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LIVER TARGETED STEAROYL-COA DESATURASE (SCD 1) INHIBITORS FOR DIABETES AND HYPERLIPIDEMIA

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Keywords:
Dyslipidemia, Lipogenesis, OATP, SREBP, The meibomian glands

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ABSTRACT

Stearoyl CoA Desaturase (SCD1) is a promising therapeutic target for the chronic treatment of metabolic disorder specifically diabetes and hyperlipidemia. The SCD1 enzyme is expressed at high levels in several human tissues and is required for the biosynthesis of monounsaturated fatty acids which are involved in many biological processes. Liver-targeted SCD inhibitors were designed to pharmacologically manipulate SCD1 activity in the liver by using OATP (organic anion transporting polypeptides) to avoid the skin and eye tissues associated adverse events.

INTRODUCTION

In the world, developed countries are now facing increased prevalence of the metabolic syndrome, which represents a collection of symptoms including insulin resistance, hyperlipidemia, hypertriglyceridemia, and low high-density lipoprotein cholesterol (HDL-C) levels [1]. Hyperlipidemia, hyperlipoproteinemia, is the condition of abnormally elevated levels of any or all lipids and/or lipoproteins in the blood. Stearoyl CoA Desaturase takes major role in hyperlipidemia. SCD 1 inhibits production of triglycerides and cholesterol. And also decrease blood glucose level, so it is used as antidiabetic and antihyperlipidemic. Stearoyl CoA Desaturase 1 (SCD1) is a microsomal iron containing enzyme that catalyzes the rate-limiting step in the biosynthesis of monounsaturated fatty acids from saturated fatty acids that are either synthesized *de novo* or derived from diet, in conjunction with cytochrome b_5 reductase, cytochrome b_5, and the cofactors NADH. SCD1 is responsible for the formation of a *cis* double bond at the Δ9-position of palmitoyl and stearoyl CoA to generate palmitoleic and oleic acids, the main substrates in triglycerides, cholesterol esters, phospholipids, wax esters and alkyldiacyglygerols [2] (Fig.1).

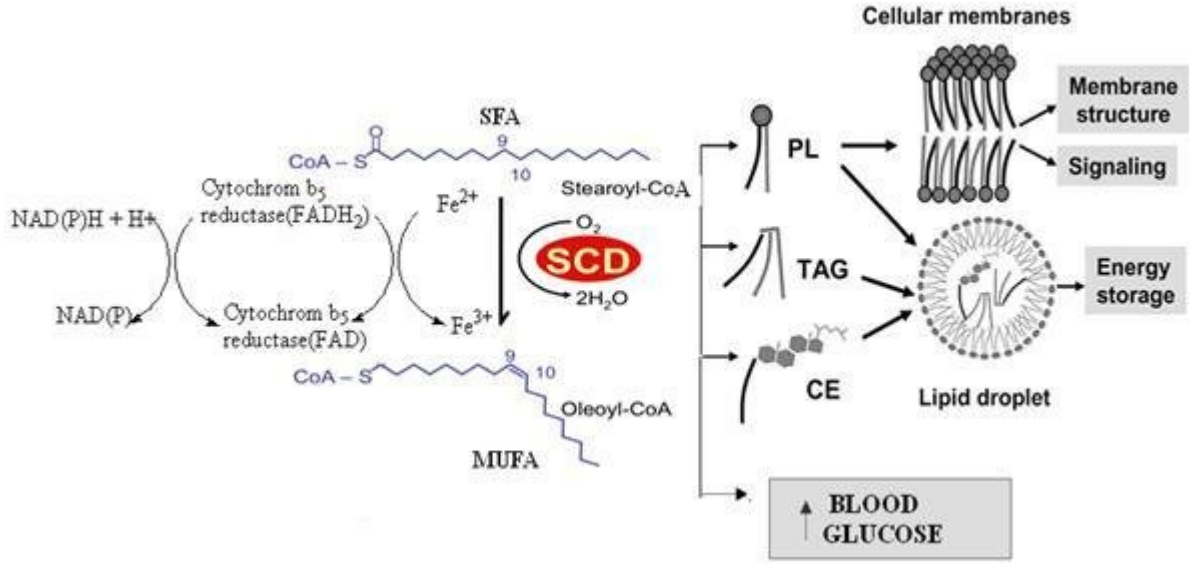


Fig.1:- **Mechanism of stearoyl CoA desaturase** .Regulation of MUFA/SFA balance in mammalian cell lipids by SCD1. CE, cholesterol esters; PL, phospholipids; TAG, triacylglycerols [6].

SCD1 activity can be measured from the ratio of SCD1 products over substrates. In the literature, this ratio is generally referred as the desaturation index [3].

Although SCD1 is ubiquitously expressed, it is predominant in liver and adipose tissues. These tissues are the principal sites of *de novo* lipogenesis as they have a high capacity to convert carbohydrate into fatty acids when glycolytic and lipogenic enzymes are induced and activated. Thus, it is postulated that the inhibition of SCD1 should reduce lipid synthesis and storage which would be beneficial for the treatment of obesity, diabetes and dyslipidemia. SCD1 inhibitor also improves glucose tolerance, which may be explained by enhanced insulin sensitivity in the liver [4], adipose tissue [5], and skeletal muscle. There are four SCD isoforms (SCD1, SCD2, SCD3, and SCD4) are present in rodents. All of which reside exclusively in the endoplasmic reticulum compartment of the cell. SCD1 is mainly expressed in liver, adipose tissue, and sebaceous glands. SCD2 is ubiquitously expressed in brain. SCD3 is restricted to skin. SCD4 is mainly expressed in the heart. SCD1, a main SCD variant found in all mammalians including humans, is present in most tissues and cells, with the highest expression displayed in brain, liver, heart and lung adipose tissue, and sebaceous glands. Human tissues contain two SCD variants, SCD1 and SCD5. SCD1 expression is remarkably sensitive to a myriad of nutrients, including carbohydrates, fatty acids, and cholesterol, and is regulated by a great number of hormones and growth factors[7]. SCD5, a recently discovered human SCD which is also present in chicken, pigs and bovines. Expression of SCD5 is higher in embryo tissues and in adult human brain and pancreas; its biological function, however, remains largely uncharacterized [8].

