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Furo[3,2-*b*]indole Derivatives. V.¹⁾ Synthesis and Structure-Activity Studies of 4-Substituted 2-(4-Methylpiperazinylcarbonyl)-6-trifluoromethylfuro[3,2-*b*]indole Derivatives with Analgesic and Antiinflammatory Activities²⁾

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Based on the quantitative structure-activity relationships (QSAR) of 4,6-disubstituted 2-morpholinocarbonylfuro[3,2-*b*]indole derivatives (53 compounds) previously reported, 4-substituted 2-(4-methylpiperazinylcarbonyl)-6-trifluoromethylfuro[3,2-*b*]indole derivatives (12 compounds) were synthesized. Their analgesic and antiinflammatory activities were examined by using the acetic acid writhing test in mice and the carrageenin edema test in rats, respectively. Most of these compounds showed potent analgesic and antiinflammatory activities as compared with tiaramide. The QSAR of the furo[3,2-*b*]indole derivatives (65 compounds) including the newly synthesized compounds was analyzed by using the adaptive least-squares method. The results confirmed that the QSARs for 2-morpholinocarbonyl derivatives and 2-(4-methylpiperazinylcarbonyl) derivatives can be expressed in one model where the steric nature of the 4- and 6-substituents mainly affects both the analgesic and antiinflammatory potencies.

Keywords—furo[3,2-*b*]indole-2-carboxamide; quantitative structure-activity relationship; adaptive least-squares method; analgesic activity; antiinflammatory activity; 4-substituted 2-(4-methylpiperazinylcarbonyl)-6-trifluoromethylfuro[3,2-*b*]indole

In the previous papers,^{1,3)} we reported the synthesis, analgesic and antiinflammatory activities, as well as quantitative structure-activity relationship (QSAR) studies, of 4,6-disubstituted 2-morpholinocarbonylfuro[3,2-*b*]indole derivatives (I). Equations 1 and 2 were formulated for the QSAR of analgesic and antiinflammatory activities, respectively.

$$Y = -0.68E_s(1) + 0.11L(2) + 1.19Nc\beta_a + 1.91D_{acyl} + 1.27D_{alkyl} - 3.10 \quad (1)$$

$n = 53 \quad n_{mis} = 6(0) \quad R_S = 0.91 \quad R_S(pred) = 0.87$

$$Y = 2.84B_1(1) - 1.70F(1) + 0.63Nc\beta_a + 0.71D_{acyl} + 1.18D_{alkyl} - 4.47 \quad (2)$$

$n = 53 \quad n_{mis} = 9(1) \quad R_S = 0.87 \quad R_S(pred) = 0.84$

I

II

Chart 1

TABLE I. 2-(4-Methylpiperazinylcarbonyl)-6-trifluoromethylfuro[3,2-*b*]indole Derivatives (II)

