NATURAL MEDICAMENTS DERIVED FROM ACETIC ACID POLYKETIDES

Large group of structurally very different compounds

Initial compound is acetylcoenzyme A, which is formatted by

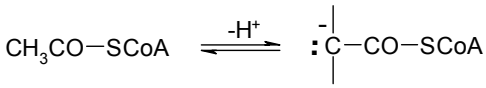
- activation of acetic acid (with help of coenzyme A and ATP)
  CH_3–COOH + HS–CoA + ATP → CH_3CO~CoA + AMP + diphosphate

- oxidative decarboxylation of pyruvic acid
  Pyruvic acid is in living organisms formed by decomposition of sugars via reaction chain of glycolysis.
  Aerobic conditions → acetylcoenzyme A
  CH_3–CO–COOH + HS – CoA + NAD → CH_3–CO~S–CoA + CO_2 + $NADH_2$

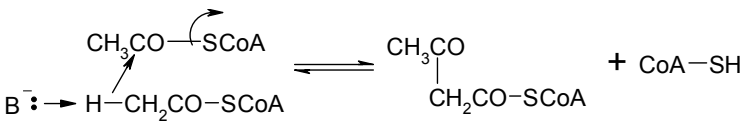
  Anaerobic conditions → reduction – lactic acid (in muscles and during milk fermentation)
  decarboxylation (alcohol fermentation)

TWO FUNCTIONAL PROPERTIES OF ACETYLCOENZYME A

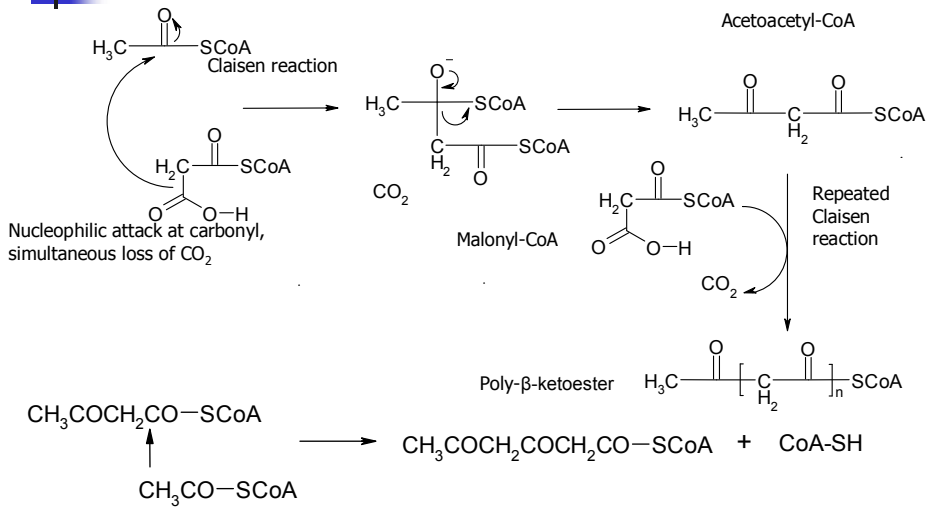
Via activation of α-hydrogen atoms of acetyl methyl group (enzymatic deprotonation) acquire carbon atom anionic character.



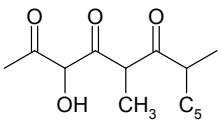
Extraordinary electrophillic character of carbonyl group of thioester provides site for nucleophilic attack; at polyketides it is anionic C atom (carbanion) of deprotonated ester.



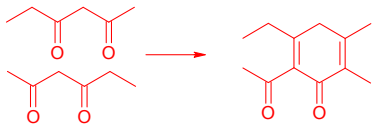
FORMATION OF β-POLYCARBONYL SUBSTANCES



POLYKETO SUBSTANCES ARE VERY REACTIVE (ethylene group located between two carbonyl groups)



alkylation or hydroxylation of methylene group



coupling via oxidative reaction of enols

including cyclisations leading to a pannel of structurally very different compounds

$—CH_2-CO-CH_2— \longrightarrow —CH_2—CHOH—CH_2—$

reduction of of ketogroup to an alcohol

$RCOCH_2COOH \xrightarrow{-CO_2} RCOCH_3$

decarboxylation leading to formation of compounds with odd number of carbon atoms

$RCOCH_2COOH \longrightarrow RCOCH_2CO-SCoA$

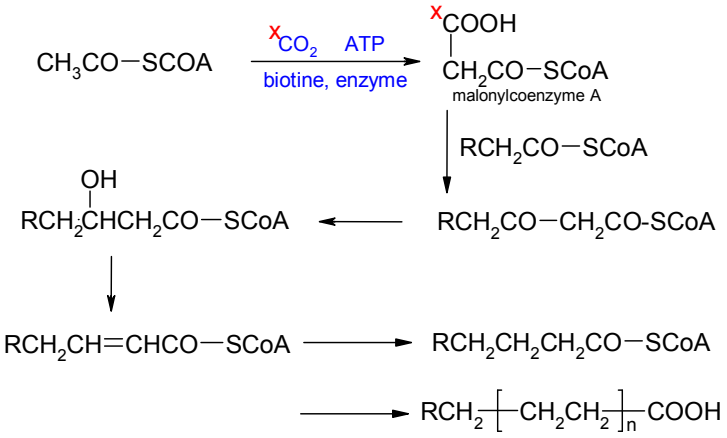
activation of COOH group via formation of thioester

DIVISIONS OF ACETOGENINS

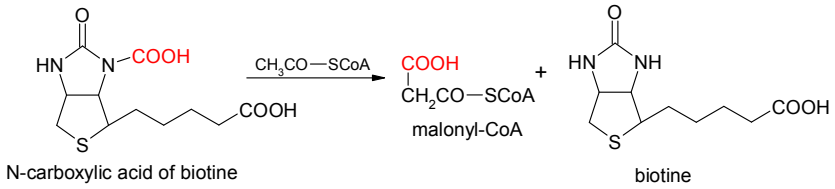
ALIPHATIC	CYCLIC
• Satturated fatty acids	• Phenols and their derivatives
• Unsattuated fatty acids	• Anthraquinones
• Polyacetylene substances	• Tetracyclines
• Prostaglandins	• Griseofulvine
	• Lichen acids
	• Phloroglucinol derivatives
	• Macrolides

ALIPHATIC ACETOGENINES

SATURATED FATTY ACIDS



ROLE OF BIOTINE DURING CARBOXYLATION OF ACETYLCOENZYME A

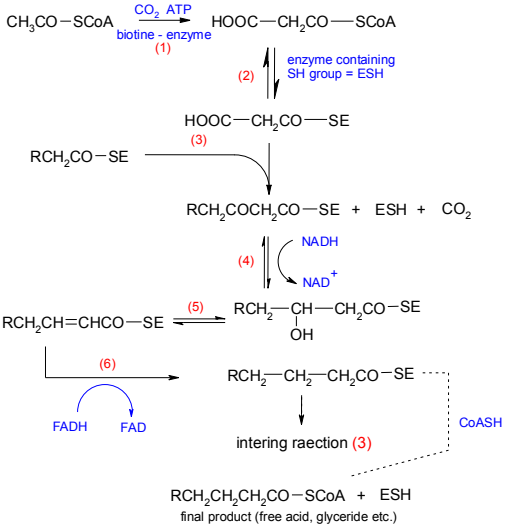


N-carboxylic acid of biotine

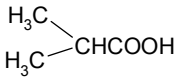
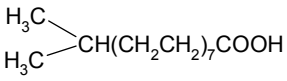
biotine

SYNTHESIS OF FATTY ACIDS

protein acyl carrier – fatty acids synthase



SUBSTITUTION OF ACETYLCOENZYME A FOR DIFFERENT ACYL-CoA
(CoA esters of propionic acid, isobutyric, isovaleric etc.)

