**Subject "Pharmaceutical chemistry 2"**

**Lecture 8. Antihyperlipidemic drugs.**

Antihyperlipidemic (lipipidemic) drugs (ATC code C10) are a group of substances, drugs to reduce the concentration of certain lipid fractions (in particular, the so-called LDL) in tissues and body fluids. These are drugs of different chemical groups with a different mechanism of action, lowering the blood cholesterol and triglycerides, which contributes to the delay in the development of atherosclerosis and its regression.

Atherosclerosis (from the Greek αθήρα - "gruel" + σκλήρωσις - "hardening") is a chronic disease of the arteries of the elastic and muscular-elastic type, which occurs as a result of a violation of lipid and protein metabolism and is accompanied by the deposition of cholesterol and some fractions of lipoproteins in the lumen of the vessels. Complications of atherosclerosis - myocardial infarction, cerebral stroke and peripheral vascular disease in 50% of cases are the cause of death of patients in different countries of the world. In the United States, one resident dies of atherosclerotic coronary heart disease every minute. In millions of people, atherosclerosis impairs the quality of life, causing angina pectoris, heart failure, intermittent claudication, and episodes of cerebrovascular accident.

Back in 1755, Geller introduced the term "atheroma" to describe vascular lesions. In 1833, Lobstein introduced the concept of "arteriosclerosis". 1912 - Russian pathologist Anichkov, Nikolai Nikolaevich and Khalatov, Semyon Sergeevich for the first time created a classic rabbit model of this disease, feeding animals pure cholesterol dissolved in sunflower oil. In 1913, N.N. Anichkov Nikolaevich created an infiltration theory of atherosclerosis morphogenesis. In 1964, K. Bloch (USA) and F. Lineen (Germany) were awarded the Nobel Prize for research into the metabolism and regulation of cholesterol. The European Atherosclerosis Society (EAS) was founded in 1964. 1985 - M. S. Brown and J. Goldstein (both USA) are awarded the Nobel Prize for research on metabolism and cholesterol regulation.

Cholesterol deposits are formed in the form of atheromatous (cholesterol) plaques. The subsequent proliferation of connective tissue in them (sclerosis), and calcification of the vessel wall lead to deformation and narrowing of the lumen up to obturation (blockage of the vessel). It is important to distinguish atherosclerosis from Menckeberg's arteriosclerosis, another form of sclerotic lesions of the arteries, which is characterized by the deposition of calcium salts in the media of the arteries, the diffuseness of the lesion (absence of plaques), the development of aneurysms (rather than blockage) of the vessels. Atherosclerosis of the heart vessels leads to the development of coronary heart disease (CHD).

Lipids are insoluble in water and are transported in the blood as part of lipoproteins.

**Lipoprotein classes**

|  |  |  |
| --- | --- | --- |
| Класс липо­протеинов | Основные липиды | Основные аполипо-протеины |
| Хиломикроны | Пищевые триглицериды | Апо В-48, Апо A-I, АпоА-И, АпоА-IV, АпоС-П/С-Ш, Апо Е |
| Липопротеины очень низкой плотности (ЛПОНП) | Эндогенные триглицериды | АпоВ-100. Апо Е. АпоС-ll/C-lll |
| Липопротеины промежуточной плотности | Эфиры холестерина, триглицериды | Апо В-100, Апо Е, Апо C-II/C-III |
| липопротеины низкой плотности (ЛПНП) | Эфиры холестерина | Апо В-100 |
| липопротеины высокой плотности (ЛПВП) | Эфиры холестерина, фосфолипиды | Апо A-I, АпоА-П. Апо C-II/C-III |
| Липопротеин (а) | Эфиры холестерина | Апо В-100. Апо (а) |

In spherical particles of lipoproteins, non-polar lipids - cholesterol esters and triglycerides form a hydrophobic core, a monolayer of polar lipids - cholesterol and phospholipids, together with amphipathic proteins - apolipoproteins, is located on the surface. Apolipoproteins give stability to lipoproteins, act as ligands for cell receptors, and determine the metabolic fate of lipoproteins.

Lipoproteins are involved in the transport of dietary lipids (exogenous pathway) and lipids synthesized in the body (endogenous pathway).

The exogenous pathway is the absorption of dietary lipids in the small intestine with the help of chylomicrons. They are synthesized in enterocytes, consist of dietary triglycerides in combination with phospholipids and apolipoproteins, enter the peripheral systemic circulation through the lymphatic thoracic duct. In the blood, chylomicron triglycerides undergo lipolysis under the influence of the vascular endothelial enzyme, lipoprotein lipase. Chylomicrons with an exhausted content of triglycerides become fragments of chylomicrons (remnant).

The endogenous system includes very low density lipoproteins (VLDL), intermediate density lipoproteins, low density lipoproteins (LDL) and high density lipoproteins (HDL).

VLDL are synthesized in the liver. They are enriched with triglycerides, also contain cholesterol and apolipoproteins. For the secretion of VLDL from hepatocytes into the blood, apo B-100 is required, then apo E and apo C-II / C-III are added to the blood. VLDL triglycerides are hydrolyzed by endothelial lipoprotein lipase (its activator is apo C-//). Triglyceride fatty acids are used for fat resynthesis in adipose tissue or oxidized in skeletal muscle. Part of VLDL is converted to LDL through the stage of intermediate density lipoproteins.

LDL containing cholesterol esters and apolipoproteins carry cholesterol from the liver to peripheral tissues. Cells that are in need of cholesterol take up LDL with the help of receptors for apo B-100. The half-life of LDL is about 2 days, their removal from the blood to the liver occurs via the receptor pathway. Patients with familial homozygous hypercholesterolemia, who lack receptors for apo B-100, do not respond to dietary and drug treatments aimed at lowering cholesterol levels.

High-density lipoproteins (HDL) are produced in the liver and intestines. They contain a core of cholesterol esters and a phospholipid disk with apolipoproteins A-I and A-II. HDL carry cholesterol from peripheral tissues and from other lipoproteins to the liver for subsequent catabolism. The blood plasma enzyme lecithin-cholesterol acyltransferase esterifies cholesterol and directs it to the HDL core, making room on the surface of the particles for new lipid molecules. HDL protect LDL from peroxidation, inhibit their capture by macrophages of the arterial wall.

Lipoprotein (a) consists of one LDL particle and a glycoprotein molecule - apo (a). The latter is a mutant form of plasminogen.

Thus, blood lipoproteins can be divided into 3 groups

depending on atherogenic properties:

• Atherogenic lipoproteins - fragments of chylomicrons. lipoproteins of intermediate density. LDL and lipoprotein (a);

• Non-atherogenic lipoproteins - chylomicrons and VLDL;

• Anti-atherogenic lipoproteins - HDL.

VLDL contains 10-15% of blood serum cholesterol, LDL - 60-70%. in HDL - 20-30%. The level of cholesterol in LDL is estimated as a more reliable indicator of the risk of coronary heart disease than the content of total cholesterol in the blood. In contrast, a 1 mg/dL increase in HDL cholesterol reduces the risk of developing coronary heart disease by 2-3%. If the content of HDL cholesterol is 60 mg / dl and above, the atherogenic effect of other lipoprotein fractions is neutralized.

Hypercholesterolemia is classified into primary, or genetically determined and secondary.

Secondary (acquired) hypercholesterolemia

|  |  |
| --- | --- |
| **Условия возникновения** | **Нарушения спектра липопротеинов** |
| Сахарный диабет | ↑ЛПОНП, ↓ЛПВП (± хиломикроны) |
| Нефротический синдром | ↑ЛПНП (±↑ ЛПОНП) |
| Уремия | ↑ЛПОНП,↓ЛПВП |
| Гипотиреоз | Т ЛПНП (±↑ ЛПОНП) |
| Обструктивные заболевания печени | ↑ липопротеина Х |
| Алкоголизм | ↑ЛПОНП (±↑ хиломикронов) |
| Прием оральных контрацептивов | ↑ЛПОНП. ↓ЛПВП |
| Прием р-адреноблокаторов | ↑ЛПОНП.↓ЛПВП |
| Прием изотретиноина (13-цисретиноевая кислота) | ↑ЛПОНП.↓ЛПВП (± хиломикроны) |

Note: VLDL - very low density lipoproteins; LDL - low density lipoproteins; HDL - high density lipoproteins; lipoprotein X is an abnormal lipoprotein enriched in cholesterol.

The treatment regimen for atherosclerosis considers both pharmacological and non-pharmacological methods.

The goals of modern lipid-lowering therapy are the normalization of elevated levels of atherogenic LDL cholesterol, the correction of hypertriglyceridemia and the increase in cholesterol content in anti-atherogenic HDL. At the beginning of the 20th century, the first work appeared in which it was experimentally (on rabbits) shown that the addition of cholesterol to food causes symptoms resembling atherosclerosis.

Subsequently, despite the very large conventionality of the model (in the normal diet of rabbits, foods containing cholesterol are usually absent), it was concluded that atherosclerosis is associated with an increased level of consumption and accumulation of cholesterol in the body. This hypothesis was confirmed in subsequent studies with animals whose natural diet includes cholesterol (rats, monkeys).

When observing large populations of people suffering from cardiovascular disease, it has also been found that there is a relationship between elevated cholesterol levels and an increased likelihood of cardiovascular disease.

The use of lipid-lowering drugs gave some statistically significant effect, but for people older than 70 years, this pattern becomes less obvious.

Classification of lipid-lowering drugs:

3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (“statins”):

Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Atorvastatin, Cerivastatin, Rosuvastatin, Pitavastatin.

Fibrates:

Clofibrate, Bezafibrate, Aluminum clofibrate, Gemfibrozil, Fenofibrate, Simfibrate, Ronifibrate, Ciprofibrate, Etofibrate, Clofibride.

Substances that increase the excretion of bile acids:

Cholestyramine, Cholestipol, Kolekstran, Kolesevelam.

Niacin and its derivatives:

Niceritrol, Niacin (nicotinic acid), Nicofuranose, Aluminum nicotinate, Nicotinyl alcohol (pyridylcarbinol), Acipimox.

Other lipid-lowering drugs:

Dextrothyroxine, Probucol, Tiadenol, Benfluorex, Meglutol, Omega-3 fatty acids, Magnesium pyridoxal 5-phosphate glutamate, Policosanol, Ezetimibe, Lecithin, Lomitapide, Phytosterols, Berberine, Red yeast rice, Boswellia serrata, L-arginine, Linseed oil.

Combined drugs.

HMG CoA reductase inhibitors in combination with other lipid-lowering drugs:

Lovastatin with nicotinic acid, simvastatin and ezetimibe.

HMG CoA reductase inhibitors, other combinations:

Simvastatin and acetylsalicylic acid, Pravastatin and acetylsalicylic acid, Atorvastatin and amlodipine.

3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors ("statins")

Statins are currently the most important among lipid-lowering drugs. The first drug - mevastatin (original name - compactin) was isolated by Endo in 1976 from the culture of fungi Penidllium citricum and Penicillium brevicompactum. Lovastatin is a waste product of the fungi Aspergillus terreus and Monascus ruber. The rest of the statins are synthetic. Researchers from the University of London have found that statins not only lower cholesterol levels, but also improve the structure and function of the heart. People taking these medications are less likely to have an enlarged heart, a sign of stress and muscle weakness. Compared to normal people, patients who took the medication had 2.4% less muscle mass in the left ventricle of the heart. The volumes of the left and right ventricles were also reduced. This class is on the World Health Organization's List of Essential Medicines, where simvastatin is on the list of medicines. The best-selling statin is atorvastatin, also known as Lipitor, which in 2003 became the best-selling pharmaceutical drug in history.

