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Imidazo[2,1-*b*]benzothiazoles. I

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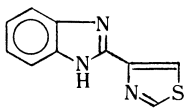
A series of [2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]acetic acid derivatives was prepared. The 2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazoles (**2a**—**e**) were first converted to the corresponding 3-(dimethylaminomethyl) Mannich bases (**3a**—**e**), which in turn were converted to the methiodide salts (**4a**—**d**) and thence to the desired products (**7a**—**e**), (see Chart 1).

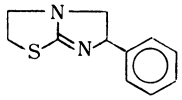
Some of the acetic acid derivatives (**7a**, **c**, **d**) were tested for analgesic and antiinflammatory activities by means of carrageenin-induced paw edema, streching induced by acetic acid and capillary permeability inhibition assays.

Keywords——imidazo[2,1-*b*]benzothiazole; Mannich reaction; analgesic activity; antiinflammatory activity

Nonsteroidal antiinflammatory drugs (NSAIDs) are a chemically heterogeneous group of compounds. The majority of such compounds are carboxylic acids, such as aroic, heteroaroic, arylalkonic and heteroarylalkonic acids.[1] Thiabendazole (I) and levamisole (II), originally developed as anthelmintics, were noted to exhibit a moderate antiinflammatory activity and to affect the immunomodulatory system.[2,3] There is also a report that a thiourea moiety in an imidazolyl ring potentiates the antiinflammatory activity.[4]



I

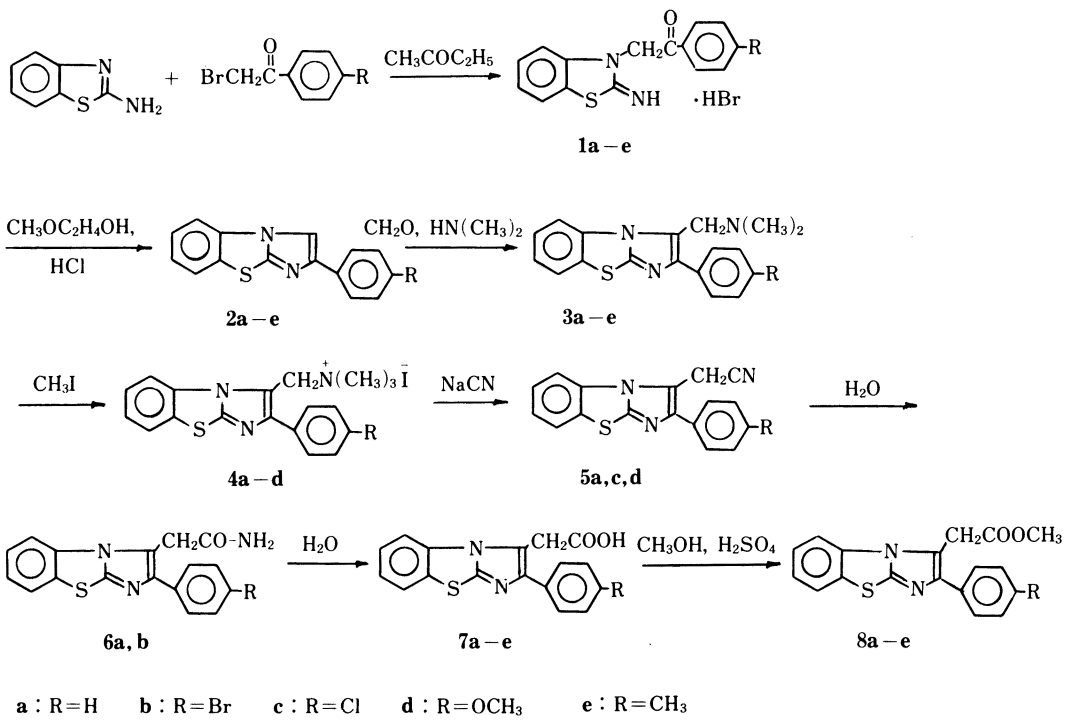


II

Thus it was of interest to incorporate a carboxyl bearing moiety into the imidazo[2,1-*b*]benzothiazole system is consistent with a proposed structural feature model (III) that appears as a common moiety in many heterocyclic derivatives with immunomodulatory and/or antiinflammatory activities.[1,5–10]

