Imidazo[2,1-*b*]benzothiazoles. II. Synthesis and Antiinflammatory Activity of Some Imidazo[2,1-*b*]benzothiazoles

Abdel-Nasser EL-SHORBAGI,[a] Shin-ichiro SAKAI,*[,a] Mahmoud A. EL-GENDY,[b] Nabil OMAR[b] and Hassan H. FARAG[b]

Faculty of Pharmaceutical Sciences, Chiba University,[a] 1-33 Yayoi-cho, Chiba 260, Japan and Faculty of Pharmacy, Assiut University,[b] Assiut, Egypt. *Received February 25, 1989*

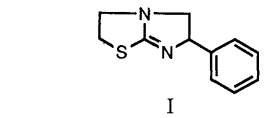
3-[2-[*p*-(Un)substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]propionic acid derivatives (2a—e) were prepared *via* the interaction of the corresponding 2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazoles (1a—e) with acrylic acid in the presence of acetic anhydride and acetic acid. Esterification of 2a—e produced methyl esters (3a—e). Upon the interaction of 3a with *m*-chloroperbenzoic acid, the *S*-dioxide (4a) was obtained. Compound 5a was prepared from 4a by alkaline hydrolysis. Vilsmeier formylation for 1a—e produced novel [2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]formaldehyde derivatives (6a—e). Derivatives 6a—e reacted with ethyl bromoacetate to give ethyl 3-hydroxy-3-[2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]propionate esters (7a—e). Compound *dl*-7a was resolved with *l*-(+)-tartaric acid.

Compounds 2a—e showed weak or no activity in the carrageenin-induced paw edema assay. Compound 4a significantly inhibited the leakage of pontamine-sky blue dye into the peritoneal cavity of mice, in the capillary permeability inhibition assay. Compound 5a inhibited the writhing by 62% in the acetic acid-induced writhing assay.

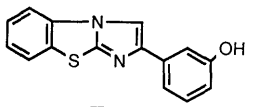
Keywords imidazo[2,1-*b*]benzothiazole; propionic acid derivative; ethyl β-hydroxypropionate ester; *S*-dioxide analogue; antiinflammatory activity; analgesic activity

Extensive research to obtain improved antiinflammatory agents to treat rheumatoid arthritis and other inflammatory diseases involving immunological abnormalities has led to compounds having a variety of structural types, though most have been arylacetic acids.[1)]

The activity of levamisole (I), an immunomodulatory[2)] and antiinflammatory agent,[1)] has been well documented. Many structurally related imidazo[2,1-*b*]thiazoles[3)] and imidazo[2,1-*b*]benzothiazoles[4-6)] have been synthesized and found to possess significant antiinflammatory and/or immunomodulatory activities. Representatives of these related compounds are structures II—V. Compound II exhibited selective immunosuppression of cell-mediated immunity, in addition to its activity in adjuvant arthritis.[4)] Compounds III—V have pronounced antiinflammatory activity.[5,6)]



I



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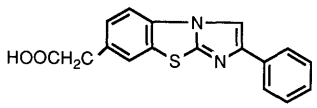
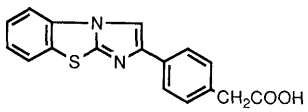
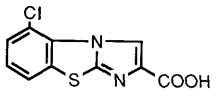


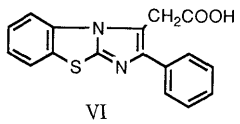
III



IV



V



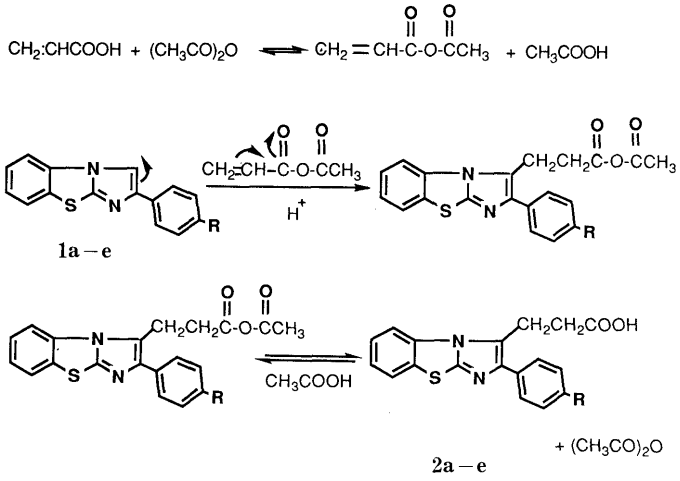
VI

In a previous paper,[7)] we reported the synthesis and the antiinflammatory and analgesic activities of a series of imidazobenzothiazoleacetic acid derivatives, among which compound VI showed a weak activity. We were interested in the effect of introducing carboxylic moieties at the 3-position of the imidazobenzothiazole system. Here, we describe the synthesis and the antiinflammatory activity of a series of imidazobenzothiazolepropionic acid derivatives.

