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An insight into advances and challenges in the development of potential stearoyl Co-A desaturase 1 inhibitors

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Stearoyl-CoA desaturase 1 (SCD1) is one of the key enzymes involved in lipid metabolism, plays a vital role in the synthesis of monounsaturated fatty acids (MUFAs) from saturated fatty acids (SFAs). Due to its promising therapeutic potential in treating metabolic disorders, cancers, and skin diseases there is an increasing interest in the development of novel inhibitors against SCD1. This review comprehensively explores the evolution of potential SCD1 inhibitors, focusing on systemic and liver-targeted inhibitors and discusses their structure–activity relationship (SAR) pattern. Among the various small molecules reported, natural products like sterculic acid have emerged as significant SCD1 inhibitors, highlighting the potential of naturally derived compounds in therapeutic development. This review also addresses the challenges in optimizing pharmacokinetic properties and reducing adverse effects, providing insights into the future directions for the development of potential novel SCD1 inhibitors with maximum therapeutic effect and minimum side effects.

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1. Introduction

The ongoing search for safe and effective synthetic inhibitors that target SCD1 has been diligently documented over the past decades by an abundance of scientific literature from more than a dozen university and industrial research organisations. Pioneering research highlighting SCD1 being a potential

therapeutic target for treating metabolic illnesses prompted this far-reaching venture into the field of chemistry. Although significant progress has been achieved in the identification of potent inhibitors across a range of scaffolds, converting these findings into effective clinical development has proven to be extremely difficult. A partial understanding of the complex biology associated with SCD1 and mechanism-based adverse effects that limit treatment efficacy are among the factors contributing to the obstacles to clinical success.¹

The focus of recent research efforts has switched to the creation of SCD1 inhibitors that are selective for certain tissues, especially the liver. This strategy is justified by the expectation of increased safety margins regarding mechanism-based side

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effects seen in animal models. Though they appear safe, these novel compounds have not yet overcome the basic obstacles that come with understanding and treating the intricacies of SCD1 biology. A paradigm change has occurred because of the difficulties in developing effective oral treatments for metabolic illnesses, with a growing focus on the assessment of SCD1 inhibitors in alternative indications.²

The goal of this review of literature is to give a thorough investigation of the structural variety and development of various scaffolds as SCD1 inhibitors, since the first drug-like SCD1 inhibitors were published in the year 2005. The following sections will describe the techniques that have been used as well as the progress that has been made in the ongoing search for new compounds that target SCD1.

Within the lipid homeostasis paradigm, SCD becomes an important participant, with complex interplay between synthesis of fatty acids or lipogenesis and fatty acid metabolism or lipolysis, affecting signalling, cellular and tissue architecture as well as energy storage.^{3–5} Situated mostly in the endoplasmic reticulum (ER) of the cell, the SCD enzyme selects and reorganises the *cis*-double bond formation between carbon 9 and 10 in saturated fatty acyl coenzyme-A esters in both regio and stereospecific manner.⁶ Palmitoyl-CoA (C16:0) and stearoyl-CoA (C18:0), the major substrates were converted into their respective MUFAs, oleoyl-CoA (C16:1) and palmitoleoyl-CoA (C16:1) (C18:1).⁷

These MUFAs were considered as necessary building blocks of membrane components – phospholipids, cholesterol esters and triglycerides. The highly regulated activity of the SCD enzyme is reliant on iron and co-factors, including cytochrome-b5, nicotinamide adenine dinucleotide (NADH), and flavoprotein cytochrome-b5 reductase.⁸

The primary human SCD isoform is called hSCD1, but hSCD5, a second SCD gene with possible developmental and

protective functions, has also been identified but not been fully explored.^{9,10}

Notwithstanding the difficulties associated with SCD1 biology, the fact that SCD1 is widely expressed in humans—especially in the liver and adipose tissues—has prompted significant efforts to create small-molecule SCD inhibitors as potential treatments for metabolic diseases.^{11,12} This is corroborated by two clinical trials in patients with non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD), which showed that Aramchol (Fig. 1A), a partial hepatic SCD1 inhibitor, significantly improved fibrosis, decreased steatohepatitis and reduced liver fat content without causing appreciable adverse drug reactions.^{13,14} Furthermore, Aramchol showed a decrease in collagen 1 (Col1 α 1) expression and secretion *via* decreasing SCD1 expression and boosting peroxisome proliferator-activated receptor γ (PPAR- γ) in hepatic stellate cells (HSCs) in mechanistic research using primary human hepatocytes. It thereby produced an anti-fibrotic effect in people with NASH.¹⁵

In pre-clinical studies, small molecules have shown persistent suppression of SCD to be linked to side effects include baldness, squinting and dry eyes. These occurrences, which are thought to be mechanism-based, highlight a crucial difficulty in creating safe, well-tolerated SCD inhibitors for use in treating humans: striking a compromise between efficacy and a large enough therapeutic margin. Suppression of SCD1 may also trigger inflammation due to accumulation of saturated fatty acids. This may be overcome by co-administration of long chain essential fatty acids.¹²

It is crucial that we critically analyse the structural variety, evolutionary history, and prospective uses of SCD1 inhibitors outside metabolic illnesses as we make our way through the complex world of these drugs. The complex relationship that exists between the onset of metabolic diseases and lipid dysregulation highlights the therapeutic target SCD1's ongoing



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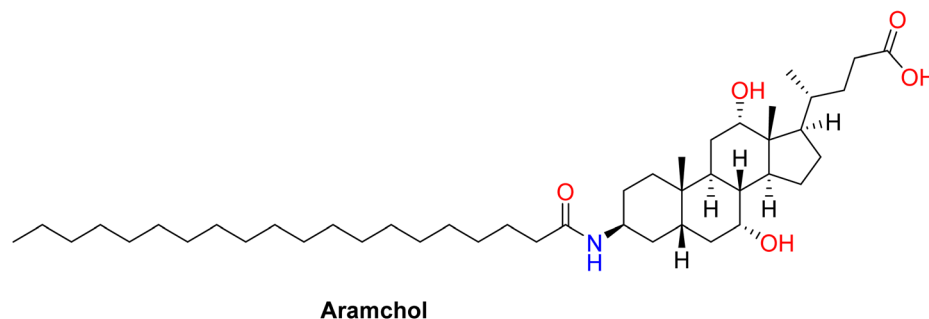
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development of non-nucleoside reverse transcriptase inhibitors for combating opportunistic infections like HIV, TB, Malaria, Leishmaniasis as well as addressing rare disorders such as Sickle Cell Disease, Gaucher's disease and lifestyle disorders such as Obesity, NAFLD and NASH.



A)



B)

