with H_2O_2; then the pH was increased to 8 with 5% Na_2CO_3, and the mixture was extracted with Et_2O. After drying ($MgSO_4$), the organic phase was evaporated and the residue was crystallized from MeOH to give **6m**. Compounds **6n** and **6o** were prepared from **6c** and **6d**.

Diols. [8a*S-(8aα,12aα,13aα)]-11β-Hydroxy-12β-(hydroxymethyl)-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-benzo[*g*]-1,3-benzodioxolo[5,6-*a*]quinolizine (6h).** $NaBH_4$ (20 g, 0.52 mol) was added slowly to keto ester **3a** (0.1 mol) in MeOH (300 mL) and CH_2Cl_2 (50 mL) at room temperature, with continuous stirring. After a further 3 h, AcOH (14 mL) was added dropwise and the solvent was evaporated. The residue was treated with H_2O, basified with 5% Na_2CO_3 to pH 8, filtered, and then separated by flash chromatography to give **6h**. Similarly, **3b** and **2a** were converted to **6i** and **5h**.

[8a*S-(8aα,12aα,13aα)]-11β-Hydroxy-2,3-dihydroxy-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-dibenzo[*a*,*g*]-quinolizine (6j).** Hydroxy compound **6c** (1 mmol) was stirred with BBr_3 (1.5 g, 6 mmol) in absolute CH_2Cl_2 (50 mL) for 1 day. The solvent was evaporated, and the residue was treated with Me_2CO; then the mixture was filtered, and compound **6j** was recrystallized from EtOH.

Ethyl [8a*S-(8aα,12aα,13aα)]-11β-Hydroxy-5,6,8a,9,10,11,12,12a,13,13a-decahydro-8*H*-benzo[*g*]-1,3-benzodioxolo[5,6-*a*]quinolizine-12-carboxylate (6p).** Hydroxy ester **6a** (1 mmol) was refluxed in EtOH (5 mL) in the presence of 4-$MeC_6H_4SO_3H$ (3 mg) for 5 h. The solvent was evaporated to one-third volume, and the crystalline product was filtered and washed (EtOH) to yield **6p**.

Pharmacology. Preparations. Rat Vas Deferens. Presynaptic α_2-Adrenoceptor Antagonist Properties. The tissue was prepared and set up in an organ bath of 3.5 mL as described by Vizi et al.[29] Cumulative concentration–response curves to xylazine were constructed in the presence and absence of antagonists. The contractions in response to field stimulation[29] were recorded isometrically on a polygraphy. After a 30-min equilibrium period, the cumulative concentration of xylazine was increased. The inhibitory effects were expressed in percentages. The antagonistic potency of the test compounds at α_2-adrenoceptors was expressed in terms of their pA_2 values. These values were obtained from the ratio of the doses of agonist producing 50% of the maximal response in the presence and absence of the test compound, according to the method of Arunlakshana and Schild.[30] The exposure time to antagonists was 20 min.

Longitudinal Muscle Strip. The longitudinal muscle strip of the guinea pig ileum was prepared as described by Paton and Vizi.[31] Guinea pigs of 400–600 g were used. The strips were suspended in organ baths of 3.5 mL and stimulated at 0.1 Hz (1 ms, supramaximal voltage, Biostim, Eltron). *l*-Norepinephrine and xylazine were used as α_2 agonists. The IC_{50} values (concentrations needed to produce 50% inhibition) for *l*-norepinephrine and xylazine were 2×10^{-6} ($n = 12$) and 8.5×10^{-7} M, respectively ($n = 12$). The time of exposure to antagonists was 20 min. The pA_2 values were calculated as described above (four to five tissues were studied at each concentration).

Postsynaptic α_1-Adrenoceptor Antagonist Properties. The rat vas deferens preparation was also used to study the potency of different compounds on postsynaptic α_1-adrenoceptors. Antagonism of *l*-phenylephrine contractions on the vas deferens was studied to determine the pA_2 values. Log dose–response curves were estimated by a curve-fitting program that gave an estimate of the IC_{50} of the agonist.

Pulmonary Artery. A dose–response curve to the contractile effect of *l*-norepinephrine, the endogenous ligand of the α_1-adrenoceptor, in the presence and absence of antagonists was tested on each preparation. The pA_2 values were calculated as described above.

The tissues described above were bathed in Krebs solution (NaCl, 118 mM; KCl, 4.7 mM; $CaCl_2$, 2.5 mM; KH_2PO_4, 1.2 mM; $MgSO_4$, 1.2 mM; $NaHCO_3$, 25 mM; dextrose, 11.2 mM), which was gassed with 95% O_2 and 5% CO_2 and maintained at 37 °C.

Registry No. (±)-**2a**, 108647-35-4; (±)-**2b**, 108647-36-5; (±)-**2c**, 108647-37-6; (±)-**3a**, 108647-32-1; (±)-**3b**, 108647-33-2; (±)-**3c**, 108647-34-3; (±)-**3d**, 108647-40-1; (±)-**3e**, 108647-41-2; (±)-**4a**, 108647-38-7; (±)-**4c**, 108647-39-8; (±)-**5a**, 108647-16-1; (±)-**5b**, 108647-18-3; (±)-**5c**, 108647-19-4; (±)-**5f**, 108647-17-2; (±)-**5h**, 108647-29-6; (±)-**5h**·HCl, 108691-30-1; (±)-**6a**, 108647-12-7; (±)-**6b**, 108647-13-8; (±)-**6c**, 108647-14-9; (±)-**6d**, 108647-15-0; (±)-**6g**, 108647-22-9; (±)-**6h**, 108647-27-4; (±)-**6h**·HCl, 108691-29-8; (±)-**6i**, 108647-28-5; (±)-**6j**, 108647-30-9; (±)-**6j**·HBr, 108691-31-2; (±)-**6k**, 108647-23-0; (±)-**6l**, 108647-42-3; (±)-**6m**, 108647-24-1; (±)-**6n**, 108647-25-2; (±)-**6o**, 108647-26-3; (±)-**6p**, 108647-31-0; (±)-**7c**, 108647-21-8; (±)-**7c**·HCl, 108691-28-7; (±)-**7e**, 108647-20-7.

