



**МЕДИЦИНСКИ УНИВЕРСИТЕТ – ПЛОВДИВ**  
**ФАКУЛТЕТ „ФАКУЛТЕТ ФАРМАЦИЯ“**  

---

**ЦЕНТЪР ЗА ДИСТАНЦИОННО ОБУЧЕНИЕ**

**Лекция №03**

**Анализ на лекарства, действащи на сърдечно-съдовата система - ACE инхибитори, AT1 антагонисти и вазодилататори,  
2 част**

**проф. Данка Обрешкова, дм, дфн**

## Клинична употреба:

- Hypertension
- Angina
- Mitral valve prolapse
- Cardiac arrhythmia
- Congestive heart failure
- Myocardial infarction
- Glaucoma
- Migraine prophylaxis
- Symptomatic control (tachycardia, tremor) in anxiety and hyperthyroidism
- Essential tremor
- Pheochromocytoma, in conjunction with  $\alpha$ -blocker
- Hypertrophic obstructive cardiomyopathy
- Acute dissecting aortic aneurysm
- Marfan syndrome
- Prevention of variceal bleeding in portal hypertension
- Possible mitigation of hyperhidrosis

**$\beta$ -блокери**

# $\beta$ -блокери

## Неселективни:

Alprenolol  
Carteolol  
Levobunolol  
Mepindolol  
Metipranolol  
Nadolol  
Oxprenolol  
Penbutolol  
Pindolol  
Propranolol  
Sotalol  
Timolol

## $\beta_1$ - селективни:

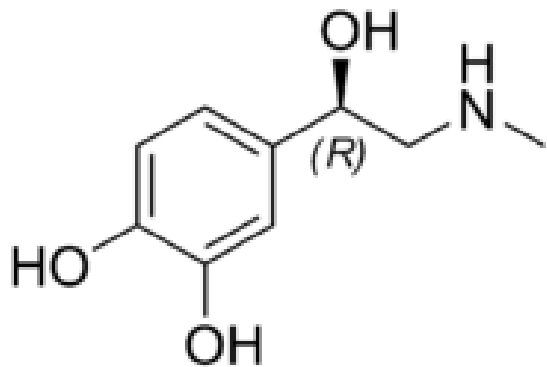
Acebutolol  
Atenolol  
Betaxolol  
Bisoprolol  
Esmolol  
Metoprolol  
Nebivolol

## Смес от $\alpha_1/\beta$ – адренергични антагонисти

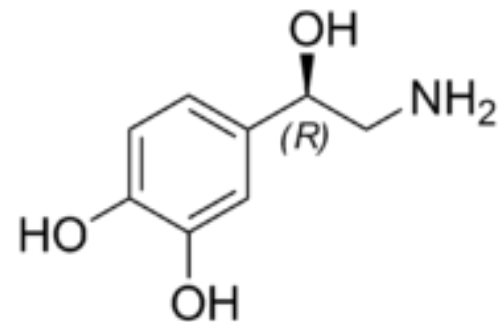
Carvedilol  
Celiprolol  
Labetalol

## $\beta_2$ - селективни

Butaxamine (weak  $\alpha$ -adrenergic agonist activity)

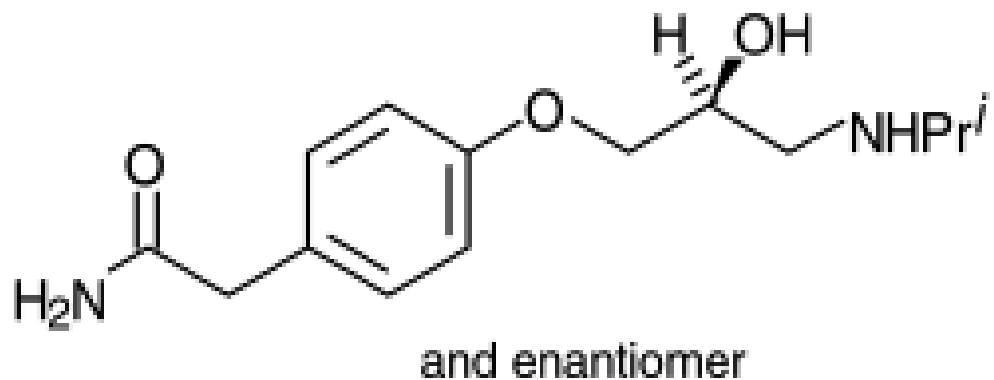


**adrenaline**



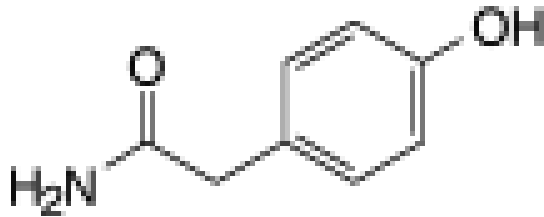
**noradrenaline**

# Atenolol

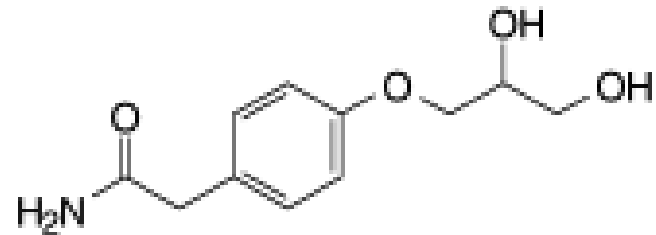


2-[4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl) amino]propoxy]phenyl]acetamide