Synthesis and Discussion

When acrylic acid and 2-substituted imidazo[2,1-*b*]benzothiazoles **1a—e** were allowed to react in acetic acid solution containing acetic anhydride, 3-[2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]propionic acid derivatives (**2a—e**) were formed. At least two equivalents of acetic anhydride were used. Although the role of acetic anhydride remains uncertain, it may form a mixed anhydride with the acrylic acid.[8)] This mixed anhydride, or an acryloyl cation produced by its dissociation, could be the reactive species that adds to C_3 of the imidazo[2,1-*b*]-benzothiazole (Chart 1).

As would be expected on the basis of the proposed mechanism, crotonic acid (*trans*-2-butenoic acid) failed to react with **1a** under the same reaction conditions. The *S*-



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

Chart 1

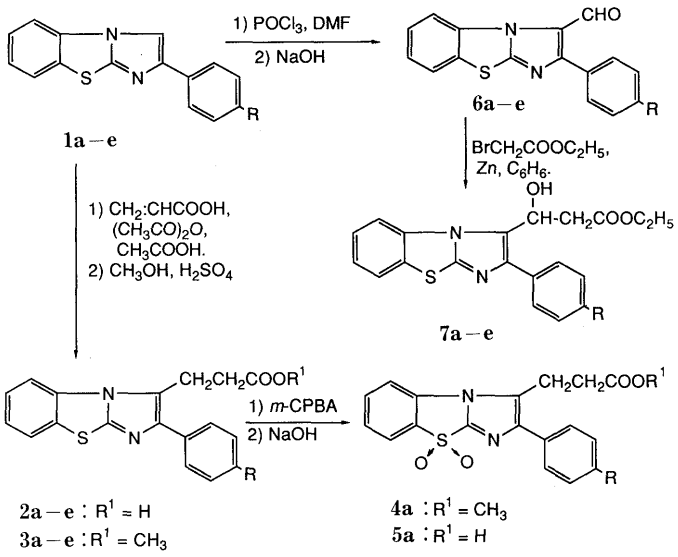


Chart 2

dioxide (**4a**) was obtained from **3a** *via* its reaction with *m*-chloroperbezoic acid (*m*-CPBA). The reaction product **4a** was separated by column chromatography. Compound **4a** yielded the corresponding free acid **5a**.

The [2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]carbaldehyde derivatives (**6a—e**) were prepared by reacting the appropriate **1a—e** with the Vilsmeier reagent prepared from dimethyl formamide and phosphorus oxychloride. The intermediate compound formed was subjected to hydrolysis in the presence of alkali without isolation to give **6a—e** (Chart 2).

The synthesis of β-hydroxy esters from carbonyl compounds and α-haloesters (Reformatsky reaction) has been reviewed.[9] The ethyl 3-hydroxy-3-[2-*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]propionate esters (**7a—e**) were prepared *via* the interaction of the novel compounds **6a—e** with ethyl bromoacetate in dry benzene. Zinc was activated before use, as reported.[10] A mixture of zinc, copper and magnesium (12:2:1), and iodine as a promoter, was effective for the reaction.

The newly synthesized compounds were prepared from the starting compounds **1a—e**,[7] according to the procedures outlined in Chart 2, and their elemental and spectral data are presented in Tables I, II and III. The decoupled spectra of **3b**, **6b** and **7a**, as representative examples, allowed assignment of the chemical shifts of the protons C_5-H, C_6-H, C_7-H and C_8-H, and those of the 2-[*p*-(un)substituted phenyl]moiety, in addition to those of the ethylene and hydroxyethylene parts.

In the spin-coupled carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **3a**, measured in $CDCl_3$, the carbon atoms of the $CH_2CH_2COOCH_3$ moiety are easily distinguished from the other carbons (in ppm downfield from tetramethylsilane (TMS): 20.88 (t, β-CH_2), 32.98 (t, α-CH_2), 51.94 (q, OCH_3) and 172.30 (s, C=O). The downfield signals at 147.20, 144.70 and 134.75 ppm were ascribed to C(9a), C(5a) and C(8a), respectively. Of the remaining three resonances, the two low-field signals at 133.40 and 131.00 ppm were assigned to C(2) and C(3), and that at 122.68 ppm was therefore assigned to C(1′). The spin-coupled spectrum of the compound also showed seven doublets representing the other part of the molecule. The four low-field signals at 128.25, 127.76, 127.41 and 126.38 ppm are assigned to C(5), C(8), C(6) and C(7), respectively. The ^{1}H-NMR signals (Table II) are consistent with the above conclusions and with data for analogous compounds.[6,11] Of the remaining three resonances, those at 124.59 and 112.70 ppm were assigned to C(2′) or C(4′) and C(3′), respectively. The signal at 124.53 ppm is therefore assigned to C(4′) or C(2′).