Aromatase Inhibition by 5-Substituted Pyrimidines and Dihydropyrimidines

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The inhibition of estrogen biosynthesis has been suggested to be an effective treatment of hormone-dependent diseases, particularly breast cancer. Several series of 5-substituted pyrimidine derivatives have been synthesized and tested for their ability to inhibit the enzyme aromatase (estrogen synthetase). Compounds were evaluated in an in vitro assay that measured the inhibition of rat ovarian microsomal aromatase activity. Greatest inhibitory activity was achieved in the cases of diarylpyrimidinemethanols and diarylpyrimidinyl methanes which were substituted in the 4- and 4′-positions with electron-withdrawing substituents, particularly Cl.

Fenarimol [α-(2-chlorophenyl)-α-(4-chlorophenyl)-5-pyrimidinemethanol (**1**)], a pyrimidinylcarbinol fungicide, acts to inhibit ergosterol biosynthesis by inhibiting the P-450 enzyme responsible for 14-demethylation.[1] It has been postulated that the inhibition occurs as a result of the binding of the pyrimidine moiety to the heme portion of the enzyme. As a result of this inhibition, the fungi lack the 14-desmethyl steroids required for the construction of the cell wall.

In reproduction studies in rats, fenarimol caused a dose-related decrease in fertility.[2] The infertility appeared to be a male-specific effect and was associated with a decrease in male sexual behavior. In the rat, gonadal androgens are metabolized to estrogens within the central nervous system (CNS) via the P-450 enzyme aromatase

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(1) Sisler, H. D.; et al. *Biochem. Biophys. Res. Commun.* **1972**, *46*(6), 2048–2053; *Pestic. Biochem. Physiol.* **1973**, *3*(1), 20–29; **1982**, *18*(1), 122–131; **1983**, *20*(3), 320–329; *Pestic. Sci.* **1973**, *4*(5), 719–728; **1984**, *15*(2), 167–176; *Plant Physiol.* **1976**, *57*(4), 640–644; *Meded Fac. Landbouwwet., Rijksuniv. Gent.* **1976**, *41*(2), 571–578, *Neth. J. Plant Pathol.* **1977**, *83* (suppl 1), 81–91; *Pestic. Chem.: Hum. Welfare, Proc. Int. Congr. Pestic. Chem. 5th* **1983**, *3*, 129–134.
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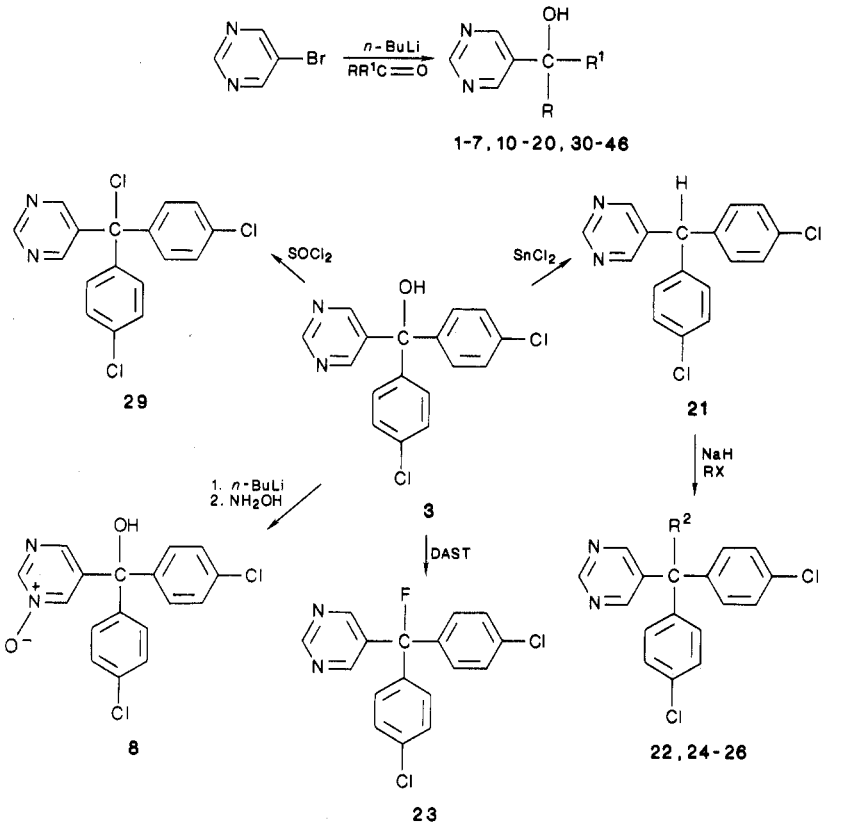
Scheme I



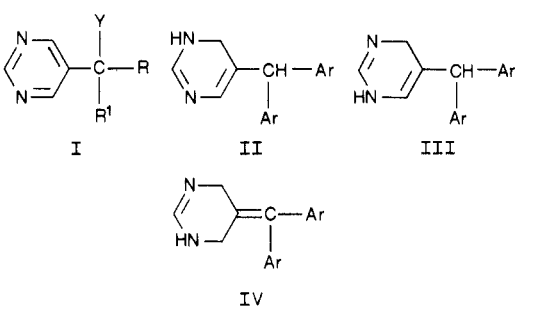
(estrogen synthetase). These estrogens play an important role in the development and eventual expression of sex-specific patterns of behavior and gonadotropin release.[3] Compounds that act to block estrogen biosynthesis have been reported to cause an absence of male sexual behavior in anatomically normal rats.[4] Effects of fenarimol on male fertility were subsequently attributed to the inhibition of aromatase activity.[5]

As a result of these observations, an examination of the diarylpyrimidinylmethanes and -methanols and other related compounds was undertaken in order to evaluate their ability to inhibit estrogen biosynthesis. The availability of a potent nonsteroidal aromatase inhibitor could provide a useful therapeutic tool for the treatment of estrogen-dependent diseases, particularly breast cancer. The oral activity and essentially nontoxic nature of fenarimol suggested that structurally related compounds would have significant advantages over aromatase inhibitors currently in clinical use.

