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A QSAR STUDY ON ATP-SENSITIVE POTASSIUM CHANNEL OPENERS : THE DERIVATIVES OF 3-ALKYLAMINO-4*H*-1, 2, 4-BENZOTHIADIAZINE 1, 1-DIOXIDE

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ABSTRACT

The structure-activity models of the myorelaxant effects of the 3-alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide derivatives have been investigated with 695 three dimensional descriptors from DRAGON software using Combinatorial Protocol in Multiple Linear Regression (CP-MLR). Among the 3D-descriptor classes in the study, the contractile activity is correlated with 3D-MoRSE, GETAWAY and WHIM class of descriptors. The models developed, and the participating descriptors suggest that the substituent groups of dioxide derivatives hold scope for further modification in the optimization of activity. The significant predictive ability of these models observed for the test-set of molecules makes these models useful for designing new compounds with good myorelaxant properties.

Key words: Quantitative structure-activity relationship (QSAR), Contractile activity of K^+-depolarized rat aorta rings, 3-Alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxide derivatives, Dragon descriptors.

INTRODUCTION

The flow of potassium ions through the cell membrane is regulated by ATP-sensitive potassium channels (K_{ATP} channels). These channels, identified in various cell types, link the metabolic state to the electric state of the cell[1-8]. Two different protein sub units in a 4 + 4 stoichiometry are involved in composition of these channels[9]. The first subunit, Kir6.x, belongs to the inwardly rectifying potassium channel family where as the second subunit known as sulfonylurea receptor (SUR) which contains the regulatory sites

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for most drugs[10]. Four variants of SUR (namely SUR1, SUR2A, SUR2B and SUR2C) have been known[11] so far. K_{ATP} channels are composed of different subunits based on tissue localization of SUR[12-17], however, the physiological roles of the different channel subtypes have not yet been thoroughly assessed [18,19]. The drugs, known as PCOs (potassium channel openers), are found to activate K_{ATP} channels[20,21]. PCOs lead to plasma membrane hyperpolarization and reduction in cell excitability which, in turn, may provoke the relaxation of smooth muscles and/or the inhibition of endocrine releases[22,23]. A large variety of K_{ATP} channels agonists, such as cromakalim[24] , pinacidil[25] and diazoxide[26] due to their broad therapeutic potential, has been developed[27, 28]. The clinical importance of selective activation of pancreatic K_{ATP} channels has been shown in the treatment of several metabolic disorders, such as type I and type II diabetes, obesity and hyperinsulinemia [29-32]. Many side effects (such as hypertrichosis, edema, headache and hypotension) are induced by diazoxide due to lack of tissue selectivity[33]. In the recent studies, structural modification in the diazoxide scaffold had been carried out with a view to obtain new pancreatic selective PCOs[34-36]. The myorelaxant effects of these compounds have been evaluated on the contractile activity of KCl-depolarized rat aorta rings. The aim of present communication is, therefore, to establish quantitative relationship between the reported contractile activity and the information rich descriptors accounting for structural modifications of diazoxide moiety.

EXPERIMENTAL

Materials and methods

Data set

The compounds used in this study comprise a series of 3-alkylamino-4H-1,2,4-benzothiadiazine 1,1-dioxide derivatives, previously shown to be pancreatic selective PCOs[34-36]. Out of the 101 reported compounds, 76 compounds were active while 25 compounds were of uncertain activity or not tested. Emphasizing the importance of different positions or the structural modifications, these compounds along with their contractile activities have been listed in Tables 1-3. The activities have been expressed in terms of pEC_{50} on molar basis, where EC_{50} is the drug concentration required to exhibit 50% relaxation of the 30 mM KCl induced contraction of rat aorta rings. Initially, a test set consisting of 25% active compounds, was generated in the SYSTAT[37] using the single linkage hierarchical cluster procedure involving the Euclidean distances of the activity values.