Mechanism of action of statins

Lovastatin and simvastatin are lactone prodrugs. In the liver, their lactone ring is hydrolyzed into the active hydroxy acid. Atorvastatin, pravastatin, fluvastatin, and cerivastatin contain an hydroxy acid in the native molecule.

The hydroxy acid in the side chain gives statins and their active metabolites a stereostructural similarity to 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA). Statins competitively block NADP-H-dependent HMG-CoL reductase, an enzyme that catalyzes the conversion of HMG-CoL to a cholesterol precursor, mevalonic acid.

Thus, statins, by reducing the synthesis of cholesterol in the liver and intestinal mucosa, cause the accumulation of cholesterol precursors. In other tissues, statins create a very low concentration and do not inhibit HMG-CoL reductase. therefore, the production of cholesterol compensatory increases.

Genes. encoding the synthesis of receptors for apo B-100 have steroid-dependent elements. With a decrease in cholesterol in the liver, gene expression occurs. The synthesis of receptors involved in the capture of apo 8-^00-containing lipoproteins - LDL and their precursors (VLDL, intermediate density lipoproteins) from the blood is increased. In liver biopsies of patients undergoing cholecystectomy and treated with pravastatin before surgery, the activity of receptors for apo B'100 almost doubled.

Statins after 2-4 weeks of course intake reduce the amount of cholesterol in the blood in LDL and intermediate density lipoproteins by 25-45%. triglycerides in VLDL - by 10-30%. increase HDL cholesterol by 8-10%. Statins (with the exception of atorvastatin) do not alter LDL levels in patients with familial homozygous hypercholesterolemia when apo B-100 receptors are absent. After liver transplantation in these patients, the therapeutic effect of statins resumes.

Statins have an anti-inflammatory effect, stabilize atherosclerotic plaques, suppress thrombosis, stimulate the production of nitric oxide in the endothelium (NO reduces the migration of foamy macrophages into the subendothelial space, the formation of free oxygen radicals, the proliferation of smooth muscle cells, and protects LDL from oxidation).

Statins are completely absorbed from the intestine, but undergo first-pass elimination, which significantly reduces bioavailability. Atorvastatin and cerivastatin, with the participation of cytochrome P-450, are converted into active metabolites. Statins are excreted in urine and bile.

Statins are prescribed for the treatment of heterozygous hyperlipidemia 11A-11B phenotypes, which does not decrease on the background of a cholesterol-free diet. Their use reduced mortality from cardiovascular diseases by 42-51%. Atorvastatin is also indicated for patients with diabetic dyslipidemia. There have been reports of successful treatment with atorvastatin in patients with homozygous hypercholesterolemia.

Statins are well tolerated by patients with long-term therapy. Only in 1% of patients they have a hepatotoxic effect with a dose-dependent increase in the activity of transaminases in the blood (monitoring of liver function is necessary). In 0.1% of patients treated with statins, myopathy develops (weakness, increased activity of creatine phosphokinase in the blood), in severe cases, rhabdomyolysis and renal failure occur. Less often than other statins, atorvastatin and cerivastatin cause myopathy. The risk of myopathy increases with the combination of statins with fibrates, nicotinic acid, cyclosporine and erythromycin.

Lipophilic drugs that cross the blood-brain barrier, lovastatin and simvastatin, can cause insomnia.

Statins are contraindicated in pregnancy, taking immunosuppressants, active liver disease, liver failure, individual intolerance. Drugs are prescribed with caution to patients with alcoholism, muscular hypotension, infectious pathology, epilepsy, with injuries and the need for major operations.

Drugs that are not recommended to be combined with statins due to the risk of developing myositis and rhabdomyolysis

• fibrates (risk of rhabdomyolysis and hepatotoxicity, possible combination with fluvastatin)

• nicotinic acid and its derivatives (risk of hepatotoxicity)

• macrolide antibiotics (erythromycin, clarithromycin in particular)

• cyclosporine

• azole antifungals

• verapamil

• amiodarone

• HIV protease inhibitors

Conditions that increase the risk of developing myositis and rhabdomyolysis when using statins:

• mature or advanced age in combination with pathology (DM and CRF)

• the presence of surgical interventions in history (it is necessary to cancel statins for the postoperative period)

• malnutrition

• liver failure

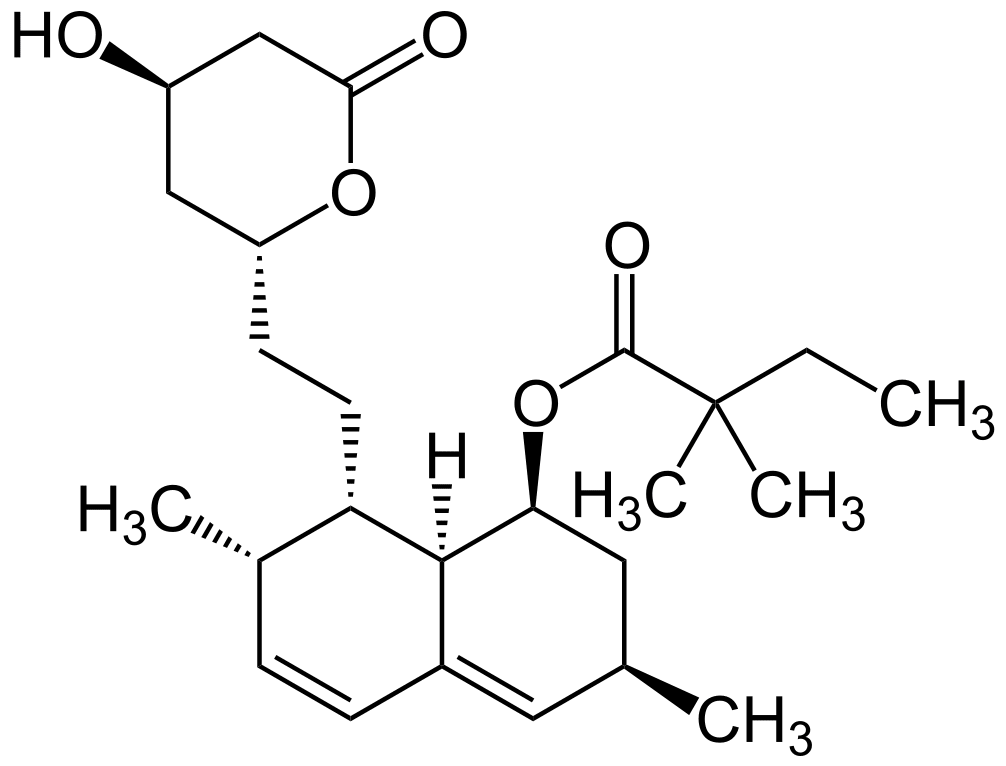
• polypharmacy

• excessive alcohol consumption

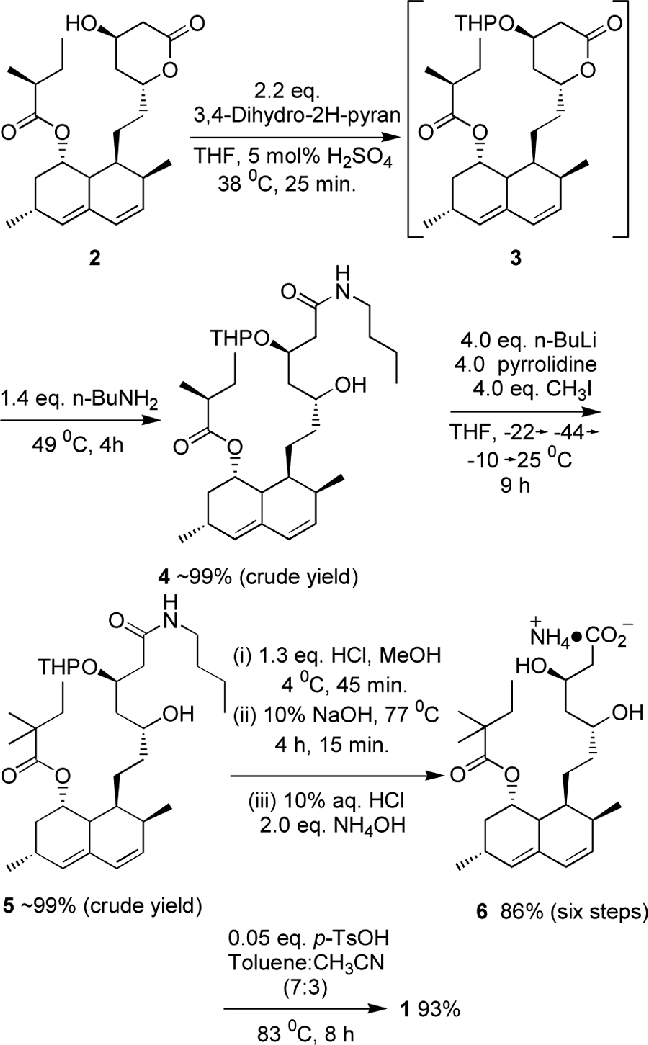
• drinking grapefruit juice

In these cases, patients should be under more careful supervision of a doctor with enzyme control (ALT, AST, GGTP, CPK) at least 2 times a month. Pharmacokinetic studies have shown that patients belonging to the Mongoloid race are more sensitive to the action of statins, therefore, in such patients, lower dosages (< 40 mg / day) should be used.

