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Quantitative structure-activity relationship of matrix metalloproteinase inhibitors based on topological descriptors

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ABSTRACT

Quantitative structure-activity relationship of nineteen matrix metalloproteinase inhibitors based on topological descriptors has been studied. For QSAR prediction, the 3D structures of the inhibitors have been drawn and their geometries have been optimized with the help of CAChe software by using PM3 hamiltonian. In developing QSAR models, topological descriptors used as independent variables and the observed biological activity in term of IC_{50} values as dependent variable. The Project Leader program associated with CAChe Pro of Fujitsu has been used for multiple linear regressions (MLR) analysis and ninety equations were developed. The study concluded that topological descriptors, connectivity index of first order in combination with valence connectivity index of zero order and kappa shape index of third order provide reliable QSAR model of rCV^2 (0.988954) and r^2 (0.996732). The model can be used to access the biological activity of the compounds of the same series.

Keywords: Matrix metalloproteinase inhibitors, QSAR, topological descriptors, PM3, CAChe software.

INTRODUCTION

Computational approaches applied in drug discovery and activity prediction often require molecular descriptors that reflect structural information and physico-chemical properties of chemicals. Predictive models in quantitative structure-activity relationship (QSAR)/quantitative structure-property relationship (QSPR) are developed by correlating the properties or activities with the structural information [1]. The structures themselves are difficult for use in the models. Therefore, the issue becomes how the structural information is represented in the models. Molecular descriptors are used to extract the structural information in the form of numerical or digital representation that is suitable for model development, serving as the bridge between the molecular structures and physico-chemical properties or biological activities of chemicals [2]. In this chapter, we present the QSAR study of MMP inhibitors using topological descriptors. The

term molecular topology [3, 4] (differing in its sense from molecular geometry) has become frequently used, although there may exist diverse viewpoints on the meaning of this concept. The key difference between topology and geometry is that in geometry the concepts of distances and angles are important, whereas in topology they are not. Instead, the essential topological properties are connectedness and continuity. Chemical structural formulas are good examples of topological models of molecules: the pattern of connectivity between atoms is essential, whereas the interatomic distances and angles are less important and may be neglected. The topological indices are molecular connectivity indices and shape index. Molecular connectivity [5-10] is a method of molecular structure quantization in which weight counts of substructure fragments are incorporated into numerical indices such as size, branching, unsaturation, hetero atom content and cyclicity which are encoded. Substructures for molecular skeleton are defined by the decomposition of the skeleton into fragments of atom (zero order, m=0) and one bond paths (first order, m=1). The calculation of indices begins with the reduction of the molecule to hydrogen-subpressed skeleton. The survey of the literatures also indicates that no QSAR model for prediction of activity of above inhibitors has been made with the help of following topological descriptors.

The molecular connectivity indices are symbolized by ${}^{m}\chi_{t}$. The connectivity index [9] is given by Eq.I

$$ {}^{m}\chi_{t} = \sum_{i=1}^{Ns} {}^{m}C_{i} \qquad \text{Eq.I} $$

and ${}^{m}C_{i}$ is given by Eq.II

$$ {}^{m}C_{i} = \prod_{k=1}^{m+1} (\delta_{k})^{-0.5} \qquad \text{Eq.II} $$

where m = 1 for first order, m = 3 for second order and m = 3 for third order.

Similarly the valence connectivity index [9] is given by Eq.III

$$ {}^{m}\chi_{t}^{V} = \sum_{i=1}^{Ns} {}^{m}C_{i}^{V} \qquad \text{Eq.III} $$

and ${}^{m}C_{i}^{V}$ is given by Eq.IV

$$ {}^{m}C_{i}^{V} = \prod_{k=1}^{m+1} (\delta_{k}^{V})^{-0.5} \qquad \text{Eq.IV} $$

where m = 1 for first order, m = 2 for second order and m = 3 for third order.

Kappa shape indices [11] are also a method of molecular structure quantization in which attributes of molecular shape are encoded into kappa values (${}^{1}K$ for first order, ${}^{2}K$ for second order, ${}^{3}K$ for third order). The first, second and third order kappa shape indices are given by Eq.V, VI, VII and VIII

$$ {}^{1}K = \frac{A(A-1)^{2}}{({}^{1}P_{i})^{2}} \qquad \text{Eq.V} $$

$$^2K = \frac{(A-1)(A-2)^2}{(^2P_i)^2} \qquad \text{Eq.VI}$$

$$^3K = \frac{(A-1)(A-3)^2}{(^3P_i)^2} \text{ if A is odd} \qquad \text{Eq.VII}$$

$$^3K = \frac{(A-3)(A-2)^2}{(^3P_i)^2} \text{ if A is even} \qquad \text{Eq.VIII}$$

where P_i is length of paths of bond length 'i' in the hydrogen suppressed molecule and 'A' is the number of non-hydrogen atoms in the molecule.

