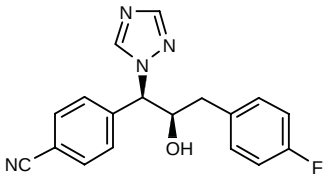
Drugs of the Future 1998, 23(10): 1071-1074

CCC: 0377-8282/98

MPV-2213ad

Antineoplastic
Aromatase Inhibitor

(±)-(*R**,*R**)-4-[3-(4-Fluorophenyl)-2-hydroxy-1-(1,2,4-triazol-1-yl)propyl]benzonitrile



$C_{18}H_{15}FN_4O$ Mol wt: 322.3415

CAS: 160146-16-7
CAS: 160146-17-8 [as racemic (*R**,*S**)-isomer]

EN: 213033

Synthesis

MPV-2213ad was synthesized by condensation of 4-(1,2,4-triazol-1-ylmethyl)benzonitrile (I) with 2-(4-fluorophenyl)acetaldehyde (II) by means of butyl lithium in THF. The two diastereomeric racemates are separated by flash chromatography (1). Scheme 1.

Introduction

Aromatase, a member of the cytochrome P450 family of enzymes, catalyzes the conversion of androgens to estrogens which leads to an increase in plasma estrogen levels. The inhibition of aromatase activity resulting in estrogen deprivation has been found to be extremely useful as a second-line therapy for estrogen-dependent metastatic breast cancer and may also be a beneficial treatment for the management of other estrogen-dependent processes and/or diseases.

The first aromatase inhibitor, aminoglutethimide (Orimeten® tablets, 250 mg; Novartis) was introduced in 1981 and is currently used as a second-line hormonal treatment of postmenopausal breast cancer (2). Aminoglutethimide affects adrenal steroid synthesis. Thus, treatment with this agent requires concommittant corticosteroid replacement therapy. Research efforts have therefore focused on the design and synthesis of more selective aromatase inhibitors. In 1992, the steroidal parenteral compound formestane (Lentaron® powder in vial, 250 mg; Novartis) was launched with the advantage of having greater selectivity without affecting adrenal steroid production.

The newest aromatase inhibitors to reach the market are the nonsteroidal orally active compounds and include Novartis' fadrozole hydrochloride (Afema® tablets, 1 mg; launched in 1995 in Japan), Zeneca's anastrozole (Arimidex® tablets, 1 mg; launched in 1995 in the U.K.) and Novartis' letrozole (Femara® tablets, 2.5 mg; launched in 1996 in the U.K.) for the treatment of postmenopausal breast cancer. Two steroidal compounds, exemestane (Pharmacia & Upjohn) and NKS-01 (Snow Brand/Nippon Kayaku), and three nonsteroidal aromatase inhibitors, vorozole (Janssen), YM-511 (Yamanouchi) and MPV-2213ad (Hormos Medical), are currently undergoing clinical trials. As shown in Table I, several aromatase inhibitors are in preclinical studies. Table II shows the aromatase inhibitory activity of these selected compounds.

Pharmacological Actions

MPV-2213ad is a new competitive, highly potent and selective nonsteroidal aromatase inhibitor which was

Scheme 1: Synthesis of MVP-2213ad

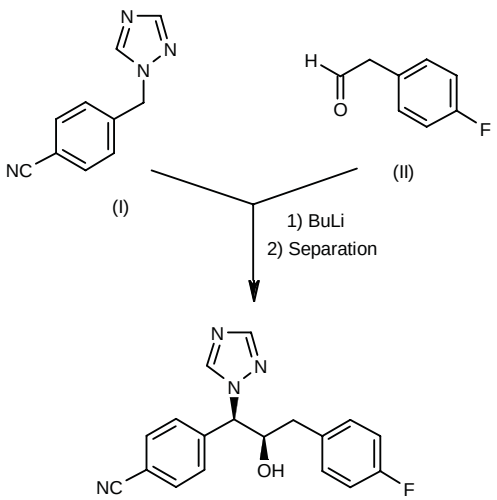


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Table I: Chemical structures of aromatase inhibitors.

