

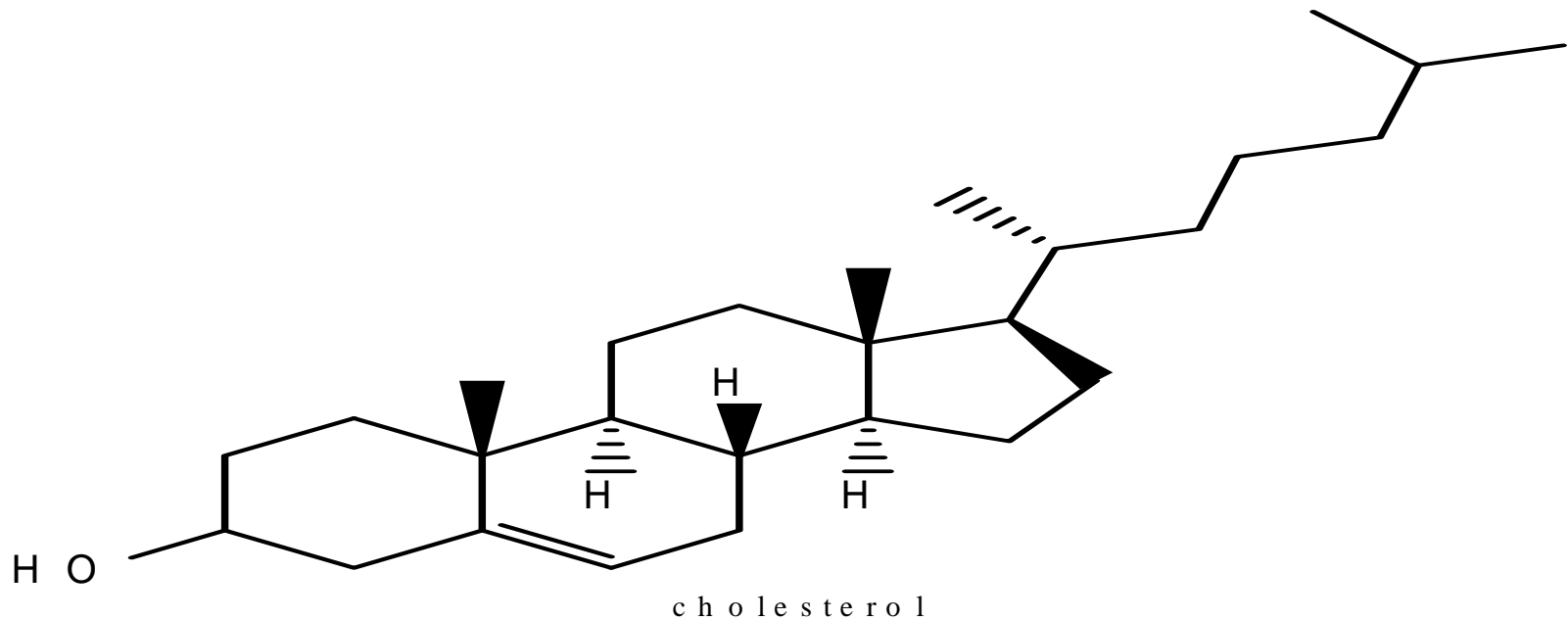


ANTI HYPERLIPIDEMIC AGENTS

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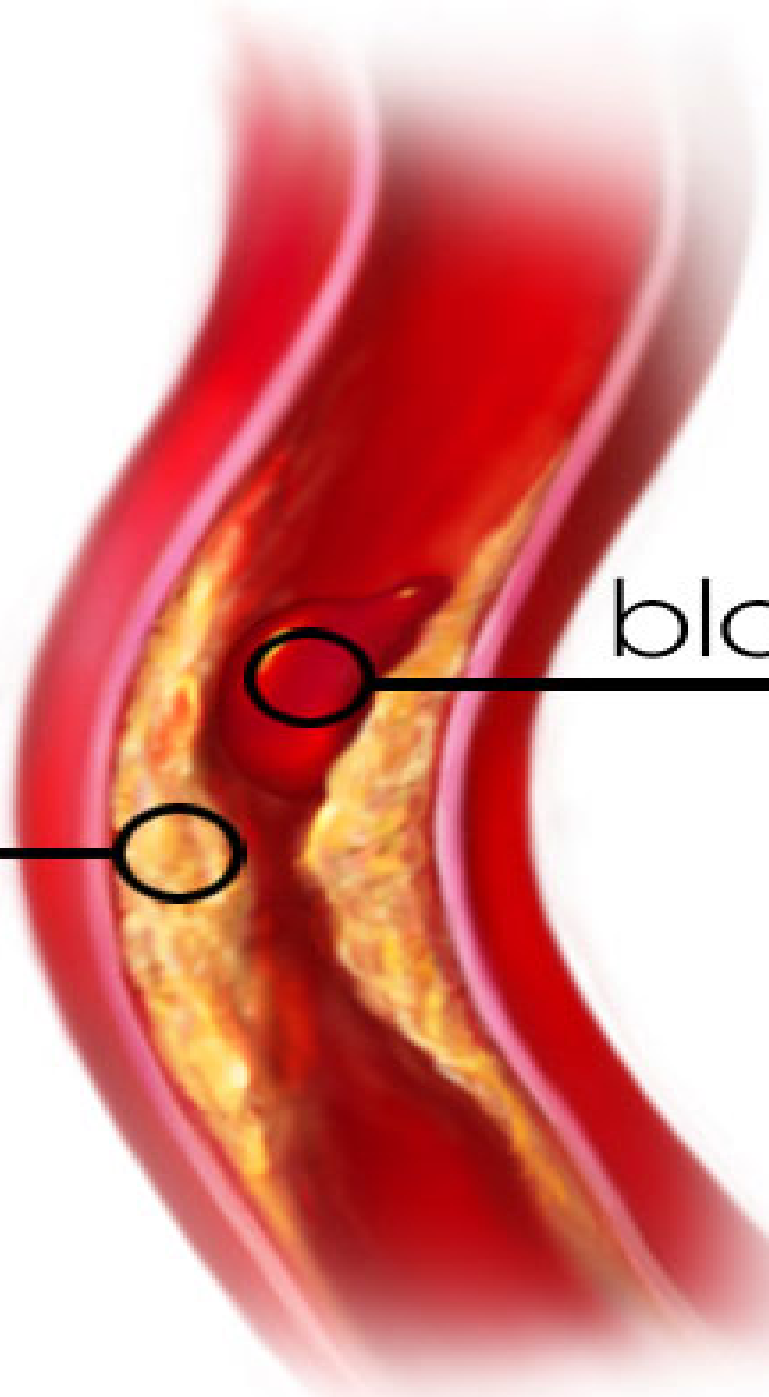
BIOMEDICAL IMPORTANCE OF CHOLESTEROL

