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Bioorganic & Medicinal Chemistry Letters 14 (2004) 3435–3439
Bioorganic & Medicinal Chemistry Letters

Exploring QSAR of melatonin receptor ligand benzofuran derivatives using E-state index

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Received 23 March 2004; accepted 23 April 2004

Abstract—Considering the recent challenge to the medicinal chemists for the development of selective melatonin receptor ligands, an attempt has been made to explore physicochemical requirements of benzofuran derivatives for binding with human MT_1 and MT_2 receptor subtypes and also to explore selectivity requirements. In this study, E-states of different common atoms of the molecules (calculated according to Kier and Hall) and physicochemical parameters (partition coefficient and molar refractivity) were used as independent variables along with suitable dummy parameters. The best equation describing MT_1 binding affinity [$n = 34$, $Q^2 = 0.670$, $R^2_a = 0.790$, $R^2 = 0.822$, $R = 0.907$, $s = 0.609$, $F = 25.8$ (df 5, 28)] suggests that the binding affinity decreases as the value of n (number of CH_2 spacer beside R_2) increases while it increases with rise in electrotopological state values of different atoms of the benzofuran ring. Again, presence of methoxy group at R_1 and hydrogen, unsubstituted phenyl or fluoro-substituted phenyl group at R_2 is conducive to the MT_1 binding affinity. The binding affinity decreases if furyl substitution at R_3 position is present. The best equation describing MT_2 binding affinity [$n = 34$, $Q^2 = 0.602$, $R^2_a = 0.755$, $R^2 = 0.792$, $R = 0.890$, $s = 0.584$, $F = 21.3$ (df 5, 28)] shows that the MT_2 binding affinity depends on the similar factors as described for MT_1 binding affinity; however, the contributions of the factors for the two affinities are different to some extent as evidenced from the regression coefficients. Among the selectivity relations, the best equation [$n = 33$, $Q^2 = 0.496$, $R^2_a = 0.681$, $R^2 = 0.721$, $R = 0.849$, $s = 0.458$, $F = 18.1$ (df 4, 28)] suggests that MT_2 binding increases with increase in value of n, presence of methoxy group at R_1, and E-state values of different atoms of the benzofuran ring, while it decreases in presence of furyl group at R_3 position.

Melatonin (N-acetyl-5-methoxyindolamine) is a derivative of tryptophan, an essential amino acid for mammals. Earlier reports indicated that melatonin was uniquely synthesized and secreted by the pineal gland in vertebrates, but recent studies[1] revealed its extrapineal origin including retina, gut ovary, testes, bone marrow and lens.

Melatonin has several important physiological actions including the control of circadian rhythms, sleep induction, regulation of seasonal reproduction and immune enhancement.[2] Melatonin was also shown to have significantly broader actions including oncostatic effects, immune system stimulation and anti-inflammatory functions.[3] Melatonin has been shown to possess both in vitro and in vivo important antioxidant activities. Further, it inhibits the activation of poly (ADP ribose) synthetase,[4,5] and several aspects of the inflammatory response.[6] Melatonin can reduce the toxicity of a wide variety of environmental and chemical insults, which initiate oxidative stress.

Melatonin is the only known chronobiotic, hormonal regulator of neoplastic cell growth. Melatonin acts as a differentiating agent in some cancer cells and lowers their invasive and metastatic status through alterations in adhesion molecules and maintenance of gap junctional intercellular communication. In some cancer types, melatonin, either alone or in combination with other agents, induces apoptotic cell death.[7]

The MT_1, MT_2 and MT_3 melatonin receptors are possible mediators of the physiological effects of melatonin,[8] and they have been expressed at central and peripheral sites. Central effects appear to be predominantly mediated by the MT_1 subtype. Activation of the

Keywords: QSAR; Melatonin receptor ligand; E-state index; Benzofuran derivatives.

