

Fibric Acid Biochemistry

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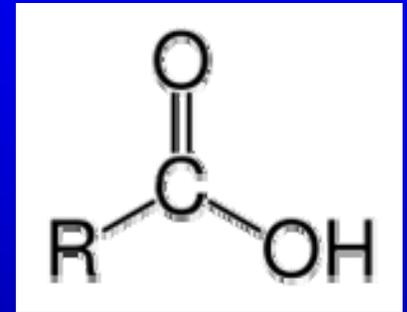
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Wayne, New Jersey**

Fibric Acids

- ▶ Fibric Acids, also referred to as fibrates are carboxylic acids that have the ability to interact (agonize or antagonize) with nuclear transcription factors which influence lipid and lipoprotein synthesis and catabolism.
 - ▶ PPAR- α , LXR, ANGPTL, SREBP
- ▶ Fibrates exist as either acids or as esters. The PPAR- α agonism requires presence of the polar carboxylic acid moiety but LXR antagonism may require the ester moiety.

Fibric Acids (Fibrates)

- **Carboxylic acids** are organic acids characterized by the presence of a carboxyl group, which has the formula -C(=O)OH, usually written -COOH or -CO₂H.



- The **fibrates** are a class of amphipathic carboxylic acids.



Have hydrophilic (polar) and hydrophobic (nonpolar) properties

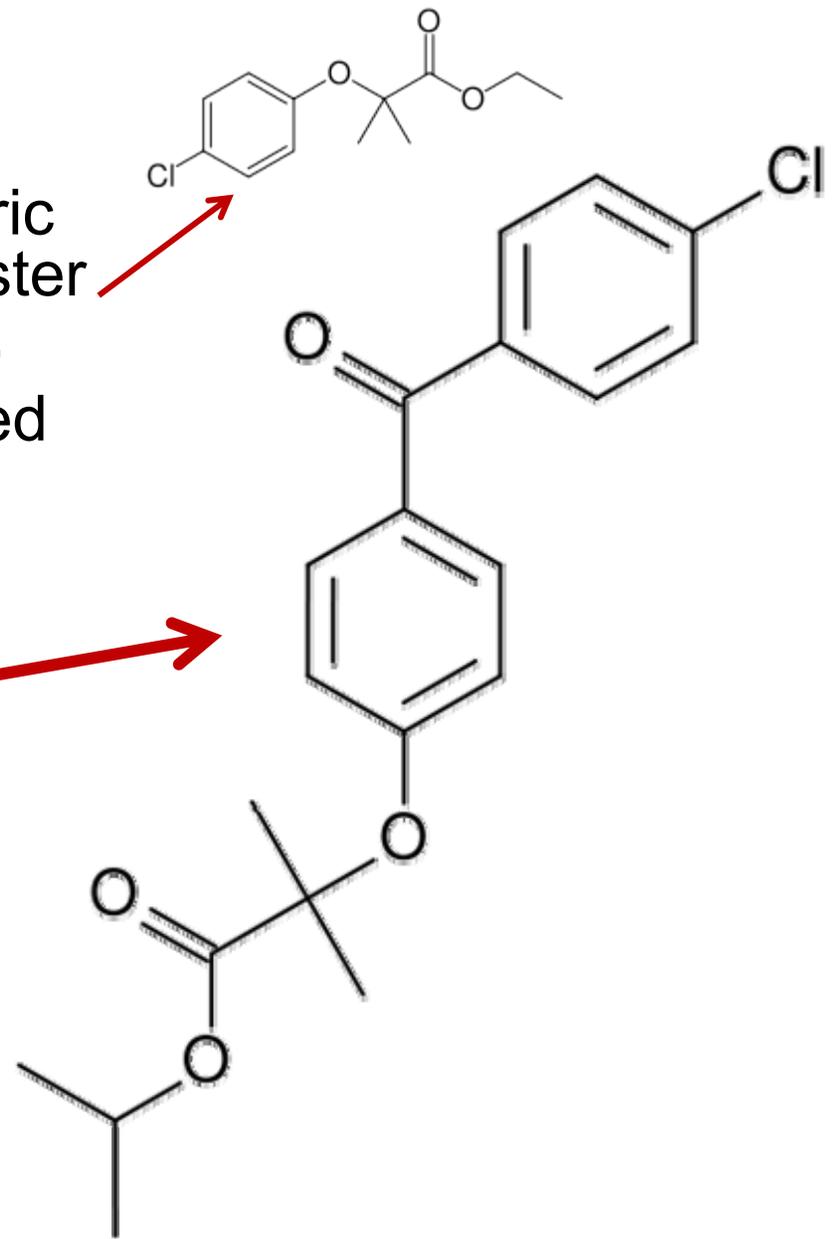
Fibrates

F Clofibrate, the prototype of fibric acids derivatives is the ethyl ester of p-chlorophenoxyisobutyrate.

F Gemfibrozil is a nonhalogenated phenoxy pentanoic acid and is thus distinct from the halogenated fibrates

F Fibric acid analogs:

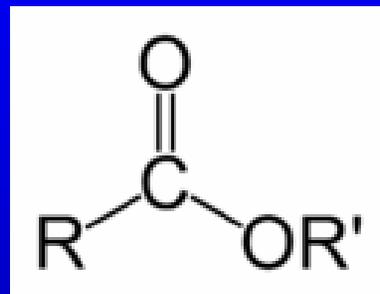
- Fenofibrate
- Bezafibrate
- Ciprofibrate



Esters

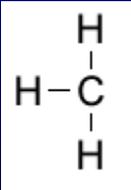
- Esters consist of an inorganic or organic acid in which at least one -OH (hydroxyl) group is replaced by an -O- alkyl group.
- Esters can be synthesized in a condensation reaction between an acid and an alcohol in a reaction known as esterification.
- Fatty acid esters form fat and lipids.

Carboxylic acid ester.