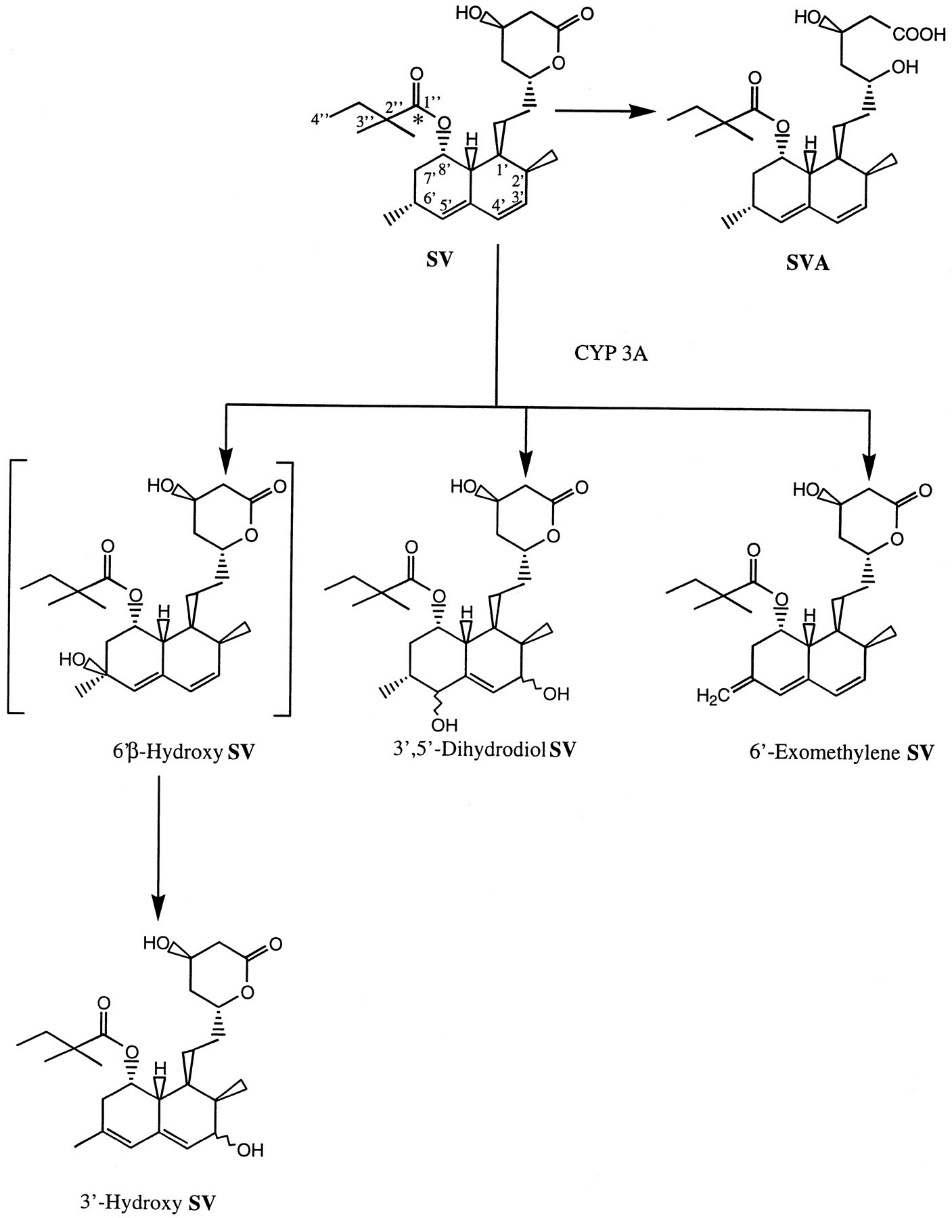
**Simvastatin**



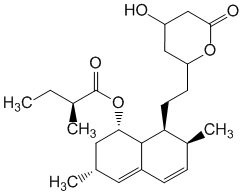
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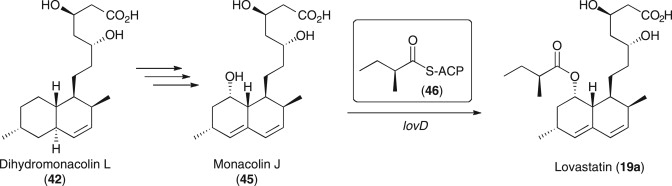
**Metabolism:**



