

# 14. Előadás

## Flavonoidok , antibiotikumok

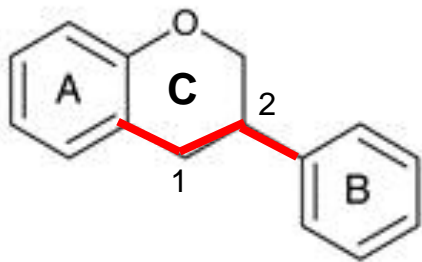
# Flavonoidok

(flavon, „flavus” latin, sárga)

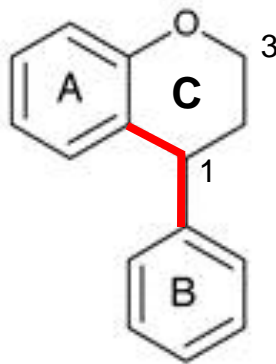


Sárga primula

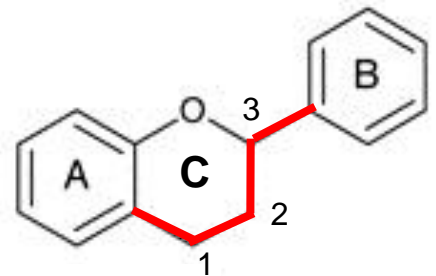
➤ 4000,  
rügy, friss hajtás,  
virág, termés



izoflavonoidváz  
(1,2-difenilpropán)

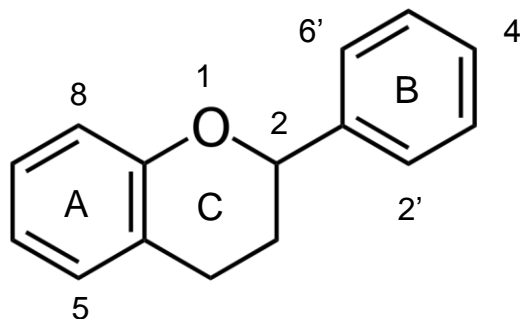


neoflavonoidváz  
(1,1-difenilpropán)



flavonoidváz  
(1,3-difenilpropán)

## Nomenklatúra

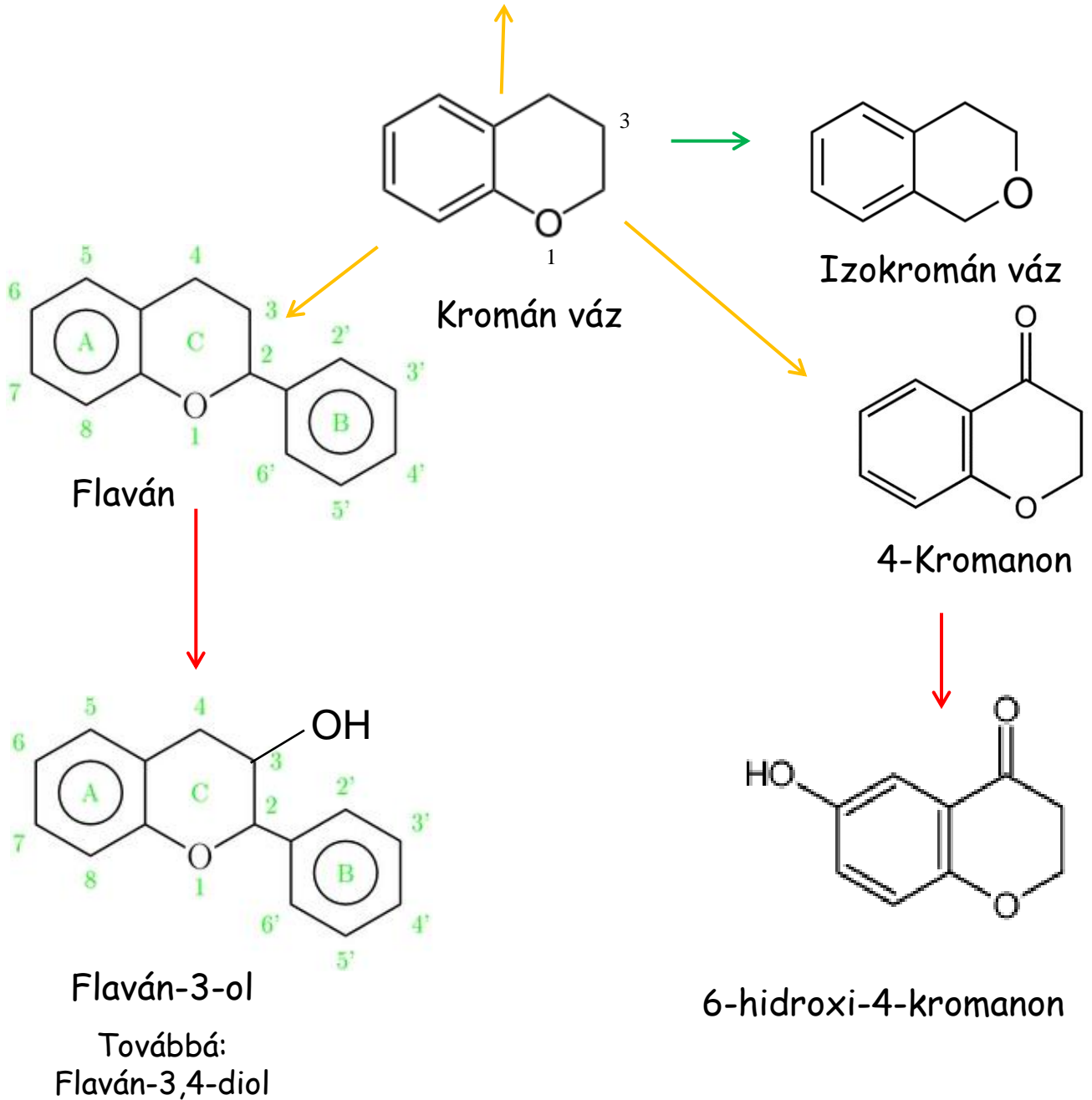
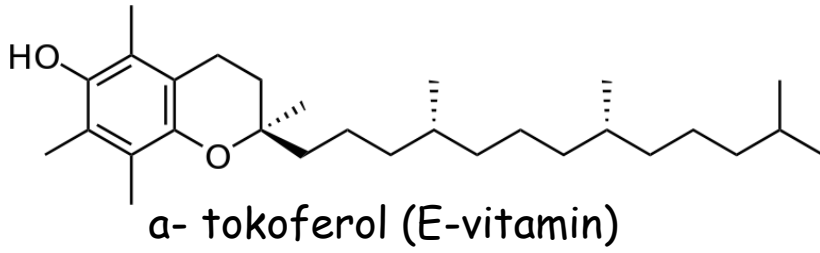


