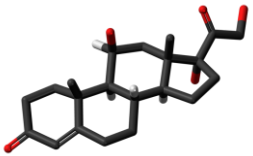
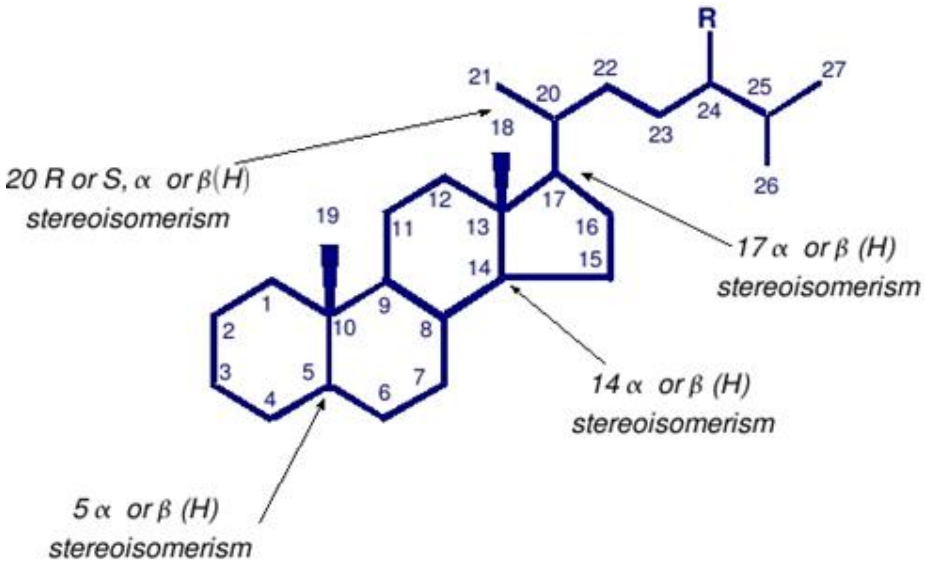
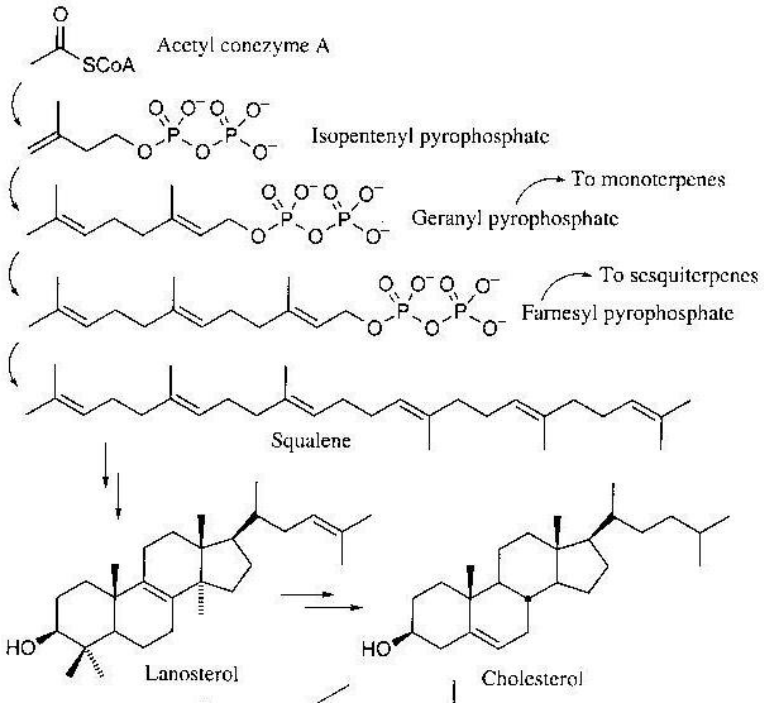
Steroids

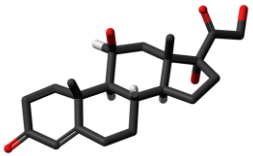


Steroid hormones: cholesterol derivatives





Steroids



Steroid hormones: endocrine classes

Corticosteroids / Adrenocorticoids:

GLUCOCORTICOIDS

MINERALOCORTICOIDS

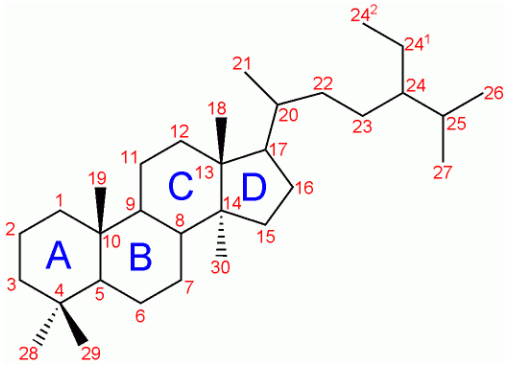
Female sexual hormones:

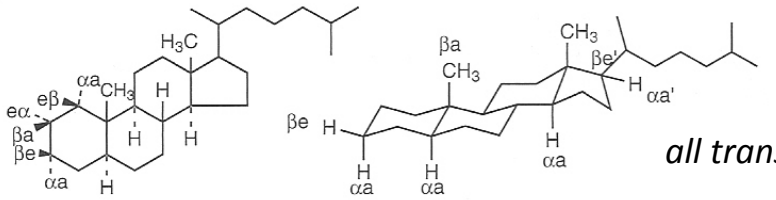
ESTROGENS

PROGESTAGENS

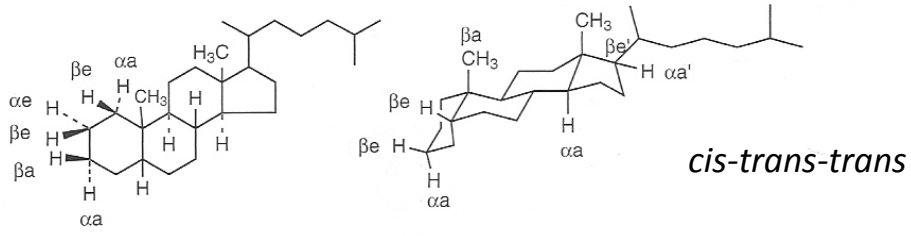
Male sexual hormones:

ANDROGENS





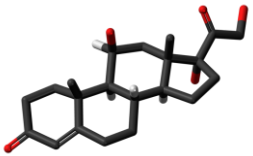
5α-Colestano — Rappresentazione della conformazione del 5α-colestano



5β-Colestano — Rappresentazione conformazionale del 5β-colestano

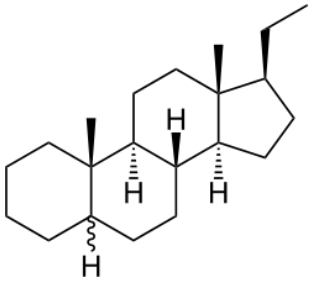
a = assiale — a' = quasi-assiale
e = equatoriale — e' = quasi-equatoriale

Steroids

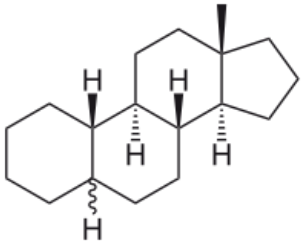


Steroid hormones: chemical classes

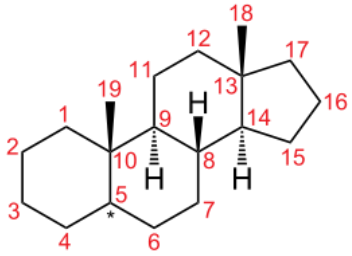
Pregnans: C21



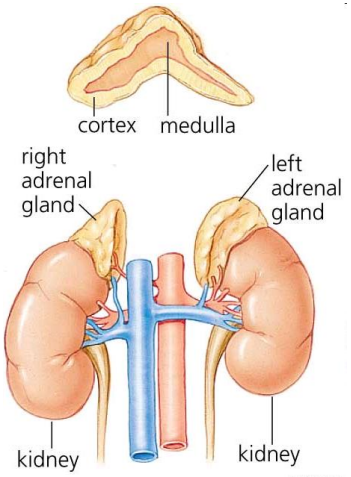
Estrans: C18



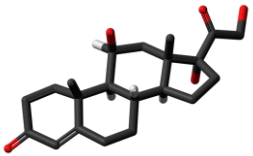
Androstans: C19

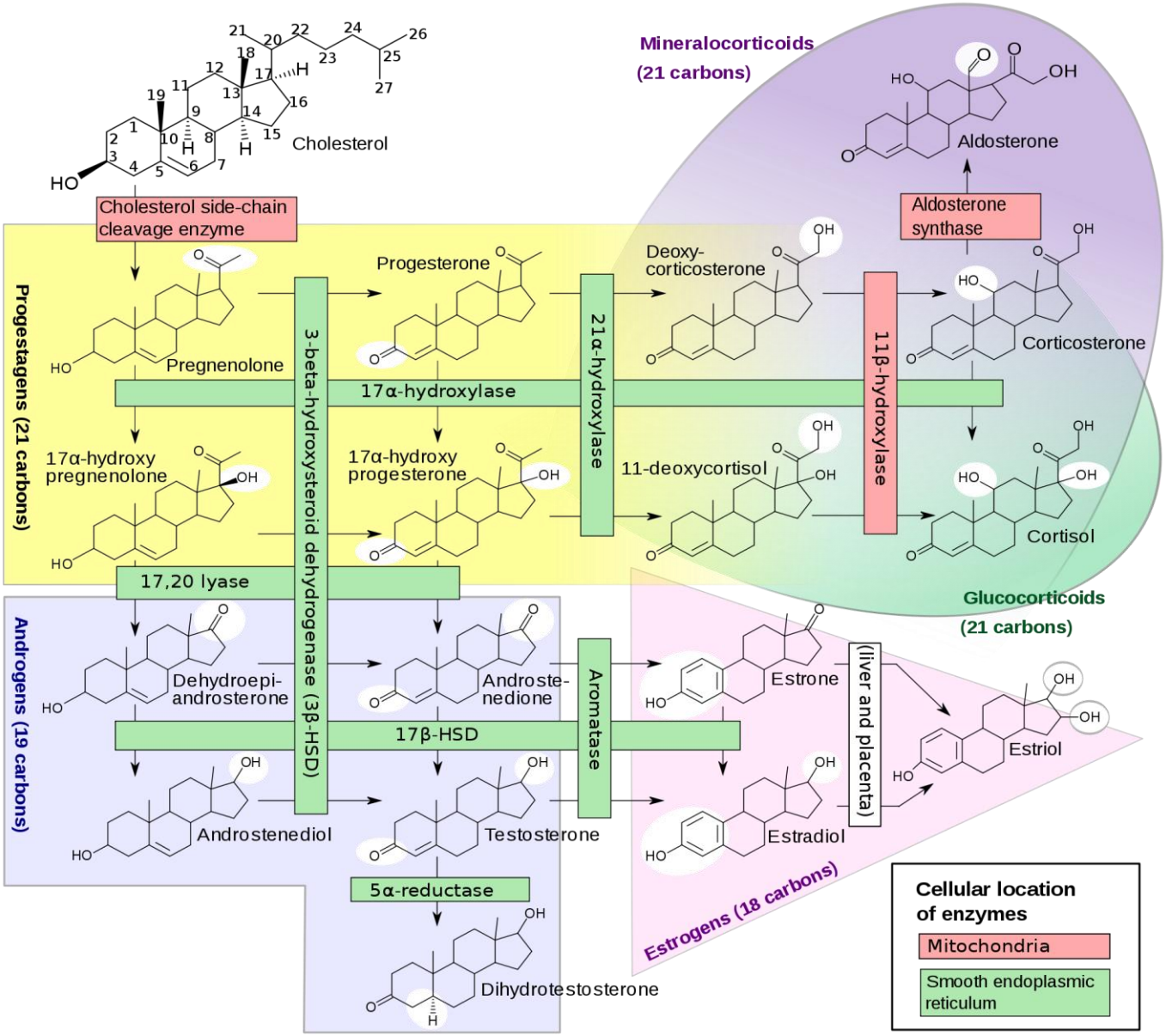


- Physiological concentration very low: 0.1-1 nM.
- Regulate protein biosynthesis.
- Production site: *surrenal/adrenal glands, (gonads and other tissues)*

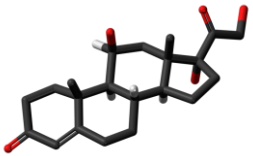


Steroids




Cholesterol
Cholesterol side-chain cleavage enzyme
Progestagens (21 carbons)
Pregnenolone
Progesterone
17α-hydroxy pregnenolone
17α-hydroxy progesterone
3-beta-hydroxysteroid dehydrogenase (3β-HSD)
17α-hydroxylase
17,20 lyase
Androgens (19 carbons)
Dehydroepi-androsterone
Androste-nedione
Androstenediol
Testosterone
17β-HSD
5α-reductase
Dihydrotestosterone
21α-hydroxylase
Aromatase
Mineralocorticoids
(21 carbons)
Deoxy-corticosterone
Corticosterone
Aldosterone
Aldosterone synthase
11β-hydroxylase
11-deoxycortisol
Cortisol
Glucocorticoids
(21 carbons)
Estrone
Estradiol
Estriol
(liver and placenta)
Estrogens (18 carbons)
Cellular location of enzymes
Mitochondria
Smooth endoplasmic reticulum

Steroids



Cholesterol: from 3 sources

- from AcCoA biosynthesis.
- ester hydrolysis in steroidogenic cells
- uptake from LDL

Hormones: from CYP / HSD metabolism

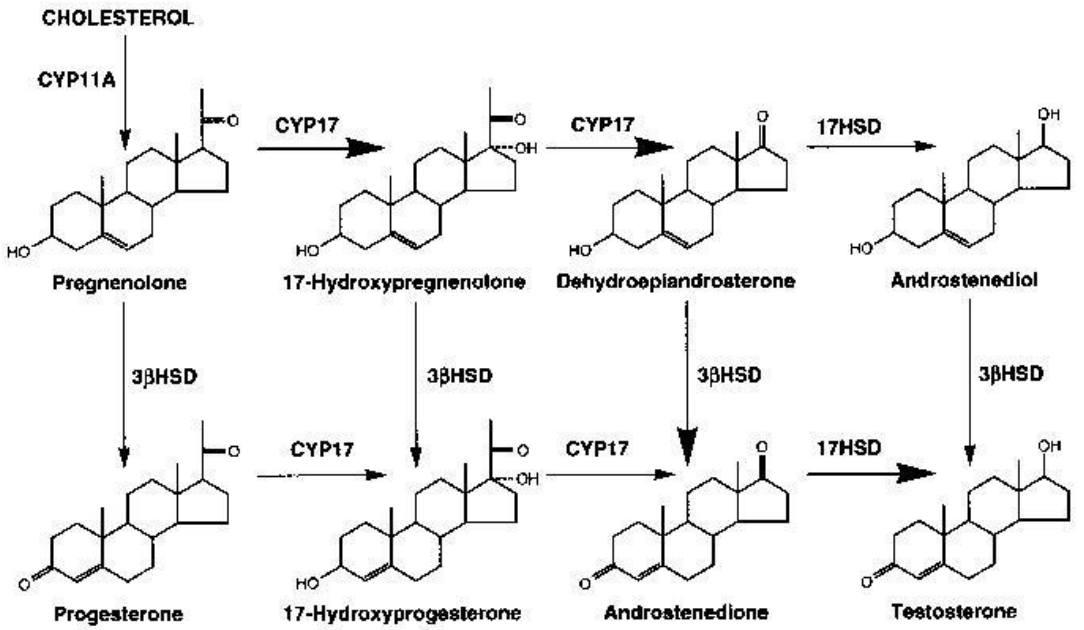
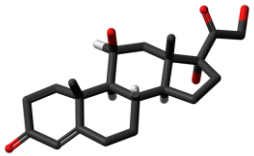
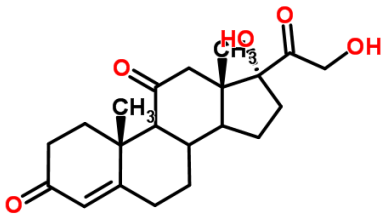


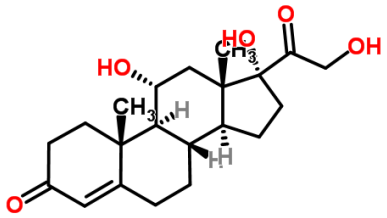
Fig. 2 The steroid biosynthetic pathway to testosterone and the enzymes involved. The *larger arrows* represent the major route in the human.
Note: in the testis, the chief isoforms of 3β-hydroxysteroid dehydrogenase/isomerase and 17β-hydroxysteroid dehydrogenase are 3βHSDII and 17βHSD3 respectively. 17βHSD3 is not expressed in the ovary but 17βHSD5 may account for the biosynthesis of testosterone in normal and abnormal states of ovarian function. 17βHSD5 can be expressed in human adrenal tumour cells but if actual synthesis of testosterone in the adrenal cortex of healthy adults does occur it appears to be minimal

Glucocorticoids (WADA S9)



Corticosteroids: GLUCOCORTICOIDS



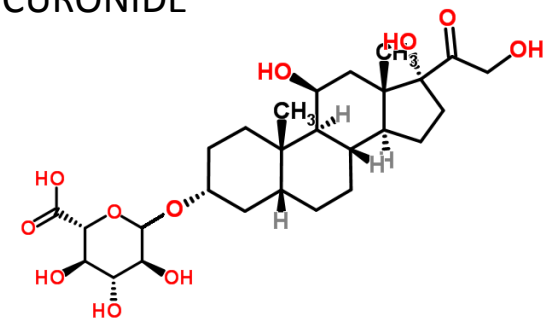


Endogenous compounds: C21 pregnans

CORTISONE, CORTISOL (HYDROCORTISONE)

Secretion by the action of peptidic hypophysis (ACTH) and hypothalamic (CRF) hormones.

