

Synthesis of 3-(2-Pyridylethyl)benzoxazolinone Derivatives: Potent Analgesic and Antiinflammatory Compounds Inhibiting Prostaglandin E₂

Cihat Safak,*† Hakki Erdoğan,† Erhan Palaska,† Rûmeysa Sunal,† and Suna Duru‡

Departments of Pharmaceutical Chemistry, Pharmacology, and Pharmaceutical Toxicology, Faculty of Pharmacy, University of Hacettepe, Ankara, Turkey. Received November 15, 1991

Fourteen new 3-[2-(2- and/or 4-pyridyl)ethyl]benzoxazolinone derivatives have been synthesized by reacting 2- and/or 4-vinylpyridine and appropriate benzoxazolinones. Their chemical structures have been proven by IR, ¹H-NMR, and elemental analysis. Analgesic activities of these compounds were investigated by a "Modified Koster's Test". Except for compounds 10 and 11, all the new derivatives showed higher analgesic activities than aspirin. Therefore the compounds were screened for their antiinflammatory activities using the carrageenan hind paw edema test. The compounds (6, 7, 8, 9, 14, and 17) that showed high antiinflammatory activity were then further screened for their ability to inhibit prostaglandin E₂ (PGE₂) induced paw edema. Although all the benzoxazolinone derivatives synthesized in this study showed higher antiinflammatory activity compared to indomethacin, those without a substituent at the 6-position of the ring were significantly more active than the rest of the group, and their ulcerogenic activities and ED₅₀ values indicate them as promising derivatives for further study.

The most prevalent side effects of the use of nonsteroidal antiinflammatory drugs is the occurrence of gastrointestinal damage with gastric upset and irritation being the major problems. Therefore, investigation of new antiinflammatory agents are still a challenge. Recently, in efforts to synthesize antiinflammatory drugs with minimal gastrointestinal side effects, benzoxazolinones have emerged as a promising group.

Shapiro and co-workers¹ prepared and demonstrated analgesic, antiinflammatory, and anticonvulsant activities of 3-[2-(2- and/or 4-pyridyl)ethyl]-1,3-benzoxazine-2,4-diones. Erdoğan and co-workers² and Erol and co-workers³ have demonstrated that some benzoxazolinone derivatives possess analgesic and antiinflammatory activities. It was therefore of interest to synthesize 14 new 3-[2-(2- and/or 4-pyridyl)ethyl]benzoxazolinone derivatives and screen them for their analgesic and antiinflammatory activities. Those with antiinflammatory activities were further investigated for their ability to inhibit prostaglandin E₂ (PGE₂) synthesis. Six potent antiinflammatory derivatives were finally assessed for their ED₅₀ and ulcerogenic activity.

Results and Discussion

Chemistry. Fourteen new 3-[2-(2- and/or 4-pyridyl)ethyl]benzoxazolinone derivatives were synthesized and evaluated for their analgesic and antiinflammatory activities. Benzoxazolinone and chlorzoxazone were acylated in PPA with appropriate carboxylic acids and then treated with 2- and/or 4-vinylpyridine (Scheme I).

Initial acylation of 2(3*H*)-benzoxazolinone could be expected to lead to formation of both the 6-acyl and also 4-acyl derivatives. However, it has been reported that the substitution is directed by the nitrogen atom of the benzoxazolinone ring and only the 6-acyl derivative is formed.⁴

The formula, melting points, % yields, and elemental analyses of the compounds are listed in Table I. All spectral data are in accordance with the assumed structures. In the IR spectra of the compounds, no absorption bands were detected at 3100–3400 cm⁻¹, indicating the absence of an NH group which is evidence for the addition reaction. In the ¹H-NMR spectrum, ethylenic and aromatic protons in all compounds are seen at expected values. The H-6 proton of the pyridine ring is seen at approximately 8.42 ppm as a doublet of doublets due to ortho and meta coupling (*J* = 1.43, 5.30 Hz). Analytical

results were within ±0.4% of the theoretical values.