III : X and Y=CH, N, S, O

The present paper describes the synthesis and antiinflammatory activity of a series of [2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]acetic acid derivatives (**7a**—**e**) which were investigated as a part of a general program designed to define the structural requirements consistent with retention of immunomodulatory and/or antiinflammatory activity of such a nucleus.



a : R=H **b** : R=Br **c** : R=Cl **d** : R=OCH_3 **e** : R=CH_3

Chart 1

The newly synthesized compounds are listed in Table I, and prepared by the methods outlined in Chart 1. Further details of the methods are given in the experimental section.

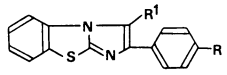
Chemistry

The synthesis of 2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazoles (**2a—e**) was achieved in alcohol[5,6] by refluxing 2-aminobenzothiazole with the appropriate *p*-(un)substituted phenacyl bromides. In recent reports,[7-9] compounds **2a—e** were prepared *via* the reaction of 2-aminobenzothiazole with the appropriate *p*-(un)substituted phenacyl bromides in methyl ethyl ketone. The products (**1a—e**) were separated and cyclized in methoxyethanol. We modified the second procedure by the addition of hydrochloric acid,[10] which improved the yield considerably.

Mannich bases (**3a—e**) were obtained by the interaction of **2a—e** with a mixture of formalin, dimethylamine and acetic acid in dioxane. The reaction of the excess sodium cyanide with the methiodide salts (**4a—e**) or the hydrochloride salts of the Mannich bases afforded derivatives (**5** and **6**). The mixtures were of different proportions and the identified compounds (Table I, **5a, c, d** and **6a, b**) were the main products separated by recrystallizations of the mixtures. No attempt to push the reaction to produce one of the products was made, except in the case of **4a**, where the main product was the 3-cyanomethyl derivative (**5a**), and prolongation of the reaction time to 8 h yielded the 3-carbamoylmethyl derivative (**6a**) as a main product.

The acetic acid derivatives (**7a—d**) were prepared *via* the hydrolysis of the corresponding **5** and/or **6** with sodium hydroxide in 80% methoxyethanol in water. Compound **7e** was obtained from the hydrochloride salt of the Mannich base (**3e**) in a one-pot reaction by addition of the hydrochloride salt to a solution of excess sodium cyanide in 80% methoxyethanol in water and refluxing the reaction mixture for 48 h.

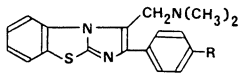
TABLE I. Physicochemical Properties of Several 2,3-Disubstituted Imidazo[2,1-*b*]benzothiazoles