Flaván váz

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

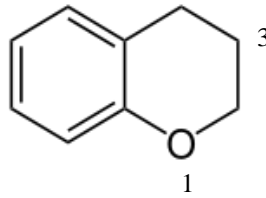
# Flavonoidok

## Kromán és származékai

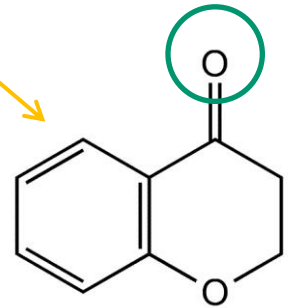


# Flavonoidok

## Kromon és származékai

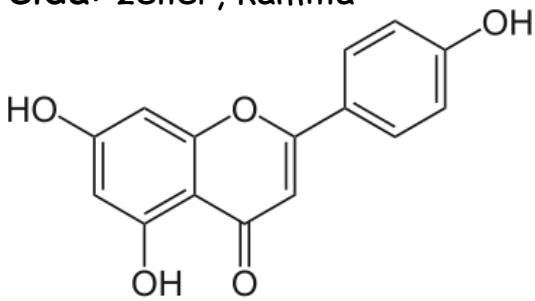


Kromán váz



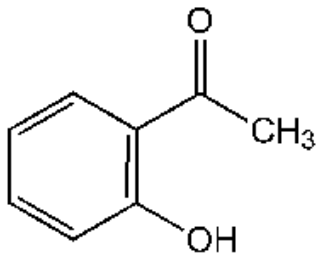
4-Kromanon

Példa: zeller, kamilla

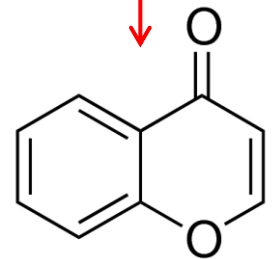
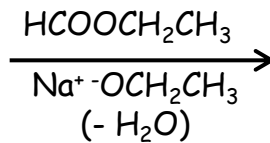


Apigenin (aglikon)

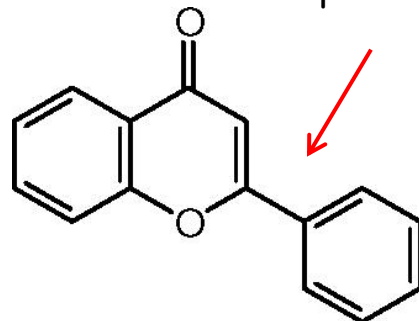
Claisen-kondenzáció



2-Hidroxiacetofenon



4-Kromon  
(halványsárga,  
op. 55-60°C)

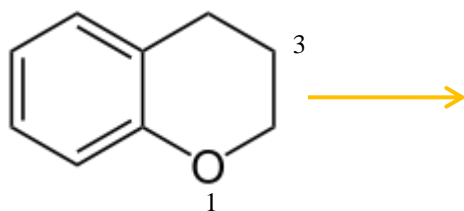


Flavon (2-fenil-kromon)

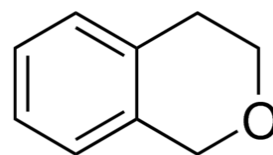
Továbbá: Izoflavon (3-fenil-kromon)

# Flavonoidok

## Kumarin és származékai

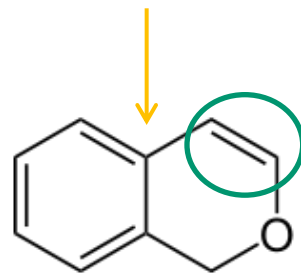


Kromán váz



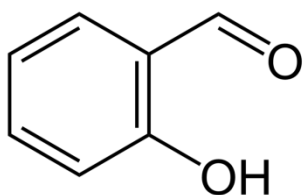
Izokromán váz

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

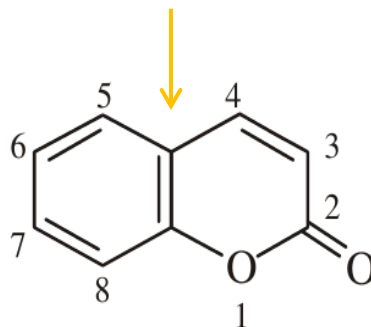
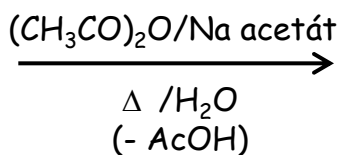


1H-isokromén  
(1H-2-benzopirán)

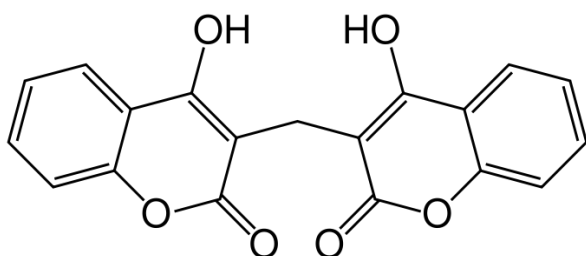
Dikumarol: izolálás (széna) 1940,  
antikoaguláns, (warfarin)  
antibakteriális (pl. lépfene)



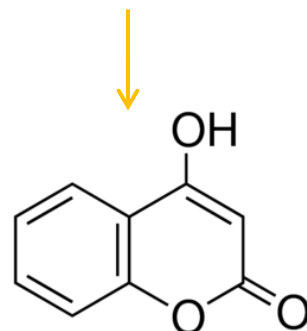
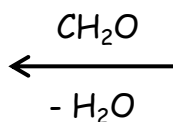
Szalicilaldehid