Pharmacology. The analgesic activity of the compounds were screened by a "Modified Koster's Test" using aspirin as a reference analgesic. As seen in Table II, the compounds synthesized (except 10 and 11) showed analgesic activities higher than aspirin. These results led us to screen the compounds for their inhibition of carrageenan induced edema (Table II). Carrageenan edema inhibition of compounds 10 and 11 were not significant when compared to measured control edema (*p* < 0.05), while inhibition of CPE (carrageenan paw edema) by compounds 16 and 19 (19.7 and 25.9%, respectively) were equivalent to indomethacin. Compounds 6–9, 12–15, 17, and 18 inhibited CPE 2-fold when compared to indomethacin. Compounds 8 and 9 showed the highest CPE inhibition, 3 times the inhibition of indomethacin (Table II).

We then screened the compounds for their activity in paw edema induced by serotonin, bradykinin, histamine, and arachidonic acid to determine which of the inflammatory agents they were inhibiting. Inhibition of serotonin induced paw edema was higher than that with indomethacin with only compounds 7, 9, 13, 14, and 19 (*p* < 0.05). But since the inhibition rate even with these compounds is less than 18% of the control values, antiinflammatory activity via serotonin inhibition was ruled out. Compounds were not effective in inhibiting histamine or bradykinin induced edemas. However, compounds 6–9, 12, 14, 15, and 17 inhibited arachidonic acid paw edema significantly (Table III).

From the results we obtained with the inhibition of edema test (induced by inflammatory agents: serotonin, bradykinin, histamine, and arachidonic acid), we concluded that the compounds are active in the CPE test via arachidonic acid synthesis inhibition.

Since our observations clearly indicate that compounds without a substituent at the 6-position of the benzoxazolinone ring have higher analgesic and antiinflammatory activities via arachidonate synthesis inhibition, we

*Department of Pharmaceutical Chemistry.

†Department of Pharmacology.

‡Department of Pharmaceutical Toxicology.

- (1) Shapiro, L. S.; Rose, I. M.; Freedman, L. Pyridylethylated Benzoxazinediones. *J. Am. Chem. Soc.* 1957, 79, 2811–2814.
- (2) Erdoğan, H.; Ünlü, S.; Sunal, R. Analgesic Activity of Some 3-Arylpiperidinomethyl-2-benzoxazolinone Derivatives. *Arch. Pharm. (Weinheim)* 1989, 322, 75–77.
- (3) Erol, D. D.; Sunal, R.; Duru, S. Synthesis and Screening of Analgesic and Antiinflammatory Activity of 6-Acyl-3-(4-substituted benzoylmethyl)-2(3*H*)-benzoxazolinones. *Arzneim.-Forsch.* 1990, 40, 478–480.
- (4) Bonte, J. P.; Lesieur, D.; Lespagnol, C.; Cazin, J. C.; Cazin, M.; Plat, M. Acyl-6-benzoxazolinones. *Eur. J. Med. Chem.* 1974, 9, 491–497.

Scheme I

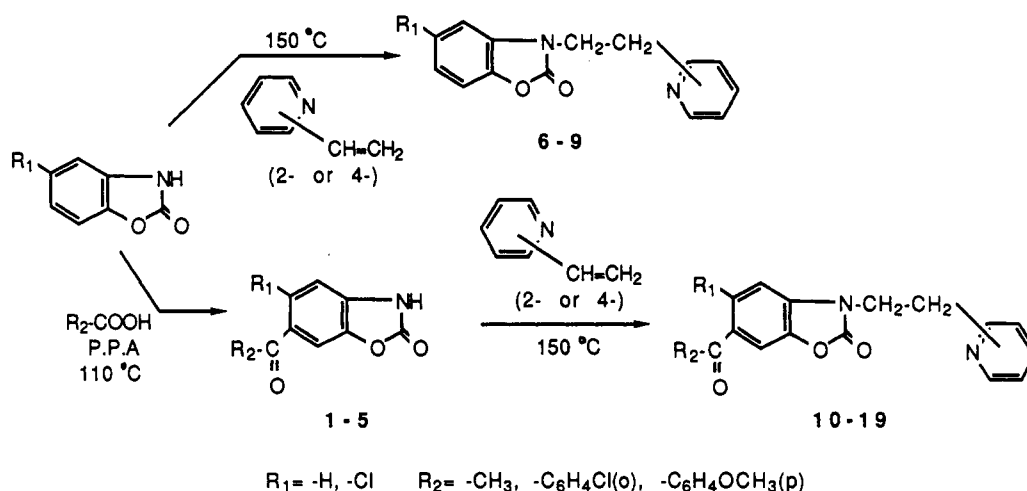
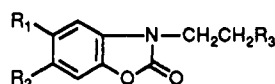


