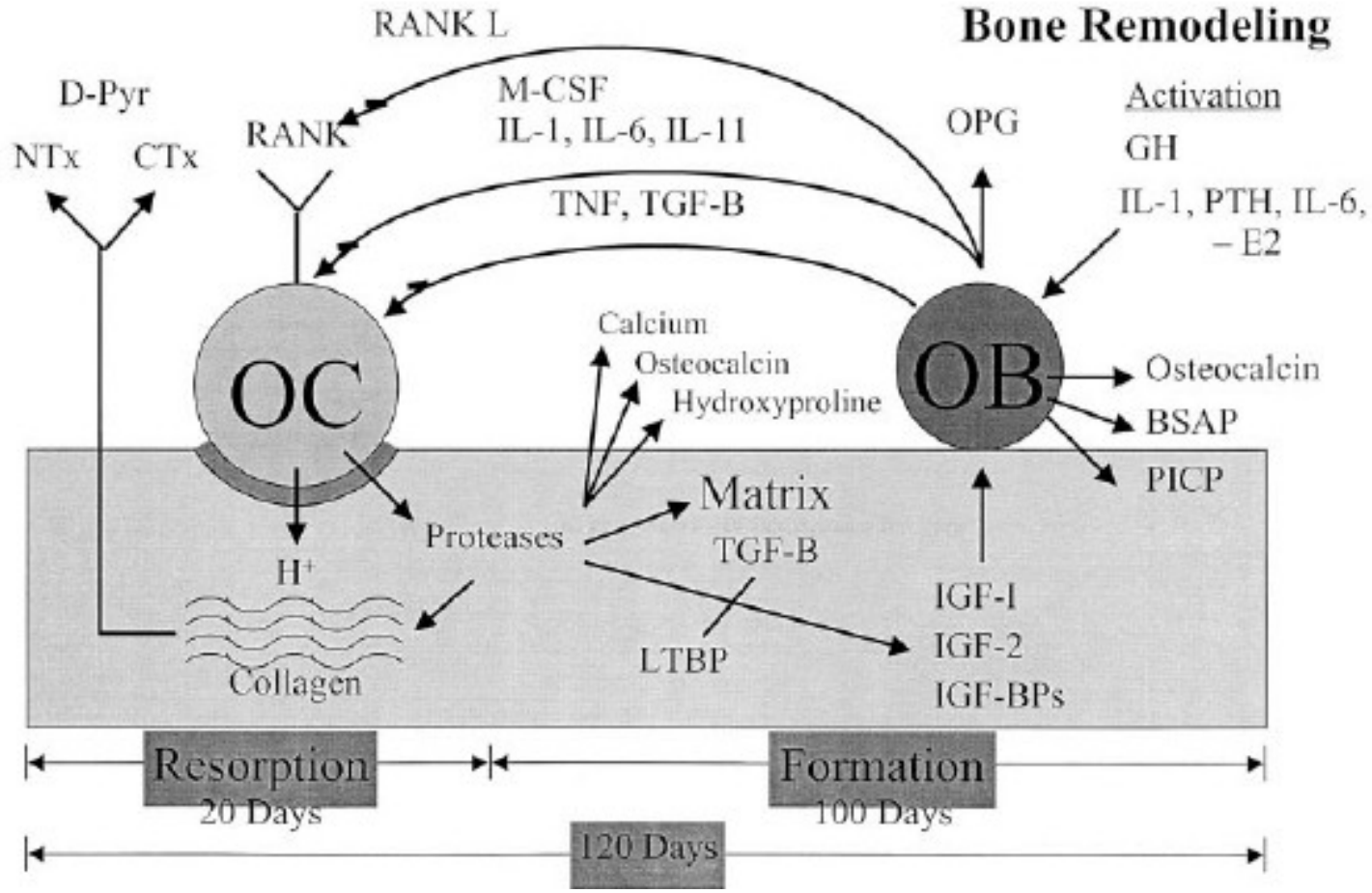
Prevention & treatment of osteoporosis

Osteoporosis =

systemic disease of skeleton characterized by low bone density and by increase of bone fragility and its predisposition to fractures

- the highest occurency in postmenopausal women
- frequent cause of fractures in elderly people



OC = osteoclast; OB = osteoblast; GH = growth hormon; IL = interleukins; E2 = oestrogens; PTH = parathormon; RANK L = receptor activator of nuclear factor kappa beta ligand (osteoprotegerin ligand); RANK = receptor for RANK L; M-CSF = macrophage colony stimulating factor etc.

„remodeling“ of 10 – 25 % bone matter per year (women in fertile age)

bone resorption > bone fromation ⇒ osteoporosis

Medicines for osteoporosis

Prevention

- Fluorides
- Calcium compounds
- Vitamine(s) D

Treatment

- Bisphosphonates
- Compounds acting on sex hormone receptors
- Parathormon, teriparatide
- Calcitonin
- Monoclonal antibodies: denosumab
- Strontium ranelate

Fluorides

NaF

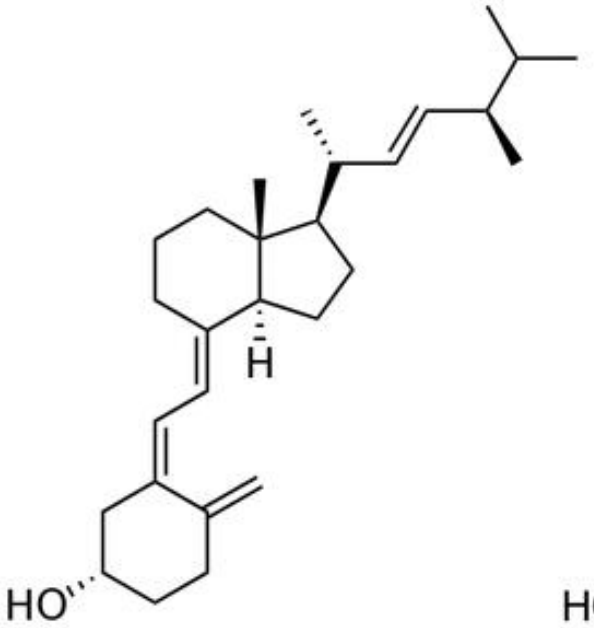
Na_2PO_3F sodium monofluophosphate – 50% ↓ of incidence of vertebral fractures

