Laxatives (or cathartics)
= drugs used in treatment of constipation or to empty bowels for a medical reason

Classification of laxatives in accordance with mechanism and site of action

1. Osmotically acting laxatives (poorly absorbable salts, oligosaccharides, sugar alcohols)
2. Compounds ↓ resorption of Na^+ in large intestine ⇒ accumulation of water therein (castor oil *Oleum ricini,* anthraglycosides, triarylmethane derivatives)
3. Softening compounds (liquid paraffin)
4. Swelling (slime forming) compounds –non-absorbable polysaccharides (linen seed *Semen lini,* wheat bran, methylcelullose)

General problems of laxatives

- possibility of addiction, necessity of chronic administration
- loss of electrolytes, namely K^+ (important except others for motility of intestines)

1. Osmotic laxatives

- cause osmotic accumulation of water in large intestine

Poorly absorbable inorganic salts

$MgSO_4$. 7 H_2O „bitter salt“

Sennagran® gra (+ laxative herbs)

Na_2SO_4.10 H_2O „Glauber salt“

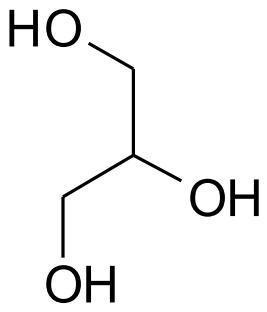
Fortrans® plv.

- also *magistraliter* preparations and mineral waters

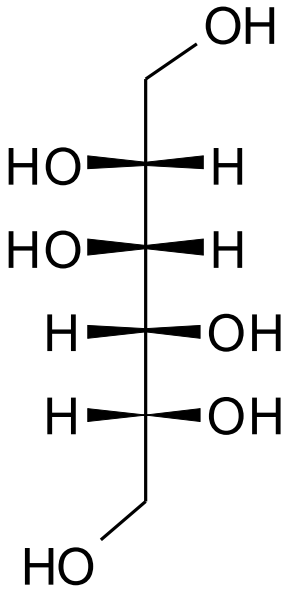
1. **Osmotic laxatives** – continued

Sugar alcohols

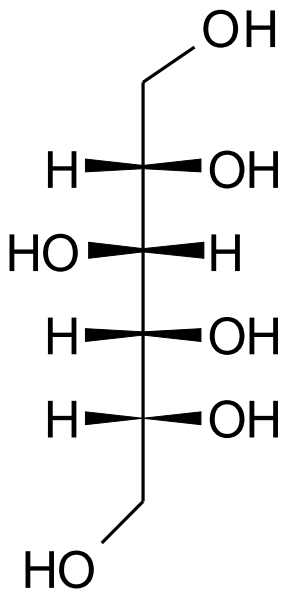
- aplication *p.o.* or *p.r.*



glycerol
glycerine suppositories
Suppositoria glycerini

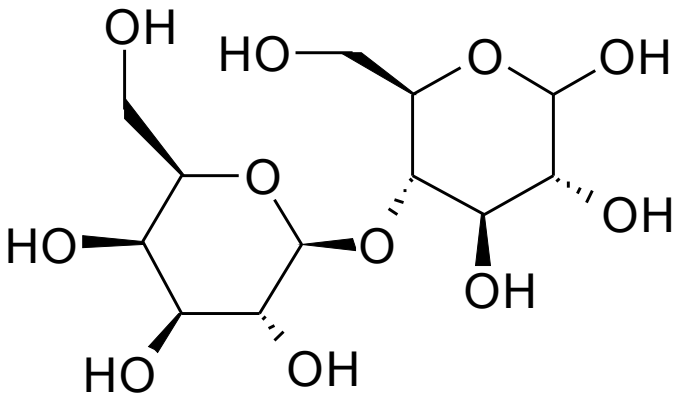


D-mannitol

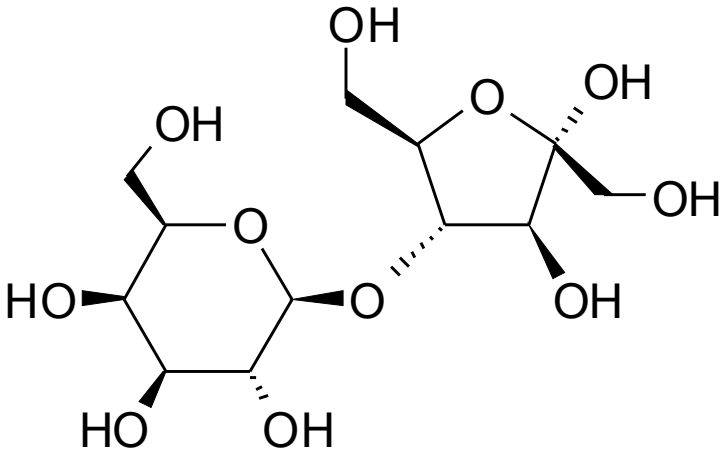


D-sorbitol
syn. **D-glucitol**
Yal® rct. sol.