Table I. 3-[2-(2- and 4-Pyridyl)ethyl]benzoxazolinones



compd	R ₁	R ₂	R ₃	mp, °C	yield, %	formula	anal.
6	H	H	2-pyr ^a	96	88	C ₁₄ H ₁₂ N ₂ O ₂	C, H, N
7	H	H	4-Pyr	95	78	C ₁₄ H ₁₂ N ₂ O ₂	C, H, N
8	Cl	H	2-Pyr	76	91	C ₁₄ H ₁₁ ClN ₂ O ₂	C, H, N
9	Cl	H	4-pyr	151	90	C ₁₄ H ₁₁ ClN ₂ O ₂	C, H, N
10	H	CH ₃ CO	2-pyr	114	76	C ₁₆ H ₁₄ N ₂ O ₃	C, H, N
11	H	CH ₃ CO	4-pyr	127	84	C ₁₆ H ₁₄ N ₂ O ₃	C, H, N
12	H	C ₆ H ₅ CO	2-pyr	138	85	C ₂₁ H ₁₆ N ₂ O ₃	C, H, N
13	H	C ₆ H ₅ CO	4-pyr	125	93	C ₂₁ H ₁₆ N ₂ O ₃	C, H, N
14	H	(o)ClC ₆ H ₄ CO	2-pyr	168	76	C ₂₁ H ₁₅ ClN ₂ O ₃	C, H, N
15	H	(o)ClC ₆ H ₄ CO	4-pyr	143	78	C ₂₁ H ₁₅ ClN ₂ O ₃	C, H, N
16	Cl	(o)ClC ₆ H ₄ CO	2-pyr	139	82	C ₂₁ H ₁₄ Cl ₂ N ₂ O ₃	C, H, N
17	Cl	(o)ClC ₆ H ₄ CO	4-pyr	132	89	C ₂₁ H ₁₄ Cl ₂ N ₂ O ₃	C, H, N
18	H	(p)CH ₃ OC ₆ H ₄ CO	2-pyr	142	90	C ₂₂ H ₁₈ N ₂ O ₄	C, H, N
19	H	(p)CH ₃ OC ₆ H ₄ CO	4-pyr	134	88	C ₂₂ H ₁₈ N ₂ O ₄	C, H, N

^a Pyr = pyridyl.Table II. Percent Analgesic Activity and Carrageenan Paw Edema (CPE) Inhibition of the Compounds^{a, b}

compound	% analgesic act.	% inhibn of CPE
6	92.17	55.2
7	96.06	59.1
8	96.96	62.3
9	100.00	68.5
10	48.74	5.6
11	38.46	10.3
12	79.49	37.1
13	85.47	46.5
14	91.74	37.1
15	84.35	38.6
16	72.67	19.7
17	92.61	49.6
18	80.34	30.8
19	75.21	25.9
aspirin ^c	58.26	—
indomethacin ^d	—	21.1

^a 95% Confidence limits. ^b n = 6. ^c 100 mg/kg po. ^d 10 mg/kg po.

evaluated these six compounds for their inhibition of PGE₂ induced edema. Compounds 6, 7, 8, 9, 14, and 17 were evaluated as potent analgesic, antiinflammatory derivatives inhibiting PGE₂ induced edemas. Results of up to 70% inhibition is a good indicator of inhibition of inflammation via PGE₂ (Table III).

