Nonsteroidal Antiinflammatory Agents. 1. 10,11-Dihydro-11-oxodibenz[b,f]oxepinacetic Acids and Related Compounds¹

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10,11-Dihydro-11-oxodibenz[b,f]oxepinacetic acids and related compounds were synthesized as potential antiinflammatory agents. Among them, 2-(8-methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl)propionic acid (16b) and its thiepin analogue (16c) showed excellent antipyretic activity together with potent antiinflammatory and analgesic properties in biological tests. Structure-activity relationships are discussed.

In recent years a number of arylacetic acid derivatives have been reported to possess potent antiinflammatory activity in animal tests,² and several of them have been clinically used.³ Shen⁴ has proposed a hypothetical antiinflammatory receptor site for indomethacin-type nonsteroidal agents, and for optimal receptor interaction, the two aromatic rings in a molecule should be out of plane. We, therefore, carried out the synthesis of the arylacetic acid derivatives containing tricyclic systems, such as dibenz[b.f]oxepin and dibenzo[b.f]thiepin, their 10,11-dihydro-11-oxo and 10,11-dihydro-11-hydroxy analogues, and 10,11-dihydro-11-oxodibenz[b,f][1,4]oxazepin, in which the two benzene rings are held in a noncoplanar orientation by the two-atom bridge, and subjected them to biological tests. Consequently, it was found that 2-(8-methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl)propionic acid (16b) and its thiepin analogue (16c) were highly active as



antiinflammatory, analgesic, and antipyretic agents. Based on these data, they have been selected for further study.

Recently, the Nippon Chemiphar group has reported an analogous study in a patent⁵ independently of our work.⁶

Chemistry. Dibenz[b,f]oxepinacetic acid derivatives (8-10) have been synthesized by the route shown in Scheme I. Ullmann reaction between 2-iodobenzoic acids 1 and ethyl hydroxybenzoates 2 gave the diphenyl ethers 3, which were reduced with lithium aluminum hydride to afford the diols 4. On chlorination, followed by reaction with sodium cyanide, 4 gave the bis(cyanomethyl) derivatives 6. Hydrolysis of 6 and subsequent cyclization with

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polyphosphoric acid (PPA) gave 10,11-dihydro-11-oxodibenz[b,f]oxepinacetic acids 8. Reduction of 8 with sodium borohydride gave the 11-ol derivatives 9, which were dehydrated with PPA to afford dibenz[b,f]oxepinacetic acids 10.

Dibenz[$b_{,f}$]oxepin- and dibenzo[$b_{,f}$]thiepinpropionic acid derivatives (16-18) have been synthesized by the general route shown in Scheme II. Ullmann reaction between 2-iodoacetophenones 11 and 4-substituted phenylpropionates 12 gave the diphenyl ethers and thioether 13, which were subjected to Willgerodt reaction, followed by acid hydrolysis, to afford the dicarboxylic acids 15. Cyclization of 15 gave the propionic acids 16, which were converted into the 11-ols 17 and their dehydrated products 18 in the similar procedure mentioned above.

Dibenz[b,f][1,4]oxazepin derivatives 25 were prepared from o-bromonitrobenzene 19 and hydroxyphenylpropionates 20, which were subjected to Ullmann reaction and then hydrogenation to afford the diphenyl ethers 22 (Scheme III). Treatment of 22 with phosgene, followed by cyclization with aluminum trichloride (AlCl₃), afforded

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the oxazepinpropionates 24, which were converted to the acids 25 by hydrolysis.

Pharmacological Results and Discussion

The antiinflammatory and analgesic activities of the compounds obtained in this study were initially measured using the carrageenan paw edema and the phenylquinone writhing assays, respectively (see the Experimental Section). Median effective doses (ED_{50}) were determined for the compounds that showed activity at 80 mg/kg for the former and at 100 mg/kg for the latter.

As to the antiinflammatory activity, 10,11-dihydro-11oxodibenz[b,f]oxepin-2-acetic acid (8a) was far more potent than the 3-acetic acid 8f. The introduction of a halogen atom on the benzene ring of 8a caused a decrease of the activity (e.g., 8b-d). However, the introduction of a methyl group at the 8-position of 8a increased the potency significantly (e.g., 8e). When a methyl group was introduced to the α -position of the acetic acid moiety of 8a, the potency increased markedly (e.g., 16a), but in the case of the 8-methyl analogue 8e, which had potent activity, such introduction did not produce a marked change in potency



(e.g., 16b). Replacement of the oxygen atom in the 5position of 16b by the often bioisosteric sulfur atom led, as expected, to a similar order of potency as the parent (e.g., 16c).