Pharmacology and Discussion

The antiinflammatory and analgesic activities of the newly synthesized compounds were examined by means of the carrageenin-induced paw edema (CIPE) assay in rats as described by Winter *et al.*[12] All of the tested compounds and the reference drugs were administered to rats ($n=3$ or 5). The results were compared with those for indomethacin and phenylbutazone (Table IV). The tested compounds showed weak or no antiinflammatory activity in the CIPE assay.

Compounds **2a**, **4a** and **5a** were investigated in the acetic acid-induced writhing (AAIW) and the capillary permeability inhibition (CPI) assays in mice ($n=5$) as described by Whittle.[13] The results were compared with those for aminopyrine at 100 mg/kg, *p.o.* Compound **4a** at 100 mg/kg, *p.o.* significantly inhibited the leakage of pontamine-sky blue dye into the peritoneal cavity of mice by 32%, in CPI assay. In AAIW assay, **5a** inhibited the writhing by 62% (Table V).

With the results of the earlier series[7] as background, and the data for the new compounds prepared in this study, the structure–activity relationship can be discussed. Regarding the phenyl moiety at C_2 of the system, the parent compound (R=H) showed the best activity. In the case of the substituent at C_3 of the imidazobenzothiazole system, the propionic acid derivative (**2a**) has slightly better activity than the corresponding acetic acid derivative (VI), and the *S*-dioxide analogues (**4a** and **5a**) exhibited the best activity among the tested compounds.

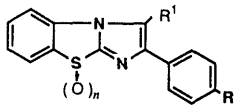
The ethyl β-hydroxy propionate derivative (**7a**) was inactive, contrary to expectation.

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 a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were determined with a Hitachi 260-10 infrared spectrophotometer. ^{1}H-NMR spectra were obtained with JEOL FX-270, JEOL GX-270 and JEOL JNM-GSX-500 spectrometers, using TMS as internal standard. Elemental analyses were performed with a Perkin-Elmer 240 elemental analyzer. Specific rotation measurements were performed on a JASCO DIP-140 polarimeter.

3-[2-[*p*-(Un)Substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]propionic Acid Derivatives (2a—e), General Procedure A solution of the appropriate *p*-(un)substituted phenylimidazo[2,1-*b*]benzothiazole, **1a—e** (8 mmol) in acetic acid (3 ml) containing acetic anhydride (1.6 ml, 16 mmol) and acrylic acid (1.3 g, 18 mmol) was heated at 130—140°C, for 10 h. The reaction mixture was allowed to stand overnight at room temperature, and then all the volatile material was removed under reduced pressure. Sodium hydroxide (1N, 50 ml) was added to the dark viscous residue. The mixture was boiled and filtered. Acetic acid (30%) was added portionwise to the filtrate, and the precipitated solid was collected by filtration. Further

TABLE I. Physicochemical Properties of Several 2,3-Disubstituted Imidazo[2,1-*b*]benzothiazoles and Their *S*-Dioxide Analogues



