Pharmaceutical colourants

-dyes, used as pharmaceutical colorants, are the same, which are approved for use in foods and beverages

Overwiev of approved and used pharmaceutical colourants

A possible classification:
1. Inorganic pigments
2. Organic dyes
2.1 Lipophilic dyes
2.1.1 Carotenoids
2.1.2 Xanthophyls
2.2 Chlorophylls and chlorophyllines
2.3 Hydrophilic dyes
2.3.1 Fused-rings glycosides, pseudoglycosides and their aglycones
2.3.2 Phenolic dyes not based on fused rings
2.3.3 Indole dyes
2.3.4 Hydrophilic azo-dyes
2.3.5 Hydrophilic triarylmethane dyes

Legislation background

EU:

DIRECTIVE 2009/35/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 23 April 2009 on the colouring matters which may be added to medicinal products:

- colouring matters approved for foodstuff can also be used in medicinal preparations
- list of approved colorants and pigments: Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council
- requirements on purity: COMMISSION REGULATION (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council

1.Inorganic pigments

•in most insoluble or poorly soluble in both water and organic solvents
•colouring of tablet mass, capsules, surface films on coated tablets
•colouring of suspension creams and oitments

$CaCO_3$, E 170

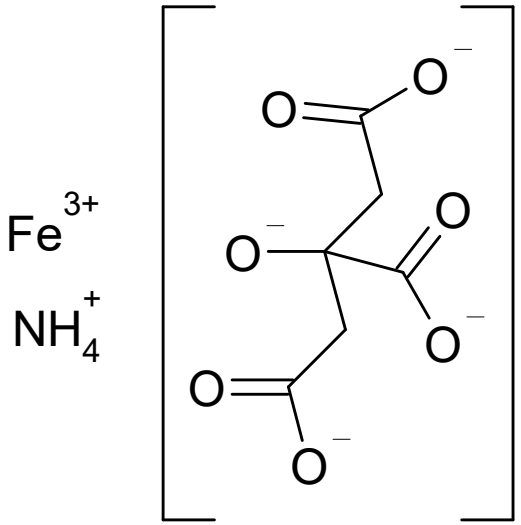
•only for surface „colouring“

TiO_2, E 171, CI 77891, titane white

•also protecting factor against UV irradiation

Iron oxides and hydroxides E 172

Ferric-ammonium citrate

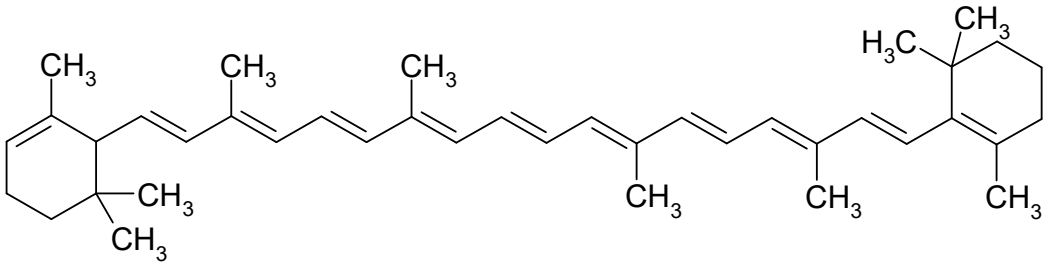


•Steinsvik S. et al.: J. Phys. Chem. Solids 58, 969 (1997)
•water soluble
•since 2002 rejected as a colourant; before 2002 approved in USA; still listed in DAC (=Deutsches Arzneimittel Codex = German Medicines Codex)

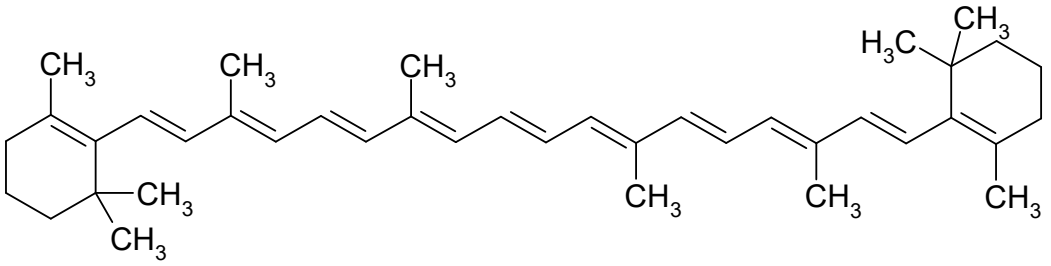
1. Inorganic pigments

Al E 173, CI 77000
•finely powdered - inflammable (pyrophoric)

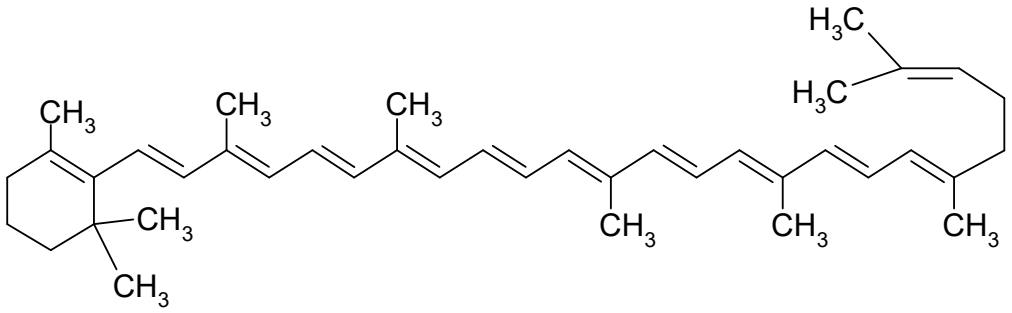
2.1. Lipophilic organic dyes
Carotenoids (together E 160)
α, β, γ-carotene together E 160a



α–carotene (β,ε–carotene)
m.p. 187,5°C
•log $P_{o/w}$ = 17.49

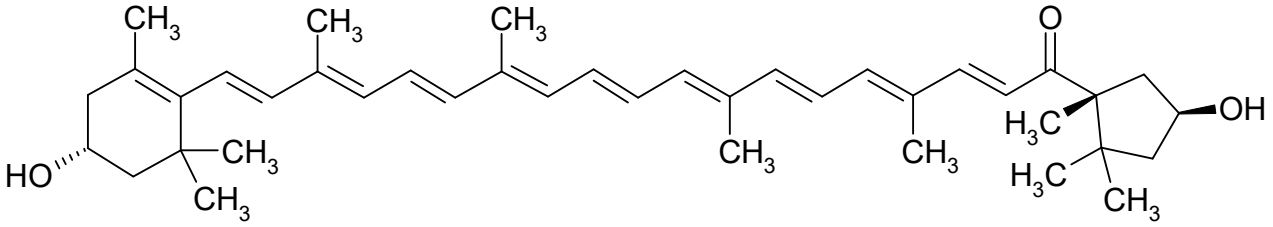


β-carotene
CI 75130 (natural), CI 40800 (syntethtic)
E 160a
m.p. 183°C
•poorly stable on air and light
•from light yellow to deep orange in dependence on concentration
•0.1% for suppositories
•log $P_{o/w}$ = 17.63

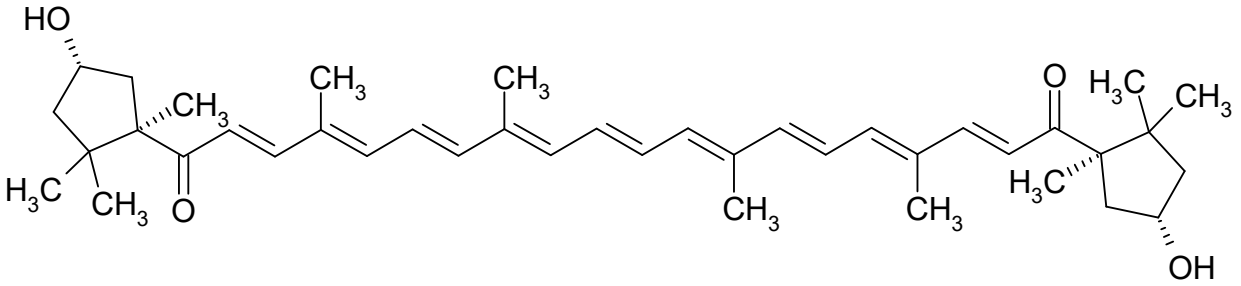


γ-carotene (β,θ–carotene)
m.p. 154°C
•log $P_{o/w}$ = 17.63

Carotenoids (together E 160) - continued

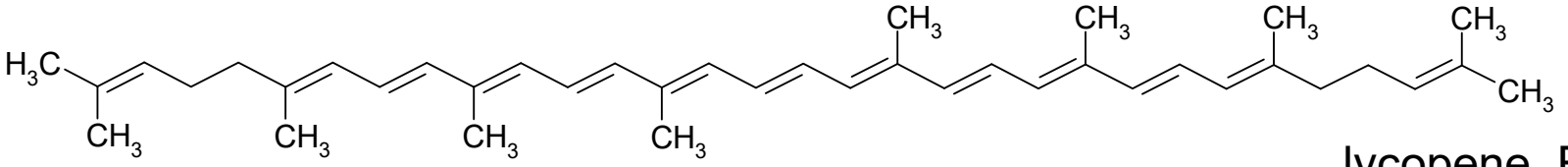


capsanthine, E 160b
•from bell peppers



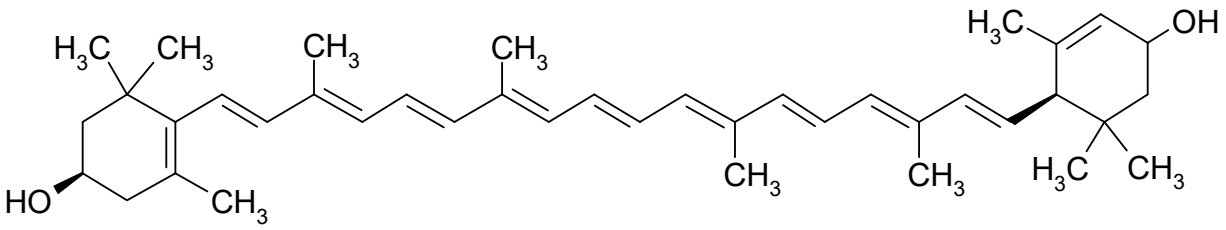
capsorubine, E 160c
•from bell peppers

(capsanthine + capsorubine = bell peppers extract, Paprika oleoresin)