Chemistry

The structures of compounds used in this study are depicted in Chart I. Preparation of simple 5-substituted pyrimidine derivatives of structure I are depicted in Scheme I. Pyrimidinylcarbinols (I with Y = OH; **1–7, 10–20, 30–46**) were prepared by the addition of 5-lithiopyrimidine (obtained by transmetalation of 5-bromopyrimidine) to the appropriately substituted aryl or alkyl ketones (method A). Compound **21** (structure I with Y = H) was obtained by stannous chloride reduction of compound **3** in glacial acetic acid (method B). The 1-oxide derivative **8** was obtained by formation of the methiodide

Chart I



salt of **3** followed by reaction with hydroxylamine (method C). Structures of type I with Y being an alkyl group (**22, 24–26**) were obtained by alkylation of the starting material **21** Y = H by using the sodium hydride in dimethyl sulfoxide alkylation procedure (method D). The Y = F analogues (**23, 27, 28**) were readily prepared from the corresponding carbinols (Y = OH) by the use of (diethylamino)sulfur trifluoride (DAST) in an inert solvent such as methylene chloride at ambient (or lower) temperature (method E). Thionyl chloride served to convert carbinol **3** to the corresponding Y = Cl compound (**29**) by the procedure of method F. Some of the above methods, or modifications thereof, have been reported previously in the patent literature[6-9].

In contrast to the simple 5-substituted pyrimidine compounds that were investigated for a fairly wide variety of R and R^1 alkyl or aryl groups, the reduced pyrimidine versions II, III, and IV were evaluated for a single case of

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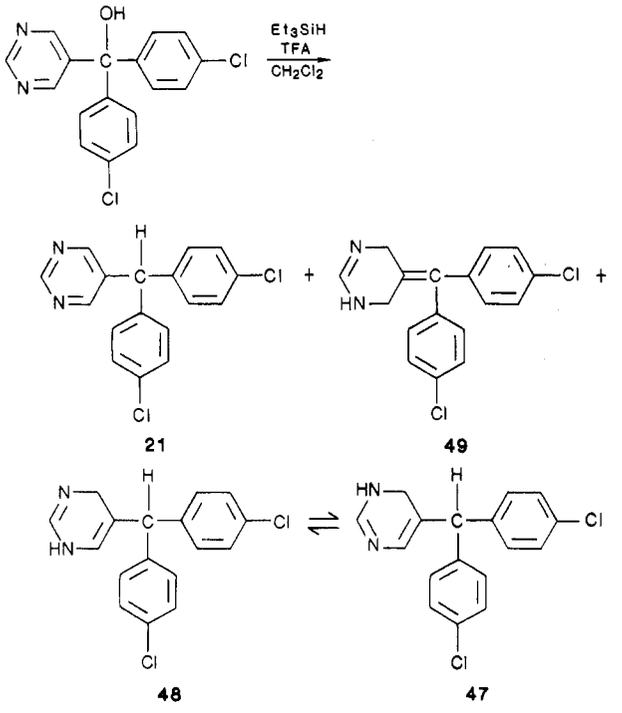
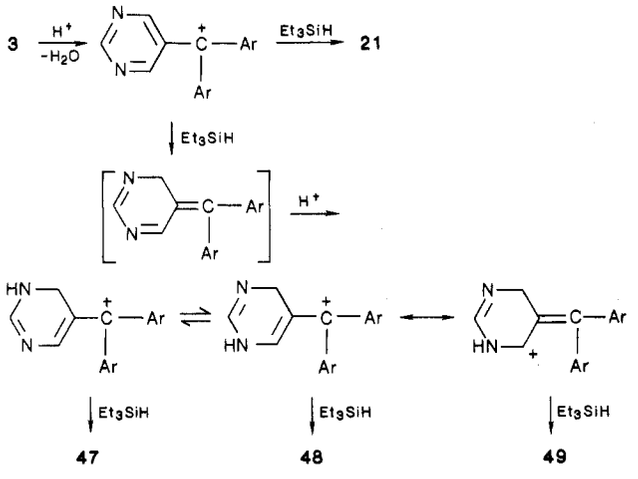
(4) Clemens, L. G.; Gladue, B. A. *Horm. Behav.* **1978**, *11*, 190–201.
(5) Hirsch, K. S.; Weaver, D. E.; Black, L. J.; MacLusky, N. J. *Toxicol. Appl. Pharmacol.*, in press.
(6) U.S. Patent 3 887 708, June 3, 1975.
(7) U.S. Patent 3 868 244, February 24, 1975.
(8) U.S. Patents 3 818 009 January 11, 1974, and 3 869 456, March 4, 1975.
(9) U.S. Patent 2 727 895, November 22, 1955.

Scheme II



Scheme III[a]



[a] Ar = 4-ClC_6H_5.

diaryl substitution expected to give a high degree of aromatase inhibition. Therefore, II, III, and the exocylic double bonded compound IV were investigated only for the specific case of Ar = 4-chlorophenyl (compounds **47**, **48**, and **49**, respectively). Preparation of the reduced analogues was accomplished by Et_3SiH/trifluoroacetic acid (TFA) reduction of compound **3** as described in the Experimental Section and shown in Scheme II. A proposed mechanism for the formation of the hydropyrimidines **47–49** as well as the pyrimidine byproduct **21** is presented in Scheme III. Compound **49** was isolated as a single crystalline entity that did not show any tendency to reoxidize to the aromatic pyrimidine **21** on standing. In contrast, a second product, isolated as an amorphous solid, undergoes air oxidation either neat or as a solution in $CHCl_3$ or Me_2SO-d_6. The NMR spectra show that this material is a single species on the NMR time scale and that it includes a methylene and methine group. We believe that this product is probably a mixture of the two tautomers **47** and **48**, although attempts to demonstrate the presence of two individual tautomers according to a recently reported method[10] using purified deuteriated solvents failed.

Biological Results and Discussion

Estrogen-dependent cancers of the breast and uterus are among the most common forms of cancer observed in women. In the United States alone there are an estimated 116 000 new cases of breast cancer diagnosed with approximately 38 000 deaths attributed to the disease. There are also 55 000 new cases of endometrial cancer with an estimated 10 000 deaths.[12] The hormone-dependence of an these diseases is attributed to the presence of estrogen and or progesterone receptors in tumor specimens. According to McGuire,[13] 61% of the mammary tumors from premenopausal women and 75% from postmenopausal women are estrogen receptor positive. In addition, 58% of the tumors also exhibit progesterone receptors. In endometrial cancer, 79% of the tumor specimens are estrogen receptor positive and 58% progesterone receptor positive.[14]

Treatment of these diseases has involved a number of therapeutic approaches including surgery, radiation, cytotoxic agents, and hormonal methods. In the past, hormonal therapy involved the administration of hormones or the surgical ablation of such tissues as the ovary, adrenal, and pituitary. Today, the most common form of endocrine therapy involves the use of antiestrogens that act to prevent the binding of estrogens to their receptors. Results from a number of clinical trials indicate that antiestrogen therapy results in objective clinical responses in 40% of patients that were unselected on the basis of steroid-receptor status of the tumor.[12] The response rate is even higher when the estrogen and progesterone status of the tumor is taken into consideration. Progestins have also been used, to some extent, particularly in endometrial cancer.[12]

