Hormones and compounds acting within the endocrinous system, if they were not refered elsewhere

1. Peptides and proteins
2. Compounds derived from a single amino acid
3. Steroids
3.1. Corticoids
3.1.1. Mineralocorticoids
3.1.2. Glucocorticoids
3.2. Sex hormones
3.2.1. Androgens
3.2.2. Estrogens
3.2.3. Gestagens
4. Prostaglandins

Classification of hormones of peptide and protein structure

1.1 Liberins a statins („releasing“&“inhibiting“)

1.2.Soma(to)tropin

1.3 Oxytocin, vasopressin and their analogues

~~1.4 Insulines, glucagon and GLP-1 analogues~~

1.5 Calcitonin

2. Blood factors of erythropoietine type

3. Colony stimulating factors

One- and three-letter symbols of L-α-amino acid rests

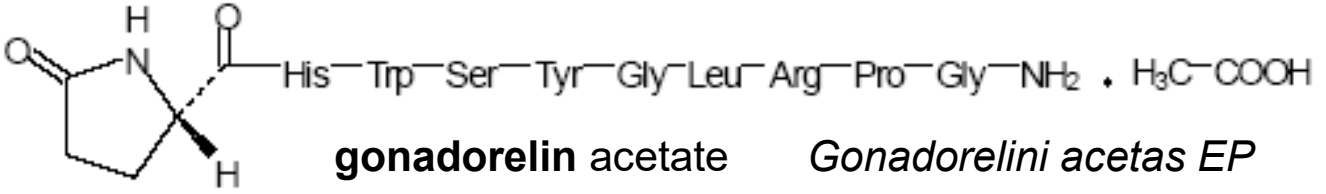
One-letter	Three-letter	
A	Ala	alanine
B	Asx	asparaginic acid or asparagine
C	Cys	cysteine
D	Asp	asparaginic acid
E	Glu	glutamic acid
F	Phe	phenylalanine
G	Gly	glycine
H	His	histidine
I	Ile	isoleucine
K	Lys	lysine
L	Leu	leucine
M	Met	methionine
N	Asn	asparagine
P	Pro	proline
Q	Gln	glutamine
R	Arg	arginine
S	Ser	serine
T	Thr	threonine
U	Sec	selenocysteine
V	Val	valine
W	Trp	tryptofane
X	Xaa	unknown or „other“ amino acid
Y	Tyr	thyrosine
Z	Glx	glutamic acid or glutamine (or compounds such as 4-carboxyglutamic acid 5-oxoproline)

1. Hormones

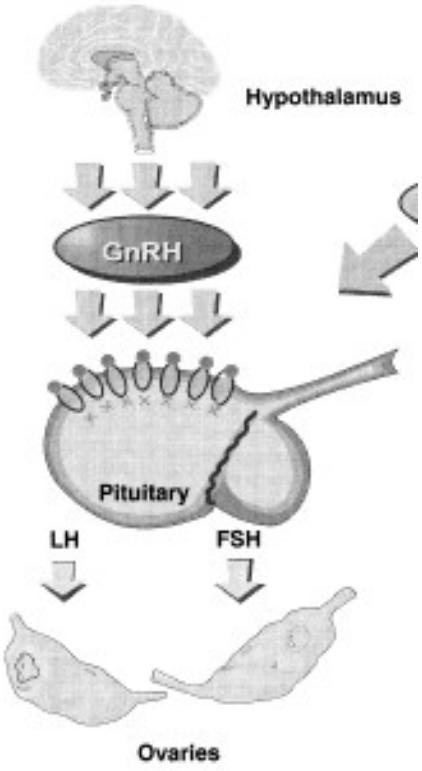
1.1 Liberins and statins („releasing“ & „inhibiting“)

Gonadorelin (GnRH = LHRH) and its analogues

- hormone of hypothalamus
- stimulates releasing of folicules stimulating hormone (FSH) and luteinizing hormone (LH) from pituitary gland; GnRH receptors also in various non-reproductive tissues

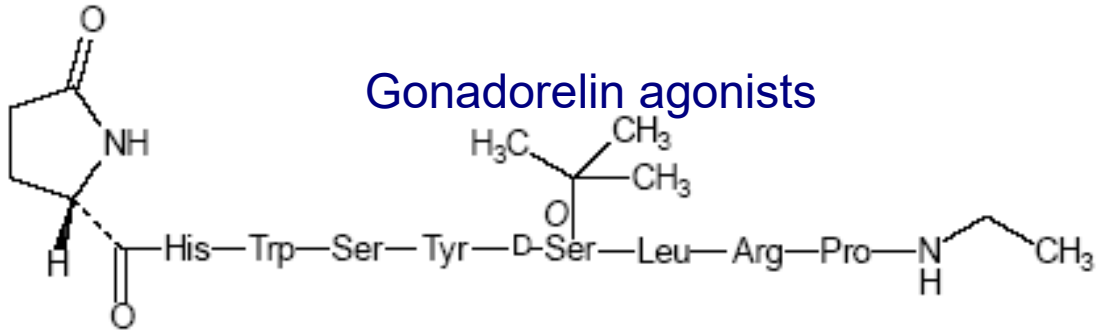


gonadorelin acetate *Gonadorelini acetas EP*



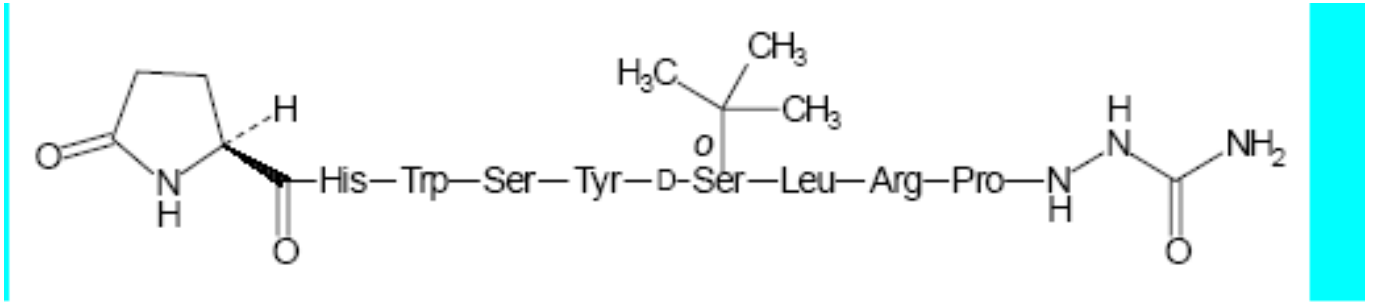
$C_{57}H_{79}N_{17}O_{15}$ M_r 1242,35

Gonadorelin agonists



$C_{60}H_{86}N_{16}O_{13}$ M_r 1239,44 CAS 57982-77-1

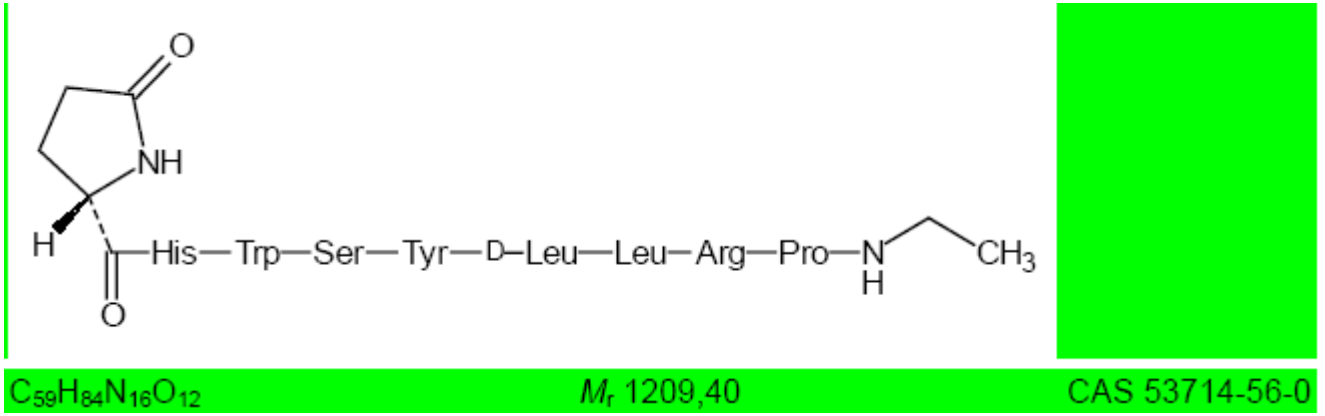
buserelin *Buserelinum EP*



$C_{59}H_{84}N_{18}O_{14}$ M_r 1269,42 CAS 65807-02-5

goserelin *Goserelinum EP*

Gonadorelin and its analogues
Agonists

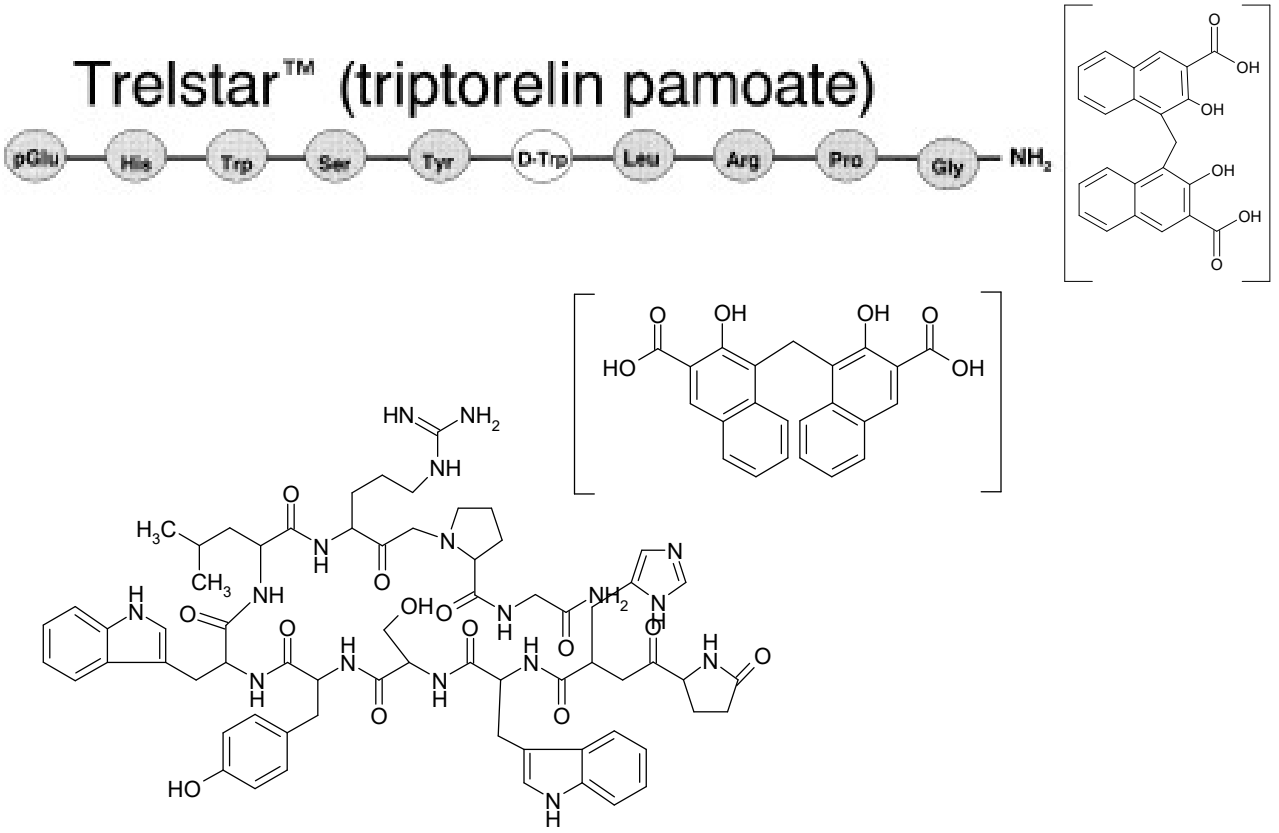


leuprorelin (syn. leuprolide) *Leuprorelinum EP*
Eligard ®

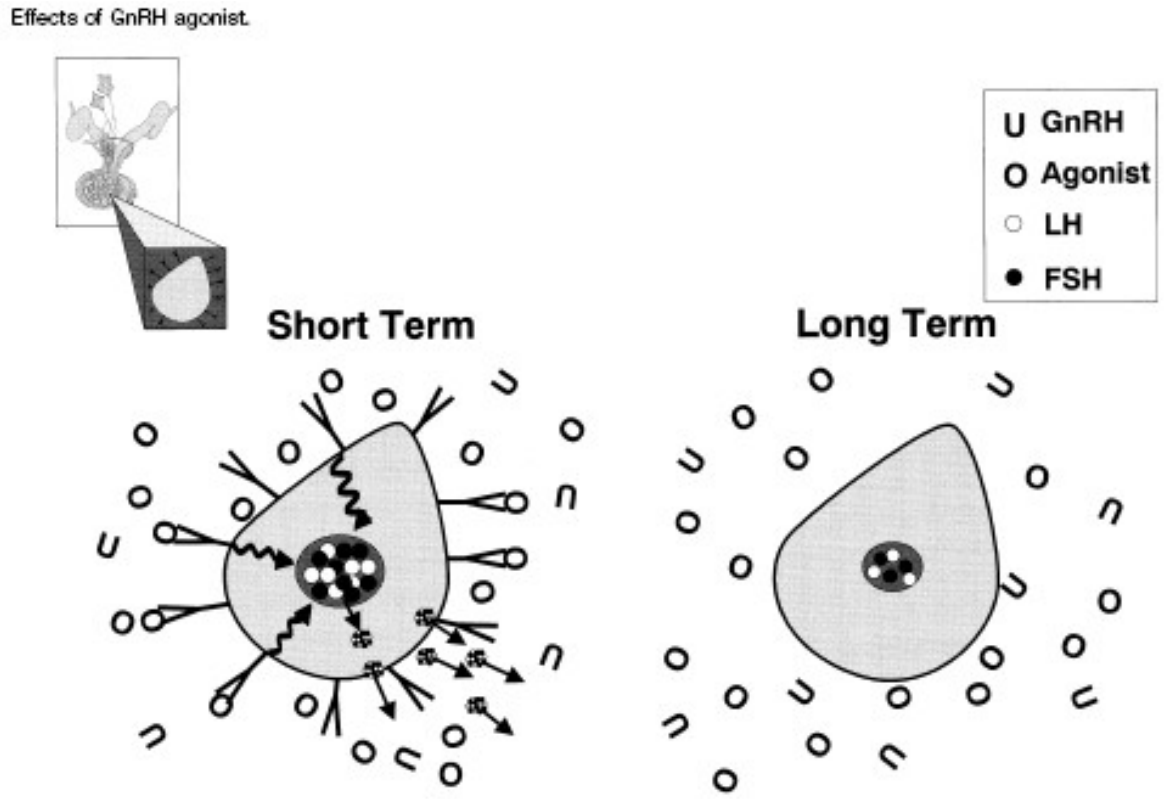
- longer-term application lowers testosterone levels ⇒ treatment of prostate cancer
  ⇒ treatment of sexual deviations

http://www.accessdata.fda.gov/drugsatfda_docs/anda/98/74728ap_appltr_prntlbl_chemr_bioeqr_micror.pdf

Gonadorelin and its analogues
Agonists



Short- and long term action of gonadorelin agonists

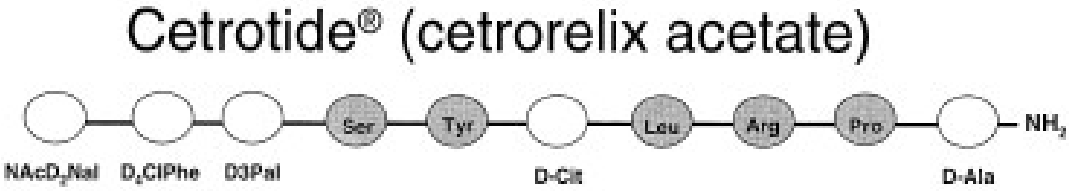


•long term action leads to receptors internalisation and stopping of the effect (due to decreasing LH and FSH levels and thus also levels of sexual hormones)

Gonadorelin analogues
Gonadorelin antagonists

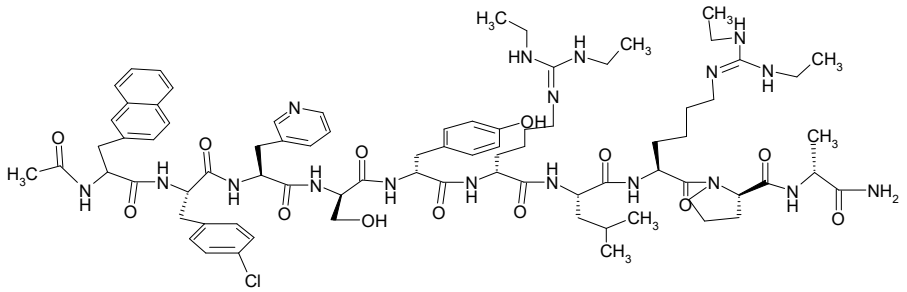
The GnRH antagonists.

. CH_3COOH

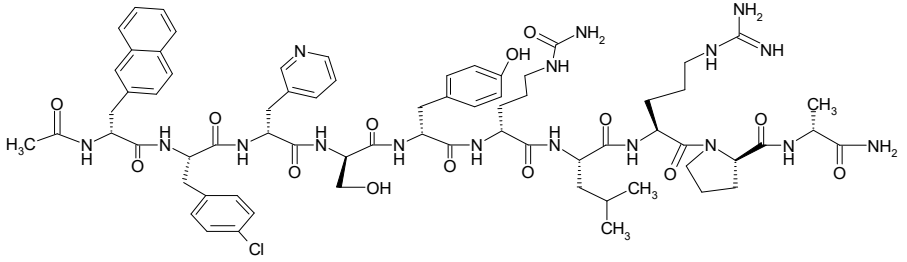


. CH_3COOH

Amino Acid Number	1	2	3	4	5	6	7	8	9	10



ganirelix



cetrorelix

Gonadorelin and its analogues

- preparation: chemical synthesis
- usage: assisted reproduction, treatment of prostate cancer, sexual deviation ...
- advantages of analogues: significantly higher stability $\Rightarrow$ longer elimination half-time $\Rightarrow$

$\Rightarrow$ possibility of application in markedly longer intervals; a single injection of an agonist can replace a continuous infusion of gonadorelin

Structure – activity relationships (SAR)

- replacement of Gly in position 6 with a more bulky amino acid leads to stability increase
- the sequence of the first three amino acids is needed for receptor binding and is kept in agonists
- antagonists have Trp in position 3 replaced with an non-physiologic amino acid, they bind to GnRH and avoid its action on receptors

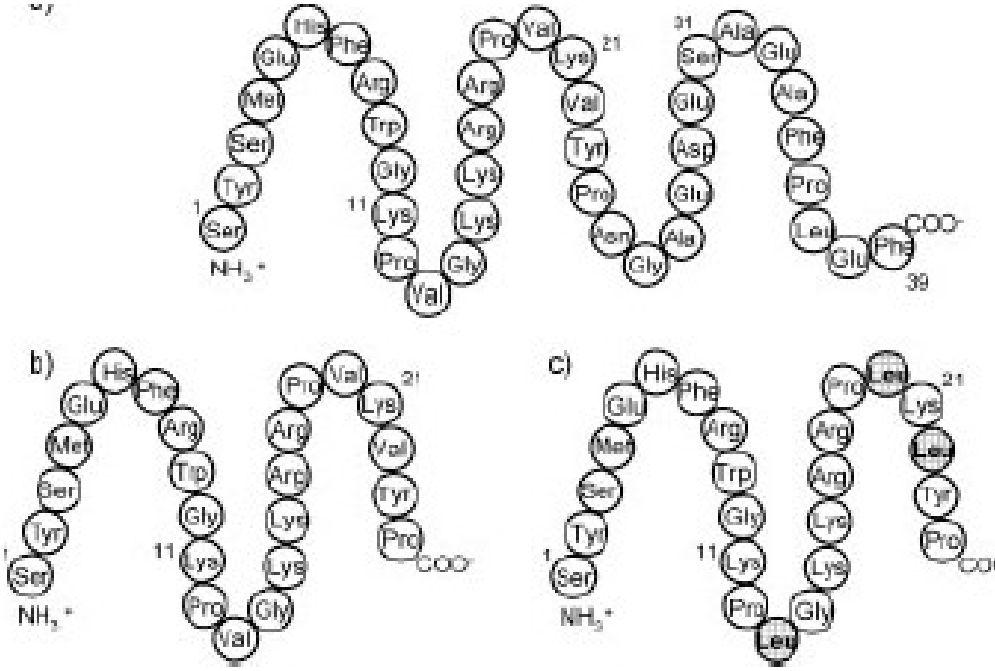
Corticotropin and its analogues

Corticotropin = Adrenocorticotrophic hormone (ACTH); an anterior pituitary hormone that stimulates the adrenal cortex and

its production of both gluco- and mineralocorticoids and growth of adrenal glands

•polypeptide of 39 amino acids; N-terminal 24 identical in all species

•N-terminal 24 AA are responsible for biologic activity; C-terminal 15 AA for immunospecificity



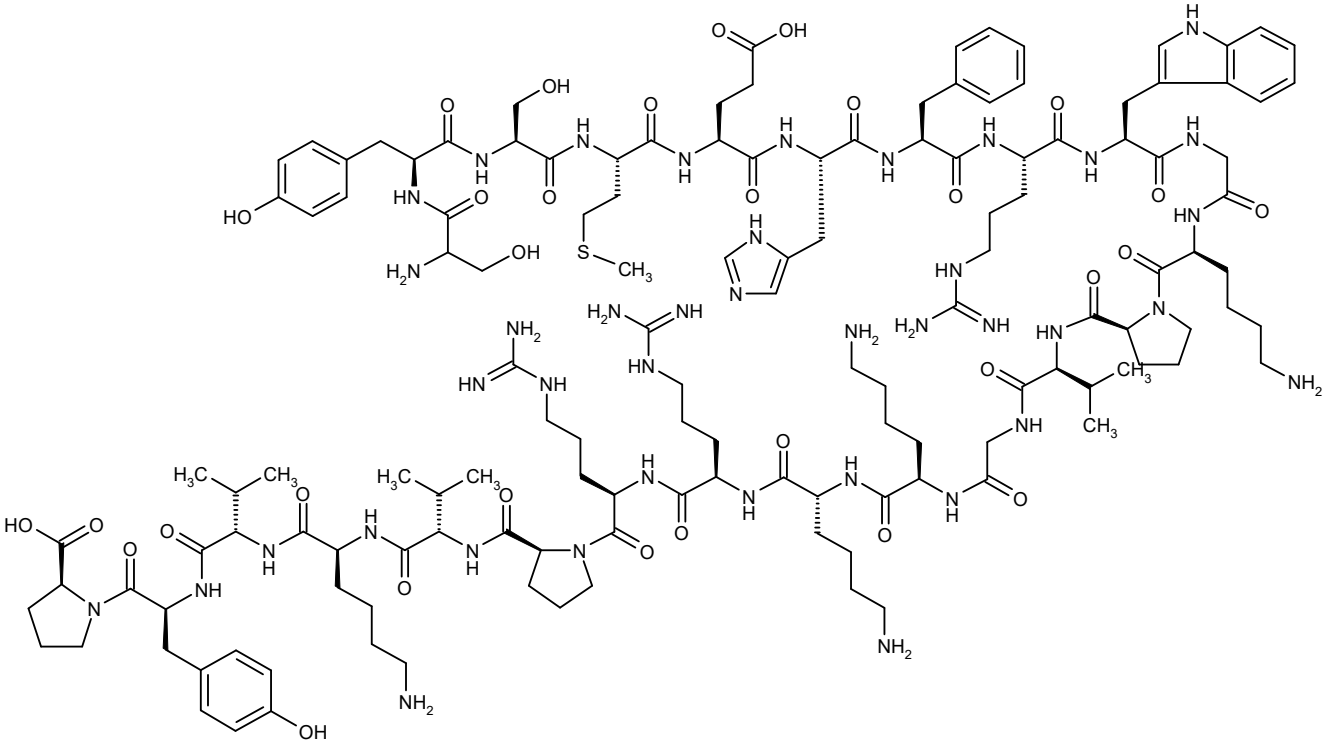
corticotropin

tetracosactide
syn. cosyntropin [USAN]
Tetracosactidum EP
Synacten®

SynVL
•compound used as a standard for determination of tetracosactide by mass spectrometry