Variation in the center ring of the 10,11-dihydro-11oxodibenz[b,f]oxepin and -dibenzo[b,f]thiepin nuclei tended to reduce the antiinflammatory activity. Reduction of the oxo group in the 11-position to an hydroxy group (e.g., 9 and 17) and the introduction of a double bond between the 10- and 11-position (e.g., 10 and 18) dramatically caused a decrease or elimination of the activity. The dibenz[b, f][1,4]oxazepinacetic acid derivatives 25, in which the methylene group at the 10-position of the 10.11-dihydro-11-oxodibenz[b,f]oxepin nucleus is replaced by an amino group, also did not retain any potency. These facts suggest that although the conformational structure to satisfy the requirements of Shen's receptor model may be very important in determining the activity at the site of action, the overall in vivo activity is also affected by pharmacodynamics and other factors.

As to the analgesic activity, 8a, 8e, 10b, and 16a-c showed potent activity. Therefore, it is suggested that the structural requirements for this activity in general seem to be parallel to those for the antiinflammatory activity. There was, however, one case (e.g., 10b) for which the analgesic potency would not have been correctly predicted on the basis of this parallelism.

In consideration of the efficacy of the compounds in both assays, **16b** and **16c** were selected for further pharmacological tests. The results obtained are shown in Table III. Measurement was made of the effect on the ultravioletinduced erythema in guinea pigs for antiinflammatory activity. Both compounds were considerably more potent Table I. Chemical Data on Various Intermediates



^a All compounds were analyzed for C, H, N, S, and halogen; analytical results were within ±0.4% of the theoretical values.

than indomethacin. As for the analgesic activity measured according to the acetic acid induced writhing and silver nitrate induced arthritic pain method, they were comparable or more active than indomethacin. The antipyretic activity was also examined in yeast-induced fever assay. They were at least ten times as potent as indomethacin. In addition, the induction of gastric ulcers was tested, and they tended to be less potent than indomethacin. They had far lower acute toxicity as compared with indomethacin.

From the pharmacological and toxicological points of view, 16b and 16c showed good potential as antiinflammatory, analgesic, and antipyretic agents. In particular, their antipyretic activities would be the strongest among the existing drugs. Further studies are in progress and will be published elsewhere.

Experimental Section

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured on a Hitachi EPI-S2 spectrometer. Organic extracts were dried over MgSO₄.

Ethyl (2'-Carboxyphenoxy)benzoates (3). A mixture of 1 (0.04 mol), 2 (0.04 mol), K_2CO_3 (8.3 g, 0.06 mol), and Cu (0.2 g) in nitrobenzene (13 mL) was heated at 140–150 °C with stirring for 30 min. After the addition of H_2O , the mixture was made acidic with dilute HCl and extracted with CHCl₃. The CHCl₃ layer was extracted with aqueous NaHCO₃ and then the extract was made acidic with dilute HCl and extracted with CHCl₃. The CHCl₃ layer was dried and concentrated. The crude product, if solid, was recrystallized; if an oil, it was purified by chromatography on silica gel with CHCl₃-MeOH (10:1).

[2'-(Cyanomethyl)phenoxy]benzyInitriles (6). A solution of 3 (0.1 mol) in dry tetrahydrofuran (THF; 100 mL) was added to a stirred suspension of lithium aluminum hydride (7.6 g, 0.2 mol) in dry THF (250 mL) at room temperature. The mixture was heated under reflux with stirring for 4 h and then cooled and treated with H_2O . The resulting mixture was concentrated, and to the residue was added dilute HCl. The solution was extracted with CHCl₃, and the extract was dried and concentrated. The oily residue (4) was used for the next step without further purification.

To a solution of crude 4 in $CHCl_3$ (150 mL) was added thionyl chloride (36 g, 0.3 mol) dropwise at room temperature, and the mixture was heated under reflux for 1 h and concentrated. To the residue was added dilute NH_4OH , and the mixture was extracted with toluene. The extract was dried and concentrated to give crude 5 as an oily product, which was used for the next step.

