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Quantitative Structure–Activity Relationship Studies on Benzylideneaminoxy Propionic Acid Anti-Inflammatory Agents

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A series of lipooxygenase inhibitors were selected and subjected to QSAR analysis using silicon graphics work station and cerius [2] software. The physicochemical parameters generated were converted to mathematical equation using stepwise multiple equations. Then genetic function approximation is also performed. The statistical parameters were satisfactory. The results indicated that contributing parameters are Connolly surface, Radius of gyration and molecular refractivity.

Keyword: Lipooxygenase Inhibitors, Stepwise Multiple Regression, Genetic Function Approximation.

1. Introduction

Non steroidal anti inflammatory agents (NSAIDS) are widely used in the treatment and management of pain and inflammation. These compounds inhibit the enzyme lipooxygenase and thus prevent the formation of prostaglandins at elevated levels causing inflammation [1]. Thus our main objective is to design specific inhibitors of lipooxygenase in the hope that these molecules may be further explored as powerful non ulcerogenic anti inflammatory agents. Forty five series of 5-Lipo Oxygenase inhibitors were selected from the literature and one series was selected for analysis based on the following facts. A wide spread biological activity, Wide variation in structure produced little variation in activity, Small variation in structure produces wide variation in activity, No QSAR have been reported.This study may help for the design and synthesis of better selective cox inhibitor

2. Materials and Methods

Structures of all compounds of series were sketched using 3D sketcher, module of Ceruis[2] . The energy calculations were done using the universal force field. All the structure were minimized by standard minimizer algorithms. In minimization process first steepest Descent (SD) method [2] was used to eliminate the bad contacts after which more accurate minimizing methods like Conjugate Gradient (CG) and Truncated Newton – Raphson (N-R) methods were used. Conformations for each compound were generated and its analysis was done using Boltzmann jump [3] method. The number of conformations were kept around 300 i.e. generate not more than 300 conformer option has been used. Further geometry of stable conformation of each compound was optimized using a semi empirical quantum mechanics module, MOPAC version 6.0 [4]. The PM-3 Hamiltonian has been used. The energies of optimized conformers of series are shown in study table 1. These

conformers were used for calculating physico chemical parameters. Semi- em-pirical calculations were performed using more accurate method: MOPAC. The PM-3 Hamiltonian of MOPAC module has been used for calculating atomic charges and electon densities on various atoms. The Connolly Surface (solvent accessible area) of the lowest energy conformer of each molecule [5] was computed and viewed on SGIIRIS Indigo using the program Cerius^2 (Version 3.5). The other 2D and 3D parameters for all compounds were calculated by standard procedure given in QSAR + module of Cerius^2. The correlation between biological activity and physico – chemical parameters was found through stepwise multiple regression analysis, also called Stepwise predicted Activity [6]. The Genetic function Approximation GFA was also used later, for getting more improved QSAR equation. Biological activity of compounds is expressed in the reference as percent inhibition of carrageen paw edema (CPE) by oral route at doses 50 mg/kg of body weight . The reported biological activity has been shown in Table No.1. Firstly step wise multiple regression analysis was performed using all the parameters. The cut off point was given for F test and the parameters having higher F test than the cut off were selected and included in the equations. Then Genetic function approximation was performed.

3. Results and Discussion

3.1 Step Wise Regression:

Equation 1:

BA = -556.639 - .6023*Connolly S + 60.4481 * Rad of Gyration + 14.2995 * MolRef + 27.0498*LUMO – 55.9255* HOMO PM_3 .

$r^2 = 0.897$, $Cvr^2 = 0.806$, n=20, F test = 24.379.

Since r^2 value is low, to improve this the electronic parameters, LUMO and HOMO- PM^3 are deleted and following equation was generated.

Equation 2:

BA = 94.3712-2.50689* Connolly + 27.8015 * Rad of Gyration + 6.96716*MolRef.

$r^2 = 0.726$, $Cvr^2 = 0.562$, n=20, F test = 14.125

This equation does not have any improved effect. Instead, the value of r^2 is decreased. To improve this equation, along with thermodynamic parameter, the electronic parameter Dipole – Y is included and following equation was obtained.

Equation 3:

BA = 74.2367 – 3.46101 * ConnollyS – 6.09089 * Dipole Y +42.9096 * Rad of Gyration + 10.2111 * MolRef

$r^2 = 0.840$ CV $r^2 = 0.699$, n= 20, F test = 18.591

The electronic parameter Dipole-Y is replaced by the shape parameter, DIFFV and following equation was got.

