and ERP (0.003–0.03 mg/kg). Compound **2** showed similar high class III activity (0.01–0.10 mg/kg). *d*-Sotalol prolonged QTc interval at doses higher than 0.10 mg/kg. The relative potency of **1** to *d*-sotalol in in vivo experiments was similar to that in the in vitro study.

The pharmacokinetic properties of compounds **1–3** were assessed in conscious dogs (Table III). All of the compounds **1–3** were orally bioavailable (56–79%) and had moderate half-lives (i.e., $t_{1/2}\beta$ = 1.3–2.9 h).

Figure 1 shows the effects of intraduodenal (id) administration of **1**, the most active compound in vivo, on QTc intervals at doses of 0.10 and 0.30 mg/kg. The changes in the QTc interval were dose-dependent. The maximum response after id administration of 0.30 mg/kg was comparable to that after iv administration of 0.10 mg/kg. The prolongation of the QTc interval was significant even after 2 h.

Compounds that selectively prolong ERP in an in vivo system are expected to prevent VF by suppressing reentrant impulses in cardiac tissue.[1] Therefore, the antiarrhythmic effects of **1** on VF were further investigated in anesthetized coronary ligated dogs (Figure 2).[20] Iv infusion (5 μg/kg per min) of **1** during the ligation reduced the incidence of VF. This result suggests the potential utility of **1** in the prevention of VF associated with acute myocardial ischemia.

In conclusion, the present study shows that 4′-[(4-piperidyl)carbonyl]methanesulfonanilides have selective class III activities. Of these, compound **1** (E-4031) is one of the most potent and bioavailable class III antiarrhythmic agents. Compound **1** is now in clinical trials. Further details of the medicinal chemistry of a series of **1–3** will be described in forthcoming publications.

Acknowledgment. We thank members of the Analytical Chemistry Section of our laboratories for interpretation of the mass spectra and elemental analysis data.

Registry No. **1** (free base), 113558-89-7; **1**·2HCl, 113559-13-0; **2** (free base), 124536-77-2; **2**·2HCl, 113559-12-9; **3** (free base), 113558-75-1; **3**·2HCl, 113559-11-8; **4**, 1197-22-4; **5**, 59084-16-1; **6**, 113558-94-4; **7**, 113559-02-7; **8**, 1122-70-9; **9**, 17944-59-1; **10**, 4226-36-2.

(19) (a) Mongrel dogs (8–16 kg) of either sex were anesthetized with enflurane and nitrous oxide. The right femoral artery and vein were cannulated to monitor aortic blood pressure and for the administration of test compound, respectively. Left ventricular pressure was monitored with use of a microtip catheter transducer into the left ventricle from left femoral artery. LV dP/dT was obtained by mechanical differential of left ventricular pressure. Heart rate (HR) was mechanically counted from the figure of the left ventricular pressure. QT interval of lead II ECG was calculated as the mean of measurments from three consecutive beats. Corrected QT (QTc) was calculated according to Bazett's formula: $QTc = QT/RR^{1/2}$. (b) In other mongrel dogs, the heart was exposed through a lateral thracotomy, and unipolar electrodes were sutured onto the surface of the left ventricle to monitor ventricular surface ECG. Effective refractory periods (ERPs) were measured by cathodal stimulation through each of three unipolar electrodes on a left ventricle with rectangular pulses of 3-ms duration at twice the diastolic threshold. A programmed single premature ventricular stimulus (S_2) was delivered after fixed-rate ventricular pacing (S_1) at a cycle length of 600 ms. The interval between S_1 and S_2 was decreased in 5-ms steps until S_2 was no longer captured. ERP was defined as the longest S_1–S_2 interval that did not elicit a ventricular capture, and ERP of an left ventricle was calculated as the mean of three sites of the left ventricular surface.

(20) Nomoto, K.; Katoh, H.; Sawada, K.; Shoji, T. *J. Mol. Cell Cardiol.* 1989, *21*, Suppl II, s-20, 60.

