

# Industrial Preparative Chromatography

Ladislav Cvak



Galena

IVAX



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# Preparativní chromatografie



1903 Michail Cvet

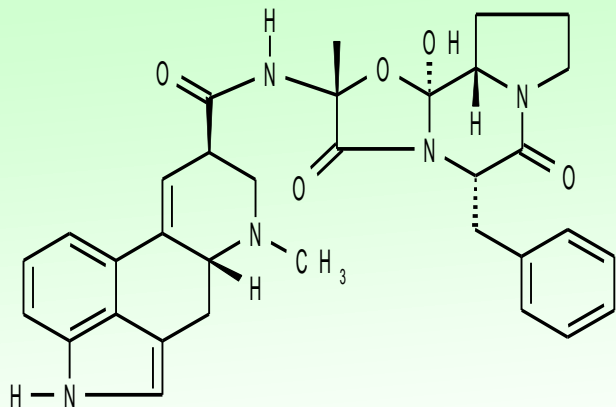
Organická syntéza  
50 – 100 násobek  
Silikagelu  
Desítky frakcí

Izolace nečistot  
Komerční systémy

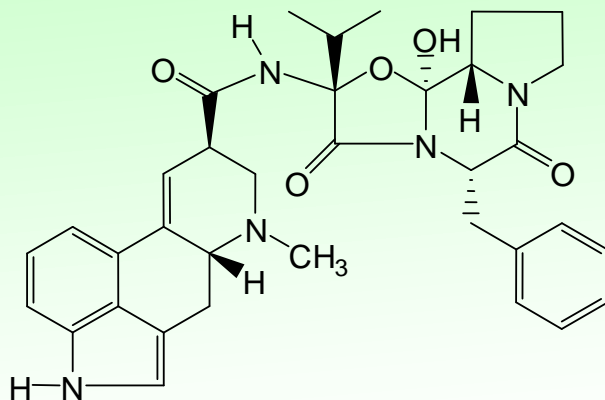
Biochromatografie



# Námelové alkaloidy



Ergotamin



Ergocristin

**Surový Ergocristin 3 – 5 % Ergotaminu**

**Chromatografie na 3 dílech silikagelu**

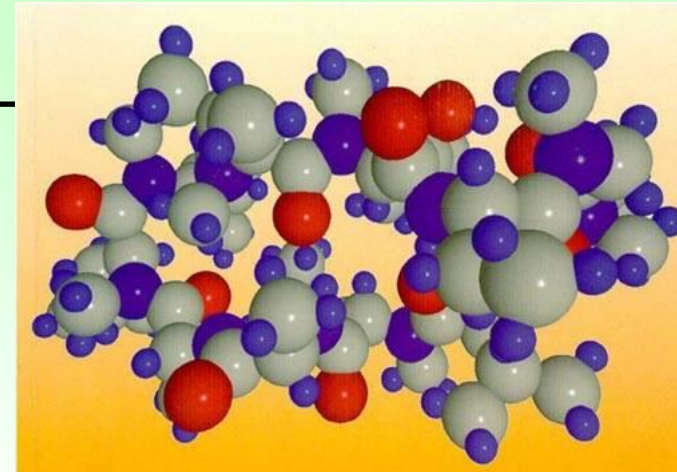
**Mobilní fáze: CH<sub>2</sub>Cl<sub>2</sub> – Ether 1 : 1**