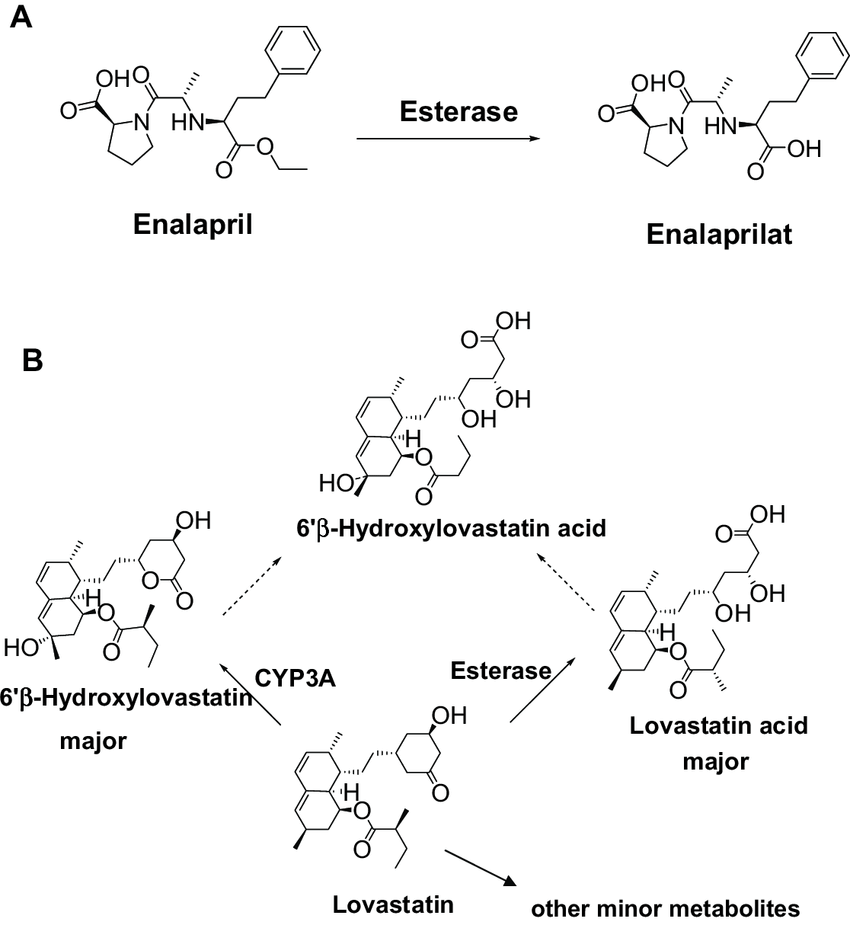
**Lovastatin**



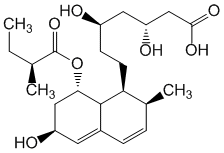
**Synthesis:**



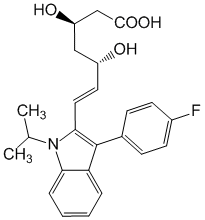
**Metabolism:**



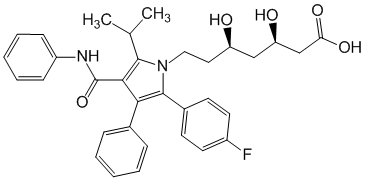
**Pravastatin**



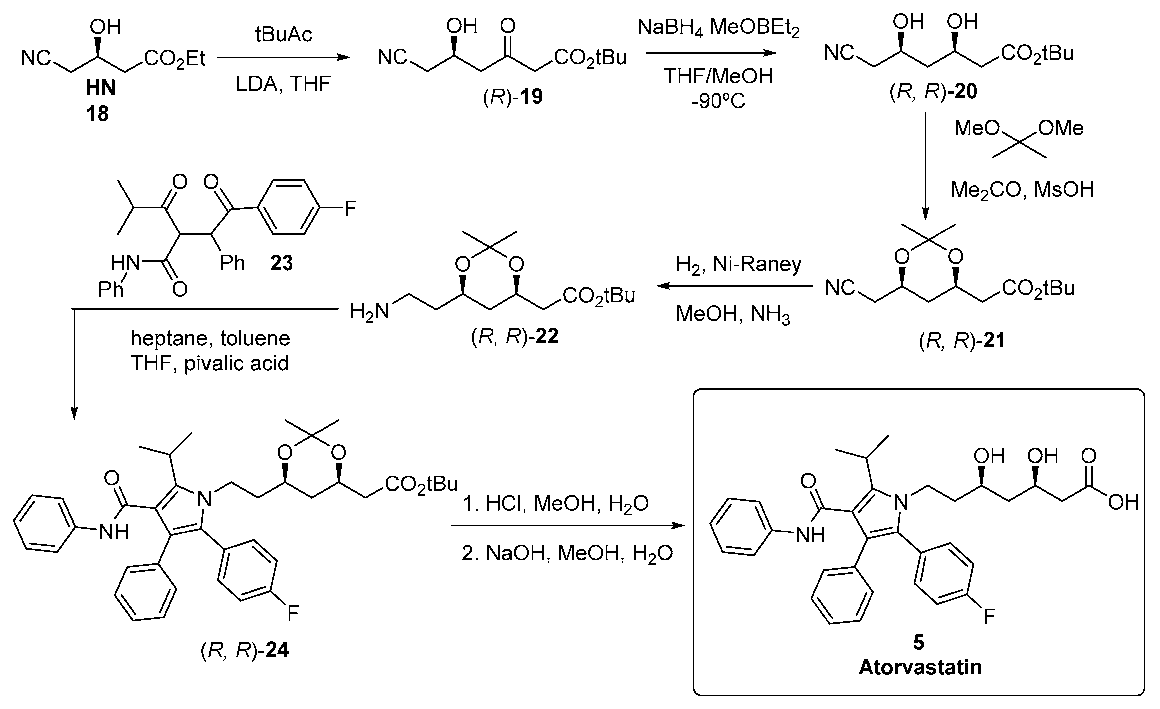
**Fluvastatin**



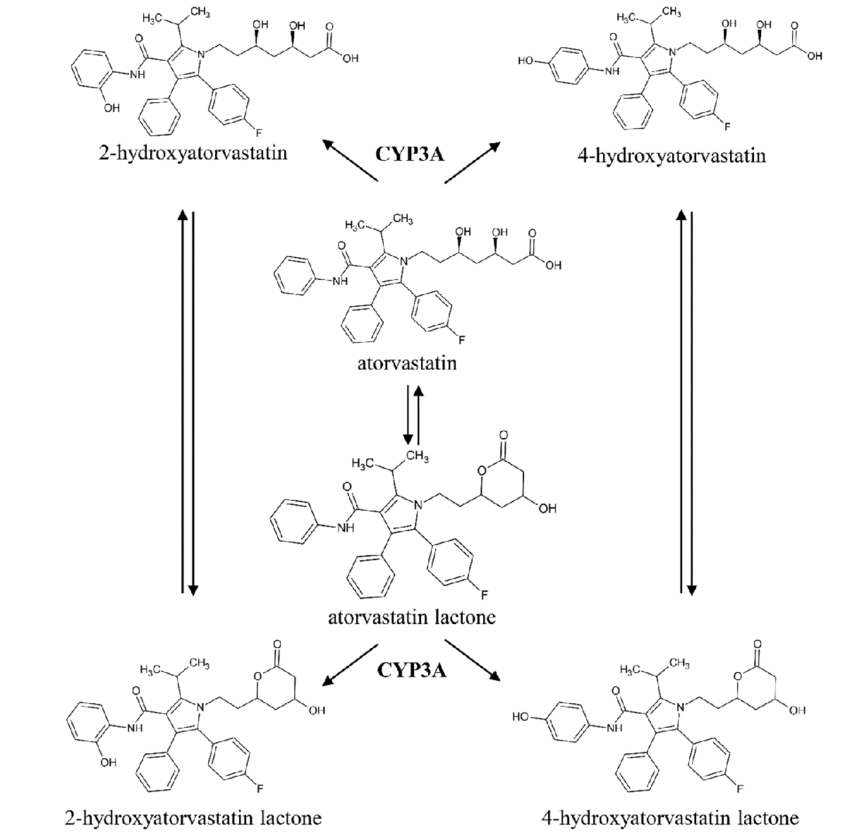
**Atorvastatin**



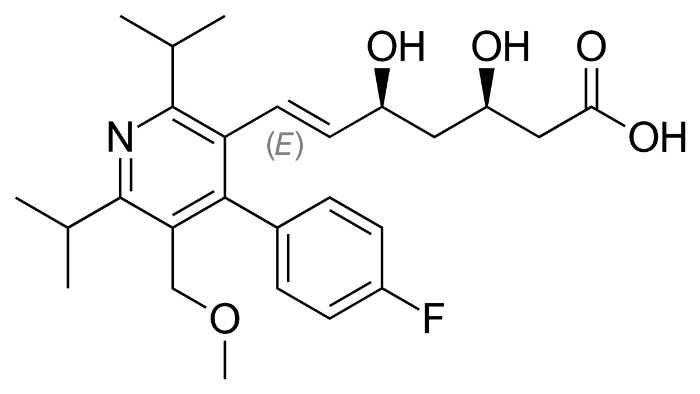
**Synthesis:**



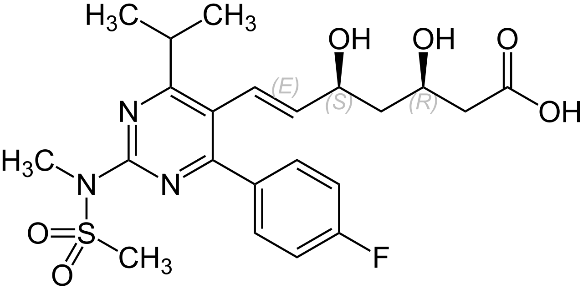
**Metabolism:**



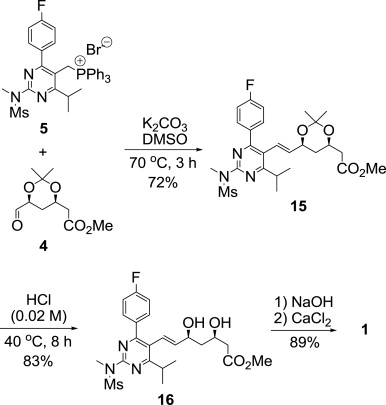
**Cerivastatin**



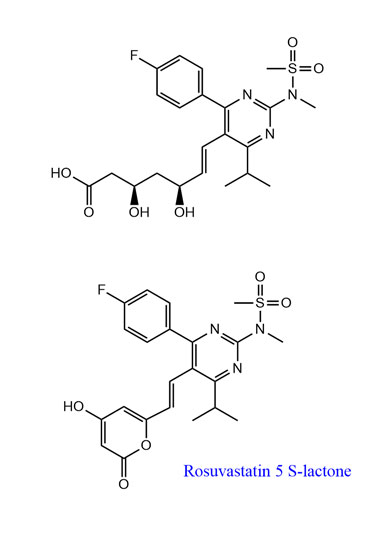
**Rosuvastatin**



**Synthesis:**



**Metabolism:**



**Pitavastatin**



**Fibrates**

The first preparation of the group of derivatives of fibroic (p-chlorophenoxy-isobutyric) acid is clofibrate. In 1967, it was recommended in the USA as a lipid-lowering agent. Currently, clofibrate is excluded from medical practice, as it increases the incidence of cholesterol gallstones and, with long-term use, increases mortality from non-cardiac diseases, in particular from oncological pathology.

Fibrates have a hypolipidemic effect after 2-4 weeks of course intake, as they reduce the content of triglycerides in VLDL and increase the amount of cholesterol in HDL. This group of drugs

• Activate lipoprotein lipase, inhibiting the synthesis in the liver of the inhibitor of this enzyme - apolipoprotein C-III, as a result, they accelerate the hydrolysis of triglycerides into VLDL and the conversion of the latter into intermediate density lipoproteins;

• They inhibit the formation of triglycerides in the liver, reducing the extraction of fatty acids from the blood and their synthesis, and also stimulate the oxidation of fatty acids in peroxisomes;

• Increase the intake of cholesterol and triglycerides in anti-atherogenic HDL (there are HDL enriched with triglycerides), improve the synthesis of apolipoprotein A-I for HDL. Fibrates ambiguously change the content of LDL, which is due to the variable fate of intermediate density lipoproteins in different patients - both accelerated degradation of intermediate density lipoproteins in the liver and their intensive conversion into LDL are possible.

Gemfibrozil activates fibrinolysis, has antiplatelet properties, inhibits the synthesis of blood coagulation factor VII (proconvertin, autopro-thrombin I); bezafibrate, fenofibrate and ciprofibrate reduce the amount of fibrinogen in the blood, gemfibrozil and bezafibrate normalize the concentration of glucose in patients with diabetes mellitus.

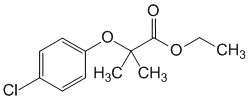
Fibrates have a high bioavailability (> 90%) when taken orally, create a maximum concentration in the blood after 2-4 hours, and are largely associated with albumin. Fibrate glucuronides are excreted in the urine (60-90%). The elimination half-life of gemfibrozil is 1.5 hours, of fenofibrate is 20 hours, of ciprofibrate is 80 hours. These drugs accumulate in diseases of the liver, kidneys and in the elderly.

Fibrates are used to treat hypertriglyceridemia when there is no effect from dietary measures and the risk of developing pancreatitis is increased (phenotypes IV and V). They are also indicated for hyperlipidemias of HA and /// phenotypes.

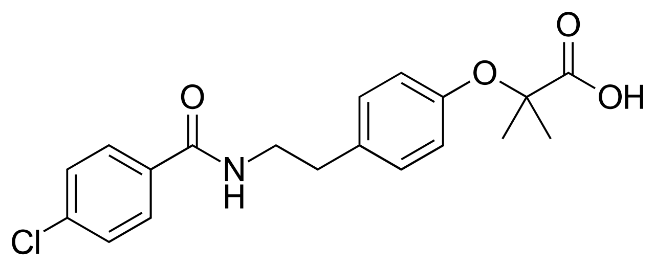
Side effects of fibrates are observed in 5-10% of patients. Liver function is impaired, dyspeptic disorders, myalgia, myositis, rhabdomyolysis occur (the risk of skeletal muscle damage increases with combined use with statins), headache. dizziness, blurred vision, cataracts, kidney failure, anemia, hair loss, impotence. In experiments on rats, gemfibrozil increased the incidence of benign and malignant tumors. Fibrates potentiate the action of indirect anticoagulants, displacing them from their association with blood proteins.

Fibrates are contraindicated in diseases of the liver, kidneys, a history of calculous cholecystitis, alcoholism, individual intolerance, pregnancy and breastfeeding. They are not given to children.

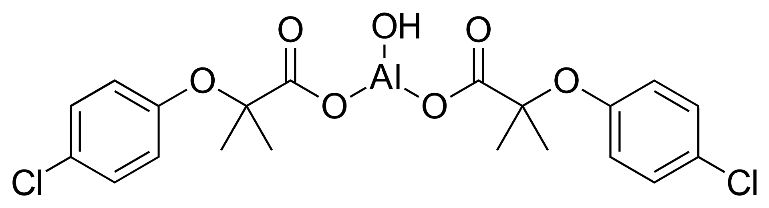
**Clofibrate**



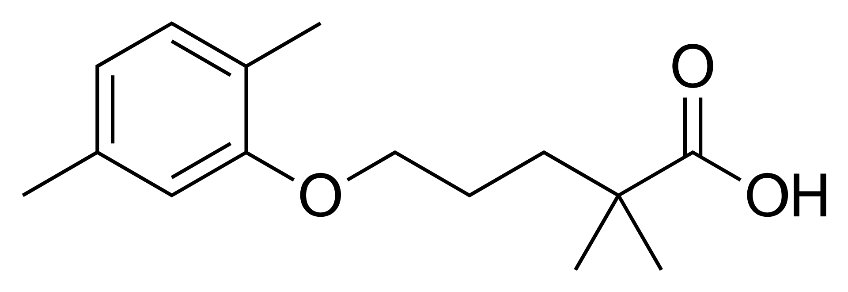
**Bezafibrate**



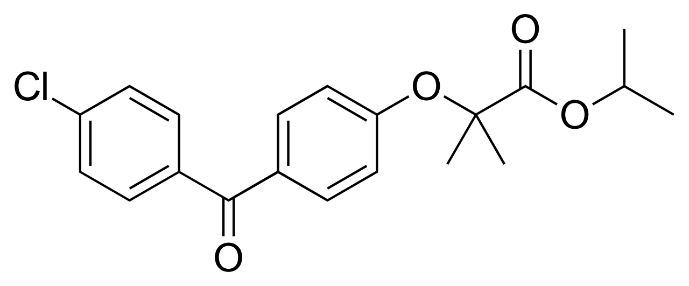
**Aluminum clofibrate**



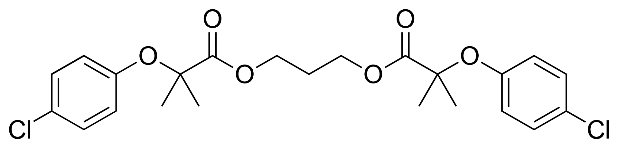
**Gemfibrozil**



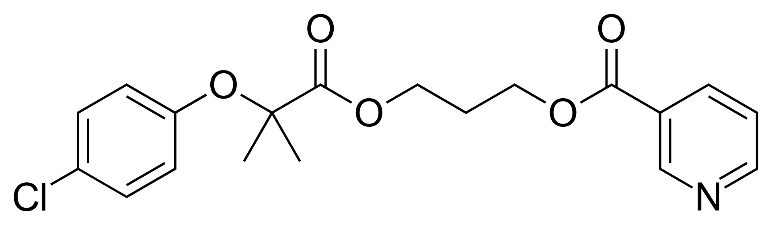
**Gemfibrozil Fenofibrate**



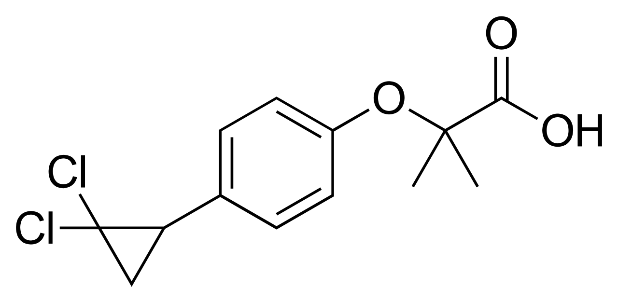
**Symfibrat**



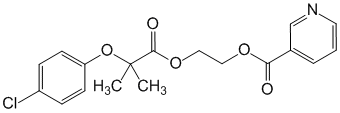
**Ronifibrate**



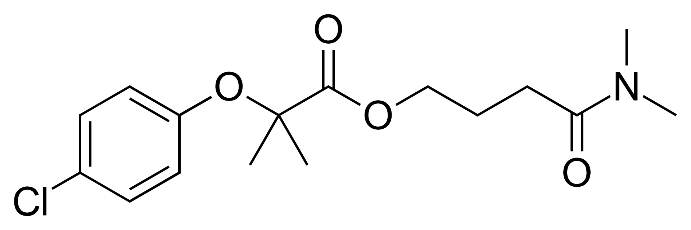
**Ciprofibrate**



**Etofibrate**



**Clofibride**



**Substances that increase the excretion of bile acids.**

Bile acid sequestrants, originally proposed for the treatment of pruritus in obstructive liver disease, are anion exchange resin hydrochlorides. Colestyramine is a base, a copolymer of styrene and divinylbenzene. contains quaternary ammonium groups. Colestipol is a copolymer of diethylenetriamine and 1-chloro-2.3-epoxypropane with secondary and tertiary ammonium groups. Both drugs are insoluble in water, but extremely hygroscopic.

