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Topological Descriptor Based QSAR Study of Benzamidine as Inhibitor of Thrombin

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ABSTRACT

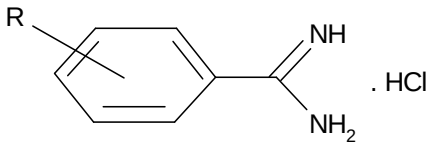
QSAR models of 22 benzamidine derivatives reported as inhibitors of thrombin have been developed using the descriptors heat of formation, valence connectivity index, shape index, solvent accessibility surface area, molar refractivity, log P and molecular weight. QSAR models, in which either heat of formation or shape index or molar refractivity is present, have good predictive powers as correlation coefficients have been found above 0.9. These descriptors alone provide good QSAR models. Best QSAR model with 0.994001 value of correlation coefficient has been obtained using the combination of descriptors heat of formation, shape index, molar refractivity and log P.

Key words: Topological descriptors, thrombin, inhibition, shape index, heat of formation, molar refractivity and log P.

INTRODUCTION

The descriptors provide quantitative information about the properties of a molecule. A large number of quantum chemical descriptors have been used for quantitative structure activity relationship (QSAR) studies [1-6]. Topological descriptors have also been developed mostly by Kier and Hall [7-11], which quantifies molecular structure, and provides information for QSAR and QSPR studies.

Essential features of blood coagulation, complement activation, fibrinolysis and digestion are the activation of trypsin, thrombin, plasmin and complement which specifically hydrolyze protein substrates [12]. All the four enzymes have been found to be competitively inhibited by benzamidine, which is a small organic molecule and is an excellent model for cationic side chain of orginine and lysine [13-14].



Benzamidine

In order to study the structural basis of the substrates-binding specificity, certain QSAR studies on the derivatives of benzamidine have been made which are listed in Table-1 [15-16]. The inhibition activities of compounds of Table-1 for the enzyme thrombin have been measured by pK_1.

MATERIALS AND METHODS

QSAR studies of the compounds listed in Table-1 have been made with the help of following topological and energy descriptors [17-23]-

1.	Heat of Formation	ΔH_f
2.	Valence Connectivity Index (order 0, standard)	κ_0
3.	Shape Index (basic kappa, order 1)	SI1
4.	Solvent Accessibility Surface Area	SA
5.	Molar Refractivity	MR
6.	Log P	Log P
7.	Molecular Weight	MW

PM3 based calculations of the above descriptors have been made on the compounds listed in Table-1 with the help of Cache Software and their relationship with the known activity of the inhibitors have been studied by developing QSAR models. The values of the descriptors have been used to prepare multilinear regression equations for predicted activities. Predicted activities obtained from the multilinear regressing equation have been compared with the known activity. The correlation coefficient and cross-validation coefficient have been evaluated to adjudge the quality of QSAR model and its predictive power.

RESULTS AND DISCUSSION

Values of topological and energy descriptors of benzamidines listed in Table-1 have been evaluated and are included in Table-2 alongwith the values of activities in terms of pK_1 for thrombin inhibition. Several QSAR models in different combination of descriptors have been tried; the models providing correlation coefficient above 0.9 are discussed below-

Best QSAR model

Best QSAR model is denoted by PA1 which is the measure of activities of benzamidines for thrombin inhibition in terms of pK_1. Combination of descriptors which provide best QSAR model is the heat of formation, shape index order 1, molar refractivity and log P. MLR equation of this QSAR model is given by

$PA1=-0.202687*\Delta H_f+0.0978225*SI1+0.11267*MR-0.0272492*Log\ P+0.581077$
$rCV^2=0.987299$
$r^2=0.994001$

Value of correlation coefficient is 0.994001 and cross-validation coefficient is 0.987299 which indicate that the predictive power of this QSAR model is very good and it can efficiently be used for the prediction of the activity of any benzamidine compound for thrombin inhibition. Values of predicted activity PA1 for benzamidine compounds is included in Table-3. Maximum difference in the values of predicted and observed activities is 0.185 and the average difference is 0.0618. Graph between observed and predicted activities PA1 is shown in Graph-1. Graph between differences in observed activities and predicted activities PA1 of benzamidines for thrombin inhibition is shown in Graph-2.