Fluocalcic® tbl. eff. (+ $CaCO_3$)

Calcium compounds

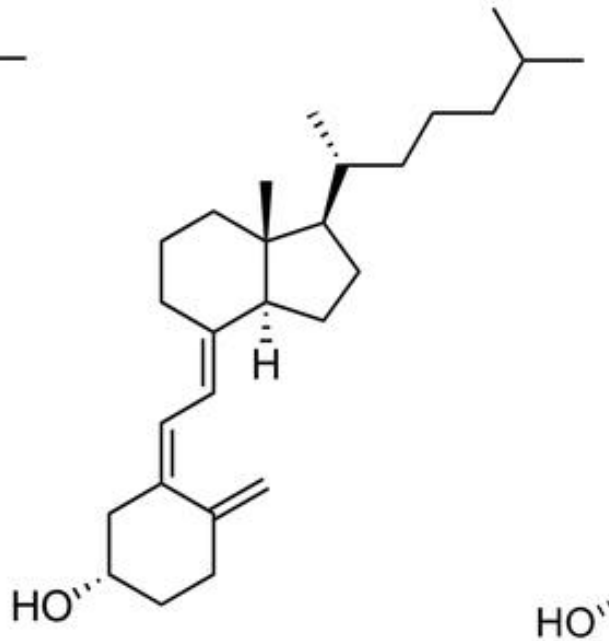
- $CaCO_3$
- cheeses, dairy products, milk
- bioavailability almost the same; from plant resources poor (phytates)

Vitamins D



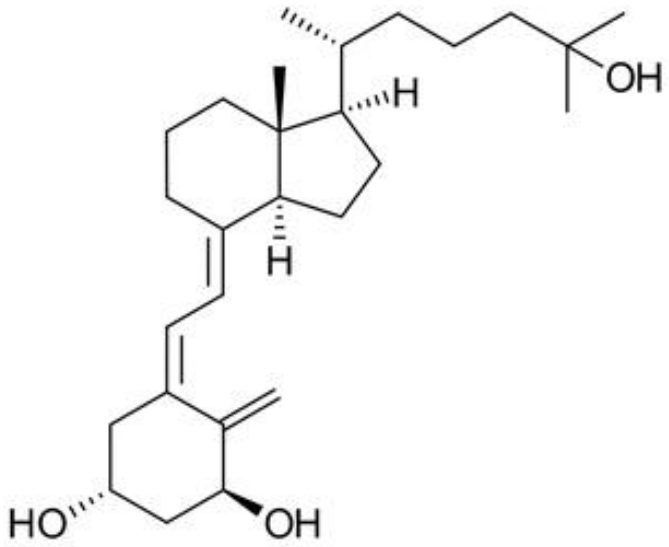
Vitamin D2 (Ergocalciferol)

Calciferol Biotika Forte ®



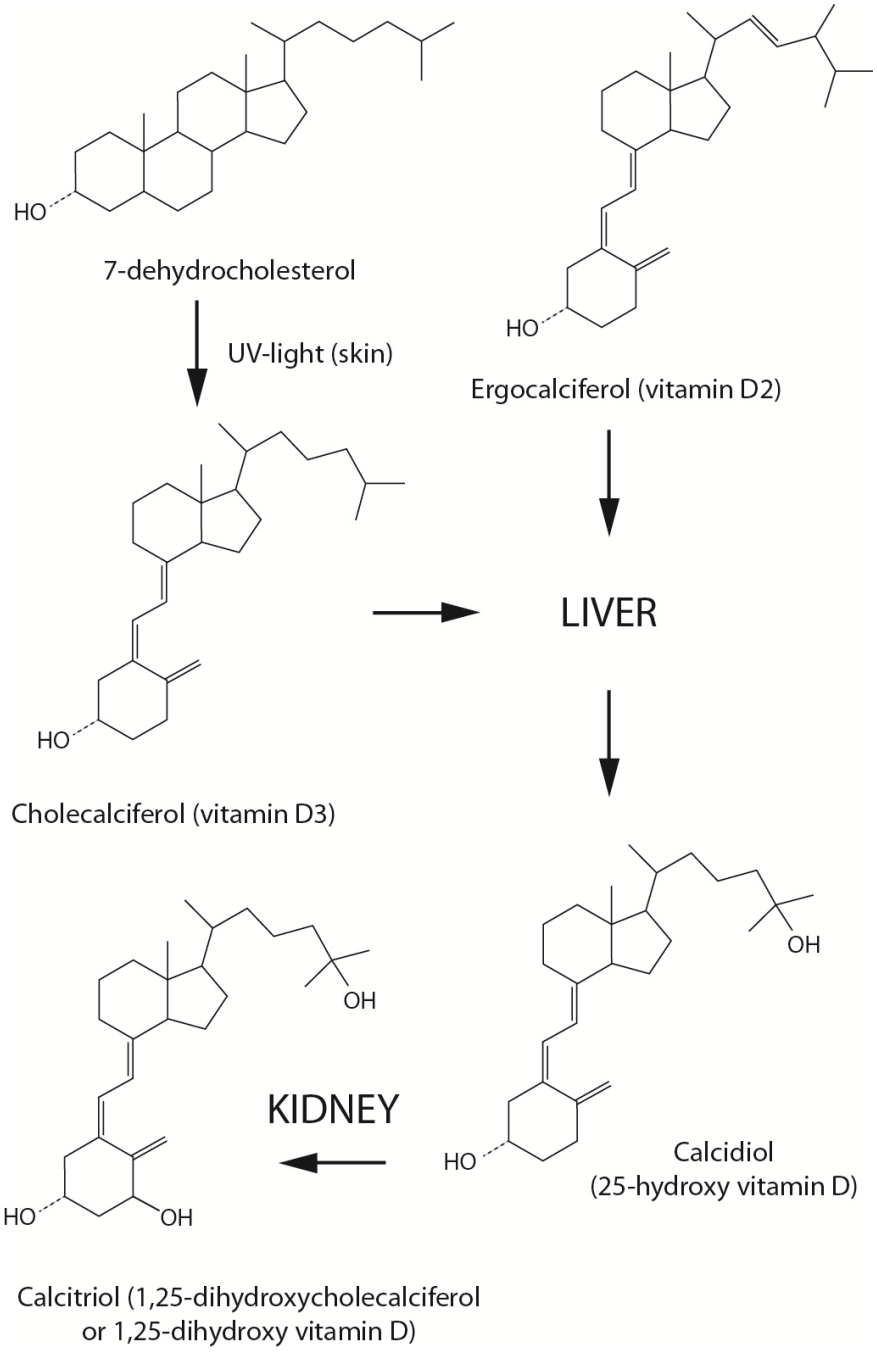
Vitamin D3 (Cholecalciferol)