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Neural Networks Applied to Structure–Activity Relationships

Sir:

The neural network is a computer-based system derived from the simplified concept of the brain in which a number of node, called processing elements or neurons, are interconnected in a netlike structure.[1] The characteristics of the neural network have been found to be suitable for data processing in which the relationship between the cause and its results cannot be exactly defined. Thus its use in biology-related responses is strongly suggested. Another prominent characteristic of the neural network is its ability to classify or grade. Therefore, we tried to apply neural networks to the study of structure–activity relationships (SAR) and obtained promising results.

Shown in Figure 1 is the neural network: the circles are neurons which are actually variables taking values ranging from 0 to 1. The number of the layers is arbitrary and the network generally consists of n layers. The data are input to A and are output from B. The value of a neuron (O_j) at the nth layer can be expressed by eq 1, where x_i is one

$$O_j = 1/[1 + \exp(-\alpha y_j)] \equiv f(y_j),\ y_j = \sum W_{ij}x_i - \theta_j \quad (1)$$

of the values of the neurons at the $n - 1$ layer; W_{ij}, an element of the weight matrix, expresses the weight value between neurons i and j; θ_j is a threshold value for neuron j; and α is a parameter which expresses the nonlinearity of the neuron's operation. On feeding the input data into A, the value of every neuron expressed by eq 1 is synchronously changed. The training is carried out according to the back-propagation algorithm[1] until

$$E = \sum(O_j - t_j)^2 \quad (2)$$

becomes small enough (where **t** is a training pattern (a vector)) to give a fixed-weight matrix. Even in the case that M sets of the input and training patterns are given, all of output patterns can be made close enough to the training patterns by the iteration through eq 1 and the back-propagation procedure. Then, the neural network has an ability to classify the input patterns into M groups.[2]

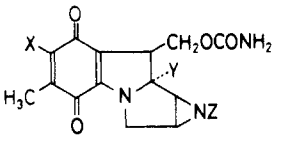
Table I. Parameters of Neural Networks

A				B			
layer	neurons	α	θ	layer	neurons	α	θ
1	6			1	7		
2	12	2.5	0.0	2	14	2.5	0.0
3	5	5.0	0.0	3	4	5.0	0.0

(1) For example: *Parallel Distributed Processing Exploration in Microstructure of Cognition*; Rumelhart, D. E., McClelland, J. L., Eds.; the MIT Press: Cambridge, MA, 1986; Vols. 1 and 2.

0022-2623/90/1833-0905$02.50/0

Table II. Structures and Observed Activities in Mitomycins, and Input Parameters, Output Patterns, and Calculated Classifications by the Neural Network[a]



									output pattern to determine rank					rank	
no.	X	Y	Z	F_x	σ_{m-x}	V_{w-x}	Y_{OMe}	Y_{OH}	E_{s-z}	3+	2+	+	+/-	-	obsd	calcd
1	NH_2	OMe	H	0.02	-0.16	0.177	1	0	1.24	0.95	0.08	0.00	0.00	0.00	3+	3+
2	NHEt	OMe	H	-0.11	-0.24	0.493	1	0	1.24	0.95	0.05	0.00	0.00	0.00	3+	3+
3	NH_2	OMe	Me	0.02	-0.16	0.177	1	0	0	0.01	0.98	0.06	0.00	0.00	2+	2+
4	NH_2	OMe	Et	0.02	-0.16	0.177	1	0	-0.07	0.00	0.98	0.10	0.00	0.00	2+	2+
5	NH_2	OMe	Ac	0.02	-0.16	0.177	1	0	-0.47	0.03	0.94	0.56	0.00	0.00	2+	2+
6	NH_2	OH	Me	0.02	-0.16	0.177	0	1	0	0.03	1.00	0.00	0.02	0.00	2+	2+
7	NMe_2	OMe	H	0.10	-0.15	0.441	1	0	1.24	0.02	0.92	0.03	0.00	0.00	2+	2+
8	NH_2	OMe	COPh-*o*-Cl	0.02	-0.16	0.177	1	0	-1.19	0.00	0.04	0.84	0.00	0.07	+	+
9	NH_2	OMe	COPh-*p*-Cl	0.02	-0.16	0.177	1	0	-1.19	0.00	0.04	0.84	0.00	0.07	+	+
10	NHPh	OMe	H	-0.02	-0.12	0.892	1	0	1.24	0.00	0.08	0.96	0.00	0.00	+	+
11	OMe	OMe	H	0.26	0.12	0.304	1	0	1.24	0.00	0.08	0.99	0.00	0.00	+	+
12	OMe	OMe	Me	0.26	0.12	0.304	1	0	0	0.00	0.07	1.00	0.00	0.00	+	+
13	OMe	OH	Me	0.26	0.12	0.304	0	1	0	0.00	0.05	0.01	0.96	0.03	+/-	+/-
14	NH_2	H	Me	0.02	-0.16	0.177	0	0	0	0.00	0.00	0.00	0.00	0.94	-	-
15	NH_2	OMe	SO_2Me	0.02	-0.16	0.177	1	0	-1.54	0.00	0.00	0.45	0.03	0.89	-	-
16	OMe	H	Me	0.26	0.12	0.304	0	0	0	0.00	0.00	0.06	0.00	0.99	-	-