SCD1 contains four *trans* membrane domains with both the NH_2 and COOH termini oriented toward the cytosol. The single cytoplasmic loop and the COOH terminus contain the eight histidine (His) residues known to form the His box, which binds iron within the catalytic center of the desaturase (Fig.2). The two ER luminal loops are relatively small compared with the cytosolic loop, which houses two of the three conserved His motifs. Purified SCD-1 migrates as a 37-kDa band on SDS PAGE with the His segments located at positions 119, 156, and 296.

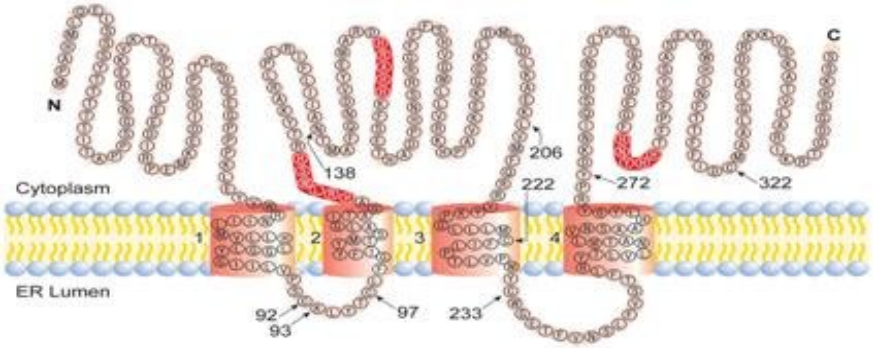


Fig.2:- Proposed model for the membrane topology of mouse SCD-1[9]

The highlighted residues represented the conserved histidine regions, which are catalytically essential. N and C represent NH_2 and COOH termini, respectively. The 5 cysteines in SCD-1 are located at residues 92, 97, 222, 233, and 322. ER, endoplasmic reticulum [10].

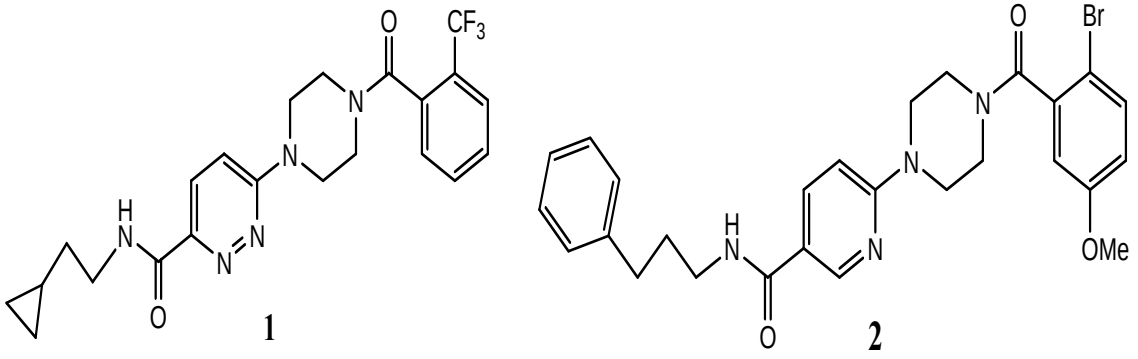
These regions are expected to be necessary to provide ligands for non heme iron within the catalytic site of the enzyme.

HISTORY OF STEAROYL COA DESATURASE 1 INHIBITORS

Despite the fact that SCD1 has been known since 1970s, the development of SCD1 inhibitors is a very recent phenomenon, largely following the further understanding of SCD1 biological function in rodents and humans. Before then, there have been scattered reports on natural product based SCD1 inhibitors, including 9-thiastearic acid, cyclopropenoid fatty acids [11], and certain conjugatedlinoleic acid isomers. These reagents are believed to inhibit SCD enzyme activity and reduce the abundance of SCD1 mRNA. Unfortunately, these SCD inhibitors are not useful at reasonable physiological doses, nor are they specific inhibitors of SCD1 biological activity, as they also inhibit other desaturases and enzymes.

The first series of SCD1 inhibitors using molecular target approach was disclosed by Xenon Pharmaceuticals in 2005[12]. The basic molecular scaffold exemplified by these compounds is the central pyridazine (1) pyridine (2) substituted by functionalized piperazine, benzamide on the one end, and a carboxamide on the other end [13].

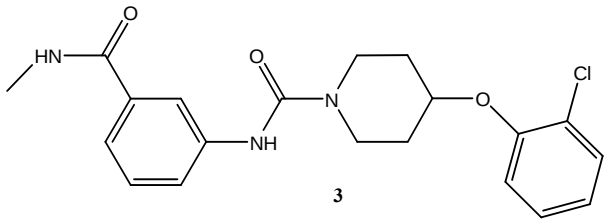
Abbott scientists disclosed studies interrogating their lead SCD1 inhibitors in diabetic and obese rodent models. At the Chicago ACS National Meeting in March 2007, the profiles of compound 3 in an efficacy study in DIO mice were reported [3].



mSCD1 IC50=100 µM (US2005/0119251)

Fig.3:- First potent and specific SCD1 inhibitors reported

In ADA scientific session in Chicago 2007, a poster discussed the effect of compound **3** in high fat (HF) fed diabetic female ZDF rats (Male Zucker diabetic Fatty rats) [14]. These animals were dosed for 3 weeks with compound. Body weights (BW), food consumption (FC), and plasma glucose were measured weekly.