Compd. No.	R	R^1	Formula	mp (°C)	Yield (%)	Cryst. solvent	Analysis (%) Calcd (Found)		
							C	H	N
3a	H	$CH_2N(CH_3)_2$	$C_{18}H_{17}N_3S$	119—123	52.5	CH_3CN–cyclohexane	70.35 (69.79)	5.58 (5.60)	13.67 (13.46)
3b	Br	$CH_2N(CH_3)_2$	$C_{18}H_{16}BrN_3S$	140—141	76.1	$CHCl_3$–methanol	55.96 (55.84)	4.17 (4.18)	10.87 (10.88)
3c	Cl	$CH_2N(CH_3)_2$	$C_{18}H_{16}ClN_3S$	153	80.2	$CHCl_3$–methanol	63.24 (62.94)	4.72 (4.73)	12.29 (12.21)
3d	OCH_3	$CH_2N(CH_3)_2$	$C_{19}H_{19}N_3OS$	144	83.0	$CHCl_3$–ethanol	67.63 (67.30)	5.68 (5.65)	12.45 (12.38)
3e	CH_3	$CH_2N(CH_3)_2$	$C_{19}H_{19}N_3S$	106—108	63.9	Ethanol	70.99 (70.66)	5.96 (5.95)	13.07 (12.88)
4a	H	$CH_2\overset{+}{N}(CH_3)_3\bar{I}$	$C_{19}H_{20}IN_3S \cdot 0.5CHCl_3$	180—182 (dec.)	56.2	$CHCl_3$	46.01 (46.02)	4.06 (4.16)	8.25 (8.23)
4b	Br	$CH_2\overset{+}{N}(CH_3)_3\bar{I}$	$C_{19}H_{19}BrIN_3S$	215—218 (dec.)	68.1	Ethanol	43.19 (43.20)	3.62 (3.61)	7.96 (7.97)
4c	Cl	$CH_2\overset{+}{N}(CH_3)_3\bar{I}$	$C_{19}H_{19}ClIN_3S$	189—190 (dec.)	71.3	Ethanol	47.17 (47.16)	3.96 (4.01)	8.68 (8.93)
4d	OCH_3	$CH_2\overset{+}{N}(CH_3)_3\bar{I}$	$C_{20}H_{22}IN_3OS$	209—211 (dec.)	75.5	Methanol	50.08 (50.17)	4.61 (4.65)	8.76 (8.76)
5a	H	CH_2CN	$C_{17}H_{11}N_3S$	209—212	57.6[a]	$CHCl_3$–methanol	70.59 (70.35)	3.83 (3.98)	14.52 (14.43)
5c	Cl	CH_2CN	$C_{17}H_{10}ClN_3S$	229—231	63.7[a]	$CHCl_3$–methanol	63.07 (63.19)	3.11 (3.22)	12.97 (13.17)
5d	OCH_3	CH_2CN	$C_{18}H_{13}N_3OS \cdot 0.5H_2O$	213—214	62.1[a]	$CHCl_3$–methanol	65.84 (65.69)	4.30 (4.53)	12.79 (12.81)
6a	H	CH_2CONH_2	$C_{17}H_{13}N_3OS \cdot H_2O$	241—242	47.6[a]	$CHCl_3$–methanol	62.77 (62.41)	4.56 (4.10)	12.91 (12.80)
6b	Br	CH_2CONH_2	$C_{17}H_{12}BrN_3OS$	214—215	53.4[a]	$CHCl_3$–methanol	52.86 (52.38)	3.89 (3.39)	10.89 (10.59)
7a	H	CH_2COOH	$C_{17}H_{12}N_2O_2S$	254—256	38.2	Precipitation	66.23 (66.26)	3.92 (4.01)	9.08 (9.05)
7b	Br	CH_2COOH	$C_{17}H_{11}BrN_2O_2S \cdot 1.25H_2O$	243—245	18.6	Precipitation	49.83 (49.67)	3.26 (3.03)	6.83 (6.39)
7c	Cl	CH_2COOH	$C_{17}H_{11}ClN_2O_2S$	267—268	48.2	Precipitation	59.58 (59.94)	3.24 (3.30)	8.17 (8.24)
7d	OCH_3	CH_2COOH	$C_{18}H_{14}N_2O_3S \cdot H_2O$	221—223	42.8	Precipitation	60.67 (61.00)	4.53 (4.33)	7.86 (7.60)
7e	CH_3[b]	CH_2COOH	$C_{18}H_{14}N_2O_2S$	217—219	26.0	Precipitation			
8a	H	CH_2COOCH_3	$C_{18}H_{14}N_2O_2S \cdot H_2O$	75—76	88.7	$CHCl_3$–methanol	63.52 (63.48)	4.74 (4.80)	8.23 (8.13)
8b	Br	CH_2COOCH_3	$C_{18}H_{13}BrN_2O_2S$	150	91.3	$CHCl_3$–methanol	53.86 (53.87)	3.26 (3.33)	6.98 (7.02)
8c	Cl	CH_2COOCH_3	$C_{18}H_{13}ClN_2O_2S$	124—126	93.0	Methanol	60.59 (60.02)	3.67 (3.66)	7.86 (7.87)
8d	OCH_3	CH_2COOCH_3	$C_{19}H_{16}N_2O_3S$	130—131	95.1	Methanol	64.76 (64.79)	4.58 (4.57)	7.95 (8.03)
8e	CH_3	CH_2COOCH_3	$C_{19}H_{16}N_2O_2S$	126—128	90.2	Methanol	66.27 (65.92)	4.98 (5.01)	8.13 (8.00)

a) Calculated as the amide. *b*) Could not be purified.