The partition coefficient is a ratio of concentrations of un-ionized compound between the two solutions. To measure the partition coefficient of ionizable solutes, the pH of the aqueous phase is adjusted such that the predominant form of the compound is un-ionized. The logarithm of the ratio of the concentrations of the un-ionized solute in the solvents is called log P. Normally one of the solvents chosen is water while the second is hydrophobic such as octanol [12]. Hence both the partition and distribution coefficient are measures of how hydrophilic ("water loving") or hydrophobic ("water fearing") a chemical substance is

$$\log P_{oct/wat} = \log\left(\frac{[solute]_{octanol}}{[solute]^{un-ionized}_{water}}\right) \qquad \text{Eq.IX}$$

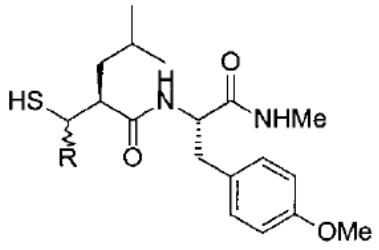
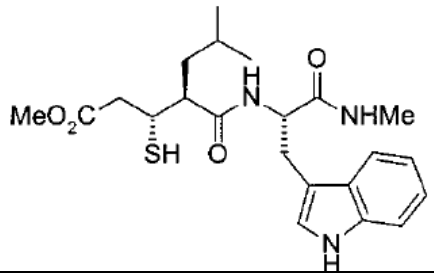
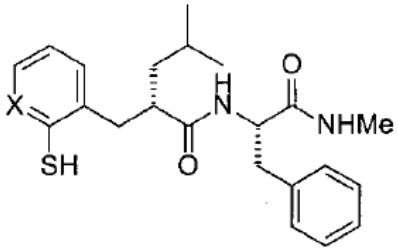
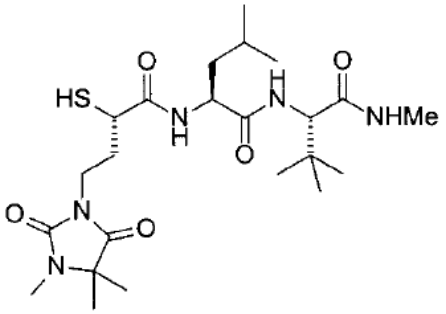
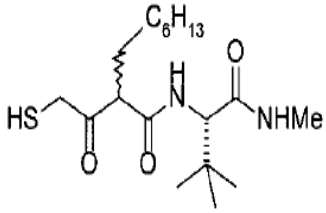
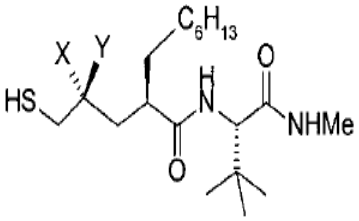
In medical practice, partition coefficients are useful for example in estimating distribution of drugs within the body. Hydrophobic drugs with high partition coefficients are preferentially distributed to hydrophobic compartments such as lipid bilayers of cells while hydrophilic drugs (low partition coefficients) preferentially are found in hydrophilic compartments such as blood serum.

