INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Hepatoprotectants

≈hepatics

Classification of hepatics

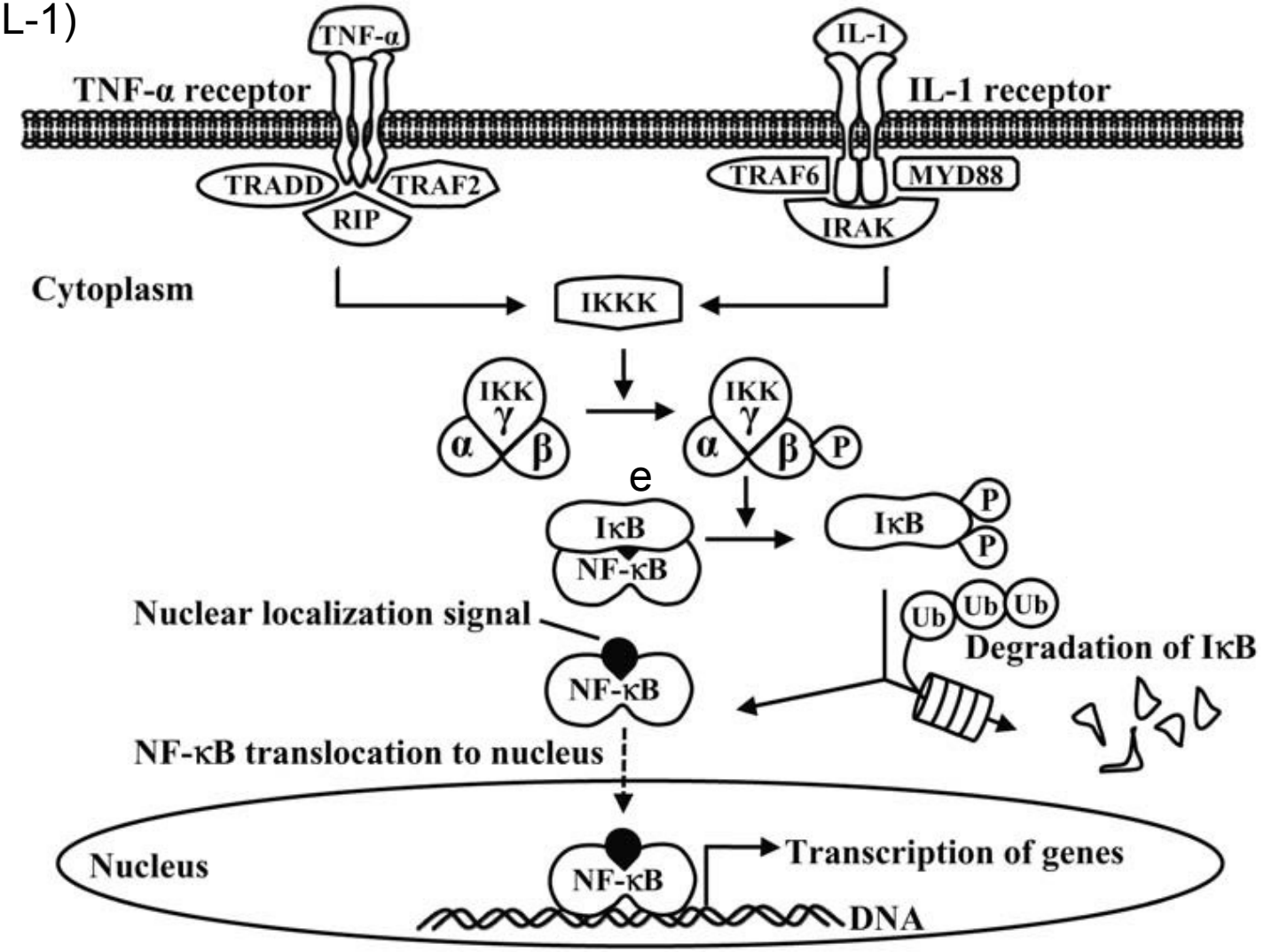
1. Inhibitors of nuclear transcription factor B (NF-κB)
2. Antifibrotics
3. Antioxidants
4. Compounds which interfere with apoptosis

•most of compounds have multiple mechanisms of action

Nuclear transcription factor B (NF-κB)
= a protein activating the immunity response of Kupfer cells of liver to harmful stimuli

