Analgetic and Antiinflammatory 7-Aroylbenzofuran-5-ylacetic Acids and 7-Aroylbenzothiophene-5-ylacetic Acids[1]

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A number of 7-benzoylbenzofuran-5-ylacetic acids and 7-benzoylbenzothiophene-5-ylacetic acids were synthesized. The compounds were generally only $^1/_2$ to 3 times as potent as phenylbutazone in the rat paw edema antiinflammatory assay. However, they show greater activity as analgetic agents. The most active compound is 7-[4-(methylthio)-benzoyl]benzofuran-5-ylacetic acid (**5g**) having 57 times the potency of aspirin in the mouse writhing analgetic assay. This compound caused virtually no gastric ulceration in rats at doses of up to 90 mg/kg.

From previous work both in this laboratory and others it has been found that arylacetic and propionic acids that contain either a benzoyl functional group such as ketoprofen or indomethacin or a benzoyl group that is fused into a seven-membered ring as in the 3-substituted dibenzotropones,[2] 2- and 3-substituted dibenzoxepins,[3,4] 3-substituted dibenzothiepins,[5] and 3-substituted dibenzoazepines[6] have antiinflammatory or analgetic activity. It has been observed that when the benzoyl functional group is forced to be noncoplanar with the ring containing the acetic or propionic[5,7] acid that there is an increase of the biological activity. We hoped to achieve a similar type of effect by fusing a heterocyclic ring ortho to the benzoyl group. We report here the preparation and bioassays of 7-substituted benzofuran- and benzothiophene-5-acetic acids.

Chemistry. The compounds were synthesized as shown in Scheme I. Friedel–Crafts acetylation of 2,3-dihydrobenzofuran gave the 5-acetyl compound (**1**; X = O), which when treated under Wilgerodt conditions gave the acetic acid (**3**; X = O, R = H). Esterification of **3** under Fischer conditions gave the ethyl ester (**3**; X = O, R = Et). Friedel–Crafts acylation of the ethyldihydrobenzofuran acetate with either benzoyl chloride or *p*-chlorobenzoyl chloride using aluminum chloride catalysis gave only the desired 7-substituted compounds. When using either *p*-methoxybenzoyl chloride or *p*-(methylthio)benzoyl chloride it was necessary to use tin(IV) chloride as a catalyst. Several of these compounds were alkylated using lithium isopropylcyclohexylamide with methyl iodide to give the propionic analogues. Basic hydrolysis then gave the corresponding acids. Bromination (NBS) followed by a spontaneous dehydrobromination gave the benzofurans. The benzothiophene compounds (**5**; X = S) were made analogously (see Experimental Section).

Biological Activity. All of the compounds showed some activity in at least one of the assays and are reported in Table I. Some trends can be discerned by looking at the reported activities. Except for one compound (**7d**) the series has very little antiinflammatory activity (rat paw edema), usually in the range of 0.4–3 times phenylbutazone; however, there was rather high analgetic (phenylquinone writhing) activity throughout the series. It is apparent that the nature of the aroyl group in a series of arylacetic acids can have a marked effect on the ratio of antiinflammatory to analgetic potency (see ref 6). The factors that determined this ratio are not readily obvious. The saturated compounds had the least activity perhaps because the saturated five-membered ring does not bind to the active site in the same manner as an aromatic ring would. The increased activity of the benzofurans over the benzothiophenes maybe due to the active site having limitations to the size of ring system that it will accomodate. In the benzofuran series of compounds, changing the *p*-benzoyl substituent seems to have little effect on potency (cf. **5c,d,e,g**), except for **5f** and **5h**, which have greatly reduced activity. It is also interesting to note that the propionic acids do not have substantially more activity than the corresponding acetic acids. Because of high analgetic activity and extremely low ulcerogenic potential (see