No.	R ₂	mp (°C)	Recrystn. solvent ^{a)}	Formula	Analysis (%)			Analgesic activity ^{b)}	Anti-inflammatory activity ^{c)}
					C	H	N		
II-1	CO ₂ iso-Pr	178—179	E-T	C ₂₁ H ₂₂ F ₃ N ₃ O ₄ ·Mal ^{d)}	54.25 (54.10)	4.74 4.73	7.59 7.66	85.5 ^{h)}	64.3 ^{h)}
II-2	COOBu	141—142	E	C ₂₂ H ₂₄ F ₃ N ₃ O ₄	58.53 (58.68)	5.36 5.54	9.31 9.28	69.4 ^{h)}	—0.6
II-3	CO ₂ iso-Bu	194.5—195.5	M	C ₂₂ H ₂₄ F ₃ N ₃ O ₄ ·Mal	55.02 (55.18)	4.97 4.98	7.40 7.50	91.7 ^{h)}	50.0 ^{g)}
II-4	CO ₂ iso-Bu	174.5—175.5	T-H	C ₂₂ H ₂₄ F ₃ N ₃ O ₃ ·Mal	56.62 (56.54)	5.12 5.12	7.62 7.60	81.6 ^{h)}	64.1 ^{h)}
II-5	Bu	174—176	T	C ₂₁ H ₂₄ F ₃ N ₃ O ₂ ·Mal	57.36 (57.45)	5.39 5.39	8.02 8.06	75.5 ^{h)}	55.0 ^{h)}
II-6	iso-Bu	170—173.5	E-M	C ₂₁ H ₂₄ F ₃ N ₃ O ₂ ·Mal	57.36 (57.09)	5.39 5.32	8.02 7.86	55.6 ^{h)}	20.1 ^{f)}
II-7	Pentyl	224—226	E-H	C ₂₂ H ₂₆ F ₃ N ₃ O ₂ ·HCl ^{e)}	57.71 (57.47)	5.94 6.22	9.17 8.96	62.5 ^{h)}	58.4 ^{h)}
II-8	Isopentyl	159—160	T	C ₂₂ H ₂₆ F ₃ N ₃ O ₂ ·Mal	58.10 (58.03)	5.63 5.60	7.82 7.71	93.5 ^{h)}	75.8 ^{h)}
II-9	Hexyl	199—200	T-H	C ₂₃ H ₂₈ F ₃ N ₃ O ₂ ·HCl	58.53 (58.30)	6.19 6.18	8.90 9.03	77.6 ^{h)}	67.2 ^{h)}
II-10	Isohexyl	144—145	E-M	C ₂₃ H ₂₈ F ₃ N ₃ O ₂ ·Mal	58.79 (58.52)	5.85 5.77	7.62 7.49	95.9 ^{h)}	54.7 ^{h)}
II-11	Heptyl	161—168	T	C ₂₄ H ₃₀ F ₃ N ₃ O ₂ ·HCl	59.34 (59.00)	6.43 6.35	8.65 8.80	85.4 ^{h)}	63.1 ^{h)}
II-12	Octyl	167.5—168.5	E-M	C ₂₅ H ₃₂ F ₃ N ₃ O ₂ ·Mal	60.09 (59.86)	6.26 6.35	7.25 7.16	45.3 ^{h)}	50.3 ^{g)}
Tiaramide					74.8 ^{h)}				52.4 ^{h)}

a) E=ether, H=hexane, M=MeOH, T=EtOH. b) % inhibition of acetic acid writhing in mice (100 mg/kg. *p.o.*). c) % inhibition of carrageenin edema in rats (100 mg/kg. *p.o.*). d) Mal=malate. e) HCl=hydrochloride. Statistically significant at *f*) *p*<0.05, *g*) *p*<0.01, *h*) *p*<0.001.

In these expressions, Y is the discriminant score for the classification of activity ratings, E_s is the Taft steric substituent parameter,⁴⁾ B_1 and L are the STERIMOL parameters,⁵⁾ F is the new Swain–Lupton field constant,⁶⁾ and $Nc\beta_a$ is the number of β -carbon atoms of the alkoxy moiety as R_2 . The figure in parentheses after the descriptor indicates the position of the substituent (R_1 or R_2 in Chart 1). The indicator variables D_{acyl} and D_{alkyl} are assigned a value of 1 for the presence of an acyl moiety and an alkyl (or alkenyl) moiety as R_2 , respectively. Further, n represents the number of compounds, n_{mis} is the number misclassified, and the figure in parentheses after the value of n_{mis} is the number misclassified by two grades, R_s is the Spearman rank correlation coefficient for the recognition, and $R_s(\text{pred})$ is that for the prediction by the use of the leave-one-out technique. These equations indicate that, as regards the substituents of the indole moiety, bulky and branched substituents are favorable for the analgesic activity, and that steric and electron withdrawing effects are required for high antiinflammatory potency. We thought that the relationship would be valid for 2-(4-methylpiperazinylcarbonyl)furo[3,2-*b*]indole derivatives (II), and this prompted us to undertake the present study.