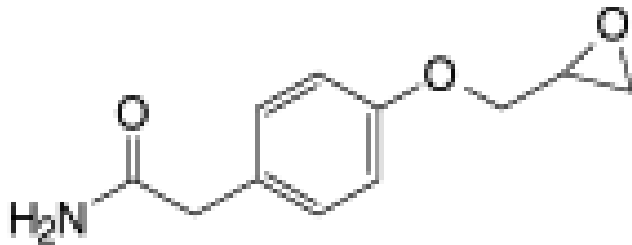
## Примеси на Atenolol



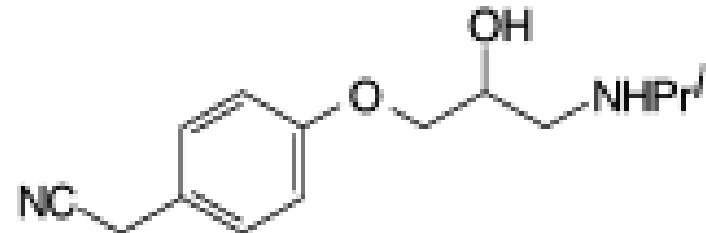
2-(4-hydroxyphenyl)acetamide,



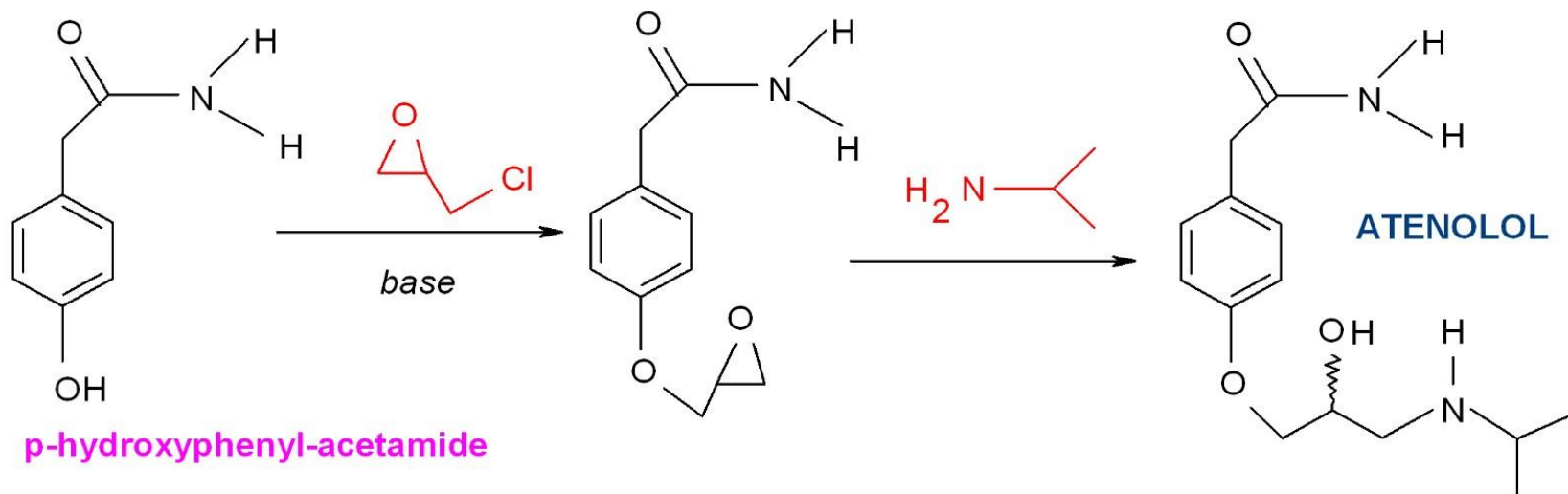
2-[4-[(2*RS*)-2,3-dihydroxypropoxy]phenyl]acetamide



2-[4-[[2*RS*]-oxiran-2-yl]methoxy]phenyl]acetamide



2-[4-[(2*RS*)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]acetonitrile



## Related substances - HPLC

The chromatographic procedure may be carried out using (a) a stainless steel column (15 cm × 4.6 mm) packed with **stationary phase C (5 µm) (Spherisorb ODS 2 is suitable)**, (b) as the mobile phase with a flow rate of 1.0 ml per minute a mixture of 20 volumes of *tetrahydrofuran*, 180 volumes of *methanol* and 800 volumes of 0.025M *potassium dihydrogen orthophosphate* containing 1.0 g of *sodium octanesulphonate* and 0.4 g of *tetrabutylammonium hydrogen sulphate* per litre and adjusted to pH 3.0 with *orthophosphoric acid* and (c) a **detection wavelength of 226 nm**.

## Chlorides

Dissolve 50 mg in a mixture of 1 ml of *dilute nitric acid R* and 15 ml of *water R*. The solution, without further addition of *dilute nitric acid R*, complies with the **limit test for chlorides (0.1 per cent)**.

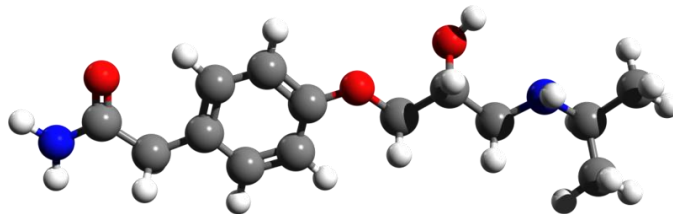


## IDENTIFICATION

The *light absorption* in the range 230 to 350 nm of the solution obtained in the Assay exhibits maxima at **275 nm and 282 nm**.

