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Furo[3,2-*b*]indole Derivatives. III. Structure–Activity Studies of 4,6-Disubstituted *N*-(3-Piperidinopropyl)furo[3,2-*b*]indole-2-carboxamide Derivatives for Analgesic and Antiinflammatory Activities[1)]

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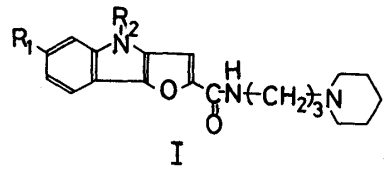
4,6-Disubstituted *N*-(3-piperidinopropyl)furo[3,2-*b*]indole-2-carboxamide derivatives possess analgesic and antiinflammatory activities. To understand how substituents affect the biological activities, the quantitative structure–activity relationships of 26 compounds were analyzed by the adaptive least-squares method. For analgesic activity, the steric effect of the substituent at the 6th position in terms of the STERIMOL length and width parameters needs to be augmented to obtain higher activity. For antiinflammatory activity, an electron-donating effect of the substituent at the 6th position seems to be favorable. On the other hand, the physicochemical factors relating to the role of the 4-substituent were not clarified. A similar correlation was obtained by Hansch analysis of analgesic ED_{50} values of 21 derivatives in mice.

Keywords——furo[3,2-*b*]indole-2-carboxamide; quantitative structure–activity relationship; adaptive least-squares method; Hansch analysis; analgesic activity; antiinflammatory activity; 4,6-disubstituted *N*-(3-piperidinopropyl)furo[3,2-*b*]indole-2-carboxamide

Compounds with the furo[3,2-*b*]indole skeleton are of interest in connection with their possible biological activities. In the previous paper,[2)] we reported the synthesis and analgesic and antiinflammatory activities of 4,6-disubstituted *N*-(3-piperidinopropyl)furo[3,2-*b*]indole-2-carboxamide derivatives (I).



I

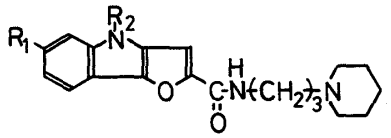
Chart 1

This paper describes an analysis of the quantitative structure–activity relationships (QSAR) of these derivatives for analgesic and antiinflammatory activities using the adaptive least-squares (ALS) method.[3-5)] In addition, the substituent effect on the analgesic activity was analyzed to confirm the correlation obtained by means of Hansch analysis[6)] based on the ED_{50} values observed in mice.

Method

Activity Classes——Twenty-six furo[3,2-*b*]indole derivatives (**1**—**26**) were classified into three groups based on

TABLE I. Structural Features and Analgesic and Antiinflammatory Activities of 26 Furo[3,2-*b*]indole Derivatives



No.	R_1	R_2	Analgesic activity			Antiinflammatory activity			Descriptor					
			Obs.[a]	Recog.[b]	Pred.[c]	Obs.[d]	Recog.[e]	Pred.[c]	$L(1)$	$B_1(1)$	$\sigma_p(1)$	$R(2)$	D_{alkyl}	D_H
1	H	H	1	1	1	2	2	2	2.06	1.0	0	0	0	1
2	H	Me	2	2	2	2	2	2	2.06	1.0	0	−0.13	1	0
3	H	Et	1	1	1	2	2	2	2.06	1.0	0	−0.10	1	0
4	H	iso-Pr	1	1	1	2	2	2	2.06	1.0	0	−0.10	1	0
5	Cl	H	1	1	1	2	2	2	3.52	1.80	0.23	0	0	1
6	Cl	Me	3	3	3	2	2	2	3.52	1.80	0.23	−0.13	1	0
7	Cl	Et	3	3	3	2	2	2	3.52	1.80	0.23	−0.10	1	0
8	Cl	iso-Pr	3	3	3	1	2	2	3.52	1.80	0.23	−0.10	1	0
9	CF_3	H	1	1	1	1	1	1	3.30	1.98	0.54	0	0	1
10	CF_3	Me	3	3	2	2	2	2	3.30	1.98	0.54	−0.13	1	0
11	CF_3	Et	3	3	3	2	2	2	3.30	1.98	0.54	−0.13	1	0
12	CF_3	iso-Pr	3	3	3	2	3	3	3.30	1.98	0.54	−0.10	1	0
13	OMe	Me	3	3	3	3	3	3	3.98	1.35	−0.27	−0.13	1	0
14	OMe	Et	3	3	3	3	3	3	3.98	1.35	−0.27	−0.10	1	0
15	OMe	iso-Pr	3	3	3	3	3	3	3.98	1.35	−0.27	−0.10	1	0
16	Me	Me	2	2	3	3	3	3	3.00	1.52	−0.17	−0.13	1	0
17	Me	Et	3	2	2	2	3	3	3.00	1.52	−0.17	−0.10	1	0
18	Me	iso-Pr	2	2	2	3	3	3	3.00	1.52	−0.17	−0.10	1	0
19	Cl	COOMe	3	2	2	2	2	2	3.52	1.80	0.23	0.15	0	0
20	Cl	COOEt	1	2	2	1	2	2	3.52	1.80	0.23	0.15	0	0
21	CF_3	COOMe	2	2	2	1	1	1	3.30	1.98	0.54	0.15	0	0
22	CF_3	COOEt	2	2	2	1	1	1	3.30	1.98	0.54	0.15	0	0
23	OMe	COOMe	2	2	2	2	2	2	3.98	1.35	−0.27	0.15	0	0
24	OMe	COOEt	1	2	2	2	2	2	3.98	1.35	−0.27	0.15	0	0
25	Me	COOMe	2	2	2	2	2	2	3.00	1.52	−0.17	0.15	0	0
26	Me	COOEt	2	2	2	1	2	2	3.00	1.52	−0.17	0.15	0	0

