

How I Got Started

Strategy

Preclinical Profiling

Aromatase (CYP19)

cytochrome P450 enzyme converts androgens to estrogens

Inhibiting estrogen production inhibits mammary cancer progression

Cytochrome P450 enzymes

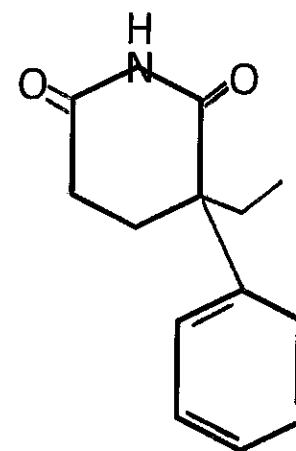
Endocrine tissues: steroids, prostaglandins

Liver: bile acids, drug metabolism, xenobiotics

AMINOGLUTETHIMIDE

Indications

1. Hypnotic sedative
2. Treatment for Cushing's Disease (Cytadren)
3. Aromatase Inhibitor (CYP19)



NH₂

Aromatase Inhibition

IC₅₀ = 0.22 μM

K_i = 0.47 μM

Relevant History

Hilton Salhanick: Demonstrated that certain imidazole cpds did not inhibit CYP11A1

Medical Adrenalectomy with Aminoglutethimide:

*Clinical Studies in Postmenopausal Patients with Metastatic
Breast Carcinoma*

SAMUEL A. WELLS, JR., M.D., RICHARD J. SANTEN, M.D., ALLAN LIPTON, M.D., DARROW E. HAAGENSEN, JR., M.D.
EDWARD J. RUBY, M.D., HAROLD HARVEY, M.D., WILLIAM G. DILLEY, Ph.D.

Pentti Siiteri: First to demonstrate aminoglutethimide inhibited aromatase

Abstract: Aminoglutethimide suppressed mammary tumors in women while raising androstenedione levels; therefore inhibition of CYP11A1 not responsible

Rationale For Project

Aminoglutethimide

aromatase inhibitor

inhibits estrogen dependent mammary tumors

Glutethimide

same CNS activities of aminoglutethimide

not an aromatase inhibitor.

CYP11A can be avoided

substitute imidazole for amino group for binding to the
Fe porphyrin nucleus of the enzyme