Scheme I

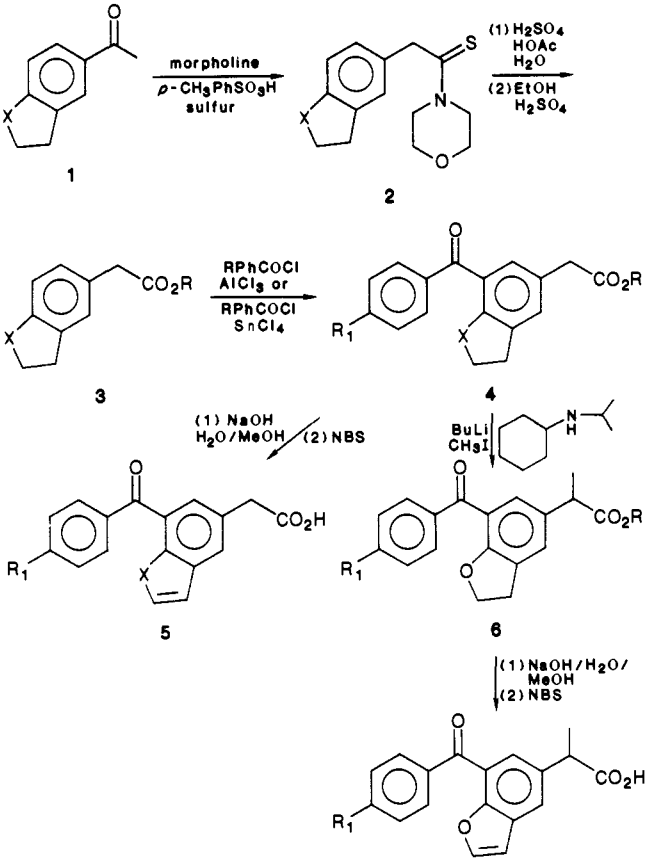

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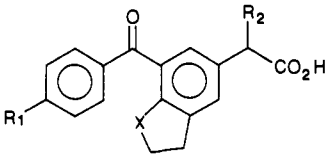
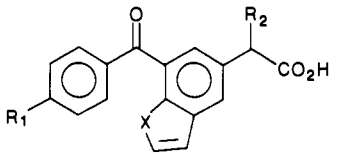
Table I. Biological Activities of Dihydrobenzofurans and Thiophenes



4a-f



5a-7d

compd	X	R_1	R_2	formula	yield, %	mp, °C	crystn solvent	anal.	rat paw assay (phenylbutazone = 1)	mouse writhing assay (aspirin = 1)	gastric errosion assay ED_{50}
4a	O	H	H	$C_{17}H_{14}O_4$	92	148–150	acetone/hexane	C, H	0.7 (0.3–2.4)[a]	0.25 (24)[b]	
4b	O	Cl	H	$C_{17}H_{13}ClO_4$	91	170–171	acetone/hexane	C, H	0.8 (0.03–4.7)[a]	7 (24)[b]	
4c	O	SCH_3	H	$C_{18}H_{16}O_4S$	91	150–152	acetone/hexane	C, H	0.2 (0–1.4)[a]	8 (24)[b]	
4d	S	H	H	$C_{17}H_{14}O_3S$	90	167–168	acetone/hexane	C, H	0.6 (0.2–1.1)[a]	<1 (24)[b]	
4e	S	Cl	H	$C_{17}H_{13}ClO_3S$	92	137–138	acetone/hexane	C, H	0.6 (0.2–1.6)[a]	0.6 (24)[b]	
5a	S	H	H	$C_{17}H_{12}O_3S$	63	152–153	acetone/hexane	C, H	0.4 (0.2–1.1)[a]	0.4 (24)[b]	
5b	S	Cl	H	$C_{17}H_{11}ClO_3S$	68	168–170	acetone/hexane	C, H	1.5 (18)[b]	7 (24)[b]	
5c	O	H	H	$C_{17}H_{12}O_4$	56	147–150	acetone/hexane	C, H	1.0 (0–4.4)[a]	40 (40)[b]	
5d	O	Cl	H	$C_{17}H_{11}ClO_4$	48	159–160	acetone/hexane	C, H	0.6 (0.2–2.0)[a]	33.9 (18.9–59.9)[a]	
5e	O	OCH_3	H	$C_{18}H_{16}O_5$	65	154–156	acetone/hexane	C, H	1.0 (0.05–3.2)[a]	33 (24)[b]	
5f	O	$SOCH_3$	H	$C_{18}H_{14}O_5S$	77	145–147	acetone/hexane	C, H	1.8 (18)[b]	7.5 (2.2–32)[a]	
5g	O	SCH_3	H	$C_{18}H_{14}O_4S$	51.5	153–154	acetone/hexane	C, H	3 (0.7–77.6)[a]	57 (43–78)[a,f]	≥90
5h	O	SO_2CH_3	H	$C_{18}H_{14}O_6S$	11	149–151	acetone/hexane	C, H	NT[e]	<1 (24)	
7a	O	H	CH_3[c]	$C_{18}H_{14}O_4$	43	114–116	acetone/hexane	C, H	1.8 (0.1–10.4)[a]	42.4 (22.4–79.6)[a]	
7b[d]	O	Cl	CH_3[c]	$C_{36}H_{29}CaCl_2O_{10.5}$	53	165	methanol/water	C, H	2.0 (0.7–7.3)[a]	42.9 (28.2–68.4)[a]	
7c[d]	O	OCH	CH_3[c]	$C_{38}H_{30}CaO_{10}$	52	185–193	methanol/water	C, H	1.3 (0.8–2.2)[a]	45 (24)[b]	
7d	O	SCH_3	CH_3	$C_{18}H_{16}O_4S$	55	132–134	acetone/hexane	C, H	18.6 (9.3–41.5)[a]	25 (24)[b]	≤1
zomepirac									NT[e]	40[g]	10 mg/kg
indomethacin									16	60[h]	3–6 mg/kg

