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Quantitative–Structure Activity Relationships on Lipoxygenase Inhibitors

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Quantitative–Structure Activity Relationships on Lipoxygenase Inhibitors[#]

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Abstract

Motivation. The control of leukotrienes biosynthesis through the inhibition of the enzyme 5–lipoxygenase represents a potential new method of treating several diseases. Several quinonoid derivatives inhibiting 5–lipoxygenase were collected from the literature. For them a quantitative structure–activity relationship study was performed in order to provide a simple description of the physicochemical parameters which are involved in the lipoxygenase–quinones site of action.

Method. The analysis was done by using the C–QSAR suite of programs (Biobyte).

Results. The evaluation of the quantitative structure–activity relationships (QSAR) revealed that the primary physicochemical feature influencing the *in vitro* LOX inhibitory potencies of these compounds is the hydrophobicity of the molecule. A significant correlation was observed between the CMR of the studied molecules and the *in vitro* inhibitory activity. The QSAR study also demonstrated that the inhibitory activity is lowered by the presence of a carboxylic or a phenyl group.

Keywords. Lipophilicity; lipoxygenase inhibitors; quantitative structure–activity relationships; quinones.

Abbreviations and notations

CMR, calculated molecular refractivity	LOX, lipoxygenase
COX, cyclooxygenase	5–LOX, 5–lipoxygenase
HPETE, hydroperoxyeicosatetraenoic acids	12–LOX, 12–lipoxygenase
HETE, hydroxyeicosatetranoic acids	15–LOX, 15–lipoxygenase
HWBL, human whole blood assay	PGs, prostaglandins
LTs, leukotrienes	QSAR, quantitative structure–activity relationships
LTC_4, leukotriene C_4	RBL–1, rat basophilic leukemia cells
LTD_4, leukotriene D_4	

1 INTRODUCTION

The biosynthetic cascade of arachidonic acid has been the object of intense research. Arachidonic acid liberated from phospholipids by various stimuli can be metabolized by the cyclooxygenase (COX) pathway to prostaglandins (PGs) and thromboxane A_2 or by lipoxygenase

[#] Dedicated on the occasion of the 70th birthday to Professor Alexandru T. Balaban.

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(LOX) pathways to hydroperoxyeicosatetraenoic acids (HPETE), hydroxyeicosatetranoic acids (HETE) and leukotrienes (LTs). Lipoxygenases (LOXs) are a family of cytosolic enzymes widely distributed in nature. They are monomeric proteins that contain a "non–heme" iron per molecule in the active site as high–spin Fe(II) in the native state, and high–spin Fe(III) in the activated state [1–3]. Arachidonic acid, their main substrate in mammals, can be cleaved from phospholipids leading to the formation of lysophospholipids [4]. Lipoxygenases as dioxygenases recognize the 1,4–pentadiene structure of polyunsaturated fatty acids and catalyze their oxygenation to corresponding lipid hydroperoxides. They differ in their specificity for placing the hydroperoxy group so 5–lipoxygenase (5–LOX) inserts oxygen on position 5 of arachidonic acid, 12–lipoxygenase (12–LOX) on position 12 and 15–lipoxygenase (15–LOX) on position 15 [5,6]. Also tissues differ in the lipoxygenase(s) that they contain; for example platelets have only 12–LOX and synthesize 12–HPETE, whereas leukocytes contain both 5–LOX and 12–LOX and produce both 5–HPETE and 12–HPETE. Lipoxygenases have a high degree of homology in the proposed iron binding region and the primary reaction they catalyze are essentially the same. It is well known that lipoxygenases are responsible for the biosynthesis of leukotrienes, eicosanoids, lipoxins, monohydroperoxy– and dihydroperoxypolyenoic fatty acids. An overproduction of these products can cause disturbances in the metabolic reactions, and are involved in some metabolic diseases and pathologies. These effects have been linked to immunological and radiation disorders, tumors, toxicoses, hypodinamy, coronary and angiological pathologies (vasospasm, thrombosis, arteriosclerosis).