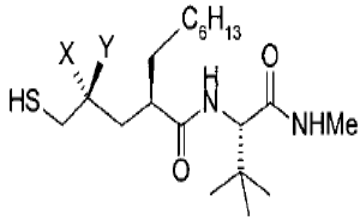
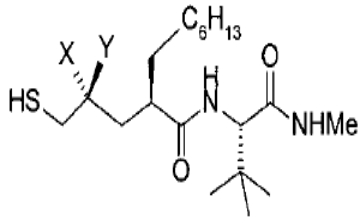
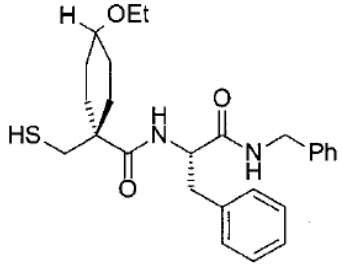
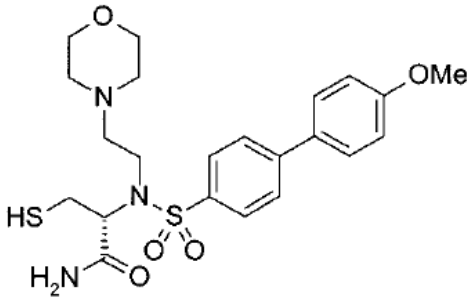
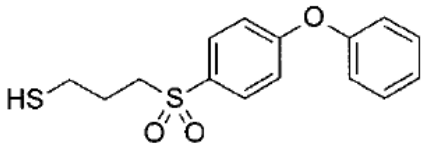
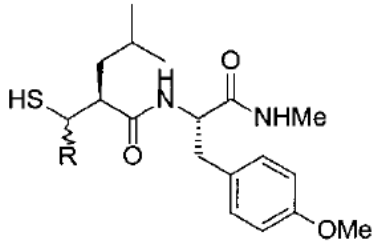
One way to provide a simple account for surface properties is to compute the solvent accessible surface area (SASA) [13]. SASA was first described by Lee and Richards in 1971 and is sometimes called Lee–Richard molecular surface. SASA is typically calculated using the rolling ball algorithm developed by Shrake and Ruplet in 1973. This approach provides a useful tool to gain insight into the over all extent of a hydrophobic region on a molecule or in the binding site of a protein, but lacks any real account of the particular atom types that make up the binding site or their positions relative to one another. In addition, it provides no means of assessing the shape of the binding because it only calculates the relative accessibility of the contributing atoms.

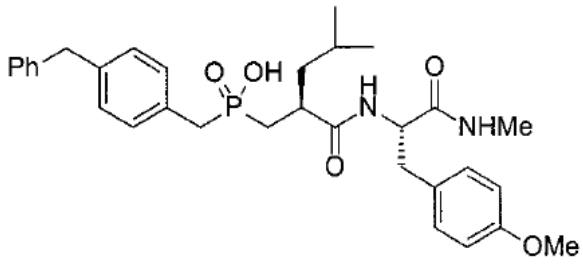
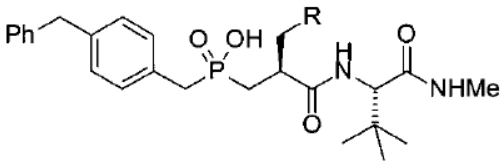
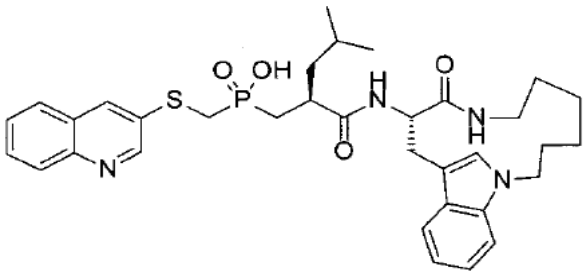
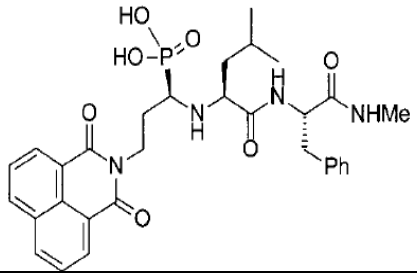
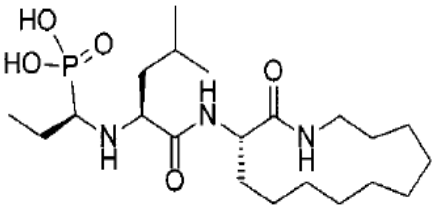
EXPERIMENTAL SECTION

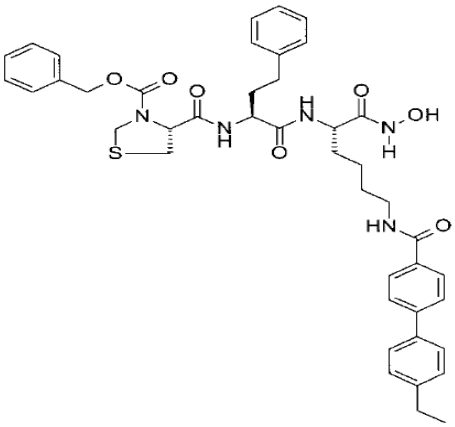
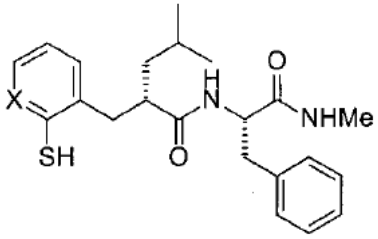
The study materials of this paper are MMP inhibitors [14] of group and are presented in Table-1. For QSAR prediction, the structures of all the above compounds have been drawn and their geometries [15] have been optimized with the help of CAChe softwareusing PM3 hamiltonian [16-18]. The values of above descriptors have been obtained from this software by solving the equations given below and the results are included in Table 2.