[a] 95% confidence limits. [b] Number of animals. [c] Racemic. [d] Tested as calcium salt. [e] Not tested. [f] ED_{50} = 1.2 mg/kg. [g] ED_{50} = 1.75 mg/kg. [h] ED_{50} = 1.16 mg/kg.

Table I) relative to other known analgetic agents, compound **5g** was selected for further biological evaluation.[8]

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. NMR spectra were obtained in deuteriochloroform unless otherwise stated, using Me_4Si as an internal standard, on Varian A60, HA 100, and EM 390 and Bruker WM 300 instruments. Chemical shifts and coupling constants are given to the nearest 0.1 Hz; NOE and resolution-enhancement experiments were run in the standard manner. Micro analytical data were within ±0.4% of theory unless otherwise stated.

2,3-Dihydrobenzothiophene was prepared from thianaphthene by the method of Bordwell et al.,[9,10] and the resulting oil was used without distillation.

5-Acetyl-2,3-dihydrobenzofuran (1a; X = O). To a solution of 2,3-dihydrobenzofuran (50.0 g, 0.41 mol) in CH_2Cl_2 (300 mL) at −10 °C was added dropwise a solution of acetyl chloride (54.8 mL, 0.77 mol) and $AlCl_3$ (54.8 g, 0.41 mol) in CH_2Cl_2 (200 mL) while maintaining the temperature below −6 °C. After addition was complete the reaction was stirred an additional 30 min at −6 °C, then added to ice (1200 mL)/concentrated HCl (200 mL) and extracted with CH_2Cl_2. The extract was dried, treated with charcoal, and evaporated, and the residue was recrystallized from hexane: yield, 59.8 g (88%); mp 61–63 °C. In a similar manner the thio analogue (**1b**; X = S) was prepared and purified by silica gel chromatography (Et_2O/hexane, 10:90) to give the product as an oil (49%).

2-(2,3-Dihydrobenzofuran-5-yl)acetothiomorpholide (2a; X = O). The acetyl compound (**1a**) (29.5 g, 0.18 mol) was heated at reflux in a mixture of morpholine (22.0 mL, 0.25 mol), sulfur (5.8 g, 0.18 mol), and *p*-toluenesulfonic acid (0.85 g, 0.004 mol) for 5 h. The reaction mixture was cooled to room temperature and, 90 mL of methanol was added. The solution was cooled in ice and filtered: yield, 24.1 g (50.3%); mp 146–149 °C. Anal. ($C_{14}H_{17}NO_2S$) C, H. Similarly, **2b** (X = S): mp 155–161 °C. Anal. Calcd for ($C_{14}H_{17}NOS_2$): C, 60.17; H, 6.13; N, 5.01. Found: C, 59.38; H, 6.02; H, 4.98.

2,3-Dihydrobenzofuran-5-ylacetic Acid (3a; X = O, R = H). The thiomorpholide (**2**; X = O) (48 g) was heated at reflux in a mixture of HOAc (200 mL), H_2SO_4 (30 mL), and H_2O (49 mL) for 4 h. The solution was added to water (1000 mL) and extracted with EtOAc, and the product was recrystallized from

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acetone/hexane: yield, 22.8 g (70%); mp 96–98 °C. Anal. ($C_{10}H_{10}O_3$) C, H. Similarly, **3b** (X = S): 78% yield; mp 132–143 °C. Anal. ($C_{10}H_{10}O_2S$) C, H.