The major products of 5–LOX, leukotrienes (LTs), are a family of important biologically active molecules. LTB_4 is a potent chemotactic agent and inflammatory mediator [7] and the peptidoleukotrienes LTC_4 and LTD_4 are powerful spasmogens in vascular and bronchial tissues [8]. Elevated levels of LTs are associated with a number of inflammatory conditions including asthma, psoriasis, ulcerative colitis, and rheumatoid arthritis, and indeed LTs have been recovered from various pathological tissues. Therefore, potent inhibitors of this enzyme are candidate drugs for the treatment of these diseases [9,10]. These inhibitors can be broadly classified into two main categories: first, competitive lipid substrate inhibitors and, second, redox–type inhibitors, which act by chelation or reduction of the Fe(III) of the active enzyme or by reaction with the fatty acid radical intermediate produced during the catalytic step [11].

2 MATERIALS AND METHODS

Many thousands of compounds have been screened as LOX inhibitors in industrial laboratories and a large number of active compounds with novel structures are undergoing clinical trials. This evaluation provides data sets suitable for quantitative structure–activity relationships (QSAR). The laboratory tests utilized in identifying lipoxygenase inhibitors are: human granulocytes, rat basophilic leukemia cells (RBL–1) and human whole blood assay (HWBL).

For drugs acting as LOX inhibitors hydrophobicity [12–16] is an important property, it is also a significant factor in the susceptibility of drugs to be attacked by the P450 enzymes [17]. In the formulation of the QSAR we have used calculated log *P* values obtained with the ClogP program [18] and denoted ClogP as well as some experimental log P_E values [18]. CMR values have been also theoretically calculated with the ClogP program. All ClogP values are for the neutral forms.

For the QSAR study a multiple regression analysis technique was employed using the C–QSAR program [18] on a VAX computer, through Internet. The best equation was selected on the basis of results of all possible equations. The biological data in Tables 1–6 are taken from literature [19–21] whereas ClogP / CMR values are theoretically calculated with the ClogP program of Biobyte. The C–QSAR (Biobyte) program was used for the derivation of equations.

3 RESULTS AND DISCUSSION

In the correlation equations, *n* is the number of compounds used in the analyses, *r* the correlation coefficient, *s* the standard deviation, q^2 defines the cross–validated r^2 and *F* is the *F* statistics significance level. A QSAR study was made for the following quinones: 2–(3–halogen–4–hydroxyphenyl)–1,4–naphthoquinone derivatives [19]; 10–aminomethylene–1,8–dihydroxy–9(10)H–anthracenones [20]; (3–pyridylmethyl)benzoquinone derivatives [21]. The negative logarithm of IC_{50} was used in the correlation analyses. Thus a higher log $1/IC_{50}$ value represents a more potent compound.

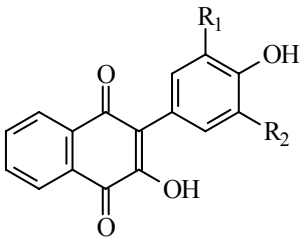
2–(3–Halogen–4–hydroxyphenyl)–1,4–Naphthoquinone Derivatives

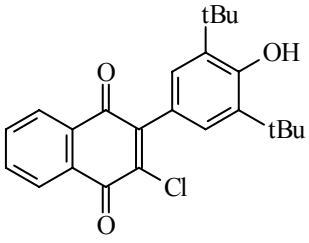
The biochemical basis for the mode of action of naphthoquinones is uncertain, but there is growing evidence that it is related to their redox activity leading to the production of free radicals and active oxygen species. Naphthoquinone derivatives possess redox properties and can be expected to inhibit the LOX reaction by inducing free radical species. For the group of 2–(3–halogen–4–hydroxyphenyl)–1,4–naphthoquinones [19] the following QSAR equation was obtained:

$$\log 1/IC_{50} = 0.058(\pm 0.033)\ \text{ClogP} + 5.023(\pm 0.162)$$
$$n = 5,\ r = 0.956,\ r^2 = 0.913,\ q^2 = 0.825,\ s = 0.036,\ F_{1,3} = 30.75,\ \alpha = 0.5 \qquad (1)$$

Equation 1 gives a good correlation between observed and calculated IC_{50} values, the greatest deviation being noted for the compound 5 (Table 1), which is one of the most active in the set, but with two bulky substituents $R_1 = R_2 = t$Bu. IC_{50} is the biological activity of the compounds for the inhibition of the production of LTB_4 in human granulocytes. The parameter ClogP represents the theoretically overall calculated lipophilicity of the molecule and governs the variations in activity, so an increase of the lipophilicity, increases the inhibitory activity of the compounds.