1. **Osmotic laxatives** – continued
Oligosaccharides



lactose
milk sugar
4-O-β-D-galactopyranosyl-D-glucose

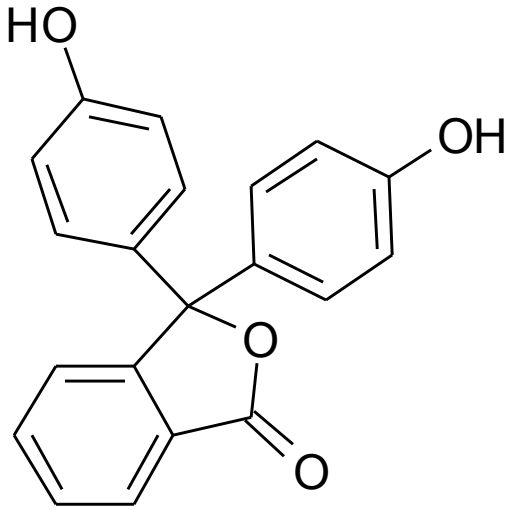


lactulose
4-O-β-D-galactopyranosyl-D-fructose
•not absorbed, human has no enzyme for cleavage of it into monosaccharides
•chronic constipation
Duplalac® sir.

2. Compounds ↓ resorption of Na^+ in large intestine

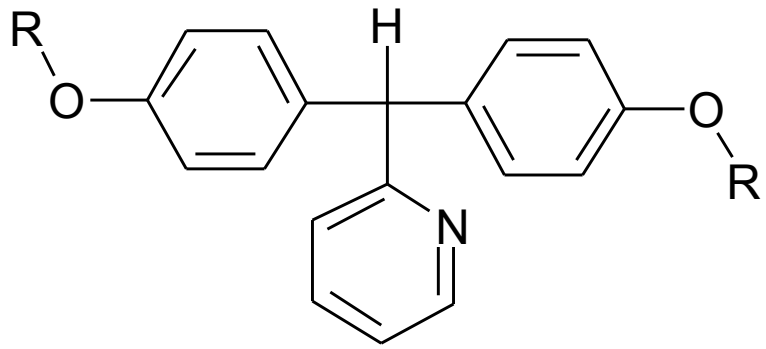
Triarylmethane derivatives

•direct interaction with Auerbach´s (or myenteric) plexus is presumed



phenolphthalein

~~Confetto falqui®~~ (+ *Pruni fructus* = dried plums as the source of K^+)



R = $-COCH_3$ **bisacodyl**

Fenolax® tbl. obd., Dulcolax ® tbl. , Stadalax ® tbl. obd.