**Jiné aplikace**

- Odbarvení reakční směsi



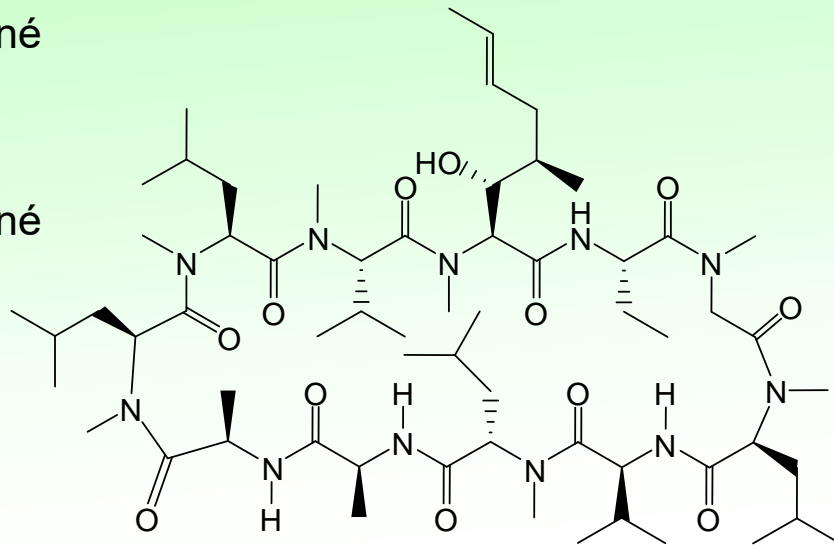
# Cyclosporin



← Nečistoty odstranitelné  
krystalizací

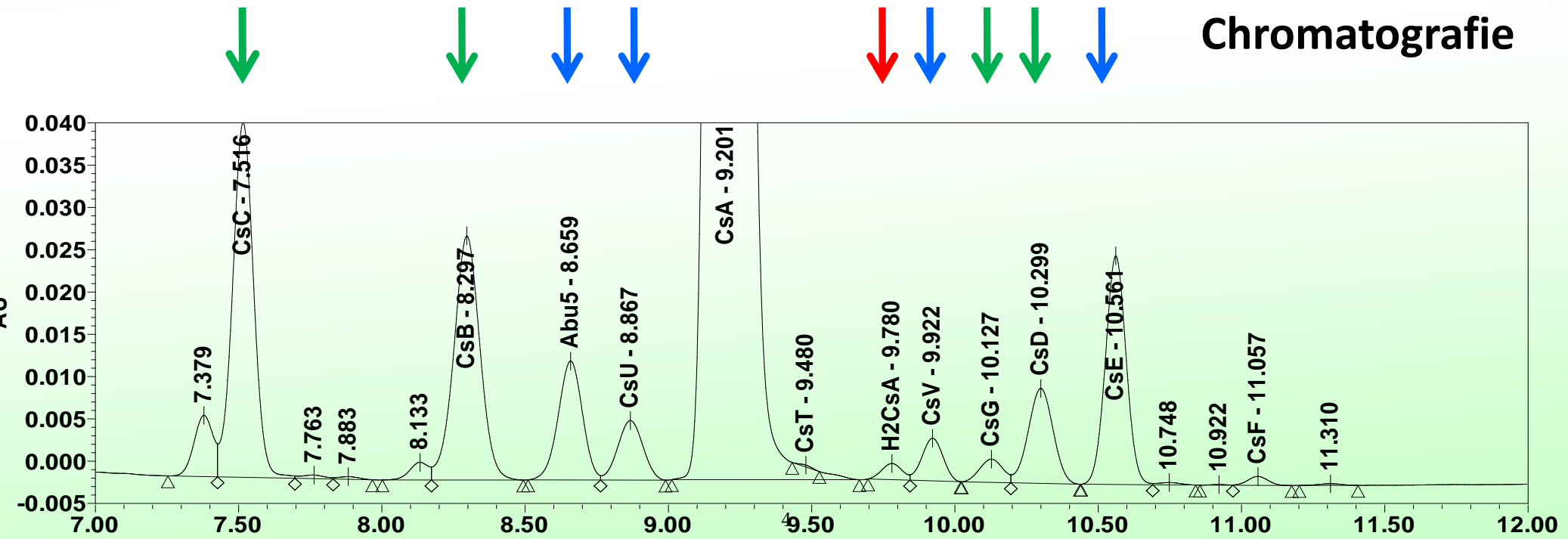
← Nečistoty odstranitelné  
chromatografií