Vigantol ® gtt.
Alendronic acid /
Vitamin D_3 Teva



1,25-dihydroxycholecalciferol (Calcitriol)

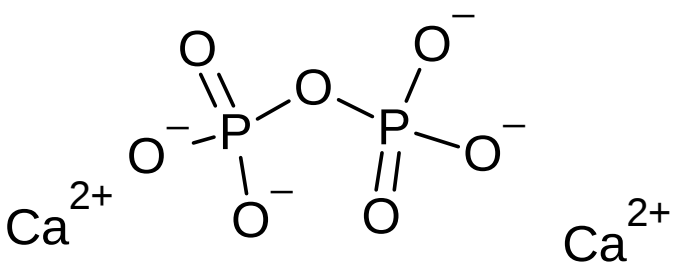
active form


HO
7-dehydrocholesterol
UV-light (skin)
HO
Ergocalciferol (vitamin D2)
HO
Cholecalciferol (vitamin D3)
LIVER
OH
HO
Calcidiol
(25-hydroxy vitamin D)
KIDNEY
OH
HO
Calcitriol (1,25-dihydroxycholecalciferol
or 1,25-dihydroxy vitamin D)

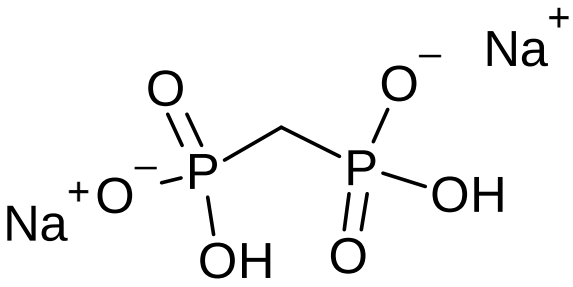
Bisphosphonates

= mainly sodium salts of monotopic bisphosphonic acids

- analogues of calcium pyrophosphate which forms the most of inorganic matter of bone
- act directly in „remodelation“; incorporated into osteoclasts
- also complexes or salts with ^{99}Tc, ^{186}Re for nuclear diagnostic



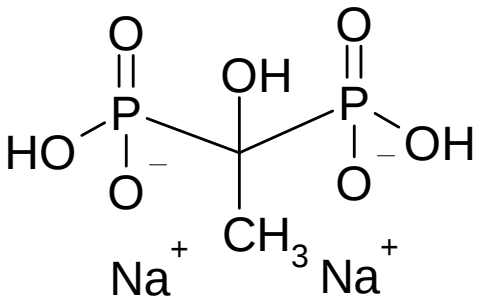
calcium pyrophosphate



medronate

1st generation“

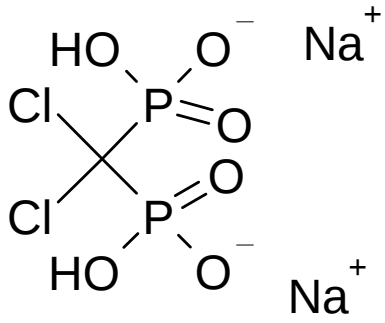
•interfere with ATP



disodium dihydrogen-1-hydroxyethyl-1,1-bis(phosphonate)

etidronate

Re-bone® inj. (+ ^{186}Re)