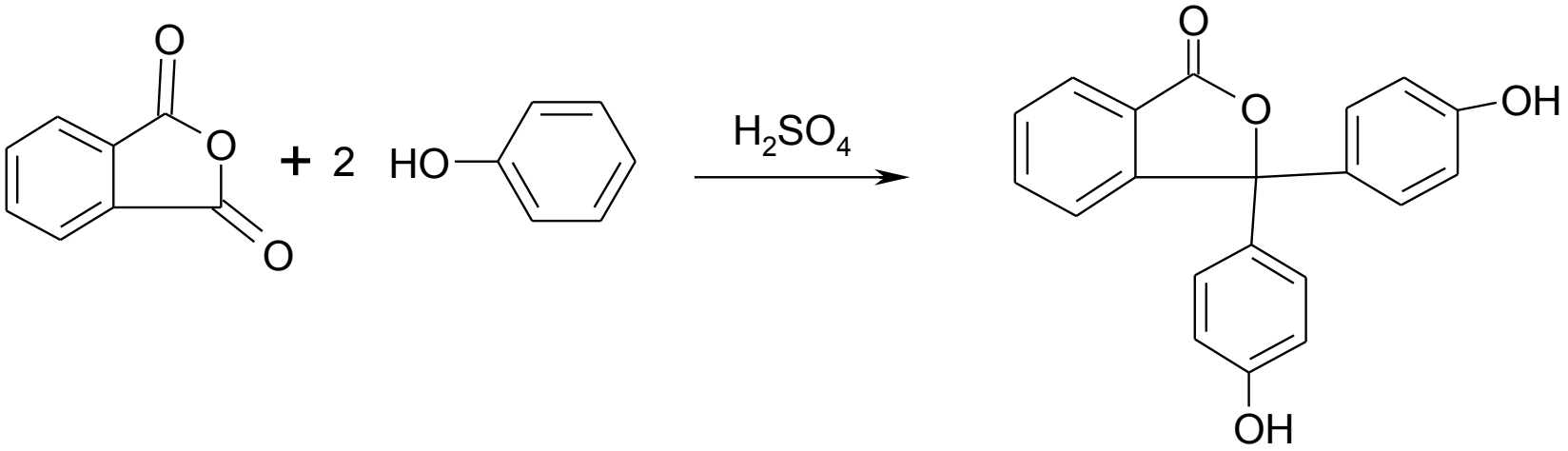
R = $-SO_3Na$ **sodium picosulfate**

~~Darmol® past.~~

•faster onset of action

•both compounds are prodrugs; the compound with 2 phenolic groups is active

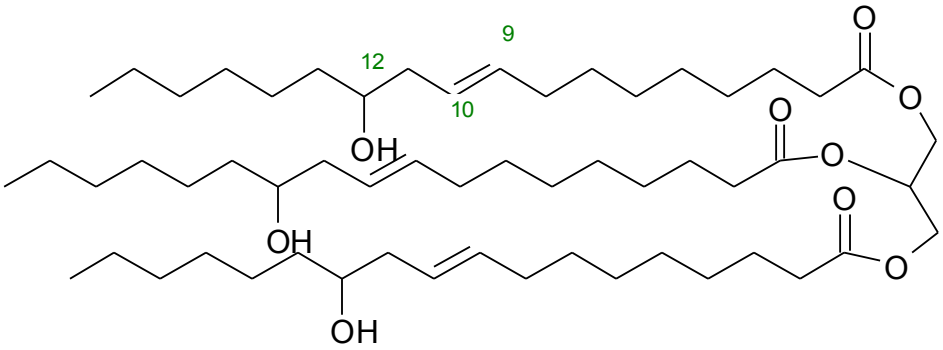
Synthesis of phenolphthalein



3,3-bis(4-hydroxyphenyl)benzo[c]furane-1(3*H*)-on

phenolphthalein

Castor oil

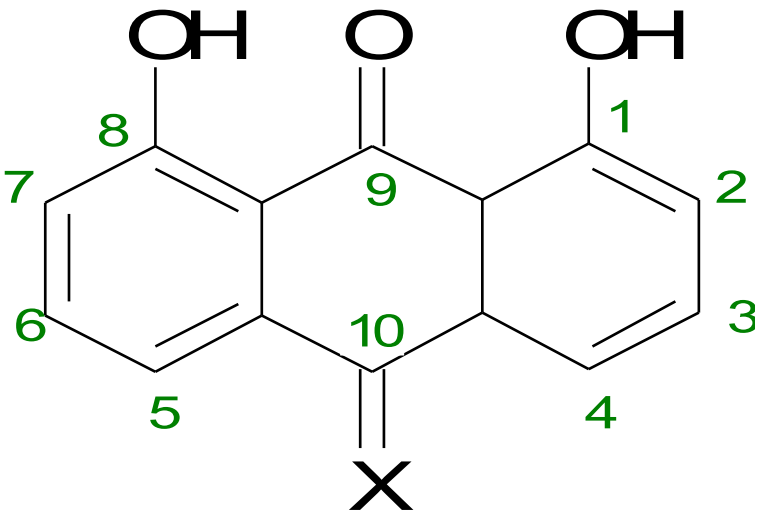


- *Ricini oleum virginale PhEur*
- oil obtained from seeds of *Ricinus communis*
- mainly glycerol triester with ricinoleic acid (85 – 92 %)

Anthraglycosides

•aglycones based on an anthrone or or anthraquinone skeleton of plant origin (*Aloe, Rheum, Cassia, Frangula ...)*

•saccharide: mostly glucose; both C-O and C-C glycosides



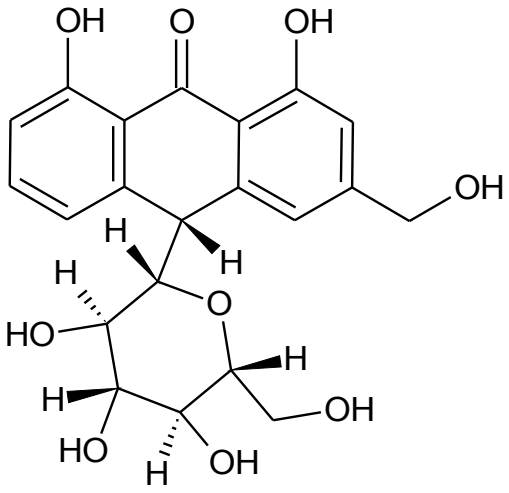
•X = H_2 **1,8-dihydroxyanthrone** = 1,8-dihydroxy-4a,10-dihydro-9a*H*-anthracene-9-on

•linking of two molecules in positions 10 and 10´leads to tetrahydroxydianthrones