Launched

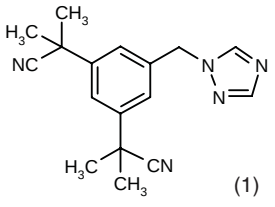
1. Anastrozole
   Arimidex
   Zeneca (1995)
2. Fadrozole HCl
   Afema
   Novartis (1995)
3. Formestane
   Lentaron
   Novartis (1992)
4. Letrozole
   Femara
   Novartis (1996)

Clinical Trials

5. Exemestane
   Pharmacia & Upjohn
6. MPV-2213ad
   Hormos Medical
7. NKS-01
   Snow Brand; Nippon Kayaku
8. Vorozole
   Rivizor
   Janssen (Johnson & Johnson)
9. YM-511
   Yamanouchi

Preclinical Testing

10. MR-20492
    CNRS; Caen Univ.
11. SEF-19
    Zenyaku Kogyo
12. TZA-2209
    Teikoku Hormone
13. ZK-138723
    Schering AG



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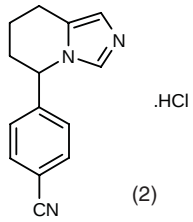

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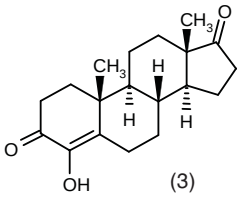

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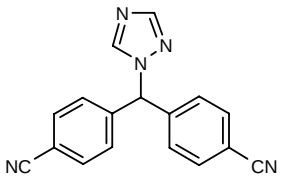

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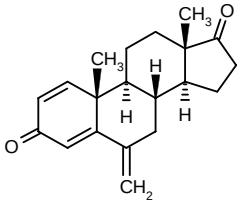

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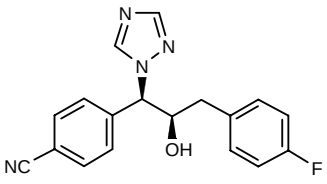

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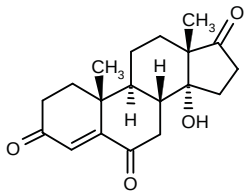

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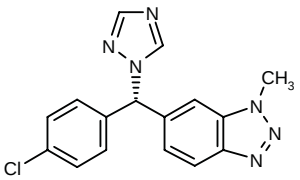

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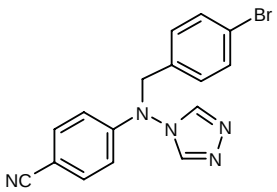

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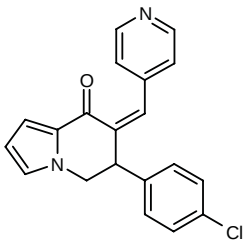

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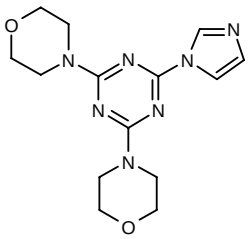

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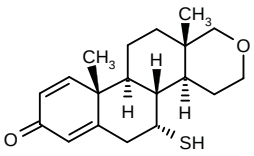

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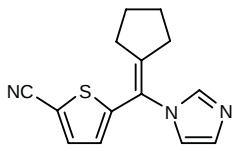

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Source: Prous Science Ensemble database.

shown to inhibit aromatase from human placental microsomes with IC_{50} values of 0.18-0.47 μM. High selectivity of the agent was demonstrated when even high concentrations of 1000 μM did not affect desmolase or human liver cytochrome P450 enzymes. It appears that administration of MPV-2213ad to rats resulted in complete suppression of ovarian aromatase activity, possibly reducing plasma estrogen to levels similar to those observed with castration. Furthermore, in rats bearing dimethylbenzanthracene-induced, estrogen-dependent mammary carcinomas, MPV-2213ad treatment induced regression of more than 80% of the tumors (3).

Clinical Studies

In a phase I open clinical trial, the selectivity and tol-

Table II: Activity of selected aromatase inhibitors.