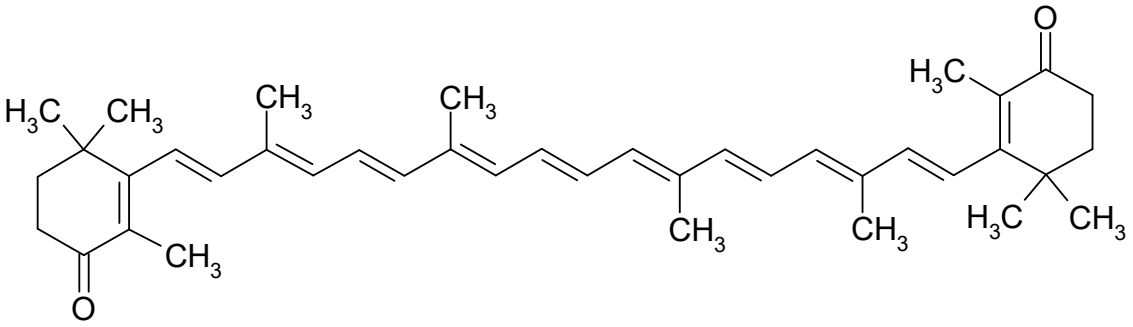


lycopene, E 160d, CI 75125
• from tomatoe
•yellow
•m.p. 175°C
•log $P_{o/w}$ = 17.64

Xanthophyls
•together E 161



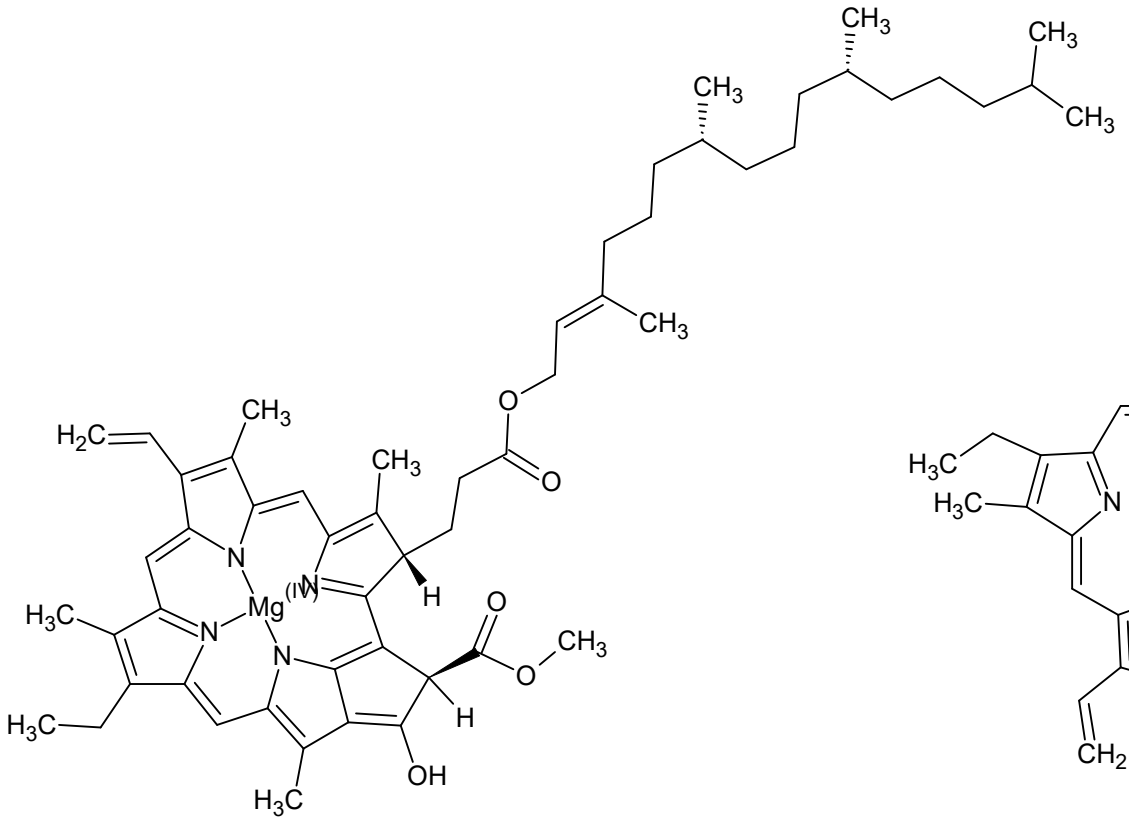
luteine, E 161b
•colourant of the egg yolk
•m.p. 196°C
•log $P_{o/w}$=14.82



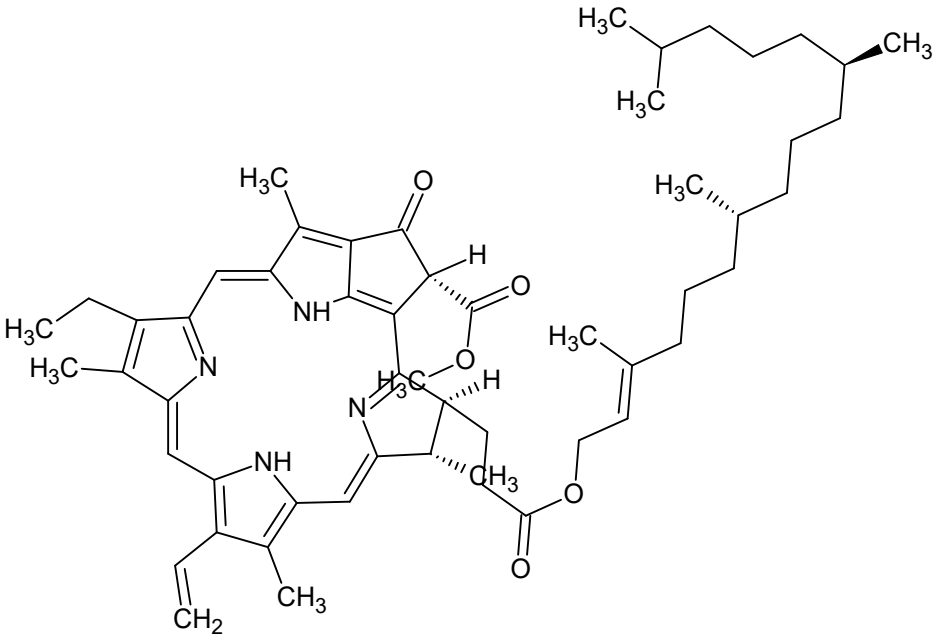
canthaxanthine, CI 40850, E 161g
•orange
•log $P_{o/w}$=14.1
•antioxidant, believed to be a cancer protectant

