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A 3D QSAR Analysis of Some Antiinflammatory 3,5-di-*tert*-Butyl-4-hydroxystyrene Derivatives

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In search of new potent NSAIDs, it was considered of interest to investigate a 3D QSAR analysis of some antiinflammatory 3,5-di-*tert*-butyl-4-hydroxystyrene derivatives. To investigate relationship molecular shape analysis has been used as a 3D QSAR formalism. Molecular modelling software Cerius2 was used to study 3D QSAR. The analysis resulted in the following 3D QSAR equation which can be used for prediction of antiinflammatory activity of new molecules.
log (BA) = 0.827(0.283) Fo + 0.007 (0.002) Energy - 0.489(0.156) ROG - 0.114(0.038) DIPOLE + 3.756 n=17
r^2=0.762 r=0.873 f=9.604 s=0.197 press=0.921 cvr^2=0.622 bsr^2=0.764

The NSAIDs represent an extremely interesting category of substances as evident from the active research going on in this area in numerous laboratories all over the world and the continuous demand for new agents for the therapeutic use, with high margin of safety and freedom from normally associated gastrointestinal side effects, notably dyspepsia, complications of peptic ulcers and renal toxicity of known antiinflammatory drugs. Following these considerations and in continuation of our search to find new potent NSAIDs[1], it was thought of importance to study a 3D QSAR analysis of some antiinflammatory 3,5-di-*tert*-butyl-4-hydroxystyrene derivatives reported Kastsumi *et al*[2]. These derivatives are structurally similar to curcumin, dehyrozingerone, ferulic acid, sinapic acid and chalcones, which have shown antiinflammatory activity[3]. All these compounds are derivatives of styryl carbonyl moiety. To investigate relationship molecular shape analysis has been used as a 3D QSAR formalism[4]. This study may contribute to a better understanding of the relationship between structure and antiinflammatory activity[5].

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EXPERIMENTAL

The antiinflammatory activity data were taken from Katsumi *et al*[2]. The biological activity of the compounds were expressed as per cent inhibition of carageenan-induced paw edema in the rat cased by 50 mg/kg of drug (CPE). These data were converted to log of per cent paw edema inhibition per millimole of drug per kilogram of body weight (log (BA).

For molecular modelling and calculation of various descriptors, different modules provided in molecular modelling software Cerius2 version 3.5 were used[6]. The structures of the compounds (1-17 in Table 1) were build using the molecular sketching facilities provided in the molecular modeling environment of Cerius2. The energy of the molecules was calculated using universal force field[7]. The energy of the molecules was minimized using conjugate gradient algorithm[8]. The minimization terminates where the root mean square (RMS) force on the model is less than 0.0001 kcal/mole/°A.

For molecular shape analysis following steps were followed:

Generate conformers:

After energy minimization, conformational analysis of each molecule was done using Boltzmann Jump method to select most stable conformers. Various possible conformations of each molecule were calculated by setting a 5 kcal/mole cutoff and the limit for maximum number of conformations which can be generated to 300.

Select a candidate shape reference compound:

The shape reference compound is the molecule that was used when the shape descriptors were calculated for all molecules. The most active compound in the series (compound 2, CPE=42) was selected as the 'shape reference compound.'

Perform pairwise molecular superpositions:

Alignment of the other molecules on the shape reference compound was done using least square fitting, with atom specified by automatic atom matching algorithm.

Measure molecular shape commonality:

shape descriptors Common overlap steric volume (COSV), Non-common overlap steric volume (NCOSV), Common overlap volume ratio (Fo), RMS to shape reference (shape RMS) and Difference volume (DIFFV) were calculated to compare the properties that two molecules have in common and to measure molecular shape commonality.

Determination of other molecular features:

Various other descriptors were also calculated to add other properties to QSAR like desolvation free energy for water (FH2O)[9,10], desolvation free energy for octanol (FOCT)[9,10], log of partition coefficient (LOGP)[9,10], molecular refractivity (MR)[10,11], molecular surface area (AREA)[12], radius of gyration (ROG), molecular density (DENSITY)[12], molecular weight (MW)[12], molecular volume (VM)[12], principal moment of inertia (PMI)[13], principal moment of inertia-x component (PMIX)[13], principal moment of inertia-y component (PMIY)[13], principal moment of inertia-z component (PMIZ)[13], number of rotatable bonds (ROTBONDS)[10], sum of atomic polariziblities (APOL)[14], dipole moment (DIPOLE)[15,16], dipole moment-x component (XDIP)[15,16], dipole moment-y component (YDIP)[15,16], dipole moment-z component (ZDIP)[15,16], energy of highest occupied molecular orbital (HOMO)[17], energy of lowest unoccupied molecular orbial (LUMO)[17], partial atomic charges[18], selected conformation energy (Energy), lowest conformation energy (LowEne) and difference between Energy and LowEne (Epenalty). The HOMO, LUMO and dipole moments calculated using MOPAC method. Partial atomic charges were calculated using charge equilibration (QEq) method[18]. Values of only those descriptors which found place in the equations are given in Table 2.