← Kritická nečistota  
– neodstranitelná

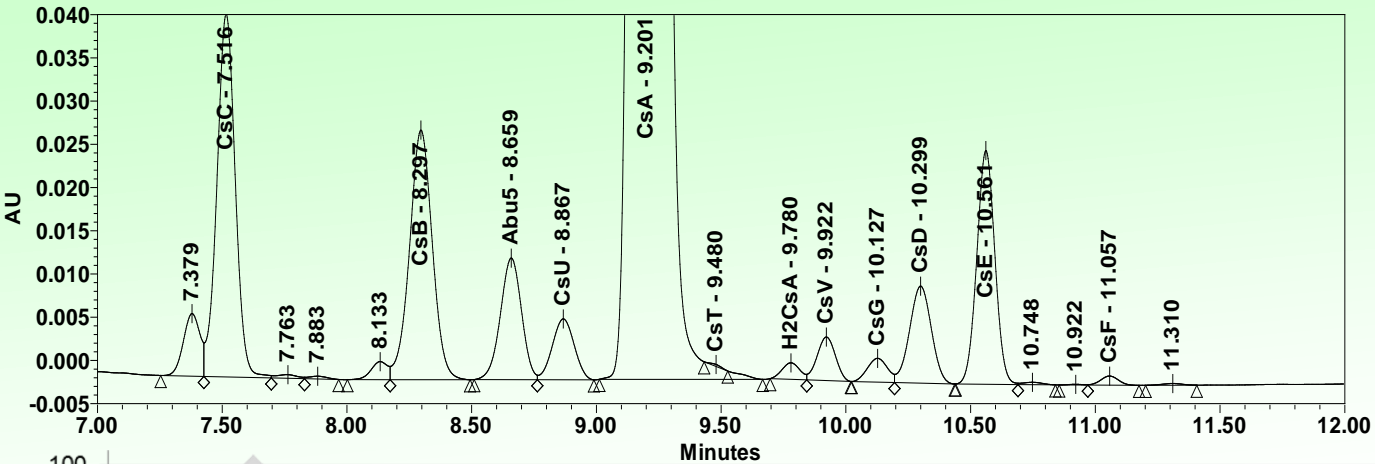


Cyklosporin A

**Krystalizace  
versus  
Chromatografie**

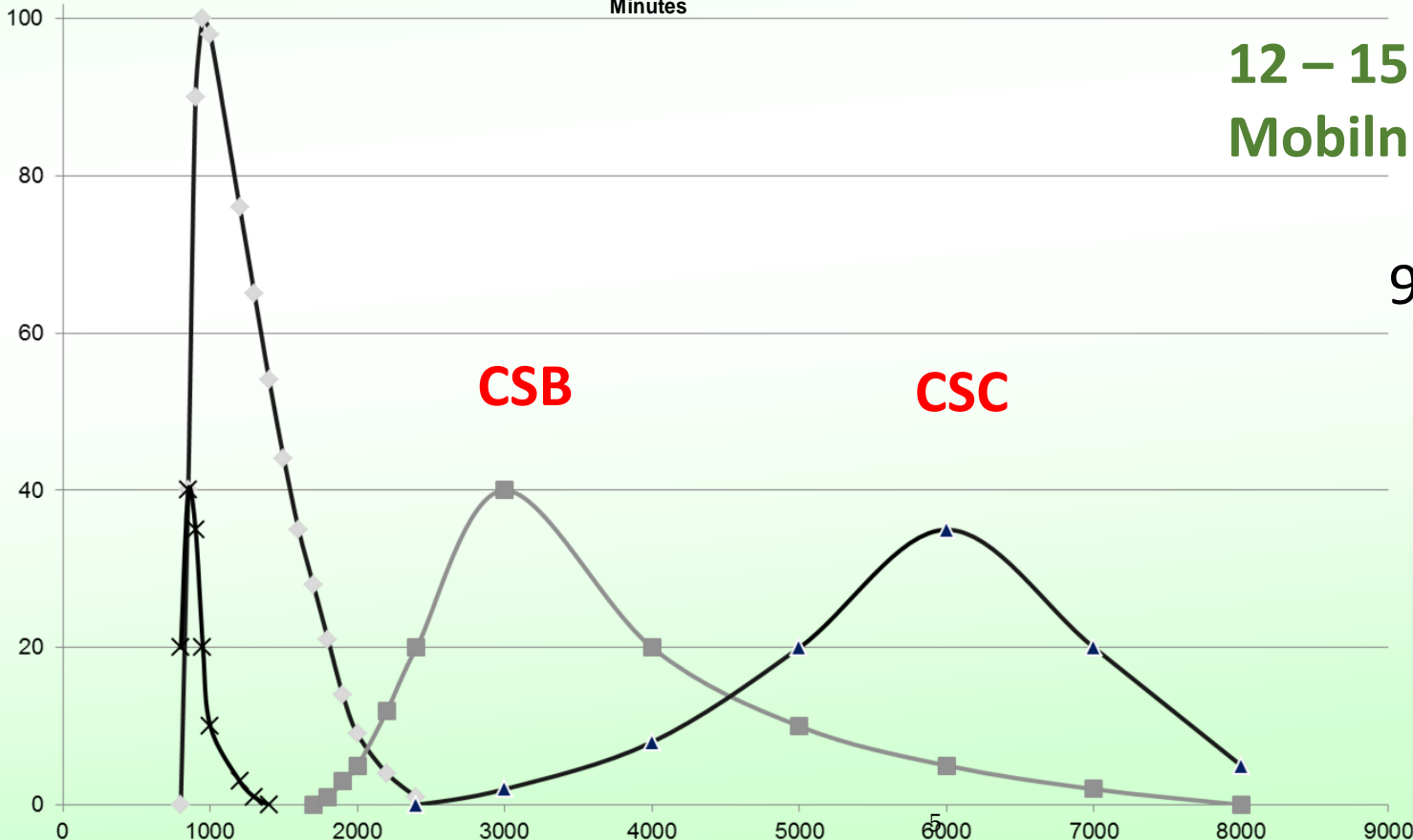


# Chromatografie of cyclosporinu



12 – 15 násobek silikagelu  
Mobilní fáze: Ethylacetát

9 m<sup>3</sup> Mobilní fáze



# Chromatografie cyclosporinu



Stará kolona  
10 bar  
250 kg silicagel  
drcený  
40 - 60 $\mu$ m  
Ethylacetát  
65 °C