[a] Me = CH_3, Et = C_2H_5, Ac = CH_3CO, Ph = C_6H_5.

We used well-studied data to compare the classification abilities of the network with those of the ALS method,[3] which may be considered to be most reliable at present. We first examined the structure–activity relationship of derivatives of carboquinone. The experimental data were taken from the literature[3] and the same compound numbers were used. The network structure and parameters are shown in Table I, under heading A.[4] Since the neurons are supposed to take values between 0 and 1, the parameters, i.e., F_x, σ_{m-x}, V_{w-x}, Y_{OMe}, Y_{OH}, and E_{s-z}, are appropriately rescaled to take the values between ca. 0.1 and 1 by the following equation

$$\tilde{x}_i = (x_i - x_{min} + 0.1)/(x_{max} - x_{min} + 0.1) \quad (3)$$

where x_{min} and x_{max} are the minimum and maximum data. The reason not to give 0 as the least value is to avoid the situation at $x_i = 0$, where W_{ij} may remain unchanged at the training phase. Each class of five ranks (from 3+ to -) of the anticarcinogenic activity was expressed with the setting 1 at one of the elements of the output patterns. For example, for the rank 2+, the training pattern is (0,1,0,0,0). The last column of Table II shows the classifications by the neutral network: the 16 derivatives are classified into five ranks in complete accord with observation. This resolution ability is found to be better than that obtained by the ALS method, in which one case of disagreement appears.[3]

Another beneficial character of the neural network is its prediction ability. We next examined such an ability: five arbitrary pieces of data (**2**, **4**, **7**, **10**, and **16**) were removed from the training patterns and the network was let go into recursive iteration until all weights settled down into a fixed connection pattern. The structure and parameters of the network are the same as before (Table I, heading A). The network thus obtained was used to classify the removed compounds. Table III shows the results of classification for the reduced training patterns together with the predictions for the removed compounds. One can see that the ranks determined by the new network are the same as those originally observed. The lower part of Table III shows that three of five compounds are correctly pre-

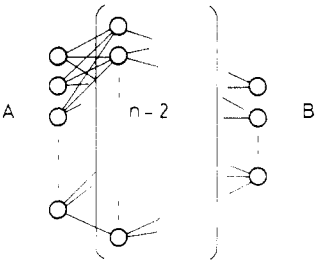


Figure 1. *n*-Layer neural network.

Table III. Output Patterns and Classification and Predictions of SAR of Mitomycins in Reduced Number of Training Patterns

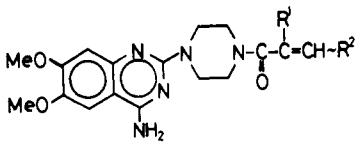
	output pattern to determine rank					rank	
no.	3+	2+	+	+/-	-	obsd	calcd
1	0.91	0.13	0.00	0.00	0.00	3+	3+
3	0.10	0.87	0.05	0.00	0.00	2+	2+
5	0.01	0.93	0.32	0.00	0.00	2+	2+
6	0.00	0.98	0.00	0.02	0.00	2+	2+
8	0.00	0.12	0.48	0.01	0.00	+	+
9	0.00	0.12	0.48	0.01	0.00	+	+
11	0.00	0.04	0.92	0.00	0.00	+	+
12	0.00	0.00	0.96	0.01	0.04	+	+
13	0.00	0.00	0.02	0.93	0.05	+/-	+/-
14	0.00	0.02	0.00	0.00	0.91	-	-
15	0.00	0.00	0.35	0.06	0.87	-	-
2	0.91	0.14	0.00	0.00	0.00	3+	3+
4	0.07	0.89	0.07	0.00	0.00	2+	2+
7	0.81	0.25	0.00	0.00	0.00	2+	3+
10	0.84	0.21	0.00	0.00	0.00	+	3+
16	0.00	0.00	0.74	0.00	0.99	-	-