Ethyl 2,3-Dihydrobenzofuran-5-ylacetate (3a; X = O, R = Et). The acid (**3**; X = O) (44 g) was heated at reflux for 3 h in a mixture of toluene (1200 mL), ethanol (240 mL), and concentrated H_2SO_4 (3 mL) with the azeotropic removal of H_2O. The reaction was then added to H_2O and the product extracted with EtOAc: yield, 49.8 g (97%) as an oil that was used without further purification. In a similar manner the thio analogue (**3b**; X = S, R = Et) was prepared as an oil and used without further purification.

Ethyl 7-[4-(Methylthio)benzoyl]-2,3-dihydrobenzofuran-5-ylacetate (4; X = O, R = Et, R_1 = SCH_3). The ethyl dihydrobenzofuranacetate (**3**; X = O, R = Et) (10.0 g, 0.049 mol) was dissolved in CH_2Cl_2 (120 mL); to this was added 4-(methylthio)benzoyl chloride (9.0 g, 0.049 mol) and $SnCl_4$ (11.5 mL, 0.137 mol), and this was heated at reflux for 2 h. The mixture was added to ice (400 g) and HCl (100 mL), then extracted with CH_2Cl_2. The crude product was chromatographed on silica gel (EtOAc/hexane, 25:75) to produce 9.8 g (56.7%) of **4** (X = O, R = Et, R_1 = SCH_3) as an oil.

7-[4-(Methylthio)benzoyl]-2,3-dihydrobenzofuran-2-ylacetic Acid (4c). Ethyl 7-[4-(methylthio)benzoyl]-2,3-dihydrobenzofuran-5-yl acetate (9.8 g, 0.0275 mol) was heated at reflux in a mixture of MeOH (40 mL), H_2O (120 mL), and NaOH (4 g, 0.1 mol). After 2 h the solution was cooled to room temperature, washed with Et_2O, and made acidic with dilute HCl. The product was extracted with EtOAc and recrystallized from acetone/hexane: yield, 8.0 g (91%); mp 150–152 °C; NMR (acetone-d_6) δ 2.52 (s, 3 H, SCH_3), 3.23 (br t, 1 H, J = 6.6, 0.9, 0.6 Hz, 3-H), 3.56 (s, 2 H, CH_2CO_2), 4.57 (t, 2 H, J = 6.6 Hz, 2-H), 7.26 (dd, 1 H, J = 1.9, 0.8 Hz, 6-H), 7.31 (dd, 1 H, J = 1.9, 1.1 Hz, 4-H) (see ref 11). Anal. ($C_{18}H_{16}O_4S$) C, H.

7-(4-Chlorobenzoyl)-2,3-dihydrobenzothiophene-5-ylacetic Acid (4e). The ethyl dihydrobenzothiopheneacetate (**3**; X = S, R = Et) (3.0 g, 0.0135 mol) was dissolved in CS_2 (45 mL), and the solution was added to a solution of benzoyl chloride (1.65 mL, 0.0135 mol) and $AlCl_3$ (5.4 g, 0.04 mol) in CS_2 (45 mL) and heated at reflux for 2 h. The mixture was added to ice and extracted with CH_2Cl_2. The crude product was chromatographed on silica gel (EtOAc/hexane, 25:75) to afford 1.5 g (34%) of the ester, which upon basic hydrolysis as previously described gave the acid **4d** (27%): mp 167–169 °C (acetone/hexane). Anal. ($C_{17}H_{13}ClO_3S$) C, H. Similarly, **4a**: mp 148–150 °C. Anal. Calcd for ($C_{17}H_{14}O_4$): C, 72.33; H, 4.99 Found: C, 71.66; H, 5.00. **4b**: mp 170–171 °C. Anal. ($C_{17}H_{13}ClO_4$) C, H. **4d**: mp 167–169 °C. Anal. ($C_{17}H_{14}O_3S$) C, H.