Compd. No.	R	R^1	*n*	Formula	mp (°C)	Yield (%)	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}
2a	H	CH_2CH_2COOH	0	$C_{18}H_{14}N_2O_2S \cdot 0.25H_2O$	257—260 (dec.)	58.2	66.15 (66.34	4.47 4.43	8.57 8.60)	1715 (C=O) 3600—2400 (OH)
2b	Br	CH_2CH_2COOH	0	$C_{18}H_{13}BrN_2O_2S \cdot 0.5H_2O$	287—289 (dec.)	46.1	52.68 (52.57	3.44 3.26	6.82 6.80)	1705 (C=O) 3200—2400 (OH)
2c	Cl	CH_2CH_2COOH	0	$C_{18}H_{13}ClN_2O_2S \cdot 1.25H_2O$	261—262 (dec.)	49.7	56.99 (56.54	4.01 3.84	7.38 7.31)	1705 (C=O) 3600—2300 (OH)
2d	OCH_3	CH_2CH_2COOH	0	$C_{19}H_{16}N_2O_3S \cdot HCl \cdot H_2O$	230—231 (dec.)	52.3	56.09 (56.06	4.71 4.35	6.88 6.41)	1705 (C=O) 3650—2300 (OH)
2e	CH_3	CH_2CH_2COOH	0	$C_{19}H_{16}N_2O_2S \cdot 0.25H_2O$	297—299 (dec.)	64.7	66.95 (66.98	4.88 4.88	8.22 8.22)	1700 (C=O) 3100—2400 (OH)
3a	H	$CH_2CH_2COOCH_3$	0	$C_{19}H_{16}N_2O_2S$	145—147	89.6	67.85 (67.63	4.80 4.84	8.32 8.68)	1735 (C=O)
3b	Br	$CH_2CH_2COOCH_3$	0	$C_{19}H_{15}BrN_2O_2S$	174—175	87.4	54.95 (54.95	3.64 3.70	6.74 6.85)	1715 (C=O)
3c	Cl	$CH_2CH_2COOCH_3$	0	$C_{19}H_{15}ClN_2O_2S$	147	91.1	61.55 (61.42	4.08 4.10	7.55 7.50)	1710 (C=O)
3d	OCH_3	$CH_2CH_2COOCH_3$	0	$C_{20}H_{18}N_2O_3S$	157—158	95.4	65.57 (65.34	4.95 5.02	7.64 7.60)	1725 (C=O)
3e	CH_3	$CH_2CH_2COOCH_3$	0	$C_{20}H_{18}N_2O_2S$	135—136	93.1	68.56 (68.28	5.18 5.19	7.99 7.91)	1740 (C=O)
4a	H	$CH_2CH_2COOCH_3$	2	$C_{19}H_{16}N_2O_4S$	125—129	34.5	61.96 (61.83	4.38 4.52	7.60 7.58)	1685 (C=O)
5a	H	CH_2CH_2COOH	2	$C_{18}H_{14}N_2O_4S$	177—180	64.0	61.01 (60.72	3.98 4.20	7.90 7.68)	1710 (C=O) 3500—2400 (OH)
6a	H	CHO	0	$C_{16}H_{10}N_2OS$	269—271	89.2	69.06 (68.70	3.62 3.68	10.06 10.01)	1665 (C=O)
6a	Br	CHO	0	$C_{16}H_9BrN_2OS$	279	62.1	53.75 (53.63	2.54 2.61	7.84 7.86)	1675 (C=O)
6c	Cl	CHO	0	$C_{16}H_9ClN_2OS$	272	91.3	61.44 (61.35	2.90 2.93	8.96 9.01)	1675 (C=O)
6d	OCH_3	CHO	0	$C_{17}H_{12}N_2O_2S$	168	90.6	66.23 (66.01	3.92 3.95	9.08 9.03)	1660 (C=O)
6e	CH_3	CHO	0	$C_{17}H_{12}N_2OS$	181—182	92.3	69.85 (69.57	4.14 4.15	9.58 9.50)	1665 (C=O)
7a	H	$CH(OH)CH_2COOC_2H_5$	0	$C_{20}H_{18}N_2O_3S$	176—177.5	61.8	65.57 (65.41	4.95 4.96	7.64 7.60)	1740 (C=O) 3500—3200 (OH)
7b	Br	$CH(OH)CH_2COOC_2H_5$	0	$C_{20}H_{17}BrN_2O_3S$	186—187	47.2	52.52 (52.38	3.89 3.89	6.12 6.00)	1740 (C=O) 3450—3350 (OH)
7c	Cl	$CH(OH)CH_2COOC_2H_5$	0	$C_{20}H_{17}ClN_2O_3S \cdot 0.25H_2O$	201.5—202.5	56.5	59.27 (59.04	4.35 4.28	6.91 6.81)	1740 (C=O) 3450—3300 (OH)
7d	OCH_3	$CH(OH)CH_2COOC_2H_5$	0	$C_{21}H_{20}N_2O_4S \cdot H_2O$	181—182	54.6	60.86 (60.65	5.35 5.40	6.76 6.91)	1740 (C=O) 3550—3400 (OH)
7e	CH_3	$CH(OH)CH_2COOC_2H_5$	0	$C_{21}H_{20}N_2O_3S \cdot 0.5H_2O$	179—181	60.6	64.79 (64.74	5.44 5.21	7.19 7.12)	1745 (C=O) 3650—3350 (OH)

purification of the product was done by dissolving the solid in sodium hydroxide (1 N), washing with chloroform (2 × 10 ml) and reprecipitating with acetic acid (30%).

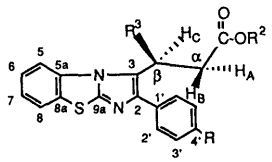
Methyl 3-[2-[*p*-(Un)Substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]propionate Esters (3a—e), General Procedure Dry methanol (0.5 ml) and sulfuric acid (3—4 drops) were added to the appropriate **2a—e** (3.1 mmol) in methylene chloride (5 ml). The reaction mixture was refluxed for 5 h. Methylene chloride (20 ml) was added to the reaction mixture, which was then washed with sodium carbonate (10%, 10 ml), and again with water. The organic layer was dried ($MgSO_4$) and evaporated under vacuum. The separated solid was recrystallized from methanol–chloroform (8:2).

3-[2-(Methoxycarbonyl)ethyl]-2-phenylimidazo[2,1-*b*]benzothiazole-*S*-dioxide (4a) *m*-CPBA (85%, 0.83 g, 4.8 mmol) was added portionwise over a period of 1 h to a solution of **3a** (0.67 g, 2 mmol) in methylene chloride (10 ml). The reaction mixture was stirred at room temperature for 3 h followed by reflux for 1 h. Methylene chloride (20 ml) was added to the reaction mixture, which was washed with saturated sodium bicarbonate solution and then with water. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica, using chloroform as the eluant. The compound eluted first was the *S*-dioxide (**4a**), which was recrystallized from 70% methanol in water.