Kumarin

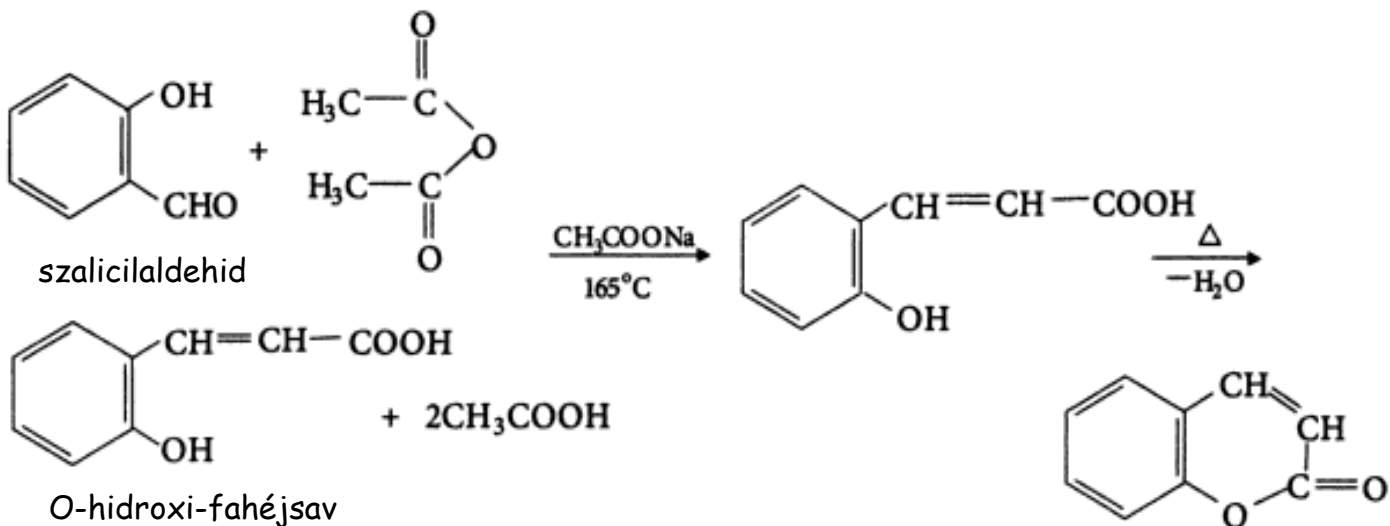


Dikumarol



4-hidroxikumarin

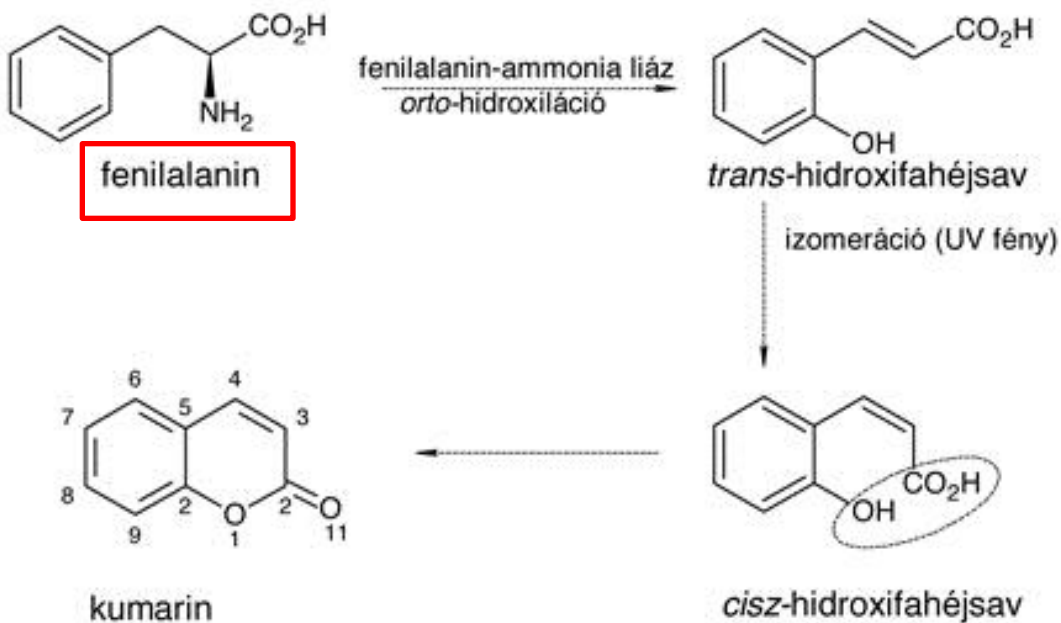
# Perkin-féle kumarin szintézis



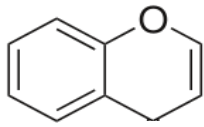
*Dipteryx odorata* (Tonka beans)

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

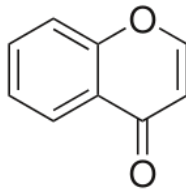
## Kumarin képződése



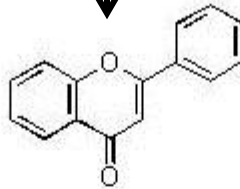
# A flavonoidok: áttekintés



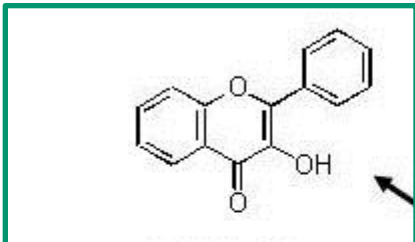
4H-Kromén



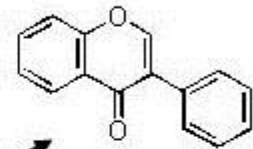
4-Kromon



Flavon (2-fenilkromon)

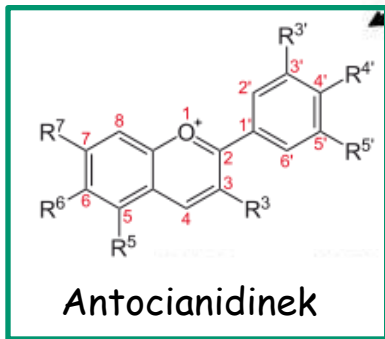
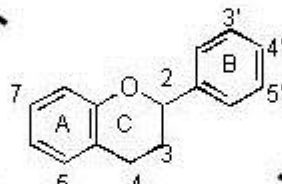


Flavonol  
(2-fenil-3-hidroxikromon)

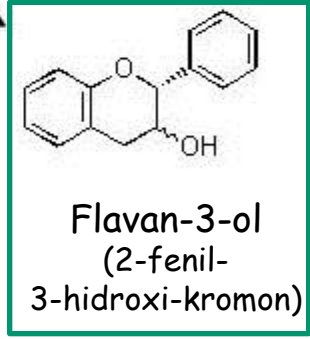


Izoflavon  
(3-fenilkromon)

1,3-difenilpropán (váz)

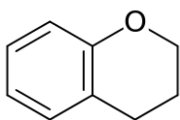


Antocianidinek

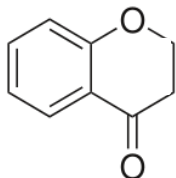
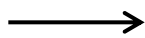


Flavan-3-ol  
(2-fenil-3-hidroxi-kromon)

Flavonon (2-fenilkromanon)



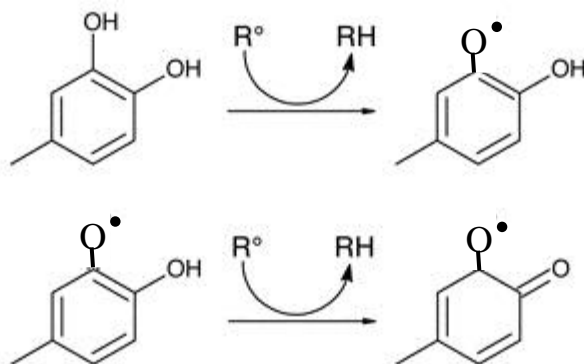
Kromán



4-Kromonon

Glikozid aglikon

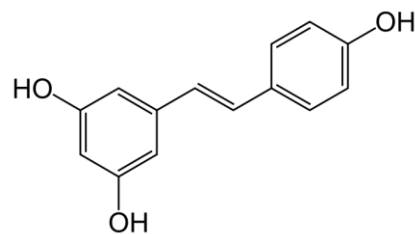
## A flavonoidok „gyökfogó” mechanizmusa



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

### Természetes antioxidánsok

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



*trans*-rezveratrol  
(NEM FLAVONOID)

Ajánlott irodalom:

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

<http://www.tankonyvtar.hu/hu/bongesztes/konyvek>



Flavonoidok , antibiotikumok

# Antibiotikumok

Definíció (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)

1.  $\beta$ (Béta)-laktám antibiotikumok
2. aminosav/peptid típusú
3. glikozid típusú
4. policiklusos
5. spirociklusos

Elnevezés:                   eredet, tulajdonság (pl. szín)

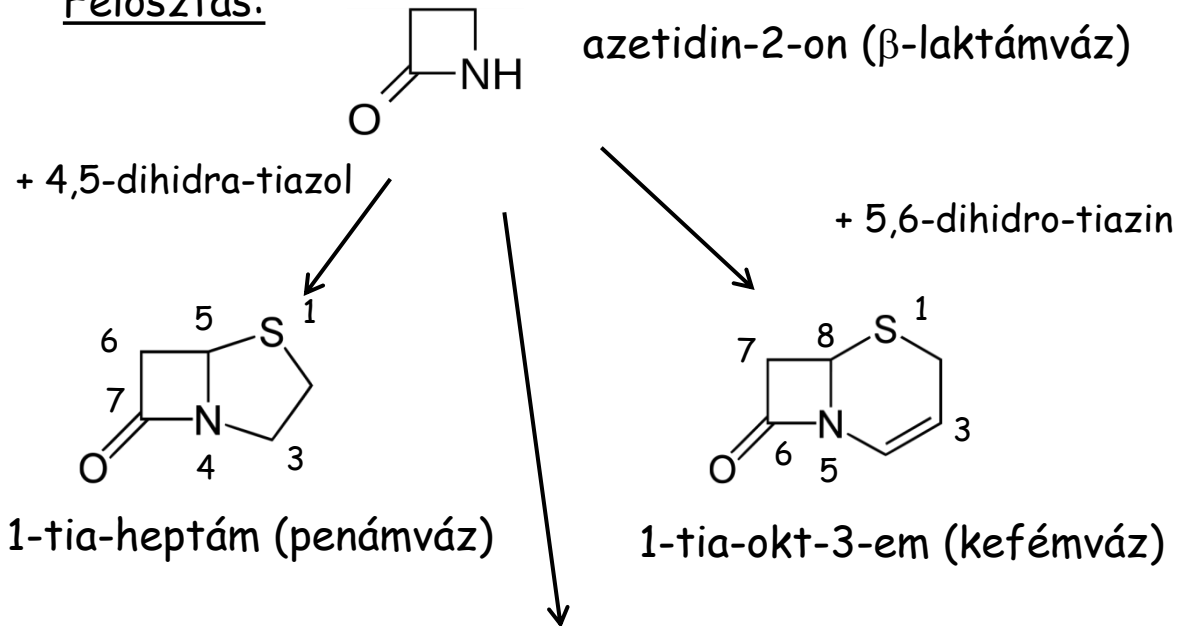
Előfordulás:               mikroorganizmusok, gombák

