A Quantitative Structure-Activity Relationship Study on Some Series of Potassium Channel Blockers

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Abstract: There has been an increasing interest in compounds that modulate potassium ion channels (K^+-channels) since they can be developed as important therapeutic agents against ischemic heart diseases. Of the diverse family of K^+-channels, the voltage-gated potassium channel Kv1.3 constitutes an attractive target for the selective suppression of effector memory T cells in autoimmune diseases. For the development of antiarrythmic drugs, the blockade of the rapidly activating delayed rectifier (I_{Kr}) and slowly activating delayed rectifier (I_{Ks}) potassium currents has been specifically studied. Since the discovery of I_{Ks}-channel, its blockers have been particularly more studied. In this communication, we present QSAR studies on a few series of Kv1.3-channel blockers and a series of I_{Ks}-channel blockers in order to provide some guidelines to the drug development.

Key Words: Quantitative structure-activity relationship study, potassium channel blockers, Kv1.3-channel blockers, I_{Ks}-channel blockers, khellinone analogs, chromanols.

INTRODUCTION

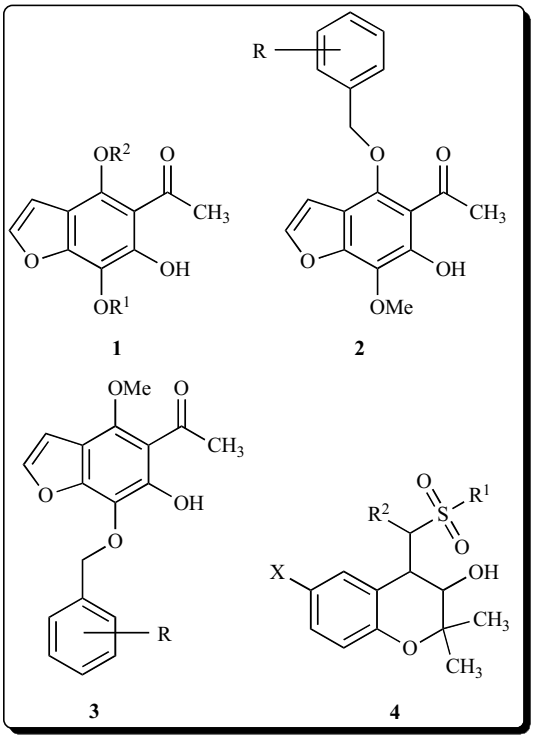
There has been an increasing interest in compounds that modulate potassium ion channels (K^+-channels) since they can be developed as important therapeutic agents [1,2]. K^+-channels are comprised of the most diverse family of ion channels so far described [3], but a very few members of the family have been exploited as the target for the development of therapeutically useful agents. Of them the voltage-gated potassium channel Kv1.3 constitutes an attractive target for the selective suppression of effector memory T cells in autoimmune diseases.

Cardiac arrhythmias in patients with ischemic heart diseases are caused by abnormalities in the electrical activity of the heart which results from excessive sympathetic stimulation and/or changes in the ionic mechanism responsible for the generation and propagation of the normal action potential. The depolarization of the membrane potential, caused by inward sodium current, is followed by a partial early repolarization caused by outward potassium current. This outward potassium current is triggered by several voltage-gated potassium channels, mainly the rapidly activating delayed rectifier (I_{Kr}) and slowly activating delayed rectifier (I_{Ks}) potassium currents [4]. Since the discovery of I_{Ks}-channel, its blockers are being studied for the development of antiarrythmic drugs.

In this communication, we present QSAR studies on a few series of Kv1.3-channel blockers and a series of I_{Ks}-channel blockers in order to explore some guidelines to the drug development.

MATERIALS AND METHOD

The three different series of compounds as represented by **1-3** were studied as the blockers of Kv1.3 by Harvey *et al*. [5] and a single series of I_{Ks}-blockers as represented by **4** was reported by Gerlach *et al*.[6]. The three series of Kv1.3



inhibitors are listed in Tables **1**-**3** and a single series of I_{Ks}-inhibitors is listed in Table **4**. Along with the compounds, in each series are listed the channel blocking potency of each compound and the physicochemical properties that were found to be relevant in the correlations. The important physiochemical parameters were the hydrophobic constant π, Verloop's STERIMOL parameters B and L, and the surface tension parameter st. The values of π, B and L were taken

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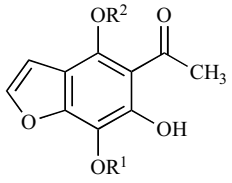
Table 1. A Series of Monoalkylated Khellinone Analogs with their Physicochemical Properties and Kv1.3 Blocking Activity [5]



