300-fold loss in binding affinity to human vascular smooth muscle cells, suggesting that the structure-activity relationships of the full molecule are quite different than those of the C-terminal hexapeptide.[27]

Previously, it was shown that D-aromatic amino acids in the 16 position of the C-terminal hexapeptide enhances receptor affinity.[7,8] The D-phenylalanine substitution (**5**) led to approximately a 3-fold enhancement in binding affinity to both receptor subtypes (cf. 4). An enhancement in binding affinity to the ET_A receptor over the ET_B receptor was realized from the D-Tyr^{16} and D-Trp^{16} (**6** and **7**) substitutions, (approximately 15-fold). A further 10-fold increase in binding was obtained by incorporation of the hydrophobic D-diphenylalanine[18-20] (D-Dip) residue in position 16.

Although, Ac-D-Dip-Leu-Asp-Ile-Ile-Trp (**8**) displayed high affinity for both the ET_A and ET_B receptors, it showed some selectivity for the ET_A receptor (IC_{50} = 15 nM and 150 nM, respectively, Table I). The enhanced binding of **8** was not simply a function of the hydrophobicity of Dip, since both the naphthyl (Nal) and biphenyl (Bip) substituted analogues (**9** and **10**) exhibited approximately 100-fold less receptor affinity.

The ability of these linear hexapeptides (**2**-**10**) to inhibit endothelin-stimulated arachidonic acid release (rabbit renal artery vascular smooth muscle cells (ET_A)) correlates well with binding to the ET_A receptor. Only **8** was a functional antagonist of ET-1-stimulated vasoconstriction in both the rabbit femoral and pulmonary artery with pA_2 values of 7.19 and 7.27, respectively. The rabbit femoral artery expresses only the ET_A receptor since SRTX-6c has no activity at concentrations up to 1.0 μM, while the rabbit pulmonary artery has predominantly an ET_B-like receptor.[12] None of the other analogues tested showed antagonism of ET-1 induced vasoconstriction at concentrations up to 10 μM.

This analogue (**8**) represents the first known functional antagonist of endothelin at both the ET_A and ET_B receptor subtypes. This compound may provide a critical tool for determining the physiological and/or pathophysiological role of endothelin.

Supplementary Material Available: Physical (proton NMR and mass spectral) data for all the peptides and a detailed description of the pharmacological assays (binding, IP_3, AAR, and vasoconstriction) is provided (23 pages). Ordering information is given on any current masthead page.

(27) Galantino, M.; de Castiglione, R.; Tam, J. P.; Liu, W.; Zhang, J.-W.; Cristiani, C.; Vaghi, F. D-Amino Acid Scan of Endothelin. In *Peptides: Chemistry and Biology. Proceedings of the Twelfth American Peptide Symposium*; Smith, J. A., Rivier, J. E., Eds.; ESCOM Science Publishers B.V.: The Netherlands, 1992; pp 404-405.

† Department of Pharmacology.
‡ Department of Signal Transduction.

Wayne L. Cody,* Annette M. Doherty,* John X. He
Patricia L. DePue, Stephen T. Rapundalo†
Gary A. Hingorani,† Terry C. Major,† Robert L. Panek†
David T. Dudley,‡ Stephen J. Haleen†
Donelle LaDouceur,† Kristen E. Hill†
Mike A. Flynn,† Elwood E. Reynolds†

Departments of Medicinal Chemistry, Pharmacology and Signal Transduction
Parke-Davis Pharmaceutical Research Division
The Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, Michigan 48106

Received June 25, 1992

Time-Dependent Inhibition of Human Placental Aromatase with a 2,19-Methyleneoxy-Bridged Androstenedione

Aromatase is the rate-limiting enzyme in the conversion of androgens to estrogens.[1] Inhibitors of aromatase have demonstrated therapeutic utility in estrogen-dependent metastatic breast cancer[2a,b] and have potential for use in the management of other estrogen-dependent processes and diseases.[2c] Several categories of steroidal aromatase inhibitors have been designed.[3,4] We recently described hydroxylated 2,19-methylene-bridged androstenediones[5]

(1) Fishman, J.; Hahn, E. F. The Nature of the Final Oxidation Step in the Aromatization Sequence. *Steroids* 1987, *50*, 339-345.