Felhasználás:             gyógyászat, agrárium

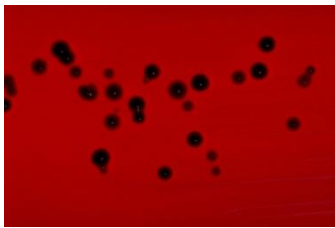
# 1. $\beta$ (Béta)-laktám antibiotikumok

(közös elem: négytagú gyűrűs savamaid)

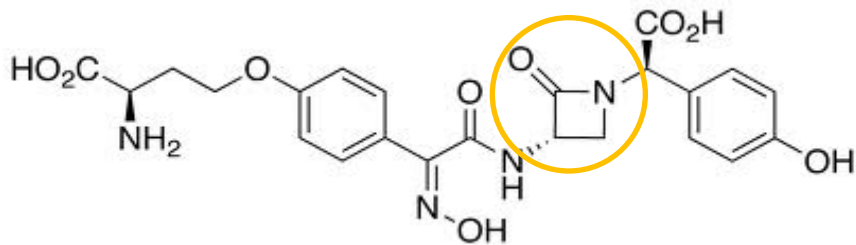
Felosztás:



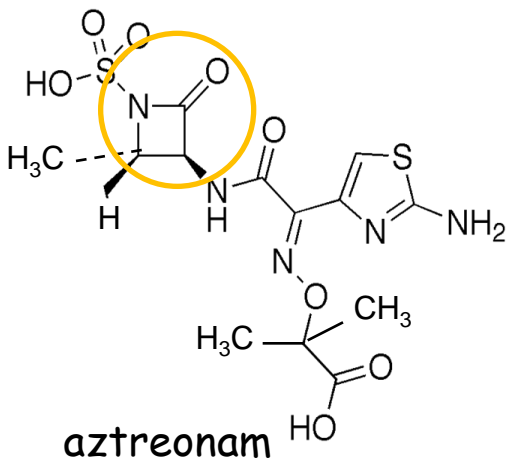
## 1.1. Monociklusos $\beta$ -laktámok (Monobaktámok)



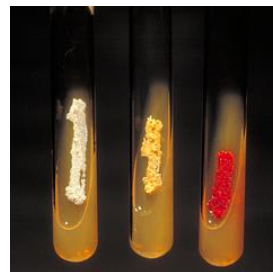
*Chromobacterium violaceum*



nocardicin A



aztreonam



*Nocardia asteroides*  
(yellow colonies)

Izolálás:  
A.H. Aoki. 1976

# 1. $\beta$ (Béta)-laktám antibiotikumok

## 1.2. Penám vázas antibiotikumok



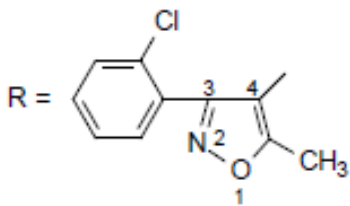
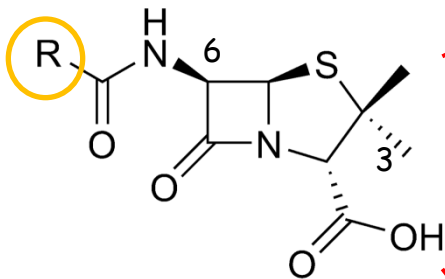
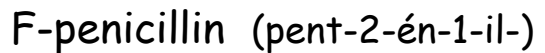
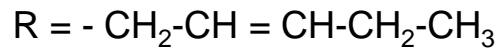
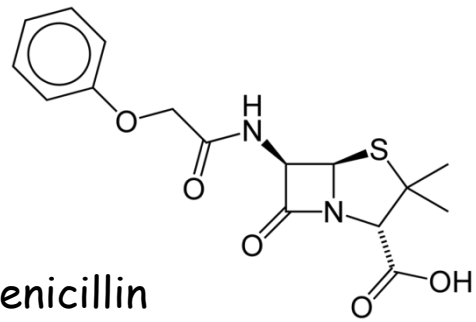
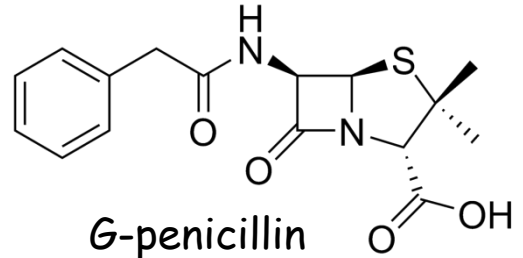
A. Fleming, E. B. Chain, H. W. Florey,  
Nobel-díj, 1945

### Penicillin (1928)

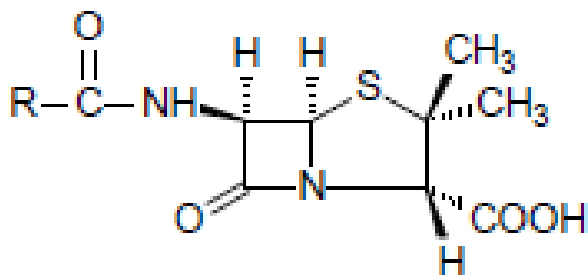
Felfedezés: Fleming  
Izolálás: Chain, Florey,  
1941