Sequestrants bind bile acids in the small intestine by replacing their chloride anions with bile acid anions. They interrupt the enterohepatic circulation of bile acids (as is known, 97% of their amount is involved in the enterohepatic circulation).

Intensive excretion of bile acids is accompanied by metabolic changes in the liver:

• Increases the conversion of cholesterol to bile acids;

• The number of LDL receptors increases;

• There is a compensatory induction of HMG-COD reductase with an increase in cholesterol synthesis;

• Increased production of triglycerides and their excretion into the blood as part of VLDL.

Bile acid sequestrants reduce the content of cholesterol in LDL by 10-35% with a maximum effect after 2 weeks of therapy, increase the amount of cholesterol in HDL by 5%. During treatment, the concentration of triglycerides initially moderately increases. but returns to normal after a few weeks.

With the combined use of sequestrants with statins, the level of cholesterol in LDL drops by an additional 20-25%. when combined with nicotinic acid, this figure decreases by 40-60%.

Bile acid sequestrants relieve itching in jaundice. eliminate diarrhea caused by excess bile acids during radiation therapy, resection of the ileum, Crohn's disease.

Drugs like resins are not absorbed into the blood from the intestines and do not have a resorptive effect.

Bile acid sequestrants are prescribed for hyperlipidemia of the HA and IV phenotypes, refractory to dietary measures for several months, as well as for the elimination of pruritus in patients with partial obstruction of the bile duct. These lipid-lowering drugs reduced mortality from coronary heart disease by 24%, the frequency of non-fatal myocardial infarction - by 19%.

The preparations in the form of powder (colestyramine) and granules (colestipol) are taken orally, either after dilution in water or juice, or together with juicy fruits. Bile acid sequestrants are not effective for very high blood cholesterol levels, familial homozygous dysbetalipoproteinemia, when LDL receptors do not function in patients (phenotype III), as well as with complete obstruction of the bile duct.

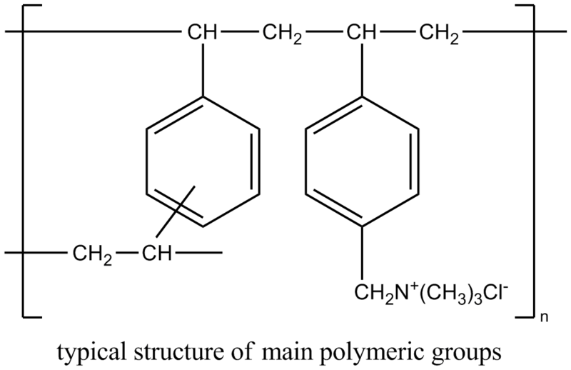
Side effects of bile acid sequestrants - constipation, peptic ulcer, flatulence, heartburn, vomiting, hiccups, steatorrhea (increased content of neutral fat in the feces), hypertransaminasemia, formation of stones in the biliary tract, cholecystitis, hypovitaminosis K with bleeding, hyperchloremic acidosis , headache, dizziness, uveitis.

Bile acid sequestrants adsorb many drugs taken orally into the intestinal lumen (other drugs are prescribed 1 hour before or 4 hours after taking sequestrants);

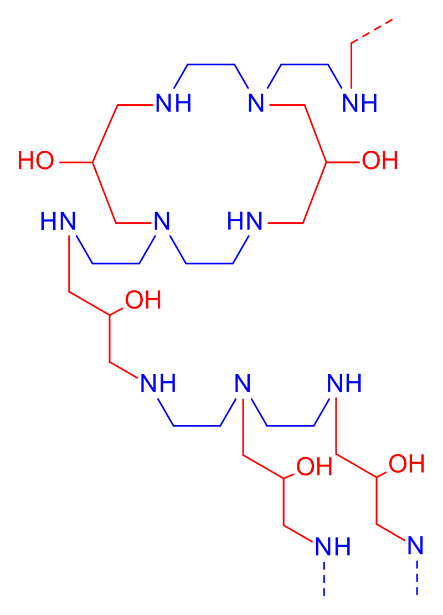
disrupt the absorption of fat-soluble vitamins D. D. E and K into the blood.

Bile acid sequestrants are contraindicated in high hypertriglyceridemia and individual intolerance.

**Cholestyramine**



**Cholestipol**



**Kolesevelam**



**Niacin and its derivatives.**

**NICOTIC ACID (NIACIN)** has been used as a hypolipidemic agent since 1955. It is pyridine-3-carboxylic acid, a water-soluble vitamin B6 or PP involved in the synthesis of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Nicotinamide is devoid of hypolipidemic effect.

Nicotinic acid in a large dose has a diverse effect on lipid metabolism:

• Inhibits lipolysis in adipose tissue, which limits the delivery of free fatty acids to the liver, ultimately inhibiting the hepatic synthesis of triglycerides and VLDL;

• Increases the breakdown of VLDL in the blood as an activator of lipoprotein lipase;

• Reduces blood levels of LDL, depleting their precursors -VLDL;

• Increases the level of HDL, delaying the elimination of apolipoprotein

to A-I along the receptor pathway in the liver.

Nicotinic acid in doses of 3-6 g / day reduces the amount of cholesterol in LDL by 15-25% after 3-5 weeks of therapy, reduces the level of triglycerides in VLDL by 20-80% after 1-4 days, increases cholesterol in HDL by 10-20%, prevents the appearance of lipoprotein (a).

In combination with bile acid sequestrants, nicotinic acid reduces the cholesterol content in LDL by 40-60%, the combination of nicotinic acid in a small dose (2 g / day), statins and bile acid sequestrants reduces this indicator by 70%.

Nicotinic acid is well absorbed from the intestine, 20% of its dose is associated with plasma proteins. It is excreted unchanged by the kidneys with a half-life of 45 minutes. Accumulation of nicotinic acid occurs in renal failure and in the elderly.

Nicotinic acid is prescribed for hypercholesterolemia in combination with hypertriglyceridemia (IV phenotype) and isolated hypertriglyceridemia. Patients subjectively better tolerate nicotinic acid in dosage forms with prolonged action - NIKOBID TEMPULES (microencapsulated tablets with fast and slow release). SLONIATSIN (compound of nicotinic acid with polygel), ENDURACIN (tropical wax matrices containing nicotinic acid).

Nicotinic acid preparations reduced mortality from coronary heart disease by 12% and overall mortality by 11%.

Only 54% of patients tolerate nicotinic acid at a dose of more than 4.5 g / day, as it causes side reactions - transient flushing and itching on the face and in the upper half of the body due to the release of vasodilating prostaglandins (in 70-80% of patients ), headache, arrhythmia (including atrial fibrillation), blurred vision, dry skin, hyperpigmentation, gastrointestinal problems, hyperglycemia, an increase in the concentration of uric acid in the blood with exacerbation of gout. A dangerous side effect is liver damage (increase in transaminase activity, jaundice, liver failure). Hepatotoxicity is significantly pronounced in nicotinic acid in long-acting dosage forms. Occasionally, after taking nicotinic acid, orthostatic collapse develops.

Nicotinic acid is contraindicated in history of bleeding, severe arterial hypertension, peptic ulcer of the stomach, diabetes mellitus, gout, liver disease, individual intolerance, pregnancy and breastfeeding.

Medicines that are not recommended for use with nicotinic acid preparations due to the risk of side effects:

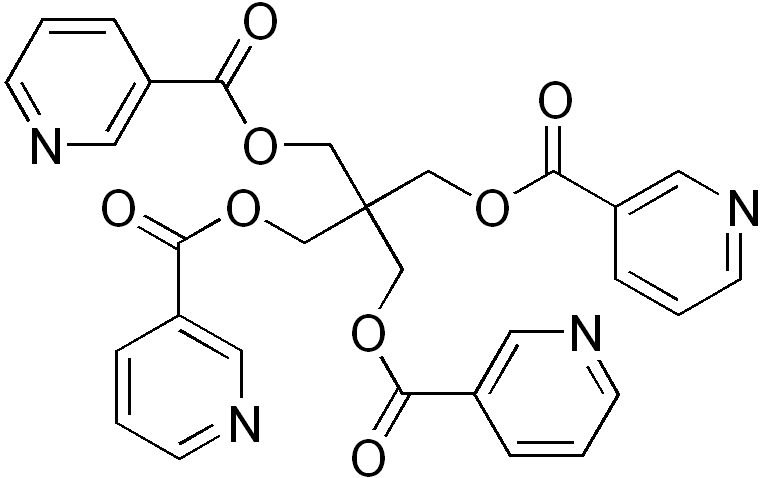
• statins (risk of hepatotoxicity)

• fibrates (risk of hepatotoxicity and rhabdomyolysis)

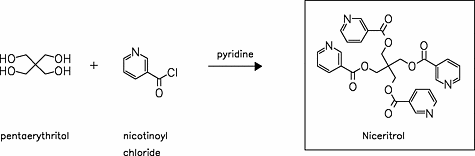
It is necessary to control ALT, AST, GGTP.

• In patients with diabetes mellitus and gout, an exacerbation of the underlying disease is possible; in this category of patients, it is necessary to avoid prescribing any form of nicotinic acid.

