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QSAR and QSTR studies for 4',5- disubstituted 3-biphenylylacetic acid derivatives

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ABSTRACT

Aryl acetic acids are widely used in the treatment of inflammation and associated with several drawbacks. QSAR approach has been useful in such cases, provide information regarding modifications required to optimize lead molecules. A series of 4',5- disubstituted 3-biphenylylacetic acid derivatives were quantitatively analyzed using TSAR software. Multiple regression analysis was carried out to find out co-relation between physicochemical parameters and the anti-inflammatory activity ($r = 0.838$, $r^2 = 0.702$, $n = 22$, $S = 0.361$, $F = 14.17$, $r^2_{CV} = 0.538$) as well as toxicity ($r = 0.870$, $r^2 = 0.757$, $n = 22$ $S = 0.113$, $F = 29.696$, $r^2_{CV} = 0.716$). The generated QSAR models revealed the importance of electronic and steric parameters. Electron withdrawing and less bulky groups at 4'and 5 positions were found important for enhancement of activity and less bulky groups and lower lipophilicity of substituents in a copmpound will give safer drugs.

KEYWORDS

Quantitative Structure Activity Relationship;
Quantitative Structure Toxicity Relationship;
Anti-inflammatory agents;
4',5- disubstituted 3-biphenylylacetic acid derivatives.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are of huge therapeutic benefit in the treatment of rheumatoid arthritis and various types of inflammatory conditions. Like Aspirin, all other NSAIDs such as Ibuprofen, Ketoprofen and Naproxen develop their mode of action by blocking cyclooxygenase. Therefore, administration of NSAIDs, for example to treat inflammatory diseases such as osteoarthritis or rheumatoid arthritis, unavoidably leads to lack of the prostaglandins required for the physiological functions also[1]. A severe side effect of NSAIDs is bronchoconstriction with resultant asthmatic events. The reduced amount of bronchodilatating PGE_2 on the one hand and a shift in the metabolic pathway from the cyclooxygenase pathway to the 5-lipoxygenase pathway on the other hand, seems to be responsible for the bronchoconstricting effect of NSAIDs[2]. The latter pathway metabolizes 'overflow' AA, which cannot be transformed by the blocked cyclooxygenase pathway. The resulting leukotrienes act as bronchoconstrictors[3]. Because of these problems, a major target of drug research is the development of NSAIDs with anti-inflammatory and analgesic activity but without side effects. Computational methods have the potential to speed the discovery of novel compounds and to guide optimization of the properties of these compounds[4].

Biphenyl acetic acid series of compounds like Flurbiprofen, Namoxyrate are proven NSAIDs and also

attempts have been made to make them COX-2 selective by modification of their structures (Figure 1)[5].

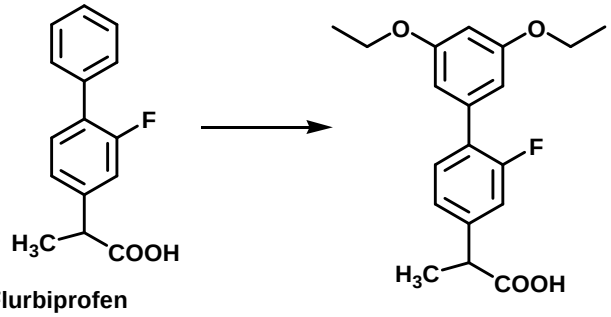


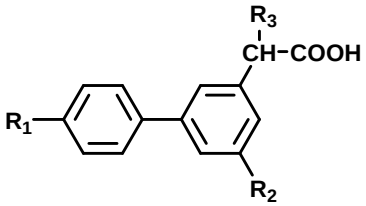
Figure 1: Strucutre of flurbiprofen and its modified derivative

However methodology used for NSAID modifications is not general and consists of extensive modification of individual compounds.

EXPERIMENTAL

Y. Tamura, et. al.[6] has disclosed synthesis of biphenylyl acetic acids and their derivatives with antiinflammatory and analgesic activities. Structures of which are presented in TABLE 1. The reported SAR is directed only to alterations of the substituents at various positions in the structure and no rationale was provided to reduce trial and error factors. Hence QSAR studies were performed correlating anti-inflammatory activity as well as acute toxicity with physicochemical properties of biphenyl series of compounds.

TABLE 1: Structures of 4',5-disubstituted 3-biphenylyl acetic acid derivatives.



