12. Előadás
Alkaloidok

Alkaloidok

Felfedezés:

1805: Sertürner morfin „növényi alkáliák"
1818: Meissner alkaloidok (= alkáli szerű)
1. növényi eredet
2. N-tartalmú, bázikus
3. fiziológiás hatás
1926: Kabay János „alkaloida"

Felosztás:

A. Eredet állati* vs növényi (pl. mák, anyarozs)

B. Szerkezet - alifás*

- heterociklusos (váz szerint)
  - pirrolidin*
  - imidazol
  - piridin, piperidin* (nikotin)
  - tropán (kokain)
  - kondenzált piridin (ópium)
  - szterán

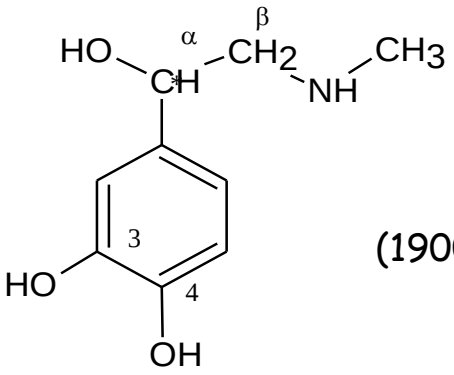
Elnevezés: -in végződés, de: sztrichnin (Strychnos)
morfin (Morpheus, álomisten)
nikotin (Nicot, francia követ)

Előfordulás: szerves savak sói

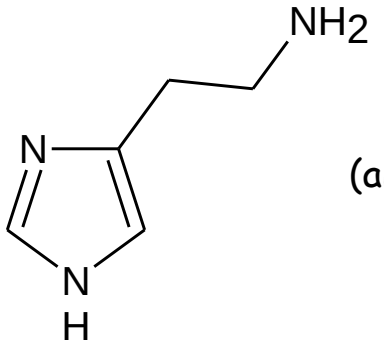
Felhasználás: gyógyászat, kábítószer

Kivételek

Állati eredetű alkaloidok (szalamandra méreg, varangy méreg)



(1900, Fürth)



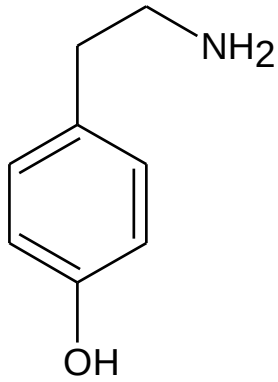
(anyarozs!)

l-α-(3,4-dihidroxi-fenil)-
-β-metil-amino-etanol
adrenalin
op.: 211-212°C

4-imidazol-etil-amin (hisztamin)
op.:83-84°C

-biogén amin
-értágító → vérnyomáscsökkenés
-allergia

mellékvese velő → hormon
-vérnyomás emelés
-glikogén mobilizálás
-vérzéscsillapítás



p-hidroxi-fenil-etil-amin (tiramin)

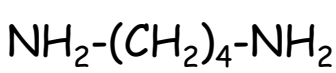
Eredet:
tirozin
hisztidin
triptofán

baktérium (sajtok)
ősszájú gerinctelenek (protostomia)
-ingerületvezetés

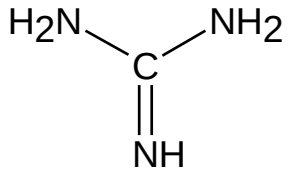
Alifás alkaloidok

(nem gyűrűbe zárt N atom)

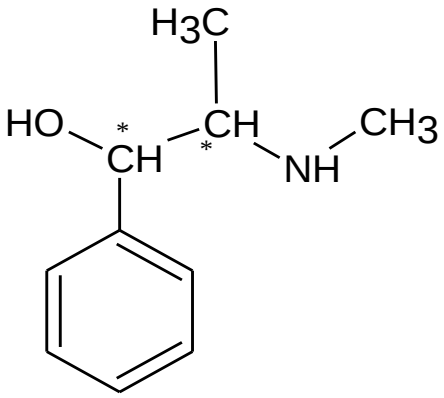
Felosztás:
- -egy N atom alkil-amin
- -több N atom alifás (pl. putreszcin, guanidin)
- -aromás alkil-amin (pl. efedrin, kapszaicin)
- -aliciklusos alkil-amin
- -alkanol-amin
- -aril-alkanol-amin váz
- -heterociklusos aminoalkohol



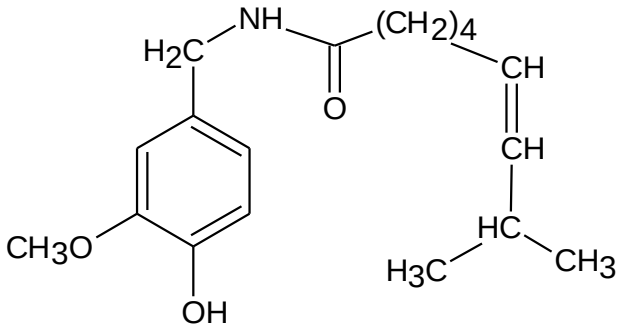
putreszcin
anyarozs (Secale cornutum)
nadragulya (Atropa belladonna)



guanidin
op.: - 50°C
répa (Beta vulgaris), szójabab
-alapanyag



1-fenil-2-metil-amino-
1-propanol (efedrin)
op.: 187-188°C
Ephedra (csikófark)
-érszűkítő, vérnyomásemelő



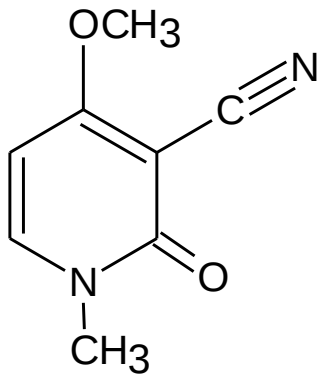
kapszaicin
op.: 64-65°C
paprika (Capsicum annuum)
-csípős

Heterociklusos alkaloidok

I. Piridin-, piperidinvázas alkaloidok

Ricinus communis mag (kutyatej féle)

(1921)

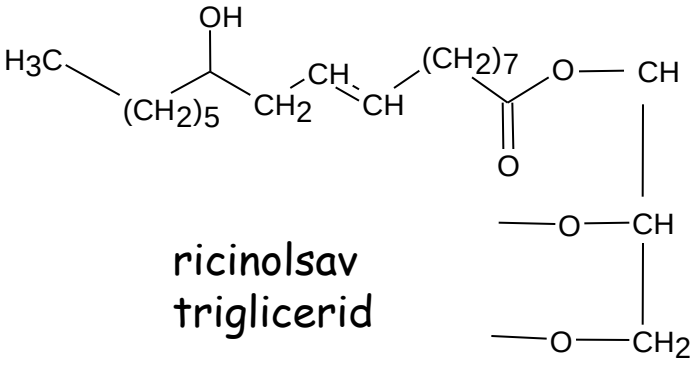


ricinin
op.: 201,5°C
(piridinváz)

ricin
fehérje
(toxin)

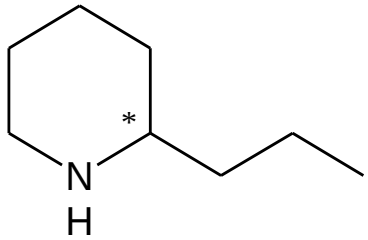
hántolás
sajtolás

ricinusolaj



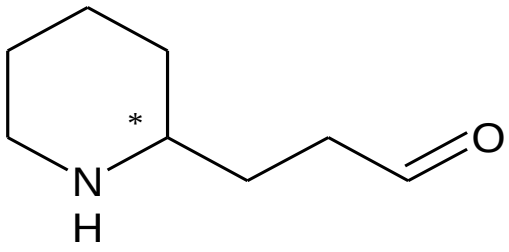
ricinolsav
triglicerid

Conium maculatum
bürök (+)
termés 2,5%-a



koniin (folyadék)
fp.: 106°C, $[\alpha]_D = \pm 15,7°$
előfordulás: almasav sója
hatás: központi idegrendszer
Szókratész kivégzése (i.e. 399)

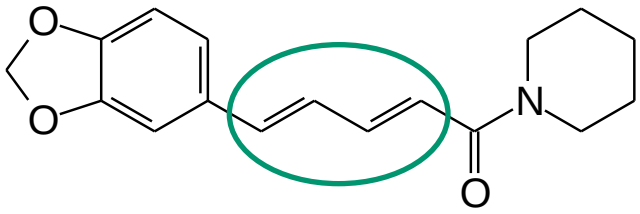
Punica granatum
gránátalmafa gyökérkérge



pelletierin
fp.: 106°C, $[\alpha]_D = -31,1°$
hatás: bélférgek (paraziták)

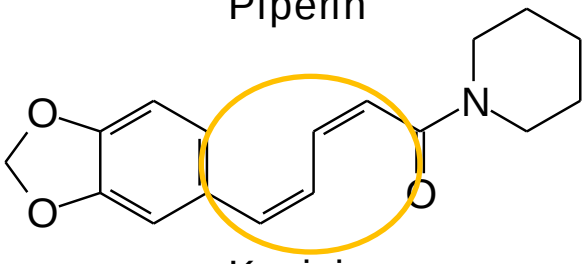
feketebors

(Piper nigrum)



E-E

Piperin

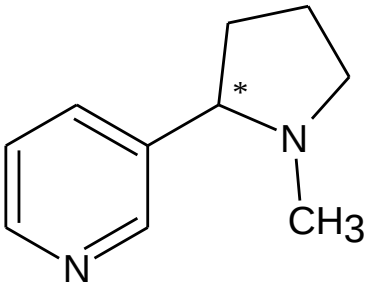


Kavicin

Z-Z

II. Dohány alkaloidok: pirrol- és piridinváz

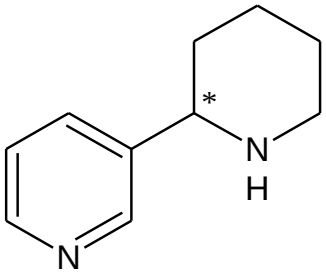
Nicotiana tabacum



(1828)

nikotin

fp.: 246°C, $[\alpha]_D$ = -169,3°



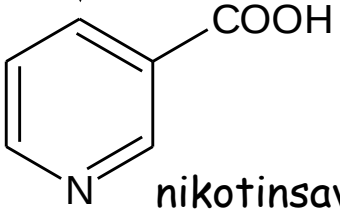
anabazin

fp.: 276°C, $[\alpha]_D$ = -82,4°

előfordulás: almasav/citromsav só

hatás: idegméreg (stimuláns), növényvédőszer, gyógyszeralapanyag

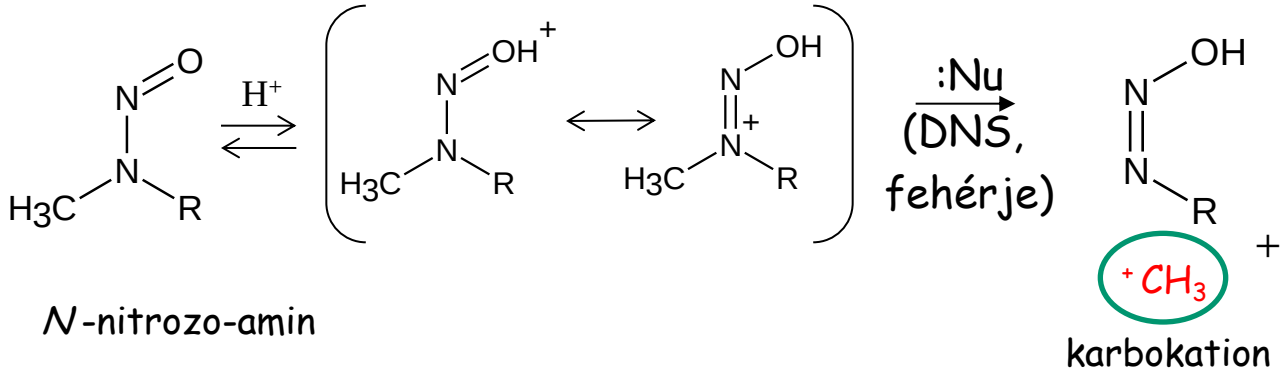
oxidáció



nikotinsav

Nikotin - karcinogenezis

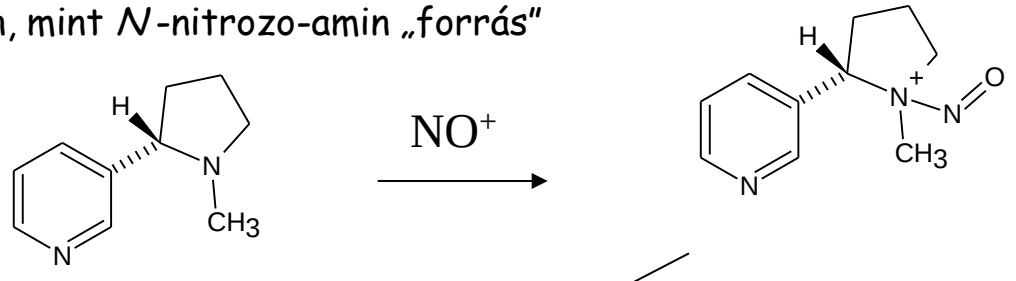
Karbokation képződés *N*-nitrozo aminból



N-nitrozo-amin

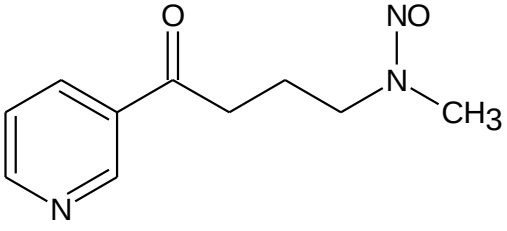
karbokation

Nikotin, mint *N*-nitrozo-amin „forrás"

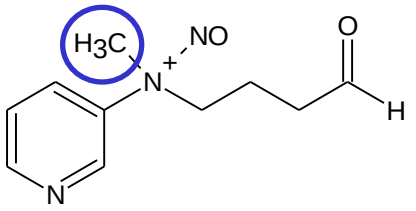


nikotin

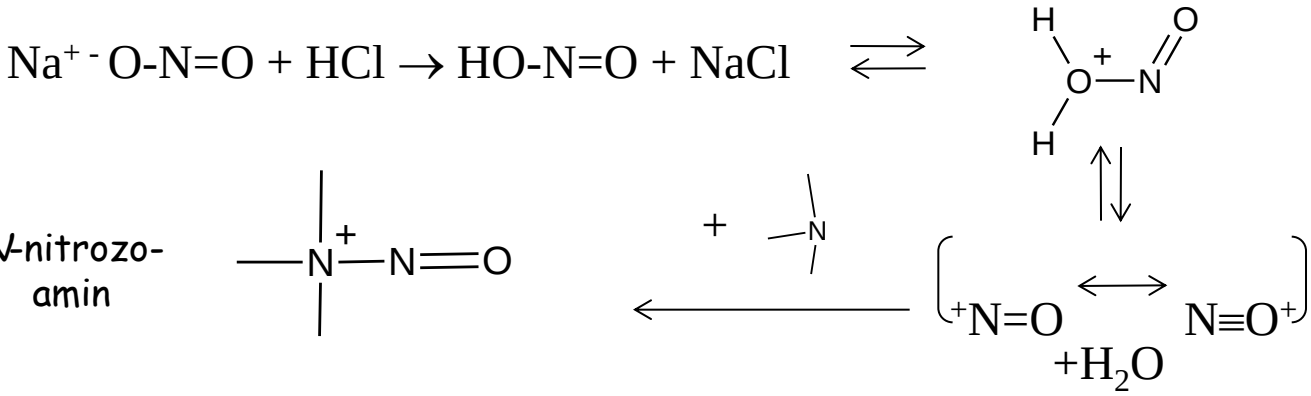
gyűrűfelnyílás (oxidáció)



4-(N-metil-N-nitrozoamino)-
-1-(3-bipiridil)-1-butanon



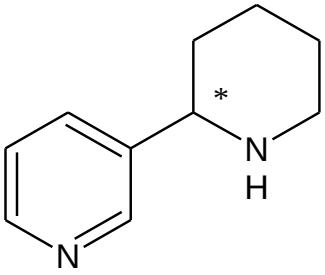
4-(N-metil-N-nitrozoamino)-
-4-(3-bipiridil)-1-butanal