Table 1: Structures[a] of benzothiadiazine 1,1-dioxide derivatives included in training set and observed and modeled contractile activity

S. No.	X	Y	Z	pEC_{50}(M)								
				Obsd[b].	Model (1)		Model (2)		Model (3)		Model (4)	
					Calc.	LOO	Calc.	LOO	Calc.	LOO	Calc.	LOO
1	H	F	$NHCH_2CH_2CH_3$	3.78	4.43	4.45	4.06	4.07	3.79	3.79	4.07	4.12
2	H	F	$NHCH(CH_3)CH_2CH_3$	4.41	4.40	4.40	4.41	4.41	4.40	4.40	4.28	4.26
3	H	F	$NHCH(CH_2)_4$	4.24	4.62	4.64	4.24	4.24	4.24	4.24	4.13	4.12
4	H	Cl	$NHCH_3$	3.85	4.22	4.27	4.30	4.34	4.14	4.17	4.08	4.11
5	H	Cl	$NHCH_2CH_3$	4.40	4.29	4.29	4.25	4.24	4.28	4.28	4.28	4.28
6	H	Cl	$NHCH_2CH_2CH_3$	4.26	4.79	4.80	4.53	4.54	4.52	4.52	4.73	4.76
7	H	Cl	$NHCH(CH_3)CH(CH_3)_2$	5.92	5.38	5.35	5.20	5.16	5.47	5.42	5.49	5.44
8	H	Cl	$NHC(CH_3)_3$	5.85	5.86	5.87	5.34	5.29	5.56	5.52	5.58	5.54
9	H	Cl	$NHC(CH_3)_2CH_2CH_3$	6.54	5.44	5.34	5.40	5.30	5.63	5.52	5.61	5.49
10	H	Cl	$NHCH(CH_2CH_3)_2$	4.03	4.53	4.58	4.63	4.66	4.79	4.89	4.72	4.78
11	H	Cl	$NHCH(CH_2)_2$	3.72	3.59	3.56	3.95	3.97	3.94	3.96	3.85	3.87
12	H	Cl	$NHCH(CH_2)_3$	4.46	4.35	4.34	4.12	4.10	4.18	4.17	4.09	4.07
13	H	Cl	$NHCH_2CH(CH_2)_2$	4.39	4.47	4.48	4.48	4.48	4.65	4.67	4.64	4.66
14	H	Cl	$NHCH_2CH{=}CH_2$	4.54	4.63	4.63	5.26	5.36	5.29	5.40	5.21	5.32
15	H	Br	$NHCH_3$	4.51	4.44	4.43	4.76	4.78	4.40	4.38	4.28	4.23
16	H	Br	$NHCH_2CH_3$	5.21	4.53	4.52	4.77	4.75	4.58	4.54	4.79	4.76
17	H	Br	$NHCH(CH_3)_2$	5.32	5.04	5.02	4.95	4.93	4.83	4.81	4.77	4.74
18	H	Br	$NHCH(CH_3)CH_2CH_3$	5.25	5.02	5.01	5.27	5.27	5.25	5.25	5.24	5.24
19	H	Br	$NHCH(CH_3)CH(CH_3)_2$	5.59	5.65	5.66	5.81	5.84	5.91	5.96	5.92	5.97
20	H	Br	$NHCH(CH_2)_2$	4.05	3.85	3.82	4.56	4.62	4.37	4.42	4.25	4.28