- High cholesterol in blood implicates cardiovascular diseases
- Atherosclerosis and coronary artery disease



plaque
in artery

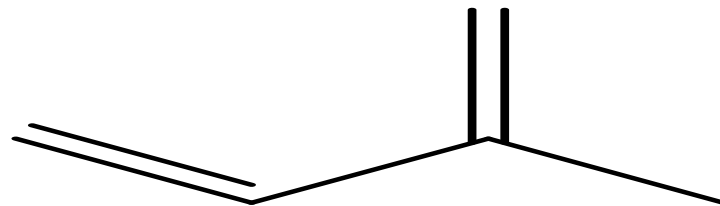
blood clot



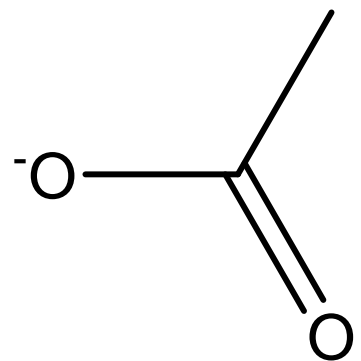
SYNTHESIS TRANSPORT AND STORAGE

- Acetate is the main precursor(released from acetyl CoA)
- Acetate converted to mevalonate
- Then mevalonate converts to squalene
- Squalene after few steps produces cholesterol

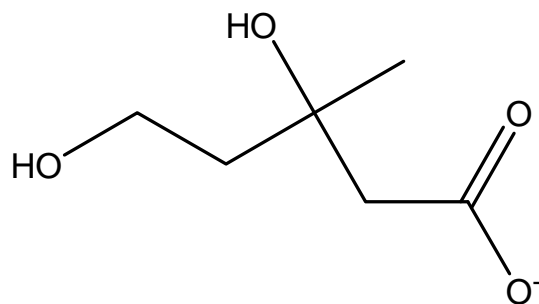
Activated isoprene units are must for cholesterol synthesis



