(28) T. Förster, *Ann. Phys. (Leipzig)*, **2**, 55 (1948).
(29) P. W. Schiller in "Biochemical Fluorescence: Concepts", Vol. 1, R. F. Chen and H. Edelhoch, Ed., Marcel Dekker, New York, N.Y., 1975, pp 285–303.
(30) P. W. Schiller, *Can. J. Biochem.*, **55**, 75 (1977).
(31) R. E. Dale and J. Eisinger in ref 29, pp 115–284.
(32) E. Haas, E. Katchalski-Katzir, and I. Z. Steinberg, private communication.
(33) C. B. Pert, A. Pert, J.-K. Chang, and B. T. W. Fong, *Science*, **194**, 330 (1976).
(34) A. R. Day, M. Lujan, W. L. Dewey, L. S. Harris, J. A. Radding, and J. R. Freer, *Res. Commun. Chem. Pathol. Pharmacol.*, **14**, 597 (1976).
(35) C. R. Beddell, R. B. Clark, G. W. Hardy, L. A. Lowe, F. B. Ubatuba, J. R. Vane, S. Wilkinson, K.-J. Chang, P. Cuatrecasas, and R. J. Miller, *Proc. R. Soc. London, Ser. B*, **198**, 249 (1977).
(36) L. Terenius, A. Wahlström, G. Lindeberg, S. Karlsson, and U. Ragnarsson, *Biochem. Biophys. Res. Commun.*, **71**, 175 (1976).
(37) D. H. Coy, A. J. Kastin, A. W. Schally, O. Morin, N. G. Caron, F. Labrie, J. M. Walker, R. Fertel, G. G. Berntson, and C. A. Sandman, *Biochem. Biophys. Res. Commun.*, **73**, 632 (1976).
(38) D. Roemer, H. H. Buescher, R. C. Hill, J. Pless, W. Bauer, F. Cardinaux, A. Closse, D. Hauser, and R. Hugenin, *Nature (London)*, **268**, 547 (1977).
(39) C. B. Pert, D. L. Bowie, B. T. W. Fong, and J.-K. Chang in "Opiates and Endogenous Opioid Peptides", H. W. Kosterlitz, Ed., North-Holland Publishing Co., Amsterdam/New York/Oxford, 1976, pp 79–85.
(40) C. Humblet and J. L. DeCoen in "Peptides, Proceedings of the Fifth American Peptide Symposium", M. Goodman and J. Meienhofer, Ed., Wiley, New York, N.Y., 1977, pp 88–91.
(41) M. Anteunis, A. K. Lala, C. Garbay-Jaureguiberry, and B. P. Roques, *Biochemistry*, **16**, 1462 (1977).
(42) H. E. Bleich, A. R. Day, R. J. Freer, and J. A. Glasel, *Biochem. Biophys. Res. Commun.*, **74**, 592 (1977).
(43) G. D. Smith and J. F. Griffin, personal communication.
(44) J. Eisinger, *Biochemistry*, 8, 3902 (1969).
(45) M. C. Fournie-Zaluski, T. Prange, C. Pascard, and B. P. Roques, *Biochem. Biophys. Res. Commun.*, **79**, 1199 (1977).
(46) P. W. Schiller, S. Natarajan, and M. Bodanszky, *Int. J. Pept. Protein Res.*, in press.
(47) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).
(48) R. Schwyzer, P. Sieber, and H. Kappeler, *Helv. Chim. Acta*, **42**, 2622 (1959).
(49) R. B. Merrifield, *J. Am. Chem. Soc.*, **86**, 304 (1964).
(50) G. R. Marshall, *Adv. Exp. Med. Biol.*, **2**, 48 (1968).
(51) S. Sakakibara in "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins", B. Weinstein, Ed., Marcel Dekker, New York, N.Y., 1971, pp 51–84.
(52) H. Matsubara and R. M. Sasaki, *Biochem. Biophys. Res. Commun.*, **35**, 175 (1969).
(53) G. W. Pasternak, H. A. Wilson, and S. H. Snyder, *Mol. Pharmacol.*, 11, 340 (1975).
(54) R. F. Chen, *Anal. Lett.*, 1, 35 (1967).
(55) J. Eisinger, B. Feuer, and A. A. Lamola, *Biochemistry*, 8, 3908 (1969).

Psychotropic Agents. 3.[1] 4-(4-Substituted piperidinyl)-1-(4-fluorophenyl)-1-butanones with Potent Neuroleptic Activity

Makoto Sato,* Masahiro Arimoto, Katsujiro Ueno,

Laboratory of Medicinal Chemistry

Hiroshi Kojima, Terukiyo Yamasaki, Takeo Sakurai, and Akira Kasahara

Laboratory of Pharmacology, Research Institute, Daiichi Seiyaku Company, Ltd., Tokyo, Japan. *Received March 13, 1978*

A series of 1-(4-fluorophenyl)-4-(1-piperidinyl)-1-butanones substituted with benzimidazole, benzotriazole, or quinoxaline at the 4 position of the piperidine ring was synthesized and subjected to neuroleptic tests. Neuroleptic activities of several compounds were comparable to those of haloperidol. In particular, 4-[4-(2,3-dihydro-2-thioxo-1*H*-benzimidazol-1-yl)-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone (**10**) was characterized by having a potent neuroleptic activity with less liability to the extrapyramidal side effect.