This paper describes the synthesis and activity of the derivatives (II) and an analysis of the QSAR of the overall compounds (I and II) for analgesic and antiinflammatory activities using the adaptive least-squares (ALS) method.^{7,8)}

Results and Discussion

Based on the results of our previous structure–activity study¹⁾ of 2-morpholino-carbonylfuro[3,2-*b*]indole derivatives (53 compounds), various 4-substituted 2-(4-methylpiperazinylcarbonyl)-6-trifluoromethylfuro[3,2-*b*]indole derivatives (12 compounds) were designed. The R_1 substituent was fixed as CF_3 , which was expected to be most favorable for the activities from its E_s , B_1 , and F values. The R_2 substituents were chosen from alkoxycarbonyl, acyl, and alkyl groups. These compounds (II-1—12) were synthesized by the method described in the previous paper,³⁾ and were examined for analgesic activity by using

TABLE II. Structural Features and Analgesic and Antiinflammatory Activities of 2-(4-Methylpiperazinylcarbonyl)-6-trifluoromethylfuro[3,2-*b*]indole Derivatives (II)

No.	R_2	Analgesic activity			Antiinflammatory activity			Descriptor		
		Obsd. ^{a)}	Recog. ^{b)}	Pred. ^{c)}	Obsd. ^{d)}	Recog. ^{e)}	Pred. ^{c)}	$E_s(1)^f$	$L(2)^g$	$Nc\beta^h$
II-1	COOiso-Pr	3	3	3	3	3	3	-2.4	5.97	2
II-2	COOBu	2	3	3	1	3	3	-2.4	8.00	1
II-3	COOiso-Bu	3	3	3	3	3	3	-2.4	6.77	1
II-4	COiso-Bu	3	3	3	3	3	3	-2.4	6.12	1
II-5	Bu	3	3	3	3	3	3	-2.4	6.17	0
II-6	Iso-Bu	2	2	2	2	3	3	-2.4	5.05	0
II-7	Pentyl	2	3	3	3	3	3	-2.4	7.11	0
II-8	Isopentyl	3	3	3	3	3	3	-2.4	6.17	0
II-9	Hexyl	3	3	3	3	3	3	-2.4	8.22	0
II-10	Isohexyl	3	3	3	3	3	3	-2.4	6.97	0
II-11	Heptyl	3	3	3	3	3	3	-2.4	9.03	0
II-12	Octyl	2	3	3	3	3	3	-2.4	10.27	0

a) Activity ratings based on the percent inhibition of acetic acid writhing at 100 mg/kg, *p.o.* in mice: class 1, 0—39; class 2, 40—69; class 3, 70—100. b) From Eq. 4. c) Using the leave-one-out technique. d) Activity ratings based on the percent inhibition of carrageenin edema at 100 mg/kg, *p.o.* in rats: class 1, less than 15; class 2, 15—49; class 3, 50—100. e) From Eq. 6. f) See ref. 4). g) See ref. 5). h) $Nc\beta$ is the number of β carbon atoms of the alkoxy or acyl moiety R_2 .

TABLE III. ALS Discriminant Functions for 65 Furo[3,2-*b*]indole Derivatives

Eq. No.	$n^a)$	Recognition		Prediction ^{b)}	
		$n_{\text{mis}}^{c)}$	$R_S^{d)}$	$n_{\text{mis}}^{c)}$	$R_S^{d)}$
Analgesic activity					
3	$Y = -0.97E_s(1) + 0.56Nc\beta - 1.99$ ($CI = 0.90$) ^{f)} (0.41) ^{f)}	65	15 (1) ^{e)}	0.75	16 (1) 0.75
4	$Y = -1.02E_s(1) + 0.04L(2) + 0.63Nc\beta - 2.32$ ($CI = 0.95$) (0.05) (0.46)	65	13 (0)	0.82	14 (0) 0.80
Antiinflammatory activity					
5	$Y = -0.87E_s(1) - 1.33$ ($CI = 0.80$)	65	14 (3)	0.78	14 (3) 0.78
6	$Y = -0.69E_s(1) + 0.04L(2) - 1.41$ ($CI = 0.64$) (0.05)	65	15 (1)	0.82	15 (1) 0.83