Cortisol (active) and cortisone (inactive) are interconverted by 11β-hydroxysteroid dehydrogenase. Urinary excretion as inactive UROCORTISOL GLUCURONIDE

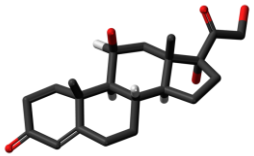


Function: regulate sugars, lipid and protein metabolism.

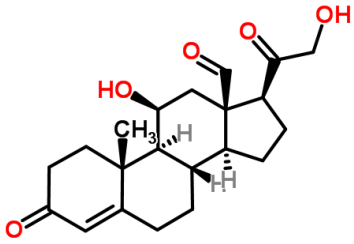
Prevent inflammation and immune reactions.

Pathologies: Addison disease (adrenal insufficiency); Cushing syndrome (hyperadrenocorticism); Conn syndrome (hyperaldosteronism).

Mineralocorticoids



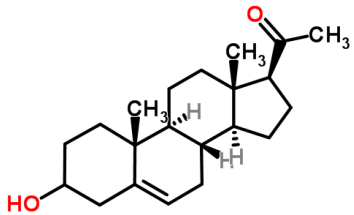
Corticosteroids: MINERALOCORTICOIDS



Endogenous compounds: C21 pregnans

ALDOSTERONE

Secretion by the action of angiotensin II. Biosynthesis from PREGNENOLONE



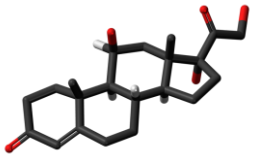
Function: regulate electrolytic balance and water reabsorption

Pathologies: Addison disease (adrenal insufficiency); Hyperaldosteronism (generally from adrenal cancers)

Antagonists: SPIRONOLACTONE

cfr diuretics

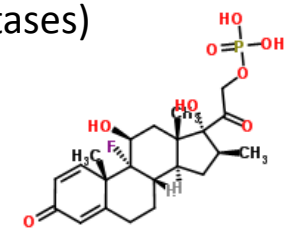
Glucocorticoids (WADA S9)



Corticosteroid drugs:

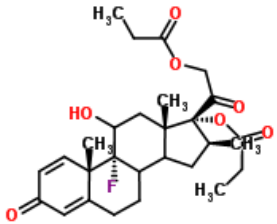
Corticosteroids for systemic use:

BETAMETHASONE PHOSPHATE, logD$^{7.4}$ -3.7, 5' halflife (phosphatases)

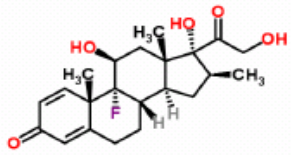


Corticosteroids for topical use:

BETAMETHASONE DIPROPIONATE, logD$^{7.4}$ 4.42

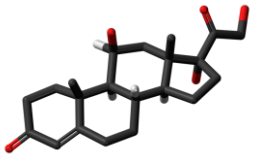


Corticosteroids for nasal use/ inhalation

Name	**BETAMETHASONE**
Structure	
Systematic name	(11β,16α)-9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione
Formula	$C_{22}H_{29}FO_5$
MW	392.4611
Monoisotopic mass	392.199902243
Mp	262-264°C
H bond acceptors	5
H bond donors	3
Acid p*Ka*	--
Basic p*ka*	--
ACD Log D pH 5.5	1.87
ACD Log D pH 7.4	1.87
Solubility	acetone, chloroform
LD50	4067 mg/Kg rat p.o.
Therapeutic cat	glucocorticoid
ATC **A07EA04** A ALIMENTARY TRACT AND METABOLISM A07 ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS A07E INTESTINAL ANTIINFLAMMATORY AGENTS A07EA Corticosteroids acting locally **C05AA05** C CARDIOVASCULAR SYSTEM C05 VASOPROTECTIVES C05A AGENTS FOR TREATMENT OF HEMORRHOIDS AND ANAL FISSURES FOR TOPICAL USE C05AA Corticosteroids **D07AC01** D DERMATOLOGICALS D07 CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS D07A CORTICOSTEROIDS, PLAIN D07AC Corticosteroids, potent (group III)	**H02AB01** H SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS H02 CORTICOSTEROIDS FOR SYSTEMIC USE H02A CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN H02AB Glucocorticoids **R01AD06** R RESPIRATORY SYSTEM R01 NASAL PREPARATIONS R01A DECONGESTANTS AND OTHER NASAL PREPARATIONS FOR TOPICAL USE R01AD Corticosteroids S03BA03 S SENSORY ORGANS S03 OPHTHALMOLOGICAL AND OTOLOGICAL PREPARATIONS S03B CORTICOSTEROIDS S03BA Corticosteroids and association with antibiotics, mydriatics, etc
Receptors	intracellular glucocorticoid receptors

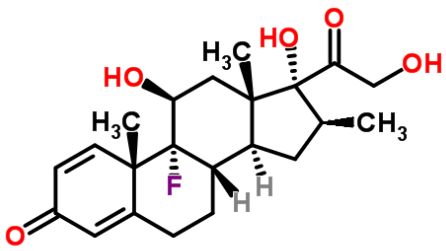
Nomi commerciali (IT)	
>40 specialità, in associazione come b. o b. estere dipropionato, fosfato, valerato, etc	

Glucocorticoids (WADA S9)

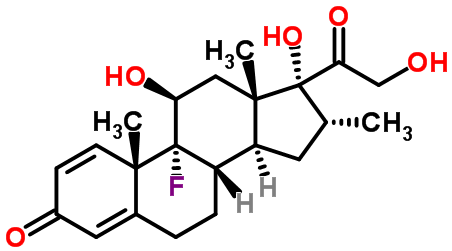


Corticosteroid drugs:

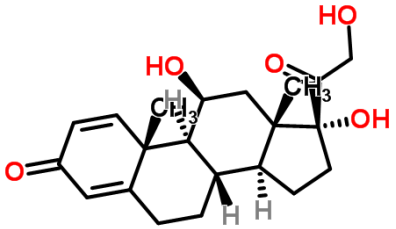
Corticosteroids for systemic use: Rheumatoid arthritis, inflammation, allergy, asthma.



BETAMETHASONE



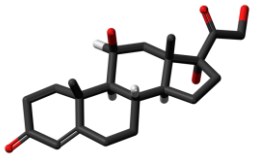
DEXAMETHASONE



PREDNISOLONE

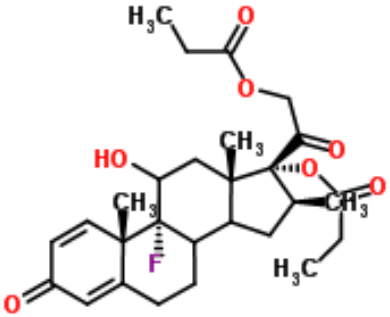
Δ_1-corticoids: hydrocortisone bacterial dehydrogenation / total synthesis. Beta/Dexa: epimers, similar activity.

Glucocorticoids (WADA S9)

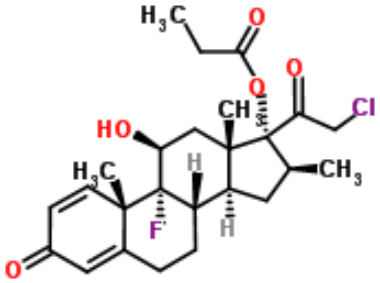


Corticosteroid drugs:

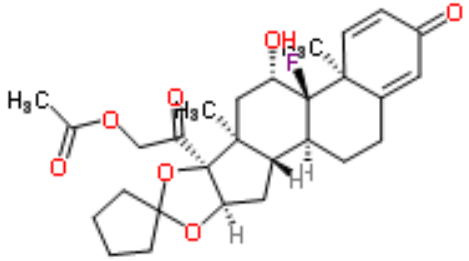
Corticosteroids for topical use: dermatosis, eczema, psoriasis.



BETAMETHASONE DIPROPIONATE



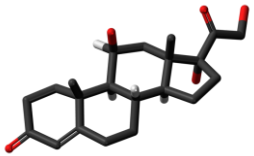
CLOBETASOL PROPIONATE



AMCINONIDE

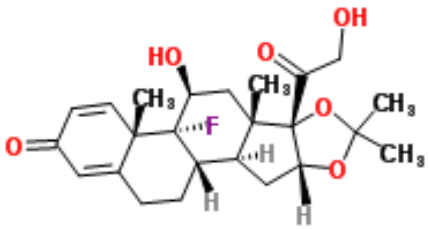
Lipophilic, used in creams/gels.

Glucocorticoids (WADA S9)

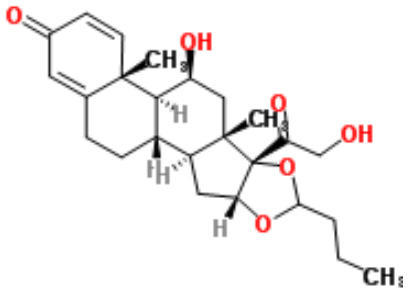


Corticosteroid drugs:

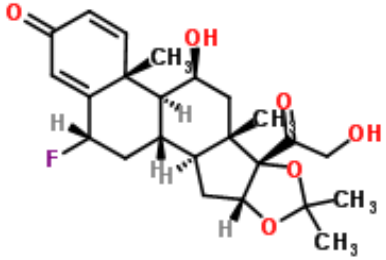
Corticosteroids for nasal use/ inhalation : *via* aerosol: rhinitis, asthma.



TRIAMCINOLONE ACETONIDE



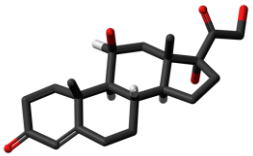
BUDESONIDE



FLUNISOLIDE

Local effect in the lungs

Sex hormones

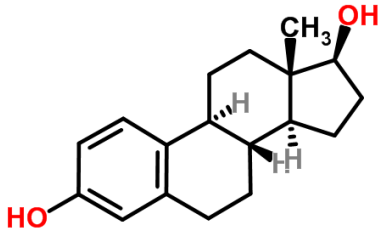


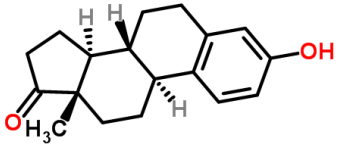
Female sex hormones : ESTROGENS

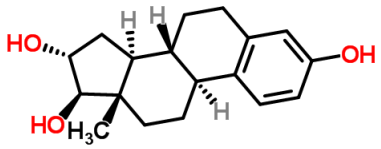
Endogenous compounds: C18 estrans

ESTRADIOL, ESTRONE, ESTRIOL

Follicular/placentar secretion by the action of peptidic hypophysis (FSH) hormones.



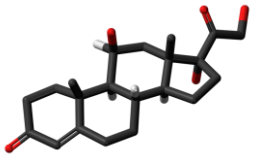




Function: development of secondary sexual characters, mammary gland stimulation, thermoregulation.

Pathologies: Menstrual diseases; hypoestrogenism, amenorrhea, dysmenorrhea, etc.

Sex hormones

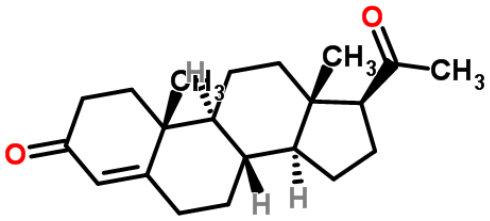


Female sex hormones : PROGESTANES

Endogenous compounds: C21 pregnans

PROGESTERONE

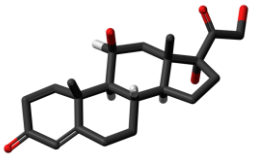
Ovary secretion by the action of peptidic hypophysis (LH) hormones *via* cAMP.



Function: action on uterus/reproduction.

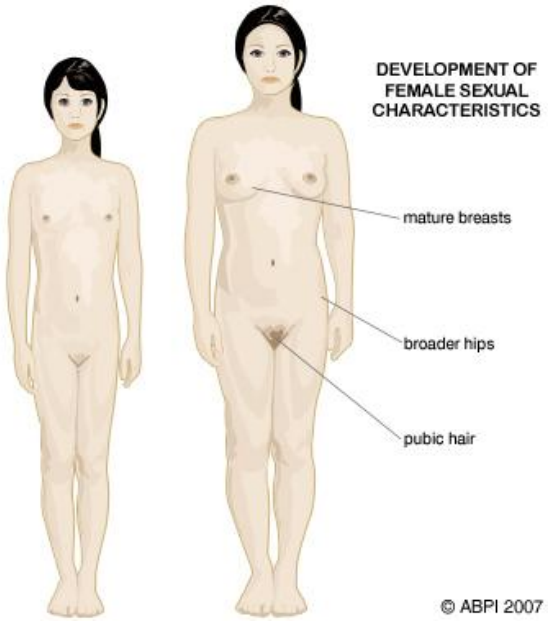
Pathologies: amenhorrea; dysmenhorrea.