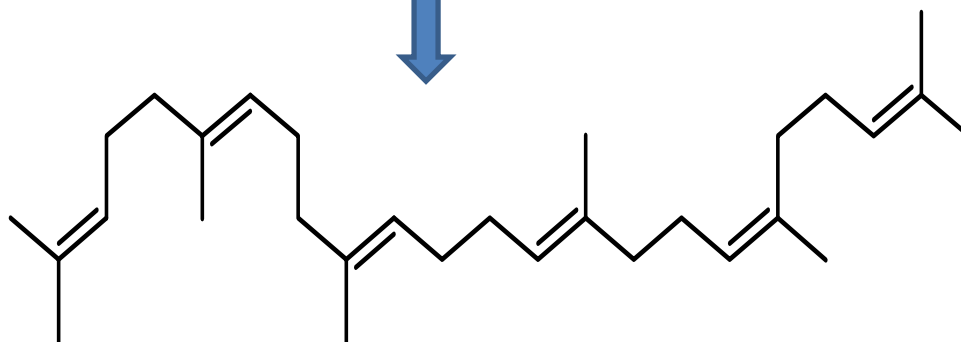
i s o p r e n e



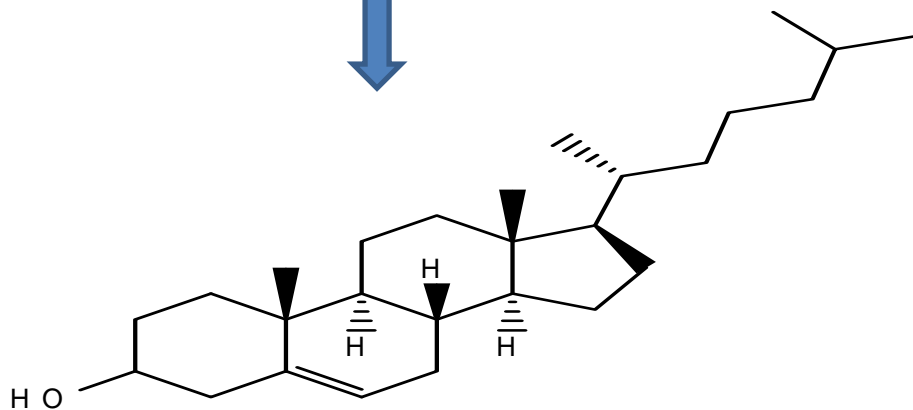
acetate



mevalonate



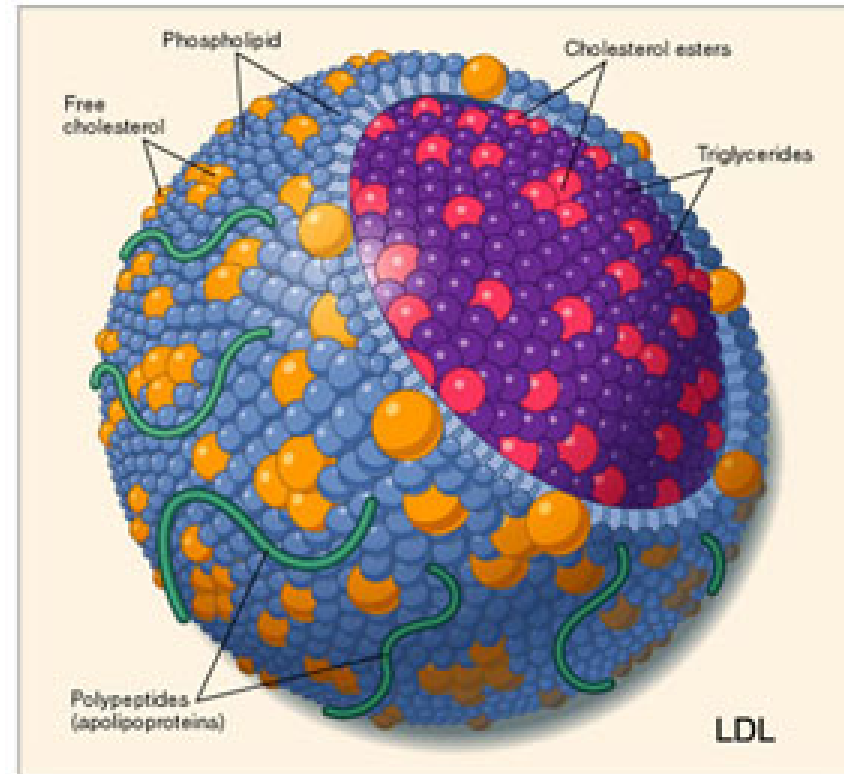
squalene



cholesterol

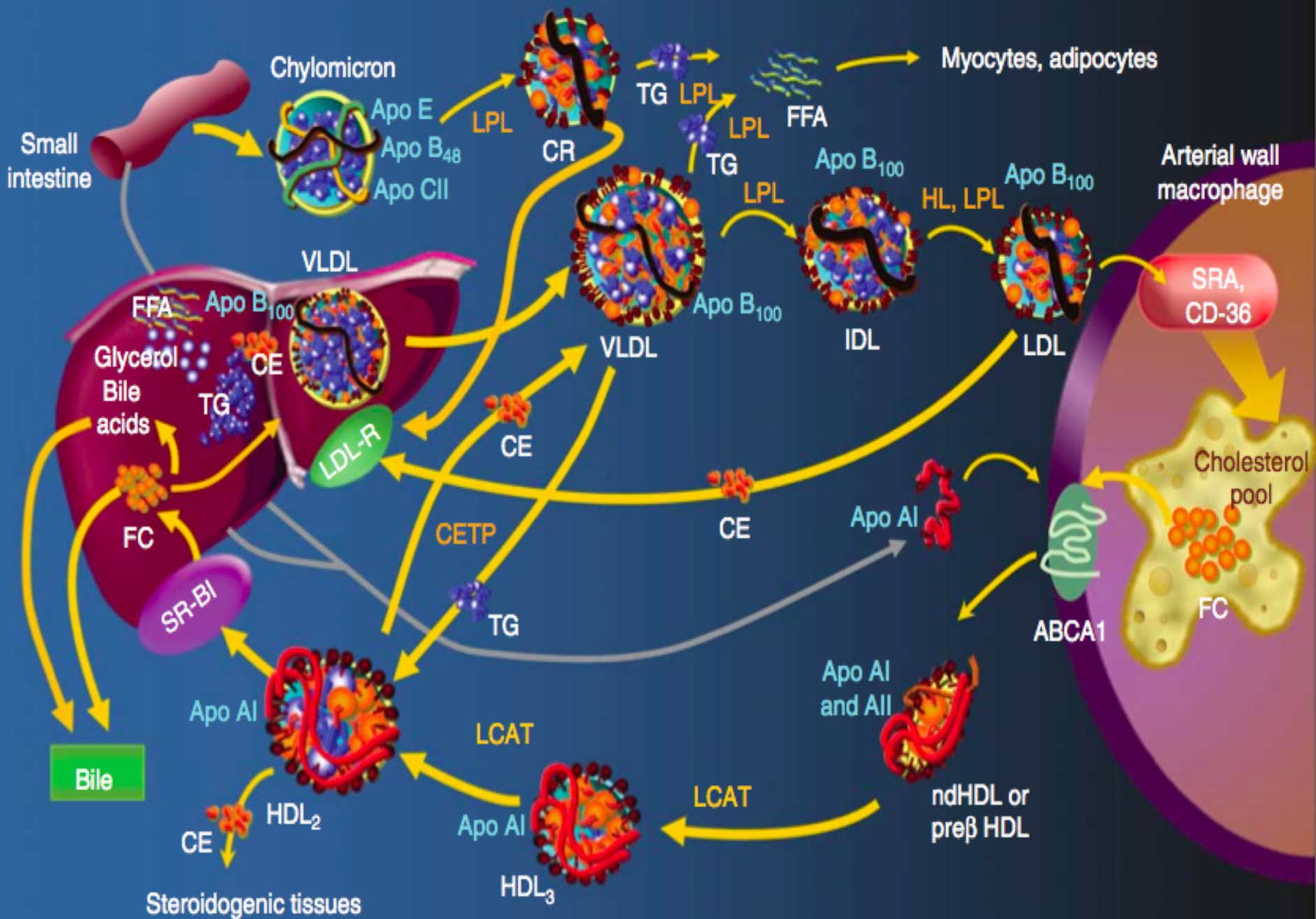
TRANSPORT AND STORAGE

- Chylomicrons (intestine)
- VLDL == VLDL(IDL)
- LDL
- HDL



UNDERSTANDING

- Fats and oils are fatty acids and tri acyl glycerol
- Apoprotein (free form) combines with lipid to form apo lipoproteins.
- They further synthesize lipoprotein bodies called as chylomicrons
- Chylomicrons transport into liver from chyle (lymph) where fatty acids are converted to TAG.
- Cholesteryl esters are formed in liver by ACAT.
- They form VLDL and move further to other tissues
- VLDL move to the extra hepatic tissue and release free fatty acids and tri acyl glycerols. Now it becomes IDL(remnant)
- Further removal of TAG produces LDL (rich in cholesterol)



HYPER LIPIDEMIC DRUGS

- **HMG Co-A REDUCTASE INHIBITORS**

1. **Lovastatin** - $t_{1/2} = 2$ hours
2. Fluvastatin
3. Simvastatin
4. Atorvastatin
5. Pitavastatin
6. Rosuvastatin

FIBRIC ACID DERIVATIVES

1. Clofibrate $t_{1/2} = 12$ hours
2. Gemfibrozil
3. Bezafibrate $t_{1/2} = 2$ hours
4. Micronized fenofibrate
5. Ciprofibrate

BILE ACID SEQUESTRANTS

1. Cholestyramine
2. Colestipol
3. Colesevelam
4. Ezetimibe
5. Ezetimibe + simvastatin

NICOTINIC ACID DERIVATIVES

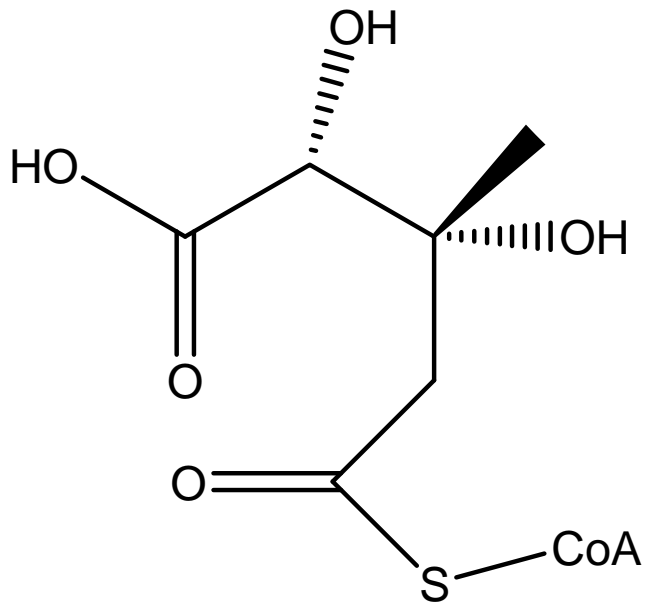
1. NIACIN
2. NIACIN + LOVASTATIN

MISCELLANEOUS DRUGS

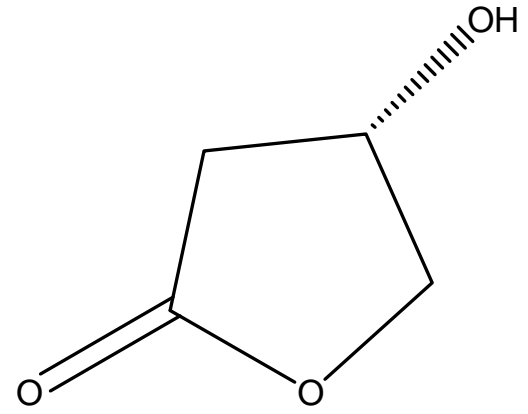
1. Probucol
2. Tamoxifen
3. Ratoxifene

HMG Co-A REDUCTASE INHIBITORS

- STATINS ARE REGARDED AS BLOCKBUSTERS IN CHOLESTEROL THERAPY
- STATINS ARE STRUCTURALLY SIMILAR TO HMG Co-A
- THEY ACT AS COMPETITIVE INHIBITORS FOR HMG Co-A REDUCTASE

