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# Antilipidaemic Drugs

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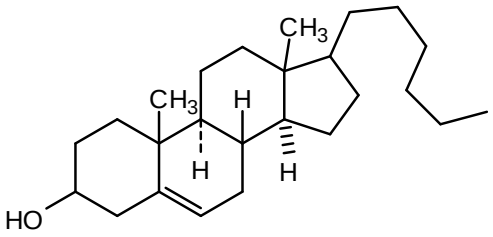
***Abstract***
*Everyone has some degree of coronary atherosclerosis. CHD is most common in affluent nations. Diets high in fats, elevated serum cholesterol levels, lack of exercise, emotional stress, hypertension and smoking all contribute to the production of this disease.*
***Keywords****: CHD, Atherosclerosis, Hypertension*

## I. INTRODUCTION

Coronary Heart Disease (CHD) is the leading cause of death in the United States. More than 650,000 people die each year from CHD in this country and about 20% of the population will develop the first symptoms before age 60[1, 2]. Although nearly everyone has some degree of coronary atherosclerosis the underlying cause of CHD is most common in affluent nations. Diets high in fats, elevated serum cholesterol levels, lack of exercise, emotional stress hypertension and smoking all contribute to the production of this disease[3 – 9].

**DRUGS OF HISTORICAL INTEREST**

During the mid-1900s, considerable interest arose in plant sterols as serum cholesterol-lowering agents. Mixtures of plant sterols, including, soybean sterols and β-sitosterol (22, 23- dihydrastigmasterol) (**1**) are among the preparations that are absorbed to a limited extent form the intestinal tract and compete for the absorption of both endogenous and exogenous cholesterol[10, 11].

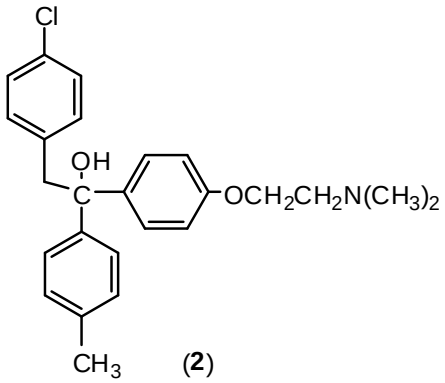



β-SITOSTEROL **(1)**

In animals (**1**) also increases the rate of cholesterol and lipid metabolism[12].

**TRIPARANOL (2)**

Triparanol (**2**) was a potent inhibitor of cholesterol biosynthesis[13, 14].

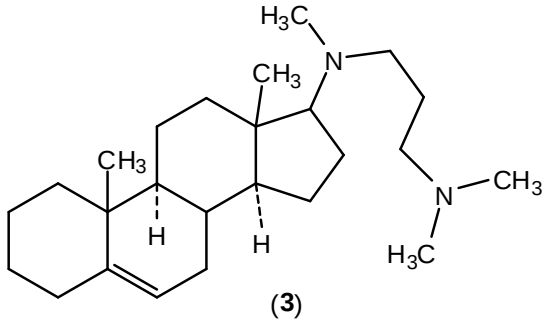



(**2**)

**DIAZACHOLESTEROLS**

It was originally suggested that diazacholesterols and related analogs, which look sufficiently like cholesterol, would bind to negative feedback enzymes because of electron rich nitrogen. Such binding would mimic cholesterol binding and inhibit cholesterol biosynthesis. Compounds such as 20, 25-diazacholesterol (**3**)

however, generally inhibit reduction of 7, 8- and 24, 25- double bonds[15] and *in vivo*, HMG-CoA reductase activity is stimulated even though serum cholesterol levels are reduced[16].