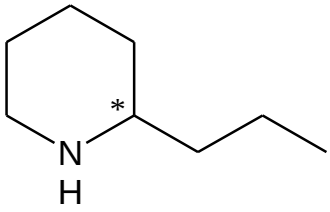
N-nitrozo-amin

Alkaloidok lizinből

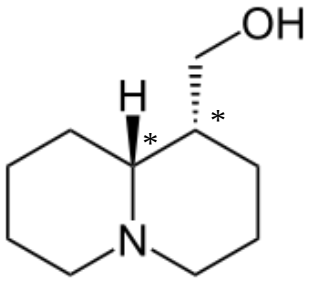
Piperidin váz



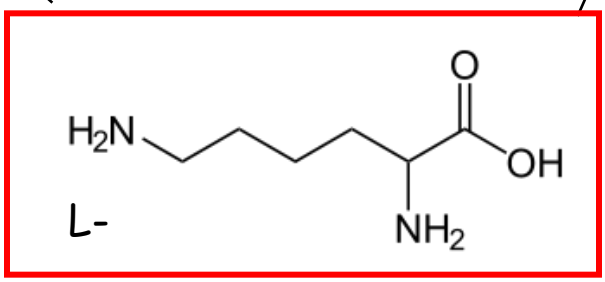
anabazin



koniin

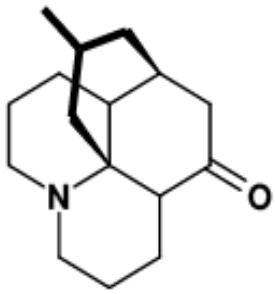


lupinin

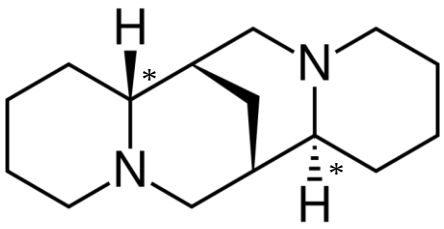


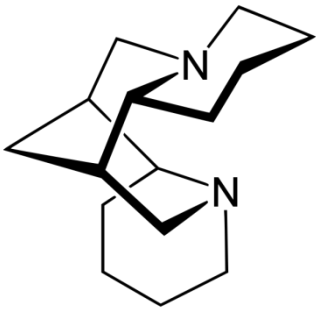
L-

Lupinus mutabilis



lycopodin





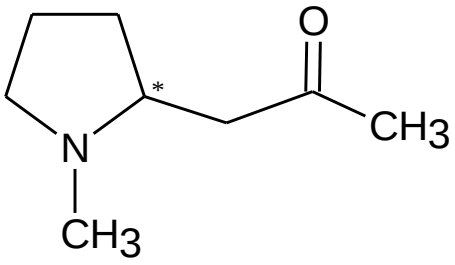
(-) - spartein (lupinidin)
- Na csatorna blokkoló, HIV
- királis sóképző

Lycopodium (kapocs korpafű)

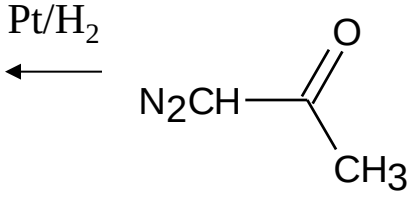
Kinolizidin váz

Továbbá: piperin, pelletierin

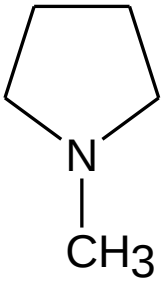
III. Pirrolidinvázas alkaloidok



(1862)



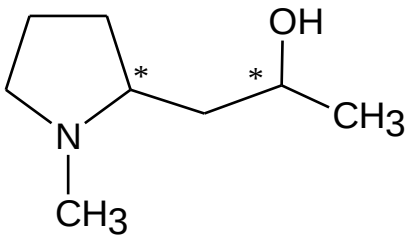
+



higrin
olaj, fp.: 193-195°C
N-metil-2-acetonil-pirrolidin
Erythroxylum coca (Peru)

diazo-aceton

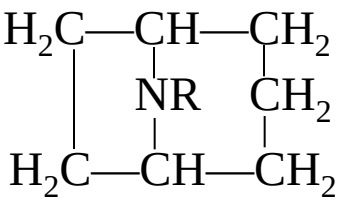
N-metil-pirrol

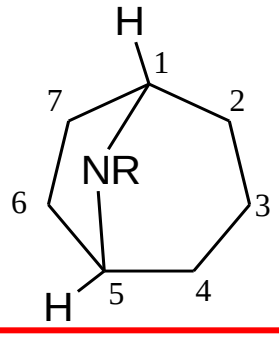


higrolin
op. 34°C
(1943)

IV. Tropán alkaloidok

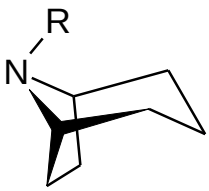
Tropán váz



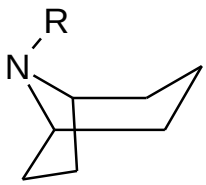


8-metil-8-aza-biciklo-[3.2.1]-oktán

R = H nortropán
R = CH_3 tropán



„szék"



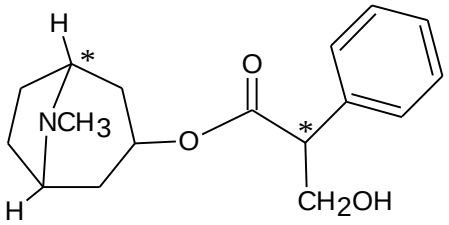
„kád"

Atropa belladonna (nadragulya, bolondfű) bogyó

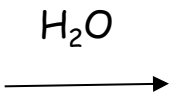
Elnevezés: Linné

Atróposz (görög) elvágja az életfonalat
belladonna (olasz) arcpír

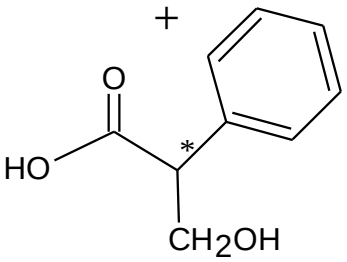
(1833)



atropin, op.: 118°C

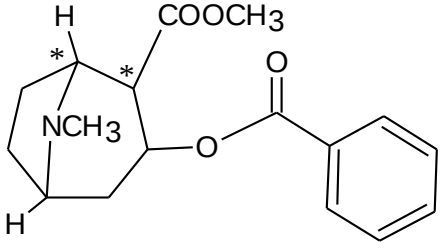


$C_8H_{15}ON$ tropin



tropasav

(1860)



kokain
op.: 98°C, $[a]_D$ = -15,8°

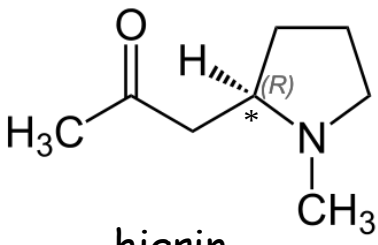
hatás: -központi idegrendszer
-stimuláns (depresszió)
-helyi érzéstelenítés

Egyebek: szkopolamin, dioszkorin

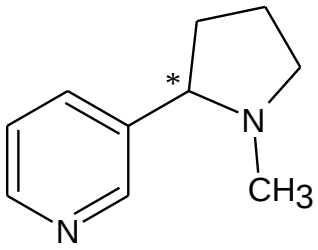
Erythroxylon coca

Alkaloidok ornitinből

Pirrolidin váz

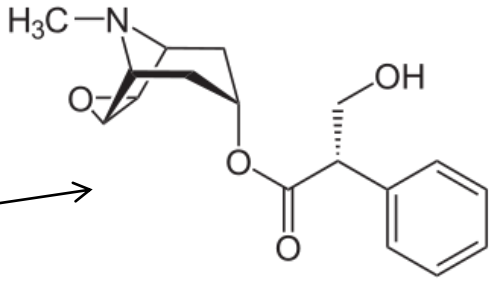


higrin
(coca levélből, 1889)

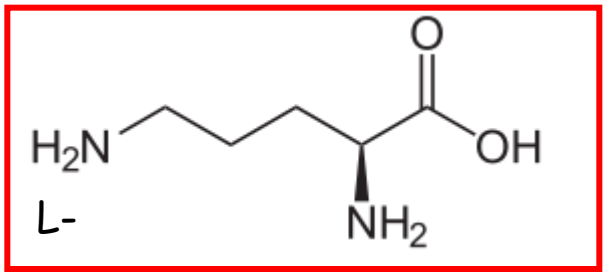


nikotin

Tropán váz



L-scopolamin

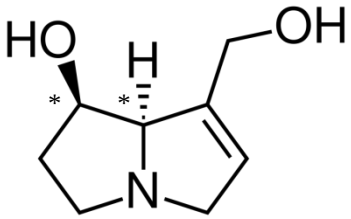


L-

Hyoscyamus niger
(beléndek)

továbbá:
kokain, atropin..

Pirrolizidin váz



retronecin

Senecio vulgaris
(közönséges aggófű)

V. Kondenzált piridingyűrűs alkaloidok

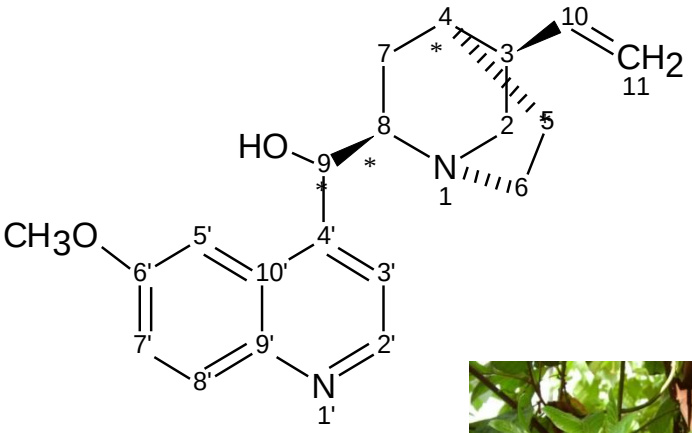
V.1. Cinchona-alkaloidok

kínafa kéreg (20)

- lázcsillapító
- malériaellenes

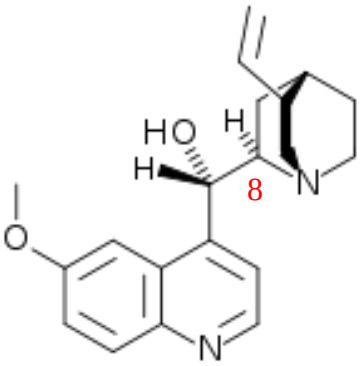
(protozoon-méreg)

1639, spanyol hódítók (Peru)



kinin (1810)
4 aszimmetriás C-atom
2^4=16

Cinchona succirubra



Térszerkezet
8α = kinin, 8β = kinidin

V.2. Ópium (mák) alkaloidok

Papaver somniferum (mák) kábítószer; görcsoldó

- -morfin (Sertürmer, 1805)
- -tebain
- -narkotin (Robiquet, 1817)
- -narcein
- -kodein (Robiquet, 1832)
- -papaverin (Merck, 1848) (Σ25)

Kabay János (1930-33)
száraz mákgubó + szalma
(2-4% morfin, 0,1-0,25% kodein)
1960: 8500 kg

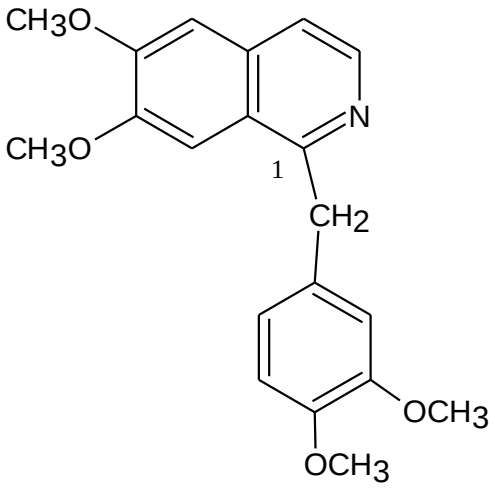
Csoportosítás – szerkezet alapján

1-benzil-izokinolin

papaverin
narkotin
narcein

fenantrénvázas alkaloidok

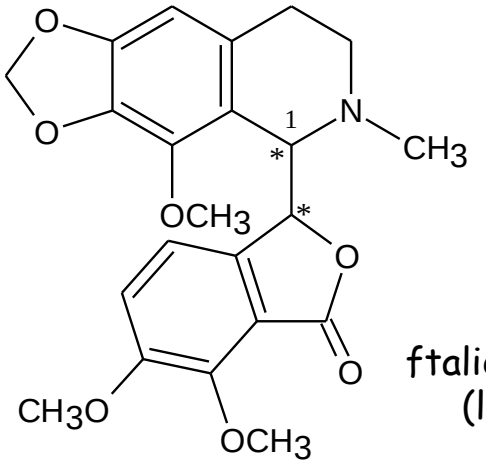
morfin
kodein
tebain



papaverin

op.: 147°C
szerkezet: 1888
szintézis: 1909

görcsoldó (simaizom)
éterkötés fontos
(etiléter = perparin)



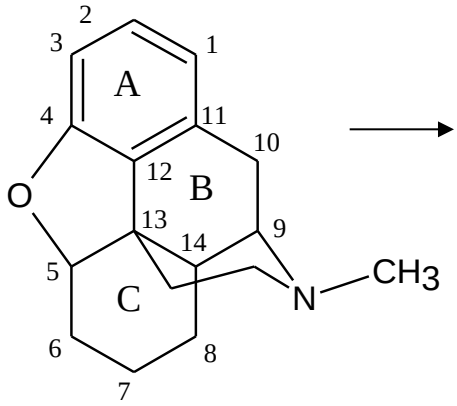
ftalid-csoport
(lakton)

narkotin
(tetrahidroizokinolin)

op.: 175°C
$[\alpha]_D$ = -200°
(1903, 1911)

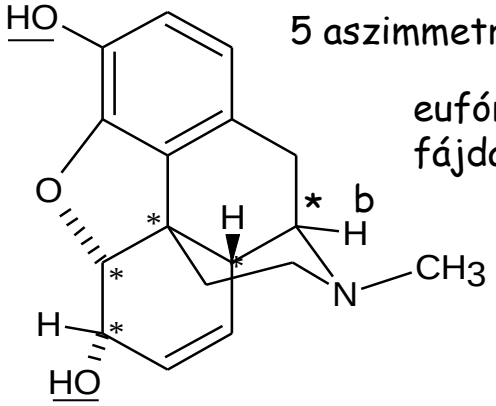
gyengébb, mint a morfin
központi idegrendszer
4 sztereoizomer
ópiumban (±) $\Rightarrow$ α-gnoszkopin

Morfin-alkaloidok



N-metil-morfinán
op.: 61°C
oktahidrofenantrén váz
gyűrűs éter a 4C és 5C között
B és C gyűrű nem planáris

fenolos



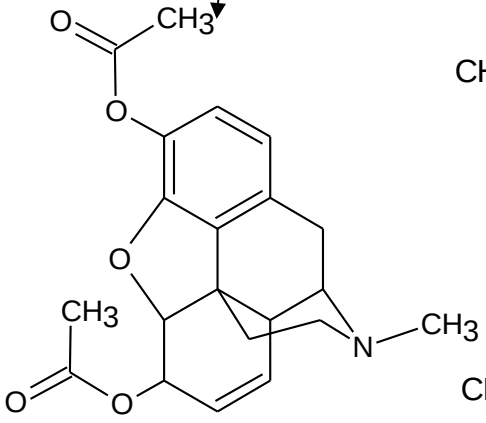
5 aszimmetriacentrum

eufória,
fájdalomcsillapítás

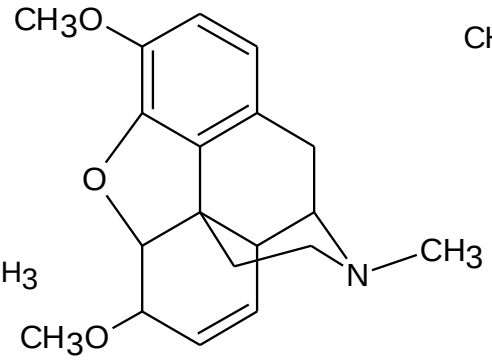
(-)-morfin
op(bp).: 254°C
$[\alpha]_D$ = - 131°

CH_3CH_2O-

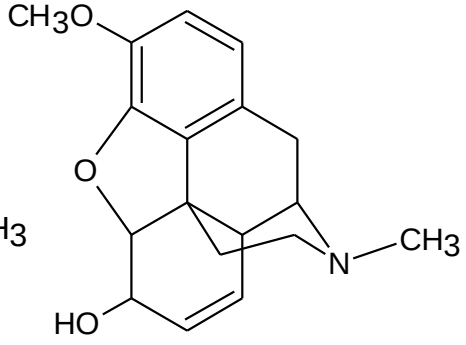
etil-morfin
fájdalom-
csillapítás



heroin
fájdalomcsillapítás



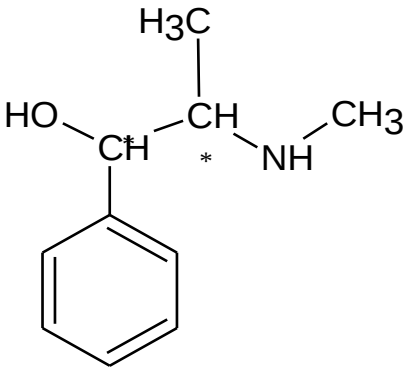
tebain
op.: 193°C
$[\alpha]_D$ = -219°
toxikus (tetanusz hatás)