Haloperidol,[2] which is the prototype of a series of chemically related butyrophenones, has been used widely in the therapy of psychic disorder, especially of schizophrenia. Two members of this series, spiroperidol and benperidol,[2] are the most potent neuroleptics known at the present time. In the previous paper,[1] we described that some modification of the side chain of haloperidol or benperidol lowered neuroleptic activity of the parent drugs. In the present study, 1-(4-fluorophenyl)-4-(1-piperidinyl)-1-butanones substituted with benzimidazole, benzotriazole, or quinoxaline derivatives at the 4 position of the piperidine ring and related compounds were prepared in order to search for new antipsychotic drugs. The structure–activity relationships of these derivatives are discussed herein and pharmacological properties of two selected compounds are described.

Chemistry. Various butanone derivatives (**4–28**) and 1,1-diphenylbutane derivatives (**30–33**) were synthesized by the general route outlined in Scheme I and listed in Table I. An intermediate, *o*-phenylenediamine (**3**), was prepared by reaction of 4-(2-nitroanilino)piperidine[3] (**1**) with 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane, followed by catalytic hydrogenation over Raney nickel of the resulting butanone derivative **2**. Cyclization of **3** with carboxylic acids or benzoyl chloride (method A), carbon disulfide (method B), sodium nitrite (method G), and pyruvic acid or oxalic acid (method H) gave benzimidazoles **4–9**, benzimidazolinethione (**10**), benzotriazole (**26**), and quinoxaline derivatives **27** and **28**, respectively. Alkylation of **10** with dimethyl sulfate (method C), alkyl halides (method D), ethylene oxide (method E), or acyl chlorides (method F) gave **11–25** in good yield. 1,1-Diphenylbutanes **30** and **31** were also synthesized from an *o*-phenylenediamine derivative[3] **29** as described above (methods A and B), and alkylation of **31** according to methods C and E gave 2-(alkylthio)benzimidazole derivatives **32** and **33**, respectively.

Structure–Activity Relationships. Table I shows experimental results expressed as ED_{50} values estimated from dose–response curves of the compounds tested. Of the compounds in which alkyl groups were introduced at the 2 position of the benzimidazole ring (**4–7**), **5** was the most potent in inhibiting SMA and MGT. This compound was almost equally effective to haloperidol, although inhibition of SMA with the former was of shorter duration than that with the latter. Compounds with a phenyl or

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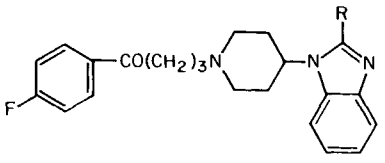
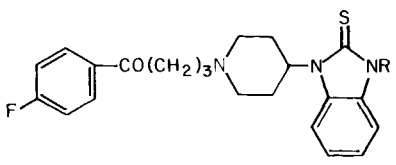
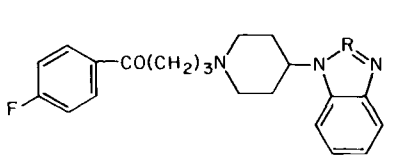
Table I. Physical Properties and Pharmacological Activities of 4-(4-Substituted piperidinyl)-1-(4-fluorophenyl)-1-butanones and Related Compounds