Sr. No.	Comp. Name	R_1	R_2	R_3	Sr. No.	Comp. Name	R_1	R_2	R_3
1.	5a	H	- $NHCOCH_3$	H	12.	5l	4 Cl -	CL	H
2	5b	4 CH_3O-	- $NHCOCH_3$	H	13.	5m	H	F	H
3.	5c	4 Cl -	- $NHCOCH_3$	H	14.	5n	4 Cl -	F	H
4.	5d	H	- NH_2	H	15.	5o	H	H	CH_3
5.	5e	4 CH_3O-	- NH_2	H	16.	5p	4 CH_3O-	H	CH_3
6.	5f	4 Cl -	- NH_2	H	17.	5q	4 Cl -	H	CH_3
7.	5g	H	H	H	18.	5r	H	Cl	CH_3
8.	5h	4 CH_3O-	H	H	19.	5s	4 CH_3O-	Cl	CH_3
9.	5i	4 Cl -	H	H	20.	5t	4 Cl -	CL	CH_3
10.	5j	H	Cl	H	21.	5u	H	F	CH_3
11.	5k	4 CH_3O-	Cl	H	22.	5v	4 Cl -	F	CH_3

MATERIALS AND QSAR METHODOLOGY

Biological activity (anti-inflammatory activity) values are reported as inhibitory activity on carrageenan paw edema (% inhibition at 3 h) and acute toxicity as LD_{50}. Pharmacological screening values therein were converted into Log (% Inh) and Log (LD_{50}) were used for multiple correlation analysis with descriptors generated using TSAR 3.3[7] software.

All molecules were drawn and imported into TSAR software window. Charges were derived using Charge 2-Derive charges option and optimized by using Cosmic-optimize 3 D option in the structure menu of the project table. Substituents were defined as shown in Figure 2 and descriptors were calculated for whole molecule as well as for the substituents. Several equations were generated correlating both Log (% Inh) and Log (LD_{50}) with physicochemical parameters (descriptors) by multiple linear regression analysis (MLR) method. Data was standardized by range and leave one out method was used for cross validation. Models were excluded if correlation was exceeding 0.9 for more rigorous analysis. Correla-

tion matrix was generated to find any intercorrelation between the descriptors.

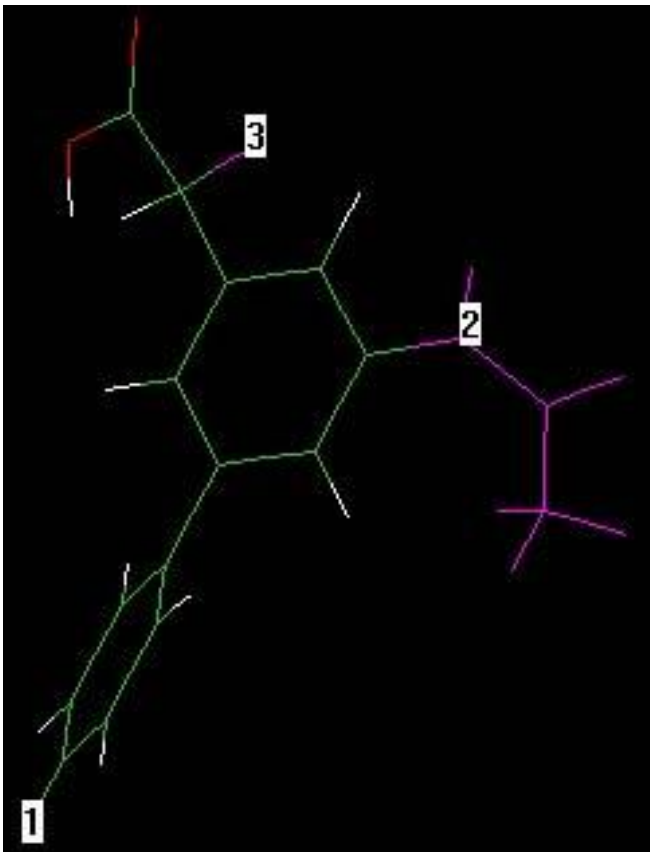


Figure 2: Substituent selection for 3-biphenylyl acetic acid derivatives

RESULTS AND DISCUSSION

Equations correlating Log (% Inh) with descriptors generated are presented in TABLE 2.