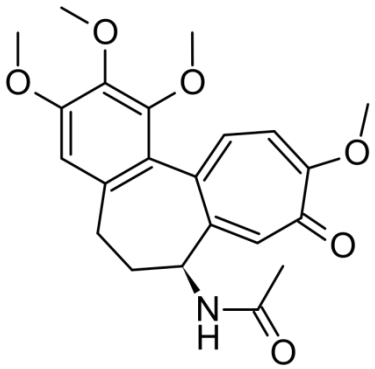
kodein
op.: 155°C
$[\alpha]_D$ = -138°
köhögés, bélhurut

heroin>morfin>kodein

Alkaloidok fenilalaninból és tirozinból

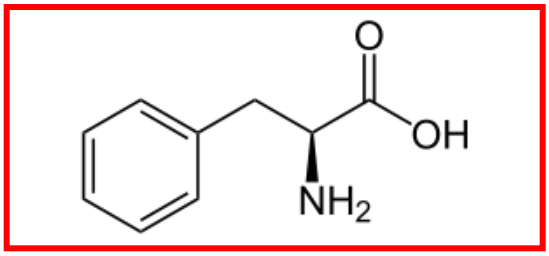


efedrin

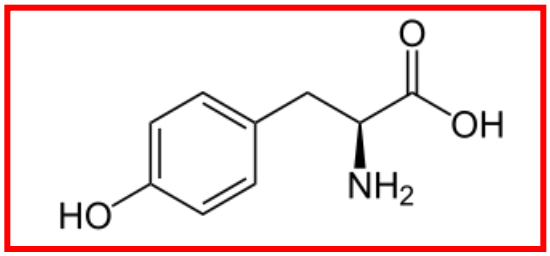


Colchicin
(köszvény)

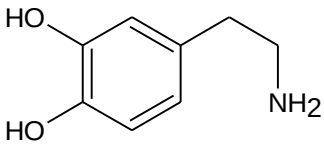
Colchicum speciosum



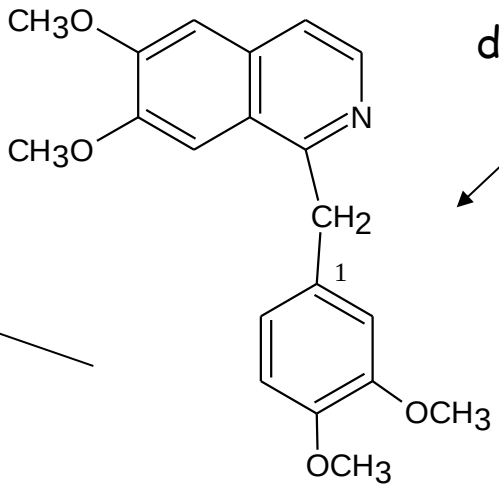
L- Phe



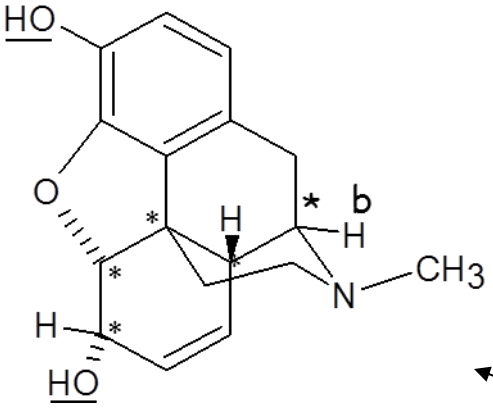
L- Tyr



dopamin

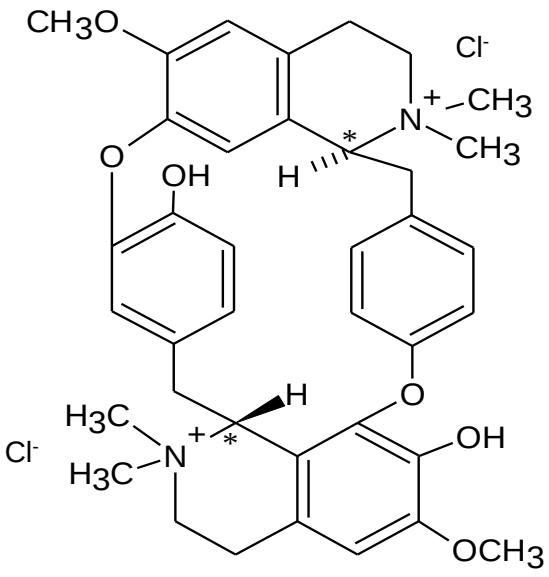


papaverin



morfin

V.3. Kuráre alkaloidok



(+)-tubokurarin-klorid
Bp.: 275°C, $[\alpha]_D$ = + 202°

- bis-benzil-izokinolin váz
- tetrahidro
- éterkötés

nyílméreg
•ingerületátvitel blokkolása
•véráram, de nem emésztőrendszer

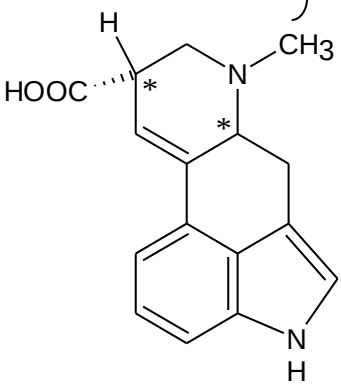
Chondrodendron tomentosum
... candicans

V.4. Anyarozs alkaloidok (>12) (Secale cornatum)

kadaverin, putreszcin, hisztamin, tiramin (1932-54)

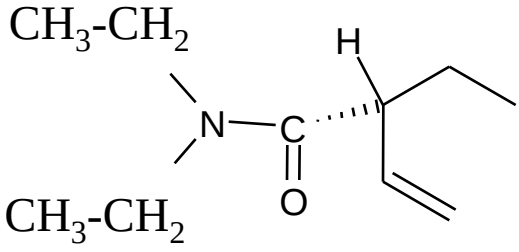
lizergsav
D-Pro
a-ketonsav (piroszőlősav)
L-a-aminosav
NH_3

hidrolízis



lizergsav
bp.: 240°C
$[\alpha]_D$ = +32°

Ergot = anyarozs
(fr, ang)

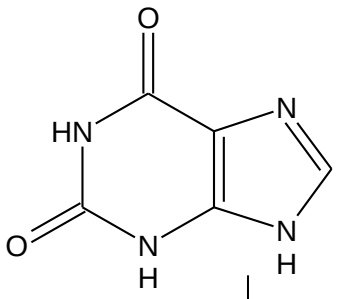


lizergsav-dietilamid
(1943)

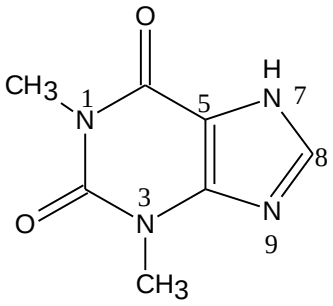
VI. Purinvázas alkaloidok

pirimidin

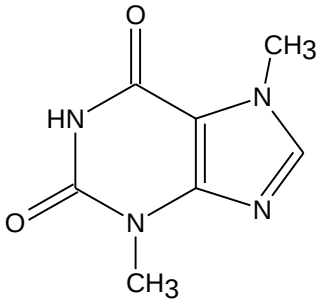
imidazol



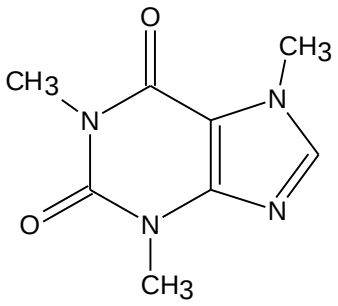
xantin



1,3-dimetil-xantin
teofilin
op.: 272°C
Kossel (1889)
tealevél
hideg vízben rosszul,
forró vízben jól,
vizelethajtó

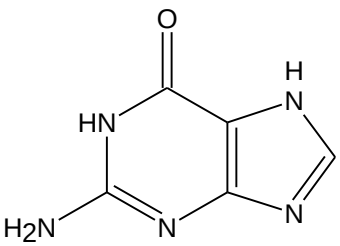


3,7-dimetil-xantin
teobromin
op.: 351°C
E. Fischer (1882)
kakaócserje
(Theobroma cacao)
kakaóbab 1,8%,
vizelethajtó



1,3,7-trimetil-xantin
koffein
op.: 237°C
Runge, Robiquet
Pelletier (1820-21)
kávészem
kávébab 1,5%
tealevél 5,0%
kóladió 2,0%
(100-150 mg/csésze)

Koffein előállítás

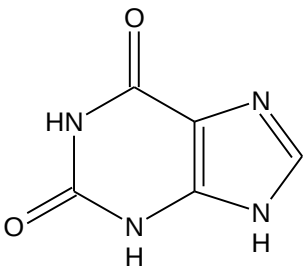


guanin

$NaNO_2/HCl$

H_2O

dezaminálás



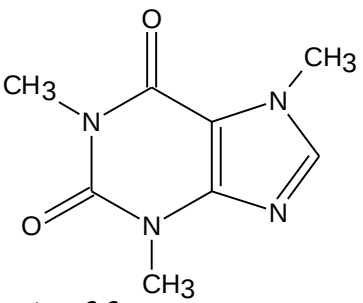
xantin

$(CH_3)_2SO_4$

pH=8-9

30-35°C

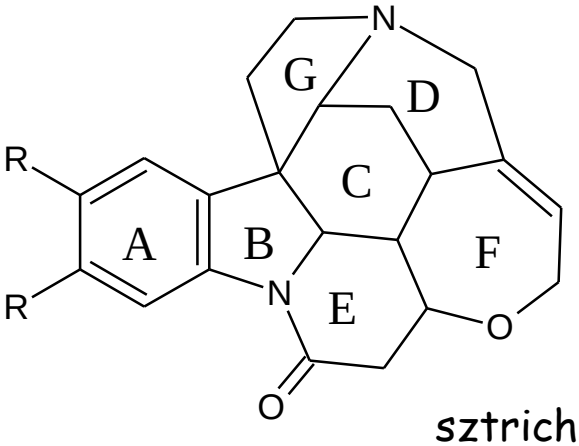
N-metilezés

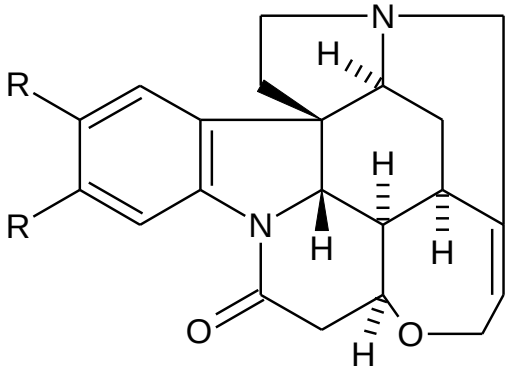


koffein

VII. Strychnos-alkaloidok

Strychnos nux vomica mag és kéreg
Pelletier és Caventou (1819)

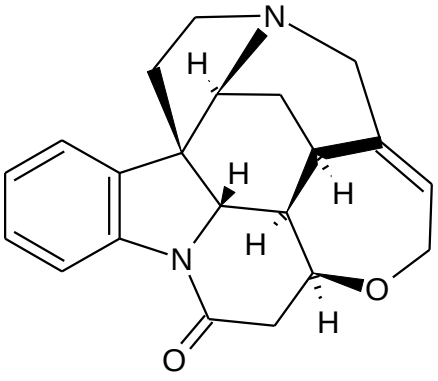




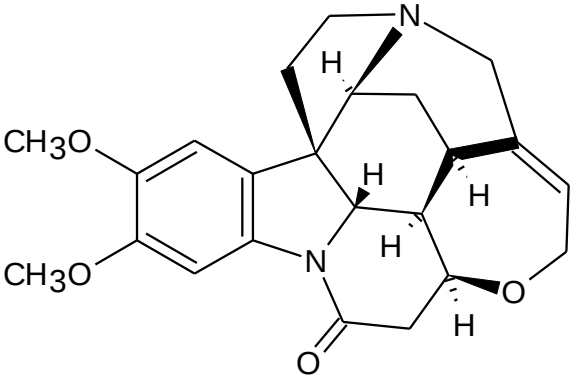
sztrichnin: R = H
brucin : R = OCH_3

A + B → indol váz
C + D → kinolin váz
F → gyűrűs éter
6 aszimmetriacentrum

szerkezet: 1948
szintézis: 1954-55
térszerkezet: 1956



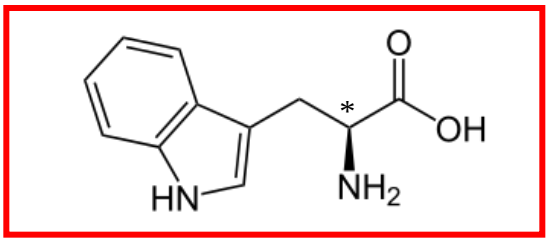
sztrichnin
op.: 286-290°C, $[a]_D$ = -139°
(5-8 mg/kg)



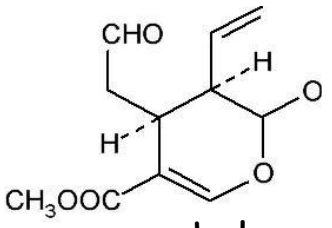
brucin
op.: 178°C
$[a]_D$ = -121°

merevgörcs

Alkaloidok triptofánból

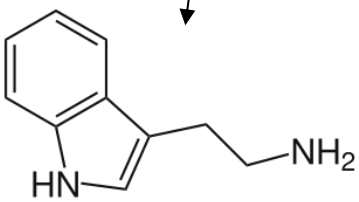


L- Trp

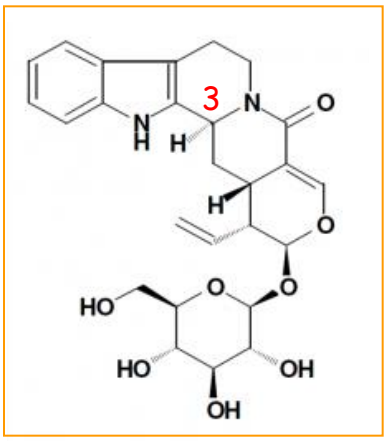


- glükóz

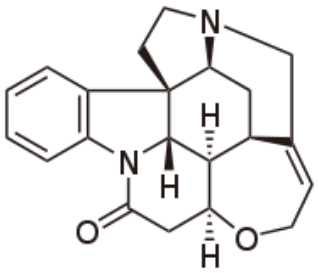
szekologanin (terpén)



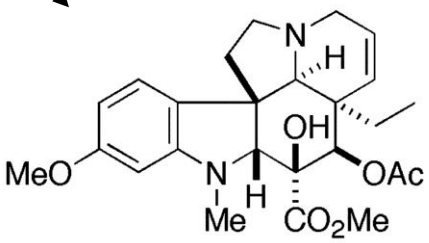
triptamin



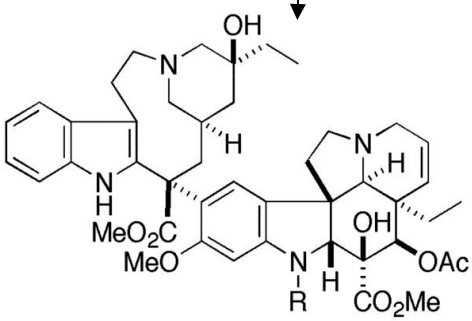
sztriktozidin (3α), vinkozid (3β)



sztrichnin



(–)-vindoline (**3**)

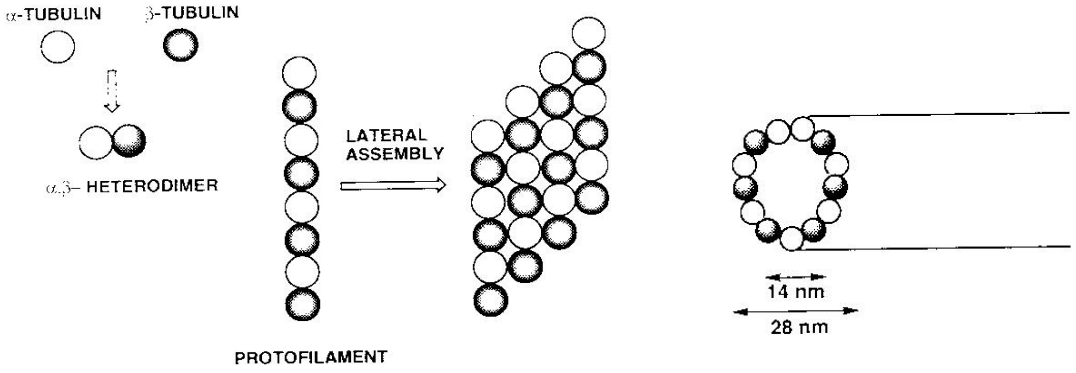


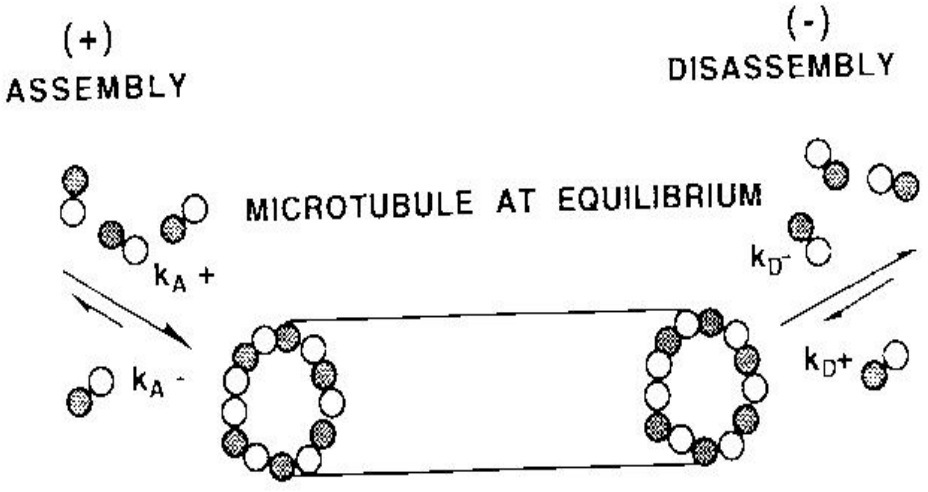
catharanthin

R = Me: (+)-vinblastine (**1**)
R = CHO: (+)-vincristine (**2**)