7-[4-(Methylthio)benzoyl]benzofuran-5-ylacetic Acid (5g). 7-[4-(Methylthio)benzoyl]-2,3-dihydrobenzofuran-5-ylacetic acid (4.1 g, 0.0125 mol) was dissolved in CCl_4 (450 mL), and to the solution was added *n*-bromosuccinimide (2.1 g, 0.0122 mol) and a catalytic amount of dibenzoyl peroxide, and the mixture was heated at reflux for 2 h, cooled to room temperature, filtered, and evaporated. The crude product was chromatographed on silica gel eluting with hexane/EtOAc/HOAc (60:40:2) to give, after recrystallization, 2.1 g (51.5%): mp 153–154 °C (acetone/hexane); NMR (Me_2SO-d_6) δ 2.55 (s, 3 H, SCH_3), 3.76 (s, 2 H, CH_2CO_2), 7.04 (d, 1 H, J =2 Hz, 3-H), 7.38 (d, 2 H, J = 8 Hz, aromatic), 7.42 (d, 1 H, J = 1.6 Hz, 6-H), 7.69 (d, 2 H, J = 8 Hz, aromatic), 7.81 (d, 1 H, J = 1.6 Hz, 4-H), 8.0 (d, 1 H, J = 2 Hz, 2-H) (see ref 11). Anal. ($C_{18}H_{14}O_4S$) C, H. Similarly, compounds **5a–f** were prepared. **5a**: mp 152–153 °C. Anal. ($C_{17}H_{12}O_3S$) C, H. **5b**: mp 168–170 °C. Anal. ($C_{17}H_{11}ClO_3S$) C, H. **5c**: mp 147–150 °C. Anal. ($C_{17}H_{12}O_4$) C, H. **5d**: mp 159–160 °C. Anal. Calcd for ($C_{17}H_{11}ClO_4$): C, 64.87; H, 3.52. Found: C, 63.73; H, 3.59. **5e**: mp 154–156 °C. Anal. ($C_{18}H_{16}O_5$) C, H. **5f**: mp 145–147 °C. Anal. ($C_{18}H_{14}O_5S$) C, H. **5h**: mp 149–151 °C. Anal. ($C_{18}H_{14}O_6S$) C, H.

7-[4-(Methylsulfonyl)benzoyl]benzofuran-5-ylacetic Acid and 7-[4-(Methylsulfinyl)benzoyl]benzofuran-5-ylacetic Acid. Compound **5g** (2.1 g, 0.0064 mol) was heated at reflux in a mixture of toluene (120 mL), ethanol (15 mL), and H_2SO_4 (0.2 mL) with the azeotropic removal of H_2O. After 3 h the solution was added to H_2O and extracted with Et_2O to give 2.2 g of ethyl 7-[4-(methylthio)benzoyl]benzofuran-5-ylacetate. The above ester (2.2 g, 0.0062 mol), was dissolved in $CHCl_3$ (50 mL) and heated at reflux with *m*-chloroperoxybenzoic acid (MCPBA) (1.06 g, 0.0061 mol) for 3 h at which point additional MCPBA (0.30 g, 0.0017 mol) was added, and after an additional 3 h of reflux the solution was added to H_2O. The organic phase was washed with 10% $NaHSO_3$ solution and 10% $NaHCO_3$ solution and dried and evaporated. The crude product was chromatographed on silica gel (30:70 EtOAc/hexane gradient dilution to 100% EtOAc) to give, after basic hydrolysis, the sulfone **5h** (252 mg, 11%), mp 149–151 °C (acetone/hexane), and the sulfoxide **5f** (1.7 g, 77%), mp 145–147 °C (acetone/hexane).

(*d*,*l*)-2-(7-[4-(Methylthio)benzoyl]-2,3-dihydrobenzofuran-5-yl)propionic Acid (6; R = Et, R_1 = SCH_3). A 1.6 M solution of *n*-BuLi in hexane (24.07 mL, 0.038 mol) was added to isopropylcyclohexylamine (6.84 mL, 0.041 mol) in THF (40 mL) at 0 °C. After 30 min the solution was cooled to −78 °C and ethyl 7-[4-(methylthio)benzoyl]-2,3-dihydrobenzofuran-5-ylacetate was added (**4**; R = Et, R_1 = SCH_3) (13.1 g, 0.037 mol) dissolved in THF (150 mL). After 30 min MeI was added (3.5 mL, 0.056 mol), and the reaction was stirred at −78 °C for 2 h, allowed to warm to room temperature, added to H_2O, and extracted with EtOAc. The crude product was chromatographed on silica gel (EtOAc/hexane, 25:75) to afford 9.7 g (71%) of the ester, which upon basic hydrolysis and recrystallization gave the above-named product: yield, 8.6 g (96%); mp 144–148 °C (acetone/hexane).