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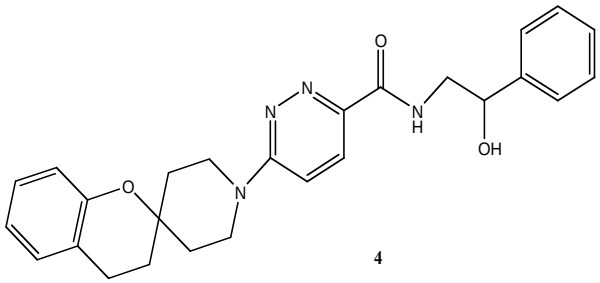
At the end of the study an insulin tolerance test was performed and fasting lipid profile was assessed. Compound 3 at 10 mg/kg caused a significant reduction in BW gain compared to vehicle (15.2±1.7 vs. 26.2±3.0 g respectively, $P<0.05$) with no change in FC. This dose had no effect on plasma or liver triglycerides, plasma cholesterol or insulin sensitivity (IS).

Additionally, progressive cranial alopecia, especially around the eyes, was observed in this group starting at 1 week of dosing. Histology performed on affected skin revealed atrophic sebaceous, epidermal hyperplasia, and dermal inflammation, as have been reported. These data, which demonstrate limited metabolic efficacy at doses that also cause mechanism-based changes in skin morphology, suggest limited potential for systemic SCD1 inhibitors in the treatment of metabolic disorders. Daiichi Sankyo also published a series of spiropiperidine derivatives 4 as SCD1 inhibitors in 2008[15].



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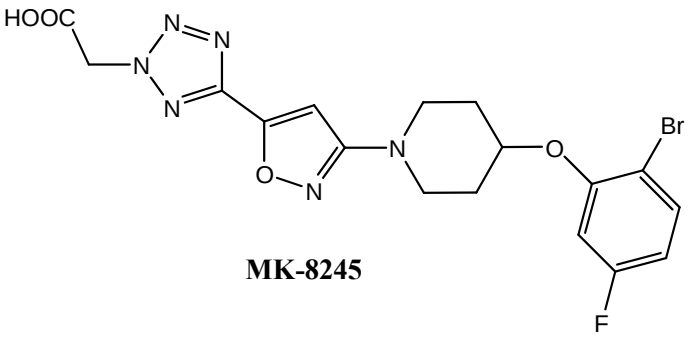
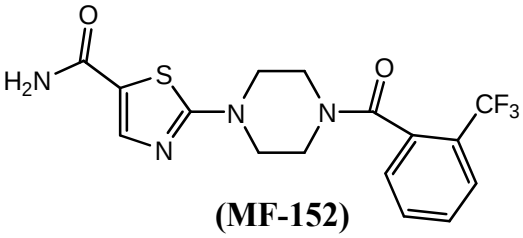
Finally in March 2011, introduce compound MK-8245 by Merck Frosst Centre for Therapeutic Research, Canada.

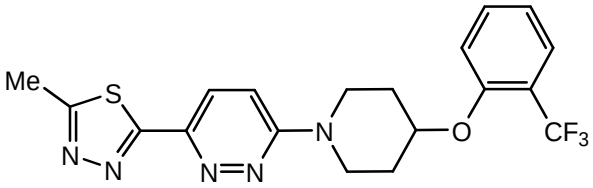
MK-8245 for the chronic treatment of diabetes and dyslipidemia has been limited by preclinical adverse events associated with inhibition of SCD in skin and eye tissues. To establish a therapeutic window, they embarked on designing liver-targeted SCD inhibitors by utilizing molecular recognition by *liver-specific organic anion transporting polypeptides (OATPs)* [16].



MK-8245



(MF-152)



(MF-438)

Another more potent compound synthesis by Merk Frost Centre for Therapeutic Research, Canada. Modification of MF-438. In October, 2011 and MF-152 in November, 2011 which gives good activity.

ROLE OF SCD1 IN LIPID BIOSYNTHESIS

It converts saturate fatty acid (SFA) to monounsaturated fatty acid (MUFA) which is responsible for increase level of triglyceride, cholesterol ester and VLDL (very large density lipoprotein). But when SCD1 inhibitors use, stop conversation of fatty acid and not create abnormal amount of lipoproteins and cholesterol**.** In the presence of SCD1, hepatic saturated fatty acids (SFA) are converted into monounsaturated fatty acids, which increase desaturase index (16:1/18:1), *sterol regulatory element-binding protein (SREBP) 1c* maturation, lipogenesis, and TG/CE synthesis. In the absence of SCD1 (SCD1-/-), the inability to desaturate hepatic SFA leads to an inability to up regulate *de novo* lipogenesis via SREBP 1c and storage as TG. Therefore, oxidation and uncoupling (not shown) increase to decrease TG and VLDL. On this way decrease synthesis of lipoproteins.

ROLE OF SCD1 IN DIABETES:-

Stearoyl CoA Desaturase increase blood glucose level and insulin résistance, when inhibitors inhibit process so improvement in insulin sensitivity. SCD1 inhibitors can use in treatment of type II diabetes.