a) Number of points used for calculations. b) Using the leave-one-out technique. c) Number of misclassified compounds. d) Spearman rank correlation coefficient with a correction of many ties; the values are all significant at $p < 0.01$. e) Number of compounds misclassified by two grades. f) Contribution index (CI).

the acetic acid writhing test⁹⁾ in mice and for antiinflammatory activity by using carrageenin edema test in rats.¹⁰⁾ The biological and physical data are summarized in Table I. Most of the obtained compounds showed potent analgesic and antiinflammatory activities. The analgesic activities of II-1, -3, -4, -8, -10, and -11 were higher than that of tiaramide. The antiinflammatory activities of II-1, -4, -8, -9, and -11 were also more potent than that of tiaramide.

Then, the QSAR of 65 furo[3,2-*b*]indole derivatives [53 2-morpholinocarbonyl compounds and 12 2-(4-methylpiperazinylcarbonyl) compounds] was analyzed by using the ALS method. The descriptors and activity ratings for the newly synthesized compounds analyzed in this study are listed in Table II. Good discriminant functions for the two kinds of activity are expressed by Eqs. 3—6 (Table III), which were derived within 20 iterations.

In these equations $Nc\beta$ is the number of β carbon atoms of the alkoxy or acyl moiety for R_2 . The figure in parentheses under the coefficient for each descriptor is the contribution index ($= |\text{coef.}| \times \text{S.D. of descriptor}$), which is a measure of the contribution of the descriptor to the discriminant score. The cross-correlation matrix of the descriptors used in Eqs. 3—6 is shown in Table IV, indicating that there is little likelihood of chance correlations.

TABLE IV. Cross-Correlation Matrix of Descriptors Used in Eqs. 3—6

	$E_s(1)$	$L(2)$	$Nc\beta$
$E_s(1)$	1.00		
$L(2)$	-0.24	1.00	
$Nc\beta$	0.21	-0.10	1.00

On the basis of Eq. 4 for the analgesic activity, a bulky substituent R_1 (in terms of $-E_s$) is favorable to the potency. For the R_2 substituent, long and more branched groups (in terms of L and $Nc\beta$) are favorable to the analgesic activity. Equation 6 for the antiinflammatory activity resembles Eq. 4, with a negative coefficient for $E_s(1)$ and a positive coefficient for $L(2)$, indicating that a bulky substituent R_1 and a long substituent R_2 enhance both potencies.

The use of an indicator variable for the distinction between the 2-morpholinocarbonyl

TABLE V. Spectral Data for 2-(4-Methylpiperazinyl)carbonyl-6-trifluoromethylfuro[3,2-*b*]indole Derivatives (II)