S.No	R^1	R^2	Σπ	st	log(1/EC_{50})		
					Obsd	Calcd eq.(1)	Predicted Loo
1	Me	Me	1.12	45.40	4.35	4.54	4.76
2	Et	Me	1.58	44.40	5.00	4.97	4.96
3	Pr	Me	2.11	43.50	5.10	5.22	5.27
4	Pn	Me	1.28	50.90	5.52	5.42	5.36
5	Bn	Me	2.57	49.70	5.92	6.02	6.19
6	2-Npm	Me	3.99	53.40	5.30	5.20	5.14
7	Me	Et	1.58	44.40	5.15	4.97	4.94
8	Me	Pr	2.11	43.50	5.30	5.22	5.20
9	Me	Pn	1.28	50.90	5.40	5.42	5.44
10[b]	Me	Bn	2.57	49.70	5.60	6.00	----
11	Me	1-Npm	3.94	53.40	5.10	5.28	5.37
12	Me	2-Npm	3.99	53.40	5.30	5.20	5.14
13	Et	Et	2.04	43.50	5.22	5.19	5.17
14[b]	Bn	Bn	4.02	52.50	5.92	5.02	-----

[b] Not used in the derivation of eq. (1).

from the literature [7] and st was calculated using the freely available software: chemsketch 10 (www.acdlabs.com). The activity parameters EC_{50} (μM) and IC_{50} (μM) in the tables are as usual the concentration of the compounds leading to 50% effect. Values for EC_{50} were determined by fitting the Hill equation to the reduction of area under the K^+ current curve [5] and the IC_{50} values were determined on human I_{Ks}-channel expressed in *Xenopus* oocytes [6].

RESULTS AND DISCUSSION

All the three series of Kv1.3-blockers listed in Tables **1**-**3** are in fact the derivatives of a natural product khellinone (**1:** R^1=R^2=Me), which was found a versatile lead molecule to develop Kv1.3-blockers [8]. A regression analysis of the compounds of Table **1** revealed the following correlation.

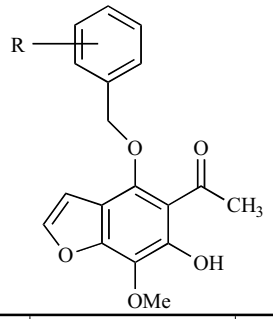
$$\log(1/EC_{50}) = 2.661(\pm0.851)\Sigma\pi - 0.541(\pm0.171)(\Sigma\pi)^2 + 0.119\ (\pm0.041)\text{st} - 3.178(\pm2.544)$$

$$n = 12,\ r = 0.942,\ r_{cv}^2 = 0.67,\ s = 0.14,\ F_{3,8} = 20.86(7.59),\ \Sigma\pi_0 = 2.46 \quad (1)$$

In this equation, n is the number of data points, r is the correlation coefficient, r_{cv}^2 is the square of cross-validated correlation coefficient obtained from leave-one-out (Loo) jackknife procedure, s is the standard deviation, F is the F-ratio between the variances of calculated and observed activities, and the data within the parentheses with ± sign are 95% confidence intervals. The figure within parenthesis for F is the standard F-value at 99% level.

Equation (1) represents a highly significant correlation between the activity and the hydrophobic property of the substituents and the surface tension of the molecule. In the equation Σπ refers to the sum of π-values of R^1- and R^2-substituents. Since there is a parabolic correlation with Σπ, an optimum value of Σπ equal to 2.46 is found, indicating that upto this value of Σπ the activity will increase with the increase in the hydrophobic property of substituents. This gives a clear indication that there may be some hydrophobic interactions of the substituents with the channel. Since Harvey *et al*. have observed that increase in the size of the alkyl groups leads to the increase in the activity [5], we may suggest from eq. (1) that these alkyl groups produce their bene-

Table 2. A Series of 4-benzyl-substituted Khellinone Analogs Along with their Physicochemical Properties and Kv1.3 Blocking Activity [5]



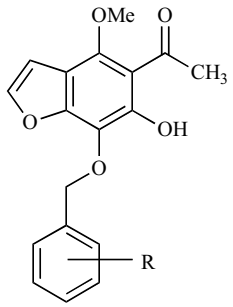
S.No	R	B_1	I_P	L	log(1/EC_{50})		
					Obsd	Calcd eq.(2)	Predicted Loo
1	2-F	1.35	0	2.65	5.77	5.78	5.78
2	2-Cl	1.80	0	3.52	5.92	5.98	5.99
3	2-Me	1.52	0	2.87	5.70	5.87	5.90
4	2-Ph	1.71	0	6.28	5.70	5.54	5.44
5	3-F	1.35	0	2.65	5.92	5.78	5.74
6	3-Cl	1.80	0	3.52	5.85	5.98	6.00
7	3-Me	1.52	0	2.87	6.00	5.87	5.85
8	3-NO_2	1.70	0	3.44	5.85	5.92	5.93
9[b]	3-OCF_3	1.35	0	4.57	6.26	5.52	----
10[b]	3-OMe	1.35	0	3.98	6.17	5.60	----
11	4-F	1.35	1	2.65	6.00	6.07	6.10
12	4-Cl	1.80	1	3.52	6.32	6.27	6.26
13	4-Br	1.95	1	3.82	6.30	6.33	6.34
14	4-CF_3	1.99	1	3.3	6.29	6.43	6.49
15	4-ipr	1.52	1	4.92	6.15	5.88	5.84
16	4-tBu	1.52	1	6.17	5.82	5.71	5.69
17	4-Ph	1.71	1	6.28	6.05	5.83	5.78
18	4-OBn	1.52	1	8.19	5.06	5.43	5.73
19	4-COPh	1.92	1	4.57	6.30	6.21	6.18
20	4-OCF_3	1.35	1	4.57	5.75	5.81	5.83
21	4-OMe	1.35	1	3.98	5.82	5.89	5.91