(2) Those procedures are programmed by the FORTRAN language for a personal computer (NEC PC-9801UV (8086cpu with the 8087 coprocessor)).

(3) Moriguchi, I. In *Structure–Activity Relationship—Quantitative Approaches*; Fujita, T., Ed.; Nankodo: Tokyo, Japan, 1986; Chapter 9.

(4) The numbers of the neurons in the input and output layers are usually set to be equal to those of the input parameters and grading classes, respectively.

Table IV. Structures and Activities of Arylacryloylpiperazines and Input Parameters, Output Patterns, and Calculated Classifications by the Neural Network



no.	R^1	R^{2a}	ΔRI	$\sum\pi$	$\sum\sigma$	I(2-OR)	$I(R^1)$	HB	output pattern to determine rank 1	2	3	4	rank obsd	calcd
19	H	4-*i*-PrPh	2.36	1.53	−0.15	0	0	0	0.989	0.090	0.001	0.000	1	1
20	H	2-MeOPh	0.49	−0.02	−0.27	1	0	1	0.989	0.159	0.000	0.000	1	1
21	H	2-EtOPh	1.18	0.38	−0.24	1	0	1	1.000	0.056	0.000	0.000	1	1
22	H	3,5-$(MeOPh)_2$	0.56	−0.04	0.24	0	0	1	0.999	0.000	0.000	0.005	1	1
23	H	3-NO_2Ph	0.03	−0.28	0.71	0	0	1	1.000	0.000	0.000	0.000	1	1
24	H	3,4-$(ClPh)_2$	2.19	1.42	0.60	0	0	0	1.000	0.001	0.000	0.000	1	1
25	H	3-CF_3Ph	1.17	0.88	0.43	0	0	0	1.000	0.008	0.000	0.000	1	1
26	H	3-MeOPh	0.28	−0.02	0.12	0	0	1	0.809	0.000	0.001	0.097	1	1
27	H	4-ClPh	1.01	0.71	0.23	0	0	0	0.992	0.073	0.004	0.000	1	1
28	H	4-BrPh	1.26	0.86	0.23	0	0	0	0.998	0.045	0.001	0.000	1	1
29	H	5-Cl-2-Th	0.89	0.39	0.26	0	0	0	0.982	0.081	0.009	0.000	1	1
30	H	3-MePh	1.01	0.56	−0.07	0	0	0	0.104	0.482	0.199	0.000	2	2
31	H	4-MePh	0.95	0.56	−0.17	0	0	0	0.009	0.621	0.425	0.000	2	2
32	H	4-*i*-PrOPh	1.53	0.82	−0.45	0	0	1	0.019	0.887	0.000	0.796	2	2
33	H	2,3,4-$(MeOPh)_3$	−0.09	−0.06	−0.42	1	0	1	0.002	0.858	0.004	0.029	2	2
34	H	5-Me-2-Th	0.69	0.24	−0.14	0	0	0	0.002	0.513	0.537	0.001	2	3
35	H	2-MePh	0.83	0.56	−0.17	0	0	0	0.005	0.597	0.485	0.000	3	2
36	Me	Ph	0.20	0.54	0	0	1	0	0.000	0.042	0.882	0.002	3	3
37	H	3-Fu	−1.29	−0.79	0.04	0	0	1	0.000	0.000	0.881	1.000	3	3
38	H	5-Me-2-Fu	0.04	−0.23	0.15	0	0	1	0.111	0.000	0.003	0.137	3	4
39	Me	2-Th	−0.13	0.22	0.03	0	1	0	0.000	0.003	0.914	0.051	3	3
40	H	3-Me-2-Th	0.48	0.24	−0.14	0	0	0	0.001	0.401	0.606	0.004	3	3
18	H	Ph	0	0	0	0	0	0	0.000	0.077	0.538	0.023	3	3
41	H	2-Th	−0.36	−0.32	0.03	0	0	0	0.000	0.005	0.565	0.396	3	3
42	H	4-MeOPh	0.19	−0.02	−0.27	0	0	1	0.000	0.030	0.070	0.993	4	4
43	H	4-EtOPh	0.92	0.38	−0.24	0	0	1	0.091	0.121	0.001	0.578	4	4
44	H	2-Fu	−0.84	−0.79	0.32	0	0	1	0.000	0.000	0.061	0.886	4	4
45	Me	2-Fu	−0.71	−0.25	0.32	0	1	1	0.000	0.000	0.071	0.989	4	4
46	H	3-Th	−0.61	−0.32	0.04	0	0	0	0.000	0.001	0.577	0.834	4	4