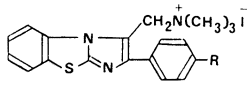
TABLE II. ^{1}H-NMR Data for Mannich Bases



Compd. No.	R	^{1}H-NMR data (δ value) measured in $CDCl_3$			
		$N(CH_3)_2$	CH_2N	R	Aromatic-H
3a	H	2.32 (6H, s)	3.94 (2H, s)	—	7.29—8.09 (9H, m)
3b	Br	2.34 (6H, s)	3.89 (2H, s)	—	7.18—8.10 (8H, m)
3c	Cl	2.22 (6H, s)	3.78 (2H, s)	—	7.12—8.05 (8H, m)
3d	OCH_3	2.17 (6H, s)	3.70 (2H, s)	3.68 (3H, s)	7.15—7.88 (8H, m)
3e	CH_3	2.31 (6H, s)	3.88 (2H, s)	2.42 (3H, s)	7.05—8.10 (8H, m)

s, singlet; m, multiplet.

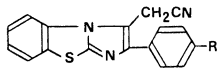
TABLE III. ^{1}H-NMR Data for the Methiodide Salts of Mannich Bases



Compd. No.	R	^{1}H-NMR data (δ value), measured in DMSO-d_6			
		$\overset{+}{N}(CH_3)_3$	$CH_2\overset{+}{N}$	R	Aromatic-H
4a	H	2.91 (9H, s)	5.34 (2H, s)	—	7.46—8.55 (9H, m)[a]
4b	Br	2.93 (9H, s)	5.33 (2H, s)	—	7.50—8.56 (8H, m)
4c	Cl	2.94 (9H, s)	5.34 (2H, s)	—	7.47—8.53 (8H, m)
4d	OCH_3	2.90 (9H, s)	5.30 (2H, s)	3.67 (3H, s)	6.93—8.12 (8H, m)

a) A singlet at δ 8.33, integrating as 0.5 proton (0.5 mol of $CHCl_3$).

TABLE IV. ^{1}H-NMR and IR Data for the 3-Cyanomethyl Derivatives



Compd. No.	R	^{1}H-NMR data (δ value), $CDCl_3$			IR (cm^{-1})
		CH_2CN	R	Aromatic-H	$\nu_{C\equiv N}$
5a	H	4.31 (2H, s)	—	7.23—8.00 (9H, m)	2240
5c	Cl	4.23 (2H, s)	—	7.15—7.80 (8H, m)	2255
5d	OCH_3	4.12 (2H, s)	3.73 (3H, s)	6.75—7.75 (8H, m)	2250

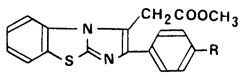
IR data were obtained in KBr.

It was difficult to measure the nuclear magnetic resonance (NMR) spectra for the free carboxylic acids due to their insolubility in deuterated solvents. Thus, methyl esters (**8a—e**) were prepared by refluxing the acids with methanol and sulfuric acid in methylene chloride.

The structures of the newly synthesized compounds (Table I) were consistent with their elemental and spectra data. Infrared (IR), ^{1}H-, and ^{13}C-NMR data are listed in Tables II—VIII.

A collective approach to the behavior of the different series of compounds in mass

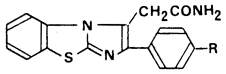
TABLE V. ^{1}H-NMR and IR Data for the Methyl Esters



Compd. No.	R	^{1}H-NMR data (δ value), $CDCl_3$				IR (cm^{-1})
		$COOCH_3$	CH_2CO	Aromatic-H	R	$\nu_{C=O}$
8a	H	3.80 (3H, s)	4.24 (2H, s)	7.31—7.78 (9H, m)	—	1730 (bs)
8b	Br	3.80 (3H, s)	4.20 (2H, s)	7.32—7.80 (8H, m)	—	1735 (bs)
8c	Cl	3.81 (3H, s)	4.20 (2H, s)	7.26—7.80 (8H, m)	—	1730 (bs)
8d	OCH_3	3.79 (3H, s)	4.20 (2H, s)	6.97—7.77 (8H, m)	3.85 (3H, s)	1730 (bs)
8e	CH_3	3.79 (3H, s)	4.22 (2H, s)	7.26—7.76 (8H, m)	2.41 (3H, s)	1730 (bs)

bs = broad and strong.