- permanent or excessive activation leads to unwanted changes ofi liver tissue (cirrhosis, fibrosis)
- under different circumstances, activation of NF-κB can lead also to liver regeneration

Activation of nuclear transcription factor B (NF-κB) by tumor necrosis factor α (TNF-α) and interleukin 1 (IL-1)

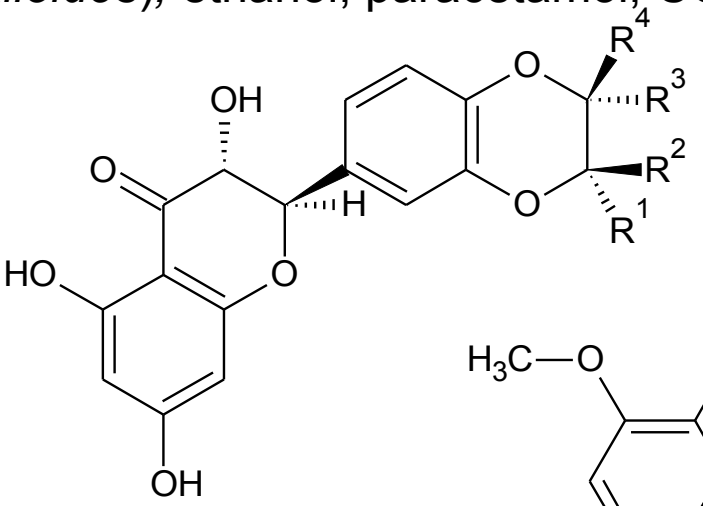


NF-κB is in the cytoplasma in its inactive form linked with protein IκB (inhibitor κB); this interaction disables transfer of NF-κB into the cell nucleus. NF-κB is activated if TNF-α or IL-1 are bound to their receptors, that leads to activation of intracellular signals and adaptor proteins, such as MyD88 (gene of primary myeloid diferentiation response 88), IRAK (IL-1R-asociated kinase) and TRAF-6 (TNF-asociated factor 6) for receptor IL-1 and TRADD (TNF-asocioated protein of death domain), RIP (receptor-interacting protein) and TRAF2 (TNF-asociated factor 2) for receptor TNF-α. These changes enable activation of IKKK (kinase of IκB kinase), which phosphorylates a activates IKK (IκB kinase), consisted from regulation subunit (IKK-γ) and two kinase subunits (IKK-α, IKK-β), that are responsible for phosphorylation of IκB. Then IκB is degraded by nuclear localisation signal and free NF-κB reaches the nucleus where it is bound to κB enhancing elements of target gene and induce their transcription.

Silymarin

= a mixture of flavanolignans gained by extraction of seeds of milk thistle(*Silybum marianum*; first referred by Pliny the Elder (= *Gaius Plinius Secundus* (23 AD – August 25, 79 AD) in 77 AD

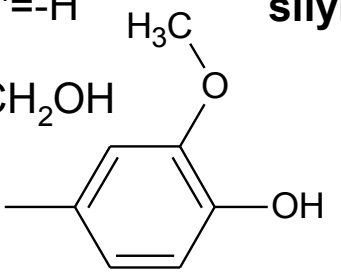
- content in seeds 1.5 – 3.5 %
- most of hepatoprotective activity is attributed to silybine (A+B) = silibinin; it represents 60 – 70 % of silymarin
- in silybin, hepatoprotective activity in liver damage by death cap (mushroom) *(Amanita phalloides*), ethanol, paracetamol, CCl_4 etc. was demonstrated.