3-[2-Carboxyethyl]-2-phenylimidazo[2,1-*b*]benzothiazole-*S*-dioxide (5a) Compound **4a** (0.3 g, 0.82 mmol) was added to a solution of sodium hydroxide (1 N, 1.7 ml) and methanol (5 ml). The reaction mixture was stirred at room temperature for 3 h after which time the solvent was evaporated off in vacuum. The residue was dissolved in water (30 ml) and the solution was washed with chloroform (3 × 5 ml). Acetic acid (30%) was added to the aqueous layer, and the separated solid was collected by filtration.

[2-[*p*-(Un)Substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]carb-

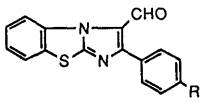
TABLE II. ^{1}H-NMR Spectral Data for 2,3-Disubstituted Imidazo[2,1-*b*]benzothiazoles



Compd. No.	R	R^2	R^3	^{1}H-NMR (δ value) $CDCl_3$ (J=Hz)
2e[a]	CH_3	H	H	2.32 (3H, s, Ar-C$\underline{H}_3$), 2.58 (2H, qi, J=8.90, 8.24, 4.29, 3.29, β-C$\underline{H}_2$), 3.41 (2H, qi, J=7.91, 8.90, 4.29, α-C$\underline{H}_2$), 7.24 (2H, d, J=7.91, $C_{3'}$-$\underline{H}$, $C_{5'}$-$\underline{H}$), 7.39 (1H, br t, J=7.58, 7.25, C_7-$\underline{H}$), 7.46 (2H, d, J=$C_{2'}$-$\underline{H}$, $C_{6'}$-$\underline{H}$), 7.54 (1H, dt, J=7.91, 1.32, C_6-$\underline{H}$), 7.82 (1H, dd, J=7.91, 0.99, C_8-$\underline{H}$), 7.94 (1H, br d, J=8.24, C_5-$\underline{H}$)
3a	H	CH_3	H	2.80 (2H, qi, J=8.54, 8.24, 3.66, 2.75, β-C$\underline{H}_2$), 3.60 (2H, qi, J=8.24, 8.54, 2.75, 3.36, α-C$\underline{H}_2$), 3.72 (3H, s, COOC$\underline{H}_3$), 7.31—7.50 (5H, m, C_6-$\underline{H}$, C_7-$\underline{H}$, $C_{3'}$-$\underline{H}$, $C_{4'}$-$\underline{H}$, $C_{5'}$-$\underline{H}$), 7.68 (2H, td, J=9.46, 1.22, 0.92, $C_{2'}$-$\underline{H}$, $C_{6'}$-$\underline{H}$), 7.72 (1H, dd, J=7.94, 0.61, C_8-$\underline{H}$), 7.78 (1H, dd, J=8.24, 0.61, C_5-$\underline{H}$)
3b	Br	CH_3	H	2.78 (2H, qi, J=8.55, 8.24, 3.36, 2.74, β-C$\underline{H}_2$), 3.58 (2H, qi, J=8.24, 8.54, 2.75, 3.36, α-C$\underline{H}_2$), 3.72 (3H, s, COOC$\underline{H}_3$), 7.36 (1H, dt, J=7.47, 1.22, 0.92, C_7-$\underline{H}$), 7.47 (1H, dt, J=7.48, 8.24, 1.53, 1.22, C_6-$\underline{H}$), 7.57 (4H, s, C_6H_4-Br-*p*-), 7.72 (1H, dd, J=7.94, 0.91, C_8-$\underline{H}$), 7.78 (1H, dd, J=7.94, 0.61, C_5-$\underline{H}$)
3c	Cl	CH_3	H	2.79 (2H, qi, J=8.54, 8.24, 3.36, 2.75, β-C$\underline{H}_2$), 3.59 (2H, qi, J=8.24, 8.24, 2.74, 3.36, α-C$\underline{H}_2$), 3.73 (3H, s, COOC$\underline{H}_3$), 7.36 (1H, dt, J=7.62, 7.80, 1.22, 0.92, C_7-$\underline{H}$), 7.43 (2H, d, J=8.55, $C_{2'}$-$\underline{H}$, $C_{6'}$-$\underline{H}$), 7.48 (1H, dt, J=7.48, 8.24, 1.52, 1.22, C_6-$\underline{H}$), 7.62 (2H, d, J=8.24, $C_{3'}$-$\underline{H}$, $C_{5'}$-$\underline{H}$), 7.73 (1H, dd, J=7.94, 0.61, C_8-$\underline{H}$), 7.78 (1H, d, J=8.24, C_5-$\underline{H}$)
3d	OCH_3	CH_3	H	2.79 (2H, qi, J=8.24, 8.24, 3.36, 3.05, β-C$\underline{H}_2$), 3.57 (2H, qi, J=8.24, 8.24, 3.05, 3.36, α-C$\underline{H}_2$), 3.73 (3H, s, COOC$\underline{H}_3$), 3.86 (3H, s, R=OC$\underline{H}_3$), 6.99 (2H, d, J=8.85, $C_{3'}$-$\underline{H}$, $C_{5'}$-$\underline{H}$), 7.33 (1H, dt, J=7.93, 7.47, 1.22, 0.92, C_7-$\underline{H}$), 7.46 (1H, dt, J=7.48, 8.09, 1.53, 1.22, C_6-$\underline{H}$), 7.60 (2H, d, J=8.85, $C_{2'}$-$\underline{H}$, $C_{6'}$-$\underline{H}$), 7.71 (1H, dd, J=7.93, 1.22, C_8-$\underline{H}$), 7.77 (1H, dd, J=8.24, 0.61, C_5-H)