No.	Yield (%)	IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1}	MS m/e (M^+)	$^1\text{H-NMR}$ Chemical shifts (δ) (in $\text{DMSO}-d_6$)
II-1	40.2	1720 1640	553	1.50 (6H, d, $J=7$ Hz), 2.86 (3H, s), 3.31 (4H, m), 4.04 (4H, m), 5.25 (1H, m), 6.15 (2H, s), 7.40 (1H, s), 7.72 (1H, dd, $J=8$, 2 Hz), 8.02 (1H, d, $J=8$ Hz), 8.52 (1H, d, $J=2$ Hz)
II-2	38.9	1750 1645	451	1.00 (3H, t, $J=7$ Hz), 1.50 (2H, m), 1.80 (2H, m), 2.25 (3H, s), 2.42 (4H, m), 3.78 (4H, m), 4.47 (3H, t, $J=7$ Hz), 7.26 (1H, s), 7.68 (1H, dd, $J=8$, 2 Hz), 7.97 (1H, d, $J=8$ Hz), 8.46 (1H, d, $J=2$ Hz)
II-3	38.9	1750 1645	567	1.06 (6H, d, $J=7$ Hz), 2.20 (1H, m), 2.83 (3H, s), 3.30 (4H, m), 4.04 (4H, m), 4.30 (2H, d, $J=7$ Hz), 6.10 (2H, s), 7.40 (1H, s), 7.73 (1H, dd, $J=8$, 2 Hz), 8.04 (1H, d, $J=8$ Hz), 8.50 (1H, d, $J=2$ Hz)
II-4	59.0	1725 1630	551	1.10 (6H, d, $J=7$ Hz), 2.18 (1H, m), 2.86 (3H, s), 3.05 (2H, d, $J=7$ Hz), 3.32 (4H, m), 4.07 (4H, m), 6.12 (2H, s), 7.70 (1H, s), 7.75 (1H, dd, $J=8$, 2 Hz), 8.04 (1H, d, $J=8$ Hz), 8.87 (1H, d, $J=2$ Hz)
II-5	98.0	1705 1615	523	0.90 (3H, t, $J=7$ Hz), 1.28 (2H, m), 1.82 (2H, m), 2.83 (3H, s), 3.29 (4H, br s), 4.44 (2H, t, $J=7$ Hz), 6.10 (2H, s), 7.48 (1H, dd, $J=8$, 2 Hz), 7.69 (1H, s), 8.00 (1H, d, $J=8$ Hz), 8.11 (1H, d, $J=2$ Hz)
II-6	30.0	1615	523	0.90 (6H, d, $J=7$ Hz), 2.25 (1H, m), 3.30 (4H, m), 4.04 (4H, m), 4.26 (2H, d, $J=7$ Hz), 6.10 (2H, s), 7.47 (1H, dd, $J=8$, 2 Hz), 7.69 (1H, s), 7.99 (1H, d, $J=8$ Hz), 8.11 (1H, d, $J=2$ Hz), 2.84 (3H, s)
II-7	66.0	1615	457	0.82 (3H, t, $J=7$ Hz), 1.27 (4H, m), 1.92 (2H, m), 2.82 (3H, s), 3.20 (2H, br s), 3.50 (4H, br s), 4.42 (2H, t, $J=7$ Hz), 4.66 (2H, d, $J=8$ Hz), 7.47 (1H, dd, $J=8$, 2 Hz), 7.69 (1H, s), 8.00 (1H, d, $J=8$ Hz), 8.09 (1H, d, $J=2$ Hz), 11.63 (1H, br s)
II-9	53.0	1620	471	0.82 (3H, t, $J=7$ Hz), 1.14 (6H, m), 1.88 (2H, br s), 2.82 (3H, s), 3.20 (2H, br s), 3.58 (4H, br s), 4.43 (2H, t, $J=7$ Hz), 4.68 (2H, br s), 7.47 (1H, dd, $J=8$, 2 Hz), 7.70 (1H, s), 8.00 (1H, d, $J=8$ Hz), 8.10 (1H, d, $J=2$ Hz), 11.66 (1H, br s)
II-10	15.0	1620	551	0.86 (6H, d, $J=7$ Hz), 1.20 (2H, m), 1.56 (1H, br s), 1.85 (2H, m), 2.84 (3H, s), 3.30 (4H, m), 4.06 (4H, m), 4.42 (2H, t, $J=7$ Hz), 6.11 (2H, s), 7.47 (1H, dd, $J=8$, 2 Hz), 7.68 (1H, s), 7.98 (1H, d, $J=8$ Hz), 8.08 (1H, d, $J=2$ Hz)
II-11	40.0	1620	485	0.81 (3H, t, $J=7$ Hz), 1.22 (8H, m), 1.82 (2H, br s), 2.82 (3H, s), 3.26 (2H, br s), 3.48 (4H, br s), 4.42 (2H, t, $J=7$ Hz), 4.66 (2H, d, $J=8$ Hz), 7.47 (1H, dd, $J=8$, 2 Hz), 7.70 (1H, s), 8.00 (1H, d, $J=8$ Hz), 8.10 (1H, d, $J=2$ Hz), 11.76 (1H, br s)
II-12	67.0	1613	579	0.83 (3H, t, $J=7$ Hz), 1.26 (10H, br s), 1.80 (2H, m), 2.83 (3H, s), 3.33 (4H, m), 4.07 (4H, m), 4.40 (2H, t, $J=7$ Hz), 6.10 (2H, s), 7.40 (1H, dd, $J=8$, 2 Hz), 7.60 (1H, s), 7.93 (1H, d, $J=8$ Hz), 8.00 (1H, d, $J=2$ Hz)