Equation 4:

BA = 660.058 – 5.0945 * ConnollyS + 42.3599 * Rad of Gyration+ 4.0539 * MolRef + 3.38212 * DIFFV

$= 0.832$, CV $r^2 = 0.692$, n= 20, F test = 18.591

The Parameter DIFFV is replaced by another shape parameter Vm and following equation was generated.

Equation 5:

BA = 124.533 – 5.0945 * ConnollyS + 42.3599 * Rad of Gyration+ 3.38212 * Vm + 4.059 * MolRef

$r^2 = 0.832$, CV $r^2 = 0.692$, n= 20, F test = 18.591

The conformational Parameter PMI-X is included along with Dipole- Y and NC-charge PM3 to get the following equation.

Equation 6:

BA = 112.037 – 375.666 * NC Charge PM3 – 6.52727* Connollys – 3.67641 * Dipole – Y + 109.154 * Rad of Gyration + 2.7135. vm + 0.423562 * PMI - X + 6.91401 * MolRef.

$r^2 = 0.952$, CV $r^2 = 0.0844$, n= 20, F test = 34.142.

Then genetic function approximation (GFA) analysis was done to get the following two equations.

3.2 GFA Regression:

Equation 1:

BA = 74.2367 + 3.46101 * ConnollyS + 10.2111 * MolRef +42.9096 * Rad of Gyration – 6.09089 * Dipole - Y

$r^2 = 0.840$, CV $r^2 = 0.699$, n= 20, F test = 19.671

Equation 2:

BA = 118.778 - 0.22681 * HF PM3 – 5.55748 *ConnollyS + 11.722 * Rad of Gyration + 11.8484 * MolRef + 0.480296 * PMI - X

$r^2 = 0.898$, CV $r^2 = 0.781$, n= 20, F test = 24.694

3.3 The Generated QSAR equationdepict

that Connolly surface and the thermodynamic parameter, Molecular Refractivity govern variations in biological activity. About 86 percent of biological activity is dominated by these two parameters. The dominant parameter, which is highly correlated with biological

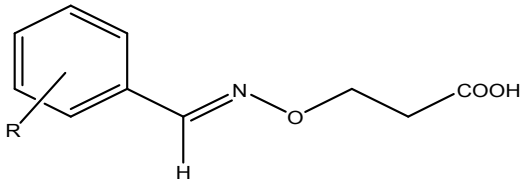
activity, is Connolly surface. Equation (2) reveals 86 percent influence of Connolly surface, on the variations in biological activity. On analyzing this equation, it has been seen that increasing Connolly surface, will decrease the biological activity. On considering the series, the compound no 25 with least Connolly surface is the most active compound. Similarly equations (3),(4),(5) and GFA equations (1) and (2) show that biological activity increases with a decrease in Connolly surface. Connolly surface is the water accessible surface. These equations suggest that a decrease in Connolly surface is needed to exhibit better biological activity. The graphs 8,9 and 10 also depict that Connolly surface is the dominant parameter.

The Second dominant parameter is Molecular Refractivity. Molecular Refractivity is a measure of the polarizability (especially electronic polarizability) and steric bulk of a molecule. The equation (1) reveals that biological activity increases with an increase in Molecular Refractivity. This suggests that for these compounds an increase in steric bulk and polarizability is needed to exhibit better biological activity. Graphs 8,9 and 10 also show the importance of Molecular Refractivity on biological activity. The conformational descriptor, Radius of Gyration also governs the biological activity. Equation (3),(4) and (5) indicate that biological activity increases with increase in Radius of Gyration. Hence for these compounds there should be more Radius of Gyration.

The Electronic descriptor Diple –Y is also contributing for activity. It is a 3D electronic descriptor that indicates the strength and orientation behavior of a molecule in an electrostatic field. The equation(3) reveals that there is inverse relationship between Diole-Y and biological activity i.e. an increase in Dipole-Y will decrease the biological activity. Its contribution towards activity is seen in graph 9. The equations suggest that for enhancing biological activity, there should be low Dipole-Y. The electronic parameters HOMO and LUMO also contribute to biological activity. According to equation (1) LUMO is contributing directly and HOMO is contributing inversely to biological activity. When these two parameters are deleted, the r^2 value is decreased from 0.897 (equation (1) to 0.726 (equation(2)). This suggests that these parameters also contribute to biological activity. Principle of moment of inertia in-X direction also contributes to activity. An increase in PMI-X increases the biological activity. This is evident from equation(6) and GFA equation(2). Hence fro enhancing biological activity, there should be more PMI-X.