Table 1. List of compounds with their observed biological activity (OBA)

No.	Compound	IC_{50}
1	 R=H	360
2		2.5
3	 X=CH	30
4		25
5		15
6	 X, Y =O	10

7	 X=OH, Y=H	140
8	 X=H, Y=OH	5
9		823
10		70
11		1500
12	 R=Me	3000

13		270
14	 R=$PhCH_2$	690
15		5
16		20
17		180

18		40
19	 X=N	100

RESULTS AND DISCUSSION

Based on above topological descriptors [3-10], the QSAR model of nineteen MMP inhibitors has been presented in this chapter. The purpose of the study is to test the suitability of the topological descriptors as possible biological activity descriptor in the development of QSAR. In developing QSAR models, topological descriptors used as independent variables and the observed biological activity in term of IC_{50} values as dependent variable. The Project Leader program associated with CAChe Pro of Fujitsu [18] has been used for multiple linear regressions (MLR) analysis [19-21] and various equations were developed for prediction of activity. We have considered 90 QSAR models using MLR analysis with the help of various combinations of the descriptors shown in Table-3. The quantities of descriptors have been taken from Table-2. In order to explore the reliability of the proposed model, we have used regression coefficient (r^2) and cross-validation coefficient (rCV^2). Out of above 90 QSAR models only 48 models have predictive powers as these have higher values (»0.5) of both rCV^2 and r^2 coefficients, while the rest have either the value of rCV^2 («0.2) or r^2 («0.5) or both much lower than their optimum values.

Table 2. Calculation of various topological descriptors of the compounds with OBA

No.	log P	$^{1}\chi_{t}$	$^{0}\chi^{v}_{t}$	$^{1}K_{\alpha}$	σ	SASA	^{1}K	OBA (IC_{50})
1	1.730	24.130	20.697	23.040	3.864	209.403	8.963	360.000
2	1.062	24.140	20.688	25.262	3.857	209.112	7.277	2.500
3	4.748	24.144	20.691	24.271	3.845	209.355	8.346	30.000
4	0.361	24.146	20.697	31.030	3.850	209.354	8.000	25.000
5	4.653	24.147	20.692	24.000	3.857	209.353	9.333	15.000
6	3.456	24.147	20.694	23.000	3.857	210.223	9.778	10.000
7	2.687	24.138	20.691	24.000	3.867	209.371	9.926	140.000
8	2.687	24.149	20.689	24.000	3.857	209.352	9.926	5.000
9	4.544	24.112	20.702	26.602	3.876	209.471	8.033	823.000
10	1.445	24.141	20.693	26.602	3.858	212.321	7.014	70.000
11	2.816	24.047	20.713	16.372	3.888	209.570	5.058	1500.000
12	2.143	23.944	20.735	24.038	3.915	209.790	9.175	3000.000
13	5.386	24.149	20.692	34.490	3.863	209.390	12.265	270.000
14	6.216	24.098	20.700	33.501	3.871	209.452	11.656	690.000
15	4.028	24.144	20.689	33.366	3.857	209.352	8.844	5.000
16	3.729	24.148	20.689	35.847	3.857	209.354	9.301	20.000
17	3.516	24.133	20.692	28.033	3.861	209.377	12.000	180.000
18	6.746	24.146	20.688	47.056	3.858	209.357	15.455	40.000
19	4.117	24.139	20.690	24.271	3.859	209.365	8.346	100.000

Where $^{1}\chi_{t}$ is connectivity index (order 1, standard), $^{0}\chi^{v}_{t}$ is valence connectivity index (order 0, standard), $^{1}K_{\alpha}$ is shape index (Kappa alpha, order 1), σ is dipole moment, SASA is solvent accessible surface area and ^{3}K is shape index (basic kappa, order 3)