Nástřik  
12 – 15 kg  
Surový CS

Detektor

Stovky cyklů



# Chromatografie cyclosporinu

## Nová kolona Separlab

60 bar

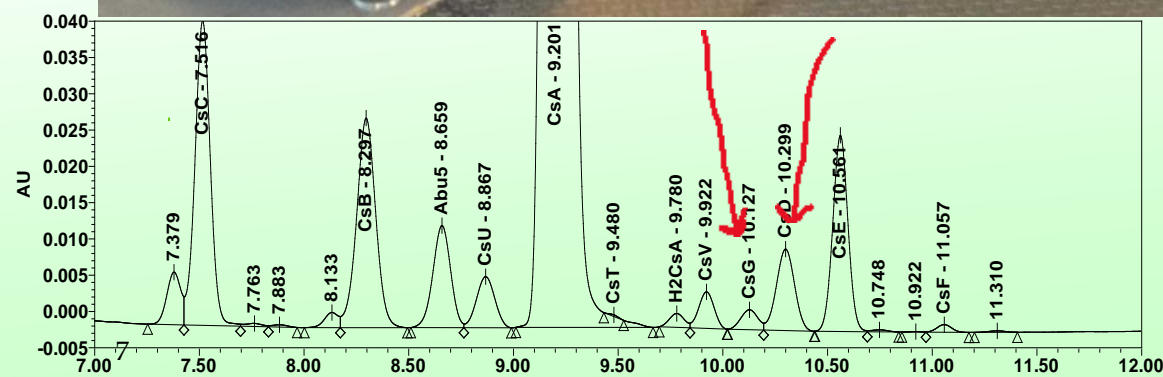
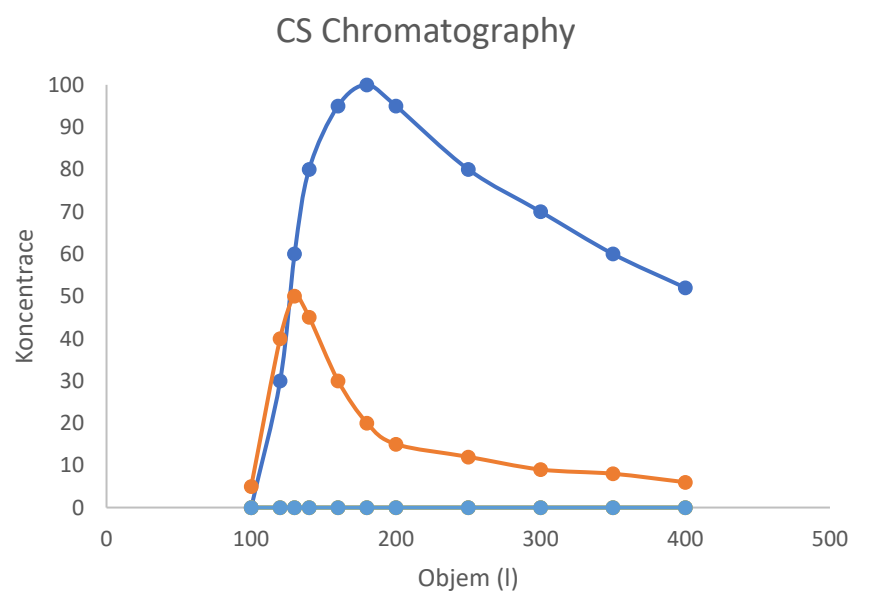
Axiální komprese