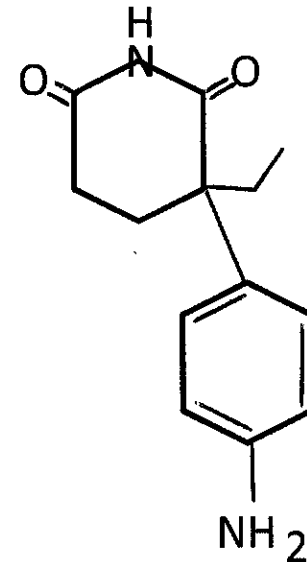
AMINOGLUTETHIMIDE

Indications

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Other Activities

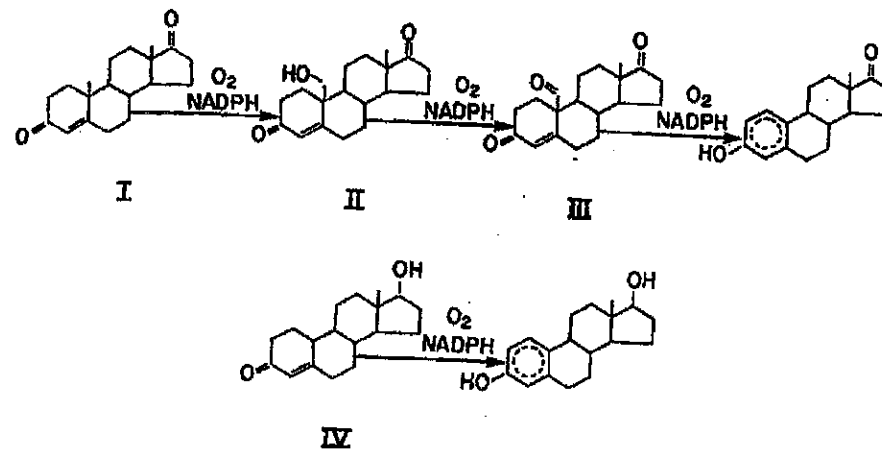
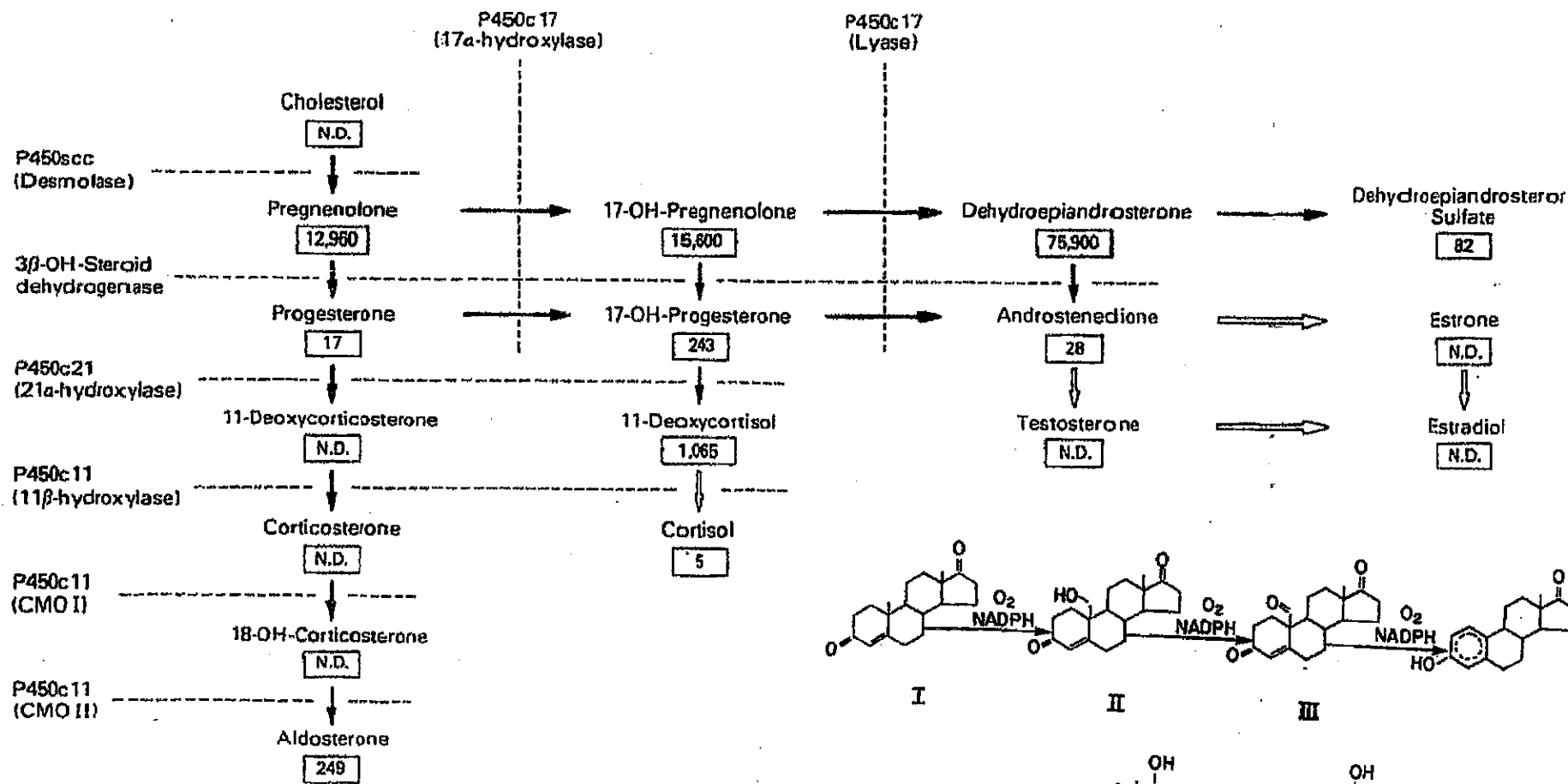
1. Inhibits CYP2D6
2. Inhibits CYP11A1
3. Inhibits CYP11B1
4. Inhibits CYP11B2