Cont…

S. No.	X	Y	Z	pEC$_{50}$(M)								
				Obsd[b].	Model (1)		Model (2)		Model (3)		Model (4)	
					Calc.	LOO	Calc.	LOO	Calc.	LOO	Calc.	LOO
21	H	Br	$NHCH_2CH{=}CH_2$	5.52	4.58	4.56	5.43	5.43	5.23	5.19	5.12	5.07
22	H	I	$NHCH(CH_3)_2$	5.11	5.26	5.27	4.90	4.84	4.86	4.79	4.97	4.92
23	H	I	$NHCH(CH_2CH_3)_2$	4.10	5.17	5.37	4.63	4.84	4.63	4.84	4.69	4.92
24	H	I	$NHCH(CH_2)_3$	4.65	4.81	4.83	4.67	4.68	4.60	4.59	4.64	4.64
25[c]	H	Cl	CH_3	4.65	4.44	4.38	3.99	3.88	4.06	3.96	4.63	4.61
26	H	CH_3	$NHCH_2CH_3$	3.68	4.12	4.15	3.93	3.96	4.14	4.20	4.03	4.08
27	H	CH_3	$NHCH(CH_3)_2$	3.70	4.48	4.52	3.99	4.01	4.05	4.08	3.91	3.93
28	H	CH_3	$NHCH(CH_3)CH_2CH_3$	4.81	4.49	4.49	4.40	4.38	4.76	4.75	4.71	4.69
29	H	CH_3	$NHCH(CH_2)_3$	4.23	4.21	4.21	3.94	3.92	4.07	4.06	4.00	3.99
30	H	C_5H_{11}	$NHC_2H_2CH_3$	5.18	5.01	4.96	4.44	4.30	4.79	4.67	4.85	4.74
31	H	C_5H_{11}	$NHCH(CH_3)_2$	4.70	5.01	5.08	4.44	4.39	4.79	4.82	4.85	4.90
32	H	OCH_3	$NHCH(CH_3)_2$	3.56	4.36	4.40	3.99	4.02	3.84	3.87	3.68	3.69
33	H	OCH_3	$NHCH(CH_3)CH_2CH_3$	4.76	4.38	4.37	4.45	4.44	4.57	4.56	4.49	4.48
34	H	OCH_3	$NHCH(CH_2)_3$	3.80	4.01	4.02	3.88	3.87	3.71	3.70	3.55	3.52
35	H	OC_2H_5	$NHCH_2CH_3$	3.79	3.67	3.64	3.80	3.81	3.63	3.61	3.65	3.62
36	H	CF_3	$NH\ CH_2CH_2CH_3$	5.54	4.77	4.75	4.75	4.71	4.57	4.49	4.70	4.63
37	H	CF_3	$NHCH(CH_3)_2$	4.88	4.71	4.70	4.73	4.72	4.68	4.68	4.64	4.62
38	H	CF_3	$NHCH(CH_3)CH_2CH_3$	5.05	4.73	4.72	5.04	5.04	5.09	5.09	5.05	5.05
39	H	CN	$NHCH(CH_3)_2$	4.37	4.73	4.75	4.31	4.30	4.17	4.16	4.07	4.08
40	H	SO_2CH_3	$NHCH(CH_3)_2$	3.90	4.46	4.49	4.10	4.12	4.23	4.26	4.19	4.22

