symmetrical maxi-K openers, we examined the effect of several bisphenols on maxi-K channels expressed in oocytes. Electrophysiological evaluations were carried out according to the previously described protocols[7] using two-electrode voltage clamp recording from *Xenopus laevis* oocytes injected with hSlo[8] cRNA. Voltage-clamp protocols ranged from a holding potential of −60 mV to a maximal

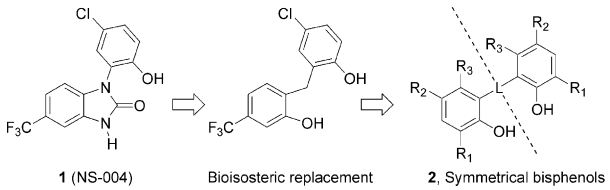

Figure 1. Symmetrical maxi-K channel modulators.

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potential of +140 mV with +20 mV increments. Using iberiotoxin, a specific blocker for maxi-K channels, the iberiotoxin-sensitive component of total outward current defined the maxi-K current and was measured in the absence or in the presence of 20 μM of drug. The increase in outward maxi-K current in the presence of drug is reported as percent of drug free control, for a voltage step to +140mV, and these data are an average of experiments conducted in at least 5 different oocytes. Under these conditions, a drug inducing current to >120% of control is considered to be a maxi-K opener.

As shown in the Table 1, several bisphenols[9,10] obtained from Bristol-Myers Squibb's collection of compounds exhibited remarkable maxi-K opening activities with statistically significant increases of the outward current to 120% or more of control. It was further confirmed that select compounds increase the maxi-K current in a dose-dependent fashion (Fig. 2), with EC_{50}'s in the low micromolar range. Although there are some subtle effects, various lengths of the linkers were tolerated, where the two phenol ring systems were separated by one bond (**4a**–**c**), two bonds (**2a**–**h**), and four bonds (**3a**–**b**). Such flexibility of the linkers is in accord with the previously observed relationship between the heterocycle and the phenolic ring system of **1**.[5]

In the methylene linker series **2a**–**f**, multi-halogen substituents on each phenol ring are pivotal for the maxi-K opening properties of bisphenols. The same is true for the thioether linker (**2g**–**h**) and biphenols **4a**–**c**. Enhanced electron-withdrawing power increases the acidity of the phenolic OH in these series of compounds, among which the maxi-K channel openers appear to require the calculated $pK_a < 8$.

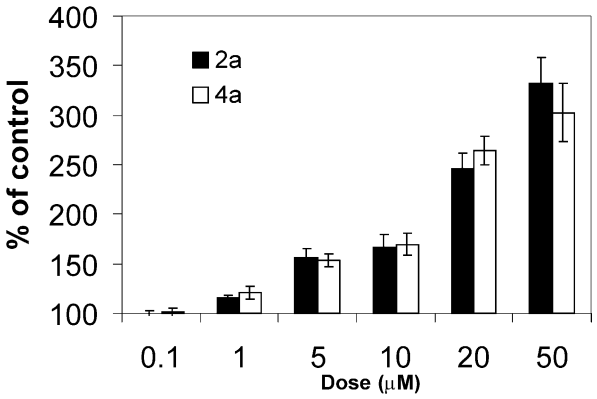
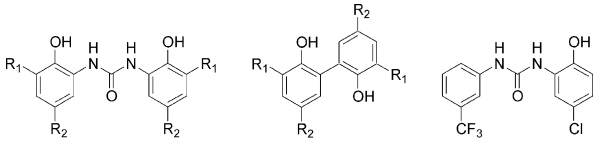


Figure 2. Dose dependent maxi-K activation by bisphenols (**2a** and **4a**).

However, mono-substitution is tolerable for the urea linker **3a**–**b**, although there is some dampening of maxi-K current. It is worth noting that the known maxi-K opener **5** (NS-1608)[4d,11] with an unsymmetrical phenol is considerably less active than the symmetrical bisphenols **3**.

In summary, we have explored the use of a simple bioisosteric replacement for the amide moiety of an imidazolone and symmetrical elements of maxi-K channel openers. Several bisphenols were identified as effective openers of cloned maxi-K channels.

Table 1. Structures and cloned maxi-K channel opening properties of bisphenols



3 4 5

Compd	R1	R2	R3	L	maxi-K opening activity[a]	calc pK_a (1st ArOH)[b]
1					131.8 (±12.8)	9.6
2a	Cl	Cl	H	CH_2	245.9 (±16.3)	7.7
2b	Cl	Cl	Cl	CH_2	237.4 (±12.2)	6.6
2c	H	Cl	H	CH_2	74.3 (±7.7)	9.3
2d	H	F	H	CH_2	83.2 (±5.8)	9.7
2e	CH_2NMe_2	Cl	H	CH_2	94.7 (±2.5)	9.6
2f	Cl	H	H	CH_2	95.9 (±6.3)	8.2
2g	Cl	Cl	H	S	198.3 (±14.5)	6.3
2h	H	F	H	S	98.8 (±5.0)	8.4
3a	Cl	Cl			196.0 (±16.1)	7.4
3b	H	Cl			149.9 (±3.2)	8.9
4a	Br	Br			264.2 (±14.5)	6.7
4b	H	Br			97.0 (±5.4)	8.6
4c	H	nPr			95.9 (±1.6)	9.3
5					124.0 (±6.5)[c]	9.3

[a]Values are means of at least five experiments measuring outward current in the presence of test compound (20 μM) as percent of control current, standard deviation is given in parentheses.
[b]pK_a calculator from Advanced Chemistry Development Inc. (http://www.acdlabs.com).
[c]Refs 4d and 11.

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9. The following selected compounds are available commercially: **2a** Tetrachlorophene (Pfaltz-Bauer); **2b** Hexachlorophene (Aldrich); **2c** 2,2′-Methylenebis-(4-chlorophenol) (Aldrich); **2g** Bithionol (Fluka); **4a** 4,4′,6,6′-Tetrabromo-2,2′-biphenol (Salor).

10. Procedure for **3b**: 5-Chloro-2-methoxyphenyl isocyanate was treated with 5-chloro-2methoxyaniline in dichloromethane to generate the urea which was treated with a 1M solution boron tribromide at 0 °C to deprotect the phenols (mp 183–185.5 °C).

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