Recently, a number of investigators have proposed the alternative that inhibition of estrogen biosynthesis might also be used in the treatment of estrogen-dependent diseases.[15-17] Aromatase (estrogen synthetase) is a P-450 enzyme complex that mediates the rate-limiting step in the conversion of androgens to estrogens. Enzyme activity has been observed in both gonadal and extragonadal sites including liver, muscle, and adipose tissues.[18] On the basis of the fact that the aromatase enzyme catalyzes the final and rate-limiting step in estrogen biosynthesis, Brodie[17] suggested that inhibitors of the enzyme might provide a method of specifically blocking the synthesis of all sources of estrogen in the treatment of estrogen-dependent diseases. This suggestion takes on particular importance with the observation that aromatase activity has been detected in specimen of both breast and endometrial cancer.[18,19] Several aromatase inhibitors have been examined in clinical trials using patients with estrogen-dependent breast cancer. The compounds have been shown to be effective in producing objective clinical responses including partial

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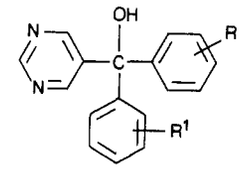
(11) Brodie, A. H. M.; Schwarzel, W. C.; Shaikh, A. A.; Brodie, H. J. *Endocrinology* **1977**, *100*, 1684–1695.
(12) Wright, J. C. **1985**, *J. Natl. Med. Assoc.* **1985**, *77*(8), 617–625.
(13) McGuire, W. L. *Cancer Res.* **1978**, *38*, 4289–4291.
(14) Ehrlich, C. E.; Young, P. C. M.; Cleary, R. E. *Am. J. Obstet. Gynecol.* **1981**, *141*, 539–546.
(15) Santen, R. J. *Cancer Res.* **1982**, *42*, 3268s.
(16) Johnston, J. O.; et al. In *Novel Approaches to Cancer Chemotherapy*; Academic: New York, 1984; pp 307–328.
(17) Brodie, A. M. *Biochem. Pharmacol.* **1985**, *34*(18), 3213–3219.
(18) Siiteri, P. K. *Cancer Res.* **1982**, *42*, 3269s–3273s.
(19) Tseng, L.; Mazella, J.; Funt, M. I.; Mann, W. J.; Stone, M. L. *Obstet. Gynecol.* **1984**, *63*, 150–154.

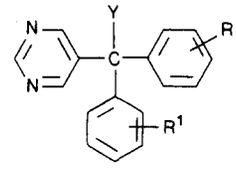
Table I. Inhibition of Aromatase by Diarylpyrimidinylcarbinols



no.	R	R¹	method of synth	mp (bp), °C	% yield	recrystn solvent[a]	formula	anal.[b]	in vitro aromatase inhibn: EC_{50},[c] μM
1	4-Cl	2-Cl	A	118–120	34	Tol/Hex	$C_{17}H_{12}Cl_2N_2O$	C, H, N	4.1
2	4-Cl	3-Cl	A	117–119	37	EtOAc/Iso	$C_{17}H_{12}Cl_2N_2O$	C, H, N	0.35
3	4-Cl	4-Cl	A	159–161	55	Tol/Hex	$C_{17}H_{12}Cl_2N_2O$	C, H, N	0.071
4	4-Cl	4-CF_3	A	139–140	16	EtOAc/Iso	$C_{18}H_{12}ClF_3N_2O$	C, H, N	0.066
5	4-Cl	4-F	A	157–158	30	Benz/SKB	$C_{17}H_{12}ClFN_2O$	C, H, N	0.18
6	4-F	4-F	A	112	27	Benz/SKB	$C_{17}H_{12}F_2N_2O$	C, H, N	0.53
7	4-CH_3	4-CH_3	A	amorph	35		$C_{19}H_{18}N_2O$	C, H, N	0.41
8	4-Cl	4-Cl (*N*-oxide)	C	148–150	60	Et_2O	$C_{17}H_{12}Cl_2N_2O_2$	C, H, N	>2.0
9	4-Cl	3-F	A	amorph	30		$C_{17}H_{12}ClFN_2O$	C, H, N	1.65
10	4-F	3-F	A	137	60	Et_2O	$C_{17}H_{12}F_2N_2O$	C, H, N	1.15
11	4-Cl	2-Cl, 4-OCH_3	A	oil	35		$C_{18}H_{14}Cl_2N_2O_2$	C, H, N, Cl	4.3
12	3,4-CH_3	3-CH_3, 4-OCH_3	A	glass	36		$C_{21}H_{22}N_2O_2$	*d*	1.4
13	H	H	A	167–170	18	EtOH/Et_2O	$C_{17}H_{14}N_2O$	C, H, N	>2.0
14	4-Cl	H	A	glass	12		$C_{17}H_{13}ClN_2O$	*e*	>2.0
15	4-F	H	A	112–115	43	Et_2O	$C_{17}H_{13}FN_2O$	C, H, N	>2.20
16	4-CF_3	H	A	125–127	40	Benz/SKB	$C_{18}H_{13}F_3N_2O$	C, H, N	1.95
17	4-OCH_3	H	A	98–99	32	EtOAc/Iso	$C_{18}H_{16}N_2O_2$	C, H, N	>2.0
18	4-NO_2	H	A	amorph	10		$C_{17}H_{13}N_3O_3$	*f*	0.27
19	3,4-Cl	H	A	amorph	48		$C_{17}H_{12}Cl_2N_2O$	*g*	1.0
20	3,4-CH_3	H	A	74–75	24	Et_2O	$C_{19}H_{18}N_2O$	C, H, N	3.20
aminoglutethimide									0.26
ATD									0.14
micronazole									0.40

[a] Iso, isooctane; Et_2O, diethyl ether; Benz, benzene; EtOH, 3A alcohol; Hex, hexane; SKB, Skellysolv B, Tol, toluene. [b] Compounds were analyzed for the elements indicated to within ±0.4% of the theoretical value except as noted. Concentration required to decrease aromatization of testosterone in the in vitro rat ovarian microsome assay by 50%. [d] *m/e* calcd 334.1679, found 334.1677. [e] *m/e* calcd 296.0717, found 296.0718. [f] *m/e* calcd 307.0948, found 307.0939. [g] *m/e* calcd 330.0327, found 330.0327.