Cont…

S. No.	X	Y	Z	pEC$_{50}$(M)								
				Obsd[b].	Model (1)		Model (2)		Model (3)		Model (4)	
					Calc.	LOO	Calc.	LOO	Calc.	LOO	Calc.	LOO
41	H	SO_2CH_3	$NHCH(CH_3)CH_2CH_3$	3.90	4.49	4.52	4.33	4.27	4.53	4.62	4.48	4.56
42	H	NO_2	$NHCH_2CH_2CH_3$	4.80	4.82	4.82	4.59	4.58	4.54	4.52	4.53	4.51
43	H	NO_2	$NHCH(CH_3)_2$	4.64	4.81	4.82	4.61	4.61	4.58	4.57	4.58	4.58
44	H	NO_2	$NHCH(CH_3)CH_2CH_3$	5.22	4.80	4.79	4.90	4.89	4.97	4.96	5.02	5.01
45	H	NO_2	$NHCH(CH_2)_3$	4.86	4.49	4.48	4.54	4.53	4.60	4.59	4.57	4.56
46	Cl	Cl	$NHCH_2CH_3$	6.00	4.99	4.94	5.42	5.73	5.43	4.39	6.21	6.39
47	Cl	Cl	$NHCH(CH_3)_2$	5.64	5.59	5.58	5.41	5.39	5.54	5.53	5.49	5.48
48	Cl	Cl	$NHCH_2CH{=}CH_2$	5.92	5.25	5.21	5.67	5.64	5.82	5.81	5.78	5.76
49	Cl	Br	$NHCH_2CH_3$	5.48	5.30	5.28	5.69	5.74	5.49	5.49	5.44	5.43
50	Cl	Br	$NHCH(CH_3)_2$	5.25	5.92	6.03	5.58	5.68	5.42	5.48	5.31	5.33
51	Cl	F	$NHCH_2CH_3$	4.37	4.50	4.51	5.10	5.10	4.92	4.98	4.89	4.95
52	Cl	F	$NHCH_2CH_2CH_3$	4.34	5.10	5.13	5.31	5.40	5.11	5.21	5.00	5.09
53	Cl	F	$NHCH(CH_3)_2$	4.38	5.13	5.16	5.11	5.18	4.92	4.99	4.79	4.85
54	F	F	$NHCH_2CH_3$	4.18	4.04	4.03	4.08	4.07	3.84	3.80	4.16	4.16
55	Cl	OCH_3	$NHCH_2CH_3$	5.09	4.28	4.22	4.89	4.87	4.83	4.81	4.71	4.69
56	Cl	OCH_3	$NHCH(CH_3)_2$	4.43	4.67	4.69	5.33	5.46	5.39	5.54	5.31	5.45
57	Cl	OCH_3	$NHCH(CH_2)_3$	4.63	4.31	4.30	4.80	4.80	4.79	4.80	4.73	4.73

[a]See Figure 1 for general structure. [b]Taken from Refernces [34-36]. [c]Diazoxide

Table 2: Structures[a] of benzothiadiazine 1, 1-dioxide derivatives included in test set with observed and modeled contractile activity, residuals and predictive r2

S. No.	X	Y	Z	pEC_{50}(M)							
				Obsd[b].	Model (1)		Model (2)		Model (3)		Model (4)	
					Calc.	LOO	Calc.	LOO	Calc.	LOO	Calc.	LOO
58	H	F	$NHCH(CH_3)_2$	4.37	4.40	–0.03	4.06	0.31	3.96	0.41	3.79	0.58
59	H	F	$NHCH(CH_3)CH(CH_3)_2$	4.58	5.02	–0.44	4.76	–0.18	4.92	–0.34	4.88	–0.30
60	H	F	$NHCH(CH_2)_3$	4.14	4.10	0.04	4.03	0.11	3.96	0.18	3.81	0.33
61	H	F	$NHCH_2CH(CH_2)_2$	3.84	4.00	–0.16	3.84	0.00	3.69	0.15	3.61	0.23
62c	H	Cl	$NHCH(CH_3)_2$	4.44	4.77	–0.33	4.44	0.00	4.52	–0.08	4.45	–0.01
63	H	Cl	$NHCH(CH_3)CH_2CH_3$	4.81	4.76	0.05	4.76	0.05	4.92	–0.11	4.89	–0.08
64	H	Br	$NHCH_2CH_2CH_3$	5.23	5.04	0.19	5.18	0.05	4.94	0.29	5.01	0.22
65	H	Br	$NHCH(CH_2)_3$	4.66	4.67	–0.01	4.91	–0.25	4.83	–0.17	4.80	–0.14
66	H	I	$NHCH(CH_3)CH_2CH_3$	5.89	5.24	0.65	5.12	0.77	5.15	0.74	5.26	0.63
67	H	I	$NHCH(CH_3)CH(CH_3)_2$	6.03	5.91	0.12	5.82	0.21	5.99	0.04	6.13	–0.10
68	H	OC_2H_5	$NHCH(CH_3)_2$	3.63	4.01	–0.38	4.08	–0.45	4.11	–0.48	4.07	–0.44
69	H	CN	$NHCH(CH_2)_3$	4.24	4.44	–0.20	4.21	0.03	4.11	0.13	4.03	0.21
70	H	$CONH_2$	$NHCH(CH_3)_2$	3.76	4.57	–0.81	4.92	–1.16	4.73	–0.97	4.58	–0.82
71	H	NO_2	$NHCH(CH_3)CH(CH_3)_2$	5.55	5.54	0.01	5.69	–0.14	5.99	–0.44	6.02	–0.47
72	Cl	Cl	$NHCH_2CH_2CH_3$	5.33	5.55	–0.22	5.51	–0.18	5.50	–0.17	5.66	–0.33
73	Cl	Cl	$NHCH(CH_2)_3$	4.90	5.28	–0.38	5.35	–0.45	5.48	–0.58	5.45	–0.55
74	Cl	Br	$NHCH(CH_2)_3$	5.18	5.58	–0.40	5.61	–0.43	5.52	–0.34	5.44	–0.26
75	Cl	F	$NHCH(CH_2)_3$	4.40	4.85	–0.45	5.08	–0.68	4.91	–0.51	4.87	–0.47
76	F	F	$NHCH(CH_3)_2$	3.99	4.64	–0.65	4.14	–0.15	4.07	–0.08	3.94	0.05
Predictive r^2					0.707		0.627		0.648		0.674	