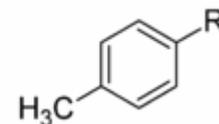
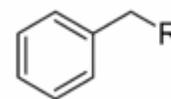
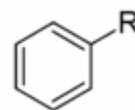


R and R' denote any alkyl (chain) or aryl (aromatic ring) group

An alkyl group is a univalent radical consisting of carbon and hydrogen atoms, arranged in a chain. (methyl, ethyl, pentyl, etc)



Aryl refers to any functional group derived from a simple aromatic ring

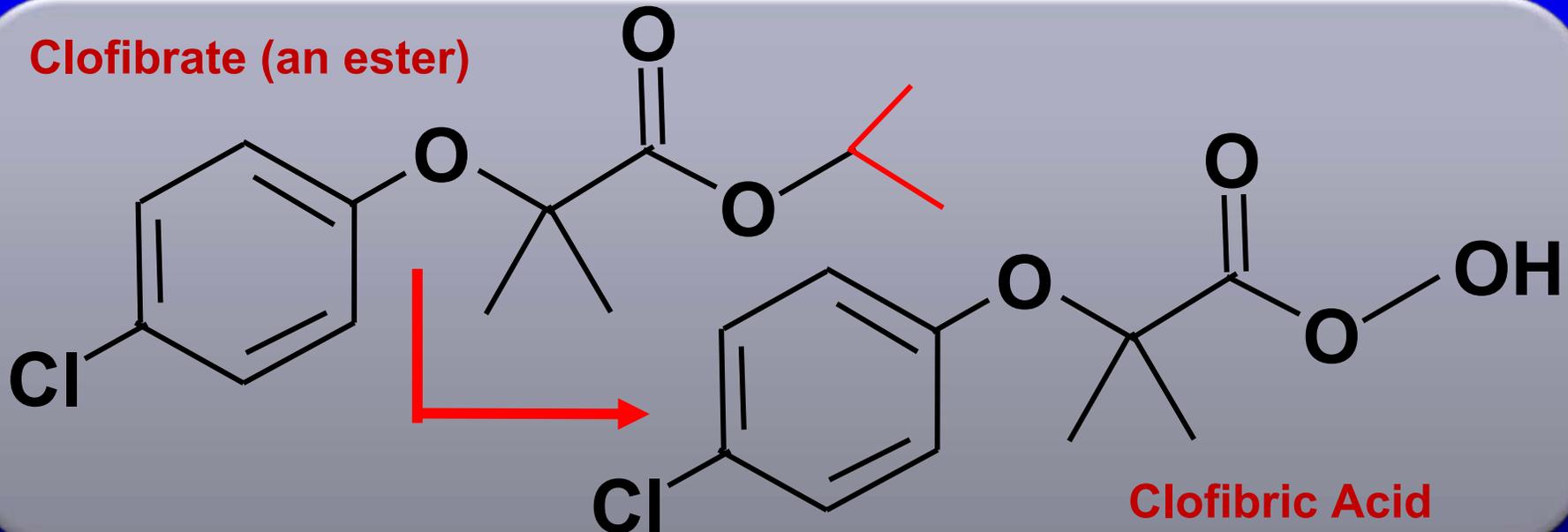


Fibrates

- F Clofibrate was the first fibrate approved for use in the US in 1967
- F The World Health Organization Trial was published in 1978 and it showed that despite a reduction in cholesterol it did not reduce fatal CV events, although nonfatal infarcts were reduced.
- F Total mortality was greater in the clofibrate group, due to multiple causes including cholelithiasis.
- F Interpretation of these negative events were clouded by failure to analyze the data according to the intention-to-treat principle.
 - A later analysis demonstrated that the apparent increase in noncardiac mortality did not persist in the clofibrate treated patients after discontinuation of the drug Lancet 1984;2:(8403):600-4

