[Chem. Pharm. Bull. 33(12)5250--5257(1985)]

# Furo[3,2-*b*]indole Derivatives. II. Synthesis and Analgesic and Anti-inflammatory Activities of 4-Alkoxycarbonyl-2-morpholinocarbonylfuro[3,2-*b*]indole Derivatives[1)]

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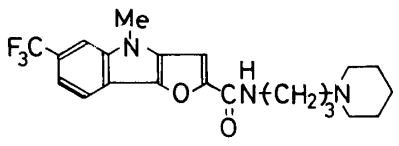
(Received April 19, 1985)

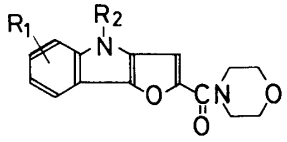
As part of a series of studies on furo[3,2-*b*]indole derivatives, 4-alkoxycarbonyl-2-morpholinocarbonylfuro[3,2-*b*]indole derivatives were synthesized, and their analgesic and anti-inflammatory activities were examined using the acetic acid writhing method in mice and the carrageenin edema method in rats. Some of these derivatives, particularly 4-isopropoxycarbonyl-2-morpholinocarbonyl-6-trifluoromethylfuro[3,2-*b*]indole, showed pronounced pharmacological activities. The structure–activity relationships are discussed.

**Keywords**——4-alkoxycarbonyl-2-morpholinocarbonylfuro[3,2-*b*]indole; 4-isopropoxycarbonyl-2-morpholinocarbonyl-6-trifluoromethylfuro[3,2-*b*]indole; analgesic activity; anti-inflammatory activity; structure–activity relationship

In a previous paper,[2)] we reported that 4,6-disubstituted-*N*-(3-piperidinopropyl)furo-[3,2-*b*]indole-2-carboxamide derivatives have potent analgesic and anti-inflammatory activities. Among these derivatives, 4-methyl-*N*-(3-piperidinopropyl)-6-trifluoromethylfuro[3,2-*b*]-indole-2-carboxamide (I) has been considered to have a potent combination of high activities and low toxicity.[3,4)]



I



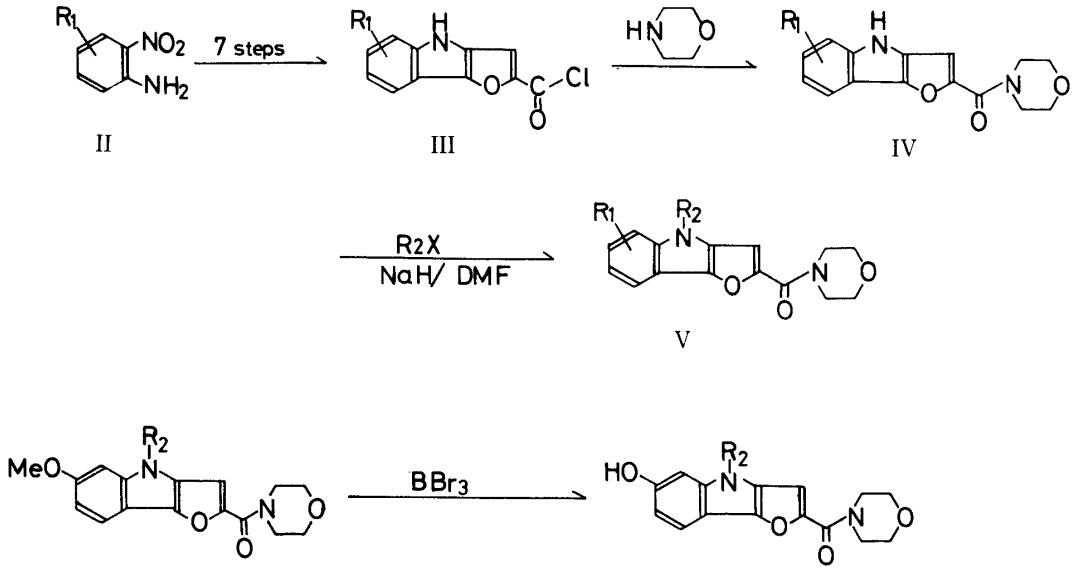
V

Chart 1

As a continuation of the above work, we have synthesized various 4-alkoxycarbonyl-2-morpholinocarbonylfuro[3,2-*b*]indole derivatives (V), and examined their analgesic and anti-inflammatory activities. The structure–activity relationships are also discussed.

## Chemistry

The general synthetic routes for preparation of the present compounds are shown in Chart 2. 6-Substituted 4*H*-furo[3,2-*b*]indole-2-carbonyl chlorides (III) were synthesized by the method reported in the previous paper.[2,5)] Acid chlorides (III) were treated with morpholine to give the corresponding amides (IV). Compounds IV were converted to the corresponding 4-alkoxycarbonyl-2-morpholinocarbonylfuro[3,2-*b*]indole derivatives (V) by alkoxycarbonylation at the 4-position with alkyl chloroformates. Further, the 7-trifluoromethylfuro[3,2-*b*]-




$R_1$: 6-H, Me, OMe, Cl, F, $CF_3$
7-$CF_3$
$R_2$: $CO_2Me$, $CO_2Et$, $CO_2n$-Pr, $CO_2$ iso-Pr
$CO_2n$-Bu, $CO_2$ iso-Bu

Chart 2

indole derivative (V-42) was similarly synthesized in 9 steps from 5-trifluoromethyl-2-nitroaniline (II).[6] 4-Substituted 6-hydroxyfuro[3,2-*b*]indole derivatives (V-37—41) were prepared by demethylation of the methoxy group of V-13—18 with $BBr_3$. Physical and analytical data for compounds IV and V are recorded in Table I.

**Biological Results and Discussion**

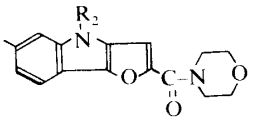
All of the 4-alkoxycarbonyl-2-morpholinocarbonylfuro[3,2-*b*]indole derivatives obtained in this study were examined for analgesic activity using the acetic acid writhing method[7] in mice and for anti-inflammatory activity using the carrageenin edema method[8] in rats, as described in the experimental section. These results are summarized in Table I, and from them the following structure–activity relationships were determined.