Construction of a trial QSAR:

The final step in MSA is to construct a trial QSAR. To generate QSAR equations stepwise multiple parameter regressions analysis method was performed using software SMRAILS[19]. The following statistical measures were used : the number of samples in the regression (n), coefficient of correlation (r), coefficient of determination (r^2), standard deviation (s), F-test for statistical significance (F), predicted sum of squared residuals (press), cross-validated r^2 (cvr^2) (leave-one out method), bootstrap r^2 (bsr^2).

RESULTS AND DISCUSSION

Following equation was generated by subjecting all calculated shape descriptors and log(BA) of compounds (1-17) to stepwise multiple parameter regression analysis:

log (BA) =0.638(0.516) Fo - 0.29(0.23) shape RMS + 0.002(0.003) DIFFV + 1.657 [1]

n=17, r=0.663, r^2=0.440, F=3.410, s=0.324, press=2.380, cvr^2=0.024, bsr^2=0.447

By subjecting all the calculated shape descriptors alongwith other molecular descriptors following equation was generated:

log(BA)=0.827(0.283) Fo + 0.007 (0.002) Energy - 0.489 (0.156) ROG
- 0.114(0.038) Dipole + 3.756 [2]

n=17, r=0.873, r^2=0.762, F=9.604, s=0.197, press=0.921, cvr^2=0.622, bsr^2=0.764

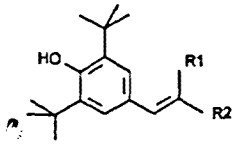
By subjecting all the calculated shape descriptors except Fo alongwith other molecular descriptors following equation was generated:

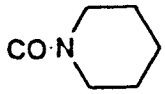
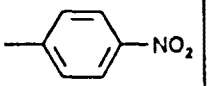
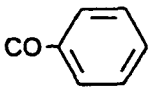
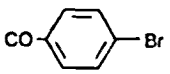
log(BA) =-0.0031(0.0008) NCOSV+0.0087(0.0029) Energy - 0.0399 (0.0253) XDIP
-0.064(0.042) DIPOLE + 2.245 [3]

n=17, r=0.813, r^2=0.661, F=5.839, s=0.263, press=1.597, cvr^2=0.345, bsr^2=0.666

To investigate other relationships shape descriptors

TABLE 1: CARRAGEENAN-INDUCED EDEMA DATA FOR 3,5-DI-*TERT*-BUTYL-4-HYDROXYSTYRENES USED IN THIS STUDY



Compound	R1	R2	CPE[a]	BA[b]	Observed log(BA)	Predicted log(BA) Equation 2	Predicted log(BA) Equation 4
1	COOH	CH_2CH_2OH	37	237.12	2.375	2.140	1.991
2	$COOCH_3$	CH_2CH_2OH	42	280.94	2.449	2.543	2.422
3	COOH	C_2H_5	13	79.15	1.898	2.151	2.025
4	$COOC_2H_5$	$COCH_3$	28	194.02	2.288	1.974	1.961
5	$CONH_2$	H	5	27.54	1.440	1.925	1.916
6	$CONHC_4H_9$	H	3	19.89	1.299	1.300	1.324
7	$CONH_2$	CN	31	186.25	2.270	2.194	2.381
8		CN	8	58.96	1.771	1.822	2.026
9	$CONHCONH_2$	CN	3	20.61	1.314	1.383	1.340
10	CN	CN	28	158.14	2.199	2.122	2.179
11		CN	5	37.85	1.578	1.683	1.789
12	SO_2CH_3	CN	18	120.75	2.082	1.907	1.966
13	$COCH_3$	H	35	192.08	2.283	2.125	2.220
14	$COCH_3$	CH_3	24	138.45	2.141	2.259	2.269
15		H	10	67.29	1.828	1.825	1.848
16		H	3	24.92	1.397	1.354	1.451
17	NO_2	H	17	94.30	1.975	1.840	1.878

[a] percentage inhibition of carrageenan-induced rat paw edema by 50 mg/kg oral dose

