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Quantitative structure-activity relationship study of ATP-sensitive potassium channel openers: Derivatives of 3-alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide

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Abstract
The inhibitory activity of glucose-induced insulin secretion on isolated rat pancreatic islets and the contractile activity of KCl-depolarized rat aorta rings of the derivatives of 3-alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide are quantitatively analyzed using multiple regression analysis. The study has helped to ascertain the role of different substituents in explaining these observed inhibitory activities. From a derived most significant correlation equation, it was concluded that a less hydrophobic 3-substituent and a less bulky 7-substituent in addition to a 3-aminoisopropyl and a 6-chloro substituent are advantageous to enhance the inhibitory action of a compound towards rat pancreatic islets. On the other hand, the more hydrophobic 6- and 7-substituents augment the contractile activity. The analysis, in this way, provided the grounds for rationalizing the substituent selection in designing the improved potency compounds in the series.

Keywords: *3-Alkylamino-4H-1,2,4-benzothiadiazine 1,1-dioxide derivatives, inhibitory and contractile activity, QSAR analysis, physicochemical parameters*

Introduction

ATP-sensitive potassium channels (K_{ATP} channels) regulate the flow of potassium ions through the cell membrane. These were identified in a wide range of cell types and are found to link the metabolic state to the electric state of the cell [1–8]. K_{ATP} channels are composed of two different protein subunits in a $4 + 4$ stoichiometry [9]. The K_{ATP} channel pore belongs to the inwardly rectifying potassium channel family, which is known as Kir6.x [10]. The second subunit, the sulfonylurea receptor (SUR) subunit, contains the regulatory sites for most drugs [10]. Four variants of SUR, namely SUR1, SUR2A, SUR2B and SUR2C have been reported [11]. K_{ATP} channels are composed of different subunits according to their tissue localization. For example, SUR1 combined with Kir6.2 forms the pancreatic K_{ATP} channels [12]. The combination of SUR2A and Kir6.2 subunits is found in cardiac and skeletal muscle whereas the smooth muscle K_{ATP} channel is composed of SUR2B and Kir6.1 or Kir6.2 subunits [13]. The pancreatic K_{ATP} channels are well-known to be involved in the insulin-releasing process [14,15] and smooth muscle K_{ATP} channels in the control of muscle tone [16,17], the physiological roles of the different channel subtypes have not yet been thoroughly assessed [18,19].

Several drugs, named as potassium channel openers (PCOs), have been found to activate K_{ATP} channels [20,21], leading to plasma membrane hyperpolarization and reduction in cell excitability. This, in turn, may provoke the relaxation of smooth muscles and/or the inhibition of endocrine release [22,23]. Due to their broad therapeutic potential, a large variety of K_{ATP} channel agonists has been developed [24,25] including chromane derivatives such as cromakalim [26], cyano-guanidine compounds such as pinacidil [27] and 1,2,4-benzothiadiazine derivatives such as diazoxide [28]. Selective activation of pancreatic K_{ATP} channels has been demonstrated to be of clinical value in the

treatment of several metabolic disorders, including type I and type II diabetes, obesity and hyperinsulinemia [29–32]. Until recently, diazoxide was the only reported compound to activate pancreatic K_{ATP} channels, but as a consequence of lack of tissue selectivity, it induces many side effects such as hypertrichosis, edema, headache and hypertension [33].

In the search for new pancreatic- selective PCOs, a series comprising of 3-alkylamino-4*H*-pyrido- and − 1,2,4-benzothiadiazine 1,1-dioxides has been developed; among them BPDZ 44 [34], BPDZ 73 [35], BPDZ 138 [36] and BPDZ 216 [37] were identified as the first potent and selective pancreatic K_{ATP} channel openers.

Recently, a series of 3-alkylamino-4*H*-1,2,4-ben-zothiadiazine 1,1-dioxides was reported [38] and were tested as putative K_{ATP} channel openers on a vascular and a pancreatic pharmacological model in order to evaluate their potency and tissue selectivity. The initial structure-activity relationship (SAR) study on these compounds was, however, directed only to alteration of the substituents at different positions of the structure but no rationale was provided to reduce the trial-and-error factors. Hence, a quantitative SAR (QSAR), on these analogues was conducted since QSAR not only provides the rationale for drug design but also illuminates their possible mechanism of action at the molecular level.