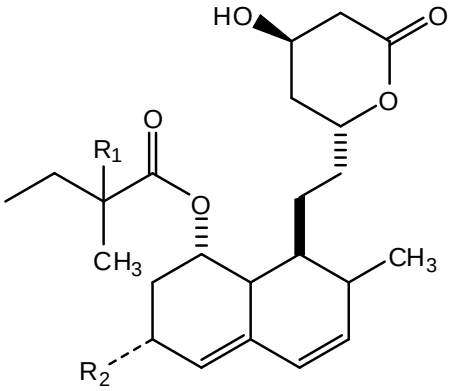


(**3**)

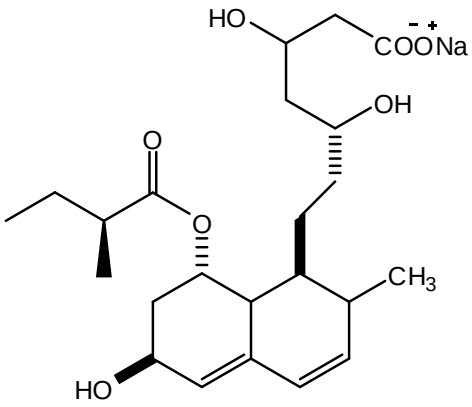
**DRUGS OF CLINICAL SIGNIFICANCE**

Statins (or vastins) represents a new class of lipid-lowering compounds that inhibit HMG-CoA reductase, the first and rate-limiting step in cholesterol biosynthesis in cells[17, 18].

Mevastatin (**4**) and lovastatin (**5**) were isolated as fungal metabolites from cultures of ***Penicillium brevicompactum*** and ***Aspergillus terreus*** respectively[19, 20]. Other closely related analogs include pravastatin (**6**) and simvastatin (**7**).

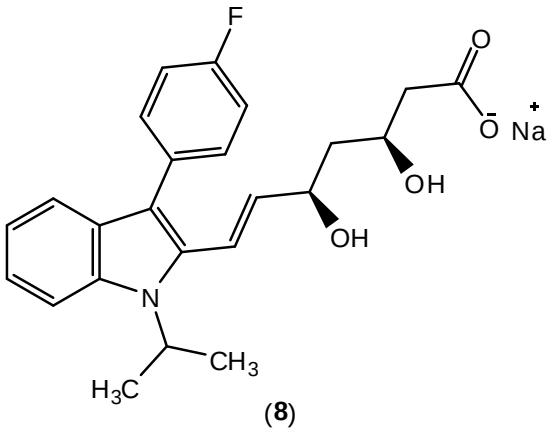


(**4**) $R_1 = H, R_2 = H$
(**5**) $R_1 = H, R_2 = CH_3$
(**6**) $R_1 = CH_3, R_2 = CH_3$



(**7**)

Fluvastatin sodium (**8**) is the most recently approved statin in the United States[21].



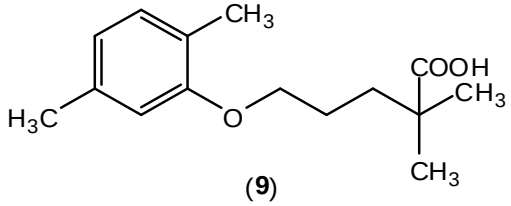
(**8**)

It is a white pale yellow, hygroscopic, powder that is freely soluble in water ethanol, and methanol. It is supplied as 20mg and 40mg capsules for oral administration.

**FIBRATES**

**GEMFIBROZIL** (**9**)

It was introduced in 1981 after the statins, and is the second most frequently presented antilipidaemic drugs. This drug is a white solid that is nearly insoluble in water and acidic solutions, and soluble at greater that 1% in dilute base[22].



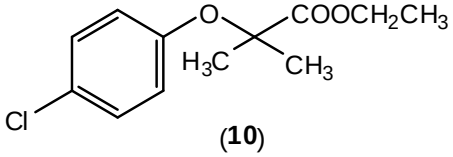

(**9**)

Overall gemfibrozil (**9**) effectively lowers plasma triglycerides, VLDL cholesterol and VLDL ApoA-I concentrations in **type II a** and **II b** hyperlipoproteinemic patients and produces a greater reduction in LDL cholesterol levels in type II a patients[23, 24].

Gemfibrozil (**9**) is rapidly and well absorbed with a peak plasma level occurring 1 to 2 hours after dosing[25]. It is extensively metabolized in humans and experimental animals[26].