[b] percentage inhibition of carrageenan-induced rat was paw edema by millimole/kg oral dose

were not considered in the analysis and only other molecular descriptors were subjected to stepwise multiple parameter regression analysis, following equation was generated:

log(BA)=-0.0012(0.0003) PMIY + 0.009(0.003) Energy - 0.146 (0.044) DIPOLE

-0.514(0.293) HOMO - 1.522 [4]

TABLE 2: CALCULATED VALUES OF THE DESCRIPTORS FOR COMPOUNDS 1-17

Compound	Energy	XDIP	HOMO	ROG	DIPOLE	PMI	PMIY	DIFFV	Shape	RMS	NCOSV Fo
1	22.048	-2.5038	-8.9134	4.1995	4.179	942.892	547.045	-9.208	0.143	26.178	0.919
2	36.211	-4.6104	-8.8448	4.3181	1.426	1026.621	599.687	8.254	0.000	8.254	0.976
3	18.934	0.7302	-8.8385	4.0939	4.423	779.174	433.753	-17.915	0.131	22.482	0.929
4	-10.759	-2.0123	-9.0738	4.3646	2.451	1046.847	605.027	17.906	0.167	50.771	0.855
5	-23.814	-4.1355	-8.9496	3.9774	3.147	744.484	406.983	-48.463	1.089	64.632	0.773
6	-1.631	1.7584	-8.9306	5.3331	3.406	1598.309	1027.312	18.999	0.992	117.99	0.667
7	-6.850	-4.2167	-9.1960	3.9925	1.468	810.653	456.775	-31.628	1.067	80.945	0.732
8	44.289	0.1600	-9.1505	4.8659	3.139	1437.862	912.810	42.213	1.125	151.706	0.596
9	-53.189	-6.9008	-9.2707	4.4923	3.188	1280.237	799.089	-1.328	1.053	107.087	0.677
10	13.096	-3.0868	-9.2877	3.7350	5.075	699.509	374.910	-44.523	0.336	51.818	0.821
11	35.378	2.9363	-9.2908	4.0264	6.883	1120.883	648.600	33.055	0.739	174.219	0.524
12	0.186	-3.6987	-9.0708	3.9679	4.011	853.383	492.272	-10.801	0.599	108.997	0.662
13	0.355	-4.1516	-8.9174	4.0689	2.442	744.827	406.573	-43.490	1.101	67.371	0.767
14	19.089	-4.1014	-8.9049	4.0734	2.965	782.172	437.282	-27.187	1.283	47.110	0.846
15	39.164	-1.5584	-8.9208	4.7417	3.628	1382.492	864.981	10.917	1.034	124.510	0.638
16	37.623	-1.7655	-9.9870	4.8387	2.624	2604.952	1762.891	29.710	1.101	362.958	0.000
17	6.538	-9.1156	-9.4738	3.7810	7.100	749.107	409.551	-55.640	0.458	43.841	0.842

n=17, r=0.855, r^2=0.731, F=8.152, s=0.209, press=0.990, cvr^2=0.594, bsr^2=0.733

By subjecting all the calculated molecular descriptors except PMIY, following equation was generated: log (BA) = -0.0009(0.0002) PMI + 0.009(0.003) Energy - 0.143 (0.045) DIPOLE

-0.501 (0.294) HOMO - 1.256 [5]

n=17, r=0.852, r^2=0.726, F=7.941, s=0.211, press=0.994, cvr^2=0.592, bsr^2=0.728

Equation 1 having poor coefficient of determination (r^2=0.440) shows that only shape descriptors are not able to explain the variation of antiinflammatory activity. Out of equations 2-5, it can be seen that equation 2 with shape descriptors alongwith all other calculated molecular descriptors is statistically more significant and it has a good prediction capability than the latter equations (4 and 5) without shape descriptors. It was also found that the independent variables in equation 2 are not significantly cross-correlated. Predicted and observed log (BA) for equation 2 and 4 can be seen in Table 1.

The study shows that shape descriptor common overlap volume ratio (Fo) alongwith other molecular descriptors conformation energy (Energy). radius of gyration (ROG) and dipole moment (DIPOLE) plays an important role in determining oral antiinflammatory activity. This also indicates that new molecules should be designed, considering the shape of reference compound and optimizing other molecular descriptors which affects spatial charge and mass distribution.

As the objective of this study is t derive a model that is optimally predictive, equation 2 was selected on the basis of its statistical significance i.e. having highest coefficient of determination (r^2 = 0.762), F-test value (F=0.873), lowest standard deviation (s=0.197) and predicted sum of squared residuals (press = 0.921) and also cross-validated r^2 (cvr^2=0.622) near to coefficient of determination (r^2=0.762). So equation 2 can be used for theoretical prediction of antiinflammatory activity of the new molecules.

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