Table-1: Benzamidines and their Thrombin Inhibition Activities

Comp	R	Thrombin Inhibition Activities in terms of pK_1
1	4-NO_2	2.5
2	3-CH_2OH	2.6
3	2-Me	1
4	3-NO_2	2.6
5	3-COOH	2.7
6	3-$CH_2C_6H_5$	3.4
7	H	2.9
8	3-NH_2	4.4
9	3-C_6H_5	3.7
10	3-$N(CH_3)_2$	3.1
11	3-OMe	3.1
12	3,4-Me_2	2.8
13	3-Br	2.8
14	3,5-Me_2	2
15	4-$CH_2COCOOH$	5.4
16	3-$O(CH_2)_3OC_6H_5$	3.8
17	4-OEt	2.8
18	4-OMe	2.7
19	3-$CH_2COCOOH$	1
20	3-naphthamidine	4
21	4-CH_2OH	2.5

Other good QSAR models

Other good QSAR models are PA2-PA8 in which correlation coefficients are greater than 0.99. MLR equations of these QSAR models is given below-

1. PA2=-0.227833*ΔH_f+0.0604503*SI1-0.00101643*SA+0.112648*MR+1.57404
rCV^2=0.983872
r^2=0.993822

2. PA3=-0.225522*ΔH_f+0.0593765*SI1+0.113489*MR-0.000397534*MW+1.46335
rCV^2=0.984591
r^2=0.993801

3. PA4=-0.22734*ΔH_f-0.00946887*κ_0+0.063374*SI1+0.112128*MR+1.52938
rCV^2=0.983912

r^2=0.993788

4. PA5=-0.253275*ΔH_f+0.0285696*κ_0-0.00380474*SA+0.11604*MR+2.65177
rCV^2=0.988729
r^2=0.993604

5. PA6=-0.229885*ΔH_f+0.0593194*SI1+0.110888*MR+1.62364
rCV^2=0.986136
r^2=0.993561

6. PA7=-0.254434*ΔH_f-0.000898703*SA+0.115565*MR-0.00318718*
Log P+2.6318
rCV^2=0.985504
r^2=0.993527

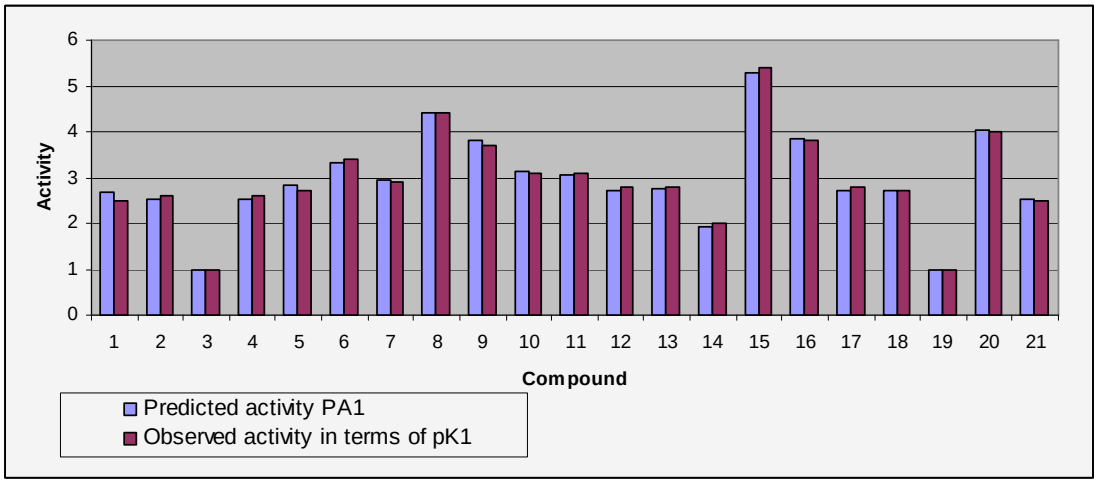
7. PA8=-0.254913*ΔH_f-0.000831554*SA+0.115485*MR-6.88344e-005*MW +2.64653
rCV^2=0.989347
r^2=0.993523

Table-2: Values of descriptors of benzamidine compounds and their activity in terms of pK_1 for thrombin inhibition