A solution of crude 5 and sodium cyanide (12 g, 0.2 mol) in a mixture of dioxane (90 mL), EtOH (90 mL), and H_2O (45 mL) was heated under reflux for 6 h and concentrated. To the residue was added toluene, and the solution was dried and concentrated. The crude product, if solid, was recrystallized from ether; if an oil, it was purified by chromatography on silica gel with CHCl₃-hexane (1:2): IR (film) ν 2250 (C=N) cm⁻¹.

[2'-(Carboxymethyl)phenoxy]phenylacetic Acids (7). A solution of 6 (0.1 mol) and KOH (40 g, 0.71 mol) in a mixture of EtOH (300 mL) and H_2O (75 mL) was heated under reflux with stirring for 16 h, and EtOH was removed in vacuo. The residue was acidified with HCl and extracted with CHCl₃. The extract was washed with H_2O , dried, and concentrated. The residue was recrystallized from EtOH and toluene to give 7.

2-[4-[2'-(Carboxymethyl)phenoxy(or phenylthio)]phenyl]propionic Acids (15). A mixture of 11 (0.05 mol), 12 (0.05 mol), K_2CO_3 (6.8 g, 0.05 mol), and Cu (1.0 g) in pyridine (15 mL) was heated at 140-150 °C with stirring for 3 h. After the mixture was cooled, CHCl₃ was added. The resulting solution was washed with dilute HCl and H₂O, dried, and concentrated to give crude 13 as an oily product.

To crude 13 were added sulfur (2.2 g, 0.069 mol) and morpholine (8.5 g, 0.1 mol), and the resulting mixture was heated at 140-150

