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Structure-Activity Study of Anti-inflammatory Trioxoperhydropyrimidine Derivatives[1]

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Regression analyses using the Free-Wilson technique were applied to the anti-inflammatory effect and the acute toxicity of 57 1,3,5-trisubstituted 2,4,6-trioxoperhydropyrimidine derivatives. Models for the orientation of substituents on the "receptor site" are presented. A significant correlation was obtained by assuming that one of the N-substituents with a high hydrophobicity always locates at a particular binding site. Further analysis of the contributions of substituents at the 5-position using the free energy related hydrophobic parameter, π revealed that acute toxicity increases with an increase in the hydrophobicity of the 5-substituents. 1-Cyclohexyl-5-butyl or -allyl derivatives seemed to be the most suitable anti-inflammatory agents in terms of their high activity and low toxicity.

A number of di- and tri-substituted 2,4,6-trioxoperhydropyrimidines, shown in Fig. 1, were synthesized by Senda, *et al.*[3a] and their anti-inflammatory effect and acute toxicity, were measured by Fujimura, *et al.*[3] Among these, 5-*n*-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine (Bucolome^R) has been widely used as an effective anti-inflammatory drug with low toxicity and few side effects. We here report the structure-activity relationship of these derivatives, including Bucolome.

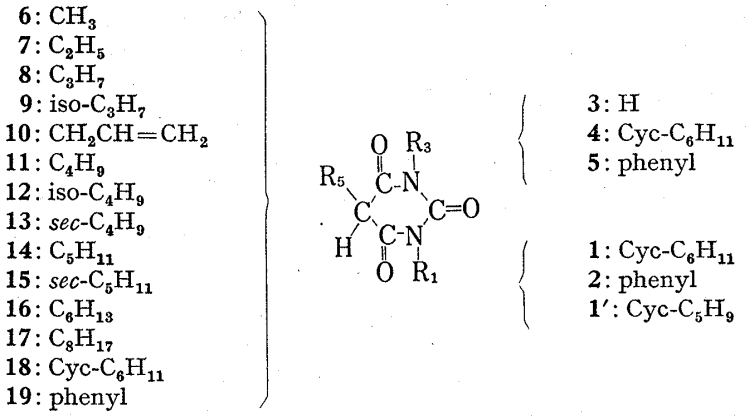

Fig. 1. Assignment of Substituents

Compounds with different substituents at the 1- and 3-positions have an asymmetric carbon atom at the 5-position. Racemic mixtures of these compounds have been used to measure the acute toxicity and anti-inflammatory effects. The pK_a value of 5-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine is reported to be 4.4.[4] We assume that other trioxoper-

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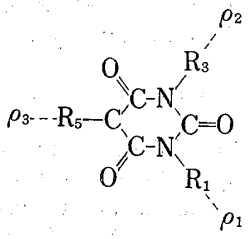
4) H. Mima, Y. Asahi, K. Terada, T. Matsuzaki, E. Mizuta, and H. Izumi, *Takeda Kenkyusho Nempo*, **24**, 1 (1965).

hydropyrimidine derivatives show nearly the same pK_a value. Therefore, these compounds will probably almost completely dissociate into ions at the 5-position in living systems under physiological conditions so that the (+)- and (−)-derivatives are no longer distinguishable from each other. This means that when administered to living systems, the racemic compounds would have the same biological activities as the individual administration of the (+)- or (−)-derivatives.

TABLE I. Models for the Location of Substituents



A			B			C		
R_1	R_3	Weight	R_1	R_3	Weight	R_1	R_3	Weight
Cyc-C_6H_{11}	H	1	Cyc-C_6H_{11}	H	1	Cyc-C_6H_{11}	H	0.5
						H	Cyc-C_6H_{11}	0.5
C_6H_5	H	1	C_6H_5	H	1	C_6H_5	H	0.5
						H	C_6H_5	0.5
Cyc-C_6H_{11}	Cyc-C_6H_{11}	1	Cyc-C_6H_{11}	Cyc-C_6H_{11}	1	Cyc-C_6H_{11}	Cyc-C_6H_{11}	1
Cyc-C_6H_{11}	C_6H_5	1	C_6H_5	Cyc-C_6H_{11}	1	Cyc-C_6H_{11}	C_6H_5	0.5
						C_6H_5	Cyc-C_6H_{11}	0.5
C_6H_5	C_6H_5	1	C_6H_5	C_6H_5	1	C_6H_5	C_6H_5	1