Among all the equations generated, equation (1), (3), (6) and GFA equation(2) are considered to be meaningful and statistically significant in terms of r^2 and cross validated r^2. Equation (1) is having r^2 value of 0.897. This shows that there is a good fit of data in the study table to QSAR model. The difference between r^2 and cross validated r^2 is only 0.09. This shows that this equation is having better predictability. Equation (3) is having value of 0.840 and cross validated r^2 is 0.699. The difference of only 0.141 and this is also having better predictability. Equation (6) is having r^2 value of 0.952 and cross validated r^2 is 0.844. Even though the number of parameters contributing the equation is more, the r^2 is more and so data is fitting well in QSAR model and the difference between r^2 and cross-validated r^2 is 0.112. So it is having better predictability. Hence this equation is also considered as best equation.

Table 1: Structure of compounds with their Reported Biological Activities.



Benzylideneaminoxy Propionic Acid

Compound No	R	Inhibition activity on CPE (Does: 50 mg / kg)
1	p-CL	29
2	m-CL	53
3	o-CL	42
4	p-F	20
5	m-F	39
6	o-F	13
7	p-CH_3	0
8	m-CH3	0
9	o-CH_3	0
10	p-CH3	15
11	m-CH3	20
12	o-CH3	15
13	p-OCH3	10
14	m-OCH3	10
15	o-OCH3	32
16	p-OC2H5	52
17	m-OC2H5	10
18	o-OC2H5	0
19	p-O-n-C3H7	0
20	m-O-n-C3H7	10
21	o-O-n-C3H7	20
22	p-O-n-C3H7	10
23	m-O-n-C4H9	15
24	o-O-n-C4H9	10
25	H	65

Table 2: Physicochemical Parameters

Str. Name	Connolly S	Dipole-mag	Dipole-X	Dipole-Y	Dipole-z	radofgyration	MW	Vm
7a	220.82	3.408050034	2.476496661	1.842002746	1.445266484	3.985027948	227.6469	190.5122324
7b	219.241	3.318889782	2.562957215	1.571053827	1.406438613	3.980721413	227.6469	190.8970092
7c	222.835	3.55615101	2.783964677	1.819550441	1.25896282	3.959363144	227.6469	190.5513775
7d	214.607	2.573316327	1.238139926	1.723851081	1.455095836	3.964306565	211.1923	182.2636091
7e	212.644	2.434780324	2.118346022	0.251212481	1.173736617	3.962239342	211.1923	181.7912463
7f	216.497	3.62145203	3.32886463	0.952448643	1.061327782	3.954446415	211.1923	182.0039522
7j	240.356	1.997936251	-0.440596039	1.337658184	1.417143244	4.32935335	261.2001	208.7114663
7k	241.614	1.800663412	1.289146863	-0.93002609	0.845896307	4.273465459	261.2001	208.6745783
7l	240.572	5.002559088	4.619597044	-1.519242788	-1.173380558	3.975995039	261.2001	207.8539459
7m	241.615	1.801160405	1.289878737	-0.9300245	0.845840456	4.273376961	261.2001	208.6728071
7n	239.041	3.086766807	0.287226955	3.069194215	0.160240029	4.35729676	223.228	202.6004804
7o	231.789	4.670199473	4.107203406	1.451686414	1.68352305	4.151788211	223.228	202.060547
7p	251.496	4.153427358	3.666732753	1.371791531	1.387161753	4.793713135	237.2548	219.240628
7q	256.622	3.801049126	2.782594096	1.951009312	1.702559021	4.633455261	237.2548	219.7560255
7t	270.282	3.645755637	1.36341516	3.352436245	0.440232311	4.744104688	251.2816	235.7768887
7u	267.017	5.212961574	4.225806842	3.045603948	0.204503062	4.523140347	251.2816	235.0643403
7v	293.95	2.741952568	1.761306828	2.095979055	0.151571578	5.520726587	265.3081	252.7391186
7w	289.106	3.853863662	2.438528604	2.629520913	1.411192099	5.041701132	265.3081	253.0452681
7x	287.667	4.83055884	4.28717564	1.099492934	1.935339511	4.713452325	265.3081	252.6209643
1	204.743	3.767113844	2.89904591	1.941695667	1.420034319	3.948346968	193.2018	177.1387927