2.2 Chlorophylls E 140 (i)

CI Natural Green 3, Magnesium chlorophyll, Magnesium phaeophytin



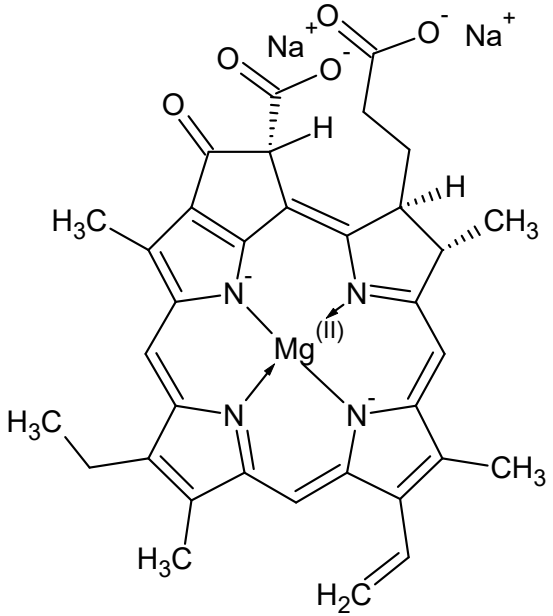
Chlorophyll a = magnesium phaeophytin a

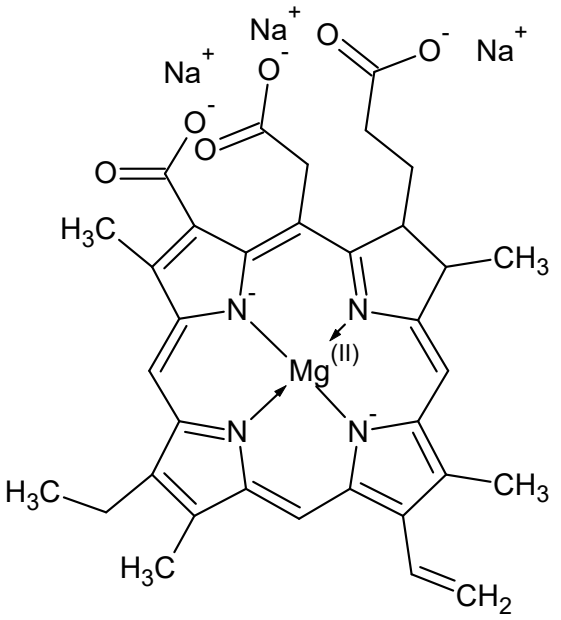


phaeophytin b

$E^{1\%}_{1cm}$ = 700 at ca. 409 nm in chloroform

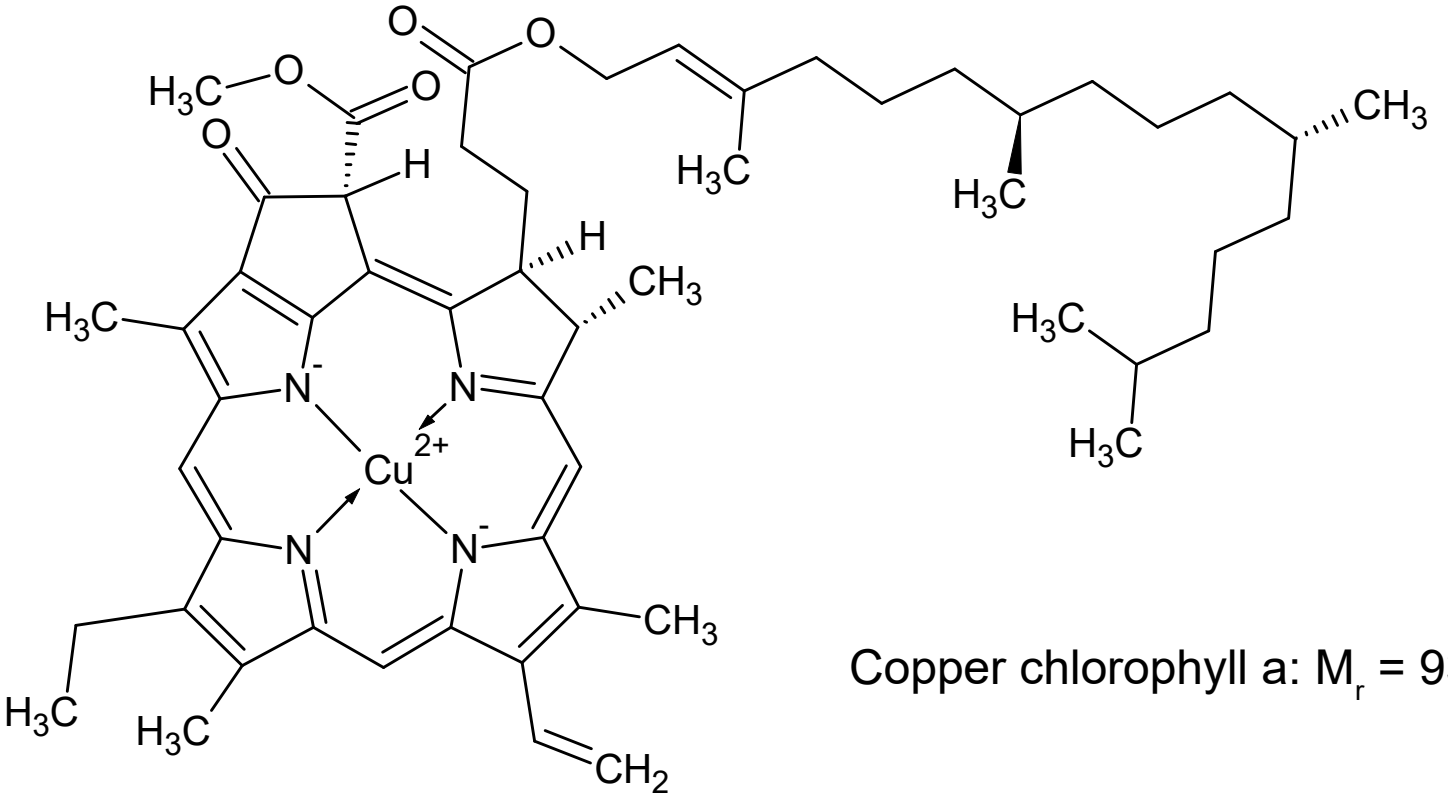
Chlorophyllins E 140 (ii)
CI Natural Green 5; Sodium Chlorophyllin; Potassium Chlorophyllin





- obtained by the saponification of a solvent extract of strains of edible plant material, grass, lucerne and nettle
- $E^{1\%}_{1cm}$ 700 at ca. 405 nm in aqueous solution at pH 9
- $E^{1\%}_{1cm}$ 140 at ca. 653 nm in aqueous solution at pH 9

E 141 (i) Copper complexes of chlorophylls
CI 75810

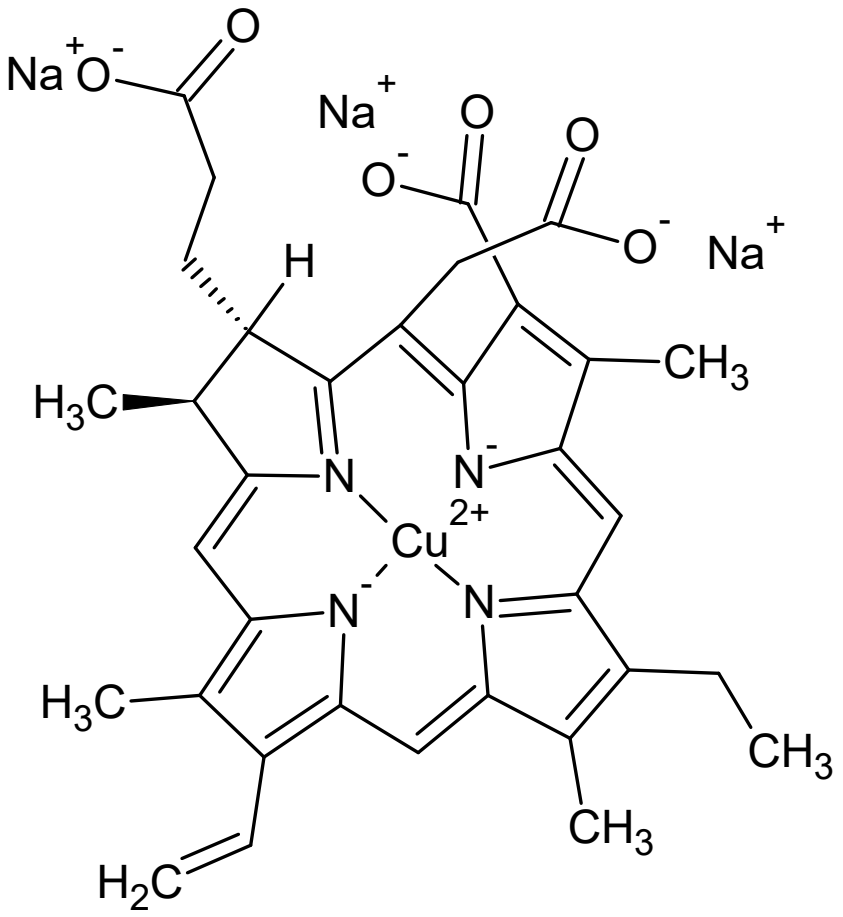


Copper chlorophyll a: M_r = 932,75

Copper chlorophylls are obtained by addition of a salt of copper to the substance obtained by solvent extraction of strains of edible plant material, grass, lucerne *(Medicago sativa),* and nettle *(Urtica dioica)*.

- $E^{1\%}_{1cm}$ = 540 at ca. 422 nm in chloroform
- $E^{1\%}_{1cm}$ 300 at ca. 652 nm in chloroform

E 141 (ii) Chlorophyllin copper sodium complex
CI 75810, [11006-34-1]



$E^{1\%}_{1cm}$ = 565 at ca. 405 nm in aqueous phosphate buffer at pH 7,5

$E^{1\%}_{1cm}$ = 145 at ca. 630 nm in aqueous phosphate buffer at pH 7,5

LD_{50} *p.o.*, mouse = 7 g / kg

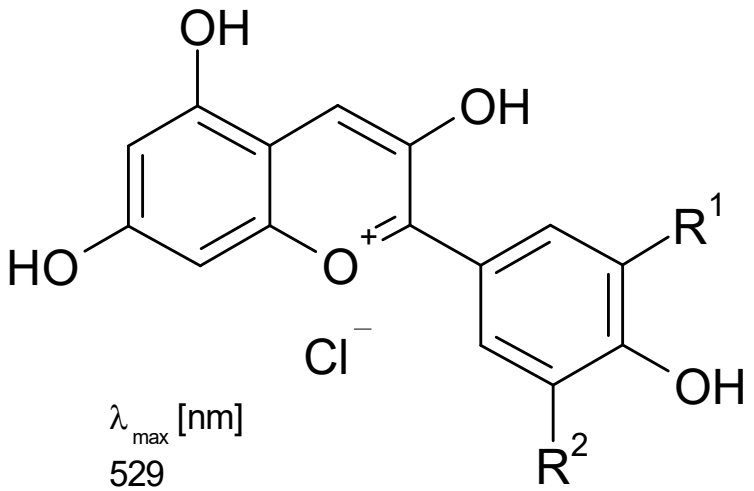
2.1 Hydrophilic organic dyes

2.1.1 Fused-rings glycosides, pseudoglycosides and their aglycones

Anthocyanidines

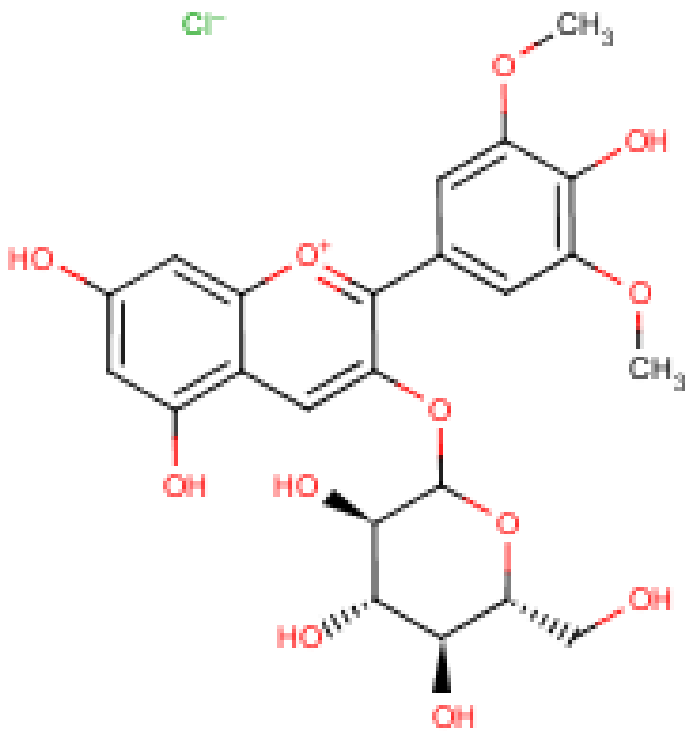
= hydroxylated and methoxylated derivatives of 2-phenylbenzopyrylium