series (I) and the 2-(4-methylpiperazinyl)carbonyl series (II) was not effective in the QSAR for the two activities. The importance of the electron-withdrawing effect of the substituent R_1 for antiinflammatory activity of 2-morpholinocarbonyl compounds¹⁾ was not significant in the present study, probably owing to a higher intercorrelation between steric and electron withdrawing properties caused by the increase in the number of compounds having a CF_3 group as R_1 in the data set. The contribution of hydrophobic character was insignificant, perhaps on account of the small difference of hydrophobicity from molecule to molecule within the set of compounds studied.

The resulting recognition and leave-one-out prediction in both activities were a little inferior to those¹⁾ for the 2-morpholinocarbonyl compounds in terms of R_s values (Table III). However, the results of prediction, which were almost equivalent to those of recognition in this study, were fairly good, and all the R_s values for Eqs. 3—6 showed a significance level of $p < 1\%$.

Thus, it was confirmed for furo[3,2-*b*]indole derivatives that the QSAR for series I and II can be expressed in one model where the steric nature of the substituents R_1 and R_2 mainly affects both the analgesic and antiinflammatory potencies.

Experimental

Melting points were determined on a Mitamura Riken micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a JASCO DS-301 spectrometer. Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were recorded on a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts are given in ppm with tetramethylsilane as an internal standard, and the following abbreviations are used: singlet (s), broad singlet (br s), doublet (d), double doublet (dd), double triplet (dt), triplet (t), quartet (q) and multiplet (m). Mass spectra (MS) were taken on a Shimadzu LKB 9000 spectrometer.

Chemistry

4-Isopentyl-2-(4-methylpiperazinylcarbonyl)-6-trifluoromethylfuro[3,2-*b*]indole Maleate (II-8)—A solution of 2-(4-methylpiperazinylcarbonyl)-6-trifluoromethyl-4*H*-furo[3,2-*b*]indole (3.5 g) in dimethylformamide (DMF) (20 ml) was added dropwise with stirring to a suspension of sodium hydride (NaH) (60% in oil, 0.16 g) in DMF (10 ml), then the mixture was stirred for 0.5 h. Isopentyl bromide (1.8 g) was added thereto, and the whole was stirred for 1 h at room temperature, then poured into ice-water. The resulting product was collected by filtration (2.6 g, 63%).

