QSAR Study of substituted 3,5-di-tert-Butyl-4-hydroxy Styrene; a series with antiinflammatory activity

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A series of 19 antiinflammatory drugs 3,5-di-tert-butyl-4-hydroxy styrene derivatives were subjected to quantitative structure activity relationship analysis with an attempt to derive a correlation between the biological activity as dependent variable and various descriptors as independent variables by using Hansch approach. The QSAR analysis showed that, the antiinflammatory activity of the analogues is significantly correlated with thermodynamic and sterimol parameters. The analysis resulted in the following 2-D equation suggest that, BA=(-0.588016) MR1+(0.2815) MR2+(-0.150769) Hdor1(- 1.322597), n=15, r=0.864, r^2=0.764, f=7.336, t=2.709, STD=0.64, a lipophillic group, which is less bulkier at R1 and more bulkier at R2, is important in determining the antiinflammatory activity along the axis of a parent skeleton, which can be used for predicting the affinity of related compound and for guiding the design of a new molecule.

The non-steroidal antiinflammatory drugs (NSAIDs) represent an extremely interesting category of drugs as evident from the active research going on in this area all over the world. It is generally, agreed that gastric irritation is associated, directly or indirectly, with acidic nature of these drugs[1]. Therefore, there is continuous demand for new therapeutic agents with high margin of safety and freedom from normally associated gastrointestinal toxic effects such as ulceration, hemorrhage and perforation. Novel category of drugs is being developed based on the new mechanism of action and pathogenesis of inflammation. Extensive research has been carried out in our laboratory[2,3] to find out new potent derivatives of NSAIDs by using Computer–aided molecular modeling. The series reported by Katsumi *et al.* 3,5-di-tert-butyl-4-hydroxystyrene to posses significant antiinflammatory activity, directed us to subject the above series to quantitative structure activity relationship (QSAR) analysis. As the part of our rational drug discovery program on novel NSAIDs, this theoretical study is aimed at determining the quantitative relationship between various substitution on 3,5-di-tert-butyl-4-hydroxy styrene and their antiinflammatory activity[4].

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In the present study, QSAR analysis was performed by conventional Hansch's extra thermodynamic multiparameter approach. The antiinflammatory data was taken from Katsumi *et al.*[5], and the data were expressed as percent inhibition of carrageenan-induced paw edema in rat, when 50 mg/kg of drug was administered. This data was converted to log of percent paw edema inhibition per millimole of drug per kilogram of body weight (log BA). We have used software SMIRAILS[6] for multiple parameter regression analysis developed and standardized on the known set. The structures of the compounds in the series were built in Table 1 by using the molecular sketching facility, provided in the modeling environment of the software. The thermodynamic, sterimol parameters were used for QSAR[7,8] analysis. The thermodynamic parameters describe free energy change during drug receptor complex formation and include log of partition coefficient (Log P), molecular refractivity (MR). Sterimol parameters describes the bulk of substituent, include length of substituent (L), width of sustituent (B1, B5) orthogonal to length have angle 90° to each other.

Stepwise multiple regression analysis method[9] was used to generate QSAR equation. Statistical measures used were: n-number of sample in the regression, r-coefficient of correlation, r^2-coefficient of determination, STD-standard devia-

TABLE 1: RAT ADJUVANT-ARTHRITIS DATA FOR 3,5-DI-TERT-BUTYL-4-HYDROXY STYRENE USED IN THIS STUDY

*R1	*R2	*BA	***Log (p/100-p)BA	# Cal Log (BA) Eqa-1	# Cal Log (BA) Eqa-2	# Cal Log (BA) Eqa-3
COOH	CH_2CH_2OH	237.12	-1.60398	-1.50	-1.62	-1.66
$COOCH_3$	CH_2CH_2OH	280.94	-1.553042	-1.74	-1.77	-1.66
COOH	C_2H_5	79.15	-1.89265	-1.50	†	†
$COOC_2H_5$	$COCH_3$	194.02	-1.696816	-1.90	†	†
$CONH_2$	H	27.54	-2.13326	-1.72	-2.20	-1.99
$CONHC_4H_9$	H	19.89	-2.30814	-2.17	-1.81	-1.96
$CONH_2$	CN	186.25	-1.665266	-1.72	-2.01	-1.96
CO-N-C_5H_{10}	CN	58.96	-2.0080	-2.09	-1.94	-1.96
$CONHCONH_2$	CN	20.61	-2.30814	-2.00	-1.08	-1.96
CN	CN	158.14	-1.69681	-1.40	-2.06	-1.99
p-C_6H_5-NO_2	CN	37.85	-2.13326	-2.18	-1.90	-1.89
SO_2CH_3	CN	120.75	-1.81507	-1.82	-1.82	-1.99
$COCH_3$	H	192.08	-1.624246	-1.68	-1.82	-1.99
$COCH_3$	CH_3	138.45	-1.74086	-1.68	-2.21	-1.99
CO-C_6H_5	H	67.29	-1.954242	-2.15	-2.27	-1.96
CO.*p*-C_6H_5- Br	H	24.92	-2.30814	-2.26	-1.89	-1.96
NO2	H	94.30	-1.829014	-1.49	-1.9990	-1.96
COOH	CH_3	8.0	-1.0606	-1.50	†	†
COOH	H	19.0	-0.62973	-1.50	†	†