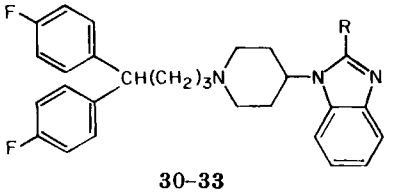
4-9, 11-23



10, 24, 25



26-28

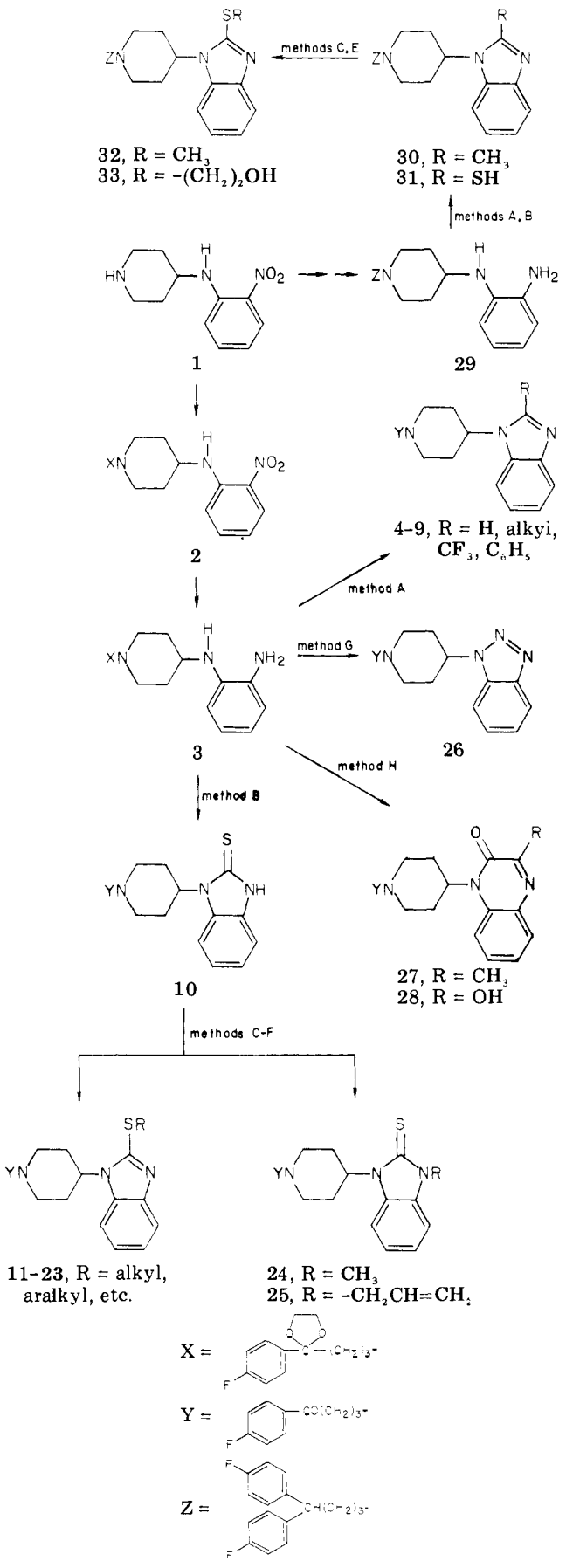


30-33

compd no.	R	method	yield, %	mp, °C	recrystn solvent	formula	ED_{50}, mg/kg po SMA test	ED_{50}, mg/kg po MGT test
4	H	A	57.9	94-95.5	Et_2O	$C_{22}H_{24}FN_3O$	4.7 (2.5-8.9)[a]	>3
5	CH_3	A	58.9	79-81.5	Et_2O	$C_{23}H_{26}FN_3O$	0.85 (0.4-1.7)	0.81 (0.36-1.80)
6	C_2H_5	A	48.5	221-225 dec	Et_2O-Me_2CO	$C_{24}H_{28}FN_3O \cdot 2HCl$	9.1 (5-16)	>3
7	n-C_4H_9	A	33.7	248-251	EtOH	$C_{26}H_{32}FN_3O \cdot 2HCl \cdot H_2O$	14 (8-23)	>3
8	C_6H_5	A	42.3	265-267 dec	EtOH-Me_2CO	$C_{28}H_{28}FN_3O \cdot 2HCl$	18 (11-29)	>3
9	CF_3	A	71.5	85.5-86	Et_2O-n-C_6H_{14}	$C_{23}H_{23}F_4N_3O$	>40	NT[b]
11	SCH_3	C	68.9	98-98.5	EtOH	$C_{23}H_{26}FN_3OS$	6.2 (3.0-12)	0.68 (0.41-1.2)
12	SC_2H_5	C	44.6	210-211 dec	MeOH	$C_{24}H_{28}FN_3OS \cdot HCl$	5.0 (2.8-9.0)	>3
13	$SCH(CH_3)_2$	D	46.5	222-224.5 dec	EtOH-$CHCl_3$	$C_{25}H_{30}FN_3OS \cdot HBr$	4.4 (1.8-11)	1.6 (1.1-2.2)
14	$S(CH_2)_2OH$	E	48.3	102-103	Me_2CO-Et_2O	$C_{24}H_{28}FN_3O_2S$	6.9 (3.5-14)	>3
15	$S(CH_2)_3CO$-C_6H_4-p-F	D	38.2	137-139	$CHCl_3$-Et_2O	$C_{32}H_{33}F_2N_3O_2S$	14 (9.3-21)	>3
16	SCH_2CO-C_6H_4-p-Cl	D	54.9	68-70	C_6H_6	$C_{30}H_{29}ClFN_3O_2S \cdot H_2O$	5.0 (3.5-7.1)	1.6 (1.0-2.5)
17	SCH_2-C_6H_5	D	67.4	124-126	Et_2O	$C_{29}H_{30}FN_3OS$	1.3 (0.76-2.3)	0.76 (0.52-1.1)
18	$SCH_2C{\equiv}CH$	D	61.4	156-158 dec	EtOH-Me_2CO	$C_{25}H_{26}FN_3OS \cdot 2HCl$[c]	1.2 (0.55-2.7)	0.74 (0.50-1.1)
19	$SCH_2COOC_2H_5$	D	67.9	217-218 dec	$CHCl_3$-EtOH	$C_{26}H_{30}FN_3O_3S \cdot HBr$	>40	NT
20	S-C_6H_4-o-NO_2	D	26.0	124-127	EtOH	$C_{28}H_{27}FN_4O_3S$	11 (6.6-19)	NT
21	$SCOOC_2H_5$	F	54.3	108-109	Et_2O-n-C_6H_{14}	$C_{25}H_{28}FN_3O_3S$	0.36 (0.17-0.77)	0.65 (0.48-0.90)
22	$SCO(CH_2)_5CH_3$	F	59.9	205-208 dec	MeOH	$C_{29}H_{36}FN_3O_2S \cdot HCl$	1.0 (0.57-1.8)	1.1 (0.80-1.5)
23	SCO-C_6H_4-p-Cl	F	64.8	221-225 dec	MeOH-C_6H_6	$C_{29}H_{27}ClFN_3O_2S \cdot HCl$	0.96 (0.34-2.7)	0.83 (0.64-1.1)
10	H	B	74.5	201-203	Me_2CO	$C_{22}H_{24}FN_3OS$	0.60 (0.35-1.02)	0.55 (0.41-0.74)
24	CH_3	C	5.4	269-271 dec	$CHCl_3$-EtOH	$C_{23}H_{26}FN_3OS \cdot HCl$	0.54 (0.22-1.35)	NT
25	$CH_2CH{=}CH_2$	D	40.0	214.5-216 dec	dioxane-Et_2O	$C_{25}H_{28}FN_3OS \cdot HBr$	0.87 (0.48-1.6)	NT
26	-N=	G	70.1	102-103	$CHCl_3$-Et_2O-n-C_6H_{14}	$C_{21}H_{23}FN_4O$	33 (19-59)	NT
27	$-COC(CH_3)=$	H	41.9	136-137	Me_2CO-n-C_6H_{14}	$C_{24}H_{26}FN_3O_2$	14.1 (8.8-22.6)	>3
28	-COC(OH)=	H	34.1	264-269 dec	H_2O-MeOH	$C_{23}H_{24}FN_3O_3 \cdot CH_3COOH$[d]	>40	>3
30	CH_3	A	40.4	125-126.5	Et_2O	$C_{29}H_{31}F_2N_3$	~40	>3
31	SH (thione)	B	63.2	224-227	Et_2O	$C_{28}H_{29}F_2N_3S$	20 (13-20)	1.0 (0.67-1.49)
32	SCH_3	C	56.3	110.5-111.5	Et_2O-n-C_6H_{14}	$C_{29}H_{31}F_2N_3S$	13 (7.4-24)	2.4 (1.7-3.5)
33	$S(CH_2)_2OH$	E	70.4	146-147	$CHCl_3$-Et_2O	$C_{30}H_{33}F_2N_3OS$	~40	>3
haloperidol[e]							0.80 (0.43-1.5)	0.32 (0.28-0.37)
benperidol[f]							0.56 (0.35-0.91)	0.63 (0.35-1.13)
pimozide[f]							7.4 (4-14)	1.1 (0.76-1.5)