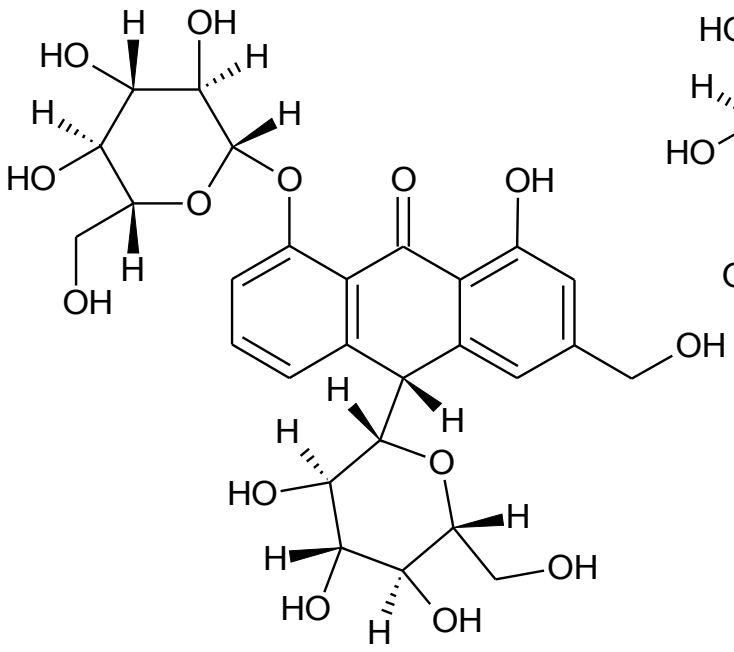
X = O **1,8-dihydroxyanthraquinone** **=** 1,8-dihydroxy-4a,9a-dihydroanthraquinone

• **-OH in positions 1 and 8 are necessary for the activity, they can be present also in other positions**

