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STUDY OF ACAT RECEPTOR WITH HETEROCYCLIC COMPOUNDS FOR DRUG DESIGNING

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ABSTRACT: ACAT enzyme is found in human body and it maintains cholesterol homeostasis in the cell. This leads to deposition of cholesterol in our body as cholesteryl esters. Freely deposited cholesterol in the membranes of the cells is cytotoxic. This deposition causes atherosclerosis, Alzheimer's disease, Xanthelasma, *etc*. The first substrate for ACAT is both medium & long fatty acyl CoA. Therefore, we studied the ACAT enzyme, its active site, location and activity to develop the inhibitors of ACAT as antihyperlipidemic agents with the heterocyclic compounds for drug designing. ACAT is having two active sites: histidine and aspargines. ACAT 1 is present in two chromosomes 1 and 7. Active site His-460 Of ACAT-I is responsible for catalysis. For docking studies these factors should be known so that the hetercyclic compound could be developed having inhibitory activity against ACAT. Further many literature review have been done to find a hetercyclic moiety having the antihyperlipidemic activity in which we found that benzene ring with thiazole and oxazole rings having side chain could get results as ACAT inhibitors.

INTRODUCTION: ACAT is also known as Acyl-Coenzyme A cholesterol Acyltransferase. It's another name is Sterol O-Acyltransferases, *i.e.* SOAT. ACATs or SOATs have a vital role in cholesterol homeostasis at the cellular level. In 2009 Chang *et. al.* [1] reviewed that these are also used in several drugs for therapeutic applications in different diseases such as atherosclerosis, Hutter *et. al.*, in 2004 [2] told about dementia especially in Alzheimer's disease and malignancy. Mammals have two genes that account for the existence of two different proteins – ACAT 1 and ACAT 2.

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MBOAT category of enzymes includes the ACAT1 and ACAT2 in conjunction to the Acyl-CoA: Diacylglycerol Acyltransferase1 (DGAT1). MBOAT enzymes utilise all medium to long fatty acyl Coenzyme A for their initial substrate They also serve as a catalyst, transporting the fatty acyl molecule to the three -OH moiety of the 1st and 2nd substrates, which are usually lipophilic in nature. A histidine can be present in long hydrophobic peptide area, and asparagines can be found in the long hydrophilic peptide section, so an MBOAT has two active sites.

There are 11 MBOAT members present in humans who have comparable catalytic processes but biological functionalism that is vastly different. There is no comprehensive crystal structure for any of the MBOAT family members available at this time. Long fatty chain acyl-coenzyme A is used by both ACAT1 and ACAT2 as the primary fatty acyl

donor in the conversion of cholesterol to cholesteryl esters. In the case of ACAT1, oleoyl coenzyme is preferred. Oleoyl coenzyme is the ideal fatty acyl-CoA in the case of ACAT1 (Chang *et al*, 2010). [3] Cholesterol does have a lipid molecule that divides efficiently inside the area of cellular membrane phospholipid bilayers. Cholesteryl esters can't split in the lipid bilayer, therefore they clump together in aqueous environments, generating cytoplasmic lipid droplets. Overabundance of cholesterol freely present in cell membranes can be harmful. As a result, ACAT contributes to the slowing down of this process. The Coenzyme Acyl All tissues have an acyltransferase 1 enzyme. It's a long-lasting enzyme found in the endoplasmic reticulum (ER). ACAT2 is primarily found in hepatocytes and the intestine. It's found in a variety of bodily tissues, but in lower amounts than ACAT1. ACAT2 generates cholesteryl esters for lipoprotein production in the stomach. Both ACAT1 and ACAT2 enzymes are found in human hepatocytes. In humans, the role of these enzymes in hepatic lipoprotein assembly is uncertain. Both enzyme homologs have been discovered in yeast S. cerevisiae as well as other species (Chang *et al*, 2011) [4].

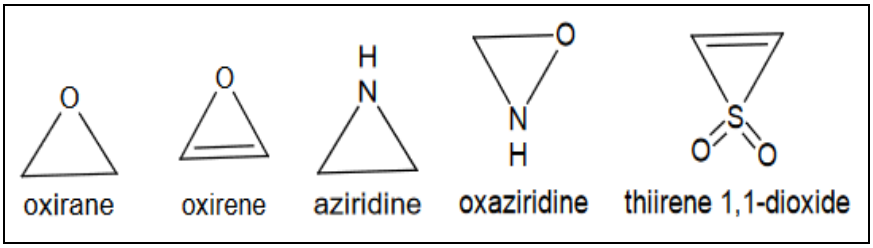
The human ACAT1 gene was found after a Chinese hamster ovary cell was successfully conjugated with a mutation that blocked ACAT activity. The human ACAT 1 is found in the two varied chromosomes – 1 and 7 where there is a distinct promoter for each site. Hu *et. al*., 2013 [5] told that the exons 1 to 16 are present in Chromosome 1&7 has the exon. The majority of ACAT1 mRNAs involve endogenous and chimeric 4.3kb ACAT1 mRNA in synthesised exon Xa to participate in a trans-splicing event.