## ASSAY

Powder 20 tablets. Transfer the powder to a 500 ml flask using 300 ml of *methanol* , heat the resulting suspension to 60° and shake for 15 minutes. Cool, dilute to 500 ml with *methanol* , filter through a fine glass micro-fibre filter paper (Whatman GF/C is suitable) and dilute a suitable volume of the filtrate with sufficient *methanol* to produce a solution containing 0.01% w/v of Atenolol. Measure the *absorbance* of the resulting solution at the maximum at 275 nm, Calculate the content of  $C_{14}H_{22}N_2O_3$  taking **53.7** as the value of **A(1%, 1 cm)** at the maximum at 275 nm.

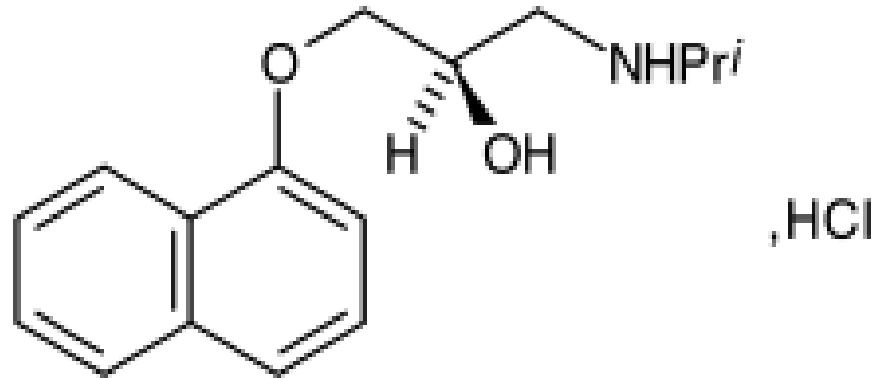


## Спектрални характеристики:

**ИЧ-спектри:** В спектрите се наблюдават ивици за валентните колебания на връзката C-N при 1020 – 1220  $\text{cm}^{-1}$  (алифатни амини). При първичните и вторичните амини се появяват ивици за N-H валентните колебания в областта 3300 – 3500  $\text{cm}^{-1}$  (положението им зависи от степента на асоциация) и за N-H деформационно трептене в областта 1550 – 1650  $\text{cm}^{-1}$ .

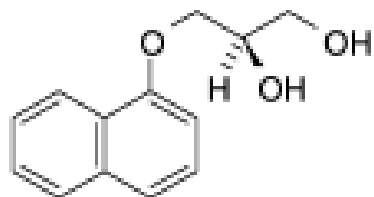
**$^1\text{H}$ -ЯМР-спектри:** Наблюдават се сигнали за amino и imino протоните обикновено като синглет при  $\delta = 1$  до 2 ppm (алифатни амини).

# Propranolol

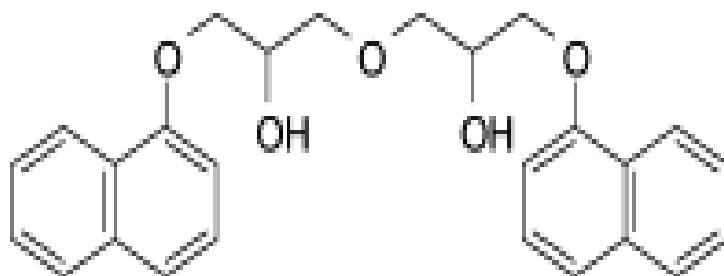
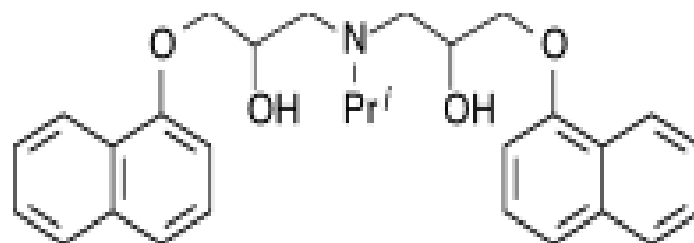


and enantiomer

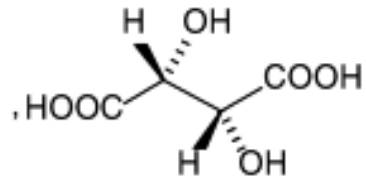
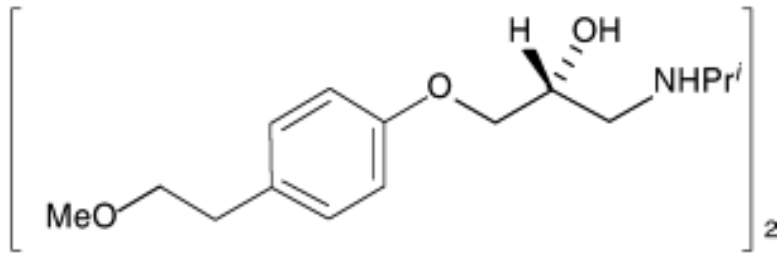
**(2*RS*)-1-[(1-methylethyl)amino]-3-(naphthalen-1-yloxy)  
propan-2-ol hydrochloride**