Clofibrate – Clofibric Acid

Ethyl 2-(4-chlorophenoxy)-2-methylpropanoate



Molecular Formula $C_{12}H_{15}ClO_3$

Molecular Weight = 242.698 g/mol

Protein Binding 92-97%

Half Life 18-22 hours

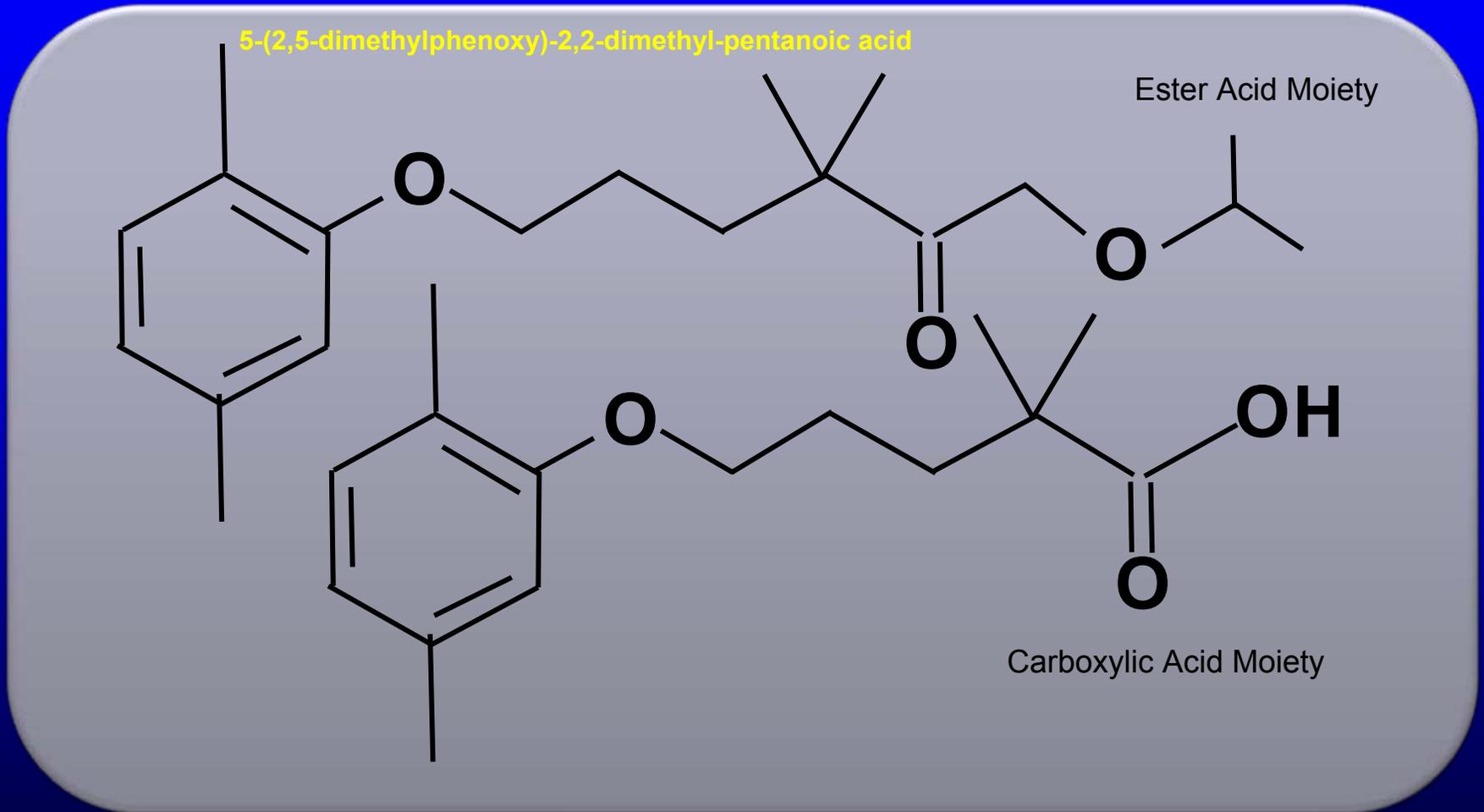
Pregnancy Category C

Hepatic glucuronidation

<http://en.wikipedia.org/wiki/clofibrate>

Thomas J, et al. J Bio Chem 278:2403-2410

Gemfibrozil - Gemfibric Acid



Molecular Formula $C_{15}H_{22}ClO_3$ Molecular Weight = 250.333 g/mol

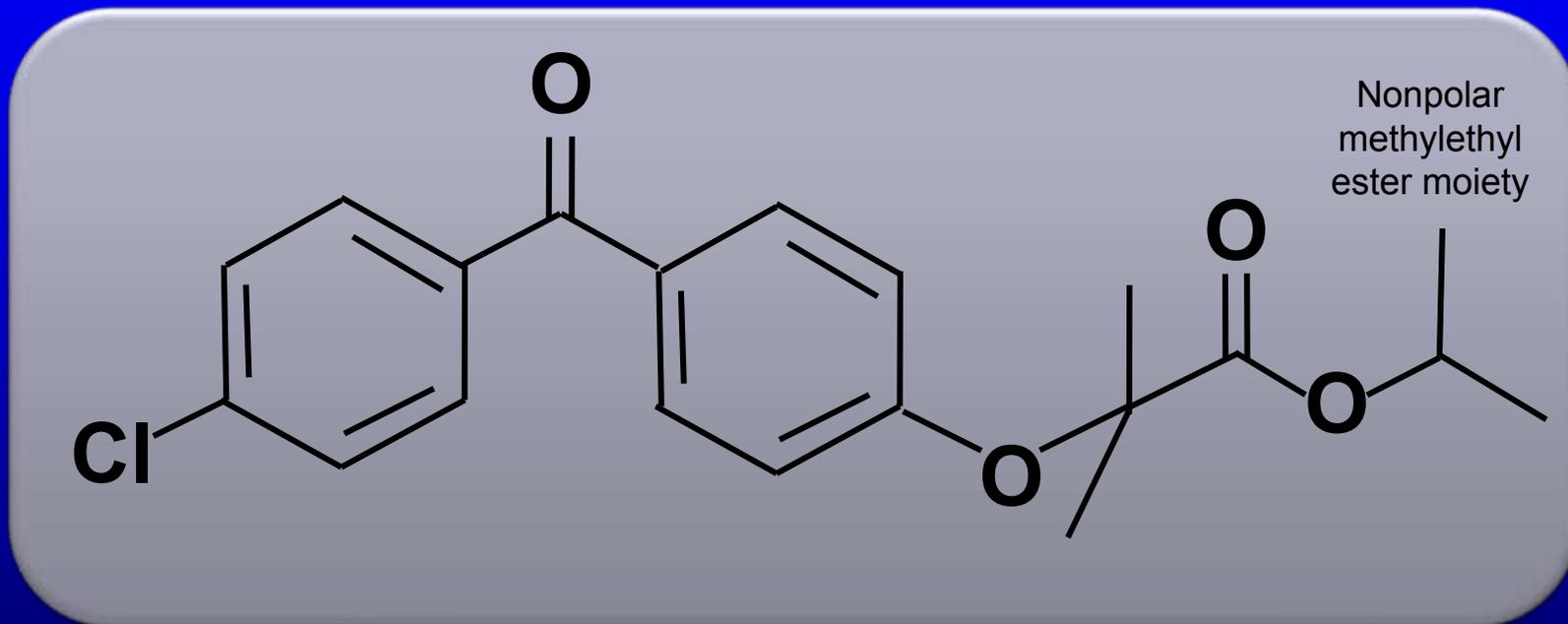
Protein Binding 95%
Half Life 1.5 hours
Pregnancy Category C

<http://en.wikipedia.org/wiki/gemfibrozil>
Thomas J, et al. J Bio Chem 278:2403-2410