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doi:10.1016/j.bmcl.2004.04.073

MT_1 melatonin receptor inhibits neuronal firing rate in the suprachiasmatic nucleus (SCN) and prolactin secretion from the pars tuberalis and induces vasoconstriction. Activation of the MT_2 melatonin receptor phase shifts circadian rhythms generated within the SCN, inhibits dopamine release in the retina, induces vasodialation, enhances splenocyte proliferation and inhibits leukocyte rolling in the microvasculature. Activation of the MT_3 melatonin receptor reduces intraocular pressure and inhibits leukotriene B4-induced leukocyte adhesion.[9]

Quantitative structure–activity relationship (QSAR) studies have been done on various derivatives acting on melatonin receptors. Comparative molecular field analysis (CoMFA) models have been reported on binding affinity within different classes of melatonin receptors of indole-based melatonin analogs,[10] 2-iodomelatonin[11] and *N*-substituted melatonin derivatives.[12] Topographical model has been used for the QSAR study of 2-N-acylaminoalkylindoles.[13] Partial least squares (PLS) and multiple regression analysis (MRA) were used as tools for QSAR studies on 2-substituted indole compounds.[14]

The present paper attempts QSAR modeling of MT_1 and MT_2 receptor binding and explores selectivity requirements for MT_2 versus MT_1 binding of benzofuran derivatives[15] using electrotopological state (E-state) index, developed by Kier and Hall.[16,17]

The E-state index is an atom level descriptor[16,17] encoding both electronic character and topological environment of each skeletal atom in a molecule. It is derived from graph theoretic approach and has two basic components: (a) intrinsic topological and electronic state of an atom; (b) effect of the environment influencing the atom (perturbation), considering differences in the intrinsic electrotopological states of different atoms and topological distance among them which determine the magnitude of the interactions. The E-state index has been projected as a useful tool in the context of QSAR studies and reported to have power to identify atoms or fragments in the molecules that are important for the biological activity.[17] The present group of authors also have used E-state index to explore QSARs of ligands acting on different pharmacologically relevant targets of contemporary interest.[18–22] In continuation of such efforts, the present communication will show here the utility of E-state index in QSAR studies by exploring selectivity requirements of MT_2 versus MT_1 binding of benzofuran derivatives using E-state index.

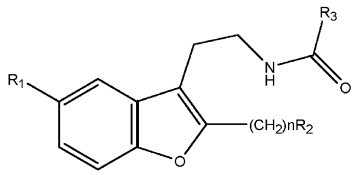
The structural features of the compounds and their melatonin receptor binding affinities are given in Table 1. In the present study, we have tried to incorporate hydrophobicity parameter (partition coefficient $\log P$), steric factor (molar refractivity MR, ignoring its polarizability component) and some indicator or integer variables along with E-state parameters to improve the quality of final relations. The physicochemical parameter values ($\log P$ and MR) were calculated by CHEM DRAW ULTRA 5.0 software[23] using Crippen's fragmentation method.[24] All compounds considered in the present study contain fourteen common atoms (excluding hydrogens). The atoms of the molecules were numbered keeping serial numbers of the common atoms same in all the compounds (as shown in Fig. 1). The E-state index values were calculated using ELECTRO1 program.[25] The program AUTOREG[25] was used to relate binding affinity with different combinations of E-state values of different atoms along with appropriate physicochemical variables and indicator variables in order to find out the best multiple regression relations. For this purpose, all possible combinations of predictor variables were tried with a restriction that predictor variables used in an equation are not much intercorrelated ($|r| < 0.5$). Using the program RRR98,[25] regression coefficients with corresponding standard errors and various statistical parameters reflecting quality[26] (like explained variance R^2_a or adjusted R^2, correlation coefficient R, standard error of estimate s, variance ratio F and average of absolute values of the residuals AVRES) of the equations were found out. Leave-one-out cross-validation[27] was done using the programs KRPRES1 and KRPRES2,[25] which generate predicted variance (Q^2), predicted residual sum of squares (PRESS), standard deviation of error of prediction (SDEP) and average of absolute values of predicted residuals ($\mathrm{Pres_{av}}$). While deriving the final relations, $\log P$ and MR values could not find place in the best equations. Though many relations were generated, only the final ones will be reported here for brevity. The regression coefficients and variance ratios of all reported equations are significant at 95% and 99% levels, respectively. For convenience, definitions of different variables appearing in the reported equations are given in Table 2.