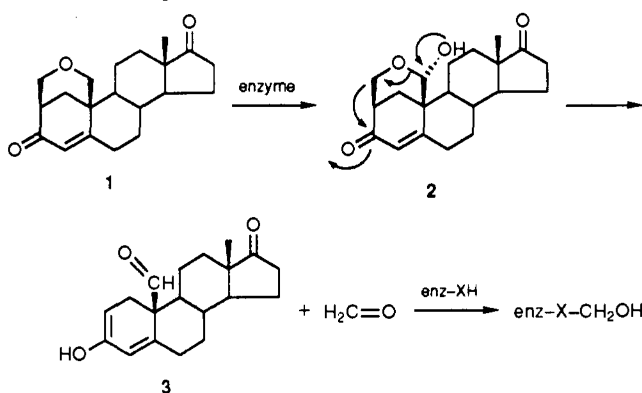
(2) (a) Covey, D. F. Aromatase Inhibitors: Specific Inhibitors of Oestrogen Biosynthesis. In *Sterol Biosynthesis Inhibitors*; Berg, D., Plempel, M., Eds.; Ellis Horwood, Ltd.: Chichester, England, 1988; pp 534-571. (b) Johnston, J. O.; Metcalf, B. W. Aromatase: A Target Enzyme in Breast Cancer. In *Novel Approaches to Cancer Chemotherapy*; Sunkara P., Ed.; Academic Press: New York, 1984; pp 307-328. (c) Henderson, D.; Habenicht, U. F.; Nishino, V.; Kerb, V.; El Etreby, M. F. Aromatase Inhibitors and Benign Prostatic Hyperplasia. *J. Steroid Biochem.* 1986, *25*, 867-876.

(3) The following androstenedione derivatives have been reported as aromatase inhibitors. (a) 19-Acetylenic: Covey, D. F.; Hood, W. F.; Parikh, V. D. 10β-Propynyl-substituted Steroids. *J. Biol. Chem.* 1981, *256*, 1076-1079. Johnston, J. O.; Wright, C. L.; Metcalf, B. W. Biochemical and Endocrine Properties of a Mechanism-Based Inhibitor of Aromatase. *Endocrinology* 1984, *115*, 776-785. (b) 19-Oxiranyl and thiiranyl: Kellis, J. T., Jr.; Childers, W. E.; Robinson, C. H.; Vickery, L. E. Inhibition of Aromatase Cytochrome P-450 by 10-Oxirane and 10-Thiirane Substituted Androgens. *J. Biol. Chem.* 1987, *262*, 4421-4426. (c) 4-Hydroxy: Brodie, A. M. H.; Schwarzel, W. C.; Shaikh, A. A.; Brodie, H. J. The Effect of an Aromatase Inhibitor, 4-Hydroxy-4-androstene-3,17-dione, on Estrogen-Dependent Processes in Reproduction and Breast Cancer. *Endocrinology* 1977, *100*, 1684-1695. (d) 7α-Arylthio: Snider, C. E.; Bruggemeir, R. W. Potent Enzyme-Activated Inhibition of Aromatase by a 7α-Substituted C_{19} Steroid. *J. Biol. Chem.* 1987, *262*, 8685-8689. (e) 6α-Bromo: Osawa, Y.; Osawa, Y.; Coon, M. J. Stereochemistry of the Functional Group Determines the Mechanism of Aromatase Inhibition by 6-Bromoandrostenedione. *Endocrinology* 1987, *121*, 1010-1016. (f) 6-One: Covey, D. F.; Hood, W. F. Enzyme-Generated Intermediates Derived from 4-Androstene-3,6,17-trione and 1,4,6-Androstatriene-3,17-dione Cause a Time-Dependent Decrease in Human Placental Aromatase Activity. *Endocrinology* 1981, *108*, 1597-1599. (g) 1-Ene: Covey, D. F.; Hood, W. F. A New Hypothesis Based on Suicide Substrate Inhibitor Studies for the Mechanism of Action of Aromatase. *Cancer Res.* 1982, *42*, 3327s. Henderson, D.; Norbisrath, G.; Kerb, U. 1-Methyl-1,4-androstadiene-3,17-dione (SH489): Characterization of an Irreversible Inhibitor of Estrogen Biosynthesis. *J. Steroid Biochem.* 1986, *24*, 302-306. (h) 1-Ene-6-methylene: Giudici, D. G.; Ornati, G.; Briatico, F.; Buzzetti, P.; Lombardi, P.; di Salle, E. 6-Methyleneandrosta-1,4-diene-3,17-dione (FCE 24304): A New Irreversible Aromatase Inhibitor. *J. Steroid Biochem.* 1988, *30*, 391-394. (i) And others: see review articles in ref 2 and 4.