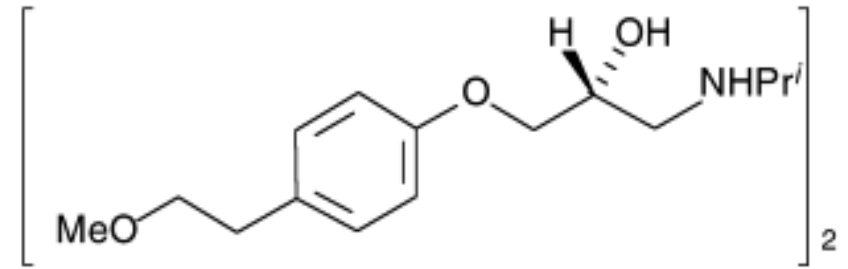
and enantiomer



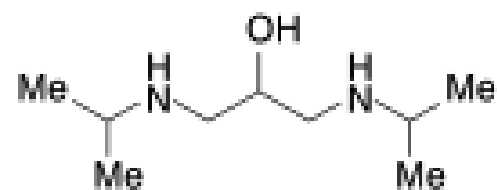
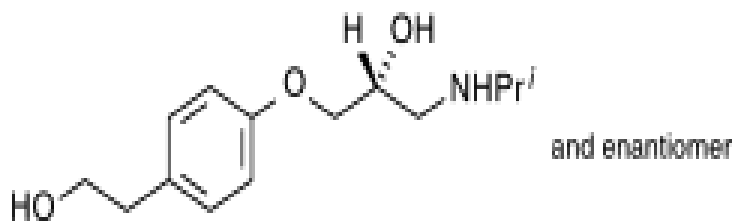
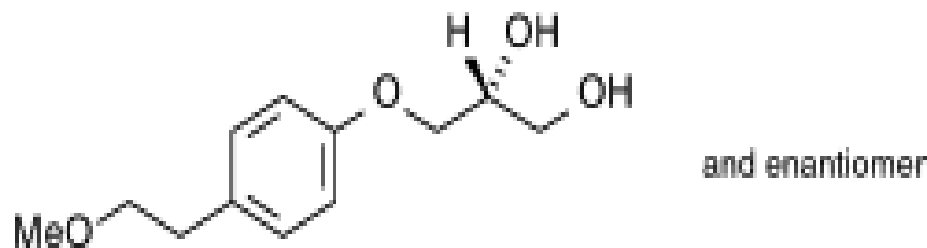
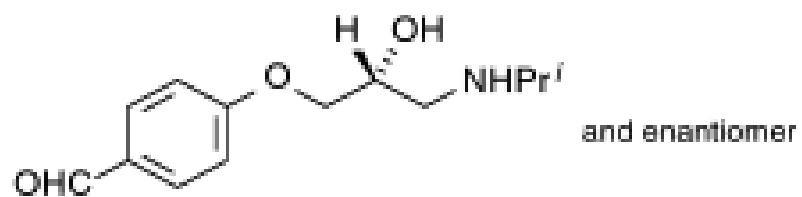
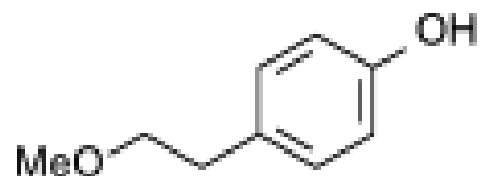
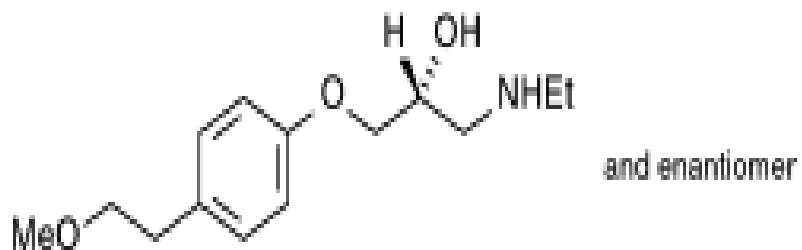
# Metoprolol (tartarate, succinate)