220 kg silicagel

Sférický 15 $\mu$ m

Ethylacetát

65 °C



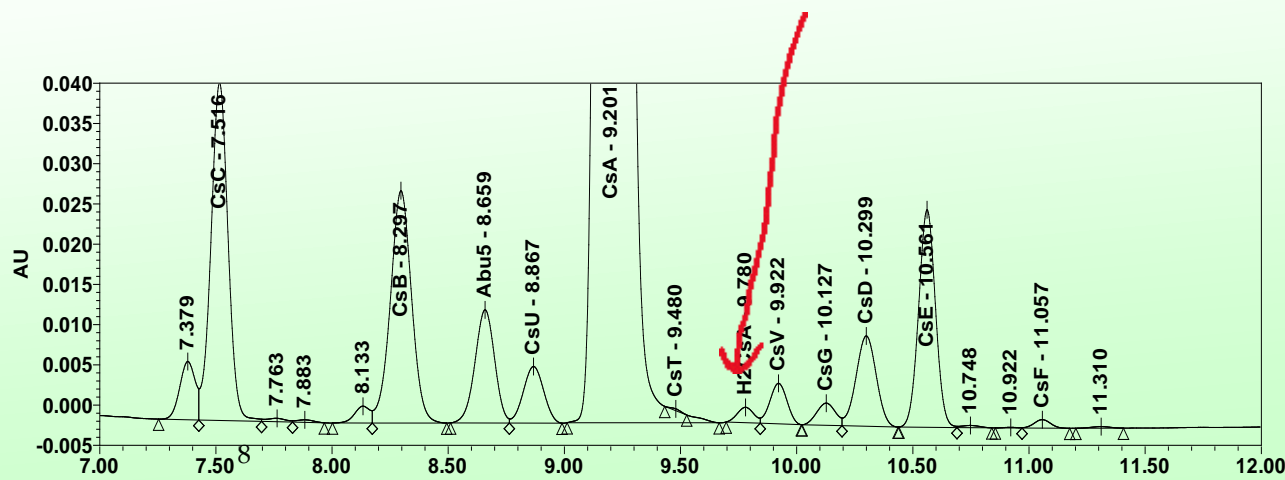


ID 1600 mm

Bed Hight 4000 mm

Bed Volume 8 m<sup>3</sup>

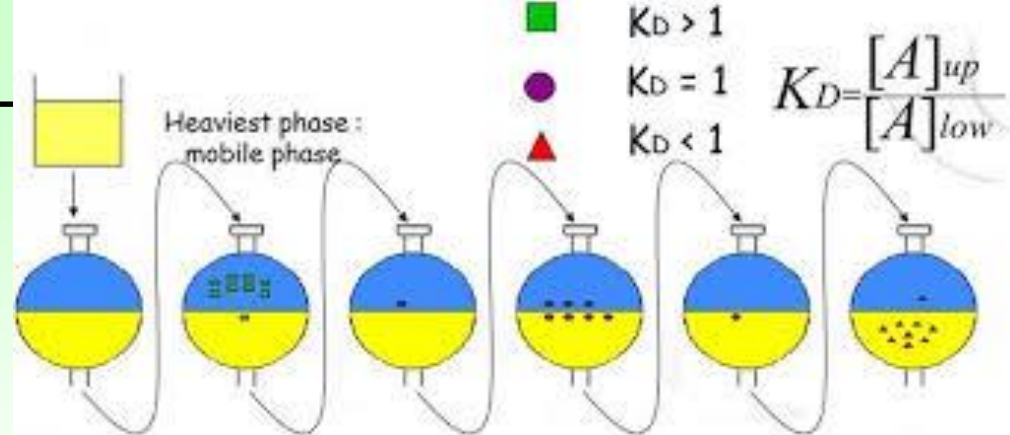
Pressure 50 bar





# CPC Centrifugal Partition Chromatography

# LL-CCC Liquid-Liquid Counter Current Chromatography

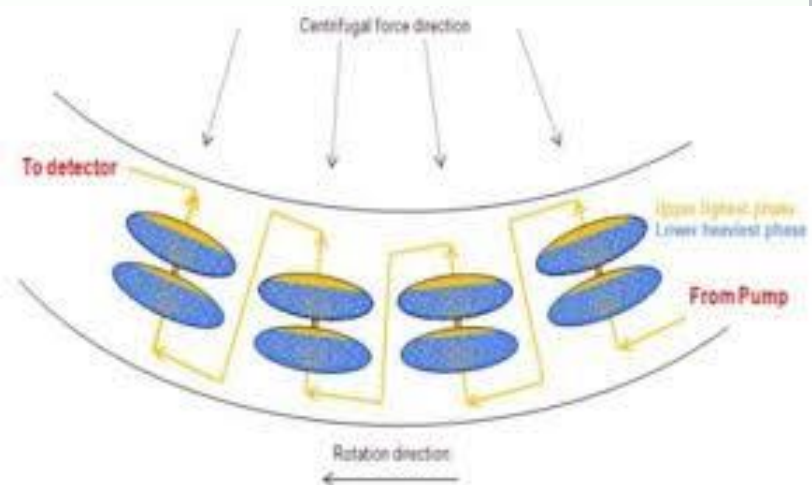


