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QSAR on a Novel Series of Indole Derived Selective ET_A Antagonists

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Abstract

A QSAR study has been made on the inhibition of some selective ET_A antagonist derivatives of indole series. Attempts have been made to correlate the inhibition potencies of these ET_A antagonists with molecular negentropy LogI, liophilicity LogP & equalized electronegativity Xeq. In the present series the $–CONH_2$ group is found as the most active group.

Introduction

Analysis of human genomic sequences has revealed the existence of ET-1, ET-2, ET-3[1] and more recently discovered ET-4[2]. G-protein coupled receptors, ET_AR[3] & ET_BR[4] and endothelin converting enzymes (ECEs) are other part of endothelin system. These endothelins are the most potent vasoconstrictor[5,6].The ET_A receptor is expressed on vascular smooth muscle cells & has high affinity for ET-1 & ET-2, ET_B receptor is expressed on vascular endothelial & smooth muscle cells & has high affinity for all the three endothelins distributed in human tissues the development of selective or non-selective endothelin antagonist is expected to be useful for the treatment of various disease including congestive heart failure[7], pulmonary hypertention[8], ,chronic renal failure[9], angina[10], asthma[11], inflammatory processes[12,13] such as airway inflammation is abrogated by ET_A inhibition[14,15]. New researches show that Endothelin receptors are new target in treatment of different types of cancer.[16-19].

Material and method

In present section QSAR has been performed on a series of twenty three compounds of indole derived selective ET_A antagonist. All the IC_{50} values of the compounds were in fact reported in nanomolar concentration .For correlation purpose we have taken -Log IC_{50} values and attempted to correlate them with parameters equalized electronegetivity(Xeq.)[20-23],negentropy (Log I)[24,25] and partition coefficient (Log P)[26,27]to describe the role of molecular properties such as electronic, topological and hydrophobic nature of drug respectively. The values are listed in Table -1.Table-2 the correlation matrix correlation between parameters as well as well between parameters & activities. The regression analysis was performed with the help of statistical program SPSS[28]version 10.

Result & Discussion

A multiple regression analysis was performed on all observed inhibition activity data using the variables as given. In Table-1 and the results obtained were as follows-

$$-\text{LogIC}_{50}=-1.234(\pm2.988)\text{Xeq}-0.634(\pm0.359)I_1 +0.635(\pm0.31)I_2 +0.908(\pm0.234)I_3+10.419$$

n=23, r=0.957, r^2=0.915, R_A^2 =0.896, $F_{(4,18)}$=48., S.E.=0.22

$$-\text{LogIC}_{50}=2.36(\pm3.868)\text{LogI}-0.685(\pm0.364)I_1 +0.61(\pm0.312)I_2+0.96(\pm0.256)I_3+2.667$$

n=23, r=0.96, r^2=0.92, R_A^2 =0.901, $F_{(4,18)}$=51.06, S.E.=0.21

$$-\text{LogIC}_{50}=0.015(\pm0.087)\text{LogP}-0.636(\pm0.374)I_1 +0.674(\pm0.154)I_2+0.89(\pm0.25)I_3+7.442$$

n=23, r =0.956, r^2=0.91, R_A^2 =0.892, $F_{(4,18)}$=46.8,S.E.=0.22

In above equations, n is the number of data points, r is the correlation coefficient, r^2 is the coefficient

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of determination, R_A^2 is the adjusted r^2, also called explained variance (E.V.), S.E. is the standard error of the estimation, F is the F ratio between the variances of the figures within parenthesis with ± sign are 95% confidence intervals.

Now it is to be noted that for IC_{50} eq(1),(2) & (3) represent almost best correlations exhibiting the dependence of inhibition activities in all the cases on the variables equalized electro negativity Xeq, negentropy, LogI, hydrophobic character LogP, and additional parameters I_1,I_2,I_3 are indicator variables that has been used with a value of 1 for the compounds having R_1={CO_2 Me(I_1) $CONH_2$(I_2)}, R_3=Me(I_3).

The correlations are highly significant and account equally well for the activity of the compounds for the inhibition of IC_{50}.

On observing all equations from 1-3 we can say that I_1(CO_2Me) & ($CONH_2$) at R_1 position and I_3(Me) at R_3 position of indole and sulfonamide ring respectively are very significant together and common for all multiple regression equations against different parameters. The positive sign of coefficient of Log I suggest that large sized and more hydrophobic substituents should be conducive while negative sign of Xeq. indicates that less electronegative groups should be more preferable in future drug designing.