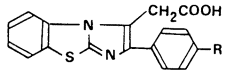
TABLE VI. IR Data for the 3-Carbamoylmethyl Intermediates



Compd. No.	R	IR (cm^{-1}), KBr	
		ν_{NH_2}	$\nu_{C=O}$
6a	H	3350 (bs)	1670 (bs)
6b	Br	3350 (br)	1675 (bs)

bs, broad and strong. br, broad.

TABLE VII. IR Data for the Free Acetic Acid Derivatives



Compd. No.	R	IR (cm^{-1}), KBr	
		ν_{O-H}	$\nu_{C=O}$
7a	H	3600—3350 (br)	1715 (bs)
7b	Br	3550—3350 (br)	1720 (bs)
7c	Cl	3520—3350 (br)	1720 (bs)
7d	OCH_3	3500—3350 (br)	1715 (bs)
7e	CH_3	3550—3400 (w)	1720 (bs)

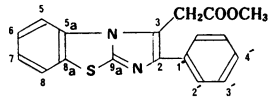
bs, broad and strong. w, weak.

specrometry is summarized in Chart 2 and Table IX. It was noticed that the molecular ion peaks [M^+] are present in all of the series of compounds with a high intensity, except in the case of the methiodide salts of the Mannich bases.

Pharmacology and Discussion

The antiinflammatory and analgesic activities of these compounds were examined by means of the carrageenin-induced paw edema (CIPE) assay in rats as described by Winter *et al.*,[12] at a dose of 100 mg/kg, *p.o.* All of the tested compounds and the reference drug were

TABLE VIII. ^{13}C-NMR Data for **8a**



Carbon No.	Chemical shift (ppm)	Carbon No.	Chemical shift (ppm)
$-CH_2-$	31.62 (t)	C-8_a	134.10 (s)
C-2	130.56 (s)	C-9_a	147.75 (s)
C-3	133.00 (s)	C-1′	116.71 (s)
C-5	128.65 (d)	C-2′	124.56 (d)
C-6	127.67 (d)	C-3′	112.82 (d)
C-7	126.12 (d)	C-4′	124.42 (d)
C-8	128.02 (d)	OCH_3	52.87 (q)
C-2′	146.50 (s)	C=O	170.37 (s)

Taken in $CDCl_3$, and measured downfield from TMS.

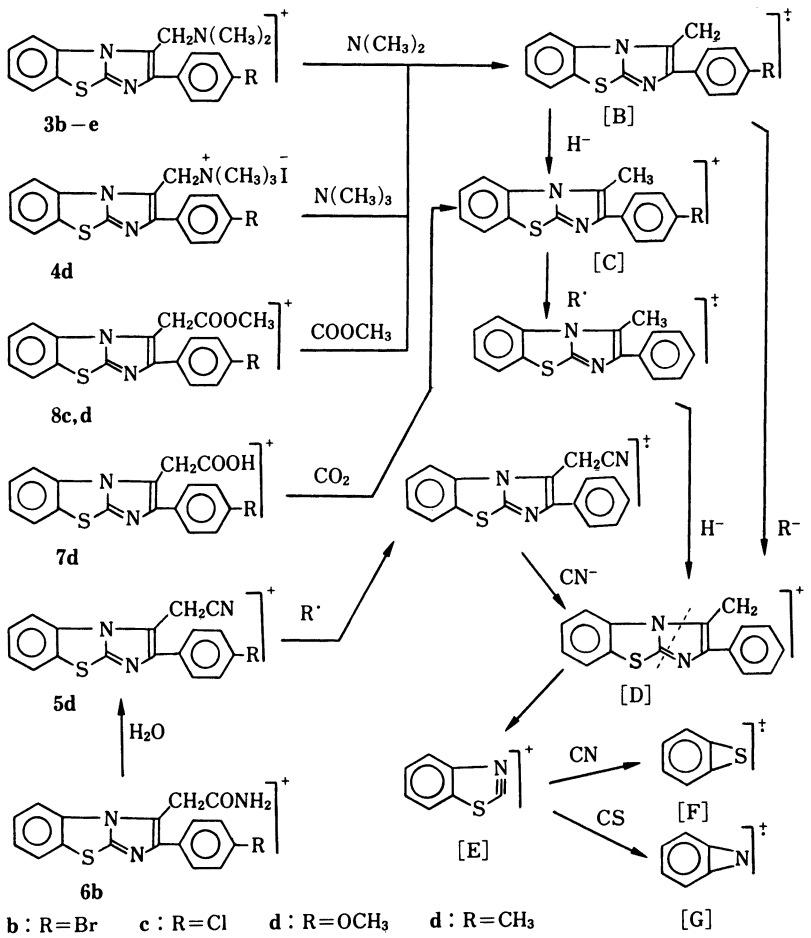
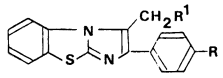