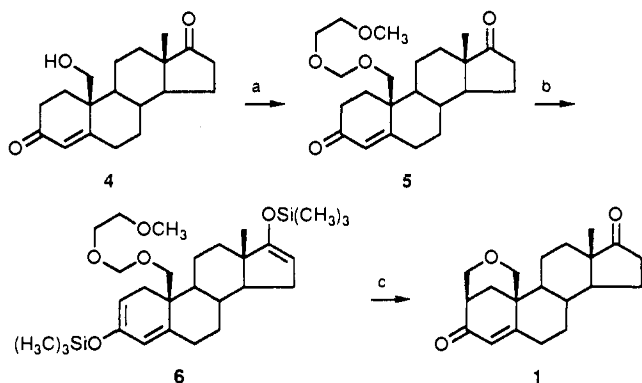
(4) (a) Johnston, J. O. Biological Characterization of 10-(2-Propynl)estr-4-ene-3,17-dione (MDL 18,962), An Enzyme-Activated Inhibitor of Aromatase. *Steroids* 1987, *50*, 105-120. (b) Van Wauwe, J. P.; Janssen, P. Is There a Case for P-450 Inhibitors in Cancer Treatment? *J. Med. Chem.* 1989, *32*, 2231-2239. (c) Cole, P. A.; Robinson, C. H. Mechanism and Inhibition of Cytochrome P-450 Aromatase. *J. Med. Chem.* 1990, *33*, 2933-2942. (d) di Salle, E.; Giudici, D.; Briatico, G.; Ornati, R. Novel Irreversible Aromatase Inhibitors. In *Steroid Formation, Degradation, and Action in Peripheral Tissues*; Castagnetta, L., d'Aquino, S., Labrie, F., Bradlow, H. L., Eds.; Annals of the New York Academy of Sciences: New York, 1990; Vol. 595, pp 357-367.

0022-2623/92/1835-3303$03.00/0 © 1992 American Chemical Society

Scheme I. Proposed Mechanism for Aromatase Inhibition by 1



Scheme II. Synthesis of 2,19-(Methyleneoxy)androst-4-ene-3,17-dione (1)[a]



[a] Reagents and conditions: (a) $ClCH_2OCH_2CH_2OCH_3$, $(Me_2CH)_2NEt$, CH_2Cl_2, 20 h, 23 °C, 76%; (b) lithium diisopropylamide, Me_3SiCl, THF, 30 min, −20 °C, 100%; (c) $TiCl_4$, CH_2Cl_2, 35 min, −20 °C, 35%.

as potential mimics of intermediates in the aromatase-mediated oxidation of androstenedione.[6] Subsequently, bridged compound 1[7] was proposed for synthesis as a potential mechanism-based inhibitor of aromatase. This report describes the synthesis of 2,19-(methyleneoxy)androst-4-ene-3,17-dione (1)[8] and its time-dependent inhibition of human placental aromatase.[9]

We reasoned that recognition of 1 by the enzyme and subsequent oxidation would give intermediate 2, which upon fragmentation of the hemiacetal as shown in Scheme I would give enol–aldehyde 3 and formaldehyde. If generated in the active site, formaldehyde would be expected to alkylate an enzyme nucleophile and inactivate the enzyme. Alternatively, intermediate 2 could open initially to a hydroxy aldehyde which could dehydrate to an enone. 1,4-Addition of an enzyme nucleophile to this enone would also lead to enzyme inactivation.