In case of MT_1 binding activity, the best relation involving all 34 compounds was the following:

$$\begin{aligned} pC_1 &= 3.357(\pm 2.334)S_3 - 1.379(\pm 0.419)n \\ &\quad + 1.712(\pm 0.591)I_{\mathrm{OMe}} + 1.170(\pm 0.466)I_{\mathrm{Ph/F}} \\ &\quad - 2.342(\pm 0.943)I_{\mathrm{Furyl}} - 5.146 \\ n &= 34,\ Q^2 = 0.670,\ R_a = 0.790,\ R^2 = 0.822, \\ R &= 0.907,\ F = 25.8(5, 28),\ s = 0.609, \\ \mathrm{AVRES} &= 0.433,\ \mathrm{SDEP} = 0.751, \\ S_{\mathrm{PRESS}} &= 0.828,\ \mathrm{PRESS} = 19.2,\ \mathrm{Pres_{av}} = 0.557 \end{aligned} \quad (1)$$

The 95% confidence intervals of the regression coefficients are shown within parentheses. Eq. 1 could predict 67.0% and explain 79.0% of the variance of MT_1 binding affinity. As E-state values of atom numbers 1, 2, 3, 4 and 9 are highly intercorrelated ($|r| > 0.9$), a new variable S_{12349} was defined as sum of E-state values of the atoms. The statistical quality of the resultant equation was comparable to that of Eq. 1.

Table 1. Structural features and melatonin receptor binding affinity of benzofuran derivatives



1-34

Sl. No.	Structural features				Melatonin receptor binding affinity								
					MT_1 binding affinity (pC_1)			MT_2 binding affinity (pC_2)			Selectivity (pC_2–pC_1)		
	n	R_1	R_2	R_3	Obs.[a]	Calc.[b]	Pred.[b]	Obs.[a]	Calc.[c]	Pred.[c]	Obs.[a]	Calc.[d]	Pred.[d]
1	0	OCH_3	H	CH_3	3.824	3.990	4.013	3.469	4.129	4.222	−0.355	−0.074	−0.023
2	1	OCH_3	C_6H_5	CH_3	2.896	2.724	2.711	4.301	3.745	3.702	1.405	1.546	1.555
3	1	OCH_3	C_6H_4(2-OCH_3)	CH_3	1.845	1.510	1.480	3.469	3.034	2.994	1.624	1.472	1.463
4	1	OCH_3	C_6H_4(3-OCH_3)	CH_3	1.391	1.518	1.530	3.495	3.053	3.012	2.104	1.489	1.451
5	1	OCH_3	C_6H_4(4-OCH_3)	CH_3	1.620	1.524	1.516	3.301	3.067	3.045	1.681	1.500	1.489
6	1	OCH_3	C_6H_4(3-F)	CH_3	3.125	2.537	2.483	3.638	3.350	3.320	0.513	1.331	1.383
7	1	OCH_3	C_6H_4(3-CF_3)	CH_3	1.097	1.094	1.094	2.932	2.179	2.033	1.835	1.035	0.878
8	1	OCH_3	C_6H_4(3-Cl)	CH_3	2.143	1.498	1.440	3.658	3.010	2.950	1.515	1.474	1.471
9	1	OCH_3	C_6H_3(2,6-Cl_2)	CH_3	1.073	1.414	1.445	1.893	2.829	2.912	0.820	1.359	1.391
10	1	OCH_3	C_6H_3(3,5-CF_3)	CH_3	0.322	0.634	0.766	0.469	1.229	2.085	0.147	0.525	1.223
11	1	OCH_3	C_6H_{11}	CH_3	1.178	1.689	1.743	2.604	3.427	3.550	1.426	1.712	1.751
12	1	OCH_3	C_5H_4N(3)	CH_3	1.538	1.513	1.511	2.452	3.040	3.095	0.914	1.497	1.533
13	3	OCH_3	C_6H_5	CH_3	1.502	0.577	−1.053	2.818	3.060	3.459	1.316	—	—
14	1	C_2H_5	C_6H_5	CH_3	1.191	1.758	1.907	2.084	2.475	2.558	0.893	1.037	1.064
15	1	C_2H_5	C_6H_4(3-OCH_3)	CH_3	0.541	0.552	0.556	1.770	1.783	1.787	1.229	0.981	0.938
16	1	H	C_6H_5	CH_3	0.810	1.572	1.728	1.975	2.295	2.356	1.165	1.024	0.998
17	1	H	C_6H_4(3-OCH_3)	CH_3	0.640	0.365	0.280	1.730	1.603	1.566	1.090	0.967	0.946
18	0	OCH_3	C_6H_5	CH_3	5.000	4.065	3.928	4.699	4.323	4.269	−0.301	−0.069	−0.026
19	1	OCH_3	C_6H_5	CH_2I	2.062	2.738	2.791	3.387	3.774	3.805	1.325	1.554	1.571
20	1	OCH_3	C_6H_5	C_3H_7	2.483	2.755	2.776	3.699	3.810	3.818	1.216	1.568	1.594
21	1	OCH_3	C_6H_5	Furyl	0.156	0.352	0.571	1.435	0.650	−0.225	1.279	0.723	0.039
22	1	OCH_3	C_6H_5	$CH{=}CH_2$	1.270	2.697	2.809	3.161	3.688	3.729	1.891	1.503	1.478
23	1	OCH_3	C_6H_4(3-OCH_3)	$CH{=}CH_2$	1.260	1.490	1.511	2.559	2.996	3.036	1.299	1.446	1.455
24	0	OCH_3	C_6H_5	$CH{=}CH_2$	4.699	4.037	3.942	5.000	4.266	4.162	0.301	−0.112	−0.187
25	0	OCH_3	C_6H_5	Furyl	1.889	1.693	1.474	0.442	1.227	2.102	−1.447	−0.891	−0.207
26	1	OCH_3	C_6H_5	$CH_2CH{=}CH_2$	2.455	2.718	2.738	4.222	3.733	3.695	1.767	1.524	1.508
27	1	OCH_3	C_6H_4(3-OCH_3)	$CH_2CH{=}CH_2$	1.666	1.512	1.498	3.959	3.041	2.955	2.293	1.468	1.419
28	0	OCH_3	C_6H_5	$CH_2CH{=}CH_2$	5.000	4.058	3.922	4.699	4.311	4.255	−0.301	−0.090	−0.051
29	0	OCH_3	C_6H_5	$CH{=}CHCH_3$	2.996	4.065	4.221	3.678	4.323	4.417	0.682	−0.085	−0.225
30	1	OCH_3	C_6H_5	$NHCH_3$	2.270	2.708	2.742	3.456	3.710	3.730	1.186	1.514	1.536
31	0	OCH_3	C_6H_5	$NHCH_3$	4.398	4.048	3.998	4.398	4.288	4.272	0.000	−0.100	−0.118
32	1	OH	C_6H_5	CH_3	0.245	0.080	−0.226	1.097	0.860	0.694	0.852	0.525	0.418
33	1	OC_5H_{11}	C_6H_5	CH_3	1.370	1.265	1.246	2.012	2.055	2.063	0.642	0.868	0.906
34	1	OC_6H_{13}	C_6H_5	CH_3	2.086	1.291	1.146	2.493	2.090	2.017	0.407	0.876	0.955