I_1 which is CO_2Me at R_1 position plays satisfactory role alone but when taken in multiple with I_2 and I_3 it gave best results.

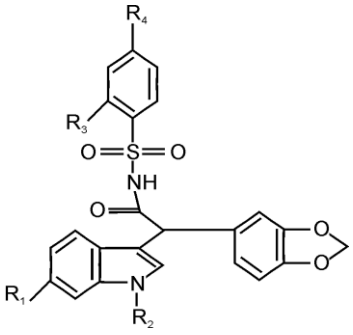
The other indicator variable I_2 which is ($CONH_2$) at the similar position R_1 is the most potent at that particular position.

The third indicator variable used is I_3 which is Me at the 4th position of sulfonamide ring is very potent compound for this series.

Overall discussion clears that for future drug designing following points may be kept in mind-

1. Less electronegative, large sized substituent and more hydrophobic and bulkier substitutions should be more effective.
2. -CO_2Me group indicator I_1 has (-)ve coefficient so it should be avoided at indole ring while -$CONH_2$ group, indicator I_2 at R_1 of indole ring and Me group, I_3, at R_4 of sulfonamide ring should be preferred as they give (+)ve coefficient.
3. Above findings about the groups which are taken as indicators are in conformity with D.J. Rawson[29] *et. al.* as they also have reported that -$CONH_2$ group is the most potent analogue at R_1 position of indole ring and Me group at R_4 of sulfonamide ring resulted an increase in ET_A affinity.

Table :1
Biological activities and physicochemical data of Endothelin receptor



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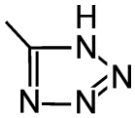
S.N	R_1	R_2	R_3	R_4	Xeq	LogI	LogP	$-LogIC_{50}$ (ET_A)	I_1	I_2	I_3
1	CO_2Me	Me	H		2.3890	2.0670	1.87	7.000	1	0	0
2	CO_2H	Me	H		2.3974	2.0266	1.64	7.6576	0	0	0
3	$CONH_2$	Me	H		2.3922	2.0046	0.41	8.6383	0	1	0
4	CH_2OH	Me	H		2.3797	2.0266	0.57	7.7212	0	0	0
5	CN	Me	H		2.3907	1.9993	1.33	7.2147	0	0	0
6	CH_2NH_2	Me	H		2.3709	2.0335	0.67	7.4202	0	0	0
7		Me	H		2.4809	2.0425	0.056	7.4559	0	0	0
8	CO_2Me	Et	H		2.3832	2.0543	2.41	6.6778	1	0	0
9	CO_2H	Et	H		2.3929	2.0423	2.18	7.4948	0	0	0
10	CO_2H	H	H		2.4115	1.9917	1.86	7.5086	0	0	0
11	$CONH_2$	Et	H		2.4000	2.0511	0.95	8.4559	0	1	0
12	CONHMe	Et	H		2.3765	2.0599	1.16	7.5229	0	0	0
13	$CONMe_2$	Et	H		2.3696	2.0799	0.93	7.1427	0	0	0
14	$C(O)NH_2$	Me	H	H	2.4227	1.9621	–2.076	7.9208	0	1	0
15	$C(O)NH_2$	Me	H	Me	2.4114	1.9859	–1.516	8.7447	0	1	1
16	$C(O)NH_2$	Me	H	Cl	2.4378	1.9621	–1.45	8.1249	0	1	0
17	$C(O)NH_2$	Me	H	CF_3	2.5227	1.9859	0.424	8.1811	0	1	0
18	$C(O)NH_2$	Me	H	OMe	2.3836	1.9763	-2.24	8.5528	0	1	0
19	$C(O)NH_2$	Me	Me	H	2.4114	1.9966	1.516	8.2840	0	1	0
20	$C(O)NH_2$	Me	OMe	H	2.4240	2.0061	2.24	8.3010	0	1	0
21	$C(O)NH_2$	Me	CO_2H	H	2.4496	2.0002	–2.24	8.5086	0	1	0
22	$C(O)NH_2$	Me	OMe	Me	2.4134	2.028	–1.66	8.9586	0	1	1
23	$C(O)NH_2$	Me	OEt	Me	2.4023	2.0315	–0.95	9.2596	0	1	1