silybin A: R^1=R^4=-H

R^2=-CH_2OH

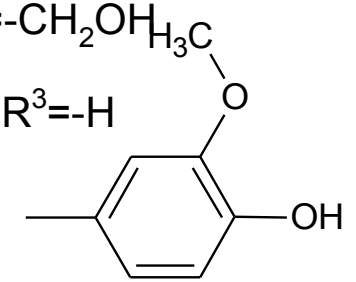
R^3=

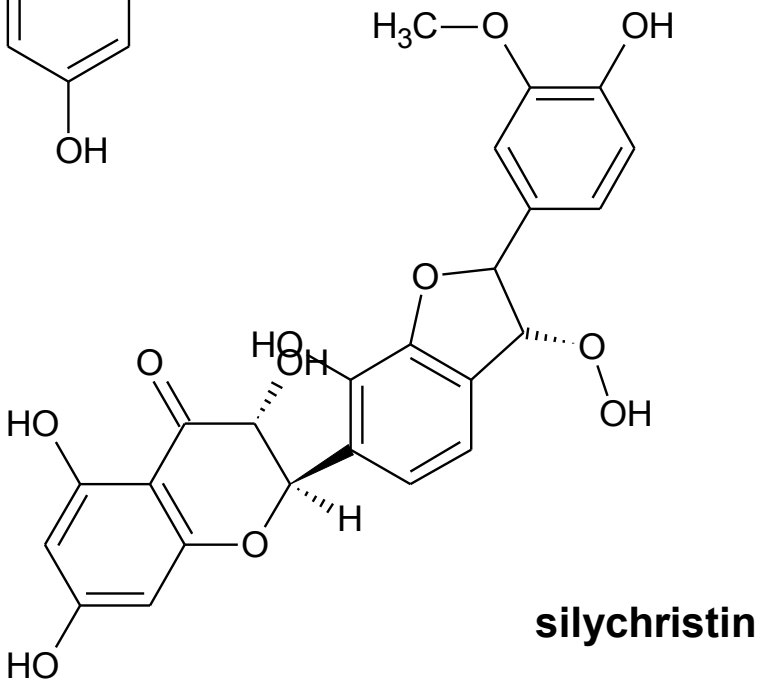


silybin B: R^1=-CH_2OH

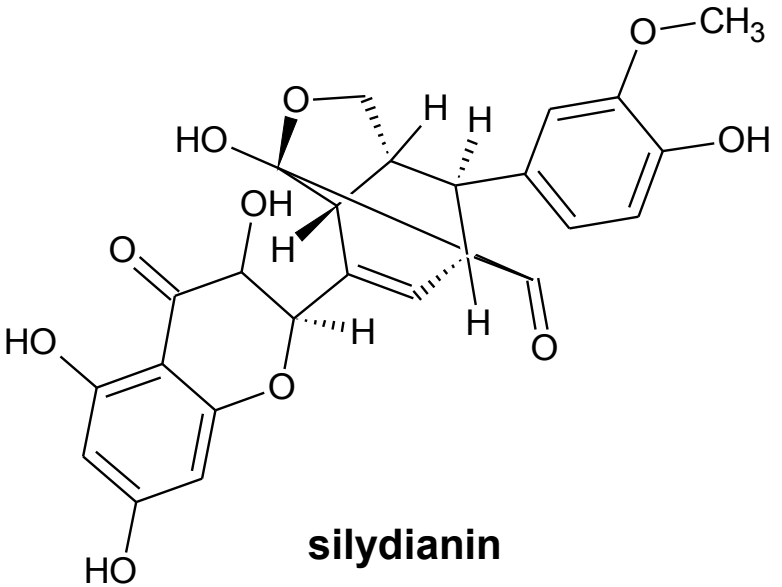
R^2=R^3=-H

R^4=





silychristin



silydianin

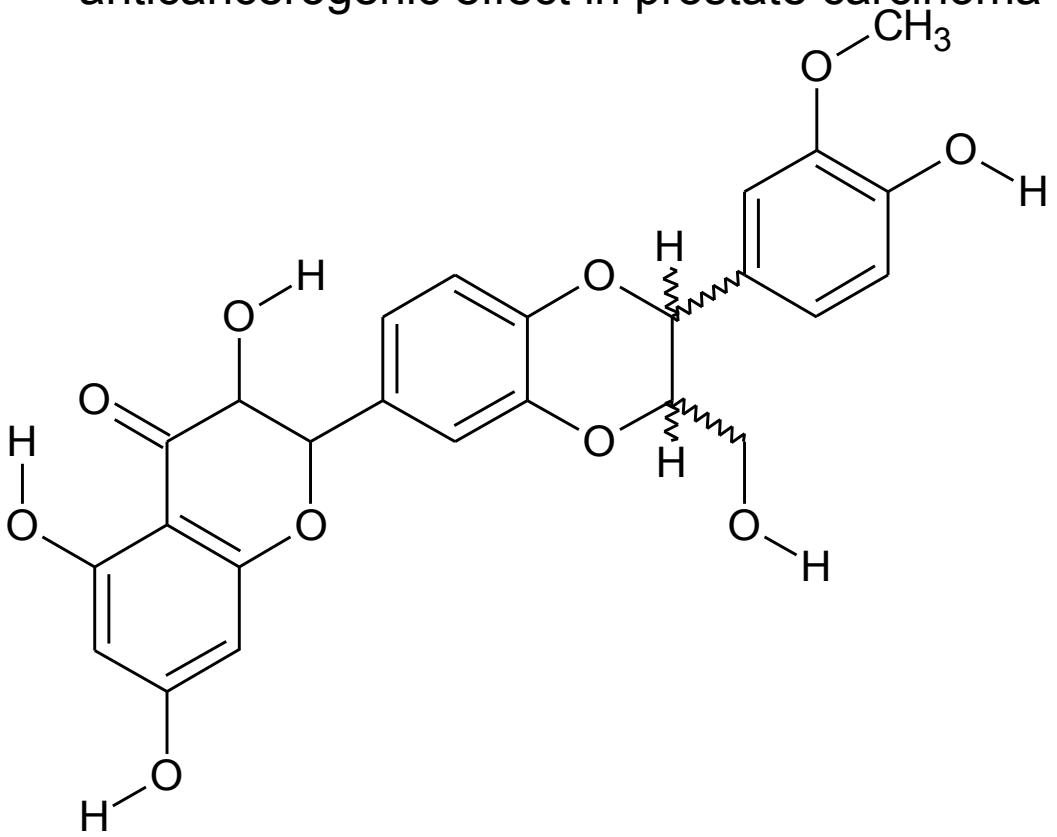
Effects of silymarin and their mechanisms

•inhibition of activation of NF-κB was demonstrated on hepatoma and lymphoma cells; probably main mechanism of action