Table II. Inhibition of Aromatase by Diarylpyrimidinylmethanes



no.	R	R¹	Y	method of synth	mp (bp), °C	% yield	recrystn solvent[a]	formula	anal.[b]	in vitro aromatase inhibn: EC_{50},[c] μM
21	4-Cl	4-Cl	H	B	oil	87		$C_{17}H_{12}Cl_2N_2$	C, H, N	0.055
22	4-Cl	4-Cl	CH_3	D	oil	25		$C_{18}H_{14}Cl_2N_2$	C, H, N	0.082
23	4-Cl	4-Cl	F	E	oil	28		$C_{17}H_{11}Cl_2FN_2$	C, H, N	0.078
24	4-Cl	4-Cl	CH_3CH_2	D	oil	20		$C_{19}H_{16}Cl_2N_2$	*d*	2.95
25	4-Cl	4-Cl	$C_6H_5CH_2$	D	152–154	12	neat	$C_{24}H_{18}Cl_2N_2$	C, H, N	1.01
26	4-Cl	4-Cl	4-$ClC_6H_4CH_2$	D	136–138	4	neat	$C_{24}H_{17}Cl_3N_2$	C, H, N	>2.0
27	2-Cl	4-F	F	E	74–75	32	Hex	$C_{17}H_{11}ClF_2N_2$	C, H, N	1.2
28	4-Cl	4-F	F	E	oil	41		$C_{17}H_{11}ClF_2N_2$	C, H, N	0.195
29	4-Cl	4-Cl	Cl	F	95–97	72	EtOAc/Iso	$C_{17}H_{11}Cl_3N_2$	C, H, N	0.275

[a] Iso, isooctane; EtOAc, ethyl acetate; Hex, hexane. [b] Compounds were analyzed for the elements indicated to within ±0.4% of the theoretical value except as noted. [c] Concentration required to decrease aromatization of testosterone in the in vitro rat ovarian microsome assay by 50%. [d] *m/e* calcd 342.0704, found 342.0718.

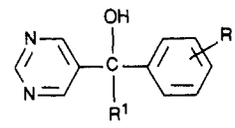
and complete remissions.[20-22]

Inhibition of aromatase activity was determined by using a modification of the rat ovarian microsome assay described by Brodie et al.[11] In this assay ovarian microsomes from rats treated with pregnant mares' serum gonadotropin were incubated with [^{3}H]androstenedione and a NADPH-generating system. Aromatization of the substrate resulted in the release of [^{3}H]water, which was quantified by liquid scintillation spectrometry.

The aromatase inhibition data for the compounds of this study are presented in Tables I–V. Also included in Table I for comparative purposes are in vitro aromatase inhibition results we have determined for the known inhibitors aminoglutethimide (AG),[23] androsta-1,4,6-triene-3,17-dione

(20) Coombes, R. C.; Goss, P.; Dowsett, M.; Gazet, J.-C.; Brodie, A. *Lancet* **1984**, *12*(1), 1237–1239.
(21) Santen, R. J. *Cancer Treat. Rev.* **1984**, *11*(4), 325–329.
(22) Ceci, G.; et al. *Tumori* **1985**, *71*, 483–489.
(23) Thompson, E. A.; Siiteri, P. K. *J. Biol. Chem.* **1974**, *249*, 5373–5378.

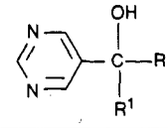
Table III. Inhibition of Aromatase by Monoarylpyrimidinylcarbinols



no.	R	R^1	method of synth	mp (bp), °C	% yield	recrystn solvent[a]	formula	anal.[b]	in vitro aromatase inhibn: EC_{50},[c] μM
30	4-Cl	cyclohexyl	A	153–154	63	EtOAc	$C_{17}H_{19}ClN_2O$	C, H, N	4.0
31	4-Cl	2-norboranyl	A	193	22	Benz	$C_{18}H_{19}ClN_2O$	C, H, N	7.80
32	4-Cl	cyclopropyl	A	112–113	57	Et_2O	$C_{14}H_{13}ClN_2O$	C, H, N	5.70
33	4-Cl	2-propyl	A	129–130	35	Et_2O	$C_{14}H_{15}ClN_2O$	C, H, N	>2.0
34	4-F	cyclopropyl	A	73–74	37	Et_2O/SKB	$C_{14}H_{13}FN_2O$	C, H, N	4.2
35	4-Br	cyclopropyl	A	122–123	30	Et_2O	$C_{14}H_{13}BrN_2O$	C, H, N	5.4
36	4-OCH_3	cyclopropyl	A	111	43	Et_2O	$C_{15}H_{16}N_2O_2$	C, H, N	>2.0
37	4-OCH_3	cyclooctyl	A	120	18	Et_2O/SKB	$C_{20}H_{26}N_2O_2$	C, H, N	6.20
38	4-OCH_3	cyclobutyl	A	158	50	Et_2O	$C_{16}H_{18}N_2O_2$	C, H, N	>2.0
39	4-OCH_3	*sec*-butyl	A	77	4	neat	$C_{16}H_{20}N_2O_2$	C, H, N	>2.0
40	4-OCH_3	*tert*-butyl	A	117–118	6	Et_2O	$C_{16}H_{20}N_2O_2$	C, H, N	>2.0
41	4-CH_3	cyclohexyl	A	139–140	43	EtOAc/Iso	$C_{18}H_{22}N_2O$	C, H, N	>2.0
42	H	2-thienyl	A	143–145	34	EtOAc	$C_{15}H_{12}N_2OS$	C, H, N	>2.0

[a] Iso, isooctane; EtOAc, ethyl acetate; Et_2O, diethyl ether; Benz, benzene; SKB, Skellysolv B. [b] Compounds were analyzed for the elements indicated to within ±0.4% of the theoretical value. [c] Concentration required to decrease aromatization of testosterone in the in vitro rat ovarian microsome assay by 50%.