Table 3. Combination of descriptors for MLR analysis

Predicted Activity	First descriptor	Second descriptor	Third descriptor	Fourth descriptor	rCV^2	r^2
PAT1	1og P	Connectivity Index (order 1, standard)	—	—	0.97122	0.98186
PAT2	1og P	Valence Connectivity Index (order 0, standard)	—	—	0.99223	0.99502
PAT3	1og P	Shape Index (Kappa alpha, order 1)	—	—	-0.18491	0.08416
PAT4	1og P	Dipole Moment	—	—	0.87444	0.93750
PAT5	1og P	Solvent Accessible Surface Area	—	—	-44.51420	0.01117
PAT6	1og P	Shape Index (basic kappa, order 3)	—	—	-0.23449	0.03621
PAT7	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	—	—	0.98300	0.99460
PAT8	Connectivity Index (order 1, standard)	Shape Index (Kappa alpha, order 1)	—	—	0.95919	0.98065
PAT9	Connectivity Index (order 1, standard)	Dipole Moment	—	—	0.97796	0.98726
PAT10	Connectivity Index (order 1, standard)	Solvent Accessible Surface Area	—	—	-44.28130	0.98060
PAT11	Connectivity Index (order 1, standard)	Shape Index (basic kappa, order 3)	—	—	0.96389	0.98085
PAT12	Valence Connectivity Index (order 0,	Shape Index (Kappa alpha, order 1)	—	—	0.99248	0.99486
PAT13	Valence Connectivity Index (order 0,	Dipole Moment	—	—	0.98888	0.99377
PAT14	Valence Connectivity Index (order 0,	Solvent Accessible Surface Area	—	—	-44.26410	0.99685
PAT15	Valence Connectivity Index (order 0,	Shape Index (basic kappa, order 3)	—	—	0.99499	0.99576
PAT16	Shape Index (Kappa alpha, order 1)	Dipole Moment	—	—	0.86111	0.93727
PAT17	Shape Index (Kappa alpha, order 1)	Solvent Accessible Surface Area	—	—	-44.56500	0.08153

PAT18	Shape Index (Kappa alpha, order 1)	Shape Index (basic kappa, order 3)	—	—	-0.18280	0.08261
PAT19	Dipole Moment	Solvent Accessible Surface Area	—	—	-44.32400	0.93707
PAT20	Dipole Moment	Shape Index (basic kappa, order 3)	—	—	0.84560	0.93939
PAT21	Solvent Accessible Surface Area	Shape Index (basic kappa, order 3)	—	—	-44.58500	0.03607
PAT22	1og P	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0,	—	0.98727	0.99619
PAT23	1og P	Connectivity Index (order 1, standard)	Shape Index (Kappa alpha, order 1)	—	0.96098	0.98189
PAT24	1og P	Connectivity Index (order 1, standard)	Dipole Moment	—	0.97592	0.98783
PAT25	1og P	Connectivity Index (order 1, standard)	Solvent Accessible Surface Area	—	-44.28330	0.98186
PAT26	1og P	Connectivity Index (order 1, standard)	Shape Index (basic kappa, order 3)	—	0.96502	0.98188
PAT27	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Shape Index (Kappa alpha, order 1)	—	0.98804	0.99576
PAT28	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Dipole Moment	—	0.98454	0.99504
PAT29	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Solvent Accessible Surface Area	—	-44.26890	0.99716
PAT30	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Shape Index (basic kappa, order 3)	—	0.98973	0.99648
PAT31	Valence Connectivity Index (order 0,	Shape Index (Kappa alpha, order 1)	Dipole Moment	—	0.99084	0.99503
PAT32	Valence Connectivity Index (order 0,	Shape Index (Kappa alpha, order 1)	Solvent Accessible Surface Area	—	-44.26390	0.99785
PAT33	Valence Connectivity Index (order 0,	Shape Index (Kappa alpha, order 1)	Shape Index (basic kappa, order 3)	—	0.99387	0.99577
PAT34	Shape Index (Kappa alpha, order 1)	Dipole Moment	Solvent Accessible Surface Area	—	-44.32770	0.93742
PAT35	Shape Index (Kappa alpha, order 1)	Dipole Moment	Shape Index (basic kappa, order 3)	—	0.83343	0.94018
PAT36	Dipole Moment	Solvent Accessible Surface Area	Shape Index (basic kappa, order 3)	—	-44.32490	0.93991