*Penicillium notatum*

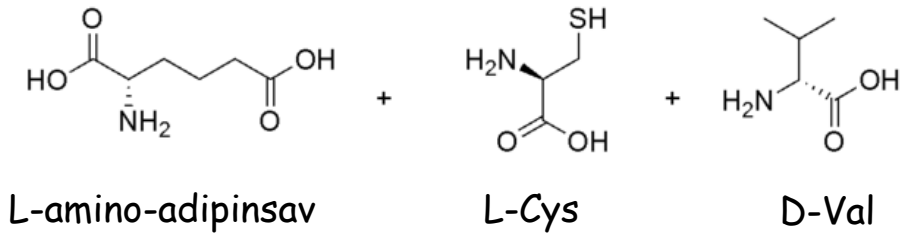


3-(2-klórfenil)-5-metiloxazolil

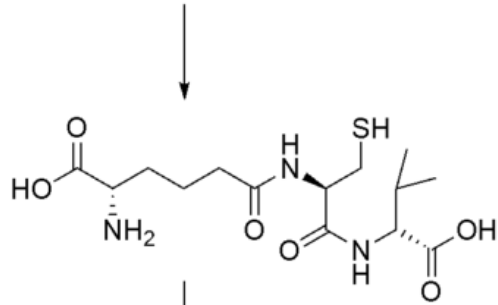


**kloxacillin**  
(félszintetikus)

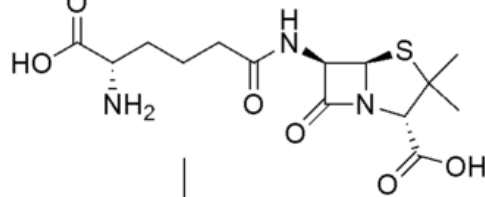
# Bioszintézis



Ala-Cys-D-Val  
tripeptid

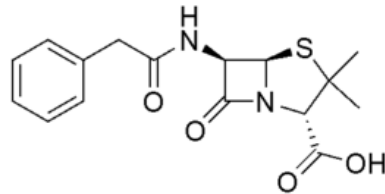


Izopenicillin N



Kefalosporin

Penicillin G



## Bioszintézis (fermentáció):



*Penicillium chrysogenum*

+ fenilecetsav = penicillin G  
+ fenoxiecetsav = penicillin V

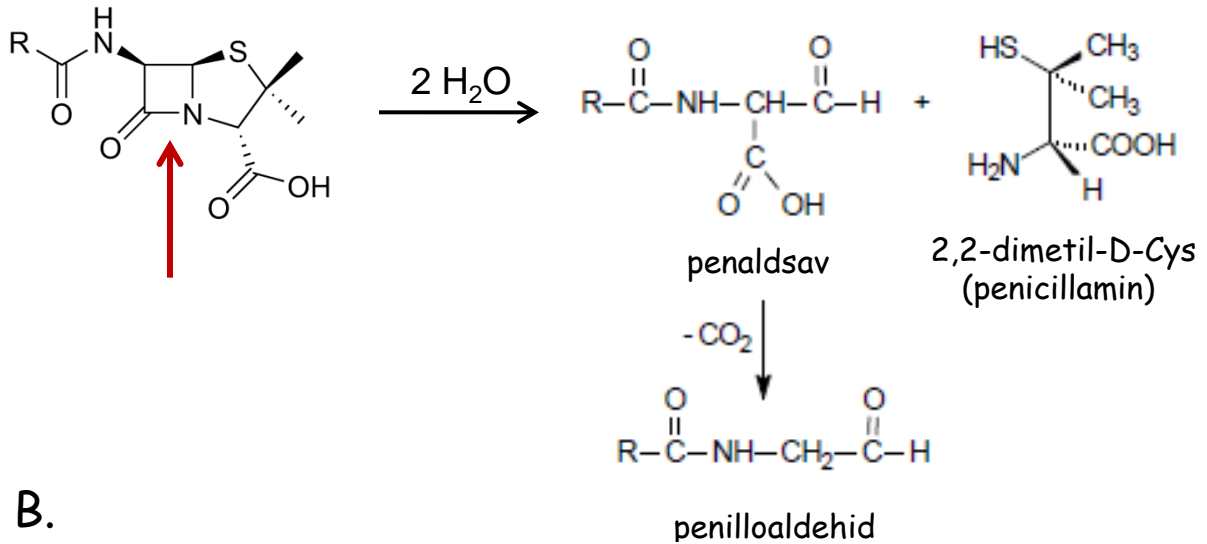
„One sometimes finds what one is not looking for.”

# 1. β(Béta)-laktám antibiotikumok

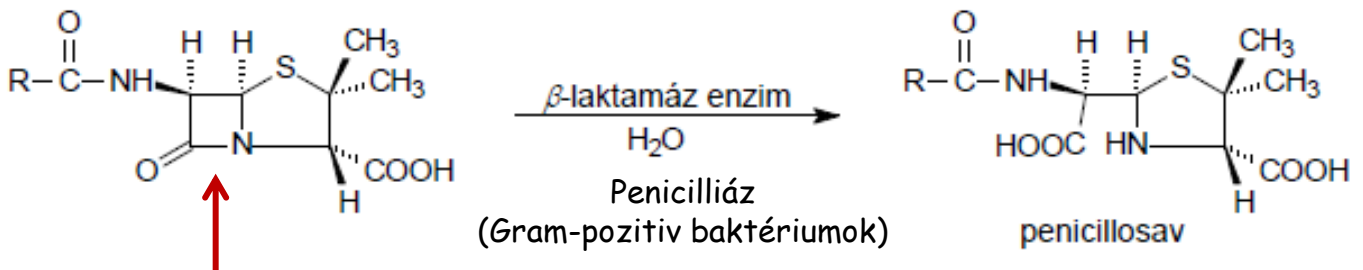
## Penicillinek

Hidrolízis, stabilitás

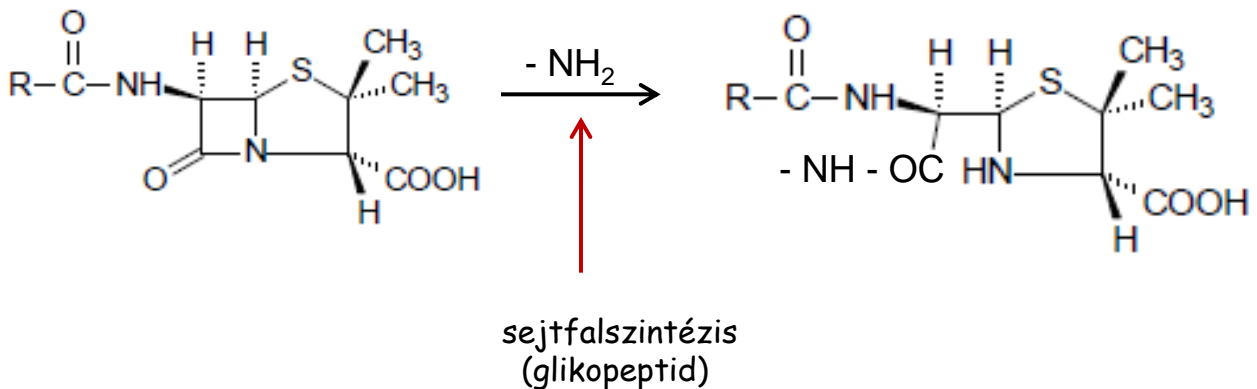
A.



B.

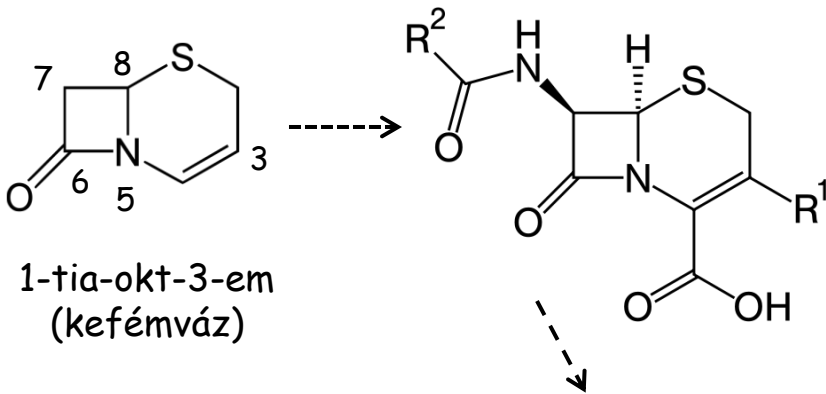


Acilezés (hatásmechanizmus)