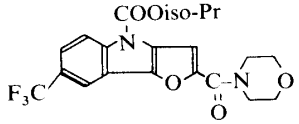
In a series of alkoxycarbonyl groups ($R_2$) on the furo[3,2-*b*]indole nitrogen, the presence of a higher alkyl or other bulky substituent tended to increase the above activities. The effect of substituents ($R_1$) on the benzene moiety of the furo[3,2-*b*]indole was rather complicated, though the 6-$CF_3$ and Cl derivatives were, in general, more potent than the 6-Me, OMe, F, OH, and H derivatives.

The analgesic activities of V-32 and -34 were more potent than that of the positive control (tiaramide), and the activities of V-10, -18, -22, -23, -33 and -35 were roughly equilvalent to that of tiaramide. The anti-inflammatory activities of V-8 and -34 were more potent than that of tiaramide, while those of V-10, -22, -32, -33 and -35 were roughly equivalent. Among these compounds, 4-isopropoxycarbonyl-2-morpholinocarbonyl-6-trifluoromethylfuro[3,2-*b*]indole (V-34) showed pronounced pharmacological activities, whereas the corresponding 7-$CF_3$ derivative (V-42) did not exhibit any marked activities. The analgesic and anti-inflammatory activities of V-34 were more potent than those of I. Moreover, on oral administration in mice, the $LD_{50}$ values of compounds I and V-34 were 332.1 mg/kg and over 1000 mg/kg (*p.o.*), respectively.

These results suggest that the analogues in this series represent a novel class of analgesic and anti-inflammatory agents with high activities. Detailed studies aimed at further evaluation are continuing.

TABLE I.



| No. | $R_1$ | $R_2$ | mp (°C) | Recrystn. solvent[a] | Formula[b] | Analgesic activity[c] | Anti-infl. activity[d] |
|---|---|---|---|---|---|---|---|
| IV-1 | H | H | 157—158[e] | T | $C_{15}H_{14}N_2O_3$ | 31.4[g] | 32.7[f] |
| V-1 | H | $CO_2Me$ | 129—131 | A | $C_{17}H_{16}N_2O_5$ | 36.0[g] | 25.9[f] |
| V-2 | H | $CO_2Et$ | 107—110 | A–H | $C_{18}H_{18}N_2O_5$ | 38.0[g] | 14.8 |
| V-3 | H | $CO_2Pr$ | 138—139 | A–H | $C_{19}H_{20}N_2O_5$ | 39.5[g] | −33.6 |
| V-4 | H | $CO_2$iso-Pr | 142—143 | A–H | $C_{19}H_{20}N_2O_5$ | 64.4[h] | 19.3 |
| V-5 | H | $CO_2Bu$ | 132—133 | A–H | $C_{20}H_{22}N_2O_5$ | 26.2[f] | 6.7 |
| V-6 | H | $CO_2$iso-Bu | 130—132 | A–H | $C_{20}H_{22}N_2O_5$ | 15.3 | 12.9 |
| IV-2 | Me | H | 198.5—199.5 | A | $C_{16}H_{16}N_2O_3$ | N.T. | N.T. |
| V-7 | Me | $CO_2Me$ | 151—153 | A | $C_{18}H_{18}N_2O_5$ | 15.5 | 24.0[f] |
| V-8 | Me | $CO_2Et$ | 120—121 | A–H | $C_{19}H_{20}N_2O_5$ | 51.3[g] | 89.8[h] |
| V-9 | Me | $CO_2Pr$ | 161—162 | A–H | $C_{20}H_{22}N_2O_5$ | 48.1[g] | −0.3 |
| V-10 | Me | $CO_2$iso-Pr | 137—139 | A–H | $C_{20}H_{22}N_2O_5$ | 75.4[h] | 65.6[h] |
| V-11 | Me | $CO_2Bu$ | 134—135.5 | A–H | $C_{21}H_{24}N_2O_5$ | 46.9[g] | 3.0 |
| V-12 | Me | $CO_2$iso-Bu | 131.5—133 | A–H | $C_{21}H_{24}N_2O_5$ | 56.6[h] | 33.6[f] |
| IV-3 | OMe | H | 161—162 | A–H | $C_{16}H_{16}N_2O_4$ | N.T. | N.T. |
| V-13 | OMe | $CO_2Me$ | 162—163 | A | $C_{18}H_{18}N_2O_6$ | 5.6 | 0.9 |
| V-14 | OMe | $CO_2Et$ | 160—162 | T | $C_{19}H_{20}N_2O_6$ | 13.3 | 12.1 |
| V-15 | OMe | $CO_2Pr$ | 131—132 | A–E | $C_{20}H_{22}N_2O_6$ | 42.9[g] | −13.0 |
| V-16 | OMe | $CO_2$iso-Pr | 164—166 | A–E | $C_{20}H_{22}N_2O_6$ | 58.2[h] | −5.3 |
| V-17 | OMe | $CO_2Bu$ | 117—118.5 | A–E | $C_{21}H_{24}N_2O_6$ | 44.0[g] | −7.1 |
| V-18 | OMe | $CO_2$iso-Bu | 96—100 | E | $C_{21}H_{24}N_2O_6$ | 75.2[h] | −8.5 |
| IV-4 | Cl | H | 228—229 | EA | $C_{15}H_{13}ClN_2O_3$ | N.T. | N.T. |
| V-19 | Cl | $CO_2Me$ | 199—201 | A | $C_{17}H_{15}ClN_2O_5$ | 11.1 | 4.8 |
| V-20 | Cl | $CO_2Et$ | 169—170.5 | A | $C_{18}H_{17}ClN_2O_5$ | 24.2[f] | 31.5[f] |
| V-21 | Cl | $CO_2Pr$ | 131—133 | A–H | $C_{19}H_{19}ClN_2O_5$ | 40.1[f] | 41.9[g] |
| V-22 | Cl | $CO_2$iso-Pr | 145.5—146.5 | A–H | $C_{19}H_{19}ClN_2O_5$ | 79.5[h] | 59.9[h] |
| V-23 | Cl | $CO_2Bu$ | 119—120.5 | A–H | $C_{20}H_{21}ClN_2O_5$ | 79.8[h] | 26.2 |
| V-24 | Cl | $CO_2$iso-Bu | 136.5—137.5 | A | $C_{20}H_{21}ClN_2O_5$ | 61.4[h] | 36.0[f] |
| IV-5 | F | H | 210.5—211.5 | A–H | $C_{15}H_{13}FN_2O_3$ | N.T. | N.T. |
| V-25 | F | $CO_2Me$ | 185—186 | A | $C_{17}H_{15}FN_2O_5$ | 2.9 | 3.5 |
| V-26 | F | $CO_2Et$ | 162.5—163.5 | A | $C_{18}H_{17}FN_2O_5$ | 29.6[f] | 2.4 |
| V-27 | F | $CO_2Pr$ | 126—127.5 | A–H | $C_{19}H_{19}FN_2O_5$ | 60.7[h] | 14.9 |
| V-28 | F | $CO_2$iso-Pr | 178—179 | A–H | $C_{19}H_{19}FN_2O_5$ | 58.7[h] | 1.8 |
| V-29 | F | $CO_2Bu$ | 118—119 | A–H | $C_{20}H_{21}FN_2O_5$ | 65.8[h] | 12.4 |
| V-30 | F | $CO_2$iso-Bu | 140.5—141.5 | A–H | $C_{20}H_{21}FN_2O_5$ | 63.8[h] | −14.6 |
| IV-6 | $CF_3$ | H | 220.5—221.5 | T | $C_{16}H_{13}F_3N_2O_3$ | N.T. | N.T. |
| V-31 | $CF_3$ | $CO_2Me$ | 200—200.5 | EA | $C_{18}H_{15}F_3N_2O_5$ | 6.1 | −17.3 |
| V-32 | $CF_3$ | $CO_2Et$ | 136.5—137.5 | A–H | $C_{19}H_{17}F_3N_2O_5$ | 87.2[h] | 66.0[h] |
| V-33 | $CF_3$ | $CO_2Pr$ | 126—127.5 | A–H | $C_{20}H_{19}F_3N_2O_5$ | 72.3[h] | 68.9[h] |
| V-34 | $CF_3$ | $CO_2$iso-Pr | 111.5—112.5 | A–H | $C_{20}H_{19}F_3N_2O_5$ | 98.5[h] | 73.4[h] |
| V-35 | $CF_3$ | $CO_2Bu$ | 115.5—116.5 | A–H | $C_{21}H_{21}F_3N_2O_5$ | 79.3[h] | 55.7[g] |
| V-36 | $CF_3$ | $CO_2$iso-Bu | 157—158 | A–H | $C_{21}H_{21}F_3N_2O_5$ | 53.5[h] | 17.8 |
| V-37 | OH | $CO_2Me$ | 231—233 | A–H | $C_{17}H_{16}N_2O_6$ | 29.5[f] | −26.9 |
| V-38 | OH | $CO_2Et$ | 222—224 | A | $C_{18}H_{18}N_2O_6$ | 50.5[h] | −30.8 |
| V-39 | OH | $CO_2Pr$ | 228.5—231.5 | A–H | $C_{19}H_{20}N_2O_6$ | N.T. | N.T. |
| V-40 | OH | $CO_2Bu$ | 217—218 | A | $C_{20}H_{22}N_2O_6$ | N.T. | N.T. |
| V-41 | OH | $CO_2$iso-Bu | 223.5—224.5 | A | $C_{20}H_{22}N_2O_6$ | N.T. | N.T. |
| V-42 |  | | 225—226 | A | $C_{20}H_{19}F_3N_2O_5$ | 44[g] | 16.5 |
| Tiaramide | | | | | | 76.2[h] | 57.4[g] |