•antioxidation effect: enhances superoxide dismutase activity in lymphocytes and erythrocytes, inhibits lipoperoxidation

•increses glutathione level

•anticancerogenic effect in prostate carcinoma



PhEur: Silybi mariani extractum siccum rafinatum et normatum

•silikristin + silidianin 20 – 45 %

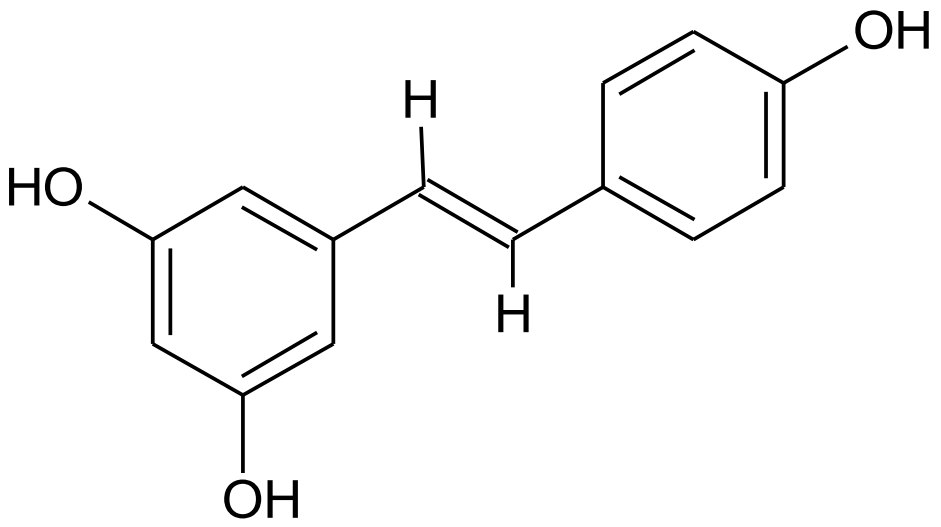
•silibinin A + B 40 – 65 %

•isosilibinin A + B 10 – 20 %

isosilybin A+B (= isosilibinin A+B)