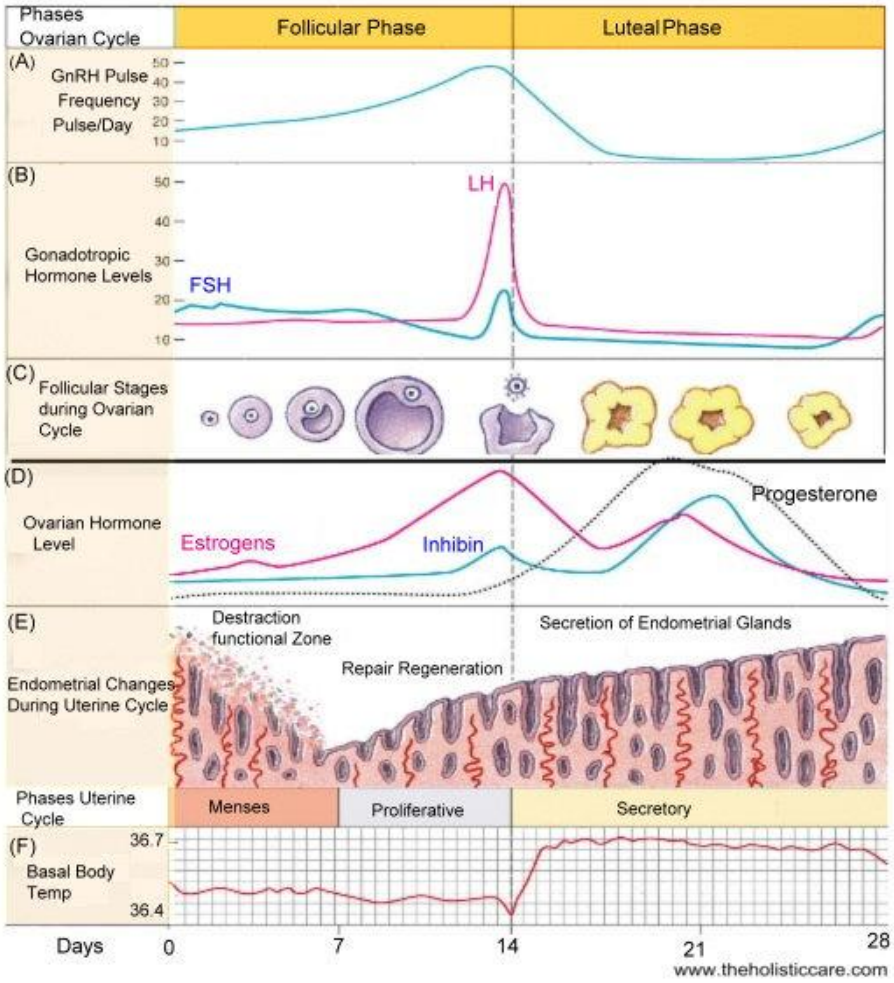
Sex hormones



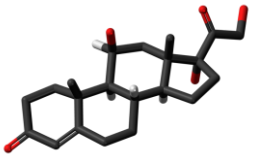
Female sex hormones :

Menstrual cycle, secondary sexual characters



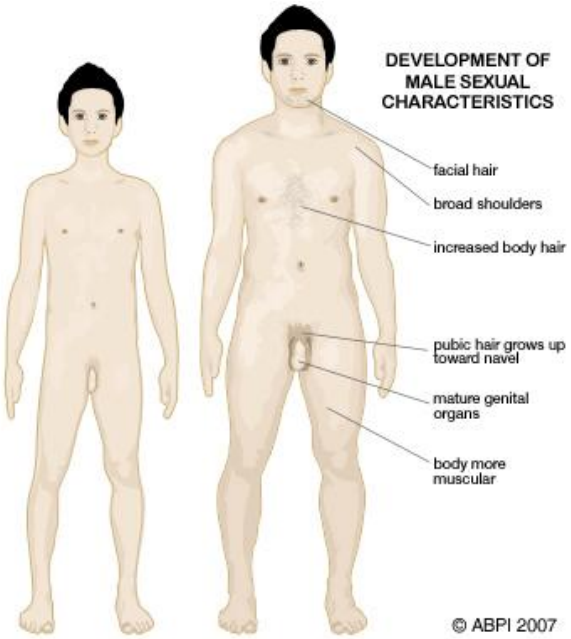


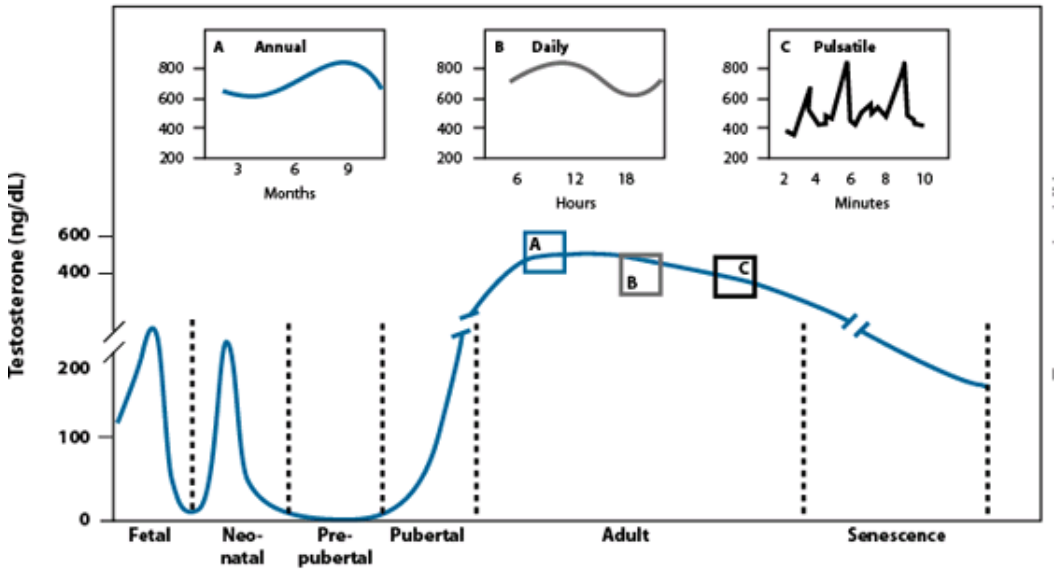
Sex hormones



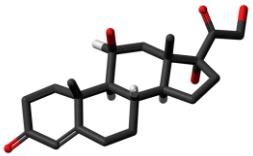
Male sex hormones :

Reproduction, secondary sexual characters

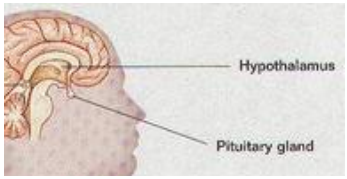




Sex hormones, Anabolic agents WADA S1

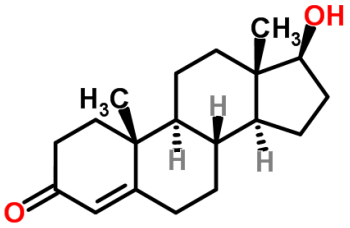


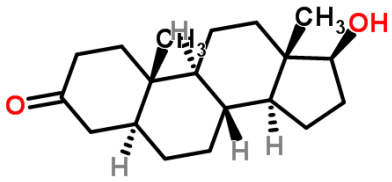
Male sex hormones : ANDROGENS

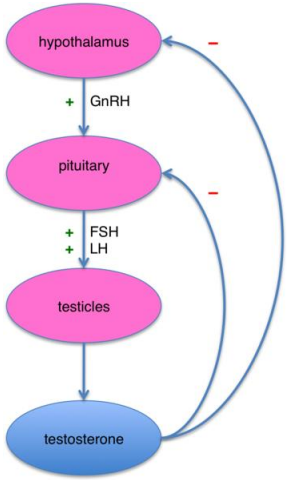


Endogenous compounds: C19 androstans

TESTOSTERONE and **5α-DIHYDROTESTOSTERONE (DHT)**







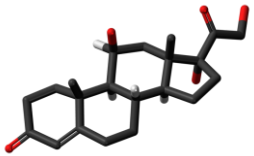
Secretion by the action of peptidic hypophysis (FSH/LH) hormones.

Negative feedback by testosterone

Function: development of secondary sexual characters (androgenic/anabolic effect), reproduction.

Pathologies: androgens insufficiency (hypogonadism); prostate/testis cancers.

Sex hormones, Anabolic agents WADA S1



Male sex hormones :

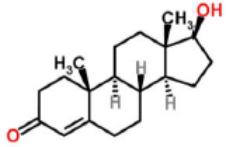
ANDROGENS

Pro-hormone (DHT is more active)

3-oxo reduction and 17-OH oxidation cause loss of activity

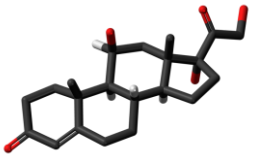
95% of biosynthesis: testicular origin (Leydig cells) 3-10 mg/day, depending on ethnic origin.

Women: 0.1-0.4 mg/day from ovaries and adrenal glands

Name	**TESTOSTERONE**
Structure	
Systematic name	(17β)-17-Hydroxyandrost-4-en-3-one
Formula	$C_{19}H_{28}O_2$
MW	288.4244
Monoisotopic mass	288.2089
Mp	154-155°C
H bond acceptors	2
H bond donors	1
Acid pK*a*	--
Basic pk*a*	--
ACD Log D pH 5.5	3.48
ACD Log D pH 7.4	3.48
Solubility	ethanol, chloroform, dioxane. Insoluble in water
LD50	1200 mg/Kg rat p.o.
Therapeutic cat	androgen
ATC	**G03BA03** G GENITO URINARY SYSTEM AND SEX HORMONES G03 SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM G03B ANDROGENS G03BA 3-oxoandrosten (4) derivatives
Receptors	AR

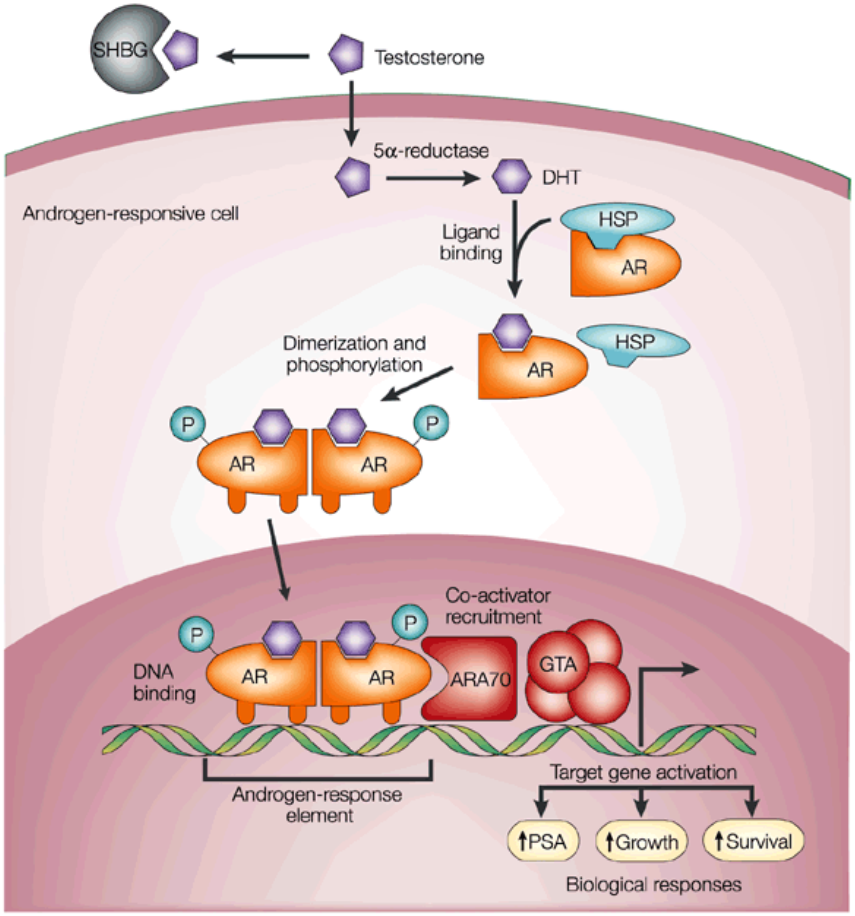
Nomi commerciali (IT)	
ANDROGEL, INTRINSA, STRIANT, TESTIM, TESTOGEL, TESTOPATCH, TOSTREX.	C, RR, compresse, gel, cerotti

Sex hormones, Anabolic agents WADA S1



Male sex hormones : ANDROGENS

Testosterone circulates in the blood bound to albumin and sex-hormone-binding globulin (SHBG), and exchanges with free testosterone. Free testosterone enters prostate (or skin) cells and is converted to **dihydrotestosterone (DHT) by the enzyme 5-reductase**. Binding of DHT to the androgen receptor (AR) induces dissociation from heat-shock proteins (HSPs) and receptor phosphorylation. The AR dimerizes and can bind to androgen-response elements in the promoter regions of target genes



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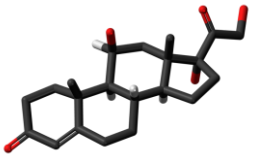
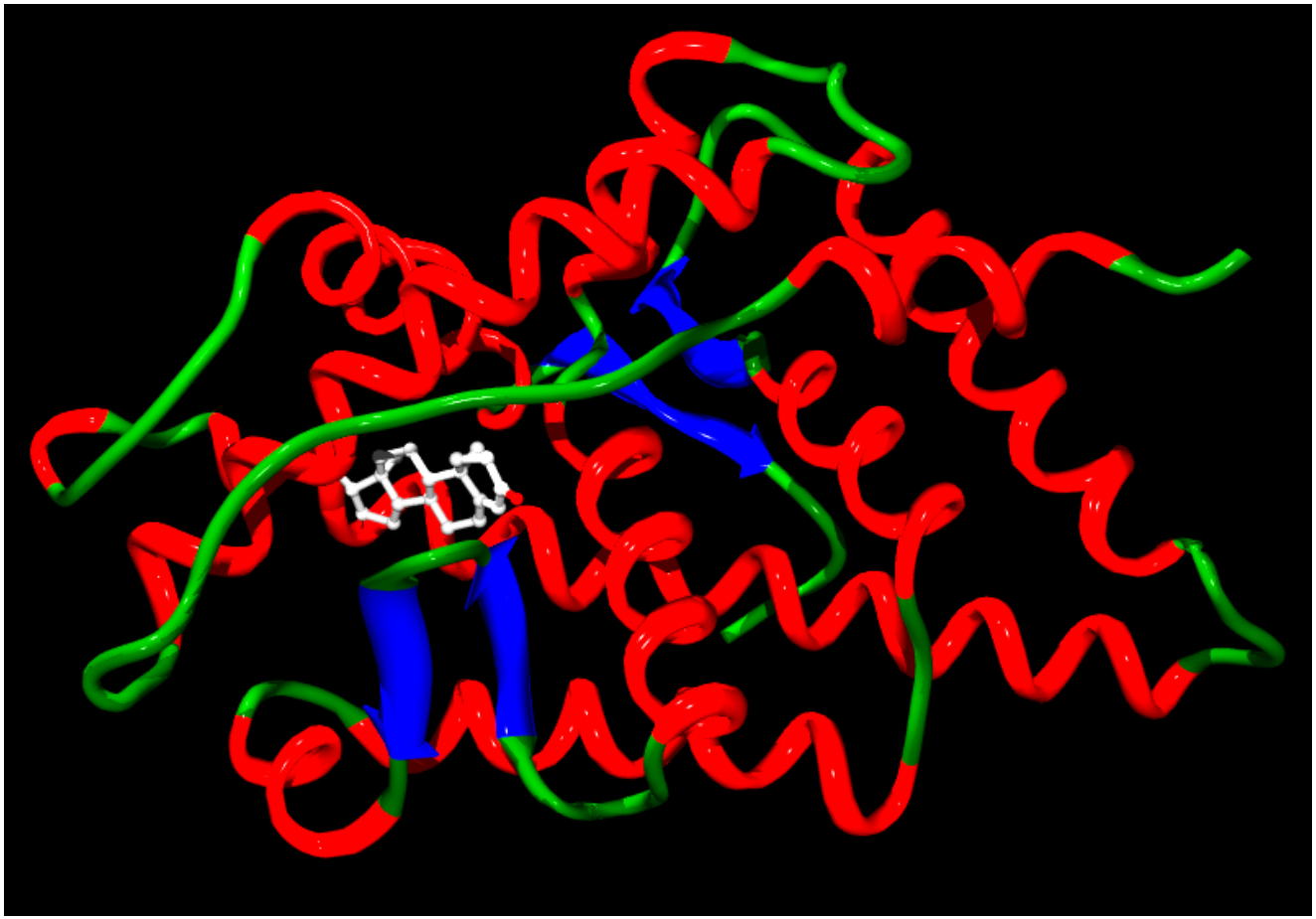
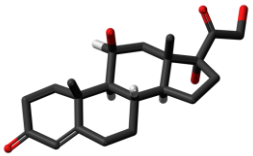