[a] Figures in parentheses indicate 95% fiducial limits. [b] NT = not tested. [c] C: calcd, 59.05; found, 58.55. [d] C: calcd, 63.95; found, 63.35. [e] Haloperidol was kindly donated from Janssen Pharmaceutica. [f] Benperidol (mp 170-171 °C) and pimozide (mp 216.5-219 °C) were synthesized in our Institute for experimental use.

Scheme I



trifluoromethyl group in this ring (**8** and **9**) were almost devoid of activity. In the case of *S*-alkyl and *S*-aralkyl analogues **11**–**19**, **17** and **18** showed high activities in both SMA and MGT tests. As seen in **11**–**13** SMA-inhibiting activity was independent of the length of the *S*-alkyl chain, while the effect against MGT was largely influenced by the chain length. It is of interest that **11** was highly effective in suppressing MGT in spite of being weak in SMA-inhibiting activity. Activities of *S*-ethoxycarbonyl and *S*-acyl derivatives (**21**–**23**) were statistically comparable to those of haloperidol, although SMA inhibition with the *S*-phenyl analogue **20** was negligible. The experiments with benzimidazolinethione analogues (**10**, **24**, and **25**) revealed that **10** had the most potent activity, almost equal to that of reference drugs, haloperidol and benperidol. Compound **24**, though highly effective, was very short lasting in SMA-inhibiting action as compared with the two reference drugs. Only weak or no activity was observed in **26**–**28** having the benzotriazole or quinoxaline moiety at the 4 position of the piperidine ring. Activities of 4,4-diphenylbutane derivatives (**30**–**33**) were almost comparable to or lower than those of pimozide. Of the compounds tested, **21**–**23** proved to be chemically unstable. In consideration of such a chemical property as well as pharmacological activities described above, **10** and **11** were selected for further pharmacological tests to clarify their profiles as neuroleptics. Measurement was made of the effect on methamphetamine- or apomorphine-induced stereotyped behavior and catalepsy-inducing activity.