Table 1. Physicochemical Parameters Used to Obtain Equation (1)





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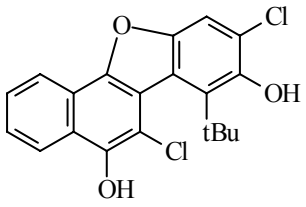

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No	R_1	R_2	log $1/IC_{50}$			ClogP
			Exp.	Calc. Eq. (1)	Res. Eq. (1)[a]	
1	*t*Bu	H	5.200	5.195	0.005	2.950
2	Br	*t*Bu	5.200	5.246	–0.046	3.830
3	*t*Bu	Cl	5.275	5.235	0.040	3.630
4	see structure **4** above		5.362	5.356	–0.060	0.006
5	*t*Bu	*t*Bu	5.409	5.302	0.107	4.780
6	see structure **6** above		5.439	5.446	5.439	0.007

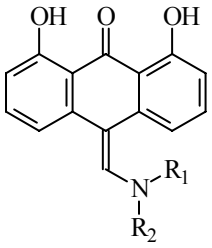
[a] Res. = Exp. – Calc.

10–Aminomethylene–1,8–dihydroxy–9(10H)–anthracenones

The equation derived shows that the inhibitory activity of the compounds depends on their lipophilicity (experimental measured lipophilicity) [20]. The negative sign indicates that the inhibitory activity increases as the lipophilicity decreases:

$$\log 1/IC_{50} = -0.995\ (\pm 0.924)\ \log P_E + 9.717\ (\pm 4.231)$$
$$n = 7,\ r = 0.778,\ r^2 = 0.605,\ q^2 = -0.307,\ s = 0.493,\ F_{1,5} = 7.66,\ \alpha = 0.05 \qquad (2)$$

Table 2. Physicochemical Parameters Used to Obtain Equation (2)



No	R_1	R_2	log $1/IC_{50}$			log P_E	ClogP
			Exp.	Calc. Eq. (2)	Res. Eq. (2)[a]		
1	CH_3	CH_3	4.678	6.544	–1.876	3.18	3.864
2	H	CH_3	5.699	6.186	–0.487	3.55	3.208
3	H	Ph	4.886	4.783	0.103	4.96	4.957
4	H	4–F–Ph	5.301	5.102	0.199	4.64	5.402
5	H	4–Cl–Ph	4.796	4.684	0.112	5.06	5.972
6	H	4–CH_3OPh	4.602	4.843	–0.241	4.90	5.059
7	H	3,4–OCH_2OPh	4.523	5.002	–0.479	4.74	4.651
8	H	4–OH–Ph	6.522	5.728	0.794	4.01	4.290
9	H	$PhCH_2$	4.620	5.550	–0.890	4.23	5.076

[a] Res. = Exp. – Calc.

Compounds 1 and 9 are outliers and were not used to derive Eq. (2). Although no specific

parameters for the substituents R_1 and R_2 have been used, all derivatives are well predicted. Two of the nine analogues are excluded from the derivation of QSAR but they don't contain any unusual structural feature. No role for an electronic effect was found. The phenyl ring with its substituents does not appear to reach a hydrophobic surface. Note that in equation (2) q^2 is quite small compared to r^2 indicating that this QSAR has a small predictive power. Attempts to derive a better equation using steric parameters did not succeed because the number of data points is small.