[a] Ph = C_6H_5, Fu = furyl(C_4H_3O), Th = thienyl(C_4H_3S).

Table V. Output Patterns and Classification and Predictions of SAR of Arylacryloylpiperazines in Reduced Number of Training Patterns

no.	output pattern to determine rank 1	2	3	4	class/ predctn
19	1.000	0.185	0.001	0.000	1
21	0.999	0.007	0.000	0.000	1
23	0.999	0.000	0.011	0.019	1
25	1.000	0.015	0.002	0.000	1
26	0.889	0.000	0.410	0.045	1
27	0.999	0.068	0.010	0.000	1
29	0.987	0.067	0.022	0.000	1
30	0.090	0.403	0.166	0.000	2
31	0.004	0.551	0.306	0.000	2
32	0.142	0.779	0.000	0.041	2
34	0.000	0.476	0.609	0.000	3
35	0.002	0.533	0.377	0.000	2
36	0.000	0.023	0.964	0.001	3
37	0.000	0.000	0.843	0.213	3
38	0.324	0.000	0.589	0.134	3
40	0.000	0.403	0.702	0.001	3
41	0.000	0.006	0.601	0.326	3
42	0.000	0.005	0.082	0.961	4
43	0.038	0.105	0.003	0.509	4
44	0.000	0.000	0.181	0.796	4
46	0.000	0.002	0.512	0.576	4
20	0.569	0.001	0.029	0.101	1
22	0.999	0.000	0.222	0.003	1
24	1.000	0.005	0.000	0.000	1
28	1.000	0.059	0.005	0.000	1
33	0.000	0.000	0.159	0.715	4
39	0.000	0.002	0.981	0.030	3
18	0.000	0.074	0.694	0.022	3
45	0.000	0.000	0.974	0.017	3

dicted, but at the same time such minor errors are also found as 2+ for 3+ (**7**) and + for 3+ (**10**).

The same method was applied to the antihypertensive activity in the derivatives of arylacryloylpiperazine[5a] since this is an example in which the ALS method faced some difficulties in grading.[5b] The results from the network are shown in Table IV, where the compound numbers are the same as those in the literature.[5b] The structure and the parameters of the network are shown in Table I, under heading B. The input data are ΔRI, $\sum\pi$, $\sum\sigma$, I(2-OR), $I(R^1)$, HB, and the constant 1.[6] As might be expected from the low quality of the given data, the convergence of the weight matrix was not easily attained: the maximum of the squared difference, $\sum (O_j^m - t_j^m)^2$ (where O_j^m and t_j^m are the output and training patterns of the mth set), was 1.0 at the 784th iteration. We tried to double the number of the neurons in the second layer. However, even at the 1410th iteration,[7] the squared difference did not converge within 1.0. This means that the difficulty of the convergence is not caused by the structure of the network but the quantity of the information included in the given data.

(5) (a) Sekiya, T.; Hirayama, H.; Hata, S.; Mizogami, S.; Hanazuka, M.; Yamada, S. *J. Med. Chem.* 1983, *26*, 411. (b) Sekiya, T. In *Structure–Activity Relationship and Drug Design*, Fujita, T., Ed.; Kagakudojin; Kyoto, Japan, 1986; Chapter 9.