Antiinflammatory compounds exhibit significant ulcerogenic potential that can be demonstrated in animal models using indomethacin as a positive control. We

therefore screened the six compounds (6-9, 14, and 17) for their ED₅₀ values and ulcerogenic activities. Gastric ulceration incidence was very low in our compounds, with only small lesions seen in high doses (with the highest rate in compounds 7 and 8; 4/8 and 5/8 at 300 mg/kg doses, respectively). Intestinal lesion incidence was even lower with compound 7; at 300 mg/kg dose level, 2/8 mice developed lesions (Table IV). We chose compounds 6-9, 14, and 17 as "leading compounds" and further experimentation is commencing.

Experimental Section

All chemicals were obtained from Aldrich Chemical Co. (Steinheim, Germany). Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 457 infrared spectrophotometer. ¹H-NMR spectra were recorded using a Bruker AC80 80 MHz spectrometer using tetramethylsilane internal standard and dimethyl-d₆ sulfoxide. All chemical shifts were reported as δ (ppm) values. Microanalyses were performed by Tubitak (Gebze, Turkey). The purity of the compounds was assessed by TLC on silica gel HF 254+366 (Merck) (benzene-methanol 95:5).

6-Acyl-2(3H)-benzoxazolinones 1-5. These were prepared by treating 2(3H)-benzoxazolinone and/or 5-chloro-2(3H)-benzoxazolinone (chlorzoxazone) and the appropriate carboxylic acid with polyphosphoric acid (PPA) according to the literature.⁴

3-[2-(2- and 4-Pyridyl)ethyl]benzoxazolinones 6-19. To 10 mmoles of benzoxazolinone derivative was added 8 mL of 2- and/or 4-vinylpyridine, and the reaction mixture was heated under reflux in an oil bath until molten and then an additional 2 h at

Table III. Effect of Compounds on Edemas Induced by Inflammatory Agents

compound	% inhibition of edema induced by:				
	bradykinin (100 µg/mL)	serotonin (250 µg/mL)	histamine (10 mg/mL)	arachidonic acid (1 mg/mL)	PGE ₂ (2 µg/mL)
6	6.0 (±0.63) ^{a,c}	10.2 (±0.22) ^e	5.5 (±0.29) ^b	41.3 (±0.32) ^c	56.2 (±1.50) ^c
7	6.4 (±0.57) ^c	9.4 (±0.14) ^c	7.6 (±0.29) ^b	38.9 (±0.25) ^c	62.2 (±2.16) ^c
8	7.0 (±0.51) ^c	10.5 (±0.30) ^e	9.0 (±0.17) ^b	42.0 (±0.34) ^c	64.8 (±1.48) ^c
9	9.0 (±0.47) ^c	13.1 (±0.10) ^c	11.0 (±0.27) ^b	51.2 (±0.26) ^d	68.0 (±1.81) ^c
12	11.0 (±0.55) ^c	9.8 (±0.32) ^b	6.0 (±0.30) ^b	32.0 (±0.26) ^b	—
13	10.0 (±0.34) ^c	14.1 (±0.14) ^c	8.5 (±0.26) ^b	36.5 (±0.28) ^e	—
14	6.4 (±0.47) ^c	18.2 (±0.53) ^c	5.0 (±0.30) ^b	46.0 (±0.27) ^c	53.0 (±1.30) ^c
15	7.0 (±0.37) ^c	10.0 (±0.11) ^e	7.4 (±0.17) ^b	39.0 (±0.38) ^c	—
16	7.6 (±0.56) ^c	9.0 (±0.17) ^b	10.0 (±0.29) ^b	37.0 (±0.24) ^e	—
17	12.0 (±0.50) ^c	8.4 (±0.07) ^b	9.3 (±0.29) ^b	43.0 (±0.25) ^c	55.0 (±1.94) ^c
18	13.0 (±0.39) ^e	9.9 (±0.13) ^b	5.4 (±0.28) ^b	40.0 (±0.24) ^e	—
19	10.0 (±0.37) ^c	15.0 (±0.24) ^c	8.0 (±0.32) ^b	32.0 (±0.24) ^b	—
indomethacin	13.4 (±0.54)	10.3 (±0.24)	14.7 (±0.35)	37.0 (±0.32)	42.0 (±2.12)

^a Results are expressed as their mean values. ^b Significantly less than indomethacin. ^c Significantly more than indomethacin (95% confidence limits, 50df). ^d Significantly more than indomethacin (99% confidence limits, 50df). ^e Nonsignificant; *n* = 6.