1,8-dihydroxyanthrone derivatives

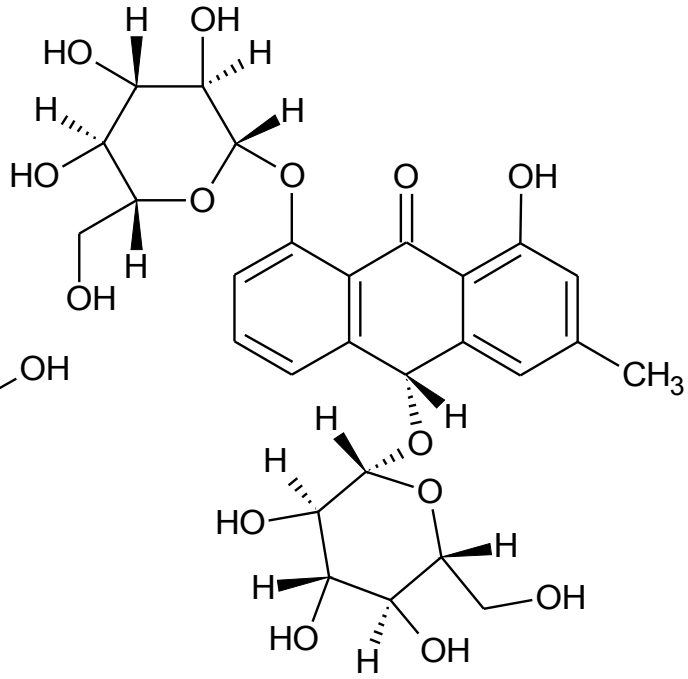


aloin
C-C glycoside



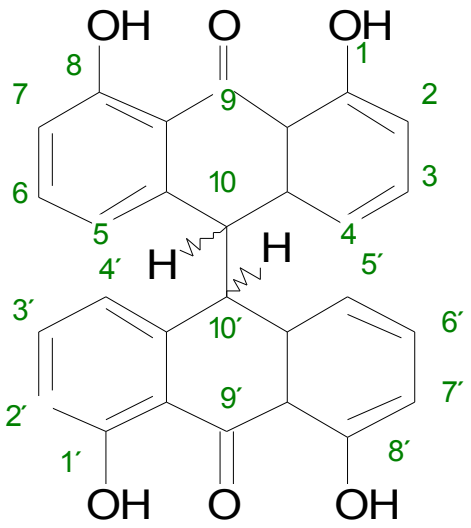
cascaroside D

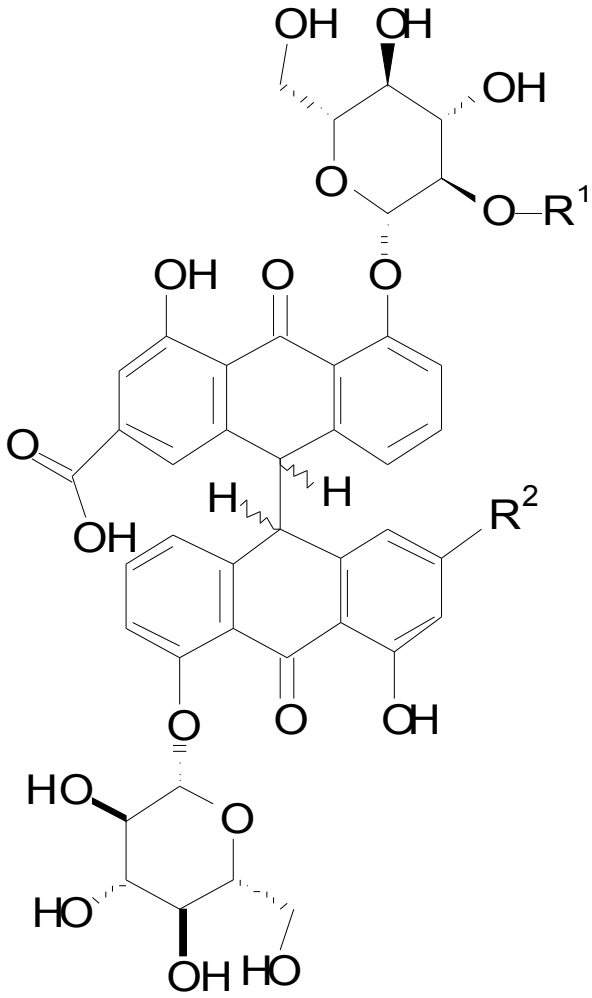
from *Rhamnus purshianus*
Krenn L. et al., Chem. Pharm.Bull.52**,** 391 (2004)



from *Rheum emodi*
Manitto P. et al.,**,** **J**.Chem. Soc. Perkin **14**, 1577(1993)

Tetrahydroxydianthrone and its derivatives





R^1= H, R^2= COOH, 10R, 10´R
sennoside A

R^1= H, R^2= COOH, 10R, 10´S
sennoside B

R^1= H, R^2= CH_2OH, 10R, 10´R

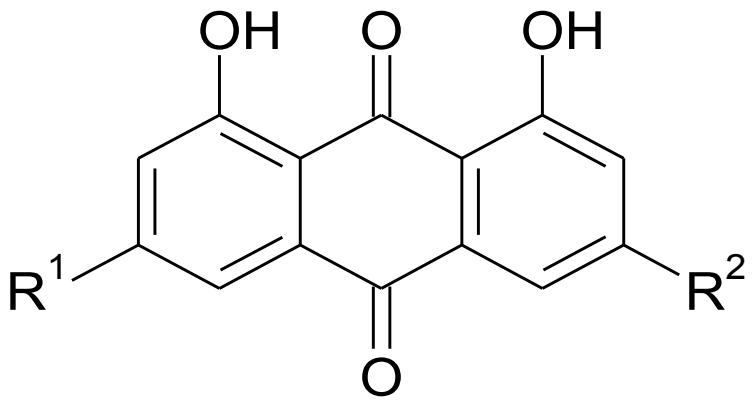
sennoside C

R^1= OCCOOH, R^2= COOH, 10R, 10´R
sennoside E

Eucarbon ® tbl.

1,8-dihydroxyanthraquinone derivatives

•aglycones, glucose bound predominantly through a phenolic hydroxyl is the most frequent sugar component



R^1	R^2		
H	CH_3	**chrysophanol** syn. chrysophanic acid	
OH	CH_3	**frangula emodin** syn. emodin	Cholagol® gtt.
H	CH_2OH	**aloe emodin**	
H	COOH	**rhein** Eucarbon ® tbl.	

Antidiarrhoics = drugs used for treatment of diarrhoea

- causes of diarrhoea: GIT infections, intoxications, alergic inflammation, tumor
- danger: water and electrolytes loss

Classification of antidiarrhoics:

- **Adsorbents** (activated charcoal, slime (mucilage) forming compounds (pectins, clays)
- **Adstringents** (tanin, basic salts of Bi, compounds of Al and Ag)

•**„Intestinal disinfectants“** – non-absorbable antibacterial chemotherapeutics acting in gastrointestinal tract

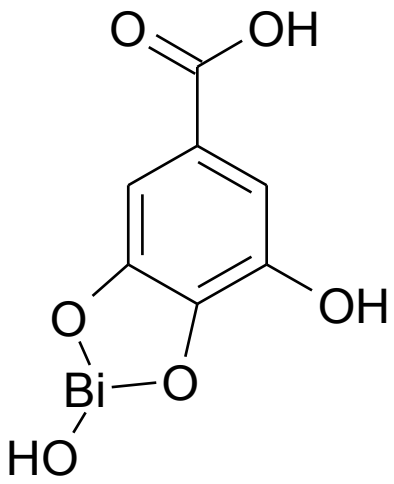
- **Intestinal peristaltic moderating compounds**