•preparations Flavobion®, Lagosa®, Legalon®, Silygal®, Silymarin AL 50®

Resveratrol

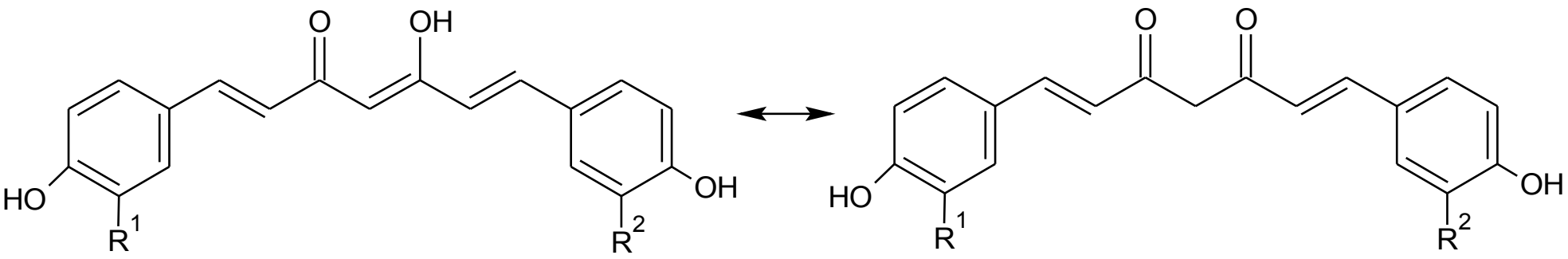


5-[(*E*)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol
3,5,4´-*trans*-trihydroxystilbene
resveratrol

- *Arachis* (peanut)*, Vitis vinifera* (grapevine)
- effects: antioxidant, anti-inflammatory, cancer prevention
- prevention of fibrose development
- protection before paracetamol toxicity and fibrosis caused by tetrachloromethane was demonstrated *in vitro*
- methylation of -OH does not decrease protective effects *in vivo*
- mechanism of action: inhibition of NF-κB activation

Curcuminoids

•*Curcuma longa, Zingiberaceae*



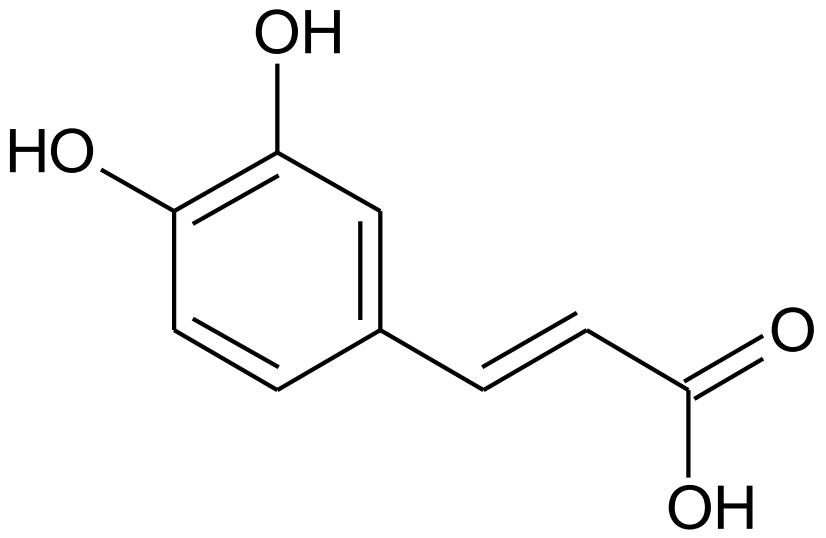
R^1=R^2=-OCH_3 **curcumin**

R^1=-H R^2=-CH_3 **demethoxycurkumin**

R^1=R^2=-H **bisdemethoxycurcumin** (syn. curcumin III)

- mechanisms of action : inhibition of NF-κB, TNF-α and IL-1β
- strong antioxidant activity, scavengers of many ROS
- lower cell membrane peroxidation
- curcumin is also the approved food additive (E 100, C.I. 75300)