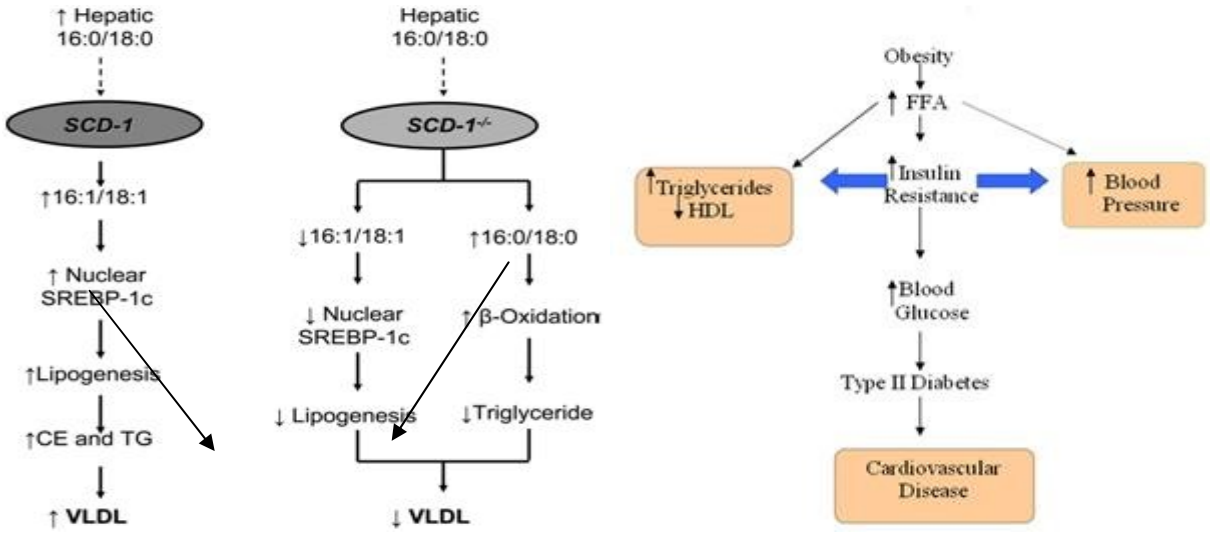


Fig.4 Role of SCD 1 in lipid biosynthesis and diabetes [18]

LIVER TARGETED STEAROYL COA DESATURASE 1 INHIBITORS

Need of Liver Targeted Stearoyl CoA Desaturase 1 Inhibitors

Inhibition of the Stearoyl CoA Desaturase 1 in mouse not only causes obesity resistance, but also severe skin and eyelid phenotypes, including alopecia, narrow eye fissure, and ptosis. This is related to the reduced production of TAG, cholesterol ester, and wax ester, increased free cholesterol in the sebaceous gland in the skin, and reduced production of meibum from the meibomian glands. Increased free cholesterol in those glands has been observed, which may contribute to the atrophy of the sebaceous and meibomian glands through cell death and atrophy. SCD inhibition in the eye lubricating Harderian glands and skin leads to reduced levels of SCD derived lipids present in the tears and skin/sebaceous glands which may be essential for eye lubrication and healthy skin. Therefore, initially hypothesized that selectively targeting the liver (where the SCD enzyme is mainly expressed), would lead to efficient inhibitors with reduced eye and skin adverse events. Indeed, this supposition was confirmed by the design of the liver-targeted SCD inhibitor MK-8245. Unfortunately, in addition to the beneficial metabolic effects observed upon SCD inhibition, chronic preclinical treatment can lead to skin and eye aberrations. These adverse events have been linked to mechanism-based depletion of essential lubricating lipids within these tissues. A paramount challenge in the development of SCD inhibitors for therapeutic application in humans is the attainment of efficacy without adversely affecting skin and eye function. To target a pharmaceutical agent to the liver, the following approaches have been studied.

(i) Nanoparticles to deliver incorporated therapeutic materials such as small molecules, proteins, genes, and siRNAs,

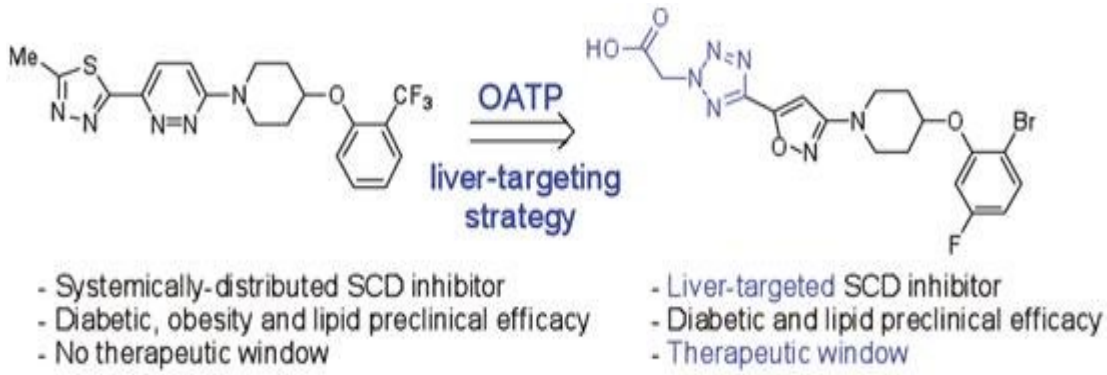
(ii) Hep Direct Cytochrome P450 activated prodrugs of certain small molecules such as nucleotides, and

(iii)Utilization of liver-pecific transport proteins. Described herein will be the strategy used to design liver-targeting SCD inhibitors and how this approach resulted in the discovery of the lead compound MK-8245, which maintains preclinical pharmacological efficacy while significantly improving the therapeutic window compared to systemically distributed SCD inhibitors[6],[21].

Liver targeted Stearoyl CoA Desaturase 1 inhibitors by using OATP (organic anion transporting polypeptides)

Recognizing that *de novo* lipogenesis occurs primarily in the liver and the liver is the organ where the SCD1 enzyme is most highly expressed, the Merck Frosst team embarked on a program to design a liver targeted, small-molecule SCD inhibitor. These efforts were recently disseminated with the disclosure of the liver-targeted SCD inhibitor MK-8245. Gratifyingly, MK-8245 demonstrates preclinical anti-diabetic and liver lipid efficacy in the absence of skin or eye adverse events in chronic dosing studies. The strategy employed in the design of MK-8245 centers on increasing transport into hepatocyte via molecular recognition by *liver-specific organic anion transporting polypeptides (OATPs) (*fig.5).

An **organic-anion-transport polypeptide** (OATP) is a membrane transport protein that mediates the transport of organic anions across the cell membrane. Organic anion-transporting proteins belong to the solute carrier family, more specific, and subfamily 21 (organic anion transporting).Organic anion transporters may carry bile acids as well as bilirubin over basolateral membrane (facing sinusoids) in hepatocytes, as well as other anions for excretion in bile.