Materials and methods

The reported series [38] consists of substituted 4*H*-1,2,4-benzothiadiazine 1,1-dioxides bearing in most cases, a short alkylamino side chain in the 3-position (Figure 1). These compounds along with their activity values for rat pancreatic islets and rat aorta rings are compiled in Table I. The activity, IC_{50}, of a compound represents its ability to inhibit glucose-induced insulin secretion and was evaluated on isolated rat pancreatic islets. The EC_{50}, on the other hand, represents the myorelaxant effect on the contractile activity of KCl-depolarized rat aorta rings. For the
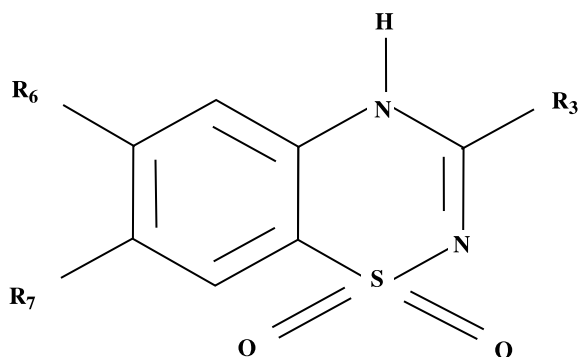

Figure 1. Structure of subsituted 4*H-1,2,*4-benzothiadiazine 1,1-dioxides.

present work, these are expressed as pIC_{50} and pEC_{50} on a molar basis. The most appropriate quantifying parameters are also listed in this Table. The physico-chemical parameter, the hydrophobicity, π, is taken from the literature [39] and the van der Waals volume for a given substituent was calculated according to the method discussed in one of our earlier publications [40]. The ClogP values for the substi-tuents at R_3 were calculated from Chemdraw software [40], following the default description of substituents. For the present work the same is, therefore, designated as $ClogP(R_3)$ to represent the descriptor as a substituent property. Additionally, indicator variables were also employed to reflect upon some special structural features of a compound. The subscripted numerals following these variables are indicative of the varying positions in the title compounds. The multiple regression analysis (MRA), employing the method of least squares, was used to derive significant correlations for further discussion. In addition to this, the final QSAR equations were subjected to a validation test [42] by the leave-one-out (LOO) method to derive the cross-validation index, q^2. For a statistical robust QSAR model, the internally validated q^2 index should have a value between 0.6 and 0.9 [43].

Results and discussion

Table I lists the compounds where the alteration in substituents occurred at different positions of the diazoxide scaffold. To account for the effects produced by such substituents, a large number of descriptors related to hydrophobic, electronic and steric interactions were initially examined for the varying positions in various possible permutations. The selected parameters for each of these positions were hydrophobicity, π or ClogP, hydrogen-bond acceptor, HA, molar refraction, MR, electronic (*para* and *meta*), σ, field, F, resonance, R, Taft's steric, Es, molecular weight, MW and van der Waals volume, Vw. The step-wise regression analysis was followed to derive QSAR equations. A large number of equations so obtained were then subjected to different statistical tests. The correlation equations, which returned the highest correlation coefficient, r and F-statistic and lowest standard deviation, $s,$ were finally retained for further discussion. The significant correlation, derived in the most appropriate quantifying parameters is shown in Equation (1)

$$pIC_{50}(\text{pancreas}) = -0.862(\pm 0.49)ClogP(R_3)$$
$$- 2.339(\pm 1.65)Vw_7$$
$$+ 0.553(\pm 0.27)I_3$$
$$+ 0.542(\pm 0.30)I_6 + 6.291$$
$$n = 24, r = 0.806, s = 0.341, F(4, 19) = 8.782,$$
$$q^2 = 0.420 \tag{1}$$

Table I. QSAR parameters and inhibitory and contractile activity of substituted 4H-1,2,4-benzothiadiazine 1,1-dioxides (See Figure 1 for structure).