[a,b]See foot note under Table 1. [c]BPDZ 73

Table 3: Structures[a] of benzothiadiazine 1,1-dioxide derivatives having uncertain activity along with predicted contractile activity

S. No.	X	Y	Z	pEC_{50}(M)				
				Obsd[b].	Predicted Model (1)	Predicted Model (2)	Predicted Model (3)	Predicted Model (4)
77	H	F	$NHCH_3$	<3.52	3.89	3.95	3.61	3.52
78	H	F	$NHCH_2CH_3$	<3.52	3.95	3.84	3.68	3.63
79	H	F	$NHCH(CH_2)_2$	<3.52	3.24	3.60	3.43	3.24
80	H	F	$NHCH_2CH{=}CH_2$	<3.52	4.21	4.70	4.52	4.39
81	H	H	$NHCH_2CH_3$	<3.52	3.86	3.76	3.78	3.72
82	H	H	$NHCH_2CH_2CH_3$	<3.52	4.38	4.05	4.04	4.02
83	H	H	$NHCH(CH_3)_2$	<3.52	4.32	3.96	3.98	3.83
84	H	H	$NHCH(CH_3)CH_2CH_3$	n.d.c	4.47	4.26	4.46	4.37
85	H	H	$NHCH(CH_2)_3$	n.d.c	4.14	3.85	3.86	3.72
86	H	C_5H_{11}	$NHCH(CH_2)_3$	<4.52	4.65	4.73	5.02	5.08
87	H	OCH_3	$NHCH_2CH_2CH_3$	<3.52	4.37	3.98	3.83	3.08
88	H	OC_2H_5	$NHCH(CH_2)_3$	<3.52	3.68	3.77	3.71	3.65
89	H	COOH	$NHCH_2CH_2CH_3$	<3.52	4.58	4.58	4.47	4.39
90	H	COOH	$NHCH(CH_3)_2$	<3.52	4.58	4.53	4.50	4.39
91	H	COOH	$NHCH(CH_3)CH_2CH_3$	<3.52	4.65	4.83	4.85	4.82
92	H	$COOCH_3$	$NHCH(CH_3)_2$	<3.70	4.26	4.76	4.77	4.67
93	H	SO_2CH_3	$NHCH_2CH_3$	<3.52	4.32	3.75	3.67	3.56
94	H	NH_2	$NHCH(CH_3)_2$	<3.52	4.12	4.22	4.18	4.07
95	H	$NHCOCH_3$	$NHCH(CH_3)_2$	<3.52	4.90	4.97	4.91	4.85
96	Cl	Cl	$NHCH(CH_2)_2$	<4.52	4.53	4.56	4.45	4.36
97	Cl	Cl	$NH(CH_2)_5CH_3$	<3.52	5.74	5.22	5.73	5.79
98	$NHCH(CH_3)_2$	F	$NHCH(CH_3)_2$	<3.70	4.86	4.27	4.41	4.38
99	$NHCH_2CH_2CH_3$	F	$NH\ CH_2CH_2CH_3$	n.d.c	4.79	4.82	4.76	4.68
100	$NHCH(CH_2)_3$	F	$NHCH(CH_2)_3$	n.d.c	4.09	3.89	3.91	3.85
101	F	F	$NHCH_2CH(CH_3)_2$	<4.52	5.39	4.94	4.97	4.96