As presented in Table II, **10** was 9.3 and 8.1 times as potent as haloperidol and benperidol, respectively, in inhibiting methamphetamine-induced stereotyped behavior. Its inhibitory effect on the behavior induced by apomorphine was also much greater than that of the reference drugs (haloperidol × 8.9, benperidol × 6.5). Although **10** had a catalepsy-inducing effect, its ED_{50} value was significantly larger than the doses (ED_{50}) inhibiting stereotyped behavior induced by methamphetamine or apomorphine. Comparison of the ratios, B/A and B/A (Table II), revealed that the separation between doses antagonizing methamphetamine or apomorphine and inducing catalepsy was much greater in **10** than in the other compounds. It has been reported that antagonistic activity of neuroleptics to amphetamine- or apomorphine-induced stereotyped behavior correlates well with their clinical antipsychotic activity[7] and that catalepsy-inducing activity of such drugs is suggestive of their ability to produce an extrapyramidal side effect in humans.[8] From these points of view, **10** seemed to be promising as a potent neuroleptic with less liability to the extrapyramidal side effect. Compounds **10** and **11** had lower acute toxicity as compared with haloperidol. Further studies of this compound are in progress and the details will be published elsewhere.

Experimental Section

Melting points were determined on a Yanagimoto melting point apparatus (Type MP-1) and are uncorrected. IR (KBr), UV (in EtOH), and mass spectra were measured on a Hitachi 285 spectrophotometer, a Hitachi 323 spectrophotometer, and a Hitachi mass spectrometer RMS-4 (direct inlet at 70 eV), respectively. NMR spectra were recorded on a Hitachi R-20B spectrometer (60 MHz) using Me_4Si as internal standard. Notations used in the descriptions are s = singlet, q = quartet, and m = multiplet. These spectral data were in accordance with the proposed structures. Where the analyses are indicated only by the symbols of the elements, the analytical results were within ±0.4% of theoretical values.

The following examples are representative of each procedure.

Method A. 1-(4-Fluorophenyl)-4-[4-(2-methyl-1*H*-benzimidazol-1-yl)-1-piperidinyl]-1-butanone (5). A mixture of **3** (400 mg, 1 mmol) and AcOH (4 mL) was refluxed for 2 h. After chilling, the reaction mixture was diluted with H_2O, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The extract was washed

Table II. Pharmacological Activities (po) of 4-(4-Substituted piperidinyl)-1-(4-fluorophenyl)-1-butanone Derivatives

compd	inhibn of methamphetamine-induced stereotyped behavior, ED_{50}, mg/kg (A)	inhibn of apomorphine-induced stereotyped behavior, ED_{50}, mg/kg (A')	catalepsy-inducing act., ED_{50}, mg/kg (B)	B/A	B/A	LD_{50}, mg/kg
10	0.054 (0.022-0.13)[a]	0.095 (0.074-0.12)	0.33 (0.17-0.64)	6.1	4.5	500 (350-710)
11	0.20 (0.07-0.54)	0.41 (0.26-0.64)	1.1 (0.46-2.6)	5.5	2.7	930 (480-1800)
haloperidol	0.50 (0.22-1.2)	0.85 (0.50-1.5)	0.88 (0.50-1.5)	1.8	1.0	240 (200-280)
benperidol	0.44 (0.20-0.97)	0.62 (0.38-1.0)	0.92 (0.50-1.7)	2.1	1.5	NT[b]

[a] Figures in parentheses indicate 95% fiducial limits. [b] NT = not tested.

with H_2O and evaporated in vacuo. To the residue were added EtOH (10 mL), H_2O (4 mL), and concentrated HCl (1 mL). The mixture was refluxed for 10 min, cooled, basified with diluted NaOH, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated. The crude product was purified by chromatography on silica gel, eluting with $CHCl_3$ containing increasing amounts of EtOH. After evaporation of the solvent, the residue was crystallized from Et_2O to give colorless prisms of **5** (229 mg, 58.9%): mp 79–81.5 °C; IR (KBr) ν 1685 cm^{-1} (C=O); UV max (EtOH) 244, 275, 282 nm; NMR ($CDCl_3$) δ 1.4–3.2 (14 H, m, methylene protons of piperidine and butanone), 2.54 (3 H, s, CH_3), 3.8–4.4 (1 H, m, methine proton of piperidine), 6.9–7.8 (6 H, m, meta protons of *p*-fluorobenzoyl and benzimidazole), 7.9–8.2 (2 H, q, ABX type, ortho protons of *p*-fluorobenzoyl). Anal. ($C_{23}H_{26}FN_3O$) C, H, N.