Cont…

Str.name.	MolRef	LUMO	HF-PM3	HOMO – PM3	LUMO – PM3	PMI-X	PMI-Y	PMI-Z
7a	56.54181671	1.475445032	-59.04648	-9.3858	-0.79553	36.35652161	672.041687	695.4512939
7b	56.54182053	1.804298043	-58.91011	-9.541	-0.74287	39.70353699	646.00485229	672.1455688
7c	56.54181671	1.742205977	-56.34824	-9.54152	-0.72955	64.88047791	513.6884766	562.8560791
7d	51.95341492	2.019197464	-95.90275	-9.67478	-0.82756	33.84542084	561.6477661	582.2662964
7e	51.95341873	1.926628947	-95.59698	-9.81375	-0.82563	35.29405212	549.15448	570.5241699
7f	51.9534111	2.041718245	-94.9499	-9.7848	-0.78308	46.54178619	484.5732117	515.3565674
7j	57.71071625	1.347784877	-210.0812	-10.15572	-1.20022	53.19347	877.8845215	903.1422119
7k	57.71072006	1.615697026	-210.25178	-10.06935	-1.03279	57.78614044	832.4448853	861.4543457
7l	57.71071625	1.839810848	-206.95021	-10.17119	-0.97039	105.2274628	568.7229614	648.2459106
7m	57.71072006	1.615686417	-21025185	-10.06936	-1.03286	57.786129	832.409668	861.4193115
7n	58.2002182	2.330083847	-89.65408	-9.21666	-0.44625	46.85160065	616.7105103	659.078064
7o	58.2002182	2.35093379	-88.37246	-9.25553	-0.45991	65.39523315	525.6196899	573.5827026
7p	62.9482193	2.343131542	-95.46928	-9.10065	-0.49392	49.28946686	776.0006714	811.1019897
7q	62.94822693	2.179725647	-94.13179	-9.25203	-0.58524	59.06924438	720.2377319	770.6799927
7t	67.42741211	2.285667181	-101.53782	-9.24614	-0.5232	91.7580719	769.6716919	824.4538574
7u	67.42741211	2.271555424	-98.82732	-9.26148	-0.55044	129.088331	641.4093018	759.4867554
7v	72.07341003	2.432414532	-105.74818	-9.01522	-0.39857	66.72148132	1112.348145	1175.899292
7w	72.07342529	2.19213748	-104.79828	-9.24465	-0.57863	108.2975464	932.7524414	1020.219116
7x	72.07342529	2.472215414	-101.97992	-9.24158	-0.42529	184.2593689	703.0252686	864.3091431
1	51.73701477	2.212932825	-52.48202	-9.609	-0.57315	30.33759499	448.4690247	465.7963562

4. Summary and Conclusion

In the present study an attempt has been made to correlate the biological activity of anti-inflammatory drugs with different thermodynamic, electronic, spatial, conformational and shape parameters.) Forty five series of 5-Lipo Oxygenase inhibitors were selected from the literature and one series was selected for analysis. Connolly Surface is the measure of water accessible area. It measures steric complementarity. The compound no.25, which is having H as substitutent, is having least Connolly Surface and it is the most active compound. Molecular refractivity is a measure of size and polariability. From equation 1 it can be seen that Connolly Surface, Radius of Gyration and Molecular refractivity are contributing more to biological activity. (r^2 value = 0.726). This shows that this equation is fitting well into the QSAR model. The value of cross validated r^2 is 0.562. The difference between r^2 and cross validated r^2 is only 0.164. This shows that this equation is having better predicatability. When the parameter DIFFV is included in equation 4 the r^2 is increased only by 0.106. This shows that this parameter is least significant and only

Connolly Surface, Radius of Gyration, Molecular refractivity are contributing more to biological activity. Molecular shape analysis depicts that there should be more difference in steric volume and reference compound. Also the common overlap steric volume of compounds in reference to most active compound should be greater.

1. The Connolly Surface is inversely proportional to activity.
2. The Radius of Gyration is directly proportional to activity.
3. The Molecular refractivity is directly proportional to activity.

Thus molecules with least Connolly Surface and higher Radius of Gyration, and Molecular refractivity will be more active.An attempt has been made to present this work in its utmost simplest and clearest form and efforts have been put to clarify each and every point in QSAR, There is still scope for more work on this series. Other approaches of drug design like COMFA, receptor surface model generation etc. may be applied for further verification of the results.

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