Usage of corticotropin and tetracosactide

- diagnosis of adrenal glands function
- substitution treatment in lack of glucocorticoids
- substitution of depot administration of glucocorticoids in a long-term treatment



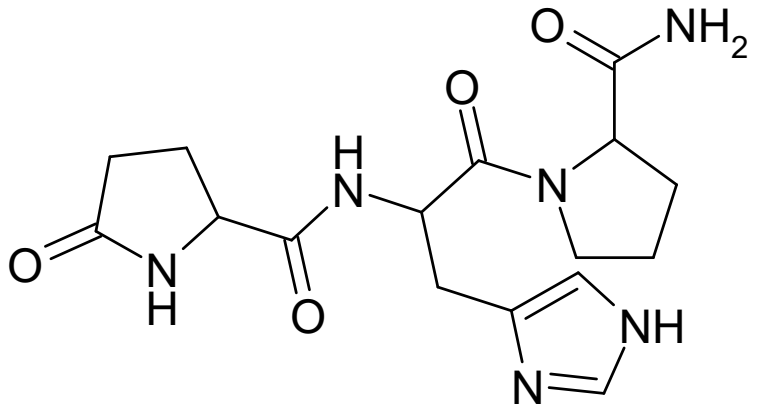
tetracosactide

- used since 1961
- prepared by synthesis
- misused for doping in sport

Protirelin – synthetic thyreotropin-releasing hormone (TRH)

•a hormone sythetized in paraventricular nucleus of hypothalamus, stimulating release of thyreotropin and prolactin from the anterior pituitary gland

•also neurotransmitter in CNS, takes part in food intake regulation, control of energy metabolism etc.



protirelin

5-oxoprolyl-histidyl-prolinamide

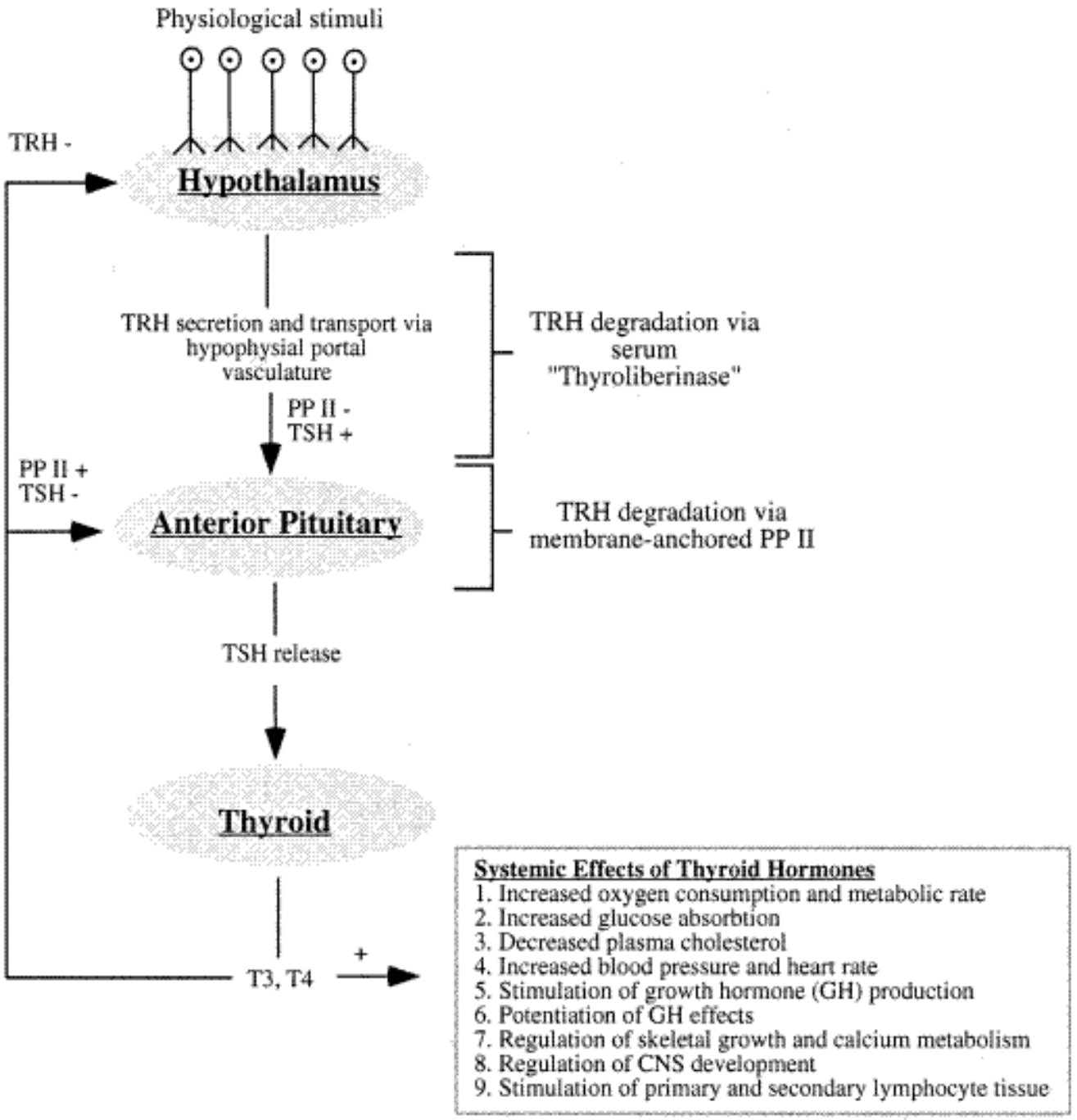
Protirelinum EP

•structure elucidated 1969, used approx. 1976 – 1991, then abandoned

•administered *p.o.*

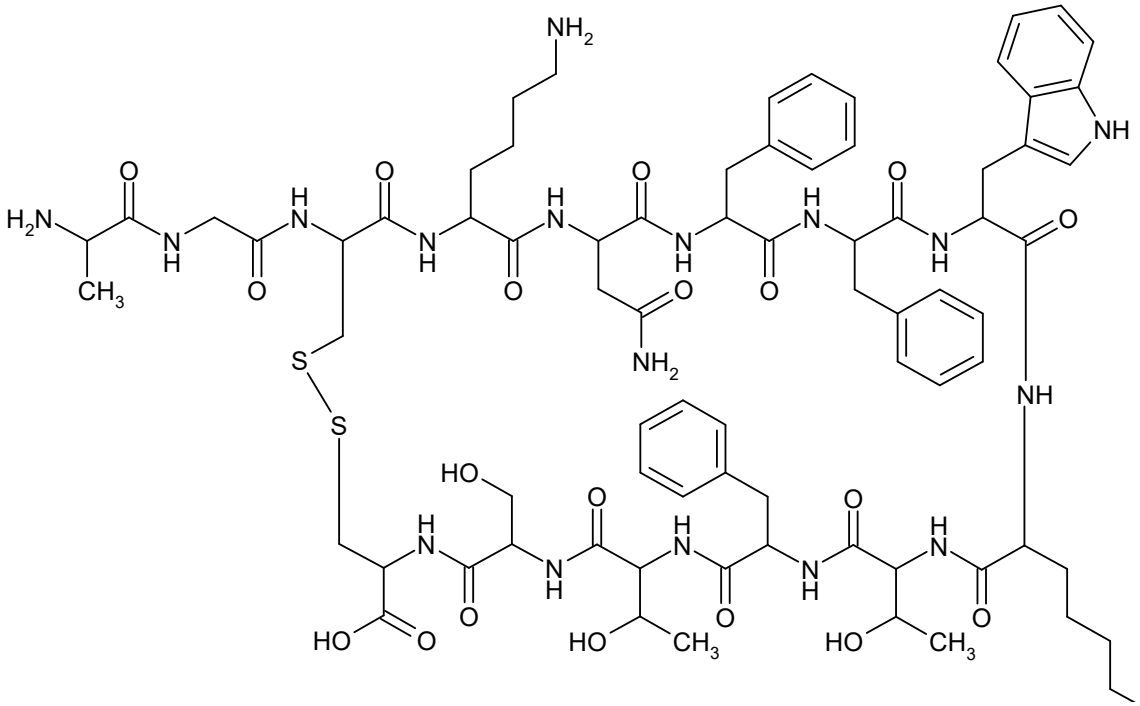
•used as cognitive functions enhacer for treatment of post-traumatic conditions in injuries of brain and spinal cord and of neurodegeneration diseases (Alzheimer, Parkinson, motoric neuronal disease etc.)

Metabolism of TRH and its regulation



Somatostatin

•cyclic tetradecapeptide formed namely in hypothalamus, but also in peripheral nervous
•system, the gut, and other organs
•inhibits pituitary growth hormone (somatotropin) release and probably also release of TRH, prolactin,insulin and glucagon
•has impact to functions of kidneys, pancreas and GIT
•also acts as neurotransmitter in CNS („neuropeptide“)



H—Ala—Gly—Cys—Lys—Asn—Phe—Phe—Trp—Lys—Thr—Phe—Thr—Ser—Cys—OH

$C_{76}H_{104}N_{18}O_{19}S_2$ M_r 1637,89 CAS 38916-34-6

somatostatin

Somatostatinum EP

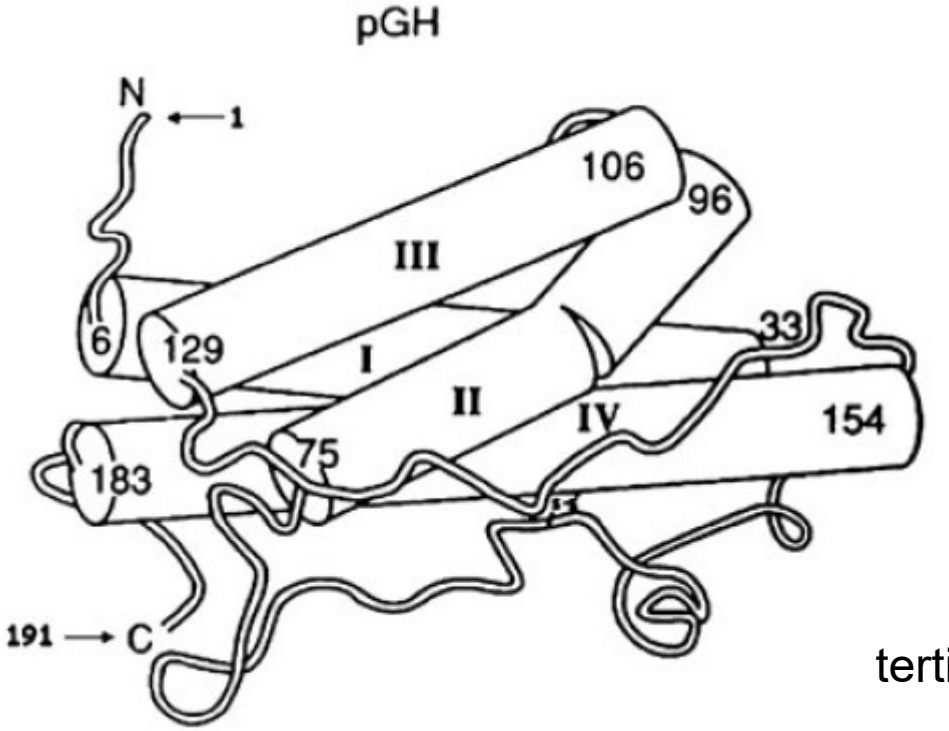
Somatostatin Eumedica® inf.

•prepared by synthesis
•treatment of acromegaly

1.2 Soma(to)tropin

= growth hormone (GH)

- peptide consisted of 191 AA secreted from anterior pituitary gland
- stimilates mitosis, growth and differentiation of cells of some tissues
- influences expression of genes and metabolism
- sequence of AA known since 1972, nucleotide sequence of the encoding gene since 1977



tertiary structure of porcine GH

somatropin

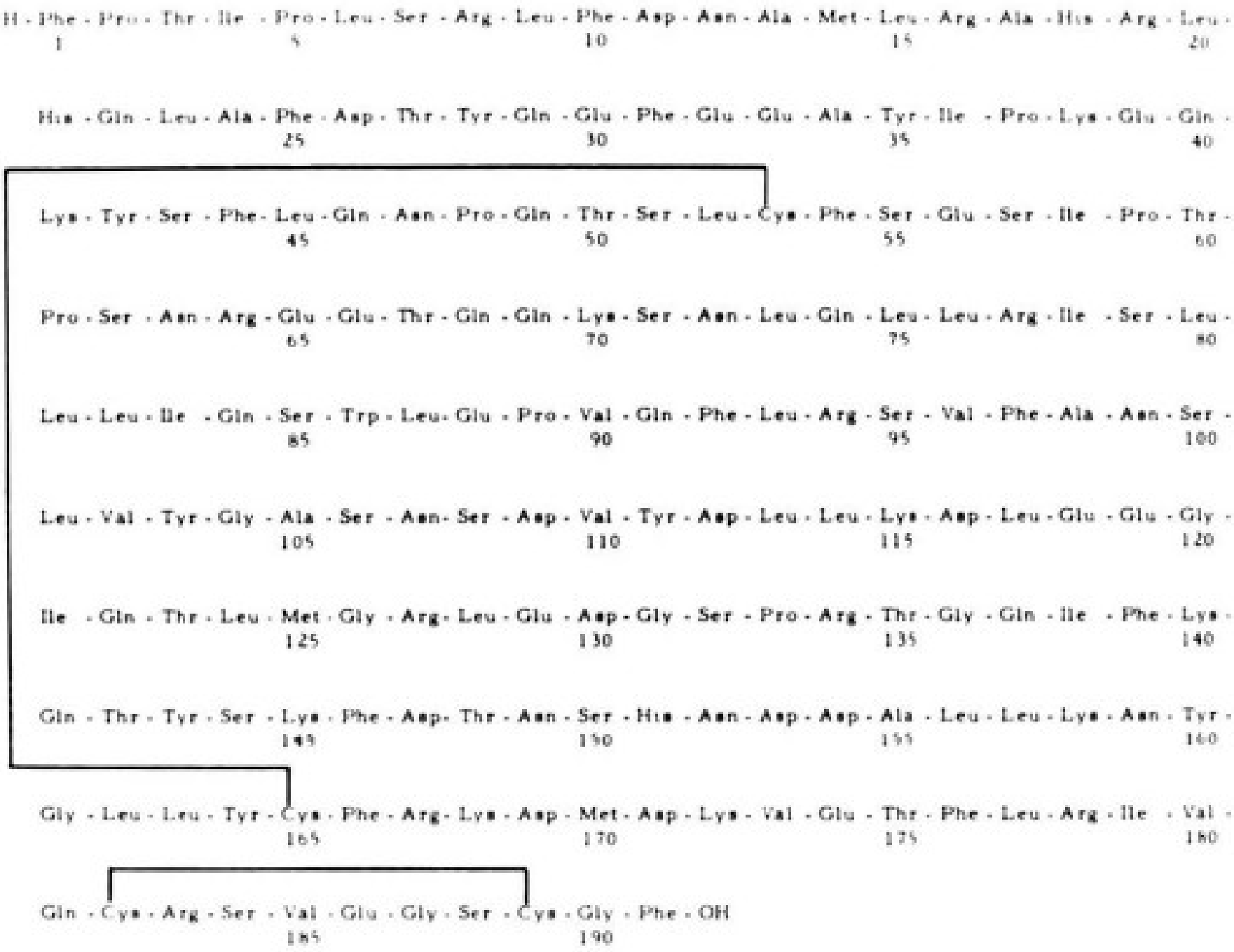
Somatropinum EP

- human, prepared by recombinant technology, used since 1985
- substitution treatment of natural GH deficiency

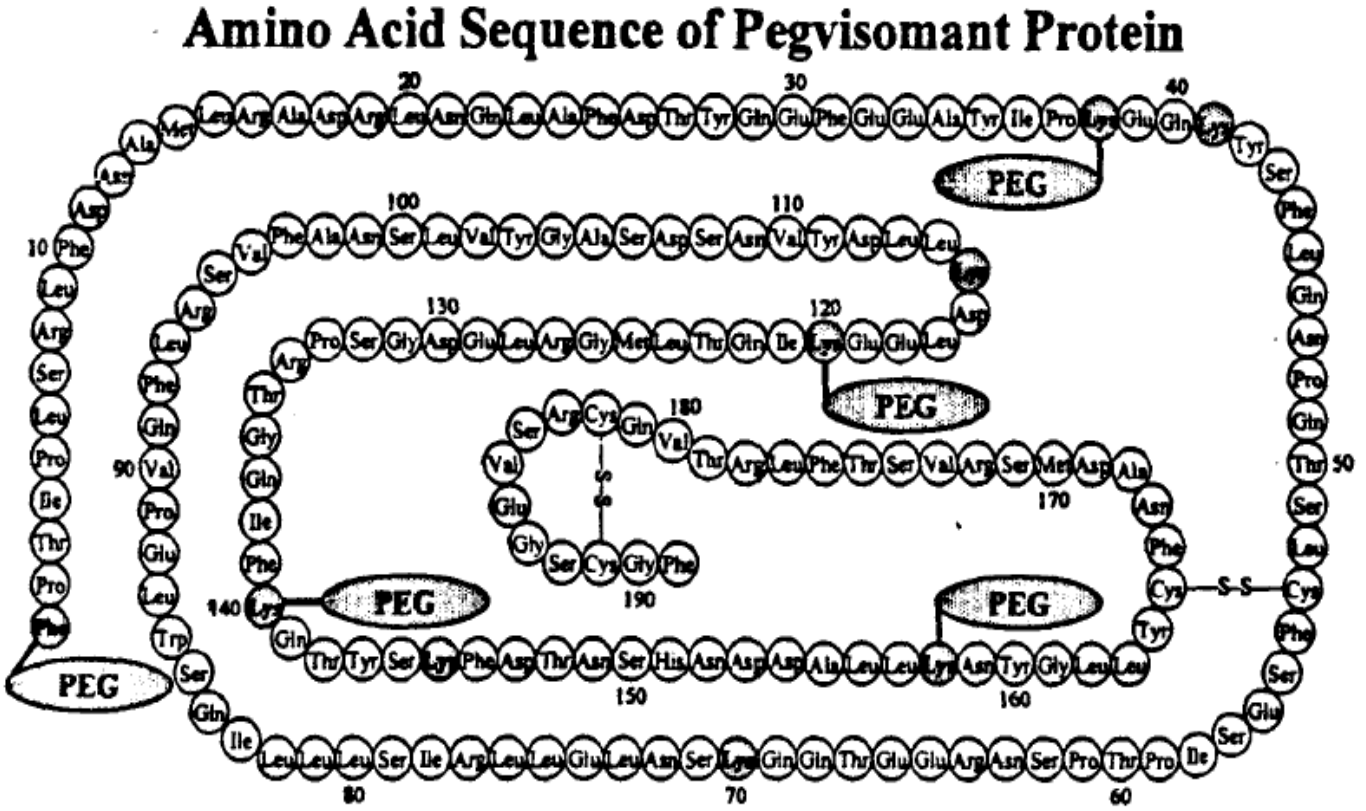
Genotropin ® , Humatrope ® , Nutropinaq ® , Omnitrope ® ...

1 MATGSRTSLL LAFGLLCLPW LQEGSAFPTI PLSRLFDNAM LRAHRLHQLA FDTYQEFEEA YIPKEQKYSF LQNPQTSLCF SESIPTPSNR EETQQKSNLE 100
101 LLRISLLLIQ SWLEPVQFLR SVFANSLVYG ASDSNVYDLL KDLEEGIQTL MGRLEDGSPR TGQIFKQTYS KFDTNSHNDD ALLKNYGLLY CFRKDMDKVE 200
201 TFLRIVQCRS VEGSCGF

Primary structure of human somatropin



Somatropin (GH) analogues



* *Stippled residues indicate PEG attachment sites (Phe_1, Lys_{38}, Lys_{41}, Lys_{70}, Lys_{115}, Lys_{120}, Lys_{140}, Lys_{145}, Lys_{158})*

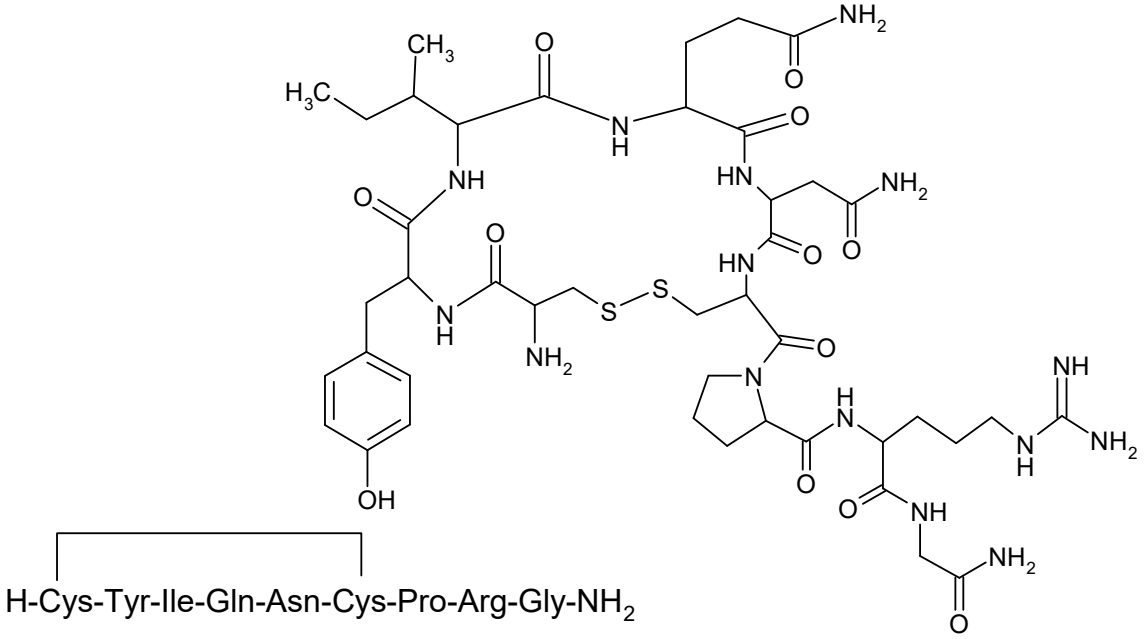
pegvisomant

- analogue – antagonist of human GH, in which 9 AA are changed, which enables it to block binding of native GH to its receptor by means of preventing receptor dimerisation
- pegylation is performed on 4 – 5 sites randomly selected from Phe_1 and various 8 Lys residues
- prepared by the recombinant technology followed by a controlled reaction with oxiran (polyadition) which results to covalent binding of 4 – 5 polyoxoethylene chains of $M_r \sim 500$
- pegylation lowers antigenicity and prolongs the biologic half-time
- using: treatment of acromegaly

1.3 Oxytocin, vasopressins and their analogues

Vasotocin

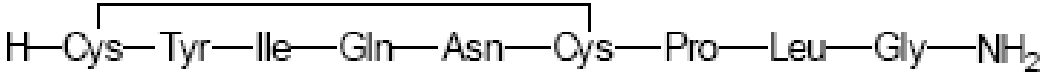
= fylogenetic precursor of oxytocine and vasopressins in organisms lower than mammals



H-Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Arg-Gly-NH_2

Oxytocin

- a cyclic nonapeptide released from the posterior pituitary gland (neurohypophysis)
- acts on smooth muscle cells, such as causing uterine contractions and milk ejection



H—Cys—Tyr—Ile—Gln—Asn—Cys—Pro—Leu—Gly—NH_2

$C_{43}H_{66}N_{12}O_{12}S_2$ M_r 1007,19 CAS 50-56-6

- prepared by synthesis
- used for triggering of the birth and enhancing of uterine contractions

Oxytocinum EP; Oxytocin Ferring-Léčiva ® inj. sol.