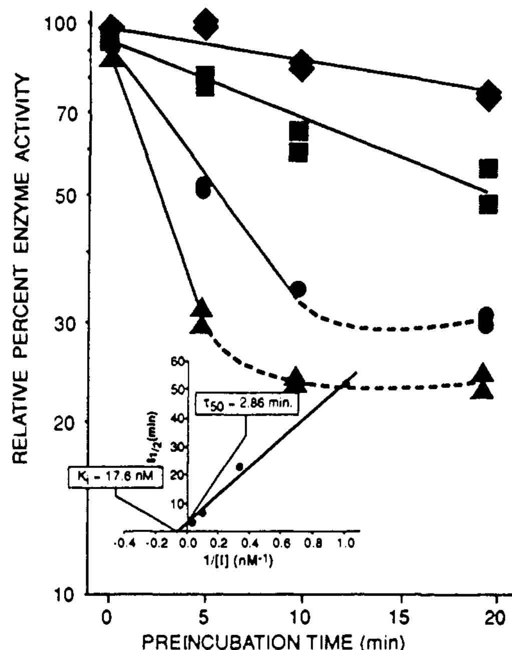


Figure 1. Aromatase inhibition by 1. Time-dependent inhibition was determined by preincubating 100 μL of compound 1 (1 nM, ♦; 3 nM, ■; 10 nM, ●; 30 nM, ▲) at intervals from 0 to 20 min with 700 μL of human placental microsomal preparation (enzyme activity = 34 ± 7 pmol of estrogen formed min^{-1} (mg of protein)$^{-1}$) and 600 μL of NADPH-generating system at 25 °C. The relative enzyme activity remaining following the preceding preincubation intervals was determined by measurement of the ^3H_2O from the stereospecific elimination of 1β-^{3}H (56.7%) from 100 μL of [1-^{3}H]androstenedione (750 pmol, 0.62 μCi) during a 10-min assay. The inherent losses of aromatase activity in buffer controls were 5% from 0 to 10 min and 12% from 10 to 20 min of preincubation. The inhibitor was solubilized in polyethylene glycol 200 to provide a 15 nM solution which was subsequently diluted with assay buffer. Assay methods have been previously described (ref 18). The data points in Figure 1 represent mean values from duplicate analyses with an interassay coefficient of variation of 1.9%. The insert represents a linear regression analysis of a Kitz–Wilson plot (ref 15) of the first-order inactivation rates ($t_{1/2}$) for preincubation intervals of 0–20 min (1–3 nM), 0–10 min (10 nM), and 0–5 min (10 nM) versus the reciprocal of inhibitor concentrations. For 1, the K_i of inactivation was 17.6 nM with τ_{50} value of 2.86 min (r = 0.995).

Treatment of 19-hydroxyandrostenedione (4) with (2-methoxyethoxy)methyl chloride (MEM chloride) and diisopropylethylamine gave MEM ether 5 (76%) as shown in Scheme II. Generation of the kinetic enolate of 5, in the presence of trimethylsilyl chloride, using lithium diisopropylamide at −20 °C gave dienol ether 6, quantitatively. Lewis acid-catalyzed intramolecular alkylation of 6 with titanium tetrachloride[10] gave bridged compound 1[11]