*substituted groups in fig.1 **percent inhibition of carrageenan induced rat paw edema by milli mole/kg of oral dose ***Log of biological activity. # calculated values obtained by using equation 1 2 3. † Outlier Compounds in deriving equations

tion, t-t-test for statistical significance and correlation matrix to show mutual correlation among the parameters (values of only those descriptors, which found place in the equation, are given in Table 2). All these derivatives in the series of 3,5-di-tert butyl-4-hydroxy styrene were subjected to QSAR with an attempt to derive a co-relation between the biological activity as dependent variable and various descriptors as independent variables. From the eight various descriptors many QSAR equations were generated. Out of the four generated equations, not all the 19 analogues showed a significant cross co-relation, one of the four generated equations is given below, which showed 72.9% of variance in the biological activity. BA= -1.088923 *MR1-0.263750*Hdor1-0.239029*Hacc1-0.256057 (1), where, n =19, r=0.729, r^2=0.537, f=3.693, t=1.922 and STD=0.337. Therefore, to obtain a significant correlation coefficient, step-by-step compounds 3, 4, 18, and 19 were eliminated, as outliers by leave one out method. BA=(-0.588016)MR1+(0.2815)MR2+(-0.150769)Hdor1(-1.322597) (2), where, n=15, r=0.864, r^2=0.764, f=7.336, t=2.709 and STD=0.64. The above Eqn. 2 obtained was found to be highly predictive and statistically significant, showing a negative value of molecular refractivity (MR) at R1 indicating stearic hindrance and a positive value of MR at R2 indicating good binding dispersion force between the analogues and the receptor. Table 1 shows the observed and the predictive values of biological activities after removal of outliers. Table 3 shows that MR is almost quantitatively equivalent in contri-

TABLE 2: CALCULATED VALUES OF DESCRIPTORS FOR THE GIVEN SERIES OF COMPOUNDS

*Log MR1	*Log MR2	**R2L	***R2B5
0.783	1.0722	0.6803	0.5289
1.073	1.0722	0.6803	0.5289
0.7803	1.01283	0.6138	0.5011
1.2242	1.01241	0.6085	0.4900
0.9916	0.01283	0.3139	0.00
1.4413	0.01283	0.3139	0.00
0.9916	0.73158	0.6263	0.2041
1.4109	0.7315	0.6263	0.2041
1.2692	0.7315	0.6263	0.2041
0.7315	0.7315	0.6263	0.2041
1.5060	0.7315	0.3139	0.00
1.1890	0.7315	0.4579	0.3096
1.0124	0.7315	0.3139	0.00
1.0124	0.0128	0.3139	0.00
1.4771	0.01283	0.3139	0.00
1.5877	0.01283	0.6263	0.2041
0.8267	0.01283	0.6263	0.2041
078031	0.75204	0.4579	0.3096
0.78031	0.01283	0.4149	0.00

*Log of molecular refractivity **Length of substituents at R2 ***Maximum width of substituents at R2 *taken from reference[5]

bution at R1, R2 but in negative and positive ways. In addition, the correlation coefficient 'r' accounts for 86.4% of variance in the biological activity.

TABLE 3: CORRELATION MATRIX FOR PARAMETERS IN EQN 2

	*BA	†Hdor	#MR1	#MR2
BA	1	0.214	0.696	0.626
Hdor		1	0.139	0.034
MR1			1	0.316
MR2				

*Biological activity, †Hydrogen donor, # Molecular refractivity.

For further investigation of MR at R2 as it is positive, additional Sterimol parameters (B5 and L) were subjected to QSAR analysis. The Eqn. obtained was,

TABLE 4: CORRELATION MATRIX FOR PARAMETERS IN EQN 3

	*BA	# R2L	**R2B1	†R2B5
BA	1	0.25	0.19	0.433
R2L		1	0.955	0.811
R2B1			1	0.749
R2B5				1

* Biological activity, # Length of substituent at R2, ** Width of substituent at R2, † Maximum width of substituent at R2

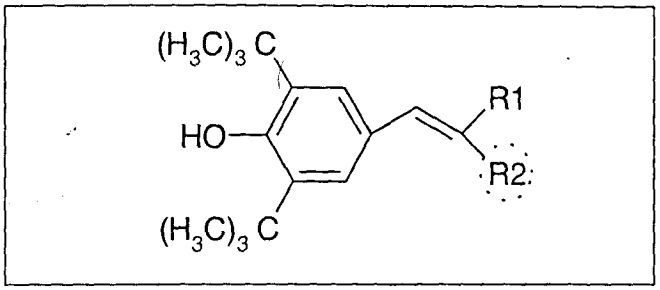

Fig. 1: 3, 5-di-tert-butyl-4-hydroxy styrene used in this study.

BA=0.19827R2L+-0.32270 R2B1+0.84462 R2B5+0.8442 (3), where, n=15, r=0.475, r^2=0.226, f=0.729, t=0.854 and STD=0.281. The above Eqn. 3 is statistically not significant having poor coefficient of determination, but it indicates that the over all value of B5 (maximum width of substituent) is more contributing than L (length of substituent) along the axis of the parent skeleton Table 4. From all the above observations, it can be concluded that, the antiinflammatory activity of the analogues is highly correlated with the thermodynamic (MR) and Sterimol (B5, L) parameters. Hence, Eqns. 2 and 3 indicates a lipophillic group, which is less bulkier at R1 and more bulkier at R2, is required for good biological activity. The above QSAR studies may throw some light on the substitutional requirement for further development of these compounds for more potent activity.

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A Modified Sensitive Micro Spectrophotometric Determination of Iron(III) by Thiocyanate Method

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A systematic study of the colour reaction formed between iron(III) and thiocyanate reagent has been carried out by using micro-scale spectrophotometric method. The optimized data resulted conditions in obtaining unusual highest sensitivity with molar absorption of 2.9565x10⁴l/mol.cm at wavelength of maximum absorption 480 nm in 0.2-1.4 N nitric acid medium containing 60%

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