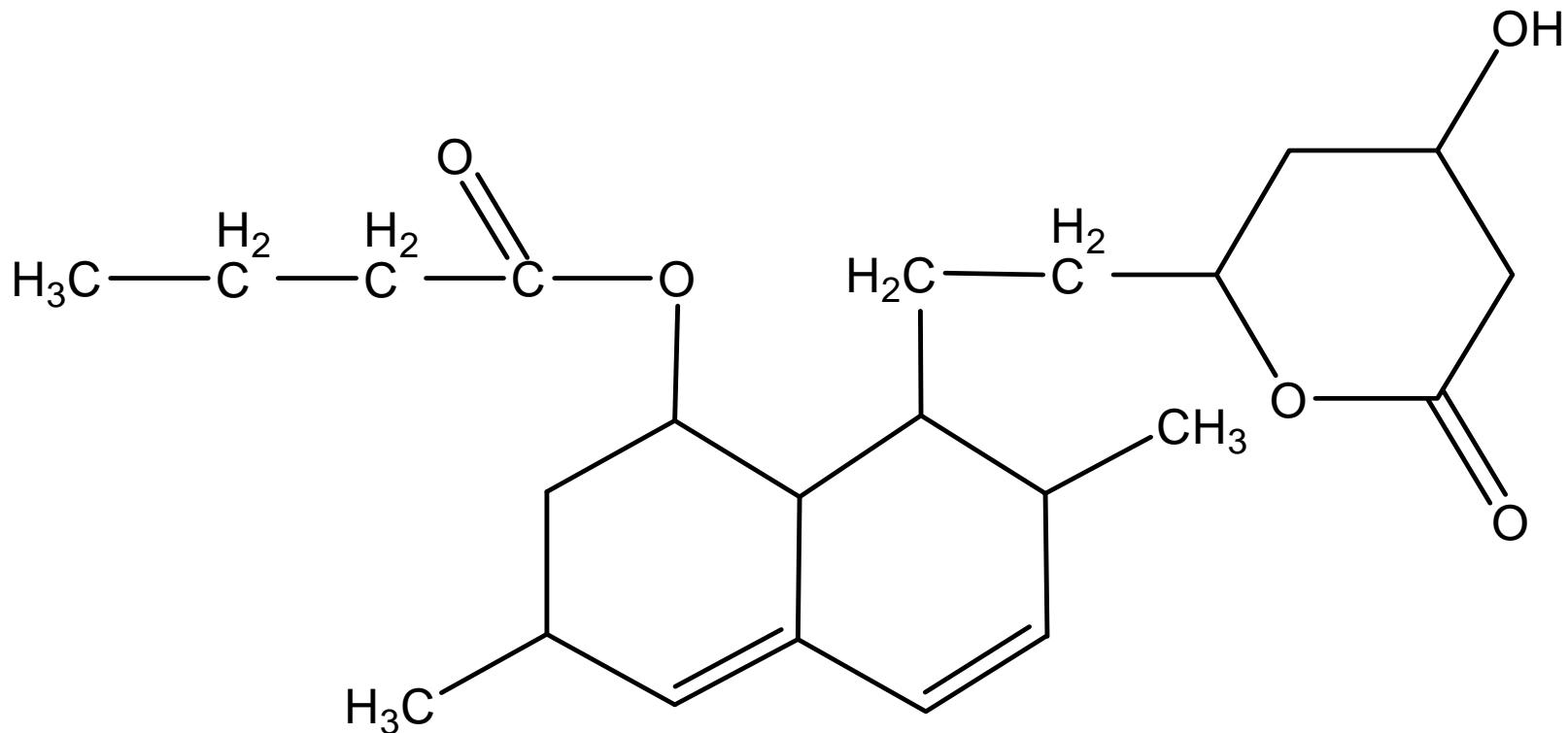


HMG Co-A



In active lactones

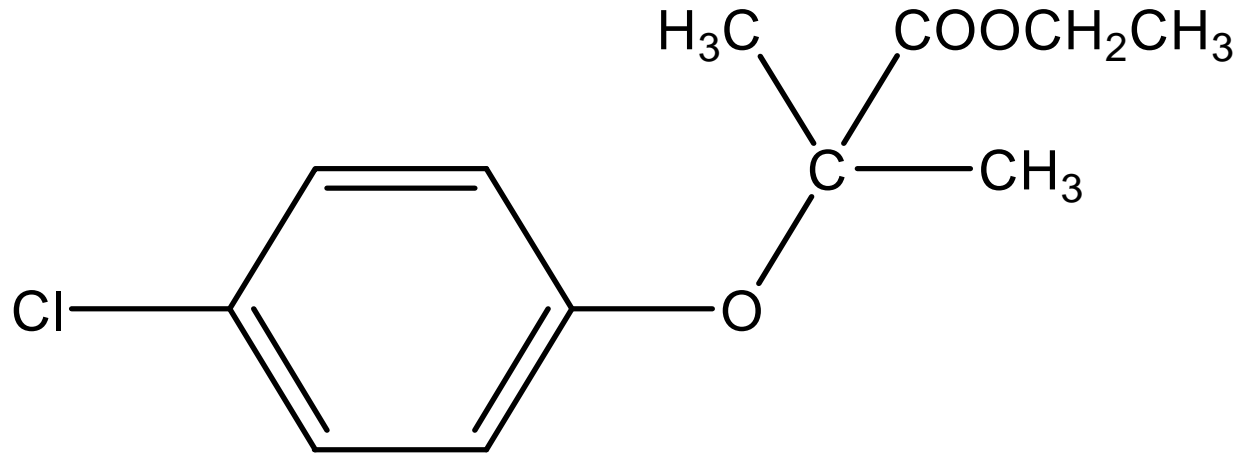
STATINS



**2-METHYL BUTANOIC ACID -1,2,3,7,8,8a- HEXA HYDRO 3,7 DIMETHYL -8-
[2-(TETRAHYDRO 4 – HYDROXY-6-OXO-2H-PYRAN-2-YL)ETHYL]-1-
NAPHTHALENYL ESTER**

