dried ($MgSO_4$), and evaporated to give, as a colorless oil, 2-(hexyloxy)benzaldehyde: yield 124.9 g (74%); IR (thin film) ν_{max} 1700 cm^{-1}.

A mixture of the aldehyde (39.7 g, 193 mmol), morpholine (25.5 g, 293 mmol), and sulfur (9.2 g, 288 mmol) was heated under reflux for 60 h. After it had been cooled, it was dissolved in ethyl acetate and the solution was washed with 2 N HCl solution and water and dried ($MgSO_4$). Evaporation of the organic layer gave crude 2-(hexyloxy)benzothiomorpholide as a dark-red oil: yield, 55.6 g (94%); IR (thin film) ν_{max} 1470, 1230 cm^{-1}.

The thiomorpholide was then converted to the corresponding dithiobenzoate (**3**, R^1 = 2-(hexyloxy)phenyl) in the same manner as that described in the synthesis of the 2-biphenylylmethyl derivative (**3**, R^1 = 2-biphenylylmethyl) (method B): yield 94%. The dithiobenzoate was converted to the chloromethyl derivative (**5**, R^1 = 2-(hexyloxy)phenyl, n = 0) by using the method described in the synthesis of the corresponding 2-biphenylyl derivative (**5**, R^1 = 2-biphenylyl, n = 0) (Scheme I): yield 62%.

A mixture of 2-(chloromethyl)-5-[2-(hexyloxy)phenyl]-1,3,4-thiadiazole (2.2 g, 7.1 mmol), methylamine (4.13 g, 133 mmol), and ethanol was heated at 55–60 °C for 2.5 h. The solution was evaporated under reduced pressure, and the residue was partitioned between ethyl acetate and 2 N HCl solution. The aqueous layer was washed with ethyl acetate, basified with 2 N NaOH solution, and extracted with ethyl acetate. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to give a red solid. This was dissolved in ethanol, and ethereal HCl was added. The resulting hydrochloride salt was filtered off and crystallized from ethanol/ether to give **17**: yield 0.4 g (17%); mp 155–157 °C. Anal. ($C_{16}H_{23}N_3OS$·HCl) C, H, N.

Acknowledgment. We thank Phil Smith for his assistance in the synthetic aspects of this work and Ginette Gray for typing the manuscript.

Registry No. **2** (R^1 = 2-biphenylyl, R^2 = H, R^3 = R^4 = phthalimide, n = 0), 104090-72-4; **3** (R^1 = 2-biphenylyl), 104090-69-9; **3** (R^1 = 2-biphenylylmethyl), 104090-75-7; **3** (R^1 = 2-(hexyloxy)phenyl), 104090-77-9; **4** (R^1 = 2-biphenylyl), 104090-70-2; **5** (R^1 = 2-biphenylyl, R^2 = H, n = 0), 104090-71-3; **5** (R^1 = 2-(hexyloxy)phenyl, R^2 = H, n = 0), 104090-78-0; **6**, 104090-42-8; **6** (free base), 104090-56-4; **7**, 104090-43-9; **7** (free base), 104090-57-5; **8**, 104090-44-0; **8** (free base), 104090-58-6; **9**, 104090-46-2; **9** (free base), 104090-45-1; **10**, 104090-47-3; **10** (free base), 104090-59-7; **11**, 104090-48-4; **11** (free base), 104090-60-0; **12**, 104090-49-5; **12** (free base), 104090-61-1; **13**, 104090-50-8; **13** (free base), 104090-62-2; **14**, 104090-51-9; **14** (free base), 104090-63-3; **15**, 104090-52-0; **15** (free base), 104090-64-4; **16**, 104090-53-1; **16** (free base), 104090-65-5; **17**, 104090-54-2; **17** (free base), 104090-66-6; **18**, 104090-55-3; **18** (free base), 104090-67-7; **19**, 104113-70-4; **19** (free base), 104090-68-8; HN=C(OEt)-CH_2Cl·HCl, 36743-66-5; 2-aminobiphenyl, 90-41-5; 2-iodobiphenyl, 2113-51-1; chloroacetonitrile, 107-14-2; 2-acetylbiphenyl, 2142-66-7; 2-biphenylacetothiomorpholide, 104090-73-5; 2-biphenylylacetothiomorpholide methiodide, 104090-74-6; salicylaldehyde, 90028; hexyl bromide, 111-25-1; 2-(hexyloxy)benzothiomorpholide, 104090-76-8; 2-(hexyloxy)benzaldehyde, 7162-59-6.

Structure–Activity Studies of 4,6-Disubstituted 2-(Morpholinocarbonyl)furo[3,2-*b*]indole Derivatives with Analgesic and Antiinflammatory Activities

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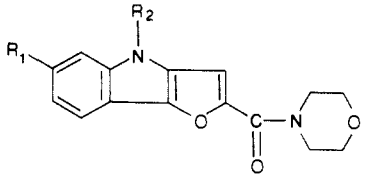
4,6-Disubstituted 2-(morpholinocarbonyl)furo[3,2-*b*]indole derivatives showed analgesic and antiinflammatory activities when assayed by the acetic acid writhing test in mice and the carrageenin edema test in rats. To understand how the substituents affect the biological activities, the quantitative structure–activity relationships (QSAR) of 38 compounds were analyzed using the adaptive least-squares method (ALS method). The resulting QSAR suggested that some chemical modifications of 4,6-disubstituted furo[3,2-*b*]indole derivatives would improve their biological activities. Thus, 15 additional compounds were synthesized to reinforce and confirm the correlation. Among these compounds, particularly 4-(2-ethylhexanoyl)-2-(morpholinocarbonyl)-6-(trifluoromethyl)furo[3,2-*b*]indole showed pronounced biological activities. This compound gave a pharmacological activity spectrum similar to that of tiaramide but exhibited much higher potency.