On the treatment with maleic acid in ethanol, the product was converted to the corresponding maleate salt and the salt was recrystallized from ethanol to give an amorphous solid. mp 159–160 °C. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 1620. MS m/e : 537 (M^+). $^1\text{H-NMR}(\text{DMSO}-d_6)$ δ : 0.94 (6H, d, $J=7$ Hz, $(\text{CH}_3)_2\text{CH}-$), 1.52 (1H, m, $(\text{CH}_3)_2\text{CH}-$), 1.74 (2H, q, $J=7$ Hz, $\text{N-CH}_2\text{CH}_2-$), 2.82 (3H, s, N-CH_3), 3.27 (4H, m, piperazinyl-H), 4.04 (4H, m, piperazinyl-H), 4.44 (2H, t, $J=7$ Hz, $\text{N-CH}_2\text{CH}_2-$), 6.08 (2H, s, maleate-H), 7.47 (1H, dd, $J=8, 2$ Hz, $\text{C}_7\text{-H}$), 7.65 (1H, s, $\text{C}_3\text{-H}$), 7.98 (1H, d, $J=8$ Hz, $\text{C}_8\text{-H}$), 8.06 (1H, d, $J=2$ Hz, $\text{C}_5\text{-H}$). Anal. Calcd for $\text{C}_{26}\text{H}_{30}\text{F}_3\text{N}_3\text{O}_6$: C, 58.10; H, 5.63; N, 7.82. Found: C, 58.03; H, 5.60; N, 7.71.

Other Compounds of This Series (II-1–7 and II-9–12)—These compounds were prepared in the same manner as II-8.

Biological Methods

Acetic Acid Writhing Method—Groups of 10 male ddY mice weighing 19–23 g were used. The test compounds and tiaramide were administered orally (100 mg/kg) 30 min before the intraperitoneal injection (10 ml/kg) of 0.7% acetic acid solution. The number of writhes of each mouse was counted during a period of 10 to 20 min after the acetic acid injection. The inhibition (percent) was calculated by comparing the number of writhes with that in the untreated control group.

Carrageenin Edema Method—Groups of 6 male Wistar rats weighing 140–170 g were used. The test compounds and tiaramide were administered orally (100 mg/kg) 30 min before the subplantar injection (0.1 ml/rat) of 1% carrageenin suspension into the left hind paw. The paw volume compared with the pre-drug volume was determined and the inhibition (percent) was calculated on the basis of the swelling percent in the control group.

Data Analysis—Student's *t*-test was used for statistical evaluation.

ALS Method

Activity Classes—Twelve furo[3,2-*b*]indole derivatives (II-1–12) were classified into three groups based on the acetic acid writhing test and the carrageenin edema test at a dose of 100 mg/kg *p.o.*, as shown in Table II, according to the same criteria as used for the 53 2-morpholinocarbonyl derivatives previously reported.¹¹⁾

ALS Method—The ALS system,^{7,8)} which is a nonparametric pattern classifier, categorizes multidimensional structural patterns into multiple ordered classes by means of a single equation. The equation (discriminant function) is formulated by a feedback adaptation procedure in a linear form, as in Eq. 7.

$$Y = w_0 + w_1x_1 + w_2x_2 + \cdots + w_px_p \quad (7)$$

where Y is the discriminant score for the classification, x_k ($k=1, 2, \cdots, p$) is the k th descriptor for the structure, and w_k ($k=0, 1, \cdots, p$) is the weight coefficient. The value of w_k is determined by the least-squares adaptation using the starting score, a_j ($j=1, 2, \cdots, m$ in the m -group case) and the correction term, $C_i(t)$. In this study, the version of 1981 (ALS 81)¹¹⁾ was used. The correction term $C_i(t)$ for misclassified compound i at the t -th iteration is given by Eq. 8.

$$C_i(t) = 0.1/[\delta_i(t) + 0.45]^2 + 0.1 \quad (8)$$

where

$$\delta_i(t) = Y_i(t) - b_k$$

In this equation, $Y_i(t)$ is the discriminant score, and b_k is the cutting point (nearer to $Y_i(t)$) of the observed class for compound i . ALS iteration was performed a maximum of 20 times. The best discriminant function was selected

according to the reported criteria.⁸⁾

Structural Descriptors—In the parametrization of structural features for the ALS study, we used the same parameters as in the previous study¹⁾ except for a few indicator variables as described in the text.

References

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