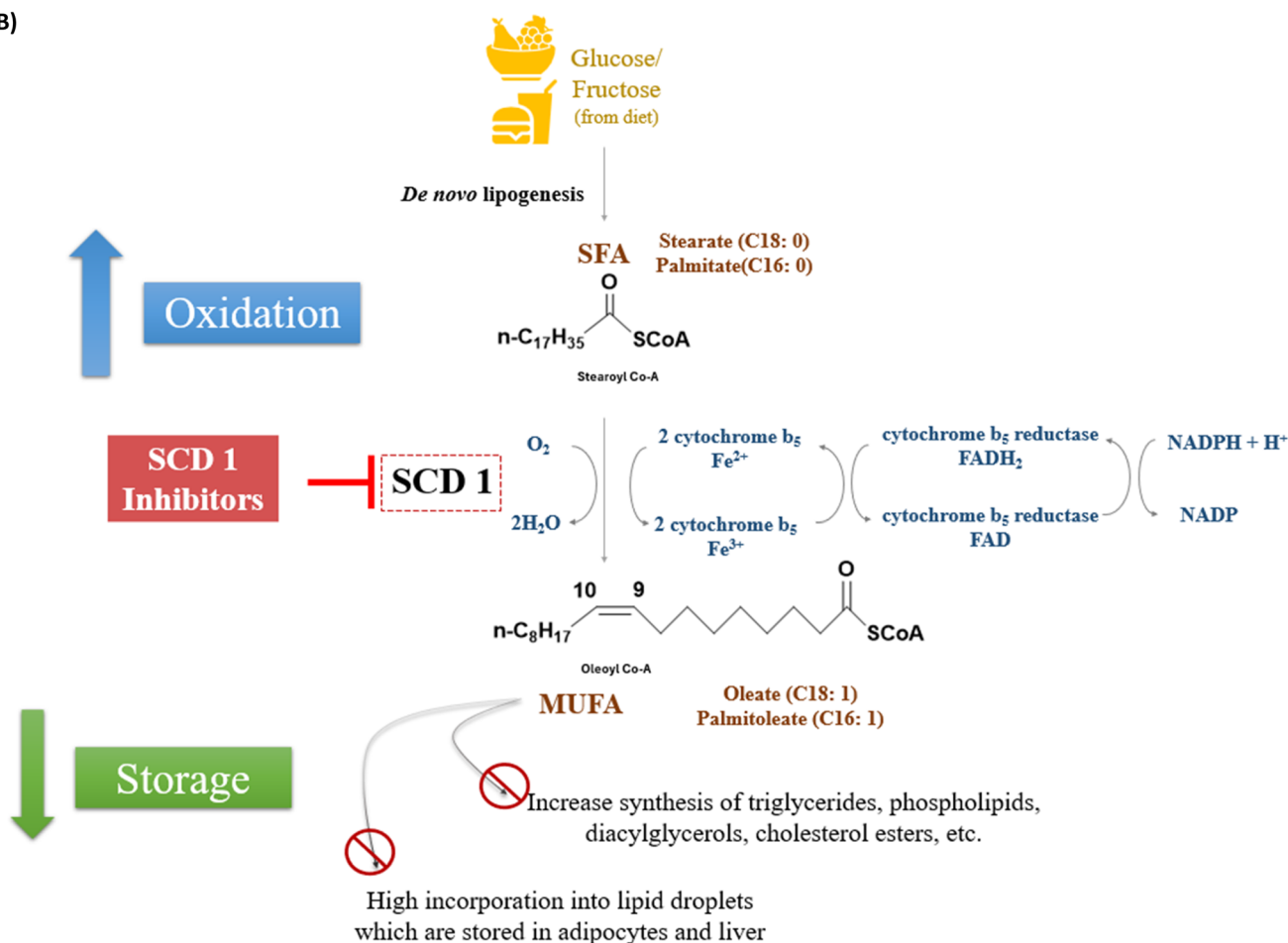


Fig. 1 (A) Structure of Aramchol (B) SCD1 converts saturated fatty acids (SFAs) to monounsaturated fatty acids (MUFAs), inhibiting SCD1 results in decreased incorporation of lipid droplets, reduced lipid storage and increased fatty acid oxidation.

relevance and importance. In the hopes that future research projects will not only decipher the complexity of SCD1 biology but also open the door for novel therapeutic treatments in the field of metabolic disorders and beyond, the search for novel, potent and well-tolerated SCD1 inhibitors continues. This thorough study aims to provide an overview of reported SCD1 inhibitors that have been created throughout the years, illuminating the structure–activity relationship, development

problems and fresh approaches for ongoing search of novel potent SCD1 inhibitors.

2. SCD1: significance and biological implications

A double bond has been created between carbon 9 and 10 in the fatty acid chain of stearoyl-CoA by the iron-containing fatty acid



desaturase SCD1, which is essential for the formation of oleoyl-CoA. Known as Δ^9 desaturase (D9D) often, SCD1 exhibits remarkable specificity by desaturating the C-9 position of the acyl chain of, stearic acid (C18:0), resulting in the production of oleic acid (C18:1n9) (Fig. 1B).¹⁶

SCD functions as an integral membrane desaturase that catalyses the first insertion of a double bond at the delta-9 position in saturated fatty acids with a carbon chain length of 12 to 19. Through an enzymatic mechanism, these fatty acids were changed into monounsaturated fatty acids (MUFAs). Membrane fluidity and cell signalling were significantly impacted by the SCD-regulated modification of the unsaturation level of cellular lipids.¹⁷

Furthermore, the monounsaturated products produced by SCD function as the main building blocks for the synthesis of complex lipids, such as wax esters, cholesterol esters, triglycerides (TGs), phospholipids and diacylglycerols. This emphasises the critical function of SCD as a very controlled and evolved conserved enzyme with a variety of isoforms that have different substrate specificities and overlapped but unique tissue distributions.

Similar to other desaturases, SCD is a non-heme Fe-containing enzyme that needs NADH, cytochrome b5, cytochrome b5 reductase or a different transport mechanism of electrons to catalyse reactions. With its N- and C-terminal facing the cytoplasm, the SCD protein binds structurally to the endoplasmic reticulum (ER) membrane *via* four transmembrane domains. Additionally, the functional integrity of the enzyme is supported by the three catalytically essential and conserved His-box motifs.¹⁸

Four recognized isoforms of SCD (SCD1–4) exist in mice, situated within a 200 kilobase region on chromosome. These isoforms encode proteins consisting of 350–360 amino acids, demonstrating identity of over 80% amino acid sequence. Variations in the 5'-flanking regions contribute to tissue specificity differences among the isoforms. SCD2 shares considerable sequence similarity with SCD1 and is expressed everywhere, with elevated levels in the mice brain, especially during the myelination period. In mice, SCD2 plays a crucial developmental role and is essential for establishing an intact skin barrier in neonates. SCD3 is in the Harderian gland and skin of mice, although at considerably lower levels than SCD1, exhibiting a preference for palmitoyl-CoA over stearoyl-CoA. Conversely, SCD4 is predominantly found in the heart and experiences significant induction in the hearts of Scd1^{-/-} mice.¹⁹

A similar reaction can be catalysed by SCD1 with substrate-CoAs that are structurally linked to saturated fatty acids. SCD1, for example, can convert palmitate (C16:0) to palmitoleate (C16:1n7), which is also a CoA conjugate. This enzymatic oxidation occurs on the inner face of the endoplasmic reticulum, partnering with NADH-cytochrome B5 reductase and employing linked electron transfers through cytochrome B5, FADH2, and NADH.²⁰ The MUFA products resulting from SCD1 desaturation may undergo further elongation, desaturation within the cell or incorporation into various complex lipids, including triglycerides, phospholipids, wax esters, and other lipid species. Since, SFA substrates are typically abundant

through diet and endogenous synthesis, the desaturation reaction catalysed by SCD1 becomes the rate-limiting step in the production and subsequent metabolism MUFAs in the body. Altering lipid composition and the ratio of SFA to MUFA has diverse impacts on cellular functioning. SCD1 enzyme is crucial in determining the balance of saturated and unsaturated lipids within cells, significantly influences membrane fluidity, impacting numerous membrane-bound biological processes and systems. Additionally, SCD1 plays a critical role in energy balance, with SFAs being preferentially utilized or oxidized over unsaturated fatty acids, which are predominantly stored as fat in tissues.

SCD1's central involvement in the *de novo* lipogenic pathway is evident as it catalyses the further transformation of fats made by fatty acid synthase into derivatives primed for integration into storage lipids, such as TGs. Moreover, its heightened expression under the influence of hormones and transcription factors like insulin and SREBP-1c underscores the crucial role of SCD1 in *de novo* lipogenesis. Notably, mice lacking SCD1 due to a targeted whole-body deletion of the enzyme exhibit remarkable resistance to obesity and hepatic steatosis induced by a high-carbohydrate diet.²¹ This resistance is attributed, in significant part, to reduction in hepatic lipogenesis. Liver-specific deletion of SCD1 through conditional knockout model confers the same protection against carbohydrate-induced obesity and hepatic steatosis as observed in whole-body SCD1 deletion.

Mice lacking SCD1 (SCD1^{-/-}) are resistant to obesity and hepatic steatosis, and they are also shielded from the harmful reduction in insulin sensitivity that is frequently linked to obesity and fatty liver.²² SCD1^{-/-} mice show enhanced insulin signalling across a variety of tissues, including skeletal muscle, liver, adipose tissue, and heart, despite having lower fasting plasma insulin levels. This is characterized by increased insulin receptor tyrosine phosphorylation and reduced Ser/Thr phosphorylation of IRS-1. Reduced ceramide formation and greater fat oxidation in SCD1^{-/-} mice may be a factor in their increased insulin sensitivity because ceramides are implicated in mediating lipid-induced alterations in insulin signalling.

SCD1 serves as a metabolic hub, orchestrating various physiological processes including glucose and lipid metabolism, inflammation, autophagy, development, and tumorigenesis by regulating the proportion of MUFAs.^{1,23} The expression of SCD1 is tightly controlled both transcriptionally and epigenetically, influenced by a myriad of factors such as glucose, insulin, sterol regulatory element binding protein 1c (SREBP-1c), peroxisome proliferator-activated receptor α (PPAR α) and liver X receptor (LXR)^{24–28} which induce its expression, while leptin, estrogen, and polyunsaturated fatty acids (PUFAs) suppress it.^{29–31}

Under pathophysiological conditions, silencing of SCD1 has been shown to promote adipose tissue browning,³² reduce lipid accumulation and enhance lipolysis, offering potential therapeutic benefits for conditions such as obesity and non-alcoholic fatty liver disease (NAFLD). However, this beneficial effect might be offset by adverse impacts on β -cell structure and function, as evidenced by decreased lipid storage capacity and increased



susceptibility to lipotoxicity in islet of β -cells. SCD1 plays a complex role in cancer biology,^{33,34} wherein SCD1 promotes metabolic balance in cancer cells that favours cell proliferation and its survival.³⁵ In cancer cells the lipotoxicity induced by saturated fatty acid accumulation is mitigated by over-expression of SCD1 enzyme. Inhibiting SCD1 would deprive this protection afforded to cancer cells from cytotoxic effects of its saturated fatty acids. Thus, SCD1 inhibitors may be potential anti-cancer agents.³⁶ SCD1 deficiency has also demonstrated cardioprotective effects against high-fat diet (HFD) induced cardiac dysfunction, underscoring its potential in addressing cardiovascular complications associated with metabolic diseases.³⁷ The multifaceted role of SCD1 in various tissues highlights its potential as a therapeutic target for a range of metabolic disorders. Advances in medicinal chemistry and structural biology, including the resolution of the crystal structures of mouse and human SCD1 have provided deeper insights into the enzyme's catalytic mechanisms and have paved the way for the rational design and development of next-generation novel SCD1 inhibitors.