Table IV. Ulcerogenic Activity and ED₅₀ Values of the Compounds 6–9, 14, and 17

compound	dose (mg/kg)	antiinflam act. CPE ^a ED ₅₀ ^b	ulceration			
			gastric ^c		intestinal ^c	
			ulcer incidence, no./grp	lesion length, mm/mice (±SE)	ulcer incidence, no./grp	lesion length, mm/mice (±SE)
indomethacin	10	7.50 (6.9–8.1)	7/8	0.6 ± 0.12	8/8	0.4 ± 0.02
6	60	55.00 (50.3–69.7)	0/8	0	0/8	0
	100		1/8	0.4 ± 0.09	0/8	0
	300		4/8	0.7 ± 0.15	0/8	0.07 ± 0.01
7	60	57.00 (52–62)	0/8	0	0/8	0
	100		0/8	0	0/8	0
	300		5/8	0.9 ± 0.21	2/8	0.1 ± 0.02
8	60	63.00 (59–67)	0/8	0	0/8	0
	100		1/8	0.2 ± 0.02	0/8	0
	300		4/8	0.9 ± 0.2	1/8	0.1 ± 0.09
9	20	18.20 (16–20.4)	0/8	0	0/8	0
	50		0/8	0	0/8	0
	100		1/8	0.4 ± 0.12	0/8	0.15 ± 0.07
14	30	25.50 (24.5–26.5)	0/8	0	0/8	0
	100		0/8	0	0/8	0
	300		2/8	0.4 ± 0.01	0/8	0.2 ± 0.03
17	30	30.00 (28–32)	0/8	0	0/8	0
	100		0/8	0	0/8	0
	300		1/8	0.4 ± 0.1	0/8	0.4 ± 0.08

^a Carrageenan paw edema. ^b Mice, mg/kg po. ^c Three oral doses; SE: standard error, *n* = 8.

150 °C. On cooling, the products were poured into crushed ice, and the solid mass which separated out was filtered, dried, and crystallized from ethanol, e.g., compound 6: IR 1765 cm⁻¹; ¹H-NMR (DMSO) 3.17 (t, 2 H, CH₂-pyr), 4.20 (t, 2 H, NCH₂), 7.07–7.78 (m, 7 H, benzoxazolinone H-4–H-7, pyridine H-3–H-5), 8.46 (dd, 1 H, *J* = 1.4, 5.3 Hz, pyridine H-6).

Pharmacology. Female albino mice, weighing 22 ± 2 g were used (local breed). The animals were housed in groups of eight with food and water ad libitum and were allowed to get accustomed to their environment for at least 2 days before the experiments.

Analgesic Activity.⁵ A "Modified Koster's Test" was used. Each compound was suspended in 5% gum arabic syrup and given orally to mice in groups of eight at a dose level of 100 mg/kg. One hour after this administration, pain was induced by ip injection of 3% solution of acetic acid at 300 mg/kg. Two control groups (*n* = 6) received gum arabic syrup 1 h prior to injection of acetic acid. Animals were placed in glass cages 5 min after acetic acid injection, and the number of "stretching" per animal was recorded during the following 10-min period; percent analgesic activity was calculated by using the formula:

$$\text{percent analgesic activity} = \frac{|n - n'|}{n} \times 100$$

(5) Koster, R.; Anderson, M.; Debeer, E. J. Acetic Acid for Analgesic Screening. *Fed. Proc.* 1959, 18, 412–420.

where *n* = average number of "stretchings" of control group, and *n'* = average number of "stretchings" of test group. Aspirin was used as a reference analgesic and administered according to the test protocol.