Vinca major
(rózsameténg)

Hatásmechanizmus: tubulin polimerizáció



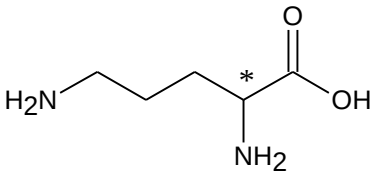


vinca alkaloidok

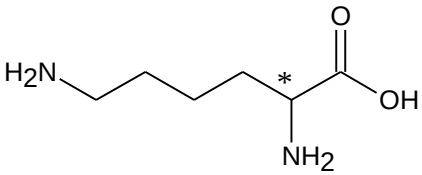
taxol

Alkaloidok bioszintézise – áttekintés

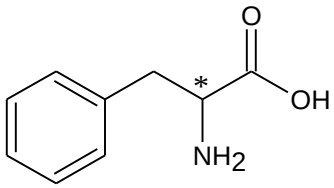
Kiindulási vegyületek



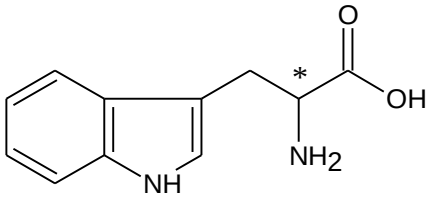
ornitin, Orn



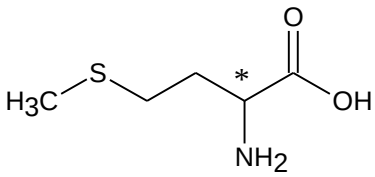
lizin, Lys (K)



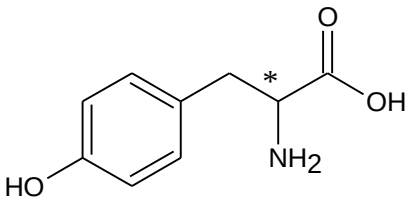
fenilalanin, Phe (F)



triptofán, Trp (W)



metionin, Met (M)



tirozin, Tyr (Y)

Reakciók (enzim)

a) NH_2-*CH*(R)-*COOH* ⟶ NH_2-CH_2 (R) + CO_2

dekarboxilezés, amin

b) NH_2-*CH*(R)-*COOH* ⟶ NH_2-CH_2 (R) ⟶ R-*CHO*

NH_2-*CH*(R)-*COOH* ⟶ *HOOC-CO*-(R) ⟶ R-*CHO*

oxidatív dezaminálás

c) R^1-*CHO* + R^2-NH_2 ⟶ R^1-*CH*=NR^2 + H_2O

Schiff-bázis reakció

d) H_2CO + $(CH_3CH_2)_2NH$ ⟶ H_2C=$N(CH_3CH_2)_2$ + H_2O

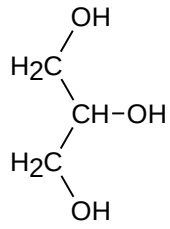
Mannich-reakció

Ornitinből képződő alkaloidok

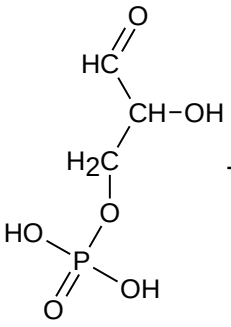
(Pirrolidin-piridin csoport)

pl. nikotin, atropin vagy kokain

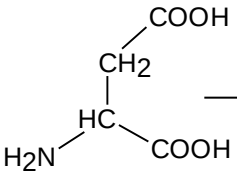
A.



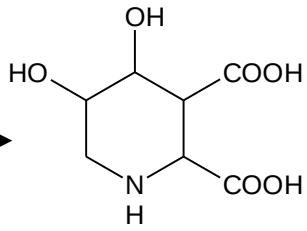
glicerin

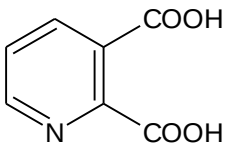


glicerin-aldehid-3-foszfát



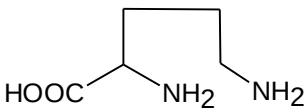
Asp





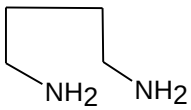
kinolinsav

B.



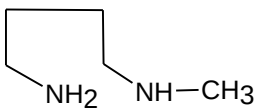
Orn

- CO_2



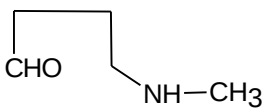
putreszcin

N-metilezés

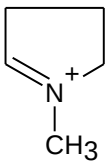


N - metil-putreszcin

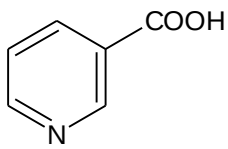
dezaminálás/oxidáció



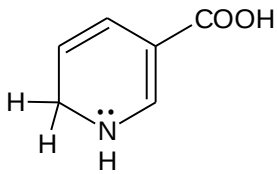
gyűrűzárás

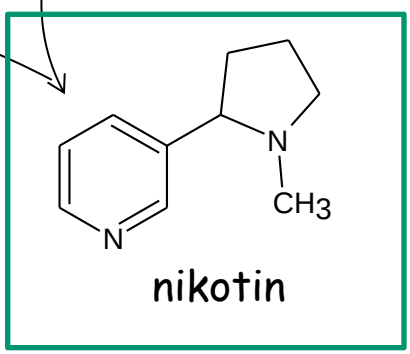


N - metil-pirrolidin



nikotinsav



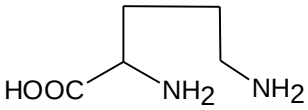


nikotin

Ornitinből képződő alkaloidok

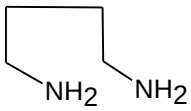
(tropánváz csoport)

pl. nikotin, atropin vagy kokain



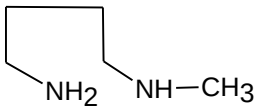
Orn

- CO_2



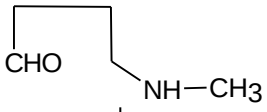
putreszcin

N-metilezés

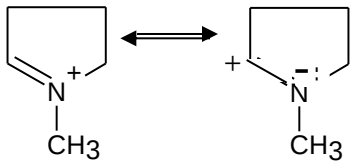


N - metil-putreszcin

dezaminálás/oxidáció



gyűrűzárás

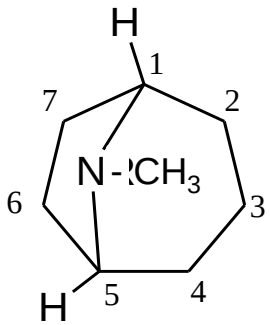


N - metil-pirrolidin

\+ H_3C-CO-CH_2-$COOH$

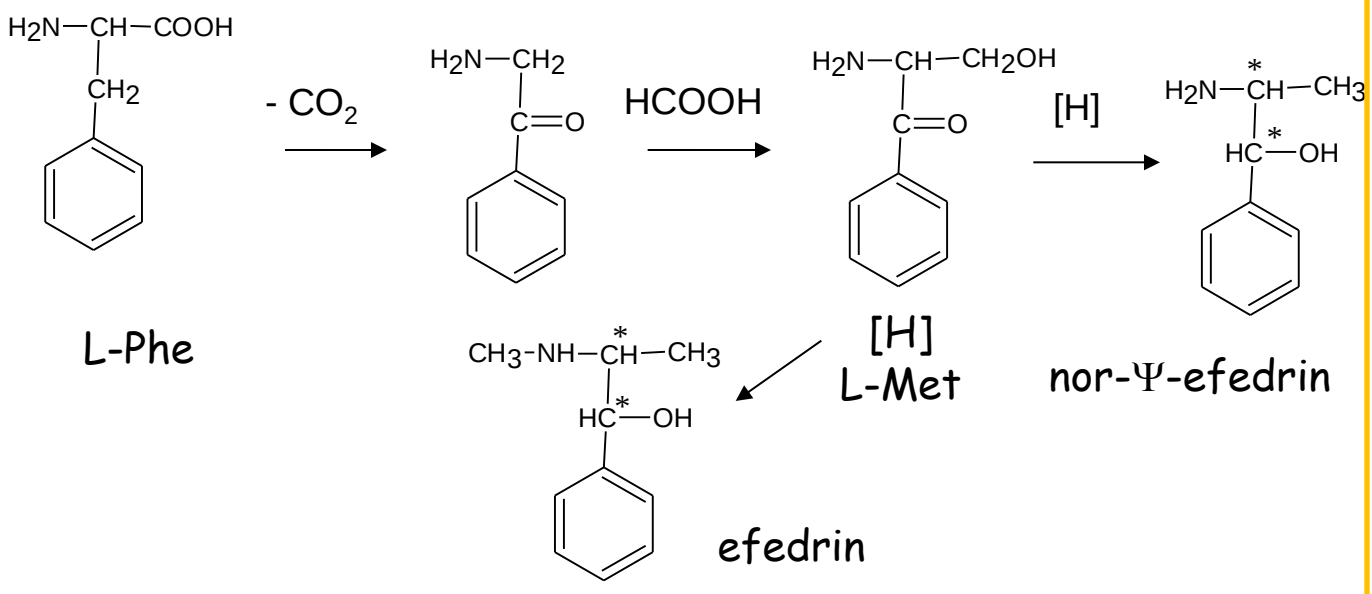
acetecetsav

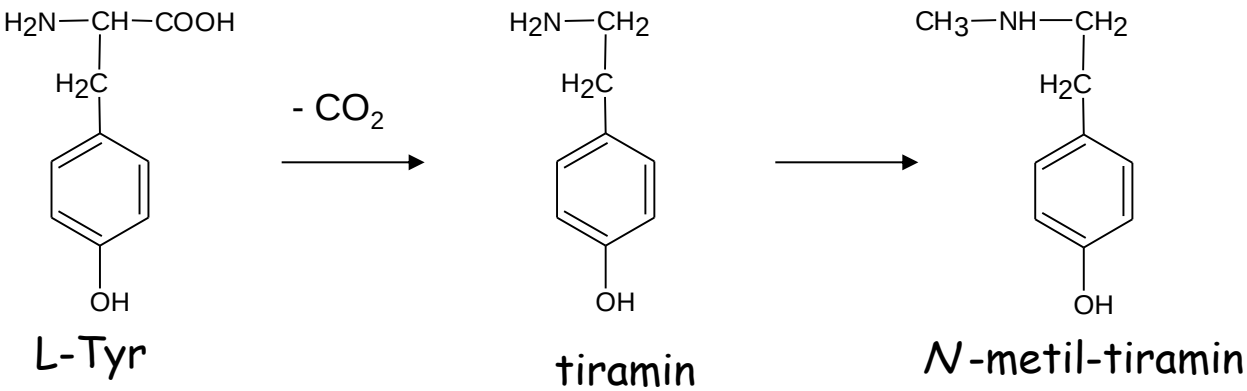
..

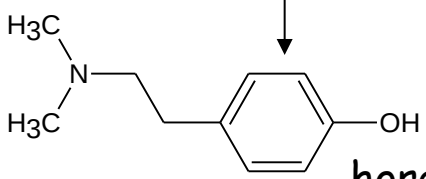


tropánváz (atropin, kokain)

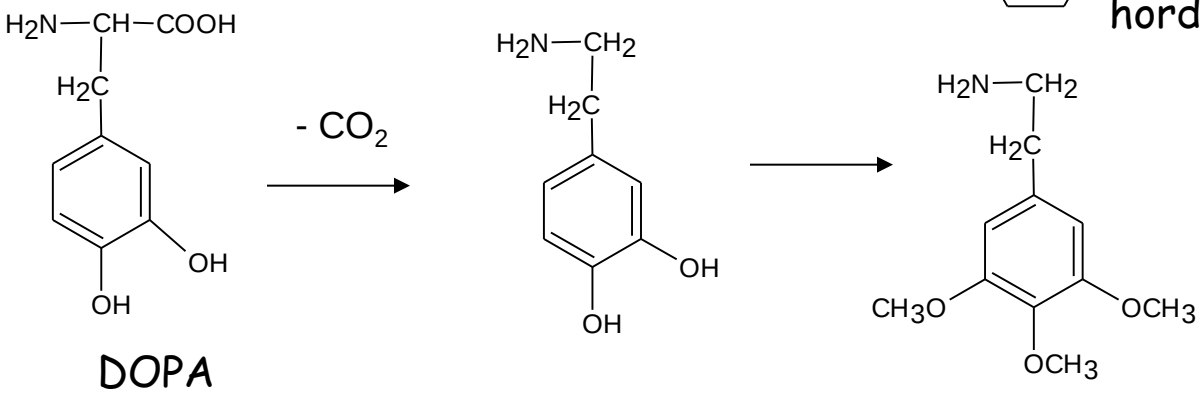
Fenilalaninból és tirozinból képződő alkaloidok





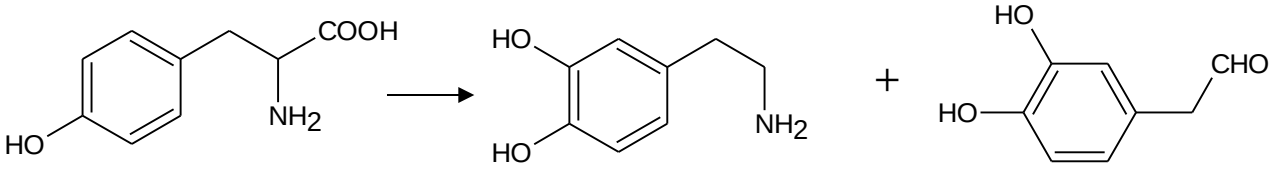


hordenin



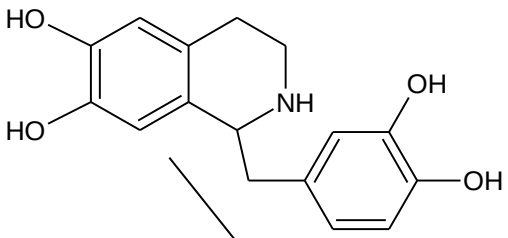
Fenilalaninból és tirozinból képződő alkaloidok

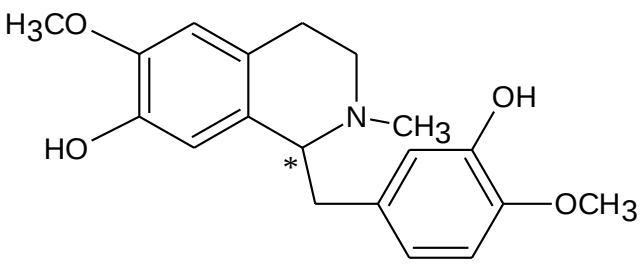
(Izokinolin/fenantrén csoport)