Initial reactant as acetyl-CoA	Produced acid	Number of C atoms
CH_3COOH	$CH_3(CH_2CH_2)_7COOH$	16
CH_3CH_2COOH	$CH_3CH_2(CH_2CH_2)_7COOH$	17
$CH_3CH_2CH(CH_3)COOH$	$CH_3CH_2CH(CH_3)(CH_2CH_2)_6COOH$	17
		18

THE MOST COMMON SATTURATED FATTY ACIDS

C_6	n-hexanoic	(capronic acid)	$CH_3(CH_2)_4COOH$
C_8	n-octanoic	(caprylic acid)	$CH_3(CH_2)_6COOH$
C_{10}	n-decanoic	(caprinic acid)	$CH_3(CH_2)_8COOH$
C_{12}	n-dodecanoic	(lauric acid)	$CH_3(CH_2)_{10}COOH$
C_{14}	n-tetradecanoic	(myristic acid)	$CH_3(CH_2)_{12}COOH$
C_{16}	n-hexadecanoic	(palmitic acid)	$CH_3(CH_2)_{14}COOH$
C_{18}	n-octadecanoid	(stearic acid)	$CH_3(CH_2)_{16}COOH$
C_{20}	n-eicosanoic	(arachidonic acid)	$CH_3(CH_2)_{18}COOH$

UNSATURATED FATTY ACIDS

Formation of unsaturated fatty acids via direct dehydrogenation

acetate + malonate

↓

$CH_3(CH_2)_{14}COOH$ palmitic acid

↓

$CH_3(CH_2)_{16}COOH$ stearic acid

↓ -2H

$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$ oleic acid (ω 9)

↓ -2H

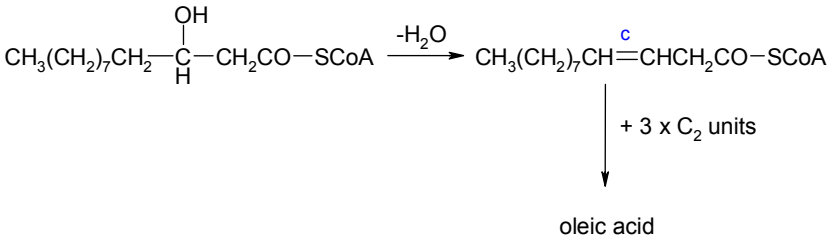
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$ linoleic acid (ω 6)

↓ -2H

$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$ linolenic acid (ω 3)

UNSATURATED FATTY ACIDS

Formation of unsaturated fatty acids via hydroxyacids



THE MOST COMMON UNSATURATED FATTY ACIDS

C_{18} cis-9-octadecenoic acid — oleic acid

$CH_3(CH_2)_7CH=CH(CH_2)_7COOH$

C_{18} cis,cis-9,12-octadecadienic acid — linoleic acid

$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$

C_{18} cis,cis,cis-9,12,15-octadecatrienic acid — linolenic acid

$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7COOH$

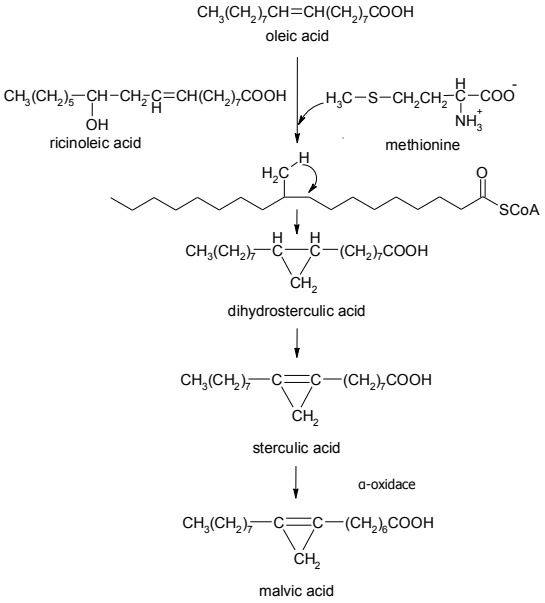
C_{18} 12-hydroxy-cis-9-octadecenoic — ricinoleic acid

$CH_3(CH_2)_5(CHOH)CH_2CH=CH(CH_2)_7COOH$

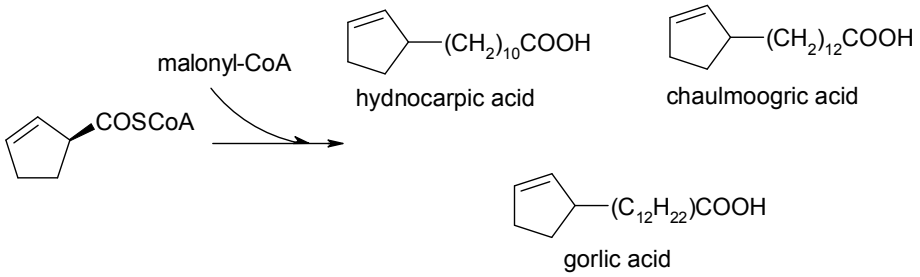
C_{22} cis-13-docosenoic — erucic acid

$CH_3(CH_2)_7CH=CH(CH_2)_{11}COOH$

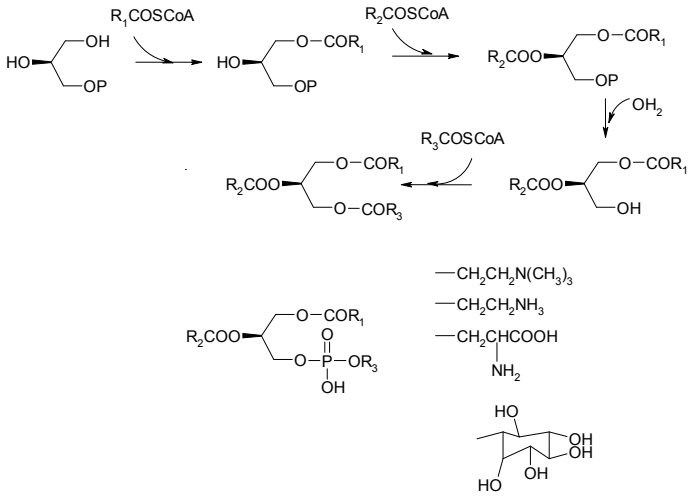
UNSATURATED FATTY ACIDS MALVACEAE, STERKULIACEAE