Adstringents

$Mg_3[Al(OH)_6]_2$

magnesium hexahydroxoaluminate

- large surface
- also effective adsorbent and antacide

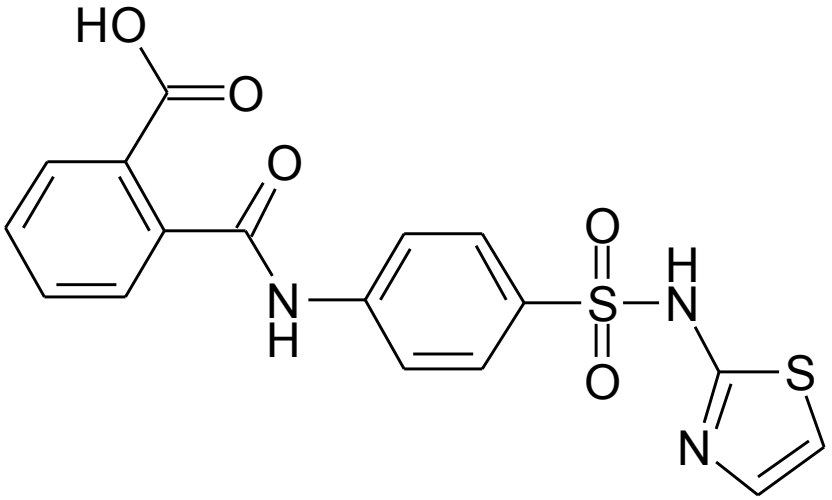


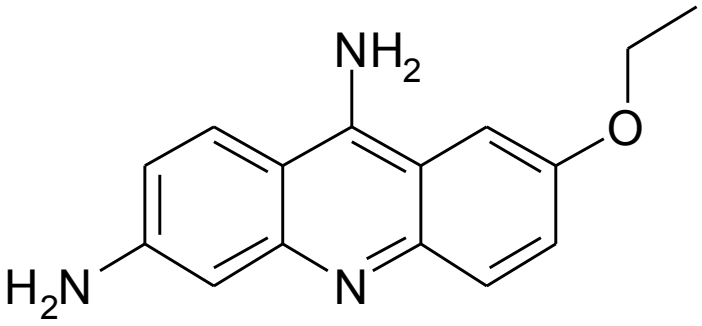
bismuth subgallate

- also antibacterial activity

Carbocit® (+ *Carbo adsorbens)*

„**Intestinal disinfectants**“ – non-absorbable antibacterial drugs



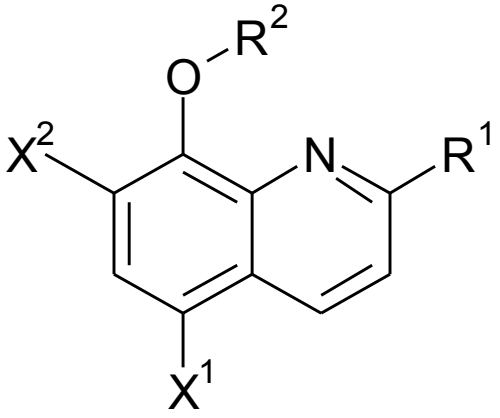


phthalylsulfathiazole
•non-absorbable N^4-acylated sulfonamide
•prodrug: free sulfathiazole is released in bacteria
•mechanism of action: inhibition of dihydropteroate synthase
~~Ftalazol® tbl.~~

ethacridine
•in most lactate
•mode of action: cation interacts with nucleic acids of a pathogen (intercalation)
•*magistraliter* preparations

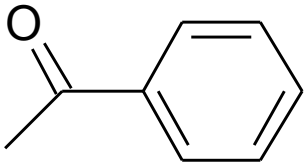
„Intestinal disinfectants“ – continued

5,7-dihalogenoquinolin-8-ol derivatives



R^1	R^2	X^1	X^2
H	H	Cl	Cl

cloroxine syn. chloroxine [USAN] (CZ, SK)
Endiaron® tbl. obd., also the substance for *magistraliter* preparations

CH_3		Br	Br

broxaldine (D…)