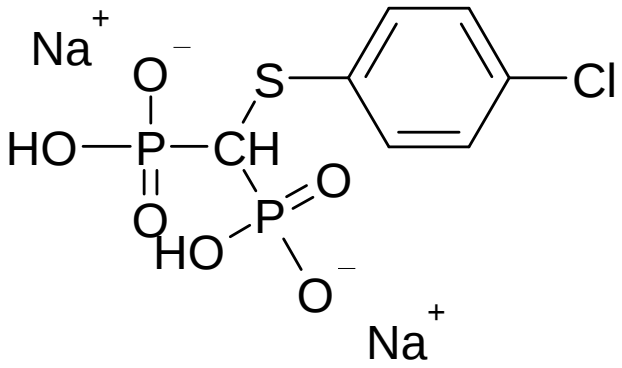


disodium dihydrogen-1,1-dichlormethan-1,1-bis(phosphonate)

clodronate

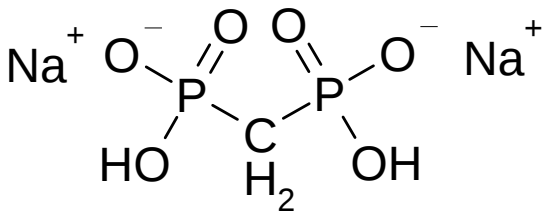
Bonefos®, Lodronat®

Bisphophonates of 1st generation continued



disodium dihydrogen-1-(4-chlorfenylsulfanyl)methan-1,1-bis(phosphonate)

tiludronate



disodium dihydrogenmethan-1,1-bis(phosphonate)

medronate

Amerscam® (+ ^{99}Tc)

Bisphosphonates

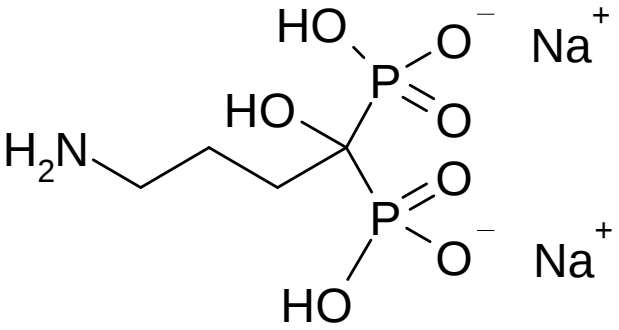
2nd generation = aminobisphosphonates

- inhibit the last step of cholesterol synthesis ⇒ ↓ activity of osteoclasts

  ↓ formation of osteoclasts

  ↑ apoptosis of asteoclasts

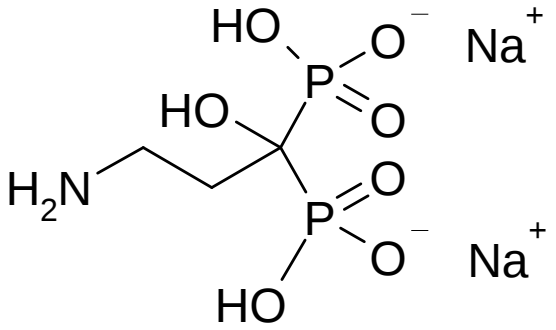
Compounds with primary amino grop



disodiumdihydrogen-4-amino-1-hydroxybutan-1,1-bis(phosphonate)

alendronate

Fosamax®, Lindron®



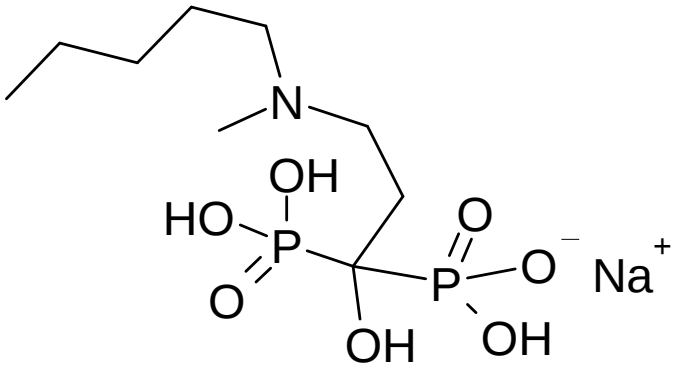
disodium dihydrogen-4-amino-1-hydroxypropan-1,1-bis(phosphonate)

pamidronate

Aredia®, Pamifos®

Bisphosphonates

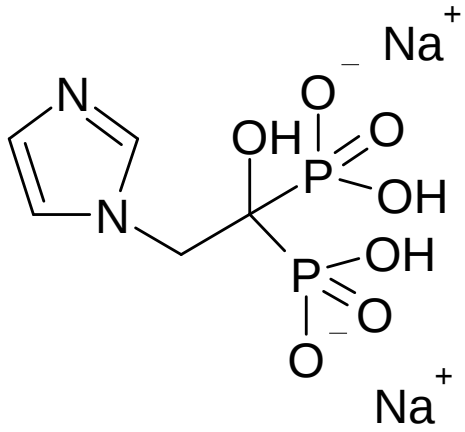
2nd generation - aminobisphosphonates with aliphtic or heterocyclic tertiary amino group



sodium trihydrogen-1-hydroxy-3-[methyl(pentyl)amino]-propan-1,1-bis(phosphonate)

ibandronate

Bondromat®



disodium dihydrogen-1-hydroxy-2-[(1H)imidazol-1-yl]ethan-1,1-bis(phosphonate)

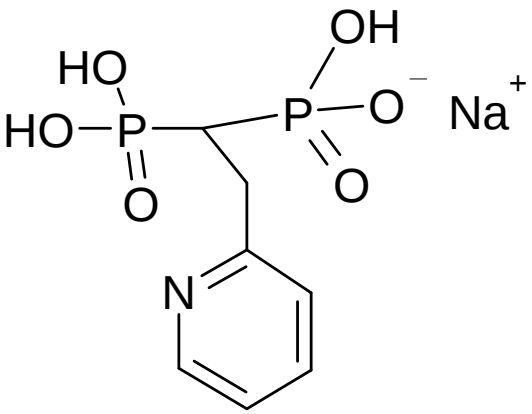
zolendronate

Zometa®

Bisphosphonates

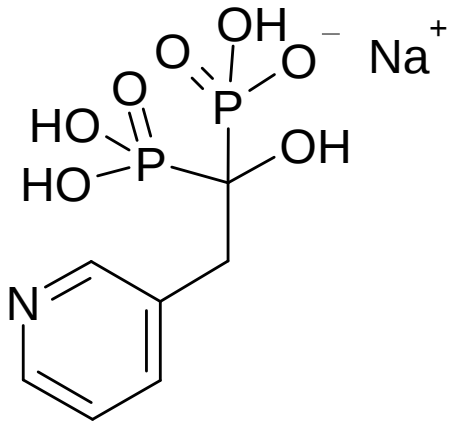
2nd generation - aminobisphosphonates
with heterocyclic tertiary amino group