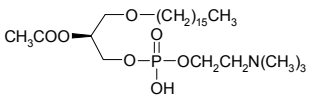
UNSATURATED CYCLIC ACIDS – HYDNOCARPACEAE



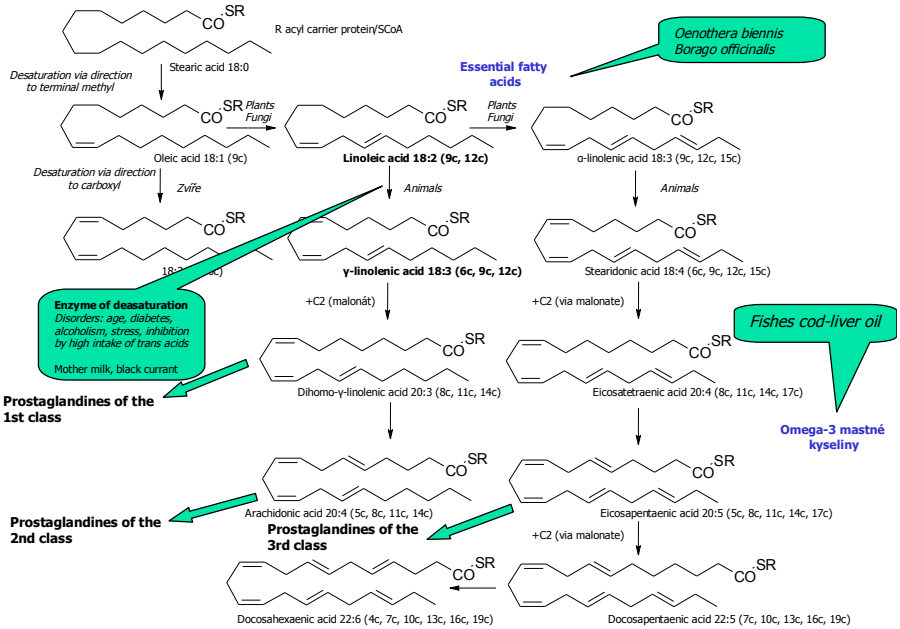
Esters with glycerol



PAF



Desaturation of stearic acid



POLYACETYLENIC SUBSTANCES, POLYINES
ASTERACEAE, DAUCACEAE, ARALIACEAE

oleic acid
linolenic acid → $CH_3(CH_2)_4-C_{54}\equiv C_{55}-CH_2CH=^{c}CH-(CH_2)_7COOH$
crepeninic acid

Polyines possess toxicological importance

$CH_3-(C\equiv C)_3-CH=^{t}CH-CH_2OH$ dehydromatricarianol

$CH_3-(C\equiv C)_3-CH=^{t}CH-COOCH_3$ dehydromatricaria-ester

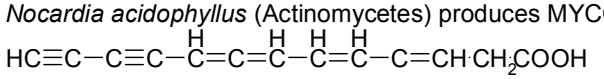
$CH_3-(C\equiv C)_4-CH=CH-CH=CH_2$ *Dahlia sp.* (Asteraceae)

$CH_3-(C\equiv C)_3-CH=CH-CH=CH-(CH_2)_2CH_2OH$

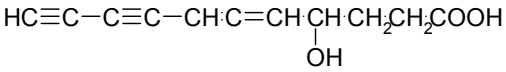
Occurrence: *Cicuta virosa,* Cowbane or Northern Water Hemlock, Apiaceae
Aethusa cynapium - Fool's Cicely or Poison Parsley (Apiaceae)

POLYACETYLENIC SUBSTANCES, POLYINES
ANTIBIOTICS

Nocardia acidophyllus (Actinomycetes) produces MYCOMYCIN

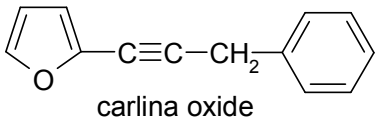


side product = nemotinic acid



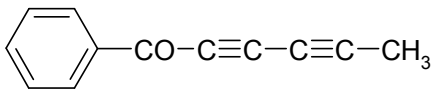
POLYACETYLENIC SUBSTANCES, POLYINES
ASTERACEAE

Carlina acaulis [root] - stemless carline thistle



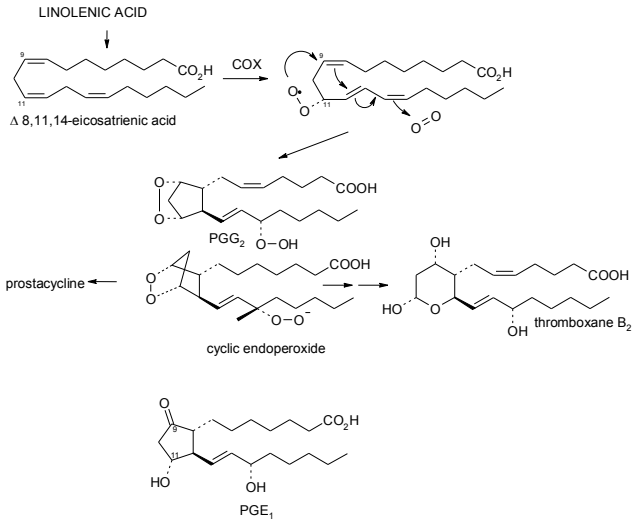
carlina oxide

r. *Artemisia* - wormwood

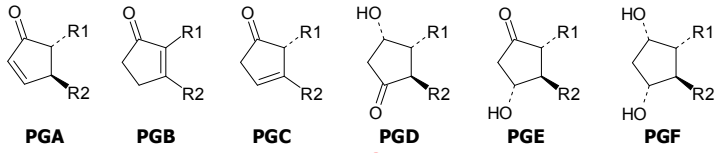


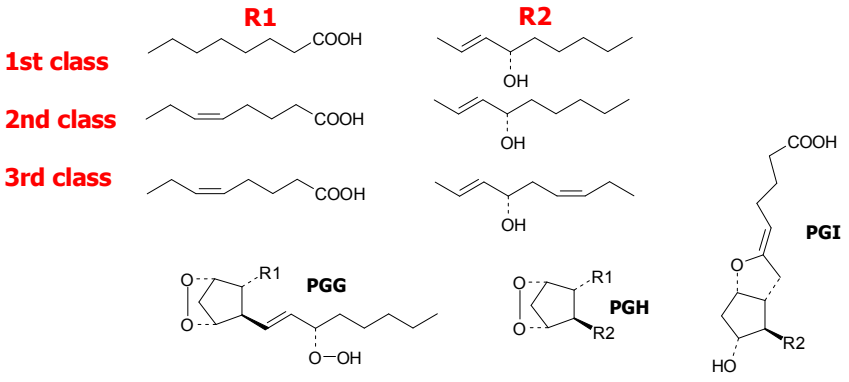
capillin (fungistatic)