- together E 163
- aglycones of anthocyanins



Name	R^1	R^2	origin	m.p. [°C]	log $P_{o/w}$	colour	λ_{max} [nm]
pelargonidine	H	H	*Pelargonium*	> 350	2.68	salmon	529
kyanidin	OH	H	*Cyanus*	> 300	2.2	red	544
delphinidine	OH	OH	*Delfinium*	> 350	2.14	blue	553
peonidine	OCH_3	H	*Peaeonia*			red	543
petunidine	OCH_3	OH	*Petunia*			blue-red	522
malvidine	OCH_3	OCH_3	*Malva*	> 300; 202-203	2.33	pink-red	553

- in plants as glycosides in most in position 3, particularly esterified with subst. cinnamic acids or acetic acid in pos. 6
- the colour of free aglycons depends on pH: blue in alkaline, red in acidic, this is not valid for glycosides
- increasing number of hydroxyles results in a more intense colour, methylation of hydroxyles shifts the shade from blue to red



malvidine-3-glucoside

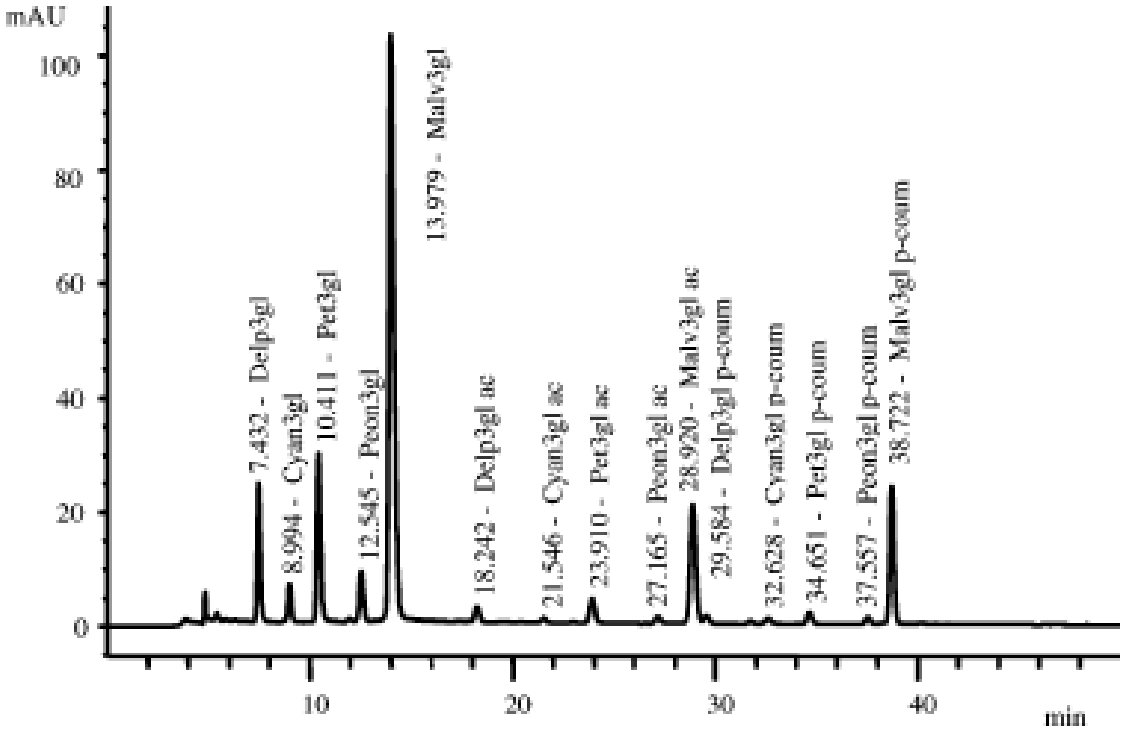
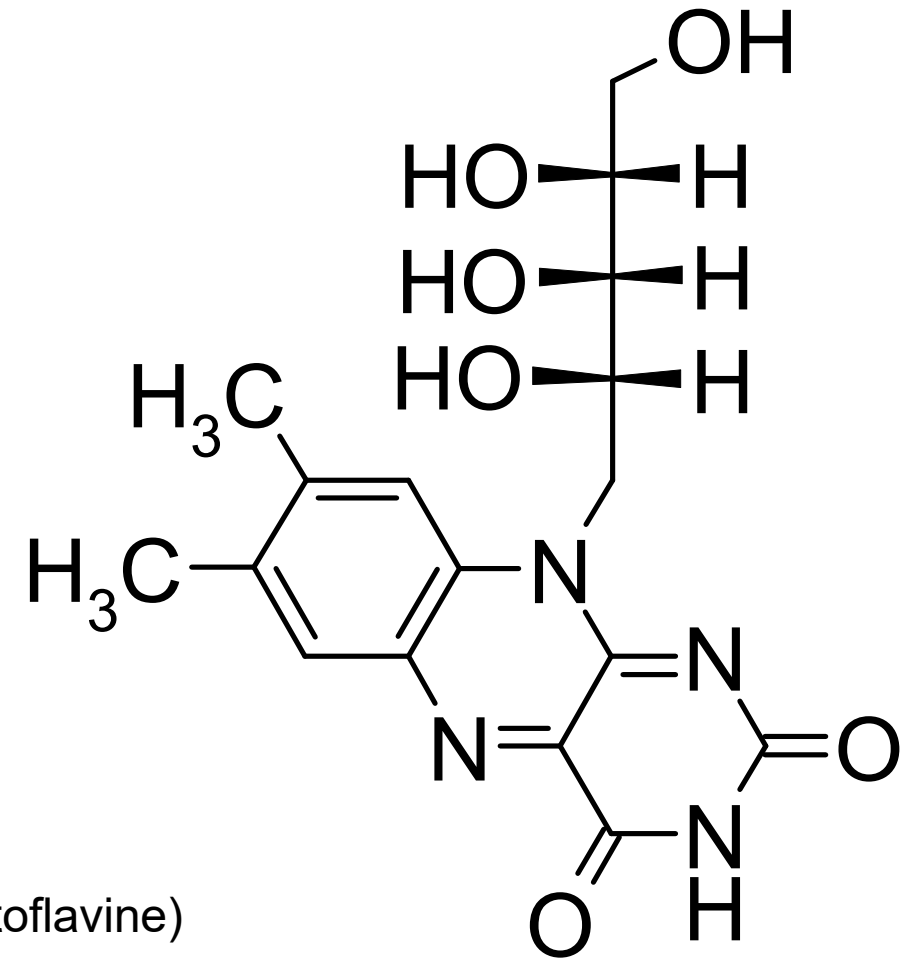
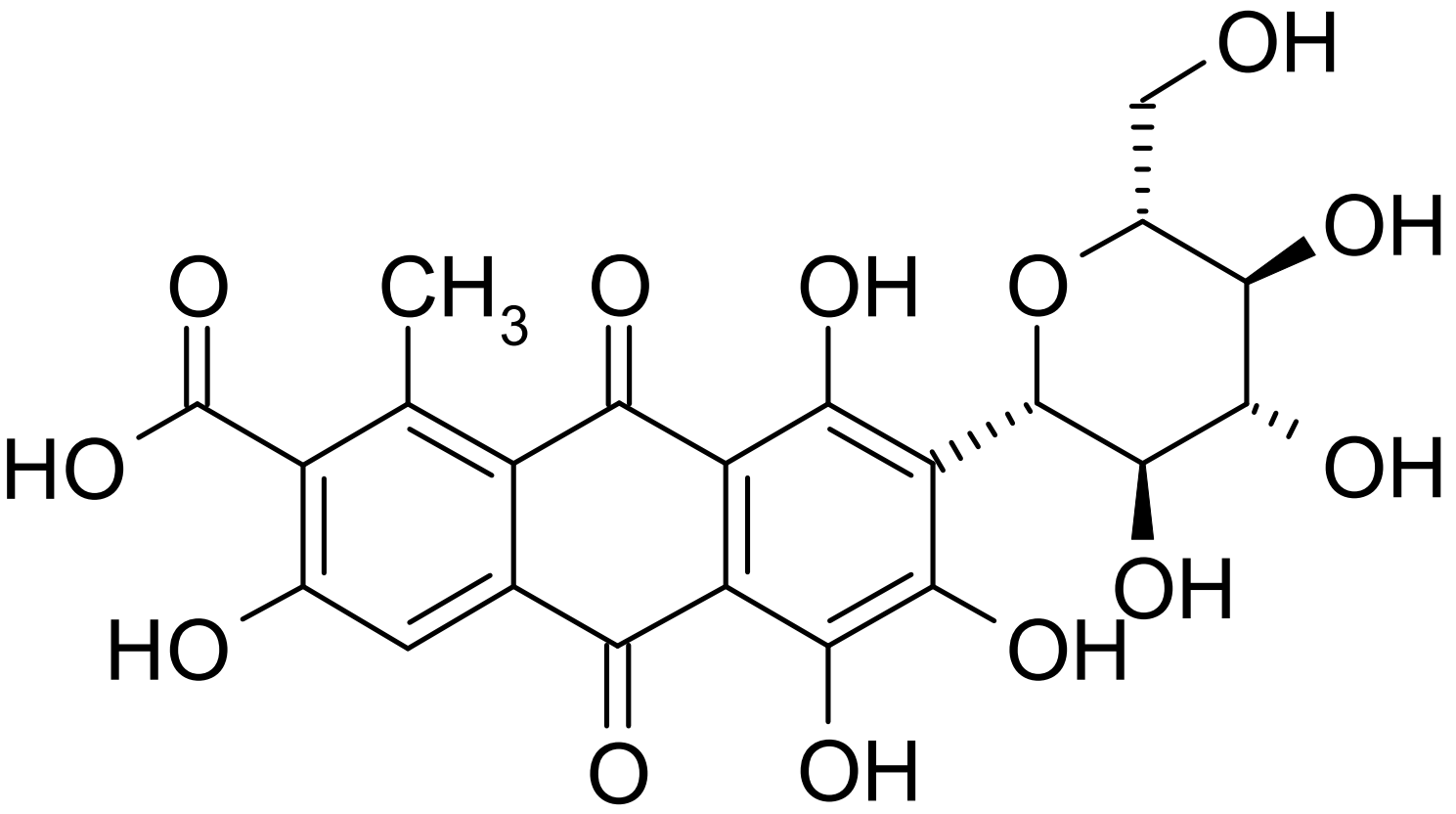


Figure 1. Representative profile of a grape extract analyzed by reversed phase HPLC at 520 nm, as described under Materials and Methods: delphinidin 3-glucoside (Delp3gl), cyanidin 3-glucoside (Cyan3gl), petunidin 3-glucoside (Pet3gl), peonidin 3-glucoside (Peon3gl), malvidin 3-glucoside (Malv3gl), and their corresponding acetic acid (ac) and *p*-coumaric acid esters (p-coum).