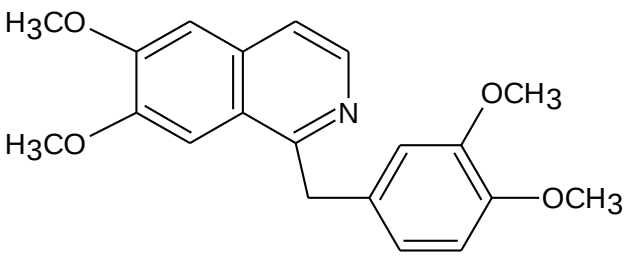
L- Tyr dopamin 3,4-dihidroxifenil-acetaldehid

norlaudanozolin

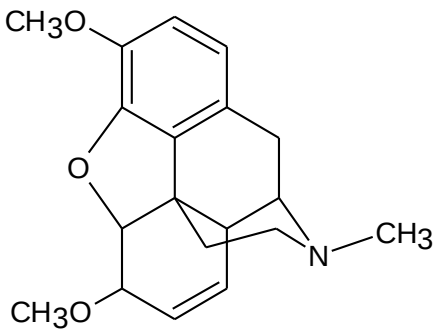




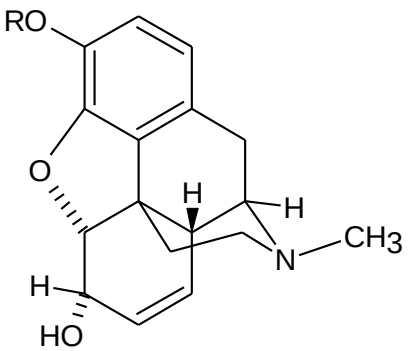
retikulin



papaverin



tebain



R = CH_3 kodein

R = H morfin

Neurotranszmitterek

1. Acetil-kolin/kolin

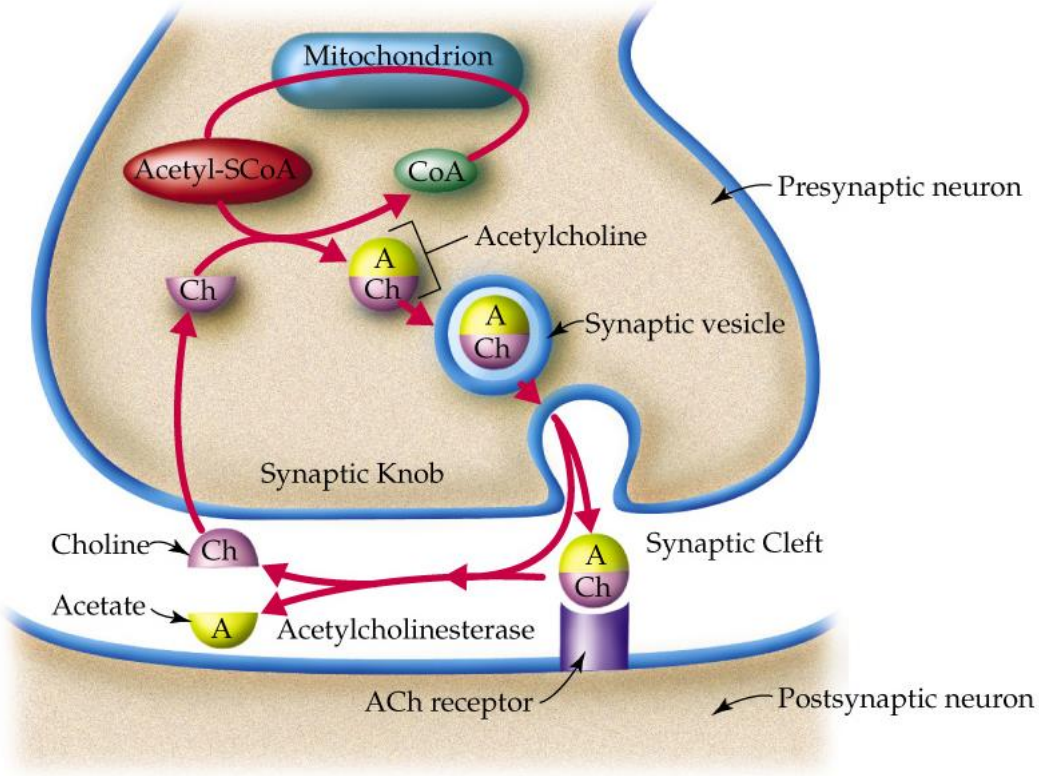
2. Biogén aminok

2.1. Katekolaminok

dopamin,
noradrenalin,
adrenalin,

2.2. Indolaminok

szerotonin,
hisztamin



Kolinerg rendszer

Monoaminerg
(Biogén aminok)

1. Acetil-kolin/kolin

$^{+}N(CH_3)_3\text{-}CH_2\text{-}CH_2\text{-}OH$ + $CH_3\text{-}CO\text{-}S\text{-}CoA$

kolin — acetil-koenzimA

↓ E: kolin acetil transzferáz

$^{+}N(CH_3)_3\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CO\text{-}CH_3$ + HS-CoA

acetil-kolin

receptor: nikotinos acetil-kolin

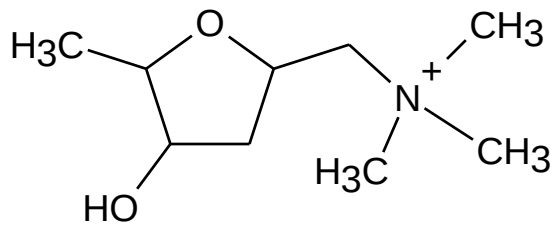
acetil-kolin → kolin + hidrolízis

E: acetil-kolin észteráz

muszkarinos acetil-kolin receptor

Muszkarin: stimulál (1957)

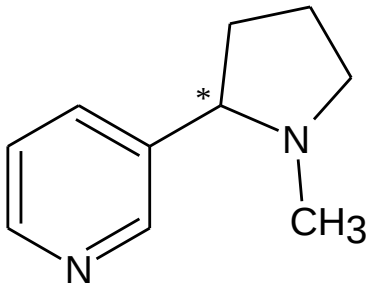
op.: 181°C



Amanita muscaria hatóanyaga

100g → 16mg

Nikotin (1828)

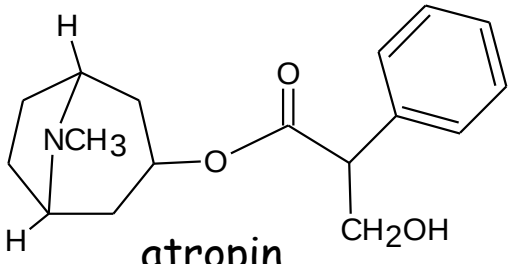


alacsony koncentráció: stimulál

magas konc.: gátol

Atropin: gátol

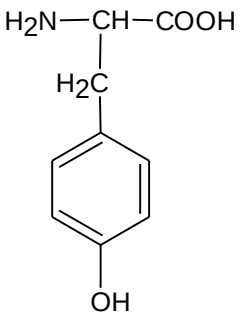
op.: 118°C



atropin

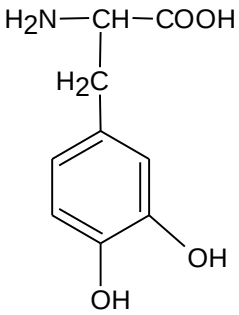
2. 1. Katekolaminok

(bio)szintézis (szimpatikus idegsejtben)



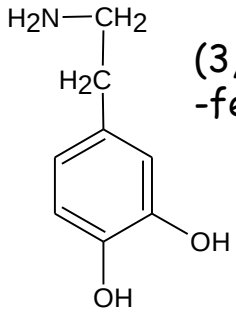
Tyr

oxidáció
hidroxilezés
E: Tyr hidroxiláz



DOPA
(3,4-dihidroxi
-fenilalanin)

E: dopa dekarboxiláz

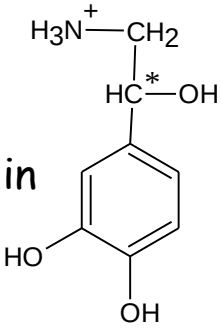


(3,4-dihidroxi-
-feniletilamin)

dopamin

oxidáció

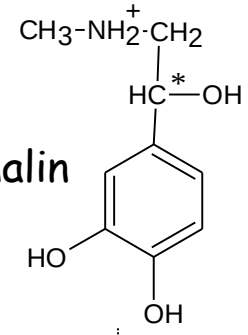
E: hidroxiláz



nor-adrenalin

metilezés
(S-adenozil-Met)
E: transzmetiláz

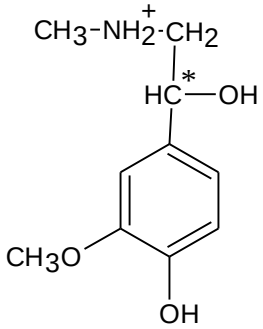
(Parkinson-ellenes szer)



adrenalin

inaktiváció

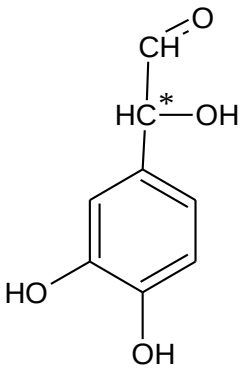
E: katekol-*O*-metil
transzferáz



3-*O*-metil
adrenalin

receptor:
adrenoreceptorok

inaktiváció
E: monoamin oxidáz



3,4-dihidroxi-
fenilglikol aldehid

α β

a_1: nyálmirigy
a_2: kp-i idegrsz.

β_1

β_2

Kábítószerek

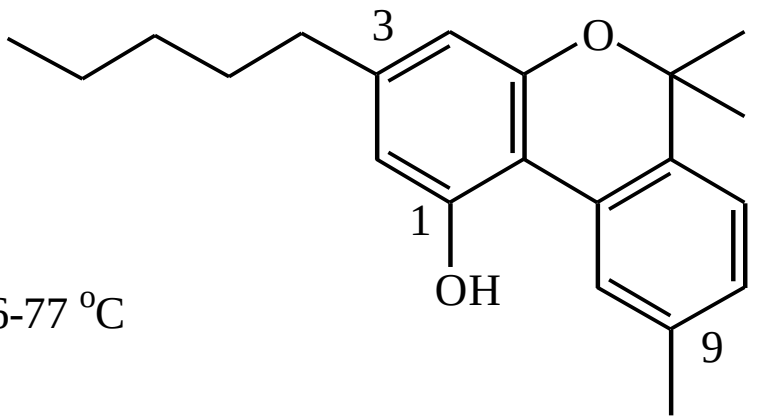
Csoportosítás (WHO)

Lágy drogok	Kemény drogok
- marihuana	- heroin
- szedativumok	- kokain
- hipnotikumok	- morfin
- antihisztaminok	

Áttekintés

1. Lágy drogok (marihuana, hasis)
2. Hallucinogének (LSD, amfetamin, meszkalin)
3. Kemény drogok (ópium, morfin, heroin, metadon)
4. Szipózásra használt (oldó)szerek:
   (éter, aceton, kloroform, benzol, toluol)

1. Lágy drogok (marihuana, hasis): indiai kender
   Cannibis saliva var. indica

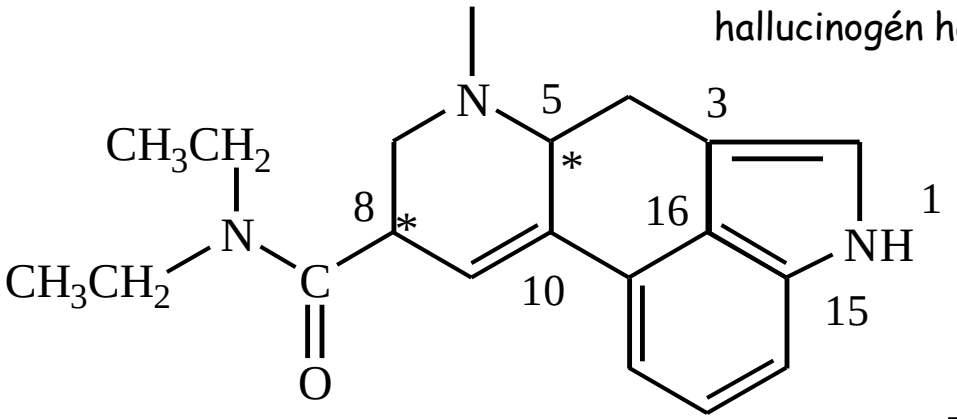


op.: 76-77 °C

Kannabinol,
1-hidroxi-3-pentil-6,6,9-trimetil-6-dibenzopirán

2. Halucinogének
(A. Stoll, A. Hofmann, 1938)

szintézis: 1938
hallucinogén hatás: 1943

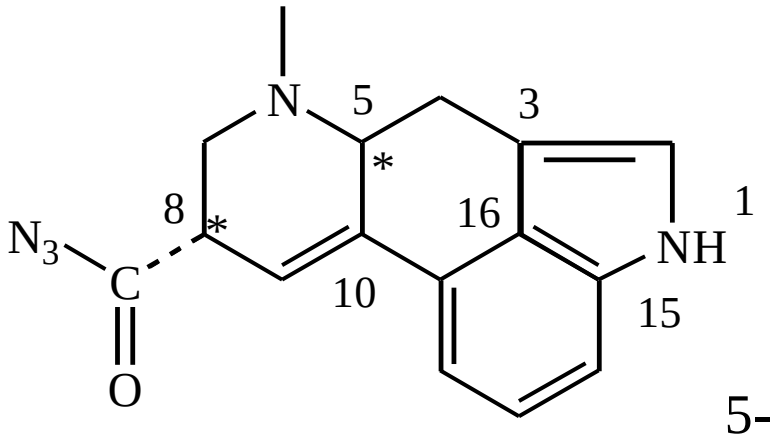


5-β, 8-β

Lizergsav dietilamid (szintetikus)

1. + CH_3-CH_2-NH-CH_2-CH_3

2. + izomerizáció

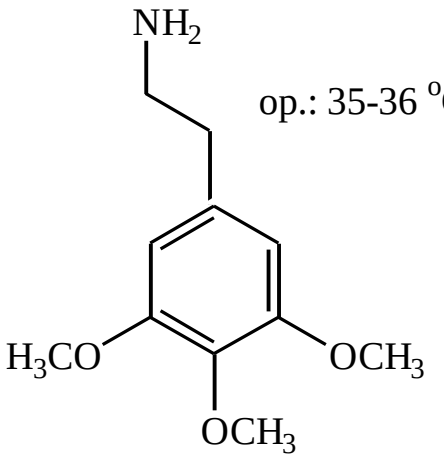


5-β, 8-α

Lizergsav azid (Ergolinváz)

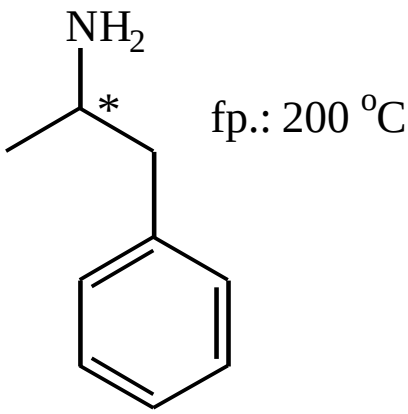
Anhalonium Lewini, kaktusz, 1886

Peyote
(Lophophora williamsii)



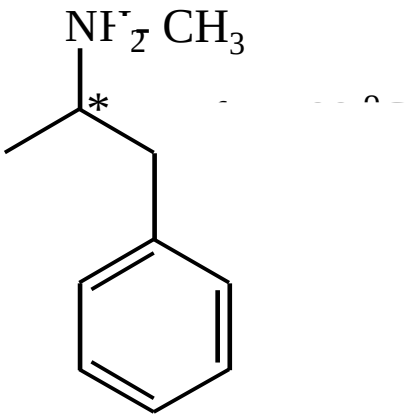
meszkalin
β-(3,4,5-trimetoxi-1-fenil)-etil-amin

Trichocereus pachanoi
(San Pedro)



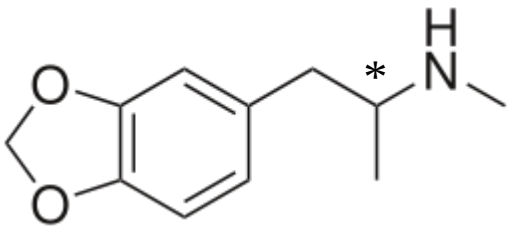
DL-amfetamin
2-amino-1-fenil-propán

Szintézis: L. Edealeno, 1887
Élettani hatás: 1910
Efedrin helyettesitő hatás: 1927
Kábitószer: 1945- 1970 i.v.
pszichostimuláns, függőség



metamfetamin
2-aminometil-1-fenil-propán

„speed"

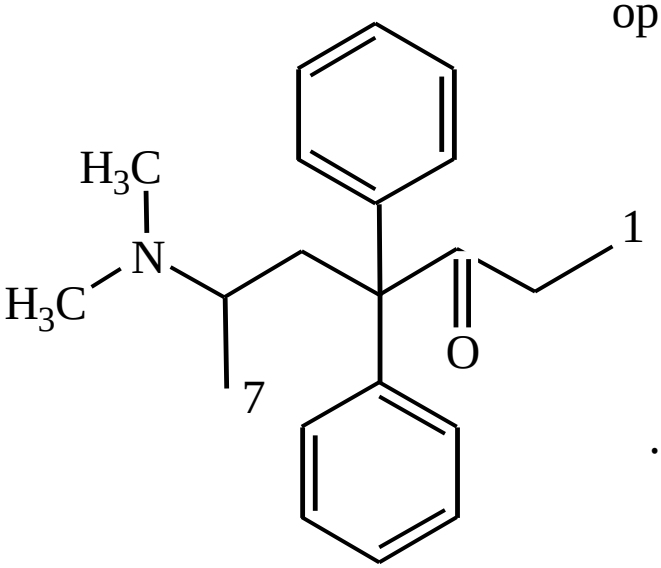


3,4-metiléndioxi-N-metil-amfetamin

„ecstasy"

3. Kemény drogok
(ópium, morfin, heroin, metadon)

op.: 232-235 ^{o}C



.HCl

Metadon
6-dimetil-amino-4,4-difenil-3-heptanon-hidroklorid
(szintetikus, opiát receptoron hat)

Flavonoidok

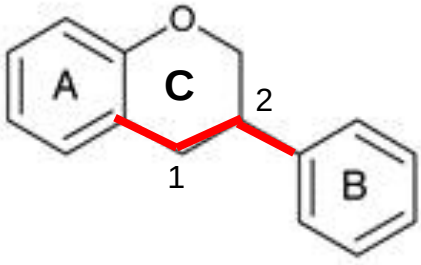
Flavonoidok

(flavon, „flavus" latin, sárga)