[b] Not included in the derivation of eq. (2).

ficial effects through their hydrophobic property which increases with the increase in the size. Additionally, eq. (1) also suggests that there should be an optimum value of the size of the substituents that may correspond to the optimum value of $\Sigma\pi$ = 2.46. The beneficial effect of hydrophobic nature of substituents may also be attributed to their contribution to the membrane permeability of the compounds.

A positive coefficient of the surface tension parameter st indicates that the surface tension of the molecule also plays an important role in blocking the Kv1.3 channel. Because of their surface tension, the molecules may be more prone to interact with the channel in order to release the surface energy.

Table 3. A Series of 7-benzyl-substituted Khellinone Analogs Along with their Physicochemical Properties and Kv1.3 Blocking Activity [5]



S.No	R	B_1	L	I_O	log(1/EC_{50})		
					Obsd	Calcd eq.(3)	Predicted Loo
1	2-F	1.35	2.65	1	5.60	5.68	5.73
2	2-Cl	1.80	3.52	1	6.15	5.98	5.85
3	2-Me	1.52	2.87	1	5.72	5.81	5.86
4[b]	2-Ph	1.71	6.28	1	5.96	5.41	-----
5	3-F	1.35	2.65	0	6.12	6.00	5.95
6	3-Cl	1.80	3.52	0	6.22	6.30	6.32
7	3-Me	1.52	2.87	0	5.92	6.14	6.18
8	3-NO_2	1.70	3.44	0	6.22	6.22	6.22
9[b]	3-OCF_3	1.35	4.57	0	6.35	5.67	-----
10	4-F	1.35	2.65	0	6.15	6.00	5.94
11	4-Cl	1.80	3.52	0	6.38	6.30	6.29
12	4-Br	1.95	3.82	0	6.40	6.40	6.40
13	4-CF_3	1.99	3.30	0	6.38	6.53	6.59
14	4-ipr	1.52	4.92	0	6.00	5.78	5.75
15	4-tBu	1.52	6.17	0	5.24	5.56	5.65
16	4-Ph	1.71	6.28	0	5.92	5.74	5.69
17	4-OBn	1.52	8.19	0	5.20	5.22	5.24
18	4-COPh	1.92	4.57	0	6.30	6.24	6.23
19[b]	4-OCF_3	1.35	4.57	0	6.22	5.67	----

[b] Not included in the derivation of eq. (3).

Table **2** represents a series of khellinone derivatives where 4-alkoxy groups have been replaced by benzyloxy groups. In this series, the variation was only in the substituents at the benzyl ring (R-substituent) and a regression analysis revealed that the steric properties of these substituents were important for the activity of the compounds (eq.2).

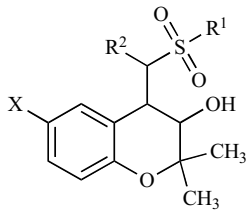
$$\log(1/EC_{50}) = 0.696(\pm0.392)B_1 + 0.290(\pm0.186)I_P - 0.137(\pm0.061)L + 5.205(\pm0.665)$$

$$n = 19,\ r = 0.852,\ r_{cv}^2 = 0.43,\ s = 0.17,\ F_{3,15} = 13.20(5.42) \quad (2)$$

In eq. (2), the positive coefficient of the width parameter B_1, defining the minimum width of the substituent, suggests that the width of the substituents will be conducive to the blocking activity of the compounds. However, the negative coefficient of length parameter L indicates that the length of the substituents will produce a negative effect. Thus, while the width of the substituent may have some kind of van der Waals interaction with the channel, the length may produce the steric problem.