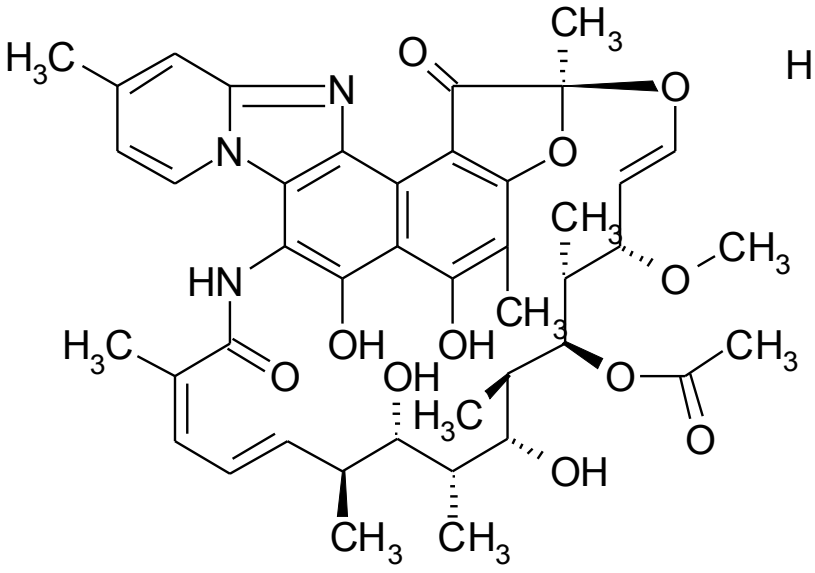
H	H	Cl	I

clioquinol (USA)
•myelooptic neuropathies

•bacteriostatic, fungistatic and antiprotozoal effects
•mechanism of action: forming of chelates with Me^{2+} important for microorganisms

„**Intestinal disinfectants**“ – continued

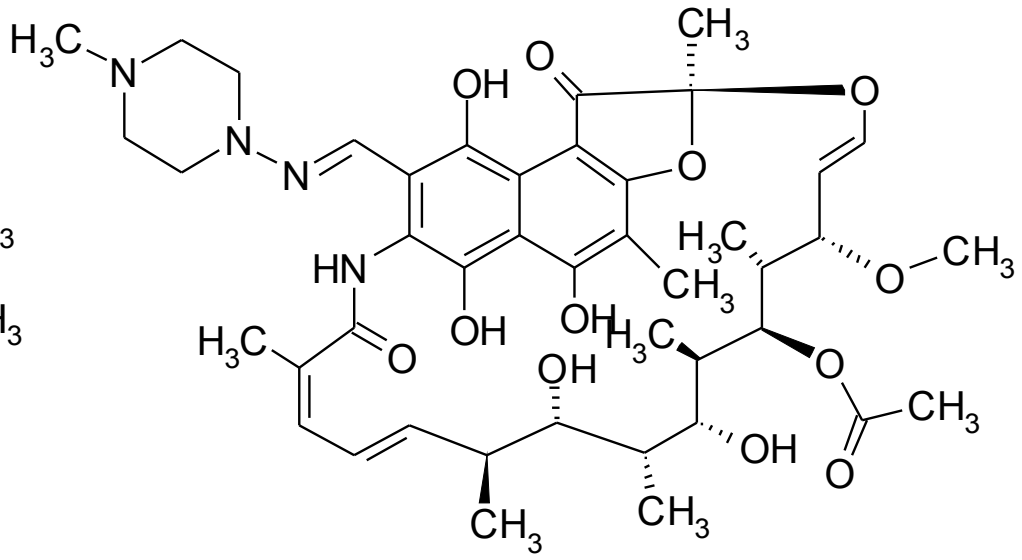
Rifaximin – poorly absorbable ansamycine antibiotic



rifaximin

•poorly absorbable ATB for treatment of infectious diarrhoea

Normix® tbl.



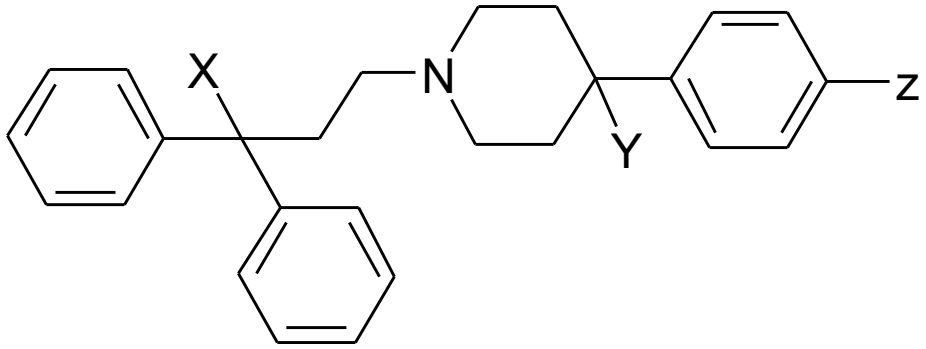
rifampicin

•ATB for treatment TBC

•mode of action: inhibition of DNA-dependent RNA-polymerase by forming of a stable complex with the enzyme ⇒ suppression of initiation of synthesis of bacterial RNA

Intestinal peristaltic moderating compounds

(also „antipropulsives“)