TABLE 2: Equations generated between log (% inh) and descriptors

Sr. No.	Equation	n	s	r	r^2	r^2_{cv}	F
1	Y = 0.398 * X1 - 0.317	22	0.528	0.54	0.291	0.132	8.226
2	Y=-0.260 * X2 - 1.323*X3 - 10.478	22	0.456	0.735	0.539	0.243	9.966
3	Y = - 0.218 * X4 - 1.576 * X3 - 13.218	22	0.433	0.765	0.585	0.412	12.008
4	Y = -0.199 *X4 - 0.229 * X2 - 1.553 * X3 - 12.575	22	0.364	0.835	0.697	0.487	13.816
5	Y = -0.227 * X4 - 1.469 * X3 - 0.414*X5 - 10.573	22	0.361	0.838	0.702	0.538	14.17

Where
Y = Log (% Inh) X1 = ClogP X2 : Verloop B4 (Subst. 2)
X3 = VAMP HOMO (Whole Molecule)
X4 = Dipole Moment Z Component (Whole Molecule)
X5 = Inertia Moment 2 Length (Whole Molecule)

The correlation coefficient of equation 1 is significantly low showing that lipophilicity is not much contributive for activity. When logp descriptor was included with other steric and electronic descriptor led to generation of equations of very low predictivity. We then generated equations using steric and electronic parameters only and obtained equations 2 to 4 with two to three terms in the final equation.

Although equation No. 4 found to be good we replaced descriptor Verloop B4 (Subst. 2) with Inertia Moment 2 Length (Whole Molecule) [intercorrelation between these two descriptors is 0.899] and found improvement in the model to get equation 5. Residual sum of squares and predictive sum of squares was found to be 2.347 and 4.434, respectively for equation 5. The graph of observed Vs predicted data for anti-inflammatory activity is presented in Figure 3.

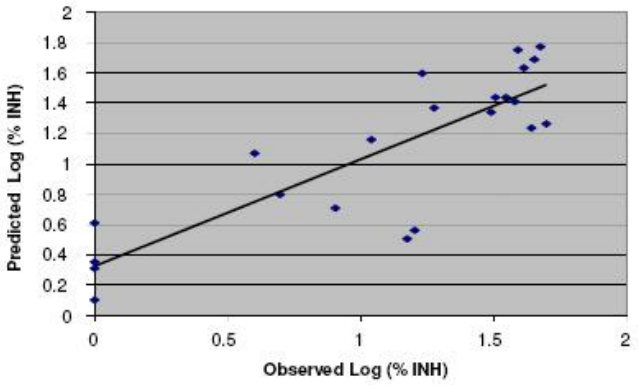


Figure 3: Correlation graph observed and predicted log (% Inh) data for 22 compounds derived from equation 5

Equations correlating Log (LD_{50}) versus descriptors generated are presented in TABLE 3.

TABLE 3: Equations generated between log (ld_{50}) and descriptors.

Sr. No.	Equation	n	S	r	r^2	r^2_{cv}	F
6.	log (LD_{50}) = -0.214 X1 + 3.388	22	0.131	0.811	0.658	0.61	38.56
7.	log (LD_{50}) = - 0.290 X1 – 0.174 X2 + 4.357	22	0.113	0.870	0.757	0.716	29.696

Where
X1 = logP and X2 = Inertia moment 2 length

The correlation coefficient of equation 6 is significantly high indicating that lipophilicity is much more responsible for the toxicity of the compounds. Further we tried to see any steric or electronic descriptor may be contributing for toxicity and found equation 7 showing improvement in the model by inclusion of steric term.

Residual sum of squares and predictive sum of squares was found to be 0.244 and 0.328, respectively for equation 7. The graph of observed Vs predicted data for acute toxicity is presented in Figure 4.

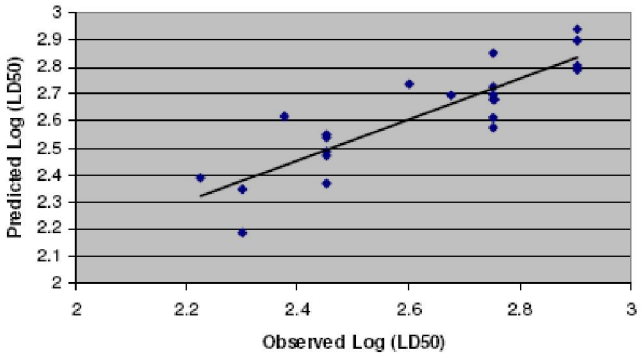


Figure 4: Correlation graph of observed and predicted log (LD_{50}) value data for 22 compounds for equation 7

CONCLUSION

From equation 5 it is observed that two electronic parameters Dipole Moment Z Component (Whole Molecule) and VAMP HOMO (Whole Molecule) and one steric parameter Inertia Moment 2 Length (Whole Molecule) contribute (-0.227, - 1.469 and - 0.414, respectively) negatively for the activity. Electron withdrawing and less bulky groups may enhance the activity (% Inh) but lipophilic contribution can not be ruled out due to considerable contribution (0.398) by logP term in the equation 1.

From equation 7 it is evident that logP and Inertia moment 2 length (Whole Molecule) contribute significantly (- 0.290 and – 0.174) for the toxicity of this series of drugs. Lower lipophilic and electron withdrawing substituents may decrease the toxicity.

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