*a*) A = acetone, H = hexane, E = ether, T = EtOH, EA = ethyl acetate. *b*) All compounds were analyzed for C, H and N: analytical results obtained for these elements were within ±0.4% of calculated values. *c*) % inhibition of acetic acid writhing (100 mg/kg *p.o.*). *d*) % inhibition of carrageenin edema (100 mg/kg *p.o.*). *e*) Ref.[5] mp 154—155 °C. Statistically significant at *f*) $p<0.05$, *g*) $p<0.01$, *h*) $p<0.001$. N.T.: not tested.

## Experimental

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. Proton nuclear magnetic resonance ($^1$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.

**Compounds IV: 2-Morpholinocarbonyl-6-trifluoromethyl-4*H*-furo[3,2-*b*]indole (IV-6)**——A solution of 6-trifluoromethyl-4*H*-furo[3,2-*b*]indole-2-carbonyl chloride (5.0 g) in acetone (50 ml) was added dropwise to a solution of morpholine (5.0 g) in dichloromethane (100 ml), then the mixture was stirred for 30 min at room temperature, concentrated, and poured into ice-$H_2O$. The resulting product was filtered off (7.2 g, 92.2%), and recrystallized from EtOH to give colorless needles, mp 220.5—221.5 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3240, 1610. MS *m/e*: 338 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.77 (8H, br s), 7.37 (1H, dd, $J$=8, 2 Hz), 7.39 (1H, s), 7.83 (1H, d, $J$=2 Hz), 7.85 (1H, d, $J$=8 Hz). *Anal.* Calcd for $C_{16}H_{13}F_3N_2O_3$: C, 56.81; H, 3.87; N, 8.28. Found: C, 57.00; H, 3.51; N, 8.21.

Compounds IV-2—5 were prepared in the same manner.

**Compounds V: 4-Isopropoxycarbonyl-2-morpholinocarbonyl-6-trifluoromethylfuro[3,2-*b*]indole (V-34)**——A solution of IV-6 (7.2 g) in dimethylformamide (DMF) (40 ml) was added dropwise with stirring to a suspension of NaH (0.51 g) in DMF (50 ml), then the mixture was stirred for 30 min. Isopropyl chloroformate (2.87 g) was added thereto, and the whole was stirred for 30 min at room temperature, then poured into ice-$H_2O$. The resulting product was filtered off (7.9 g, 88%). Recrystallization from hexane–acetone gave colorless prisms, mp 111.5—112.5 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1740, 1620. MS *m/e*: 424 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.46 (6H, d, $J$=7 Hz), 3.74 (8H, br s), 5.16 (1H, m), 7.22 (1H, s), 7.58 (1H, dd, $J$=8, 2 Hz), 7.89 (1H, d, $J$=8 Hz), 8.39 (1H, d, $J$=2 Hz). *Anal.* Calcd for $C_{20}H_{19}F_3N_2O_5$: C, 56.60; H, 4.51; N, 6.60. Found: C, 56.60; H, 4.57; N, 6.43.

Compounds V-1—33, -35, -36 and -42 were prepared in the same manner.