The structure of the furo[3,2-*b*]indole skeleton is of particular interest in connection with its possible relationship with biological activity. In a previous paper[1] we reported the synthesis and analgesic and antiinflammatory activities of 4-(alkoxycarbonyl)-2-(morpholinocarbonyl)-furo[3,2-*b*]indole derivatives I. When structure–activity



I

relationships of the derivatives were considered, it appeared that CF_3 and Cl as substituent R_1 were associated with an increase in the potency. Although the effect of substituent R_2 seemed rather complicated, a bulky substituent (R_2) tended to enhance the analgesic and antiinflammatory activities. This consideration prompted us to attempt a quantitative structure–activity analysis to develop more potent compounds.

This paper described the analysis of the quantitative structure–activity relationships (QSAR) of these derivatives for analgesic and antiinflammatory activities using the adaptive least-squares (ALS) method[2-4] and the design

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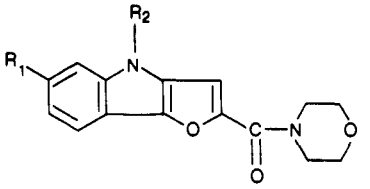
Table I. Structural Features and Analgesic and Antiinflammatory Activities of 38 Furo[3,2-*b*]indole Derivatives



			analgesic act.			antiinfl act.			descriptor				
no.	R_1	R_2	obsd[a]	recog[b]	pred[c]	obsd[d]	recog[e]	pred[c]	Es(1)	$B_1(1)$	$F_1(1)$	$L(2)$	$Nc\beta_a$
1	H	COOMe	1	1	1	2	1	1	0	1.0	0	4.85	0
2	H	COOEt	1	1	1	1	1	1	0	1.0	0	5.96	1
3	H	COOPr	1	1	1	1	1	1	0	1.0	0	6.90	1
4	H	COO-*i*-Pr	2	2	2	2	2	1	0	1.0	0	5.97	2
5	H	COOBu	1	1	1	1	1	1	0	1.0	0	8.00	1
6	H	COO-*i*-Bu	1	1	1	1	1	1	0	1.0	0	6.77	1
7	Me	COOMe	1	1	1	2	2	2	−1.24	1.52	−0.01	4.85	0
8	Me	COOEt	2	2	2	3	2	2	−1.24	1.52	−0.01	5.96	1
9	Me	COOPr	2	2	2	1	2	2	−1.24	1.52	−0.01	6.90	1
10	Me	COO-*i*-Pr	3	3	2	3	3	3	−1.24	1.52	−0.01	5.97	2
11	Me	COOBu	2	2	2	1	2	2	−1.24	1.52	−0.01	8.00	1
12	Me	COO-*i*-Bu	2	2	2	2	2	2	−1.24	1.52	−0.01	6.77	1
13	F	COOMe	1	1	1	1	1	1	−0.46	1.35	0.74	4.85	0
14	F	COOEt	1	1	1	1	1	1	−0.46	1.35	0.74	5.96	1
15	F	COOPr	2	2	2	1	1	1	−0.46	1.35	0.74	6.90	1
16	F	COO-*i*-Pr	2	2	2	1	1	1	−0.46	1.35	0.74	5.97	2
17	F	COOBu	2	2	2	1	1	1	−0.46	1.35	0.74	8.00	1
18	F	COO-*i*-Bu	2	2	2	1	1	1	−0.46	1.35	0.74	6.77	1
19	Cl	COOMe	1	1	1	1	1	2	−0.97	1.80	0.72	4.85	0
20	Cl	COOEt	1	2	2	2	2	2	−0.97	1.80	0.72	5.96	1
21	Cl	COOPr	2	2	2	2	2	2	−0.97	1.80	0.72	6.90	1
22	Cl	COO-*i*-Pr	3	3	3	3	3	3	−0.97	1.80	0.72	5.97	2
23	Cl	COOBu	3	3	2	2	2	2	−0.97	1.80	0.72	8.00	1
24	Cl	COO-*i*-Bu	2	2	2	2	2	2	−0.97	1.80	0.72	6.77	1
25	CF_3	COOMe	1	1	1	1	2	2	−2.40	1.98	0.64	4.85	0
26	CF_3	COOEt	3	2	2	3	3	3	−2.40	1.98	0.64	5.96	1
27	CF_3	COOPr	3	3	3	3	3	3	−2.40	1.98	0.64	6.90	1
28	CF_3	COO-*i*-Pr	3	3	3	3	3	3	−2.40	1.98	0.64	5.97	2
29	CF_3	COOBu	3	3	3	3	3	2	−2.40	1.98	0.64	8.00	1
30	CF_3	COO-*i*-Bu	2	3	3	2	3	3	−2.40	1.98	0.64	6.77	1
31	OMe	COOMe	1	1	1	1	1	1	−0.55	1.35	0.54	4.85	0
32	OMe	COOEt	1	2	2	1	1	1	−0.55	1.35	0.54	5.96	1
33	OMe	COOPr	2	2	2	1	1	1	−0.55	1.35	0.54	6.90	1
34	OMe	COO-*i*-Pr	2	2	2	1	2	2	−0.55	1.35	0.54	5.97	2
35	OMe	COOBu	2	2	2	1	1	1	−0,55	1.35	0.54	8.00	1
36	OMe	COO-*i*-Bu	3	2	2	1	1	1	−0.55	1.35	0.54	6.77	1
37	OH	COOMe	1	1	1	1	1	1	−0.55	1.35	0.46	4.85	0
38	OH	COOEt	2	1	1	1	1	1	−0.55	1.35	0.46	5.96	1

[a] Acetic acid writhing (mice); percent inhibition of writhing at 100 mg/kg, po: class 1, 0–39; class 2, 40–69; class 3, 70–100. [b] From eq 3. [c] Using leave-one-out technique. [d] Carrageenin edema (rats); percent inhibition of edema at 100 mg/kg, po: class 1, less than 15; class 2, 15–49; class 3, 50–100. [e] From eq 4.

and synthesis of 4,6-disbustituted 2-(morpholinocarbonyl)furo[3,2-*b*]indole derivatives on the basis of this analysis. High potency was observed with the resulting compounds.