ANDROGEN RECEPTOR

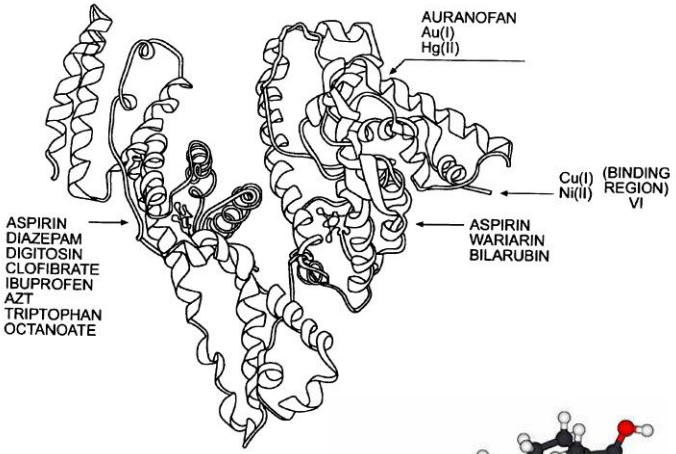


Sex hormones, Anabolic agents WADA S1

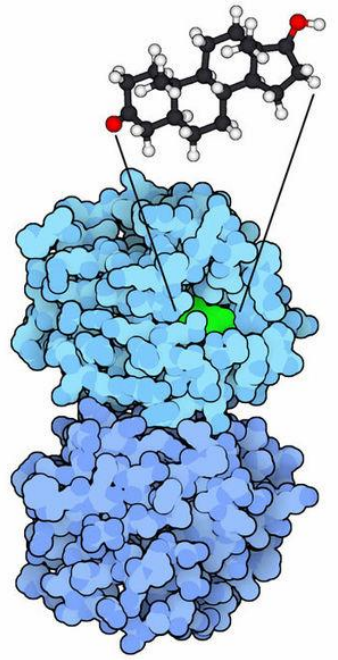


ANDROGEN TRANSPORTERS

Albumin: 66 Kda, 585 Aas, 200 negative charges at pH 7.4, 0.8 mM in plasma



Sex hormone Binding Globulin: 85.6 Kda, glycoprotein (14% sugar), 1 nM in plasma



Sex hormones, Anabolic agents WADA S1

ANDROGENS

Metabolism:

Urine: only 3% unbound **T**

40 ng/mL **T**, after glucuronidase hydrolysis

1000-4000 ng/mL **AN** + **ET**

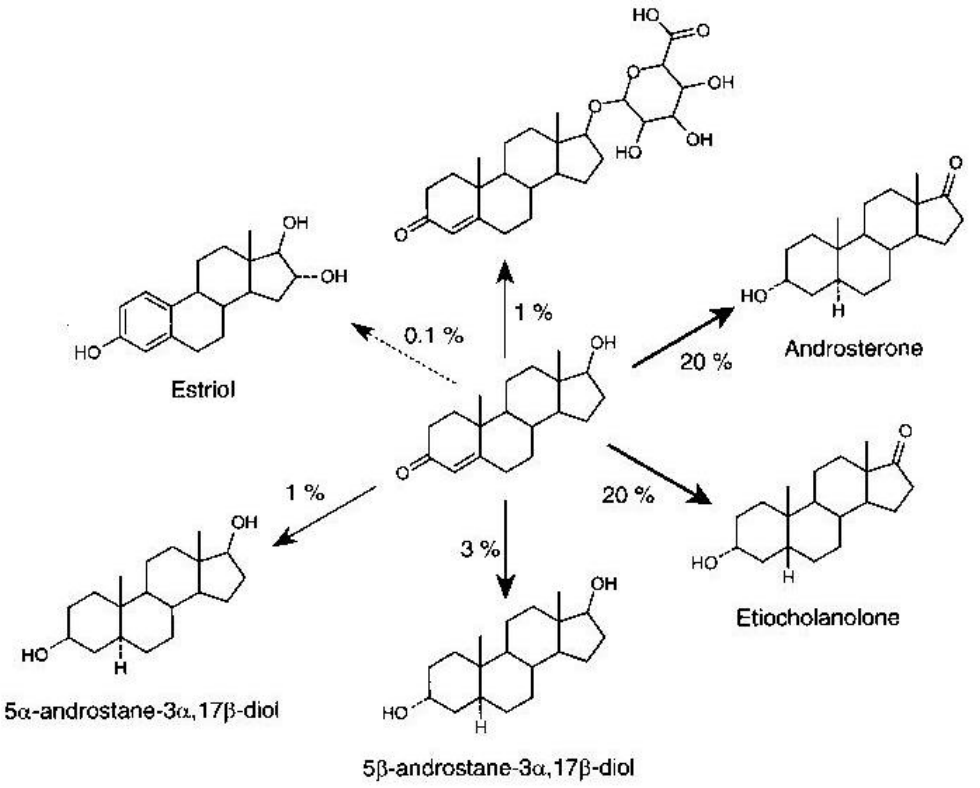


Fig. 9 Metabolism of testosterone, with figures attached to the arrows indicating the approximate proportion of testosterone which is metabolized by that route (Brooks 1975). All steroids are excreted predominantly as conjugates but only the glucuronide conjugate of testosterone is shown

Sex hormones, Anabolic agents WADA S1

ANDROGENS

Metabolism:

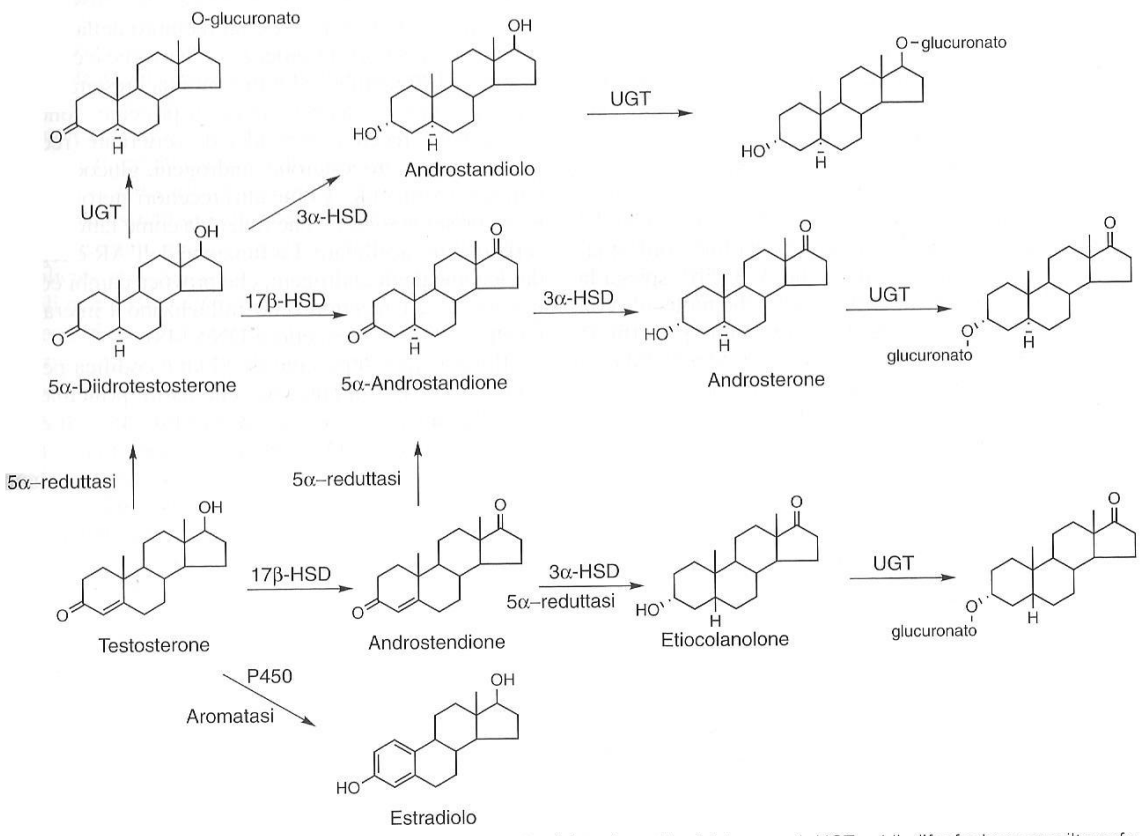


Fig. 45.5. Metabolismo del testosterone. G, glucuronide; HSD, idrossisteroide deidrogenasi; UGT, uridindifosfoglucuronosiltransferasi.

Sex hormones, Anabolic agents WADA S1

ANDROGENS

Co-Metabolism:

Epitestosterone (17-epimer) is weakly anti-androgenic.

Synthetic testosterone: $\delta\ ^{13}C < -29$ ‰

11-Ketoandrosterone: endogenous reference of isotopic ratio because unaffected by testosterone administration.

Epimerization metabolism (T to E) is negligible. T/E ratio is independent from dilution

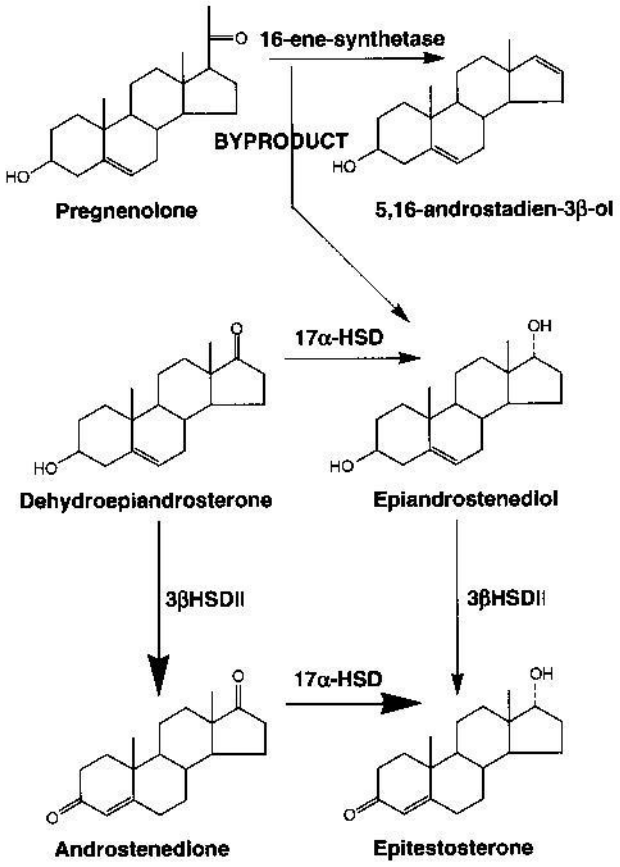
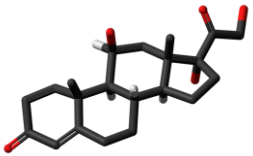


Fig. 5 Proposed synthetic pathways to epitestosterone. Note: 5,16-androstadien-3β-ol = androsta-5,16-dien-3β-ol, under the revised nomenclature of steroids of 1989 (IUPAC/IUB); the former name is used in papers describing the putative pathways

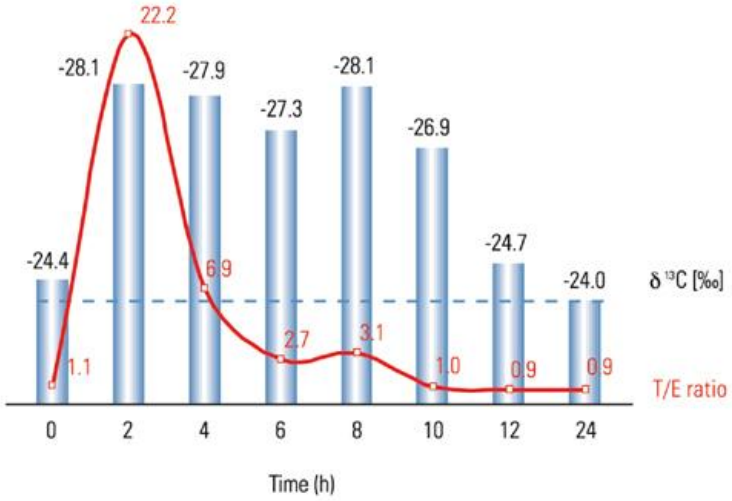
Sex hormones, Anabolic agents WADA S1

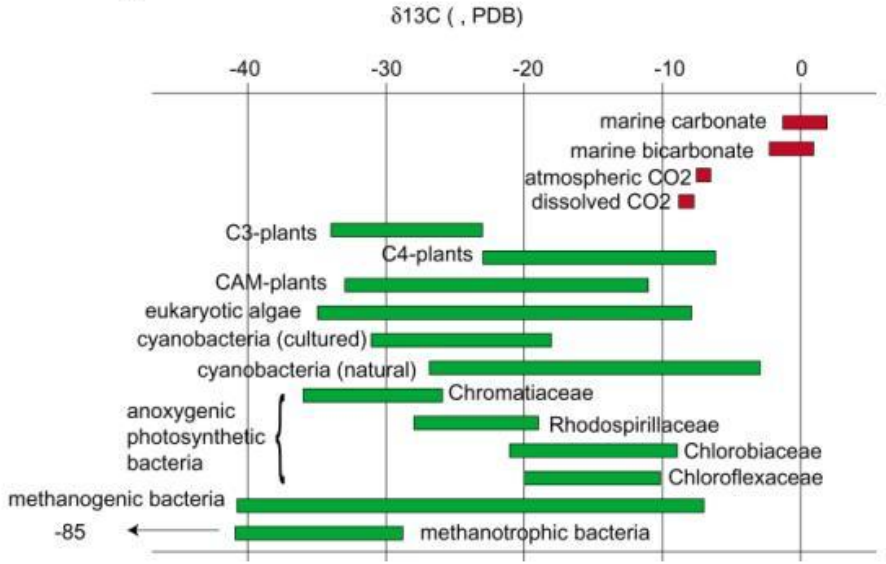


ANDROGENS

Exogenous administration:

$$\delta^{13}C = \left(\frac{\frac{^{13}C}{^{12}C_{sample}}}{\frac{^{13}C}{^{12}C_{standard}}} - 1 \right) \times 1000$$

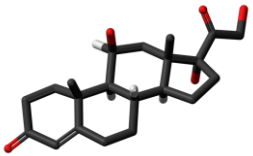




T/E ratio (after glucuronidase hydrolysis ≈1) is independent from dilution. WADA limit: 4.