Hepatic CYP3A4 Metabolism

Fenofibrate

1-methylethyl 2-[4-(4-chlorobenzoyl) phenoxy]- 2-methyl-propanoate



Molecular Weight = 360.831 g/mol

Molecular Formula $C_{20}H_{21}ClO_4$

Protein Binding 99%

Half Life 20 hours

Pregnancy Category C

Fenofibrate Tablet Pharmacokinetics

- F Fenofibrate is readily absorbed from the gastrointestinal tract
- F Following oral administration fenofibrate is rapidly hydrolyzed to by esterases to the active metabolite fenofibric acid
- F No unchanged fenofibrate is detected in the serum
- F Fenofibric acid is primarily conjugated with glucuronic acid and excreted in the urine
- F Neither fenofibrate nor fenofibric acid undergo oxidative metabolism by CYP450 enzymes
 - They are weak inhibitors of CYP2C19, CYP2A6 and mild-moderate inhibitors of CYP2C9 and may potentiate coumarin-type anticoagulants

Fenofibric Acid

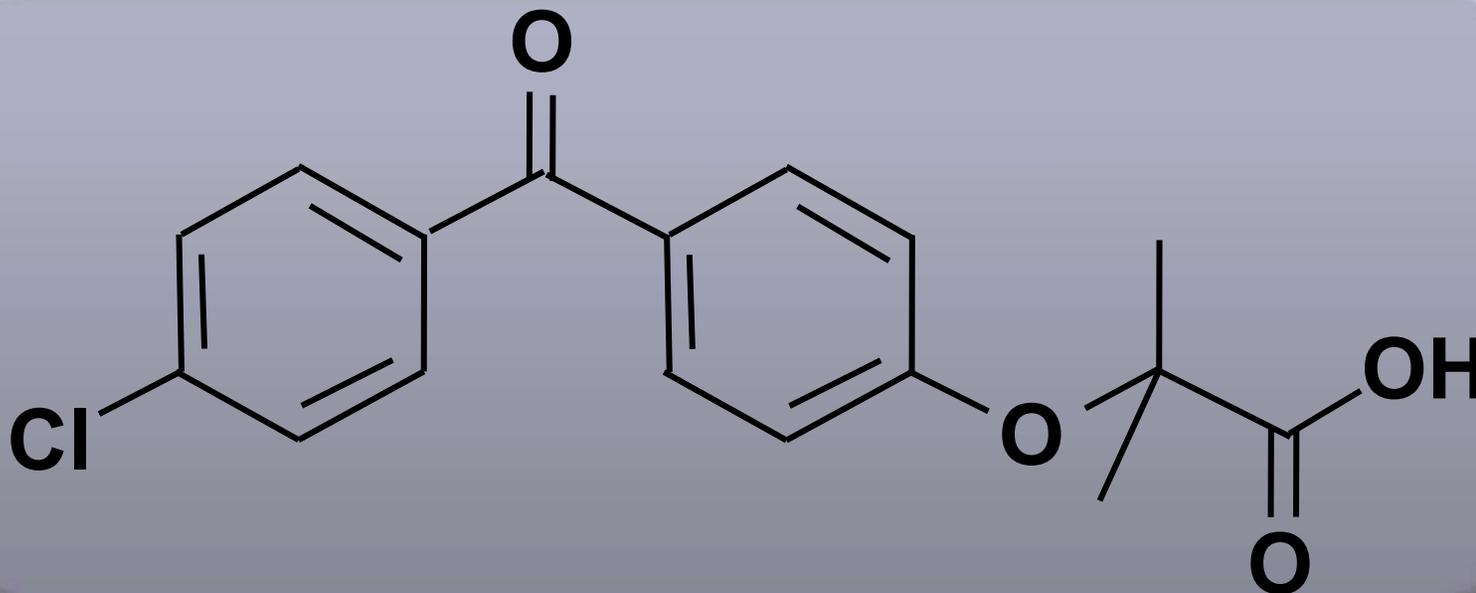
In December 2008 the FDA approved a newly developed fibrate that is the choline salt of fenofibric acid.

. This agent is unique in that it dissociates to free fenofibric acid within the gastrointestinal tract, allowing fenofibric acid to be rapidly and directly absorbed without requiring first-pass metabolism.

In contrast, fenofibrate is an ester of fenofibric acid and requires enzymatic cleavage via first-pass metabolism to form fenofibric acid. Fenofibric acid, the active metabolite of fenofibrate, contains a carboxylic acid moiety instead of an ester moiety and has relatively low potential for interaction with statins..

Fenofibric Acid

2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid; 2-[4'-(p-Chlorobenzoyl)phenoxy]-2-methylpropionic acid