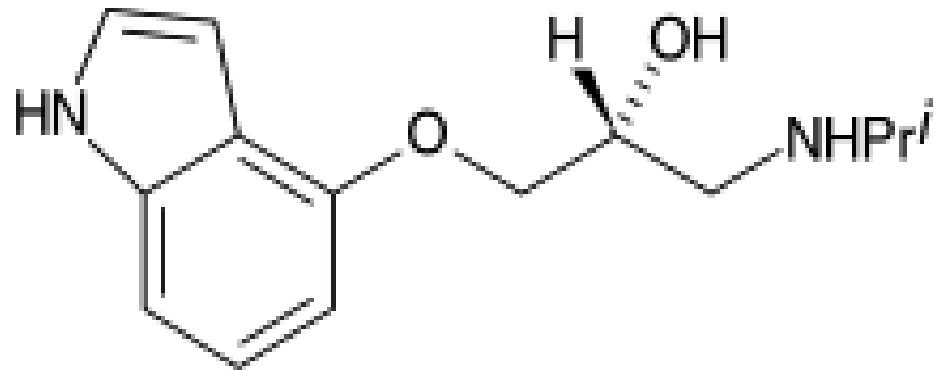
and enantiomer



and enantiomer



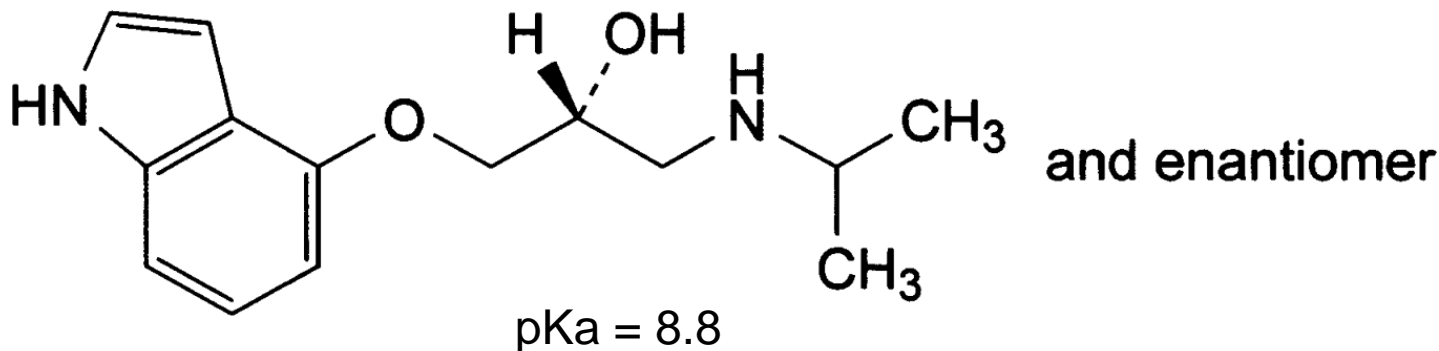
# Pindolol



and enantiomer

# Pindolol

(2*RS*)-1-(1*H*-indol-4-yloxy)-3-[(1-methylethyl)amino]propan-2-ol



## ASSAY

Dissolve 0.200 g in 80 ml of *methanol R*. Titrate with 0.1 M *hydrochloric acid*, determining the end-point potentiometrically (2.2.20).

1 ml of 0.1 M *hydrochloric acid* is equivalent to 24.83 mg of C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>.

## STORAGE

Store protected from light.



## IMPURITIES

A. 1-[7-(2-hydroxy-3-isopropylaminopropyl)-indol-4-yloxy]-3-isopropylamino-2-propanol,

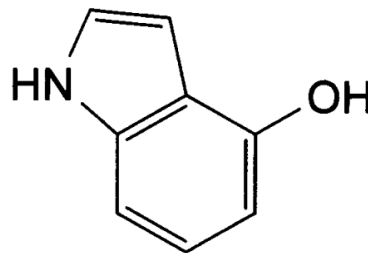
B. 1-[1-(2-hydroxy-3-isopropylaminopropyl)-indol-4-yloxy]-3-isopropylamino-2-propanol,

C. 3,3-bis(indol-4-yloxy)- *N*-isopropyl-1,1-imino-bis-(2-propanol)hydrogen malonate,

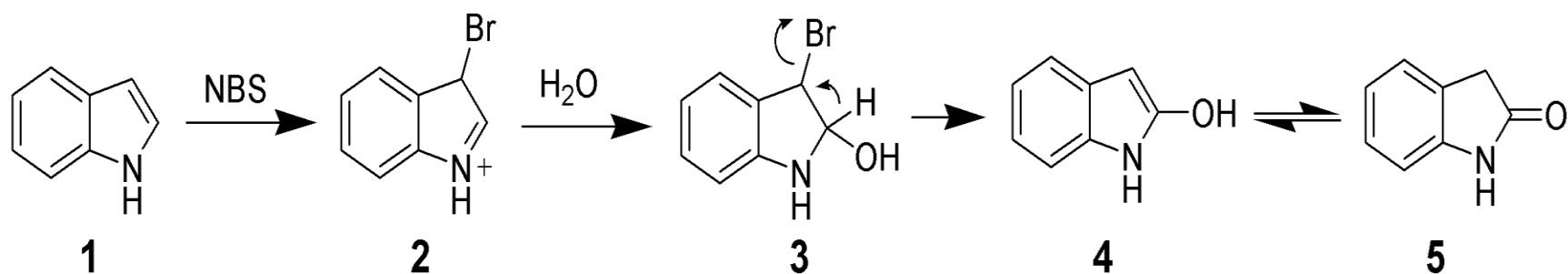
D. 4-(2,3-dihydroxypropoxy) indole,

E. 4-hydroxyindole,

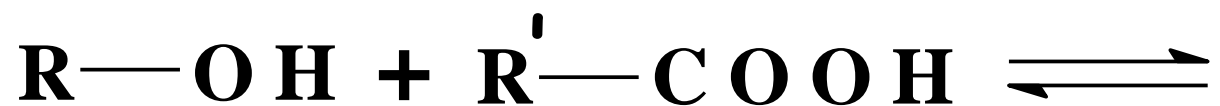
F. 4-(2-hydroxy-3-chloropropoxy) indole.