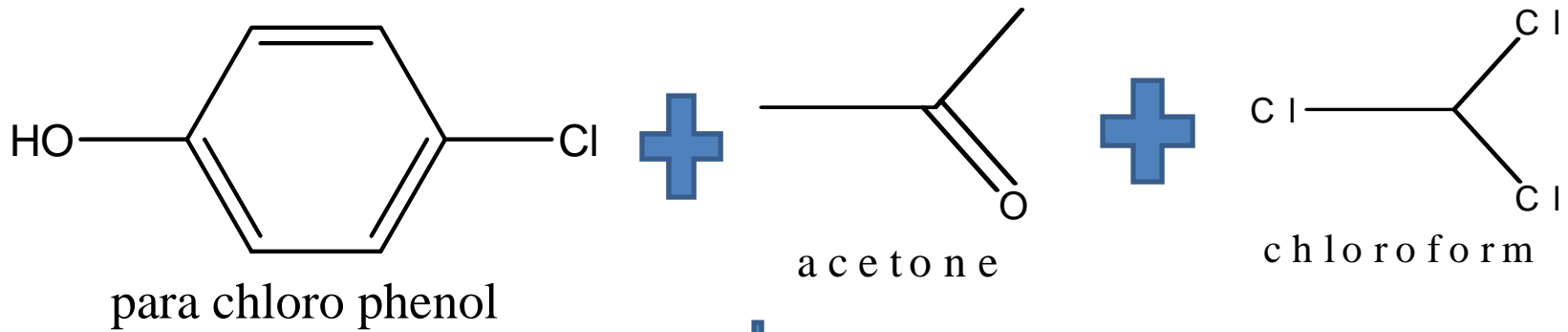
- OBTAINED FROM FERMENTATION OF *ASPERGILLUS TERRERS AND MONASCUS PURPUREUS*
- THEY REDUCE LDL CHOLESTEROL
- LOVASTATIN 80 mg reduces 40% of LDL