3e	CH_3	CH_3	H	2.40 (3H, s, R=C$\underline{H}_3$), 2.79 (2H, qi, J=8.24, 8.54, 3.66, 3.05, β-C$\underline{H}_2$), 3.59 (2H, qi, J=8.55, 8.24, 2.74, 3.66, α-C$\underline{H}_2$), 3.73 (3H, s, COOC$\underline{H}_3$), 7.26 (2H, d, J=8.55, 0.61, $C_{3'}$-$\underline{H}$, $C_{5'}$-$\underline{H}$), 7.34 (1H, dt, J=7.93, 7.48, 1.22, 0.92, C_7-$\underline{H}$), 7.46 (1H, dt, J=7.94, 7.79, 1.52, 1.22, C_6-$\underline{H}$), 7.57 (2H, d, J=8.24, $C_{2'}$-$\underline{H}$, $C_{6'}$-$\underline{H}$), 7.71 (1H, td, J=7.94, 0.91, 0.61, 0.92, C_8-$\underline{H}$), 7.77 (1H, br d, J=7.93, C_5-$\underline{H}$)
7a	H	C_2H_5	OH	1.24 (3H, t, J=7.15, $OCH_2C\underline{H}_3$), 2.68 (1H, dd, J=16.50, 3.57, α-$\underline{H}_B$), 3.23 (1H, dd, J=16.36, 10.72, 10.45, α-$\underline{H}_A$), 4.17 (2H, m, $OC\underline{H}_2CH_3$), 4.28 (1H, d, J=2.75, O$\underline{H}$ (exchanged by D_2O)), 5.81 (1H, dt, J=10.18, 3.30, 3.03, β-$\underline{H}_C$), 7.20—7.35 (4H, m, C_7-$\underline{H}$, $C_{3'}$-$\underline{H}$, $C_{4'}$-$\underline{H}$, $C_{5'}$-$\underline{H}$), 7.46 (1H, td, J=8.25, 7.43, 1.10, C_6-$\underline{H}$), 7.50 (2H, dd, J=8.38, 1.37, 1.10, $C_{2'}$-$\underline{H}$, $C_{6'}$-$\underline{H}$), 7.66 (1H, dd, J=7.97, 0.83, C_8-$\underline{H}$), 8.43 (1H, br d, J=7.97, C_5-$\underline{H}$)
7b	Br	C_2H_5	OH	1.27 (3H, t, J=7.15, $OCH_2C\underline{H}_3$), 2.67 (1H, dd, J=16.64, 3.57, 3.30, α-$\underline{H}_B$), 3.24 (1H, dd, J=16.77, 10.73, α-$\underline{H}_A$), 4.05 (1H, d, J=2.75, O$\underline{H}$), 4.20 (2H, m, $OC\underline{H}_2CH_3$), 5.77 (1H, td, J=6.88, 6.60, 4.68, 3.03, β-$\underline{H}_C$), 7.43 (6H, m, C_6-$\underline{H}$, C_7-$\underline{H}$, C_6H_4-Br-*p*-), 7.69 (1H, dd, J=7.97, 0.82, C_8-$\underline{H}$), 7.41 (1H, d, J=7.70, C_5-$\underline{H}$)
7c	Cl	C_2H_5	OH	1.25 (3H, t, J=7.15, $OCH_2C\underline{H}_3$), 2.66 (1H, dd, J=16.50, 3.57, α-$\underline{H}_B$), 3.21 (1H, dd, J=16.50, 10.44, α-$\underline{H}_A$), 4.19 (2H, m, $OC\underline{H}_2CH_3$), 4.50 (1H, br s, O$\underline{H}$), 5.75 (1H, dd, J=10.45, 3.57, β-$\underline{H}_C$), 7.21 (2H, d, J=8.53, $C_{3'}$-$\underline{H}$, $C_{5'}$-$\underline{H}$), 7.36 (1H, br t, J=7.42, C_7-$\underline{H}$), 7.38 (2H, d, J=8.53, $C_{2'}$-$\underline{H}$, $C_{6'}$-$\underline{H}$), 7.47 (1H, td, J=7.83, 6.88, 1.10, 0.82, C_6-$\underline{H}$), 7.66 (1H, dd, J=7.97, 0.83, C_8-$\underline{H}$), 8.40 (1H, d, J=8.25, C_5-$\underline{H}$)
7e	CH_3	C_2H_5	OH	1.27 (3H, t, J=7.15, $OCH_2C\underline{H}_3$), 2.37 (3H, s, Ar-C$\underline{H}_3$), 2.68 (1H, dd, J=16.64, 3.57, 3.30, α-$\underline{H}_B$), 3.25 (1H, dd, J=16.64, 10.99, 10.72, α-$\underline{H}_A$), 3.81 (1H, d, J=2.20, O$\underline{H}$), 4.20 (2H, m, $OC\underline{H}_2CH_3$), 5.83 (1H, dt, J=8.12, 2.47, 2.20, β-$\underline{H}_C$), 7.21 (2H, d, J=7.97, $C_{3'}$-$\underline{H}$, $C_{5'}$-$\underline{H}$), 7.35 (1H, t, J=7.42, 6.88, 1.10, C_7-$\underline{H}$), 7.48 (3H, m, C_6-$\underline{H}$, $C_{2'}$-$\underline{H}$, $C_{6'}$-$\underline{H}$), 7.68 (1H, dd, J=7.97, 1.10, C_8-$\underline{H}$), 8.42 (1H, d, J=8.24, C_5-$\underline{H}$)