Vasopressin(s)

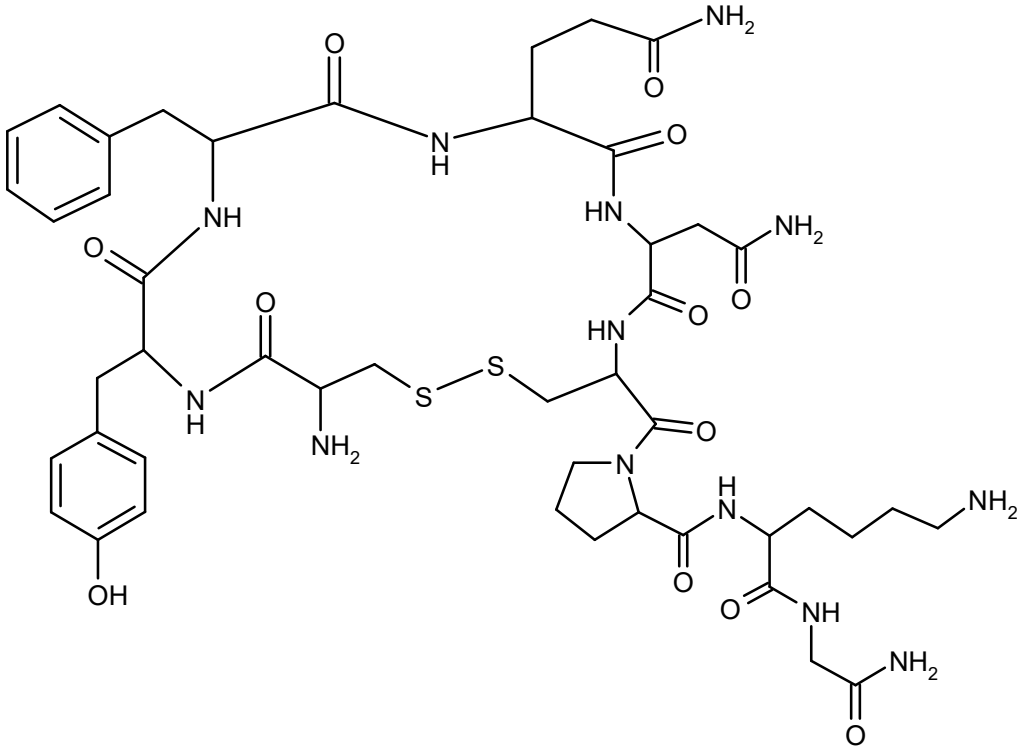
=antidiuretic hormone(s) (ADH)

•octapeptides released from the neurohypophysis of all vertebrates (precursor synthetized in hypothalamus)

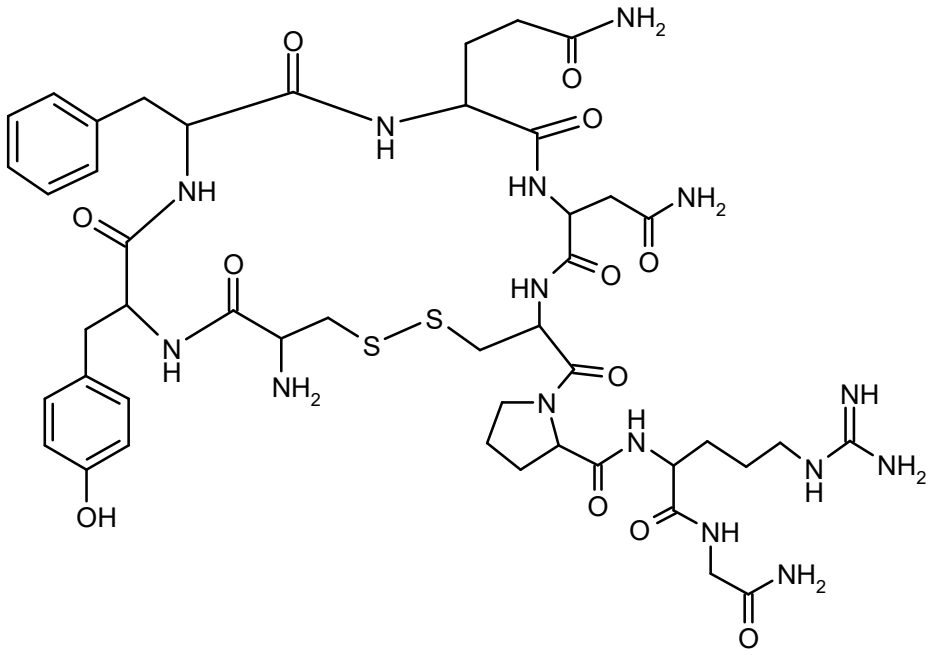
•control body water content (regulation of kidneys, lungs etc.)

•potential neurotransmitters

•semi-synthetic derivatives used predominantly



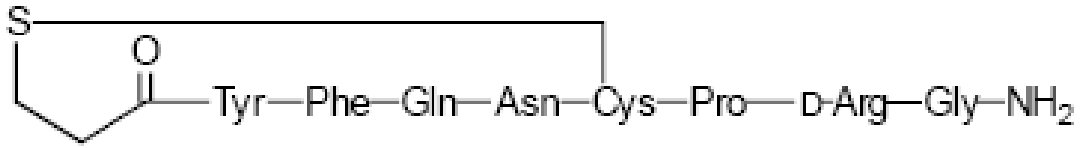
lysine-vasopressin
lypressin
•*Suidae* family only



arginine-vasopressin
argipressin
•predominant form of mammalian ADH

•treatment of *diabetes insipidus* and low blood pressure

Vasopressin analogues
Desmopressin



$C_{46}H_{64}N_{14}O_{12}S_2$ M_r 1069,22 CAS 16679-58-6

Desmopressinum EP
- cyclic pseudononapeptide
- prepared by synthesis
- antidiuretic (*enuresis nocturna*, ...)

Vaspressin analogues

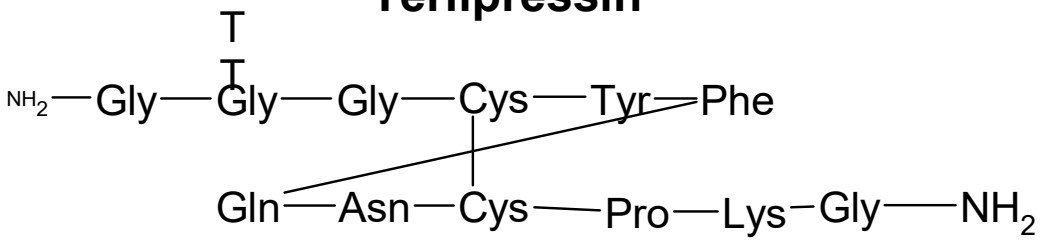
Felypressin

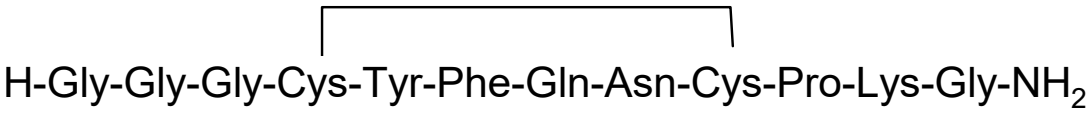
$C_{46}H_{65}N_{13}O_{11}S_2$ M_r 1040,22 CAS 56-59-7

Felypressinum EP

•vasoconstrictor with reduced antidiuretic activity

Terlipressin





•vasoconstrictor, treatment of variceal bleeding, circulation and septic shock
Glypressin ® inj., Remestyp ® inj.

Calcitonin

•released from thyroidal C-cells (= parafolicular cells – Baber 1876), in lower vertebrates from ultimobranchial bodies, originated from 5th branchial fissure

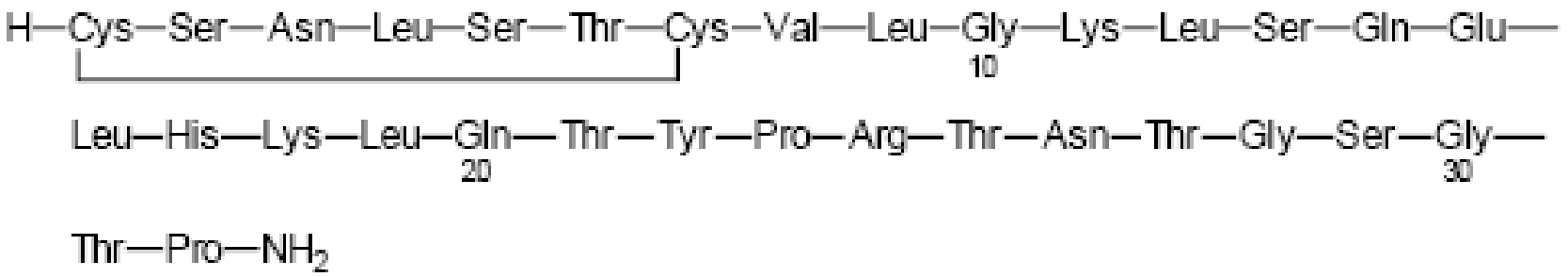
•peptide from 32 amino acid residues (salmon's – *Onchorhyncus kisutch;* human has 139 AA)

•receptors on osteoclasts (also in kidneys and brain)

•↓ excretion of Ca^{2+} from the bone (⇒ ↓ calcaemia)

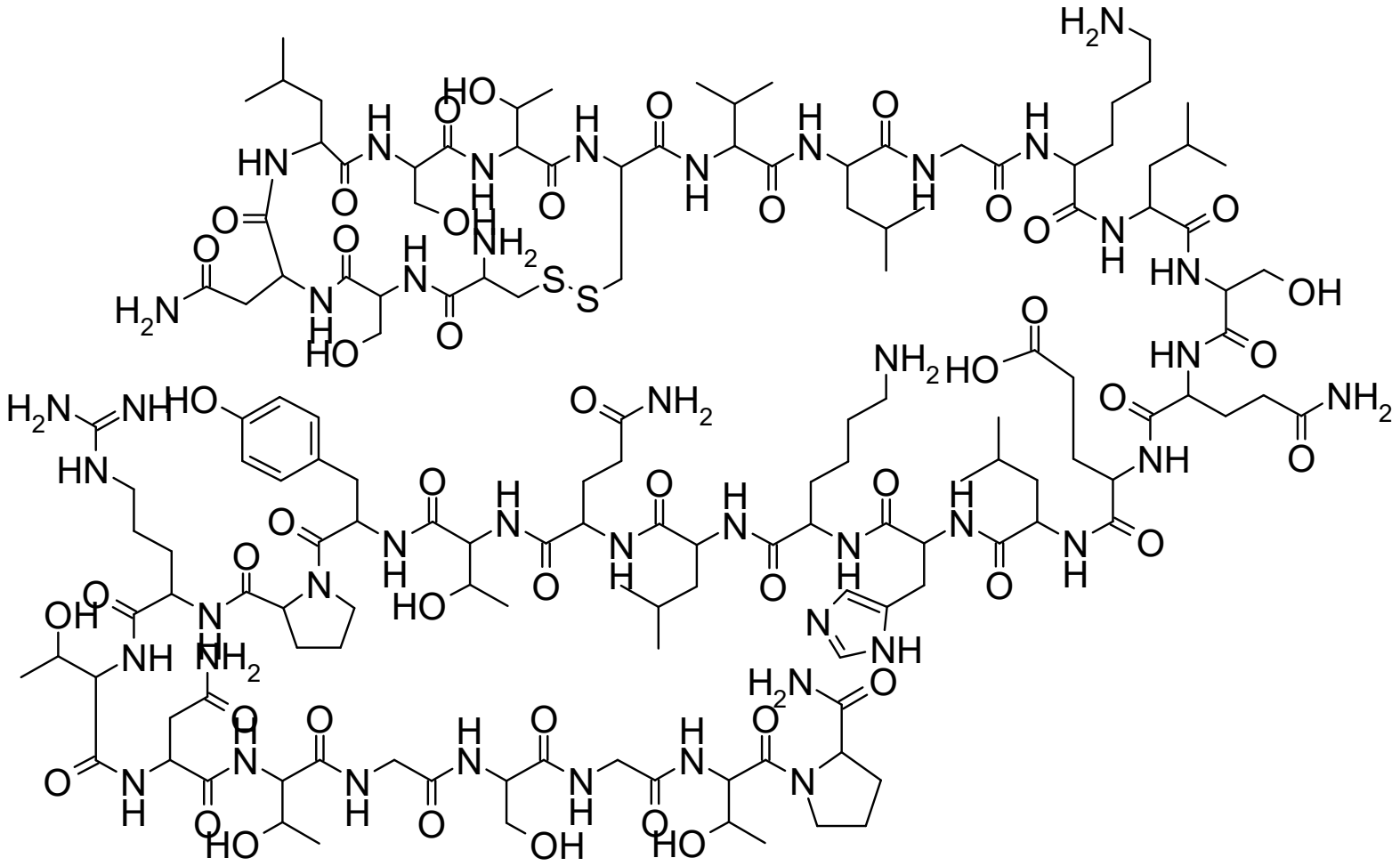
•↓ osteoclasts formation

•used together with Ca^{2+} for treatment of osteoporosis



$C_{145}H_{240}N_{44}O_{48}S_2$ M_r 3431,88 CAS 47931-85-1

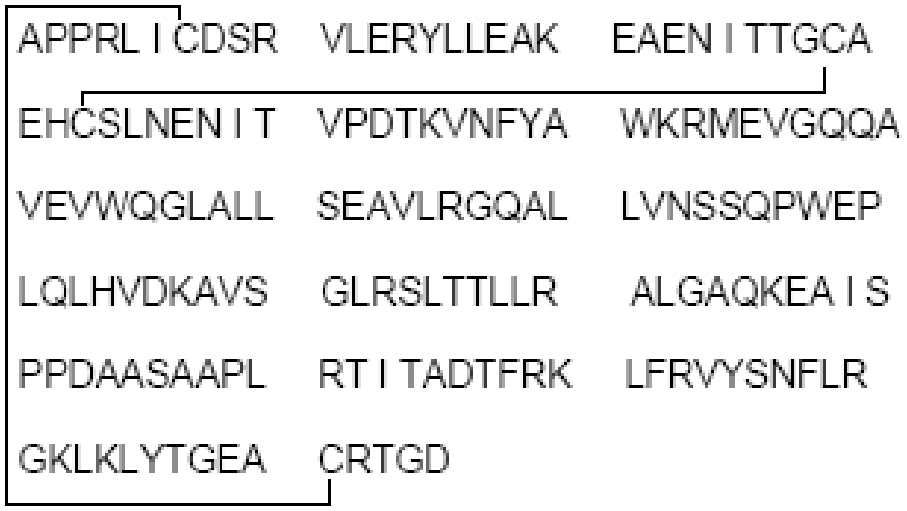
Calcitonin



Calcitoninum salmonis EP **= calcitonin salmon** (synthetic; AA sequence coresponds with salmon hormon)

Miacalcic® inj., nasal; Osteodon®; Tonocalcin®

2. Blood factors of erythropoetine type



M_r about 30 600 CAS 113427-24-0

erythropoietin
= glycosylated protein from 165 AA
Erythropoietini solutio concentrata EP
= a solution containing a group of closely related glycoproteins, which are not to distinguish from the natural human erythopoietin (urine erythropoietin) from the point of view of 165 amino acids sequence and their average profile of glycosylation
•naturally released from kidneys of adults and in liver of foetus
•stimulates stem cells of bone marrow to proliferation and differentiation
•produced *in vitro* in rodent cell lines by a method based on the recombinant DNA technology
•treatment of haematopoietic disorders, misused for doping

3. Colony stimulating factors

APARSPSPST QPWEHVNAIQ EARRLLNLSR

DTAAEMNETV EVISEMFDLQ EPTCLQTRLE

LYKQGLRGSL TKLKGPLTMM ASHYKQHCPP

TPETSCATQI ITFESFKENL KDFLLVIPFD

CWEPVQE

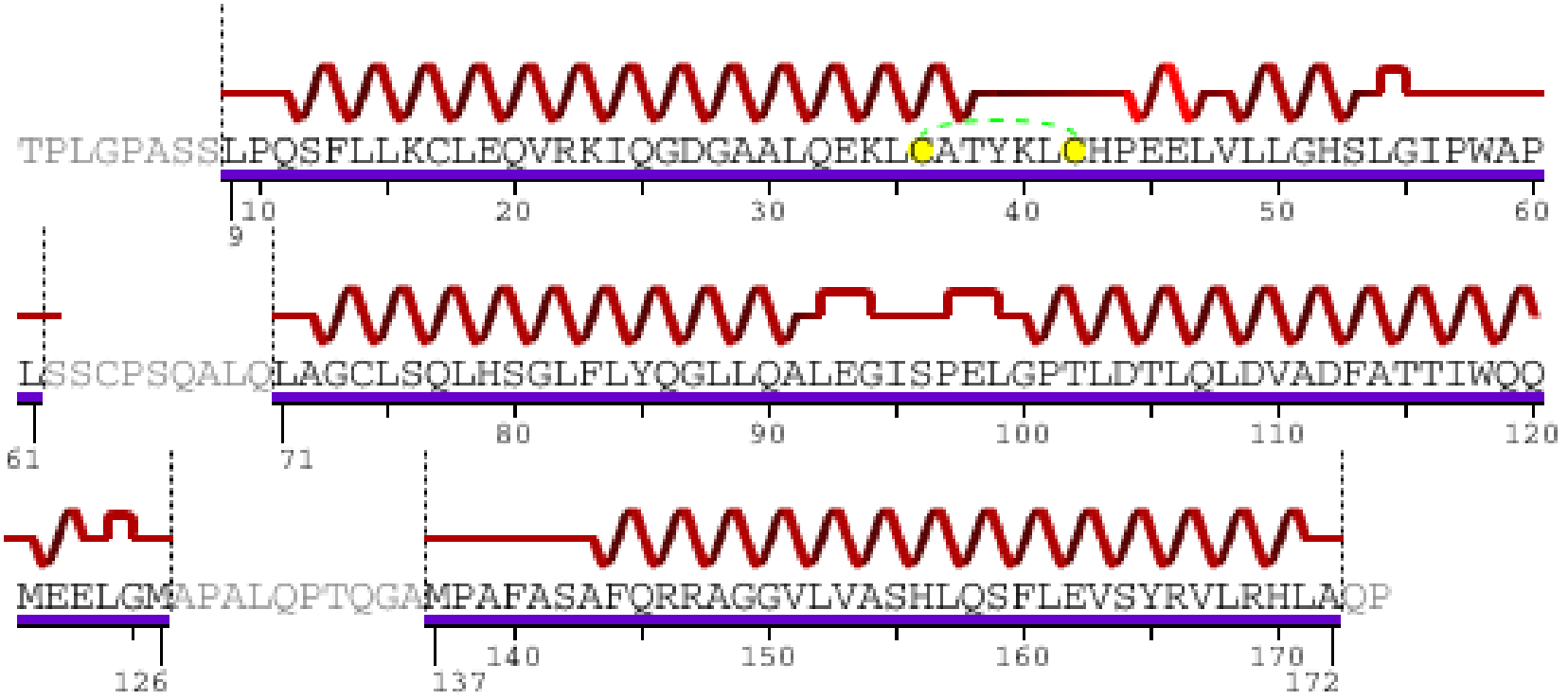
$C_{639}H_{1007}N_{171}O_{196}S_8$ M_r 14 477,49 CAS 99283-10-0

molgramostim
= a factor stimulating granulocytes and macrophages colonies released from various kinds of blood cells
•not glycosylated
•stimulates differentiation and proliferation of leukocyte pluripotent stem cells into matured granulocytes and macrophages
•production by a recombinant technology using bacteria as host cells
• treatment of leukopenia in cancer chemotherapy or HIV infections

Filgrastim and pegfilgrastim

Filgrastim = human granulocytes colony-stimulating factor (G-CSF); glycosylated, 174 AA