Its value could be enhanced due to inter-ethnic variation (genetic polymorphism)

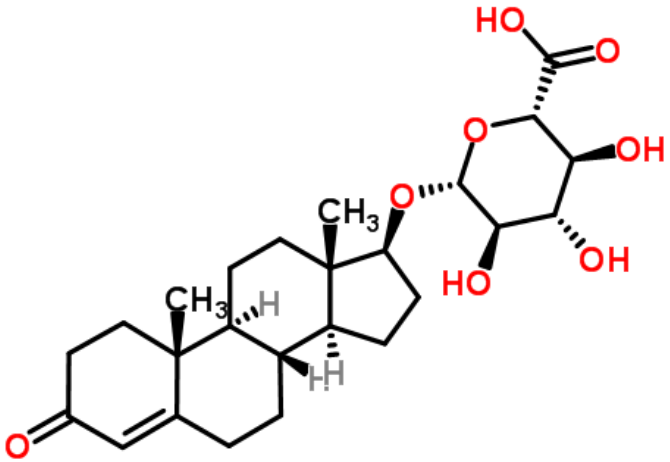
Sex hormones, Anabolic agents WADA S1



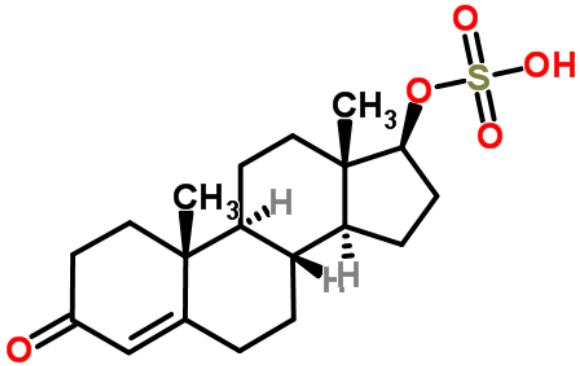
ANDROGENS

Metabolism: phase II

There are 19 UGTs (529-534 Aas)



Testosterone glucuronide, logD pH 7.4: -2.26



Testosterone sulphate, logD pH 7.4: -0.23

Sex hormones, Anabolic agents WADA S1

ENDOGENOUS ANABOLIC AGENTS

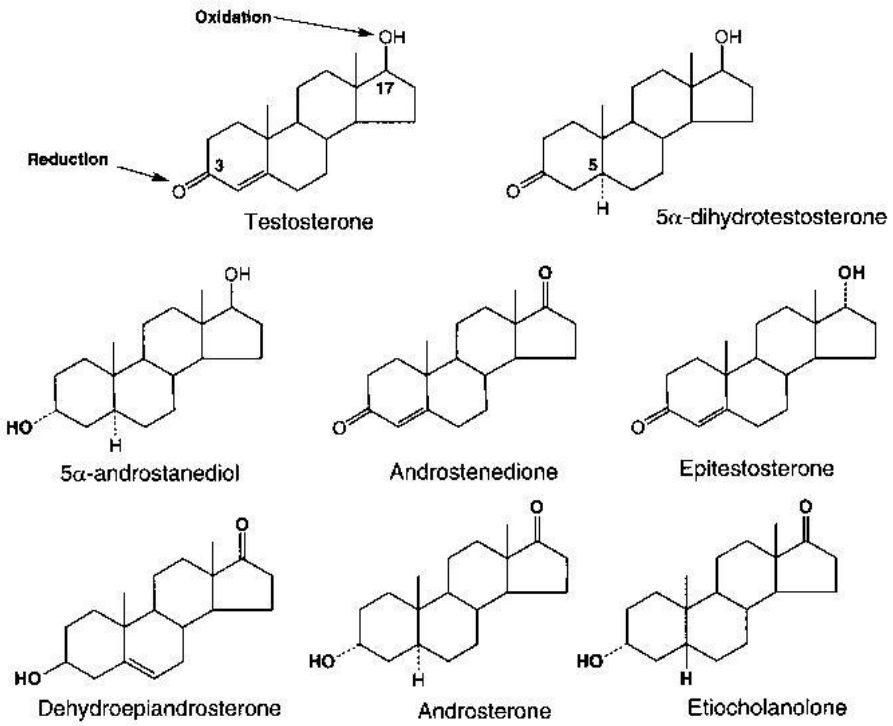
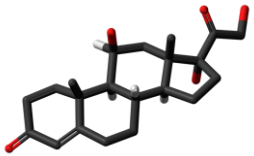


Fig. 1 Structures of endogenous androgens. The groups in *bold text* highlight the changes compared to testosterone and DHT. Testosterone and 5α-dihydrotestosterone (DHT) are displayed in the top row. Oxidation of the 17β-hydroxyl group of these androgens or reduction of the 3-oxo group results in a loss of activity (middle row) as does conversion of both groups (bottom row). Epitestosterone is a 17α-epimer of testosterone and has no androgenic activity, and neither do the 5β-reduced androgens, such as etiocholanolone

Sex hormones, Anabolic agents WADA S1



ENDOGENOUS/EXOGENOUS ANABOLIC AGENTS

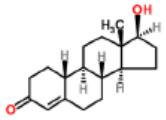
NANDROLONE

WADA S1a (exogenous)

Endogenously measured (< 2 ng/mL)

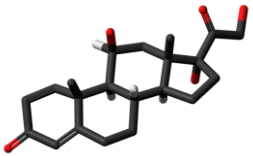
Porcine urine: 27 ng/mL

(J.F. Kay Analyses for Hormonal Substances in Food Producing Animals, RSC Pub, London 2009)

Name	**NANDROLONE**
Structure	
Systematic name	(17β)-17-Hydroxyestr-4-en-3-one
Formula	$C_{18}H_{26}O_2$
MW	274.3980
Monoisotopic mass	274.1933
Mp	112°C
H bond acceptors	2
H bond donors	1
Acid pK*a*	--
Basic pk*a*	--
ACD Log D pH 5.5	2.78
ACD Log D pH 7.4	2.78
Solubility	ethanol, chloroform, dioxane. Insoluble in water
LD50	3200 mg/Kg rat p.o.
Therapeutic cat	androgen
ATC	**A14AB01** A ALIMENTARY TRACT AND METABOLISM A14 ANABOLIC AGENTS FOR SYSTEMIC USE A14A ANABOLIC STEROIDS A14AB Estren derivatives **S01XA11** S SENSORY ORGANS S01 OPHTHALMOLOGICALS S01X OTHER OPHTHALMOLOGICALS S01XA Other ophthalmologicals
Receptors	AR

Nomi commerciali (IT)	
DECADURABOLIN (decanoato)	C, RR, fiale

Sex hormones, Anabolic agents WADA S1



ENDOGENOUS/EXOGENOUS ANABOLIC AGENTS

Metabolism: Aromatase and NANDROLONE

Gem-diol oxidation: elimination of formic acid.

Nandrolone could form as by-product of aromatization (gestation, reported 1 up to 5 ng/mL)

WADA 2004 36% of doping-positive samples

WADA 2007 5% of doping-positive samples (4th after testosterone, amphetamine, cannabis)

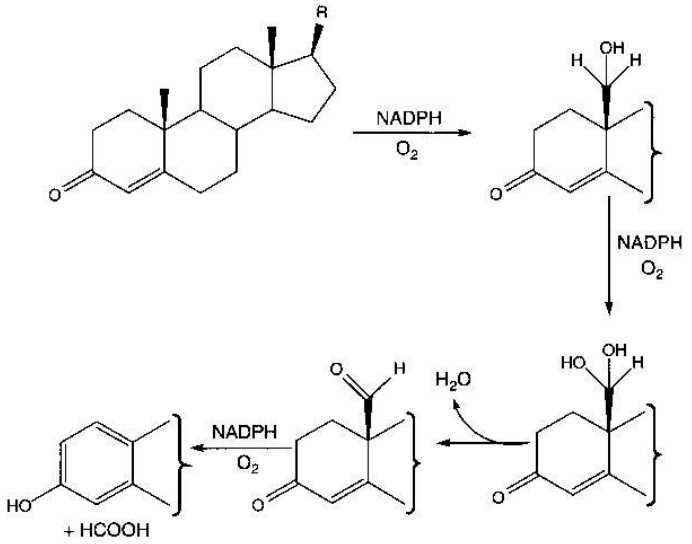


Fig. 3 Classical aromatization pathway. R is a 17-oxo group in androstenedione and a 17β-OH group in testosterone, these androgens being aromatized to estrone and estradiol respectively

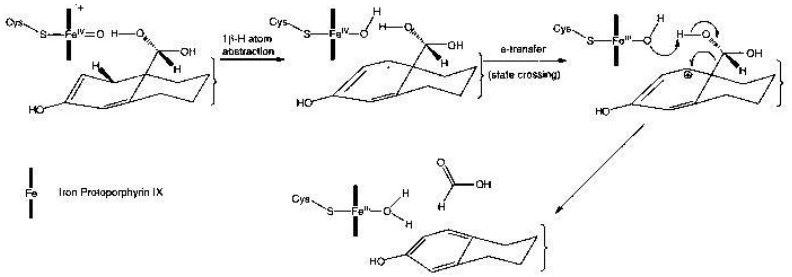


Fig. 4 A proposed mechanism of the final aromatization step, which can be summarized by

Sex hormones, Anabolic agents WADA S1

ENDOGENOUS/EXOGENOUS ANABOLIC AGENTS

NANDROLONE

Criteria for issuing an ADVERSE ANALYTICAL finding:

1) NA (norandrosterone) > 2 ng/mL (quantitative cut-off)

2) No pregnancy

3) No contraceptive drugs administration

4) Urine “stability”

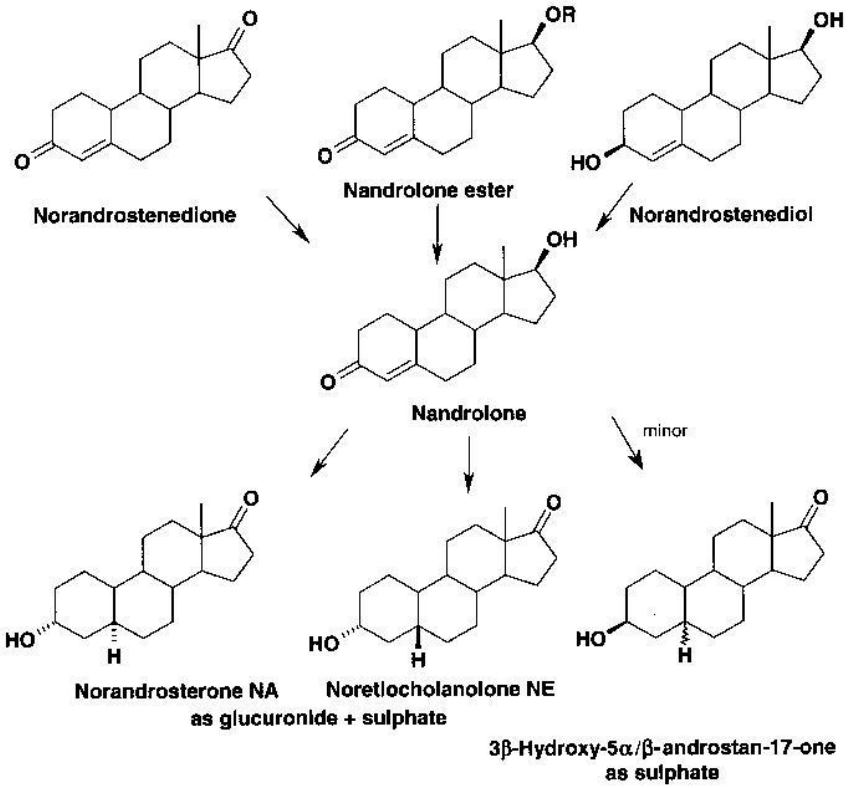


Fig. 3 Phase I metabolism and urinary excretion of nandrolone and the nandrolone-related steroids

Sex hormones, Anabolic agents WADA S1

ENDOGENOUS/EXOGENOUS ANABOLIC AGENTS

NANDROLONE interferences

Pregnancy

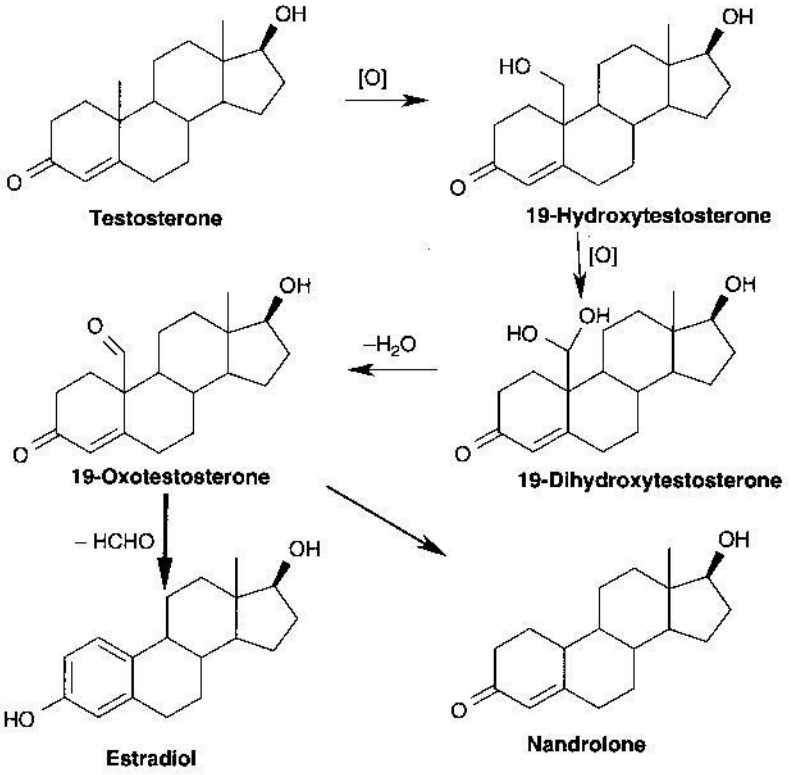
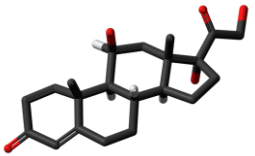


Fig. 11 Proposed synthesis path (simplified) for the formation of nandrolone as a side reaction to the aromatisation of testosterone to estradiol

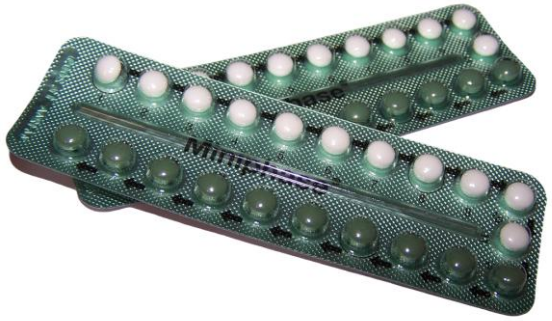
Sex hormones, Anabolic agents WADA S1



ENDOGENOUS/EXOGENOUS ANABOLIC AGENTS

NANDROLONE interferences

Contraceptive drugs metabolism



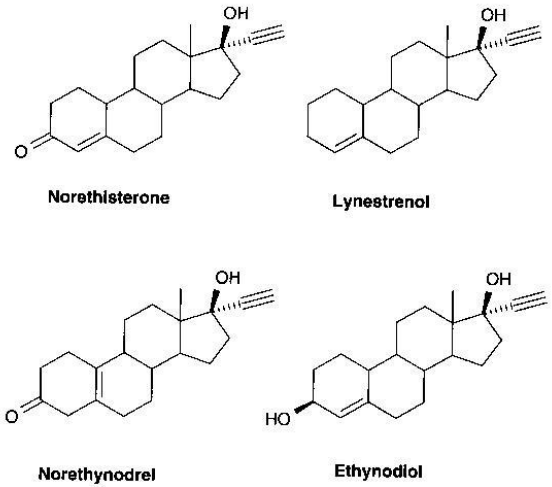


Fig. 8 Norethisterone and its prodrugs

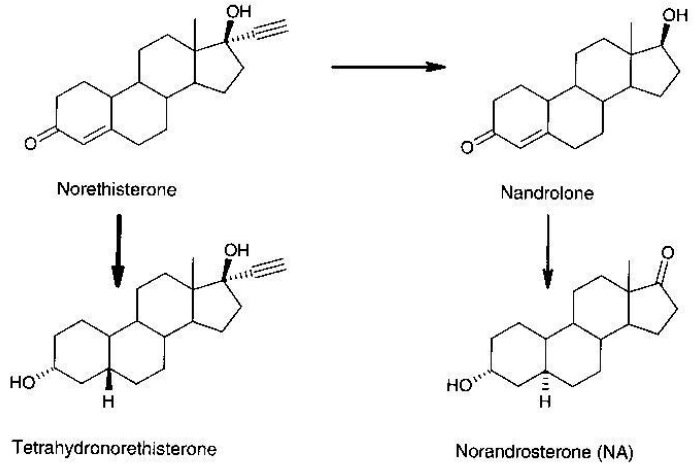


Fig. 9 Scheme of norethisterone metabolism: the A-ring reduction of norethisterone gives mainly the 5β-isomer of tetrahydronorethisterone, whereas after de-ethynylation to nandrolone to a minor degree the 5α-isomer norandrosterone (NA) is excreted into urine. A more detailed investigation of the norethisterone metabolism has recently been published (Walker et al. 2009b)