Abbreviations: s, singlet; d, doublet; dd, double doublet; dt, double triplet; td, triple doublet; br d, broad doublet; br t, broad triplet; qi, quintuplet. *a*) Measured in CD_3OD, D_2O and NaOD (40%) in D_2O.

TABLE III. ^{1}H-NMR Spectral Data for 2-[*p*-(Un)Substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]formaldehyde Derivatives



Compd. No.	R	^{1}H-NMR (δ value), $CDCl_3$, (J=Hz)
6a	H	7.30—7.90 (8H, m, $C_6\underline{H}_5$, C_6-$\underline{H}$, C_7-$\underline{H}$, C_8-$\underline{H}$), 9.10 (1H, d, J=8.24, C_5-$\underline{H}$), 9.73 (1H, s, C$\underline{H}$O)
6b	Br	7.44 (1H, td, J=7.94, 1.22, C_7-$\underline{H}$), 7.54 (1H, td, J=7.94, 7.79, 1.52, 1.22, C_6-$\underline{H}$), 7.65 (4H, s, $C_6\underline{H}_4$-Br-*p*-), 7.73 (1H, dd, J=8.24, 1.53, 0.92, C_8-$\underline{H}$), 9.20 (1H, br d, J=8.24, C_5-$\underline{H}$), 9.86 (1H, s, C$\underline{H}$O)
6e	CH_3	2.44 (3H, s, R=C$\underline{H}_3$), 7.32 (2H, d, J=7.94, $C_{3'}$-H, $C_{5'}$-H), 7.41 (1H, td, J=7.94, 7.32, 1.22, C_7-$\underline{H}$), 7.53 (1H, td, J=8.40, 1.22, 0.91, C_6-$\underline{H}$), 7.66 (2H, d, J=7.94, $C_{2'}$-$\underline{H}$, $C_{6'}$-$\underline{H}$), 7.72 (1H, dt, J=7.94, 0.91, C_8-$\underline{H}$), 9.20 (1H, dd, J=7.94, 0.61, C_5-$\underline{H}$), 9.86 (1H, s, C$\underline{H}$O)

aldehyde Derivatives (6a—e), General Procedure A solution of dimethylformamide (2.9 g, 40 mmol) in 1,2-dichloroethane (10 ml) was cooled in an ice-salt bath. Phosphorus oxychloride (0.86 g, 5.6 mmol) was added to the stirred and cooled solution over a period of 30 min. The suspension of white solid was then stirred at room temperature for 15 min. The suspension was cooled in ice and a solution of the appropriate **1a—e** (5 mmol) in 1,2-dichloroethane (40 ml) was added over a period of 20 min. The reaction mixture was then allowed to warm to room temperature over 1 h, after which the temperature was raised to 45—50°C for 2 h. The reaction mixture was stripped of solvent at less than 30°C. A solution of

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

Compd. No.	Dose (mg/kg, *p.o.*)	*n*	Edema weight (mg) (mean ± S.E.)	Inhibition (%)	Compd. No.	Dose (mg/kg, *p.o.*)	*n*	Edema weight (mg) (mean ± S.E.)	Inhibition (%)
2a	100	3	654 ± 20	12.4	Indomethacin	3	3	388 ± 75	48.1
2b	100	3	839 ± 77	−12.3	Control	—	3	747 ± 71	—
2c	100	3	926 ± 67	−24.0	**4a**	50	5	793 ± 29	11.1
2d	100	3	745 ± 72	−0.3	Phenylbutazone	50	5	416 ± 42[a]	53.4
2e	100	3	806 ± 15	−19.1	Control	—	5	892 ± 35	—

a) $p<0.01$ *vs.* control in multiple comparison.