Table IV. Inhibition of Aromatase by Pyrimidinylcarbinols That Lack a Phenyl Ring



no.	R	R^1	method of synth	mp (bp), °C	% yield	recrystn solvent[a]	formula	anal.[b]	in vitro aromatase inhibn: EC_{50},[c] μM
43	2-thienyl	2-thienyl	A	80–81	49	Et_2O/Iso	$C_{13}H_{10}N_2OS_2$	C, H, N	>2.0
44	2-thienyl	cyclopropyl	A	oil	90		$C_{12}H_{12}N_2OS$	C, H, N	>2.0
45	2-(5-methylthienyl)	isopropyl	A	oil	70		$C_{13}H_{16}N_2OS$	C, H, N	>2.0
46	cyclopentyl	cyclopropyl	A	92	65	neat	$C_{13}H_{18}N_2O$	C, H, N	>2.0

[a] Et_2O, diethyl ether; Iso, isooctane. [b] Compounds were analyzed for the elements indicated to within ±0.4% of the theoretical value except as noted. [c] Concentration required to decrease aromatization of testosterone in the in vitro rat ovarian microsome assay by 50%.

Table V. Inhibition of Aromatase by Reduced Pyrimidine Analogues

no.	in vitro aromatase inhibn:[a] ED_{50}, μM
47 + 48	0.05
49	2.7

[a] Concentration required to decrease aromatization of testosterone in the in vitro rat ovarian microsome assay by 50%.

(ATD),[24] and miconazole.[25]

Variation of Aromatic Substituents. In Table I the results of moving and varying the aromatic substituents can be seen. Moving the chlorine from position 2 to 3 (compound **2**) resulted in increased activity over that of the lead compound **1**. Placement of both chlorines in the 4-position (compound **3**) also gave increased activity, producing one of the most active compounds of the series. Replacement of one chlorine with a proton reduced activity (compound **14**), but a CF_3 (**4**) was about equal to a chlorine in efficacy. Fluorine was slightly less effective than chlorine (compounds **5**, **6**, **9**, **10**). Activity is maintained, but to a lesser degree, with other substituents on the ring (examples **7**, **12**) as long both 4-positions are occupied. As mentioned above, replacement of the substituent on one ring with a proton (examples **14–20**) results in greatly reduced activity except in the case of nitro. With both rings unsubstituted (compound **13**) the molecule is ineffective. Conversion of the pyrimidine to its *N*-oxide (compound **8**) also reduces activity.

Variation of Y Substituents. Table II shows the effects of modifying Y with the aryl groups being 4-chlorophenyl or 4-fluorophenyl. In general, there appears to be little change when Y is a small group (compounds **21–23**, **28**), but as the size increases to ethyl (**24**) and other large groups (**25**, **26**) activity is reduced or lost.

Requirement of Aryl Groups. Replacement of one phenyl group by either an alkyl or cycloalkyl group, even with the phenyl substituted in the 4-position, results in greatly reduced activity as seen in Table III (**30–42**). As one might expect, a similar effect is noted when both phenyl groups are replaced (Table IV).

Variation of Pyrimidine Ring Oxidation State. The in vitro aromatase inhibition data for reduced analogues **47** + **48** and **49** are shown in Table V. In the case of **49**, the enzyme-inhibiting activity was reduced by at least 1 order of magnitude as compared to that of the corresponding aromatic pyrimidine oxidation state (compound **21**). However, the mixture of **47** + **48** exhibited activity at a degree comparable to compound **21**. This similarity in activity suggests that **47** + **48** is undergoing oxidative conversion to **21** under the conditions of the in vitro assay.

In summary, our results clearly demonstrate that certain 5-substituted pyrimidine derivatives provide extremely

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effective inhibitors of rat ovarian microsomal aromatase activity in vitro. The most active inhibitor of the pyrimidine series that has been found to date (compound **21**) has an EC_{50} value of 0.055 μM. The known inhibitors of aromatase activity, aminoglutethimide, ATD, and micronazole, exhibit corresponding values of 0.26, 0.14, and 0.40 μM, respectively. We are currently evaluating **21** and other analogues in a number of in vivo assay systems in order to determine whether the in vitro data correlate with in vivo aromatase-inhibiting activity.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were taken at 270 MHz on a Bruker WM-270 machine or at 360 MHz on a Bruker WM-360 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained on a Finnegan MAT731 spectrometer in the EI mode with samples introduced directly into the ion source for spectral determination. Although only selective spectral data are presented herein, all new compounds exhibited IR, UV, and NMR spectra consistent with the structures assigned them. Microanalyses were performed at Eli Lilly and Co.

Method A. Synthesis of α,α-Bis(4-chlorophenyl)-5-pyrimidinemethanol (3). A solution of 5-bromopyrimidine (19.9 g, 0.125 mol) and 4,4′-dichlorobenzophenone (31.4 g, 0.125 mol) in tetrahydrofuran (350 mL) was cooled to −95 °C, resulting in a white slurry. Over 1 h, 1.6 M *n*-BuLi in hexane (0.125 mol) was added dropwise and the reaction mixture became a thick paste. After the reaction mixture was allowed to warm slowly to ambient temperature, it was cooled to −20 °C and water (80 mL) was added. The lower aqueous layer was separated and the upper organic phase was stripped down to a gum. The gum was dissolved in hot toluene (90 mL) and washed with water (50 mL) containing concentrated HCl (1.75 mL), followed by water (4 × 50 mL). The toluene was evaporated to an amorphous solid, which was the desired product containing approximately 10% of the starting material ketone. Two recrystallizations from toluene/hexane provided 22.6 g (55%) of the desired carbinol **3**, mp 159–161 °C, which was free of the starting material as judged by TLC (silica gel; toluene/EtOAc, 1:1) and NMR spectroscopy. Anal. ($C_{17}H_{12}Cl_2N_2O$) C, H, N.

Additional pyrimidine carbinols **1–7**, **10–20**, and **30–46** were prepared in a similar fashion by the addition of 5-lithiopyrimidine to the appropriate starting material ketone.