a) Activity ratings based on the percent inhibition of acetic acid writhing (in mice) at 100 mg/kg, *p.o.*: class 1, 0—39; class 2, 40—69; class 3, 70—100. *b*) From Eq. 5. *c*) Using the leave-one-out technique. *d*) Activity ratings based on the percent inhibition of carrageenin edema (in rats) at 100 mg/kg, *p.o.*: class 1, less than 15; class 2, 15—49; class 3, 50—100. *e*) From Eq. 6.

their analgesic and antiinflammatory activities[2] in the acetic acid writhing test in mice and the carrageenin edema test in rats, at a dose of 100 mg/kg *p.o.* The details are shown in Table I.

ALS Method——The ALS system, which is a nonparametric pattern classifier, categorizes multidimensional structural patterns into multiple ordered classes by means of a single discriminant function. In this study, the 1981 version (ALS 81)[5] was used. The correction term $C_i(t)$ for the adaptation of a misclassified compound i at the tth iteration is given by Eq. 1.[5]

$$C_i(t)=0.1/[\delta_i(t)+0.45]^2+0.1 \quad (1)$$

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.[4]

ED_{50} Value of Analgesic Activity——The ED_{50} values for 21 derivatives were estimated by means of the acetic acid writhing test. Groups of 10 male ddY mice weighing 19—23 g were used. The test compounds 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 in the test group with that in the untreated control group. The ED_{50} values and 95% confidence limits were calculated by using the method of Litchfield and Wilcoxon.[7]

Hansch Analysis——Correlation of structural features to $-\log ED_{50}$ was studied by multiple regression analysis with a descriptor selection utilizing the every-possible-combination technique.

Structural Descriptors——In the parametrization of structural features for the ALS study and Hansch analysis, we investigated physicochemical parameters[8] generally used in QSAR studies and indicator variables as detailed in the text.

Results and Discussion

ALS Study

The compounds analyzed in this study are listed in Table I along with the descriptors and activity ratings. The good discriminant functions derived with 2—4 descriptors are expressed by Eqs. 2—6 (Table II), which were generated within 20 iterations.

In Eqs. 2—6, L and B_1 are the STERIMOL length and width parameters, respectively, R is the Swain–Lupton substituent resonance constant, and σ_p is the Hammett substituent constant. The figure in parentheses after the descriptor refers to the position of the substituent

TABLE II. ALS Recognition and Prediction of Furo[3,2-*b*]indole-2-(*N*-piperidinopropyl)carboxamides