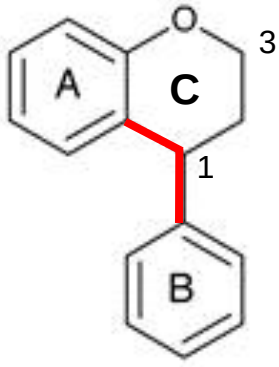
Sárga primula

- 4000,

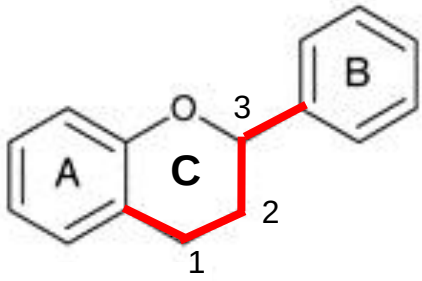
rügy, friss hajtás,
virág, termés



izoflavonoidváz
(1,2-difenilpropán)

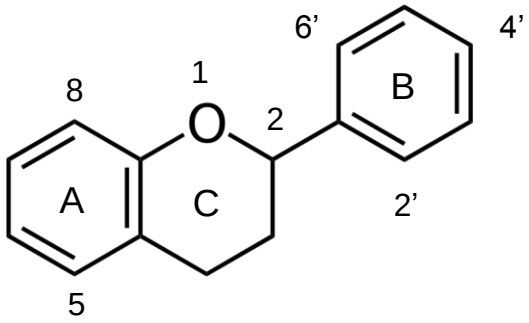


neoflavonoidváz
(1,1-difenilpropán)



flavonoidváz
(1,3-difenilpropán)

Nomenklatúra

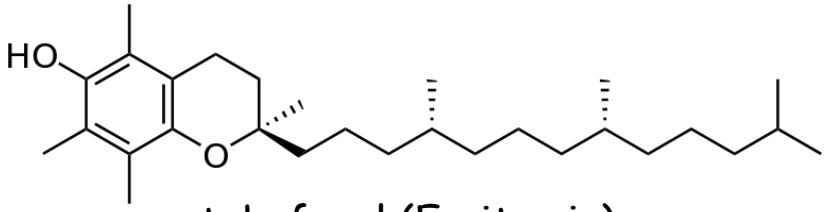


Flaván váz

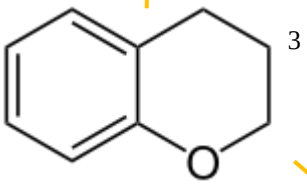
Növényi festékek
- polifenolok
- konjugált rendszerek (UV védelem)
- antioxidáns

Flavonoidok

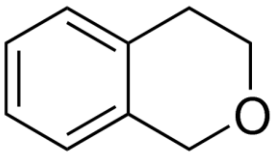
Kromán és származékai



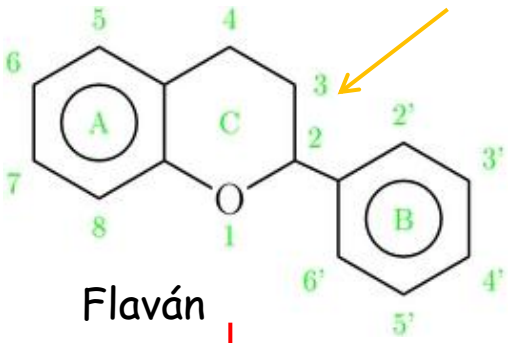
a- tokoferol (E-vitamin)



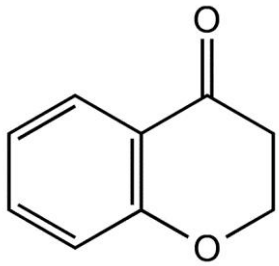
Kromán váz



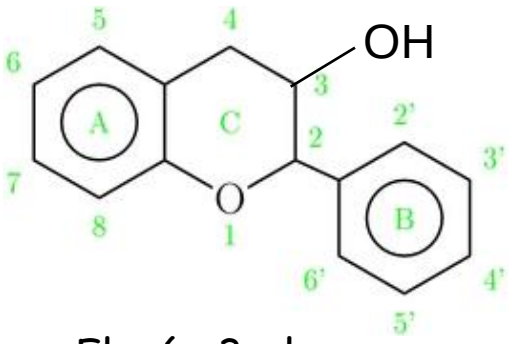
Izokromán váz



Flaván

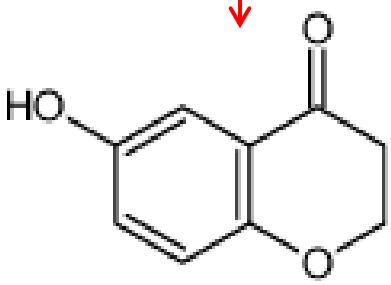


4-Kromanon



Flaván-3-ol

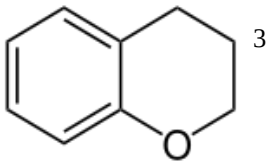
Továbbá:
Flaván-3,4-diol



6-hidroxi-4-kromanon

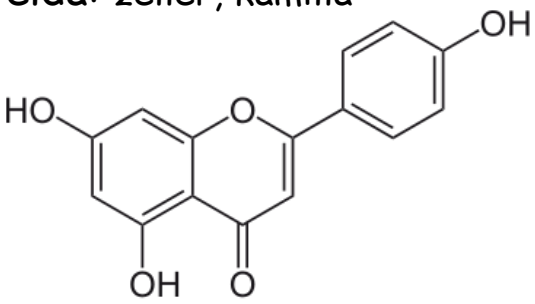
Flavonoidok

Kromon és származékai

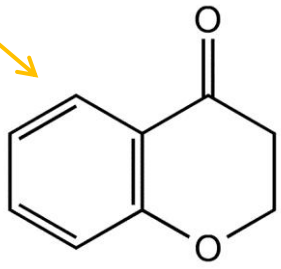


Króman váz

Példa: zeller, kamilla

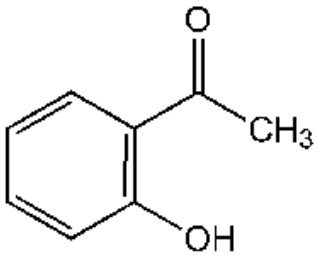


Apigenin (aglikon)

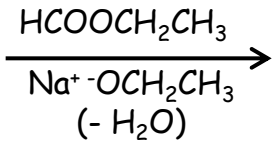


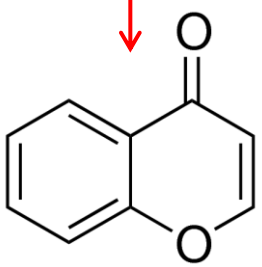
4-Kromanon

Claisen-kondenzáció



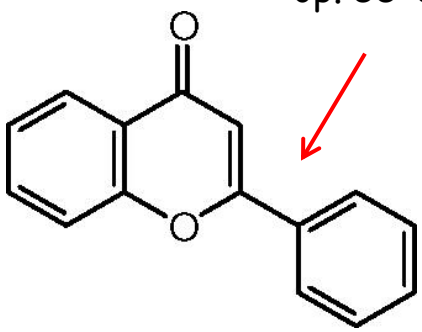
2-Hidroxiacetofenon





4-Kromon

(halványsárga, op. 55–60°C)

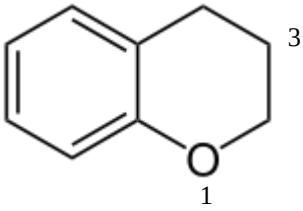


Flavon (2-fenil-kromon)

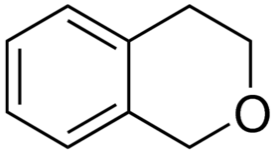
Továbbá: Izoflavon (3-fenil-kromon)

Flavonoidok

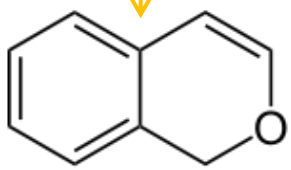
Kumarin és származékai



Kromán váz



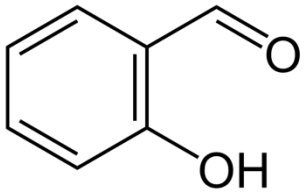
Izokromán váz



1*H*-isokromen

Kumarin: izolálás A. Vogel, 1820
asztma, lymphedema
eper, barack

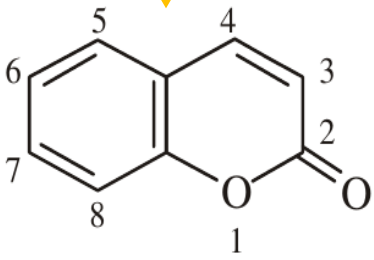
Dikumarol: izolálás (széna) 1940,
antikoaguláns, (warfarin)
antibakteriális (pl. lépfene)



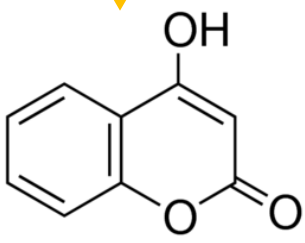
Szalicilaldehid

$(CH_3CO)_2O$/Na acetát

Δ /H_2O
(- AcOH)



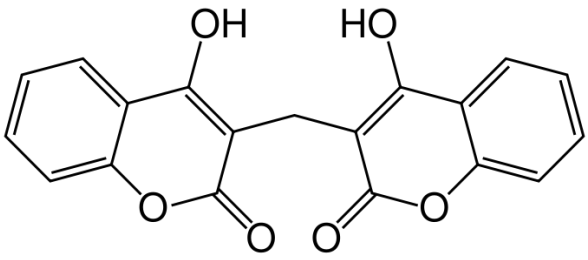
Kumarin



4-hidroxikumarin

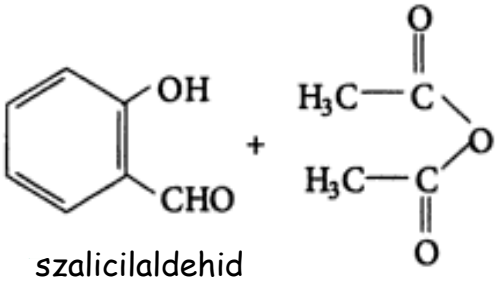
CH_2O

- H_2O

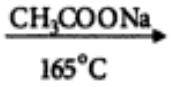


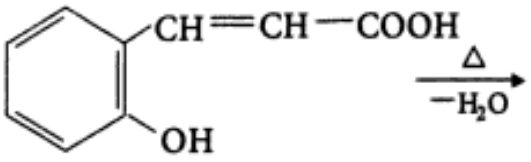
Dikumarol

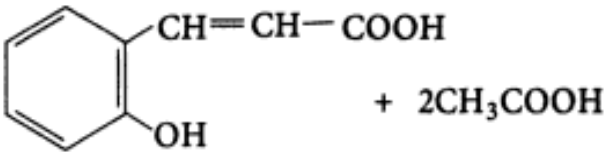
Perkin-féle kumarin szintézis



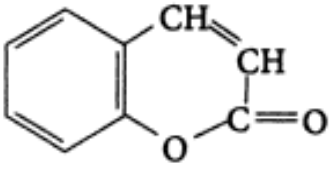
szalicilaldehid







O-hidroxi-fahéjsav

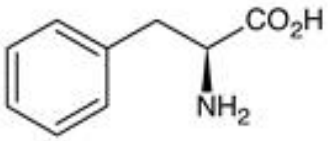


kumarin

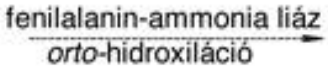
Dipteryx odorata (Tonka beans)

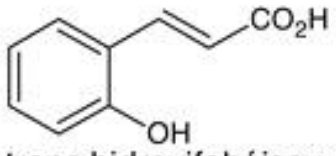
Szintézis: W. H. Perkin, 1868
Gyári méret: Haarmann & Reimer, 1869
Kozmetikum: 1882

Kumarin képződése

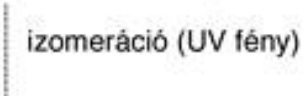


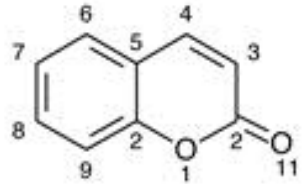
fenilalanin



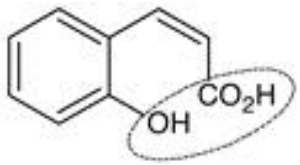


trans-hidroxifahéjsav



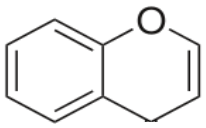


kumarin

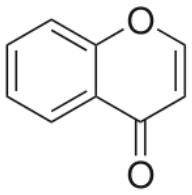


cisz-hidroxifahéjsav

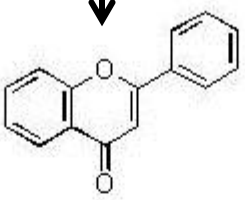
A flavonoidok: áttekintés



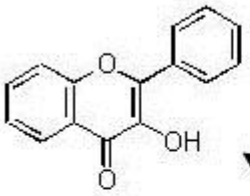
4*H*-Kromén



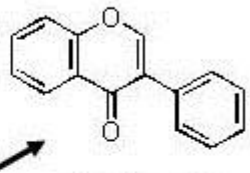
4-Kromon



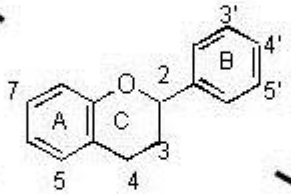
Flavon (2-fenilkromon)

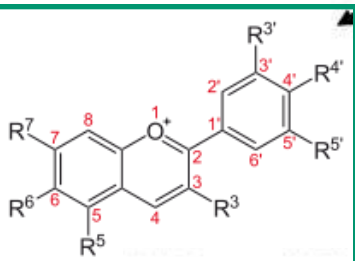


Flavonol
(2-fenil-3-hidroxikromon)

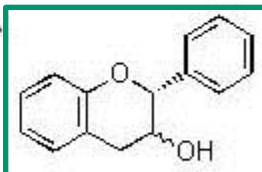


Izoflavon
(3-fenilkromon)

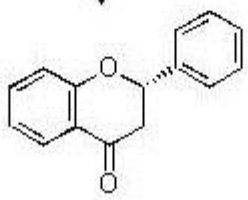




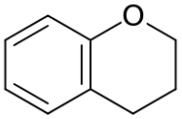
Antocianidinek



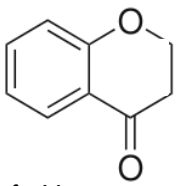
Flavan-3-ol
(2-fenil-
3-hidroxi-kromon)



Flavonon (2-fenilkromanon)



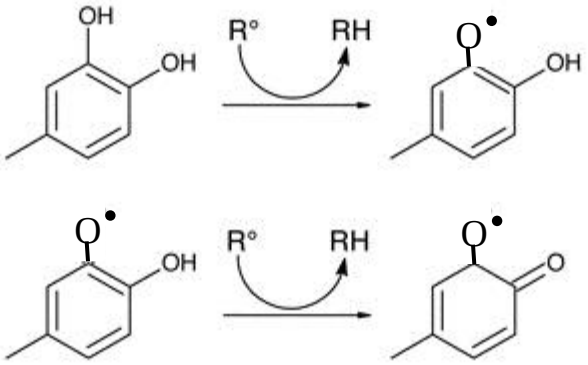
Kromán



4-Kromonon

Glikozid aglikon

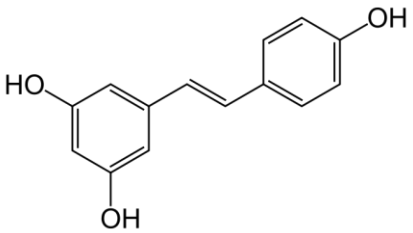
A flavonoidok „gyökfogó" mechanizmusa



Antioxidáns (oxidáció gátló): szabadgyökök elektronját felveszik, gyökké alakulnak (stabilabb, hosszabb életidő), újabb elektron felvételével stabil vegyület lesz.

Természetes antioxidánsok

aszkorbinsav (C-vitamin),
retinol (A-vitamin),
tokoferol (E-vitamin),
flavonoidok,
rezveratrol,
többszörösen telítetlen vegyületek
(karotinoidok, a telítetlen zsírsavak)
szelén



transz-resveratrol
(NEM FLAVONOID)

Ajánlotti irodalom:

Szőke Éva et al. (2012): Gyógynövény és Drogismeret
Hajós Györgyi et al. (2008): Élelmiszerkémia, Akadémiai Kiadó

http://www.tankonyvtar.hu/hu/bongeszes/konyvek

Antibiotikumok

Antibiotikumok

Definició (klasszikus): **antibiotikum** olyan vegyület, amelyet mikroorganizmus (gomba) termel és képes más mikroorganizmus (gomba) elpusztítására (baktericid hatás) vagy a szaporodás gátlására (bakteriosztatikus hatás).