Caffeic acid

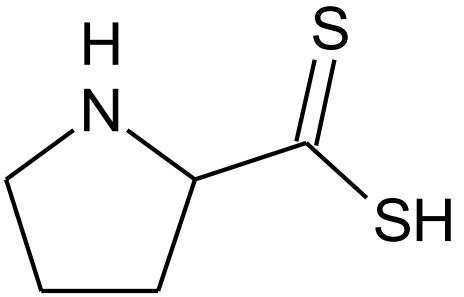


3-(2,3-dihydroxyphenyl)prop-2-enoic acid

caffeic acid

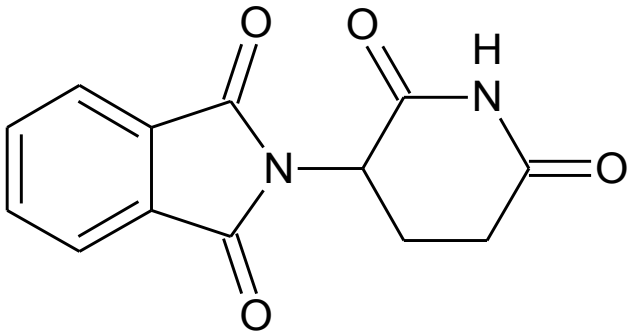
- protection against damage by CCl_4
- mechanisms of action:
  1. inhibition of lipoxygenase 5 (which produces leucotriens damaging the liver)
  2. inhibition NF-κB activation
  3. free radicals scavenging

Pyrrolidine-2-carbodithioic acid

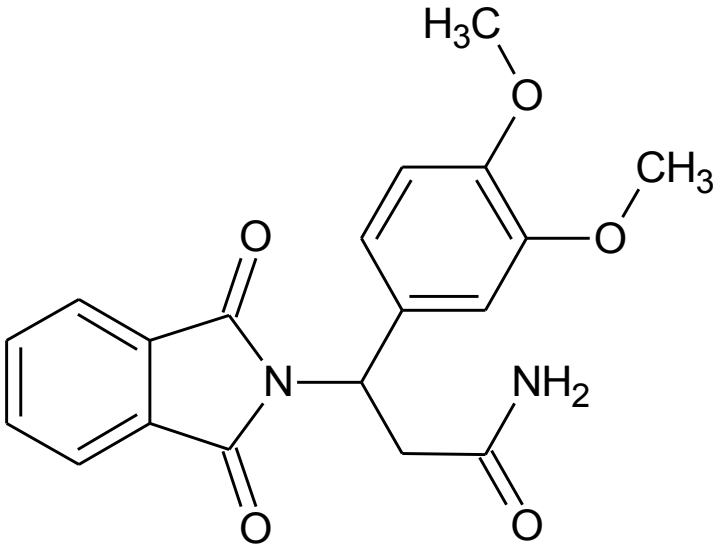


•syn. pyrrolidine-2-dithiocarboxylic acid,**"pyrrolidine dithiocarbamate", „prolinedithiocarbamate"**, **PDTC**, dithioproline
•known at least since 1958 (Zuman, Zahradník)
•mechanisms of action: 1.antioxidant by complexation of metal cations which catalyse generation of free radicals
2. inhibits activation of NF-κB

Thalidomide and its analogues



2-(2,6-dioxopiperidine-3-yl)-1*H*-isoindole-1,3(2*H*)-dion
α-(N-phtalimido)glutarimide
thalidomide

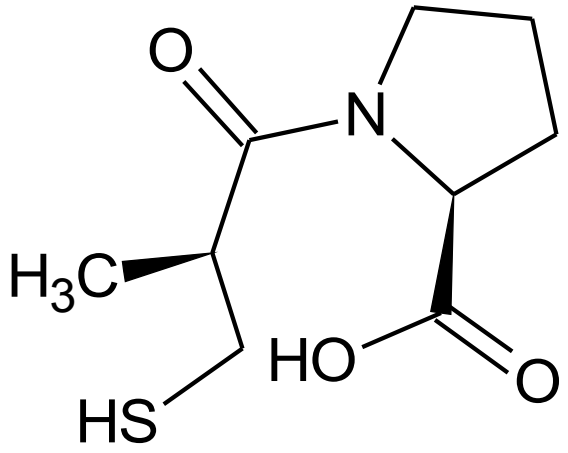


3-(3,4-dimethoxyphenyl)-3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)propanamide
3-(phtalimido)-3-(3,4-dimethoxyphenyl)propanamide
PDP

- originally hypnotic
- strong teratogene (Contergan®)
- abandoned in 1970th , now used in cancer therapy
- anti-inflammatory, antifibrotic and anticirrhotic activity
- efficient inhibitor NF-κB