•pyridine derivatives



sodium trihydrogen-2-(pyridin-2-yl)ethan-1,1-bis(phosphonate)

piridronate

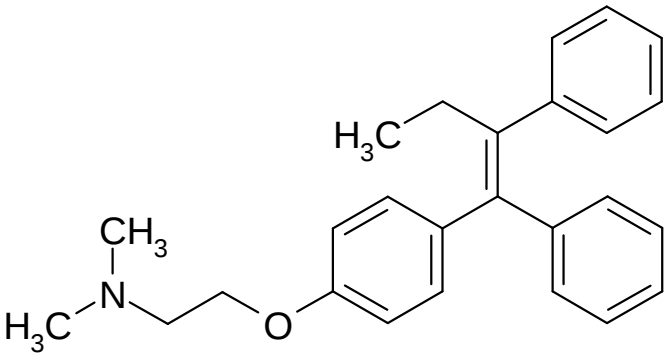


sodium trihydrogen-1-hydroxy-2-(pyridin-3-yl)ethan-1,1-bis(phosphonate)

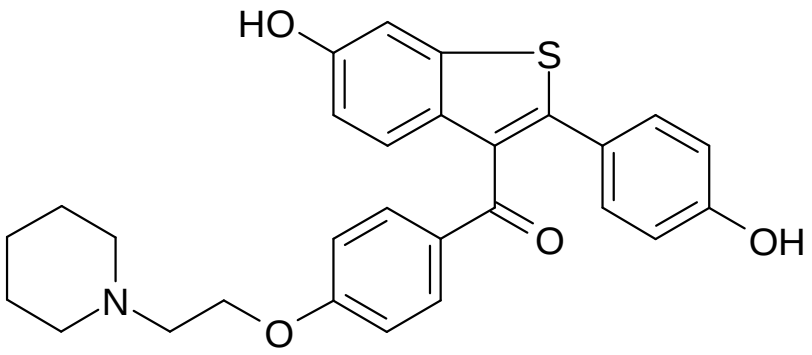
risendronate

~~Actonel®~~

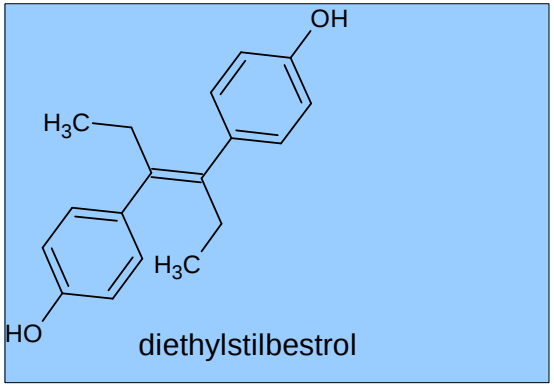
Compounds interacting with estrogenic receptors: selective estrogen receptors modulators (SERM)



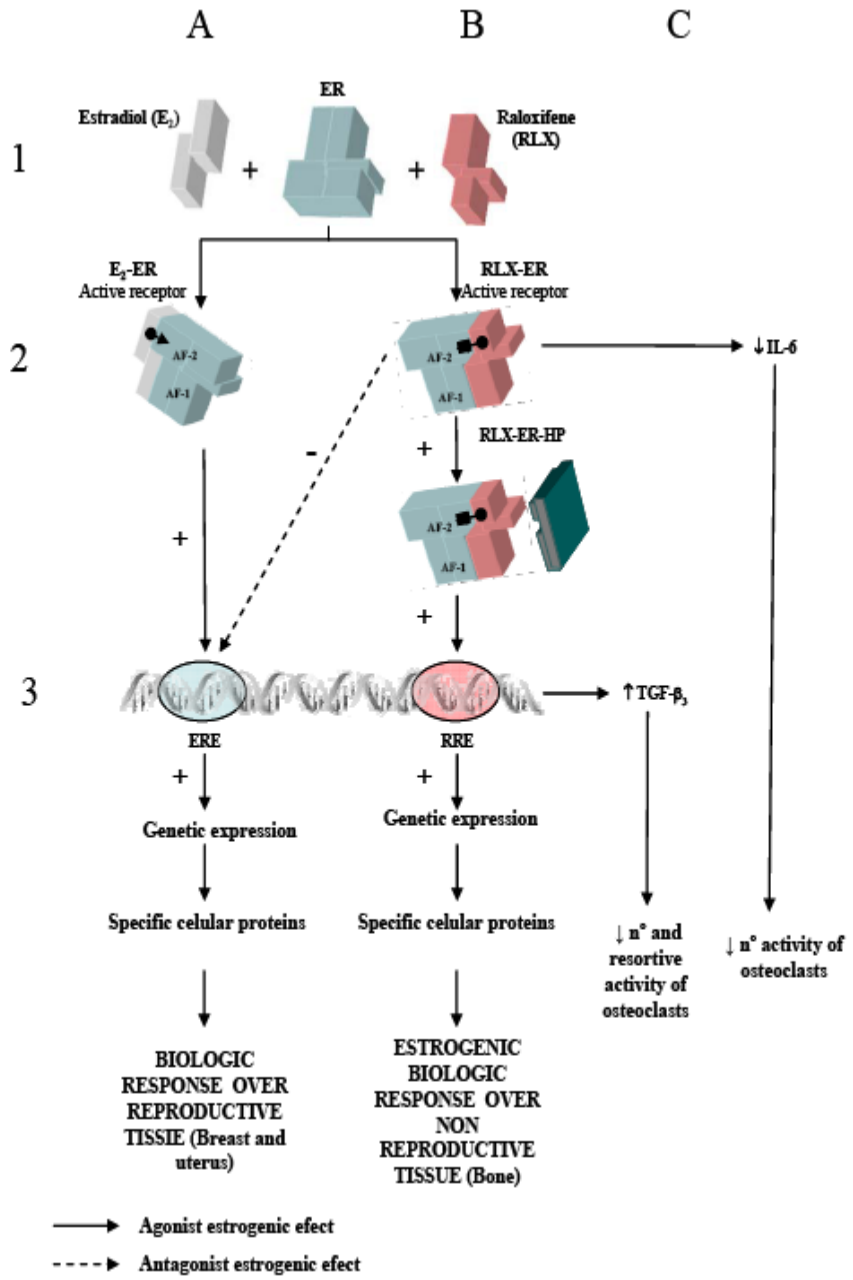
tamoxifene
•**rather anti-cancer *I* estrogen antagonist**
Tamoxifeni citras PhB