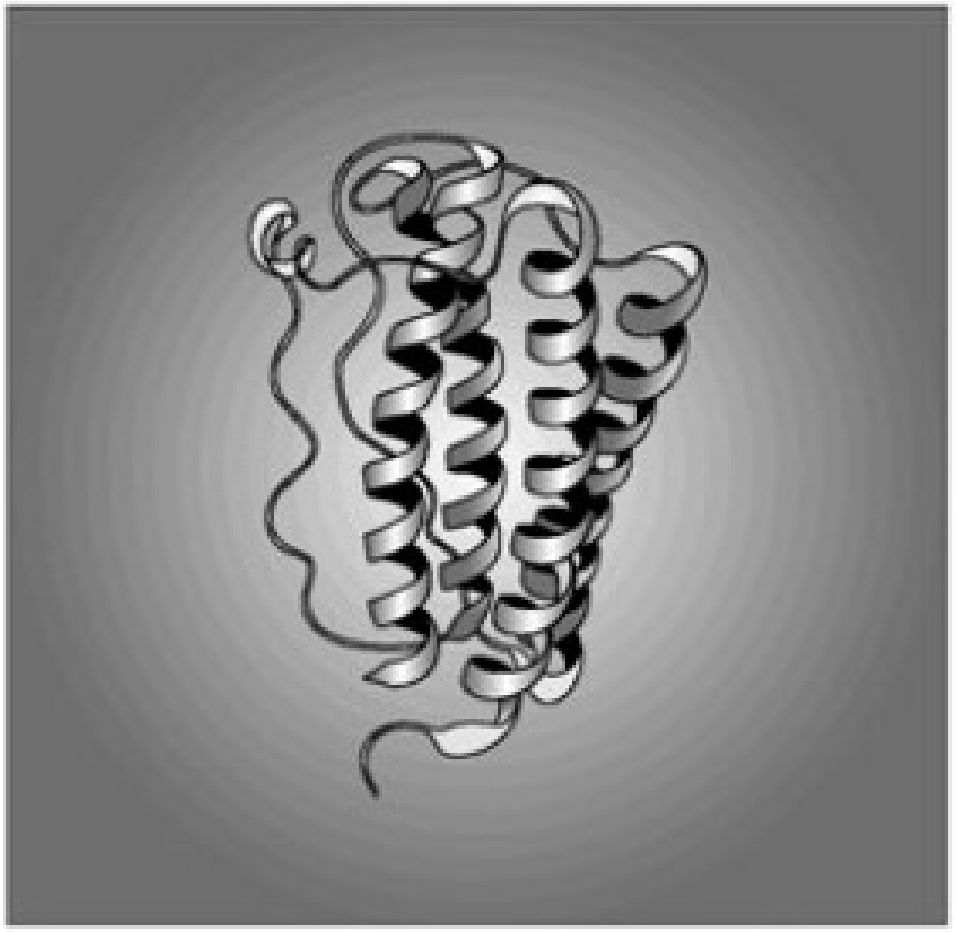
Sequence of filgrastim precursor



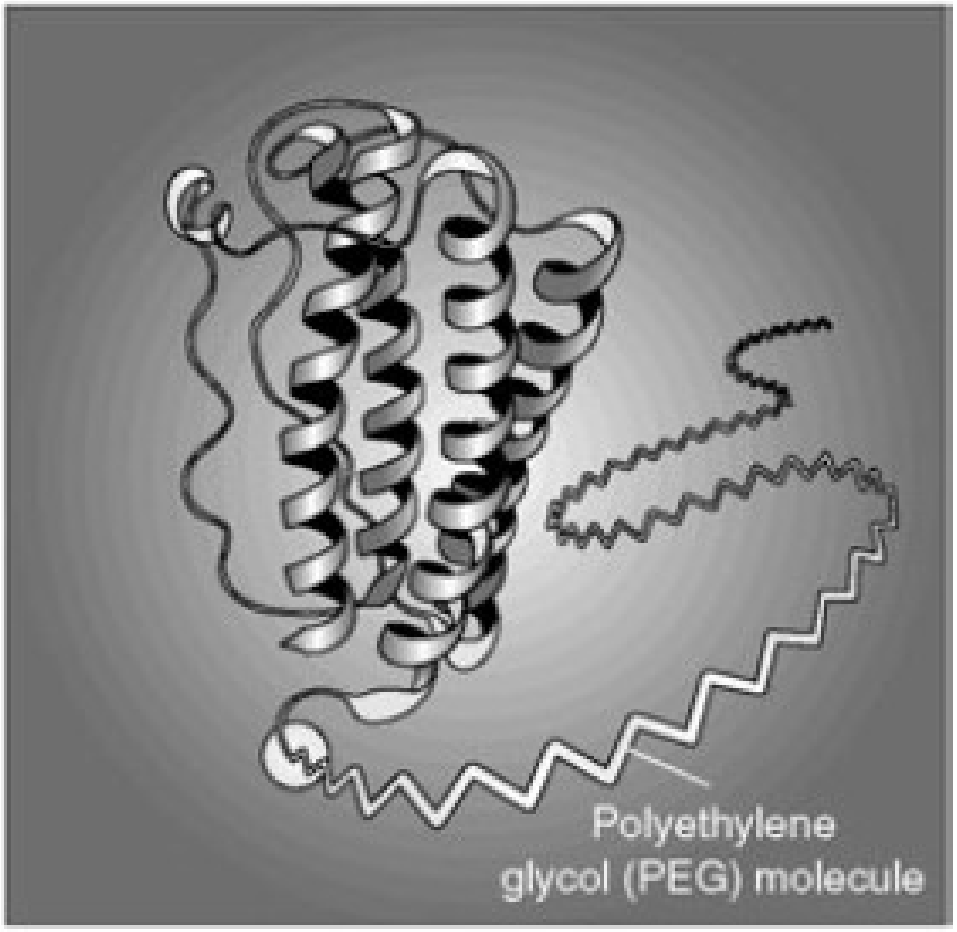
•treatment of neutropenia in cancer chemotheapy and in AIDS

Pegfilgrastim has covalently attached PEG chain of M_r cca 20 000 on N-terminus

- longer elimination half-time
- recombinant and semi-synthetic production



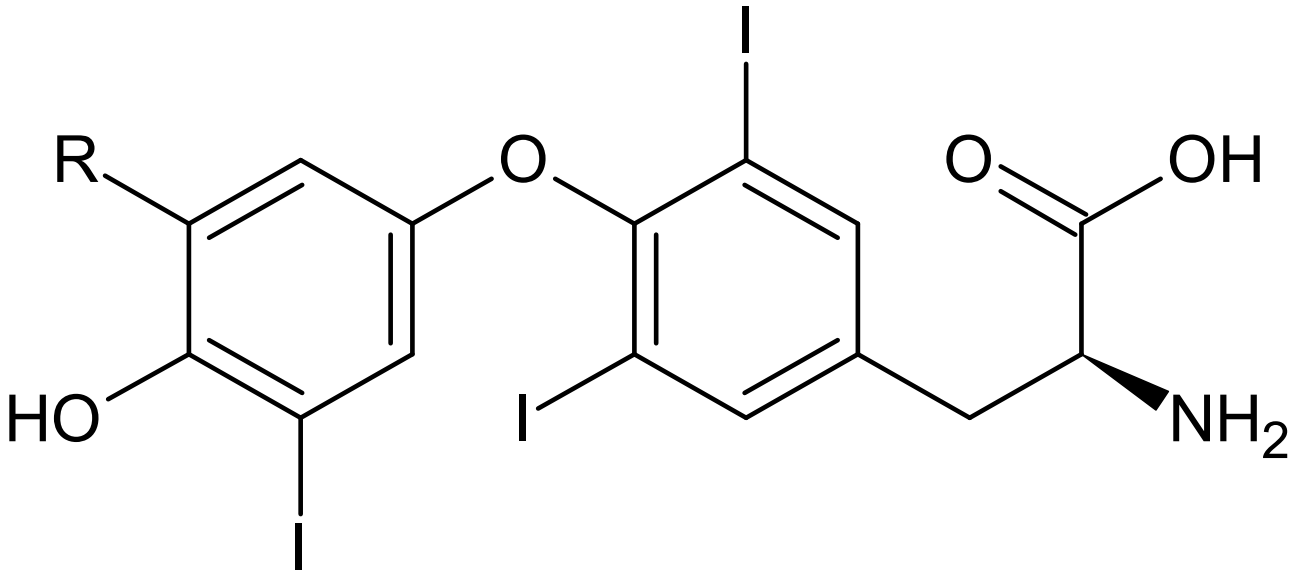
Filgrastim



Pegfilgrastim

2. Hormones derived from a single amino acid

Thyroid hormones



R = -H

liothyronine, syn. L-3,5,3´-trijodothyronine, T3

R = -I

levothyroxine, syn. L-3,5,3´,5´-tetrajodothyronine, T4

Levothyroxinum natricum hydricum PhEur

•Thyroid hypofunction caused by lack of thyroxine

Drugs used in thyroid dysfunctions
Thyrotropics

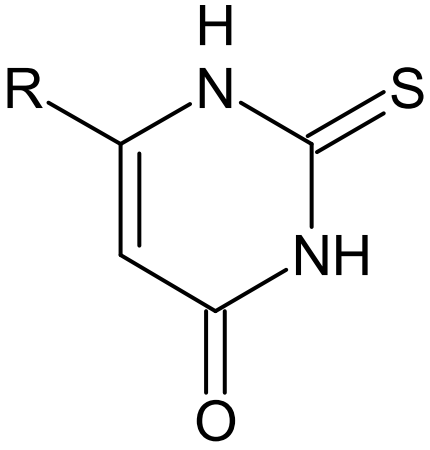
KI
potassium iodide
- prevention of thyroid hypo-function due to lack of iodine (goitre, cretinism) – additive to NaCl
- prevention of striking by radioactive I_2 in a potential nuclear power plant accident: JODID DRASELNÝ 65 VULM

Drugs used in thyroid dysfunctions
Thyrostatics

$KClO_4$

potassium perchlorate
Kalii perchloras PhEur

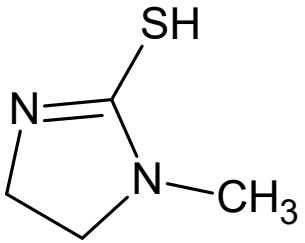
Thiouracil derivatives



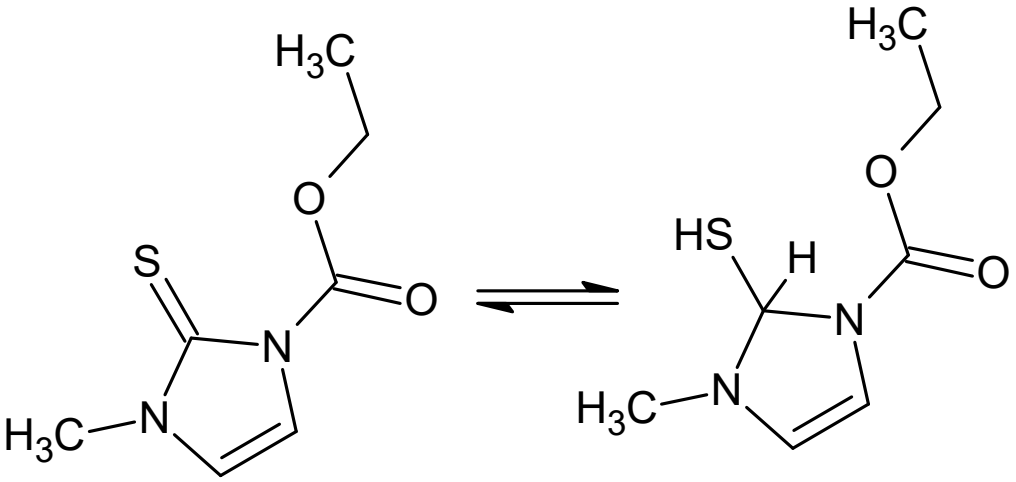
R = $-CH_3$ **methylthiouracil**

R = $-C_3H_7$ **propylthiouracil**
Propylthiouracilum PhEur

2-mercaptoimidazole derivatives



thiamazol
syn. **methimazol** [USAN, BAN]



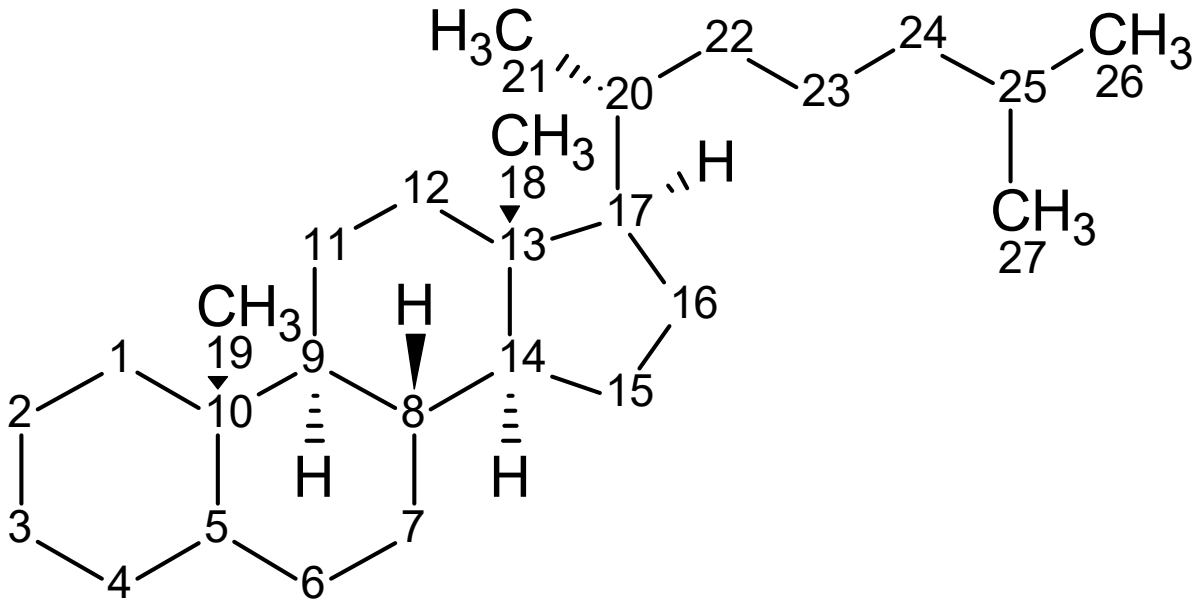
carbimazole

- Mode of action of both thiouracils and mercaptoimidazoles: inhibition of thyroidal peroxidase $\Rightarrow \downarrow$ 2 $I^- \rightarrow I_2 \Rightarrow \downarrow$ embedding of I_2 into tyrosyl rests $\downarrow$ T3 and T4 formation
- common structural fragment: thiourea

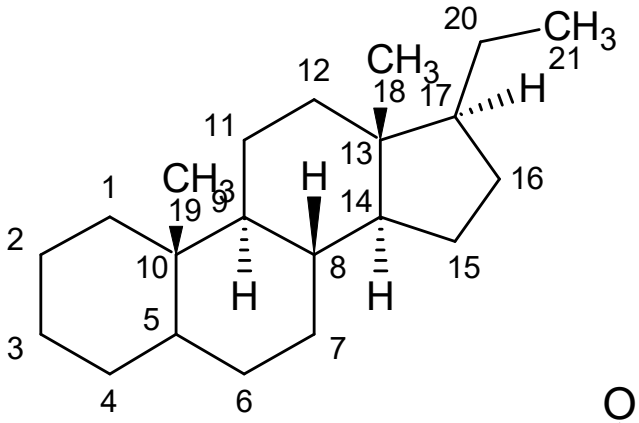
„Radiothyrostatics“ and thyroid diagnostics

- $Na^{131}I$ for radio-therapeutic purposes: treatment of thyroid carcinoma including metastases, diagnose of cancers
- ^{123}I, ^{99}Tc: diagnoses of benign conditions

3. Steroid hormones



cholestane – the largest steroid skeleton of the human organism

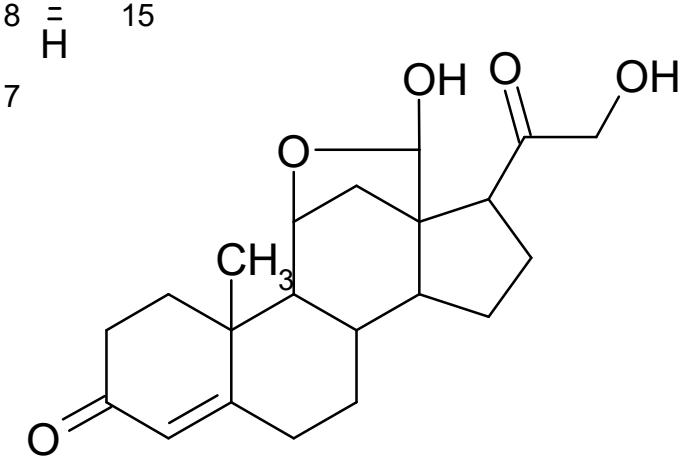


pregnane

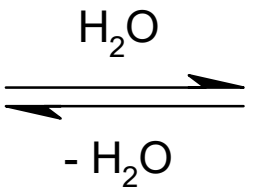
3.1. Corticoids = adrenal cortex hormones

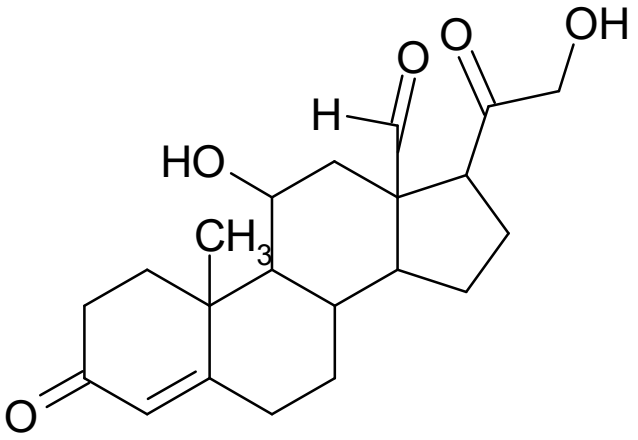
3.1.1. Mineralocorticoids

•secreted from *Zona glomerulosa* of supra-renal glands cortex



(cyclo)hemiacetal form





aldosterone

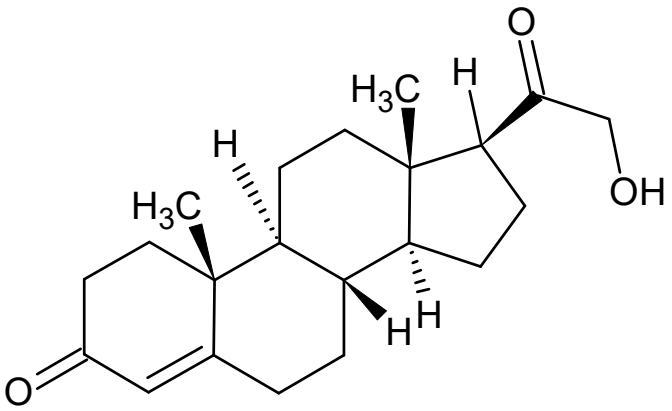
•control of ratio Na^+/K^+ and water distribution in tissues

•↑ tubular back resorption of Na^+ $\Rightarrow$ ↓ water excretion by kidneys and ↑ excretion of both K^+ and H^+ by change for Na^+

•secretion of aldosterone is controlled by angiotensin II and probably also by osmotic and volume receptors

•„adversary“: atrial natriuretic factor (ATF); a polypeptide formed in the heart

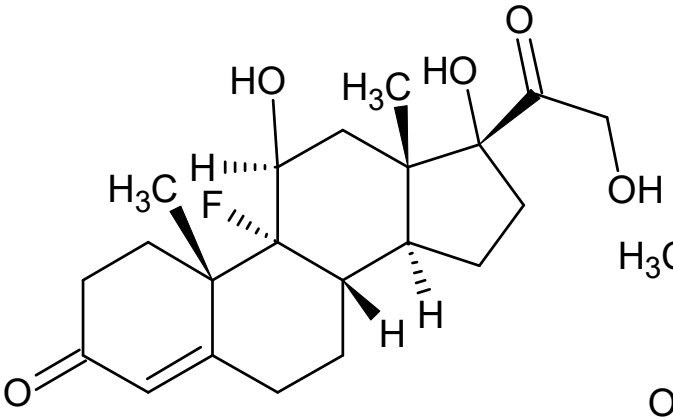
Further mineralocorticoids



desoxycortone

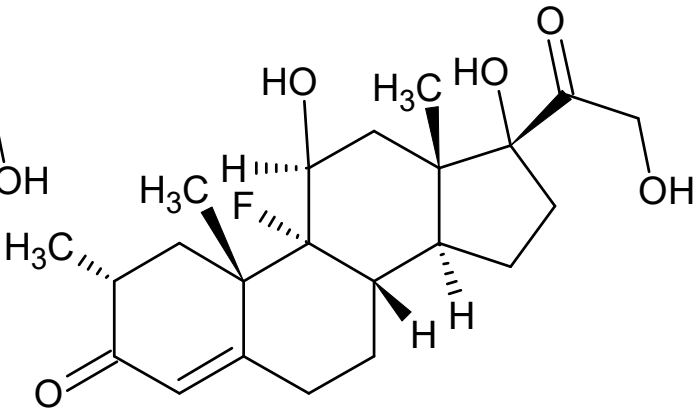
syn. desoxycorticosterone [USAN]

- •natural
- •biosynt. intermediate of glucocorticoide corticosterone
- *Desoxycortoni acetas PhEur*



fludrocortisone

- •subst. treatment in supra-renal insufficiency
- Astonin-H®



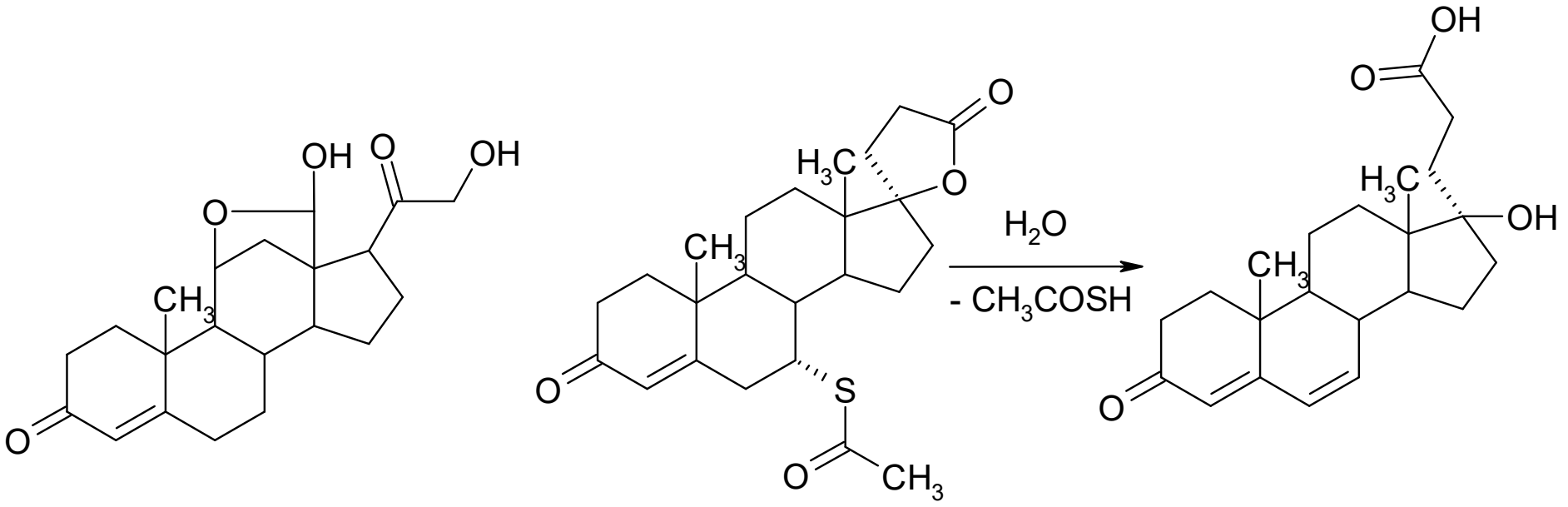
9α–fluoro-2α-methylcortisol

Structure-activity relationships (SAR)

- introduction of F into pos. 9α strengthens mineralocorticoid activity, -CH_3 in pos. 2α also and more $\Rightarrow$ 9α–fluoro-2α-methylcortisol is 30x more active than aldosterone

Aldosterone antagonists = „potassium conserving“ diuretics

inhibit reabsorbtion of Na^+ in distal tubule; simultaneously retention of K^+ occurs

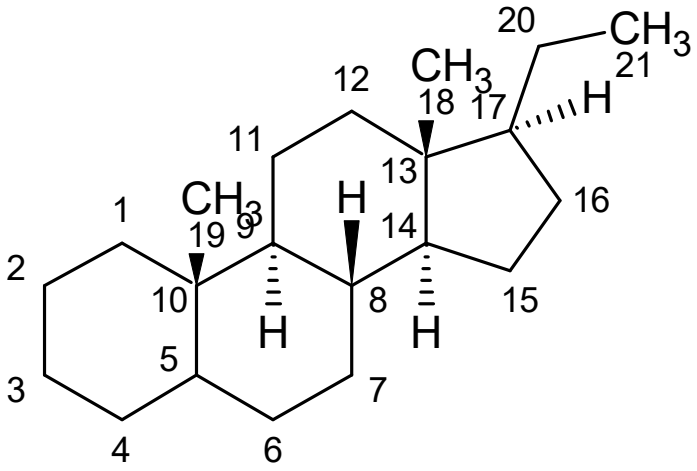


aldosterone

spironolactone
prodrug of canrenoic acid
for oral application

Verospiron® tbl.