Recent findings indicate that due to wide distribution of SCD1 throughout the body, indiscriminate inhibition of SCD1, on a systemic scale may not be advisable due to the potential heightened susceptibility to cellular inflammation and side effects like alopecia and partial eye closure. While developing safe and effective SCD1 inhibitors, we should consider the metabolic consequences arising from systemic SCD1 inhibition and the indirect impacts of SCD1 inhibition in peripheral tissues such as skin. Taking this into consideration various efforts have been made to design molecules that have preferential liver distribution over other tissues giving liver targeted SCD1 inhibition in order tackle the side effects of systemic

SCD1 inhibition. In this context, the availability of various *in silico* techniques, *in vitro* models and rodent models provide an immense scope for rational design of potential molecules that can target SCD1 with maximum potency and favourable pharmacokinetic profiles as well as with minimum side effects. Following, we present the reported systemic and liver-targeted SCD1 inhibitor across a variety of scaffolds from the available literature.

3. Small molecules as SCD1 inhibitors

In the present review, the development of SCD1 inhibitors has been broadly categorized into: (A) systemic inhibitors and (B) liver-targeted inhibitors. The scaffold of most of the SCD1 inhibitors exhibited a central ring system that were either (i) monocyclic, (ii) bicyclic or (iii) spirocyclic. These inhibitors were modified on their sidechains in order to enhance their potency. It is emphasized here that the liver targeted SCD inhibitors necessarily bear a tetrazole acetic acid side chain which facilitates directed distribution of the inhibitor molecule to the liver cells (Fig. 2). In the following section, the structural details of the various scaffolds in the reported molecules, along with their activity correlations, have been discussed.

3.1 Systemic SCD1 inhibitors

Researchers at Xenon took compound **1** (Fig. 3), a potent hit obtained from library screening and produced compound **2a** as a hit-to-lead effort.³⁸ Compound **2a** was chosen to start SAR investigation, and the goal was to substitute heterocycles containing nitrogen for the pyridin-2-yl moiety. Analogues of pyrimidine and pyrazine (compound **2b** and **2c**) exhibited

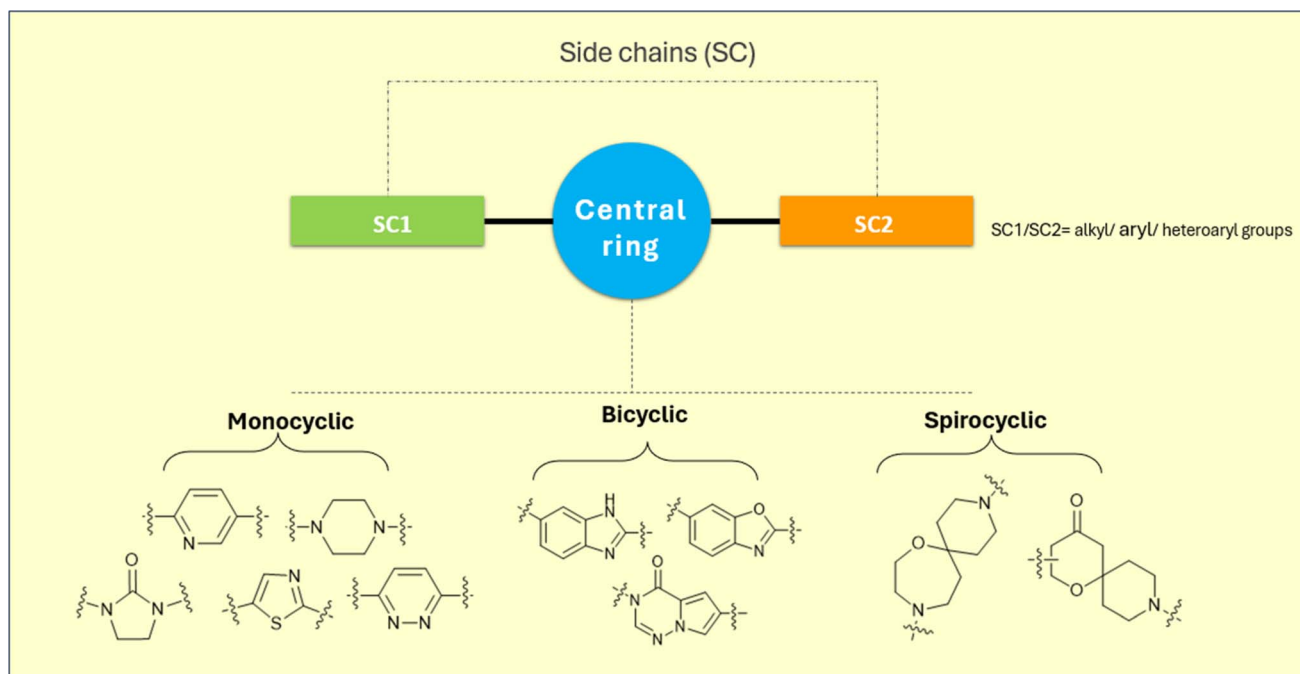


Fig. 2 General structural representation of SCD1 inhibitors.



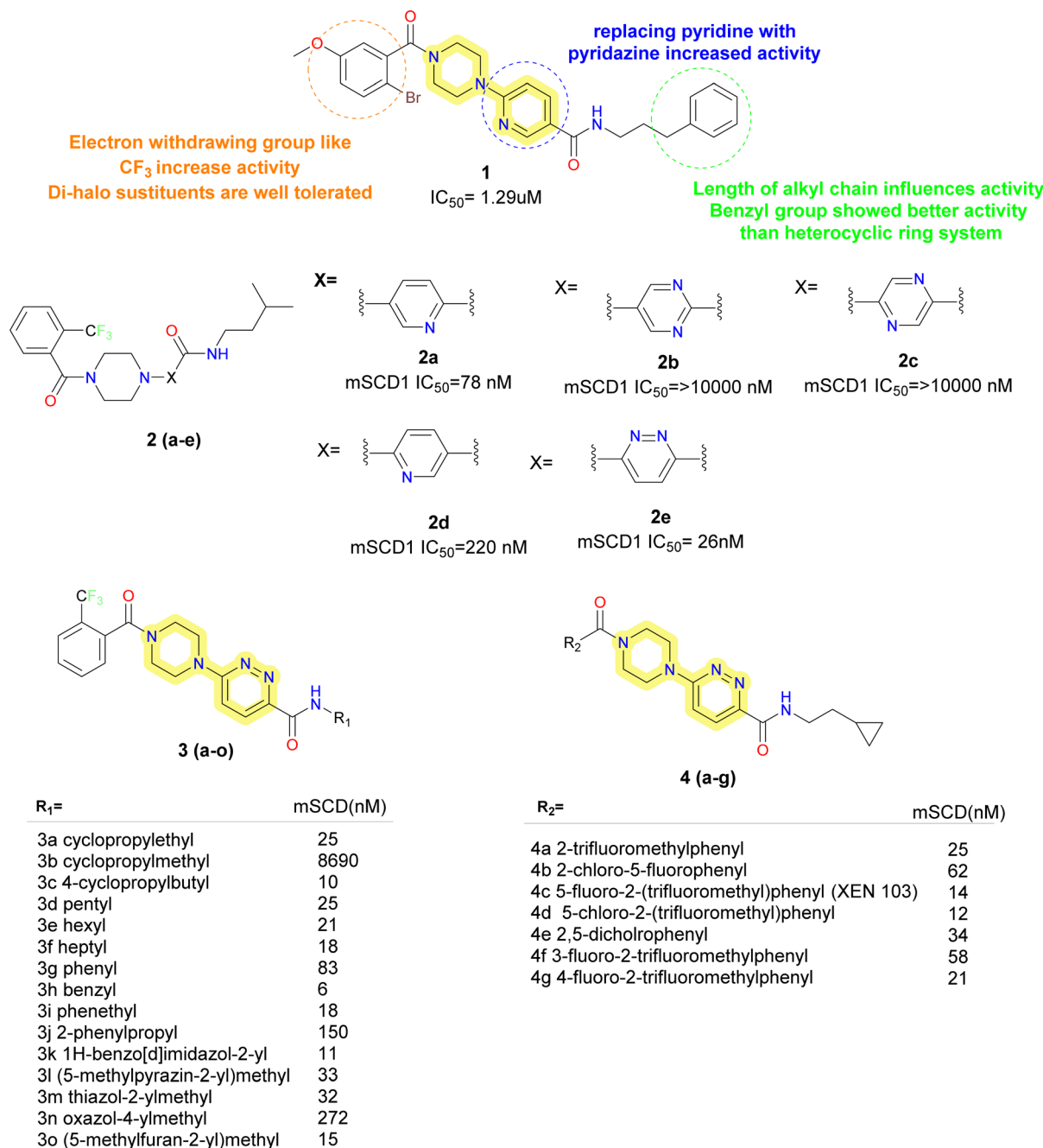


Fig. 3 Monocyclic SCD1 inhibitors: piperazinyl – pyridazine based SCD1 inhibitors as reported by Xenon.