PAT37	Connectivity Index (order 1, standard)	Shape Index (Kappa alpha, order 1)	Dipole Moment	—	0.97350	0.98739
PAT38	Connectivity Index (order 1, standard)	Shape Index (Kappa alpha, order 1)	Solvent Accessible Surface Area	—	-44.29220	0.98077
PAT39	Connectivity Index (order 1, standard)	Shape Index (Kappa alpha, order 1)	Shape Index (basic kappa, order 3)	—	0.95443	0.98085
PAT40	Connectivity Index (order 1, standard)	Dipole Moment	Solvent Accessible Surface Area	—	-44.28010	0.98742
PAT41	Connectivity Index (order 1, standard)	Dipole Moment	Shape Index (basic kappa, order 3)	—	0.97738	0.98728
PAT42	Connectivity Index (order 1, standard)	Solvent Accessible Surface Area	Shape Index (basic kappa, order 3)	—	-44.28310	0.98091
PAT43	Valence Connectivity Index (order 0,	Dipole Moment	Solvent Accessible Surface Area	—	-44.26420	0.99692
PAT44	Valence Connectivity Index (order 0,	Dipole Moment	Shape Index (basic kappa, order 3)	—	0.99448	0.99576
PAT45	Valence Connectivity Index (order 0,	Solvent Accessible Surface Area	Shape Index (basic kappa, order 3)	—	-44.26290	0.99810
PAT46	1og P	Valence Connectivity Index (order 0, standard)	Shape Index (Kappa alpha, order 1)	—	0.99284	0.99543
PAT47	1og P	Valence Connectivity Index (order 0, standard)	Dipole Moment	—	0.99159	0.99512
PAT48	1og P	Valence Connectivity Index (order 0, standard)	Solvent Accessible Surface Area	—	-44.26380	0.99750
PAT49	1og P	Valence Connectivity Index (order 0, standard)	Shape Index (basic kappa, order 3)	—	0.99393	0.99590
PAT50	1og P	Shape Index (Kappa alpha, order 1)	Dipole Moment	—	0.78787	0.93753
PAT51	1og P	Shape Index (Kappa alpha, order 1)	Solvent Accessible Surface Area	—	-44.68050	0.08420
PAT52	1og P	Valence Connectivity Index (order 0, standard)	Shape Index (Kappa alpha, order 1)	Shape Index (basic	0.99293	0.99591
PAT53	1og P	Dipole Moment	Solvent Accessible Surface Area	—	-44.32980	0.93778
PAT54	1og P	Dipole Moment	Shape Index (basic kappa, order 3)	—	0.81041	0.93952
PAT55	1og P	Solvent Accessible Surface Area	Shape Index (basic kappa, order 3)	—	-44.64750	0.03641

PAT56	Shape Index (Kappa alpha, order 1)	Solvent Accessible Surface Area	Shape Index (basic kappa, order 3)	—	-44.60630	0.08261
PAT57	1og P	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0,	Shape Index (Kappa	0.98859	0.99644
PAT58	1og P	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0,	Dipole Moment	0.98728	0.99635
PAT59	1og P	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0,	Solvent Accessible Surface	-44.26730	0.99790
PAT60	1og P	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0,	Shape Index (basic	0.98895	0.99673
PAT61	1og P	Connectivity Index (order 1, standard)	Shape Index (Kappa alpha, order 1)	Dipole Moment	0.96791	0.98783
PAT62	1og P	Connectivity Index (order 1, standard)	Shape Index (Kappa alpha, order 1)	Solvent Accessible Surface	-44.29310	0.98190
PAT63	1og P	Connectivity Index (order 1, standard)	Shape Index (Kappa alpha, order 1)	Shape Index (basic	0.95444	0.98189
PAT64	1og P	Connectivity Index (order 1, standard)	Dipole Moment	Solvent Accessible Surface	-44.28020	0.98787
PAT65	1og P	Connectivity Index (order 1, standard)	Dipole Moment	Shape Index (basic	0.97443	0.98799
PAT66	1og P	Connectivity Index (order 1, standard)	Solvent Accessible Surface Area	Shape Index (basic	-44.28410	0.98189
PAT67	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Shape Index (Kappa alpha, order 1)	Dipole Moment	0.98917	0.99602
PAT68	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Shape Index (Kappa alpha, order 1)	Solvent Accessible Surface	-44.26720	0.99808
PAT69	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Shape Index (Kappa alpha, order 1)	Shape Index (basic	0.98950	0.99650
PAT70	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Dipole Moment	Solvent Accessible Surface	-44.26860	0.99728
PAT71	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Dipole Moment	Shape Index (basic	0.98991	0.99652
PAT72	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Solvent Accessible Surface Area	Shape Index (basic	-44.26630	0.99832
PAT73	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Dipole Moment	Solvent Accessible Surface	-44.26440	0.99787
PAT74	Connectivity Index (order 1, standard)	Valence Connectivity Index (order 0, standard)	Dipole Moment	Shape Index (basic	0.99241	0.99578