Molecular Weight = 318.76

Molecular Formula $C_{17}H_{15}ClO_4$

Protein Binding 99%

Half Life 20 hours

Pregnancy Category C

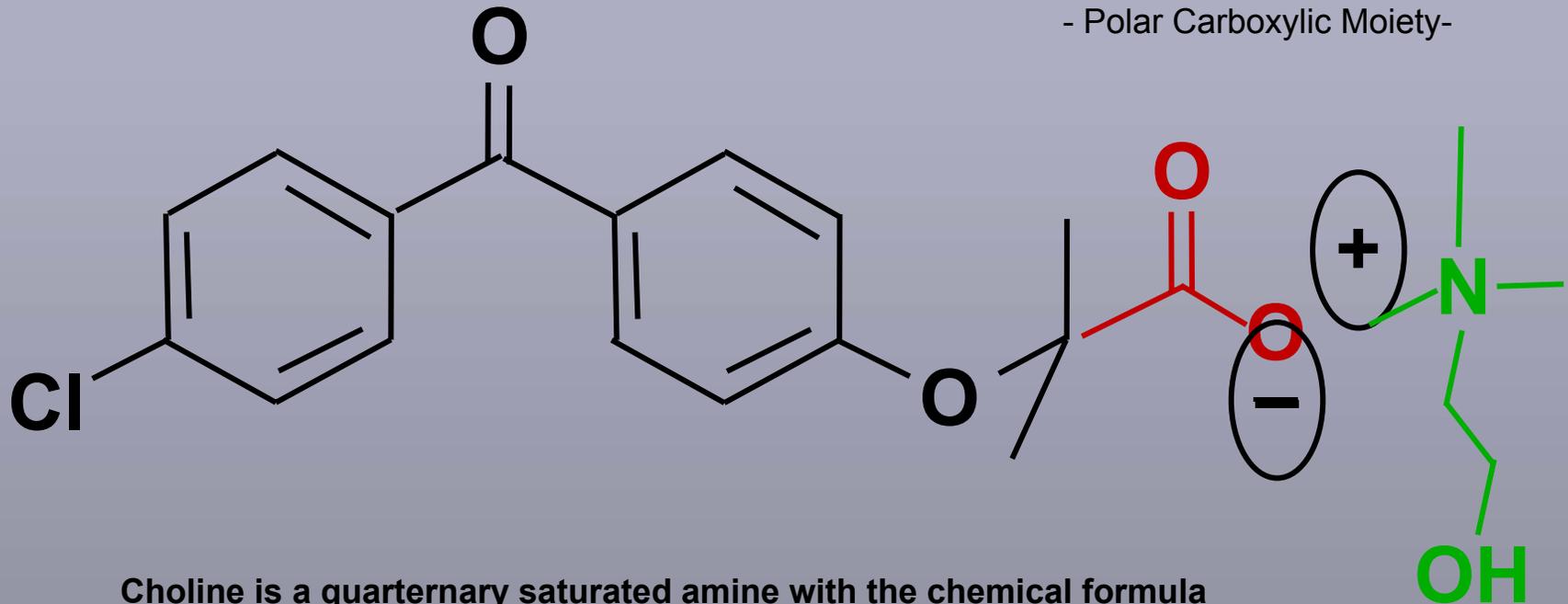
Fenofibric Acid

Unlike fenofibrate, fenofibric acid contains a carboxylic acid moiety instead of an ester moiety.

This polar moiety plays an important role in the formation of a rare acid-to-ketone hydrogen-bond-type packing interaction. The lack of an isopropyl group in fenofibric acid aligns the carboxyl group on the same side as the ketone carbonyl group; this conformation may play an important role in discrimination between the acid and the fenofibrate molecule in molecular recognition.

Choline Salt of Fenofibric Acid

Cholin Fenofibric Acid ic Acid



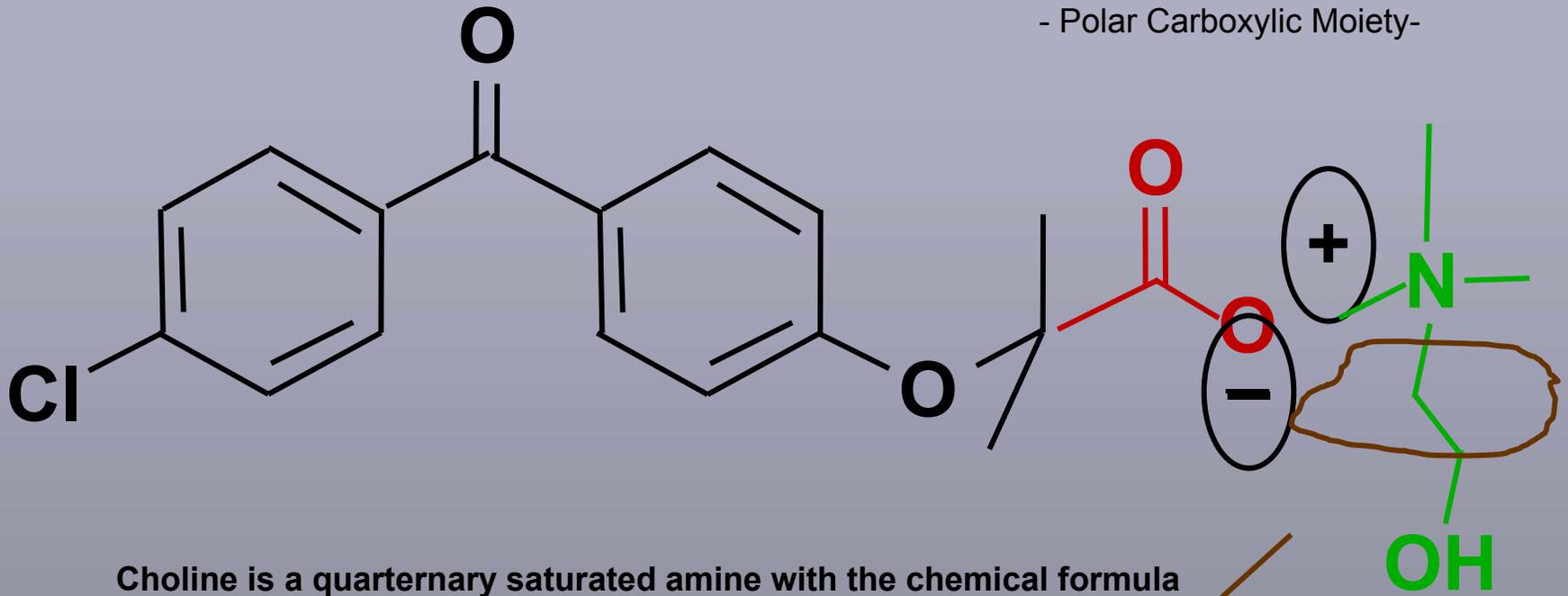
Choline is a quarternary saturated amine with the chemical formula $(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CH}_2\text{OHX}^-$, where X^- is a counterion such as chloride.