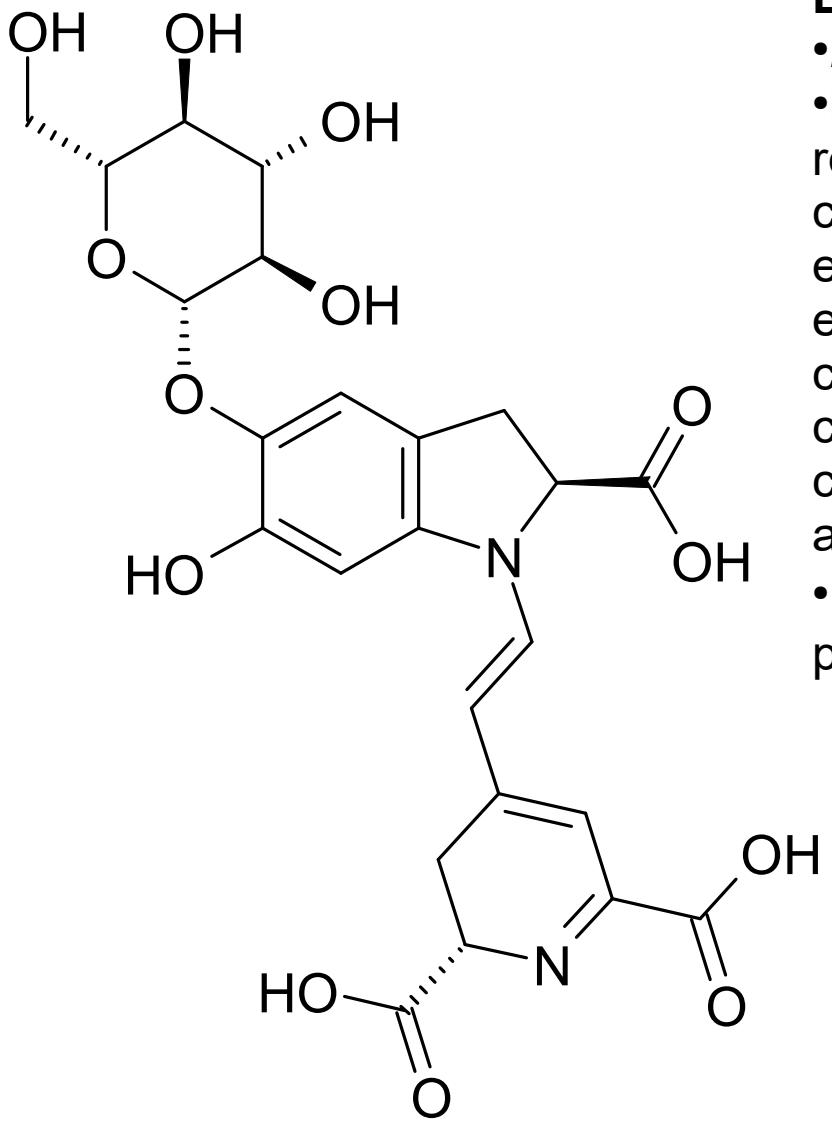
Riboflavine (vitamin B2, lactoflavine)
E 101

- yellow
- listed in PhEur, CzP2009, BP, USP, JP
- Relative absorbance $A_{373\ nm} / A_{267\ nm} = 0.31 – 0.33$, $A_{444\ nm} / A_{267\ nm} = 0.36 – 0.39$



Carmine (= carminic acid, coccinellin, cochineal extract, CI 75470, E 120)

- deeply red
- fruit odour
- water solubility cca 30 g / l
- obtained from aqueous, aqueous alcoholic or alcoholic extracts from Cochineal, which consists of the dried bodies of the female insect *Dactylopius coccus* Costa.
- λ_{max} (buffer pH = 3) = 490 – 493 nm; cca 494 in diluted HCl
- $E^{1\%}_{1cm}$ 139 at peak around 494 nm in diluted HCl



betanin

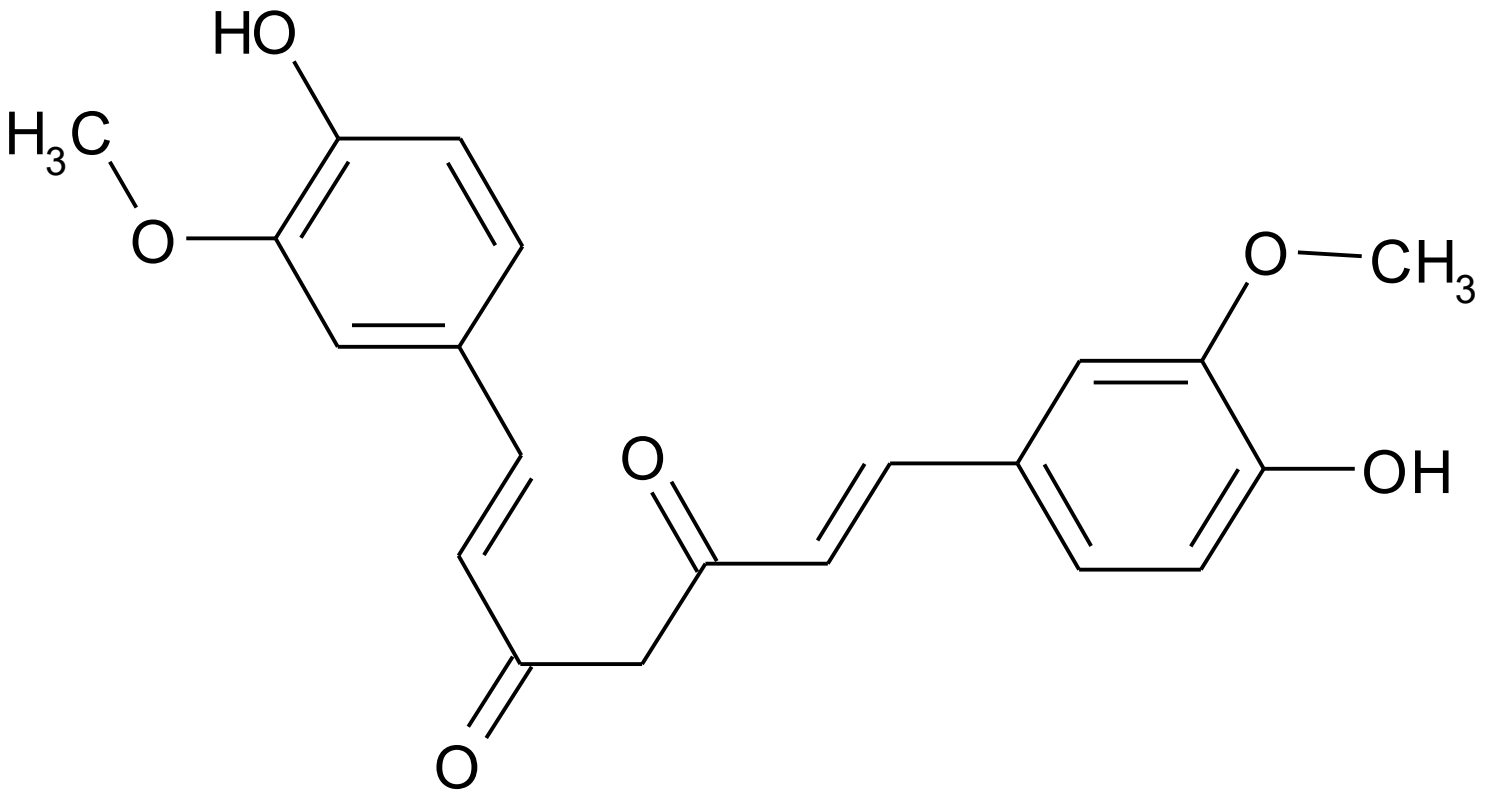
Beetroot red, Betanin, E 162, beet red

•*Beta vulgaris*

•**Beet red** is obtained from the roots of strains of red beets (*Beta vulgaris* L. *var. rubra*) by pressing crushed beet as press juice or by aqueous extraction of shredded beet roots and subsequent enrichment in the active principle. The colour is composed of different pigments all belonging to the class betalaine. The main colouring principle consists of betacyanins (red) of which **betanin** accounts for 75-95 %.