The ALS system, which is a nonparametric pattern classifier, has been devised (a) to formulate a QSAR in a single mathematical equation irrespective of the number of activity classes and (b) to categorize multidimensional structural patterns into multiple ordered classes by means of the equation. The equation (discriminant function) is formulated by a feedback adaptation procedure in a linear form as eq 1, where L is the discriminant score for the

$$L = w_0 + w_1x_1 + w_2x_2 + ... + w_px_p \quad (1)$$

classification, x_k (k = 1, 2, ..., p) is the kth descriptor for the structure, and w_k (k = 0, 1, ..., 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, ..., m in the m group case) and the correction term $C_i(t)$ (see the Experimental Section). In the parameterization of structural features for the ALS study, we examined physicochemical parameters[5] and indicator variables.

Results and Discussion

QSAR of 4-(Alkoxycarbonyl)furo[3,2-*b*]indole Derivatives (38 Compounds). The compounds first analyzed by ALS are listed in Table I along with descriptors and activity ratings. The resulting discriminant functions are expressed as eq 2–4 (Table II), where n stands for 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.

In eq 2–4, Es is the Taft steric substituent parameter,[6] B_1 and L are the STERIMOL parameters,[7] $Nc\beta_a$ is the

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Table II. ALS Recognition and Prediction of 38 Derivatives

eq no.		n	recognition n_{mis}	recognition R_s	prediction[a] n_{mis}	prediction[a] R_s
	Analgesic Activity					
2	$L = -0.69Es(1) + 0.16L(2) + 1.30Nc\beta_a - 3.08$ (0.52)[b] (0.15) (0.76)	38	5 (0)	0.88	9 (0)	0.77
3	$L = 1.96B_1(1) + 0.28L(2) + 1.12Nc\beta_a - 5.90$ (0.62) (0.27) (0.66)	38	5 (0)	0.89	7 (0)	0.85
	Antiinflammatory Activity					
4	$L = -1.78F(1) + 3.06B_1(1) + 0.64Nc\beta_a - 4.29$ (0.95) (0.55) (0.37)	38	7 (0)	0.83	10 (0)	0.74

[a] Using leave-one-out technique. [b] Contribution index (CI).

Table III. Squared Cross-Correlation Matrix of Descriptors for Equations 2–4

	Es(1)	$B_1(1)$	$F_1(1)$	$L(2)$	$Nc\beta_a$
Es(1)	1.00				
$B_1(1)$	0.81[a]	1.00			
$F_1(1)$	0.07	0.28	1.00		
$L(2)$	0.00	0.00	0.00	1.00	
$Nc\beta_a$	0.00	0.00	0.00	0.14	1.00

[a] Es(1) and $B_1(1)$ were not used simultaneously in eq 2–4.

number of β-carbon atoms of alkoxy moiety, and F is the new Swain–Lupton substituent constants.[8] The figure in parentheses after the descriptor is assigned the position of substituent (R_1, R_2). The figure in parentheses under the coefficient is the contribution index (= |coef| × SD of descriptor), which is a measure of the contribution of the descriptor to the discriminant score.[3] The squared cross-correlation matrix of the descriptors used in eq 2–4 is shown in Table III. On the basis of eq 2 and 3 on analgesic activity, the bulky substituent R_1 (in terms of Es or B_1) and the long and more branched substituent R_2 (in terms of L and $Nc\beta_a$) are favorable to the activity. The validity and predictive power of descriptors were investigated by leave-one-out technique. The descriptor set in eq 3 gave the best predictive result.

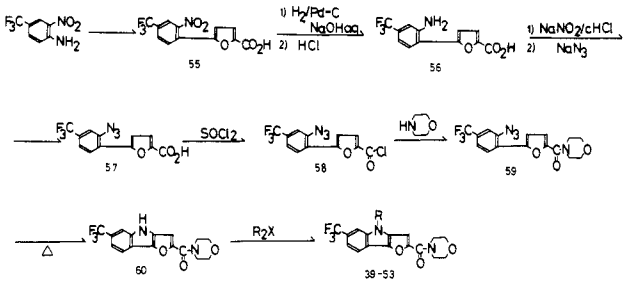
In eq 4 on antiinflammatory activity, the steric and electron-withdrawing effects (B_1 and F for the substituent R_1 and $Nc\beta_a$ for the substituent R_2) are required to improve the potency.

The resulting recognition and leave-one-out prediction in both activities were reasonably good in terms of R_s (Table II), all of which indicated the significance level of 1%.

Chemical Synthesis and Assay. On the basis of obtained QSAR models, 15 additional compounds were synthesized to reinforce and confirm the correlation. The R_1 substituent was fixed to be CF_3, which is the most favorable for the activities. The R_2 substituents were chosen from acyl, alkyl, and alkenyl moieties.

The general synthetic routes for preparing the additional compounds are shown in Scheme I. Preparation of the 4*H*-furo[3,2-*b*]indole derivatives has been previously described in a series of papers by Tanaka et al.[9] 5-[4-(Trifluoromethyl)-2-nitrophenyl]-2-furancarboxylic acid (**55**) was synthesized by the method reported in the previous paper.[10] By catalytic reduction of nitro group,

Scheme I



followed by treatment with HCl–$NaNO_2$ and NaN_3, compound **55** led to **57**. Chlorination of **57** with $SOCl_2$ gave an acid chloride (**58**), which was treated with morpholine to give a carboxamide (**59**). Compound **60** was obtained by thermolysis of **59**. 4-Substituted 2-(morpholinocarbonyl)-6-(trifluoromethyl)furo[3,2-*b*]indole derivatives **39–53** were obtained by the reaction of **60** with acyl chlorides, alkyl halides, and alkenyl halide under basic condition. Their syntheses are described in detail in the Experimental Section.

Activities of the newly synthesized congeneres were examined by the acetic acid writhing test in mice and the carrageenin test in rats. The biological data are shown in Table IV. Most of the designed compounds showed potent analgesic and antiinflammatory activities.