ma. ^c PQW = phenyl-	CPE = carrageenan paw ede	etical values. 🧳	thin ±0.4% of the theor se ref 15.	esults were wi m ether. ^g Se	analytical r E = petroleu	, H, N, S, and halogen; mits. ^e See ref 5. ^f P	ds were analyzed for C g. ^d 95% confidence li	ll compoun ne writhing	a A quinc
0.62 (0.61-0.63)	3.30 (2.10-7.30)		-				I	nethacin	indor
>100	>80	C ₁₅ H ₁₁ NO ₄	dil MeOH	223 - 224	87		$3-CH_2CO_2H$		25c
>100	> 80	C ₁₆ H ₁₃ NO ₄	dil MeOH	205 - 206	96		2-CH(CH ₃)CO ₂ H		25b
>100	>80	C ₁₅ H ₁₀ NO	dil MeOH	241-242	68		2-CH ₃ CO ₃ H		25a
>100	>80	$C_{1a}H_{1b}SO_2$	ether-PE	120 - 123	25	$2-CH(CH_3)CO_2H$	8-CH	s	18c
>100	>80	C ₁₈ H ₆ O	toluene	158 - 160	15	$2-CH(CH_3)CO_2H$	8-CH ₃	0	18b
>100	≥80	C ₁₇ H ₁₆ O ₃	toluene	162 - 164	16	$2-CH(CH_3)CO_2H$	Н	0	18 a
>100	>80	C ₁₆ H ₁₂ O ₃	toluene	169 - 171	44	$3-CH_2CO_2H$	H	0	10f
	>80	C ₁₇ H ₁₄ O ₃	acetone	175-179	15	$2 - CH_{3} CO_{3} H$	8-CH ₁	0	10 e
>100	>80	C,"H,"FO,	EtOH	212 - 214	68	$2 - CH_{3}CO_{3}H$	8-F	0	10d
>100 `	>80	C, H, CIO	dil EtOH	195-197	83	2-CH,CO,H	8-CI	0	10c
9.53 (5.34-17.0)	61.4(15.8-239)	C, H, CIO	THF-ether	210 - 213	68	2-CH,CO,H	7-CI	0	10b
>100	28.3 (20.2-39.6)	Ċ, H, O	toluene-EtOH	193 - 195	56	2-CH,CO,H	, H	0	$10a^g$
>100	>80	$C_{H}^{1}O_{S}^{1}$	$ether-PE^{f}$	180-182	87	2-CH(CH,)CO,H	8-CH.	0 00	17c
× 100	× × ×	$C_{17}^{17}H_{0}^{4}$			66	2-CH(CH)CO H	8-CH		176
100	> 80		toluene-EtOH	144-147	51 2	9-CH/CH JCO H	H		17a 17a
>100	> 80		ether	101-001	0.) 0.)	2-CH ² CO ² H	8-CH ₃	0	9e
>100	> 80	$\tilde{\mathbf{C}}_{\mathbf{h}} \tilde{\mathbf{H}}_{\mathbf{h}} \tilde{\mathbf{F}} 0_{\mathbf{q}}$	dil EtOH	161 - 162	80	2-CH ₂ CO ₂ H	8-F	0	P6
>100	>80	C ₁₆ H ₁₃ ClO	dil EtOH	184 - 185	86	$2-CH_2CO_2H$	8-CI	0	9c
>100	>80	C,"H,"CIO	toluene-MeOH	130-132	79	$2-CH_{3}CO_{3}H$	7-CI	0	6
44.6 (13.7-146)	24.3(8.73-67.6)	Ċ, H, O,	toluene-EtOH	172 - 174	72	2-CH,CO,H	Н	0	9a
3.10(1.42-6.76)	2.08(1.29 - 3.36)	C, H, O,S	toluene	157-159	63	2-CH(CH,)CO,H	8-CH	S	16c
6.51(2.44-17.4)	3.38(2.17 - 5.27)	C,H,O,	toluene	128 - 129	64	2-CH(CH,)CO,H	8-CH,	0	16b
17.8 (4.19-75.2)	3.65(1.65-8.08)	$C_{L}^{M}H_{L}^{12}O_{L}^{4}$	toluene	152 - 154	70	2-CH(CH,)CO,H	H	0	01 16a ^e
≥100 ≥100	569(140-231)	$C H O^{4}$	toluene	143-145	56	3-CH ² CO ¹ H	H H	C	e e
>100 138(573-744)	≶80 2 20 (1 00-4 82)		all EtOH toluene-EtOH	11/1-119 154-155	008	2-CH ₂ CO ₂ H 2-CH CO H	8-CH		
≥100 ≥100	× 80	C ₁₆ H ₁₁ ClO	EtOH	191-193	85 00	$2-CH_2CO_2H$	5.	00	8 8
>100	10.8 (3.44-34.0)~ ≥80	C,H ¹² Co	toluene-bton EtOH	183-185	00 65	2-CH ₂ CO ₂ H 2-CH ₂ CO ₂ H	7-CI	00	sa 8b
M & I	3		Lecty sul solvent	urp, c	yıtıtı, /o	1 L 2	I n I	4	.01
g/kg po	ED _{so} , m				2	ł	ſ	;	
		62		9, 17		8, 16			
			10, 18	HO	10				
	R1	ZI	Ř ₂ Ř ₁ – R2	ſ	- R2 R2	K 9 10 1			
	Ł			2		B C C C C C C C C C C C C C C C C C C C			
					Ĩ				
			X		4	× %			

Table II. Chemical and Pharmacological Data on Tricyclic Acetic Acids

				, ^{сн}	CHICH	l ₃)CO2H			
				ED 50,	∩ mg/kg po			gastric ulcer	
no.	x	CPE <i>a</i> (rats)	UV erythema (guinea pigs)	PQW ^b (mice)	acetic acid writhing (rats)	AgNO ₃ pain (rats)	yeast fever (rats)	UD _{so} , mg/kg (rats), po	LD ₅₀ , mg/kg (rats), po
16b	0	3.38	0.30	6.51	0.28	2.60	0.021	13.8	147
16 c	ß	$(2.17-5.27)^{\circ}$ 2.08	(0.079 - 1.10) 0.85	(2.44-17.4) 3.10	(0.128-0.591) 0.84	(1.25-6.86) 1.41	(0.012 - 0.036) 0.015	(8.96-21.3) 11.3	$(99.0-217) \ge 100$
indome	ethacin	(1.29-3.36) 3.30	(0.35 - 3.55) 9.12	(1.42-6.76) 0.62	(0.54-1.30) 0.44	(0.62 - 3.20) 4.30	(0.007-0.029) 0.22	8.0	18.5
		(2.10 - 7.30)	(5.73 - 14.5)	(0.61-0.63)	(0.224 - 0.870)	(2.00 - 8.10)	(0.104 - 0.480)		(13.0-23.7)

10,11-Dihydro-11-oxodibenz[b,f]oxepinacetic Acids

°C with stirring for 5 h. After the mixture was cooled, $CHCl_3$ was added to the reaction mixture. The solution was washed with dilute HCl and H₂O and concentrated to give crude 14.