raloxifene
•SERM



SERM



Mechanism of action of raloxifene

- 2 types of receptor proteins: ERα, ERβ
- ERα is activated by binding of estradiol but inhibited by activated ERβ

- genes transcription under estrogenic control then proceeds in non-reproductive tissue only

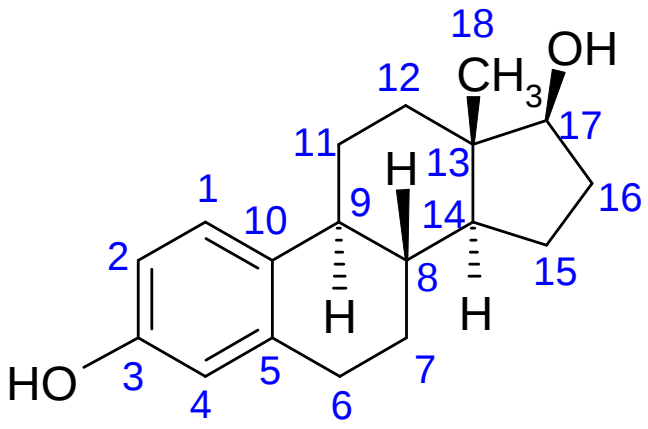
Sex hormones and their synthetic analogues

Estrogens

•2nd line prevention and treatment of o. in women in and after menopause

↑ risk of cancer of uterus ⇒ usually with gestagens (subfysiol. dose)

•often TTS

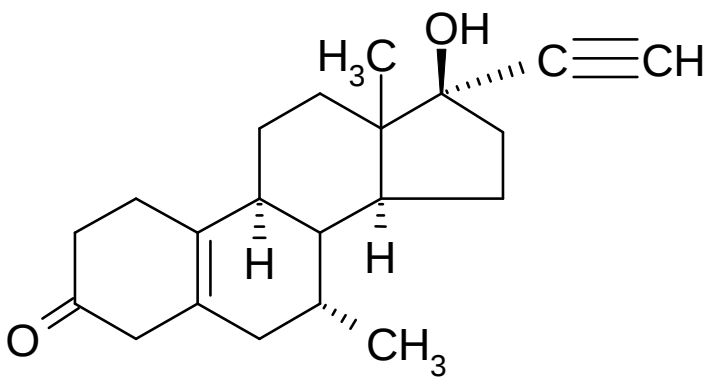


estra-1,3,5(10)-trien-3,17β-diol

estradiol

Avaden®, Climara® emp., Dermestril ®TTS emp., Oestrogel®

Estrogen analogues



17β-hydroxy-6α-methyl-19-norpregn-5(10)en-20-in-3-on

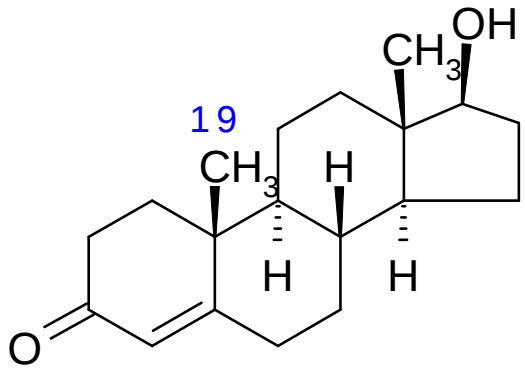
tibolon

Ladybon®, Livial®

- evidence for increse of bone matter during one year of treatment
- no action in endometrium