•$E^{1\%}_{1cm}$ 1 120 at ca. 535 nm in aqueous solution at pH 5

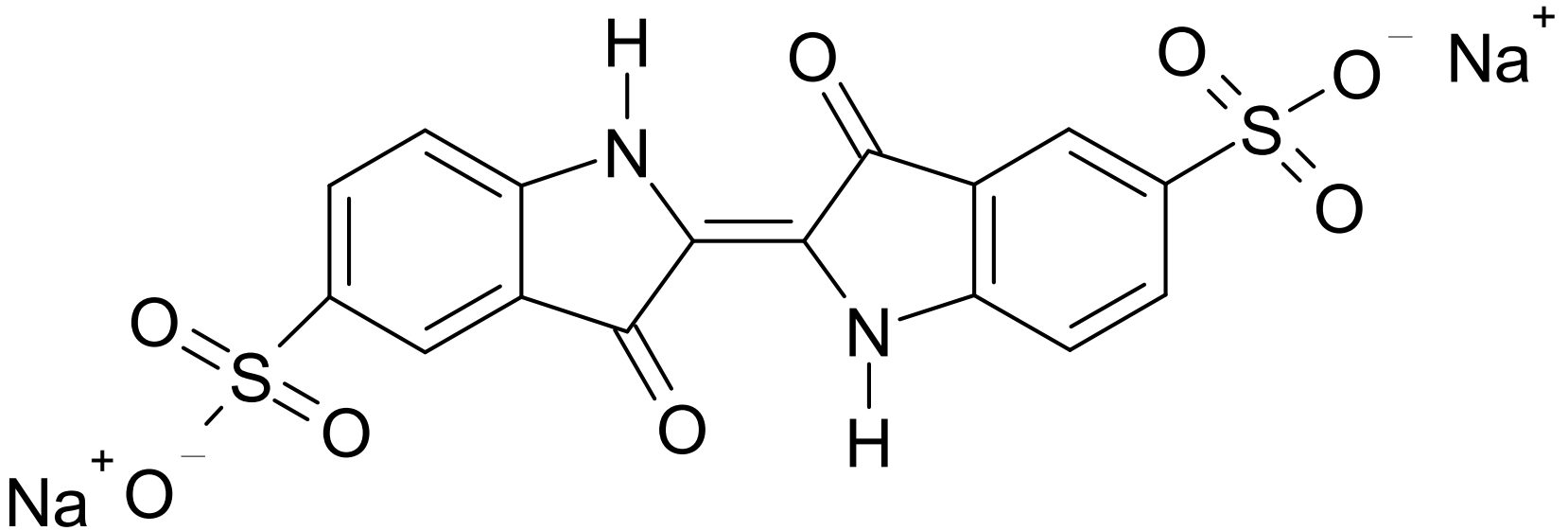
2.2.2 Phenolic dyes not based on fused rings



Curcumin

E 100
- yellow-orange
- approved in EU
- from turmeric root (*Curcuma longa*)

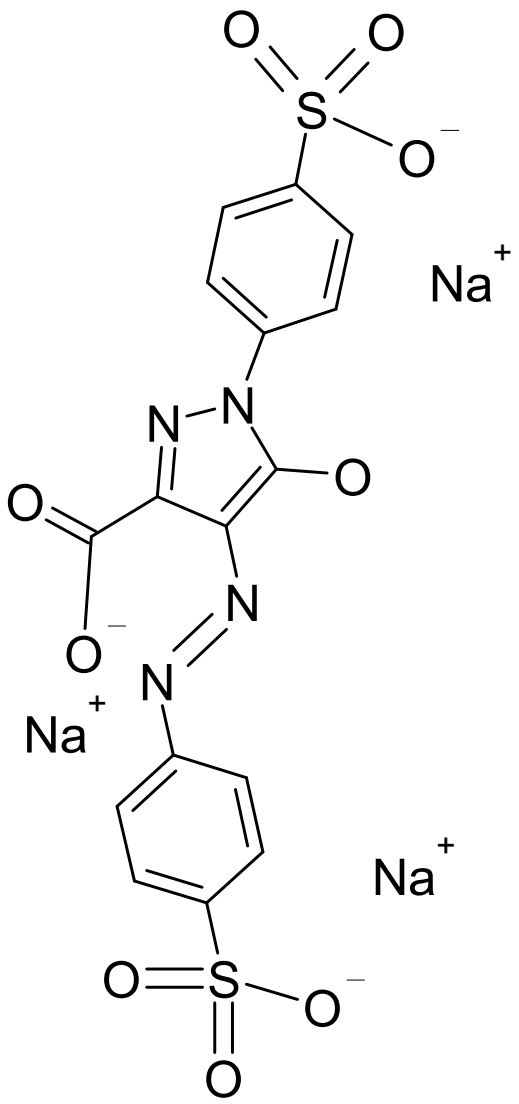
2.2.3 Indole dyes



indigo carmine
indigotin disulfonate sodium [USP]
E 132, CI 73015, FD&C blue #2
Disodium 3,3′-dioxo-2,2′-bi-indolylidene-5,5′-disulfonate

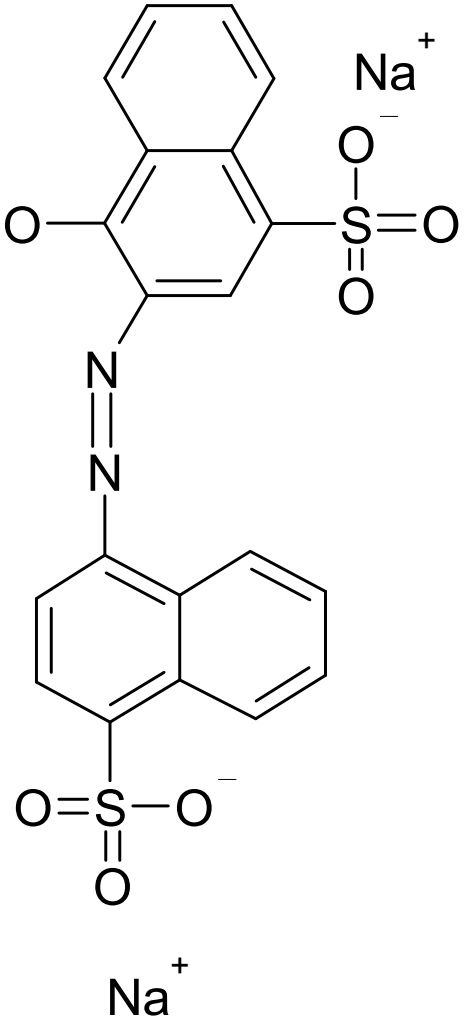
- deeply blue powder, aqueous solutions are blue or blue-purple
- λ_{max} = 610 nm in aquaeous solution
- $E^{1\%}_{1cm}$ = 480 at ca. 610 nm in aqueous solution
- LD_{50} *p.o.*, rat = 2g / kg

2.2.4 Hydrophilic azo-dyes



tartrazine, CI 19140, E 102,
acidic yellow 23, egg yellow A

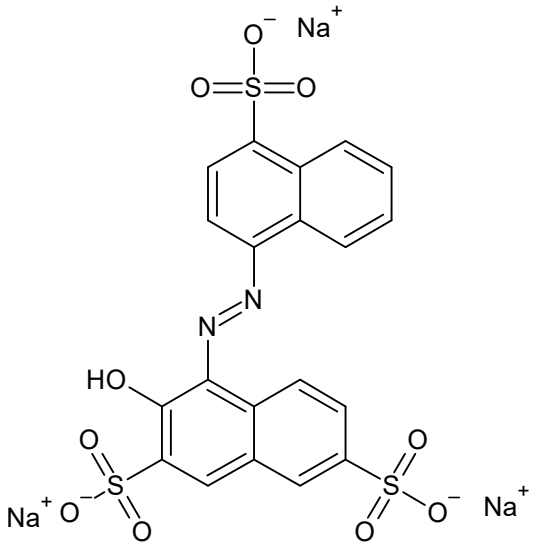
- orange-yellow
- log $P_{octanol/water}$ = -10.17
- $E^{1\%}_{1cm}$ = 530 at ca. 426 nm in aqueous solution



carmoisine, azorubin, E 122,CI 14720, C.I. Acid Red 14, chromotrop FB

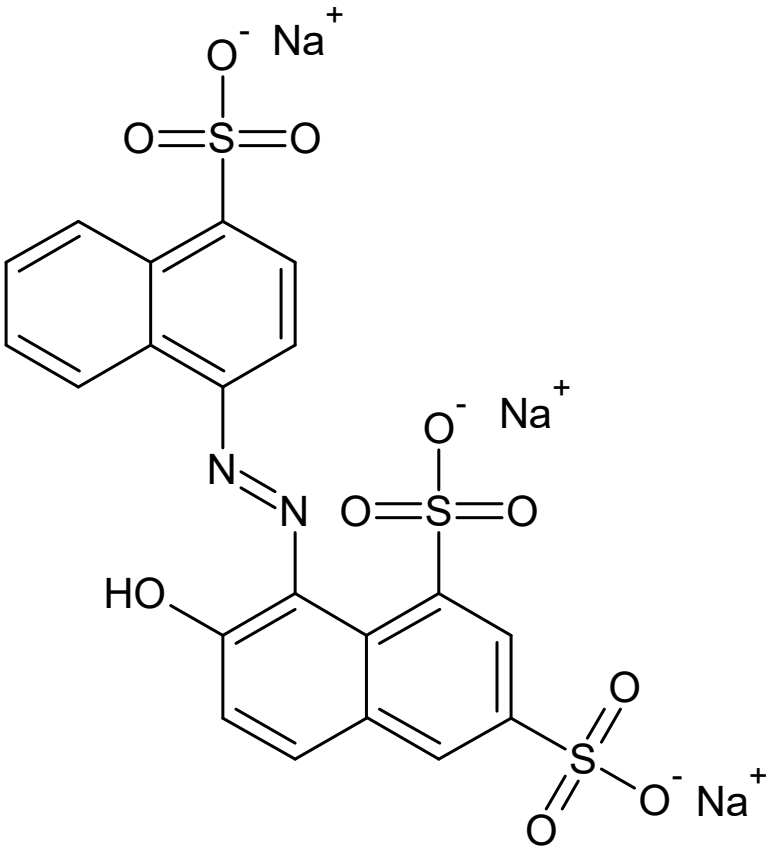
- LD_{50}(*p.o.*, mouse) = 8 g / kg
- $E^{1\%}_{1cm}$ = 510 at ca. 516 nm in aqueous solution