The selection of the test set from the generated cluster tree was done in such a way to keep the test compounds at a maximum possible distance from each other. In this way, the test set represents different cross-sections of entire series. The compounds included in training set and test set are mentioned in Table 1 and 2, respectively, whereas compounds with uncertain activity are listed in Table 3.

Table 4: Descriptor class, symbols and definition of descriptors emerged in models (1-4) through CP-MLR.

Descroptor's class	Symbol	Meaning
3D MoRSE	Mor04v	3D MoRSE signal 04/weighted by atomic van der Waals volumes
	Mor24u	3D MoRSE signal 24/unweighted
	Mor04m	3D MoRSE signal 04/weighted by atomic masses
	Mor10m	3D MoRSE signal 10/weighted by atomic masses
	Mor13e	3D MoRSE signal 10/weighted by atomic masses
GETAWAY	H3v	H autocorrelation of lag 3/weighted by atomic van der Waals volumes
	HATS4e	leverage-weighted autocorrelation of lag 4/weighted by atomic Sanderson electronegativities
WHIM	G3u	3rd component symmetry directional WHIM index/unweighted
	L1m	1st component size directional WHIM index/weighted by atomic masses

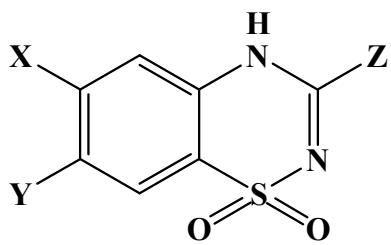

Figure 1: General structure of benzothiadiazine 1,1-dioxide derivatives.

Computational procedure

The structures of the compounds under study have been drawn in 2D Chem. Draw[38] using the standard procedure. The drawn structures were then converted into 3D modules using the default conversion procedure implemented in the CS Chem3D Ultra. The generated 3D-structures of the compounds were subsequently subjected to energy minimization in the MOPAC module, using the AM1 procedure for closed shell systems, implemented in the CS Chem3D Ultra. This will ensure a well defined conformer relationship among the compounds of the study. All these energy minimized structures of respective compounds have been ported to DRAGON software[39] for the computation of descriptors for the compounds in Tables 1-3. This software offers several hundreds of descriptors from different perspectives corresponding to 0D-, 1D-, 2D- and 3D-descriptor modules. Subsequently, the myorelaxant activity of the titled compounds had been attempted to correlate with 0D-, 1D-, 2D-descriptors using combinatorial protocol-multiple linear regression (CP-MLR) computational procedure. However, no significant model was obtained from these descriptors. Thus, a data file consisting of 695 descriptors from 3D-class was generated and was analyzed next through CP-MLR. The brief description of this procedure is given below.