At this point, the endogenous 4.3 kb mRNA undergoes a second trans-splicing process with an exogenous transcript encoded by Amp (rantisense)'s strand (as Amp). The new mRNA species leads to the formation of 56-kDa protein. 50-kDa protein is having low Acyl coenzyme A acyl transferase activity than 56-kDa protein. According to Hu *et. al*, 2013 [5] Farese and colleagues developed and characterised ACAT1 and ACAT2 mutant mice having the chimeric 4.3 kb ACAT1 mRNA that is found in humans with 17 exons on chromosome and Human ACAT2 that is located on chromosome 12 and produces a single 46-kDa protein on SDS-PAGE. Lipoprotein metabolism, neurological illness and atherosclerosis studies have all benefited from the use of these animals. In humans, the recombinant 50-kDa ACAT1 is extracted to ensure homogeneity and complete preservation of enzymatic activity (Miller, 2008) [6]. Because the enzyme responds to cholesterol in micelles and reconstituted liposomes in a sigmoidal fashion. The cholesterol is also sigmoidally reacted by the ACAT2 enzyme. As substrates, ACAT1 and ACAT2 can use a number of sterols, according to other support kinetic studies. Cholesterol is the best activator and sterol among the different sterols that have been investigated, including plant sterols, oxysterols, synthetic sterols and yeast sterols. Such sterols are excellent ACAT activators as well as substrates for steroid ring A with a 3 hydroxyl group. The recombinant 50-kDa ACAT1 is isolated in humans to assure homogeneity and full enzymatic activity conservation (Miller, 2008) [7].

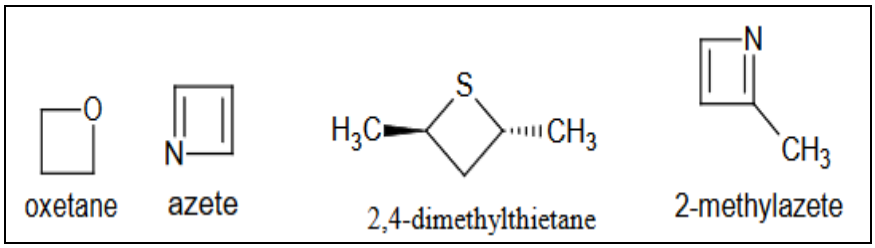
Because the enzyme reacts sigmoidally to cholesterol in micelles & reconstituted liposomes so ACAT 2 enzyme also reacts with cholesterol in a sigmoidal manner. According to previous support kinetic investigations, ACAT1 and ACAT2 can use a variety of sterols as substrates. Cholesterol is one of the best promoter in phytosterols, oxysterols, synthetic sterols and yeast sterols. ACAT enhancers and substrates for steroid ring too with a 3 hydroxyl group, are effective. Because the molecule was absent, sitosterol was used as a substrate to investigate the structural features of various sterols in the form of catalysts. Tagawa *et al.* in 2006 [8] told that sterol can be used as an activator as sitosterol was used as the substrate in the ACAT activation test.

Heterocyclic Compounds: A heterocyclic compound is a form of cyclic molecule that has rings made up of atoms from two different elements (Coffey, 2010) [9]. The counterparts of the heterocyclic compounds can be found in the form of the homocyclic compounds or the rights that are comprised of a single element. In most of the cases, it has been seen that the heterocyclic compounds happen to be inorganic which in maximum cases still contains a single carbon.

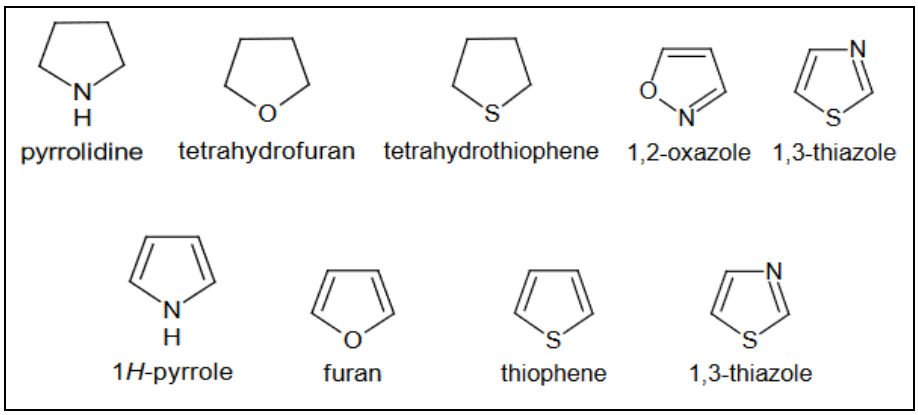
In the realm of organic chemistry, it has been seen that no carbons are often required to replace the carbon atoms hence they are referred to as heteroatom which means that they are different from carbon and also that of hydrogen. Heterocyclic compounds may be classified on the basis of their electronic structure. Heterocyclic that is saturated acts like acyclic derivatives. Hence the tetrahydrofuran and piperidine are the conventional amines and ethers that are altered atomic profiles. Hence the research of heterocyclic chemistry is mainly concentrated upon the derivatives that are unsaturated and also includes the preponderance of applications and works that includes unrestrained rings with 5 – 6 members. In this you can find thiophene, pyridine, furan and pyrrole included. Another major class of heterocycles is fused in the benzene rings. Quinoline, benzothiophene, indole, benzofuran, benzthiazole, benzimidazole and benzoxazole are respectively, for pyridine, thiophene, pyrrole and furan. Another big family of chemicals the acridine, dibenzothiophene, carbazole, and dibenzofuran, is formed by the fusion of two benzene rings. The participation of the heteroatom in the pi-system can be used to classify unsaturated rings. The nature of the ring strain with three atoms makes then more reactive in Heterocycles. The ones that have a single heteroatom are considerably more stable. Those with a couple of heteroatoms happens to be more reactive Common 3-membered heterocycles with one heteroatom are aziridine, azirine, oxirane, oxirene, thiirane, thiirene *etc.*