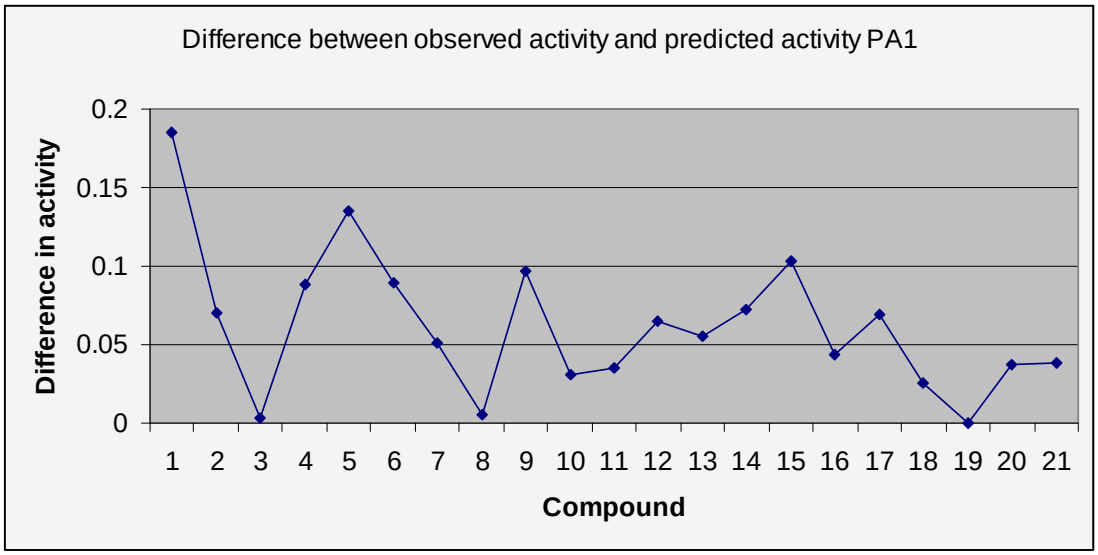
Benzamidine compound	Heat of Formation (kcal/mole)	Valence Connectivity Index (order 0, standard)	Shape Index (basic kappa, order 1)	Solvent Accessibility Surface Area	Molar Refractivity	Log P	Molecular Weight	Activity in terms of pK_1
1	22.550	6.150	10.039	90.652	50.876	1.465	165.151	2.500
2	22.409	6.041	10.127	86.390	49.034	0.882	150.180	2.600
3	24.853	5.887	8.124	79.635	41.803	1.885	134.180	1.000
4	22.409	6.150	10.127	90.637	49.012	1.465	165.151	2.600
5	22.253	6.242	10.224	89.629	51.432	1.116	164.163	2.700
6	21.897	8.981	10.905	113.527	54.998	3.498	210.278	3.400
7	21.765	4.964	10.418	75.062	51.485	1.418	120.154	2.900
8	19.641	5.464	11.877	81.130	59.114	0.634	135.168	4.400
9	20.134	8.274	11.987	104.830	55.110	3.102	196.251	3.700
10	21.123	7.334	10.613	93.141	51.822	1.682	163.222	3.100
11	21.621	6.295	10.613	86.857	52.012	1.165	150.180	3.100
12	22.189	6.809	10.921	88.062	50.123	2.352	148.207	2.800
13	22.342	6.851	10.321	90.339	50.975	2.209	199.050	2.800
14	23.321	6.809	9.543	89.427	46.187	2.352	148.207	2.000
15	18.112	7.858	12.112	106.143	64.065	0.586	206.201	5.400
16	20.153	11.211	11.293	141.222	56.098	2.833	270.330	3.800
17	22.097	7.002	10.321	94.703	50.234	1.507	164.207	2.800
18	22.250	6.295	10.224	86.695	50.465	1.165	150.180	2.700
19	24.851	7.858	8.571	107.858	41.119	0.586	206.201	1.000
20	20.261	11.836	11.488	139.502	57.913	3.182	289.336	4.000
21	22.551	6.041	10.030	86.680	49.446	0.882	150.180	2.500

Values of predicted activities PA2-PA8 are included in Table-3. Values of predicted activities are very close to the observed activities; hence, the predictive power of all above QSAR models is very good and can be utilized in the prediction of activity of any benzamidine compound. QSAR models in decreasing order of predictive powers are included in Table-4 alongwith the descriptors used to develop the model.

Graph-1: Graph between observed and predicted activities PA1 of benzamidines for thrombin inhibition



Graph-2: Graph between differences in observed activities and predicted activities PA1 of benzamidines for thrombin inhibition



QSAR models using single descriptor

QSAR model developed using molar refractivity possesses the value 0.983893 of correlation coefficient and its MLR equation is given by PA9=0.188668*MR-6.7899

rCV^2=0.979374

r^2=0.983893

Clearly, the descriptor molar refractivity alone is sufficient to predict the activity of any benzamidine compound and all the combinations in which molar refractivity is present form good QSAR models. Values of predicted activities PA9 of benzamidines are included in Table-3.