In the present study we assumed that the substituents R_1, R_3 and R_5 of the trioxoperhydropyrimidine derivatives play specific roles at each position. This is easily understandable if we speculate, for example, that the substituents interact with different binding areas ρ_1, ρ_2 and ρ_3, respectively, on the receptor site. Based on this assumption, three models A, B, and C are presented for the orientation of substituents as shown in Table I. In model A substituent R_1, which has an affinity for the ρ_1 area, is always more lipophilic than substituent R_3. In model B, the ρ_1 area prefers an aromatic group to a lipophilic one. In the symmetric C model, the ρ_1 and ρ_2 areas have no such selectivities as in models A and B. Substituents R_1 and R_3 interact with the binding areas ρ_1 and ρ_2 with the same probability. In Table I, the figures of the column, weight, show the probability with which each substituent pair interacts with the binding sites, ρ_1 and ρ_2. We have attempted to analyze the structure-activity relationship by using these three models to estimate the contribution of substituents to biological activity. Note that ρ_1, ρ_2 and ρ_3 are not necessarily the true binding areas on the receptor site. They merely represent the location of substituents classified according to their roles in eliciting biological activity.

Calculations

Regression analyses using the Free-Wilson method[5] assume that the biological activity of a compound is the mathematical sum of the contributions of the substituents and parent skeleton, as represented by Eq. 1. In this equation, Y represents the magnitude of the biological activity. G_i is the log activity

5) S.H. Free, Jr. and J.W. Wilson, *J. Med. Chem.*, **7**, 395 (1964); T. Fujita and T. Ban, *ibid.*, **14**, 148 (1971).

$$\log Y = \sum G_i X_i + c \qquad \text{Eq. 1}$$

contribution or the log activity enhancement factor of the i-th substituent. X_i takes the value of 1 or 0, depending on the presence or absence of the i-th substituent at each position. The numbering of the substituents is shown in Fig. 1. Unfortunately, no biological activities for the unsubstituted compound have been observed. Therefore, analyses based on Eq. 1 were performed by employing the overall average of the log activity values in this set of compounds for the term c.

Results

1) Acute Toxicity of Trioxoperhydropyrimidine Derivatives

The acute toxicity of 49 trioxoperhydropyrimidine derivatives have been reported by Senda, *et al.*[3a] The reciprocals of the LD_{50} values (mM/100 g) used in the present analysis were calculated from their data. Eq. 2 was obtained by applying Eq. 1 to the symmetric C model. Eqs. 3 and 4 were derived from applications

With model C:

	n	r	s	F	$\binom{(\phi_1)}{(\phi_2)}$	
$\log Y = \sum G_i X_i + c$	49	0.457	0.303	0.58	$\binom{(15)}{(33)}$	Eq. 2

With model A:

$\log Y = \sum G_i X_i + c$	49	0.739	0.234	2.40	$\binom{(16)}{(32)}$	Eq. 3

With model B:

$\log Y = \sum G_i X_i + c$	49	0.457	0.308	0.53	$\binom{(16)}{(32)}$	Eq. 4

of Eq. 1 for models A and B, respectively. In all the equations n is the number of compounds included in the analysis, r is the correlation coefficient and s is the standard deviation. Correlations between the observed and calculated activities in Eqs. 2 and 4 were poor and their correlation coefficients were not significantly different from zero. A fairly good correlation was observed in Eq. 3 obtained for model A. In equation 3, the F ratio between the variances of the calculated and observed activities was significant at the 97.5% level. Thus, it is conceivable that one of the 1- and 3-substituents, which is more hydrophobic than the other, plays a similar role in biological activity. One of the two binding areas, ρ_1 or ρ_2, may have a stronger affinity for lipophilic substituents than the other. When substituent R_5 is a phenyl or cyclohexyl group and is identical or closely resembles substituent R_1 or R_3 (Compounds No. **13**, **14**, **20**, **21**, **31**, **32**, **40**, **48**, and **49** in Table II), large differences are found between the observed and calculated values as shown in Table II. Some of these are predicted to be more toxic and others less toxic than was observed. These differences may be attributed to the steric limitation of the ρ_3 area. Another possibility might be that a quasi symmetry is involved in these compounds. Substituent R_5 may play a role which would otherwise be that of hydrophobic R_2 or the R_3 substituent.