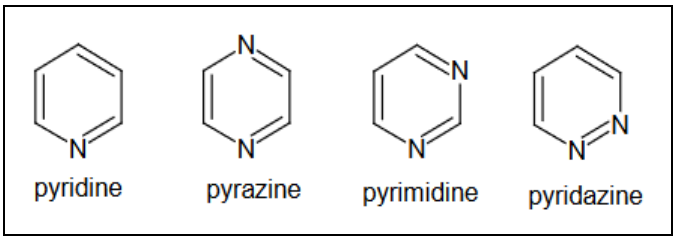
Heterocycles Containing Four-membered Ring Compounds are as follows: The heterocycles that have five atoms, the unsaturated compounds happen to be more stable because of aromaticity.



Saturated five-membered rings with one heteroatom are Pyrrolidine, tetrahydrofuran, tetrahydrothiophene and unsaturated five-membered rings with one heteroatom are pyrrole, furan, thiophene and borole. These unsaturated five-membered ring compounds are aromatic in nature.



Compounds with 5 membered ring often contain a couple of heteroatoms where at least one of them happens to be nitrogen and are collectively referred to as azoles Sulfur and nitrogen atoms are found in the ring of thiazoles and isothiazoles. There are two sulphur atoms in dithiolanes. Unsaturated six-membered nitrogen heterocyclic compounds with stable aromatic rings include pyridine, pyrazine, pyrimidine, and pyridazine.



Picolines, lutidines, and collidines are pyridines with a single, two, or three bonded methyl groups, respectively named mono, di and trimethylpyridines. The methyl group positions are usually represented by the numbers 2, 4. 6-collidine. The acids picolinic, nicotinic (produced from nicotine and an oxidation product) and isonicotinic have all been renamed. Pyidine can be discovered in bone oil and coal tar among the lutidines, picolines, and collidines. Pyridine chemicals have numerous biological applications. Nicotinic acid is has the same nutritional properties as niacin and niacinamide.

The Coenzyme II:
Nicotine Adenine Dinucleotide Phosphate (NADP) and coenzyme I: Nicotinamide Adenine Dinucleotide (NAD) are the couple of coenzymes which happens to be involved in some really important metabolic reactions within cells. Both of these coenzymes are made up of nicotinamide and pyridoxal phosphate. These are physiologically active version of pyridoxine. The nicotine and piperine are sharp-tasting ingredients of white and black pepper, (Piper nigrum) are one of alkaloids with a piperidine or pyridine ring structure. Pyridine which was earlier commercially extracted from coal tar in the current times happens to get prepared in a catalytic manner out of ammonia and tetrahydrofurfuryl alcohol. It happens to be a significant solvent and is used in the process of making other compounds. Vinyl pyridines, on the other hand, is important in the production of plastics and is entirely saturated with piperidine, pyridine, and is utilised in rubber manufacturing as well as a chemical raw component.“Nevirapine an anti-AIDS drug, Isoniazid (Isonicotinic acid hydrazide) an anti- tubercular drug, and the vasodilator Nicorandil, used to treat angina, as well as the anti-inflammatory Sulfa drug 1-(1-phenyl cyclohexyl) Piperidine (PCP, Phencyclidine), which was previously used as an anaesthetic but whose strong hallucinogenic Diflufenican, as well as Diquat, Paraquat, and Clopyralid are well-known pyridine compounds used as herbicides.