2.2.4 Hydrophilic azo-dyes



amaranth, E123, CI Food Red 9, Amaranth [USP]
$E_{1\%}^{1cm}$ = 440 at cca. 520 nm in aqueous solution
LD_{50} *i.p., i.v.* rat = 1 g / kg

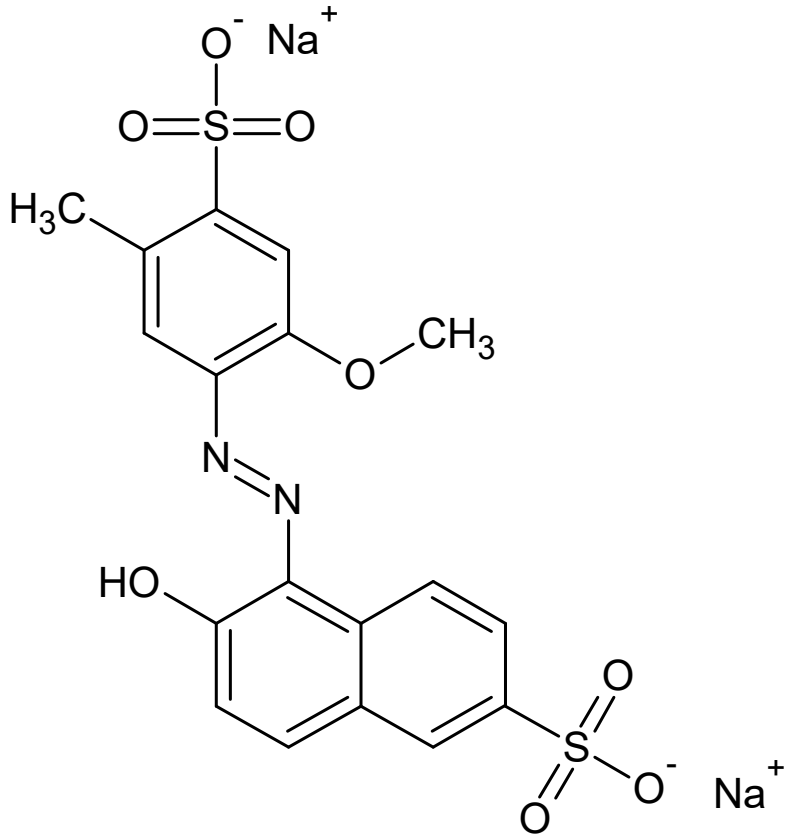
2.2.4 Hydrophilic azo-dyes



ponceau 4R, cochineal red A, E 124, Acid Red 18

$E^{1\%}_{1cm}$ = 430 at λ_{max} cca. 505 nm in aqueous solution

LD_{50} *p.o.*, *mouse* = 8 g/kg

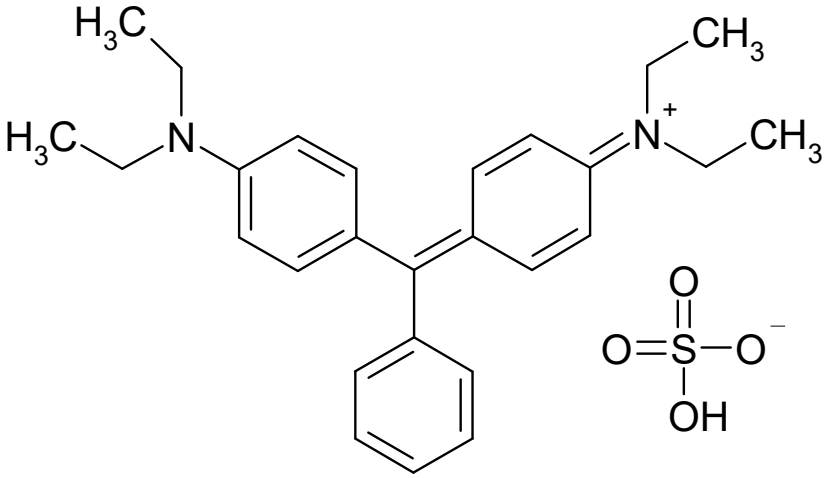


allura red AC, CI Food Red 17, E 129

$E^{1\%}_{1cm}$ 540 at λ_{max} cca. 504 nm in aqueous solution at pH 7

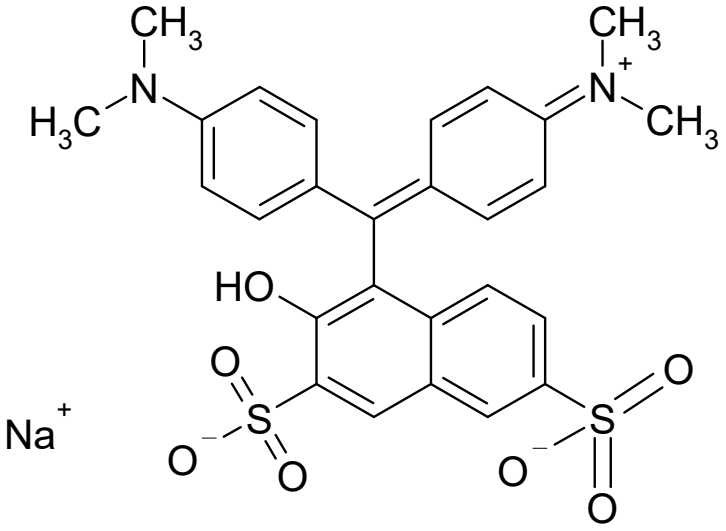
LD_{50} *p.o.*, *dog* > 5 g/kg

2.2.5 Hydrophilic triarylmethane dyes



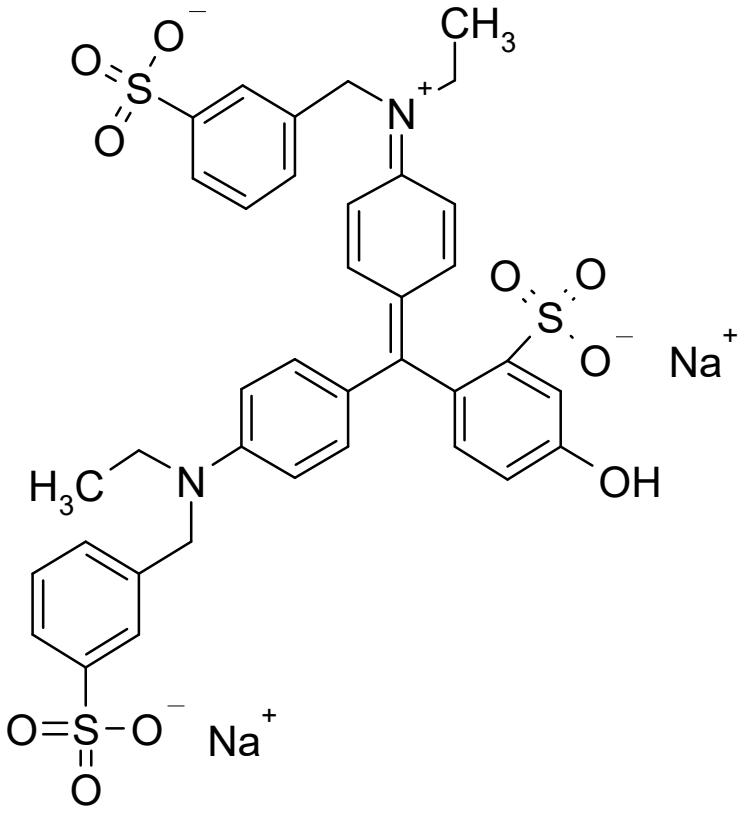
Brilliant Green, CI 42040, *Viride nitens*, Malachite Green G, Emerald Green

- not approved as medicines and food colorant, but listed in many pharmacopoeias as a therapeutic (antiseptic)
- m.p. 210°C
- log $P_{o/w}$=2.01
- LD_{50} = 3 - 8 mg / kg



- **Acid Green 50,** Green S, CI 44090, E 142, Brilliant Acid Green BS, Food Green S
- LD_{50} *p.o.*, rat = 2 g / kg
- $E^{1\%}_{1cm}$ = 1 720 at ca. 632 nm in aqueous solution

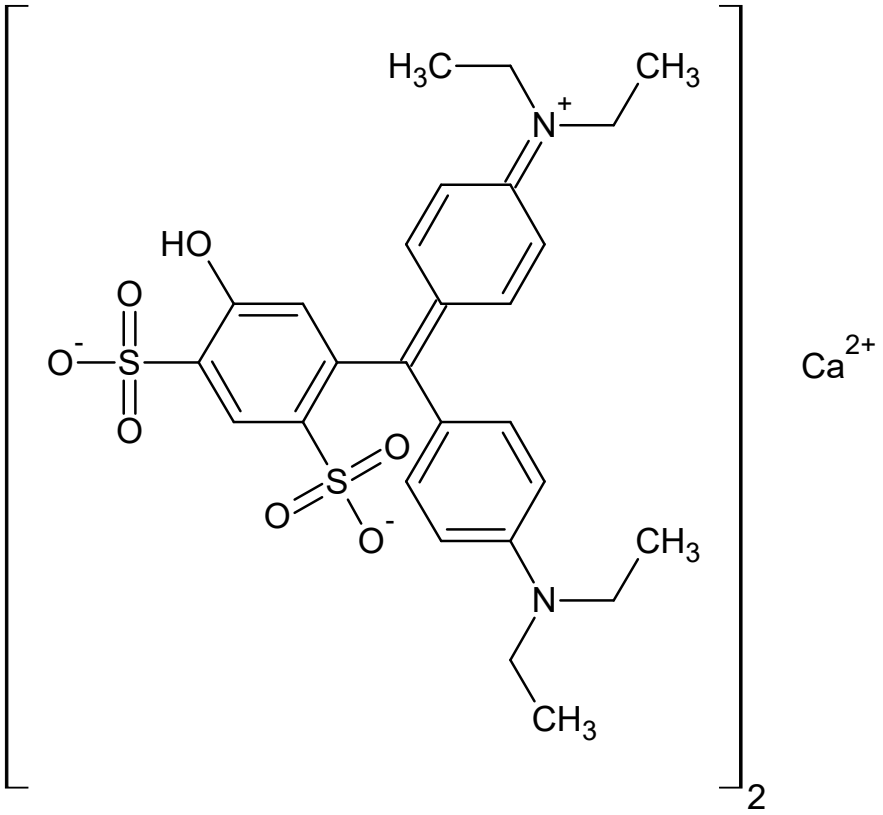
2.2.5 Hydrophilic triarylmethane dyes (continued)