(*d*,*l*)-2-(7-[4-(Methylthio)benzoyl]benzofuran-5-yl)propionic Acid (7d). To a solution of **6** (R = Et, R_1 = SCH_3) in CCl_4 (1200 mL) was added NBS (5.8 g, 0.032 mol) and a catalytic quantity of dibenzoylperoxide. The mixture was heated at reflux for 2 h, cooled to room temperature, filtered, and evaporated. Chromatography on silica gel (30:70:2 EtOAc/hexane/HOAc) was performed and gave **7d** (5.8 g, 55%): mp 132–134 °C (acetone/hexane). Anal. ($C_{18}H_{16}O_4S$) C, H. **7a**: mp 114–116 °C. Anal. Calcd for ($C_{18}H_{14}O_4$): C, 73.46; H, 4.79. Found: C, 72.24; H, 4.19. **7b**: mp 165 °C. Anal. ($C_{36}H_{29}CaCl_2O_{10.5}$) C, H; **7c**: mp 185–193 °C. Anal. ($C_{38}H_{30}CaO_{10}$) C, H.

Inhibition of Carrageenan-Induced Paw Edema. This was carried out essentially as described in a previous publication[2] (see also ref 12). Thus, 80–90-gram female rats were given the test agent orally 1 h prior to the injection of 0.05 mL of 1% carrageenan into the right hindpaw. The test agents were in a vehicle containing 0.9% sodium chloride, 0.5% sodium carboxymethyl cellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol, and 97.3% distilled water. The rats were sacrificed 4 h after drug administration, and both hindpaws were excised and weighed separately. The potencies relative to phenylbutazone were determined by dose–response plots of the mean percent increase in weight of the treated over the nontreated paw. Six rats were used for each dose group. Relative potencies were calculated according to standard statistical procedures employing an analysis of variance.[13] The dose–response curves for the test materials and reference standard were linear and parallel. At least four dose levels were used to obtain the dose–responses on which the relative potencies are based.

Inhibition of Phenylquinone-Induced Writhing. The assay was performed as described in ref 14, modified as described in ref 2. Thus, 18–20-g male mice were given the test agent orally in the aqueous vehicle noted above, 20 min prior to an intraperitoneal injection of phenylquinone. The mice were observed for the next 10 min, and the potencies, relative to aspirin, were

(11) Unexpectedly, the resonance of the H-6 was upfield from that of the H-4. The relative positions of the two protons were determined by using the NOE difference technique. This upfield shift of the H-6 is probably due to the benzoyl ketone being out of plane of the aromatic ring (see ref 5). Long-range couplings were observed between the H-3 and H-4 and H-3 and H-6 in compound **4c** in the resolution-enhanced 300-MHz ^1H NMR.

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determined as described above. Eight mice were used for each dose group.

Chronic Gastrointestinal Erosive Activity. This assay was effected as described by Rooks et al.[15,16] Thus, male rats weighing 190–220 g (Cox/SD obtained from Laboratory Supply Co., Indianapolis, IN) were acclimated for ca. 1 week. The animals (groups of 5 rats/dose) were given the test material po daily in phosphate-buffered saline (1 mL/100 g of body weight) for 7 consecutive days. One day after the last dose, the rats were sacrificed. Body weights were obtained on the first day of dosing and at sacrifice. Food, but not water, was removed from the cages in the last day of dosing. At necropsy, the stomach and small intestine were removed from each rat and examined blindly for lesions, which were scored as follows:

focal		diffuse
0	no gastric changes	
1	minimal, rare	2
3	slight, low, few	4
5	moderate, medium, several	6
7	marked, severe, many	8

In addition, a score of 10 was assigned to those rats that died during the test from complications due to gastrointestinal erosion. The scores for each rat ranged from 0 to 10; the scores for each dosage group ranged from 0 to 50. Arbitrarily, the dose giving a score of 5 (1/rat) was assigned as the minimum effective dose and that dose giving a score of 25 (5/rat) was the median effective erosive dose.