The crude thiomorpholide 14 was dissolved in a mixture of acetic acid (90 mL), concentrated H_2SO_4 (16 mL), and H_2O (30 mL), and the solution was heated under reflux for 6 h. The reaction mixture was poured into H_2O , and the resulting mixture was extracted with CHCl₃. The CHCl₃ layer was washed with H_2O and then extracted with aqueous NaHCO₃. The extract was made acidic with dilute HCl and extracted with CHCl₃. The CHCl₃ layer was dried and concentrated. The residual solid was recrystallized from a suitable solvent to give 15.

Tricyclic 11-Oxo Acetic Acids (8 and 16). A mixture of 7 (or 15) (0.02 mol) and PPA (50 g) was heated at 130 °C with stirring for 30 min. The solution was poured into ice- H_2O , and the resulting mixture was extracted with ethyl acetate. The extract was washed with H_2O , dried, and concentrated. The residue was recrystallized from a suitable solvent to give 8 (or 16).

Tricyclic 11-Hydroxy Acetic Acids (9 and 17). To a solution of 8 (or 16) (0.01 mol) in EtOH (30 mL) was added sodium borohydride (0.013 mol) with ice cooling, and the resultant solution was heated under reflux for 1 h. The solution was concentrated, and to the residue was added dilute HCl. The mixture was extracted with CHCl₃, and the extract was dried and concentrated. The crude product, if solid, was recrystallized from a suitable solvent; if an oil, it was purified by chromatography on silica gel with CHCl₃-MeOH (5:1).

Tricyclic Unsaturated Acetic Acids (10 and 18). A mixture of 9 (or 17) (0.01 mol) and PPA (30 mL) was heated at 110 °C with stirring for 1.5 h. The mixture was poured into ice- H_2O , and the resulting mixture was extracted with CHCl₃. The extract was dried and concentrated. The residue was recrystallized from a suitable solvent to give 10 (or 18).

Methyl (2'-Nitrophenoxy)phenylacetates (21). Compound 19 (6.8 g, 0.034 mol) was added slowly to a mixture of 20 (0.034 mol) and KOH (1.89 g, 0.034 mol) at 150 °C with stirring, and the mixture was stirred at the same temperature for 30 min. After the addition of H_2O , the mixture was made acidic with dilute HCl and extracted with ether. The extract was washed with H_2O , dried, and concentrated. To the residue were added MeOH (100 mL) and concentrated H_2SO_4 (0.2 mL), and the resulting solution was heated under reflux for 30 min. The solution was poured into ice- H_2O , and the mixture was extracted with ether. The extract was dried and concentrated. The residue was chromatographed on silica gel (50 g), and the fraction eluted with toluene gave 21 as an oily product.

Methyl 10,11-Dihydro-11-oxodibenz[b,f][1,4]oxazepin-2acetates (24). To a solution of 21 (0.03 mol) in MeOH (50 mL) was added PtO₂ (70 mg), and the mixture was submitted to catalytic hydrogenation under ordinary pressure. After the theoretical amount of H₂ was absorbed, the catalyst was removed by filtration. The filtrate was concentrated to give crude 22 as an oily product in quantitative yield.

Into a solution of crude 22 in toluene (60 mL) was passed COCl_2 under ice cooling for 30 min and then on the water bath for 30 min, and the resulting solution was concentrated. The oily residue (23) was used for the next step: IR (film) ν 2230 (NCO) cm⁻¹.

A solution of crude 23 in o-dichlorobenzene (35 mL) was added to a suspension of pulverized AlCl₃ (4 g, 0.03 mol) in o-dichlorobenzene (35 mL) at 100 °C with stirring during 15 min, and the mixture was heated at 150 °C with stirring for 1 h. The resulting mixture was poured into ice-H₂O and extracted with CHCl₃. The extract was washed with H₂O, dried, and concentrated. The residue was chromatographed on silica gel (100 g) and eluted with CHCl₃. The crude product was recrystallized from ether to give 24.