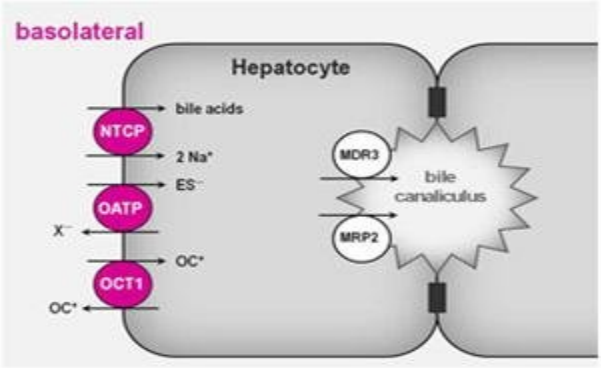


Fig.5:-Organic-anion-transport-polypeptide (OATP) membrane

A second critical component is to minimize exposures in off-target tissues and cells associated with adverse events (skin and eye) by decreasing the extent of passive cell diffusion.In general, carboxylic acids are preferred substrates for OATPs, however, only a few known acid containingmolecules have been confirmed as demonstrating OATP mediated transport.

The key structural element present in MK-8245 which imparts OATP transport is a tetrazole acetic acid moiety. Herein we describe the use of a similar liver-targeting strategy which employs a differential and unique OATP recognition moiety [16].

Strategy to Design a Liver-Targeted SCD Inhibitor

The Goal of design a Liver-Targeted SCD inhibitor was to increase drug exposure in liver (target organ) by engaging active transport into heptocytes via the liver-specific organic anion transporting polypeptides (OATPs).Our goal was to incorporate key transporting elements into SCD inhibitors to enable recognition by the OATP transport proteins while maintaining SCD potency. Moreover, we also sought to decrease the extent of unselective passive cell diffusion in order to minimize exposures in off-target tissues and cells (skin and eye). Fortunately, polar and acidic moieties used to engage the active transporters generally impart reduced passive cell penetration. Nonetheless, required a research operating procedure (ROP) that would allow us to funnel potential compounds and help us identify compounds which may exhibit a liver targeting tissue distribution profile. The ROP to select for liver-targeted SCD inhibitors is depicted in Figure and can be summarized as follows. (i) Determine if compounds are SCD inhibitors via an *in vitro* rat microsomal enzyme assay, (ii) Test active SCD inhibitors in two cell assays, one devoid of active OATPs (HepG2 cell line) and one containing functional, active OATPs (rat hepatocyte), (iii) Conduct mouse tissue distribution studies on those compounds which are at least 4 to 5 fold more potent in the OATP vs non OATP cell assays.

The first task was to determine where an acidic moiety could be appended onto existing SCD inhibitors to impart recognition by OATPs, decrease passive cell diffusion while at the same time maintaining SCD potency. Starting with SCD inhibitor MF-438 **1**acidic moieties were placed on either the right- or left-hand side of the molecule. It became evident that acidic moieties were only tolerated on the left hand side of the molecule **2**, appendage of acids on the right hand side produced compounds completely devoid of SCD inhibition **3.**

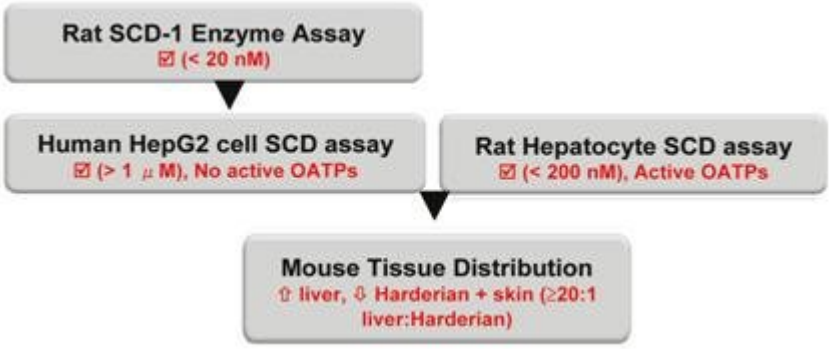


Fig.6:- Strategy to identify liver-targeting SCD inhibitors.

HepG2 cell SCD assay is a gauge of the extent of passive cell diffusion; rat hepatocyte SCD assay identifies compounds which are actively transported into the liver; mouse tissue distribution is a measure of the extent of liver-targeting.

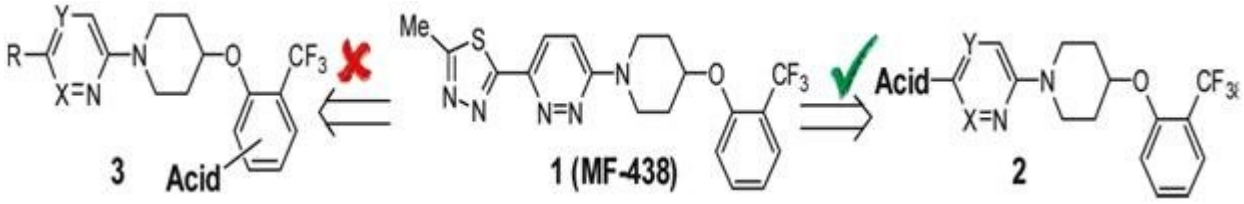


Fig.7:- Chemical structure of systemically distributed 1

Compounds of general structures 2 and 3 were assessed for potency vs the rat microsomal SCD1 enzyme.20 Compounds of general structure 2 inhibited the rat SCD1 enzyme (IC50s < 1 μM), whereas compounds of general structure 3 were inactive vs rat SCD1 (IC50s > 10 μM).