S. No.	R_3	R_6	R_7	ClogP(R_3)	π_6	π_7	Vw_7 (10^2 Å^3)	I_3	I_6	pIC$_{50}$(M)[a]			pEC$_{50}$(M)[b]		
										Obsd	Calcd Eq(2)	Prctd LOO	Obsd	Calcd Eq(4) Prctd	LOO
1	NH-Et	Cl	Cl	−0.09	0.71	0.71	0.244	0	1	6.60	6.54	6.53	5.96	5.39	5.32
2	NH-Pr	Cl	Cl	0.43	0.71	0.71	0.244	0	1	5.86	5.89	5.89	5.33	5.39	5.40
3	NH-iPr	Cl	Cl	0.21	0.71	0.71	0.244	1	1	6.55	6.62	6.63	5.64	5.39	5.36
4	NH-allyl	Cl	Cl	0.15	0.71	0.71	0.244	0	1	5.72	6.24	6.29	5.85	5.39	5.34
5	NH-cPr	Cl	Cl	−0.27	0.71	0.71	0.244	0	1	5.48	_c	_c	_d	_d	_d
6	NH-cBu	Cl	Cl	0.29	0.71	0.71	0.244	0	1	5.90	6.06	6.08	4.90	_c	_c
7	NH-Et	Cl	Br	−0.09	0.71	0.86	0.287	0	1	6.57	6.45	6.42	5.57	5.61	5.61
8	NH-Pr	Cl	Br	0.21	0.71	0.86	0.287	1	1	6.59	6.52	6.51	5.25	5.61	5.67
9	NH-cBu	Cl	Br	0.29	0.71	0.86	0.287	0	1	5.92	5.97	5.98	5.18	5.61	5.68
10	NH-iPr	H	Cl	0.21	0.00	0.71	0.244	1	0	6.14	6.11	6.10	4.44	4.80	4.89
11	NH-iPr	H	Br	0.21	0.00	0.71	0.287	1	0	6.33	6.02	5.93	5.32	5.01	4.91
12	NH-Et	Cl	F	−0.09	0.71	0.14	0.115	0	1	6.70	6.82	6.87	4.37	4.57	4.59
13	NH-Pr	Cl	F	0.43	0.71	0.14	0.115	0	1	6.28	6.17	6.14	4.34	4.57	4.60
14	NH-iPr	Cl	F	0.21	0.71	0.14	0.115	1	1	6.80	6.90	6.95	4.38	4.57	4.59
15	NH-cBu	Cl	F	0.29	0.71	0.14	0.115	0	1	6.64	6.35	6.28	4.40	4.57	4.59
16	NH-Et	F	F	−0.09	0.14	0.14	0.115	0	0	6.43	6.32	6.23	4.18	4.09	4.08
17	NH-iPr	F	F	0.21	0.14	0.14	0.115	1	0	6.52	6.39	6.36	3.99	4.09	4.11
18	NH-iBu	F	F	0.83	0.14	0.14	0.115	0	1	5.25	5.16	5.11	_d	_d	_d
19	NH-Et	Cl	OMe	−0.09	0.71	−0.02	0.304	0	1	6.32	6.41	6.43	_c	_c	_c
20	NH-iPr	Cl	OMe	0.21	0.71	−0.02	0.304	1	1	6.62	6.49	6.45	4.43	4.34	4.32
21	NH-cBu	Cl	OMe	0.29	0.71	−0.02	0.304	0	1	6.29	5.93	5.87	4.63	4.34	4.28
22	NH-iPr	H	F	0.21	0.00	0.14	0.115	1	0	6.12	6.39	6.47	4.37	3.97	3.88
23	NH-iPr	H	OMe	0.21	0.00	−0.02	0.304	1	0	5.76	5.98	6.05	3.56	3.74	3.80
24[e]	CH$_3$	H	Cl	0.88	0.00	0.71	0.244	0	0	4.65	4.82	4.95	4.65	4.80	4.83

[a] pIC$_{50}$ expressed as negative logarithm on molar basis, represents the inhibition of glucose-induced insulin secretion evaluated on isolated rat pancreatic islets; [b] pEC$_{50}$ expressed as negative logarithm on molar basis, represents the contractile activity of KCl-depolarized rat aorta rings; taken from Ref. [38]; [c] "Outlier" compound in the present study; [d] Uncertain activity; [e] Reference compound: diazoxide.