Chart 2. Summary of Mass Spectrometric Behavior

TABLE IX. Principal Mass Spectral Peaks



R^1	R	M^+ m/z (%)	B m/z (%)	C m/z (%)	D 262 (%)	E 134 (%)	F 108 (%)	G 90 (%)
$N(CH_3)_2$	Br	385 (13.25)	341 (100)	342 (31.00)	77.57	9.48	5.11	4.65
		387 (13.33)	343 (99.98)	344 (30.79)				
$N(CH_3)_2$	Cl	341 (16.17)	297 (100)	298 (40.45)	49.33	8.23	3.7	3.35
		343 (5.98)	299 (63.81)	300 (16.35)				
$N(CH_3)_2$	OCH_3	337 (28.43)	293 (100)	294 (54.11)	10.23	4.18	2.94	3.39
$N(CH_3)_2$	CH_3	321 (16.85)	277 (100)	278 (50.07)	13.43	6.11	3.73	3.38
$\overset{+}{N}(CH_3)_3 \cdot \bar{I}$	OCH_3	—	293 (36.82)	294 (100)	2.30	5.57	4.96	5.16
CN	OCH_3	319 (100)	276 (22.20)	277 (7.77)	—	3.47	3.46	2.45
$CONH_2$	Br[a]	385 (32.67)	367 (44.97)	341 (72.26)	87.85	11.71	11.20	8.33
		387 (34.39)	369 (52.20)	343 (74.59)				
COOH	OCH_3	338 (13.32)	293 (37.67)	294 (100)	2.32	4.73	4.27	5.37
$COOCH_3$	Cl	356 (40.56)	297 (100)	298 (19.98)	41.40	8.61	4.26	5.37
		358 (15.56)	299 (38.02)	300 (7.24)				
$COOCH_3$	OCH_3	352 (41.26)	293 (100)	294 (21.27)	5.80	2.92	1.95	3.18

a) The base peak appeared at $m/z=261$ (100%).

TABLE X. Activity in Carrageenin-Induced Paw Edema in Rats

Compd. No.	Dose (mg/kg, *p.o.*)	Edema weight (mg) (mean ± S.E.)	Inhibition (%)
7a	100	731 ± 60	−7.9
7c	100	715 ± 65	−5.7
7d	100	701 ± 45	−3.5
Indomethacin	3	280 ± 54	58.7
Control	—	677 ± 96	—

The number of animals used was three.

TABLE XI. SIAA and CPI Assays in Mice

Compd. No.	Dose (mg/kg, *p.o.*)	*n*	SIAA test		CPI test	
			Stretchs (20 min)	Inhibition (%)	Pontamine-sky blue (%)	Inhibition (%)
7a	100	5	35 ± 6	13	81 ± 5	19
Aminopyrine	100	5	1 ± 1	98	40 ± 5	60
Control	—	5	40 ± 9	—	100 ± 11	—

administered to rats ($n=3$). The results were compared with that for indomethacin (3 mg/kg, *p.o.*), and are listed in Table X. The tested compounds did not show any activity.