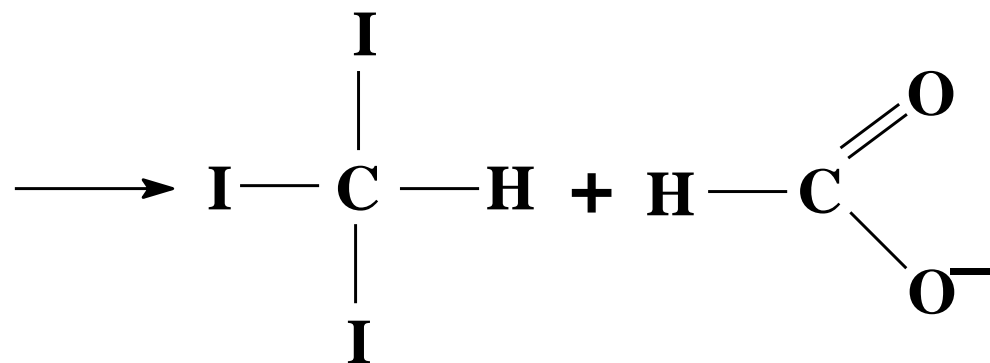
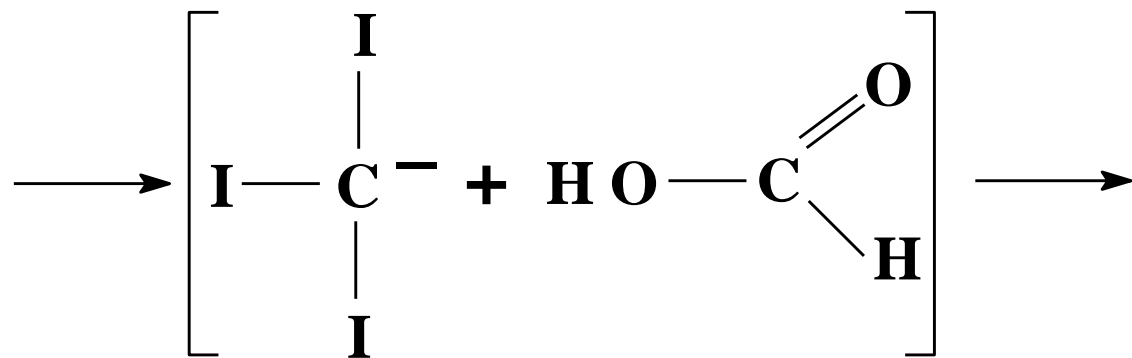
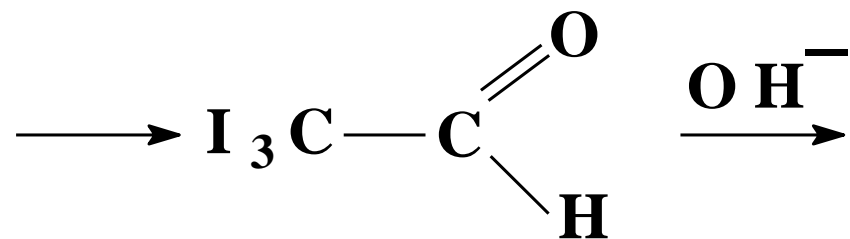
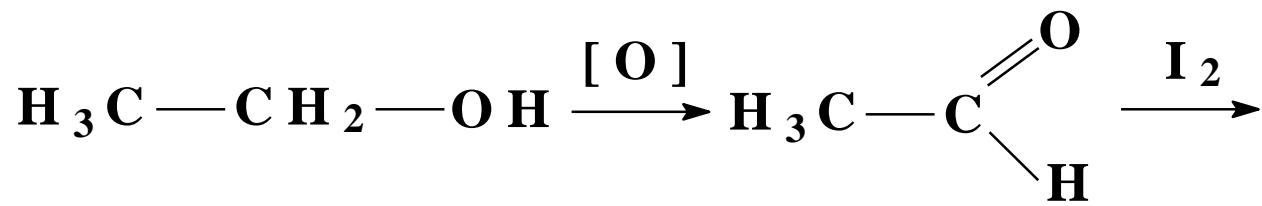


Due to the electron-rich nature of indole, it is easily oxidized. Simple oxidants such as *N*-bromosuccinimide will selectively oxidize indole 1 to oxindole (4 and 5).

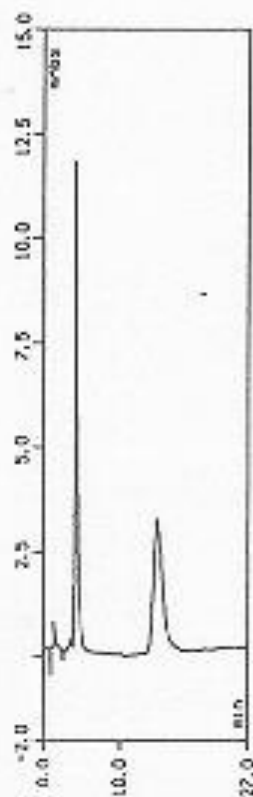
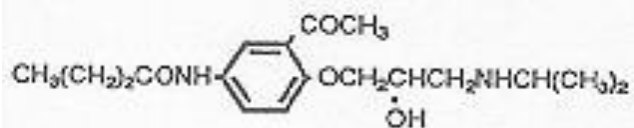


Анализ на  $\beta$ -блокери,  
съдържащи алкохолна група





## ACEBUTOLOL

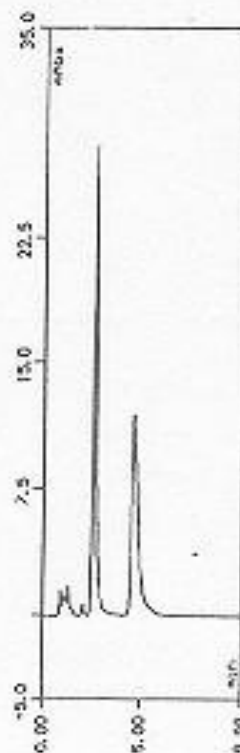
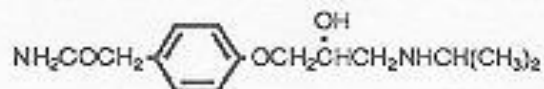