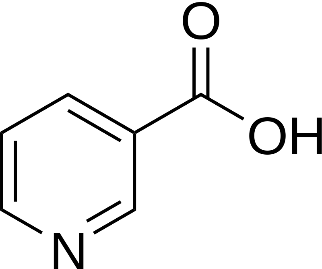
**Niceritrol**



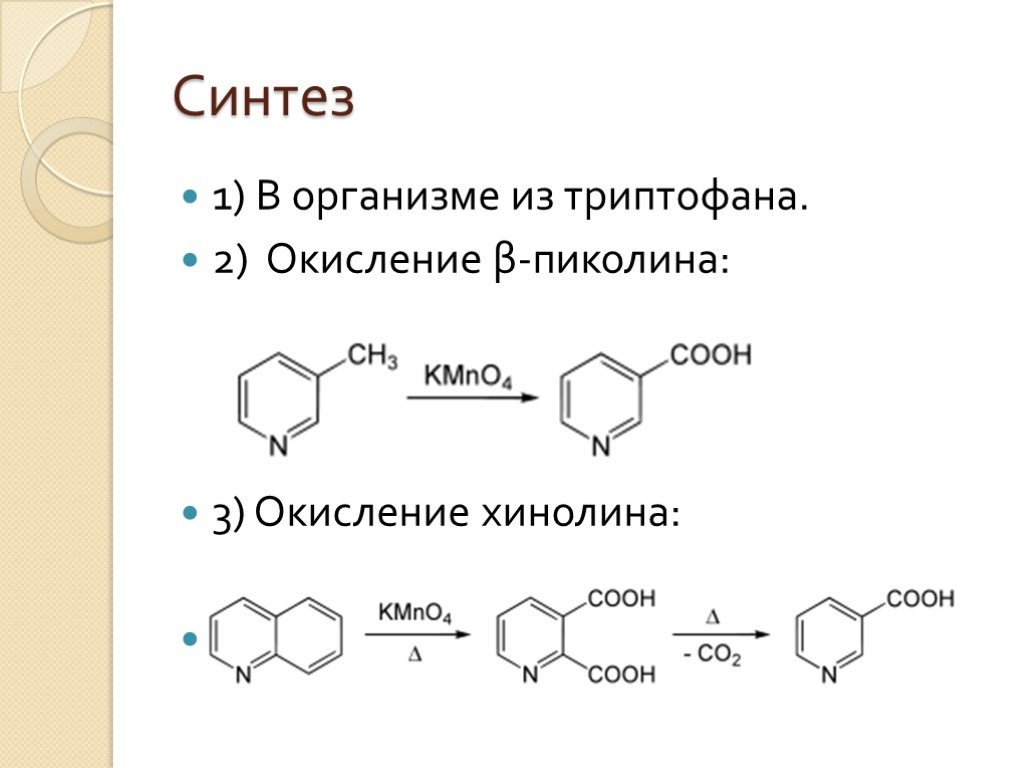
**Synthesis:**



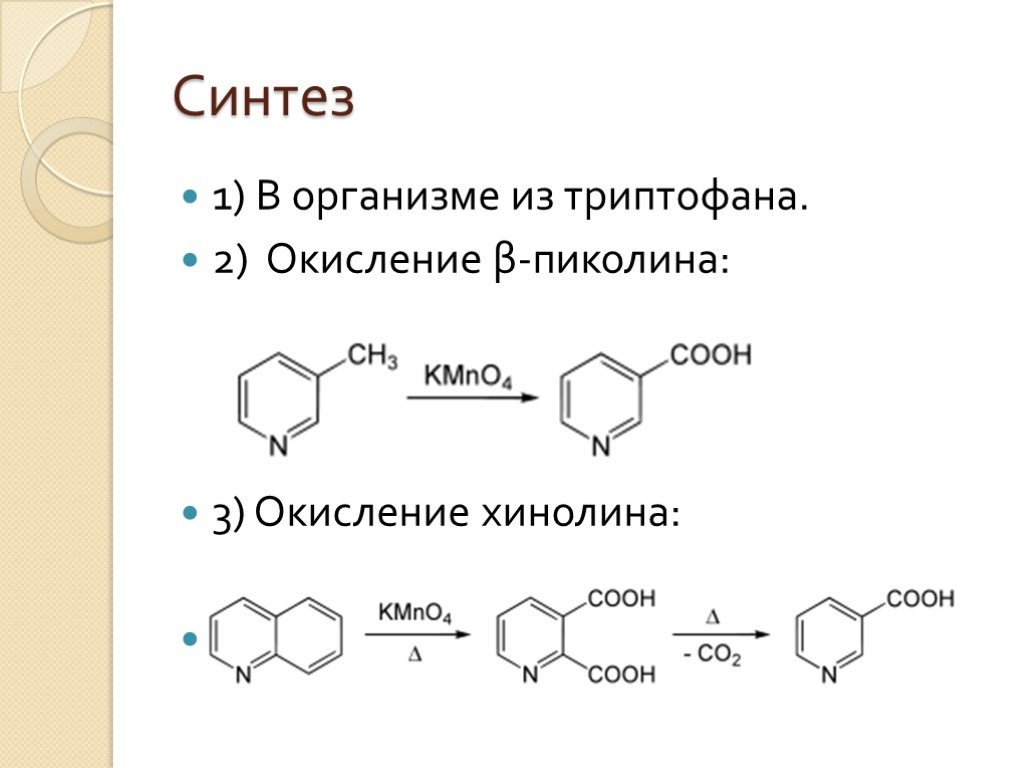
**Niacin (nicotinic acid)**



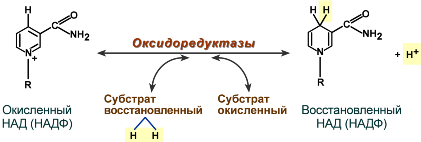
**Synthesis:**



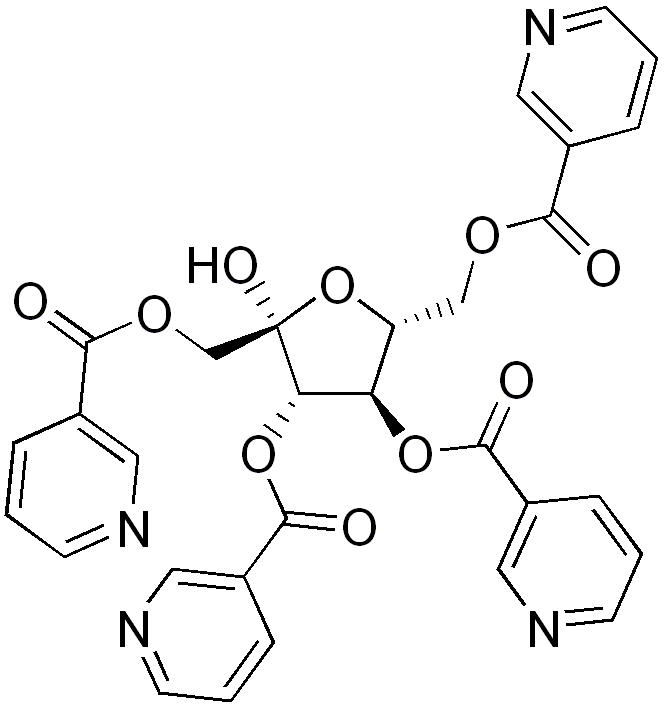
**Metabolism:**



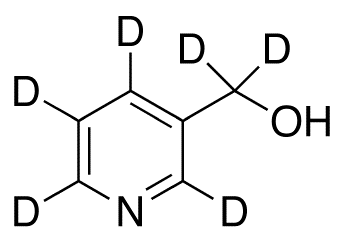
**Nicofuranose**



**Nicotinyl alcohol (pyridylcarbinol)**



**Acipimox**



Acipimox (trade name Olbetam in Europe) is a nicotinic acid derivative used as a lipid-lowering agent. It lowers triglycerides and raises HDL cholesterol levels. It may have fewer side effects than niacin, although it is not clear if the recommended dose is as effective as standard doses of niacin. Acipimox (trade name Olbetam in Europe) is a nicotinic acid derivative used as a lipid-lowering agent. It lowers triglycerides and raises HDL cholesterol levels. It may have fewer side effects than niacin, although it is not clear if the recommended dose is as effective as standard doses of niacin.

**Other lipid-lowering drugs**

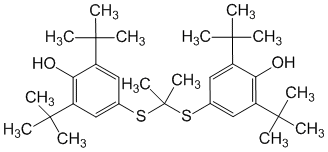
**Dextrothyroxine**



Dextrothyroxine (d-thyroxine) is a stereoisomer of natural thyroid α-thyroxine. In the form of sodium salt, it is well absorbed in the digestive apparatus. It is used in the treatment of hyperlipoproteinemia (HLP) II and III types. Most effective for reduced thyroid function. Its lipid-lowering effect is more pronounced when combined with clofibrate and nicotinic acid.

The mechanism of action of dextrothyroxine is associated with an increase in the degradation of low-density lipoproteins (LDL). Under the influence of the drug, the synthesis of cholesterol in the liver increases, but to an even greater extent - oxidation and the release of its decay products (bile acids) with feces. In patients with type II HLP, dextrothyroxine reduces cholesterol levels by 20–30%, and leads to resorption of skin and tendon xanthomas. Long-term (6 months to 3 years) use of dextrothyroxine in euthyroid patients with HLP types II and III does not lead to hyperthyroidism. After stopping the drug, no additional effect on the pituitary-thyroid gland system is required to eliminate its inhibition caused by dextrothyroxine, since it is transient.

**Probucol**



Lipophilic antioxidant PROBUCOL (LIPOMAL, LORELKO, LURSELL) - tertiary butyloxytoluene. In its symmetrical molecule, 2 fragments are connected by an S - C - S bridge.

The mechanism of action of probucol:

• Changes the structure of LDL in such a way that facilitates their hepatic elimination without the participation of receptors for apolipoprotein B-100 (effective in patients with homozygous hypercholesterolemia);

• Reduces HDL cholesterol content. disrupting the synthesis of apolipoprotein A-I, stimulates the conversion of HDL into other lipoproteins, more accessible for elimination in the liver;

• Activates the flow of free cholesterol to the liver, regardless of lipoproteins;

• It has an anti-atherosclerotic effect, not associated with a hypolipidemic effect - as an antioxidant, it counteracts the transformation of macrophages into foam cells loaded with peroxide-modified lipids.

Probucol reduces cholesterol in LDL by 8-15%, in HDL by 25-30% (Table 48.5). The latter effect is considered as undesirable (HDL plays the role of an endogenous anti-atherosclerotic factor). The hypocholesterolemic effect of probucol develops after 2-3 months of course administration and persists for six months after cancellation.

With the combined use of probucol with bile acid sequestrants, the level of cholesterol in LDL decreases by an additional 10%. When combined with lovastatin, the cholesterol content in LDL remains the same as with the action of probucol alone. however, as part of HDL, it falls by an additional 25-30%. Fibrates potentiate the decrease in the content of HDL in the blood caused by probucol.

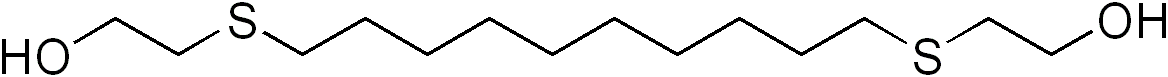
The bioavailability of probucol when taken orally is only 2-8%. In the blood, 95% of its molecules are associated with lipoproteins. The drug is excreted unchanged in the bile (half-life is 12 hours or more), it can be deposited in adipose tissue for 6 months.

Probucol is used as a second-line hypocholesterolemic agent with the ineffectiveness of other drugs, if the expected hypocholesterolemic effect in a patient exceeds the risk of an adverse effect on the level of HDL.

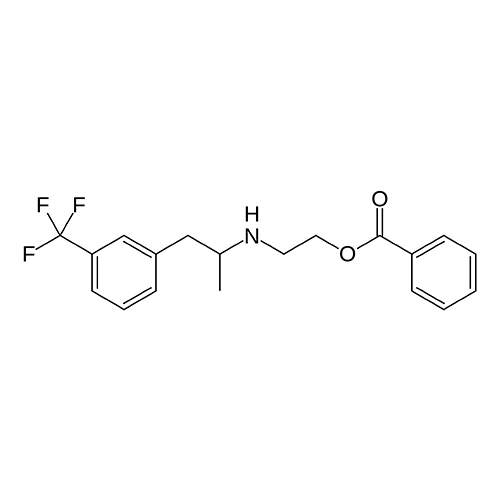
Side effects of probucol are dyspepsia, headache, dizziness, insomnia, hematological problems. These disorders occur in 10% of patients. A serious danger is the prolongation of the interval 07 "on the ECG, which can cause ventricular tachycardia (torsades de pointes) and ventricular fibrillation. Cases of sudden death due to the arrhythmogenic effect of probucol are described. It is unacceptable to use it in conjunction with drugs that lengthen the OT interval, - antiarrhythmic drugs (including -blockers), neuroleptics of the phenothiazine group, tricyclic antidepressants, cardiac glycosides.

Probucol is contraindicated in fatty foods, coronary heart disease (especially acute myocardial infarction), arrhythmias, bradycardia, prolongation of the OT interval, impaired atrioventricular conduction, hypokalemia, hypomagnesemia, primary biliary cirrhosis of the liver, inflammatory processes. The drug is not prescribed for women during pregnancy and breastfeeding, as well as children.