The analysis of the structure-activity relationship based on model A, excluding these nine derivatives, led to Eq. 5.

	n	r	s	F	$\binom{(14)}{(25)}$	
$\log Y = \sum G_i X_i + c$	40	0.879	0.169	6.08		Eq. 5

The correlation was much improved over that of Eq. 3. The F ratio between the variances of the calculated and observed activities was significant at the 99.5% level. The log activity

contribution values G_is using Eqs. 3 and 5 for the acute toxicity are listed in Table III. The calculated total activity of each compound is shown in Table II.

TABLE II. Observed and Calculated -log LD_{50} Values of Trioxoperhydropyrimidine Derivatives

	R_1	R_3	R_5	Obsd.	Calcd. from Eq. 3	Calcd. from Eq. 5
1	Cyc-C_6H_{11}	H	CH_3	0.647	0.752	0.729
2			C_2H_5	0.995	0.785	0.762
3			C_3H_7	0.875	0.843	0.820
4			iso-C_3H_7	0.789	0.942	0.884
5			$CH_2CH=CH_2$	0.809	0.878	0.855
6			C_4H_9	0.685	0.883	0.860
7			iso-C_4H_9	0.887	0.863	0.881
8			*sec*-C_4H_9	0.908	0.731	0.749
9			C_5H_{11}	0.936	0.924	0.890
10			*sec*-C_5H_{11}	0.985	0.775	0.793
11			C_6H_{13}	1.067	1.067	1.067
12			C_8H_{17}	1.141	1.141	1.141
13			Cyc-C_6H_{11}	1.003	0.945	
14			C_6H_5	1.025	0.829	
15	C_6H_5	H	CH_3	0.483	0.492	0.445
16			C_2H_5	0.255	0.524	0.478
17			C_3H_7	0.467	0.583	0.536
18			$CH_2CH=CH_2$	0.442	0.618	0.571
19			C_4H_9	0.666	0.623	0.576
20			Cyc-C_6H_{11}	1.145	0.685	
21			C_6H_5	0.243	0.569	
22	Cyc-C_6H_{11}	Cyc-C_6H_{11}	CH_3	0.646	0.525	0.466
23			C_2H_5	0.501	0.557	0.498
24			C_3H_7	0.427	0.616	0.557
25			$CH_2CH=CH_2$	0.857	0.650	0.591
26			C_4H_9	0.691	0.656	0.597
27			iso-C_4H_9	0.612	0.636	0.618
28			*sec*-C_4H_9	0.326	0.503	0.485
29			C_5H_{11}	0.569	0.697	0.626
30			*sec*-C_5H_{11}	0.338	0.548	0.530
31			Cyc-C_6H_{11}	0.740	0.718	
32			C_6H_5	0.998	0.602	
33	Cyc-C_6H_{11}	C_6H_5	CH_3	1.155	1.023	1.099
34			C_2H_5	1.135	1.055	1.132
35			C_3H_7	1.198	1.114	1.190
36			iso-C_3H_7	1.061	1.213	1.254
37			$CH_2CH=CH_2$	1.296	1.149	1.225
38			C_4H_9	1.140	1.154	1.230
39			C_5H_{11}	1.112	1.195	1.260
40			Cyc-C_6H_{11}	0.628	1.216	
41	C_6H_5	C_6H_5	CH_3	0.622	0.763	0.815
42			C_2H_5	0.831	0.795	0.848
43			C_3H_7	1.044	0.854	0.906
44			iso-C_3H_7	1.257	0.953	0.970
45			$CH_2CH=CH_2$	0.778	0.889	0.941
46			C_4H_9	1.028	0.894	0.946
47			C_5H_{11}	1.134	0.935	0.976
48			Cyc-C_6H_{11}	1.003	0.956	
49			C_6H_5	0.574	0.840	

TABLE III. Calculated Group Contributions, G Values, of Trioxoperhydropyrimidine Derivatives