## Rotachrom

Craig

$\text{CH}_2\text{Cl}_2 - \text{MeOH} - \text{H}_2\text{O}$

Hexan - EtAc - MeOH-  $\text{H}_2\text{O}$



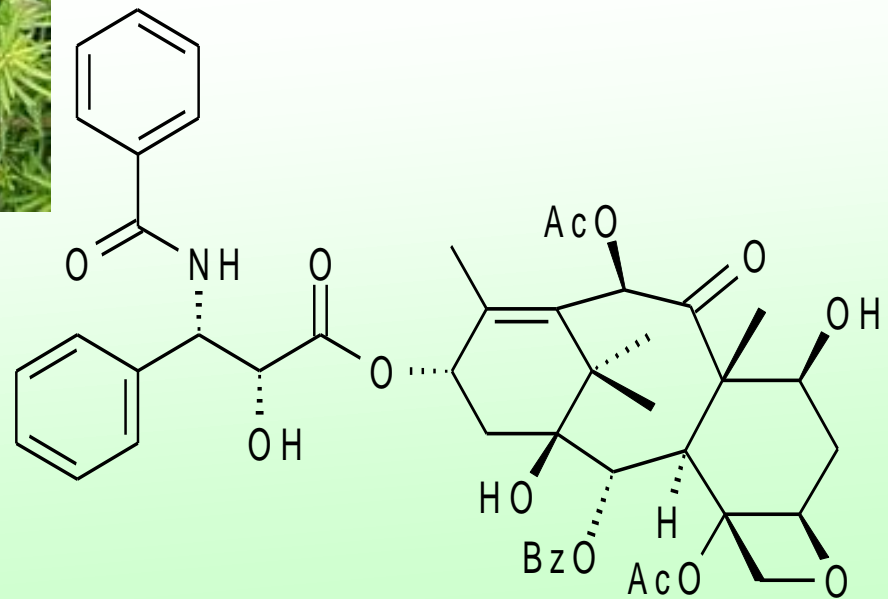
# Paclitaxel



9-DHB



Paclitaxel, Taxol ®

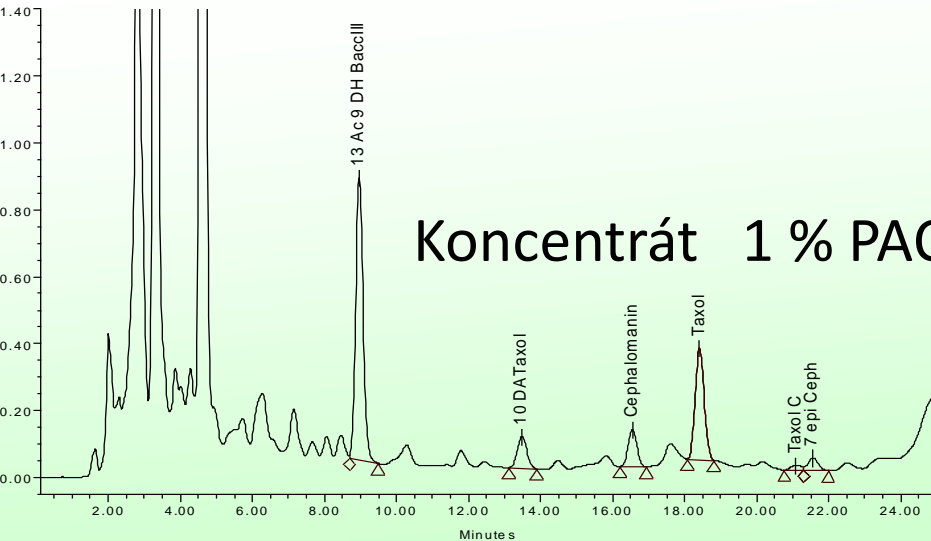
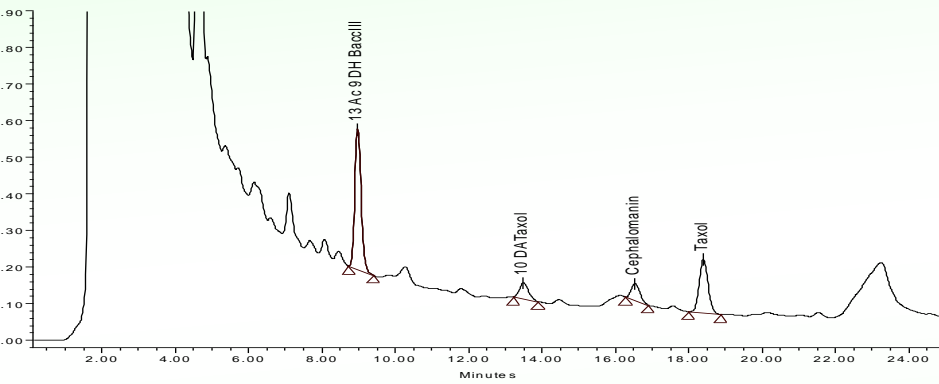