a reduction in potency. In the SCD1 inhibition assay, compound **2d** (pyridin-3-yl substitution) maintained its activity but lost some of its potency. In conclusion, it was observed that replacing the pyridine group with pyridazine (compound **2e**) increased the potency by almost three-fold.

With piperazinyl pyridazine as the focal point, further optimization was conducted. On the right (R_1), various amines were investigated while keeping the 2-trifluoromethyl benzoyl group constant on the right. SCD1 activity was dependent on the linker lengths of the cycloalkyl and alkyl groups (compounds **3a–f**). The cyclopropyl group with ethyl chain showed far more potency than that of methyl group containing analogues.

Further with increase in chain length up to butyl group, potency increased whereas with hexyl and pentyl, heptyl it was less than butyl but comparable to that of ethyl group. Groups containing phenyl ring (compounds **3g–3j**) showed strong potency and ideal chain lengths. Benzyl group showed good potency compared to directly attached phenyl group, increasing the aliphatic chain attached to the aromatic group decreased the activity. The potency of benzimidazol-2-yl (compound **3k**) was preserved. In case of 5-membered heterocycles as side chain, furan and thiazole were active, whereas oxazole and pyrazole (compounds **3l–3o**) were not as much as active.



The left-hand side's (R2) SAR study revealed strict tolerance for alterations. For strong SCD1 inhibitory activity, the 2-trifluoromethyl phenyl group (compound **4a**) turned out to be the best choice. Electron withdrawing groups showed increased activity, whereas compounds with di-halo substitution (compounds **4b-4g**) showed improved potency. Compound **4c** (XEN 103) demonstrated good potency ($IC_{50} = 14$ nM), strong enzymatic inhibition and good oral bioavailability ($F = 49\%$). These inhibitors were found to be highly potent and orally bioavailable SCD1 inhibitors. Promising *in vivo* tests using Zucker fatty rats, verified significant decreases in visceral fat pad weight and body weight growth without lowering lean body mass. Subsequent research revealed that it was possible to substitute the piperazine moiety with piperidine and the amide linkage with carbonyl, ether, amino or alkyl without significantly altering the inhibitory potential of SCD1. In 2006, Xenon made these findings public through several patent filings.³⁹⁻⁴⁴

Based on these proposed scaffolds using scaffold design strategies, scientists at Abbott developed pyridazine heteroaryl-based potent and orally bioavailable SCD1 inhibitors.⁴⁵ Replacing pyrazine with piperidine aryl ethers (compounds **5a-**

b) (Fig. 4), characteristically fluorinated phenoxypiperidine (compound **5b**) showed improved potency over un-substituted phenoxy piperidine analogue. Further, using various substituted analogues for SAR exploration, it was observed that either 2 or 2,5-disubstituted phenoxypiperidine were preferred, which has added advantage of 2-substitution to avoid the oxidation of phenoxy ring. Although good potency was achieved, but the molecules failed to show metabolic stability. It was hypothesized that the isoamyl group is responsible for the metabolic instability. Replacing isoamyl amide with methyl amide (compound **6a**) improved the metabolic stability in rat liver microsomes. Primary amide substitution (compound **6b**) showed similar potency to that of methyl amide. Further SAR was explored using heteroarylmethylamines based pyridazine carboxamides. 3-Pyridinylmethyl (compound **6d**) analogue showed good potency against mSCD1 but not human SCD1, this could be recovered by using 3-methyl isoxazole, pyrazole and imidazole amides (compounds **6e-g**). But these molecules showed decreased hepatic microsomal stability compared to smaller amides. Further replacement of the amide group was done with different heterocyclic systems (compounds **7a-d**).

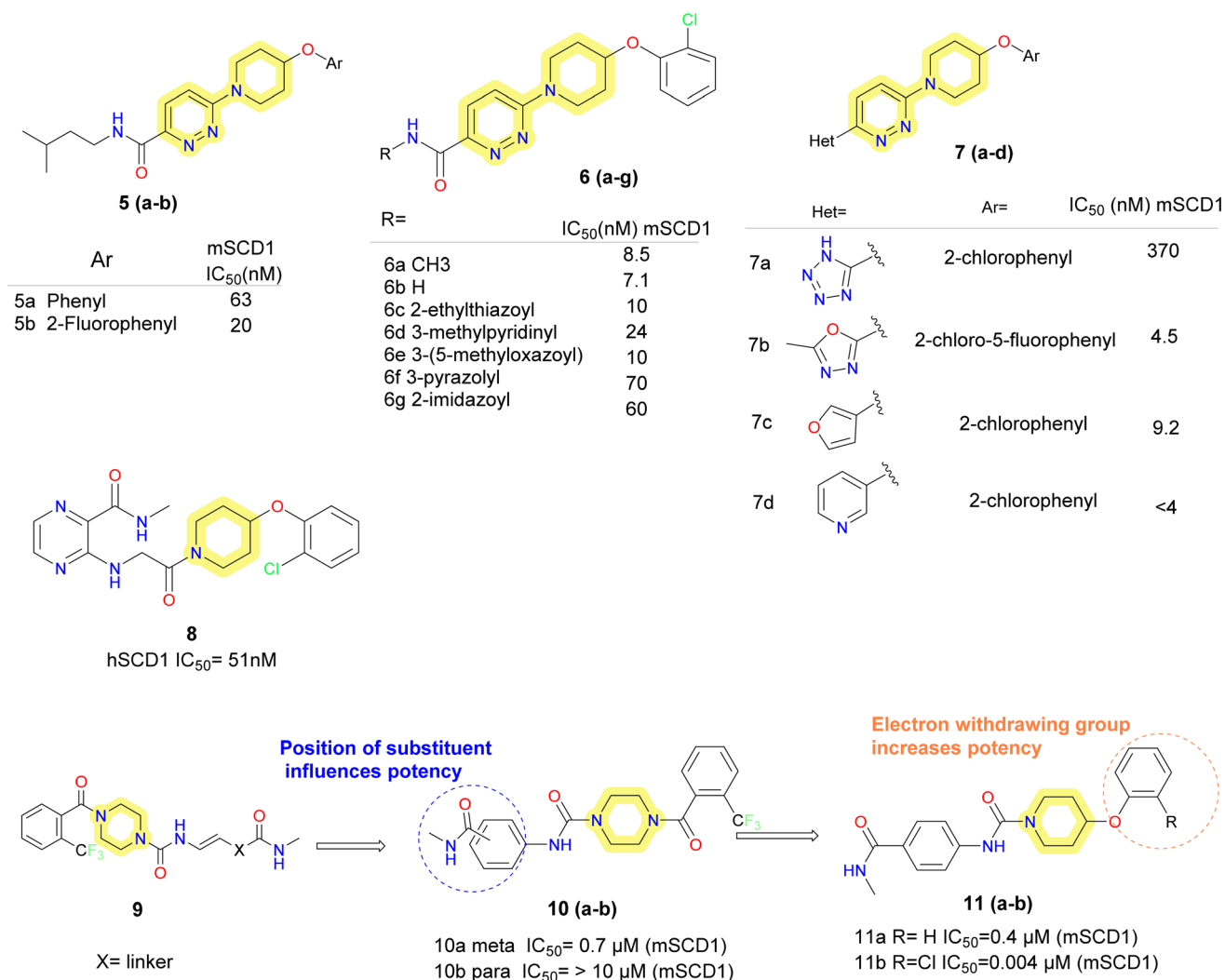


Fig. 4 Monocyclic SCD1 inhibitors: six-membered piperazinyl based SCD1 inhibitors.



Compound **7b** was found as lead, which showed good microsomal stability.

Further on exploration, modification of the scaffold was done and series of 1-(4-phenoxy-piperidin-1-yl)-2-arylaminoethanone, piperidine aryl urea-based inhibitors were reported.⁴⁶ It yielded potent molecules like compound **8** but did not improve the potency compared to lead (compound **6a**) taken.