We have tried to correlate the experimental values of lipophilicity log P_E to the theoretically calculated ClogP values. Equation (3) is derived which is not a significant correlation, in terms of r^2 (0.698) and F. In order to have a significant equation, it would be desirable to have more experimental values.

$$\begin{gathered}\text{ClogP} = 1.043(\pm 0.614)\ \log P_E + 0.167(\pm 2.075) \\ n = 9,\ r = 0.835,\ r^2 = 0.698,\ q^2 = 0.441,\ s = 0.489,\ F_{1,7} = 1.796\end{gathered} \tag{3}$$

(3–Pyridylmethyl)benzoquinone derivatives

3–Pyridylmethyl)benzoquinone derivatives [21] inhibit thromboxane A_2 synthase and leukotriene biosynthesis enzymes. For the inhibition of 5–LOX the experiments were made in human blood (human whole blood assay). The following QSAR model is obtained with the data reported in Table 3:

$$\begin{gathered}\log 1/IC_{50} = 0.490(\pm 0.234)\ CMR - 1.914(\pm 0.421)\ I_{COOH} - 1.641(\pm 0.535)\ I_{Ph} + 2.174(\pm 2.077) \\ n = 19,\ r = 0.957,\ r^2 = 0.916,\ q^2 = 0.858,\ s = 0.359,\ F_{3,15} = 6.949,\ \alpha = 0.01\end{gathered} \tag{4}$$

where CMR is the overall calculated molecular refractivity. Since MR is primarily a measure of the bulk of the substituent, the positive coefficient for this term indicates that molecules are contacting polar space in the enzyme [22], not hydrophobic space. No considerable collinearity was found to exist between CMR and ClogP (CMR *vs*. ClogP 0.109). A positive coefficient might suggest an interaction depending on the polarizability of the substituents although there is a little evidence for the importance of such an effect. On the other hand I_{COOH} and I_{Ph} (indicator variables having a value of 1 when R has a carboxylic or phenyl group) have negative signs, which means that the presence of these groups decreases the inhibition of LOX.

However, if the experimental measured lipophilicity log P_E is used in place of CMR equation (5) is obtained:

$$\begin{gathered}\log 1/IC_{50} = 0.498(\pm 0.149)\ \log P_E - 1.439(\pm 0.562)\ I_{Ph} + 4.461(\pm 0.533) \\ n = 19,\ r = 0.921,\ r^2 = 0.849,\ q^2 = 0.810,\ s = 0.467,\ F_{2,16} = 33.118,\ \alpha = 0.01\end{gathered} \tag{5}$$

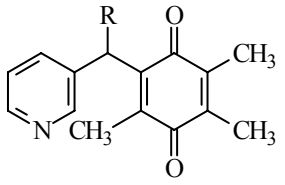
For the compounds in Table 4, equation (6) is derived:

$$\begin{gathered}\log 1/IC_{50} = 0.586(\pm 0.240)\ \log P_E + 5.473(\pm 0.396) \\ n = 6,\ r = 0.959,\ r^2 = 0.920,\ q^2 = 0.859,\ s = 0.324,\ F_{1,4} = 45.843,\ \alpha = 0.01\end{gathered} \tag{6}$$

Equation (6) shows that there is a linear relationship between the biological activity log $1/IC_{50}$

and log P_E (experimental lipophilicity). Compound 7 is an outlier and was not used to derive Eq. (6). This compound is an ester and can be easily hydrolyzed under the experimental conditions in the biological assay. Since log *P* is by far the most important parameter, it would seem that the simple linear relationship is associated with the positive diffusion of the compounds to the active site. No considerable collinearity was found to exist between log P_E and ClogP (log P_E *vs*. ClogP is 0.281).

Table 3. Physicochemical Parameters Used to Obtain Equations (4) and (5)