Model development

The CP-MLR is a 'filter'-based variable selection procedure for the development of statistical models in high dimensional QSAR studies[40-43]. It involves a combinatorial strategy with appropriately placed 'filters' interfaced with MLR and extracts diverse models having unique combination of descriptors from the dataset. The filters set the thresholds for the descriptors in terms of inter-parameter correlation cutoff limits in subset regressions (filter-1), t-values of the regression coefficients (filter-2), internal explanatory power (filter-3; square root of adjusted multiple correlation coefficient of regression equation, r-bar), and the external consistency (filter-4; Q^2 i.e. cross-validated R^2 from the leave-one-out procedure). Throughout this study, the thresholds for the filters-1, 2 and 4 were assigned as 0.3, 2.0, and $0.3 \leq Q^2 \leq 1.0$, respectively while the filter-3 was assigned an initial value of 0.50. In order to collect the descriptors with higher information content, the threshold of filter-3 was successively incremented with increasing number of descriptors (per model) by considering the r-bar value of the preceding optimum model as the new threshold for the next generation.

Further, to find out any chance correlations associated with the models recognized in CP-MLR, each cross-validated model has been subjected to randomization test[44,45] by

scrambling of the biological responses. The datasets with scrambled response vector have been reassessed by multiple regression analysis. The resulting regression equations, if any, with correlation coefficients better than or equal to the one corresponding to unscrambled response data were counted. Every model has been subjected to 100 such simulation runs. This has been used as a measure to express the percent chance correlation of the model under scrutiny. The CP-MLR protocol has been applied with default filter thresholds to identify the all possible models that could emerge from the descriptors under consideration.

For each model, derived in n data points, a number of statistical parameters were obtained to access its overall statistical significance. These are the multiple correlation coefficient, r, the standard deviation, s, the F-value representing the ratio of the variances of calculated to observed activities, the cross-validated Q^2LOO (obtained by LOO method) and Q^2L5O (leave five out) , addressing the external consistency (or the robustness) of the model. Additional statistical parameters such as, the Akaike's information criterion, AIC[46,47], the Kubinyi function, FIT[48,49] and the Friedman's lack of fit, LOF[50], have also been calculated to further validate the derived models. The AIC takes into account the statistical goodness of fit and the number of parameters that have to be estimated to achieve that degree of fit. The FIT, closely related to the F-value, proved to be a useful parameter for evaluating the quality of the models. A model which is derived in k independent descriptors, its F-value will be more sensitive if k is small while it becomes less sensitive if k is large. The FIT, on the other hand, will be less sensitive if k is small whereas it becomes more sensitive if k is large. The model that produces the lowest AIC value and highest FIT value is considered potentially the most useful and the best. The LOF factor takes into account the number of terms used in the equation and is not biased, as are other indicators, toward large number of parameters. A minimum LOF value infers that the derived model is statistically sound.

RESULTS AND DISCUSSION

The QSAR models were obtained for 57 compounds in the training set using a total number of 695 3D-Dragon descriptors through CP-MLR. The threshold of filter-3 was successively incremented with increasing the number of descriptors (per model) by considering the r-bar value of the preceding optimum model as the new threshold for the next generation.

The model having highest predictive power, amongst eight models emerged through CP-MLR of the 4H-1,2,4-benzothiadiazine 1,1-dioxide derivatives in three

descriptors is given below.

$pEC_{50} = 0.456 + 0.702(0.242)\ Mor04v + 3.531(0.764)\ H3v + 3.429(0.745)\ HATS4e$

$n = 57, r = 0.716, s = 0.500, F = 18.604, FIT = 0.846, LOF = 0.290, AIC = 0.287, Q^2_{LOO} = 0.441, Q^2_{LGO} = 0.413$ …(1)