Compound	Aromatase inhibition IC_{50} (nM)	Material	Ref.
Aminoglutethimidine	3800	Human placenta	4
	3900	Rat granulosa cells	5
	5000	Human breast cancer cells	6
Anastrozole	14.60	Human placenta	7
Exemestane	30	Human placenta	4
	40	Rat ovary	4
Fadrozole	1.00	Human breast cancer cells	8
	1.48*	Rat ovary	9-11
	5.40	Human placenta	7
	6.91*	Human placenta	9, 11, 12
Formestane	270	Pig placenta	13
	590	Rat ovary	13
	3500	Human placenta	12
Letrozole	0.39*	Human placenta	9, 11
	1.81*	Rat ovary	10, 11
MPV-2213ad	180-470	Human placenta	3
NKS-01	550*	Human breast cancer cells	6, 8
Vorozole	1.4	Rat granulosa cells	14
YM-511	0.4*	Rat ovary	9-11, 15
	0.125*	Human placenta	9, 11, 15, 16

*Mean value from different references which used the same experimental method. Source: Prous Science MFLine database.

erability of MVP-2213ad were examined in 39 healthy subjects. After overnight fasting, subjects were orally administered MVP-2213ad (0.003, 0.03, 0.3, 3, 9, 30, 100, 300 or 600 mg) with doses escalated if preceding dosages were well tolerated. Although results obtained from subjects receiving the low doses of 0.003 and 0.03 mg MVP-2213ad were inconsistent, estrogen plasma levels were dose-dependently suppressed by 58-65% in individuals receiving 0.3-30 mg MVP-2213ad with a maximum reduction of 83% observed in subjects receiving 300 mg; nadir values were obtained at 8 h and 20 h for 0.3 mg and 300 mg, respectively. Duration of suppression of estrogen levels was longer at higher doses of MVP-2213ad, with levels returning to baseline values within 2-4 days with doses of 100, 300 and 600 mg. The maximum suppression of estrogen levels observed with MVP-2213ad treatment is comparable to the estrogen-reducing activities observed with other aromatase inhibitors such as anastrozole and CGS-20267 (letrozole). MVP-2213ad treatment also reduced plasma estrone levels by 19-29%

Box 1: Efficacy and safety of MPV-2213ad (3).

Study Design	Open clinical trial
Study Population	Healthy male volunteers (n = 39)
Intervention Groups	MPV-2213ad, 0.003 mg (n = 3) MPV-2213ad, 0.03 mg (n = 3) MPV-2213ad, 0.3 mg (n = 3) MPV-2213ad, 3 mg (n = 3) MPV-2213ad, 9 mg (n = 3) MPV-2213ad, 30 mg (n = 3) MPV-2213ad, 100 mg (n = 3) MPV-2213ad, 300 mg (n = 10) MPV-2213ad, 600 mg (n = 8)
Significance of Results	Serum E_2 levels (change) at 24 h: 0.003, 15; 0.03, 9; 0.3, -12; 3, -53; 9, -86; 30, -101; 100, -80; 300, -82; 600, -68 pmol/l (testosterone, androstenedione, 17-hydroxyprogesterone, LH and FSH increased after 100-600 mg MPV-2213ad)
Conclusions	MPV-2213ad is effective in clearing serum E_2 and is well tolerated

Source: Prous Science CTLine database.

at 8 h; levels were maintained for 4 days with 100, 300 and 600 mg doses. In addition, significant increases in testosterone, androstenedione, 17-OH-progesterone, LH and FSH were also noted in subjects receiving doses of 100, 300 and 600 mg. However, basal serum aldosterone and cortisol of MVP-2213ad-treated subjects were maintained throughout the study, indicating that there was no inhibition of hydroxylase enzymes. No adrenocortical suppression or hematological or biochemical toxicity was observed, indicating good clinical tolerability. Only transient mild to moderate adverse effects were observed, including hot flashes, vertigo, nausea, acne and gastrointestinal discomfort (3) (Box 1).

Manufacturer

Hormos Medical Ltd. (FI); licensed from Orion Pharma (FI).

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