[a] Obs. = Observed (Ref. 15), Calc. = Calculated, Pred. = Predicted.
[b] From Eq. 1.
[c] From Eq. 3.
[d] From Eq. 6.

$$pC_1 = 0.584(\pm 0.412)S_{12349} - 1.395(\pm 0.423)n + 1.704(\pm 0.592)I_{OMe} + 1.156(\pm 0.469)I_{Ph/F} - 2.322(\pm 0.946)I_{Furyl} - 3.231$$
$$n = 34,\ Q^2 = 0.673,\ R_a^2 = 0.789,\ R^2 = 0.821,$$
$$R = 0.906,\ F = 25.6(5, 28),\ s = 0.611,$$
$$\text{AVRES} = 0.433,\ \text{SDEP} = 0.749,$$
$$S_{\text{PRESS}} = 0.825,\ \text{PRESS} = 19.1,\ \text{Pres}_{\text{av}} = 0.551 \qquad (2)$$

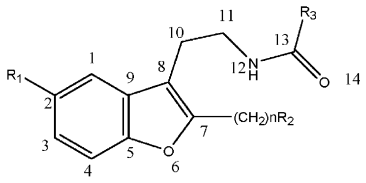


Figure 1. General structure of benzofuran derivatives: the common atoms have been numbered 1 through 14.