The cyanine dyes, which are used as sensitizers in silver halide photographic emulsions, as well as the quinophthalone dyes, which are used in plastics, textiles, polymers, cosmetics, paper, transfer printing processes, electronic photography and laser dyes, are significant benzo- and dibenzopyridines synthetic derivatives. Antiseptics such as the coal-tar dye- Acriflavine, antibacterial agents -ciprofloxacin, antimalarial agents - Mepacrine (quinacrine). Pyrone derivatives can be found in a variety of natural goods. As an example, Kojic acid is an antibiotic produced by the action of some moulds on sugars or other carbohydrates. The steroid "Bufotalin" and its lethal ester "Bufotoxin" are produced by the skin glands of toads. A wide range of natural substances begins with the benzopyryliumcation.

Despite the fact that chroman, also known as 3,4-dihydro-2H-1-benzopyran, is not found in nature. It can be found in a number of natural chemicals eg; Vitamin E (-tocopherol), a substituted chroman, is found in plant oils and green vegetable leaves. Coumarin, commonly known as 2H-1-benzopyran-2-one, is a flavouring and fragrance ingredient. The blood anticoagulant Dicoumarin is derived from live organisms. The realm of the chemistry of chalcones has given rise to exhaustive scientific researches worldwide. The domains of synthesis and biodynamic activities of chalcones seem to have harnessed a special flicker of interest. Kostanecki and Tambor came up with the name "Chalcones." Benzalacetophenone and benzyl-ideneacetophenone are other names for these compounds. An aliphatic three-carbon chain connects two aromatic rings in chalcones. Chalcone's versatility allows for the development of a wide range of new heterocycles with promising pharmacological properties. Chalcones are

unsaturated ketones that have the reactive keto-ethylenic group –CO-CH=CH-.

The presence of the chromophore -CO-CH=CH- gives these compounds their colour, which is further influenced by the presence of other auxochromes. The preparation of Chalcones can be done in a variety of ways (Martin and Zekter, 2013) [10]. The most convenient method is 'Claisen-Schmidt condensation' of equimolar quantities of aryl-methyl ketone with aryl aldehyde in the presence of alcoholic alkali.

Flavones, pyrazolines, 3-chlrochromones and 1, 5-benzothiazepines are only a few of the derivatives made from chalcones having different heterocyclic ring systems **Fig. 1.**

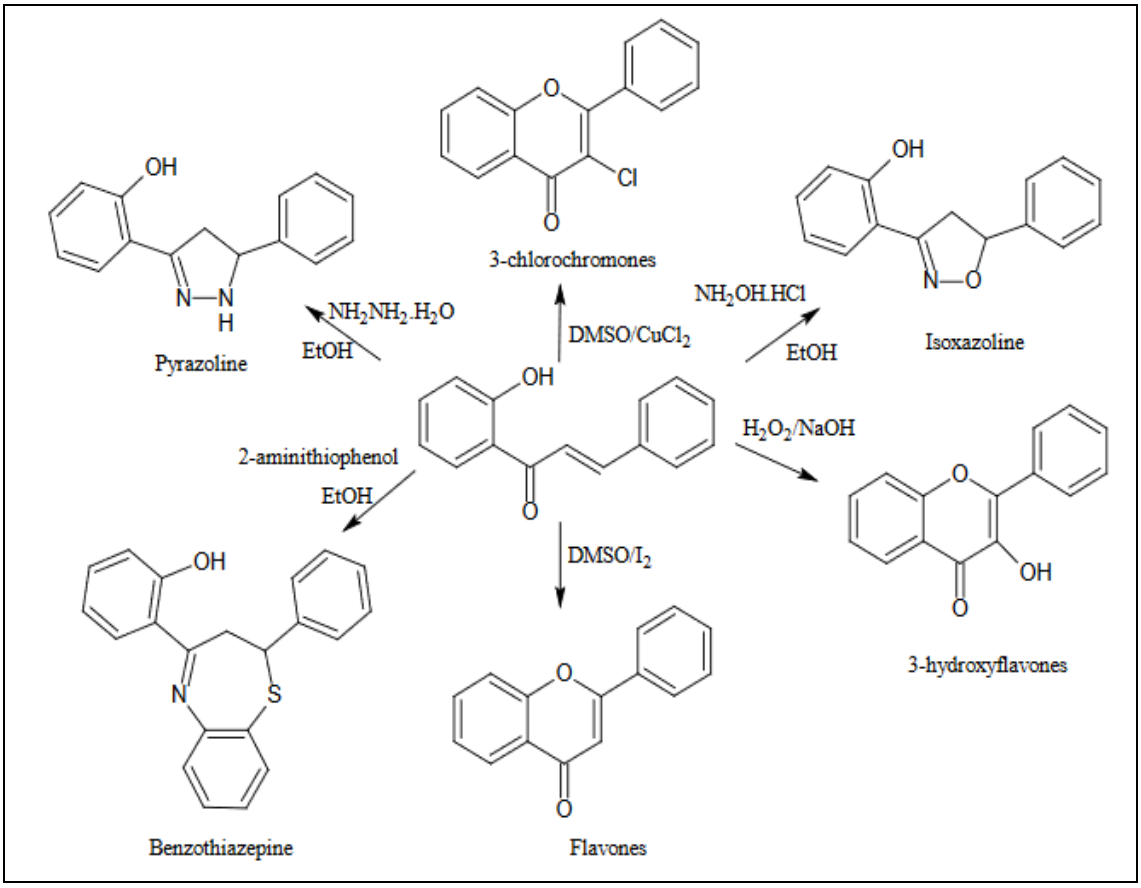


FIG. 1: CHALCONES AS A PRECURSOR FOR DIFFERENT HETEROCYCLES

The Pyrazolines are another set of imperative nitrogen heterocyclic compounds that contain five-member. These rings happen to be a significant group of five-membered aromatic heterocycles which are the subunits of several drug molecules.