In above equation, the values given in the parentheses are the standard errors of the regression coefficients. The model as such could explain the 51 percent of variance in observed activity. The emerged descriptor in above model, Mor04v belongs to 3D MoRSE class and H3v and HATS4e from GETAWAY class of descriptors. 3D-MoRSE (3D-Molecule Representation of Structures based on Electron diffraction) descriptors are based on the idea of obtaining information from the 3D atomic coordinates by the transformations used in electron diffraction studies for preparing theoretical scattering curves. The appeared descriptors in models are indicative of the role for different atomic properties such as the atomic mass, the van der Waals volume, the Sanderson atomic electronegativity and the polarizability in electron diffraction signals. The GETAWAY (GEometry, Topology, and Atom-Weights AssemblY) are geometrical descriptors encoding information on the effective position of substituents and fragments in the molecular space. They are independent of molecule alignment and, at some extent, account also for information on molecular size and shape as well as for specific atomic properties. These descriptors have been derived by applying some traditional matrix operators and concepts of information theory both to the molecular influence matrix and the influence/distance matrix. Most of these descriptors are simply calculated only by the leverages used as the atomic weightings. The other GETAWAY descriptors are based on the spatial autocorrelation formula, weighting the molecule atoms by physicochemical properties together with 3D information encoded by the elements of the molecular influence matrix and influence/distance matrix. The physical interpretations of these descriptors have been outlined in Table 4.

The individual descriptors of all three-descriptor models were pooled to discover the higher models for the activity. The following models are the representative of higher models.

$pEC_{50} = 4.100 - 1.224(0.380)\ Mor24u + 0.795(0.145)\ Mor04m - 0.431(0.110)\ Mor10m + 0.135(0.020)\ L1m$

$n = 57, r = 0.774, s = 0.458, F = 19.379, FIT = 1.063, LOF = 0.259, AIC = 0.250, Q^2LOO = 0.506, Q^2LGO = 0.480$ …(2)

pEC50 = 4.444 – 1.527(0.370) Mor24u + 0.833(0.136) Mor04m – 0.415(0.103) Mor10m + 0.658(0.225) Mor13e + 0.137(0.018) L1m

n = 57, r = 0.810, s = 0.428, F = 19.482, FIT = 1.188, LOF = 0.241, AIC = 0.226, Q^2LOO = 0.564, Q^2LGO = 0.562 …(3)

pEC_{50} = 3.927 – 1.581 (0.342) Mor24u + 0.875(0.126) Mor04m – 0.387(0.096) Mor10m + 0.843(0.216) Mor13e + 2.159(0.688) G3u + 0.151(0.018) L1m

n = 57, r = 0.844, s = 0.428, F = 20.695, FIT = 1.335, LOF = 0.219, AIC = 0.200, Q^2LOO = 0.628, Q^2LGO = 0.635 …(4)

Above equations were further subjected to randomization process, where 100 simulations per model were carried out but none of the identified models has shown any chance correlation. Additionally, the above equations were also validated through a test set containing 19 compounds listed in Table 2. The residuals of the predictions and the corresponding predictive r^2 of test set have been given in the same table. The predictions corresponding to all the test set compounds are within the reasonable limits of their actual values (Table 2). These equations were further used to predict activity values of the compounds having uncertain or unreported activity. The same are given in Table 3.

The other descriptor class emerged in above models is WHIM class of descriptors. The G3u and L1m descriptors are representative of this class, which played significant role to explain the variance in activity. The physical interpretations of all of these descriptors have been outlined in Table 4. WHIM descriptors (Weighted Holistic Invariant Molecular descriptors) are geometrical descriptors based on statistical indices, calculated on the projections of the atoms along principal axes. These descriptors are built in such a way as to capture relevant molecular 3D information regarding molecular size, shape, symmetry and atom distribution with respect to invariant reference frames. A fundamental role in the calculation of WHIM descriptors is played by the eigenvalues of the weighted covariance matrix of the molecular atomic coordinates. Each eigenvalue represents a dispersion measure (i.e., the weighted variance) of the projected atoms along the considered principal axis, thus accounting for the molecular size along that principal direction. The relationships among the eigenvalues are used to describe the molecular shape.

CONCLUSIONS

QSAR models for 4H-1,2,4-benzothiadiazine 1,1-dioxide derivatives with statistical significance and predictive abilities by using 3D-Dragon descriptors were

developed and validated. The significant predictive ability of these models observed for the test-set of molecules makes these models useful for designing new compounds with good myorelaxant properties.

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