Sex hormones, Anabolic agents WADA S1

ENDOGENOUS/EXOGENOUS ANABOLIC AGENTS

NANDROLONE interferences

Urine “stability”

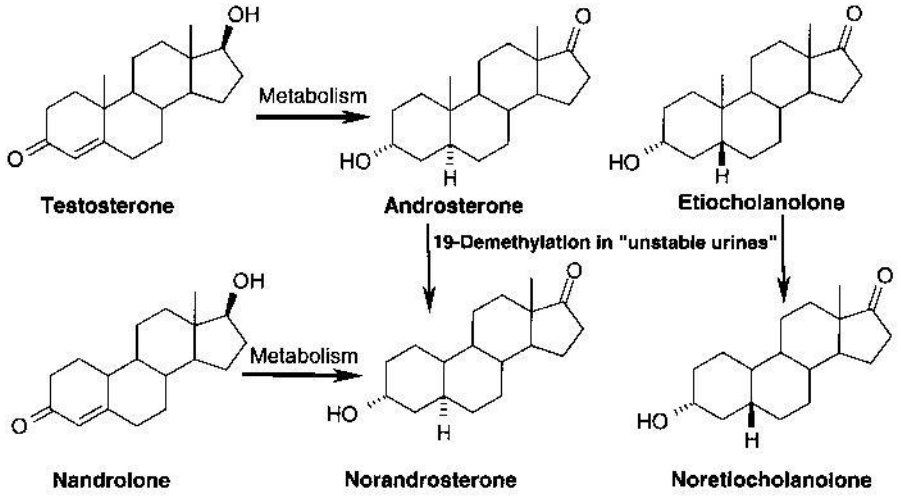
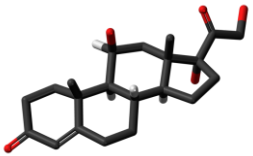


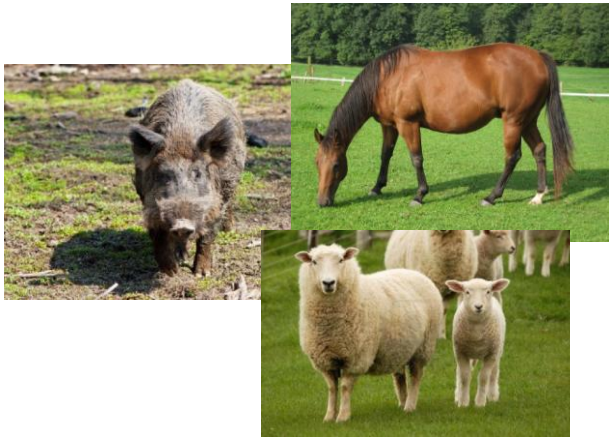
Fig. 12 Scheme of the rare in situ formation of the nandrolone metabolites NA and NE in urine by 19-demethylation from the testosterone metabolites androsterone and etiocholanolone (Grosse et al. 2005)

Sex hormones, Anabolic agents WADA S1



ENDOGENOUS/EXOGENOUS ANABOLIC AGENTS

other NANDROLONE interferences



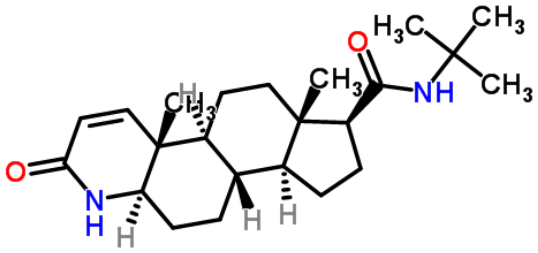
False positives:

from “contaminated” food (wild boar, horse, sheep meat)

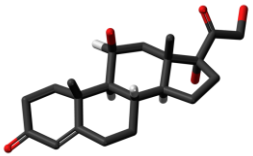
False negatives:

5-α-reductase inhibitors : **FINASTERIDE**:

Used for benignal prostatic hypertrophy, alopecia



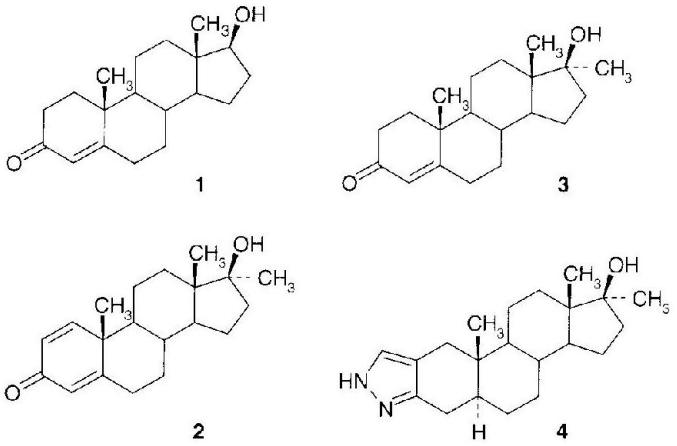
Anabolic agents WADA S1



EXOGENOUS ANABOLIC AGENTS

Synthetic anabolic steroids

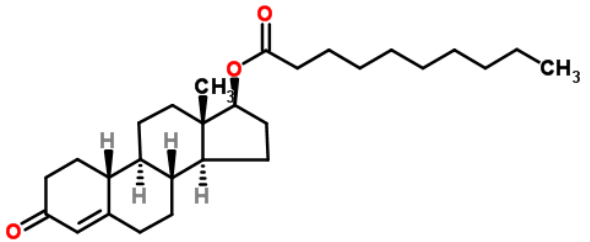
Should be orally active and not be substrates fo reductase and aromatase. Orally administered testosterone show limited bioavailability.



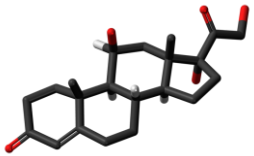
Scheme 1 Chemical structures of testosterone (**1**, mol wt=288), methyltestosterone (**3**, mol wt=302), metandienone (**2**, mol wt=300) and stanozolol (**4**, mol wt=328)

17-α-METHYLTESTOSTERONE could not be transformed into 17-keto: decelerated metabolism. Also **METANDIENONE** and **STANOZOLOL** display longer halflife and improved bioavailability.

NANDROLONE and esters: **DECANOATE** logP 8.28**,** etc.



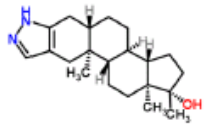
Anabolic agents WADA S1



EXOGENOUS ANABOLIC AGENTS

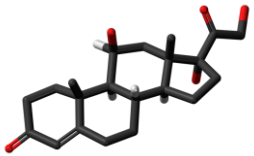
STANOZOLOL: pyrazo-steroid. High anabolic activity.

Ben Johnson 1988

Name	**STANOZOLOL**
Structure	
Systematic name	(1S,3aS,3bR,5aS,10aS,10bS,12aS)-1,10a,12a-Trimethyl-1,2,3,3a,3b,4,5,5a,6,7,10,10a,10b,11,12,12a-hexadecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-ol
Formula	$C_{21}H_{32}N_2O$
MW	328.4916
Monoisotopic mass	328.2515
Mp	242°C
H bond acceptors	3
H bond donors	2
Acid p*Ka*	--
Basic p*ka*	2.42 ($N_{pyrazol}$)
ACD Log D pH 5.5	5.52
ACD Log D pH 7.4	5.53
Solubility	Ethanol, chloroform. Insoluble in water
LD50	3200 mg/Kg rat p.o.
Therapeutic cat	androgen
ATC	**A14AA02** A ALIMENTARY TRACT AND METABOLISM A14 ANABOLIC AGENTS FOR SYSTEMIC USE A14A ANABOLIC STEROIDS A14AA Androstan derivatives
Receptors	AR

Nomi commerciali (IT)	
STARGATE, SUNGATE, WINSTROL.	veterinario, compresse, iniettabile

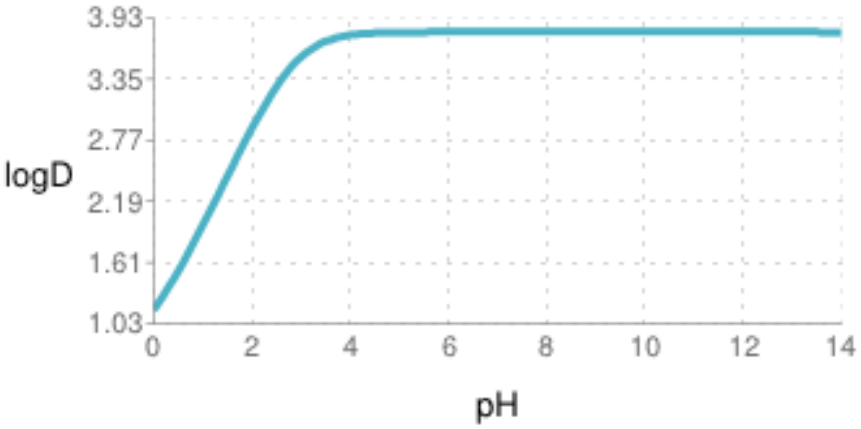
Anabolic agents WADA S1

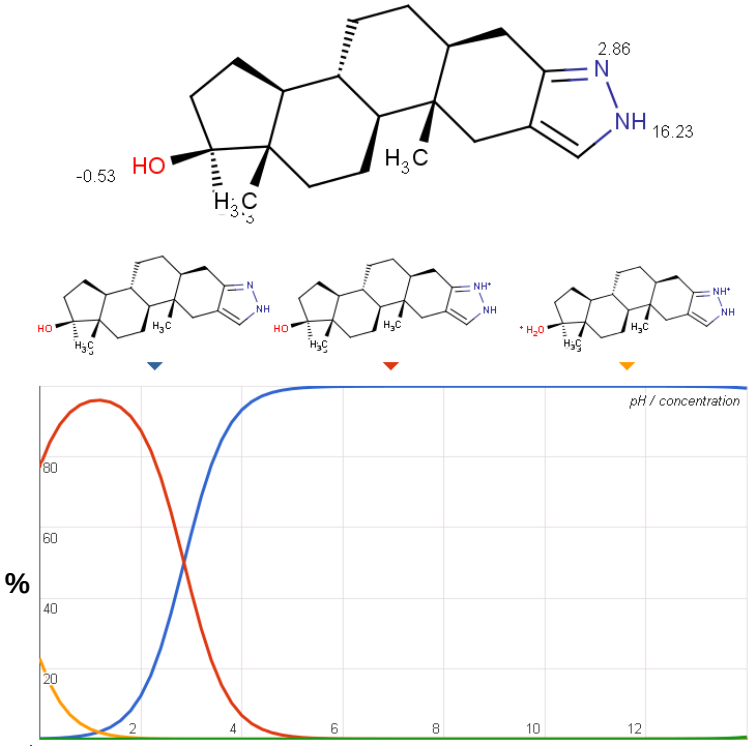


EXOGENOUS ANABOLIC AGENTS

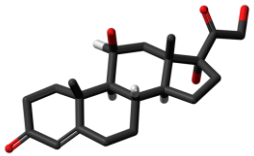
STANOZOLOL

pH/logD and pH/species





Anabolic agents WADA S1



EXOGENOUS ANABOLIC AGENTS

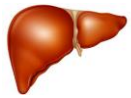
Synthetic anabolic steroids

Undesiderable effects:

☠ CARDIOVASCULAR ISSUES: cardiac hypertrophy; myocardial infarction and stroke

☠ ENDOCRINE ISSUES: testicular atrophy (LH decrease); infertility; feminization

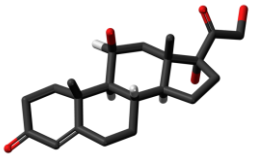
☠ HEPATIC ISSUES: liver toxicity; hepatocarcinoma



☠ PSYCHIATRIC ISSUES: mood; aggressive behavior; depression

☠ MUSCOLO-SKELETAL ISSUES

Anabolic agents WADA S1



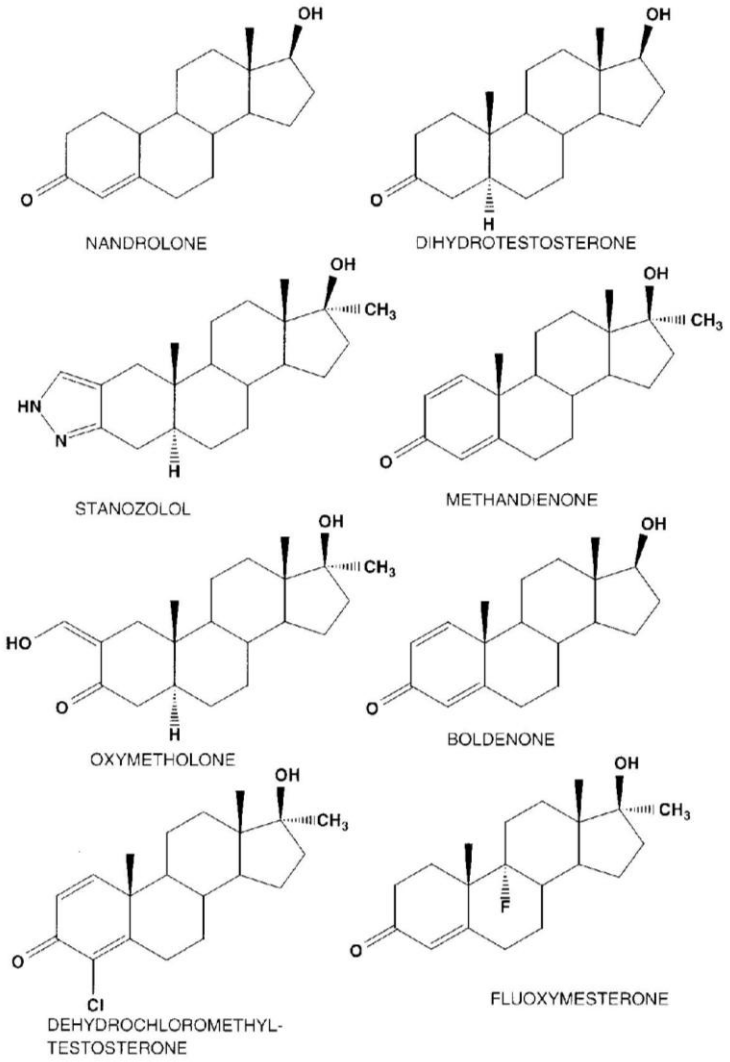
EXOGENOUS ANABOLIC AGENTS

Commercially available steroids:

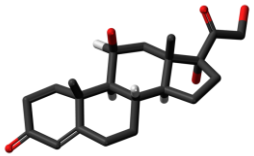
Testosterone esters for prolonged activity: **T DECANOATE, UNDECANOATE, PROPIONATE, ENANTHATE, CYPIONATE.**

Double bond in 1,2 (**METHANDIENONE**, DIANABOL, **BOLDENONE**) increases activity

C17- (**FLUOXYMESTERONE**) and C7-methyl (**MENT**) derivatives display high biological activity.