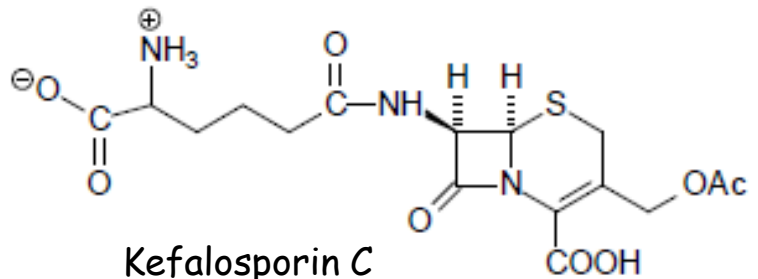
# 1. $\beta$ (Béta)-laktám antibiotikumok

## 1. 3. Kefémvázás antibiotikumok (kefalsporinok)

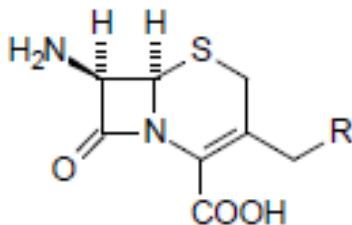
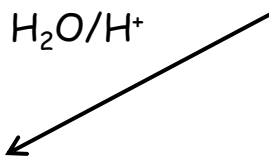


*Acremonium falciforme*  
(*Cephalosporium*)

$R^1 = -CH_2O-COCH_3$   
 $R^2 = -(CH_2)_3-CH(NH_2)-COOH$   
 acil csoport: L-amino-adipinoil



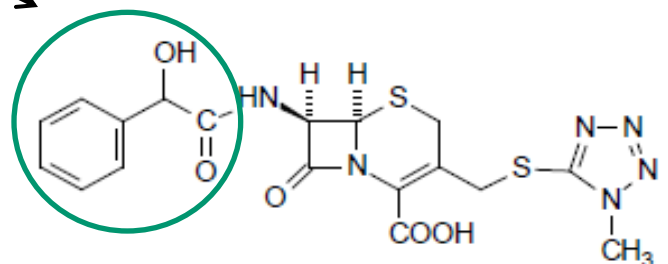
G. Brotzu, Szardínia, 1948  
 Szerkezet: E.P. Abraham, D. Hodgkin, 1961  
 Hatás: Gram pozitív és negatív  
 Ellenálló: penicillináz enzim



### Félszintetikus kefalsporinok

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

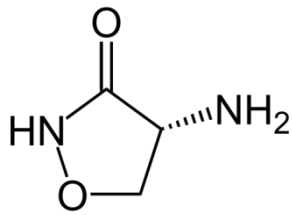
acilezés



cefamandol

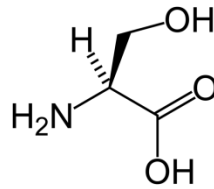
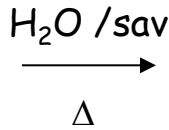
## 2. Aminosav és peptid típusú antibiotikumok

Streptomyces törzsek termelik

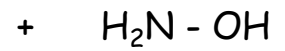


cikloszerin (1955)

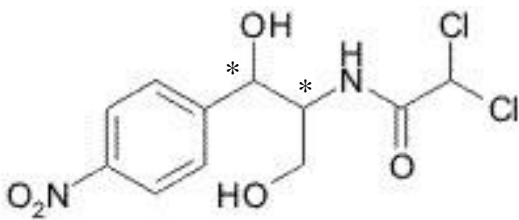
((R)-4-amino-1,2-oxazolidin-3-on)



L-szerin

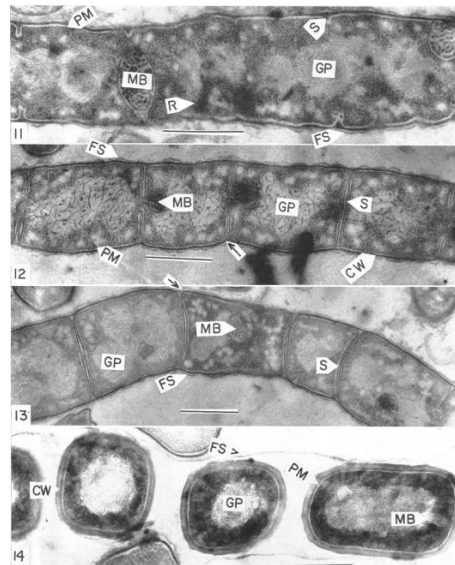


hidroxilamin



klóramfenikol (1947)

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

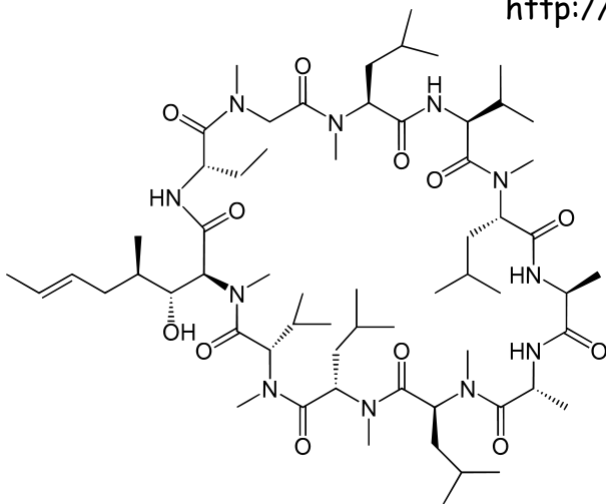


<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC315171/>

### Ciklosporin-A (1972)

11 aminosav

Immunszuppresszáns:  
első transzplantáció  
1980 március, USA



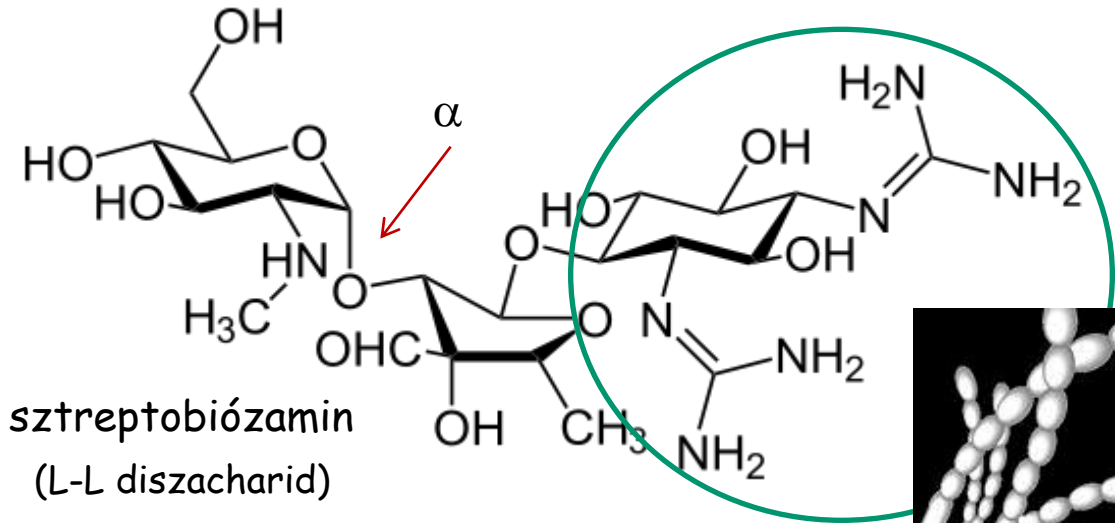
Tolyocladium inflatum (gomba)



# 3. Glikozid típusú antibiotikumok

## 3.1. Aminoglikozidok (fehérjeszintézis gátlás)

sztreptidin  
(ciklohexán váz)