Androgens

- in men with o. caused by hypogonadism only



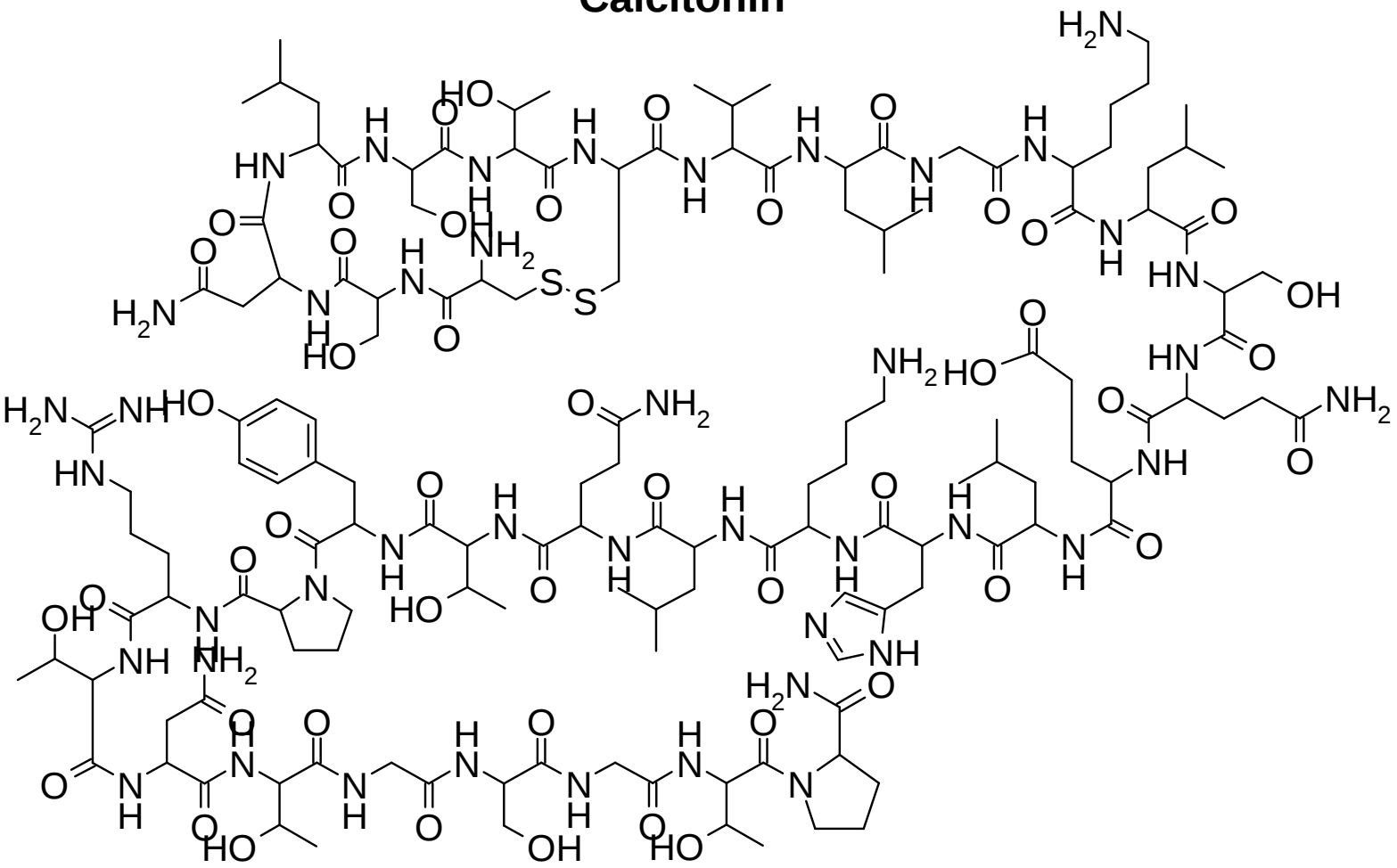
17β-hydroxyandrost-4-en-3-on

testosterone

Sustanon® inj. sol. (mixture of propionate, isocapronate, phenylpropionate and decanoate of testosteronu)

Understore ® cps. (undecanoate)

Calcitonin

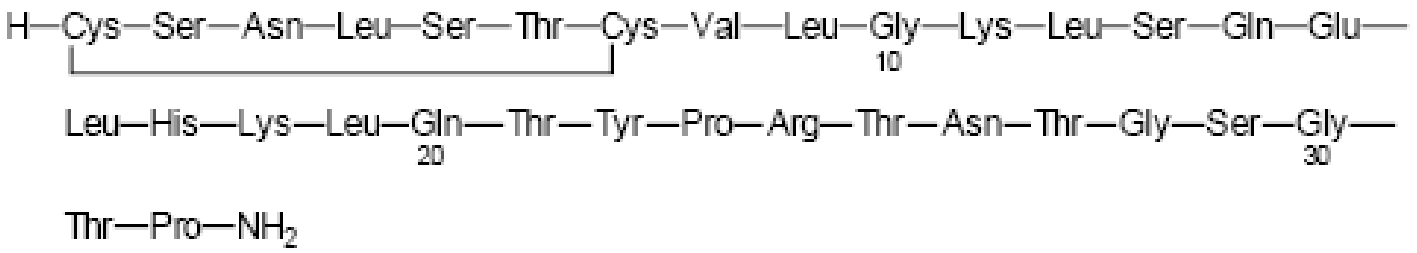


***Calcitoninum salmonis EP* = salmon´s calcitonin** (syntetic; AA sequence identical with salmon´s hormone; 32 AA)

~~Miacalcic® inj., nasal; Osteodon®; Tonocalcin®~~ withdrawn due to increase of incidence of nasal septum cancer after administration