Anabolic agents WADA S1

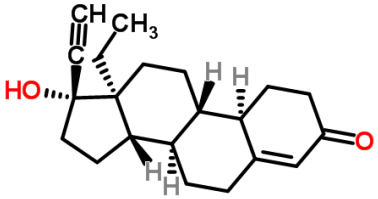


EXOGENOUS ANABOLIC AGENTS

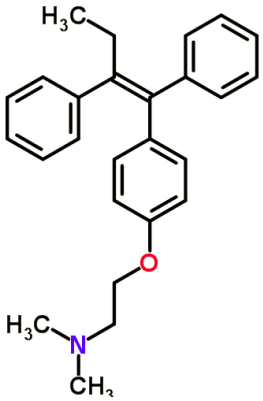
Designer steroids

3-keto reduction decreases anabolic activity and increases the androgenic one.

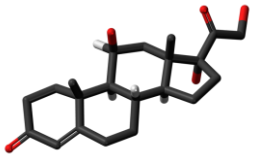
19-NORsteroids are less androgenic and equally myothropic.



13-ethylgonan **LEVONORGESTREL** (birth control pill) caused feminization side effect: association with **TAMOXIFEN** (antiestrogenic)

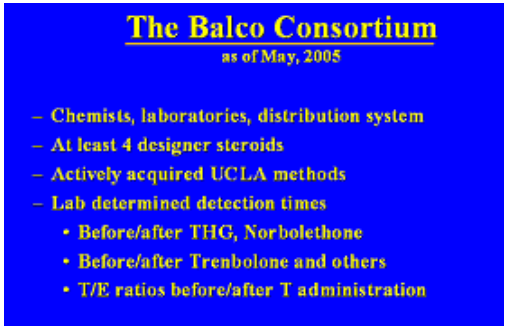


Anabolic agents WADA S1



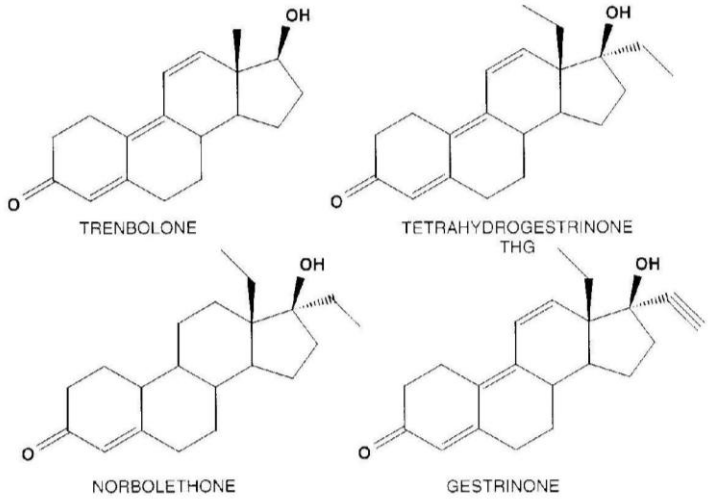
EXOGENOUS ANABOLIC AGENTS

Designer steroids



BALCO scandal: 23/09/2003

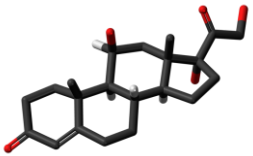
Bay-area laboratory cooperative. No test. Mix T/E to have normal ratio.



NORBOLETHONE was discovered by Don Catlin laboratory in 2002.

GESTRINONE: weak androgenic / progestogen. **THG**: (Balco “CLEAR”)

Anabolic agents WADA S1



EXOGENOUS ANABOLIC AGENTS

Designer steroids: halogenated (**DHCMT**: DDR state-controlled doping program) / heterocyclic

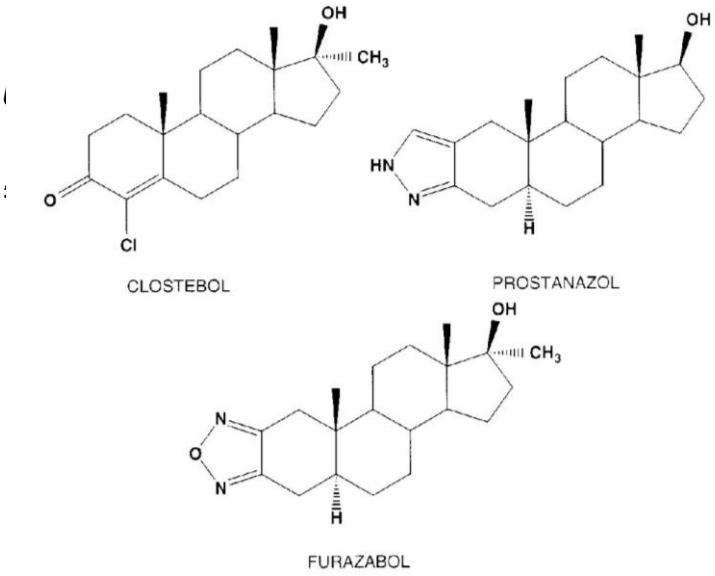


Fig. 6 Halogenated and heterocyclic steroids

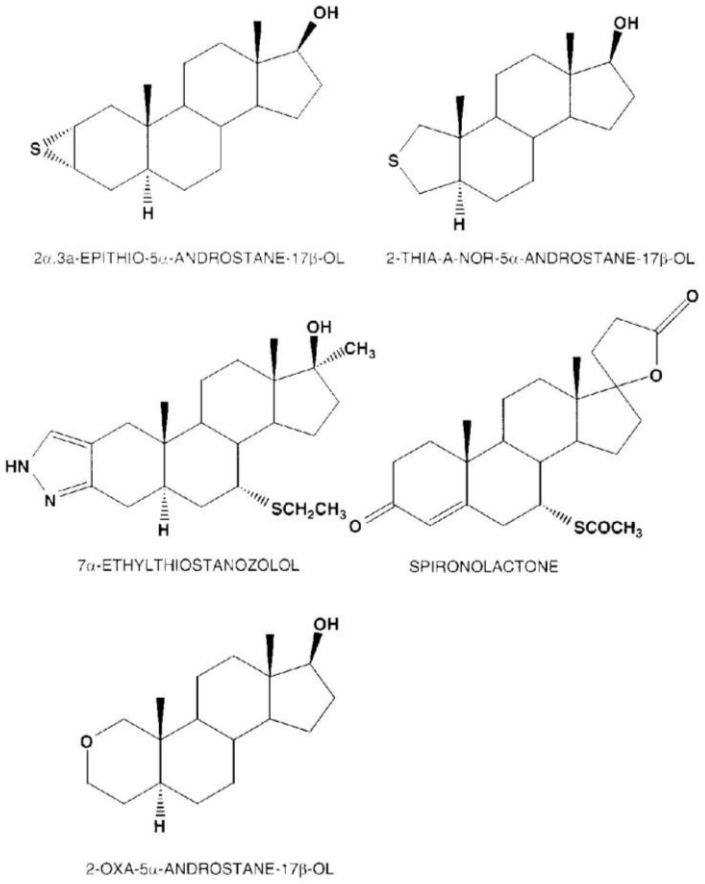
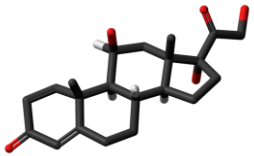


Fig. 7 Heteroatom-substituted steroids studied for anabolic adrenergic activity

Anabolic agents WADA S1

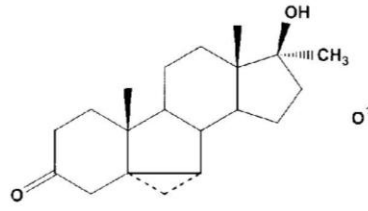


EXOGENOUS ANABOLIC AGENTS

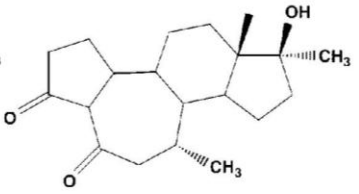
Designer steroids

Modified steroid ring:

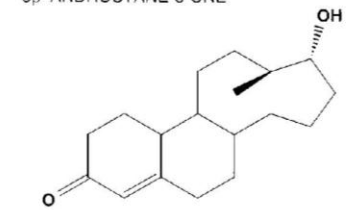
7-cyclosteroids, B-homosteroids, no experimentation as drugs



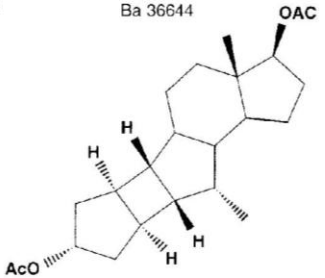
17β-HYDROXY-17α-METHYL-5,7β-CYCLO -5β-ANDROSTANE-3-ONE



Ba 36644



17-HYDROXY-13,14-SECO-ANDROST -4-EN-3-ONE

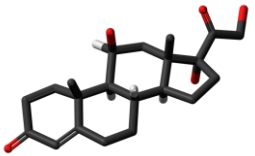


"CYCLOBUTANE STEROID"

Additional risk:

Contamination and side effects. Byproducts. Mixed or poorly characterised products.

Anabolic agents WADA S1.2

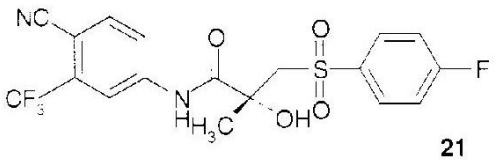


EXOGENOUS ANABOLIC AGENTS

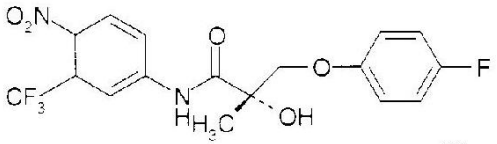
Selective androgen receptor modulators (SARMs)

S1: “related pharmacologically and chemically”

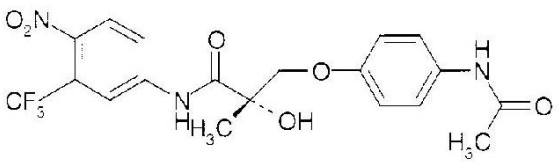
BICALUTAMIDE : AR antagonist, for treatment of prostate cancer and hirsutism.



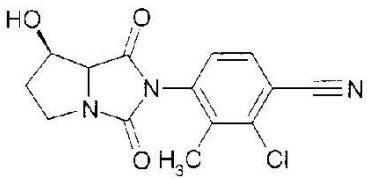
21



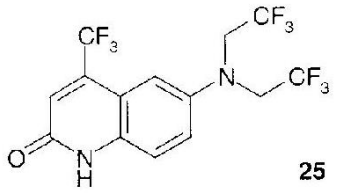
ANDARINE 22



23



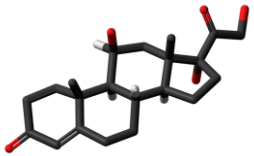
BICALUTAMIDE 24



25

Scheme 4 Chemical structures of selected SARMs: bicalutamide (**21**, mol wt = 430), propionanilides (**22**, mol wt = 402, and **23**, mol wt = 441), bicyclic hydantoin BMS-564929 (**24**, mol wt = 305), and 2-quinolinone LGD 2226 (**25**, mol wt = 392)

Anabolic agents WADA S1.2



EXOGENOUS ANABOLIC AGENTS

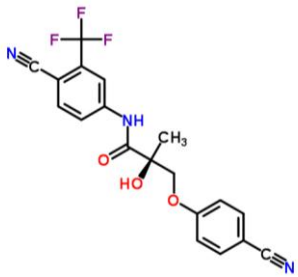
Selective androgen receptor modulators

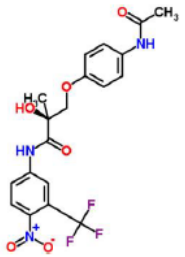
S1: “related pharmacologically and chemically”.

Not being substrates for 5-α-reductase or aromatase they display less androgenic/estrogenic side effects

ANDARINE: AR partial agonist

OSTARINE (ENOBOSARM):



Name	**ANDARINE**
Structure	
Systematic name	(2S)-3-(4-Acetamidophenoxy)-2-hydroxy-2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide
Formula	$C_{19}H_{18}F_3N_3O_6$
MW	441.3579
Monoisotopic mass	441.1148
Mp	70-74°C
H bond acceptors	9
H bond donors	3
Acid pK*a*	12 (p-nitroanilide), 14 (tertiary OH)
Basic pk*a*	--
ACD Log D pH 5.5	4.01
ACD Log D pH 7.4	4.01
Solubility	Ethanol, DMSO. 1.2 mg/mL in water
LD50	--
Therapeutic cat	antiBPH (benign prostatic hypertrophy)
ATC	Investigational new drug
Receptors	AR partial agonist

Anabolic agents WADA S1.2

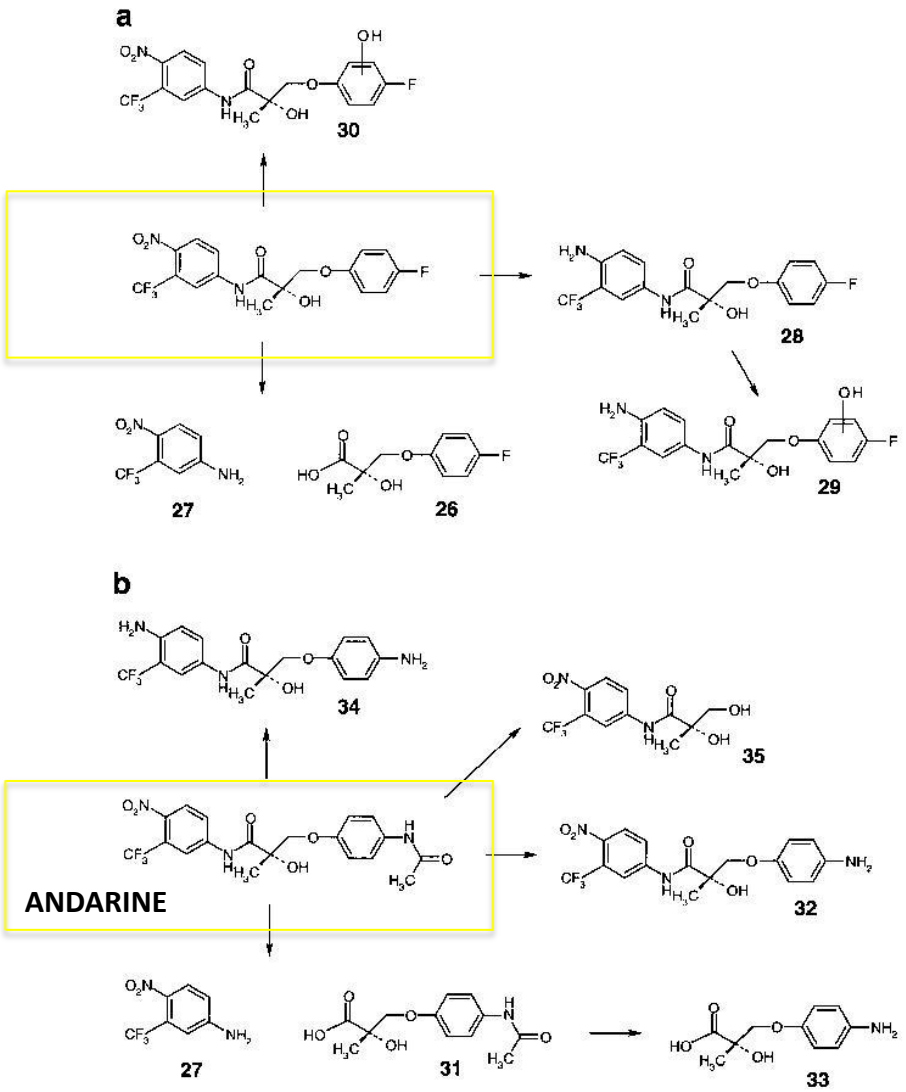
EXOGENOUS ANABOLIC AGENTS

Selective androgen receptor modulators

Andarine metabolism:

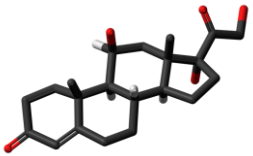
Amide hydrolysis (central amide / deacetylation).