**6-Hydroxy-4-methoxycarbonyl-2-morpholinocarbonylfuro[3,2-*b*]indole (V-37)**——Boron tribromide ($BBr_3$) (25 g) was added dropwise to a solution of V-13 (4.5 g) in dichloromethane (100 ml) below −70 °C, then the solution was stirred for 30 min at −70 °C and filtered. The filtrate was concentrated and extracted with chloroform. The extract was washed with aq. $NaHCO_3$ and $H_2O$, then dried ($MgSO_4$), and concentrated to give crystals (1.5 g, 34.7%). Recrystallization from hexane–acetone gave colorless prisms, mp 231—233 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3280, 1710, 1630. MS *m/e*: 344 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.70 (8H, br s), 3.99 (3H, s), 6.79 (1H, dd, $J$=8, 2 Hz), 7.29 (1H, s), 7.52 (1H, d, $J$=8 Hz), 7.68 (1H, d, $J$=2 Hz), 9.77 (1H, s). *Anal.* Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.08; H, 4.80; N, 7.85.

Compounds V-38—41 were prepared in the same manner. Compound V-16 was treated with $BBr_3$, but gave only IV-3 (1%).

Data for compounds IV and V are listed in Table II.

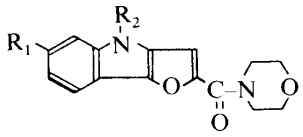
**5-(2-Nitro-5-trifluoromethylphenyl)-2-furancarboxylic Acid (VI-1)**——A mixture of 2-nitro-5-trifluoromethylaniline (60 g) and conc. HCl (300 ml) was heated at 60 °C, then cooled in an ice bath. A solution of $NaNO_2$ (21 g) in $H_2O$ (100 ml) was added dropwise to the cold solution below −10 °C. After the mixture had been stirred at −10 °C for 30 min, it was added dropwise to a stirred mixture of 2-furancarboxylic acid (34 g), $CuCl_2$ (12 g) and $H_2O$ (1000 ml) at 50 °C. The resulting product was filtered off, then washed with $H_2O$ and benzene to give crystals (30.7 g, 35.0%). Recrystallization from EtOH gave colorless prisms, mp 171—174 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 2800, 1700. MS *m/e*: 301 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.17 (1H, d, $J$=4 Hz), 7.34 (1H, d, $J$=4 Hz), 7.98 (1H, dd, $J$=8, 2 Hz), 8.16 (1H, d, $J$=8 Hz), 8.23 (1H, d, $J$=2 Hz). *Anal.* Calcd for $C_{12}H_6F_3NO_5$: C, 47.85; H, 2.01; N, 4.64. Found: C, 48.00; H, 1.70; N, 4.92.

**5-(4-Fluoro-2-nitrophenyl)-2-furancarboxylic Acid (VI-2)**——A diazonium salt of 4-fluoro-2-nitroaniline prepared in the same manner as above was added dropwise to a stirred mixture of 2-furancarboxylic acid, $CuCl_2$ and 87.5% aq. acetone at 60 °C. The resulting product was filtered off (30.6%). Recrystallization from EtOH gave pale yellow prisms, mp 176—177 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3200, 1680. MS *m/e*: 251 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.07 (1H, d, $J$=4 Hz), 7.39 (1H, d, $J$=4 Hz), 7.7—8.1 (3H, m), 13.35 (1H, br s). *Anal.* Calcd for $C_{11}H_6FNO_5$: C, 52.60; H, 2.41; N, 5.57. Found: C, 52.30; H, 2.60; N, 5.51.

**Ethyl 5-(2-Nitro-5-trifluoromethylphenyl)-2-furancarboxylate (VII-1)**——A mixture of VI-1 (35 g), conc. $H_2SO_4$ (9 ml) and EtOH (200 ml) was refluxed for 10 h, then concentrated, and poured into ice-$H_2O$. The resulting product was filtered off (35.4 g, 92.5%), and recrystallized from EtOH to give pale yellow prisms, mp 110—112.5 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1710. MS *m/e*: 329 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.29 (3H, t, $J$=7 Hz), 4.28 (2H, q, $J$=7 Hz), 7.23 (1H, d, $J$=4 Hz), 7.38 (1H, d, $J$=4 Hz), 7.95 (1H, dd, $J$=8, 2 Hz), 8.12 (1H, d, $J$=8 Hz), 8.22 (1H, d, $J$=2 Hz). *Anal.* Calcd for $C_{14}H_{10}F_3NO_5$: C, 51.07; H, 3.06; N, 4.25. Found: C, 51.00; H, 3.22; N, 4.02.

Ethyl 5-(4-fluoro-2-nitrophenyl)-2-furancarboxylate (VII-2) was prepared in the same manner, mp 79—80.5 °C (hexane–acetone). Yield 90%. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1720, 1610. MS *m/e*: 279 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.40 (3H, t, $J$=7 Hz), 4.38 (2H, q, $J$=7 Hz), 6.68 (1H, d, $J$=4 Hz), 7.23 (1H, d, $J$=4 Hz), 7.38 (1H, dt, $J_d$=2 Hz, $J_t$=8 Hz), 7.57 (1H,

TABLE II.