(6) The constant was added to increase the recognition ability of the network: this effect is equivalent to the effect of having the parameter θ_j set to be the best value.

(7) The iteration took ~7 h.

The network gave minor errors such as classifying 34, 35, and 38 into, respectively, rank 3, 2, and 4 instead of the observed ranks 2, 3, and 3. It may be generally said that output patterns with one of the elements being close to 1 and other elements being close to 0 steadily give reliable results. The rate of correct grading was 26/29 (= 0.90), which is far better than those of ALS method (0.62–0.76).

We again tried the prediction ability of the network: eight arbitrary data points were removed from the original data to make the weight matrix, then the removed data were fed to the network to get the results. Good convergence was not obtained: the maximum squared difference was 0.723 at the 1381st iteration. The results are shown in Table V. The rate of correct classification was 19/21 (=0.90) and that of correct prediction was 6/8 (=0.75).

Thus we found that the neural network makes best use of the information included in the given data, resulting in an excellent grading compared to other conventional methods. Moreover, the prediction ability in addition to the easy operation indicated that the neural network will be a valuable tool in developing new drugs.

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Articles

Antioxidant-Based Inhibitors of Leukotriene Biosynthesis. The Discovery of 6-[1-[2-(Hydroxymethyl)phenyl]-1-propen-3-yl]-2,3-dihydro-5-benzofuranol, a Potent Topical Antiinflammatory Agent

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The leukotrienes, metabolites of arachidonic acid produced through the action of the enzyme 5-lipoxygenase, are important mediators of immediate hypersensitivity and inflammation. Among the variety of diseases in which the leukotrienes may play a symptomatic or causative role is the dermatological condition psoriasis, a chronic proliferative disease of the skin. This study reports the synthesis and comparative biological activities of various ortho-substituted phenols including 4-methoxyphenols, 6-hydroxy-1,2,3,4-tetrahydrobenzopyrans, 2,3-dihydro-5-benzofuranols, and 5-benzofuranols. The phenols prepared in this study were evaluated for their ability to inhibit the production of leukotriene B_4(LTB_4) in isolated human polymorphonuclear leukocytes (PMNs) and to inhibit a topical inflammatory response in the topical mouse ear (TME) model. In the former case, when the log IC_{50} was plotted versus the log of the octanol/water partition coefficient (log P), to eliminate the effect of lipophilicity, the 2,3-dihydro-5-benzofuranol ring system was shown to be more potent than the other ring systems examined throughout the range of partition coefficients studied. The ability to inhibit leukotriene production in vitro in human PMNs can be rationalized on the basis of a model that suggests that the observed inhibition is dependent on the kinetic ability of the inhibitor to reduce a radical species and on the fraction of inhibitor that is partitioned into the cell membrane. While the in vivo antiinflammatory activity as measured by the TME did not correlate with the in vitro data, it was felt that the TME represented a valuable measure of the ability of a compound to penetrate the skin to the site of an ongoing inflammatory response. Of the compounds synthesized in this study, 6-[1-[2-(hydroxymethyl)phenyl]-1-propen-3-yl]-2,3-dihydro-5-benzofuranol (1, L-651896) was chosen for further development.

The leukotrienes, metabolites of arachidonic acid produced through the action of the enzyme 5-lipoxygenase, are important mediators of immediate hypersensitivity and inflammation.[1] In particular leukotriene C_4 (LTC_4) and LTD_4 cause a prolonged constriction of bronchial smooth muscle and have been identified as the slow-reacting substances of anaphylaxis (SRSAs).[2] Leukotriene B_4 is a potent chemotactic agent for polymorphonuclear leukocytes (PMNs), which are also a rich source of LTB_4.[3]

Among the variety of diseases in which the leukotrienes may play a symptomatic or causative role is the dermatological condition psoriasis. Psoriasis is a chronic proliferative disease of the skin whose lesions are characterized by the accumulation of PMNs.[4] Leukotriene B_4, along with other metabolites of arachidonic acid, has been found in elevated concentration in the involved skin of psoriatic patients.[5] It therefore seemed reasonable to hypothesize that a potent topical inhibitor of leukotriene biosynthesis

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