PAT75	Valence Connectivity Index (order 0,	Shape Index (Kappa alpha, order 1)	Solvent Accessible Surface Area	Shape Index (basic	-44.26340	0.99818
PAT76	Shape Index (Kappa alpha, order 1)	Dipole Moment	Solvent Accessible Surface Area	Shape Index (basic	-44.33380	0.94083
PAT77	1og P	Valence Connectivity Index (order 0, standard)	Shape Index (Kappa alpha, order 1)	Dipole Moment	0.98837	0.99552
PAT78	1og P	Valence Connectivity Index (order 0, standard)	Shape Index (Kappa alpha, order 1)	Solvent Accessible Surface	-44.26370	0.99797
PAT79	1og P	Valence Connectivity Index (order 0, standard)	Shape Index (Kappa alpha, order 1)	Shape Index (basic	-0.23329	0.24258
PAT80	1og P	Valence Connectivity Index (order 0, standard)	Dipole Moment	Solvent Accessible Surface	-44.26380	0.99751
PAT81	1og P	Valence Connectivity Index (order 0, standard)	Dipole Moment	Shape Index (basic	0.99238	0.99591
PAT82	1og P	Shape Index (Kappa alpha, order 1)	Dipole Moment	Solvent Accessible Surface	-44.36200	0.93781
PAT83	1og P	Shape Index (Kappa alpha, order 1)	Dipole Moment	Shape Index (basic	0.78211	0.94025
PAT84	1og P	—	—	—	-0.04297	0.01116
PAT85	Connectivity Index (order 1, standard)	—	—	—	0.97262	0.98044
PAT86	Valence Connectivity Index (order 0,	—	—	—	0.94976	0.95997
PAT87	Shape Index (Kappa alpha, order 1)	—	—	—	-0.04885	0.08148
PAT88	Dipole Moment	—	—	—	0.88058	0.93697
PAT89	Solvent Accessible Surface Area	—	—	—	-44.52750	0.00093
PAT90	Shape Index (basic kappa, order 3)	—	—	—	-0.15713	0.03578

Out of 48 models the top five models are as below:

I. Top First QSAR model: The top first QSAR model is obtained when multi linear regression analysis is done by taking log P as first descriptor, connectivity index (order 1, standard) as second descriptor, valence connectivity index (order 0, standard) as third descriptor and shape index (basic kappa, order 3) as fourth descriptor. The regression equation is given below:

PAT60=8.95699×log P-2849.41×$^{1}\chi_{t}$ +52561.1×$^{0}\chi^{v}_{t}$ +10.2767×^{3}K -1.01876e+006
rCV^2=0.988954
r^2=0.996732 Eq.X

The values of the predicted activity PAT60 of all the compounds are listed in the Table-15.

II. Top Second QSAR model: The top second QSAR model is obtained when multi linear regression analysis is done by taking connectivity index (order 1, standard) as first descriptor, valence connectivity index (order 0, standard) as second descriptor, dipole moment as third descriptor and shape index (basic kappa, order 3) as fourth descriptor. The regression equation is given below:

PAT71=-2725.99×$^{1}\chi_{t}$ +51505.1×$^{0}\chi^{v}_{t}$ +1204.77× σ +13.9663×^{3}K -1.00454e+006
rCV^2=0.989905
r^2=0.99652 Eq.XI

The values of the predicted activity PAT71 of all the compounds are listed in the Table-18

III. Top Third QSAR model: The top third QSAR model is obtained when multi linear regression analysis is done by taking connectivity index (order 1, standard) as first descriptor, valence connectivity index (order 0, standard) as second descriptor, Shape index (Kappa alpha, order 1) as third descriptor and shape index (basic kappa, order 3) as fourth descriptor. The regression equation is given below:

PAT69=-2643.72×$^{1}\chi_{t}$ +53518.2×$^{0}\chi^{v}_{t}$ +0.681296×$^{1}K_{\alpha}$ +13.3094×^{3}K -1.04354e+006
rCV^2=0.9895
r^2=0.9965 Eq.XII

The values of the predicted activity PAT69 of all the compounds are listed in the Table-17.