CLOFIBRATE

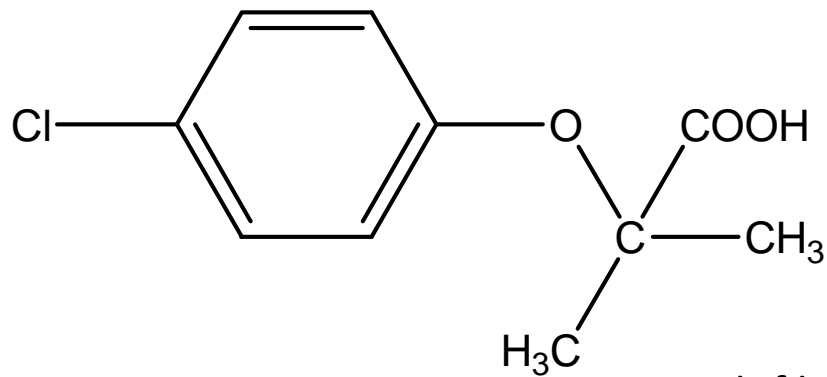


Ethyl -2- (p-chloro phenoxy)-2- methyl propionate

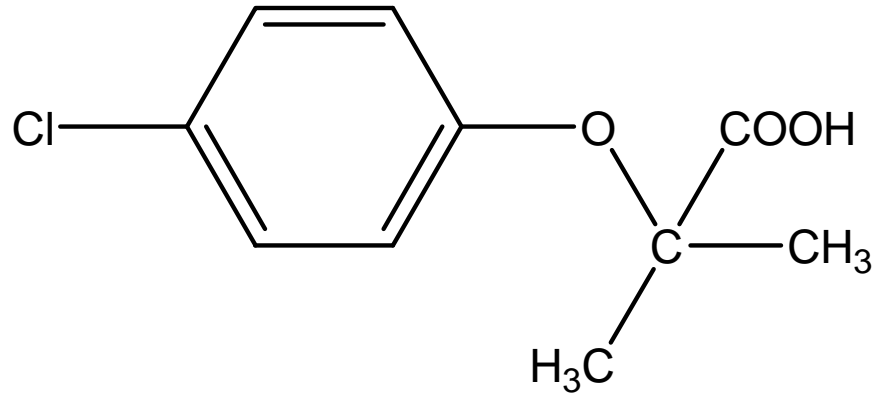
SYNTHESIS



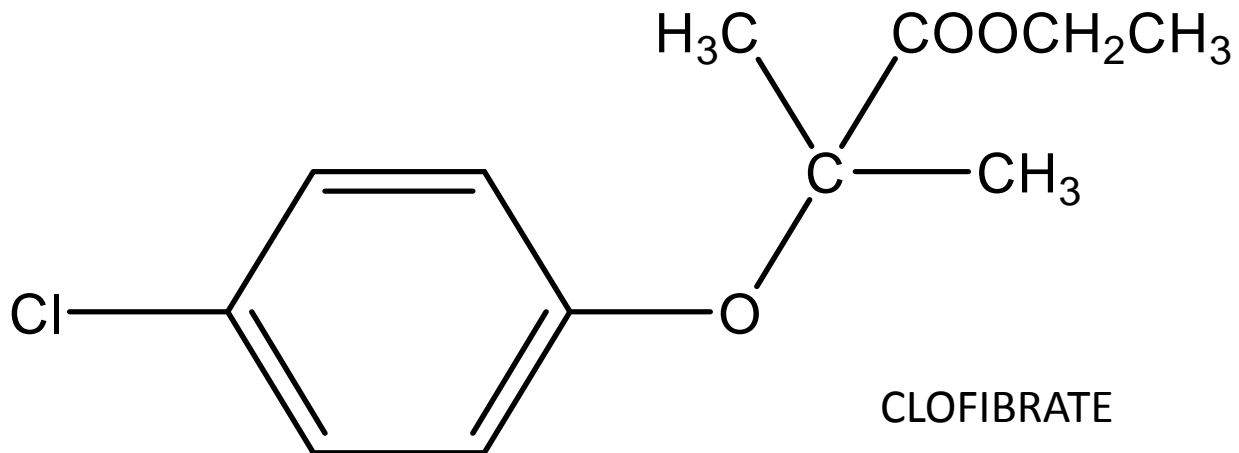
Sodium
chloride/acid
reflux