10,11-Dihydro-11-oxodibenz[b, f][1,4]oxazepin-2-acetic Acids (25). To a solution of 24 (0.01 mol) in a mixture of MeOH (25 mL) and dioxane (20 mL) was added 10% NaOH (20 mL), and the solution was stirred at room temperature for 30 min. The resulting solution was made acidic with dilute HCl under ice cooling. The precipitate was collected and recrystallized from dilute MeOH to give 25.

Pharmacology Methods. Materials. Test compounds were dissolved or suspended in 0.5% aqueous tragacanth and administered.

Statistics. ED_{50} values were calculated according to the method of Litchfield and Wilcoxon.⁷

Carrageenan-Induced Paw Edema (CPE).⁸ Five to ten male rats of the Wistar strain, weighing 120–150 g, were used per dose. Hind paw edema was induced by a subcutaneous injection of a 1% carrageenan aqueous solution into the left hind paw. ED_{50} was determined 3 h after carrageenan injection.

Phenylquinone-Induced Writhing (PQW).⁹ Five to fifteen female mice of the ddN strain, weighing 18-22 g, were used per dose. The writhing was induced by an intraperitoneal injection of phenylquinone (0.03%), and the number of writhes was calculated for 15 min.

Ultraviolet-Induced Erythema.¹⁰ Erythema was induced on the depilated skin of the dorsal trunk of female guinea pigs of the Hartlet strain (350-450 g). ED₅₀ was determined 3 h after irradiation of ultraviolet light.

Acetic Acid Induced Writhing.¹¹ The writhing was induced by an intraperitoneal injection of a 1% acetic acid aqueous solution in male Wistar rats (90–120 g).

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Silver Nitrate Induced Arthritic Pain.¹² Arthritis was induced by an injection of a 1% silver nitrate aqueous solution into the ankle joint of right hind leg of male Wistar rats (130–180 g).

Antipyretic Assay.¹³ Hyperthermia was induced by a subcutaneous injection of a 15% yeast suspension in male Wistar rats (350-500 g).

Gastric Ulcer Assay.¹⁴ Male Wistar rats were used. The rats, fasted for 24 h, were sacrificed 6 h after a single oral administration of test compounds, and the stomach was removed and macroscopically observed. The dose (UD_{50}) producing ulcers in 50% of the rats was calculated according to the regression line of each compound.

Acute Lethal Toxicity. LD_{50} was determined from the 7-day mortality in male Wistar rats (150-230 g).

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1,1,2-Triphenylbut-1-enes: Relationship between Structure, Estradiol Receptor Affinity, and Mammary Tumor Inhibiting Properties

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1,1,2-Triphenylbut-1-enes, which are substituted with acetoxy groups on one, two, or three aromatic rings in the para and/or meta positions, were synthesized. The identity of the occurring E and Z isomers were established by ¹H NMR spectroscopy. A study on structure-activity relationships was carried out with regard to estradiol receptor affinity and to inhibiting effects on the growth of a postmenopausal human mammary carcinoma implanted in nude mice. The para-substituted compounds generally exhibited a higher receptor affinity and a better antitumor activity than the corresponding meta-substituted ones. The E isomers were superior to the respective Z isomers in those two properties. The tumor-inhibiting effect of the mono- and disubstituted compounds was better than that of the trisubstituted ones. Except for the trisubstituted compounds, they all showed a good correlation between estradiol receptor affinity and antitumor activity. One of the compounds was also tested on the 9,10-dimethylbenz[a]-anthracene-induced, hormone-dependent mammary carcinoma of the Spraque–Dawley rat, and the results corresponded to those obtained in the xenograft tumor.

Many compounds of the triarylethylene type have been tested with regard to their mammary tumor inhibiting properties.¹ One of these compounds, tamoxifen, is now widely used for the treatment of advanced breast cancer.¹ It is of great interest that the E isomer of tamoxifen² and the metabolite hydroxytamoxifen² show contrasting biological properties concerning estradiol receptor affinity,

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uterotrophic and antiuterotrophic activity, and mammary tumor inhibiting effects. For example, the estradiol receptor affinity of tamoxifen (Z configuration) is higher than that of its E isomer.³ Furthermore, compared with ta-

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