In many cases,[9,13] including some imidazo[2,1-*b*]benzothiazole derivatives,[9] compounds do not show any activity in the CIPE test, but do show good activity in other tests for antiinflammatory and/or immunomodulatory activities. For this reason, **7a** was further investigated for analgesic and antiinflammatory activities in the stretching induced by acetic acid (SIAA) assay in mice ($n=5$), and the result was compared with that for aminopyrine

(100 mg/kg, *p.o.*). Compound **7a** was also tested for capillary permeability inhibitory activity in mice ($n=5$), as described by Whittle.[14] The result was compared with that of aminopyrine at 100 mg/kg, *p.o.* Compound **7a** showed weak activity in both tests (Table XI).

Experimental

Precoated Silica gel 60 F-254 plates from Merck were used for thin layer chromatography; spots were detected under ultraviolet (UV) light. Melting points were determined by using Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were determined with a Hitachi 260-10 infrared spectrophotometer. ^{1}H-NMR spectra were obtained with R-24B (60 MHz), JEOL-FX-270 and JEOL-GX-270 spectrometers. ^{13}C-NMR spectra were obtained with a JEOL-FX-270 (67.8 MHz) spectrometer, using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were obtained with a Hitachi-60 mass spectrometer. Elemental analyses were performed with a Perkin-Elmer 240 elemental analyzer.

A Modified Procedure for the Preparation of 2-[*p*-(Un)substituted phenyl]imidazo[2,1-*b*]benzothiazoles (2a—e)——2-Aminobenzothiazole (5 g, 33.3 mmol) and the appropriate *p*(un)substituted phenacyl bromide (33.3 mmol) in methyl ethyl ketone (30 ml) were stirred at 50—55 °C for 4 h. The precipitated solid was collected by filtration, washed with methyl ethyl ketone and dried. Methoxyethanol (30 ml) and hydrochloric acid (3.5 ml) were added to the dry solid. The mixture was heated at 120—130 °C for 5 h. The reaction mixture was then cooled and concentrated to 1/2 of its original volume under reduced pressure. Ammonia (14%, 20 ml) was added dropwise and the separated crystals were filtered off, washed with aqueous methanol (30%) and recrystallized from chloroform–methanol (3 : 1).

3-[Dimethylaminomethyl]-2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazoles (3a—e)——The appropriate 2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazole (10 mmol) in dioxane (10 ml) was added to a stirred mixture of dimethylamine (40%, 12 mmol), formalin (35%, 12 mmol) and acetic acid (3 ml) in dioxane (10 ml). The reaction mixture was stirred for 1 h at room temperature, followed by 5 h at 70—80 °C. The solvent was evaporated off and a solution of sodium carbonate (10%, 40 ml) was added to the viscous residue. The precipitated solid was extracted with chloroform (30, 10, 10 ml), treated with charcoal and concentrated under vacuum. The residude was recrystallized from the appropriate solvent.

Methiodide Salts of 3-[Dimethylaminomethyl]-2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazoles (4a—d)——Methyl iodide (14 mmol) was added to the appropriate 3-[dimethylaminomethyl]-2-[*p*-(un)substituted phenyl]-imidazo[2,1-*b*]benzothiazole (10 mmol) in a mixture of methylene chloride and acetonitrile (10 ml, 3 : 1). The reaction mixture was left overnight then refluxed for 2 h, and cooled. The precipitated crystals were collected and recrystallized.

3-[Cyanomethyl]- and 3-[Carbamoylamethyl]-2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazoles (5a, c, d and 6a, b)——A solution of the appropriate methiodide salt of 3-[dimethylaminomethyl]-2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazole (10 mmol) in methoxyethanol (20 ml) was added in portions to a refluxing solution of sodium cyanide (2.48 g, 50 mmol) in methoxyethanol–water (10 ml, 1 : 1). The reaction mixture was refluxed for 5 h, after which time the solvent was removed *in vacuo*. The residue was extracted with methylene chloride (50 ml) and washed with water. The organic layer was treated with charcoal then evaporated to leave a residue, which was recrystallized from the appropriate solvent.