| No. | Yield (%) | IR $\nu_{max}^{KBr}$ cm$^{-1}$ | | MS *m/e* ($M^+$) | NMR Chemical shift (in DMSO-$d_6$) $\delta$ |
|---|---|---|---|---|---|
| V-1 | 76.0 | 1740 | 1610 | 328 | 3.74 (4H, br s), 3.80 (4H, br s), 4.04 (3H, s), 7.34 (1H, s), 7.38 (1H, t, $J$=8 Hz), 7.42 (1H, t, $J$=8 Hz), 7.73 (1H, d, $J$=8 Hz), 8.20 (1H, d, $J$=8 Hz) |
| V-2 | 80.0 | 1735 | 1615 | 342 | 1.46 (3H, t, $J$=7 Hz), 3.74 (4H, br s), 3.80 (4H, br s), 4.50 (2H, q, $J$=7 Hz), 7.32 (1H, s), 7.42 (1H, t, $J$=8 Hz), 7.45 (1H, t, $J$=8 Hz), 7.78 (1H, d, $J$=8 Hz), 8.24 (1H, d, $J$=8 Hz) |
| V-3 | 83.3 | 1735 | 1610 | 356 | 1.02 (3H, t, $J$=7 Hz), 1.84 (2H, m), 3.72 (8H, br s), 4.34 (2H, t, $J$=7 Hz), 7.16 (1H, s), 7.30 (2H, m), 7.62 (1H, m), 8.15 (1H, m) |
| V-4 | 79.6 | 1740 | 1625 | 356 | 1.45 (6H, d, $J$=7 Hz), 3.72 (8H, br s), 5.15 (1H, m), 7.20 (1H, s), 7.32 (2H, m), 7.70 (1H, m), 8.15 (1H, m) |
| V-5 | 83.8 | 1740 | 1615 | 370 | 0.96 (3H, t, $J$=7 Hz), 1.70 (4H, m), 3.72 (8H, br s), 4.40 (2H, t, $J$=7 Hz), 7.20 (1H, s), 7.33 (2H, m), 7.70 (1H, m), 8.15 (1H, m) |
| V-6 | 91.1 | 1735 | 1610 | 370 | 1.04 (6H, d, $J$=7 Hz), 2.15 (1H, m), 3.72 (8H, br s), 4.18 (2H, d, $J$=7 Hz), 7.16 (1H, s), 7.30 (2H, m), 7.65 (1H, m), 8.12 (1H, m) |
| IV-2 | 71.3[a] | 3240 | 1615 | 284 | 2.43 (3H, s), 3.73 (8H, br s), 6.93 (1H, dd, $J$=8, 2 Hz), 7.27 (1H, d, $J$=2 Hz), 7.28 (1H, s), 7.58 (1H, d, $J$=8 Hz), 10.83 (1H, s) |
| V-7 | 83.1 | 1755 | 1610 | 324 | 2.42 (3H, s), 3.80 (4H, br s), 3.85 (4H, br s), 4.02 (3H, s), 7.15 (1H, d, $J$=8 Hz), 7.26 (1H, s), 7.51 (1H, dd, $J$=8, 2 Hz), 7.89 (1H, d, $J$=2 Hz) |
| V-8 | 73.4 | 1740 | 1625 | 356 | 1.46 (3H, t, $J$=7 Hz), 2.47 (3H, s), 3.77 (4H, br s), 3.83 (4H, br s), 4.50 (2H, q, $J$=7 Hz), 7.21 (1H, dd, $J$=8, 2 Hz), 7.30 (1H, s), 7.62 (1H, d, $J$=8 Hz), 8.05 (1H, d, $J$=2 Hz) |
| V-9 | 68.0 | 1740 | 1615 | 370 | 1.05 (3H, t, $J$=7 Hz), 1.87 (2H, m, $J$=7 Hz), 2.49 (3H, s), 3.75 (8H, br s), 4.40 (2H, t, $J$=7 Hz), 7.14 (1H, dd, $J$=8, 2 Hz), 7.23 (1H, s), 7.62 (1H, d, $J$=8 Hz), 8.02 (1H, d, $J$=2 Hz) |
| V-10 | 49.0 | 1735 | 1630 | 370 | 1.46 (6H, d, $J$=7 Hz), 2.48 (3H, s), 3.75 (8H, br s), 5.18 (1H, m), 7.16 (1H, dd, $J$=8, 2 Hz), 7.23 (1H, s), 7.62 (1H, d, $J$=8 Hz), 8.05 (1H, d, $J$=2 Hz) |
| V-11 | 54.0 | 1735 | 1610 | 384 | 0.95 (3H, t, $J$=7 Hz), 1.70 (4H, m), 2.43 (3H, s), 3.70 (8H, br s), 4.39 (2H, t, $J$=7 Hz), 7.12 (1H, dd, $J$=8, 2 Hz), 7.19 (1H, s), 7.56 (1H, d, $J$=8 Hz), 7.98 (1H, d, $J$=2 Hz) |
| V-12 | 47.0 | 1735 | 1630 | 384 | 1.00 (6H, d, $J$=7 Hz), 2.12 (1H, m), 2.43 (3H, s), 3.72 (8H, br s), 4.18 (2H, d, $J$=7 Hz), 7.10 (1H, dd, $J$=8, 2 Hz), 7.17 (1H, s), 7.56 (1H, d, $J$=8 Hz), 7.95 (1H, d, $J$=2 Hz) |
| IV-3 | 58.6[a] | 3180 | 1635 | 300 | 3.74 (8H, br s), 3.83 (3H, s), 6.75 (1H, dd, $J$=8, 2 Hz), 6.97 (1H, d, $J$=2 Hz), 7.25 (1H, s), 7.58 (1H, d, $J$=8 Hz), 10.90 (1H, s) |
| V-13 | 78.2 | 1740 | 1640 | 358 | 3.72 (4H, br s), 3.80 (4H, br s), 3.85 (3H, s), 4.04 (3H, s), 6.99 (1H, dd, $J$=8, 2 Hz), 7.32 (1H, s), 7.64 (1H, d, $J$=8 Hz), 7.74 (1H, d, $J$=2 Hz) |
| V-14 | 77.9 | 1740 | 1635 | 372 | 1.44 (3H, t, $J$=7 Hz), 3.72 (4H, br s), 3.80 (4H, br s), 3.84 (3H, s), 4.48 (2H, q, $J$=7 Hz), 6.98 (1H, dd, $J$=8, 2 Hz), 7.26 (1H, s), 7.63 (1H, d, $J$=8 Hz), 7.74 (1H, d, $J$=2 Hz) |
| V-15 | 83.1 | 1750 | 1640 | 386 | 1.02 (3H, t, $J$=7 Hz), 1.83 (2H, m), 3.73 (8H, br s), 3.79 (3H, s), 4.31 (2H, t, $J$=7 Hz), 6.84 (1H, dd, $J$=8, 2 Hz), 7.09 (1H, s), 7.49 (1H, d, $J$=8 Hz), 7.59 (1H, d, $J$=2 Hz) |
| V-16 | 85.7 | 1735 | 1615 | 386 | 1.45 (6H, d, $J$=7 Hz), 3.71 (8H, br s), 3.83 (3H, s), 5.15 (1H, m), 6.92 (1H, dd, $J$=8, 2 Hz), 7.20 (1H, s), 7.61 (1H, d, $J$=8 Hz), 7.72 (1H, d, $J$=2 Hz) |
| V-17 | 80.2 | 1730 | 1635 | 400 | 0.98 (3H, t, $J$=7 Hz), 1.70 (4H, m), 3.73 (8H, br s), 3.80 (3H, s), 4.35 (2H, t, $J$=7 Hz), 6.85 (1H, dd, $J$=8, 2 Hz), 7.10 (1H, s), 7.50 (1H, d, $J$=8 Hz), 7.60 (1H, d, $J$=2 Hz) |