*Streptomyces griseus*

Izolálás: A. Schatz, 1943 (diák), Rutgers University

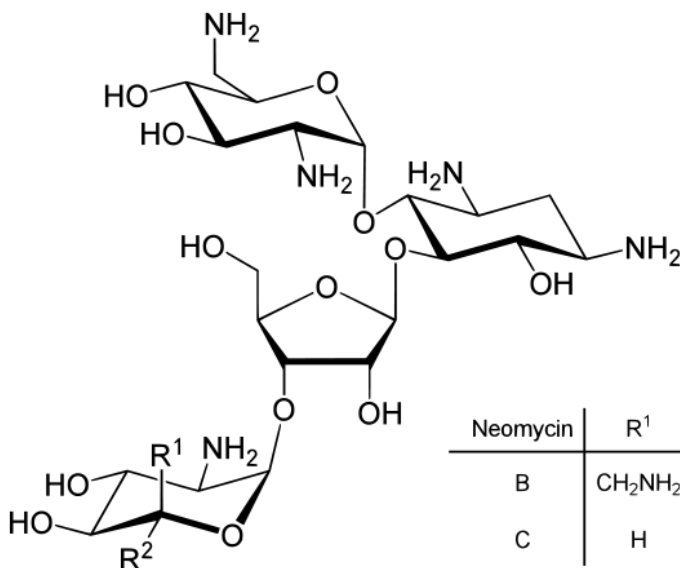
Hatás: anti-TB, peszticid, fungicid

Izolálás: S. Waksman, 1949

H. Lechevalier (diák)

Rutgers University

Hatás: helyi fertőzések

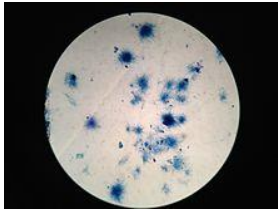


Neomycin	R <sup>1</sup>	R <sup>2</sup>
B	CH <sub>2</sub> NH <sub>2</sub>	H
C	H	CH <sub>2</sub> NH <sub>2</sub>

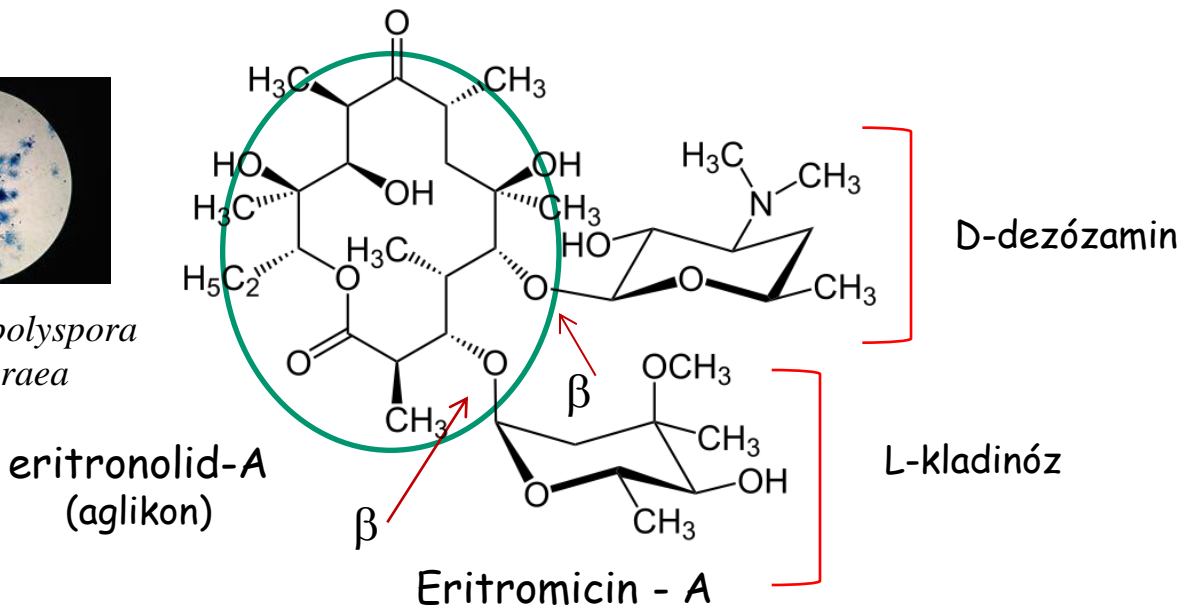
Neomycin

### 3. Glikozid típusú antibiotikumok

#### 3.2. Makrolid vegyületek (makrociklusos lakton)



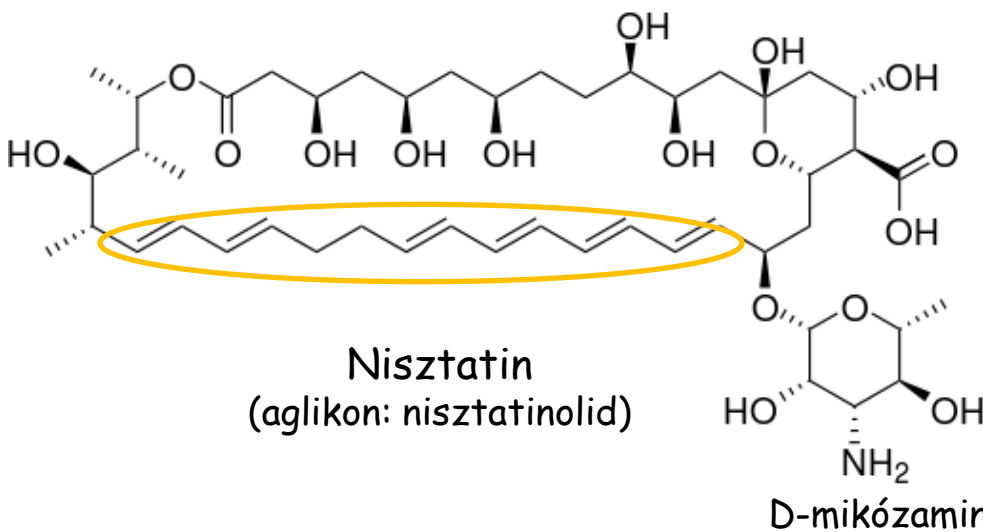
*Saccharopolyspora erythraea*



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

#### 3.3. Polién makrolid vegyületek (gyűrűs ketál)

38 tagú aglikon



*Streptomyces noursei*

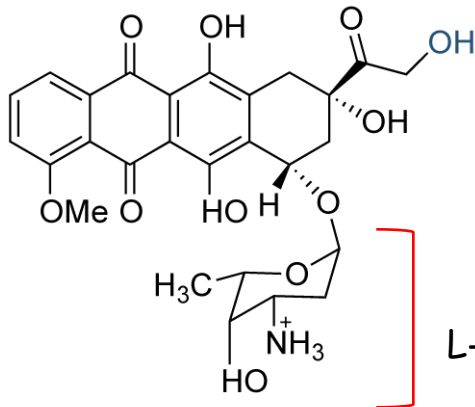
Izolálás: R. Fuller Brown és E. Lee Hazen, 1950  
Hatás: gomba ellenes (*Candida*)