For compound **7e**, the reaction was done on the hydrochloride salt of the Mannich base (**3e**). Thus, **3e** (10 mmol) was dissolved in a mixture of chloroform and methanol (15 ml, 3 : 1) and hydrochloric acid (1.4 ml) was added dropwise. The reaction mixture was left overnight and the separated crystals, without further purification, were allowed to react with sodium cyanide by the aforementioned procedure. The reflux was continued for 48 h. The solvent was evaporated off, and the residue was dissolved by boiling with sodium hydroxide solution (1 N, 50 ml) and filtered while hot. The filtrate was acidified with acetic acid (30%). The precipitated solid was collected and washed with water and methanol.

[2-[*p*-(Un)substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]acetic Acid Derivatives (7a—d)——A solution of sodium hydroxide (1 g, 25 mmol) in water (5 ml) was added to the appropriate 3-(cyanomethyl)- and/or 3-(carbamoylmethyl)-2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazole (5 mmol, calculated as the amide) in methoxyethanol (20 ml). The reaction mixture was refluxed for 48 h. The solvent was evaporated off, the residue was dissolved by boiling with sodium hydroxide solution (1 N, 30 ml) and the solution was filtered while hot. The filtrate was acidified with acetic acid (30%) and the precipitated solid was collected and washed with water and methanol.

3-[Methoxycarbonylmethyl]-2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazoles (8a—e)——Dry methanol (0.5 ml) and sulfuric acid (3 drops) were added to the appropriate [2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]acetic acid (0.25 mmol) in methylene chloride (5 ml). The reaction mixture was refluxed for 5 h. Methylene chloride (15 ml) was added to the reaction mixture, which then washed with sodium carbonate solution (10%, 10 ml) and again with water. The organic layer was dried ($MgSO_4$) and evaporated under vacuum. The separated solid was recrystallized from the appropriate solvent.

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References and Notes

1) R. A. Scherrer and M. W. Whitehouse, eds., "Antiinflammatory Agents," Vol. 1, Academic Press, New York, 1974, p. 46.
2) C. G. Van Arman and W. C. Cambell, *Tex. Rep. Biol. Med.*, **33**, 303 (1975).
3) J. G. Lambardino, "Annual Reports in Medicinal Chemistry," Vol. XIII, Academic Press, New York, 1978, p. 167.
4) J. W. Black and M. E. Parsons, Ger. Offen. 2320121 (1973) [*Chem. Abstr.*, **80**, 19564*k* (1974)].
5) M. Patra, S. K. Mahapatra and B. Dash, *J. Indian Chem. Soc.*, **L1**, 1031 (1974).
6) N. P. Grin, A. N. Krasovskii and P. M. Kochergin, *Khim. Geterotsikl. Soedin*, **9**, 1271 (1972) [*Chem. Abstr.*, **77**, 164598*s* (1972)].
7) Yamanouchi Pharmaceutical Co., Ltd., Jpn Kokkai Tokkyo Koho Japan. Patent 82, 40492 (1982) [*Chem. Abstr.*, **97**, 110003*p* (1982)].
8) K. Murase, T. Mase and K. Tomioka, Ger. Offen. DE, 3030982 (1981) [*Chem. Abstr.*, **96**, 6724*t* (1982)].
9) T. Mase, H. Arima, K. Tomioka, T. Yamada and K. Murase, *J. Med. Chem.*, **29**, 386 (1986).
10) E. S. Hand and W. W. Paudler, *Tetrahedron*, **38**, 49 (1982).
11) S. N. Sawhney, D. R. Kodali, G. S. Dhindsa and S. P. Singh, *Indian J. Chem. Sect. B*, **21B**, 134 (1982).
12) C. A. Winter, E. A. Risley and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
13) E. S. Lazer, M. R. Matteo and G. J. Possanza, *J. Med. Chem.*, **30**, 726 (1987).
14) B. A. Whittle, *Brit. J. Pharmac.*, **22**, 246 (1964).