**Tiadenol**



**Benfluorex**



Benfluorex, sold under the brand name Mediator, is an anorectic and lipid-lowering agent structurally related to fenfluramine (a substituted amphetamine). It may improve glycemic control and reduce insulin resistance in people with poorly controlled type 2 diabetes.

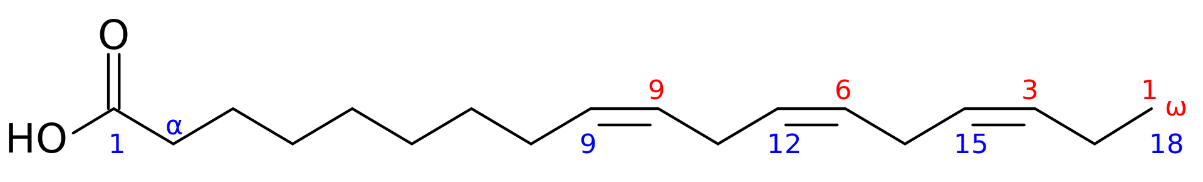
**Meglutol**



Meglutol (INN, also known as 3-hydroxy-3-methylglutaric acid, β-hydroxy-β-methylglutaric acid, and dicrotalic acid) is a lipid-lowering agent.

It is in the free state and is associated with (pyrrolizidine alkaloid).

**Omega 3 fatty acids**



An example of the chemical structure of a ω−3-polyunsaturated fatty acid (alpha-linolenic acid is shown). The linear chain of carbon atoms linked by single and double bonds ends on the left with a carboxyl group -COOH, on the right with a methyl group -CH3. The letter alpha (α) denotes the first atom of the chain, counting in the direction from the carboxyl group; the letter omega (ω), the last in the Greek alphabet, is the last atom from the carboxyl group (that is, the carbon atom of the methyl group). Looking backwards at the bonds between carbon atoms, the first double bond is in third place from the methyl end, that is, at position ω−3 ("omega minus three"). The definition of "polyunsaturated" means that there are at least two double (that is, unsaturated) bonds in the carbon skeleton of the molecule.

Omega-3 polyunsaturated fatty acids (PUFAs) belong to the family of unsaturated fatty acids that have a carbon-carbon double bond in the omega-3 position, that is, after the third carbon atom, counting from the methyl end of the fatty acid chain.

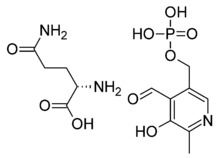
Omega-3 polyunsaturated fatty acids are part of cell membranes and blood vessels, are not synthesized in the right quantities in the human body and are one of the essential components of a complete healthy diet. The main food source is fish, as well as chia seeds, flax seeds, seaweed and microalgae, and so on.

The potential of ω3 fatty acids to reduce insulin resistance in type 2 diabetes has been shown in in vitro and mouse experiments and needs to be tested in humans.

In obese people, omega-3 supplements improved the quality of life, and, presumably, could increase life expectancy. (In 2012, researchers suggested that ω3, by neutralizing the action of ω6, reduces the rate of DNA telomere shortening.).

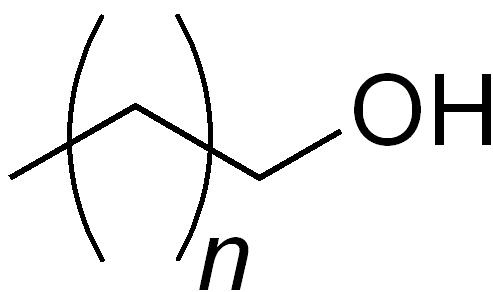
Omega-3 fatty acids are used to lower very low density lipoprotein (VLDL) levels. By inhibiting the esterification of fatty acids, they delay the synthesis of triglycerides in the liver. The decrease in triglyceride levels is facilitated by a decrease in the amount of free fatty acids available for triglyceride synthesis. When taking omega-3-unsaturated fatty acids, there is a slight temporary increase in the level of high-density lipoprotein (HDL), significantly less than after taking fibrates.

**Magnesium pyridoxal 5-phosphate glutamate**



Pyridoxal-5-phosphate magnesium glutamate (trade name sedalipide) is a lipid-lowering agent.

**Policosanol**



Policosanol is a general term for a mixture of long chain alcohols isolated from vegetable waxes. Included in a number of nutritional supplements.

It was first produced in Cuba in the early 1990s. Policosanol supplements have been approved in over 25 countries, mainly in South America and the Caribbean

According to a meta-analysis of a number of studies, the effectiveness of policosanol is not statistically different from placebo when trying to use it to reduce "bad" cholesterol (low density cholesterol) and increase "good" cholesterol (high-density lipoprotein (HDL, HDL)), as well as to prevent atherosclerosis.

• Lipid-lowering effect is achieved by suppressing cholesterol synthesis at the moment between the formation of acetate and mevalonate and stimulating the breakdown of LDL cholesterol in hepatocytes by activating lipases.

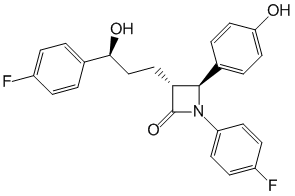
• Vasoprotective effect is provided by increasing the level of "protective" HDL cholesterol. Policosanol also prevents the oxidation of LDL cholesterol.

• The antiplatelet effect is achieved, according to the creators of the drug, by preventing platelet aggregation by influencing the synthesis of prostaglandins (policosanol reduces the level of thromboxane A2 in serum and increases the level of prostacyclin) and reduces the risk of thrombosis. At the same time, policosanol does not affect coagulation parameters.

The ineffectiveness of this supplement has been shown in several studies, in some cases conflicting results have been obtained. In particular, the results of a 2006 study show that in patients with hypercholesterolemia or combined hyperlipidemia, policosanol at regular and high doses is no more effective than placebo. Some studies conducted also did not find any positive effects.

There is an opinion that positive results were obtained only in studies conducted in Cuba by the Dalmer Laboratories group, which is associated with the Center for Scientific Research (the manufacturer of the product). A number of their results could not be repeated by other groups.

**Ezetimibe**



The mechanism of action of ezetimibe differs from that of other classes of lipid-lowering compounds (eg, statins, bile acid sequestrants, fibrates, and plant styrenes).

Ezetimibe is localized in the brush border of the small intestine and prevents the absorption of cholesterol, which leads to a decrease in the flow of cholesterol from the intestine to the liver, thereby reducing the reserves of cholesterol in the liver and increasing its excretion from the blood. Ezetimibe does not increase the excretion of bile acids (unlike drugs that bind bile acids), does not inhibit the synthesis of cholesterol in the liver (unlike statins).

The molecular target of ezetimibe is the transporter protein of cholesterol and phytosterols in enterocytes - the so-called. Niemann-Pick type C1 protein (Niemann-Pick C1-Like1, NPC1L1), which is involved in the intracellular transport of cholesterol. By reducing the absorption of cholesterol in the intestine, ezetimibe reduces the flow of cholesterol to the liver. Statins reduce cholesterol synthesis in the liver. Due to two different mechanisms of action, the drugs of these two classes, when administered together, provide an additional reduction in cholesterol levels. Ezetimibe, given in combination with statins, lowers total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo-B), and triglycerides (TG) and increases high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolemia to a greater extent than ezetimibe or simvastatin, administered separately.

Indications: Primary hypercholesterolemia - is prescribed in combination with HMG-CoA reductase inhibitors (statins) or as monotherapy in addition to diet to reduce elevated levels of TC, LDL-C, apo-B and TG, as well as to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia. Homozygous familial hypercholesterolemia - in combination with a statin is recommended to reduce elevated levels of TC and LDL cholesterol in patients with homozygous familial hypercholesterolemia; patients may also receive adjunctive treatment (eg LDL apheresis). Homozygous familial sitosterolemia (or phytosterolemia - elevated plasma plant styrenes with elevated or normal cholesterol levels and normal TG levels) - is recommended to reduce elevated sitosterol and campesterol levels.

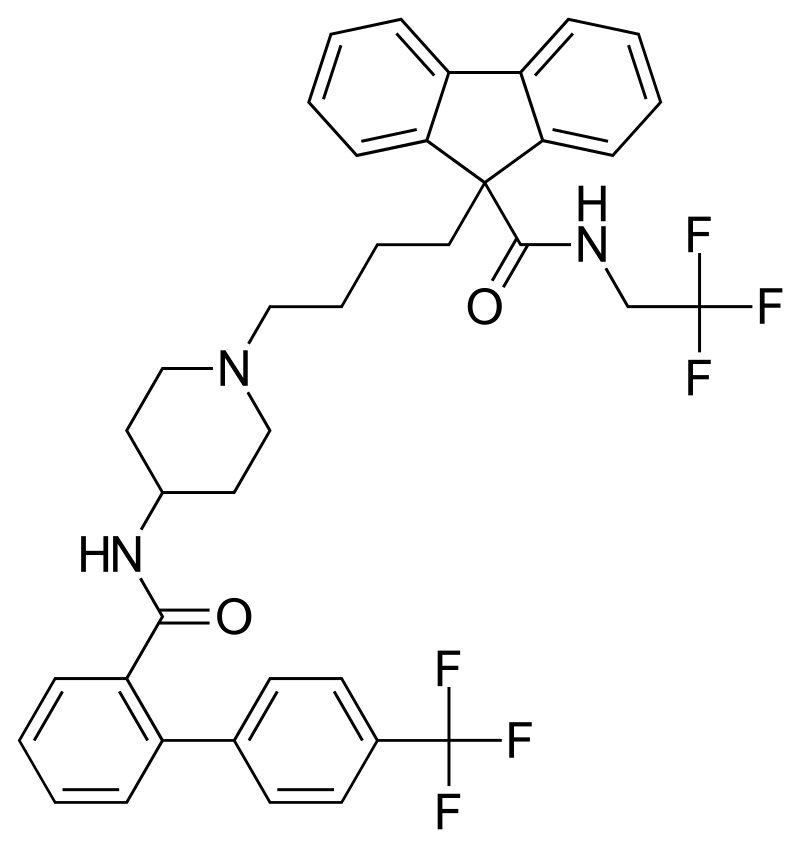
**Lecithin**

Lecithins (from the Greek λέκιθος - yolk) - the common name for a group of fat-like substances, which is a mixture of phospholipids (65-75%) with triglycerides and a small amount of other substances. It is widely used in the food and cosmetic industries as it is a natural emulsifier. First isolated in 1845 by the French chemist Gobley from egg yolk (hence the name). Commercial lecithin is obtained primarily from soybean oil.

Lecithins are esters of the amino alcohol choline and diglyceride phosphoric acids. Due to the fact that lecithin is based on phospholipids, these terms are sometimes used interchangeably. The main phospholipids contained in soy lecithin are phosphatidylcholine (19-21%), phosphatidylethanolamine (8-20%), inositol-containing phosphatides (20-21%) and phosphatidylserine (5.9%).

Lecithin is the active substance of the so-called hepatoprotectors, designed to prevent liver diseases. On the basis of phospholipids, the preparations "Essentiale Forte", "Essentiale N", "Esliver Forte", "Our Lecithin", a number of dietary supplements are produced.