Eq. No.		n[a]	Recognition		Prediction[b]	
			n_{mis}[c]	R_s[d]	n_{mis}[c]	R_s[d]
Analgesic activity						
2	$Y=1.09L(1)-4.02R(2)-3.53$ $(CI=0.64)$[e] (0.47)[e]	26	6 (0)[f]	0.83	10 (0)[f]	0.73
3	$Y=1.12L(1)-3.99R(2)-1.37D_H-3.60$ $(CI=0.66)$ (0.47) (0.44)	26	4 (0)	0.88	7 (0)	0.81
4	$Y=1.20L(1)-0.77D_H+1.06D_{alkyl}-4.42$ $(CI=0.71)$ (0.24) (0.52)	26	5 (0)	0.86	10 (0)	0.73
5	$Y=0.55L(1)+1.28B_1(1)-3.97R(2)-1.77D_H-3.72$ $(CI=0.33)$ (0.43) (0.47) (0.57)	26	4 (0)	0.88	5 (0)	0.84
Antiinflammatory activity						
6	$Y=-1.33\sigma_p(1)+1.03D_{alkyl}-0.46$ $(CI=0.40)$ (0.51)	26	5 (0)	0.79	5 (0)	0.79

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*) Contribution index (CI). *f*) Number of compounds misclassified by two grades.

TABLE III. Squared Cross-Correlation Matrix of Descriptors for Eqs. 2—6

	$L(1)$	$B_1(1)$	$\sigma_p(1)$	$R(2)$	D_H	D_{alkyl}
$L(1)$	1.00					
$B_1(1)$	0.23	1.00				
$\sigma_p(1)$	0.00	0.57[a]	1.00			
$R(2)$	0.04	0.03	0.00	1.00		
D_H	0.03	0.00	0.04	0.00	1.00	
D_{alkyl}	0.01	0.03	0.01	0.85[b]	0.18	1.00

a) $\sigma_p(1)$ and $B_1(1)$ were not used simultaneously. *b*) $R(2)$ and D_{alkyl} were not used simultaneously.

(R_1 or R_2). The indicator variables D_H and D_{alkyl} were assigned a value of 1 corresponding to the presence of hydrogen and alkyl moieties, respectively, at R_2. The figure in parentheses under the coefficient is the contribution index (=|coefficient|×S.D. of descriptor),[4] which is a measure of the contribution of the descriptor to the discriminant score (Y). The squared cross-correlation matrix of the descriptors used in Eqs. 2—6 is shown in Table III. These seems to be no problem due to cross-correlation between descriptors in these equations.

On the basis of Eqs. 2—5 for the analgesic activity, a long and wide R_1 substituent in terms of $L(1)$ and $B_1(1)$ is favorable to the activity. The effect of the R_1 substituent on the analgesic activity is mainly steric in nature. For the R_2 substituent, the negative coefficient for $R(2)$ may indicate that π-electron-donating groups enhance the activity. However, since the range of $R(2)$ values for the 26 compounds is rather small (−0.13—0.15), the contribution of electronic effect is not certain. Replacing $R(2)$ with the indicator variable D_{alkyl} lowered the predictive power (Eqs. 3 and 4). Hydrogen for R_2 seemed to be unfavorable for the potency. The positive coefficient for D_{alkyl} and the negative coefficient for D_H in these equations may indicate that hydrophobicity of the molecule plays some role, possibly in the absorption and the transport process to the active site. However, the use of the hydrophobic parameter π for the R_2 substituent was not significant in the analysis. The validity and predictive power of descriptors were investigated by the leave-one-out technique. The descriptor set used in Eq. 5 gave the best predictive result.

In Eq. 6 for the antiinflammatory activity, a stronger electron-donating property ($-\sigma_p$) of the substituent R_1 is required to improve the potency. In this case, the contribution of the electronic effect seems reliable, because the range of σ_p values was not so small (−0.27—0.54). On the other hand, the effect of the substituent R_2 was not clear, although alkyl for R_2 seemed to be favorable to the activity.

Hansch Analysis

The ED_{50} values of 21 compounds were obtained by using the acetic acid writhing test. The values were analyzed by means of the Hansch analysis to confirm the correlation derived by the ALS method. The data are shown in Table IV and the results obtained by regression analysis are summarized in Table V. The analgesic activities of the 21 compounds are described by Eqs. 7 and 8, which are roughly equivalent. These equations are similar to those of the ALS method, including a positive term $L(1)$ for the R_1 substituent and a negative term $R(2)$ or a positive term D_{alkyl} for the R_2 substituent. For the substituent R_2, the physical meaning of the indicator variable (D_{alkyl}) and whether or not the resonance effect ($R(2)$) really contributes to the activity are not clear. To establish these points, it would be necessary to examine many more compounds having various R_2 substituents.