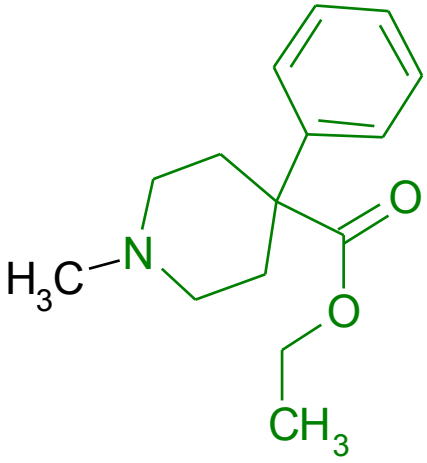
X	Y	Z		
-CN	-COOEt	H	**diphenoxylate**	Reasec® tbl. (+ atropin)
-CN	-COOH	H	**diphenoxine**	
$-CON(CH_3)_2$	-OH	Cl	**loperamid**	Imodium® cps.

•structural similarity with methadone and pethidine (*Tinctura opii* was formerly used also as antidiarrhoic)

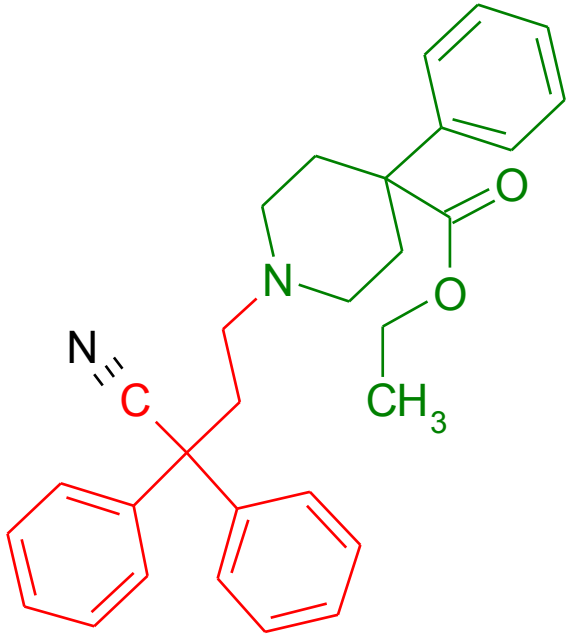
•mechanism of action: interaction with opioid receptors in the intestine (supposed σ,δ - receptors; natural agonist is enkephaline)

Intestinal peristaltic moderating compounds

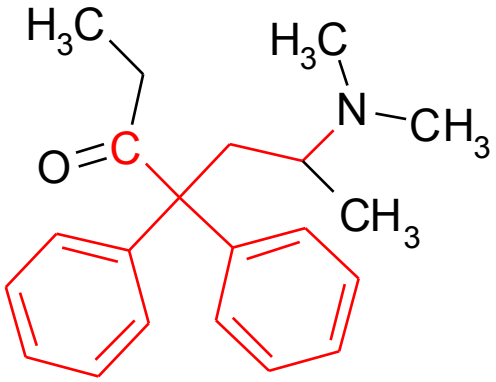
Comparison of structures of diphenoxylate, methadone and pethidine



pethidine
syn. meperidine



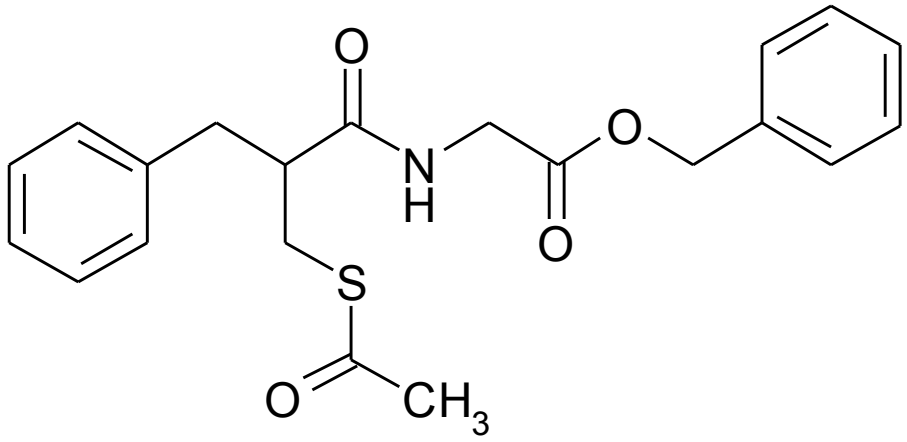
diphenoxylate



methadone

Intestinal peristaltic moderating compounds

Inhibitor of enkephalinase, i.e. indirect agonist of σ-, δ-receptors



racecadotril

syn. **acetorphan**

•clinical trials of the Phase III for acute diarrhoea in infants finished