Unlike fenofibrate, fenofibric acid contains a carboxylic acid moiety instead of an methylethyl ester moiety.

Choline salt

Choline Salt of Fenofibric Acid

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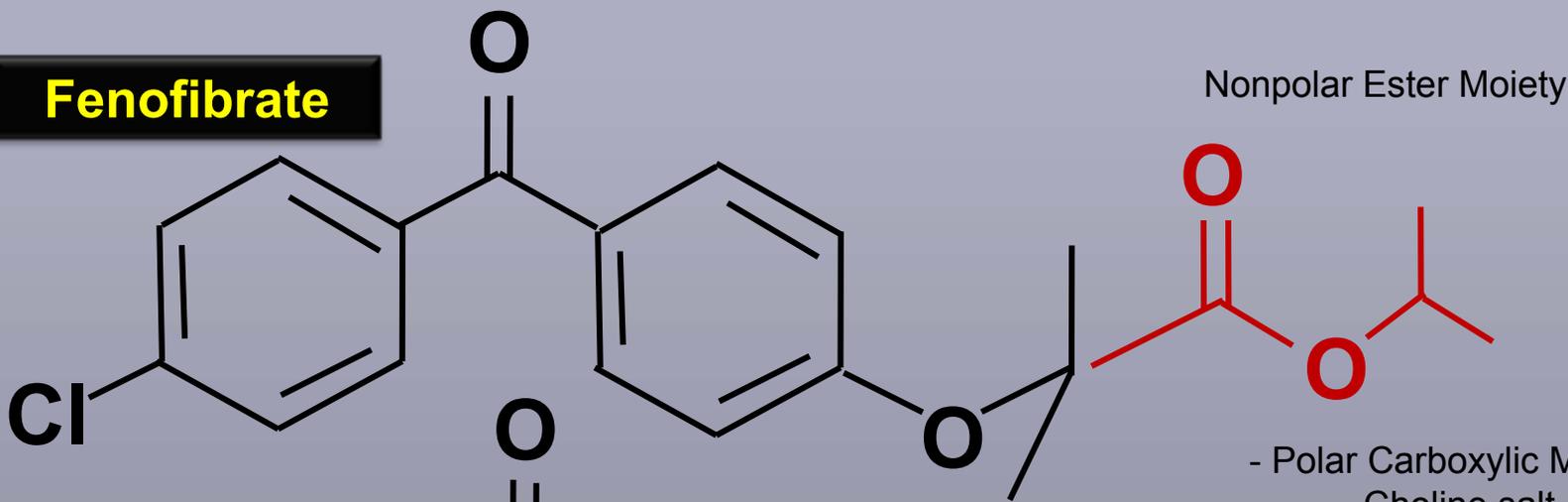
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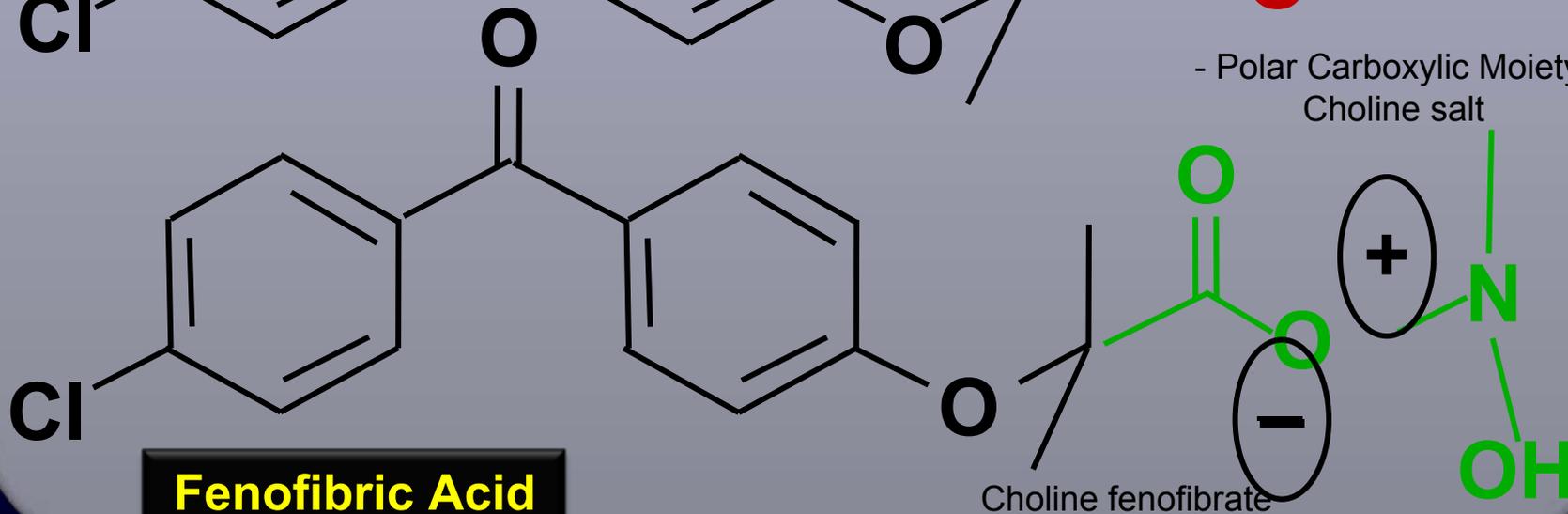
Fenofibrate vs Fenofibric Acid

Unlike fenofibrate fenofibric acid contains a carboxylic acid moiety instead of an methylethyl ester moiety.