Method B. 4-[4-(2,3-Dihydro-2-thioxo-1*H*-benzimidazol-1-yl)-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone (10). A mixture of **3** (9.99 g, 0.025 mol), KOH (2.80 g, 0.05 mol), CS_2 (5.70 g, 0.075 mol), H_2O (5 mL), and EtOH (25 mL) was heated at 80 °C for 3 h in a sealed tube. After evaporation of the solvent, EtOH (250 mL), H_2O (100 mL), and concentrated HCl (25 mL) were added to the residue and refluxed for 10 min. After chilling, the reaction mixture was made alkaline with NH_4OH, concentrated in vacuo, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel using $CHCl_3$ and the eluate gave a white solid which was crystallized from Me_2CO yielding **10** (7.40 g, 74.5%): mp 201–203 °C; mass spectrum M^+ 397; IR (KBr) ν 1675 cm^{-1} (C=O); UV max (EtOH) 226.5, 246, 309 nm; NMR ($CDCl_3$) δ 1.6–3.3 (14 H, m, methylene protons of piperidine and butanone), 4.9–5.5 (1 H, m, methine proton of piperidine), 7.0–7.6 (6 H, m, meta protons of *p*-fluorobenzoyl and benzimidazole), 7.9–8.2 (2 H, q, ABX type, ortho protons of *p*-fluorobenzoyl). Anal. ($C_{22}H_{24}FN_3OS$) C, H, N.

Method C. 1-(4-Fluorophenyl)-4-[4-[2-(methylthio)-1*H*-benzimidazol-1-yl]-1-piperidinyl]-1-butanone (11) and 4-[4-(2,3-Dihydro-3-methyl-2-thioxo-1*H*-benzimidazol-1-yl)-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone (24). To a stirred solution of **10** (15.9 g, 0.04 mol), NaOH (3.20 g, 0.08 mol), and H_2O (24 mL) in MeOH (200 mL) was added Me_2SO_4 (7.06 g, 0.056 mol) dropwise during 3 h at room temperature, and the reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was made alkaline with diluted NaOH and extracted with $CHCl_3$. The extract was washed with H_2O and dried over Na_2SO_4. After removal of the solvent, the residue was passed through a silica gel column using $CHCl_3$. The oily residue was solidified with Et_2O–*n*-C_6H_{14} and recrystallized from EtOH to yield colorless crystals of **11** (3.24 g, 19.6%): mp 98–98.5 °C; UV max (EtOH) 245.5, 292.5 nm. Anal. ($C_{23}H_{26}FN_3OS$) C, H, N.

The mother liquor was acidified with HCl–MeOH and concentrated to dryness. The residue was recrystallized from EtOH to yield colorless crystals of **11**·2HCl (9.55 g, 49.3%), mp 179–180 °C dec. Anal. ($C_{23}H_{26}FN_3OS$·2HCl) C, H, N.

The filtrate was concentrated and crystallized from H_2O to give colorless crystals, which were recrystallized from $CHCl_3$–EtOH to afford colorless crystals of **24** (1.03 g, 5.7%): mp 269–271 °C dec; UV max (EtOH) 231, 246.5, 310.5 nm. Anal. ($C_{23}H_{26}FN_3OS$·HCl) C, H, N.

Method D. 1-(4-Fluorophenyl)-4-[4-[2-(isopropylthio)-1*H*-benzimidazol-1-yl]-1-piperidinyl]-1-butanone (13). A mixture of **10** (398 mg, 1 mmol) and isopropyl bromide (2 mL) in dioxane (5 mL) was heated at 120 °C for 38 h in a sealed tube. After cooling, the precipitate was collected and washed with dioxane. The crude product was recrystallized from $CHCl_3$–EtOH to give colorless plates of **13** (242 mg, 46.5%): mp 222–224.5 °C dec; UV max (EtOH) 246, 286.5, 293 nm. Anal. ($C_{25}H_{30}FN_3OS$·HBr) C, H, N.

Method E. 1-(4-Fluorophenyl)-4-[4-[2-(hydroxyethylthio)-1*H*-benzimidazol-1-yl]-1-piperidinyl]-1-butanone (14). A mixture of **10** (597 mg, 1.5 mmol), ethylene oxide (176 mg, 4 mmol) in THF (1 mL), and dioxane (5 mL) was heated at 80 °C for 8.5 h in a sealed tube. The reaction mixture was concentrated in vacuo. The residue was chromatographed on Al_2O_3 with C_6H_6 and $CHCl_3$ as an eluant. Removal of the solvent afforded a colorless solid, which was recrystallized from Me_2CO–Et_2O to yield 320 mg (48.3%) of **14** as colorless prisms: mp 102–103 °C; IR (KBr) ν 3300, 3110 (OH), 1680 (C=O); UV max (EtOH) 244, 285, 293 nm. Anal. ($C_{24}H_{28}FN_3O_2S$) C, H, N.

Method F. 1-(4-Fluorophenyl)-4-[4-[2-(*n*-heptanoylthio)-1*H*-benzimidazol-1-yl]-1-piperidinyl]-1-butanone (22). A mixture of **10** (596 mg, 1.5 mmol), *n*-heptanoyl chloride (669 mg, 4.5 mmol), and triethylamine (304 mg, 3 mmol) in dry benzene (50 mL) was refluxed for 2 h. After cooling, the reaction mixture was washed with diluted Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated. The residue was treated with HCl–MeOH to give a colorless solid, which was recrystallized from MeOH to afford colorless needles of **22** (491 mg, 59.9%): mp 205–208 °C; IR (KBr) ν 1720, 1675 cm^{-1} (C=O). Anal. ($C_{29}H_{36}FN_3O_2S$·HCl) C, H, N.