Liver Targeted Tissue Distribution Profile

To determine if strategy to select compounds based on their shift in the HepG2 vs hepatocyte assays resulted in compounds which exhibit a liver-targeted tissue distribution profile, the inhibitors were dosed in mice and 6 h post dose the animals were euthanized and the concentration of compound in select tissues (plasma, liver, skin, and the eye-lubricating Harderian glands) was measured. The liver to Harderian gland ratio was used as a measure of the

degree of liver-targeting.The initial strategy employed in the design of liver-selective compounds centers on exploring the addition of polar acidic moieties which are recognized by organic anionic transporters (OATPs), such as tetrazoles or carboxylic acids, on SCD inhibitors to obtain the desired in vivo properties: a high liver concentration (target organ for efficacy) and a low systemic concentration to minimize exposures in off-target tissues and cells associated with adverse events (skin and eye).In addition to generating OATP substrate affinity, liver targeting strategy required the minimization of passive cell diffusion to prevent the penetration of any circulating SCD inhibitor to off-target tissues.MK-8245 was distributed mainly to the liver, with low exposure in tissues associated with potential adverse events (i.e.,skin,eye lubricating glands).

Pharmacological Efficacy of the Liver Targeted SCD Inhibitor:-

To assess the diabetic efficacy, lipid efficacy, and safety profile of a systemically distributed vs. liver-targeted SCD inhibitor, the following models were used

(i) Acute oral glucose tolerance in DIO mice (oGTT) to assess glucose clearance

(ii) Chronic administration in DIO mice to assess body weight effects and lipid profile as well as evaluating the adverse event profiles in skin and eyes [16].

Structural requirement for SCD 1 inhibitors:-

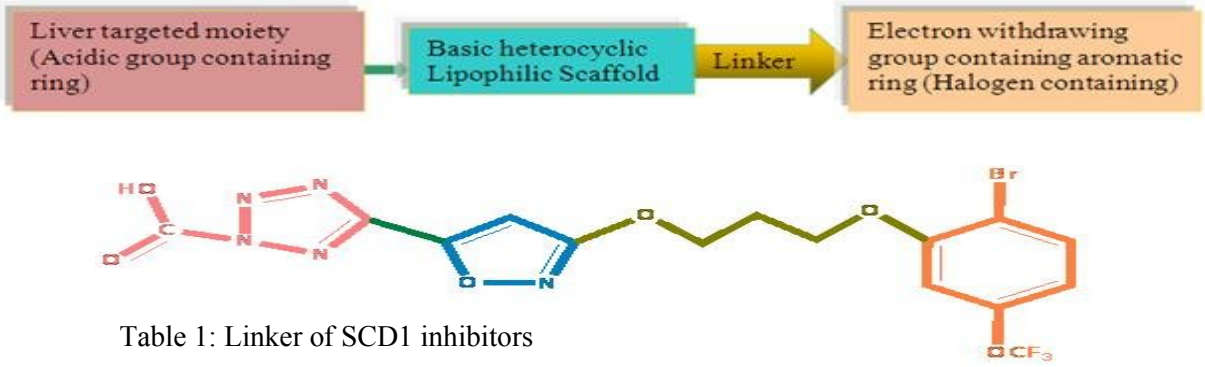


Table 1: Linker of SCD1 inhibitors

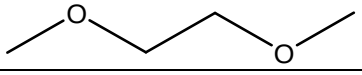
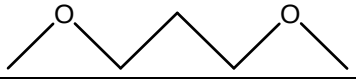
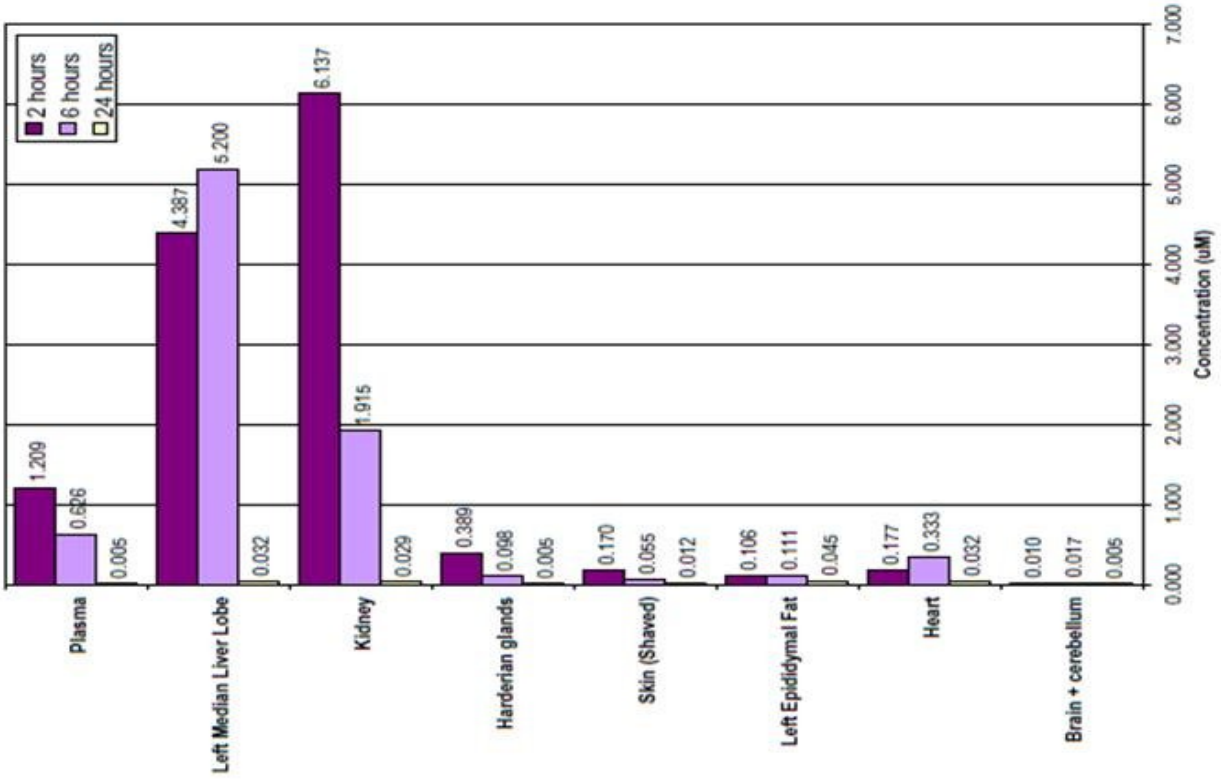
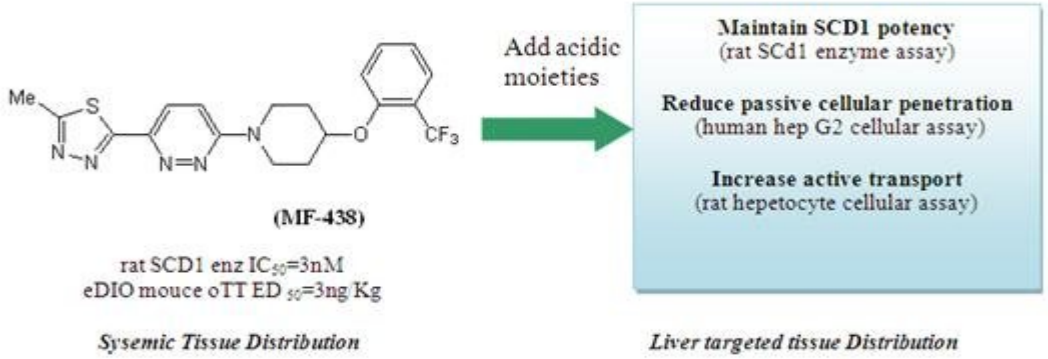
Sr.No	LINKER
1.	-O-(ether)
2.	-CONH-(amide)
3.	-CO-(ketone)
4.	
5.	
6.	