Based on the nicotinamide SCD1 inhibitor (compound **2a**) researchers at Abbott decided to replace the central aminopyridine with urea group, while conserving its polarity and geometry.⁴⁷ Although, *trans* olefin seems to be a suitable linker (compound **9**) (Fig. 4), but due to stability problem, benzene was incorporated in the structure. *Meta*-substituted derivative (compound **10a**) showed promising results whereas *para*-substituted derivative (compound **10b**) failed to show any potency. Replacing piperazine benzamide with piperidine ether

conserved the potency. It was found that on the phenoxy ring, *o*-substituted halogen derivative showed improved activity with increase in bulkiness. Improved inhibitory activity was correlated with increased lipophilicity on the phenoxy ring.

The urea containing analogue, compound **11b** (A-939572), was an effective and selective SCD1 inhibitor with an IC_{50} of 4 nM in (mouse SCD1) mSCD1 and 37 nM in hSCD1 enzymatic assays.⁴⁷ Compound **11b** also exhibited good PK profiles, a dose dependent desaturation index reduction in obese mice models and decrease in body weight, plasma insulin, plasma and liver triglycerides and an increase in insulin sensitivity, in a diet-induced obesity model in mice. However, the target-related adverse effects such as alopecia, eye apoptosis and sebaceous gland atrophy were observed 2 weeks of oral administration.⁴⁶

Further researchers at Daiichi Sankyo replaced the piperazine moiety of the molecules proposed by Xenon using piperidine moiety and obtained a series of potent SCD1 inhibitors.⁴⁸ It

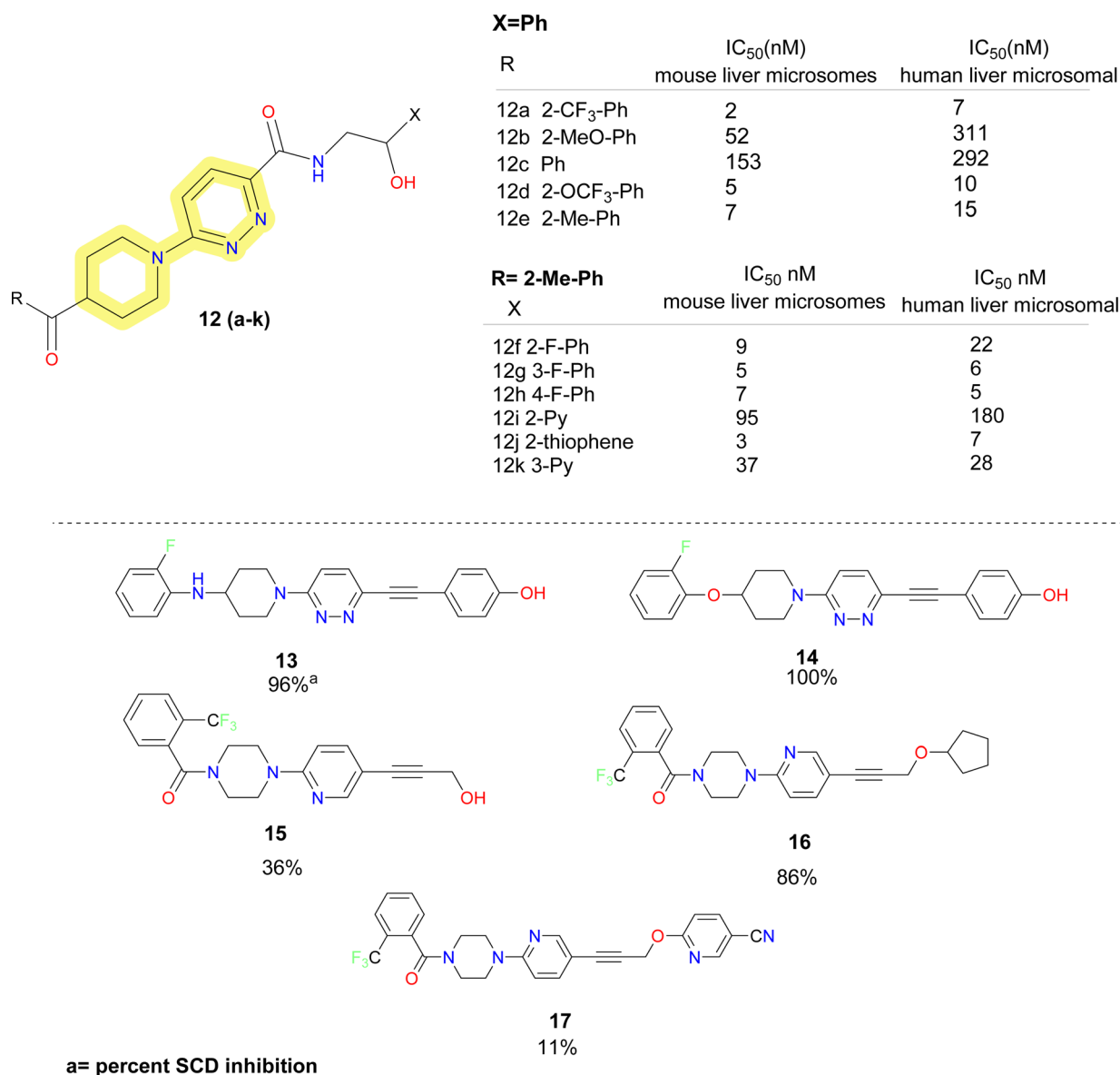


Fig. 5 Monocyclic SCD1 inhibitors: pyridazine based carboxamide and acetylene linker containing SCD1 inhibitors.



was found that replacing the pyridazine resulted in substantial loss in activity. So, keeping the pyridazine core constant they explored the piperazine fragment. SAR obtained for the benzoyl piperidine based SCD1 inhibitor depicted that electron withdrawing groups (compounds **12a–e**) (Fig. 5) showed better activity in both mouse and human cell microsomal SCD1. Similar pattern was observed in the SAR development on the right-hand side aryl moieties. Fluro-phenyl derivatives (compounds **12f–h**) showed better potency than pyridine analogue (compound **12i**). Fluorine at *meta* position (compound **12f**) did not improve inhibition in humans but at *ortho* and *para* (compounds **12g–h**), it showed improved results. Replacing phenyl group with bio isostere thiophene (compound **12j**) improved the potency. Compound **12k** demonstrated plasma triglyceride-lowering effects in Zucker fatty rats in a dose-dependent manner after a 7 days administration. Further, this benzoyl piperidine (compound **12k**) was explored by cyclization to form a spiro-piperidine ring. These reported compounds showed excellent potency.⁴⁹

In the year 2008, researchers at Glenmark reported acetylene derivatives of piperidine–pyridazine based SCD1 inhibitors (compounds **13–17**) (Fig. 5).⁵⁰ Titrated water release assay at 10 μM was performed for the synthesized compounds to determine the percent SCD inhibition. No IC_{50} values were disclosed.

Based on the determined percent inhibition, it was observed that amino and ether linkage showed better inhibition than carbonyl linkage and piperine and azetidine ring are better tolerated than piperazine moiety. Further, they reported acetylene containing spirocyclic SCD1 inhibitors. No biological data was disclosed.⁵¹

Researchers at Forest Laboratories also reported various piperazine based SCD1 inhibitors in various patent application, but no biological evaluation data was reported for these compounds.^{52–55}

von Roemeling *et al.* introduced a pioneering computational-driven strategy for drug discovery, integrating machine learning and functional assessment to devise novel inhibitors of the lipogenic enzyme SCD1.⁵⁶ This methodology, characterized by the creation of a new compound library based on reported molecules and in house fragments, and the integration of sophisticated *in silico* scoring techniques encompassing shape analysis, docking simulations and QSAR parameters. This method led to the identification of compound **18** (SSI-4) (Fig. 6), a pyridine–piperidine carboxamide analogue, showcasing potent SCD1 inhibitory property $\text{IC}_{50} = 1.9 \text{ nM}$ and anti-tumour property.