2. Antifibrotics

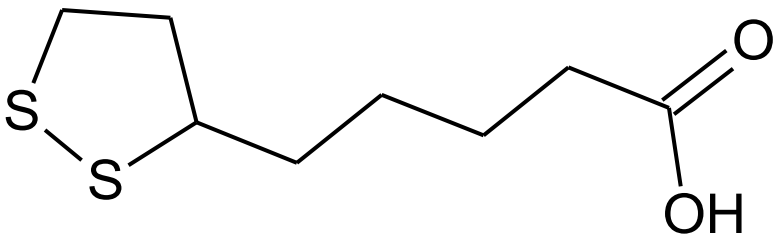
- angiotensin II (AT-II) a ACE play probably important roles in formation of liver firbrose
- transforming growth factor β (TGF-β) plays a dominat role in fibrose initiation; it can be supported by AT-II
- angiotensin receptor 1 antagonists lowers the portal pressure in hepatic cirrhosis
- hypothesis: inhibition of AT-II leads to NF-κB inactivation



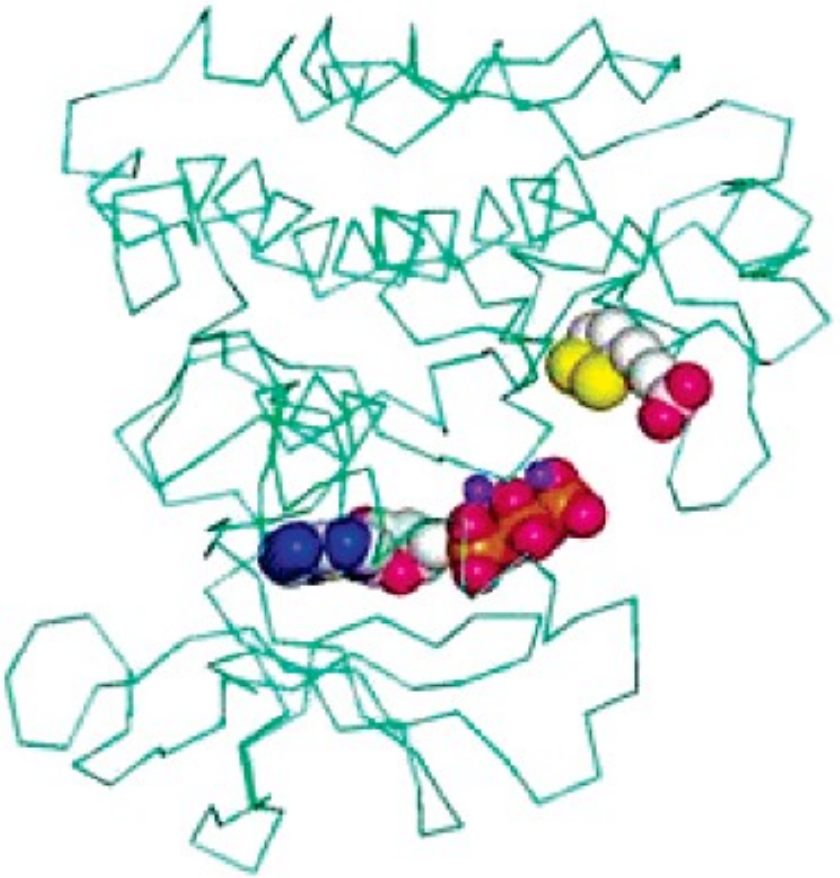
(2*S*)-1-[(2*S*)-2-methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid c**aptopril**

(normally used as an anti-hypertensive agent)