Table : 2
Correlation matrix

	Xeq	Log I	Log P
Xeq	1.00		
Log I	-0.42	1.00	
Log P	-0.256	0.525	1.00

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Table: 3

Observed and Calculated activities of Endothelin receptor antagonists

S.N.	Observed - $LogIC_{50}$ (ET_A)	Equation(1)		Equation(2)		Equation(3)	
		Calculated	Residual	Calculated	Residual	Calculated	Residual
1.	7.000	6.85	0.15	6.83	0.17	6.834	0.166
2.	7.6576	7.44	0.2176	7.46	0.1976	7.470	0.1876
3.	8.6383	8.355	0.2833	8.37	0.2683	8.340	0.2983
4.	7.7212	7.44	0.2812	7.48	–0.2412	7.450	0.2712
5.	7.2147	7.40	–0.1853	7.47	–0.2553	7.460	–0.2453
6.	7.4202	7.46	–0.0398	7.49	–0.0698	7.450	–0.0298
7.	7.4559	7.48	–0.0241	7.36	0.0959	7.440	–0.0159
8.	6.6778	6.82	–0.1422	6.842	–0.1642	6.840	0.1622
9.	7.4948	7.48	0.0148	7.464	0.0308	7.470	0.0248
10.	7.5086	7.36	0.1486	7.44	0.0686	7.470	0.0386
11.	8.4559	8.465	–0.0091	8.364	0.0919	8.349	0.1069
12.	7.5229	7.521	0.0019	7.485	0.379	7.459	0.0639
13.	7.1427	7.569	0.4263	7.493	–0.3503	7.456	–0.3133
14.	7.9208	8.255	–0.3342	8.336	–0.4152	8.302	–0.3812
15.	8.7447	8.919	–0.1743	8.984	–0.2393	8.980	–0.235
16.	8.1249	8.255	–0.1301	8.317	–0.1921	8.312	–0.1871
17.	8.1811	8.311	–0.1299	8.212	–0.0309	8.341	–0.1599
18.	8.5528	8.289	–0.2638	8.384	0.1688	8.300	0.2528
19.	8.2840	8.336	–0.052	8.349	0.065	8.357	–0.073
20.	8.3010	8.359	–0.058	8.334	0.033	8.369	–0.068
21.	8.5086	8.345	0.1636	8.303	–0.2056	8.300	0.2086
22.	8.9586	9.018	–0.0594	8.983	–0.0244	8.983	–0.024
23.	9.2596	9.026	0.2336	8.994	–0.2656	8.994	0.2656

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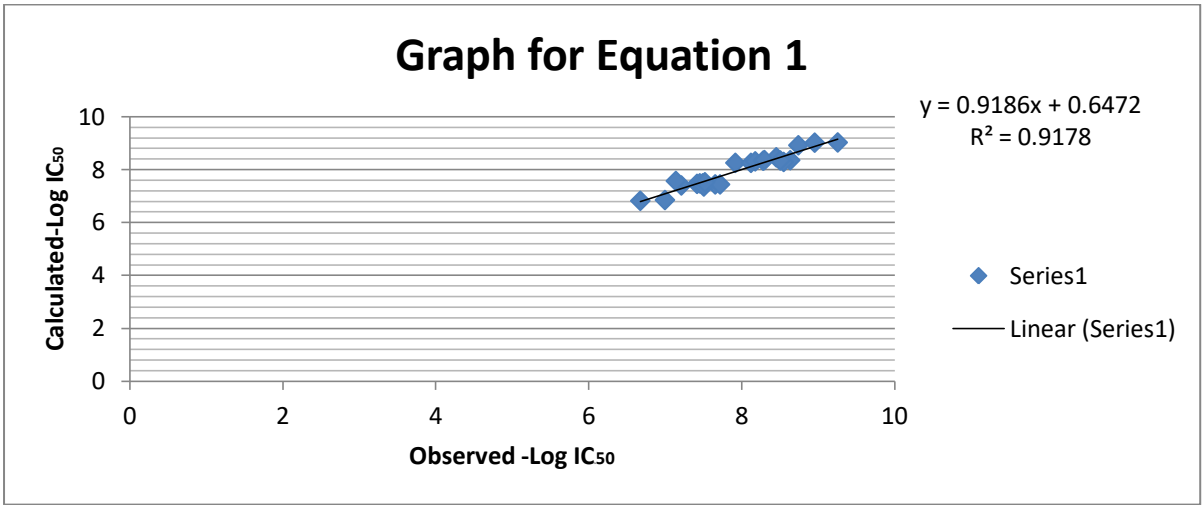