In 2020 Yumanity Therapeutics, Inc. reported a series of pyridazine and pyridine carboxamide molecules (compound

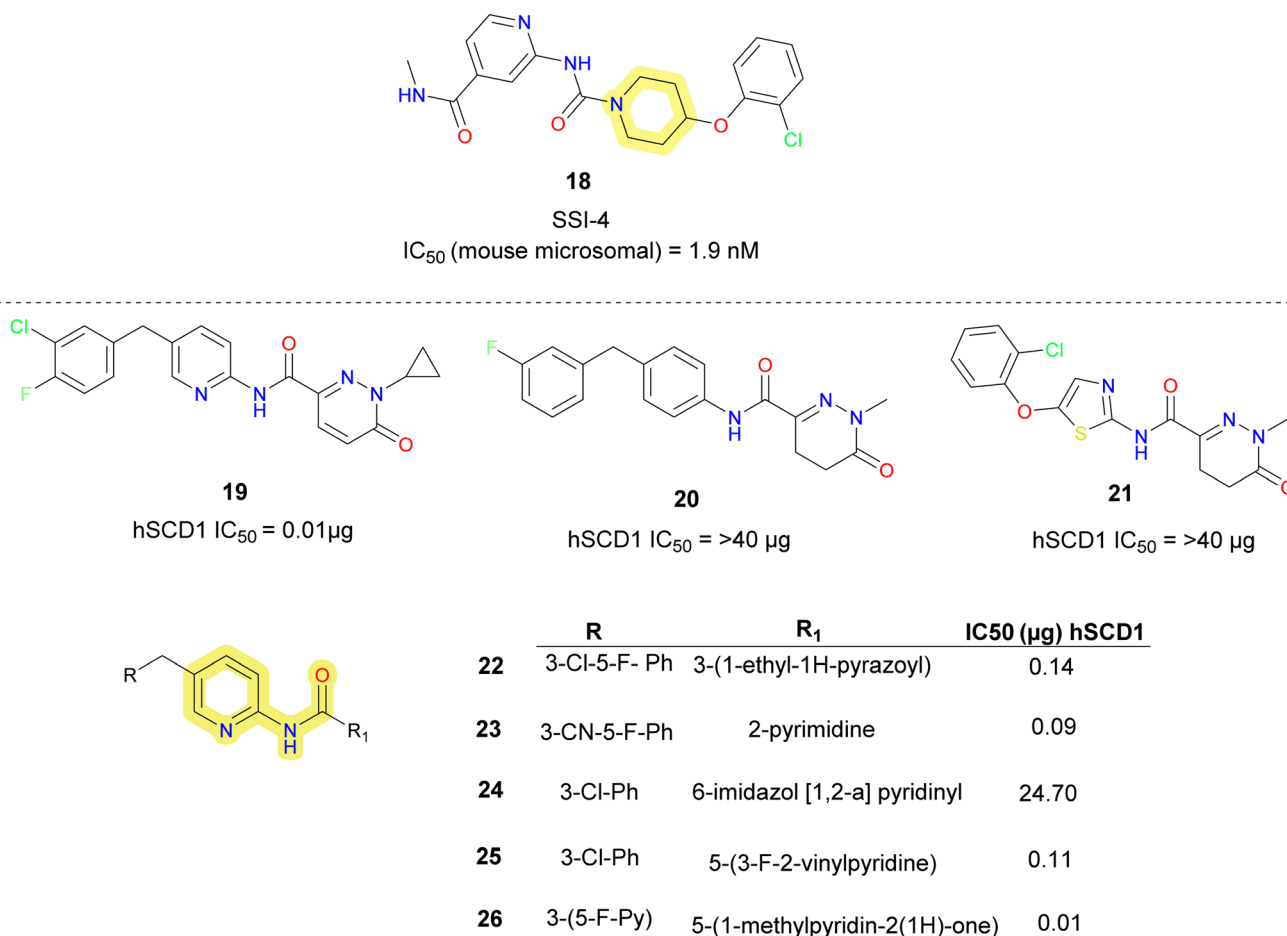


Fig. 6 Monocyclic SCD1 inhibitors: piperidine based SSI-4 and pyridine based SCD1 inhibitors.



19–26) (Fig. 6) as SCD modulators.⁵⁷ Compound 19 showed good potency, replacement of the central pyridine with groups like phenyl (compound 20), thiazole (compound 21) reduced the potency. Dihalo-substituted benzyl group (compounds 19, 22) as side chain showed better potency than mono-substituted derivatives. It was observed that pyrimidine (compound 23) and pyridine (compound 26) were well tolerated substituents for the side chain benzyl group. Imidazole (compound 23), pyridine (compound 26) was well tolerated substituent for pyridazinone side chain, whereas replacing it with dihydro imidazopyridine (compound 25) on its place decreased the potency.

Researchers at Takeda Pharmaceutical Company identified a lead compound 27 (Fig. 7), which exhibited high SCD1 binding affinity but lacked favorable PK properties, researchers pursued the design of novel derivatives based on molecular modeling studies.⁵⁸ Through iterative SAR analysis, they identified compound 28a and subsequently explored various substitutions on the piperidine scaffold to optimize binding affinity and potency. Notably, hydrophilic substitutions like

amino (compound 28b), hydroxy (compound 28c) and methoxy (compound 28d) were tolerated in terms of binding affinity, but lipophilic trifluoromethyl group (compounds 28e, 28i) showed a 5-fold increase in potency. Further optimization including substitution at the phenyl ring showed that lipophilic substitutions enhanced potency and regio isomers of the oxadiazole showed that 1,3,4-oxadiazole (compound 29b) and thiadiazole (compound 30b) showed excellent PK profiles and potency. Ultimately, compound 29b (T-3764518) emerged as a promising candidate, demonstrating high binding affinity, GI activity and metabolic stability, warranting further investigation for its therapeutic potential in metabolic disorders.⁵⁹

Yang *et al.* discovered 4-bicyclic heteroaryl-piperidine derivatives as potent inhibitors of SCD1 (compounds 30–36) (Fig. 7).⁶⁰ Initially, compounds with *N*-methylpyrazole-4-yl substitution were synthesized and tested, revealing that potency was significantly influenced by the type and position of substituents on the bicyclic heteroaryl ring.⁶¹ Halogen substitution at the 6-position of indoline rings (compounds 32–36)

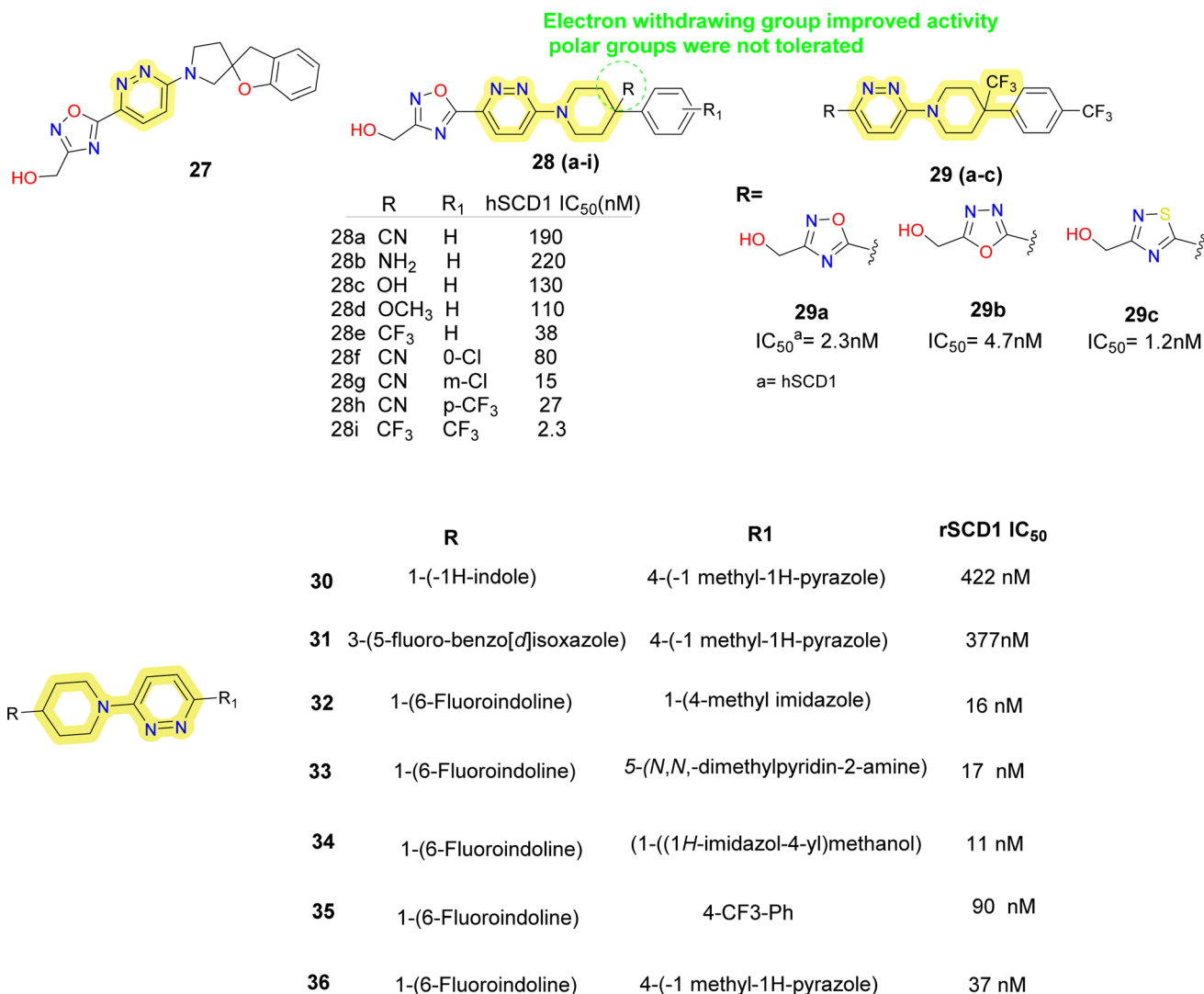


Fig. 7 Monocyclic SCD1 inhibitors: pyridazine–piperidine containing SCD1 inhibitors reported by Takeda Pharmaceuticals and Yang *et al.*⁶⁰