**Column:**  
CHIRAL-CBH  
100 x 4.0 mm

**Mobile phase:**  
5% 2-propanol in  
10 mM sod.ac.b.  
pH 5.5 + 50  $\mu\text{M}$  di-  
sodium EDTA

**Sample conc.:**  
0.03 mg/ml

## ATENOLOL

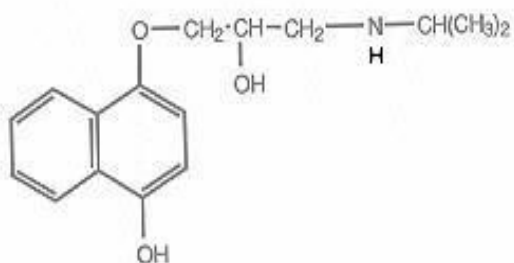
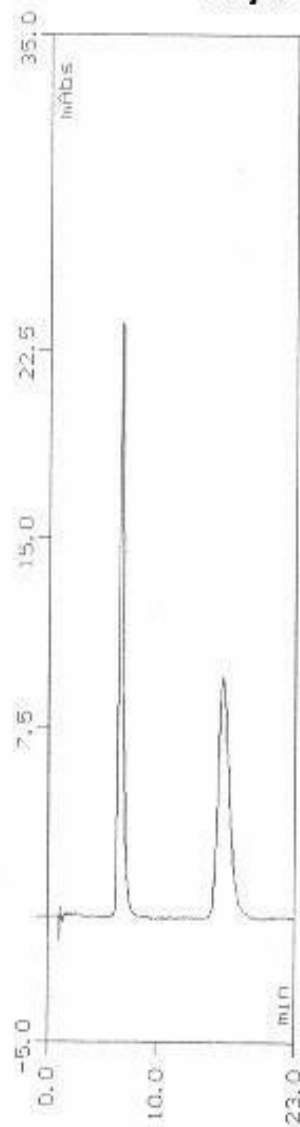


**Column:**  
CHIRAL-CBH  
100 x 4.0 mm

**Mobile phase:**  
5% 2-propanol in  
10 mM sod.ph.b.  
pH 6.0 + 50  $\mu\text{M}$  di-  
sodium EDTA

**Sample conc.:**  
0.03 mg/ml

## 4-hydroxypropranolol



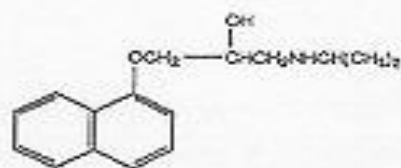
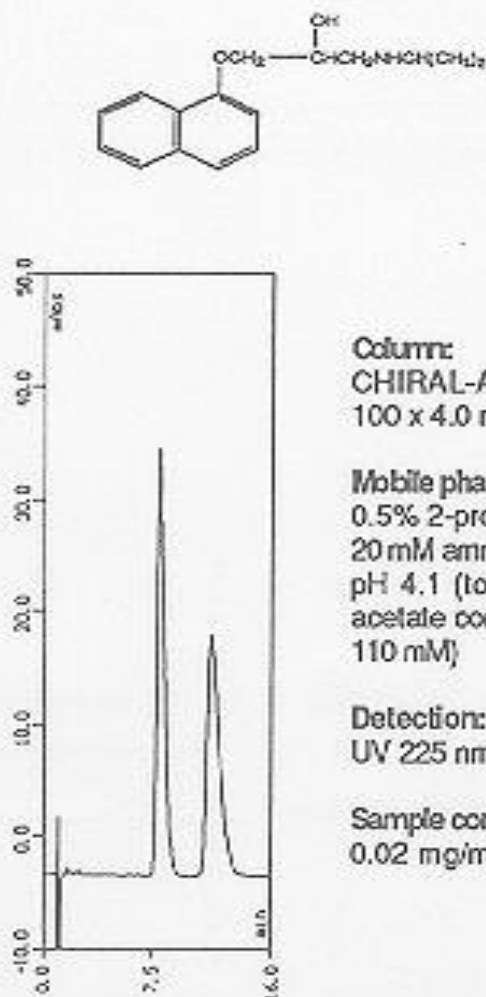
**Column:**  
CHIRAL-CBH  
100 x 4.0 mm

**Mobile phase:**  
5% Isopropanol in  
10 mM sod.ac. buffer  
pH 5.0

**Flow:**  
0.9 ml/min

**Detection:**  
UV 210nm

## PROPRANOLOL



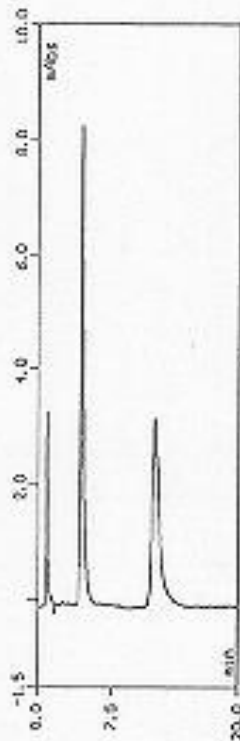
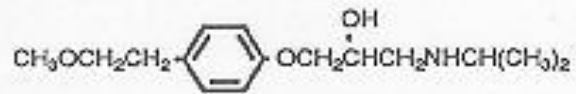
**Column:**  
CHIRAL-AGP  
100 x 4.0 mm