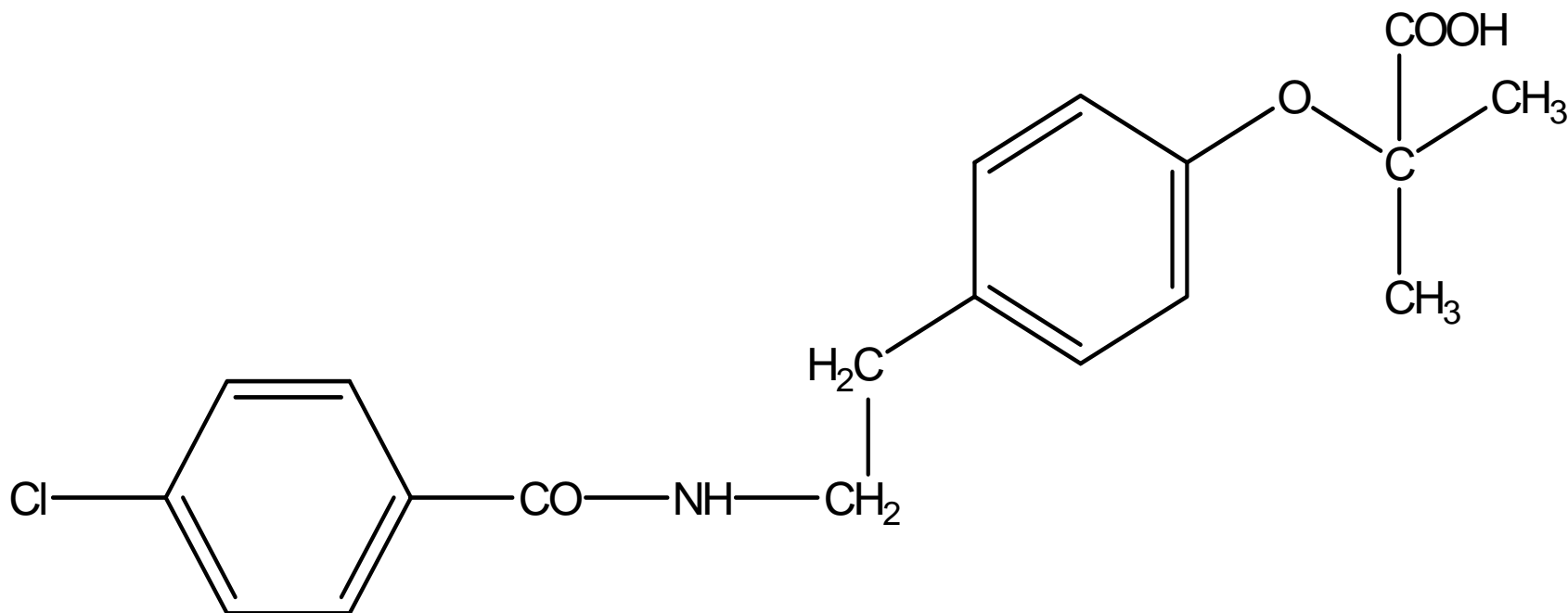
Clofibric acid



ESTERIFICATION

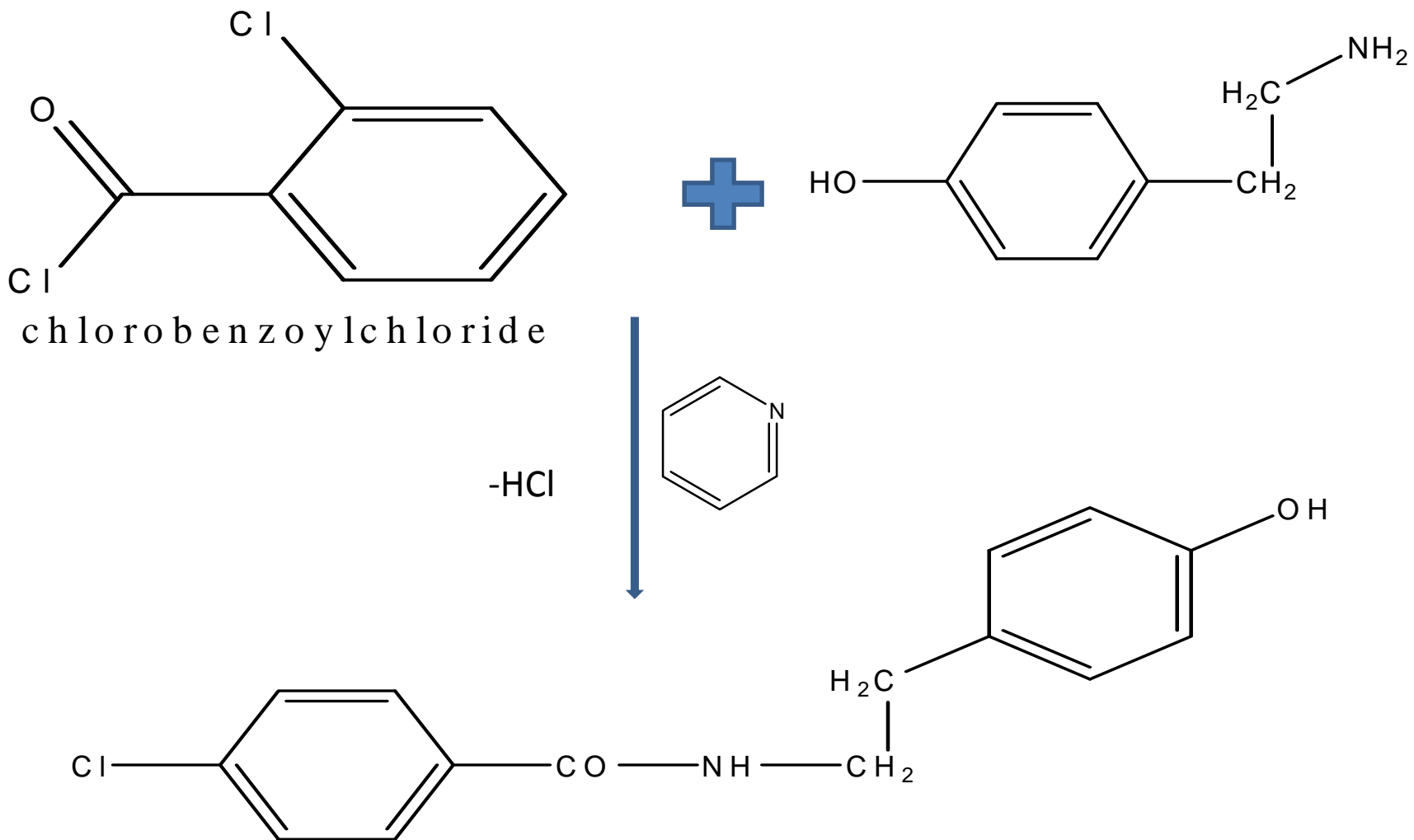


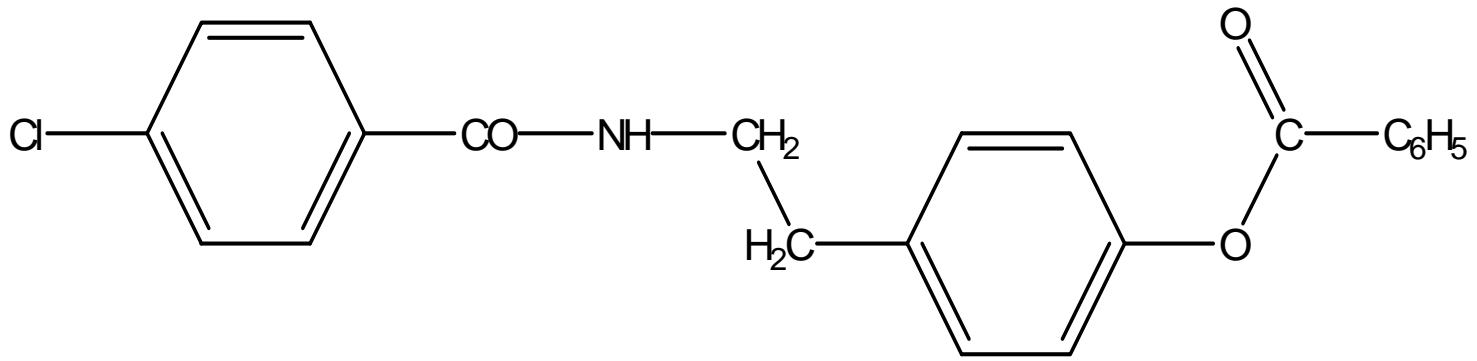
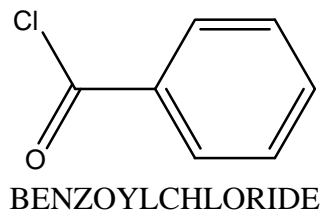
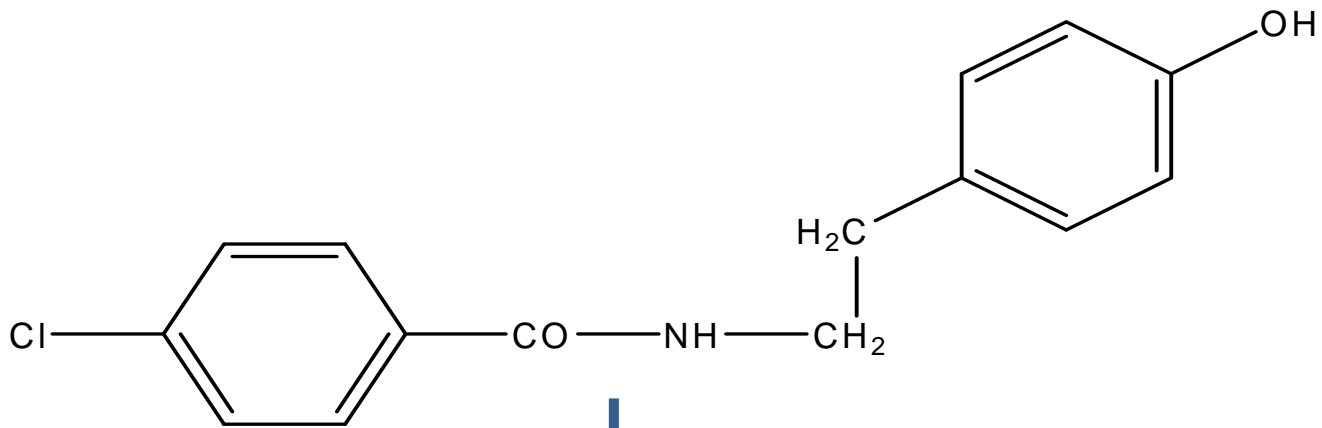
BENZAFIBRATE