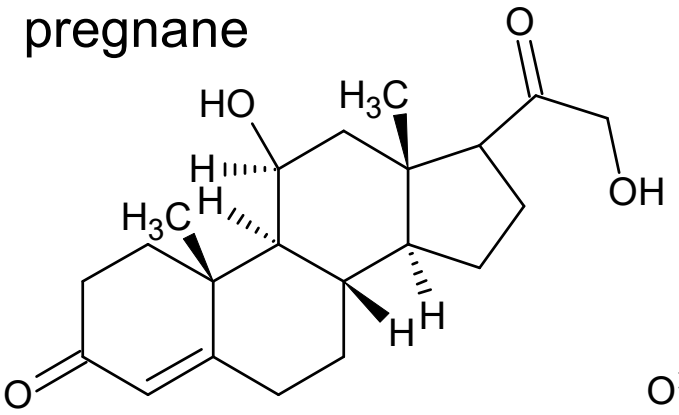
canrenoic acid
real active compound
Aldactone® inj. – K^+ salt for parent. application *(kalii canrenoas)*



pregnane

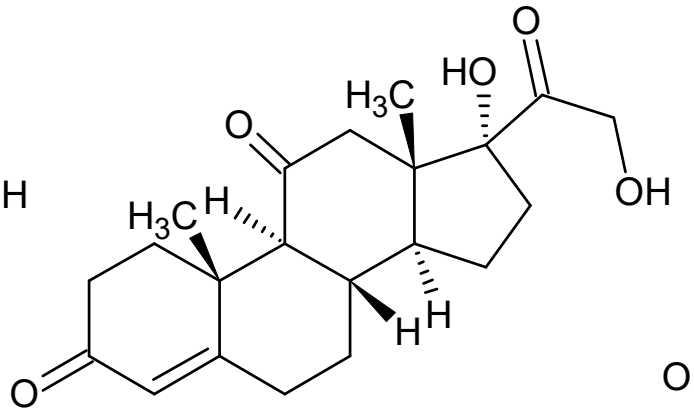
3.1.2. Glucocorticoids

•secreted from *Zona fasciculata* of supra-renal glands cortex



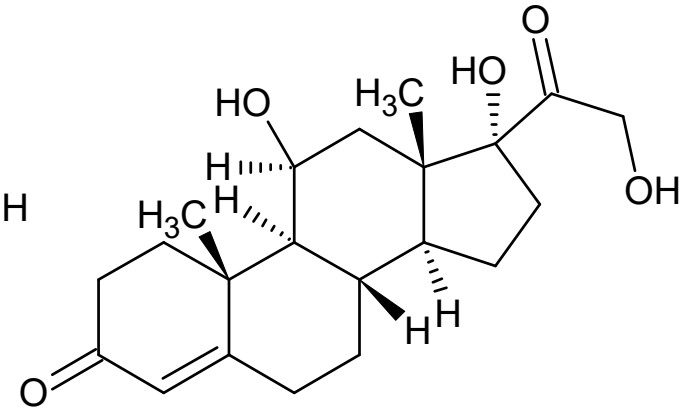
corticosterone

•first isolated by Reichstein 1936



cortisone

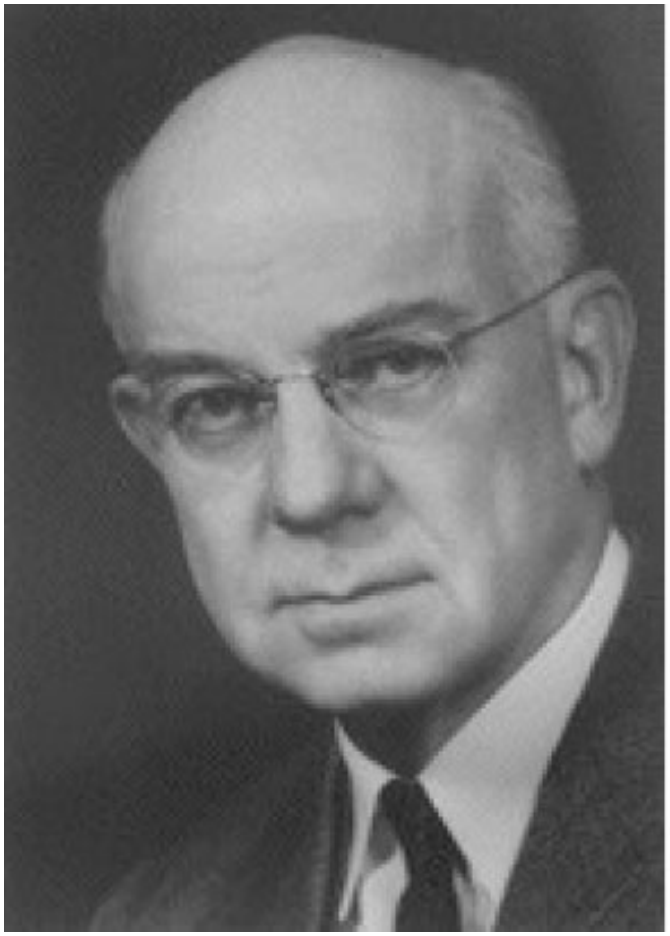
•first isolated simultaneously by Reichstein and Kendall (1939)



hydrocortisone, syn. **cortisol**

•first used by Hench for Addison disease and rheumatism treatment (1950)
(rel. anti-inflammatory activity = 1)

Nobel prize for physiology and medicine holders (1950)



Edward C. Kendall

Philip S. Hench

Tadeus Reichstein

Effects of glucocorticoids

- ↑ gluconeogenesis from amino acids, which are formed by proteins cleavage; a portion of glukose stored in glycogen, a portion released into the blood (⇒ „steroid diabetes“)
- block all inflammatory processes
- cortisol excretion ↑ in stress conditions as a protective reaction („energy emergency“)

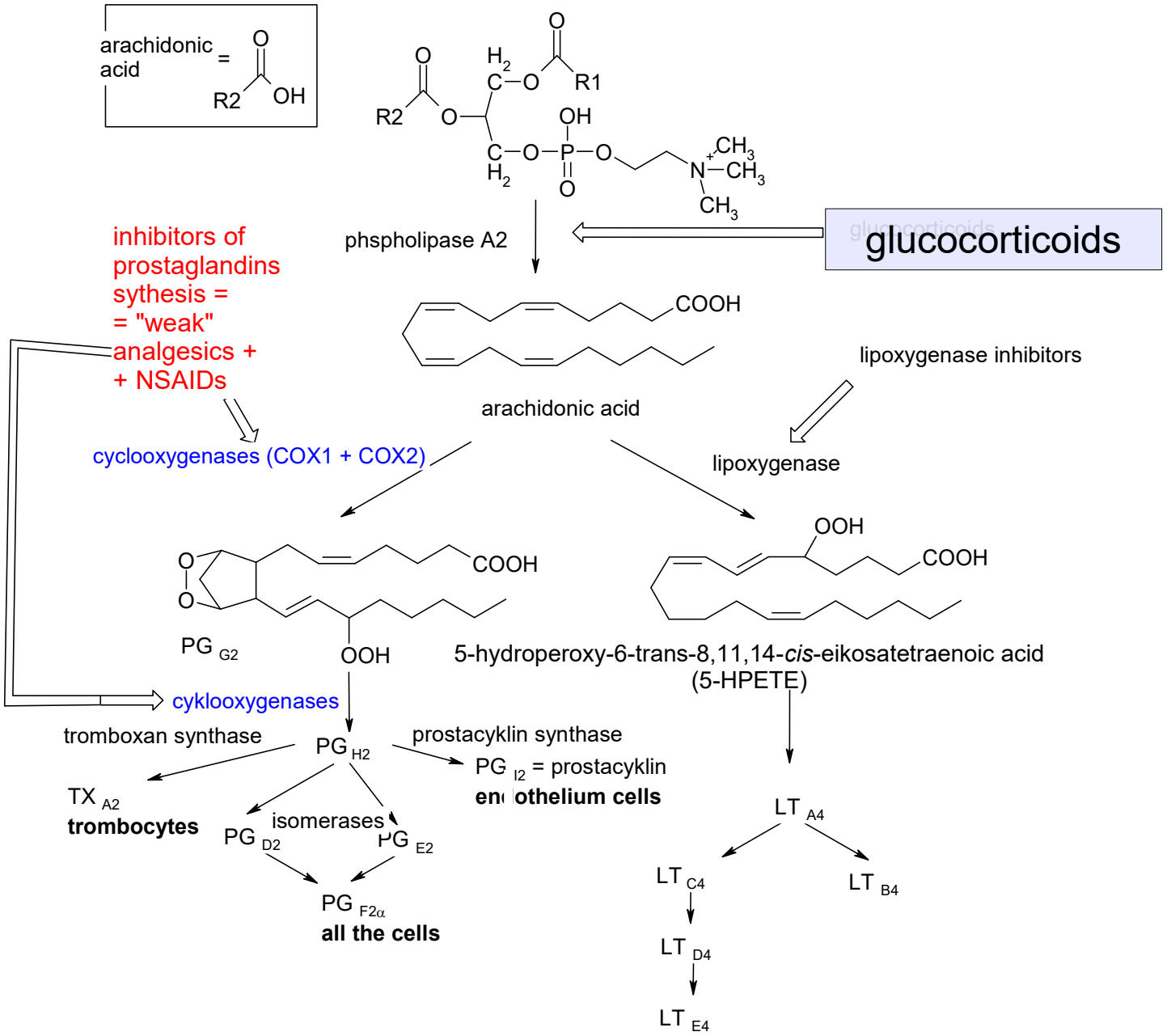
Target structures – sites of action:

- steroid receptor is in cell nucleus, stimulation ⇒ ↑ neo-formation of enzymes taking part in proteins metabolism (e.g. tyrosinaminotransferase) and sugars e.g. pyruvatecarboxylase)
- binding site also on GABA-receptor
- etc.

Usage: anti-inflammatory drugs, anti-rheumatics, anti-asthmatics, immunosuppressants, treatment of multiple sclerosis, *lupus erythematodes,* substitution therapy (Addison´s disease) etc.

Adverse effects: Cushing syndrome

The role of glucocorticoids in metabolism of eicosanoids



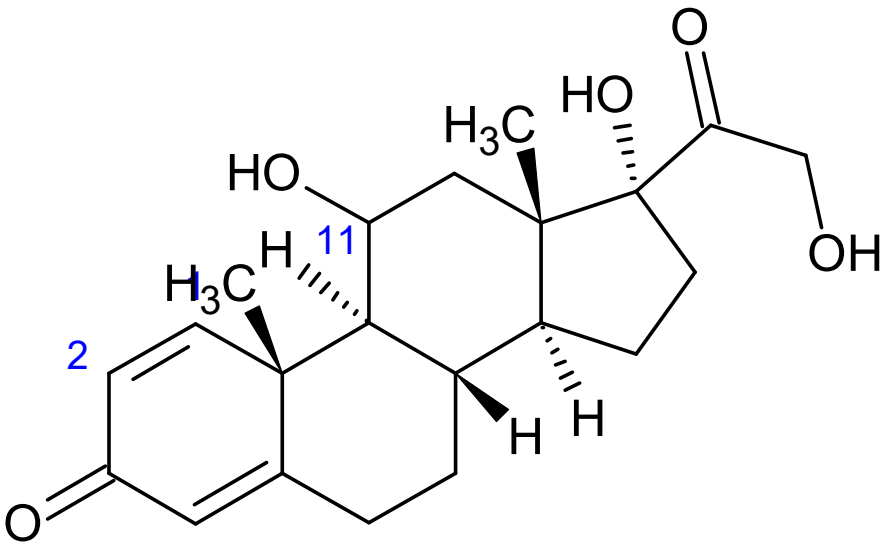
Structure-activity relationships (SAR)

- the "upper" β-side of the skeleton is more important for the interaction with the steroid receptor
- ketonic group in ring A conjugated with double bond is necessary for the activity
- α-ketol group in position 17 also
- an oxygenous group in pos. 11 also
- hydroxyl in pos. 17α increases the activity

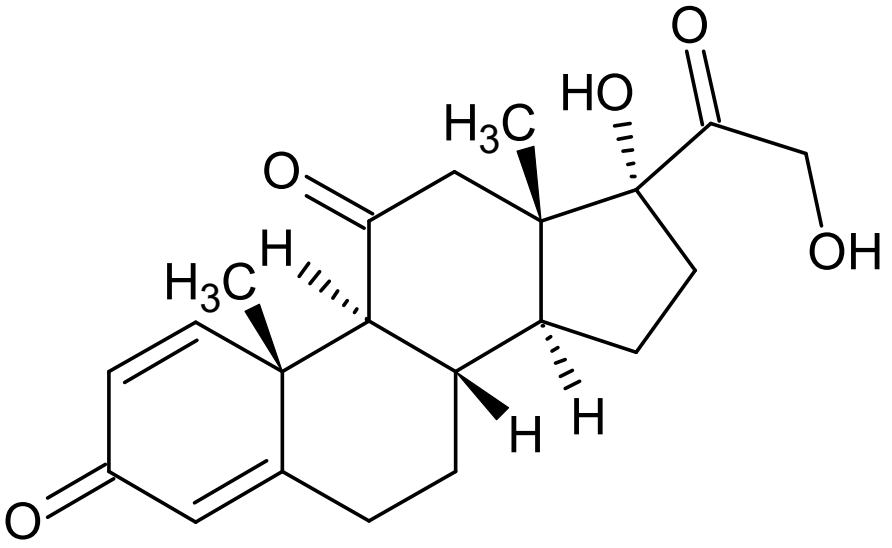
Synthetic changes for more suitable profile of activity

- further double bond in pos. resulted to ↑ anti-inflammatory activity 4x, mineralocorticoid one ↓ about 2/3 (⇒ prednisolone, prednisone)
- fluorination in pos. 9α ↑ preferably mineralocorticoid activity, glucocorticoid effect also growths; it ↑ with electronegativity and ↓ with bulkiness of a substituent (for 9α–Cl 5x greater); this effect is not caused by simple ↑ of acidity 11β-OH as a result of elektronacceptor effect of the substituent in pos. 9α, because affinity of 9α–Cl a 9α–F derivatives to the receptor does not differ
- fluorination in pos. 6α has similar, but weaker impact; methylation in this position ↑ glucocort. activity 10x, the mineralocort. one is mildly lowered
- 9α/β-methylation ↑ further glucocort. activity; mineralocort. activity is almost lost (fluocortolone, dexamethasone, betamethasone...); hydroxylation has the same effect (triamcinolone, fluocinolone)

Glucocorticoids – steroidal anti-inflammatory drugs



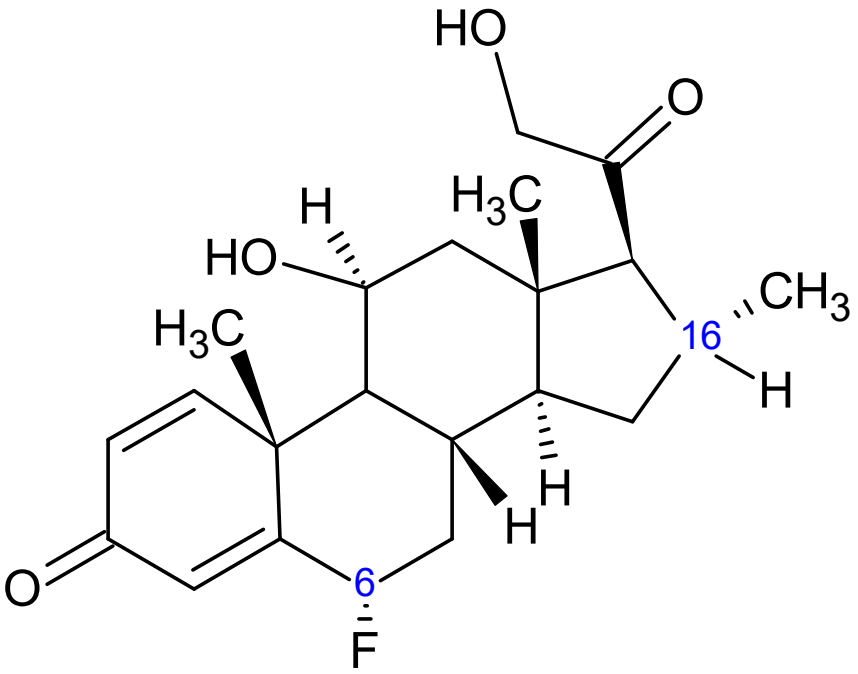
prednisolone



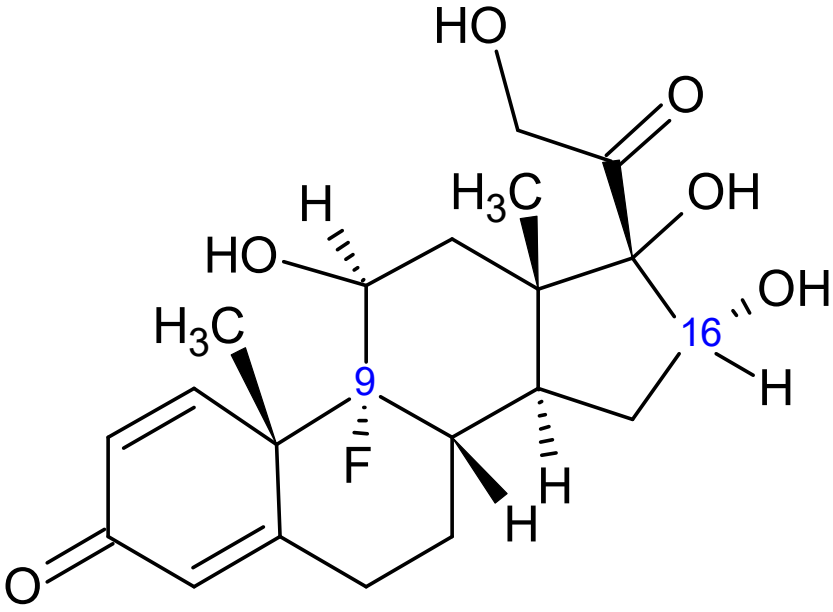
prednisone

•rel. activity = 4

Glucocorticoids – steroidal anti-inflammatory drugs

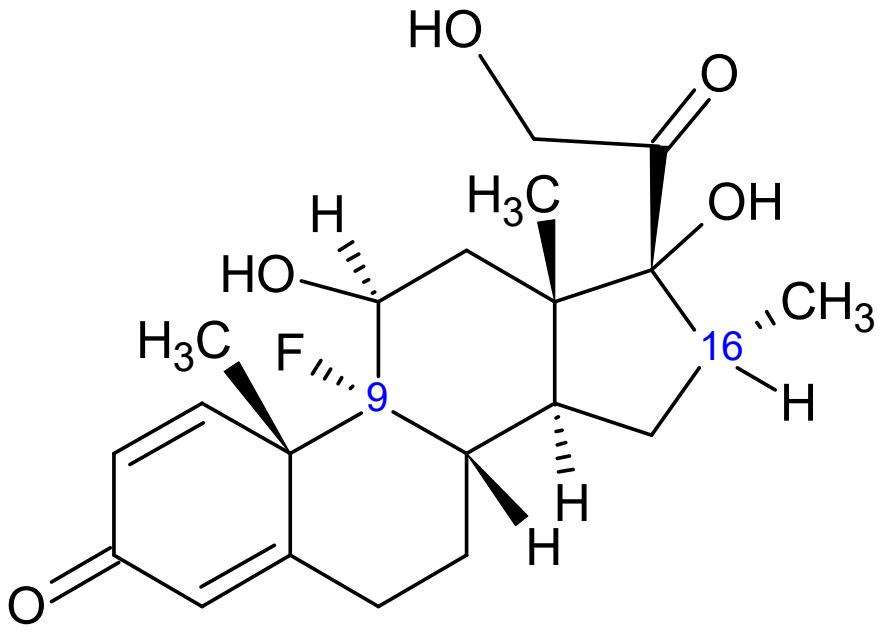


fluocortolone
•5

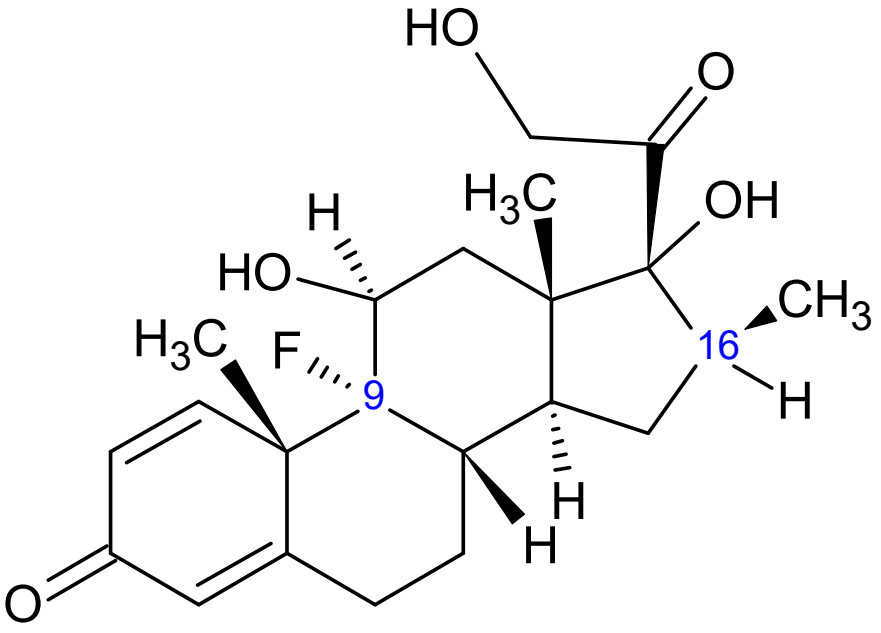


triamcinolone
•6

Glucocorticoids – steroidal anti-inflammatory drugs

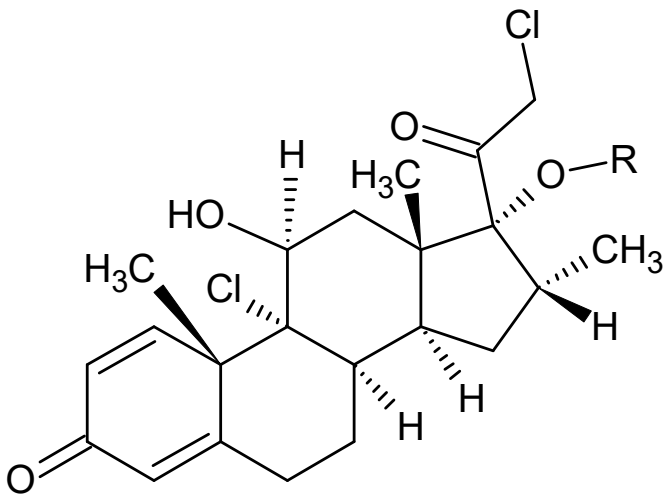


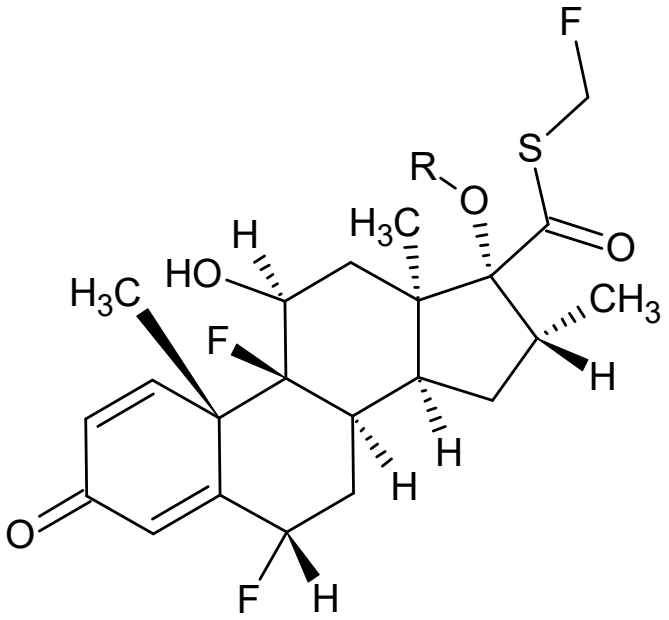
dexamethasone
•30



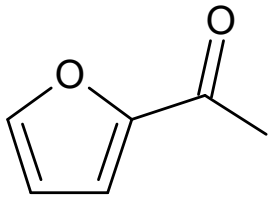
betamethasone
•30

Glucocortikoids – antialergics, antiasthmatics and their prodrugs





R = H- **mometasone**

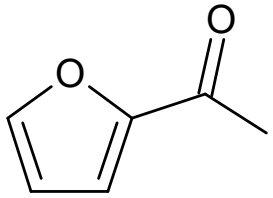
R =  **mometasone furoate**

Asmanex$^{(R)}$ 200 μg inh. plv.