No	R	log 1/IC_{50}					CMR	I_{COOH}	I_{Ph}	log P_E
		Exp.	Calc. Eq. (4)	Res. Eq. (4)[a]	Calc. Eq. (5)	Res. Eq. (5)[a]				
1	Me	5.022	5.633	–0.641	5.854	–0.832	7.119	0	0	2.85
2	CH_2Me	6.180	5.890	0.290	6.098	0.082	7.582	0	0	3.35
3	$(CH_2)_3Me$	6.081	6.344	–0.263	6.587	–0.506	8.510	0	0	4.35
4	$(CH_2)_5Me$	7.137	6.799	0.338	7.075	0.062	9.438	0	0	5.35
5	$=CH(CH_2)_4Me$ (Z)	6.585	6.824	–0.239	6.929	–0.344	9.488	0	0	5.05
6	$=CH(CH_2)_4Me$ (E)	6.658	6.824	–0.166	6.929	–0.271	9.488	0	0	5.05
7	$(CH_2)_4OH$	7.000	6.419	0.581	6.020	0.980	8.663	0	0	3.19
8	$(CH_2)_5OH$	7.000	6.647	0.353	6.264	0.736	9.127	0	0	3.69
9	$(CH_2)_4OAc$	6.602	6.891	–0.289	6.455	0.147	9.626	0	0	4.08
10	$(CH_2)_5OAc$	7.060	7.119	–0.059	6.699	0.361	10.090	0	0	4.58
11	$(CH_2)_3COOH$	5.000	4.523	0.477	4.632	0.368	8.699	1	0	0.35
12	$(CH_2)_4COOH$	4.222	4.750	–0.528	4.867	–0.654	9.163	1	0	0.85
13	$(CH_2)_5COOH$	5.032	4.977	0.055	5.121	–0.089	9.626	1	0	1.35
14	$(CH_2)_6COOH$	5.155	5.205	–0.050	5.365	–0.210	10.090	1	0	1.85
15	$=CH(CH_2)_4COOH$ (E+Z)	5.143	5.002	0.141	4.974	0.169	9.677	1	0	1.05
16	Ph	5.119	5.024	0.095	5.211	–0.092	9.166	0	1	4.48
17	PhCH=C(Me)COOH	4.000	4.249	–0.249	4.038	–0.038	11.489	0	1	2.08
18	PhCH=CHCOOH	4.060	4.021	0.039	3.892	0.168	11.025	0	1	1.78
19	$Ph(CH_2)_2COOH$	4.000	3.885	0.115	4.038	–0.038	10.746	0	1	2.08

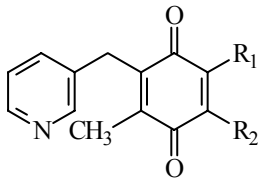
[a] Res. = Exp. – Calc.

The quality of the correlation varies considerably in term of the number of data points supporting an equation, the range in parameter values and the reliability of the various terms. Most researchers regard five data points/parameter as the maximum to support an equation. The reliability of the regression parameters in the QSAR model has been assessed with the F–test. We have provided F–tests at the generally used 0.95 level of significance and for the more stringent 0.99 level of significance for all terms in all equations. All terms pass at the 0.95 level.

Small structural features (*e.g.* σ) influencing how the inhibitor reacts with the enzyme are overshadowed by the penetration problem. With the isolated enzyme and with cells having a transport system, only molecules with log *P* < log P_o make full hydrophobic contact (log P_o is the

optimum value for lipophilicity). We are not able to formulate a QSAR with a bilinear model of log *P*, and the linear log *P* term is the most significant one. For some structural features, namely in equations (4) and (5) we have used indicator variables as a device to account for the effect of a specific feature that cannot be accounted for by a more specific parameter. The results support the older idea that lipophilicity as well as some steric requirements can be helpful in the design of potent LOX inhibitors.

Table 4. Physicochemical Parameters Used to Obtain Equation (6)



No	R_1	R_2	log $1/IC_{50}$			log P_E
			Exp.	Calc. Eq. (6)	Res. Eq. (6)[a]	
1	Me	Me	7.208	6.968	0.240	2.550
2	–CH=CHCH=CH–		7.097	7.086	7.097	–0.011
3	OMe	OMe	5.284	5.831	–0.547	0.610
4	Me	$(CH_2)_2COOH$	5.301	5.092	0.209	–0.650
5	Me	CH=CHCOOH	5.056	4.916	0.140	–0.950
6	Me	CH=C(Me)COOH	5.060	5.092	–0.032	–0.650
7	Me	CH=CHCOOEt	6.097	7.396	–1.299	3.280

[a] Res. = Exp. – Calc.

4 CONCLUSIONS

In conclusion, our results firmly establish the importance of hydrophobic interaction for LOX inhibitors. The *p*–quinone fragment is responsible for the LOX inhibiting activity while various types of substituents modulate the intensity of the biological activity. By the use of global hydrophobic parameter log *P* (experimental or theoretically calculated) three cases are found where the lipophilicity is important. In one case hydrophobicity was found to be less important than the steric effects of the substituents. In all these QSAR models the redox nature of the *p*–quinone moiety is not expressed through an electronic term.

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