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Original article

QSAR studies on benzopyran potassium channel activators

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Abstract

QSAR studies on a series of benzopyrans as potassium channel activators have been carried out using a large set of distance-based topological indices. In addition, the molecular descriptors namely: negentropy and molecular redundancy indices have also been used. The relaxant potency in rat trachea, expressed as pEC_{50} was used for biological characterization of the benzopyrans. The results have shown that pEC_{50} can be modeled excellently in multiparametric model in that we have to include an indicator parameter. The predictive powers of the proposed models are discussed on the bases of cross-validation parameters.

Keywords: Potassium channel activators; QSAR; Negentropy; Topological indices; Benzopyrans

1. Introduction

Three families of potassium ion channels have been described to date [1]. Compounds interacting with these families of proteins may control various diseases, and research was reported for the synthesis of compounds which can activate or block K_{ATP}-dependent potassium channels [1]. Recently, much interest have been shown towards the K (potassium) channel activators (KCA) which have been found to be smooth muscle relaxants with their main utility in hypertension and bronchodilators [1].

In their paper Mannhold et al. [1] reported the synthesis, vasodilator properties and multivariate analysis of 6-substituted benzopyrans as KCAs. Initially they started with 34 compounds and in the end deleted two compounds from regression procedure as outliers (Fig. 1 and Table 1). Their regression analysis explained the variance in biological activity to 82% in the tracheal test system. They observed that low values of substituent size are favorable for high potency. However, they have not used topological indices in their analysis, have not mentioned statistical models along with their quality and also have not attempted estimation of predictive power of the proposed models.

Our earlier reports [2–11] indicated that the distance-based topological indices can be successfully used in such studies as mentioned above. Topological based studies gave better results than those in which indices other than topological indices are used for characterizing the biological activity.

We report in the present study a large set of molecular descriptors along with topological indices used to model pEC_{50} of the benzopyran K-channel activators reported in [1] (Fig. 1 and Tables 1 and 2). It is interesting to mention that in the Mannhold et al.'s paper [1], from which the data have been taken, the activity is recorded in two systems: aortic and tracheal. The former system showed much more dependence on

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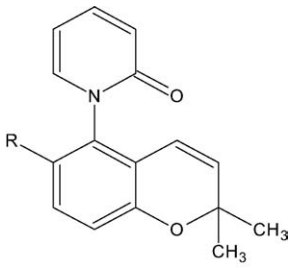

Fig. 1. Benzopyrans KCAs used in the present study.

the size of the substituents. The topological indices chosen in the present study will be much more useful for modeling aortic system. Consequently, the present study deals with the same.

2. Results and discussion

The initial regression analysis has shown that compounds **1**, **6**, **9**, **16**, **29** and **32** are outliers. Therefore, they are deleted from the process of regression. Thus, our methodology relates in 28 compounds only. At present we can't offer convincing proof for the deletion of six compounds. Maybe it is due to the ultimate result of regression and/or they have different type of mechanism than the remaining 28 compounds. It is worthy to mention that our set of compounds include compounds **13**, **34** and **35** which otherwise were deleted by Mannhold et al. [1] from their regression analysis.

The biological activity (pEC_{50}) of the present set of 34 compounds along with the indicator parameters used is given in Table 1. The data show that the biological activity (pEC_{50}) ranges between 4.63 and 7.84 and that little degeneracy is observed in the activity.

A perusal of Table 1 shows that pEC_{50} activity follow the following sequence in increasing order of pEC_{50}.

$$\begin{aligned} 29 > 33 > 30 > 34 > 3 > 19 > 11 > 15 > 18 > 17 > 13 \\ > 14 > 31 > 9 > 4 > 5 > 2 > 7 > 32 \\ > 10 > 12 > 6 > 16 > 21 > 27 > 20 \\ > 1 > 25 > 24 = 26 > 28 > 22 > 23 \end{aligned} \quad (1)$$

This shows that fluorosulfonyloxy substitution at R has highest effect on the exhibition of pEC_{50} while the substitution of 4-fluorophenacyloxy has most retarding effect. The above sequence (Eq. (1)), however, does not show any correlation between structure and activity.

Consequent to above, we have attempted regression analysis using the data recorded in Tables 1 and 2 shows that degeneracy (high to low) is present in these topological indices as they belong to first- and second-generation topological indices [11]. Balaban has shown that such indices in spite of their degeneracy can be used successful in QSPR/QSAR studies. This is the case in the present study also.

In order to arrive at the most significant model we have used maximum R^2 method [12]. The results have shown that

Table 1
Compounds used in the present study, their pEC_{50} and indicator values

Compound No	Compound	EC_{50}	I_{r1}
1[a]	H	5.43	0
2	Methoxy	6.55	1
3	Acetyl	7.37	0
4	Propionyl	6.63	0
5	Benzoyl	6.61	0
6[a]	4-Methoxybenzoyl	6.15	0
7	2-Thienoyl	6.40	0
8	2-Furoyl	6.49	0
9[a]	4-Hydroxybenzoyl	6.65	0
10	4-Nitrobenzoyl	6.20	0
11	2-Fluorobenzoyl	7.08	0
12	2-Nitrobenzoyl	6.17	0
13	2-Methylbenzoyl	6.83	0
14	2-(Trifluoromethyl)benzoyl	6.76	0
15	2,6-Difluorobenzoyl	6.97	0
16[a]	Aminohydroxyiminomethyl	5.99	0
17	Formyl	6.91	0
18	2,2-Dicyanoethenyl	6.95	0
19	2,5-Dimethyl-1-pyrrolyl	7.27	0
20	Hydroxy	5.44	1
21	Acetoxy	5.60	1
22	Phenacyloxy	5.05	1
23	4-Fluorophenacyloxy	4.63	1
24	Phenylcarbamoyloxy	5.30	1
25	2-Fluorophenylcarbamoyloxy	5.38	1
26	4-Fluorophenylcarbamoyloxy	5.30	1
27	2-(Trifluoromethyl) phenylcarbamoyloxy	5.58	1
28	4-(Trifluoromethyl) phenylcarbamoyloxy	5.10	1
29[a]	Fluorosulfonyloxy	7.95	1
30	Cyno	7.67	0
31	4-Pyridyl	6.68	0
32[a]	Thiocarboxamid	6.21	0
33	Bromo	7.84	0
34	Trifluoromethyl	7.61	0

$Ip_1 = 1$, when oxy group is present otherwise 0.

Balaban index [13] (J) is the promising index for this purpose. At this stage it is worthy to mention that compared to Wiener [14] (W) and Randic connectivity indices (Kier and Hall [15]), little attention is paid for the use of Balaban index [13] (J) in QSPR/QSAR studies. Same is the case with the molecular redundancy index MRI [16].

The perusal of Table 3 shows that except for MRI [16] all other topological indices are linearly correlated with each other. They are, therefore, autocorrelated. This means any combination of these indices in regression procedure may result into the defect due to co-linearity. However, such cases are well dealt with Randic [17] and we will follow his recommendation in those cases when auto correlated indices are involved in the model.

The data presented in Table 3 also show that W [14], Sz [18,19] and logRB [20] indices are best suited for monoparametric regression. The initial regression analysis indicated that the model containing J though of the low statistics, is better than the other models. Therefore, our methodology is centered on the use of J and related multiparametric models. As stated earlier another reason in favor of J is that very little attention is paid to this most discriminating index (Tables 4–6).