Fenofibrate



- Polar Carboxylic Moiety-
Choline salt

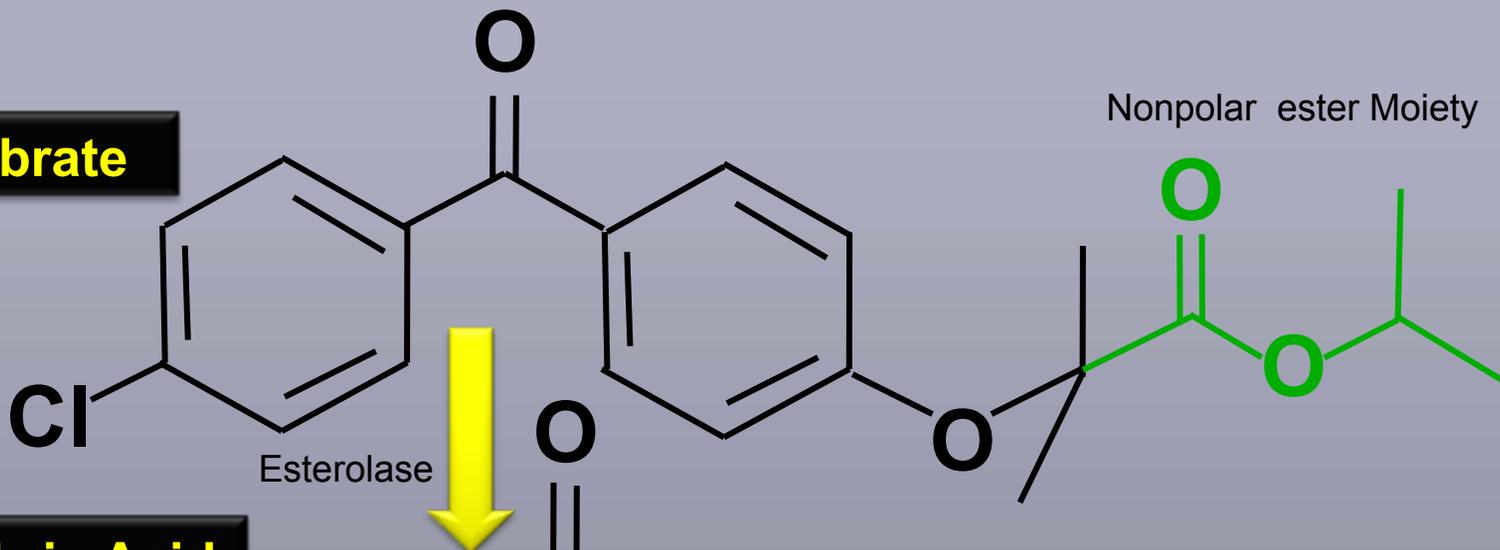


Fenofibric Acid

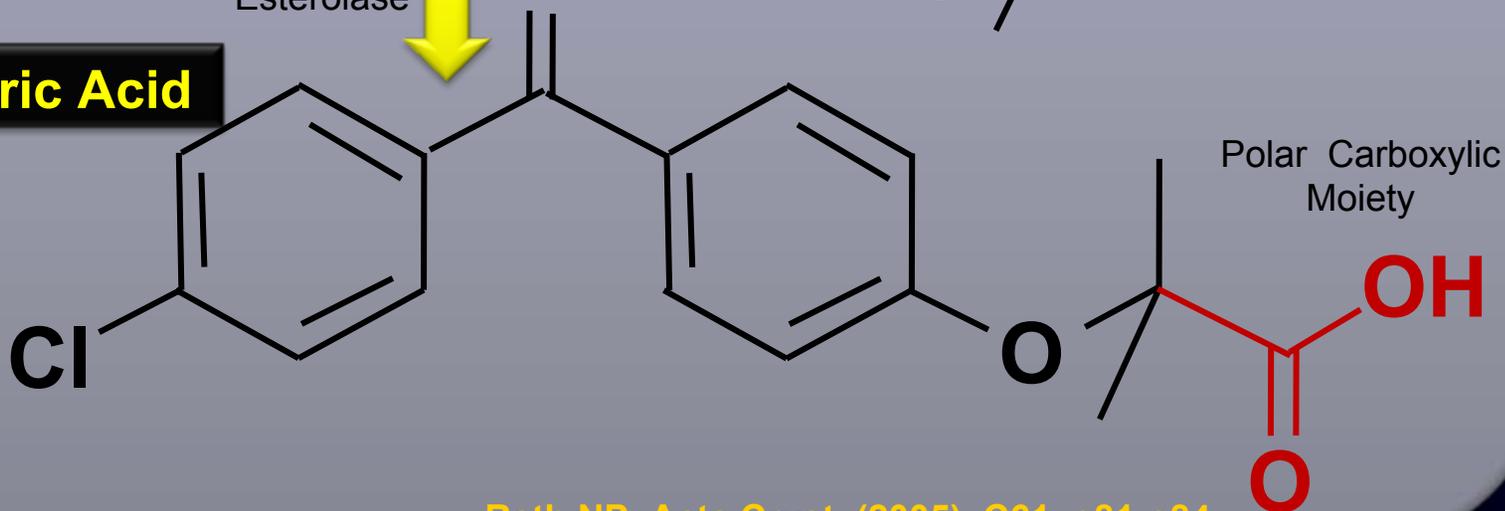
Fenofibrate vs Fenofibric Acid

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Fenofibrate



Fenofibric Acid



Fenofibric Acid

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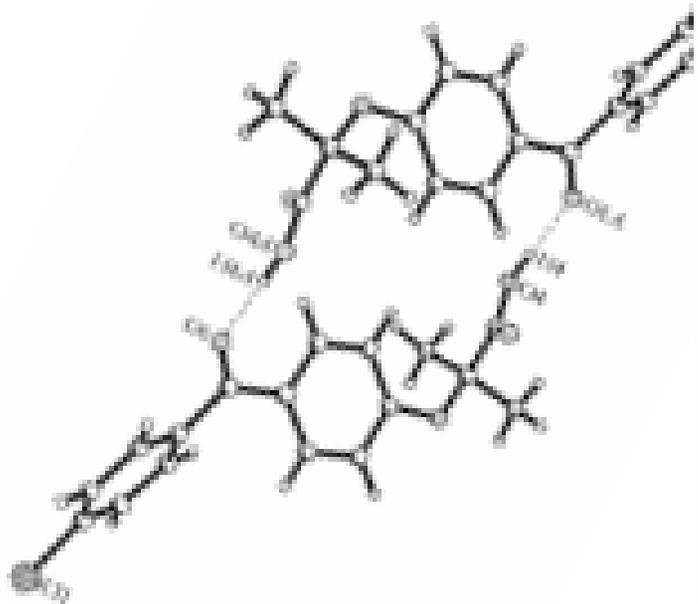
Fenofibric Acid