Position	i	Substituent	Acute toxicity		Anti-inflammatory effect		
			Calculated from Eq. 3	Eq. 5	Oval-bumin	Dextran	Carra-geenin
R_1	1′	Cyc-C_5H_9					0.433
	1	Cyc-C_6H_{11}	0.085	0.085	0.086	0.038	0.351
	2	C_6H_5	−0.175	−0.199	−0.178	−0.078	−0.361
R_3	3	H	−0.043	−0.070	0.020	−0.012	0.041
	4	Cyc-C_6H_{11}	−0.270	−0.334	−0.072	0.006	−0.474
	5	C_6H_5	0.228	0.300	0.022	0.011	0.104
R_5	6	CH_3	−0.110	−0.106	0.055	0.060	0.005
	7	C_2H_5	−0.077	−0.073	0.018	−0.050	−0.018
	8	C_3H_7	−0.018	−0.015	−0.034	0.001	−0.051
	9	iso-C_3H_7	0.080	0.049	−0.041	−0.043	−0.051
	10	$CH_2CH=CH_2$	0.016	0.020	0.101	0.163	0.043
	11	C_4H_9	0.022	0.025	0.032	0.090	0.015
	12	iso-C_4H_9	0.002	0.046	0.011	0.102	
	13	*sec*-C_4H_9	−0.131	−0.086	−0.081	−0.328	
	14	C_5H_{11}	0.063	0.055	0.007	−0.032	−0.083
	15	*sec*-C_5H_{11}	−0.086	−0.041	−0.118	0.010	−0.248
	16	C_6H_{13}	0.206	0.232	−0.127	−0.658	
	17	C_8H_{17}	0.279	0.306	−0.127	0.019	
	18	Cyc-C_6H_{11}	0.083		0.106	0.053	0.089
	19	C_6H_5	−0.032		−0.166	−0.062	−0.018
	20	c	0.819	0.820	1.601	1.533	1.275

We analyzed the G values obtained for substituents at the 5-position using a free energy related hydrophobic substituent parameter, π.[6,7] Using the G values calculated from Eq. 5; Eqs. 6 and 7 were obtained by the method of least squares. In Eq. 6 the G values of the cyclohexyl and phenyl groups were excluded, and in Eq. 7 the exclusion was extended to the *sec*-butyl and *sec*-pentyl groups. The fact that the *sec*-butyl and *sec*-pentyl

	n	r	s	
$G = 0.110\pi - 0.1205$	12	0.847	0.069	Eq. 6
$G = 0.114\pi - 0.1037$	10	0.942	0.045	Eq. 7

groups were the most poorly predicted substituents by Eq. 6 suggests that the steric effect of the 5-substituent plays a role in toxicity. Eq. 7 rationalized 88.7% of the variance in the data. The G values calculated from Eq. 7 are given in Table IV, in comparison with their original values and hydrophobic parameters, π. Eq. 7 indicates that the more hydrophobic the substituent at the 5-position, the stronger the acute toxicity.

2) Anti-inflammatory Effect of Trioxoperhydropyrimidine Derivatives

The anti-inflammatory effect of the trioxoperhydropyrimidine derivatives, shown in Table V, on rat paw edema induced by dextran, ovalbumin and carrageenin was measured by Senda, Izumi and Fujimura.[3a] In their report, the inhibitory effect of these compounds was divided into five grades, ⫼, ⫲, ⫩, +, ±, corresponding to 100—66%, 65—51%, 50—26%, 25—16%, and 15—0% inhibition, respectively. Intermediate values for the per cent of inhibition in the individual grades were adopted for the analysis. Thus, Y values of 83, 58, 38, 21 and 8 were assigned to the activities expressed as ⫼, ⫲, ⫩, + and ±, respectively.

6) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
7) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem.*, **86**, 5175 (1964).

Table IV. Group Contribution Values and the Hydrophobicity of Substituent R_5

R_5 Substituent	π[a]	G value	
		Original	Calcd. from Eq. 7
CH_3	0.0	−0.106	−0.104
C_2H_5	0.5	−0.073	−0.047
C_3H_7	1.0	−0.015	0.011
iso-C_3H_7	0.8	0.049	−0.012
$CH_2CH=CH_2$	0.7	0.020	−0.024
C_4H_9	1.5	0.025	0.068
iso-C_4H_9	1.3	0.046	0.045
C_5H_{11}	2.0	0.055	0.125
C_6H_{13}	2.5	0.232	0.182
C_8H_{17}	3.5	0.306	0.296

a) π values were recalculated from those in Ref. 7 by shifting the standard to a CH_3-group (π CH_3=0).