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Registry No. **1a** (X = O), 90843-31-5; **1b** (X = S), 7019-66-1; **2a** (X = O), 97483-11-9; **2b** (X = S), 34104-91-1; **3a** (X = O, R = H), 69999-16-2; **3a** (X = O, R = CH_3CH_2), 69999-18-4; **3b** (X = S, R = H), 34104-86-4; **3b** (X = S, R = CH_3CH_2), 104172-39-6; **4a**, 97483-15-3; **4b**, 97483-16-4; **4c**, 97483-14-2; **4c** (ethyl ester), 97483-12-0; **4d**, 104172-31-8; **4e**, 97483-28-8; **5a**, 104172-32-9; **5b**, 97483-27-7; **5c**, 97483-18-6; **5d**, 97483-23-3; **5e**, 97483-19-7; **5f**, 104172-33-0; **5g**, 97483-17-5; **5g** (ethyl ester), 104172-37-4; **5h**, 104172-34-1; (±)-**6a**, 97483-21-1; (±)-**6b**, 97483-22-2; (±)-**6c**, 104172-38-5; (±)-**6d**, 97509-14-3; (±)-**6d** (ethyl ester), 97483-13-1; (±)-**7a**, 97483-24-4; (±)-**7b**, 104172-35-2; (±)-**7c**, 104172-36-3; (±)-**7d**, 97483-25-5; 2,3-dihydrobenzofuran, 496-16-2; 4-(methylthio)benzoyl chloride, 1442-06-4; 4-chlorobenzoyl chloride, 122-01-0.

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Synthesis and Antiallergic Activity of a Novel Series of 5-Lipoxygenase Inhibitors

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A series of novel substituted [[(phenoxymethyl)phenyl]amino]oxoalkanoic acid esters have been synthesized. These compounds were tested in vitro for their ability to inhibit the synthesis of 5-hydroxyeicosatetraenoic acid and leukotriene (LT) B_4 from rat polymorphonuclear leukocytes (PMN) and in vivo as inhibitors ovalbumin- (OA) and LTD_4-induced bronchospasm in the guinea pig. Compounds **5–12** and **25** had IC_{50}'s between 1 and 5.6 μM in the rat PMN 5-lipoxygenase assay. Compounds **1**, **3**, and **16** inhibited OA-induced bronchoconstriction (61%, 64%, and 57%, respectively), but only **1** showed activity against LTD_4-induced bronchoconstriction. When tested against LTD_4-induced contraction of isolated guinea pig tracheal spiral strips, **1** was a competitive inhibitor with a pK_B of 4.94.

Slow reacting substance of anaphylaxis (SRS-A) has long been known as an important mediator of anaphylactic and other immediate hypersensitivity reactions.[1] It is now believed that leukotriene (LT) C_4, LTD_4, and LTE_4 account for the biological properties of SRS-A.[2] LTs are derived from arachidonic acid via the 5-lipoxygenase (LO) biosynthetic pathway and are classified as the cysteine-containing LTs (LTC_4, LTD_4, LTE_4, and LTF_4) and the nonpeptidic LTs of which LTB_4 has stimulated the most interest. In vitro LTB_4 is a potent chemotactic agent and aggregating substance for migrating cells and stimulates cell accumulation and increases vascular permeability in vivo.[3] LTC_4 and LTD_4 induce smooth muscle contraction and constriction of small airways, promote secretion of mucus, enhance leakage from postacpillary venules, and cause vasoconstriction and edema formation.[4] The ubiquitous nature of LTs coupled with the variety and potency of their actions justifies the search for agents that block their actions and/or their synthesis.

The first reported antagonist of SRS-A was FPL-55712[5] (Figure 1). Since its discovery in 1973 FPL-55712 has been used extensively to delineate the role of cysteine-containing LTs in allergic responses of animals and man.[6] Over the last 12 years many analogues of FPL-55712 have been prepared for which LT antagonism is claimed.[7,8] With few exceptions, these analogues were obtained through substantial modification of the chromone side of the bisaryl system of FPL-55712 while retaining the hydroxyacetophenone moiety. For example, Wy-44,329 (Figure 1), which inhibits bronchoconstriction in the guinea pig induced by either LTC_4, LTD_4, or ovalbumin (OA), contains the hydroxyacetophenone fragment but employs a trisubstituted benzene ring in place of the chromone ring.[9]

In 1981 Kadin revealed that certain meta-substituted (phenylamino)-4-oxobutanoic acid derivatives (e.g., Pfizer, Figure 1) antagonized the effects of SRS-A,[10] although no

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