Alignment of the sp² ketone moiety (the C4/C7/O1/C8 plane) of fenofibric acid and the corresponding plane in the fenofibrate molecule reveals that the carboxyl moiety is positioned almost on the same side as the ketone carbonyl group in fenofibric acid

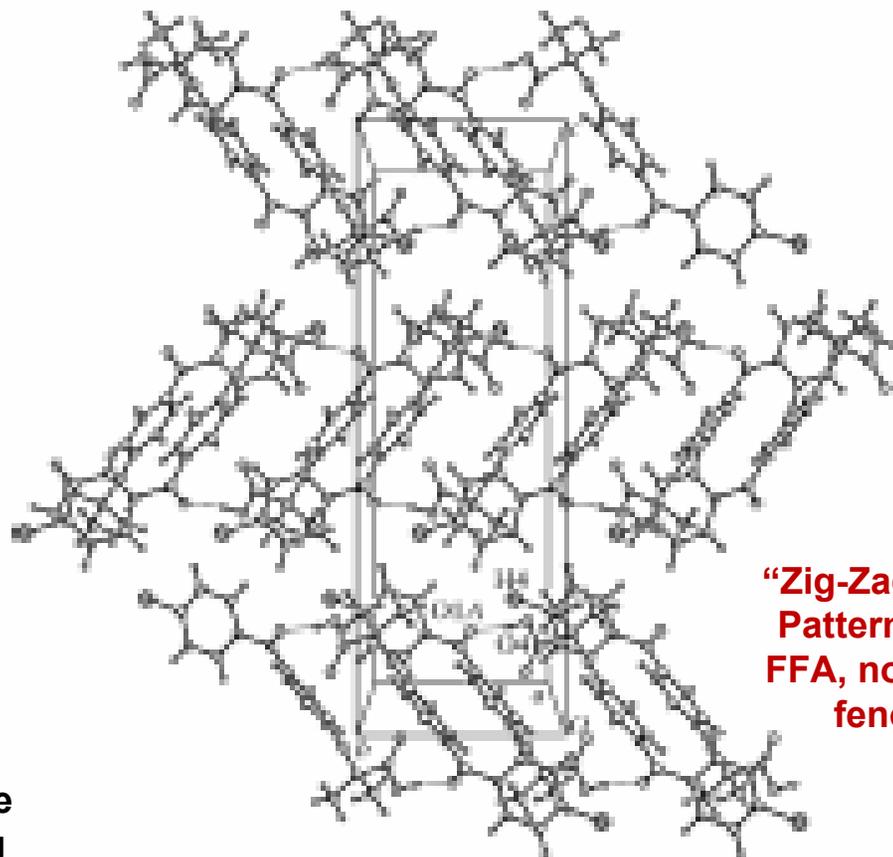
This conformation may facilitate the formation of intermolecular C – O --- H - O hydrogen bonding over the carboxyl OH dimer. However, the carboxyl moiety of the fenofibrate molecule is located away from the ketone carbonyl group, at the back of the molecule.

This conformation may be due to steric effects and packing interactions, which are caused by the presence of the isopropyl group. This phenomenon may play a significant role in distinguishing fenofibric acid as an activator of PPAR over fenofibrate. In general, if polar groups, such as the carbonyl and carboxyl groups in fenofibrate and fenofibric acid, are involved in the formation of specific interactions with their target molecules, the orientation of these moieties will alter the binding affinities.

Fenofibric Acid



A dimer of fenofibric acid, showing the rare acid-to-ketone hydrogen bonding pattern. The symmetry operator (-x, -y, 1-z) was used to generate atoms labeled with the suffix A.



**“Zig-Zag” Stacking
Pattern unique to
FFA, not seen with
fenofibrate**

A packing diagram of fenofibric acid, in the orthorhombic space group Pbca, viewed along the a axis.

Fibrate Esters vs Fibrate Acid

- F The fenofibrate ester is rapidly converted into the carboxylic acid form by esterases in the liver and plasma. It has been assumed that the pharmacologically relevant form of fenofibrate is the acid form due to its specificity for PPAR- α and the lack of detectable ester in the plasma.
- F The fibrate esters bound only to the LXRs, whereas the fibric acids were specific for PPARs
- F The ester/acid moiety acts as a switch that determines LXR *versus* PPAR- α affinity, yet the remaining portion of the ligand seems to have relatively little impact on this selectivity.
- F Fenofibrate ester, **antagonizes LXR and represses lipogenic gene expression in liver, but not** members of the ABC transporter gene family (ABCA1, ABCG5, and ABCG8).

Fibrate Esters vs Fibrate Acid

- F Not only does the fibrate class of hypolipidemic compounds function through activation of PPAR- α , leading to induction of genes that control fatty acid -oxidation; they also decrease SREBP1 and FAS gene expression by antagonizing LXR-mediated transcription.
- F Fibrate esters display LXR partial agonist/antagonist activity that is dependent on the target gene context. This data ascribes a novel regulatory function to the clinically utilized fibrate drugs and have therapeutic implications for identification of compounds that increase cellular cholesterol efflux through LXR yet counteract the accumulation of triglycerides by utilizing a promoter-selective mode of action.