A detailed study of the chemistry of pyrazole was attempted in the last 30 to 50 years which has been noted down within the domain of the literature of the field.

All the Pyrazoline derivatives contains a large spectrum of biological activities such as antihistaminic, tranquilizing, muscle relaxant, anticonvulsant, psycho analeptic, anticonvulsant, antihypotensive, antifungal, antibacterial, antitubercular, antidepressant, antitumor, insecticidal, antidiabetic (Kalsi, 2004) [11], Pyrazolines are employed vastly on the form of synthons in organic synthesis.

It is employed not only in the domain of drug chemistry but also in agro-chemistry. Some of these pyrazole derivatives are once again employed as herbicides, insecticides or fungicides.

A powerful fungicidal for plants containing 4-chloro-3- (3,5-dichlorophenyl)-1H-pyrazole has been patented. Some of the important pyrazole containing drug molecules that are in common use are shown below **Fig. 2.**

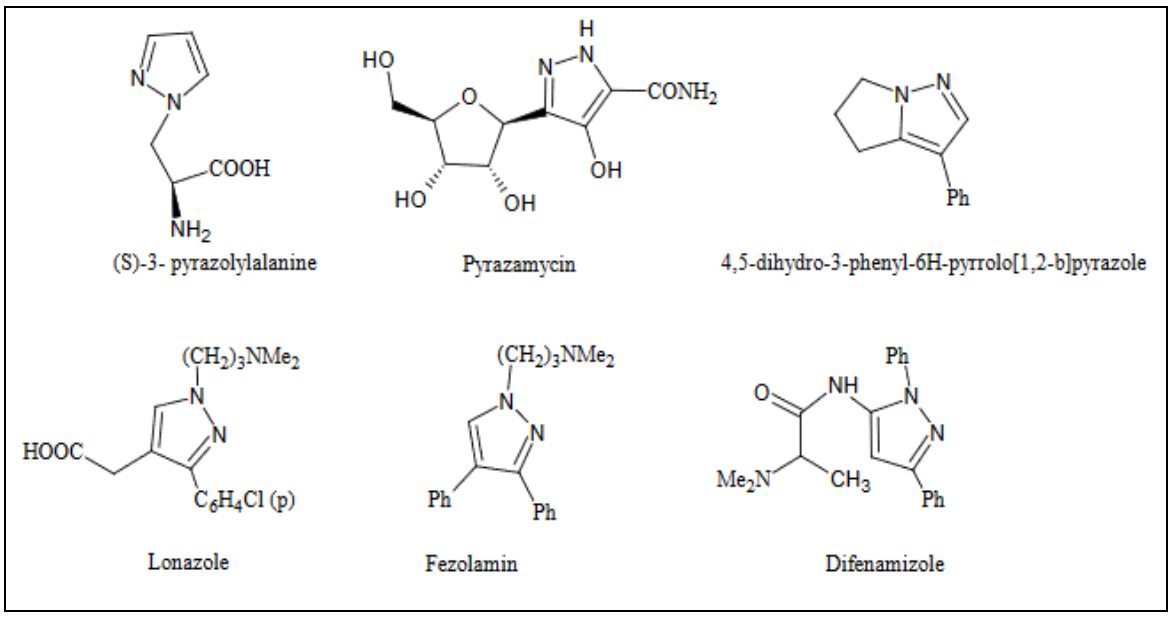


FIG. 2: PYRAZOLE CONTAINING DRUGS AVAILABLE IN THE MARKET

Acyl-Coenzyme A: Cholesterol O-acyltransferase (ACAT): ACAT has three identical members: acyl-coenzyme A: diacylglycerol acyltransferase I (DGAT-l), acyl-coenzyme A: cholesterol O-acyltransferase I and acyl-coenzyme A: cholesterol O-acyltransferase II. ACAT has received a lot of interest as a viable technique for examining both non-lipid and lipid pathways in atherosclerosis. There were also 18 prior biochemical investigations using cell partition studies to demonstrate that ACAT activity can only be identified in the microsomal portion and not the soluble portion. ACAT is a membrane-bound enzyme, according to this information.