Table II.   Stepwise development of Equation (2) $pIC_{50}(pancreas) = a_0 + a_1ClogP(R_3) + a_2Vw_7 + a_3 I_3 + a_4 I_6$

a_0	a_1	a_2	a_3	a_4	r	s	$F_{k,n-k-1}$[a]	q^2	steps
6.553	$-1.533(\pm 0.50)$				0.755	0.344	27.783	0.453	(i)
6.864	$-1.584(\pm 0.49)$	$-1.381(\pm 1.56)$			0.784	0.334	15.943	0.463	(ii)
6.777	$-1.551(\pm 0.46)$	$-1.486(\pm 1.46)$	$0.263(\pm 0.23)$		0.824	0.312	13.426	0.517	(iii)
6.455	$-1.254(\pm 0.28)$	$-2.184(\pm 0.86)$	$0.454(\pm 0.14)$	$0.505(\pm 0.16)$	0.920	0.223	24.662	0.765	(iv)

[a] The F statistics for n ($= 23$) data-points and k ($= 1, 2, 3$ & 4) independent variable(s).

As given above, n is the number of data points, F-statistic is the F-ratio between the variances of calculated and observed activities, and the $\pm$ data within the parentheses are the 90% confidence intervals. The arbitrarily chosen indicator variables, I_3 and I_6, stand to account, respectively for an aminoisopropyl substituent at the 3-position and a chloro substituent at the 6-position. Thus a value either 1 or 0 for I_3, in that order, indicates the presence or absence of an aminoisopropyl substituent at the 3-position of diazoxide scaffold. Likewise, $I_6 = 1$ or 0 indicates, respectively, the presence or absence of a 6-chloro substituent.

From Equation (1), it appears that the 3-substituents are engaged in a hydrophobic interaction while the 7-substituents are involved in a steric/polar interaction. In addition, the presence of the 3-aminoisopropyl and 6-chloro substituents are prerequisite for inhibitory action. The statistical parameters of the above equation, however, do not represent a sound model as the r^2 value accounts for 65% of the variance and q^2 is below the specified level of significance, though the F-value remained significant at 99% [$F_{4,19}(0.01) = 4.500$] level. These observations merely reflect upon the parametric requirements of the substituents in a compound that may lead to agonistic activity for K_{ATP} channel. In order to improve upon the significance levels of Equation (1), all data points in Table I, were further analyzed for their deviation from a regular trend. The lone compound **5** (Table I), having a 3-NH-cPr substituent, showed unusual behavior. At present, no plausible explanation could be assigned for such an abnormality. After removal of this compound the QSAR analysis, through successive steps (Table II), has revealed correlation Equation (2)

$$pIC_{50}(pancreas) = -1.254(\pm 0.28)ClogP(R_3)$$
$$- 2.184(\pm 0.86)Vw_7$$
$$+ 0.454(\pm 0.14)I_3$$
$$+ 0.505(\pm 0.16)I_6 + 6.455$$
$$n = 23, r = 0.920, s = 0.223, F(4, 18) = 24.662,$$
$$q^2 = 0.765 \tag{2}$$

Now both the r- and F-values were increased to account for 85% ($r^2 = 0.846$) of variance in the observed activities and 99% level of significance [$F_{4,18}(0.01) = 4.579$], respectively. Also, the s-value

and 90% confidence intervals ($\pm$ data within parentheses) associated with regression coefficients were significantly lowered. Additionally, the higher value obtained for q^2 expressed a reasonable QSAR model. That the variables used in deriving Equation (2) had no mutual correlation is shown in Table III. The calculated activity values, using this equation and listed in Table I, are in close agreement with the observed ones. The predicted activity values, using Equation (2), are also listed in this Table for the sake of comparison. The plot of observed versus calculated and predicted pIC_{50} values, is shown in Figure 2. Such a plot is useful to understand the goodness of fit and to identify the systematic trend. From Equation (2), it appeared that a less hydrophobic 3-substituent and a less bulky 7-substituent are advantageous to improve the pIC_{50} value. In addition, the presence of 3-aminoisopropyl and 6-chloro substituents are favorable to enhance the activity.