The predictor variables used in Eqs. 1 and 2 are not much intercorrelated (Table 3). The variable S_{12349} in Eq. 2 implies the importance of electron density distribution of different atoms of the benzofuran nucleus, which is in turn dependent on the R_1 substituent The negative coefficient of n indicates the MT_1 binding affinity

Table 2. Definitions of variables

Variable	Definition
S_3	E-state value of atom no. 3
S_4	E-state value of atom no. 4
S_8	E-state value of atom no. 8
S_{12349}	Sum of E-state values of atom nos. 1, 2, 3, 4 and 9
S_{4589}	Sum of E-state values of atom nos. 4, 5, 8 and 9
I_{OMe}	Indicator variable having value 1 in presence of methoxy group at R_1 position, value 0 otherwise.
$I_{Ph/F}$	Indicator variable having value 1 in presence of hydrogen, unsubstituted phenyl or fluoro-substituted phenyl group at R_2 position, value 0 otherwise.
I_{Furyl}	Indicator variable having value 1 in presence of furyl substitution at R_3 position, value 0 otherwise.
n	Number of CH_2 spacer beside R_2

decreases on increase of number of CH_2 spacer (n) beside R_2. Again, the positive coefficients of I_{OMe} and $I_{Ph/F}$ indicate that presence of methoxy group at R_1 and hydrogen, unsubstituted phenyl or fluoro-substituted phenyl group at R_2, respectively, are conducive to the MT_1 binding affinity. Further, the negative coefficient of I_{Furyl} denotes that MT_1 binding affinity decreases if furyl substitution at R_3 position is present. The calculated and predicted MT_1 binding affinity values according to Eq. 1 are given in Table 1.

In case of MT_2 binding activity, the best relation was the following:

$$\begin{aligned} pC_2 &= 5.742(\pm 2.781)S_4 - 0.670(\pm 0.400)n \\ &\quad + 1.988(\pm 0.556)I_{OMe} + 0.615(\pm 0.454)I_{Ph/F} \\ &\quad - 3.033(\pm 0.904)I_{Furyl} - 9.287 \\ n &= 34,\ Q^2 = 0.602,\ R_a^2 = 0.755,\ R^2 = 0.792, \\ R &= 0.890,\ F = 21.3(5,28),\ s = 0.584, \\ \text{AVRES} &= 0.466,\ \text{SDEP} = 0.733, \\ S_{\text{PRESS}} &= 0.808,\ \text{PRESS} = 18.3,\ \text{Pres}_{\text{av}} = 0.606 \end{aligned} \quad (3)$$

Eq. 3 could predict 60.2% and explain 75.5% of the variance of MT_2 binding affinity. The predictor variables of Eq. 3 are not much intercorrelated (Table 3). As E-state values of atom numbers 4, 5, 8 and 9 are highly intercorrelated ($|r|>0.9$), a new variable S_{4589} was defined as sum of E-state values of the atoms. The statistical quality of the resultant equation was comparable to that of Eq. 3.

$$\begin{aligned} pC_2 &= 1.198(\pm 0.599)S_{4589} - 0.671(\pm 0.406)n \\ &\quad + 1.924(\pm 0.554)I_{OMe} + 0.564(\pm 0.467)I_{Ph/F} \\ &\quad - 2.955(\pm 0.915)I_{Furyl} - 4.008 \\ n &= 34,\ Q^2 = 0.590,\ R_a^2 = 0.749,\ R^2 = 0.787, \\ R &= 0.877,\ F = 20.7(5,28),\ s = 0.591, \\ \text{AVRES} &= 0.469,\ \text{SDEP} = 0.744, \\ S_{\text{PRESS}} &= 0.820,\ \text{PRESS} = 18.8,\ \text{Pres}_{\text{av}} = 0.613 \end{aligned} \quad (4)$$

The variable S_{4589} in Eq. 4 implies the importance of electron density distribution of the benzofuran nucleus, which is in turn dependent on the R_1 substituent. The impact of the variables n, I_{OMe}, $I_{Ph/F}$ and I_{Furyl} shows similar trend as found in case of MT_1 binding but only differing in the numerical value of the corresponding coefficient. This is also supported by the high intercorrelation between MT_2 and MT_1 binding affinity for the present set of compounds (Table 3). The calculated and predicted MT_2 binding affinity values according to Eq. 3 are given in Table 1.