For substantial and difficult functions, ACAT-I and ACAT-2 are required for *in-vivo* lipid homeostasis. They frequently assist in the single-cell avoidance of the build-up of free excessive lipoprotein in cell membranes. Both ACAT1 and 2 are involved in the physiological synthesis of cholesteryl esters from membrane lipids cargo, which is then aggregated in VLDLs, chylomicrons and cholesterol-laden macrophages. These macrophages turn into foam cells, which are a feature of initial atherosclerosis lesions.

Identification of ACAT Isozymes: The ACAT function was well-known as soon as 1970; however, due to the presence of small amounts of the enzyme in various tissues, the enzyme isolation procedure failed. In 1993, Chang's lab at Dartmouth College used the first ACAT-deficient Chinese hamster ovary (CHO) cell culture to clone the entire cDNA of mammalian ACAT-I. This was regarded as a turning point in the domain. Decreased lipoprotein ester levels in the adrenal glands and peritoneal macrophages are linked to decreased sterol esterification in hematopoietic cells with adrenocortical membrane surface, indicating that ACAT-I is important in these tissues.

ACAT Enzymes' Membrane Structure: According to TMD algorithms, the ACAT family enzymes seem to be essential ER surface proteins with many envelope proteins (TMDs). Understanding the substrate binding and catalytic response of transmembrane enzymes necessitates knowledge of cell wall structure. As a consequence, a range of practical methods for studying membrane topology have now been devised. A range of methodologies have been used to investigate the transmembrane morphology of ACAT-positive cells. In 1999, *I. Lin et. al.,* constructed the first 7-TMD framework for ACAT-I based on the results of HA-tag inclusion and immunofluorescence studies after specific downregulation of the cell surface and ER outer layer. Researchers told that the ER lumen has two long hydrophobic polypeptide stretches as well as one long hydrophilic polypeptide sequence with conserved sequences. A year later, depending on the C-terminal truncation technique, suggested a 5-TMD model of ACAT-I.

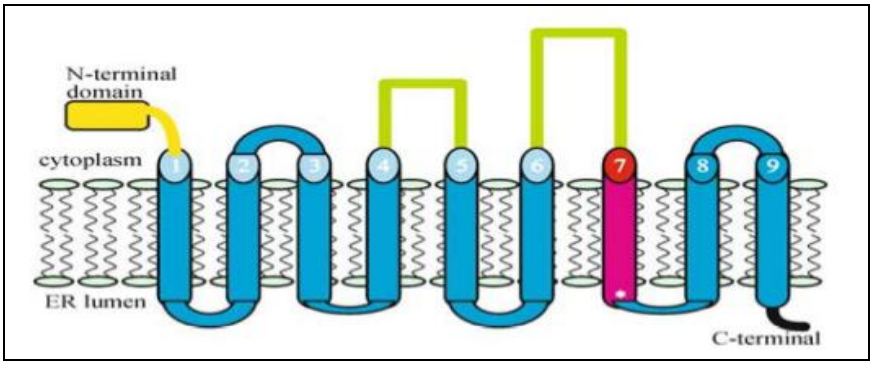


FIG. 3: A GENERAL ER MEMBRANE TOPOLOGY MODEL FOR ACAT FAMILY ENZYMES. THE POSSIBLE CHOLESTEROL/DIACYGLYCEROL- REGIONS BINDING REGION (TMD7) IS SHOWN IN RED AND OTHER TMDS ARE SHOWN IN BLUE. THE POSSIBLE ACYL-COENZYME A-BINDING THE LOOP BETWEEN TMD6 AND TMD7 AND THE LOOP BETWEEN TMD4 AND TMD51 ARC SHOWN IN GREEN, THE POSITION OF THE ACTIVE SITE HIS IN TMD7 IS INDICATED BY A WHITE STAR

They discovered three hydrophobic polypeptide sequences inside the cytosol under this model. Using cysteine-scanning mutagenesis & subsequent cysteine-specific modification method, Guo *et al.* proposed a 9- TMD model for ACAT-1 in 2005. All lengthy hydrophobic polypeptide stretches are embedded in the biological membrane inside the 9-TMD topology model **Fig. 3**. In this concept, the cytosol contains a lengthy polypeptide sequence between TMD6 and TMD7 that is rich in invariant hydrophilic and hydrophobic residues. This peptide sequence may serve as a binding site for acyl-coenzyme A, a cytosol-produced molecule that is impenetrable to the ER membrane. The so-called active site His-460 of ACAT-I is positioned in a membrane bound area at the luminal end of TMD7 in the 9-TMD model. This site appears to be in charge of catalysis. ACAT-2 membrane topology has also been investigated experimentally utilising two different ways. "A 2-TMD model resulted from the insertion of an HI-tag and subsequent immunofluorescence observation, whereas a 5-TMD model resulted from the C-terminal truncation technique. ACAT-2, on the other hand, comprises nine long hydrophobic peptide sequences that correlate to nine TMDs of ACAT-I, according to sequence analysis **Fig. 3**. As a result, ACAT-2 is likely to have nine TMDs. All lengthy hydrophobic peptide lengths of ACAT-2 are immersed in the membrane bilayer in the suggested 9-TMD model; the putative acyl-coenzyme-A binding site in TMD6 and TMD7 is in the cytosol; with active site His-434 is at the luminal end of TMD7 **Fig.3.** A broad topological model **Fig. 3** has been proposed for the ACAT family of enzymes. TMD7 is particularly important since it is thought to play a role in substrate binding and catalysis. The retained residues in TMD7 are abundant. An active site is thought to be the completely preserved His-460 at the luminal end. Cholesterol/diacylglycerol binding is likely to be mediated by additional conserved regions. ACAT group enzymes can utilise membrane-bound cholesterol with diacylglycerol as substrates since cholesterol and diacylglycerol are water insoluble. There are several conserved hydrophobic and hydrophilic residues in two lengthy cytosolic loops (between TMD6 and TMD7 and between TMD4 and TMD5) which are most likely involved in the binding of acyl-coenzyme A, which is produced in the cytosol but is not permeable to Endosomal membrane.

