**Lecture 3.**

**Pharmeceutical chemistry 4.**

**Topic:** Piperazine and pyrimidine derivatives Piperazine derevatives. Pyrimidine ­2,4 ­ dion derivatives. Cytostatic and antiviral preparations as pyrimidine nucleosides.



**Piperazine (Piperazine Adipate)**

N

H

N

H

C

H

2

C

H

2

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C

O

O

H

C

H

2

C

H

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C

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a

C

4

H

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N

2

C

6

H

1

0

O

4

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**Cinnarizine (Stugeron)**

**Flunarizin**

**Trimetazidine (Preductal)**

C

H

R

1

R

2

N

N

2

H

C

H

C

C

H

1

2

4

3

1

2

3

C

H

2

O

C

H

3

O

C

3

H

O

3

H

C

N

N

H

2

H

C

l

.

**Cytarabine**

**(Cytosar)**

M.w.243,2

O

O

O

H

O

H

N

H

2

N

N

C

H

2

O

H

**İdoxuridine**

**(İduviran)**

O

O

I

N

H

N

O

O

H

C

H

2

H

O

1

2

3

4

5

6

1

2

3

4

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**Zidovudine**

**(Azidothymidin, Retrovir)**

O

O

3

H

C

N

H

N

O

N

C

H

2

H

O

1

2

3

4

5

6

1

2

3

4

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N

N

**Lamivudin**

N

O

H

O

C

H

2

O

S

N

N

H

2

**Stavudine**

**(Zerit)**

N

O

H

O

C

H

2

O

H

N

O

C

H

3

**Quinazoline derivatives**

**Prazosin**

N

N

H

2

O

3

H

C

O

3

H

C

N

N

C

O

N

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H

C

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MEDICINAL SUBSTANCES, WHICH ARE DERIVATIVES OF URACIL

Uracil is a hydrolytic product of nucleic acids. It undergoes lactam-lactim tautomerism:

O

O

N

N

H

H

O

H

O

H

N

N

Derivatives of uracil are assuming an increasing importance in, medicine; they exert their effects by interfering with normal metabolic processes.

thiouracils (methylthiouracil and thiouracil) decrease the thyroid acytivity, but uracils themselves (especially fluorine-containing) have the ancer activity.

**Methyluracilum**

O

O

N

N

H

H

C

3

H

6-Metyluracil or 2,4-dioxo-6-methyl-l,2,3)4-tetrahydropyrimidine

**Properties.** A white, crystalline powder, odourless. It is slightly soluble in water and in ethanol.

**Identification.** 1. UV-spectrum has max at 275 nm.

1. The acidic properties of uracil derivatives are confirmed with the salt of heavy metals — AgN03 and HgCl2 they form white preci­pitates; with the salts of cobalt — a violet colouring.
2. It discharges bromine water-; with p-nitrodiazobenzene it forms a red-orange colouring.

**Assay.** 1. Alkalimetry in the non-aqueous medium (dimethylform- amide). The indicator is thymol blue; s=1:

O

H

N

N

C

3

H

O

H

+

N

a

O

H

O

N

a

N

N

C

3

H

O

H

+

H

2

O

2. Iodchlorimetry, back titration with a blank titration; s=1:

+

H

C

l

N

N

H

C

3

H

O

H

+

I

C

l

O

N

N

H

C

3

H

O

H

O

I

I

C

l

+

K

I

I

2

+

K

C

l

I

2

+

2

N

a

2

S

2

O

3

2

N

a

I

+

N

a

2

S

4

O

6

**Usage.** Stimulant of leukopoiesis

**Storage.** Store protected from light

**Phthorafurum**

F

O

N

H

O

N

O

N'-(2-furanidyl)-5-fluorouracil

**Properties**. A white, crystalline powder, odourless. It is very slightly soluble in water and in ethanol.

**Identification**. 1. UV-spectrum has max at 270 nm.

1. With the salts of heavy metals — AgN03 and HgCl2 it forms white precipitates; with the salts of cobalt — a violet colouring.
2. Phthorafurum educes ammonia while heating with 30 % sodium

hydroxide solution in the presence of zinc.

1. Fluorine in phthorafurum is detected: a) dissolve the residue after mineralization and add calcium chloride at pH = 4.0—5.0; a white opalescence is obtained:

2F- + CaCl2 → CaF2↓ + 2Cl-

1. after ignition in the presence of H202 fluoride-ions discharge the red colouring of Fe(CNS)3 forming of the complex:

Fe(SCN)3 + 6F- → [FeF6]3- + 3SCN-

1. in the medium of hydrochloric acid in the presence of fluoride- ions the colour of the red-violet solution becomes yellow:

O

O

O

H

S

O

3

N

a

O

+

6

F

O

O

H

O

H

S

O

3

N

a

O

+

Z

r

F

6

2

alizarin-zircon complex

**Assay. 1.** Bromatometry, back titration; s=3:

K

B

r

O

3

+

5

K

B

r

+

6

H

C

l

3

B

r

2

+

6

K

C

l

+

3

H

2

O

+

B

r

2

B

r

+

2

K

I

I

2

+

2

K

B

r

O

F

N

O

N

H

+

H

B

r

O

F

N

O

N

H

r

B

O

I

2

+

2

N

a

2

S

2

O

3

2

N

a

I

+

N

a

2

S

4

O

6

2. UV-spectrophotometry.

**Usage.** Use in the treatment of gastric and intestinal cancer.

**Storage.** Store protected from light.

**Fluorouracil**

**(Fluorouracil), Ph.Eur.**

O

N

H

O

N

F

H

5-Fluoropyrirnidine-2,4(lH,3H)-dione

Properties. A white or almost white, crystalline powder, sparingly soluble in water, slightly soluble in alcohol, practically insoluble in ether.