TABLE II. (continued)

| No. | Yield (%) | IR $\nu_{max}^{KBr}$ cm$^{-1}$ | | MS *m/e* ($M^+$) | NMR Chemical shift (in DMSO-$d_6$) $\delta$ |
|---|---|---|---|---|---|
| V-18 | 83.0 | 1735 | 1620 | 400 | 1.04 (6H, d, $J$=7 Hz), 2.10 (1H, m, $J$=7 Hz), 3.73 (8H, br s), 3.80 (3H, s), 4.16 (2H, d, $J$=7 Hz), 6.85 (1H, dd, $J$=8, 2 Hz), 7.10 (1H, s), 7.50 (1H, d, $J$=8 Hz), 7.60 (1H, d, $J$=2 Hz) |
| IV-4 | 82.7[a)] | 3260 | 1610 | 304 | 3.73 (8H, br s), 7.08 (1H, dd, $J$=8, 2 Hz), 7.32 (1H, s), 7.52 (1H, d, $J$=2 Hz), 7.71 (1H, d, $J$=8 Hz), 10.92 (1H, s) |
| V-19 | 70.1 | 1750 | 1615 | 362 | 3.71 (4H, br s), 3.78 (4H, br s), 4.06 (3H, s), 7.39 (1H, s), 7.42 (1H, dd, $J$=8, 2 Hz), 7.79 (1H, d, $J$=8 Hz), 8.19 (1H, d, $J$=2 Hz) |
| V-20 | 80.9 | 1740 | 1630 | 376 | 1.46 (3H, t, $J$=7 Hz), 3.72 (4H, br s), 3.78 (4H, br s), 4.51 (2H, q, $J$=7 Hz), 7.29 (1H, s), 7.39 (1H, dd, $J$=8, 2 Hz), 7.74 (1H, d, $J$=8 Hz), 8.18 (1H, d, $J$=2 Hz) |
| V-21 | 78.0 | 1750 | 1620 | 390 | 1.02 (3H, t, $J$=7 Hz), 1.75 (2H, m), 3.71 (8H, br s), 4.32 (2H, t, $J$=7 Hz), 7.10 (1H, s), 7.24 (1H, dd, $J$=8, 2 Hz), 7.60 (1H, dd, $J$=8 Hz), 7.98 (1H, d, $J$=2 Hz) |
| V-22 | 85.6 | 1735 | 1616 | 390 | 1.45 (6H, d, $J$=7 Hz), 3.71 (8H, br s), 5.13 (1H, m), 7.15 (1H, s), 7.25 (1H, dd, $J$=8, 2 Hz), 7.65 (1H, d, $J$=8 Hz), 8.05 (1H, d, $J$=2 Hz), |
| V-23 | 81.0 | 1740 | 1640 | 404 | 0.98 (3H, t, $J$=7 Hz), 1.70 (4H, m), 3.73 (8H, br s), 4.33 (2H, t, $J$=7 Hz), 7.03 (1H, s), 7.19 (1H, dd, $J$=8, 2 Hz), 7.52 (1H, d, $J$=8 Hz), 7.89 (1H, d, $J$=2 Hz) |
| V-24 | 86.8 | 1740 | 1620 | 404 | 1.02 (6H, d, $J$=7 Hz), 2.15 (1H, m), 3.75 (8H, br s), 4.17 (2H, d, $J$=7 Hz), 7.10 (1H, s), 7.22 (1H, dd, $J$=8, 2 Hz), 7.56 (1H, d, $J$=8 Hz), 7.94 (1H, d, $J$=2 Hz) |
| IV-5 | 86.5 | 3220 | 1630 | 288 | 3.75 (4H, br s), 3.85 (4H, br s), 7.05 (1H, dt, $J_d$=2 Hz, $J_t$=8 Hz), 7.37 (1H, dd, $J$=8, 2 Hz), 7.40 (1H, s), 7.85 (1H, dd, $J$=8, 5 Hz), 11.20 (1H, s) |
| V-25 | 67.7 | 1735 | 1630 | 346 | 3.75 (4H, br s), 3.82 (4H, br s), 4.10 (3H, s), 7.33 (1H, dt, $J_d$=2 Hz, $J_t$=8 Hz), 7.45 (1H, s), 7.87 (1H, dd, $J$=8, 5 Hz), 8.02 (1H, dd, $J$=8, 2 Hz) |
| V-26 | 62.9 | 1735 | 1630 | 360 | 1.46 (3H, t, $J$=7 Hz), 3.75 (4H, br s), 3.82 (4H, br s), 4.52 (2H, q, $J$=7 Hz), 7.32 (1H, dt, $J_d$=2 Hz, $J_t$=8 Hz), 7.35 (1H, s), 7.85 (1H, dd, $J$=8, 5 Hz), 7.97 (1H, dd, $J$=8, 2 Hz) |
| V-27 | 71.0 | 1740 | 1620 | 374 | 1.02 (3H, t, $J$=7 Hz), 1.85 (2H, m), 3.72 (8H, br s), 4.38 (2H, t, $J$=7 Hz), 7.20 (1H, dt, $J_d$=2 Hz, $J_t$=8 Hz), 7.21 (1H, s), 7.73 (1H, dd, $J$=8, 5 Hz), 7.86 (1H, dd, $J$=8, 2 Hz) |
| V-28 | 64.0 | 1735 | 1615 | 374 | 1.47 (6H, d, $J$=7 Hz), 3.74 (8H, br s), 5.18 (1H, m), 7.18 (1H, dt, $J_d$=2 Hz, $J_t$=8 Hz), 7.22 (1H, s), 7.73 (1H, dd, $J$=8, 5 Hz), 7.91 (1H, dd, $J$=8, 2 Hz) |
| V-29 | 58.0 | 1745 | 1625 | 388 | 0.96 (3H, t, $J$=7 Hz), 1.70 (4H, m), 3.73 (8H, br s), 4.40 (2H, t, $J$=7 Hz), 7.17 (1H, dt, $J_d$=2 Hz, $J_t$=8 Hz), 7.19 (1H, s), 7.70 (1H, dd, $J$=8, 5 Hz), 7.85 (1H, dd, $J$=8, 2 Hz) |
| V-30 | 43.0 | 1740 | 1625 | 388 | 1.02 (6H, d, $J$=7 Hz), 2.20 (1H, m), 3.73 (8H, br s), 4.24 (2H, d, $J$=7 Hz), 7.18 (1H, s), 7.20 (1H, dt, $J_d$=2 Hz, $J_t$=8 Hz), 7.21 (1H, s), 7.74 (1H, dd, $J$=8, 5 Hz), 7.89 (1H, dd, $J$=8, 2 Hz) |
| V-31 | 73.0 | 1760 | 1625 | 396 | 3.74 (4H, br s), 3.80 (4H, br s), 4.09 (3H, s), 7.46 (1H, s), 7.72 (1H, dd, $J$=8, 2 Hz), 8.02 (1H, d, $J$=8 Hz), 8.50 (1H, d, $J$=2 Hz) |
| V-32 | 72.0 | 1740 | 1625 | 410 | 1.47 (3H, t, $J$=7 Hz), 3.74 (4H, br s), 3.81 (4H, br s), 4.52 (2H, q, $J$=7 Hz), 7.34 (1H, s), 7.69 (1H, dd, $J$=8, 2 Hz), 7.96 (1H, d, $J$=8 Hz), 8.46 (1H, d, $J$=2 Hz) |
| V-33 | 88.0 | 1750 | 1615 | 424 | 1.02 (3H, t, $J$=7 Hz), 1.85 (2H, m), 3.72 (8H, br s), 4.38 (2H, t, $J$=7 Hz), 7.23 (1H, s), 7.58 (1H, dd, $J$=8, 2 Hz), 7.90 (1H, d, $J$=8 Hz), 8.37 (1H, d, $J$=2 Hz) |
| V-35 | 86.0 | 1740 | 1645 | 438 | 1.00 (3H, t, $J$=7 Hz), 1.70 (4H, m), 3.76 (8H, br s), 4.43 (2H, t, $J$=7 Hz), 7.21 (1H, s), 7.58 (1H, dd, $J$=8, 2 Hz), 7.87 (1H, d, $J$=8 Hz), 8.36 (1H, d, $J$=2 Hz) |
| V-36 | 87.5 | 1740 | 1625 | 438 | 1.02 (6H, d, $J$=7 Hz), 2.10 (1H, m), 3.71 (8H, br s), 4.20 (2H, d, $J$=7 Hz), 7.18 (1H, s), 7.55 (1H, dd, $J$=8, 2 Hz), 7.85 (1H, d, $J$=8 Hz), 8.32 (1H, d, $J$=2 Hz) |