Antiinflammatory Activity.^{6,7} Carrageenan induced mouse paw edema (CPE) was measured using a Peacock dial thickness gauge (0.01–10 mm). Six mice per group were used. Sixty minutes after oral administration of the compound (100 mg/kg), 0.01 mL of 2% carrageenan was injected subcutaneously into the plantar surface of the right hind paw. Three hours later the volume of the edema was measured with a dial thickness gauge.

Bradykinin, Arachidonic Acid, Histamine, Serotonin Induced Edema. Six mice per group were used. Sixty minutes after oral administration of the compound (100 mg/kg), 0.01 mL of each phlogistic agent was injected subcutaneously into the plantar surface of the right hind paw and the volume of the resulting edema was measured with a dial thickness gauge. The

- (6) Ackrell, J.; Antonio, Y.; Franco, F.; Landeros, R.; Leon, A.; Muchowski, J. M.; Maddox, M. L.; Nelson, P. H.; Rooks, W. H.; Roszkowski, A. P.; Wallach, M. B. Synthesis and Antiinflammatory Activity of 6,11-Dihydro-11-oxodibenzo[*b,e*]thiepinalkanoic Acids and Related Compounds. *J. Med. Chem.* 1978, 21, 1035–1044.
- (7) Dunn, J. P.; Muchowski, J. M.; Nelson, P. H. Antiinflammatory 5,6-Dihydro-11-oxodibenzo[*b,e*]azepine-3-acetic Acids. *J. Med. Chem.* 1981, 24, 1097–1099.

antiedematous effects of the drugs were estimated in terms of percent inhibition.

PGE₂ Induced Edema. Six mice per group were used. Sixty minutes after oral administration of drugs (100 mg/kg), PGE₂ (20 µg/0.01 mL) was injected subcutaneously into the plantar surface of the right hind paw and the volume of the resulting edema was measured with a dial thickness gauge. The antiedematous effects of the drugs were estimated in terms of percent inhibition.

Gastrointestinal Ulceration Studies.⁸ Gastric Ulceration. Mice were fasted for 24 h (with water ad libitum). Compounds were suspended in a methyl cellulose vehicle and administered orally by gavage in a volume of 0.5 mL/100 g of body weight. The animals were sacrificed after 4 h, and the stomachs were examined for lesions under a dissecting microscope.

Intestinal Ulceration: Compounds were administered to normal, fed rats by gavage for 3 consecutive days. The mice were sacrificed 24 h after the last dosing and examined for intestinal ulcers.

Statistical Analysis:⁹ Student's *t*-test and analysis of variance [ANOVA, two factors (pharmacologic calculation system version 4.1)] were employed.

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Registry No. 1, 54903-09-2; 2, 54903-12-7; 3, 72766-68-8; 4, 95637-40-4; 5, 76751-95-6; 6, 139101-47-6; 7, 139101-48-7; 8, 139101-49-8; 9, 139101-50-1; 10, 139101-51-2; 11, 139101-52-3; 12, 139101-53-4; 13, 139101-54-5; 14, 139101-55-6; 15, 139101-56-7; 16, 139101-57-8; 17, 139101-58-9; 18, 139101-59-0; 19, 139101-60-3; 2-vinylpyridine, 100-69-6; 4-vinylpyridine, 100-43-6.

Supplementary Material Available: A table of IR and ¹H-NMR spectral data of compounds 6–19 (2 pages). Ordering information is given on any current masthead page.

(8) Sancilio, L. F.; Nolan, J. C.; Wagner, L. E.; Ward, J. W. The Analgesic and Antiinflammatory Activity and Pharmacologic Properties of Bromfenac. *Arzneim.-Forsch.* 1987, 37, 513–519.

(9) Bliss, C. I.; White, C. In *The Vitamins*, 2nd ed.; Gyorgy, P., Pearson, W. N., Eds.; Academic Press: New York, 1967; Vol. 6, pp 50–78.