Antibiozis vs. szimbiózis (Paul Vuillemin, 1889)

Felosztás:

Eredet

Szerkezet - gyűrűrendszer (váz szerint)

- β(Béta)-laktám antibiotikumok
- aminosav/peptid típusú
- glikozid típusú
- policiklusos
- spirociklusos

Elnevezés: eredet, tulajdonság (pl. szin)

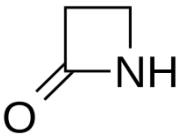
Előfordulás: mikroorganizmusok, gombák

Felhasználás: gyógyászat, agrárium

β(Béta)-laktám antibiotikumok

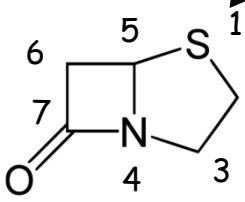
(közös elem: négytagú gyűrűs savamaid)

Felosztás:



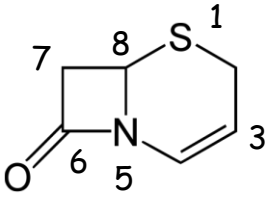
azetidin-2-on (β-laktámváz)

+ 4,5-dihidra-tiazol



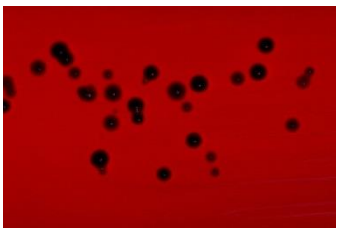
1-tia-heptám (penámváz)

+ 5,6-dihidro-tiazin

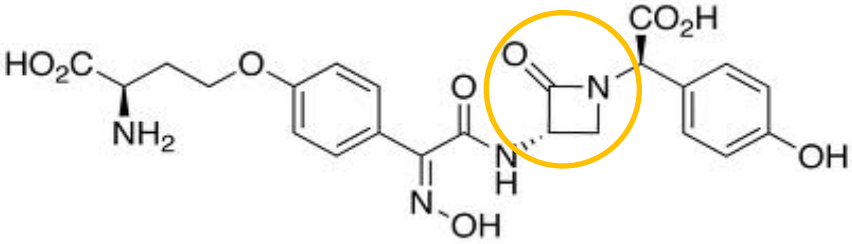


1-tia-okt-3-em (kefémváz)

1. Monociklusos β-laktámok (Monobaktámok)

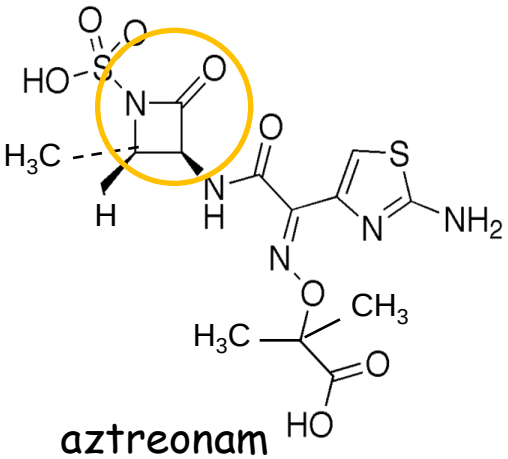


Chromobacterium violaceum

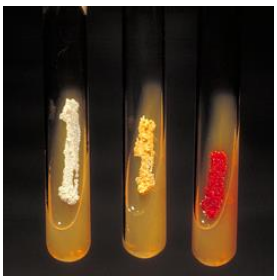


nocardicin *A*

Izolálás:
A.H. Aoki. 1976



aztreonam



Nocardia asteroides
(yellow colonies)

β(Béta)-laktám antibiotikumok

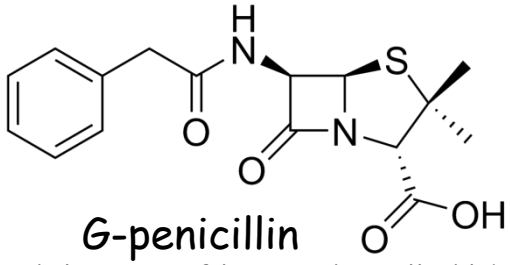
2. Penám vázas antibotikumok

A. Fleming, E. B. Chain, H. W. Florey,
Nobel-díj, 1945

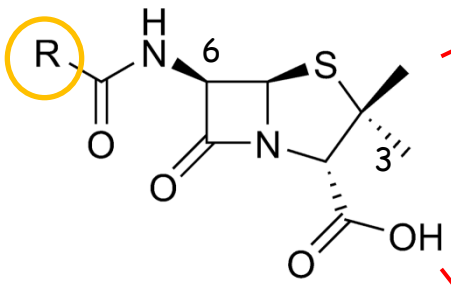
Penicillin (1928)

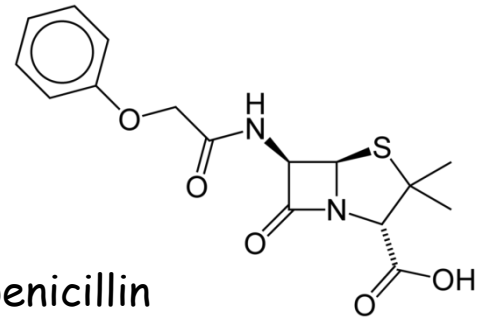
Felfedezés: Fleming
Izolálás: Chain, Florey, 1941

Penicillium notatum



G-penicillin
(pl. agyhártya, szifilisz, tüdőgyulladás)

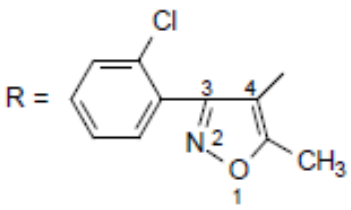




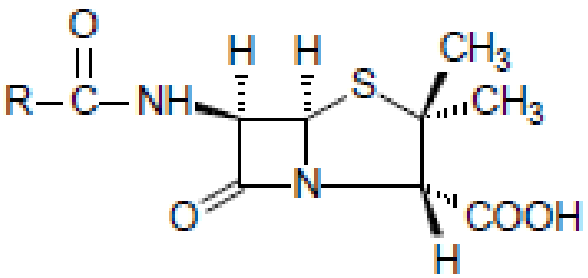
V-penicillin
(pl. torok, mandula gyulladás)

R = - CH_2-CH = CH-CH_2-CH_3

F-penicillin (pent-2-én-1-il-)



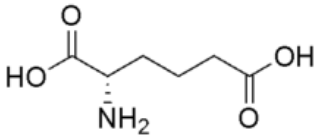
3-(2-klórfenil)-5-metiloxazolil



kloxacillin
(félszintetikus)

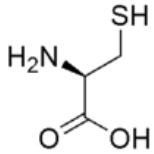
http://www.smithsonianmag.com/

Bioszintézis



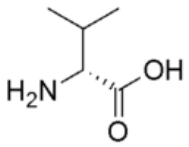
L-amino-adipinsav

\+



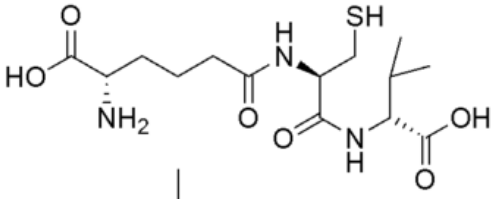
L-Cys

\+

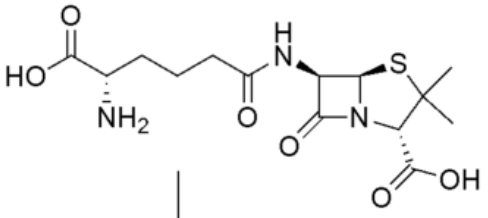


D-Val

Ala-Cys-D-Val tripeptid

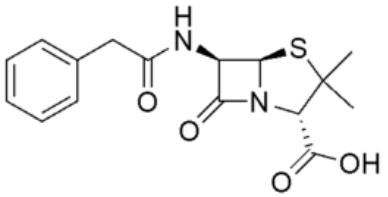


Izopenicillin N



Kefalosporin

Penicillin G



Bioszintézis (fermentáció):

Penicillium chrysogenum

\+ fenilecetsav = penicillin G
\+ fenoxiecetsav = penicillin V

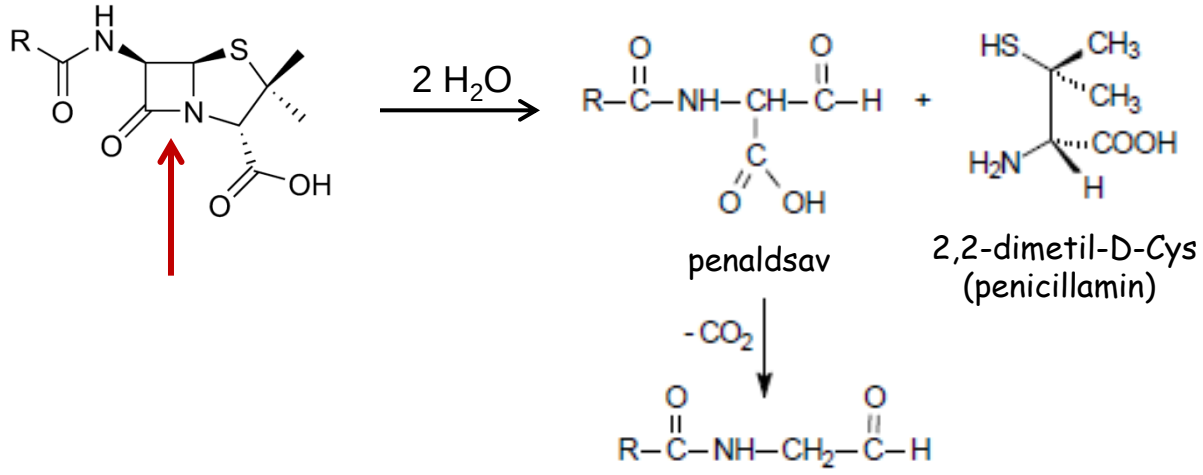
„One sometimes finds what one is not looking for."

β(Béta)-laktám antibiotikumok

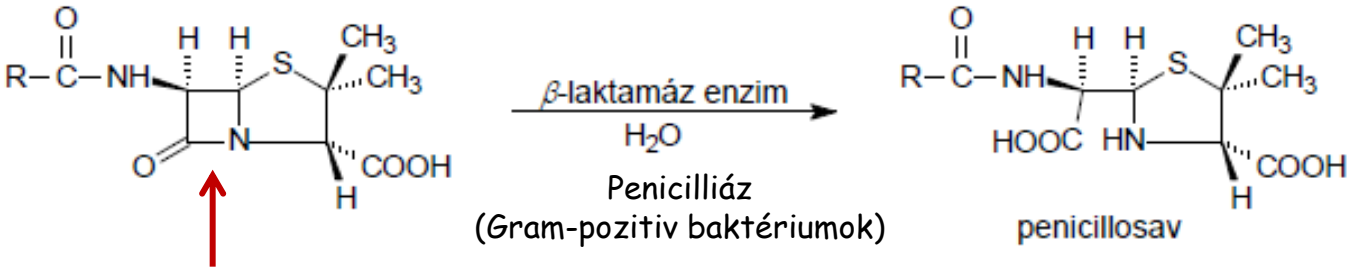
Penicillinek

Hidrolizis, stabilitás

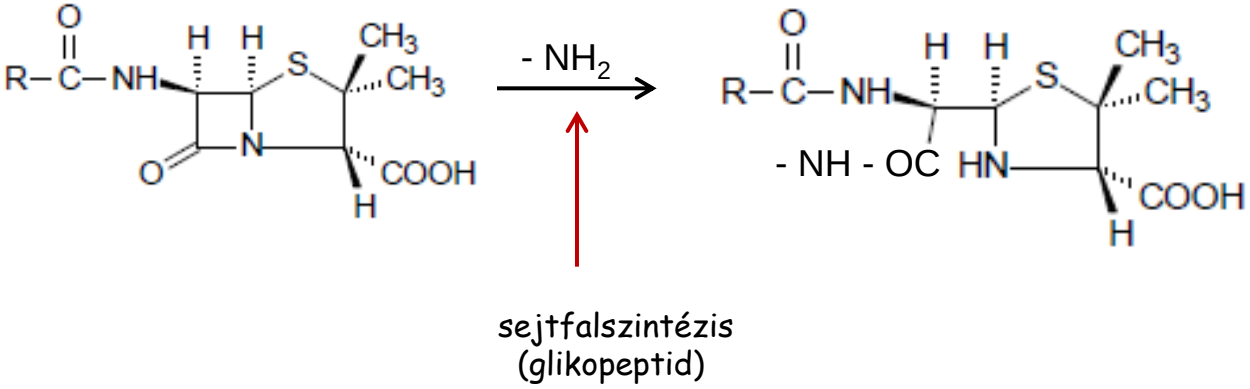
A.



B.

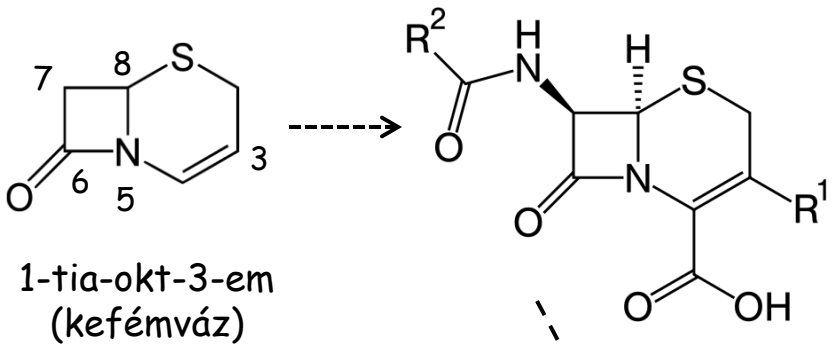


Acilezés (hatásmechanizmus)



β(Béta)-laktám antibiotikumok

3. Kefémvázas antibiotikumok (kefalosprorinok)

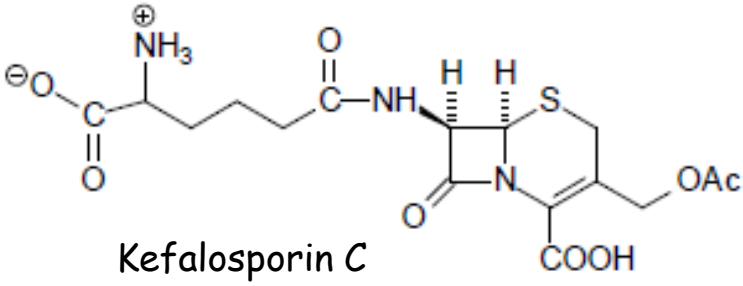


1-tia-okt-3-em
(kefémváz)

Acremonium falciforme
(Cephalosporium)

R^1 = - CH_2O-$COCH_3$
R^2 = - $(CH_2)_3$-$CH(NH_2)$-$COOH$

acil csoport: L-amino-adipinoil

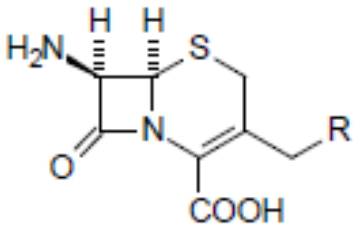


Kefalosporin C

H_2O/H^+

G. Brotzu, Szardinia, 1948
Szerkezet: E.P. Abraham, D. Hodgkin, 1961

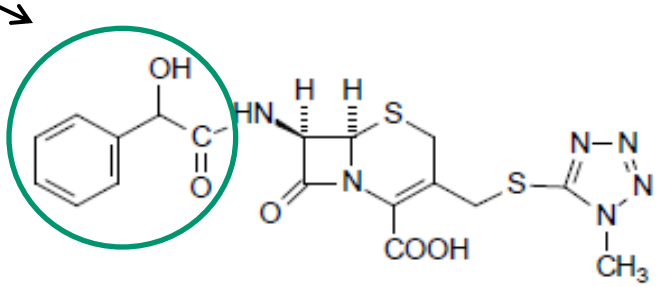
Hatás: Gram pozitiv és negativ
Ellenálló: penicillináz enzim



Félszintetikus kefalosprorinok

acilezés

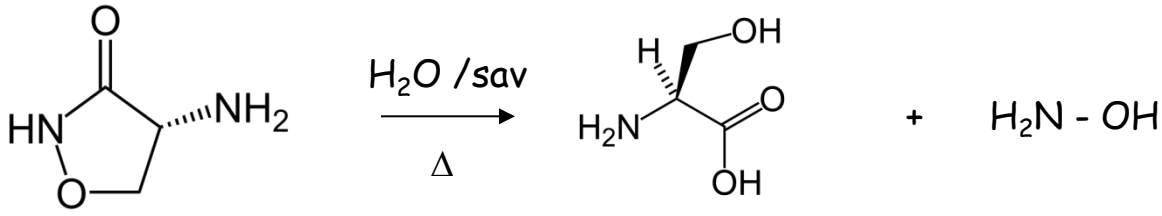
7-aminokefalosporinsac, R = - O-$COCH_3$
7-amino-3-dezacetoxisporánsav, R = - H



cefamandol

Aminosav és peptid tipusú antibiotikumok

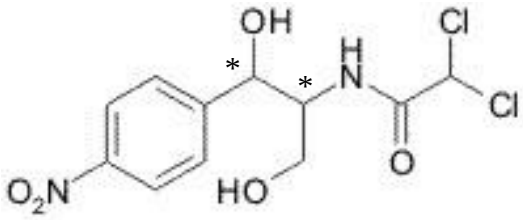
Streptomyces törzsek termelik



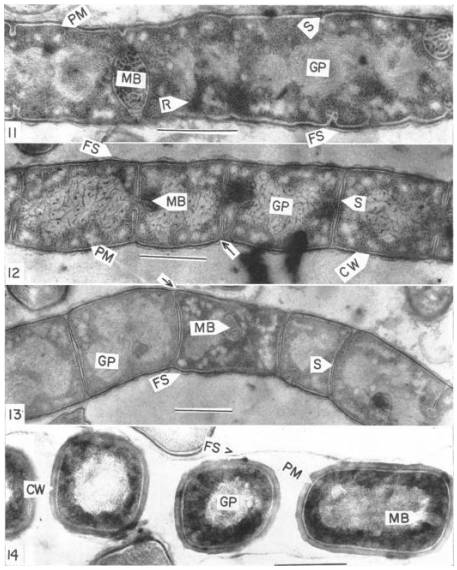
cikloszerin (1955)
((R)-4-amino-1,2-oxazolidin-3-on)