(5) Burkhart, J. P.; Peet, N. P.; Wright, C. L.; Johnston, J. O. Novel Time-Dependent Inhibitors of Human Placental Aromatase. *J. Med. Chem.* **1991**, *34*, 1748–1750.
(6) Although the first two hydroxylations at the 19-methyl group of androstenedione are well-understood, the nature of the third hydroxylation remains elusive. A model reaction for this third hydroxylation has recently been described: Cole, P. A.; Robinson, C. H. Mechanistic Studies on a Placental Aromatase Model Reaction. *J. Am. Chem. Soc.* **1991**, *113*, 8130–8137.
(7) 2,19-Bridged steroids with oxygen atoms in the bridge and directly connected to position 2 have been reported: (a) Kocovsky, P. A Stereospecific Silver (I)-Assisted Solvolysis of Cyclic Halo Ethers. Evidence for a Push-Pull Mechanism Involving Neighboring Group Participation. *J. Org. Chem.* **1988**, *53*, 5816–5819. (b) Njar, V. C. O.; Spiteller, G.; Wicha, J.; Caspi, E. Observations on the Preparation of 2β-Hydroxy-19-oxoandrost-4-ene-3,17-dione; Synthesis of a 2β-19-oxa-androst-4-ene-3,17-dione. *Heterocycles* **1989**, *28*, 1051–1060.
(8) *Chemical Abstracts* nomenclature for 1: (4α,10α)-4,19-cyclo-A-dihomo-2-oxaandrost-4b-ene-4a,17-dione.
(9) A Patent Evaluation on compound 1 has appeared: Alteration of Adrenal Steroid Biosynthesis by an Aromatase Inhibitor. *Curr. Opinion Ther. Pat.* **1991**, *1*, 1434–1436.
(10) (a) Walker, D. M.; Logusch, E. W. Preparation of Heterocyclic Amino Acids via Intramolecular Mukaiyama Aldol Condensation: Synthesis of a Novel Cycloleucine Analogue. *Tetrahedron Lett.* **1989**, 1181–1184. (b) Nishiyama, H.; Itoh, K. Reaction of 2-Methoxyethyl Hemiacetals with Allylsilanes in the Presence of Titanium Tetrachloride: Regioselective C–O Bond Cleavage of Unsymmetrical Acetals. *J. Org. Chem.* **1982**, *47*, 2496–2498.

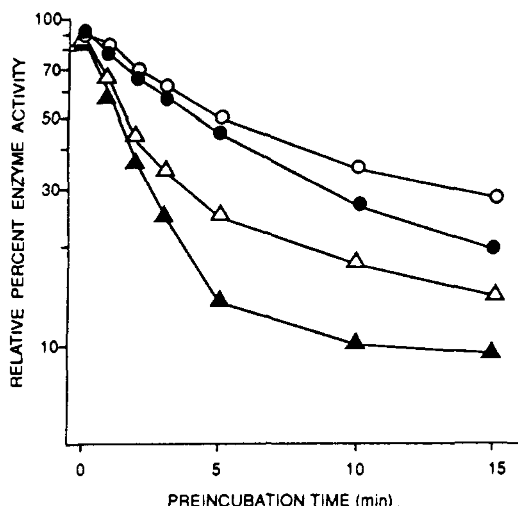


Figure 2. Preincubation of 1 with and without NADPH. Inhibition of aromatase activity at two concentrations of 1 (10 nM without NADPH, ○; 10 nM with NADPH, ●; 30 nM without NADPH; △, 30 nM with NADPH, ▲) was measured by preincubation of enzyme with inhibitor in the presence or absence of NADPH for various time intervals followed by incubation with substrate (750 pmol of [^{3}H]androstenedione) in the presence of added NADPH for 4 min. Each point represents the average of duplicate analyses of duplicate assays with an interassay coefficient of variation of 2.2%. The inhibition curves at each concentration with and without NADPH were statistically different ($p < 0.01$).