# PACLITAXEL

Jehličí *Taxus canadensis*

0,03 % PAC 0,08 % DHB

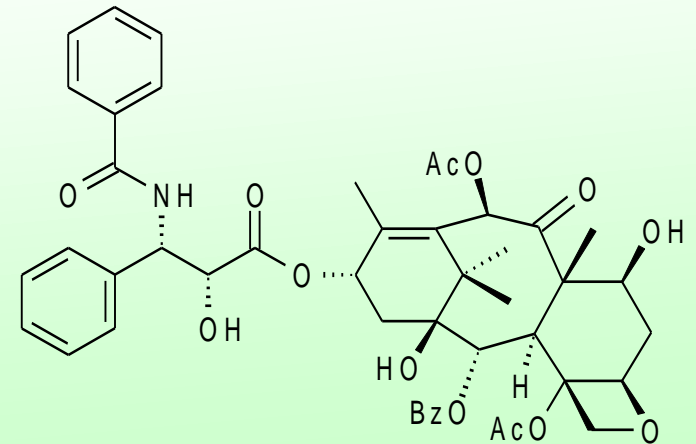
Extrakt 0,1 % PAC 0,25 % DHB



Koncentrát 1 % PAC a 2,5 % DHB



**Extrakce pevnou fází**



# PACLITAXEL

Koncentrát č.1 1 % PAC a 2,5 % DHB  
v Toluenu

## Chromatografie 1

Koncentrát č.2 6 % PAC a 15 % DHB

## Chromatografie 2

Koncentrát č. 3 25 % PAC

Koncentrát č. 4 50 % DHB

## Krystalizace



## Chromatografie 1

**100 kg sušiny**

250 kg silicagel

Toluen s gradientem acetonu

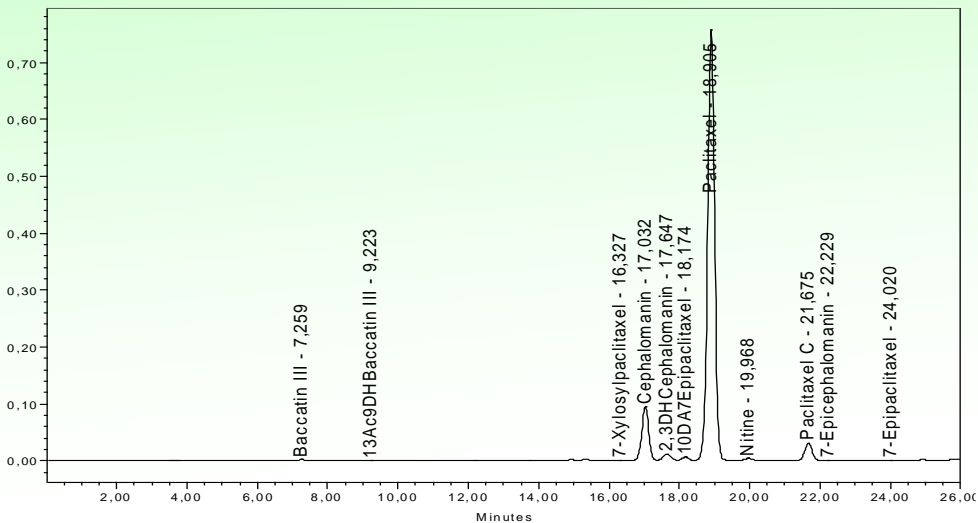
## Chromatografie 2

200 kg Polyamidu

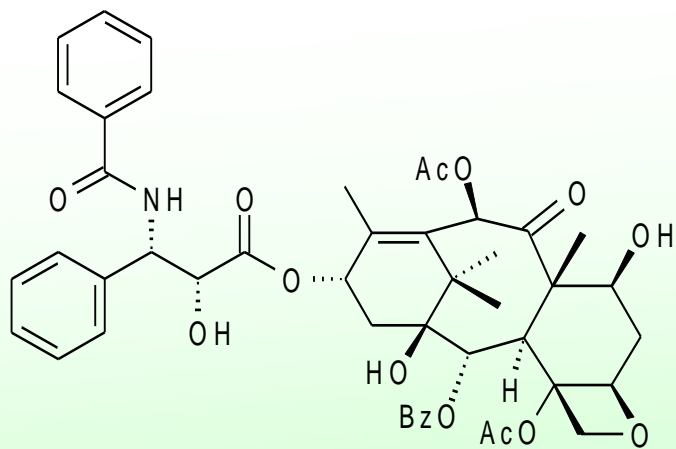
Toluen s gradientem acetonu

# PACLITAXEL

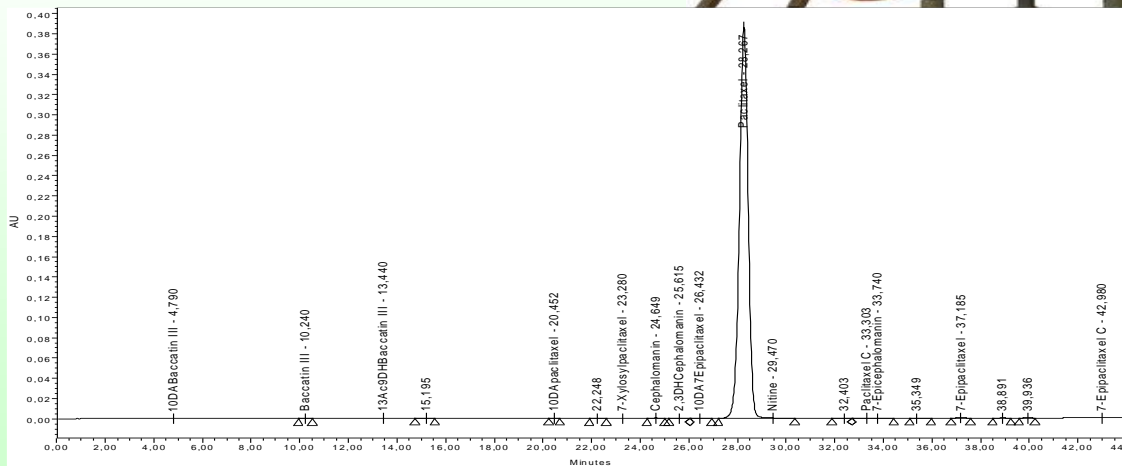
Surový paclitaxel, cca 75 %



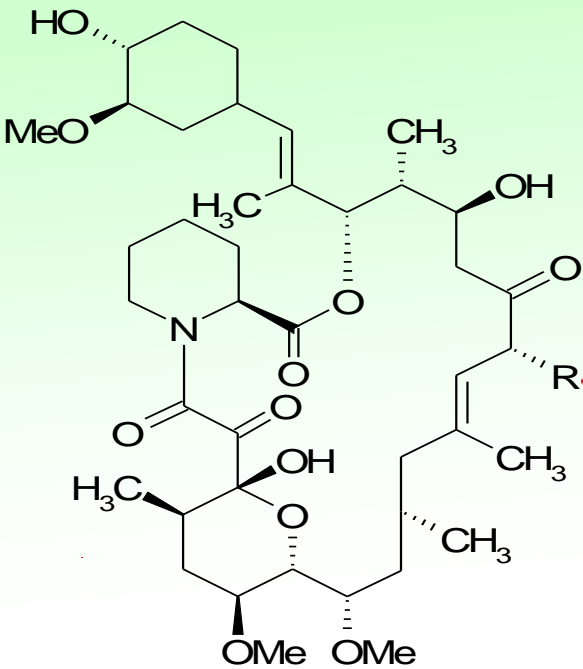
Kolona 400 x 1000 mm  
60 kg sférický silikagel, 15 µm  
Mobilní fáze  
Toluen – MIBK 60 : 40  
Nástřik 1 kg Surový paclitaxel



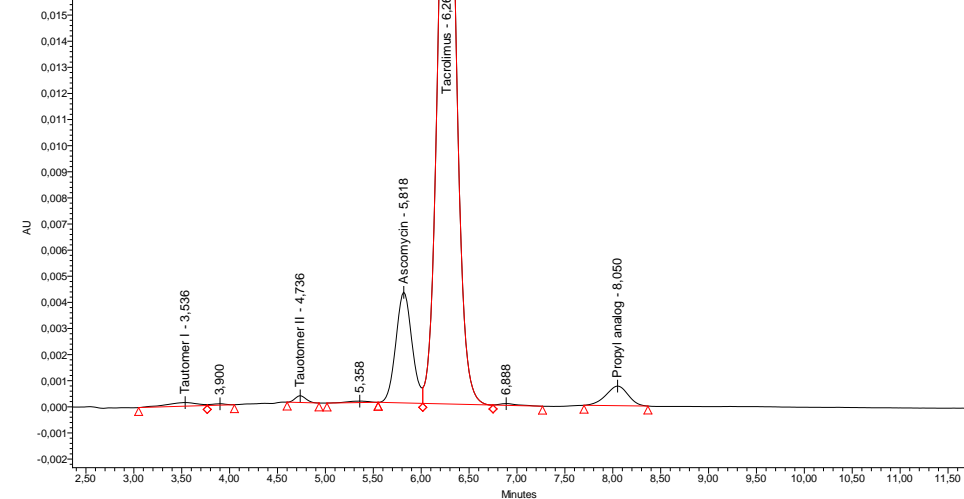
Paclitaxel USP 99,8 %



# TACROLIMUS



**Tacrolimus**  
R = -CH<sub>2</sub>-CH=CH<sub>2</sub>  
**Ascomycin**  
R = -CH<sub>2</sub>-CH<sub>3</sub>  
**Dihydrortacrolimus**  
R = -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>