Table II. (continued)

| No. | Yield (%) | IR $\nu_{max}^{KBr}$ cm$^{-1}$ | MS *m/e* ($M^+$) | NMR Chemical shift (in DMSO-$d_6$) $\delta$ |
|---|---|---|---|---|
| V-38 | 30.1[b] | 3200 1735 1625 | 358 | 1.41 (3H, t, $J$=7 Hz), 3.70 (8H, br s), 4.42 (2H, q, $J$=7 Hz), 6.78 (1H, dd, $J$=8, 2 Hz), 7.19 (1H, s), 7.49 (1H, d, $J$=8 Hz), 7.67 (1H, d, $J$=2 Hz), 9.78 (1H, s) |
| V-39 | 7.3[c] | 3240 1740 1630 | 372 | 1.00 (3H, t, $J$=7 Hz), 1.75 (2H, m), 3.70 (8H, br s), 4.33 (2H, t, $J$=7 Hz), 6.76 (1H, dd, $J$=8, 2 Hz), 7.16 (1H, s), 7.50 (1H, d, $J$=8 Hz), 7.65 (1H, d, $J$=2 Hz), 9.78 (1H, s) |
| V-40 | 6.3[d] | 3200 1730 1630 | 386 | 0.98 (3H, t, $J$=7 Hz), 1.70 (4H, m), 3.72 (8H, br s), 4.40 (2H, t, $J$=7 Hz), 6.80 (1H, dd, $J$=8, 2 Hz), 7.16 (1H, s), 7.50 (1H, d, $J$=8 Hz), 7.67 (1H, d, $J$=2 Hz), 9.80 (1H, s) |
| V-41 | 5.5[e] | 3240 1740 1620 | 386 | 1.01 (6H, d, $J$=7 Hz), 2.10 (1H, m), 3.71 (8H, br s), 4.17 (2H, d, $J$=7 Hz), 6.78 (1H, dd, $J$=8, 2 Hz), 7.14 (1H, s), 7.48 (1H, d, $J$=8 Hz), 7.65 (1H, d, $J$=2 Hz), 9.80 (1H, s) |
| V-42 | 81.0 | 1740 1620 | 424 | 1.47 (6H, d, $J$=7 Hz), 3.72 (4H, br s), 3.80 (4H, br s), 5.25 (1H, m), 7.36 (1H, s), 7.79 (1H, dd, $J$=8, 2 Hz), 8.28 (1H, d, $J$=2 Hz), 8.46 (1H, d, $J$=8 Hz) |

*a*) Yield from compounds III. *b*) Yield from V-14. *c*) Yield from V-15. *d*) Yield from V-17. *e*) Yield from V-18.

dd, $J$=8, 2 Hz), 7.86 (1H, dd, $J$=8, 5 Hz). *Anal.* Calcd for: $C_{13}H_{10}FNO_5$: C, 55.92; H, 3.61; N, 5.01. Found: C, 56.00; H, 3.38; N, 5.03.

**Ethyl 5-(2-Amino-5-trifluoromethylphenyl)-2-furancarboxylate (VIII-1)**——A mixture of VII-1 (35.4 g), 10% Pd–C (1.1 g) and EtOH (1200 ml) was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated to give crystals (26.9 g, 83.2%), which were recrystallized from EtOH to give yellow prisms, mp 101—102.5 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3500, 3370, 1705. MS *m/e*: 299 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.36 (3H, t, $J$=7 Hz), 4.37 (2H, q, $J$=7 Hz), 6.28 (2H, br s), 7.05 (1H, d, $J$=8 Hz), 7.14 (1H, d, $J$=4 Hz), 7.46 (1H, d, $J$=4 Hz), 7.48 (1H, dd, $J$=8, 2 Hz), 7.82 (1H, d, $J$=2 Hz). *Anal.* Calcd for: $C_{14}H_{12}FNO_3$: C, 64.37; H, 4.63; N, 5.36. Found: C, 64.51; H, 4.61; N, 5.51.