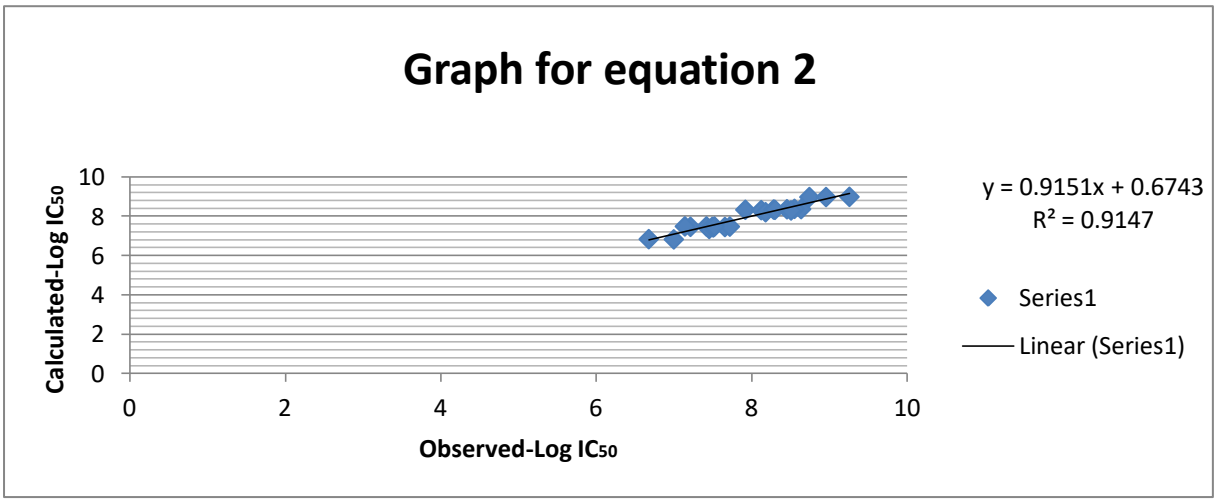

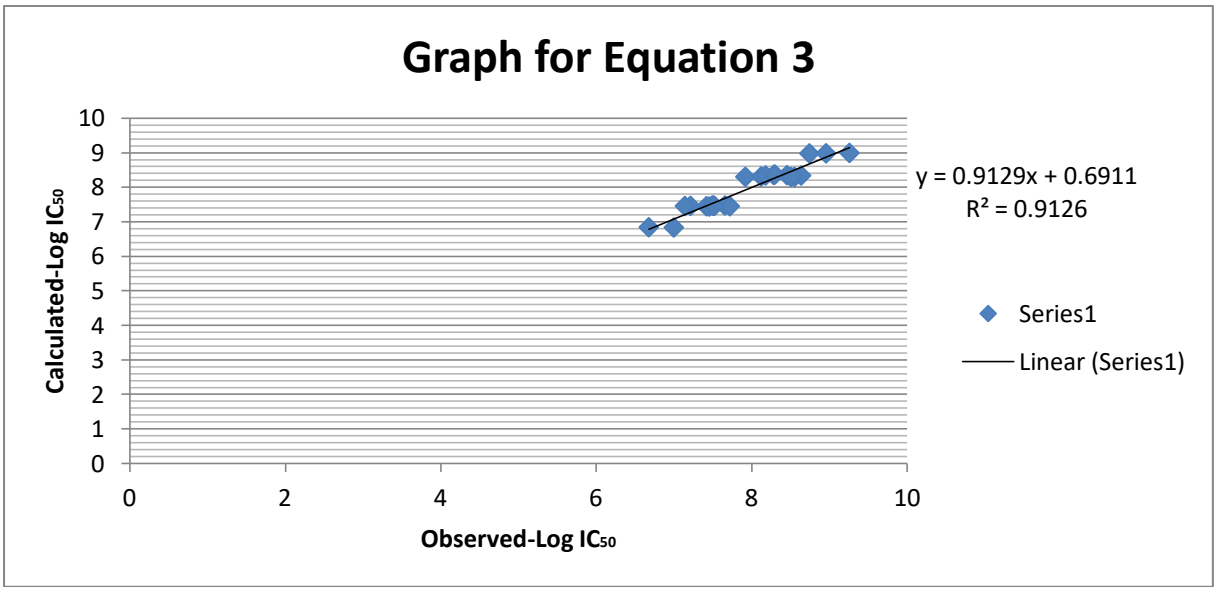

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