notably improved potency, while substitutions at other positions decreased activity. Subsequent modifications focused on exploring SAR by varying the pyrazole ring with various substituted 5-membered heteroarenes (compounds 32, 34), revealed promising inhibitory activities. Replacement of the pyrazole ring with *para*-substituted 6-membered rings such as phenyl (compound 35) or pyridine (compound 33) showed improved inhibitory activity, imidazole with hydroxymethyl substitution (compound 34) also improved the potency. Despite the potency of these inhibitors, some suffered from low microsomal stabilities or significant affinity towards CYP450 inhibition and/or human ether-a-go-go related gene (hERG) channel binding, limiting further development. Notably,

compound 36 demonstrated *in vivo* efficacy by decreasing body weight gain and plasma fatty acid desaturation index (DI) in Zucker *fa/fa* rats, suggesting its potential as a therapeutic agent. The study highlights the importance of SAR analysis in the rational design of SCD1 inhibitors and suggests that plasma fatty acid DI could serve as a biomarker for SCD1 inhibition, warranting further investigation into the pharmacological effects of these compounds.

Some pyridazine containing SCD1 inhibitors were reported by Xenon (compounds 37–41) (Fig. 8).⁶² These molecules indicated that sulphide and sulfoxide linkages are tolerated as a substitute to ether linkages and phenyl side chain improves potency rather than an aliphatic side chain.

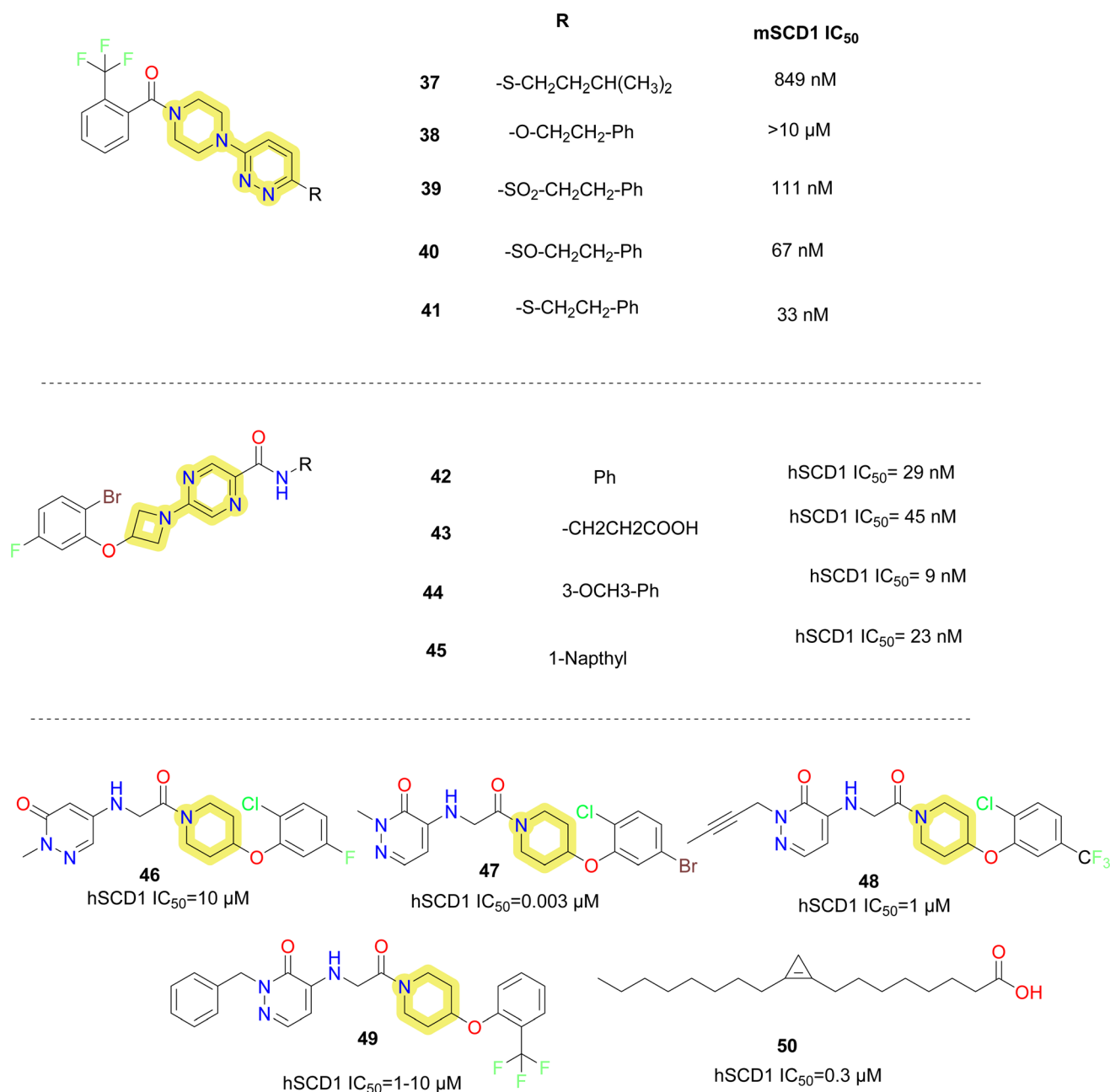


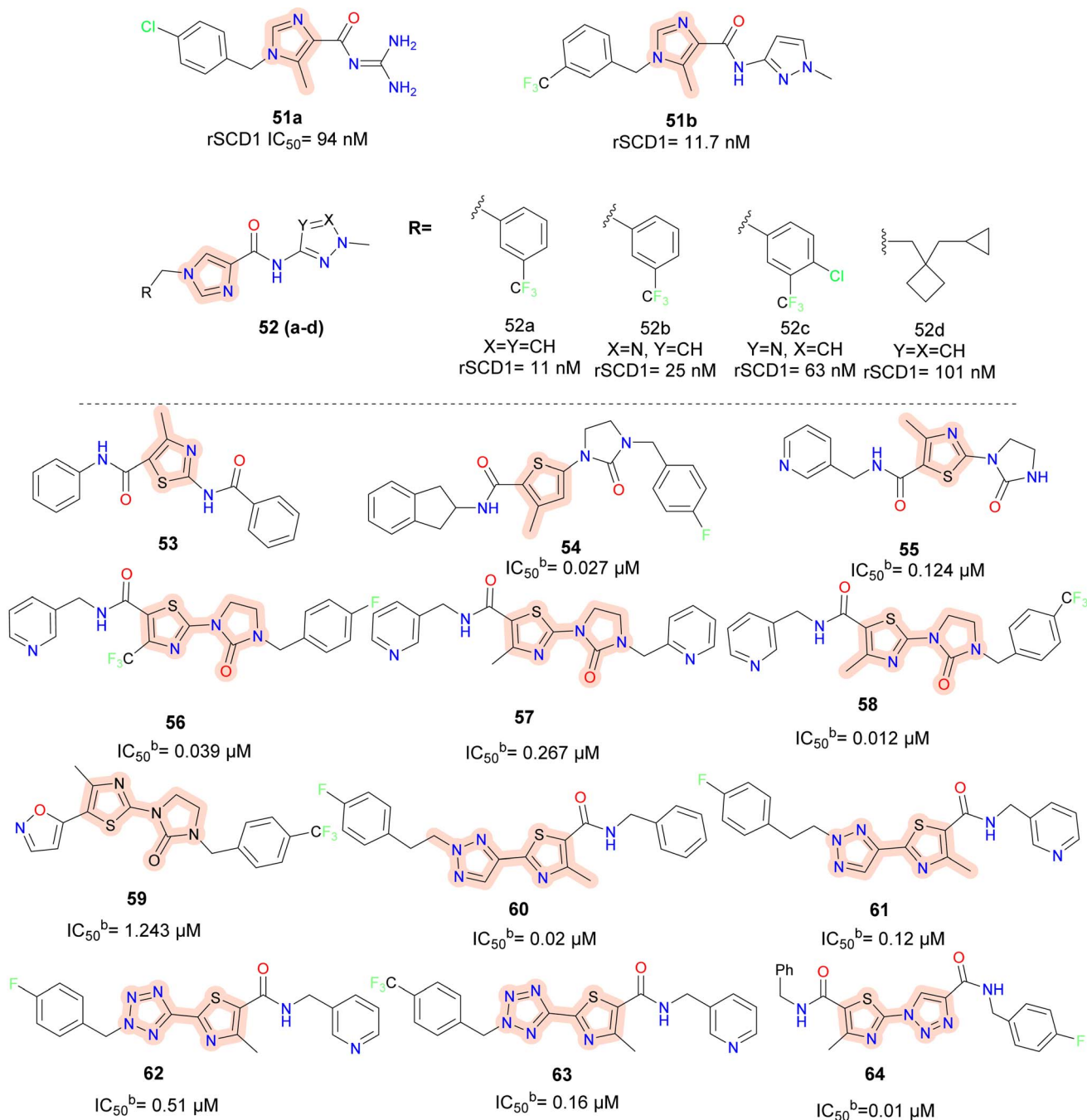
Fig. 8 Monocyclic SCD1 inhibitors: SCD1 inhibitors reported by Xenon and Merck.