Among these derivatives, 4-methyl-*N*-(3-piperidinopropyl)-6-trifluoromethyl-furo[3,2-*b*]indole-2-carboxamide (**10**) was considered to have a hopeful profile for high activity and low toxicity.[9,10] With these results in mind, we are searching for new types of analgesic and

TABLE IV. Analgesic Activities of 21 Furo[3,2-*b*]indole Derivatives

No.	R_1	R_2	ED_{50} (mg/kg)	Confidence limit (95%) (mg/kg)	$-\log ED_{50}$[a]	Eq. 7		Eq. 8	
						Calcd	(Diff)[b]	Calcd	(Diff)[b]
1	H	H							
2	H	Me	47.2	34.6— 63.8	3.86	3.80	(0.06)	3.78	(0.08)
3	H	Et							
4	H	iso-Pr							
5	Cl	H							
6	Cl	Me	29.5	18.0— 50.1	4.10	4.06	(0.04)	4.03	(0.07)
7	Cl	Et	56.4	23.4—118.1	3.84	4.01	(−0.17)	4.03	(−0.19)
8	Cl	iso-Pr	68.4	36.8—112.4	3.77	4.01	(−0.24)	4.02	(−0.25)
9	CF_3	H							
10	CF_3	Me	26.5	16.0— 43.8	4.19	4.02	(0.17)	3.99	(0.20)
11	CF_3	Et	50.0	19.9—120.8	3.93	3.98	(−0.05)	3.99	(−0.07)
12	CF_3	iso-Pr	68.3	37.1—126.1	3.80	3.98	(−0.18)	3.99	(−0.19)
13	OMe	Me	25.0	13.6— 46.0	4.17	4.15	(0.02)	4.11	(0.06)
14	OMe	Et	18.0	10.3— 41.2	4.33	4.10	(0.23)	4.11	(0.22)
15	OMe	iso-Pr	23.0	13.4— 42.0	4.24	4.10	(0.14)	4.11	(0.13)
16	Me	Me	35.0	25.0— 36.2	4.00	3.97	(0.03)	3.94	(0.06)
17	Me	Et	40.0	20.6— 70.4	3.96	3.92	(0.04)	3.94	(0.02)
18	Me	iso-Pr	60.0	35.0— 82.8	3.80	3.92	(−0.12)	3.94	(−0.14)
19	Cl	COOMe	56.0	27.1—114.3	3.87	3.60	(0.27)	3.61	(0.26)
20	Cl	COOEt	134.6	71.2—253.4	3.51	3.60	(−0.09)	3.61	(−0.10)
21	CF_3	COOMe	139.2	72.6—261.5	3.51	3.56	(−0.05)	3.57	(−0.06)
22	CF_3	COOEt	105.0	47.2—240.2	3.65	3.56	(0.09)	3.57	(0.08)
23	OMe	COOMe	86.0	40.5—154.2	3.68	3.69	(−0.01)	3.69	(−0.01)
24	OMe	COOEt	145.0	66.6—313.7	3.47	3.68	(−0.21)	3.69	(−0.22)
25	Me	COOMe	130.0	61.9—248.7	3.49	3.51	(−0.02)	3.52	(−0.03)
26	Me	COOEt	105.0	59.0—192.4	3.59	3.51	(0.08)	3.52	(0.07)

a) ED_{50} in mol/kg. *b*) Difference between observed and calculated values.

TABLE V. Hansch Analysis for Analgesic Activity (ED_{50} value)

Eq. No.		n[a]	r[b]	s[c]	F[d]
7	$-\log ED_{50} = 0.18(\pm 0.15)$[f] $L(1) - 1.64(\pm 0.54)R(2) + 3.22$	21	0.84	0.15	22.22[e]
8	$-\log ED_{50} = 0.17(\pm 0.16)L(1) + 0.42(\pm 0.15)D_{alkyl} + 3.85$	21	0.83	0.16	19.41[e]

a) Number of points used for calculations. *b*) Correlation coefficient. *c*) Standard deviation. *d*) Overall F test for significance of regression. *e*) Statistically significant at $p < 0.01$. *f*) Figures in parentheses are 95% confidence intervals.

antiinflammatory agents of higher potency.

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