Systematic Literature Review: Researcher conducted a systematic review to determine docking studies and computer based drug designing for some novel heterocyclic compounds against ACAT receptor using different studies shown in **Table 1**. This systematic review was based on published peer-reviewed articles that were publically available. Thus, it was not submitted to an ethics board for review.

TABLE 1: DOCKING STUDIES AND COMPUTER BASED DRUG DESIGNING FOR SOME NOVEL HETERO-CYCLIC COMPOUNDS AGAINST ACAT RECEPTOR

S. no.	Topic	Results	Reference
1	Acyl CoA: cholesterol acyltransferase (ACAT)	*In-vitro* potency was studied between the heterocyclic groups and their diarylimidazole counterparts. Data was also gathered	12

	inhibitors: ureas bearing heterocyclic groups bioisosteric for an imidazole	for the purposes of QSAR. Our goal is to develop a systemic ACAT inhibitor that could be used to treat hypercholesterolemia and atherosclerosis	
2	Heterocyclic Amides: Inhibitors of Acyl-CoA: CholesterolO-Acyl Transferase with Hypocholesterolemic Activity in Several Species and Antiatherosclerotic Activity in the Rabbit	In cholesterol-fed rat, rabbit, as well as dog models of pre-existing hyperlipidemia, compounds 13a and 16a reduced total cholesterol. At a dose of 1 mg/kg, compound 13a proved effective in decreasing the formation of cholesteryl ester-rich thoracic aortic plaques in the damaged cholesterol-fed rabbit model of atherosclerosis, lowering lesion coverage by 53%.	13
3	QSAR study of a series of acyl coenzyme A (CoA): Cholesterol acyltransferase inhibitors using genetic function approximation	Molecules with larger substituents are more likely to increase potency, according to the positive contribution of molecular shadow descriptors. The internal and external cross-validation statistics of the developed models revealed that they were predictive	14
4	Inhibitors of Acyl-CoA: CholesterolO-Acyltransferase. 2. Identification and Structure−Activity Relationships of a Novel Series of N-Alkyl-N-(heteroaryl-substituted benzyl)-N‘-arylureas[1]	Compound 3aq (FR186054) was identified as a new, orally effective ACAT inhibitor after optimization of the combination with the N-alkyl group (R) and the N-aryl group (Ar3). It showed potent in vitro ACAT inhibitory activity (rabbit intestinal microsomes IC_{50} = 99 nM) and excellent hypocholesterolemic effects in cholesterol-fed rats, regardless of administration mode (ED_{50} = 0.046 mg/kg dosed via the Furthermore, when tested at a single dose of 10 mg/kg po, compound 3aq was found to be harmless to the adrenal glands of dogs in a toxicological assessment	15
5	Ureidopyridazine Derivatives as Acyl-CoA: cholesterol acyltransferase Inhibitors	On the enzyme produced from rat liver microsomes, their inhibitory activity against acyl-CoA: cholesterol acyltransferase (ACAT) was examined. Theoretical investigations were conducted to link their activity to structural characteristics.	16
6	The Nine Lives of ACAT Inhibitors	However, a study published in this edition of Arteriosclerosis, Thrombosis and Vascular Biology by Bell *et al* reintroduces the idea of targeting ACAT enzymes and raises an important unsolved question: Can ACAT2-specific inhibitors help treat or prevent atherosclerosis by lowering plasma cholesterol?	17
7	Acyl-CoenzymeA (CoA): Cholesterol Acyltransferase Inhibition in Rat and Human Aortic Smooth Muscle Cells Is Nontoxic and Retards Foam Cell Formation	The Fujire bio chemical F1394 inhibited ACAT, which decreased CCC-induced foam cell production in rat and human ASMC but did not cause significant cytotoxicity. ASMC may be more resistant to the negative effects of FC than macrophages	18
8	Human Acyl-CoA: cholesterol Acyltransferase (ACAT) and its Potential as a Target for Pharmaceutical Intervention against Atherosclerosis	There are several reviews that cover various elements of ACAT and ACAT inhibitors. This paper quickly summarises what is currently known about the biochemical features of human ACATs before delving into the merits of ACAT as a therapeutic target for atherosclerosis treatment	19
9	Acyl-coenzyme A:cholesterol acyltransferases	In diverse tissues, ACATs serve a crucial role in cellular cholesterol homeostasis. In two sections, this chapter highlights current information on ACAT-related research: 1) ACAT genes and proteins as pharmacological targets for atherosclerosis and Alzheimer's disease; 2) ACAT enzymes as drug targets for atherosclerosis and Alzheimer's disease	20
10	Effect of probucol on blood cholesterol and basal and lovastatin-induced 3hydroxy-3-methylglutaryl coenzyme A reductase activity in mice	The findings raise the possibility that some patients with hypercholesterolemia may benefit from combined therapy with lovastatin plus probucol	20
11	Impact of subdermalnorgestrel on hepatic acyl-coenzyme A:cholesterol- acyltransferase	A dose-related threshold and drug-drug interaction for this effect is suggested by significantly elevated ACAT estradiol or norgestrel alone or in a lower dose combination. These findings	22