Phase II glucuronidation.



Scheme 5 Major unconjugated metabolites of selected SARMs: (**a**) **22** yields 3-(4-fluorophenoxy)-2-hydroxy-2-methyl propanoic acid (**26**, mol wt=206), 4-nitro-3-(trifluoromethyl)aniline (**27**, mol wt =214), 4-amino-**22** (**28**, mol wt=372), hydroxylated 4-amino-**22** (**29**, mol wt = 388), and hydroxy-**22** (**30**, mol wt=418); (**b**) (**23**) yields 3-(4-acetylamino-phenoxy)-2-hydroxy-2-methyl propanoic acid (**31**, mol wt=253), 4-nitro-3-(trilluoromethyl)aniline (**27**, mol wt=214), deacetylated compound **23** (**32**, mol wt=399), 3-(4-amino-phenoxy)-2-hydroxy-2-methyl propanoic acid (**33**, mol wt=211), deacetylated 4-amino-**23** (**34**, mol wt=369), and the *O*-dephenylation product (4-nitro-3-(trifluoromethyl))-2,3-dihydroxy-2-methyl-propionanilide (**35**, mol wt=308)

Sex hormones



Female sex hormones related drugs:

Estrogenic compounds:

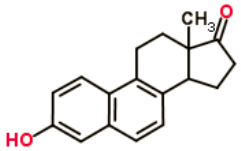
ETHYNYLESTRADIOL

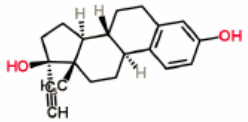
Contraceptive (in association with progestinics)/antineoplastic. Ethynyl group prevents metabolic hydroxylation.

Ester prodrugs: valerate, cipionate

Equine estrogens: major potency.

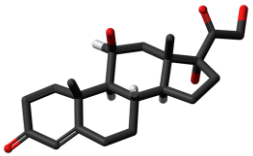
EQUILENINE



Name	**ETHINYLESTRADIOL**
Structure	
Systematic name	(17β)-17-ethynylestra-1,3,5(10)-triene-3,17-diol
Formula	$C_{20}H_{24}O_2$
MW	296.4034
Monoisotopic mass	296.177630012
Mp	142-146°C
H bond acceptors	2
H bond donors	2
Acid pK*a*	10 (phenol)
Basic pk*a*	--
ACD Log D pH 5.5	4.52
ACD Log D pH 7.4	4.52
Solubility	methanol, diethyl ether, acetone. Very slightly soluble in cold water
LD50	1200 mg/Kg rat p.o.
Therapeutic cat	contraceptive
ATC **L02AA03** L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L02 ENDOCRINE THERAPY L02A HORMONES AND RELATED AGENTS L02AA Estrogens	**G03CA01** G GENITO URINARY SYSTEM AND SEX HORMONES G03 SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM G03C ESTROGENS G03CA Natural and semisynthetic estrogens, plain
Receptors	ER-α / ER-β

Nomi commerciali (IT)	
ARIANNA, ESTINETTE, ETINILESTRADIOLO/GESTODENE, FEDRA, FEMODETTE, GESTODIOL, GINODEN, HARMONET, KIPLING, MILVANE, MINESSE, MINIGESTE, MINULET, TRIMINULET (associazione con gestodene [mestrenolo])	C, RR, compresse

Sex hormones, metabolic modulators, WADA S4



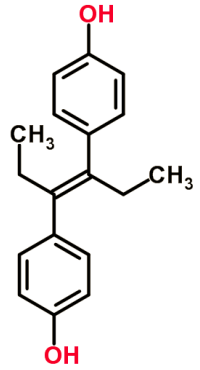
Female sex hormones related drugs:

Non-steroidal estrogenic compounds:

DIETHYLSTILBESTROL (DES):

trans 10 times more potent than *cis*.

Not used because of ***toxicity*** (vaginal tumor).



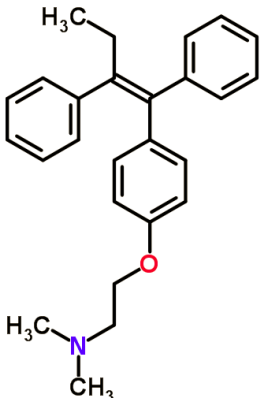
Non-steroidal anti-estrogenic compounds:

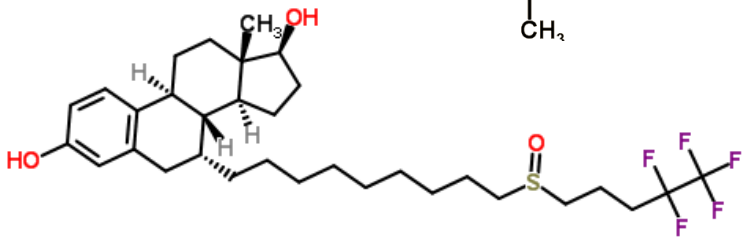
Z-TAMOXIFEN

antineoplastic. Residual estrogenic action:

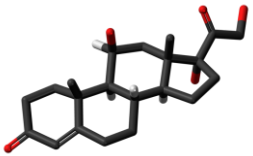
SERMs: selective estrogenic receptor modulators: agonist in some tissues / antagonists in some other.

FULVESTRANT anti-breast-cancer in the case of resistance to tamoxifene. Pure antagonist.





Sex hormones, metabolic modulators, WADA S4



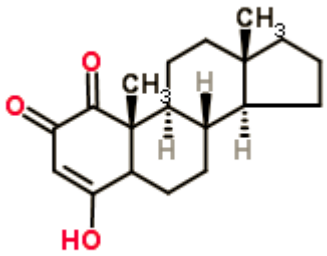
Female sex hormones related drugs:

Non-steroidal anti-estrogenic compounds:

Aromatase inhibitors

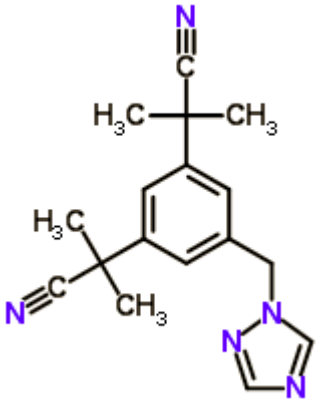
anti-estrogen-dependent tumor.

4-HYDROXYANDROSTENEDIONE

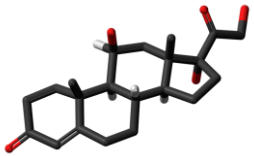


ANASTROZOLE

Triazole interacts with Fe-heme of the enzyme.



Sex hormones

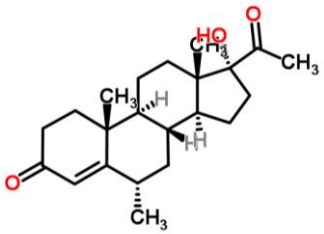


Female sex hormones related drugs:

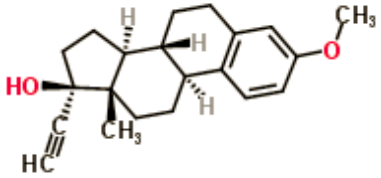
Progestin compounds: action on endometrium/placenta.

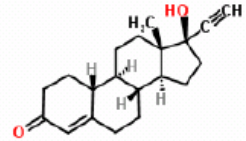
Contraceptive / anticancer (breast/ endometrium). Possible conversion to NANDROLONE

MEDROXYPROGESTERONE first synthetic



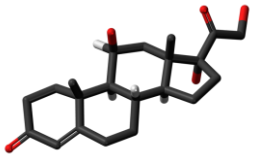
MESTRANOL (GESTODENE):



Name	**NORETHISTERONE (NORETHINDRONE)**
Structure	
Systematic name	(17β)-17-ethynyl-17-hydroxyestr-4-en-3-one
Formula	$C_{20}H_{26}O_2$
MW	298.4192
Monoisotopic mass	298.193280076
Mp	203-204°C
H bond acceptors	2
H bond donors	1
Acid pK*a*	--
Basic pk*a*	--
ACD Log D pH 5.5	3.38
ACD Log D pH 7.4	3.38
Solubility	ethanol, acetone, chloroform, pyridine, and dioxane
LD50	6000 mg/Kg mouse p.o.
Therapeutic cat	contraceptive
ATC	**G03AC01** G GENITO URINARY SYSTEM AND SEX HORMONES G03 SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM G03A HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE G03AC Progestogens
Receptors	

Nomi commerciali (IT)	
ACTIVELLE, ESTALIS (associazione con estradiolo). PRIMOLUT NOR	A, RNR, compresse, cerotti

Sex hormones

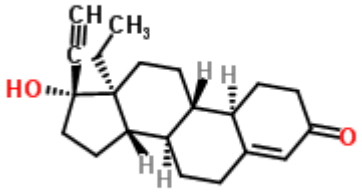


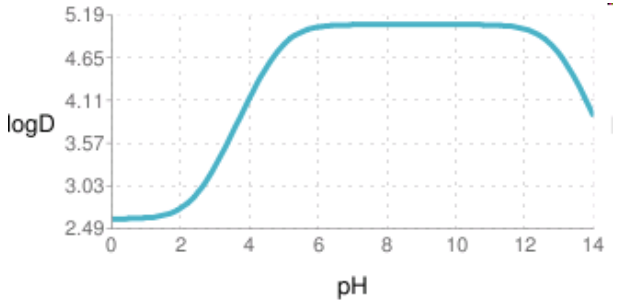
Female sex hormones related drugs:

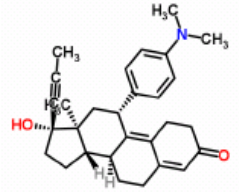
Progestinic antagonists:

MIFEPRISTONE (RU-486) abortive.

Day-after pill: **LEVONORGESTREL**

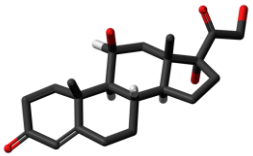




Name	**MIFEPRISTONE**
Structure	
Systematic name	(11β,17β)-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(prop-1-yn-1-yl)estra-4,9-dien-3-one
Formula	$C_{29}H_{35}NO_2$
MW	429.5937
Monoisotopic mass	429.266779369
Mp	150°C
H bond acceptors	3
H bond donors	1
Acid p*Ka*	12.87 (OH)
Basic p*ka*	4.89
ACD Log D pH 5.5	4.66
ACD Log D pH 7.4	4.94
Solubility	ethanol, DMSO, and dimethylformamide
LD50	4640 mg/Kg rat p.o.
Therapeutic cat	emergency contraceptive
ATC	**G03XB01** G GENITO URINARY SYSTEM AND SEX HORMONES G03 SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM G03X OTHER SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM G03XB Antiprogestogens
Receptors	progestogens

Nomi commerciali (IT)	
MIFEGYNE	H, OSP1, compresse

Sex hormones

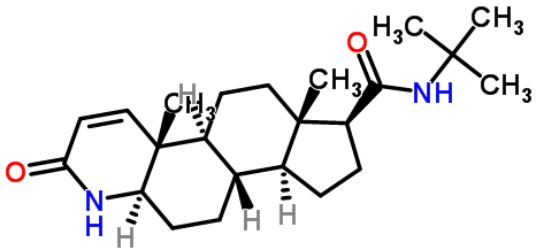


Male sex hormones related drugs:

DHT biosynthesis inhibitors

FINASTERIDE: inhibits 5α-reductase.

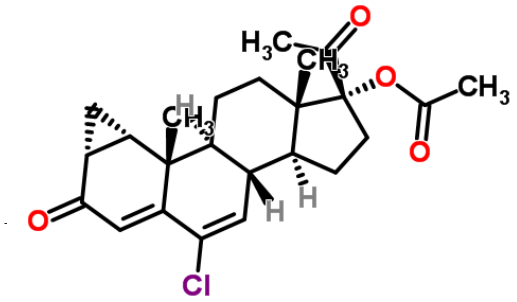
Used for benignal prostatic hypertrophy and alopecia



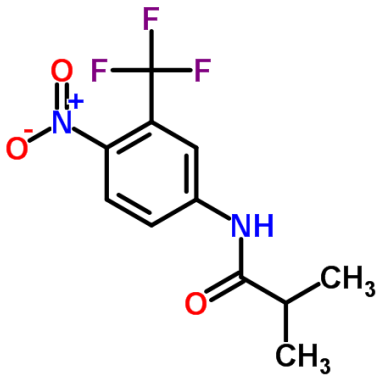
Androgen antagonists

Used in prostatic cancer treatment.

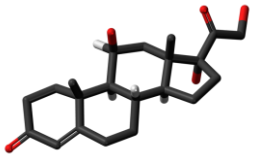
***Steroidal*: CYPROTERONE ACETATE**



***Non-steroidal*: FLUTAMIDE**

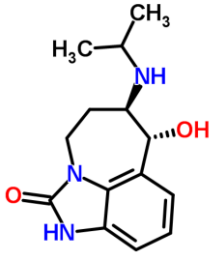


Other anabolic agents, WADA S1.2



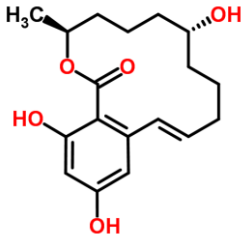
Anabolic β-agonists:

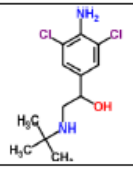
ZILPATEROL: used to increase the size of cattle



Non-steroidal estrogen agonists:

ZERANOL: used as a growth promoter in livestock



Name	**CLENBUTEROL**
Structure	
Systematic name	1-(4-Amino-3,5-dichlorophenyl)-2-[(2-methyl-2-propanyl)amino]ethanol
Formula	$C_{12}H_{18}Cl_2N_2O$
MW	277.1901
Monoisotopic mass	276.0796
Mp	174-175°C
H bond acceptors	3
H bond donors	4
Acid p*Ka*	--
Basic p*ka*	1.4 (aniline); 9.6 (amine)
ACD Log D pH 5.5	-0.44
ACD Log D pH 7.4	0.56
Solubility	Water, ethanol, methanol
LD50	--
Therapeutic cat	bronchodilator
ATC	**R03AC14** R RESPIRATORY SYSTEM R03 DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES R03A ADRENERGICS, INHALANTS R03AC Selective beta-2-adrenoreceptor agonists **R03CC13** R RESPIRATORY SYSTEM R03 DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES R03C ADRENERGICS FOR SYSTEMIC USE R03CC Selective beta-2-adrenoreceptor agonists
Receptors	β_2-adrenergic agonist

Nomi commerciali (IT)	
MONORES, VENTIPULMIN, BERESTIM, BRONCODIL	C, RR, compresse, spray, sciroppo, iniettabile