Table V. Observed and Calculated Anti-inflammatory Effects of Trioxoperhydropyrimidine Derivatives

	R_1	R_3	R_5	Ovalbumin			Dextran			Carrageenin		
				Obsd.		Calcd.	Obsd.		Calcd.	Obsd.		Calcd.
1	Cyc-C_6H_{11}	H	CH_3	###	###	1.761[a]	###	##	1.621[b]	—	—	—[c]
2			C_2H_5	###	###	1.724	##	##	1.510	—	—	—
3			C_3H_7	###	##	1.673	##	##	1.562	—	—	—
4			iso-C_3H_7	##	##	1.666	+	##	1.517	—	—	—
5			$CH_2CH=CH_2$	###	###	1.807	###	###	1.724	###	###	1.709
6			C_4H_9	###	##	1.738	###	##	1.651	###	###	1.681
7			iso-C_4H_9	###	###	1.717	###	##	1.663	—	—	—
8			*sec*-C_4H_9	##	##	1.625	±	+	1.233	—	—	—
9			C_5H_{11}	###	###	1.713	+	##	1.529	—	—	—
10			*sec*-C_5H_{11}	###	##	1.588	##	##	1.571	—	—	—
11			C_6H_{13}	##	##	1.580	±	±	0.903	—	—	—
12			C_8H_{17}	##	##	1.580	##	##	1.580	—	—	—
13			Cyc-C_6H_{11}	###	###	1.813	##	##	1.613	—	—	—
14			C_6H_5	+	##	1.541	##	##	1.499	—	—	—
15	C_6H_5	H	CH_3	##	##	1.497	+	##	1.505	±	±	0.959
16			C_2H_5	+	##	1.460	+	+	1.395	±	±	0.936
17			C_3H_7	+	+	1.409	##	##	1.446	±	±	0.903
17′			iso-C_3H_7	—	—	—	—	—	—	±	±	0.903
18			$CH_2CH=CH_2$	##	##	1.543	###	##	1.608	±	±	0.997
19			C_4H_9	+	##	1.474	##	##	1.535	±	±	0.969
19′			C_5H_{11}	—	—	—	—	—	—	±	±	0.871
20			Cyc-C_6H_{11}	##	##	1.549	##	##	1.498	±	±	1.043
21			C_6H_5	+	+	1.277	+	+	1.383	±	±	0.936
22	Cyc-C_6H_{11}	Cyc-C_6H_{11}	CH_3	###	##	1.670	###	##	1.638	+	±	1.156
23			C_2H_5	##	##	1.633	+	##	1.528	—	—	—
24			C_3H_7	##	##	1.582	##	##	1.579	—	—	—
25			$CH_2CH=CH_2$	##	###	1.716	##	###	1.741	—	—	—
26			C_4H_9	###	##	1.647	##	##	1.668	±	±	1.166
27			iso-C_4H_9	##	##	1.626	##	##	1.680	—	—	—
28			*sec*-C_4H_9	##	##	1.534	##	##	1.250	—	—	—
29			C_5H_{11}	##	##	1.622	##	##	1.546	—	—	—
30			*sec*-C_5H_{11}	+	##	1.497	##	##	1.589	±	±	0.903
31			Cyc-C_6H_{11}	###	###	1.722	##	##	1.631	—	—	—
32			C_6H_5	##	##	1.450	##	##	1.516	—	—	—

	R_1	R_3	R_5	Ovalbumin Obsd.	Ovalbumin Calcd.		Dextran Obsd.	Dextran Calcd.		Carrageenin Obsd.	Carrageenin Calcd.	
33	Cyc-C_6H_{11}	C_6H_5	CH_3	###	###	1.764	###	##	1.643	—	—	—
34			C_2H_5	###	###	1.727	##	##	1.533	—	—	—
35			C_3H_7	###	##	1.676	##	##	1.584	—	—	—
36			iso-C_3H_7	##	##	1.669	##	##	1.540	—	—	—
37			$CH_2CH=CH_2$	###	###	1.810	###	###	1.746	##	###	1.772
38			C_4H_9	##	###	1.741	##	##	1.673	##	###	1.744
39			C_5H_{11}	##	###	1.716	##	##	1.551	—	—	—
40			Cyc-C_6H_{11}	###	###	1.815	##	##	1.636	—	—	—
41	C_6H_5	C_6H_5	CH_3	+	##	1.500	+	##	1.528	±	±	1.023
42			C_2H_5	##	##	1.463	##	##	1.418	—	—	—
43			C_3H_7	+	+	1.412	+	##	1.469	—	—	—
44			iso-C_3H_7	##	+	1.405	##	##	1.425	—	—	—
45			$CH_2CH=CH_2$	##	##	1.546	##	##	1.631	+	±	1.061
46			C_4H_9	+	##	1.477	+	##	1.558	±	±	1.032
47			C_5H_{11}	##	##	1.452	##	##	1.436	±	±	0.935
48			Cyc-C_6H_{11}	##	##	1.551	##	##	1.521	+	±	1.107
49			C_6H_5	+	+	1.279	+	+	1.406	—	—	—
50	Cyc-C_5H_9	H	CH_3	—	—	—	—	—	—	###	###	1.754
51			C_2H_5	—	—	—	—	—	—	###	###	1.731
52			$CH_2CH=CH_2$	—	—	—	—	—	—	###	###	1.792
53			C_4H_9	—	—	—	—	—	—	###	###	1.764
54			Cyc-C_6H_{11}	—	—	—	—	—	—	###	####	1.838
55			C_6H_5	—	—	—	—	—	—	###	###	1.731