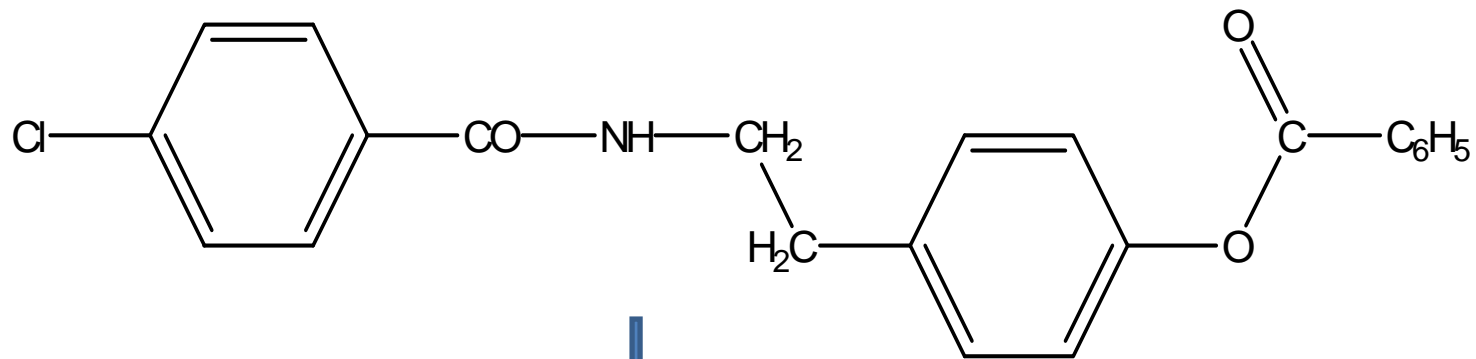


**2-{p-[2-(p-chlorobenzamido)ethyl]phenoxy}-2-methyl
propanoic acid**

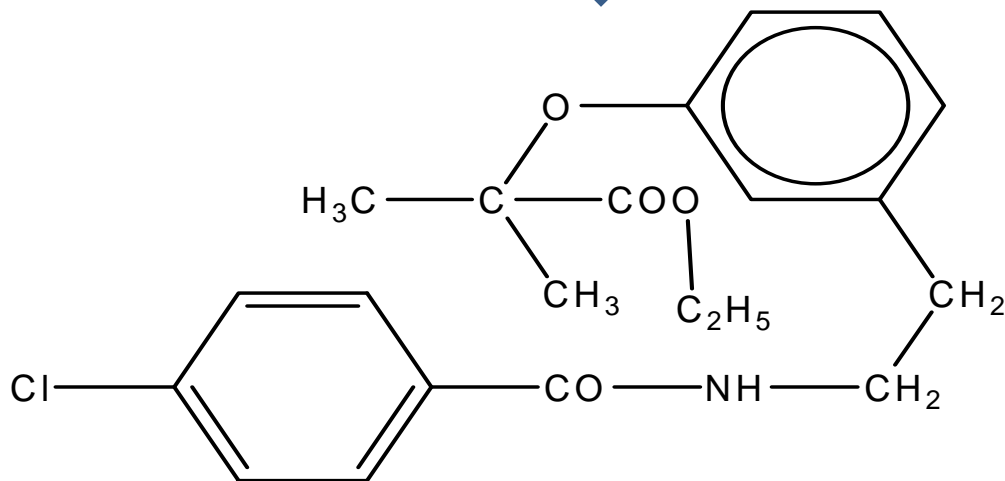
SYNTHESIS







CONDENSATION



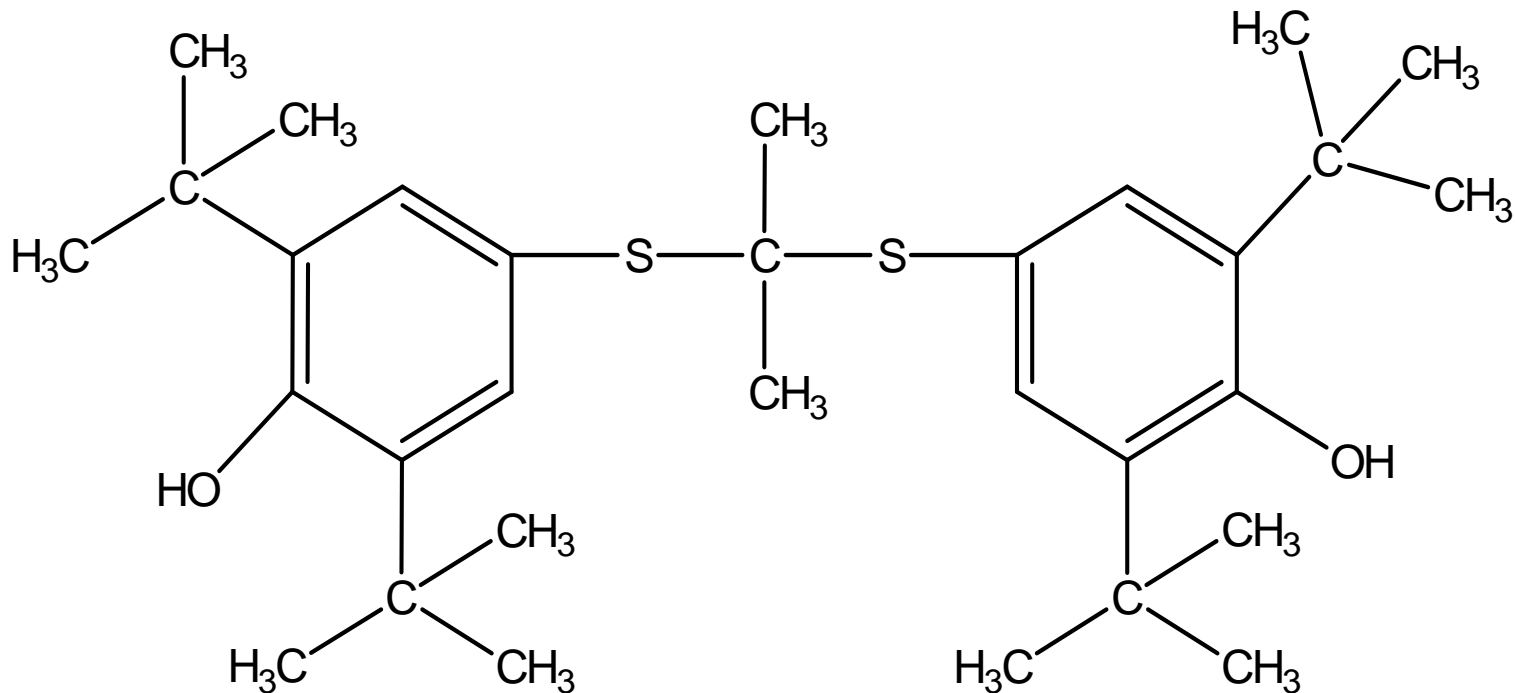
KOH
HYDROLYSIS



DRUG

MISCELLANEOUS DRUGS

- **PROBUCOL**



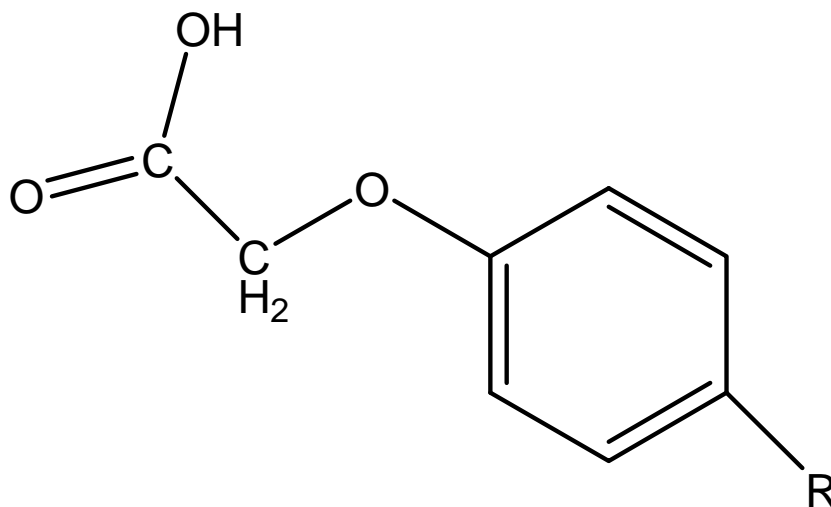
4,4 [(1-methyl ethylidene)bis (thio) bis [2,6 bis (1,1 dimethyl ethyl) phenol

STRUCTURAL ACTIVITY RELATIONSHIP

- Statins exploit *conformational flexibility* of enzyme HMG Co-A to create a *hydrophobic pocket* near the active site for hydrophobic ring system of inhibitor thus occupies both HMG binding pocket and Co-A pocket
- Lactonic group is essential for activity. This biotransforms into open carboxylic acid
- Synthetic statins contain 4- fluoro phenyl moieties
- *Atorvastatin* contains polar side chains that form *hydrogen bonding to Ser 565*

SAR OF FIBRATES

- Fibrates contain common fibrate head which is necessary for action.



CONCLUSION

- STATINS ARE STILL THE BEST SOURCE FOR LOWERING CHOLESTEROL IN BLOOD
- STATINS IN COMBINATION WITH NIACIN IS THE PERFECT CHOICE FOR MAINTAINING CHOLESTEROL LEVELS
- FIBRATES ARE REDUCED IN USE DUE TO RHABDOMYLOMA
- MISCELLANEOUS DRUGS ARE GIVEN WHENEVER NECESSARY

REFERENCES

- BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY VOL-3 ; 343
- STATINS – BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY VOL-3 ; 345
- SYNTHETIC PART – MEDICINAL CHEMISTRY VOL-2 BY K. ILANGO AND P. VALENTINA; 278
- ILLUSTRATION REFERENCE – BURGER'S MEDICINAL CHEMISTRY VOL-3 ; Fig 7.1 ; 359

THANK YOU