R = H- **fluticasone**

R = CH_3CH_2CO- **fluticasone propionate**

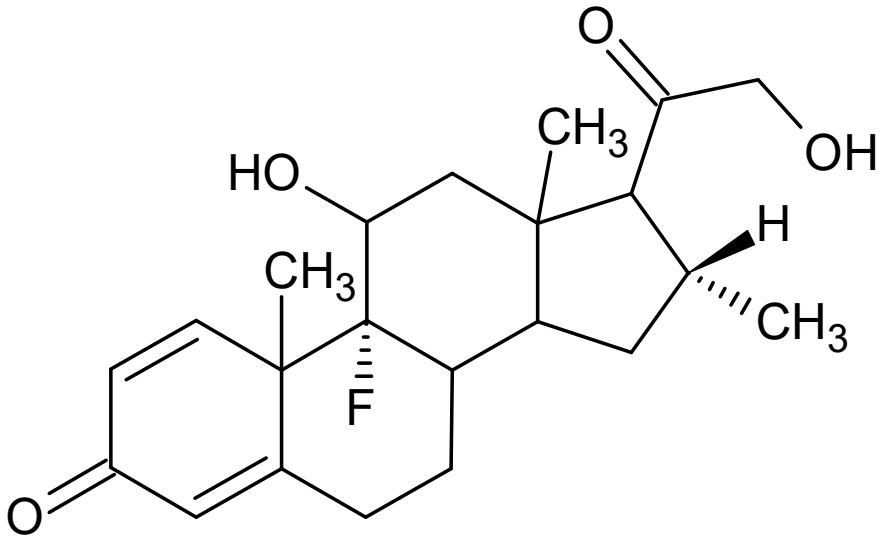
Seretide$^{(R)}$ Inhaler (+ salmeterol)

R =  **fluticasone furoate**

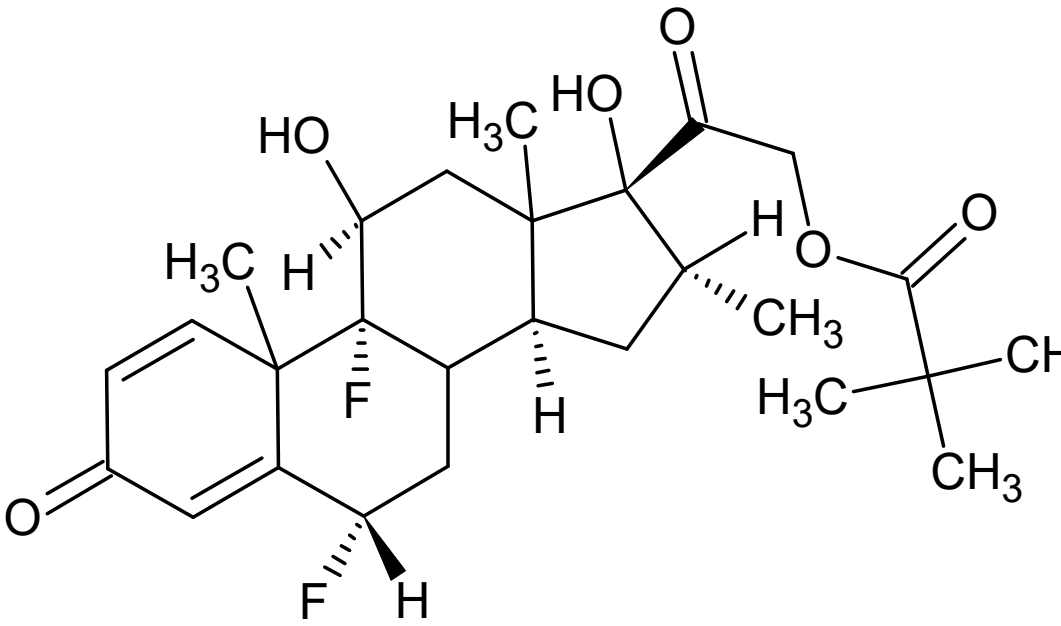
Avamys$^{(R)}$ 27,5 μg susp. - nasal spray

Topically administered steroid anti-inflammatory drugs

- ↑ lipofillicity desirable ⇒ prodrugs of ester or acetal type

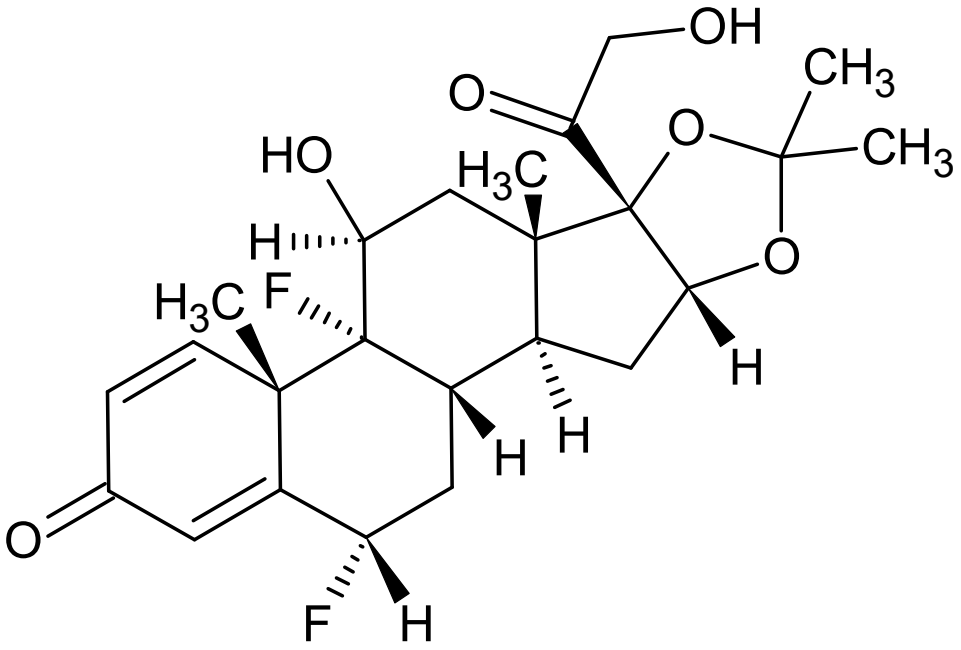


doximethason

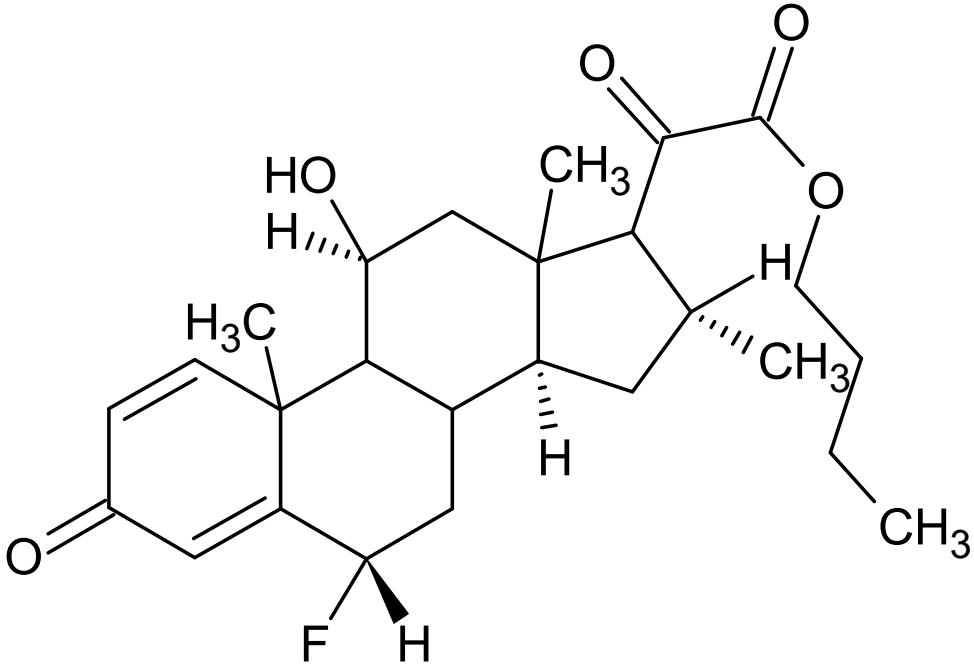


flumethasone pivalate

Topically administered steroid anti-inflammatory drugs (continued)



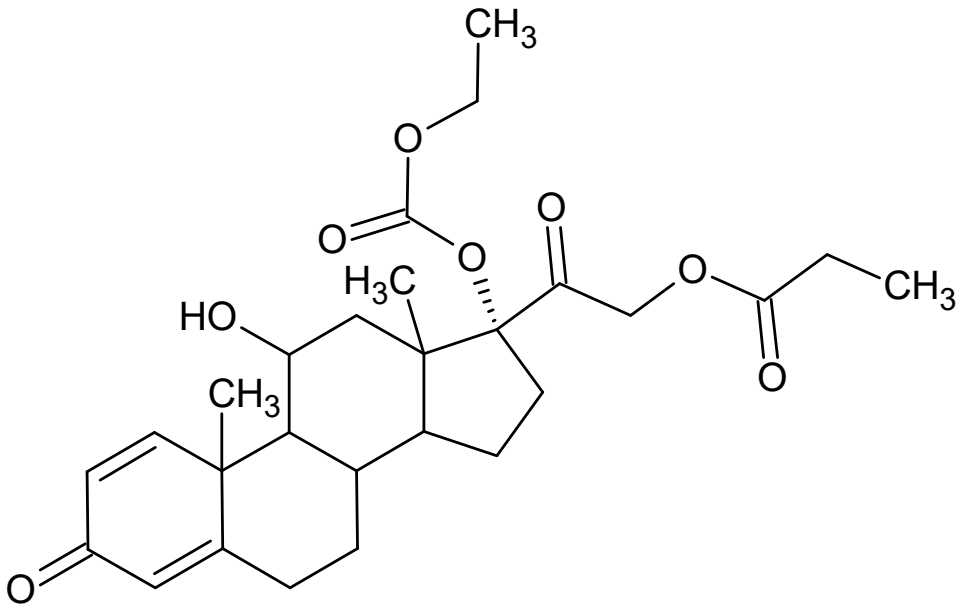
fluocinolone acetonide



fluorocortin butylester

•rapidly hydrolysed to inactive free carboxylic acid by esterases of the skin ⇒ no system activity

Topically administered steroid anti-inflammatory drugs (continued)

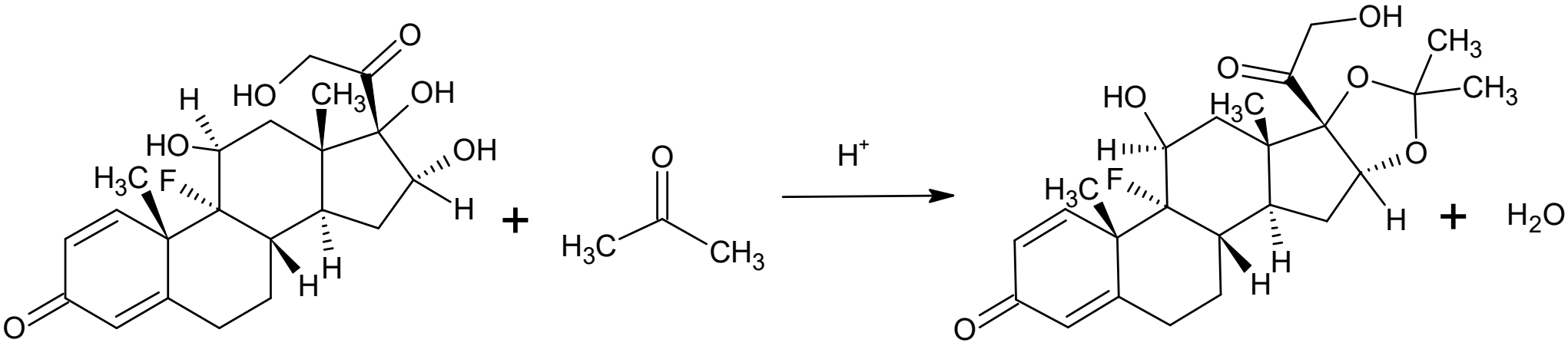


prednicarbate

- fast hydrolysis and further inactivation by biotransformation $\Rightarrow$ minimal systemic effect

Prodrugs of glucocorticoids

- esters with shorter alkanoic acids (acetic, propionic, valeric, caproic, pivaloic) at C17 and/or C21 for topical skin administration
- monoesters with polyhydric acids (succinic, H_3PO_4) usually at C21 for injection administration in the form of a salt
- acetals bridging C16 and C17

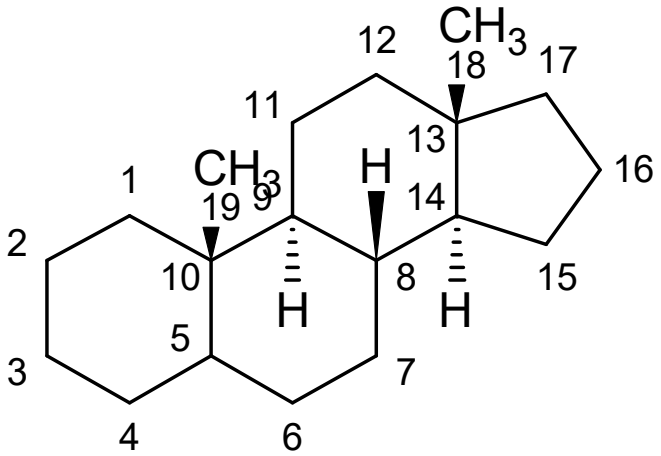


triamcinolone

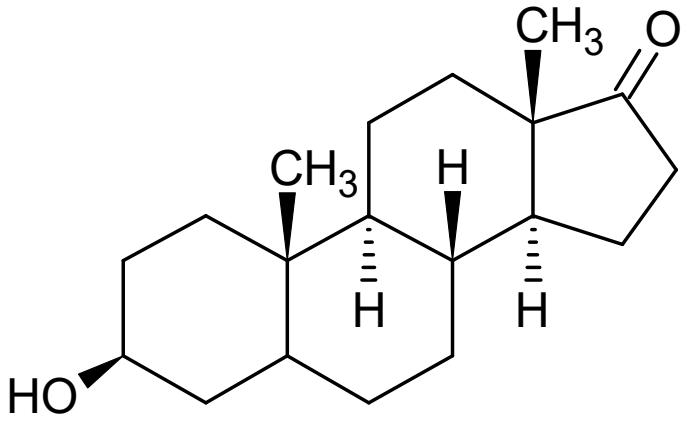
triamcinolone acetonide

Example of preparation of an acetal prodrug

3.2. Sex hornomes
3.2.1. Androgens

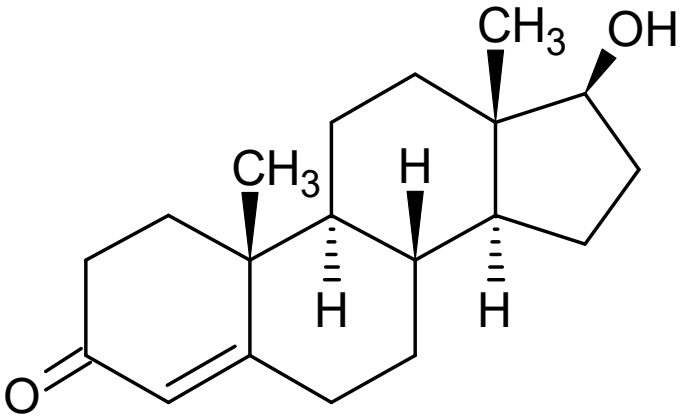


androstane



androsterone

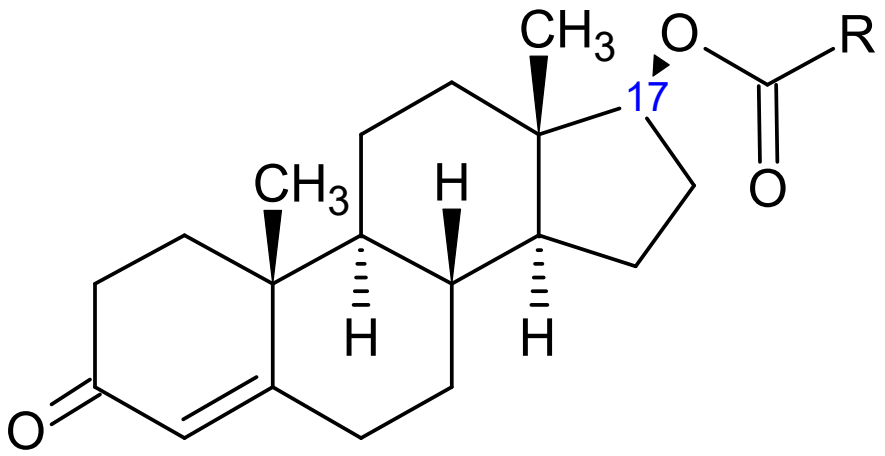
- a metabolite of testosterone
- 1st isolated male sex hormone (Butenandt 1931)

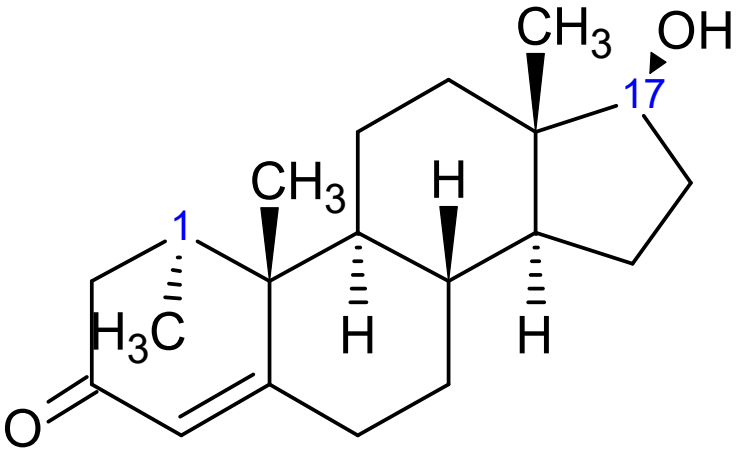


testosterone

- 1935
- 10x more efficient
- $T_{1/2}$ = 10 min $\Rightarrow$ ester prodrugs needed
- *p.o.* inactive due to high first-pass effect

Androgens – therapeutics in use





R = -C_2H_5 **testosterone propionate**

R = -$(CH_2)_2CH(CH_3)_2$ **testosterone isocaproate**

R = -C_6H_{13} **testosterone enanthate**

etc.