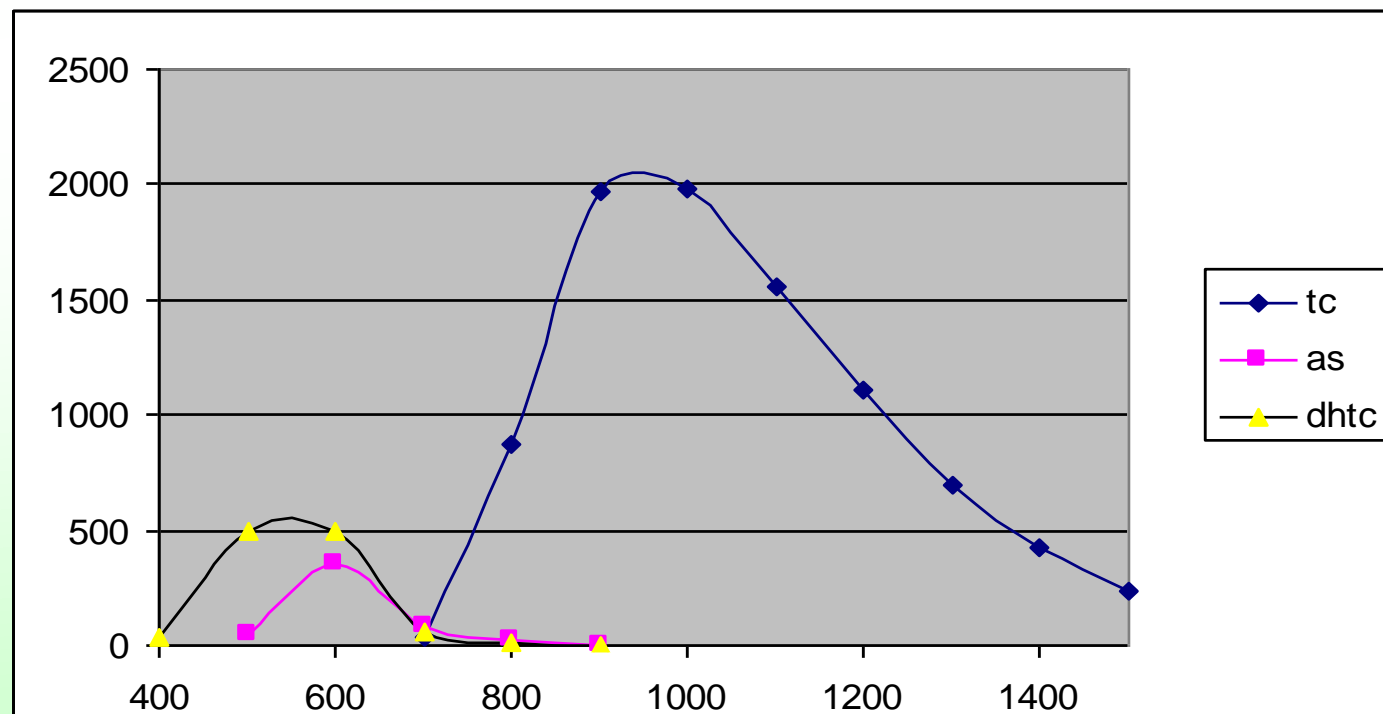


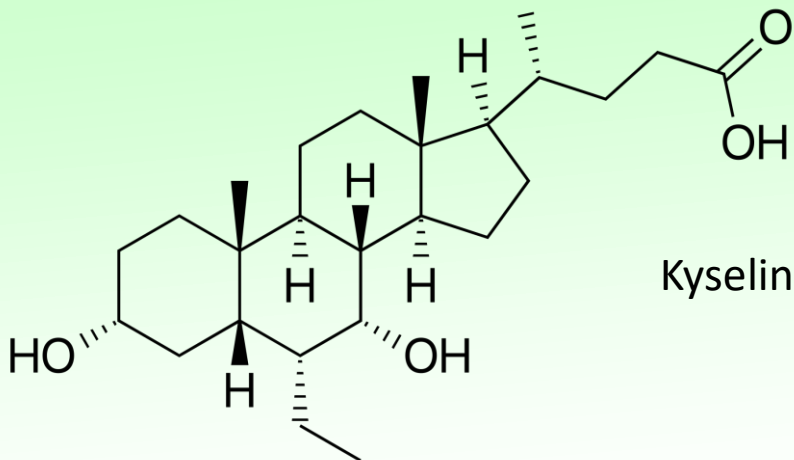
Kolona: 150 x 1500 mm  
8 kg CN-Silikagel + 10 % AgNO<sub>3</sub>

Nástřik: 200 g SurTC

Mobilní fáze:  
Aceton – Hexan 4 : 6  
Sycení AgNO<sub>3</sub>

Zachytávání AgNO<sub>3</sub>





Kyselina obeticholová

## Postup 1

Chromatografie na silikagelu  
Toluen a gradient Acetonu

Krystalizace z Toluenu

**Patentová ochrana polymorfie**

## Postup 2

Chromatografie na silikagelu  
Toluen a gradient Acetonu

Chromatografie na reversní fázi  
Voda a Acetonitril