3. Antioxidants

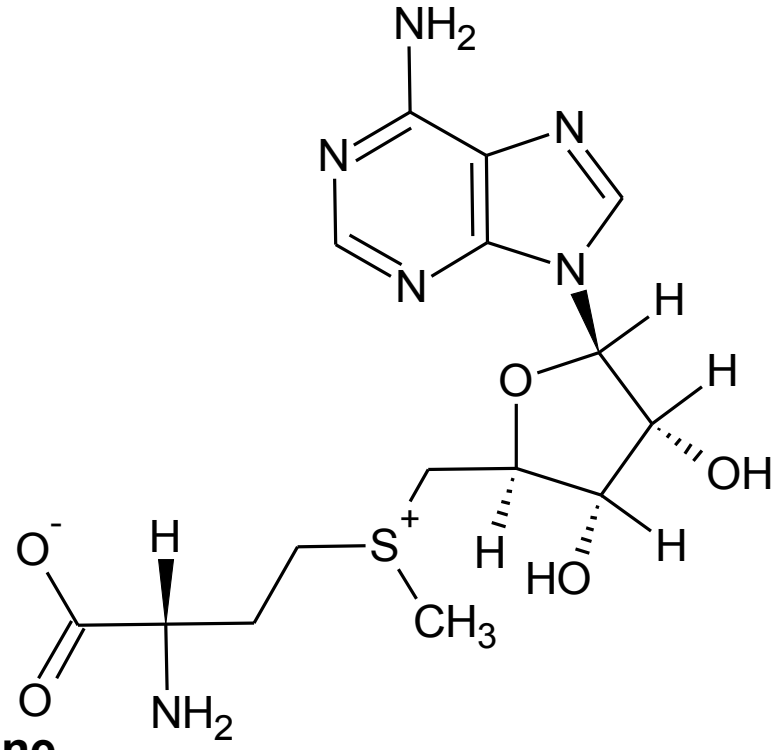


5-(1,2-dithiolan-3-yl)pentanoic acid
thioctic acid
lipoic acid



- inhibition of apoptosis of hepatocytes which had been induced by actinomycine D and TNF-α was demonstrated
- mechanism of action: activation of the insulin receptor by binding to thyrosinkinase domain
- used and authorised for long time as a drug for diabetic polyneuropathy (Thioktacid®, Thiogamma®)

4. Compounds which interfere with apoptosis



S-adenosylmethionine

SAME, SAM, AdoMet

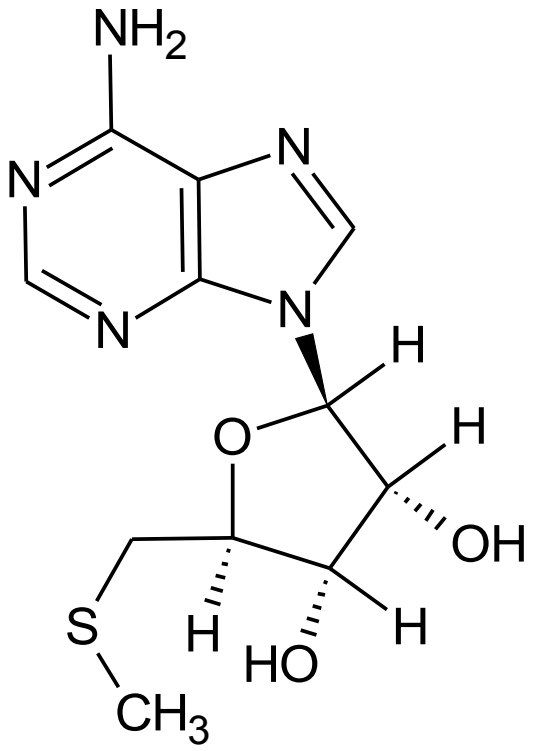
•endogenous compound, a donor of methyl

•synthesized from Met and ATP by the reaction catalyzed by methionine adenosyltransferase (MAT)

•regulates liver growth

•anti-apoptic in normal cells, induces apoptosis in cancer cells; a mechanism of action related to proteins Bcl-x was proposed (Bcl-x belong to BCl-2c family, members of this family are central regulators of apoptosis); posttranslation splicing of Bcl-x protein can lead to Bcl-x_L, that is anti-apoptic, or to Bcl-x_S which is proapoptic; SAME and methionyladenosin (MTA) induced selectively Bcl-x_S in HepG2 cancer cells; the alternative splicing is modulated by proteinphosphatase 1 (PP1) and its inhibitors block the ability of SAME and MTA induce Bcl-x_S

•SAME and MTA increased the amount of mRNA for the catalytic subunit PP1 in HepG2 cells, but not in normal hepatocytes
•SAME is freely available in food supplements in the USA



methylthioadenosine (MTA)
5´-deoxy-5´-methylsulfanyladenosine
•a side product of SAME metabolism gained in polyamines synthesis

The hepatal metabolism of S-adenosylmethionine (SAME)