QSAR of Furo[3,2-*b*]indole Derivatives (53 Compounds). The QSAR for all the 53 compounds was analyzed by the ALS method. The descriptors used for the additional 15 compounds are listed in Table IV. Satisfactory discriminant functions using 3–5 descriptors were obtained as eq 5–10 (Table V), where $Nc\beta_b$ is the number of β-carbon atoms of the acyl moiety. The indicator variables D_{acyl} and D_{alkyl} were assigned a value of 1 corresponding to the presence of an acyl or alkyl (or alkenyl) moiety on R_2, respectively. These indicator variables were assigned a value of 0 for 38 compounds in Table I, and $Nc\beta_a$ was assigned 0 for the 15 congeners in Table IV. The squared correlation matrix for the descriptors included in eq 5–10 appears in Table VI. Combinations of the descriptors were validated by leave-one-out technique. In the investigation by leave-one-out technique, the descriptor sets in eq 7 on analgesic activity and eq 10 on antiinflammatory activity gave best predictive results. Taking into account the effect of acyl and alkyl moieties, these models were similar to those obtained for the 38 compounds. The steric effects of the R_1 and R_2 substituents are dominant for both activities, and the electron-attracting effect of substituent R_1 is also required for the antiinflammatory

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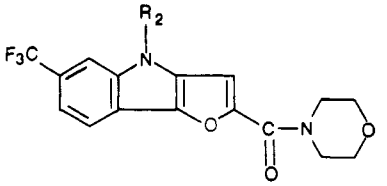
(10) Nakashima, K.; Kawashima, K.; Amanuma, F.; Sota, K.; Tanaka, A.; Kameyama, K. *Chem. Pharm. Bull.* **1984**, *32*, 4271.

Table IV. Structural Features and Analgesic and Antiinflammatory Activites of 15 Additional Derivatives



		analgesic act.			antiinfl act.			descriptor						
no.	R_2	obsd[a]	recog[b]	pred[c]	obsd[d]	recog[e]	pred[c]	Es(1)	$B_1(1)$	$F_1(1)$	$L(2)$	$Nc\beta_b$	D_{alkyl}	D_{acyl}
39	CO-*i*-Pr	3	3	3	3	3	3	−2.40	1.98	0.64	4.84	2	0	1
40	COBu	3	3	3	3	3	3	−2.40	1.98	0.64	6.92	1	0	1
41	CO-*i*-Bu	3	3	3	3	3	3	−2.40	1.98	0.64	6.12	1	0	1
42	COCHEt(Bu)	3	3	3	3	3	3	−2.40	1.98	0.64	8.17	2	0	1
43	$COCMe_3$	3	3	3	1	3	3	−2.40	1.98	0.64	4.87	3	0	1
44	CO-octyl	3	3	3	2	3	3	−2.40	1.98	0.64	11.03	1	0	1
45	Bu	3	3	3	3	3	3	−2.40	1.98	0.64	6.17	0	1	0
46	*i*-Bu	2	2	2	3	3	3	−2.40	1.98	0.64	5.05	0	1	0
47	pentyl	3	3	3	3	3	3	−2.40	1.98	0.64	7.11	0	1	0
48	*i*-pentyl	3	3	3	3	3	3	−2.40	1.98	0.64	6.17	0	1	0
49	hexyl	3	3	3	3	3	3	−2.40	1.98	0.64	8.22	0	1	0
50	*i*-hexyl	3	3	3	3	3	3	−2.40	1.98	0.64	6.97	0	1	0
51	heptyl	3	3	3	3	3	3	−2.40	1.98	0.64	9.03	0	1	0
52	octyl	2	3	3	3	3	3	−2.40	1.98	0.64	10.27	0	1	0
53	$CH_2CH{=}CHMe_2$	3	3	3	3	3	3	−2.40	1.98	0.64	6.39	0	1	0

[a,c,d] See footnotes in Table I. [b] From eq 7. [e] From eq 10.

Table V. ALS Recognition and Prediction of 53 Derivatives

eq no.		n	recognition n_{mis}	recognition R_s	prediction[a] n_{mis}	prediction[a] R_s
	Analgesic Activity					
5	$L = -1.12Es(1) + 0.11L(2) + 0.81Nc\beta_a + 0.35Nc\beta_b - 2.91$ (1.03)[b] (0.15) (0.54) (0.20)	53	7 (0)	0.89	9 (0)	0.86
6	$L = -1.12Es(1) + 0.11L(2) + 0.81Nc\beta_a + 0.62D_{acyl} - 2.88$ (1.03) (0.15) (0.53) (0.20)	53	7 (0)	0.89	9 (0)	0.86
7	$L = -0.68Es(1) + 0.11L(2) + 1.19Nc\beta_a + 1.91D_{acyl} + 1.27D_{alkyl} - 3.10$ (0.62) (0.15) (0.79) (0.61) (0.48)	53	6 (0)	0.91	8 (0)	0.87
8	$L = 2.05B_1(1) + 0.21L(2) + 1.11Nc\beta_a + 1.15Nc\beta_b + 1.19D_{alkyl} - 6.01$ (0.71) (0.28) (0.73) (0.67) (0.45)	53	6 (0)	0.91	13 (0)	0.79
	Antiinflammatory Activity					
9	$L = -1.00Es(1) - 1.17F(1) + 0.16Nc\beta_a - 0.78$ (0.92) (0.33) (0.10)	53	9 (2)	0.83	12 (2)	0.79
10	$L = 2.84B_1(1) - 1.70F(1) + 0.63Nc\beta_a + 0.71D_{acyl} + 1.18D_{alkyl} - 4.47$ (0.98) (0.47) (0.42) (0.22) (0.44)	53	9 (1)	0.87	11 (1)	0.84

[a] Using leave-one-out technique. [b] Contribution index (CI).

Table VI. Squared Cross-Correlation Matrix of Descriptors for Equations 5–10

	Es(1)	$B_1(1)$	$F_1(1)$	$L(2)$	$Nc\beta_a$	$Nc\beta_b$	D_{alkyl}	D_{acyl}
Es(1)	1.00							
$B_1(1)$	0.88[a]	1.00						
$F_1(1)$	0.17	0.35	1.00					
$L(2)$	0.04	0.04	0.01	1.00				
$Nc\beta_a$	0.22	0.17	0.04	0.00	1.00			
$Nc\beta_b$	0.14	0.11	0.03	0.00	0.12	1.00		
D_{alkyl}	0.27	0.21	0.05	0.05	0.23	0.02	1.00	
D_{acyl}	0.17	0.13	0.03	0.01	0.14	0.82	0.03	1.00

[a] Es(1) and $B_1(1)$ were not used simultaneously in eq 5–10.

activity. Acyl and alkyl groups for substituent R_2 enchance the potency.