IV. Top Fourth QSAR model: The top fourth QSAR model is obtained when multi linear regression analysis is done by taking connectivity index (order 1, standard) as first descriptor, valence connectivity index (order 0, standard) as second descriptor and shape index (basic kappa, order 3) as third descriptor. The regression equation is given below:

PAT30=-2644.43×$^{1}\chi_{t}$ +53453×$^{0}\chi^{v}_{t}$ +14.7358×^{3}K -1.04217e+006
rCV^2=0.989725
r^2=0.996484 Eq.XIII

The values of the predicted activity PAT30 of all the compounds are listed in the Table-9.

Table 4. Predicted activities of compounds as obtained by Eq.X to Eq.XIV

No.	PAT60	PAT71	PAT69	PAT30	PAT57	OBA
1	399.138	413.208	412.575	415.135	382.933	360.000
2	-29.375	-15.545	-18.350	-19.249	-21.184	2.500
3	26.459	-3.293	8.273	9.542	36.047	30.000
4	-26.309	-11.687	-1.311	-5.136	-18.167	25.000
5	14.537	4.745	0.401	3.277	12.467	15.000
6	4.158	6.690	1.334	5.531	-9.738	10.000
7	134.251	152.689	139.592	143.189	117.692	140.000
8	-11.130	-0.957	-5.603	-1.872	-28.173	5.000
9	782.462	773.329	772.362	770.790	793.779	823.000
10	187.535	194.343	199.430	196.971	198.177	70.000
11	1493.498	1483.438	1479.923	1480.413	1510.925	1500.000
12	2984.887	2992.890	2995.011	2994.785	2976.112	3000.000
13	201.436	199.298	200.025	199.743	191.162	270.000
14	762.220	746.129	747.902	746.947	764.307	690.000
15	4.006	-2.442	-0.407	-4.598	25.283	5.000
16	7.301	5.829	9.699	4.452	26.599	20.000
17	210.457	220.252	217.041	220.810	185.372	180.000
18	44.697	40.331	44.894	40.863	39.623	40.000
19	95.271	86.254	82.709	83.908	102.283	100.000

V. Top Fifth QSAR model: The top fifth QSAR model is obtained when multi linear regression analysis is done by taking log P as first descriptor, connectivity index (order 1, standard) as second descriptor, valence connectivity index (order 0, standard) as third descriptor and Shape index (Kappa alpha, order 1) as fourth descriptor. The regression equation is given below:

$PAT57=13.3015\times \log P-3108.01\times {}^{1}\chi_{t}+51473.2\times {}^{0}\chi^{v}_{t}+2.14395\times {}^{1}K_{\alpha}-989982$
rCV^2=0.988591
r^2=0.99644 Eq.XIV

The values of the predicted activity PAT57 of all the compounds are listed in the Table-15.

In order to explore the reliability of the proposed model we have used regression coefficient (r^2) and cross-validation coefficient (rCV^2). The regression summary of these models is as shown below

QSAR	rCV^2	r^2	Variable Used	Variable Count
PAT60	0.988954	0.996732	log P, ${}^{1}\chi_{t}$, ${}^{0}\chi^{v}_{t}$, ${}^{3}K$	4
PAT71	0.989905	0.996520	${}^{1}\chi_{t}$, ${}^{0}\chi^{v}_{t}$, σ, ${}^{3}K$	4
PAT69	0.989500	0.996500	${}^{1}\chi_{t}$, ${}^{0}\chi^{v}_{t}$, ${}^{1}K_{\alpha}$, ${}^{3}K$,	4
PAT30	0.989725	0.996484	${}^{1}\chi_{t}$, ${}^{0}\chi^{v}_{t}$, ${}^{3}K$	3
PAT57	0.988591	0.99644	log P, ${}^{1}\chi_{t}$, ${}^{0}\chi^{v}_{t}$, ${}^{1}K_{\alpha}$	4

From the above study it is clear that the QSAR model PAT30 has highest predictive powers as it has highest values of rCV^2 (0.988954) and r^2 (0.996732) among the five QSAR models

CONCLUSION

The study concluded that topological descriptors, connectivity index of first order in combination with valence connectivity index of zero order and kappa shape index of third order provide reliable QSAR model of rCV^2 (0.988954) and r^2 (0.996732). The model can be used to access the biological activity of the compounds of the same series.

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