Development of 2,3-Dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol (L-670,630) as a Potent and Orally Active Inhibitor of 5-Lipoxygenase

Cheuk K. Lau,*† Patrice C. Bélanger,† Claude Dufresne,† John Scheigetz,† Michel Therien,† Brian Fitzsimmons,† Robert N. Young,† Anthony W. Ford-Hutchinson,† Denis Riendeau,§ Danielle Denis,§ Jocelyne Guay,§ Stella Charleson,† Hanna Piechuta,† Cyril S. McFarlane,† Suet-Hing Lee Chiu,|| Diana Eline,|| Raul F. Alvaro,|| Gerald Miwa,|| and John L. Walsh||

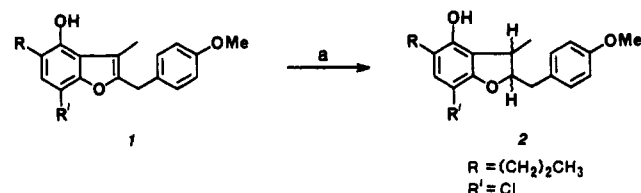
Departments of Medicinal Chemistry, Pharmacology and Biochemistry, Merck Frosst Centre For Therapeutic Research, P.O. Box 1005, Pointe Claire-Dorval, Quebec, H9R 4P8, Canada, and Department of Animal Drug Metabolism, Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065. Received August 19, 1991

Leukotrienes are potent biological mediators of allergic and inflammatory diseases and are derived from arachidonic acid through the action of the 5-lipoxygenase. In this study, the syntheses and comparative biological activities of three series of 2,3-dihydro-2,6-disubstituted-5-benzofuranols with various substituents on position 3 are described. Compounds from each series were evaluated for their ability to inhibit the production of leukotriene B₄ (LTB₄) in human peripheral blood polymorphonuclear (PMN) leukocytes and the 5-lipoxygenase reaction in cell-free preparations from rat PMN leukocytes. The structure–activity relationships of each series in vitro and in vivo are presented. The bioavailability, metabolism, and toxicity profile of each series are discussed. The series with no substituent at position 3 was the most potent and among the compounds in that series 2,3-dihydro-6-(3-phenoxypropyl)-2-(2-phenylethyl)-5-benzofuranol (46, L-670,630) was chosen for further development.

Leukotrienes are potent biological mediators derived from arachidonic acid through the action of the 5-lipoxygenase. The peptidoleukotrienes LTC₄, LTD₄, and LTE₄, are potent spasmogenic agents and have been implicated in the pathology of allergic diseases. Leukotriene B₄, being a potent chemotactic agent, has been considered to be an important mediator of inflammation.¹ Thus, a selective inhibitor of 5-lipoxygenase could become a new class of therapeutic agents for the treatment of such conditions. Recently, a number of hydroxamic acid derivatives² and benzofuranols^{3,4} have been reported to be potent 5-lipoxygenase inhibitors.

In our continuing quest for a potent and orally active inhibitor of 5-lipoxygenase, we were also interested in the 2,3-dihydrobenzofuranols, as an extension of our earlier work on the 4-benzofuranols.⁴ We now report our studies

Scheme I^a



a) Et₃SiH, TFA

in this area in which the structure–activity relationship of substitution pattern at positions 2, 3, 4, 5, and 6 are

* Department of Medicinal Chemistry.

† Department of Pharmacology.

§ Department of Biochemistry.

|| Department of Animal Drug Metabolism.

(1) For reviews on the leukotrienes, see: (a) Rokach, J., Ed. *Leukotrienes and Lipoxygenases Chemical, Biological and Clinical Aspects*; Elsevier: Amsterdam, 1989. (b) Taylor, G. W.; Clarke, S. R. The Leukotriene Biosynthetic Pathway a Target for Pharmacological Attack. *Trends Pharmacol. Sci.* 1986, 7, 100–103. (c) Sirois, P. Pharmacology of the Leukotrienes. *Adv. Lipid Res.* 1985, 21, 79–101.