Biological Results of Compound 42. Among all the compounds, compounds **10**, **22**, **26–29**, **39–42**, **45**, **47–51**, and **53** showed pronounced (class 3) analgesic and antiinflammatory activities. Then, we investigated the ED_{50} values of these compounds in the mouse acetic acid writhing test. As shown in Table VII, 4-(2-ethylhexanoyl)-2-(morpholinocarbonyl)-6-(trifluoromethyl)furo[3,2-*b*]indole (**42**) had a much higher potency than other compounds. So, compound **42** was selected for the additional evaluation in order to define the spectrum of analgesic, antiinflammatory, and antipyretic activities. The pharmacological results were summarized in Table VIII along with those for tiaramide, which is a typical basic nonsteroidal antiinflammatory agent.[11]

The analgesic activity of **42** was 16–100 times as potent as that of tiaramide in the acetic acid induced writhing test in mice, pressure test in mice, Randall–Selitto test in rats,

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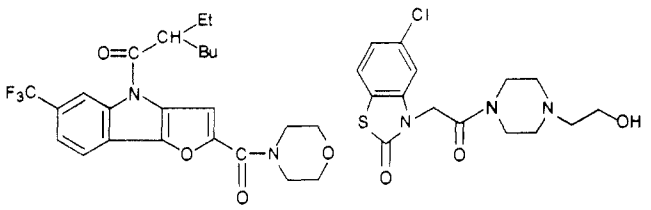
Table VII. ED_{50} Values of Acetic Acid Writhing Test

no.	ED_{50} (95% CL), mg/kg po	no.	ED_{50} (95% CL), mg/kg po
10	26.0 (13.8–49.0)	42	0.7 (0.5–1.4)
22	21.4 (10.6–41.6)	45	29.5 (15.3–56.9)
26	35.6 (18.8–67.6)	47	10.9 (5.5–21.6)
27	34.6 (20.3–58.7)	48	5.1 (2.9–12.4)
28	4.7 (1.9–11.2)	49	7.7 (5.0–11.8)
29	21.4 (10.2–44.9)	50	6.0 (3.8–9.4)
39	7.3 (3.8–14.0)	51	17.8 (10.9–29.0)
40	34.5 (15.8–75.2)	53	10.1 (7.1–14.4)
41	6.0 (2.9–12.4)		

Table VIII. Analgesic, Antiinflammatory, and Antipyretic Activities of Compound 42 and Tiaramide



42

tiaramide

	method (species)	ED_{50} (95% CL), mg/kg po: 42	tiaramide
1	analgesic activities		
	acetic acid writhing (mice)	0.7 (0.5–1.4)	74.0 (44.0–146.0)
	pressure (mice) Randall–Sellito (rats)	7.0 (3.7–13.3)	116.0 (59.5–224.8)
	normal foot	5.9 (3.1–11.4)	>160.0
	inflamed foot	1.7 (0.5–5.7)	94.6 (49.1–182.1)
	adjuvant induced-arthritic pain (rat)	1.7 (0.8–3.7)	176.4 (69.4–448.5)
2	antipyretic activity		
	yeast induced fever (rats)	0.059 (0.037–0.092)	170.7 (79.7–356.6)
3	antiinflammatory activity		
	carrageenin edema (rats)	5.4 (3.5–8.2)	119.2 (55.0–258.3)

and adjuvant-induced arthritic pain in rats. Moreover, in the Randall–Selitto test, only compound **42** showed a significant analgesic effect in a normal foot (ED_{50} value 5.9 mg/kg, po), without the appearance of central nervous system depressant activity such as sedation and decrease of locomoter activity. These results may indicate that compound **42** acts not only peripherally but also centrally.

The antipyretic potency of **42** was about 3000 times as high as that of tiaramide in rats with yeast-induced fever. The effective dose of antipyretic potency of **42** (ED_{50} value 0.059 mg/kg, po) was the lowest of the available data. In addition, compound **42** had no effect on normal body temperature at a dose of 20 mg/kg.

The antiinflammatory activity of **42** was 22 times as potent as that of tiaramide in carrageenin edema test. Compound **42** and tiaramide had little or no ulcerogenic activity in rats. It is known that acidic nonsteroidal antiinflammatory drugs such as indomethacin did produce marked ulcerogenic activity.[12-14] In general, it is considered that ulceration is due to the inhibition of prostaglandin (PG) biosynthesis.[15] Moreover, compound **42** has no effect on the cotton pellet granuloma (chronic inflammatory model) and ultraviolet erythema, which are both inhibited by nonsteroidal antiinflammatory agents having an inhibitory effect on the PG biosynthesis.[16] Therefore, compound **42** has no inhibitory effect on the PG biosynthesis.

In conclusion, compound **42** has potent analgesic and antipyretic activity, has an inhibitory effect on acute inflammatory swelling, but has little or no ulcerogenic activity. In acute toxicity, compound **42** caused general depression in mice at an oral dose of more than 50 mg/kg and did not kill at an oral dose of 100 mg/kg. The observed pharmacological properties exhibited that compound **42** is a new-type nonsteroidal antiinflammatory agent.

Experimental Section

Melting points were determined on a Mitamura Rikken micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Jasco DS-301 spectrometer. ^1H nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-200 spectrometer. Chemical shifts are given (ppm) with tetramethylsilane as an internal standard, and the following abbreviation are used: singlet (s), broad singlet (br s), doublet (d), double doublet (dd), triplet (t), multiplet (m). Mass spectra (MS) were taken on a Shimadzu LKB 9000 spectrometer.