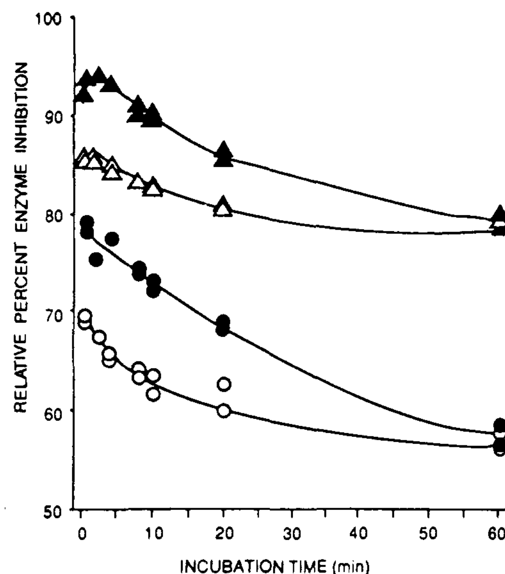


Figure 3. Incubation of 1 following preincubation with and without NADPH. Two concentrations of 1 with and without NADPH (10 nM with NADPH, ●; 10 nM without NADPH, ○; 30 nM with NADPH, ▲; 30 nM without NADPH, △) were preincubated with enzyme for 10 min, substrate (750 pmol of [^{3}H]androstenedione) and NADPH added and enzyme activity measured at the incubation time intervals shown. Each data point represents the average of duplicate analyses with an interassay coefficient of variation of 5.6%. Data are expressed as percent enzyme inhibition relative to respective buffer controls.

(35%). The tetrahydropyran ring of 1 was shown by spectroscopy to prefer a chair conformation in solution.[12] The ether oxygen of 1 may be positioned to efficiently interact with the enzyme heme, although such an interaction does not occur with 19-methoxyandrostenedione,[4c] the acylic analog of 1. Alternatively, it is known that the 19-*pro-R* hydrogen atom of 19-hydroxyandrostenedione is stereospecifically replaced by a hydroxyl group in the second enzymatic hydroxylation.[13] Perhaps 1 could be viewed as a conformationally restricted version of 19-hydroxyandrostenedione in which the optimal position of the hydroxyl oxygen atom is duplicated by the ether oxygen atom in the rigid 1.

The inhibitory curves for aromatase from human placenta generated with bridged compound 1 are shown in Figure 1. Incubation of the aromatase preparation[14] to which an NADPH-generating system had been added, for varying time periods with different concentrations of 1 gave a time-dependent loss of enzyme activity. A Kitz–Wilson plot[15] of the reciprocal of inhibitor concentration versus enzyme half-life at these concentrations (Figure 1 inset) gave an apparent $K_{i(inactivation)}$ value of 17.6 nM for 1. The calculated enzyme half-life (τ_{50}) at infinite inhibitor concentration was 2.86 min.

A substrate protection study[16] with 1 (10 nM) showed that enzyme inactivation was reduced from $t_{1/2}$ of 7.5 min to 18.0 min to 622 min by the addition of increasing levels of androstenedione (0, 45, and 135 nM, respectively) in the preincubation medium. Thus, the inhibition by 1 was active site directed.

At saturating substrate concentration (500 nM of androstenedione) there was a modest but significant ($p \leq 0.05$) reduction in time-dependent loss of enzyme activity with 1 in the absence of the NADPH-generating system.[17] This experiment prompted us to study cofactor dependence. In Figure 2 is shown a set of aromatase inhibition curves generated with 1 at two concentrations (10 and 30 nM) following preincubation of 1 and enzyme for several different times in the absence and presence of NADPH. Following the preincubations, substrate and NADPH were added, the preparations were incubated for 10 min, and percent relative enzyme activities were determined. Even though most of the inhibition is occurring in the absence of NADPH, it is evident from the curves that cofactor is playing a role during the preincubation. Inhibition of