TABLE V. Activity in Acetic Acid-Induced Writhing (AAIW) and Capillary Permeability Inhibition (CPI) Assays in Mice

Compd. No.	Dose (mg/kg, *p.o.*)	*n*	AAIW test		CPI test	
			Writhes (20 min)	Inhibition (%)	Pontamine-sky blue (%)	Inhibition (%)
2a	100	5	55 ± 8	−38	93 ± 8	7
4a	100	5	32 ± 5	20	68 ± 8[a]	32
Aminopyrine	100	5	1 ± 1[a]	98	40 ± 5[b]	60
Control	—	5	40 ± 9	—	100 ± 11	—
5a	100	5	10 ± 5	62	79 ± 11	21
Aminopyrine	100	5	3 ± 3	88	39 ± 7[b]	61
Control	—	5	26 ± 10	—	100 ± 20	—

a) $p<0.05$. *b*) $p<0.01$ *vs.* control in multiple comparison.

sodium hydroxide (3 g) in water (30 ml) was added portionwise to the Vilsmeier complex prepared above. The reaction mixture was refluxed for 2 h. After cooling, the precipitated solid was filtered off and washed with water, and then recrystallized from chloroform–methanol (4 : 1).

Ethyl 3-Hydroxy-3-[2-[*p*-(un)substituted phenyl]imidazo[2,1-*b*]benzothiazol-3-yl]propionates(7a—e) A mixture of activated zinc powder, copper powder and magnesium turnings (12 : 2 : 1), (0.27 g, 3.3 mg atoms of zinc), iodine (0.02—0.03 g) and dry benzene (2 ml) was stirred and heated to reflux. A solution of the appropriate **6a—e** (1.1 mmol) and ethyl bromoacetate (0.55 g, 3.3 mmol) in dry benzene (15 ml) was added portionwise during a period of 1 h. When the addition was complete, the reaction mixture was heated for an additional 5 h under reflux. Benzene (20 ml) was added and the reaction mixture was decanted, filtered to remove the solid and washed with saturated sodium bicarbonate solution. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was chromatographed on silica, using chlorofom as the eluant. The separated compounds were crystallized from chloroform–methanol (1 : 1).

(−)Ethyl 3-Hydroxy-3-[2-phenylimidazo[2,1-*b*]benzothiazol-3-yl]propionate[(−)-7a] A mixture of racemic (±)-**7a** (0.4 g, 1.1 mmol) and [2*R*, 3*R*]-(+)-tartaric acid (0.17 g, 1.11 mmol) in methanol (10 ml) was heated, and the solution obtained was then left at room temperature until crystallization was complete to give(−)-**7a** as the bitartrate salt (0.28 g, 50.1%). Liberation of the ester from the bitartrate salt gave(−)-**7a** (98.2%): mp 180—181°C, $[\alpha]_D^{21}$ −4.65 ± 0.3° ($c=0.7$, $CHCl_3$).

(+)-Ethyl 3-Hydroxy-3-[2-phenylimidazo[2,1-*b*]benzothiazol-3-yl]propionate[(+)-7a] The residue on evaporation of the filtrate in the preceding resolution gave (+)-**7a** (97.8%): mp 177—178°C, $[\alpha]_D^{21}$ +4.48 ± 0.4° ($c=0.7$, $CHCl_3$).

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References

1) For a review and leading references, see: J.G.Lombardino, "Annual Reports in Medicinal Chemistry," Vol. XIII, Academic Press, New York, 1978, p. 167.
2) G. Renoux and M. Renoux, *C. R. Hebd. Seances Acad. Sci., Ser. D*, **272**, 349 (1971); through C. Bell and P. H. L. Wei, *J. Med. Chem.*, **19**, 524 (1976).
3) E. Abignente, F. Arena, P. De Caprariis and L. Parente, *Farmaco-Ed. Sc.*, **31**, 880 (1976).
4) T. Mase, H. Arima, K. Tomioka, T. Yamada and K. Murase, *J. Med. Chem.*, **29**, 386 (1986).
5) S. N. Sawhney, D. R. Kodali, G. S. Dhindsa and S. P. Singh, *Indian J. Chem., Sect. B*, **21B**, 134 (1982).
6) E. Abignente, F. Arena, P. De Caprariis, C. Fereri, E. Marmo, R. Ottavo, F. Rossi and M. Giasi, *Farmaco-Ed. Sc.*, **36**, 893 (1981).
7) A. El-Shorbagi, S. Sakai, M. A. El-Gendy, N. Omar and H. H. Farag, *Chem. Pharm. Bull.*, **36**, 4760 (1988).
8) H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **25**, 569 (1960).
9) R. L. Shriner, *Org. React.*, **1**, 1 (1942).
10) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, John Wiley and Sons, Inc., New York, 1967, p. 1285.
11) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra," Wiley-Interscience, New York, 1972.
12) C. A. Winter, E. A. Risley and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
13) B. A. Whittle, *Br. J. Pharmacol.*, **22**, 246 (1964).