The myorelaxant effects, reported in terms of the contractile activity of KCl-depolarized rat aorta rings, of these diazoxides were also correlated with quantifying parameters. The derived correlation for the same, is shown in Equation (3)

$$pEC_{50}(rat\,aorta) = 0.873(\pm 0.41)\pi_6$$
$$+ 1.265(\pm 0.37)\pi_7 + 3.841$$
$$n = 22, r = 0.853, s = 0.350, F(2, 19) = 25.418,$$
$$q^2 = 0.637 \tag{3}$$

This equation analyzes the importance of 6- and 7-substituents while the 3-substituents remained silent. Compound **6** and **19** could not fit into the model and are ignored to derive an improved QSAR Equation (4)

Table III.   Intercorrelation matrix[a] amongst independent variables of Equation (2).

	$ClogP(R_3)$	Vw_7	IR_3	IR_6
$ClogP(R_3)$	1.000	0.115	0.069	0.303
Vw_7		1.000	0.071	0.232
IR_3			1.000	0.350
IR_6				1.000

[a] Matrix elements are the r-values.
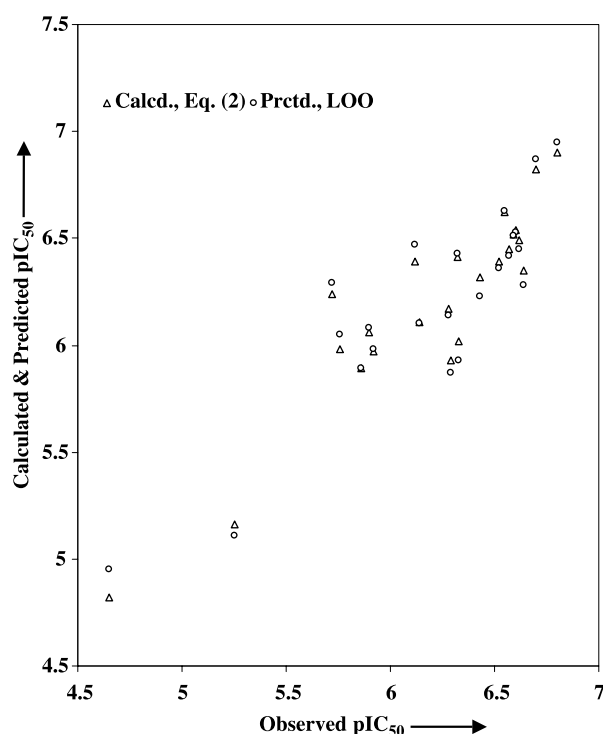
Figure 2. Plot of observed versus calculated and predicted pIC_{50} values.

compared to Equation (3)

$$pEC_{50}(\text{rat aorta}) = 0.837(\pm 0.37)\pi_6$$
$$+ 1.443(\pm 0.35)\pi_7 + 3.772$$
$$n = 20, r = 0.900, s = 0.307, F(2, 17) = 36.270,$$
$$q^2 = 0.737 \quad\quad\quad (4)$$

All the statistical parameters, including 90% confidence intervals, of this equation have significantly improved over that of Equation (3). The *r*-value now accounts for 81% of the variance and the *s*-value is lowered. In addition, the *F* value remained significant at 99% level, and the q^2 index, explaining a satisfactory statistical model, are both increased. The calculated pEC_{50} values using Equation (4), and predicted pEC_{50} values, using the LOO method, listed in Table I, are in close agreement with the observed ones. The independent variables of this equation fulfill the mutual orthogonality condition (π_6 *vs* $\pi_7 = 0.071$). From Equation (4), it appears that more hydrophobic substituents present at 6- and 7-positions augment activity.

The conclusions deduced from Equations (2) and (4) may be used as guidelines to obtain more potent compounds in the further synthesis of similar compounds.

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