Method G. 4-[4-(1*H*-Benzotriazol-1-yl)-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone (26). To a solution of **3** (400 mg, 1 mmol) in H_2O (5 mL) and AcOH (180 mg, 3 mmol) was added $NaNO_2$ (76 mg, 1.1 mmol) on ice cooling. The reaction mixture was stirred for 5 min at the same temperature and then heated at 80 °C for 10 min. To the mixture were added MeOH (2 mL) and concentrated HCl (1 mL), and the mixture was heated at 80 °C for 10 min. After cooling, the reaction mixture was made alkaline with Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was passed through an Al_2O_3 column using Et_2O and Et_2O–$CHCl_3$ (1:1 v/v), and the eluate was evaporated to afford a pale yellow solid. Recrystallization from $CHCl_3$–Et_2O–*n*-C_6H_{14} gave colorless prisms of **26** (257 mg, 70.1%): mp 102–103 °C; IR (KBr) ν 1675 cm^{-1} (C=O). Anal. ($C_{21}H_{23}FN_4O$) C, H, N.

Method H. 1-(4-Fluorophenyl)-4-[4-(3-methyl-2-oxo-1,2-dihydro-1*H*-quinoxalin-1-yl)-1-piperidinyl]-1-butanone (27). A mixture of **3** (1.05 g, 2.6 mmol) and pyruvic acid (227 mg, 3.1 mmol) in dry *o*-dichlorobenzene (5 mL) was refluxed for 2 h. After cooling, the reaction mixture was extracted with diluted HCl, and the aqueous layer was made alkaline with Na_2CO_3, extracted with $CHCl_3$, and concentrated. EtOH (15 mL), H_2O (5 mL), and concentrated HCl (1.5 mL) were added to the residue, and the mixture was refluxed for 10 min. After chilling, the reaction mixture was made basic with diluted NH_4OH, evaporated in vacuo, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography on silica gel with Et_2O and recrystallized from Me_2CO–Et_2O to give 448 mg (41.9%) of colorless needles (**27**): mp 136–137 °C; mass spectrum M^+ 407; IR (KBr) ν 1690, 1650 cm^{-1} (C=O). Anal. ($C_{24}H_{26}FN_3O_2$) C, H, N.

2-(4-Fluorophenyl)-2-[4-(2-nitroanilino)piperidin-1-ylpropyl]-1,3-dioxolane (2). A mixture of **1** (24.4 g, 0.11 mol), 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane (24.5 g, 0.1 mol), Na_2CO_3 (5.30 g, 0.05 mol), and KI (0.3 g, 1.8 mmol) in *n*-BuOH (30 mL) was refluxed with stirring for 24 h and concentrated in vacuo. The residue was chromatographed on Al_2O_3 using $CHCl_3$ and the eluate afforded yellow crystals, which were recrystallized from Et_2O–*n*-C_6H_{14} to give yellow needles of **2** (32.06

g, 74.6%), mp 78–80.5 °C. Anal. ($C_{23}H_{28}FN_3O_4$) C, H, N.

2-[4-(2-Aminoanilino)piperidin-1-ylpropyl]-2-(4-fluorophenyl)-1,3-dioxolane (3). A mixture of **2** (4 g, 9.3 mmol) and Raney nickel (4 mL) in MeOH (100 mL) was submitted to catalytic hydrogenation at ordinary temperature and pressure. After the theoretical amount of H_2 was absorbed, the catalyst and the solvent were removed. The residue was crystallized from Et_2O to give needles of **3** (3.18 g, 85.4%), mp 111–113 °C. Anal. ($C_{23}H_{30}FN_3O_2$) C, H, N.

Pharmacological Methods. Use was made of male mice of the STD-ddY strain weighing 20–28 g and male albino rats of the Wistar strain weighing 110–220 g. Test compounds were suspended in 0.5% CMC and given orally in a volume of 10 mL/kg to mice and 2 mL/kg to rats. ED_{50} values with 95% fiducial limits were calculated according to the Litchfield–Wilcoxon method.[4]

(a) Spontaneous Motor Activity (SMA) Test. Ten mice were used in each group. One hour after the administration of test compounds, the mouse was placed in the wheel cage, 210 mm in diameter and 40 mm in width (Kishimoto IKa Co., Kyoto). The number of revolutions of the cage which the mouse rotated for 5 min was taken as an index for spontaneous motor activity. ED_{50}, the dose which decreased the number of revolutions by 50%, was determined.

(b) Antagonism to Methamphetamine Group Toxicity (MGT). The experiment was carried out by a modification of method of Sharma et al.[5] Twenty mice were used in each group. The animals were kept aggregated in a metallic cage (22 × 32 × 10.5 cm). Each group was treated with test compounds 1 h before subcutaneous injection of 25 mg/kg of methamphetamine hydrochloride. ED_{50}, the dose required to protect 50% of the animals from death due to methamphetamine, was determined from mortality of the animals at 24 h after methamphetamine injection.