5-[2-Amino-4-(trifluoromethyl)phenyl]-2-furancarboxylic Acid (56). A mixture of 5-[2-nitro-4-(trifluoromethyl)-phenyl]-2-furancarboxylic acid (50 g), 10% Pd–C (0.5 g), and 1.5% aqueous NaOH (500 mL) was hydrogenated at 40 °C and atmospheric pressure. The catalyst was filtered, and the filtrate was acidified with concentrated HCl. The product that resulted was filtered (44 g, 98.0%) and recrystallized from EtOH to give **56** as needles: mp 175–176 °C; IR (KBr) 3470, 3370, 1660 cm^{-1}; MS m/e 271 (M^+); NMR (Me_2SO-d_6) δ 7.76 (1 H, d, J = 8 Hz, C_6-H), 7.41 (1 H, d, J = 4 Hz, C_3-H), 7.24 (1 H, s, C_3-H), 7.12 (1 H, d, J = 4 Hz, C_4-H), 6.98 (1 H, d, J = 8 Hz, C_5-H), 6.03 (2 H, br s, NH_2). Anal. ($C_{12}H_8N_1O_3F_3$) C, H, N.

5-[2-Azido-4-(trifluoromethyl)phenyl]-2-furancarboxylic Acid (57). A solution of **56** (44 g), 1.5% aqueous NaOH (500 mL), and $NaNO_2$ (12.5 g) was added to concentrated HCl (500 mL) at −10 °C. After the solution had been stirred at −10 °C for 30 min, a solution of NaN_3 (25 g) in H_2O (200 mL) was added thereto, and the temperature was allowed to rise to room temperature. The product that resulted was filtered and washed with H_2O to give **57** as crystals, 47.7 g (99%). Recrystallization from EtOH gave **57** as needles: mp 174–175 °C; IR (KBr) 2900, 2120, 1690 cm^{-1}; MS m/e 297 (M^+); NMR (M_2SO-d_6) δ 8.04 (1 H, d, J = 8 Hz, C_5-H), 7.70 (1 H, s, C_3-H), 7.65 (1 H, d, J = 8 Hz, C_6-H), 7.41 and 7.36 (1 H each, d, J = 4 Hz, C_3- and C_4-H). Anal. ($C_{12}H_6N_3O_3F_3$) C, H, N.

5-[2-Azido-4-(trifluoromethyl)phenyl]-2-furancarbonyl Chloride (58). A mixture of **57** (47.7 g), $SOCl_2$ (90 g), pyridine (4.5 g), and $CHCl_3$ (450 mL) was heated at reflux for 1.5 h, then concentrated in vacuo, and diluted with hexane. The product that resulted was filtered; 49.7 g (98%). Recrystallization from hexane–acetone gave **58** as needles: mp 98.5–99.5 °C; IR (KBr) 2100, 1735 cm^{-1}; MS m/e 317 (M^+ + 2), 315 (M^+); NMR (Me_2SO-d_6) δ 8.05 (1 H, d, J = 8 Hz, C_5-H), 7.72 (1 H, s, C_3-H), 7.66 (1 H, d, J = 8 Hz, C_6-H), 7.38 and 7.42 (1 H each, d, J = 4 Hz, C_3- and C_4-H). Anal. ($C_{12}H_5N_3O_2F_3Cl_1$) C, H, N.

5-[2-Azido-4-(trifluoromethyl)phenyl]-2-(morpholinocarbonyl)furan (59). A solution of **58** (49.7 g) in CH_2Cl_2 (180 mL) was added to a solution of morpholine (35 g) in CH_2Cl_2 (270 mL) at 0 °C; then, the mixture was stirred for 30 min at room temperature, concentrated, and poured into ice–H_2O. The resulting product was filtered; 56.7 g (98.0%). Recrystallization from hexane–acetone gave needles: mp 104.5–106.5 °C; IR (KBr) 2100, 1630 cm^{-1}; MS m/z 366 (M^+); NMR (Me_5SO-d_6) δ 7.98 (1 H, d, J = 8 Hz, C_5-H), 7.70 (1 H, s, C_3-H), 7.62 (1 H, d, J = 8

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Table IX. Physical and Analytical Data for Compounds 40–53

no.	formula	mp, °C	recryst[a]	yield, %	anal.
40	$C_{21}H_{21}N_2O_4F_3$	141–142.5	H-A	68.0	C, H, N
41	$C_{21}H_{21}N_2O_4F_3$	146.5–147	H-E	64.0	C, H, N
42	$C_{24}H_{27}N_2O_4F_3$	107–108	H-A	56.0	C, H, N
43	$C_{21}H_{21}N_2O_4F_3$	138–139	I	69.0	C, H, N
44	$C_{25}H_{29}N_2O_4F_3$	114–115	I	72.0	C, H, N
45	$C_{20}H_{21}N_2O_3F_3$	127–129	H-A	77.2	C, H, N
46	$C_{20}H_{21}N_2O_3F_3$	154–156	H-A	77.5	C, H, N
47	$C_{21}H_{23}N_2O_3F_3$	102–103	H-A	77.0	C, H, N
48	$C_{21}H_{23}N_2O_3F_3$	122.5–123	E	55.2	C, H, N
49	$C_{22}H_{25}N_2O_3F_3$	69–72	H-A	74.8	C, H, N
50	$C_{22}H_{25}N_2O_3F_3$	100–102	H-A	68.1	C, H, N
51	$C_{23}H_{27}N_2O_3F_3$	72–74.5	H-A	67.2	C, H, N
52	$C_{24}H_{29}N_2O_3F_3$	87–89	H-A	75.1	C, H, N
53	$C_{21}H_{21}N_2O_3F_3$	150.5–151.5	H-A	97.0	C, H, N

[a] Key: H = hexane, A = acetone, E = ether, I = isopropyl alcohol.

Hz, C_6-H), 7.38 and 7.18 (1 H each, d, J = 4 Hz, C_3- and C_4-H), 3.73 and 3.68 (4 H each, br s, NCH_2CH_2O). Anal. ($C_{16}H_{13}N_4O_3F_3$) C, H, N.