	(ACAT) activity: possible antiatherogenic effect	demonstrate that norgestrel, when applied subdermally, reduces ACAT activity significantly, suggesting that it could be used as an antiatherogenic medication	
12	Mechanism of Action of Fenofibrate: New Data	Hypercholesterolemia and its effects have been successfully controlled by inhibiting cholesterol production and esterification. As a result, utilising fenofibrate, studies were conducted on these two metabolic pathways	23
13	Recent Advances in Cancer Vaccines: An Overview	The three main factors for the development of therapeutic cancer vaccines appear to be a customised approach to stimulate immune responses, the use of chemotherapy to defeat robust malignancies, and altering objectives from tumour reduction to overall survival	24
14	ACAT Inhibition: Bad for Macrophages, Good for Smooth Muscle Cells?	Furthermore, in murine models, removing macrophage ACAT-1 is linked to an increase in atherosclerotic lesion formation. 8 Rong et al. point to SMCs as a possible explanation for the seemingly paradoxical effects of ACAT inhibition in this issue of Arteriosclerosis, Thrombosis and Vascular Biology	25
15	Identification of putative active site residues of ACAT enzymes	The tyrosine residue of the highly conserved FYXDWWN motif was found to be critical for ACAT activity through mutational research. Furthermore, Y518 was required for ACAT1 activity but not for ACAT2's comparable residue, Y496, which was not. The available evidence suggests that the amino acid requirements for ACAT activity for the two ACAT isozymes may vary	26
16	Inhibitors of Acyl CoA: Cholesterol Acyltransferase	The discovery of multiple effective inhibitors of acyl CoA: cholesterol acyltransferase was made possible by conformational limitation of previously published acyclic (diphenylethyl) diphenylacetamides (ACAT). The most powerful ACAT inhibitor discovered was cis-[2-(4-Hydroxyphenyl)-1-indanyl] diphenylacetamide (4a) (IC_{50} = 0.04 microM in an in vitro rat hepatic microsomal ACAT assay, ED50 = 0.72 mg/kg/day in cholesterol-fed hamster)	27
17	Novel 3,5-Diaryl Pyrazolines as Human Acyl-CoA: Cholesterol Acyltransferase Inhibitors	The acyl-CoA: cholesterol acyltransferase activities of a range of pyrazoline derivatives were tested. 3-(3,5-Di-tert-butyl-4-hydroxyphenyl)-5-(3,5-Di-tert-butyl-4-hydroxyphenyl)-5-(3,5-Di-ter (multi-substituted 4-hydroxyphenyl) *In-vitro* inhibitory action of -2-pyrazolines 4a-i on hACAT-1 and -2 was demonstrated	28
18	Heterocyclic compounds from *Chrysanthemum coronarium* L. and their inhibitory activity on hACAT-1, hACAT-2, and LDL-oxidation	This is the first time these chemicals have been isolated from *C. coronarium* L. Compound 1 had IC_{50} values of 0.16 mM and 0.19 mM for human Acyl-CoA: cholesterol acyltransferase (hACAT)-1 and hACAT-2, respectively. Compound 2 reduced the oxidation of low-density lipoprotein (LDL) with an IC_{50} of 7.7 M	29

CONCLUSION: The findings of this systematic literature review indicate that the heterocyclic groups were compared in terms of *in-vitro* potency against ACAT enzyme.

Our goal is a systemic ACAT inhibitor, which would be a potential antihypercholesterolemic and antiatherosclerotic agent. Positive contribution of molecular shadow descriptors suggests that molecules with bulkier substituents are more likely to improve the potency. Developed models were found to be predictive as evidenced from their internal and external cross-validation statistics.

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CONFLICT OF INTEREST: The author declares there is no conflict of interest.

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