(11) For 1: mp 214–217 °C (ethanol); ^{1}H NMR ($CDCl_3$) δ 6.11 (s, 1 H, vinyl), 3.89 (ddd, 1 H, J = 11.2, 1.8, and 1.8 Hz), 3.78 (dd, 1 H, J = 10.8 and 2.6 Hz), 3.60 (d, 1 H, J = 10.8 Hz), 3.50 (dd, 1 H, J = 11.2 and 2.5 Hz), 0.91 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 219.8, 200.5, 165.5, 129.2, 68.8, 67.5, 51.2, 50.7, 47.3, 44.2, 40.4, 36.6, 35.6, 35.4, 32.1, 31.6, 29.4, 21.6, 20.7, 13.6; IR (KBr) 1734 (cyclopentanone C=O), 1658 (enone C=O) cm^{-1}; MS (CI, CH_4) m/z (rel intensity) 315 (MH^+, 100), 297 (10). Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.14; H, 8.48.

(12) A W coupling constant of J = 1.8 Hz was observed between the C3-equatorial hydrogen and the α-hydrogen of the C19-methylene bridge. Likewise, coupling (J = 2.6 Hz) was observed between the C1-equatorial hydrogen and the α-hydrogen of the C19-methylene bridge. As can be seen from a molecular model, these W couplings are only consistent with a chair conformation for the tetrahydropyran portion of 1. The numbering used in the above description derives from the *Chemical Abstracts* nomenclature for 1 (see ref 8).

(13) Wright, J. N.; Akhtar, M. Studies on Estrogen Biosynthesis Using Radioactive and Stable Isotopes. *Steroids* **1990**, *55*, 142–151.

(14) Metcalf, B. W.; Wright, C. L.; Burkhart, J. P.; Johnston, J. O. Substrate-Induced Inactivation of Aromatase by Allenic and Acetylenic Steroids. *J. Am. Chem. Soc.* **1981**, *103*, 3221–3222.

(15) Kitz, R.; Wilson, I. B. Esters of Methanesulfonic Acid as Irreversible Inhibitors of Acetylcholinesterase. *J. Biol. Chem.* **1962**, *237*, 3245–3249.

(16) This study was conducted as described in the following reference: Johnston, J. O.; Wright, C. L.; Metcalf, B. W. Biochemical and Endocrine Properties of a Mechanism-Based Inhibitor of Aromatase. *Endocrinology* **1984**, *115*, 776–785.

(17) Loss of enzyme activity was not due to a reduction in total microsomal protein concentration, which was monitored during this study.

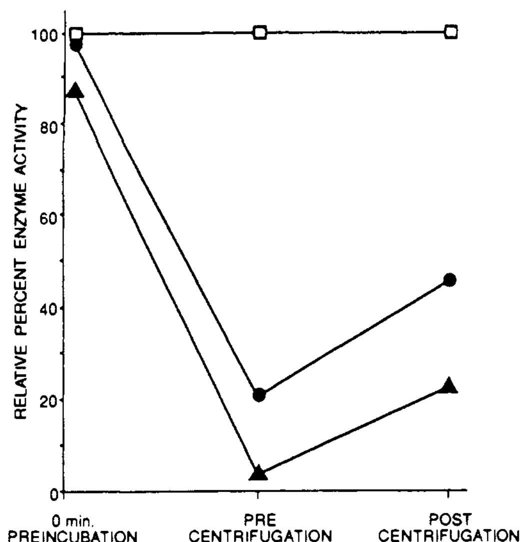


Figure 4. Reversibility of aromatase binding with 1. An NADPH-generating system was present during the 15-min preincubation period. Partial recovery of aromatase activity following isolation by centrifugation and reconstitution of human placental microsomal preparations previously treated with two concentrations of 1 (10 nM, ●; 30 nM, ▲; buffer, □). Each point represents the average of four replicates with duplicate determinations. The interassay coefficient of variation was 3.3%.

enzyme activity is statistically ($p < 0.01$) enhanced at both concentrations with the preparations containing NADPH during the preincubation periods with respect to those preparations without NADPH.