2-(Morpholinocarbonyl)-6-(trifluoromethyl)-4*H*-furo[3,2-*b*]indole (60).[10] A mixture of **59** (56.2 g) and o-dichlorobenzene (90 mL) was stirred at 170 °C for 30 min. The resulting product was filtered off, and washed with hexane to give crystals (42.4 g, 81%).

4-Isobutyryl-2-(morpholinocarbonyl)-6-(trifluoromethyl)furo[3,2-*b*]indole (39). A solution of **60** (2 g) in dimethylformamide (DMF; 10 mL) was added dropwise with stirring to a suspension of NaH (0.16 g) in DMF (10 mL). The mixture was stirred for 30 min at room temperature, isobutyryl chloride (0.7 g) was added thereto, and then the mixture was concentrated and poured into ice–H_2O. The resulting product was filtered; 1.8 g (74%). Recrystallization from hexane–acetone gave needles: mp 156–157 °C; IR (KBr) 1720, 1625 cm^{-1}; MS m/e 408 (M^+); NMR (Me_2SO-d_6) δ 8.92 (1 H, s, C_5-H), 8.06 (1 H, d, J = 8 Hz, C_8-H), 7.76 (1 H, d, J = 8 Hz, C_7-H), 7.72 (1 H, s, C_3-H), 3.80 and 3.73 (4 H each, br s, NCH_2CH_2O), 3.58, 1.28 (1 H, m; 6 H, d, J = 7 Hz, i-Pr H). Anal. ($C_{20}H_{19}N_2O_4F_3$) C, H, N.

Compounds **40–53** were synthesized in the same manner. Data for **40–53** are listed in Table IX.

Analgesic Effect. (a) Acetic Acid Induced Writhing Test.[17] Groups of 10 male ddY mice weighing 19–24 g were used. The drugs were administered orally 30 min before intraperitoneal injection (10 mL/kg) of 0.7% acetic acid solution. The number of writhes was counted in each mouse during a period of 10–20 min after the acetic acid injection. The inhibitory percent was calculated by comparison with the number of writhes in a control group. The ED_{50} values and their 95% confidence limits (CL) were calculated by the method of Litchfield and Wilcoxon.[18]

(b) Pressure Test.[19] Groups of 10 male ddY mice weighing 19–24 g were used. The drugs were administered orally, and the pain threshold was measured every 30 min for 120 min. Animals in which the pain threshold of the postdrug values was raised more than 50% as compared with the pain threshold of the predrug values were regarded as positive for analgesic activity. The ED_{50} values and their 95% confidence limits (CL) were calculated by the method of Litchfield and Wilcoxon.[18]

(c) Randall–Selitto Test.[20] Groups of six male Wistar rats weighing 90–110 g were used. The drugs were administered orally 120 min after the subplantar injection (0.1 mL/rat) of 20% yeast suspension into the right hind paw. The pain threshold was measured every 60 min for 240 min. Animals in which the postdrug pain threshold was raised more over 50% as compared with the threshold in a control group were regarded as positive for analgesic activity. The ED_{50} values and their 95% confidence limits (CL) were calculated by the method of Litchfield and Wilcoxon.[18]

(d) Adjuvant-Induced Arthritic Pain Test.[21] Groups of six male SD rats weighing 160–200 g were used. Rats were given an intradermal injection (0.1 mL/rat) of 0.5% *Mycobacterium butyricum* suspension into the distal portion of the tail. After 15–18 days, the drugs were administered orally to rats showing a pain response (vocalization) by gentle flexion, and the pain response was measured every 60 min for 300 min. Animals that did not show any pain response were regarded as positive for analgesic activity. The ED_{50} values and their 95% confidence limits (CL) were calculated by the method of Litchfield and Wilcoxon.[18]

Antipyretic Activity. Yeast Induced Fever Test.[22] Groups of six male Wistar rats weighing 190–210 g were used. The body temperature of the animal was measured automatically by a personal computer system (PC-8001, NEC). The drugs were administered orally 180 min after a subcutaneous injection (10 mL/kg) of 7.5% yeast suspension to rats showing a body temperature increase of more over 1 °C. The body temperature was measured every 60 min for 360 min. The inhibitory percent was calculated by comparison with the body temperature in a control group. The ED_{50} values and their 95% confidence limits (CL) were calculated by the method of Litchfield and Wilcoxon.[18]

Antiinflammatory Activity. Carrageenin Induced Edema.[23] Groups of six male Wistar rats weighing 130–170 g were used. The drugs were administered orally 60 min before the subplantar injection (0.1 mL/rat) of 0.5% λ-carrageenin suspension into the left hind paw. The foot volume was measured every 60 min for 360 min. The swelling percent was calculated by comparison with that in a control group. The ED_{50} values and their 95% confidence limits (CL) were calculated by the method of Litchfield and Wilcoxon.[18]

ALS Method. The ALS method includes an error-correcting feedback algorithm, and the details have been described elsewhere.[2-4] In this study, the version of 1981 (ALS 81)[4] was used. ALS 81 differs from the old version[3] in only two respects: the correction term and the maximum iteration times. The correction term $C_i(t)$ for misclassified compound i at the tth iteration is given as

$$C_i(t) = 0.1/(\delta_i(t) + 0.45)^2 + 0.1$$

where

$$\delta_i(t) = |L_i(t) - b_k|$$

In this equation, $L_i(t)$ is the discriminant score, and b_k is the cutting point [nearer to $L_i(t)$] of the observed class for compound i. ALS iteration is performed maximum 20 times. The best discriminant function is selected according to the Spearman rank correlation coefficient and the value (apparent variance of errors) detailed in ref 3.

The results of the ALS calculation were validated by the leave-one-out prediction.[24] The measure of the predictive ability is obtained by leaving out one compound and using the remaining compounds as the training set. The discriminant function developed from the training set is used to predict the potency class of the compound left out. This procedure is continued until each compound of the data set has been left out of the training set once. The predictive results were given as the number misclassified and the Spearman rank correlation coefficient for the overall leave-one-out classification.