PROSTAGLANDINS

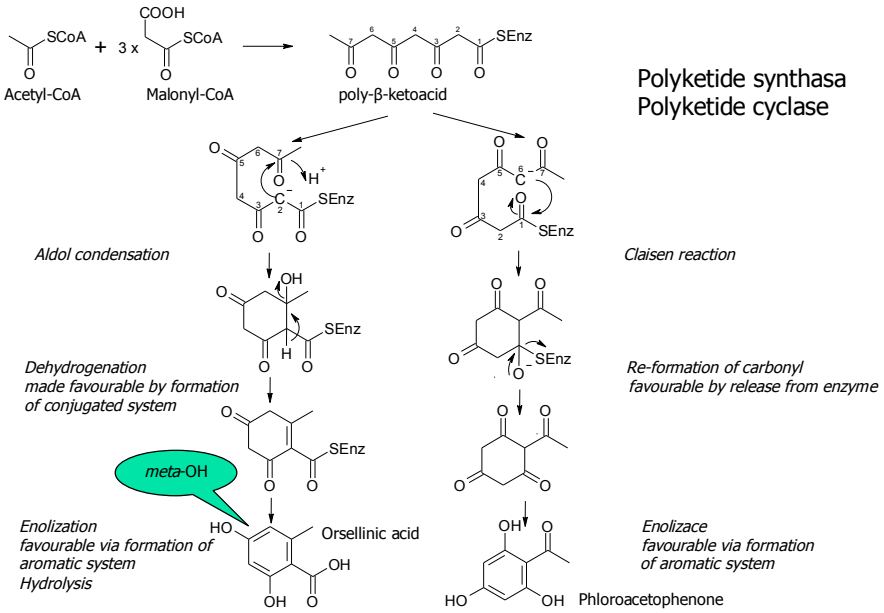


Prostaglandins



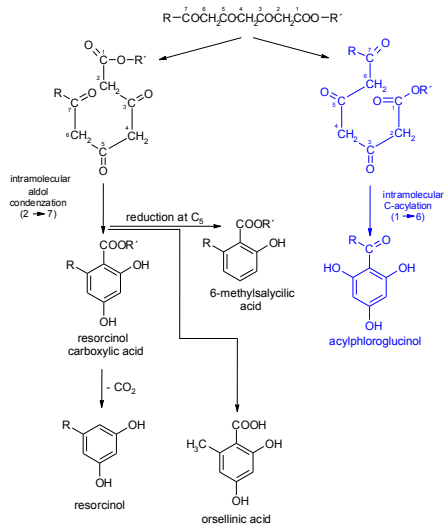


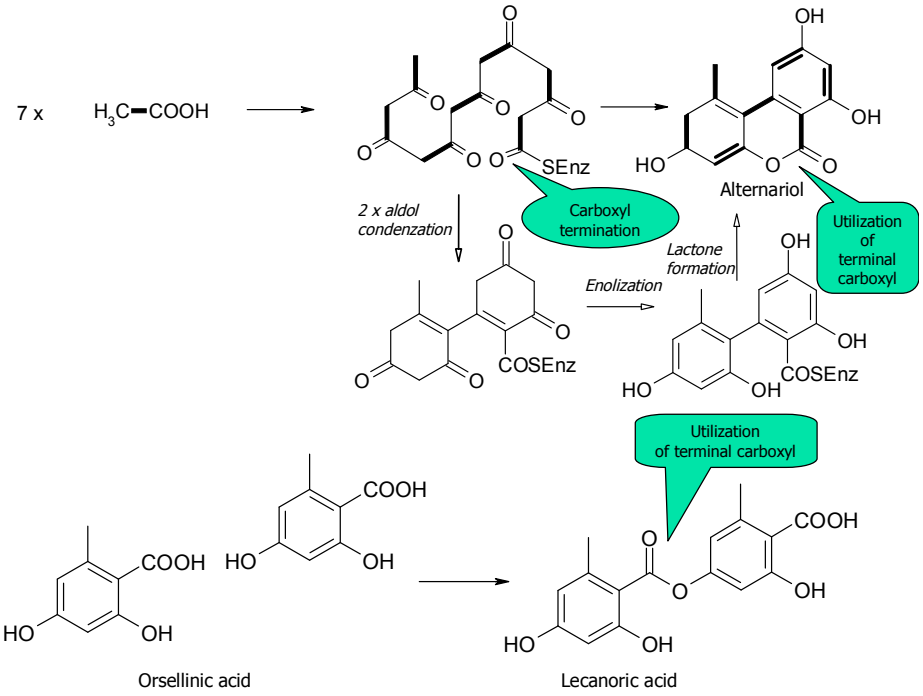
Acetate cyclization – formation of simple phenols