Fig.8:- Structural requirement for Liver targeted Stearoyl Coa Desaturase Inhibitors [19]

Examples of Liver targeted SCD Inhibitors

Recently find out Nicotinic acids: Liver-targeted SCD inhibitors with preclinical anti-diabetic efficacy:- Structural variations in the acid moiety or adjacent heterocycles can have a significant impact on tissue-distribution profiles. Overall, the demonstrated molecular recognition of the nicotinic acid and the confirmed liver-targeted tissue distribution profile in mice serves to depend the understanding of known chemical entities for OATP-mediated transport and liver-targeted delivery. Tissue distribution of nicotinic acid show in fig.9. Nicotinic acid derivatives efficacious in improving glucose clearance in a mouse model. So, it gives antidiabetes activity.





Sysemic Tissue Distribution *Liver targeted tissue Distribution*

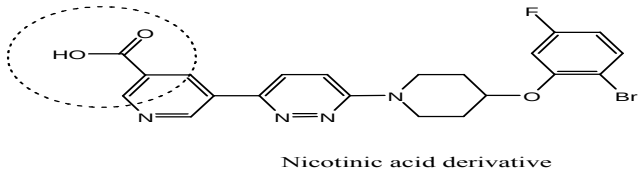


Fig.9:- Liver targeted Nicotonic acid SCD inhibitor: Tissue-distribution profile of nicotinic acid derivative in C57/BL6 mice. Compound10 was administered orally in 1% Methocel (30 mg/kg, 10 mL/kg) and 2, 6 or 24 h post dose, mice were sacrificed, tissues were harvested and drug concentrations were determined by LC–MS analysis using an internal standard, n = 3 mice per time point[20]. Conversion of systemically-distributed triazole-based stearoyl CoAdesaturase (SCD) uHTS hits into liver-targeted SCD inhibitors[17]. During an ultra high throughput screening (uHTS) campaign identified a structurally distinct class of potent SCD inhibitors.To avoid potential eye and skin adverse events, it was converted the systemically distributed triazole-based compound into liver targeting inhibitors by the incorporation of a tetrazole acetic acid moiety and a pyridine linker. Further modifications of the middle ring linker allowed to modulate in vitro (increased potency) and in vivo (increased liver exposure) properties and generated isoxazole, a potent liver selective SCD inhibitor (Fig.10). Unfortunately, despite the good liver selectivity and drug exposure, no significant in vivo inhibition was observed. Further studies are underway to identify more efficient and potent liver-targeting inhibitors of SCD.