# 4. Policiklusos antibiotikumok

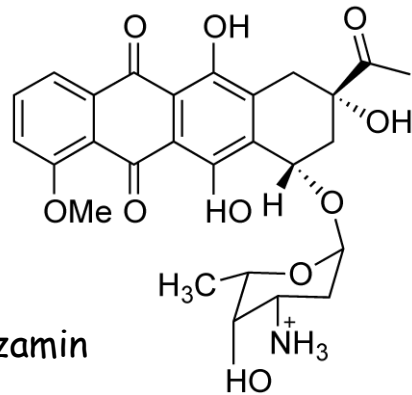
## Antraciklin-glikozidok



*Streptomyces peucetius*



doxorubicin (adriamycin)



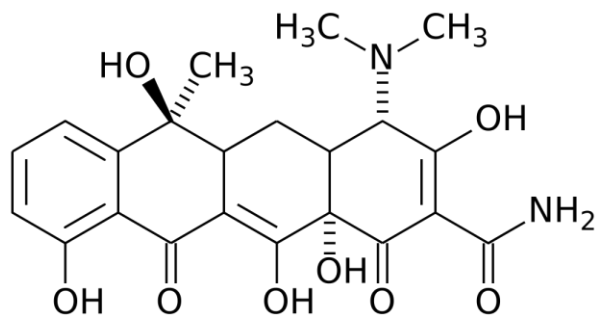
L-daunózamin

daunorubicin (daunomycin)

## Tetraciklin (nem-glikozid)



*Streptomyces*



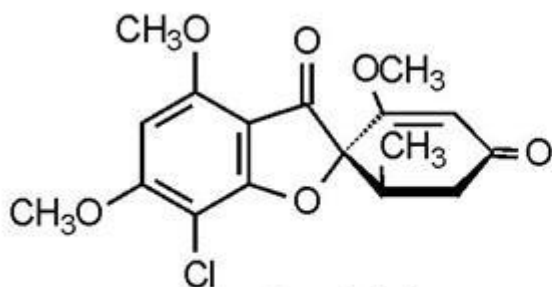
5-oxitetraciklin (amfoter)

Izolálás: Benjamin M. Duggar, Lederle Labs, 1945

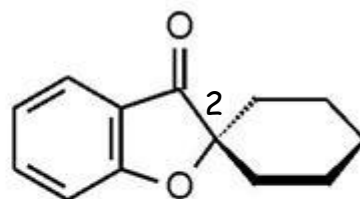
Szerkezet: 8 tagú team, 1952

Hatás: széles spektrum, kolera

## 5. Spirociklusos antibiotikumok



grizeofulvin



grizánváz

*Grizeofulvin*: gombaellenes hatású (*Penicillium grizeofulvum*)

Spiroszerkezet:

3-kumara-non gyűrűhöz 2-helyzetben gyűrű kapcsolódik

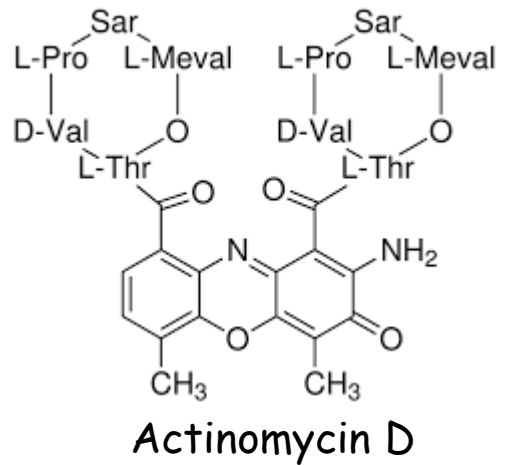
*Grizeofulvin*: az aromás gyűrűhöz klóratom is kapcsolódik. (ritka)

# Tumorellenes hatású antibiotikumok

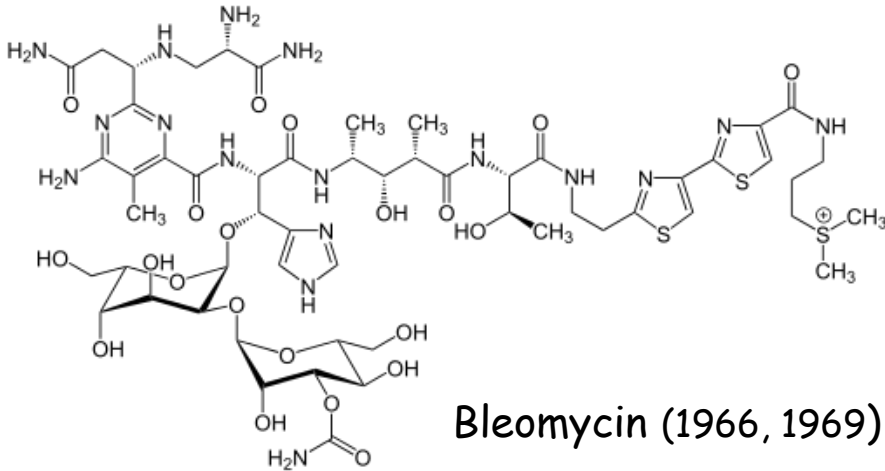
## Policiklusos antibiotikumok

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

*Streptomyces*



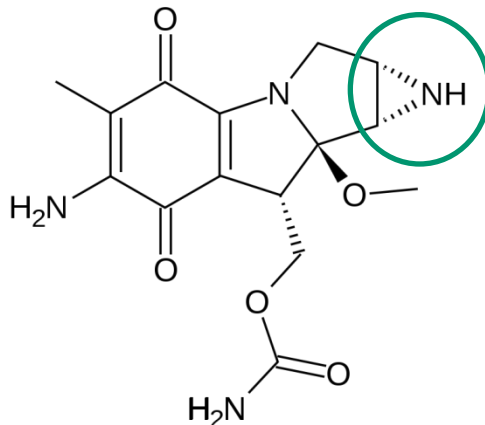
## Peptid (glikozid) antibiotikum



*Streptomyces verticillus*

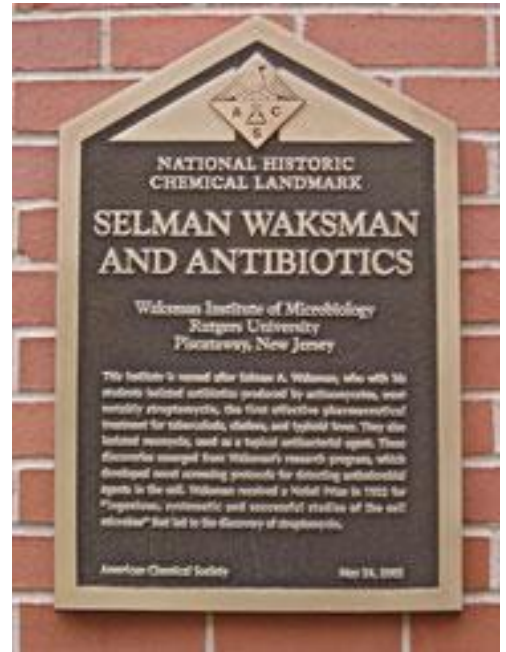
## Aziridin gyűrű tartalmú antibiotikum

Mitomycin C  
*Streptomyces lavendulae*



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

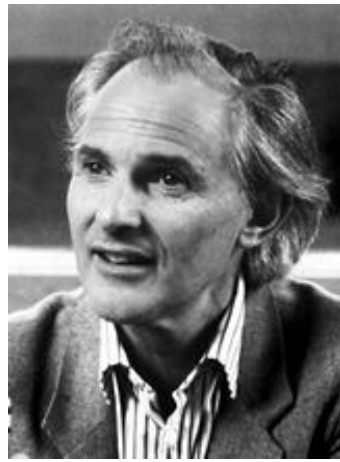
Selman A. Waksman  
(1888 - 1973), 15 vegyület



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