CYCLIC ACETOGENINS

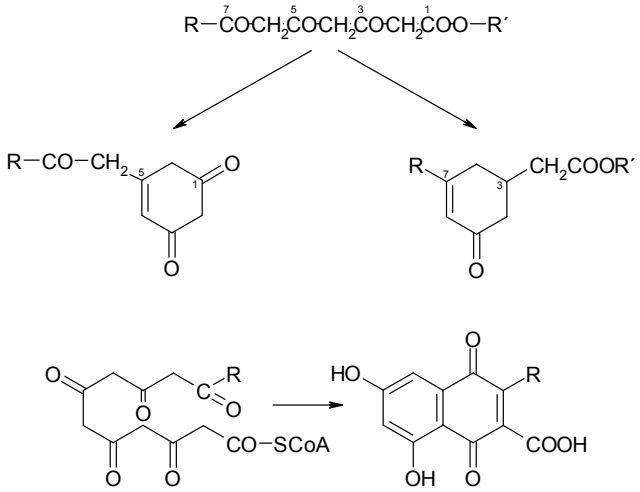
PHENOLS AND THEIR DERIVATIVES





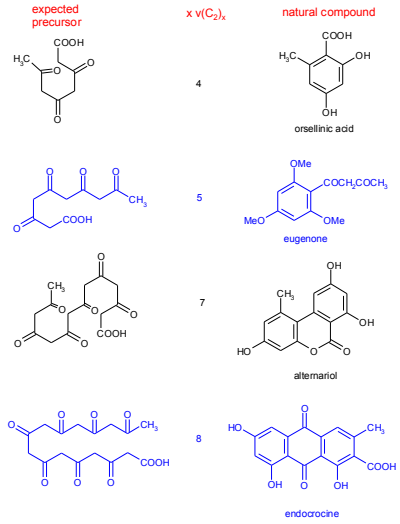
CYCLIC ACETOGENINS

DERIVATIVES OF PYRONES AND NAPHTOQUINONES

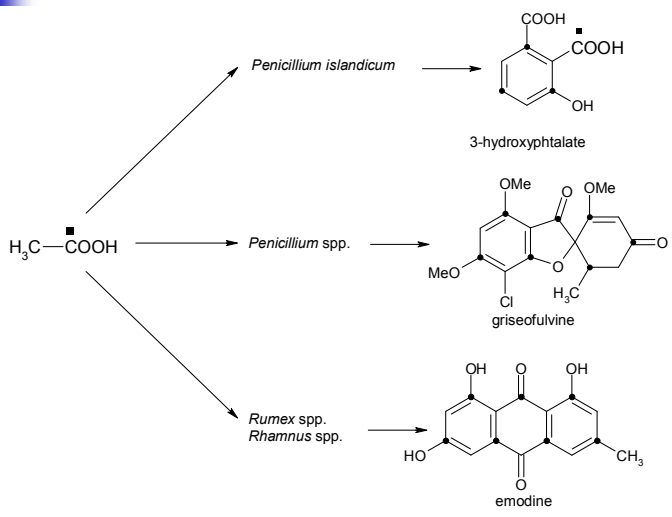


EXAMPLES OF POLY-β-KETO-SUBSTANCES CYCLISATION

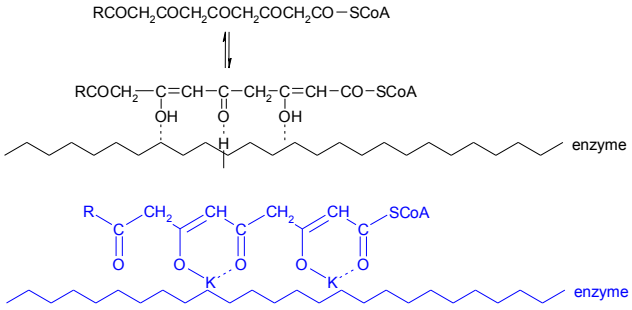
with numerous secondary transformations



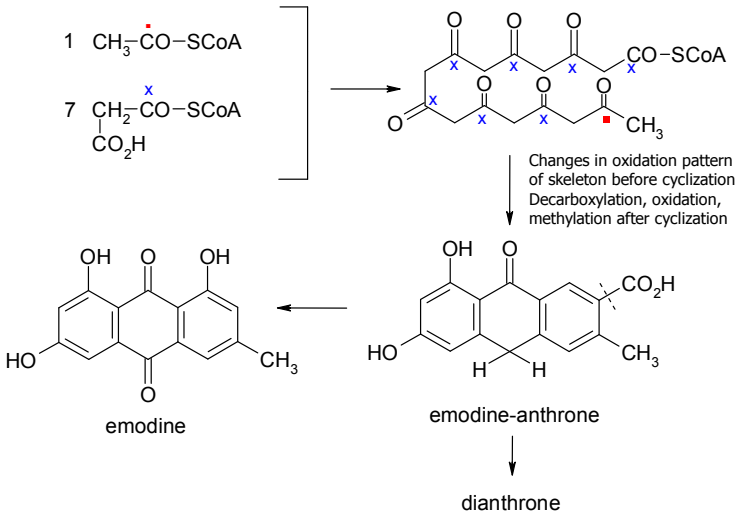
ACETATE ORIGIN OF NATURAL COMPOUNDS



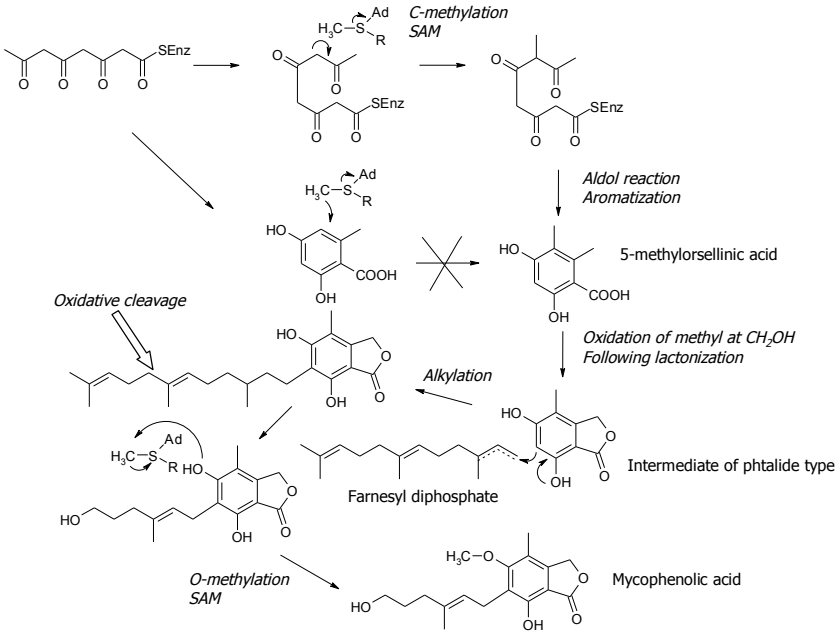
POLY-β-KETO CHAIN STABILISATION



ANTHRAQUINONE DERIVATIVES

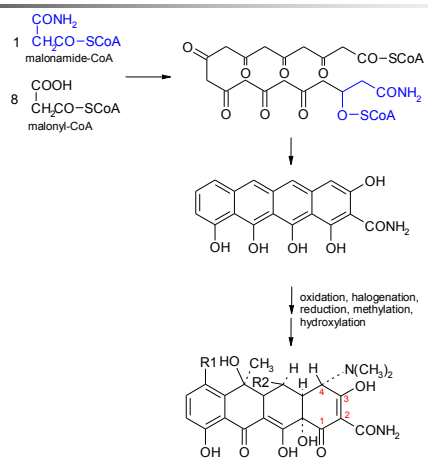


C-alkylation reactions



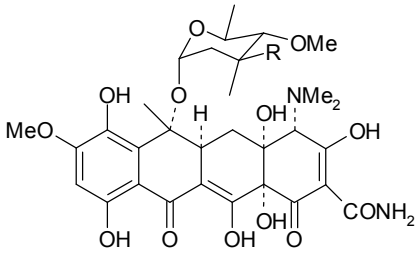
ANTIBIOTICS OF POLYKETIDE TYPE

TETRACYCLINES – product of actinomycetes *Streptomyces* spp.