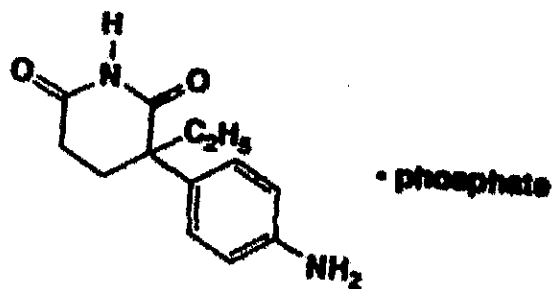
Aromatase Inhibition

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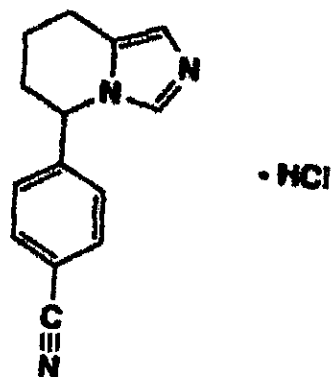
K_i = 0.47 μM



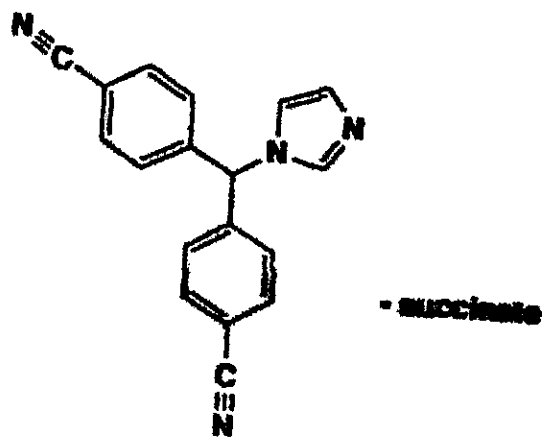
AMINOGLUTETHIMIDE



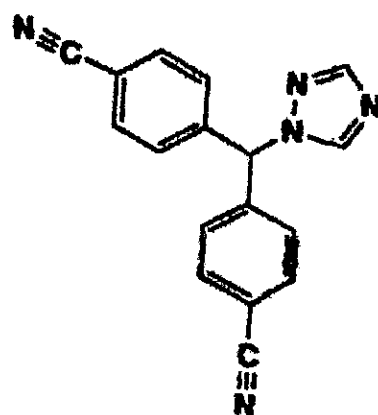
CGS 16949A



CGS 18320B



CGS 20267



Aminoglutethimide

Fadrozole

Tritiated H₂O Assay
Human Placenta

Ovarian Estrogen Content
In Vivo Rat

ED₅₀ = 10-30 mg/kg ED₅₀ = 13-26 µg/kg

Product Isolation Assay
Human Placenta

IC₅₀ = 220 nM IC₅₀ = 1.4 nM
K_i = 470 nM K_i = 1.5 nM

Inhibition Corticosterone
In Vivo Rat

Vehicle = 609 ± 31 ng/ml
FAD 4mg/kg = 602 ± 28 ng/ml

Endocrine Organ wts
In Vivo Rat (4mg/kg)

Endocrine Organ Weights
In Vivo Rat (4mg/kg)

Treatment (n = 10)	Bwt. (g)	mg/100 g body weight			
		Ovaries	Uterus	Adrenals	Pituitary
Control	202.7	37.7	165.6	24.5	5.8
S.E.	-3.4	2.1	10.1	1.4	0.4
Fadrozole	223.4*	48.3*	84.1*	21.8	3.8*
S.E.	3.5	3.1	7.4	2.0	0.2

*p<0.05 [Dunnett]

Fadrozole

clinically developed in U.S. and Europe
never registered

Registered in Japan 1994 (Afema)

Letrozole (Femara)

Registered in U.S. and Europe 1997

MA-17 study

Tamoxifen 5 yrs + additional 5yrs Femara

Early stage hormone receptor positive breast cancer

reduced risk of cancer return

reduced risk of cancer spreading

2011 FDA approved generic version for 11 companies