•*i.m.* administration

mestrenolon

•applicable *p.o.*

Effects of androgens

- formation of secondary sex signs, spermatogenesis, libido
- anabolic: ↑ biosynthesis of proteins of the muscle tissue (sex independent)

Usage as therapeutics

- substitution treatment of hypogonadism
- breast cancer treatment

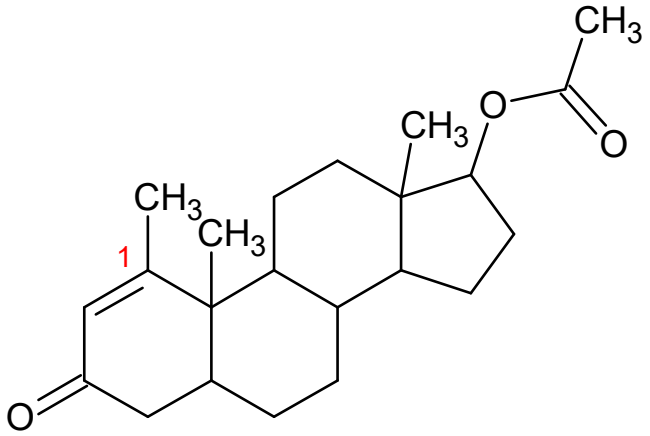
Anabolics

•analogues of testosterone, in which anabolic effect is ↑ and androgenic one is ↓ by changes of the structure

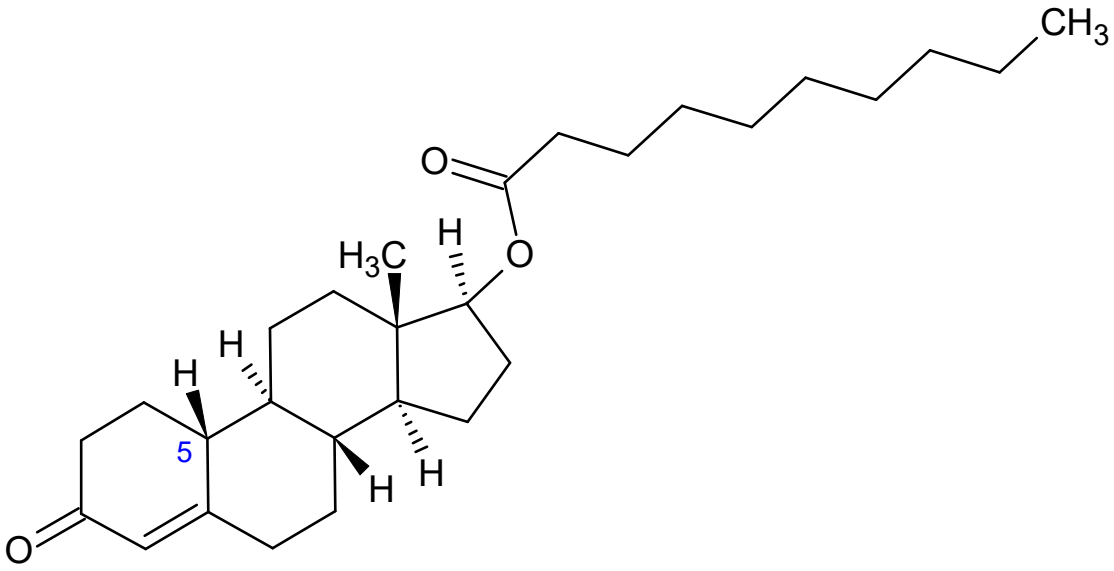
•impact also metabolism of carbohydrates and minerals

•androgenic effect in part kept ⇒ virilization in women (1st sign: change of position of voice)

• therapeutic indications: anorexia, serious protein deficiency

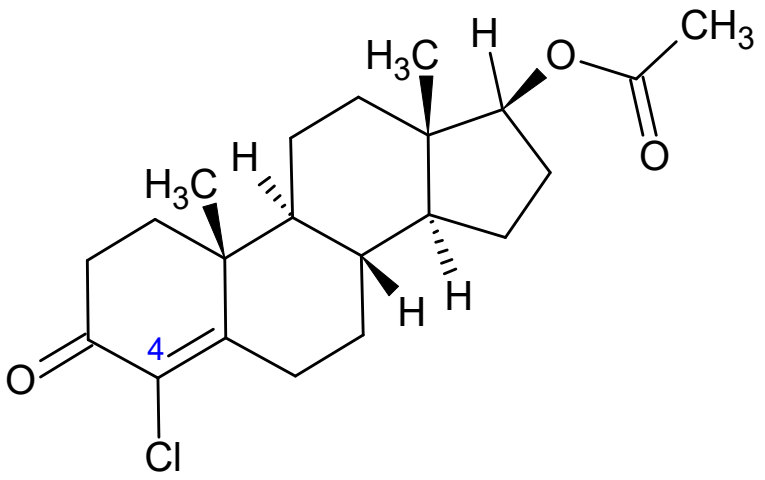


methenolone acetate



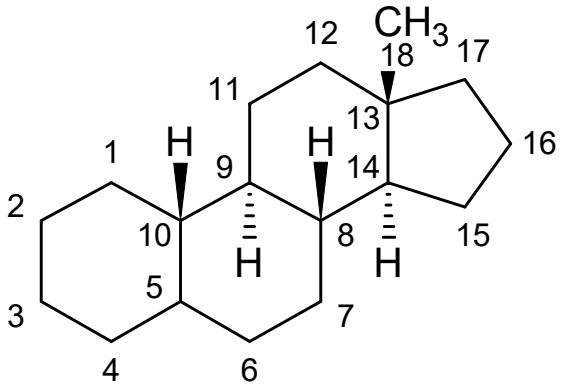
19-nortestosterone decanoate
nandrolone decanoate
Nandroloni decanoas PhEur

Anabolics

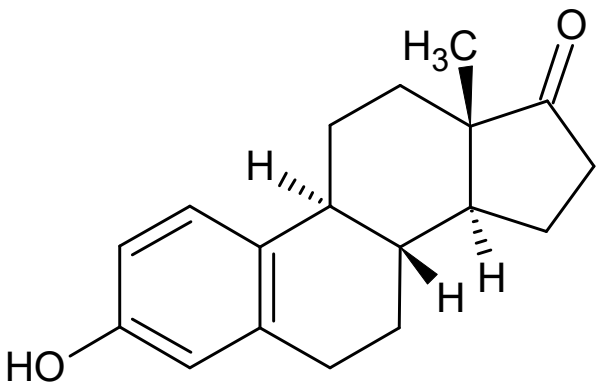


clostebol acetate
syn. turinabol

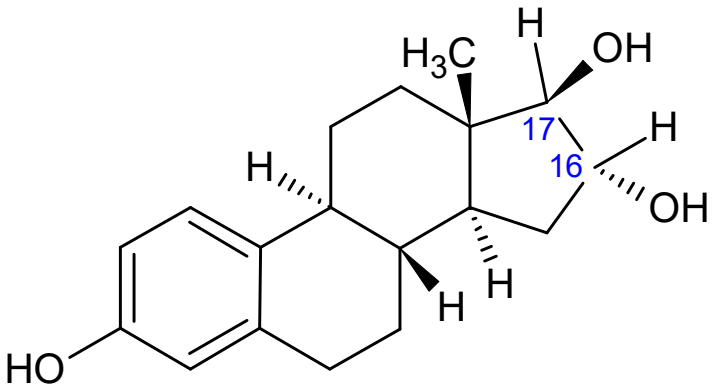
3.2.2. Oestrogens



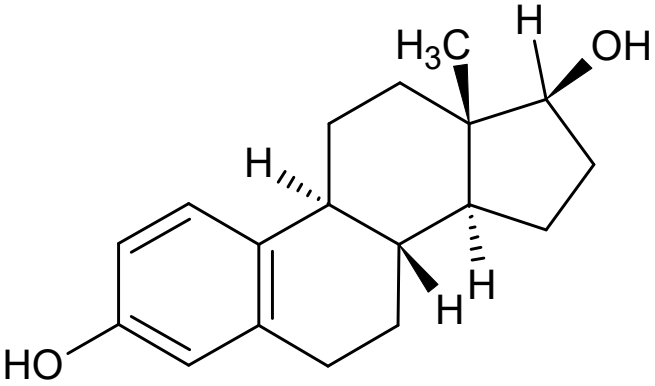
estrane



estrone
- 1st isolated oestrogen (Doisy and Butenandt 1929)
- structure elucidated 1932 (Butenandt)
- 30% activity



estriol
- metab. product
- 10% activity



estradiol
- „true“ hormon
- 100% activity

Oestrogens

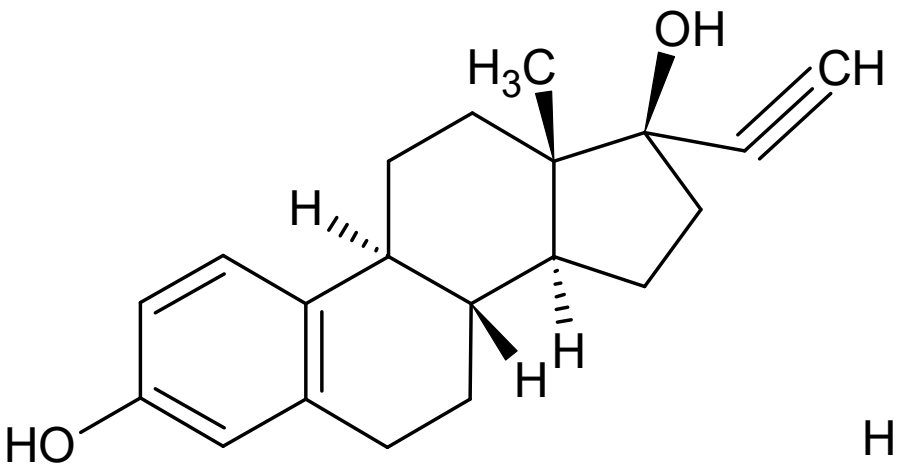
Effects and usage

- development and keeping of female sex signs
- also extra-genital lipid-anabolic effect $\Rightarrow$ development of subcutaneous fat tissue
- substitution therapy in hypogonadism
- prevention and treatment of osteoporosis in climacteric women
- lactation termination
- treatment of prostate cancer
- a component of hormonal contraception

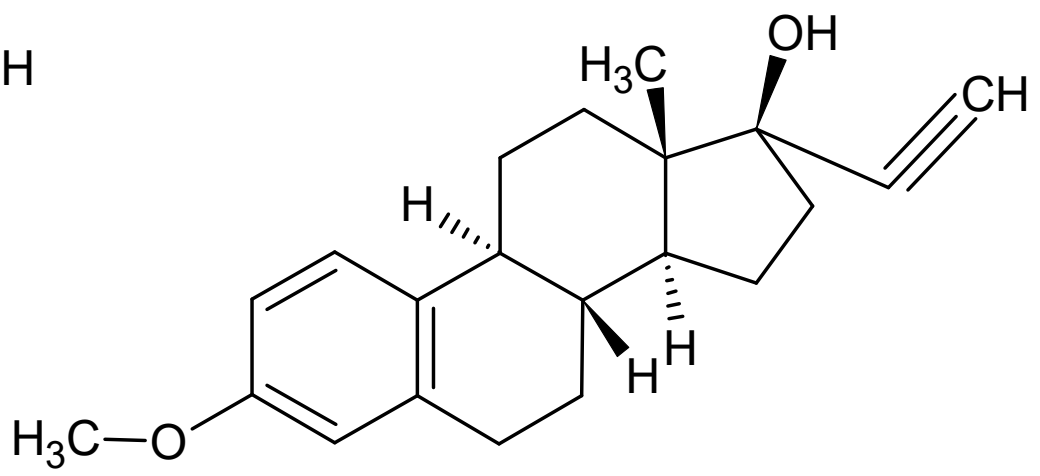
SAR

- among natural ostrogens, only little active estriol is applicable *p.o.* $\Rightarrow$ changes of the structure or estradiol in transdermal therapeutic systems (TTS)
- ethinyl to 17α position $\Rightarrow$ good *p.o.* activity; only slow degradation in liver
- $T_{1/2}$ of estradiol in parenteral application only 50 min $\Rightarrow$ ester prodrugs
- also stilbene derivatives; today only for treatment of prostate cancer; they damage the tissue with oestrogen receptors
- fytooestrogens: „non-hormonal“ compounds of plant origin, used for relief of climacteric problems; some of them are also stilbene derivatives (carcinogenicity)

Orally active oestrogens

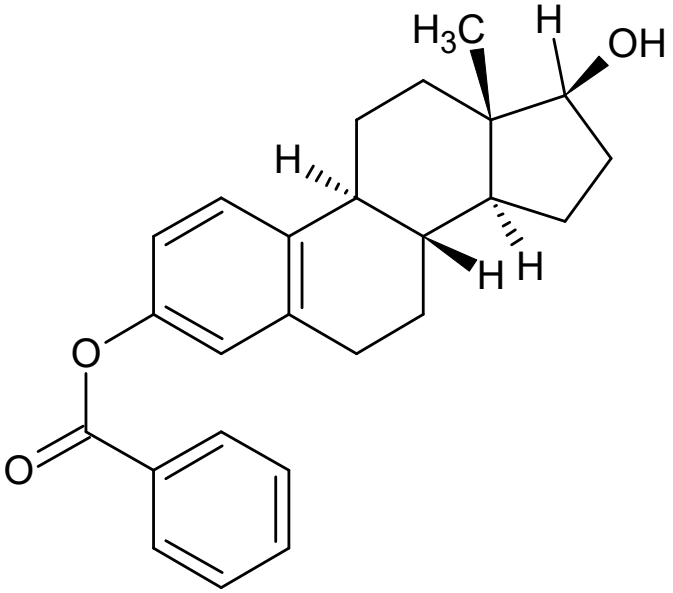


ethinylestradiol

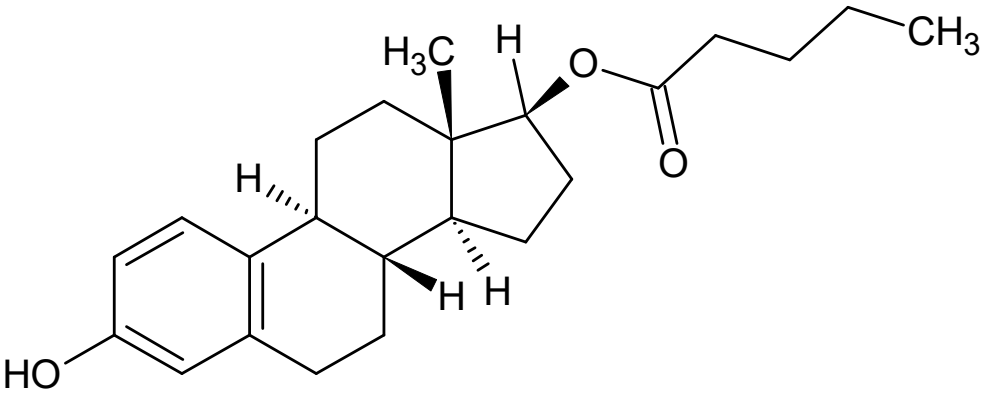


mestranol

Examples of ester prodrugs of oestrogens pro depot *i.m.* application



estradiol-3-benzoate

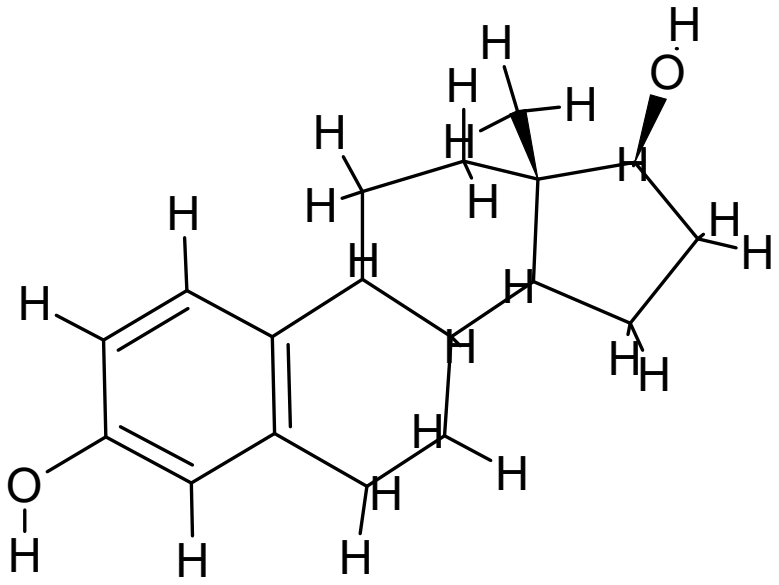


estradiol-17β-valerate

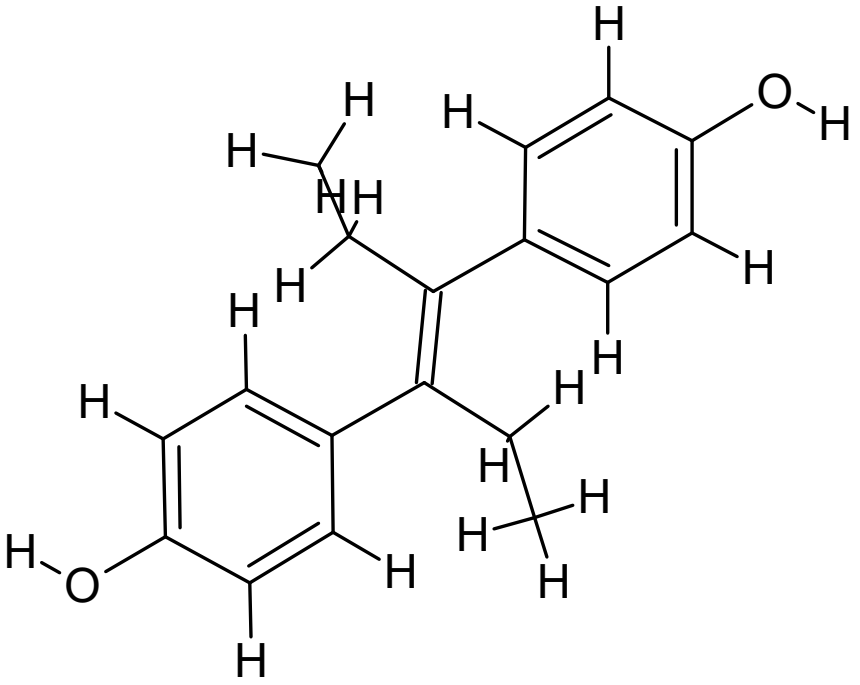
•oil solutions for *i.m.* injections

Steroid and non-steroid oestrogens

•the distance between -OH groups is essetial for interaction with oestrogen receptor

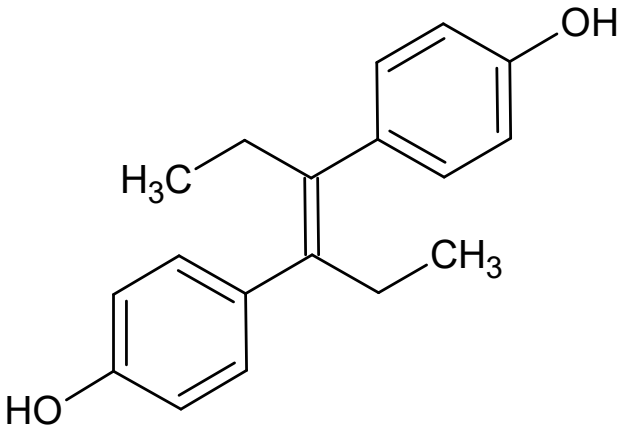


estradiol
distance between -OH(C3) a -OH(C17) 11.109 Å



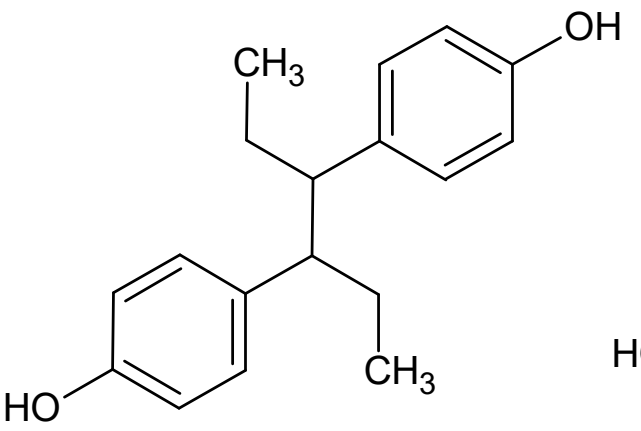
diethylstilbestrol
distence of phenolic -OH 12.342 Å

Non-steroid oestrogens



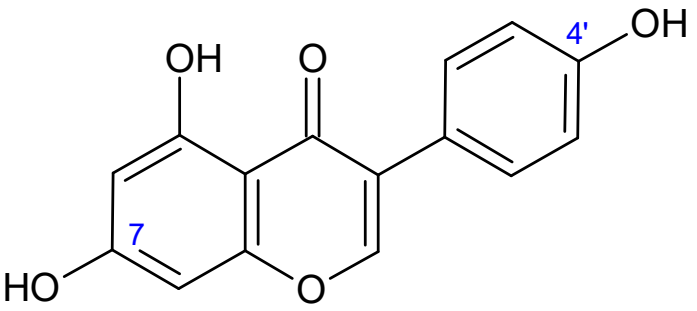
diethylstilbestrol

- a component of the 1st generation contraceptives
- today prostate cancer treatment only
- toxic, carcinogenic, damages the tissue containing oestrogen receptors, alters expression of many genes, ↑ incidence of uterus cancer even in low doses, genetic harm is transferred to the offspring
- „endocrine disruptor“
- model compound for study of negative oestrogenic effects of many compounds to the environment



hexestrol

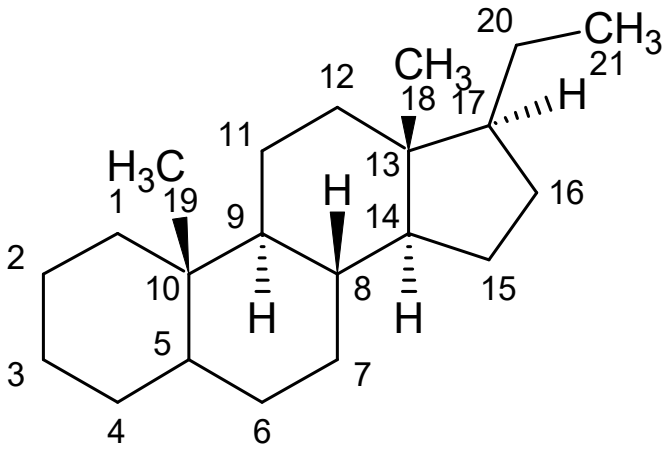
- lower activity



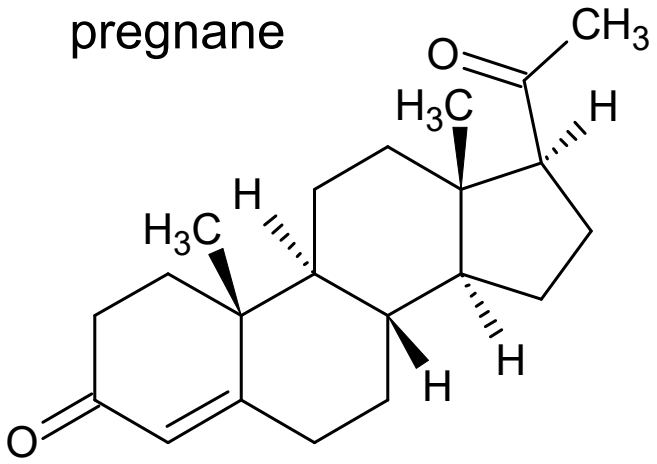
genistein

- isoflavonoid
- in plants (in the food) in form of glycosides, which are cleft by intestinal microflora, good absorption
- ±prevention of climacteric problems
- distance 7-OH and 4´-OH 13.161 Å

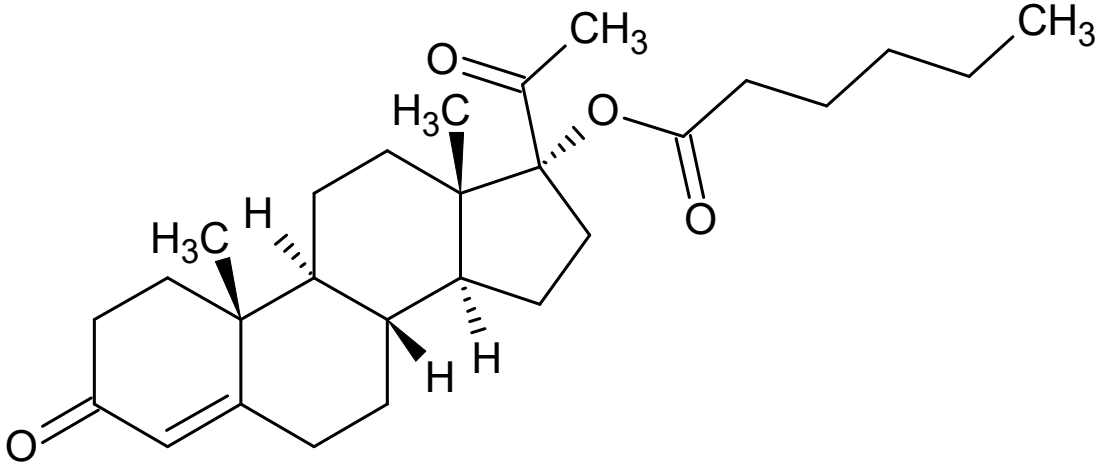
3.2.3. (Pro)gestagens



pregnane



4-pregnene-3,20-dion
progesterone
Progesteronum PhEur
•isolated 1934 from yellow bodies of pregnant sows (female pigs), structure elucidated by Slotta 1935
•intermediate of corticoids and androgens biosynthesis
•*p.o.* little active
•$T_{1/2}$ = 20 min $\Rightarrow$ *i.v.* shortly active