**Lomitapide**

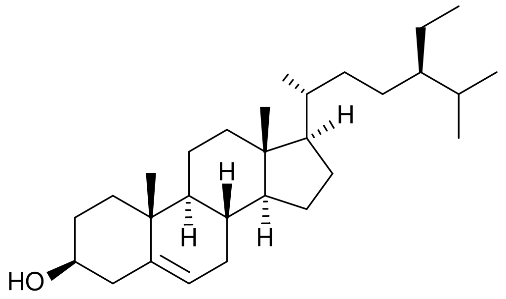


Lomitapide, sold under the brand name Juxtapid in the US and Lojuxta in the EU, is a drug used as a lipid-lowering agent for the treatment of familial hypercholesterolemia developed by Aegerion Pharmaceuticals. It has been clinically tested as monotherapy and in combination with atorvastatin, ezetimibe, and fenofibrate.

Lomitapide inhibits the microsomal triglyceride transport protein (MTP or MTTP), which is required for the assembly and secretion of very low density lipoproteins (VLDL) in the liver.

In December 2012, drug maker Aegerion announced that they had been approved by the FDA as "an adjunct to a low-fat diet and other lipid-lowering therapies ... in patients with homozygous familial hypercholesterolemia (HoFH)".

**Phytosterols**

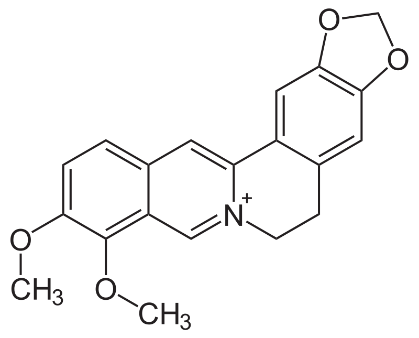


Phytosterols (phytosterols; also plant sterols/sterols) are a group of steroidal alcohols naturally present in plants. They look like a non-solid white powder with a characteristic odor, insoluble in water and soluble in alcohol. Phytosterols are widely used in medicine, cosmetics, and as food additives.

As a food component or as a special dietary supplement, phytosterol has the property of reducing cholesterol (reducing the amount of absorption in the intestine) and may work as a cancer prevention agent. Phytosterols are present in small amounts in vegetable oils, especially sea buckthorn (1640 mg/100 g oil), corn (968 mg/100 g) and soybean (327 mg/100 g oil). As a dietary supplement, the substance cholestatin is used, which exists separately from vegetable oils and is a mixture of campesterol, stigmasterol and brassicasterin. Sterols can reduce the concentration of cholesterol in the human body by more than 15%.

The mechanism by which phytosterol reduces cholesterol is as follows: the penetration of cholesterol into micelles in the digestive tract is inhibited, as a result, the total amount of absorbed cholesterol is reduced. This property of phytosterol helps to control the level of cholesterol in the human body. The quality of the control is determined by the ability to modify HDL (high density lipoprotein), LDL (low density lipoprotein) and TAG levels.

**Berberine**



Berberine (previously also yamaicin and xanthopicrit) is an alkaloid of the composition C20H17NO4, found in various parts of many plants belonging to the most diverse families, so from this side it can be considered one of the most common in the plant kingdom. In addition to the barberry (Berberis vulgaris), it is found in the roots of the colombus (Radix Colombo), belonging to the plant Cocculus palmatus Dec., in the bark of Geoffroya inermis and Xanthoxylum clava Herculis (whence its former names yamaicin and xanthopicrit), etc. At present, its obtained from the roots of the cultivated medicinal plant Coptis chinensis.

Since berberine has many valuable pharmacological properties, scientists are looking for ways to use it to treat and prevent various diseases, including cancer, heart disease, and diabetes.

Berberine has geroprotective properties, it protects the body from cardiovascular disease, diabetes and age-related learning loss. In particular, berberine can inhibit the accumulation of cholesterol in atherosclerotic plaque-producing foam cells by suppressing the activity of the AP-1 complex and activating the Nrf2/HO-1 pathway, and thus counteract the development of atherosclerosis.

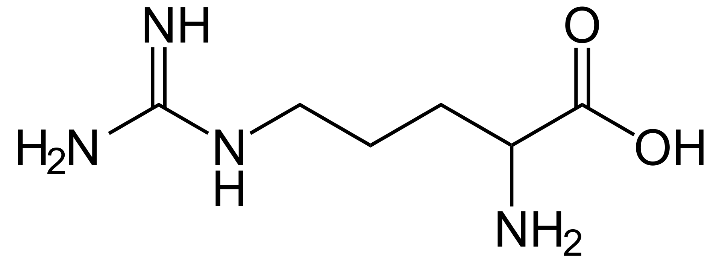
**Red Yeast Rice**

Red yeast rice (red fermented rice, red koji rice, red koji rice, an-ka, ang-kak) is a red-colored fermented rice that stains as a result of the cultivation of the mold Monascus purpureus. More commonly referred to as "red koji rice" in Japanese literature; in relation to China, the term "red yeast rice" is preferred.

In the late 1970s, researchers in the United States and Japan isolated lovastatin from Aspergillus and monacolins from Monascus, which are used to make red yeast rice when cultivated under carefully controlled conditions. Chemical analysis showed that lovastatin and monacolin K are identical chemical compounds. Lovastatin was patented as a prescription drug Mevacor. Red yeast rice is sold as an over-the-counter dietary supplement in the United States and other countries.

Lovastatin and other prescription statin drugs inhibit cholesterol synthesis by blocking the action of the HMG-CoA reductase enzyme. As a result, total cholesterol and LDL cholesterol levels are reduced by 24-49% depending on the amount of statin and dosage. Different strains of the Monascus mold produce different amounts of monacolins. The 'Went' Monascus purpureus strain, when properly fermented and processed, produces dry red yeast rice powder with monacolins in the order of 0.4%, about half of which is monacolin K (chemically identical to lovastatin).

**L-arginine**

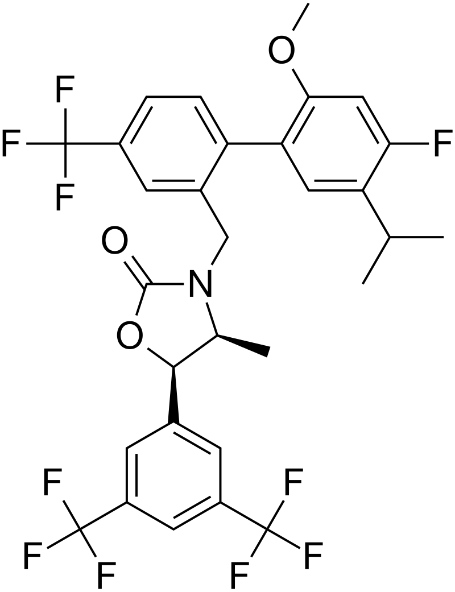


Arginine (2-amino-5-guanidinepentanoic acid) is an aliphatic basic α-amino acid. Optically active, exists in the form of L and D-isomers. Arginine is a non-essential amino acid synthesized in the liver; however, in moments of stress or injury, arginine becomes indispensable. This amino acid is necessary for the normal functioning of the pituitary gland. Along with ornithine, phenylalanine, and other nervous system chemicals, arginine is required for the synthesis and release of pituitary growth hormone.

Arginine is the direct precursor of endogenous nitric oxide, which is synthesized by vascular endothelial cells. The importance of this function of arginine cannot be overestimated, since endogenous nitric oxide has a pronounced vasodilating and antiaggregatory effect and mediates the physiological effects of many vasodilatory hormones and drugs. In most patients with cardiovascular diseases, there is a sharp decrease in the production of endogenous nitrogen, as a result, the content of arginine is sharply reduced, since under conditions of atherosclerotic endothelial damage, most of the arginine is metabolized into dimethylarginine.

**Investigated classes of lipid-lowering drugs:**

**Anacetrapib**

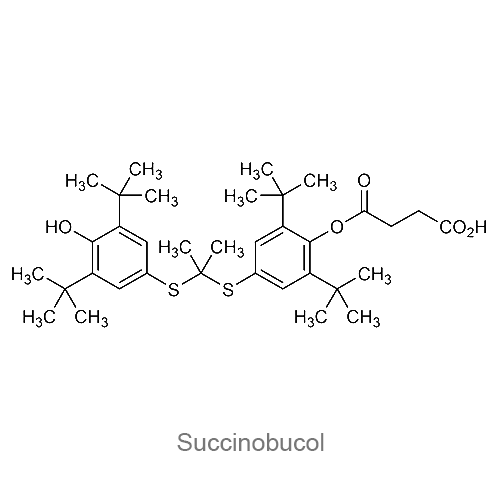


Anacetrapib is a cholesterol ester transport protein (CETP) inhibitor that has been developed to treat elevated cholesterol levels to prevent cardiovascular disease. In 2017, Merck abandoned its development. In the 2017 REVEAL study, anacetrapib was shown to reduce the risk of recurrent heart attacks in high-risk patients with a history of acute coronary events.

ApoA-1 Milan

Apolipoprotein A-1 Milano (also ETC-216, now MDCO-216) is a naturally occurring mutant variant of the apolipoprotein A1 protein found in human HDL, a lipoprotein particle that transports cholesterol from tissues to the liver and is associated with protection against cardiovascular diseases. ApoA1 Milano was first identified by Dr. Cesare Sirtori in Milan, who also demonstrated that its presence significantly reduces the risk of cardiovascular disease, even though it causes a decrease in HDL levels and an increase in triglycerides. Apo AI Milano has been shown to reduce atherosclerosis in animal models and in a small phase 2 human trial. Recombinant adeno-associated virus 8 (AAV8) mediated by Apo AI Milano gene therapy combined with a low cholesterol diet causes rapid and significant regression atherosclerosis in mice.

**Succinobucol**



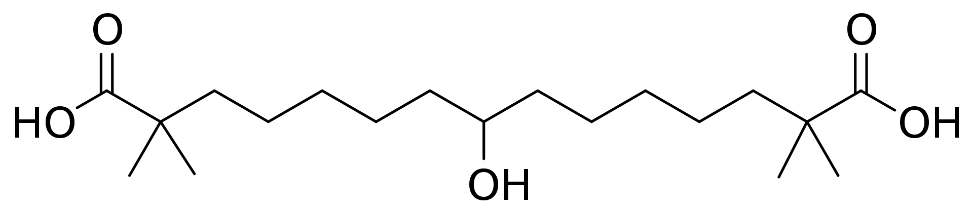
**A new antioxidant that failed phase III trials.**

**Mipomersen**

Mipomersen (Kinamro) is a first-in-class inhibitor of ApoB synthesis that reduces Lp(a) levels in patients with heterozygous familial hypercholesterolemia (heHC) and high baseline Lp(a) levels.

Indications: In addition to dietary therapy and other lipid-lowering therapies, to lower low-density lipoprotein (LDL) cholesterol, total cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia.

**Bempedoic acid**



Bempedoic acid (Nexletol), is a medicine for the treatment of hypercholesterolemia. In the US, bempedoic acid is indicated for the treatment of hypercholesterolemia in combination with diet and most tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or with established atherosclerotic cardiovascular disease who require additional LDL cholesterol lowering.

In the European Union, bempedoic acid is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia as an adjunct to diet in combination with statins or statins with other lipid-lowering drugs in patients unable to achieve target LDL-cholesterol levels. with the maximum tolerated dose of a statin; either alone or in combination with other lipid-lowering drugs in patients with statin intolerance or contraindications.