Method B. Synthesis of 5-[Bis(4-chlorophenyl)methyl]-pyrimidine (21). To a solution of **3** (110.3 g, 0.3 mol) in glacial acetic acid (1 L) was added solid anhydrous stannous chloride (113.7 g, 0.6 mol) followed by concentrated HCl (350 mL) to produce a clear, amber solution. As the reaction mixture was heated to reflux, a precipitate formed and then redissolved. After the mixture was refluxed, the resulting clear yellow solution was allowed to cool slowly overnight to ambient temperature. The pale yellow granulated solid that had precipitated was collected on a filter, sucked dry, washed on the filter with water (3 × 100 mL), and vacuum dried at 50 °C to a constant weight of 141.2 g (92.2% of theory for the $SnCl_2$ complex of **21**). The dry granular solid was dissolved in THF (420 mL) and the resulting clear yellow solution was treated dropwise with pyridine (23.7 g, 24.1 mL, 0.3 mol) in THF (50 mL) to break the tin complex. After the mixture had been allowed to stir for 30 min, the precipitate was collected, washed with THF (100 mL), and dried in vacuo at 50 °C to a constant weight of 65.0 g (89.2% of the theoretical amount of pyridine $SnCl_2$). The THF filtrate from breaking the complex was refiltered and stripped down to a gum. The gum was dissolved in toluene (500 mL) and washed with 10% aqueous HCl (100 mL) and by water (3 × 200 mL). After drying of the toluene phase over anhydrous $MgSO_4$ and removal of toluene on the rotary evaporator, the resulting oil was heated on a steam bath under vacuum to constant weight of 82.6 g (87%). By TLC (silica gel; toluene/EtOAc, 1:1) and NMR spectroscopy, the product was essentially pure. To obtain analytical material, 61 g of the oil was chromatographed on 300 g of silica gel in a 6 × 27 cm column eluting with 1:1 EtOAc/toluene. Appropriate fractions were pooled and concentrated to constant weight to provide **21** as an oil (56.0 g), which resisted all attempts to induce its crystallization. Anal. ($C_{17}H_{12}N_2Cl_2$) C, H, N.

Method C. Synthesis of α,α-Bis(4-chlorophenyl)-5-pyrimidinemethanol 1-Oxide (8). Compound **3** (10.0 g, 0.03 mol) was refluxed overnight in methyl iodide (100 mL). The reaction mixture was then cooled and filtered to provide the crude methiodide salt of **3** in a yield of 12.8 g (90% of theoretical). The crude salt was used without further purification. To the pyrimidinium methiodide (10 g, 0.021 mol) was added a solution of hydroxylamine hydrochloride (6.95 g, 0.1 mol) in water (20 mL) and $NaHCO_3$ (9.24 g, 0.11 mol), followed by 3A ethanol (200 mL). The reaction mixture was refluxed for 2 h, and then it was cooled, poured into water, and extracted with ether. The ether extract was dried over anhydrous Na_2CO_3, filtered, and evaporated to a thick oil, which was purified by chromatography over silica gel with EtOAc as eluent. Appropriate fractions were combined and evaporated to provide the *N*-oxide **8** as 4.4 g (60%) of a white solid, mp 148–150 °C. Anal. ($C_{17}H_{12}Cl_2N_2O_2$) C, H, N.

Method D. Synthesis of 5-[1,1-Bis(4-chlorophenyl)-ethyl]pyrimidine (22). A solution of **21** (1.8 g, 0.0057 mol) in dimethyl sulfoxide (20 mL) was added at ambient temperature to a slurry of 67% NaH in mineral oil (250 mg, 0.0069 mol of NaH) in dimethyl sulfoxide (20 mL). The mixture was stirred until a deep red color formed. Methyl iodide (10 drops) was added and the color disappeared and then returned after about 10 min. The addition of methyl iodide was repeated over the course of several hours until the red color no longer formed. The reaction was then quenched by the addition of ethanol followed by water. The product was extracted into ether, washed with water, dried over $MgSO_4$, and evaporated to a thick oil, which was chromatographed over silica gel with gradient elution ((EtOAc/hexane, 1:9, changing to EtOAc/hexane, 2:8). Concentration of the appropriate fractions provided the desired alkylated product **22** as 0.47 g (25%) of a viscous liquid. Anal. ($C_{18}H_{14}Cl_2N_2$) C, H, N.

Compounds **24–26** were prepared similarly from **21** and the appropriate alkylating agents (ethyl iodide, benzyl chloride, and 4-chlorobenzyl chloride, respectively).

Method E. Synthesis of 5-[Bis(4-chlorophenyl)fluoromethyl]pyrimidine (23). To a solution of carbinol **3** (5.0 g, 0.015 mol) in CH_2Cl_2 (40 mL) was added (diethylamino)sulfur trifluoride (2.5 g, 0.015 mol). The reaction mixture was allowed to stir at ambient temperature for 75 h. The solution was washed with water (100 mL) and with saturated aqueous $NaHCO_3$ solution until basic. After the organic phase was dried over anhydrous $MgSO_4$, the solvent was evaporated and the residual oil was purified by chromatography over silica gel with gradient elution (pentane changing to hexane/EtOAc, 5:1). Appropriate fractions provided 1.4 g (28%) of oily **23**, which did not crystallize. Anal. ($C_{17}H_{11}Cl_2FN_2$) C, H, N.

Also prepared by the reaction of (diethylamino)sulfur trifluoride with the appropriate carbinol were compounds **27** and **28**.

Method F. Synthesis of 5-[Bis(4-chlorophenyl)chloromethyl]pyrimidine (29). Carbinol **3** (12.0 g, 0.036 mol) in CH_2Cl_2 (200 mL) was treated with thionyl chloride (16.7 g, 10 mL, 0.14 mol). After the mixture was stirred for 2 h, most of the solid went into solution. An additional 10 mL of thionyl chloride was added, and after an additional 2h, a clear yellow solution was obtained. After evaporation of the solvent and excess thionyl chloride, the residue was taken up in fresh CH_2Cl_2, washed with cold Na_2CO_3 solution, and dried over anhydrous $MgSO_4$. Evaporation of the solvent provided an oil, which was chromatographed over silica gel with 20% EtOAc in toluene. Appropriate fractions provided 9.1 g (72%) of **29** as essentially pure material as judged by NMR spectroscopy. An analytical sample was obtained by recrystallization initially from CH_2Cl_2/ether and finally from EtOAc/isooctane to provide pale yellow crystals, mp 95–97 °C. Anal. ($C_{17}H_{11}Cl_3N_2$) C, H, N.

Method G. Part I. Synthesis and Isolation of 5-[Bis(4-chlorophenyl)methyl]-1,6-dihydropyrimidine (47) and 5-[Bis(4-chlorophenyl)methyl]-1,4-dihydropyrimidine (48). To a mixture of carbinol **3** (6.00 g, 0.0181 mol), Et_3SiH (4.23 g, 0.0364 mol), and CH_2Cl_2 (9 mL) maintained under a dry N_2 atmosphere was added anhydrous trifluoroacetic acid (40 mL). The reaction mixture was stirred overnight and most of the TFA was removed by rotary evaporation at temperatures not exceeding 35 °C. The residual pale yellow oil was added in small portions to an excess

of saturated $NaHCO_3$ solution. When basification was complete, CH_2Cl_2 (150 mL) was added and the mixture was stirred for 1 h. During this time, a white amorphous solid formed between the organic and aqueous layers. The solid was collected, washed well with water, and vacuum dried at 25 °C overnight. This material amounted to 1.72 g of a 2:1 mixture of **49** and (**47** + **48**) as determined subsequently by NMR spectroscopy.