QSAR models developed using heat of formation and shape index separately have very good predictive powers. MLR equations of these models are given by-

PA10=-0.623281*ΔH_f+16.5595
rCV^2=0.968632
r^2=0.973055
and
PA11=0.961037*SI1-7.1196
rCV^2=0.868034
r^2=0.91362

Table-3: Values of predicted activities PA1-PA11 of benzamidine compounds in terms of pK_1

Compound	PA1	PA2	PA3	PA4	PA5	PA6	PA7	PA8	PA9	PA10	PA11
1	2.685	2.682	2.682	2.685	2.675	2.677	2.688	2.687	2.809	2.505	2.528
2	2.530	2.516	2.516	2.518	2.510	2.510	2.516	2.515	2.461	2.592	2.613
3	0.997	1.031	1.032	1.026	1.073	1.028	1.062	1.063	1.097	1.069	0.688
4	2.512	2.510	2.508	2.514	2.494	2.508	2.508	2.508	2.457	2.592	2.613
5	2.835	2.825	2.824	2.826	2.821	2.818	2.829	2.828	2.914	2.690	2.706
6	3.311	3.324	3.331	3.324	3.312	3.335	3.303	3.307	3.586	2.912	3.360
7	2.951	2.968	2.969	2.967	2.970	2.947	2.972	2.973	2.924	2.994	2.893
8	4.405	4.394	4.394	4.394	4.384	4.368	4.391	4.390	4.363	4.318	4.294
9	3.797	3.813	3.811	3.813	3.785	3.817	3.774	3.778	3.608	4.010	4.400
10	3.131	3.146	3.146	3.141	3.170	3.144	3.157	3.158	2.987	3.394	3.080
11	3.065	3.060	3.061	3.059	3.061	3.050	3.060	3.059	3.023	3.084	3.080
12	2.735	2.736	2.737	2.733	2.708	2.729	2.692	2.695	2.667	2.730	3.376
13	2.745	2.758	2.744	2.755	2.760	2.752	2.750	2.749	2.827	2.634	2.800
14	1.928	1.950	1.953	1.947	1.959	1.950	1.948	1.951	1.924	2.024	2.052
15	5.297	5.289	5.287	5.288	5.319	5.282	5.330	5.326	5.297	5.271	4.520
16	3.844	3.841	3.848	3.848	3.840	3.881	3.851	3.852	3.794	3.999	3.734
17	2.731	2.726	2.729	2.726	2.724	2.726	2.725	2.725	2.688	2.787	2.800
18	2.726	2.720	2.720	2.718	2.722	2.711	2.721	2.720	2.731	2.692	2.706
19	1.000	0.953	0.952	0.959	0.943	0.979	0.962	0.956	0.968	1.070	1.118
20	4.037	4.034	4.034	4.033	4.048	4.069	4.034	4.034	4.136	3.931	3.921
21	2.538	2.524	2.525	2.525	2.521	2.517	2.528	2.526	2.539	2.504	2.519

Values of predicted activities PA10 and PA11 are shown in Table-3. Any combination of descriptors in which either heat of formation or shape index is present is capable to form good QSAR model.

Table-4: Values of cross-validation coefficient, regression coefficient and descriptors used in QSAR models

Predicted Activity	rCV^2	r^2	Descriptors used in QSAR model
PA1	0.987299	0.994001	heat of formation, shape index order 1, molar refractivity and log P
PA2	0.983872	0.993822	heat of formation, shape index order 1, molar refractivity and solvent accessibility surface area
PA3	0.984591	0.993801	heat of formation, shape index order 1, molar refractivity and molecular weight
PA4	0.983912	0.993788	heat of formation, shape index order 1, molar refractivity and valence connectivity index order 0
PA5	0.988729	0.993604	heat of formation, solvent accessibility surface area, molar refractivity and valence connectivity index order 0
PA6	0.986136	0.993561	heat of formation, shape index order 1 and molar refractivity
PA7	0.985504	0.993527	heat of formation, solvent accessibility surface area and molar refractivity
PA8	0.989347	0.993523	heat of formation, molar refractivity, molecular weight and solvent accessibility surface area
PA9	0.979374	0.983893	molar refractivity
PA10	0.968632	0.973055	heat of formation
PA11	0.868034	0.913620	shape index order 1

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