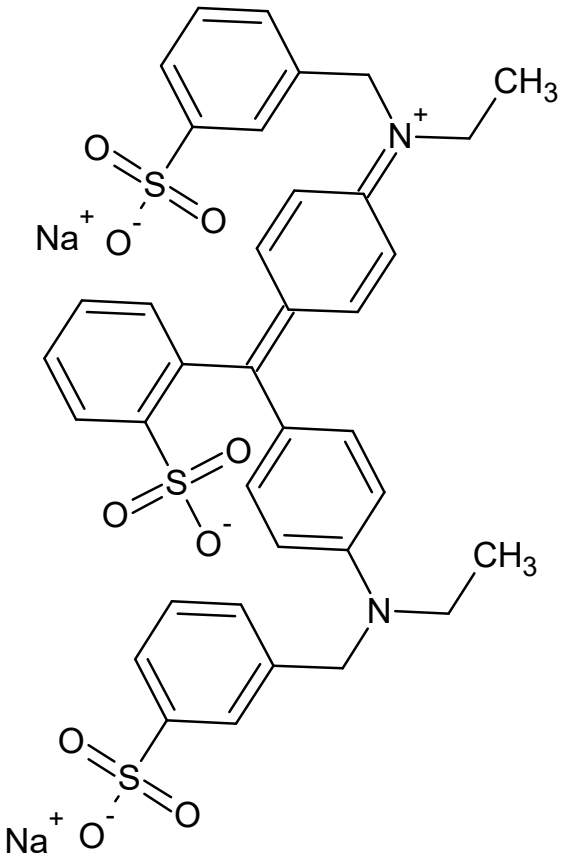
Fast green FCF, CI 42053, Solid Green FCF, Food Green 3

- λ_{max}(ethanol 50 %) 622 - 626 nm
- spec. absorbance $A^{1\%}_{1cm}$ (λ_{max}; 0.003 g/l; ethanol 50%) = 1360 – 1610
- log P o/w = -5.42

2.2.5 Hydrophilic triarylmethane dyes (cntinued)

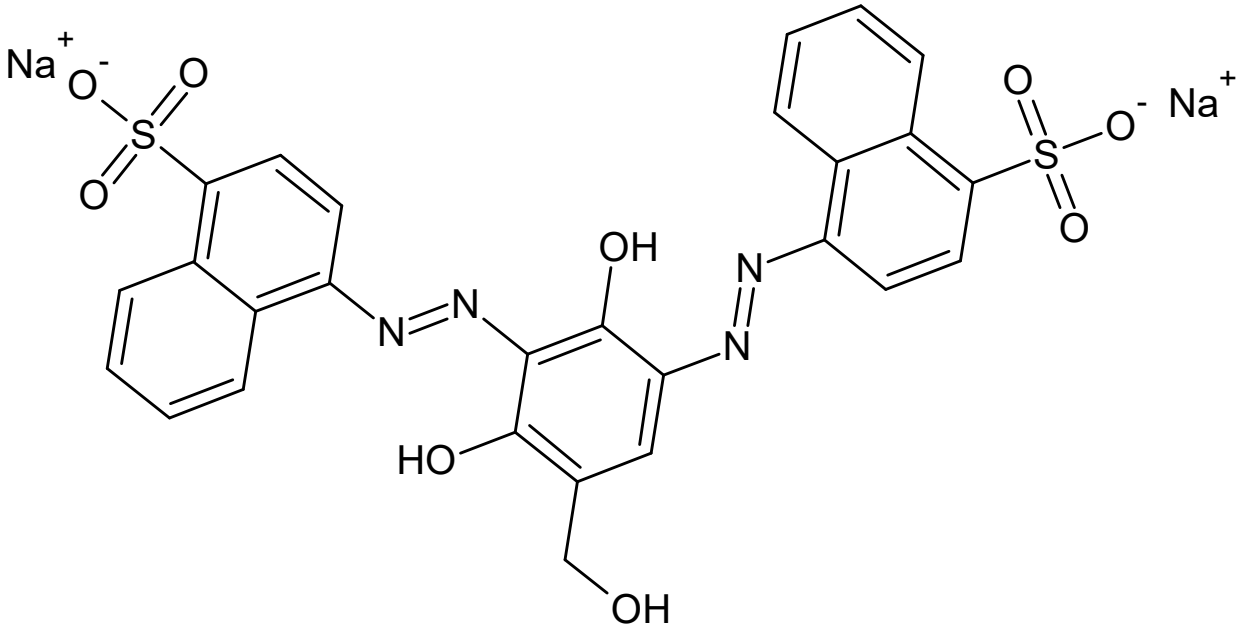


patent blue V, CI Food Blue 5, E 131, acid blue 3
$E^{1\%}_{1cm}$ = 2 000 at ca. 638 nm in aqueous solution at pH 5
LD_{50} *i.v.*, mouse = 1,2 g/kg



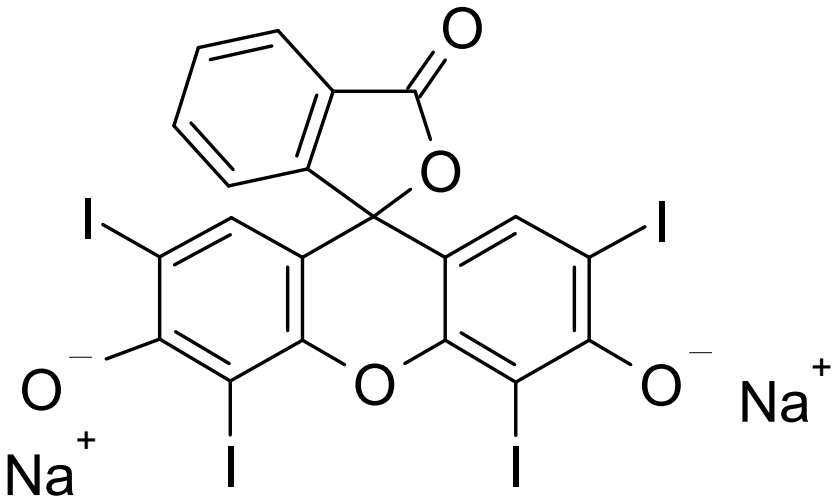
brilliant blue FCF, CI Food Blue 2, E 133
$E^{1\%}_{1cm}$ = 1 630 at ca. 630 nm in aqueous solution
LD_{50} *s.c.*, mouse = 4,6 g/kg

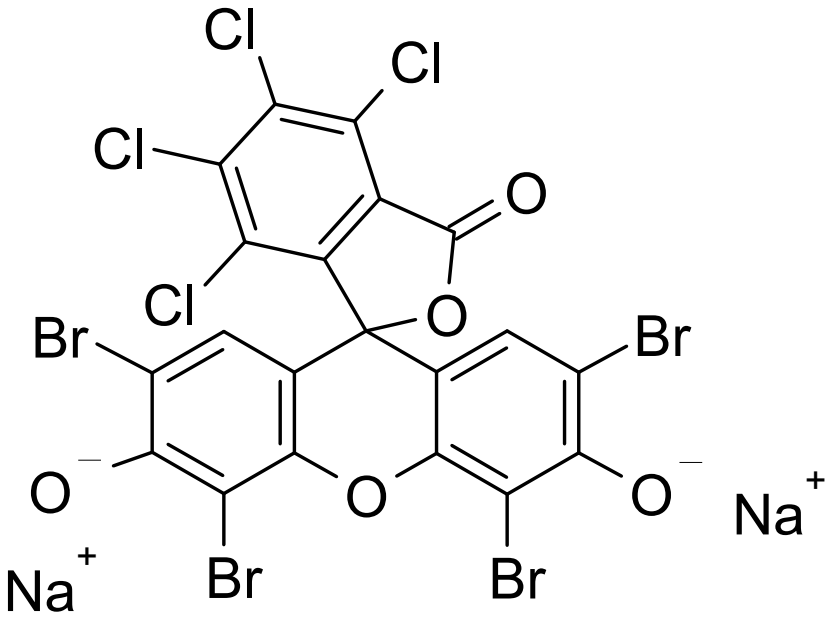
2.2.5 Hydrophilic triarylmethane dyes (continued)



E 155 Brown HT, Chocolate brown HT, CI Food Brown 3

- reddish-brown powder or granules
- $E^{1\%}_{1cm}$ = 403 at ca. 460 nm in aqueous solution at pH 7
- LD_{50} *p.o.* rat, mouse > 2 g / kg





Erythrosine (erythrosine B, CI 45430, E 127)

CI Food Red 14

reddish-brown

λ_{max} (water) = 524 - 527 nm

specific absorbance

$E^{1\%}_{1cm}(\lambda_{max}$; water; pH = 7) = 1100

LD_{50}(*p.o.*, rat) = 1.84 g / kg

log P = -0,29

Phloxine B (CI45410, D&C red #28, Eosine Blue)

not approved in EU

deeply brown

λ_{max} (ethanol 50%) = 546 – 560 nm

$A_{1cm}(\lambda_{max}$; 0.005 g/l; ethanol 50%) = 930 - 1400

LD_{50}(*p.o.*, rat) = 8.4 g / kg