In Figure 3 are shown two sets of curves where the enzyme was preincubated with 10 and 30 nM concentrations of 1 for a fixed time (10 min), with and without NADPH. The preparations were then incubated in the presence of 500 nM androstenedione and added NADPH for 60 min with periodically monitored enzyme activity. At the early incubation timepoints the preparations with NADPH in the preincubation phase showed a greater amount of enzyme inhibition. At the 60-min assay timepoint, the effects of preincubating the enzyme and inhibitor without NADPH were not evident, as expected, since the cofactor was present during the incubation phase. We conclude from these studies that a statistically significant ($p < 0.01$) portion of the aromatase inhibition displayed by bridged steroid 1 is attributed to a cofactor-dependent process.

To further define the mechanism of inhibition of 1 we performed a reversibility assay. Two concentrations of 1 were incubated with human placental microsomes and aromatase activity was assayed as shown in Figure 4. The inhibited microsomes were isolated by centrifugation and the microsomal pellets were rinsed with assay buffer, resuspended in the assay medium, and assayed for percent relative enzyme activity. A portion of the inhibitor was removed during the centrifugation-rinsing process and a portion remained enzyme bound, as shown by the partial recovery of enzyme activity. For a strictly competitive inhibitor which did not exhibit time-dependency, we have shown a complete removal of inhibitor from the microsomes by centrifugation and rinsing. Also, for an inhibitor which irreversibly binds to aromatase, we have shown that the enzyme remained inactivated following the centrifugation-rinsing process.[18]

In summary, we have shown that A-ring bridged steroid 1 is a potent, time-dependent, and active site directed inhibitor of human placental aromatase. The inhibition appears to be mainly a tight-binding competitive process. However, a portion of the inhibitory activity is NADPH dependent and is consistent with the mechanism-based oxidative process proposed for this compound. It is recognized that other factors may be responsible for the NADPH-dependent behavior of 1, such as a conformational change in the enzyme active site induced by NADPH binding, or an NADPH-mediated oxidation of 1 to give a higher affinity competitive inhibitor.

Acknowledgment. We thank Linda C. Meyer for technical assistance with aromatase assays.

(18) We have recently described this assay. See: Burkhart, J. P.; Weintraub, P. M.; Wright, C. L.; Johnston, J. O. Novel Silylated Steroids as Aromatase Inhibitors. *Steroids* **1985**, *45*, 357–374.

Norton P. Peet,* Joseph P. Burkhart
C. Lee Wright, J. O'Neal Johnston*
Organic Chemistry/Cancer Biology
Marion Merrell Dow Research Institute
2110 East Galbraith Road
Cincinnati, Ohio 45215-6300
Received March 27, 1992

Book Reviews

Books of Interest

Writing Reaction Mechanisms in Organic Chemistry. By Audrey Miller. Academic Press, Inc., San Diego, CA. 1992. x + 488 pp. 16 × 23 cm. ISBN 0-12-496711-6. $34.95 (pbk).

Crystallization of Nucleic Acids and Proteins. A Practical Approach. Edited by A. Ducruix and R. Giege. Oxford University Press, New York. 1992. xxiv + 331 pp. 15.5 × 23 cm. ISBN 0-19-963245-6. $50.00 (pbk).

The Cytoskeleton. A Practical Approach. Edited by K. L. Carraway and C. A. C. Carraway. Oxford University Press, New York. 1992. xviii + 268 pp. 15.5 × 23 cm. ISBN 0-19-963256-1. $40.00 (pbk).

Pharmaceutical Biotechology. A Programmed Text. Edited by S. William Zito. Technomic Publishing Company, Inc., Lancaster, PA. 1992. x + 177 pp. 17 × 25 cm. ISBN 0-87762-911-0. $45.00.

Clinical Pharmacology. Seventh Edition. Edited by D. R. Laurence and P. N. Bennett. Churchill Livingstone, Inc., New York. 1992. xii + 686 pp. 18.5 × 24 cm. ISBN 0-443-04388-4. $54.00.

Medical Microbiology. Third Edition. Edited by Samuel Baron. Churchill Livingstone, Inc., New York. 1991. xx + 1340 pp. 20.5 × 26 cm. ISBN 0-443-08671-0. $59.95.