Ethyl 5-(2-amino-4-fluorophenyl)-2-furancarboxylate (VIII-2) was prepared in the same manner, mp 120.5—121.5 °C (EtOH). Yield 88.8%. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3485, 3380, 1710. MS *m/e*: 249 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.34 (3H, t, $J$=7 Hz), 4.32 (2H, q, $J$=7 Hz), 6.38 (1H, dd, $J$=8, 2 Hz), 6.42 (1H, dt, $J_d$=2 Hz, $J_t$=8 Hz), 6.54 (1H, d, $J$=4 Hz), 7.18 (1H, d, $J$=4 Hz), 7.40 (1H, dd, $J$=8, 2 Hz). *Anal.* Calcd for: $C_{13}H_{12}FNO_3$: C, 62.65; H, 4.85; N, 5.62. Found: C, 62.28; H, 4.60; N, 5.55.

**Ethyl 7-Trifluoromethyl-4*H*-furo[3,2-*b*]indole-2-carboxylate (IX-1)**——A mixture of VIII-1 (26.9 g) and conc. HCl (250 ml) was heated at 70 °C, then cooled in an ice bath. A solution of $NaNO_2$ (6.9 g) in $H_2O$ (100 ml) was added dropwise to the cold solution below −5 °C. After the solution had been stirred at −5 °C for 30 min, a solution of $NaN_3$ (13.0 g) in $H_2O$ (50 ml) was added dropwise thereto, and the temperature was raised to room temperature. The resulting product was filtered off, and washed with $H_2O$ and hexane to give ethyl 5-(2-azido-5-trifluoromethylphenyl)-2-furancarboxylate as crude crystals (17.3 g, 59%), then a mixture of the azide derivative and *o*-dichlorobenzene (40 ml) was stirred at 160—170 °C for 30 min. The resulting product was filtered off, and washed with hexane to give crystals (13.5 g, 85.3%).

Recrystallization from EtOH gave colorless prisms, mp 275.5—277 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3360, 1700. MS *m/e*: 297 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.38 (3H, t, $J$=7 Hz), 4.39 (2H, q, $J$=7 Hz), 7.59 (1H, dd, $J$=8, 2 Hz), 7.66 (1H, s), 7.73 (1H, d, $J$=8 Hz), 8.25 (1H, d, $J$=2 Hz), 11.7 (1H, s). *Anal.* Calcd for $C_{14}H_{10}F_3NO_3$: C, 56.57; H, 3.39; N, 4.71. Found: C, 56.80; H, 3.36; N, 4.50.

Ethyl 6-fluoro-4*H*-furo[3,2-*b*]indole-2-carboxylate (IX-2) was prepared in the same manner. Azide (crude crystals), yield 90.5%. IX-2: mp 209—210 °C (EtOH). Yield 68.9%. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1710. MS *m/e*: 247 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.33 (3H, t, $J$=7 Hz), 4.33 (2H, q, $J$=7 Hz), 7.00 (1H, dt, $J_d$=2 Hz, $J_t$=8 Hz), 7.29 (1H, dd, $J$=8, 2 Hz), 7.49 (1H, s), 7.78 (1H, dd, $J$=8, 5 Hz). *Anal.* Calcd for $C_{13}H_{10}FNO_3$: C, 63.16; H, 4.08; N, 5.66. Found: C, 63.40; H, 4.00; N, 5.44.

**7-Trifluoromethyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid (X-1)**——A mixture of IX-1 (13.5 g), 10% aq. NaOH (40 ml) and acetone (100 ml) was stirred for 1 h at room temperarure, then diluted with $H_2O$ and acidified with conc. HCl. The resulting product was filtered off (11.5 g, 94.0%), and recrystallized from EtOH to give colorless needles, mp 206—210 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3420, 2800, 1675. MS *m/e*: 269 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.57 (1H, dd, $J$=8, 2 Hz), 7.60 (1H, s), 7.73 (1H, d, $J$=8 Hz), 8.20 (1H, d, $J$=2 Hz), 11.70 (1H, s). *Anal.* Calcd for $C_{12}H_6F_3NO_3$: C,

53.54; H, 2.24; N, 5.20. Found: C, 53.55; H, 2.45; N. 5.42.

6-Fluoro-4*H*-furo[3,2-*b*]indole-2-carboxylic acid (X-2) was prepared in the same manner, yield 96%. mp 235—236 °C (EtOH). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3420, 3400, 2800, 1660. MS *m/e*: 219 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.10 (1H, dt, $J_d$ = 2 Hz, $J_t$ = 8 Hz), 7.38 (1H, dd, $J$ = 8, 5 Hz), 7.55 (1H, s), 7.87 (1H, dd, $J$ = 8, 5 Hz), 11.40 (1H, s), 13.10 (1H, br s). *Anal.* Calcd for $C_{11}H_6FNO_3$: C, 60.28; H, 2.76; N, 6.39. Found: C, 60.02; H, 3.11; N, 6.45.

**2-Morpholinocarbonyl-7-trifluoromethyl-4*H*-furo[3,2-*b*]indole (IV-7)**——A mixture of X-1 (11.5 g), $SOCl_2$ (17 ml) and benzene (250 ml) was refluxed for 1 h, then concentrated *in vacuo*, and the resulting product was filtered off to give 7-trifluomethyl-4*H*-furo[3,2-*b*]indole-2-carbonyl chloride as crude crystals (11.2 g, 91.0%). A solution of the acid chloride in dichloromethane (50 ml) was added dropwise to a solution of morpholine (8 g) in dichloromethane (30 ml), then the mixture was stirred for 30 min at room temperature, concentrated, and poured into ice-$H_2O$. The resulting product was filtered off (9.9 g, 77%), and recrystallized from $Et_2O$ to give colorless needles, mp 222.5—225.5 °C. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3400, 3250, 1605. MS *m/e*: 338 ($M^+$). $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.72 (4H, br s), 3.82 (4H, br s), 7.43 (1H, s), 7.53 (1H, dd, $J$ = 8, 2 Hz), 7.71 (1H, d, $J$ = 8 Hz), 8.17 (1H, d, $J$ = 2 Hz). *Anal.* Calcd for $C_{16}H_{13}F_3N_2O_3$: C, 56.81; H, 3.87; N, 8.28. Found: C, 56.77; H, 3.91; N, 8.28.

**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 inhibitory 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 inhibitory percent was calculated as compared with the swelling percent in the control group.

## References and Notes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