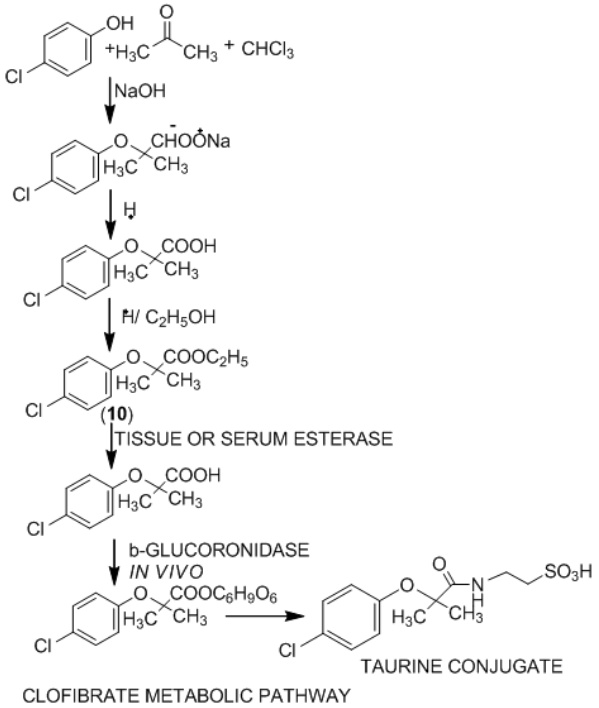
**CLOFIBRATE (10)**

It was the first fibrate introduced in the United States. It is nearly colourless, oily liquid, insoluble in water and miscible with organic solvents[27].



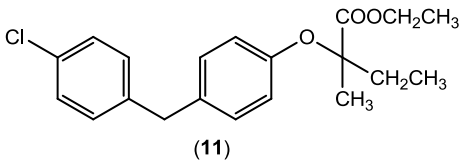

(**10**)

Serum cholesterol lowering by clofibrate (**10**) in animals is related to changes in liver cholesterol through blockade of HMGCoA reductase[28]. Serum cholesterol catabolism remains unchanged in human after clofibrate treatment[29], however, acidic and neutral sterol excretion into bile is increased by its treatment[30].

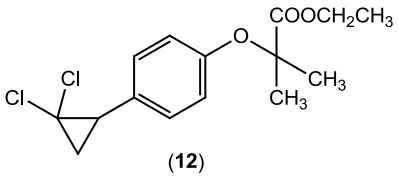



CLOFIBRATE METABOLIC PATHWAY

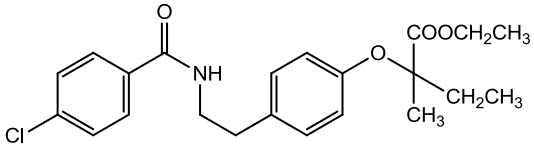
Other fibrates which have got clinical applications are beclobrate (**11**), bezafibrate (**12**), Ciprofibrate (**13**) and fenofibrate (**14**).



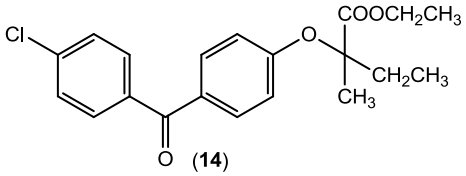

(**11**)




(**12**)




(**13**)




(**14**)

## II. CONCLUSION:

**ANTIATHEROSCLEROSIS DRUGS IN DEVELOPMENT**

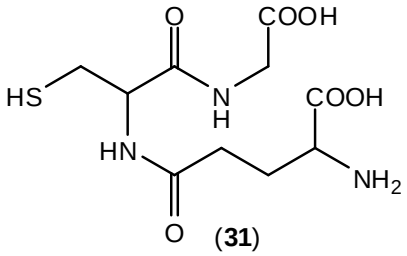
Atherosclerotic fatty streaks occur through cholesterol ester engorgement by cells. This takes place after uptake of $LDL_{ox}$ or modified LDL. This lesion proceeds to a fibrous plaque and then to a complicated thrombus-involved atheroma which may block arterial blood flow and produce clinically manifested CHD[5zyy].