a) Calculated from *G* values obtained from Eq. 8, shown in Table III.
b) Calculated from *G* values obtained from Eq. 9, shown in Table III.
c) Calculated from *G* values obtained from Eq. 10, shown in Table III.

As with acute toxicity, the most significant correlations were obtained for regression analysis based on model A. Eqs. 8, 9 and 10 were derived by using this model for the anti-inflammatory effect on rat paw edema induced by dextran, ovalbumin and carrageenin, respectively. In each of these three equations,

For ovalbumin induced edema:

	n	r	s	F	(ϕ_1) (ϕ_2)	
$\log Y = \sum G_i X_i + c$	49	0.807	0.122	3.73	(16) (32)	Eq. 8

For dextran induced edema:

$\log Y = \sum G_i X_i + c$	49	0.746	0.156	2.51	(16) (32)	Eq. 9

For carrageenin induced edema:

$\log Y = \sum G_i X_i + c$	27	0.958	0.161	11.03	(13) (13)	Eq. 10

the F ratio between the variances of the calculated and observed activities was significant at the 97.5% level. The activity contribution values, G, for each of the anti-inflammatory effects obtained using Eqs. 8, 9 and 10 are given in Table III. The calculated total activities of each compound from Eqs. 8, 9 and 10 are shown in Table V.

Discussion

The G values for acute toxicity, shown in Table III, clearly indicate that compounds which have a phenyl group at the 1-position, R_1; and a cyclohexyl group at the 3-position, R_3;

may be expected to have the least toxicity. However, when these compounds are administered, they will dissociate into ions and the cyclohexyl group, which is the more lipophilic of the two substituents, will bind to the ρ_1 area on the receptor site resulting in the same toxicity as the corresponding compounds with a cyclohexyl group at the 1-position and a phenyl group at the 3-position have. Consequently they must be fairly toxic contrary to our initial expectation.

For the compounds used in the present work, there are five possible pairs of substituents at the 1- and 3-positions. The weakest toxicity is expected for derivatives having a phenyl group and a hydrogen atom at the 1- and 3-positions, respectively, but their anti-inflammatory effect will be very weak as well. In contrast, the strongest anti-inflammatory effect is expected for derivatives having cyclohexyl and phenyl groups at the 1- and 3-positions, respectively; but they will be very toxic. The best pair of substituents for the 1- and 3-positions would be a cyclohexyl group and hydrogen atom since a moderately weak toxicity and moderately strong anti-inflammatory effect are predicted for this pair.

As for substituent R_5, it is obvious from Eqs. 6 and 7 that methyl and ethyl groups which are less lipophilic than other groups contribute to a weakening of the toxicity, whereas a large lipophilic substituent, *i.e.* hexyl and octyl groups, leads to fairly toxic compounds. Anti-inflammatory activities seem to have no direct relation to the lipophilicity of substituent R_5. Allyl, butyl, cyclohexyl and methyl groups at the 5-position enhance the anti-inflammatory effect. Thus, as the most suitable anti-inflammatory agents in terms of their activity and toxicity, 1-cyclohexyl-5-methyl, -5-allyl, and -5-butyl derivatives would be selected from this series of compounds. In fact, the clinically used, anti-inflammatory agent, Bucolome^R, belongs to this group.

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