The CH_2Cl_2 layer was separated, dried over anhydrous $MgSO_4$, and evaporated to 7.8 g of a yellow oil. The crude product was purified by SiO_2 chromatography with a Waters Prep 500A (Milford, MA) instrument. The column was eluted initially with 2 L of 9:1 $CHCl_3$/MeOH. Then solvent polarity was increased in a step-gradient fashion to a solution of 5% triethylamine (TEA) in 9:1 $CHCl_3$/MeOH. (For each 200 mL eluent, the TEA was increased by 1%.) Finally, the column was eluted with 1.5 L of 5% TEA in 9:1 $CHCl_3$/MeOH; 200-mL fractions were collected throughout the gradient-elution procedure. Under these conditions, compound **49** was retained on the column. Fractions 3 and 4 provided 3.0 g of a colorless oil from which 1.93 g (34%) of **21** was obtained after removal of unidentified volatile silicon containing materials by vacuum distillation. Fractions 16–20 provided after evaporation and vacuum drying 0.96 g (16%) of a colorless foam, which was a single spot on silica gel TLC (TEA/$CHCl_3$/MeOH, 1:8:2). Mass spectral analysis was consistent with the dihydro derivative(s) of **21** with *m/e* 316.05243 (calculated 316.05340 for $C_{17}H_{14}Cl_2N_2$) and elemental analysis was also consistent with this formulation (calculated for $C_{17}H_{14}Cl_2N_2$ (C, H)). Proton NMR spectrum of freshly prepared material assigned to be a mixture of the tautomers **47** + **48** (270 MHz, $CDCl_3$): δ 3.92 (s, 2 H, CH_2), 4.42 (s, 1 H, $CHAr_2$), 5.50 (s, 1 H, N=C*H*C), 7.09 (s, 1 H, N=C*H*N), 7.09 (d, *J* = 10 Hz, 4 H, Ar H), 7.28 (d, *J* = 10 Hz, 4 H, Ar H). On standing, oxidation of **47** + **48** to the fully aromatic **21** was observed by virtue of the appearance of the following peaks attributable to **21**: δ 5.47 (s, 1 H, C*H*Ar_2), 7.02 (d, *J* = 10 Hz, 4 H, Ar H), 7.32 (d, *J* = 10 Hz, 4 H, Ar H), 8.48 (s, 2 H, N=C*H*C), 9.13 (s, 1 H, N=C*H*N).

Method G. Part II. Synthesis and Isolation of 5-[Bis(4-chlorophenyl)methylene]-1,4,5,6-tetrahydropyrimidine (49). The reduction of **3** described above was repeated on a 2.00-g scale with the same reaction conditions. An identical workup was used except that a larger quantity of CH_2Cl_2 (500 mL) was utilized so that no undissolved solid appeared between the layers. The crude product (2.73 g) obtained in this manner was purified by the use of a Waters Semiprep column packed with Woelm activity I alumina and 5% TEA in MeOH as the elution solvent. Fractions (approximately 30 mL) were assayed by TLC (Al_2O_3; 10% TEA in MeOH). After collection of **21** (0.50 g; 26%) and a mixture of **47** and **48** (0.42 g; 22%) there was obtained as single spot material 810 mg (42%) of **49**. Recrystallization from EtOAc/isooctane was rather inefficient, yielding only 240 mg (13%) of colorless crystals, mp 113–120 °C. The high-resolution mass spectrum showed the material to be a dihydro derivative with *m/e* 316.05160 (calculated 316.05340 for $C_{17}H_{14}Cl_2N_2$). Proton NMR (360 MHz, $CDCl_3$): δ 4.06 (S, 4 H, CH_2), 5.76 (s, 1 H, NH), 7.02 (d, *J* = 10 Hz, 4 H, Ar H), 7.33 (d, *J* = 10 Hz, 4 H, Ar H α to Cl), 8.26 (s, 1 H, N=CHN).

Aromatase Inhibition in Vitro. The ability of compounds to inhibit aromatase was evaluated in vitro by using a modification of the rat ovarian microsome assay described by Brodie et al.[11] Ovarian microsomes were prepared from rats treated with pregnant mares serum gonadotropin (PMSG, Sigma Chemical Co., St. Louis, MO) every other day for 12 days. Sample vials contained the microsomes (protein = 665 μg per vial), a drop of propylene glycol, 0.1 μM androstenedione (Steraloids Inc., Wilton, NH), 100 000 dpm [1,2-^{3}H]androstenedione (46.1 Ci/mmol), New England Nuclear Corp., Boston, MA), and fenarimol (0.05–10.0 μM) dissolved in a total volume of 2.5 mL of 0.1 M phosphate buffer, pH 7.4, containing 0.0012% dithiothreitol. The reaction was initiated by the addition of an NADPH-generating system (0.5 mg of $NADP^+$, 1.0 mg of glucose 6-phosphate, 3 IU glucose-6-phosphate dehydrogenase, Sigma). After a 10-min incubation at 37 °C in an atmosphere of 95% O_2/5% CO_2, the reaction was stopped by the addition of 10.0 mL of chloroform, and the samples were stored overnight at 4 °C. A 1.0-mL aliquot of the aqueous phase was incubated with 1.0 mL of a 2.5% charcoal suspension (Norit charcoal (neutral) (Sigma) in phosphate buffer for 10 min. The samples were centrifuged at 600*g* for 10 min and 1.0 mL of the supernatant was added to a vial containing 10 mL of Beckman Ready-Solv MP (Beckman Instruments, Inc., Irvine, CA). Samples were analyzed by liquid scintillation spectrometry. In this assay the aromatization of the labeled androstenedione results in the release of [^{3}H]H_2O. The extent of aromatization was quantified on the basis of the difference between vials incubated in the presence and absence of test compound and a correction for the spontaneous release of labeled water. Activity is expressed as concentration of the test compound that inhibits 50% of the enzyme activity (EC_{50}).

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