17α-hydroxyprogesterone hexanoate
•*i.m.* depot injections

Gestagens

Effects and usage

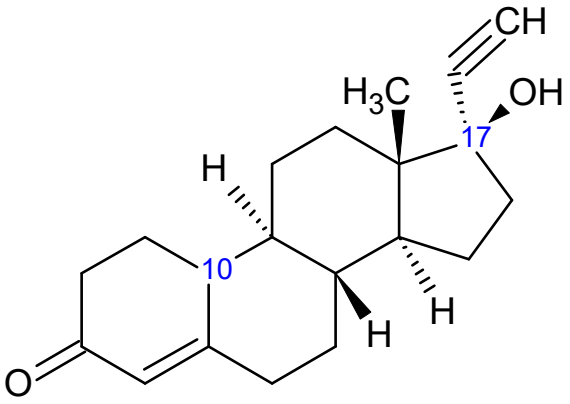
- progesterone is responsible for control of all the reproduction processes in woman
- keeping of the pregnancy (*gestare* = lat. carry)
- synthesised in yellow body in the 2nd half of the cycle, during pregnancy mostly in placenta
- therapeutically used together with oestrogens for normalisation of cycle anomalies
- shift of menstruation out of a “unsuitable” time
- with oestrogens in *p.o.* hormonal contraception

SAR

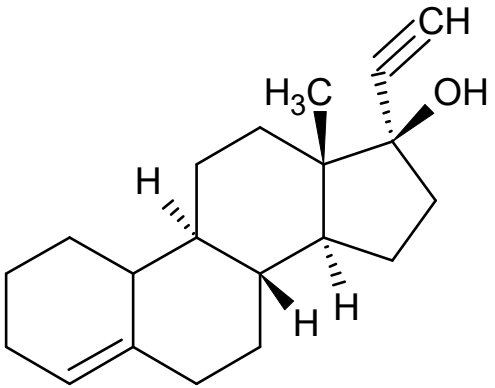
- usually C=O in position 3, methyl 19, CH_3CO- in pos. 17; although, none of these fragments is absolutely necessary for gestagene activity
- CH_3CO- in pos. 17 can be repaced with ethinyl without loss of activity
- 19-nortestosterone derivatives have high gestagene activity (norethisteron)
- compounds without ketonic group in pos. 3 are also active (lynestrenol)
- replacement of methyl at C13 (C18 methyl) with ethyl ↑ *p.o.* activity (norgestrel)
- introduction of double bond into the ring B to C6 also ↑ *p.o.* activity (megestrol, chlormadinon)
- methylation on C6 to α-position results also in *p.o.* aplicable compound ; $T_{1/2}$ ↑ by introduction of 17β-OH and its esterification (medroxyprogesterone acetate)

P.o. applicable gestagens

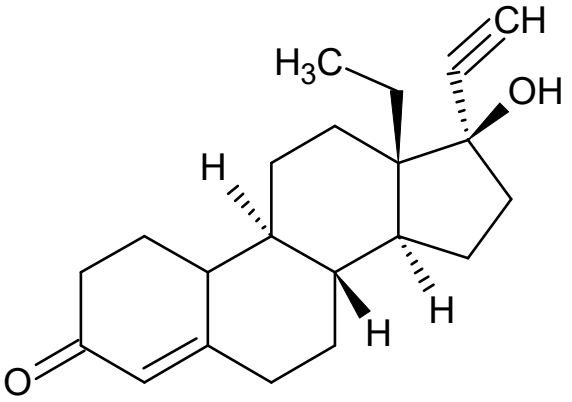
17α-ethinyl-17β-hydroxyderivatives



norethisterone
•acetate is official
Norethisteroni acetas PhEur



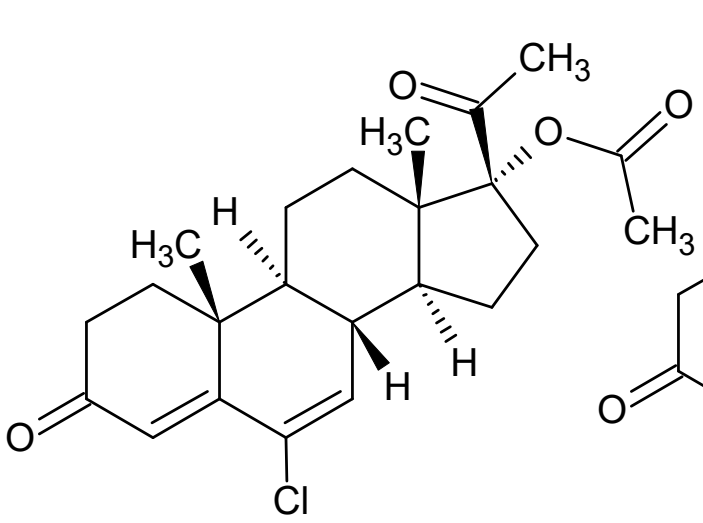
lynesterol



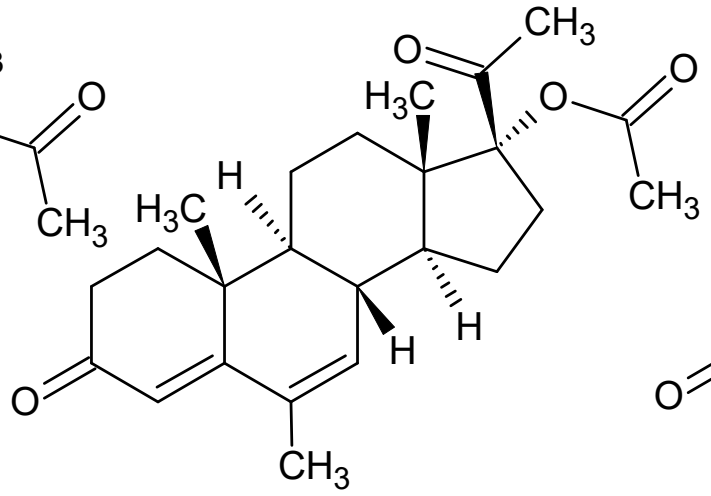
D-(-)-norgestrel
levonorgestrel
Levonorgestrelum PhEur

P.o. applicable gestagens

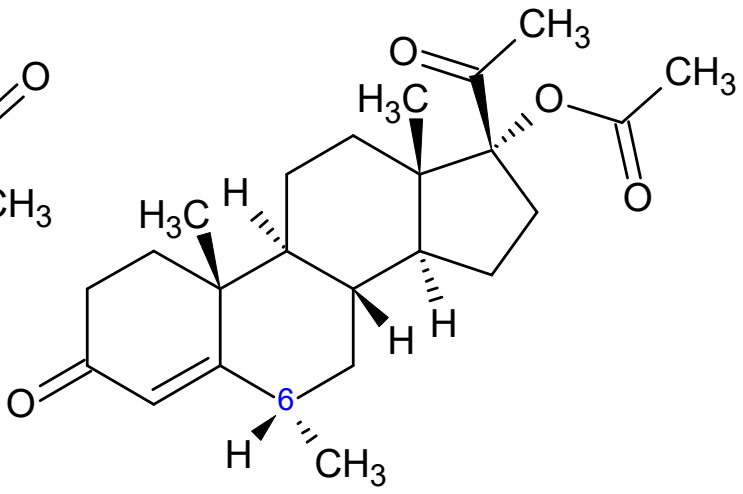
Compounds changed in ring B



chlormadinone acetate



megestrol acetate
Megestroli acetas PhEur

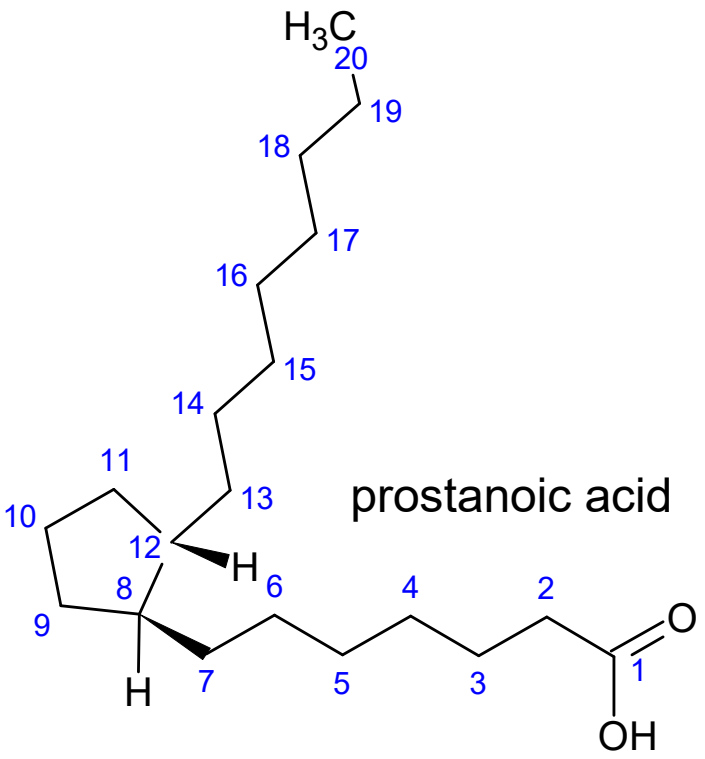


medroxyprogesterone acetate
Medroxyprogesteroni acetas PhEur
Provera®

Hormonal contraceptives

- gestagen is the main component
- antigonadotropic effect: prevention of ovulation; furthermore prevention of nidation
- ↑ viscosity of mucus of cervix avoids penetration of spermcells
- purely gestagen preparations do not prevent ovulation, only ↑ viscosity of cervical mucus, therefore less reliable

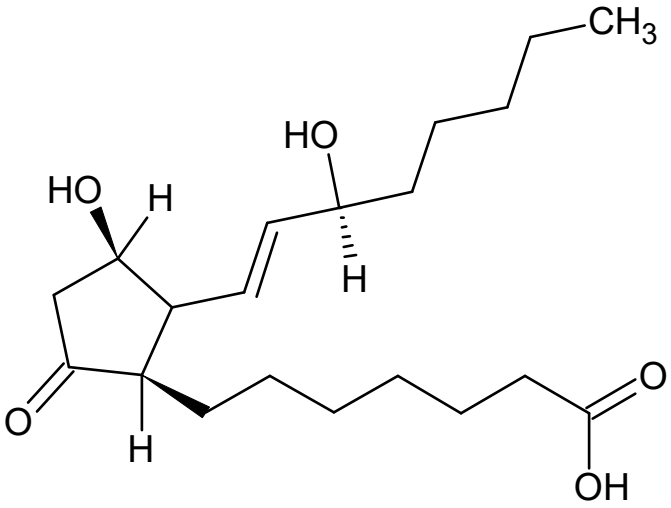
4. Prostaglandins



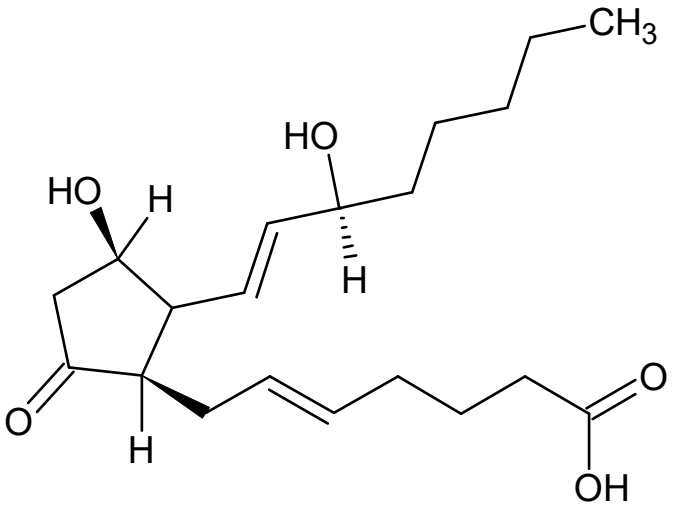
prostanoic acid

- prostanoic acid derivatives
- discovered by Euler 1934, isolated from sperma by Bergström 1957
- differ one from each other by substitution on cyclopentane rings and/or by positions and number of double bondns in side chains
- all natural ones have double bond on C13 and -OH on C15
- primary prostaglandins: D, E, F
- secondary ones are formed by their dehydratation and isomerisation

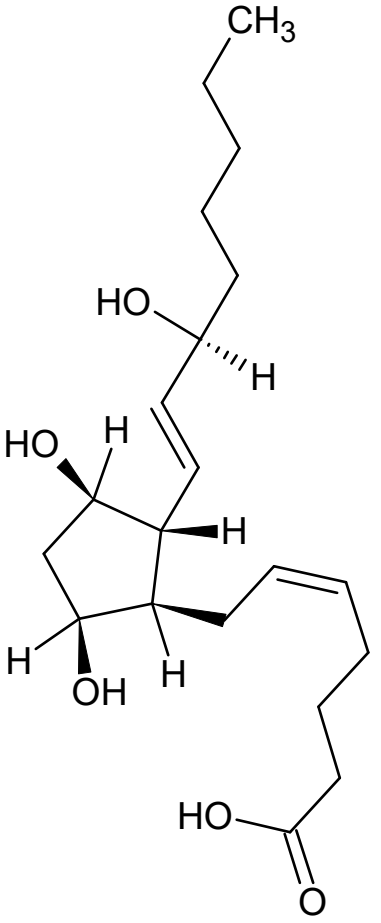
Primary prostaglandins



PGE_1

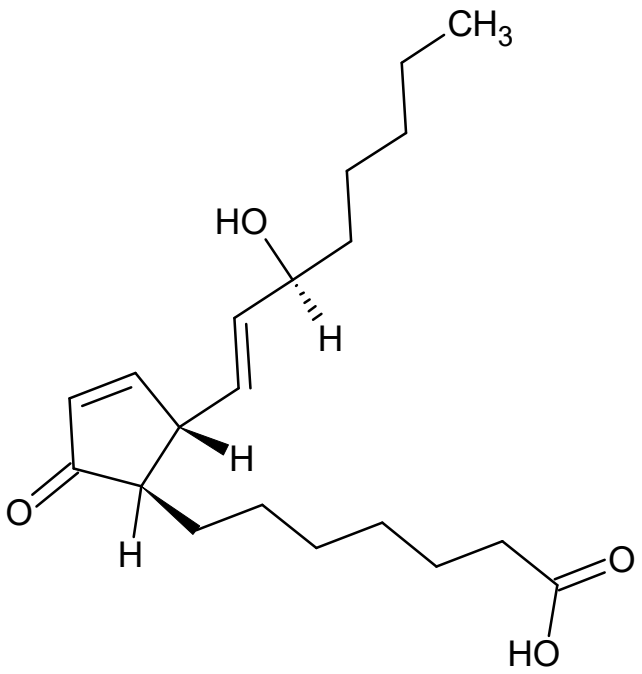


PGE_2
alprostandil

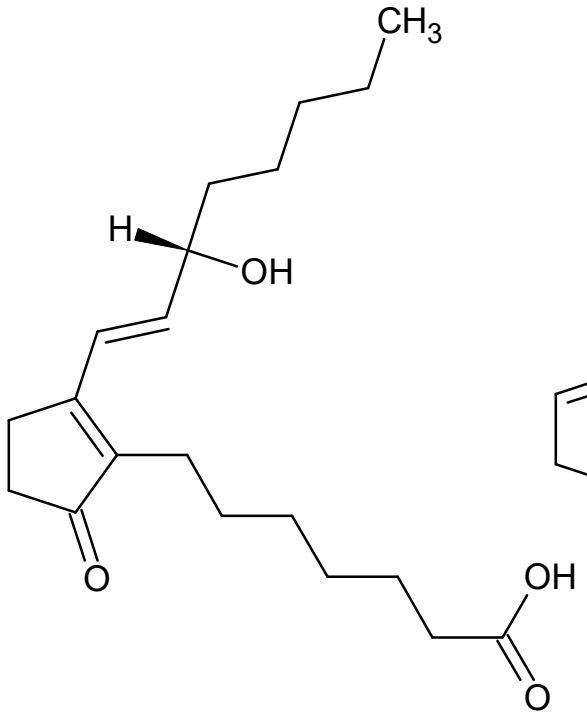


$PGF_{2\alpha}$
dinoprost
Enaprost F ® , Prepidil ® ,
Prostin E2 ®
•induction of birth

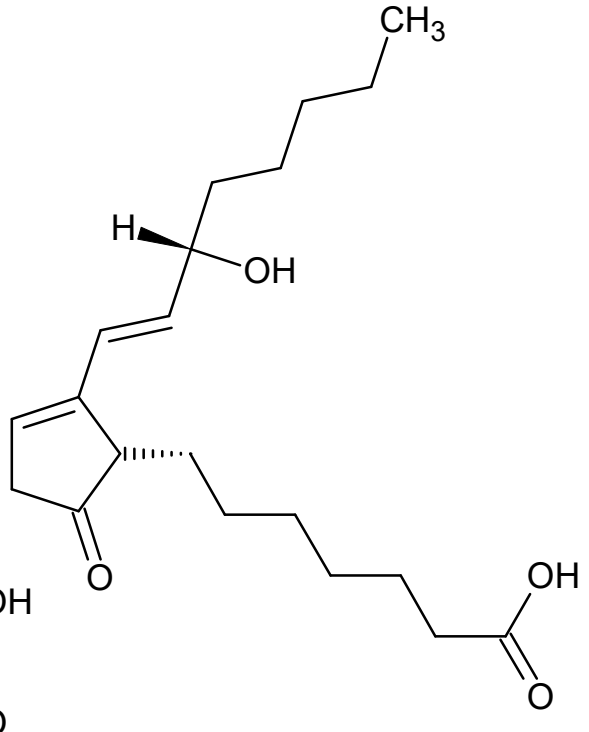
Secondary prostaglandins



PGA_1



PGB_1

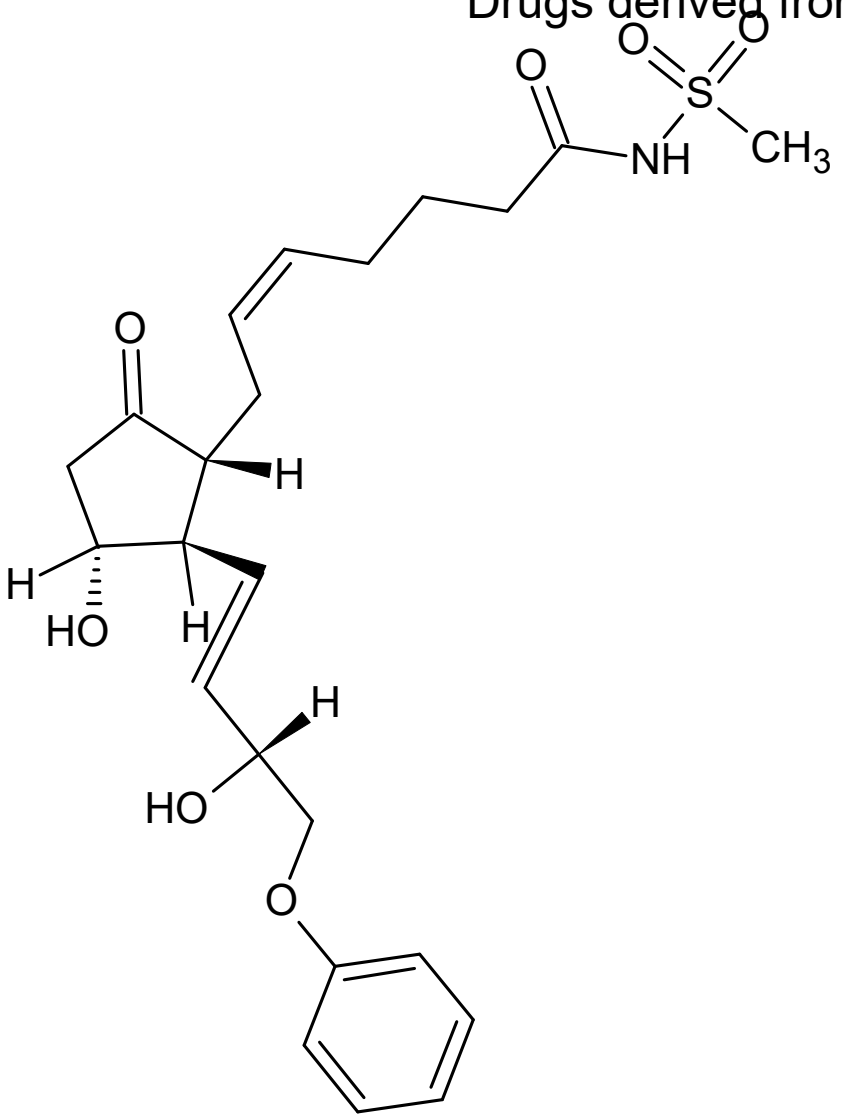


PGC

Effects of prostaglandins

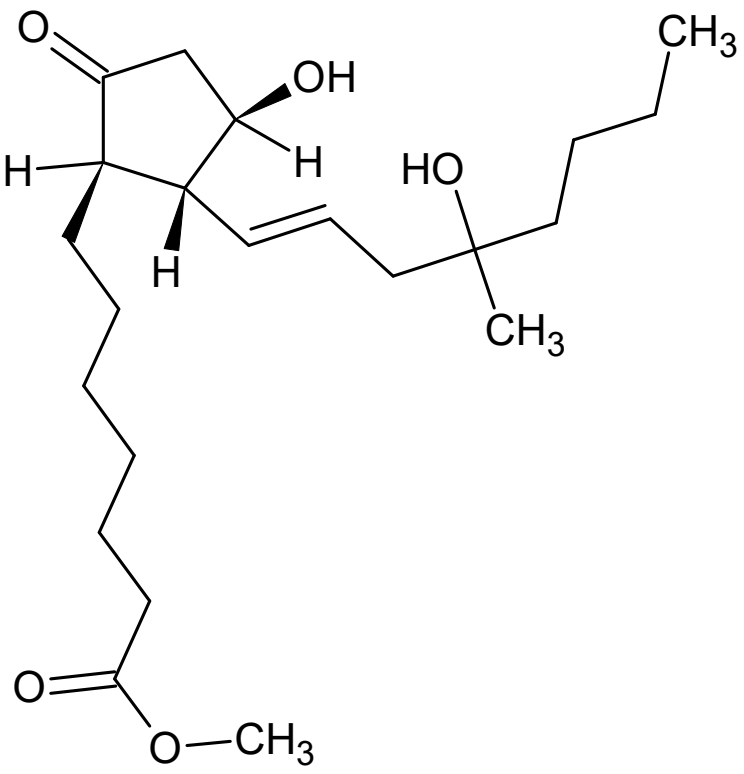
- activities are extensive, complex and not completely elucidated till now
- participate in inflammatory processes, senzitize nociceptors
- PGE affects smooth vascular musculature directly and lowers blood pressure; dilates bronchi
- PG2α cause bronchoconstriction
- both PGE2 and PGF2α causes contraction of uterus; birth initiation ($\Rightarrow$ sulproston)
- PGE acts on the mucous membrane of the stomach as cytoprotective agent ($\Rightarrow$ misoprostol)

Drugs derived from prostaglandins



sulproston

•initiation of birth



misoprostol

•PGE_1 methyl ester

•gastric protectant

•inhibits gastric HCl and pepsin secretion

•delivery (=chlidbirth) induction; abortive