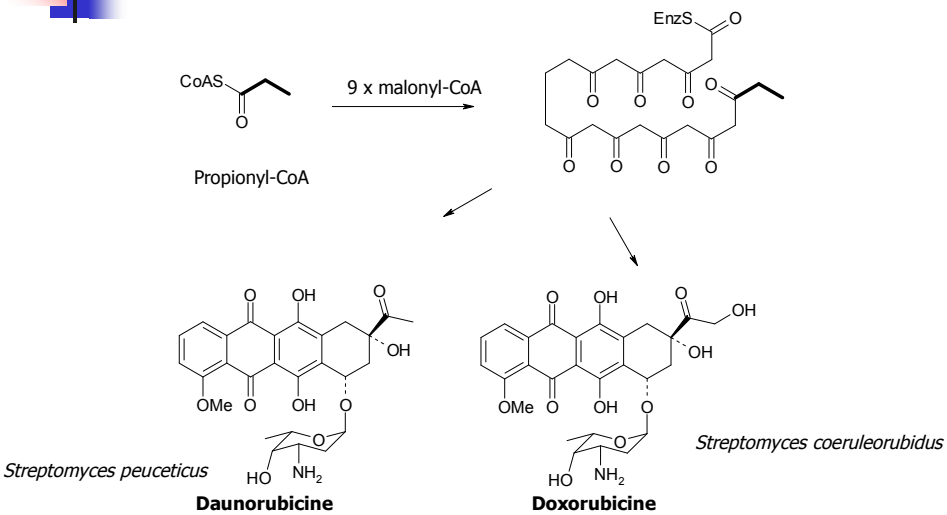


	R1	R2
tetracycline	H	H
chlorotetracycline	Cl	H
oxytetracycline	H	OH

Dactylocyklines

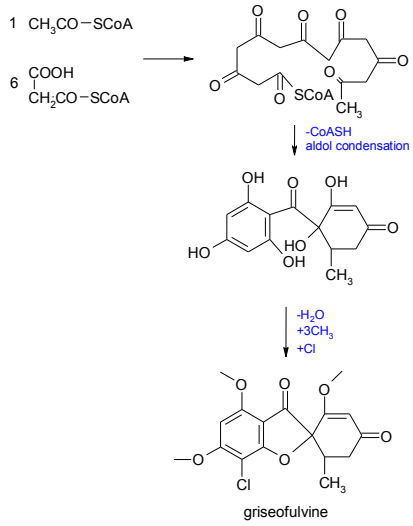


Anthracycline antibiotics



ANTIBIOTICS OF POLYKETIDE TYPE

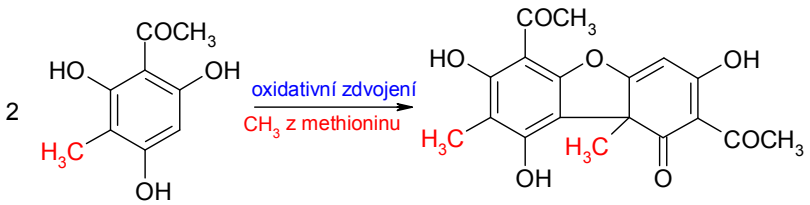
GRISEOFULVINE – product of *Penicillium griseofulvum* and others, examples of biosynthetic application of oxidative phenolic conjugation



griseofulvine

LICHEN ACIDS

usnic acid

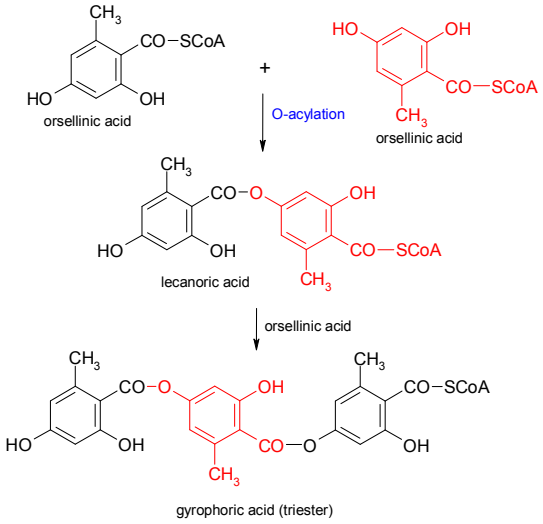


substituted phloroglucinol

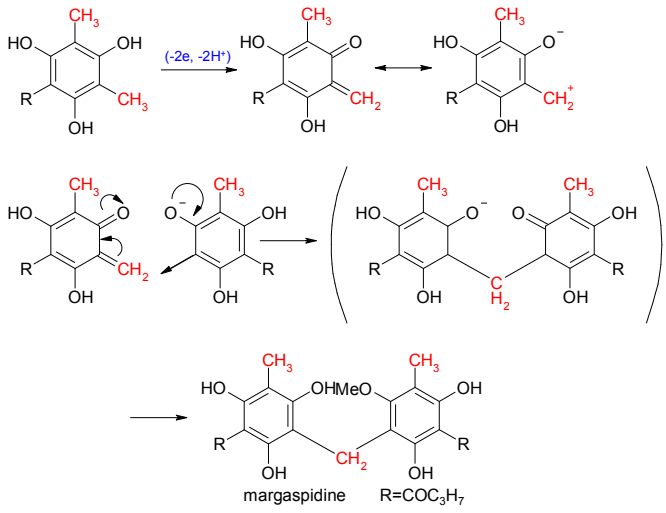
usnic acid

LICHEN ACIDS

symbionts of fungi and algae, produce mainly depsides and depsidones

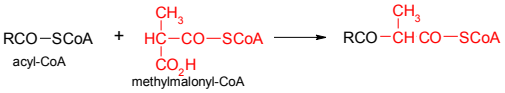


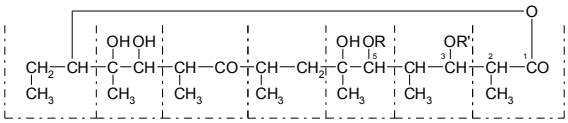
PHLOROGLUCINE DERIVATIVES PRESENT AT FERNS



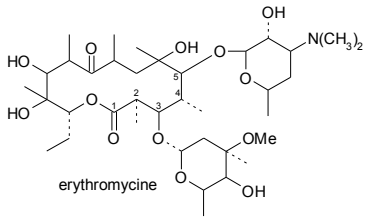
MACROLIDES OF ERYTHROMYCINE GROUP

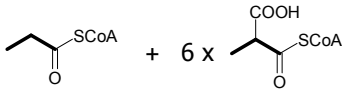
formed *via* incorporation of propionic acid in form of methylmalonylcoenzyme A





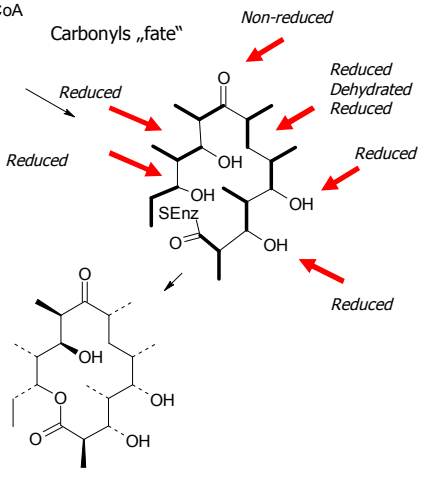
erythromycine (R=desosamine, R'=cladinose)

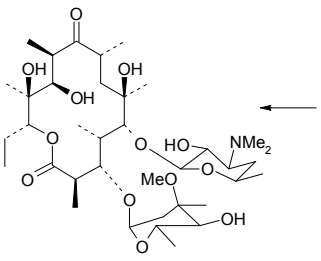




Carbonyls „fate"