Preparation. The initial products are sodium formylfluoracetic ester and S-methylisothiourea:

S

C

H

3

F

N

C

H

3

S

N

H

O

C

C

O

O

C

2

H

5

F

C

H

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N

a

+

C

N

H

N

H

2

H

C

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F

N

O

N

H

O

H

sodium formyl- S-methyl­ isothiourea 2 methylthio- 5-fluorouracil

fluoroacetic ester 5-fluorouracil

**Identification.** 1. IR-spectrum.

1. Thin layer chromatography.
2. After heating with the chromic acid cleansing mixture until white fumes appear in the upper part of the tube the solution wets the side of the tube and there is no appearance of greasiness. Add the substance and heat again in a naked flame until white fumes appear. The solution does not wet the sides of the tube.
3. Detection of fluorine — see phthorafurum.

**Assay.** 1. Alkalimetry in the medium of dimethylformamide. Titrant is 0.1 M tetrabutylammonium hydroxide solution (the indicator is thymol blue). Carry out a blank titration; s= 1:

+

N

(

C

4

H

9

)

4

O

H

N

O

N

H

O

F

H

+

N

(

C

4

H

9

)

4

+

N

O

N

H

O

F

+

H

2

O

2. Indirect alkalimetry method. The indicator is phenol red; s = 1/2:

+

2

A

g

N

O

3

N

O

N

H

O

F

H

2

H

N

O

3

+

F

N

O

A

g

N

O

A

g

H

N

O

3

N

a

O

H

N

a

N

O

3

H

2

O

+

+

3.Differential UV-spectrophotomtery.

4. Photocolorimetry (for fluoride-ions after the reaction with arsenaso-1 and thorium nitrate solutions).

**Usage.** Use in the treatment of gastric and intestinal cancer. Fluororacil Ampules, Efudex, 5-FU is effective in the palliative management of carcinoma of the breast, colon, pancreas, rectum, and stomach in patients who cannot be cured by surgery or other means. The topical formulations are used with favourable results for the treatment of premalignant keratoses of the skin and protected superficial basal-cell carcinomas.

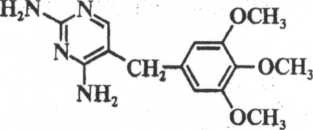
Strorage. It should be stored at the room temperature and protected from light.

**Usage.** Antiviral. Zidovudine is active against retroviruses, a group of RNA viruses responsible for AIDS and certain types of leukemia. It is recommended for the management of adult patients with sympto­matic human immune deficiency virus (HIV) infection (AIDS or ARC).

**Storage.** Store protected from light.

Trimethoprim

(Trimethoprimum), Ph. Eur.



5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine

**Properties.** A white or yellowish-white powder. Very slightly solu­ble in water, slightly soluble in alcohol.

**Preparation**

O

C

O

O

C

3

H

C

H

3

C

H

3

O

H

+

O

C

N

C

H

3

3,4,5-trimethoxybenzaldehyde 3-ethoxypropionitrile

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C

H

3

O

O

C

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H

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H

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C

N

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3,4,5-trimethoxybenzaldehyde 3-ethoxy-  
methyl-3-(3,4,5-trometoxyphenyl)-acrylonitryle

O

C

H

3

O

O

C

3

H

C

H

3

N

N

H

2

N

N

H

2

5 - (3,4,5 - trimethoxybenzyl)pyrimidine-  
2,4-diamine

Identification. 1. The melting point.

1. UV-spectrum.
2. IR-spectrum.

4 To the solution of the substance in sulphuric acid in the presence of potassium permanganate, sodium hydroxide solution and formaldehyde add sulphuric acid and methylene chloride. The organic layer examined in UV-light at 365 nra shows green fluorescence.

**Assay.** Von-aqueous titration. Titrate in the medium of acetic acid whith 0,1 M perchloric acid determining the end-point potentiometriflly: s1.

N

2

H

N

N

N

H

2

C

H

2

O

C

H

3

O

C

H

3

O

C

H

3

+

H

C

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O

4

N

2

H

N

N

N

H

2

C

H

2

O

C

H

3

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C

H

3

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C

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H

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4

**Usage.** Bacteriostatic. Trimethoprim is marketed by itself and in mbination with sulfonamides (e. g., it is used with sulfamethoxazole the combination products Biseptol, Bactrim, Septra, and others) marily as an antibacterial product, but subsequent tests showed it to active as an antimalarial agent.

**Storage.** Store protected from light.