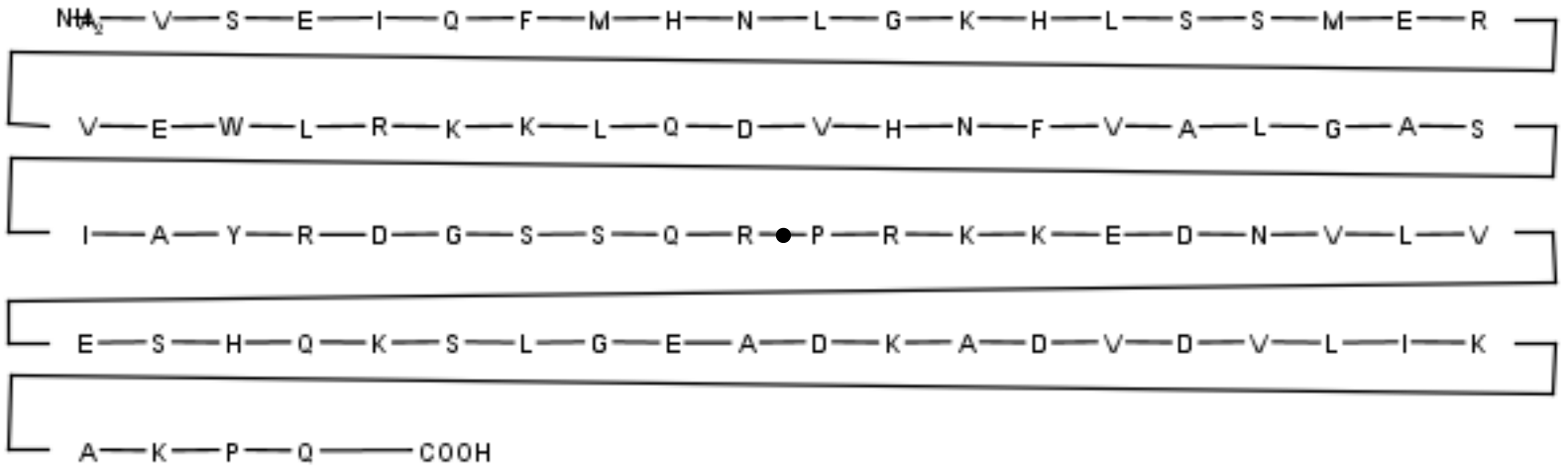
Calcitonin

- peptide of 32 AA (salmon´s – *Onchorhyncus kisutch;* human 139 AA)
- secreted from C-cells of thyroid gland (= parafolicular cells – Baber 1876), in lower vertebrates by ultimobranchial bodies originated from 5th gills slot
- receptors on osteoclasts (but also kidneys, brain)
  - ↓ excretion of Ca^{2+} from bone (⇒ ↓ calcemia)
  - ↓ osteoclasts formation
- applied together with Ca^{2+}



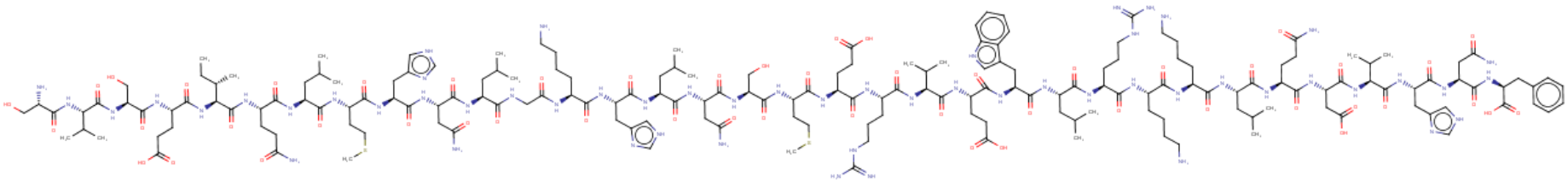
$C_{145}H_{240}N_{44}O_{48}S_2$ M_r 3431,88 CAS 47931-85-1

Parathyroid hormone



- produced in parathyroidal bodies
- protein of 84 AA
- evidence for anabolic effect in bone but continous aplication causes bone destruction
- therapeutic usage limited, new drug forms???

Teriparatide

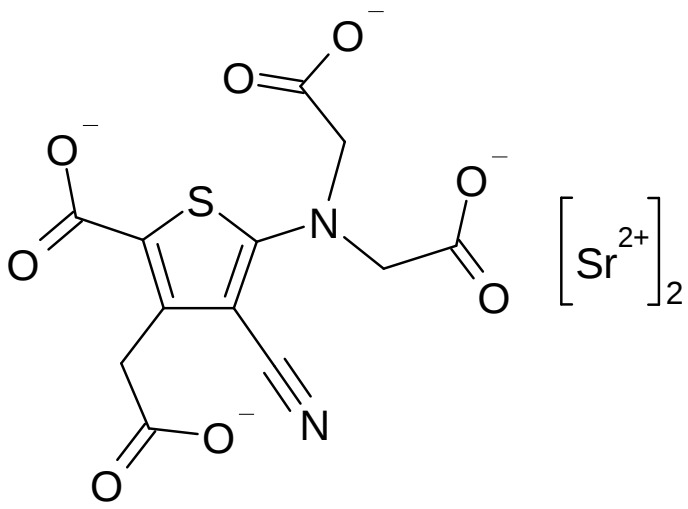


- N-terminal sequence 1 – 34 of parathyroid hormone
- produced by a recombination technology
- intermitent aplication preferably stimulates new bone formation by osteoblasts
- used in postmenopausal women when a previous treatment lasting at least 2 years failed

denosumab

- completely human monoclonal antibody
- IgG_2
- against RANKL = receptor activator of nuclear factor kappa beta ligand (or osteoprotegerin ligand)
- binds to RANKL specifically and blocks its binding to RANK ⇒ inhibition of osteoclast formation ⇒ decrease of bone resorption
- 10years treatment keeps low incidency of both vertebral and non-vertebral fractures
- Prolia ®, Xgeva ®

Strontium ranelate



- Sr^{2+} is the active part, ranelic acid is not absorbed
- incorporation of traces of Sr^{2+} into bone phosphates ⇒↑ density and strength
- used in postmenopausal women in whom other drugs are contraindicated or intolerated
- evidence for decrease of fractures