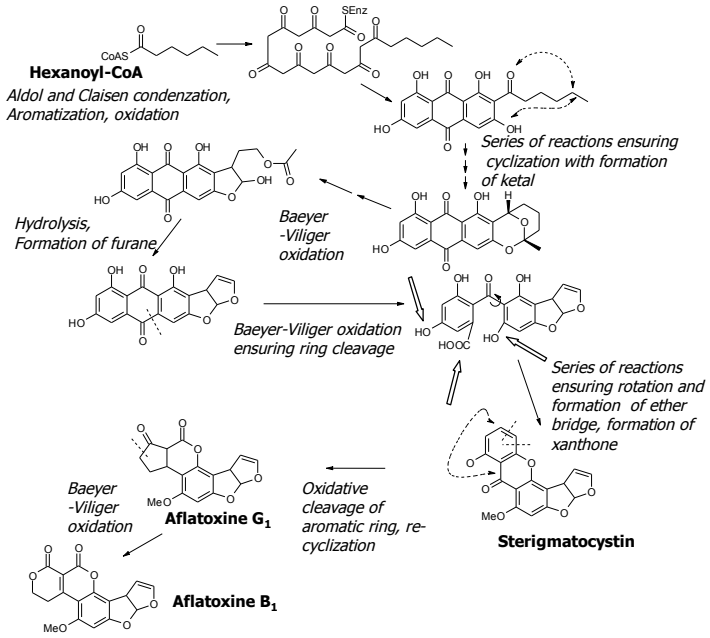
Saccharopolyspora erythrea





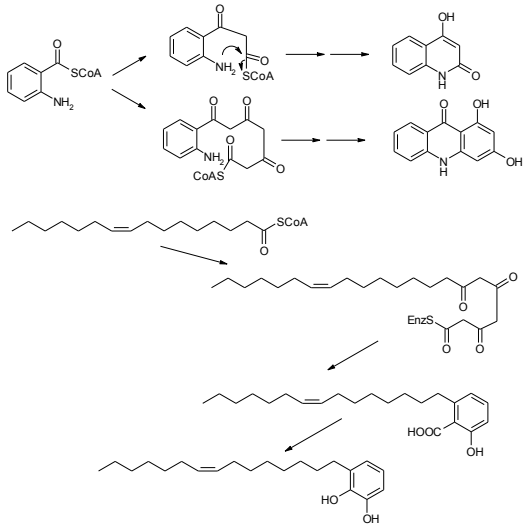
COMPOSITE ACETOGENINS

formed except of acetogenine from constituent of other biogenetic origin



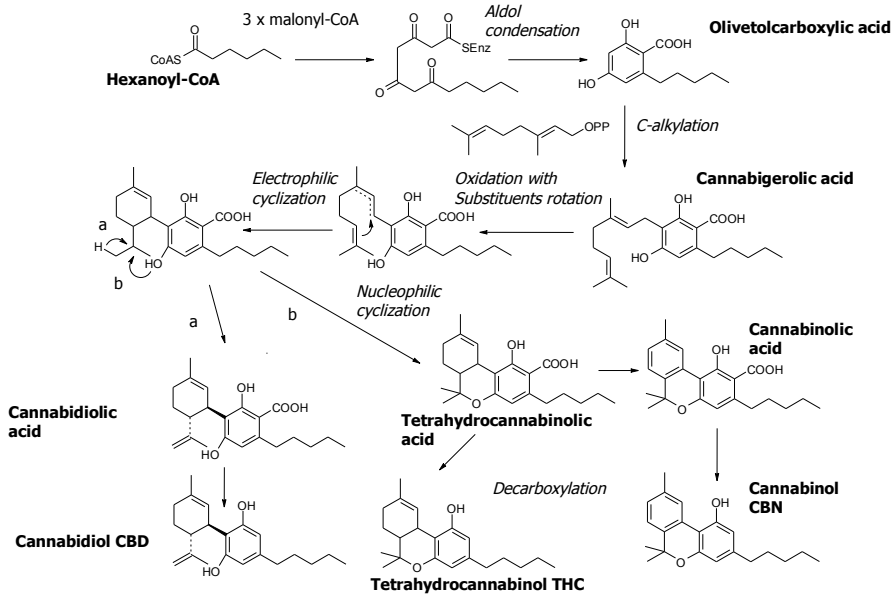
COMPOSITE ACETOGENINS

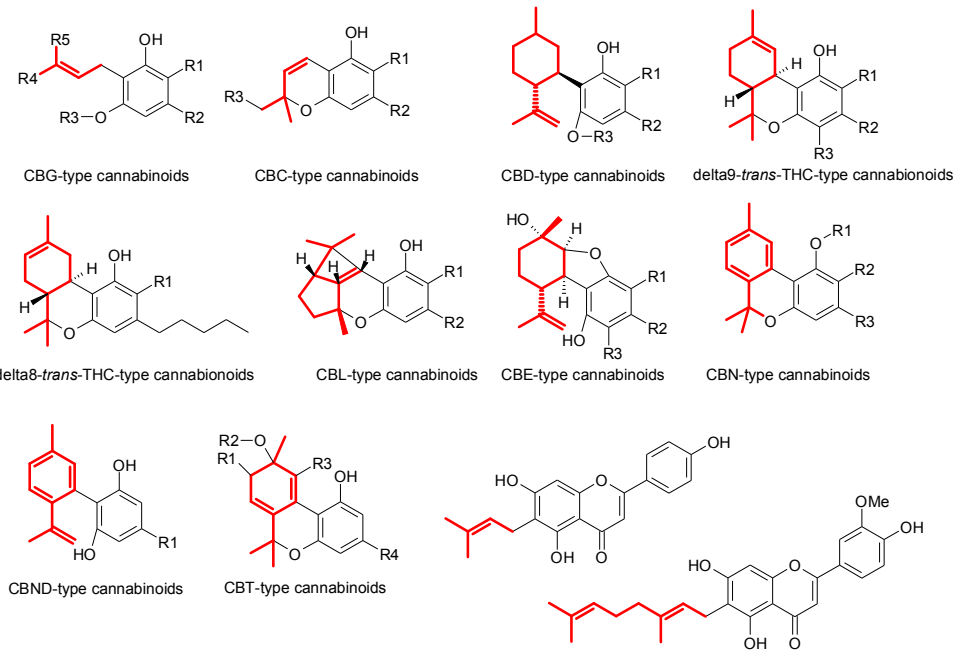
formed except of acetogenine from constituent of other biogenetic origin



COMPOSITE ACETOGENINS

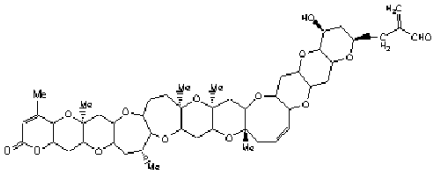
formed except of acetogenine from constituent of other biogenetic origin