L-szerin

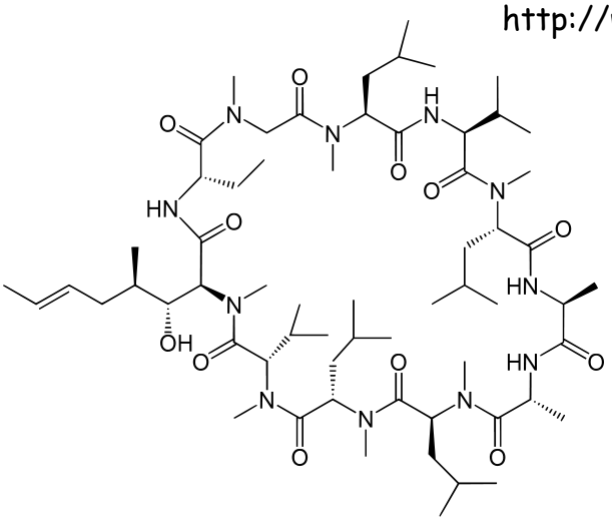
hidroxilamin



klóramfenikol (1947)
((R)-4-amino-1,2-oxazolidin-3-on)



http://www.ncbi.nlm.nih.gov/pmc/articles/PMC315171/



Tolypocladium inflatum (gomba)

Ciklosporin-A (1972)

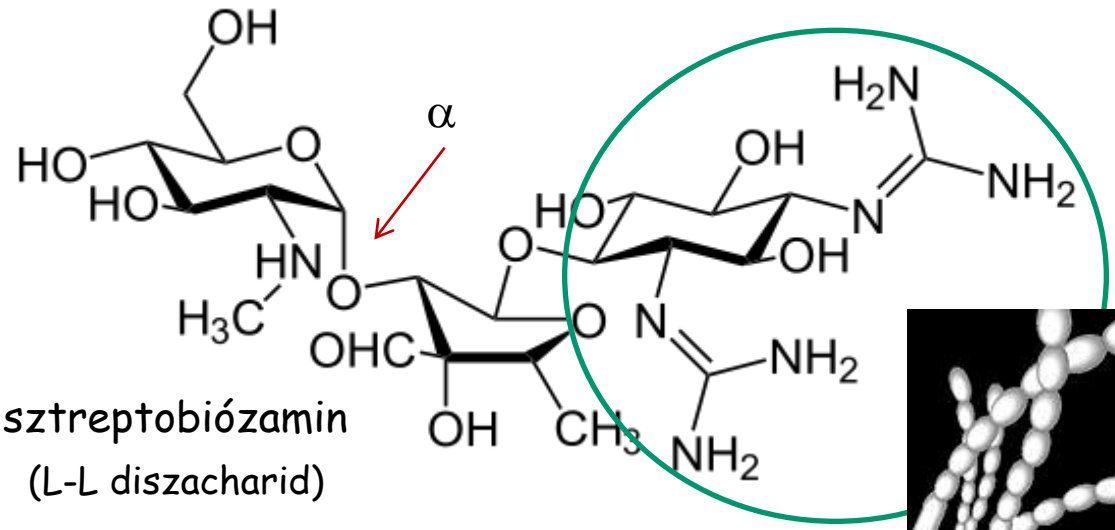
11 aminosav

Immunszuppresszáns:
első transzplantáció
1980 március, USA

Glikozid tipusú antibiotikumok

Aminoglikozidok (fehérjeszintézis gátlás)

sztreptidin
(ciklohexán váz)

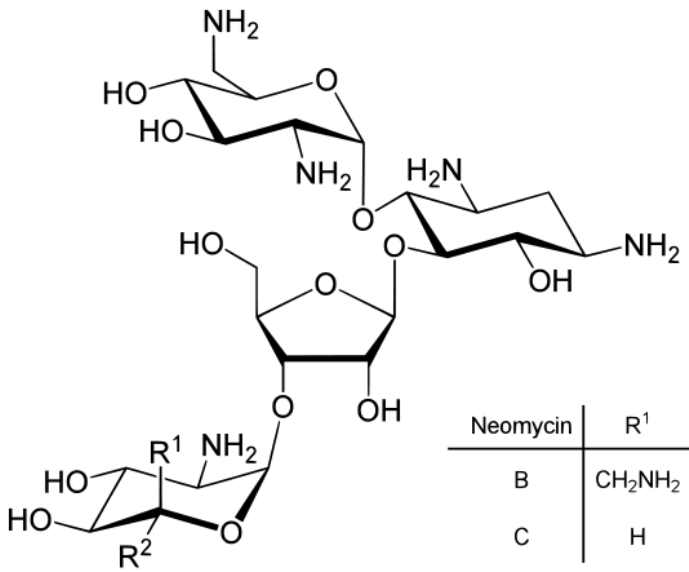


sztreptobiózamin
(L-L diszacharid)

Sztreptomicin

Streptomyces griseus

Izolálás: A. Schatz, 1943 (diák), Rutgers University
Hatás: anti-TB, peszticid, fungicid



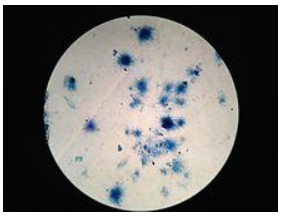
Neomycin	R^1	R^2
B	CH_2NH_2	H
C	H	CH_2NH_2

Neomicin

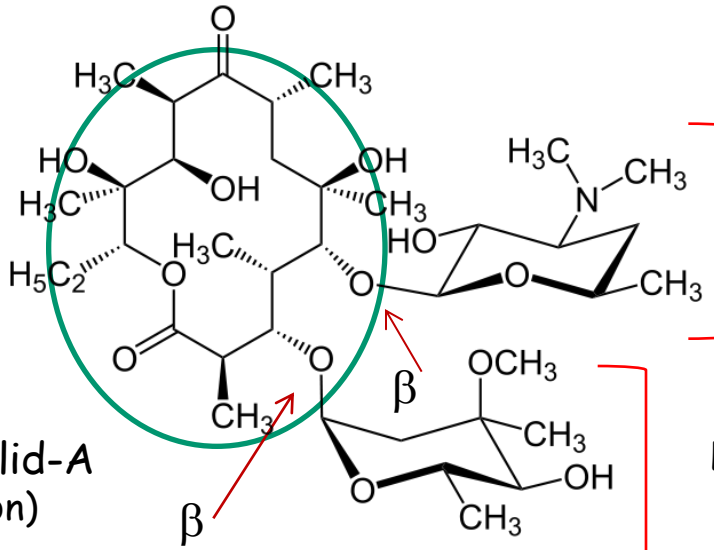
Izolálás: S. Waksman, 1949
H. Lechevalier (diák)
Rutgers University
Hatás: helyi fertőzések

Glikozid tipusú antibiotikumok

Makrolid vegyületek (makrociklusos lakton)



Saccharopolyspora erythraea



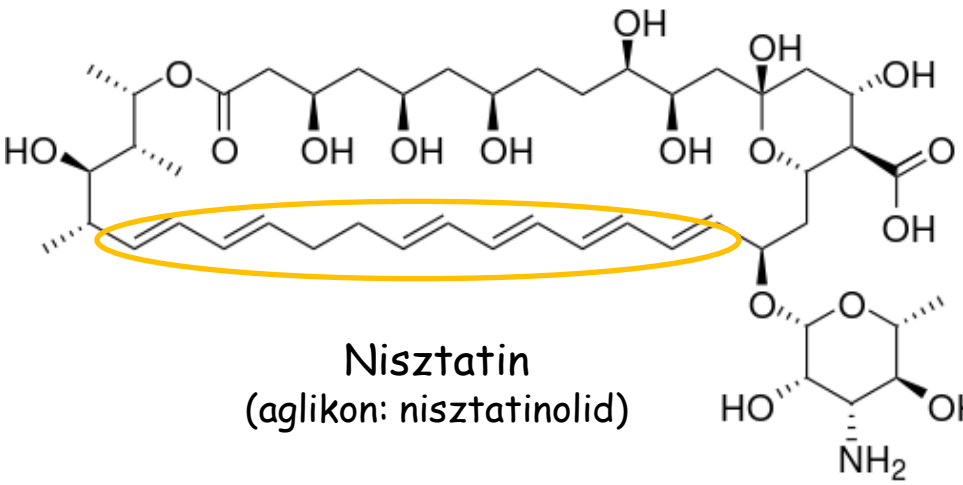
eritronolid-A
(aglikon)

Eritromicin - A

Izolálás: J. M. McGuire, 1949 (diák), Eli Lilly
Szintézis: R. B. Woodward, 1981

Polién makrolid vegyületek (gyűrűs ketál)

38 tagú aglikon



Nisztatin
(aglikon: nisztatinolid)

D-mikózamin

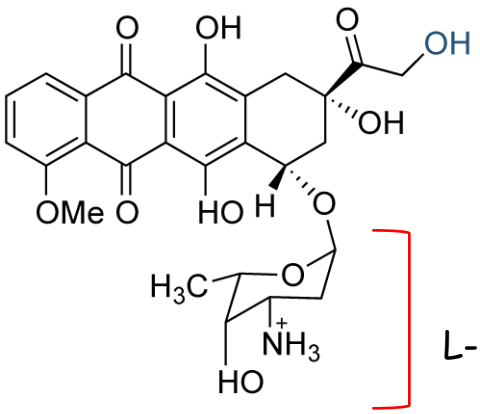
Streptomyces noursei

Izolálás: R. Fuller Brown és E. Lee Hazen, 1950
Hatás: gomba ellenes (Candida)

Policiklusos antibiotikumok

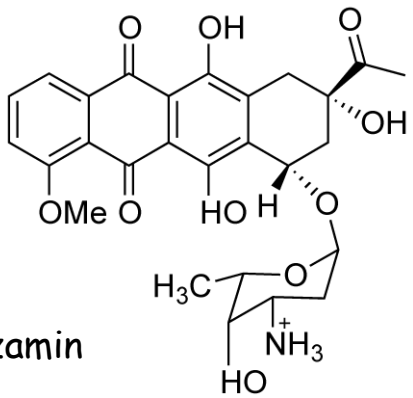
Antraciklin-glikozidok

Streptomyces peucetius



doxorubicin (adriamycin)

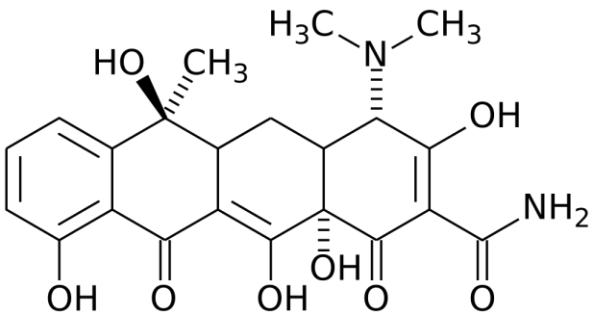
L-daunózamin



daunorubicin (daunomycin)

Tetraciklin (nem-glikozid)

Streptomyces



5-oxitetraciklin (amfoter)

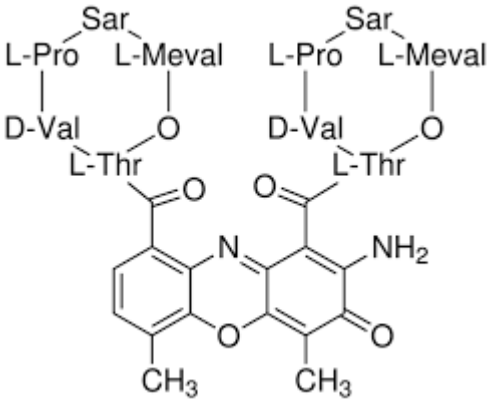
Izolálás: Benjamin M. Duggar, Lederle Labs, 1945
Szerkezet: 8 tagú team, 1952
Hatás: széles spektrum, kolera

Tumorellenes hatású antibiotikumok

Policiklusos antibiotikumok

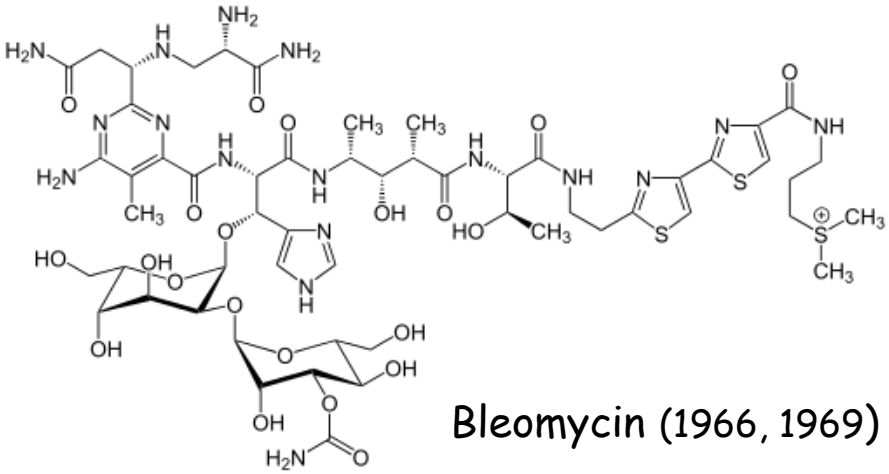
Selman A.Waksman, (1940)
(első mikrobiális , FDA 1964)

Streptomyces



Actinomycin D

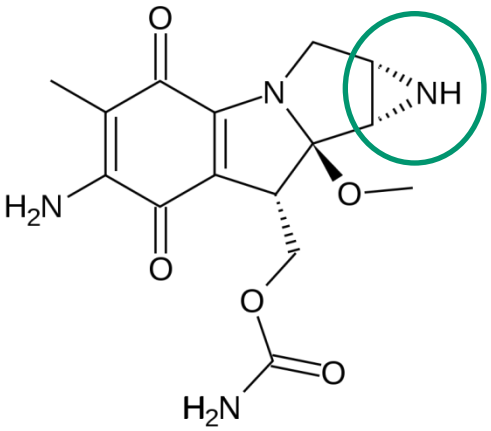
Peptid (glikozid) antibiotikum



Bleomycin (1966, 1969)

Streptomyces verticillus

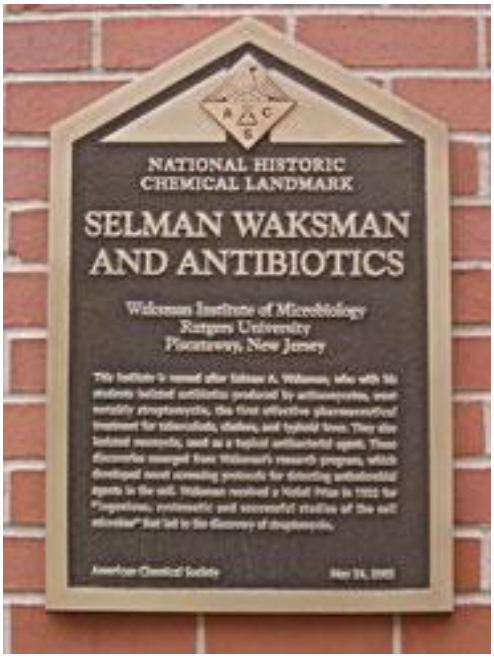
Aziridin gyűrű tartalmú antibiotikum



Mitomycin *C*
Streptomyces lavendulae

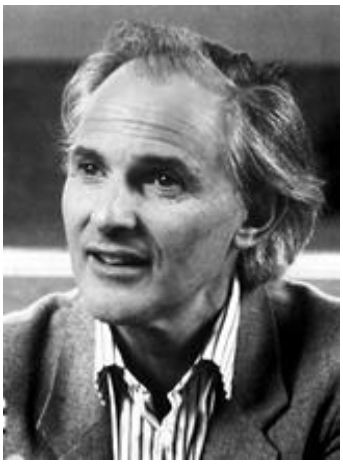
Továbbá:
puromycin
idarubicin,
epirubicin,
pirarubicin,
zorubicin,
aclarubicin,
carminomycin

Selman A. Waksman
(1888 – 1973), 15 vegyület



1952: orvosi Nobel díj
in recognition "for his discovery of "streptomycin,
the first antibiotic active against tuberculosis."

Waksman Institute of Microbiology
State University of New Jersey, Rutgers



"My advice is

to do something which interests you or which you enjoy (though I am not sure about the definition of enjoyment) and do it to the absolute best of your ability….
With this recipe, whatever your limitations, you will almost certainly still do better than anyone else. Having chosen something worth doing, never give up and try not to let anyone down."

Harold W. Kroto

From Les Prix Nobel 1996