$LDL_{ox}$ identified in both human and atherosclerotic animal model arteries and in the bloodstream results from a free-radical reaction sequence with LDL lipids[59]. This produces endothelial cytotoxicity modified platelet functionality, increased monocyte adherence to and chemotaxis through the endothelium. This results in accumulation of arterial foam cells and enhanced smooth muscle proliferation[60].

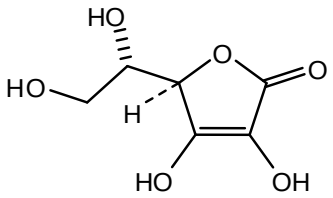
Superoxide anion radicals ($O_2$) are continuously generated in normal cells by reduction of dioxygen ($O_2$). Defense mechanisms against $O_2$ include radical scavengers as such ascorbate and vitamin E and enzymes, superoxide dismutase (SOD), and catalase, among others. $O_2$ is the anionic form of HOD; having a $pK\alpha = 4.8$. Both $O_2$ and $HOO^{\cdot}$ are reactive species but are not as reactive species but are not as reactive as their metabolites $O_2$ upon dismutation catalyzed by SOD yields $H_2O$ and $H_2O_2$. Preferably, $H_2O_2$ converts to $H_2O$ and $O_2$ through the action of catalase.

When normally protective mechanisms cannot handle accumulation of $H_2O_2$, a Fenton's reaction with ferrous ion ($Fe^{2+}$) may cause further reduction to produce both hydroxyl radical ($OH^{\cdot}$) and hydroxy anion ($OH^{-}$). $H_2O_2$ and especially $HO^{\cdot}$ are highly toxic substances with macromolecules such as DNA, enzymes, proteins and lipoproteins (i.e., LDL). Such free radical reactions may result in pathologic conditions such as CHD, cancer, liver damage, rheumatoid arthritis, immunologic incompetence, among others.

Lipid peroxidation involves highly reactive radicals. Thus, radicals ($R^{\cdot}$) generated under conditions undergo reaction with lipid side-chains (LH) to generate new radicals ($L^{\cdot}$). When $L^{\cdot}$ is an unsaturated chain, reaction with $O_2$ produces allylic peroxides ($RCH = CH\text{-}CH_2OOH$) and epoxides (oxiranes, RCH-CH) which are also reactive species. For example, peroxides may react with LH to generate $L^{\cdot}$, which produces more $LOO^{\cdot}$ and $LOOH^{\cdot}$ Additionally, $O_2$ may react with LH by an insertion mechanism, lead to $H_2O_2$ and $HO^{\cdot}$, LOOH may undergo reduction by $Fe^{2+}$ or oxidation by ferric ion ($Fe^{3+}$) in reinitiation reactions, in which $LO^{\cdot}$ and $LOO^{\cdot}$, respectively, are product. Glutathione (**31**) and other reducing agents such as ascorbic acid (**32**) may remove LOOH through generation of LOH and $H_2O$. Unfortunately, ascorbate can also reduce $Fe^{3+}$ generating $Fe^{2+}$, which serves to increase concentrations of $HO^{\cdot}$ in Fenton's reaction.

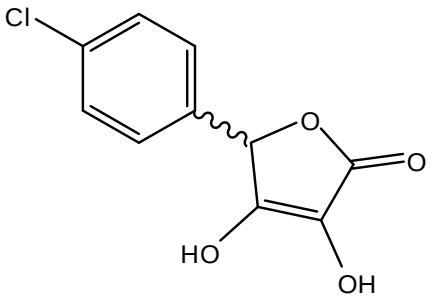



(**31**)




(**32**)

4- (4- Chlorophenyl) - 2- hydroxy-tetronic acid (CHTA) (**33**) is very effective hypolipidemic drug *in vivo* and an antioxidant *in vitro*[34].




(**33**)

In the future, such experimental antiatherosclerotic drugs may more effectively fulfill the antioxidant ascorbate function of protecting endogenous LDL antioxidants.

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