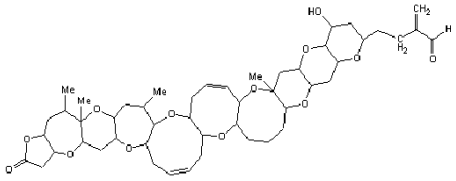


Brevetoxins

- *Gymnodinium breve* (*Ptychodiscus brevis*)
  - So called red tide
    - Massive death of fishes
    - Mexican gulf, Australia, coast of North America
  - Polycyclic ethers
    - Lipophilic
    - 10 and 11 rings
    - All-*trans* arrangement
    - Relatively stabile compounds (high and low pH cause decomposition)
  - Mechanism
    - Depolarization, opening of voltage-directed channels Na+
    - Uncontrolled influx Na+ into cell
    - Change of voltage opening channels, hyperexcitability
  - Symptoms:
    - Often mis-changed as intoxication with ciguatoxins
    - Tingling of face, throat, fingers
    - Tremor, nausea, vomiting, diarrhoea, headache
    - Mydriasis
    - Bradycardia
    - No death causing cases



BREVETOXIN-A, a type I brevetoxin



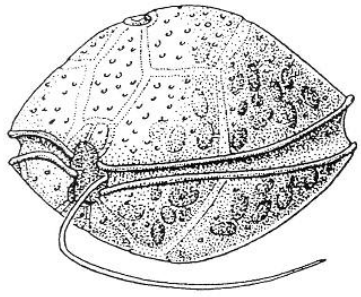
BREVETOXIN-B, a type II brevetoxin

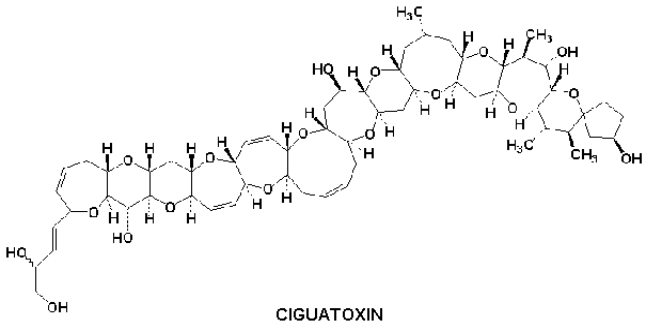
Ciguatera toxins

- Mixture of substances
- Present: 24 related compounds (ciguatoxin, maitotoxin, scaritoxin, okadaic acid)
- Dinoflagellate *Gambierdiscus toxicus*
  - On corral reefs
- Found in Pacific fishes
  - Tropics and subtropics
- Low-molecular lipid polyethers
- Temperature resistant
- Stimulation of Na+ passage through membrane

Neurotoxins

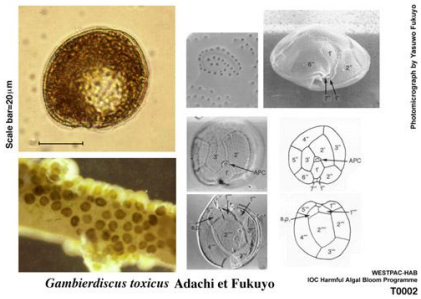
- 4 sets of symptoms
  - Neurologic 7 days
  - Cardiovascular
  - Gastrointestinal 1-2 days
  - General 1-7 days





CIGUATOXIN

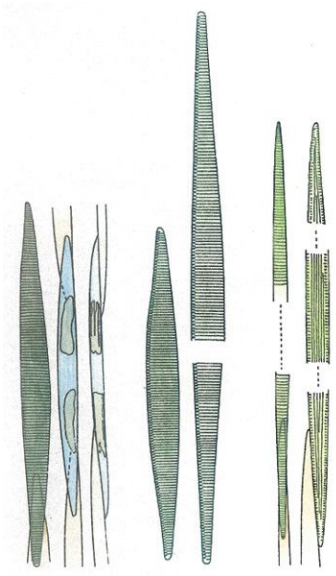
- Nástup otravy:
  - 10 minut to 12 hours after first contact, after požití of contamined fishes upto 36 hours
- Begging of intoxication
  - Vomiting, diarrhoea, general weakness
  - Decreased sensitivity to painfull podnětům
  - Tingling and burning of fingers
  - Sense of changing of cold and heat
- Further stadia
  - Hypotension, mydriasis, arhytmia
  - Convulsions, circulatory colaps, respiratory colaps, death



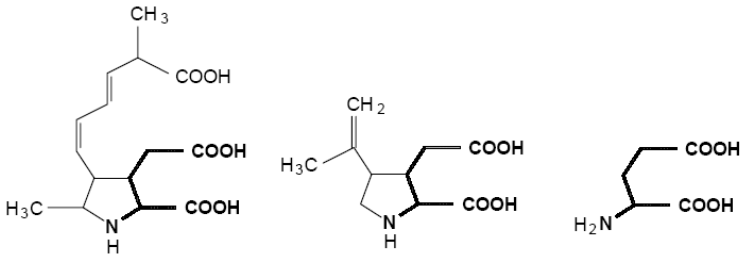
- Possibility of symptoms persistance
  - Bad differential diagnostics from other NSP
  - First aid
    - Manitol – diuresis
    - Function control
    - No antidote
    - Curing of long-termed symtoms
      - Amitriptilin, gabapentin

Domoic acid

- *Nitzchia pungens*
- Amnestic shellfish poisoning (ASP)
  - Poisoning corresponded by neurologic disorders
    - Hallucinations, time and space disorientation
    - Deterioration of short-termed memory
- Symptoms of intoxication
  - Vomiting, stomach convulsions, diarrhoea, headaches
  - ASP
- Cumulation of toxin in hepatopancreas, gills, so called siphone of mollusces
- Mollusces resistant, meat becomes toxic
- New Zealand, Canada coast, Mexico
- Red tide
- Tricarboxylic acid
- Proline derivative
- Structural similarity with excitation aminoacids (cainate, glutamate)
- Mechanism of effect:
  - Excitation AMA
  - 100times effective than glutamate
    - Ring rigidity
  - Bond to NMDA receptor
    - Affection of Ca channels, Ca influx
      - Stimulation of processes → neuronal damage
    - Loss of memory



http://www.regione.emilia-romagna.it/laguna/immagine_dettaglio.asp?id_img=1002



kyselina domoová kyselina kainová kyselina glutamová

Obr. 1: Strukturální podobnost neurotoxinů ze skupiny excitačních aminokyselin (domoové a kainové) s kyselinou glutamovou, přirozeným agonistou NMDA-glutamátových receptorů.

KYSELINA DOMOOVÁ, NEBEZPEČNÝ NEUROTOXIN

Plk. v zál. prof. MUDr. Vratislav HRDINA, CSc.,[1,2] prof. RNDr. Jiří PATOČKA, DrSc.,
plk. v zál. doc. RNDr. Vladimír MĚRKA, CSc.,[3] doc. MUDr. Radomír HRDINA, CSc.