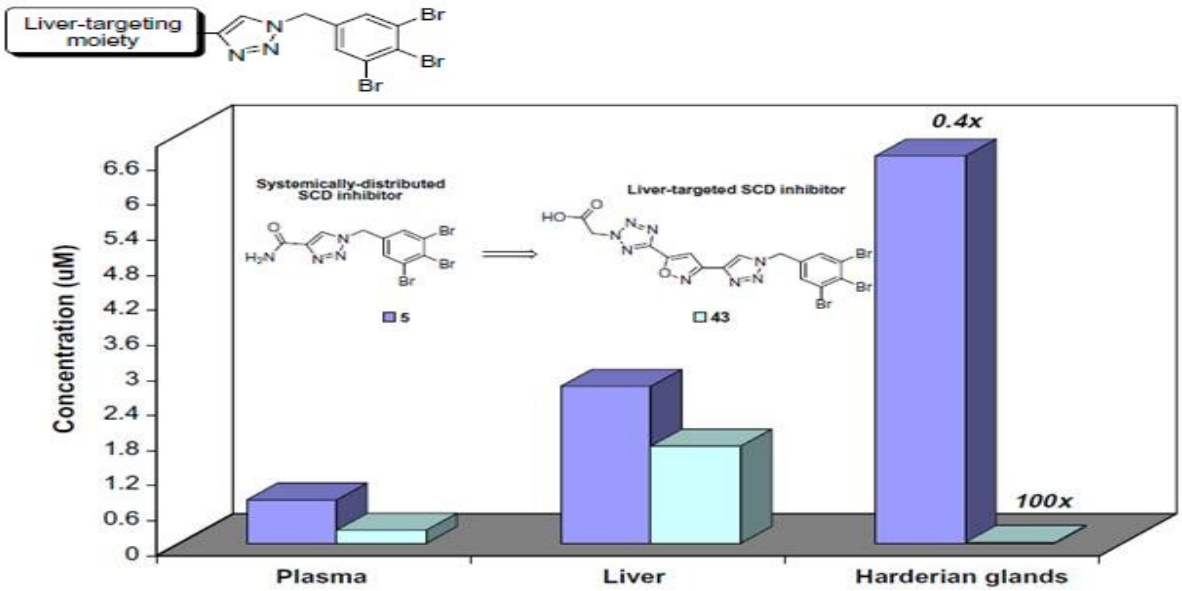


Fig.10:- **SCD1 inhibitors from systemic lead to liver-targeted inhibitor**

PHARMACOLOGICAL EVALUATION OF SCD INHIBITORS

Rat SCD Hepatocyte Assay:-

Male Sprague Dawley rats were fed a high carbohydrate diet (Ren's Feed & Supplies Ltd. no. 7576) for 2 days to obtain SCD1 induced liver (175-200 g). Rat hepatocytes were isolated by collagenase perfusion. Cells were plated, 100 µL of 4 $x10^6$ cells/mL cells per well on a 96 well plate (NUNC). Then 1.2 µL of compound was added to each well and incubated for 15 min at 37°C/5 $\%CO_2$. Then 20 µL of ^{14}C-stearic acid (final concentration 0.5 µCi/ml) was added and incubated for 1 h, shaking in an Eppendorf shaker set at 400 rpm with 37°C/5 $\%CO_2$. Hepatocytes were spun down and washed three times with PBS buffer to remove the tracer in medium. Complete hydrolysis was done by incubation at 75°C for 1 h with 2N NaOH. Cell lysate was acidified with phosphoric acid and then the lipids were extracted with acetonitrile. The quantification of the resulting radiolabeled oleic acid and stearic acid in the final organic phase was done by HPLC, using a C18 reverse phase column (Zorbax extended C18 (4.6 mm x 75 mm), eluting with a 3% water (0.1% formic acid)/ acetonitrile to 100%. Acetonitrile gradient (0.1% formic acid) at a flow rate of 2 mL/min in 4 min, detection via a Packard Flow scintillation analyzer.

Tissue Distribution Analysis Method

Compound was administered orally to fed C57BL6 mice (n = 2), male Sprague Dawley rats (n = 3), female rhesus monkeys (n = 2), or fasted male beagle dogs (n =2) using 0.5% methylcellulose as vehicle and 6 h post dose, the animals were sacrificed, tissues were harvested, and the concentration of compound in tissues was analyzed following the procedure outlined below. For Mice and Rats. Requested tissues (less than 0.2 g) were weighed and put in a blue 96-well plate for tissues (strips of 12, attached, 1.1 mL microtubes in microracks from National Scientific Supply Co.) and frozen at 78 °C. Tissues were thawed and diluted with 3.5 volumes of a 2.5:1 MeCN: H_2O mixture containing internal standard. To this mixture was added 125-150 mg of silicon carbide chips and a small (4 mm) stainless steel bead (bead must be added to the 96-well plate prior to the addition of the tissue). The 96 well plate was capped (Marsh bio plug caps, polyethylene for microtubes, strips of 12) and shaken at 1500-1700 strokes per min using a GenoGrinder for 20 min. The plate was then centrifuged for 15 min and the supernatant was transferred to a mass spec vial and the concentration of compound was determined by LC-MS. Quantification involved the preparation of a standard curve using blank plasma instead of tissue (i.e., 10 µL of blank plasma +10 µL of MeCN (with internal standard) containing different concentrations of compound + 10 µL of water + 15 µL of MeCN (with

internal standard). Because of the small size of mouse Harderian glands (i.e., 10 mg/gland), a similar procedure was used, except 2 volumes of water and 4 volumes of acetonitrile were added to the well containing the Harderian gland (final concentration was adjusted based on increased initial dilution).

For skin, tissue homogenization was not performed with the GenoGrinder. Instead, to an 8 mL vial containing a weighed piece of shaved skin was added 3.5 volumes of a 2.5:1 MeCN:H_2O mixture containing internal standard. The skin was then homogenized using a tissue tearor from Biospec Products Inc., followed by centrifugation and analysis as above.

GTT Study in DIO Mice with compound.

Male C57/Bl6 mice were fed a high fat diet (Bio-Serv F3283) for at least 14 weeks starting at 6 weeks of age. The obese mice were fasted for 16 h, and the SCD inhibitors were given orally to DIO mice 1 h before administration of oral glucose (2 g/kg). Blood glucose levels were monitored at t = -60 min, 0 min, 20 min, 40 min, 60 and 120 min post glucose challenge[16].

SCD 1 INHIBITOR IN DRUG DEVLOPMENT:-

GRC 9332 GRC 9332 a Stearoyl CoA Desaturase-1 (SCD-1) inhibitor is Glenmark's the lead candidate for obesity and dyslipidemia. GRC 9332 is currently under pre- clinical development stage and is expected to enter clinics by Q3 FY09. The Company targets launching the molecule in 2013 and aims to be an early launcher in this class.

CONCLUSION

In this review, a liver-targeting strategy was successfully implemented which resulted in the discovery of potent, liver-targeted SCD inhibitor with excellent in vitro and preclinical in vivo efficacy. Systemically distributed Stearoyl CoA Desaturase inhibiters were used in obesity, diabetes like metabolic disorders, But it was produce some severe skin and eyelid phenotypes, including alopecia, narrow eye fissure, ptosis. This is related to the reduced production of TAG, cholesterol ester, and wax ester, increased free cholesterol in the sebaceous gland in the skin, and reduced production of meibum from the meibomian glands. So, Merck Frosst Therapeutic Research Centre introduces firs time New Liver Targeted Stearoyl CoA Desaturase 1 inhibitor by using OATP (organic anion-transporting polypeptide)**.** Liver targeting OATP approaches have been used to improve the therapeutic window of pharmaceutical agents such as statins, to the best of our knowledge. Liver-targeting SCD 1 inhibitor to demonstrate maximal liver SCD inhibition while sparing inhibition in the skin and eye tissues associated with adverse events. This ultimately resulted in an improved safety profile for the liver-targeted SCD1-inhibitor.

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