(c) Antagonism to Methamphetamine-Induced Stereotyped Behavior. Rats were separately kept in individual cages (26 × 42.5 × 15 cm) made of plastic. Each group of five rats was administered test compounds 2 h before the treatment with methamphetamine hydrochloride (10 mg/kg ip). Stereotyped behavior induced by methamphetamine hydrochloride was scored 1, 2, and 3 h after methamphetamine injection as 0 (sleeping), 1 (squating), 2 (looking about), 3 (preening and grooming), 4 (ambulating), 5 (rearing), 6 (sniffing), 7 (neck shaking), 8 (licking, biting, and gnawing), 9 (body shaking, walking back, and rotating), and 10 (hard ataxia and death). ED_{50}, the dose which reduced the total scores by 50%, was determined.

(d) Antagonism to Apomorphine-Induced Stereotyped Behavior. The experiment was carried out by a modification of the method of Janssen et al.[2] Rats were kept in the same manner as described in the preceding item (c). Each group of six rats was administered test compounds 2 h before the treatment with apomorphine hydrochloride (1.25 mg/kg iv). The effect against apomorphine was taken as positive when, 20 min after apomorphine injection, gnawing behavior was not observed during an observation period of 1 min. ED_{50}, the dose which produced a positive effect in 50% of the animals, was determined.

(e) Catalepsy Test. The test was carried out according to the method of Costall et al.[6] Six rats were used in each group. The animals were subjected to the catalepsy test 8 h after medication by placing both front limbs on a horizontal bar set up at a height of 12 cm from the floor. When the animals showed catalepsy for more than 1 min, the cataleptic syndrome was regarded as positive. ED_{50}, the dose which produced a positive effect in 50% of the animals, was determined.

(f) LD_{50}. Ten mice were used for each dose level. LD_{50} values were determined from 7-day mortality.

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References and Notes

(1) M. Sato, M. Kitagawa, F. Uchimaru, K. Ueno, H. Kojima, and T. Yamasaki, *Chem. Pharm. Bull.*, submitted for publication.
(2) P. A. J. Janssen, C. J. E. Niemegeers, and K. H. L. Schellekens, *Arzneim.-Forsch.*, **15**, 104 (1965).
(3) H. K. F. Hermans, Japanese Patent 7267 (1972).
(4) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(5) V. N. Sharma, R. L. Mital, S. P. Benerjee, and H. L. Sharma, *Jpn. J. Pharmacol.*, **19**, 211 (1969).
(6) B. Costall and R. J. Naylor, *Psychopharmacologia*, **32**, 161 (1973).
(7) J. M. Van Rossum, P. A. J. Janssen, J. R. Boissier, L. Julou, D. M. Loew, I. Moller Nielsen, I. Munkvad, A. Randrup, G. Stille, and D. H. Tedeschi in "Modern Problems in Pharmacopsychiatry; The Neuroleptics", Vol. 5, D. P. Babon, P. A. J. Janssen, and J. Babon, Ed., S. Karger, Basel, 1970, p 23.
(8) L. Julou in ref 7, p 50.

Benzopyrones.[1] 14. Synthesis and Antiallergic Properties of Some *N*-Tetrazolylcarboxamides and Related Compounds

G. P. Ellis,* G. J. P. Becket, D. Shaw, H. K. Wilson,

Department of Chemistry, University of Wales Institute of Science and Technology, Cardiff CF1 3NU, United Kingdom

C. J. Vardey, and I. F. Skidmore*

Biochemistry Department, Allen and Hanburys Research Limited, Ware, Herts SG12 ODJ, United Kingdom.
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A series of chromones containing an acidic group has been synthesized and screened for the ability to inhibit passive cutaneous anaphylaxis and the release of histamine from mast cells of the rat. Many of the chromones contain the *N*-(5-tetrazolyl)carboxamido group, a novel source of acidity. Others contain a carboxyl, *C*-(5-tetrazolyl), 5-(4*H*)-oxotetrazolinyl, or *N*-(5-tetrazolyl)sulfonamido function. The compounds were compared with cromolyn sodium (sodium cromoglycate) and many were found to be powerful inhibitors of anaphylaxis. The most potent was 7-methoxy-4-oxo-*N*-(5-tetrazolyl)-4*H*-1-benzopyran-2-carboxamide (**15**). Structure–activity relationships among the chromones and also some related compounds are discussed.

Many derivatives of chromones have been shown to inhibit the release of spasmogens which usually follows an antigen–antibody interaction.[2-5] Although the mechanism of action of these compounds is not fully understood, the presence of an acidic group at C-2 or C-3 is characteristic of most of the active chromones. The majority of these contain a carboxyl group,[2,5,6] but its replacement by a 5-tetrazolyl ring has been shown to result in some com-

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