In eq.(2), there is an additional indicator parameter I_P used with a value of unity for a para-substituent. For other

Table 4. A Series of Chromanols Along with their Physicochemical Properties and I_{Ks}-Channel Blocking Activity [6]



S.No	X	R^1	R^2	π_X	I_{CN}	I_{Cf}	log (1/IC_{50})		
							Obsd	Calcd eq.(5)	Predicted Loo
1	CN	Et	Me	-0.57	1	0	5.16	4.62	4.41
2	CN	Et	Me	-0.57	1	1	5.30	5.20	5.13
3	CN	Et	Me	-0.57	1	0	4.35	4.62	4.72
4	CN	Bu	Me	-0.57	1	0	4.24	4.62	4.76
5	H	Et	Me	0	0	0	5.51	5.64	5.68
6	F	Et	Me	0.14	0	0	5.92	5.71	5.66
7	F	Et	Me	0.14	0	1	6.15	6.30	6.40
8	F	Et	Me	0.14	0	0	5.66	5.71	5.73
9	Cl	Me	Me	0.71	0	0	5.96	6.01	6.01
10	OPr	Me	Me	1.05	0	0	6.05	6.18	6.19
11	OBn	Me	Me	2.08	0	0	6.70	6.71	6.71
12	OBn	Et	Me	2.08	0	1	7.30	7.30	7.29
13	OBn	Et	Me	2.08	0	0	6.40	6.71	6.81
14	Obu	Me	Me	1.52	0	0	6.60	6.42	6.40
15	$O(CH2)_3 CF_3$	Me	Me	1.26	0	0	6.62	6.29	6.25
16	$O(CH2)_3 CF_3$	Me	Me	1.26	0	1	6.92	6.87	6.86
17	$O(CH2)_3 CF_3$	Me	Me	1.26	0	0	6.36	6.29	6.28

substituents it is zero. A positive coefficient of it suggests a favorable role of para-substituents as compared to ortho- or meta-substituents. The para-substituents may have the proper orientation towards the active site of the channel. Equation (2), however, is not so highly significant and its r_{cv}^2 value is not very satisfactory (r_{cv}^2 should be greater than 0.60 to define the predictive ability of the equation), but we were not able to get any better correlation. However, this equation does reflect the role of steric properties of the substituents since the coefficients of all the parameters were statistically significant at 95% confidence level. This indication was significantly supported when we analyzed the third series of khellinone derivatives (Table **3**), where the benzyloxy substituents were substituted at the 7-position. For this series, the correlation obtained was highly significant (eq.3). While eq.(3) indicated the same role of B_1 and L as eq.(2), it also indicated exclusively an steric effect of the ortho-substituent through the indicator parameter I_0 used for it.

$$\log(1/EC_{50}) = 1.001(\pm0.453)B_1 - 0.173(\pm0.064)L - 0.325(\pm0.258)I_0 + 5.111(\pm0.811)$$

$$n = 16, r = 0.915, r_{cv}^2 = 0.71, s = 0.17, F_{3,12} = 20.58(5.95) \quad (3)$$

The ortho-substituents in this case might have some hindrance in the possible involvement of the 6-OH group in the hydrogen bonding with the receptor. For I_{Ks}-channel blockers (Table **4**), the activity of compounds was found to be significantly correlated with the hydrophobic property of the X-substituent as shown by the equation:

$$\log (1/IC_{50}) = 0.760(\pm0.226)\,\pi_X + 5.441(\pm0.263)$$

$$n = 17, r = 0.880, s = 0.42, F_{1,15} = 51.53(8.68) \quad (4)$$

Thus the hydrophobic property of the X-substituents seems to be crucial for the activity. These substituents may have strong hydrophobic interaction with the active site of the channel.

The correlation expressed by eq.(4) was, however, found to be further improved significantly when two indicator variables I_{CN} and I_{Cf} were used (eq.5). I_{CN} was used with a value of 1 for X=CN and I_{Cf} was used with a value of 1 for the compounds with configuration (3R,4S). A negative coefficient of I_{CN} indicates that X being a CN group will be detrimental to the activity and it may be probably due to CN being more electronic rather than hydrophobic in nature. However, the positive coefficient of I_{Cf} indicates that the compounds with (3R,4S) configuration will possess more activity than those having any other configuration or being racemic.

$$\log (1/IC_{50}) = 0.514(\pm 0.203)\,\pi_X - 0.732(\pm 0.453)\, I_{CN} + 0.585(\pm 0.312)\, I_{Cf} + 5.642(\pm 0.268)$$

$$n = 17, r = 0.961, r_{cv}^2 = 0.87, s = 0.26, F_{3,13} = 52.80 \quad (5)$$

Equation (5) represents an excellent correlation in that it has very high predictive value as its $r_{cv}^2 >> 0.60$ and that it did not encounter any outlier. In eqs. (1) –(3), however, there were some outliers as indicated in the respective tables. However, no satisfactory reasons could be found to explain their aberrant behavior. In QSAR analysis of these compounds we had tried several other physicochemical and topological parameters, but the best equations that we could find were only those discussed above.

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