While exploring selectivity relations, compound **13** had to be deleted because of its outlier behavior. The following best relation was obtained:

$$\begin{aligned} pC_2 - pC_1 &= 1.924(\pm 1.542)S_8 + 1.533(\pm 0.419)n \\ &\quad + 0.716(\pm 0.443)I_{OMe} - 0.743(\pm 0.697)I_{Furyl} \\ &\quad - 2.874 \\ n &= 33,\ Q^2 = 0.492,\ R_a^2 = 0.682, \\ R^2 &= 0.722,\ R = 0.850,\ F = 18.2(4,28), \\ s &= 0.457,\ \text{AVRES} = 0.357,\ \text{SDEP} = 0.569, \\ S_{\text{PRESS}} &= 0.618,\ \text{PRESS} = 10.7,\ \text{Pres}_{\text{av}} = 0.460 \end{aligned} \quad (5)$$

As E-state values of atom numbers 4, 5, 8, 9 are highly intercorrelated ($|r| > 0.9$), S_{4589} as defined previously was used:

$$\begin{aligned} pC_2 - pC_1 &= 0.575(\pm 0.465)S_{4589} + 1.551(\pm 0.420)n \\ &\quad + 0.744(\pm 0.453)I_{OMe} - 0.754(\pm 0.698)I_{Furyl} \\ &\quad - 3.612 \\ n &= 33,\ Q^2 = 0.492,\ R_a^2 = 0.681, \\ R^2 &= 0.721,\ R = 0.849,\ F = 18.1(4,28), \\ s &= 0.458,\ \text{AVRES} = 0.359,\ \text{SDEP} = 0.568, \\ S_{\text{PRESS}} &= 0.616,\ \text{PRESS} = 10.6,\ \text{Pres}_{\text{av}} = 0.459 \end{aligned} \quad (6)$$

Table 3. Intercorrelation ($|r|$) among important descriptors

	pC_2	pC_2–pC_1	S_3	S_4	S_8	S_{12349}	S_{4589}	n	I_{OMe}	$I_{Ph/F}$	I_{Furyl}
pC_1	0.802	0.475	0.023	0.041	0.073	0.025	0.072	0.765	0.404	0.463	0.190
pC_2		0.144	0.049	0.149	0.221	0.055	0.196	0.357	0.474	0.219	0.435
pC_2–pC_1			0.110	0.152	0.206	0.123	0.171	0.744	0.030	0.444	0.326
S_3				0.941	0.775	0.995	0.857	0.082	0.475	0.070	0.032
S_4					0.937	0.950	0.976	0.061	0.427	0.169	0.011
S_8						0.807	0.989	0.067	0.353	0.228	0.045
S_{12349}							0.883	0.081	0.482	0.078	0.044
S_{4589}								0.046	0.391	0.214	0.034
n									0.269	0.418	0.179
I_{OMe}										0.115	0.132
$I_{Ph/F}$											0.205

Table 4. Results of leave-20%-out cross-validation[a]

Eq. No.	Q^2	PRESS
1	0.721	16.3
2	0.720	16.3
3	0.588	18.9
4	0.576	19.5
5	0.458	11.4
6	0.446	11.7

[a] Compounds were deleted in five cycles in the following manner: **1**, **6**, **11**,. . .,**31**; **2**, **7**, **12**,. . ., **32**; . . .; **5**, **10**,. . .,**30**.

The predictor variables of Eqs. 5 and 6 are not much intercorrelated (Table 3). Eq. 6 could predict 49.6% and explain 68.1% of the variance of selectivity for binding with MT_2 over MT_1. The variable S_{4589} in Eq. 6 indicates that electron density distribution of different atoms of the benzofuran ring is important for the selective binding with MT_2 over MT_1 receptor type. Moreover, the positive coefficient of n indicates the MT_2 selectivity increases on increase of number of CH_2 spacer (n) beside R_2. Further, the positive coefficient of I_{OMe} indicates that the MT_2 selectivity increases in presence of methoxy group at R_1. Again, the negative coefficient of I_{Furyl} denotes that MT_2 selectivity decreases if furyl substitution at R_3 position is present. The calculated and predicted selectivity values according to Eq. 6 are given in Table 1.

Leave-20%-out cross-validation was applied on all reported equations and the results are reported in Table 4.

The present QSAR study could throw some light on the physicochemical requirements of benzofuran derivatives for binding with MT_2 and MT_1 receptor types. The study also shows the utility of E-state index in developing statistically acceptable model having direct physicochemical significance. However, more data points covering wider features of substitution pattern need to be considered to reach a conclusion.

Acknowledgements

One of the authors (K.R.) thanks the All India Council for Technical Education (AICTE), New Delhi for financial grant under the Career Award for Young Teachers (CAYT) scheme.

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