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Registry No. 1, 101372-11-6; 2, 101372-12-7; 3, 101372-13-8; 4, 101372-14-9; 5, 101372-15-0; 6, 101372-16-1; 7, 100284-84-2; 8, 100284-85-3; 9, 100284-86-4; 10, 100284-87-5; 11, 100284-88-6; 12, 100284-89-7; 13, 100284-96-6; 14, 100284-97-7; 15, 100284-98-8; 16, 100284-99-9; 17, 100285-00-5; 18, 100285-01-6; 19, 100284-79-5; 20, 100284-80-8; 21, 100303-52-4; 22, 100284-81-9; 23, 100284-82-0; 24, 100284-83-1; 25, 100284-74-0; 26, 100284-75-1; 27, 100284-76-2; 28, 101372-20-7; 29, 100284-77-3; 30, 100284-78-4; 31, 100284-90-0; 32, 100284-91-1; 33, 100284-92-2; 34, 100284-93-3; 35, 100284-94-4; 36, 100284-95-5; 37, 100284-61-5; 38, 100285-02-7; 39, 91260-70-7; 40, 97682-54-7; 41, 91260-71-8; 42, 91260-69-4; 43, 97682-55-8; 44, 97682-00-3; 45, 97681-41-9; 46, 97681-42-0; 47, 97681-43-1; 48, 97681-44-2; 49, 97681-45-3; 50, 97681-46-4; 51, 97681-47-5; 52, 97681-48-6; 53, 97681-49-7; 55, 95611-89-5; 56, 103534-07-2; 57, 103534-08-3; 58, 103534-09-4; 59, 103534-10-7; 60, 91260-68-3.

Synthetic 1,4-Disubstituted-1,4-dihydro-5*H*-tetrazol-5-one Derivatives of Fentanyl: Alfentanil (R 39209), a Potent, Extremely Short-Acting Narcotic Analgesic

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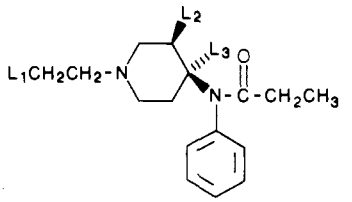
The synthesis of a series of *N*-1,4-disubstituted-1,4-dihydro-5*H*-tetrazol-5-one piperidinyl derivatives of fentanyl (**10**), carfentanil (**11**), and sufentanil (**12**) is described. The 1-substituted tetrazolinones **2** were essentially prepared via the addition reaction of aluminum azide to isocyanates or acid chlorides in tetrahydrofuran. Alkylation of **2** under neutral or weakly basic conditions afforded almost exclusively the 1,4-disubstituted tetrazolinone isomer **3**. N-Alkylation of the piperidine derivatives **4** with **3** in dimethylformamide yielded **9a–v**. The morphinomimetic activity in rats, after intravenous injection of the compounds, was evaluated in the tail withdrawal reflex test. The fentanyl analogues **9a–c** (R_4 = H) are inactive at the measured dose of 2.5 or 10 mg/kg (iv). For the carfentanil analogues (R_4 = $COOCH_3$) maximal narcotic activity is found when R_1 represents a lower alkyl group (**9d–f**) or a thienylethyl group (**9n**). The sufentanil analogues (R_4 = CH_2OCH_3) show the same structure–activity relationship (SAR) profile as the carfentanil derivatives (R_4 = $COOCH_3$). The structural requirements for optimal activity are in good agreement with earlier observations in the series of **10–12**. From the series the ethyl tetrazolinone derivative **9r**, alfentanil (R 39209), was selected for clinical investigation. As an analgesic in rats, **9r** is 140 times more potent than pethidine **15** and 72 times more potent than morphine **14**. Alfentanil reaches its peak effect within 1 min after injection, and its duration of action is very short; at 2 times its MED_{50}, **9r** has a duration of action of 11 min. This duration is 30 min for **10** and 90 min for **14**. Compared to **10**, alfentanil **9r** is about 4 times faster but 3 times shorter acting. Structurally, **9r** shows most resemblance to sufentanil **12**, since it differs only by substitution of a 4-ethyltetrazolinone ring for the thiophene ring. The considerable differences in their pharmacological profiles were explained in terms of marked variations in physicochemical and, hence, pharmacokinetic properties.

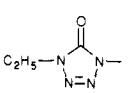
Neuroleptanalgesia[1] has become a popular technique in anesthesia, largely on account of the stable cardiovascular situation associated with it. The narcotic analgesics most commonly used intravenously are morphine and fentanyl.[2,3]

New surgical techniques have created the need for other morphinomimetic compounds characterized by a rapid onset of action, a duration of analgesic activity that can be adapted to the particular clinical situation, a well-defined dose–response relationship, and a maximal margin of safety. Our initial strategy for the attainment of these objectives was directed toward the discovery of narcotic analgesics of increased potency, not for the sake of potency itself but because specificity and safety are directly related to potency.

Chemical modification of the fentanyl structure at the C-4 position of the piperidine ring proved to be a successful approach (Table I).[4,5] Thus, introduction of a carbomethoxy group gave carfentanil **11**, whereas addition of a methoxymethylene group coupled with isosteric replacement of the phenyl ring of the phenethyl substituent by a thienyl ring led to sufentanil **12**. Both carfentanil and sufentanil are very potent and long-acting analgesics. Stereospecific introduction of a methyl group at the C-3 position of the piperidine moiety of the carfentanil molecule resulted in the extremely potent and long-acting compound lofentanil **13**.

Table I. Structures of Fentanyl and Related Compounds



compd	L_1	L_2	L_3
fentanyl (**10**)	Ph	H	H
carfentanil (**11**)	Ph	H	$COOCH_3$
sufentanil (**12**)	2-thienyl	H	CH_2OCH_3
lofentanil (**13**)[a]	Ph	CH_3	$COOCH_3$
alfentanil (**9r**)		H	CH_2OCH_3

[a] Cis-(−) enantiomer.

Changing the piperidine ring system or modifying the propionanilido moiety was less rewarding. Thus, contraction of the piperidine ring to a 3-anilinopyrrolidine[6]

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