**Mobile phase:**  
0.5% 2-propanol in  
20 mM amm.ac.b.  
pH 4.1 (total  
acetate conc. =  
110 mM)

**Detection:**  
UV 225 nm

**Sample conc.:**  
0.02 mg/ml

## METOPROLOL

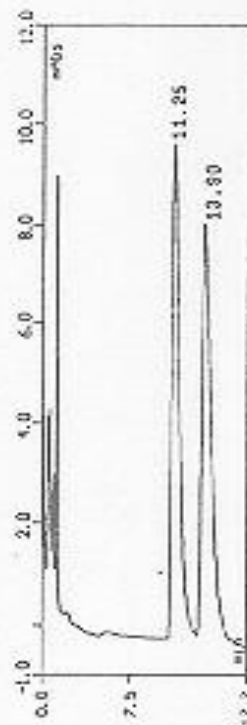
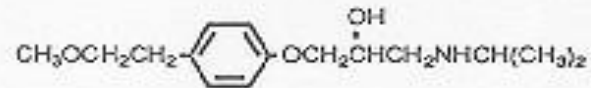


**Column:**  
CHIRAL-CBH  
100 x 4.0 mm

**Mobile phase:**  
5% 2-propanol in  
10 mM sod.ph.b.  
pH 6.0 + 50  $\mu$ M di-  
sodium EDTA

**Sample conc.:**  
0.03 mg/ml

## METOPROLOL



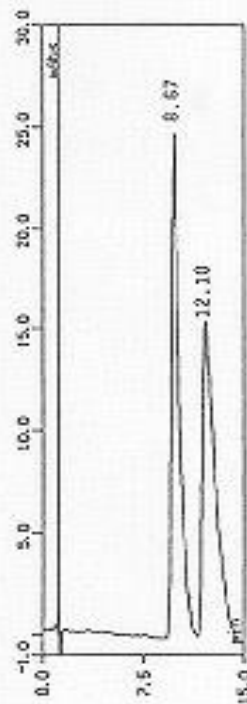
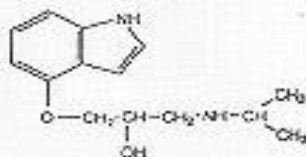
**Column:**  
CHIRAL-AGP  
100 x 4.0 mm

**Mobile phase:**  
0.5% 2-propanol  
in 0.01 M sod.ph.b.  
pH 7.0

**Detection:**  
UV 225 nm

**Sample conc.:**  
0.02 mg/ml

## PINDOLOL



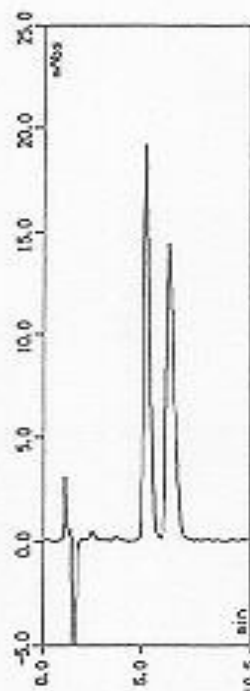
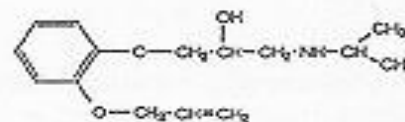
Column:  
CHIRAL-AGP  
100 x 4.0 mm and  
CHIRAL-AGP  
guard column  
10 x 3.0 mm

Mobile phase:  
10% acetonitrile  
in 10 mM sod.ph.b.  
pH 7.0

Detection:  
UV 225 nm

Sample conc.:  
0.02 mg/ml

## OXPRENOLOL



Column:  
CHIRAL-AGP  
100 x 4.0 mm

Mobile phase:  
1% 2-propanol  
in 10 mM sod.ac.b.  
pH 4.5 (total  
acetate conc. =  
25 mM)

Detection:  
UV 225 nm

Sample conc.:  
0.02 mg/ml



## A chiral HPLC-column for direct resolution of enantiomers

Cellobiohydrolase (CBH) is a very stable enzyme, which has been immobilized onto 5 micrometer spherical silica particles. This is a reversed-phase column, used for the direct separation of enantiomers. The column is preferentially used for the separation of enantiomers of basic drugs from many compound classes. CHIRAL-CBH separates preferentially compounds containing one or more **basic nitrogen** together with one or more hydrogen accepting or hydrogen donating groups (**alcohol**, phenol, carbonyl, amide, ether, sulphoxide, ester etc.).

### Application Areas

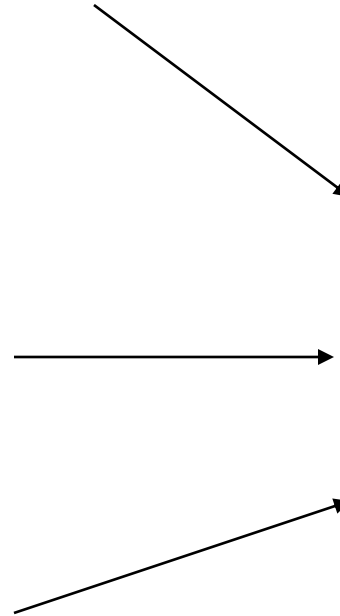
At pharmaceutical companies, hospitals, universities and chemical industry CHIRAL-CBH is used for the analysis of enantiomeric purity and for bioanalysis. An interesting and fast growing area is isolation of pure enantiomers on semipreparative columns.

### Mobile Phases

The mobile phases are mixtures of phosphate or acetate buffers and organic solvents as 2-propanol or acetonitrile containing 50mM disodium EDTA. The retention and the enantioselectivity can be regulated by changes in pH, buffer concentration and organic modifier (nature and concentration).

# Оптимизиране на енантоселективността и ефективността на колоната

- **pH**
- **Модификатор:**
  - вид;
  - концентрация.
- **Буфер:**
  - вид;
  - концентрация.



**ВАЛИДИРАНЕ;  
РЕВАЛИДИРАНЕ**