Researchers at Merck reported azetidine containing pyridazine carboxamide SCD1 inhibitors (compounds **42–45**) (Fig. 8),⁶³ where dihalo-phenoxy moiety on the azetidine was fixed, on the right hand it is observed that phenyl group substituted with electron donor groups like methoxy (compound **44**), alkyl (compounds **42, 45**) showed better activity than withdrawing groups like carboxylic acid (compound **43**). PF Medicament reported 2*H*-pyridazin-3-one derivatives as SCD1 inhibitors (compounds **46–50**) (Fig. 8).⁶⁴ Smaller groups

like methyl (compounds **46, 47**) were tolerated on the pyridine nitrogen whereas bulky groups like benzyl (compound **50**) resulted in decrease of potency. Compound **47** was reportedly 100 times more potent than reference sterculic acid (**50**).

Pfizer researchers took compound **51a** (Fig. 9) as the lead molecule and postulated that the benzyl group linked to imidazole was comparable to the halo substituted group by employing Rapid-Fire High Throughput Mass Spectrometry (RF-MS) experiment and acyl guanidine (compound **51a**) as the



b = mouse liver microsomes

Fig. 9 Monocyclic SCD1 inhibitors: SCD1 inhibitors containing 5-membered rings as central moiety.



starting point.⁶⁵ The guanidine moiety was replaced out for the more potent *N*-methyl pyrazole. Results improved when benzylic tail moieties were substituted for the tail amide region; this was superior to phenyl substitutions. Additionally, a single *meta* substituent Cl or CF₃ on the benzyl moiety was shown to produce ligand-efficient inhibitors.

However, this did not help with the objective of *in vivo* activity because the increase in log *P* that accompanied the alteration frequently led to decreased microsomal stability and solubility. Tail substituents were also accepted in certain instances by highly specialised aliphatic groups (compound **52d**). For the amide area, similar patterns were seen. The preference was for small, five-membered amino heterocycles (compounds **52a–c**). While some six-membered amino heterocycles and aliphatic cyclic (data not shown) amines (compound **52d**) were tolerated, their potency was typically lost by one to two orders of magnitude. In rats fed with a low essential fatty acid (LEFA) diet, compound **51b** produced a high exposure *in vivo* to cause dose-dependent alteration of the plasma desaturation index (DI). All dosage groups did, however, see minor to moderate effects on the ocular tissues.

To develop potential SCD1 inhibitors to treat metabolic diseases, researchers from Novartis and Xenon collaborated in the year 2004. By starting with the pyridazine molecule, HTS was carried out to create a novel scaffold.⁶⁶ Compound **53** (amino thiazole) was obtained as a HIT, following this various patent of thiazole along with imidazolidinones, pyridinones, triazinones, piperidinones and other heteroaryl containing SCD1 inhibitors were reported (compounds **53–64**) (Fig. 9).^{67–71} In thiazolyl imidazolidinone⁶⁷ molecules reported (compounds **55–59**), on the left side of thiazole methyl-pyridinyl and other six membered aromatic moiety were well tolerated, whereas molecules containing un-substituted NH in imidazole (compound **55**) were less potent than the molecules where the hydrogen of NH was substituted with benzyl substituents. Electron withdrawing trifluoromethyl phenyl group (compound **58**) showed better activity than mono-fluoro substituted phenyl (compound **56**) and pyridinyl (compound **57**) substituted compounds. Further, replacing imidazole with triazole, thiazole improved the activity.⁶⁸ Benzyl group on left showed better potency than pyridine substitution and trifluoromethyl phenyl showed better activity than mono-fluoro substituted phenyl analogue.

In 2006 Merck Frosst reported thiazole and thiadiazole analogues as SCD1 inhibitor (compounds **65–68**) (Fig. 10).^{72,73} Compared to oxadiazole and triazoles, thiadiazole demonstrated superior efficacy when substituted for thiazole. Analogs of pyrazine and piperidine with ether and carbonyl linkers (compound **67**) shown superior efficacy than those with alkyl and sulfoxide linkers. Whereas urea, thiadiazole and carboxamide reduced the potency, amide and hydroxyl-oxadiazole substitution on the thiazole ring preserved the potency. The potency of compound **68** was 100 times higher than that of compound **67**. Even though its potency improved, it had adverse effects on the skin and eyes. Compound **67** was synthesized by substituting the piperazinyl-pyridazine analogues' five-membered thiazole ring for the six-membered pyridazine ring, as previously reported. This drug showed no $\Delta 5$ and $\Delta 6$

desaturase activity and IC₅₀ values of 0.1 μM against rSCD and 0.3 μM against hSCD1 against SCD1, indicating it's *in vitro* potency against SCD1. In an acute trial, compound **67** reduced the mouse liver SCD activity index in a dose-dependent manner following oral dosing, with an ED₅₀ of 3.0 mg kg⁻¹. Additionally, compound **67** reduced body weight increase in a 7 weeks chronic mice study by 73%; however, after 14 days of therapy, partial eye closure and progressive baldness has been developed.⁷⁴ The optimization efforts yielded compound **68**, a highly effective SCD inhibitor (HepG2 IC₅₀ = 1 nM). With an ED₅₀ of 0.3 mg kg⁻¹, compound **68** showed a dose-dependent decrease in the liver SCD activity index in mice. In rats given a high-fat diet, compound **68** showed a strong 24% reduction in body weight growth in a 4 weeks chronic testing with oral dosage at 0.2 mg kg⁻¹. Changes in insulin and glucose levels demonstrated an improved metabolic profile along with this outcome, although unfavourable effects on the skin and eyes depending on the mechanism were also noted. Researchers at Glenmark in 2010 reported a series of thiazole containing SCD1 inhibitors.⁷⁵ Electron withdrawing groups (compound **69a**) on the amide showed improved potency compared to electron donating groups such as phenyl (compounds **69b–c**) (Fig. 10).

Sun *et al.*, utilized bio isostere strategies to replace the amide bond at the C2-position in the lead obtained compound **70**, leading to the identification of potent SCD1 inhibitors.⁷⁶ The replacement of the amide moiety at the C2-position with various heterocycles revealed that SCD1 potency was highly dependent on the nature of the heterocyclic replacements (compounds **71a–e**) (Fig. 10). Imidazolidinone analogues emerged as the most potent compound, while other substitutions such as oxadiazole and triazoles, exhibited decreased potency. Halogen substitution at the 6-position of the aromatic ring notably improved the activity. However, substitutions at other positions or with different groups led to decreased potency, emphasizing the importance of substituent type and position. The study also highlighted the significance of thiazolyl imidazolidinone core structure, where analogues (compounds **72a–h**) with certain aryl or heteroaryl groups displayed good potency, while longer chain lengths at specific positions led to decreased the activity.

Moreover, the potent and novel (compound **72d**) XEN723 was found, exhibiting significant *in vivo* pharmacodynamic (PD) effects, and demonstrating an enhancement in SCD1 *in vitro* potency of approximately 560-fold over the original HTS hit compound **70**.

While demonstrating potent inhibition and *in vivo* efficacy, XEN723 was associated with undesirable skin and eye adverse events (AEs), prompting the exploration of alternative chemical space to mitigate these AEs. The synthesis and SAR analysis of a series of triazolone-based SCD1 inhibitors (compounds **73, 74**) (Fig. 11) led to the discovery of compound **74a**,⁷⁷ exhibiting improved AEs profile and promising *in vivo* efficacy. The study systematically modified the chemical structure, particularly focusing on the R2 side chain, to optimize potency and metabolic stability. Replacement of the thiazole core with a pyrazole group in compound **74a** resulted in decreased permeability but maintained potency and demonstrated good *in vivo* efficacy. Furthermore, SAR analysis highlighted the importance of



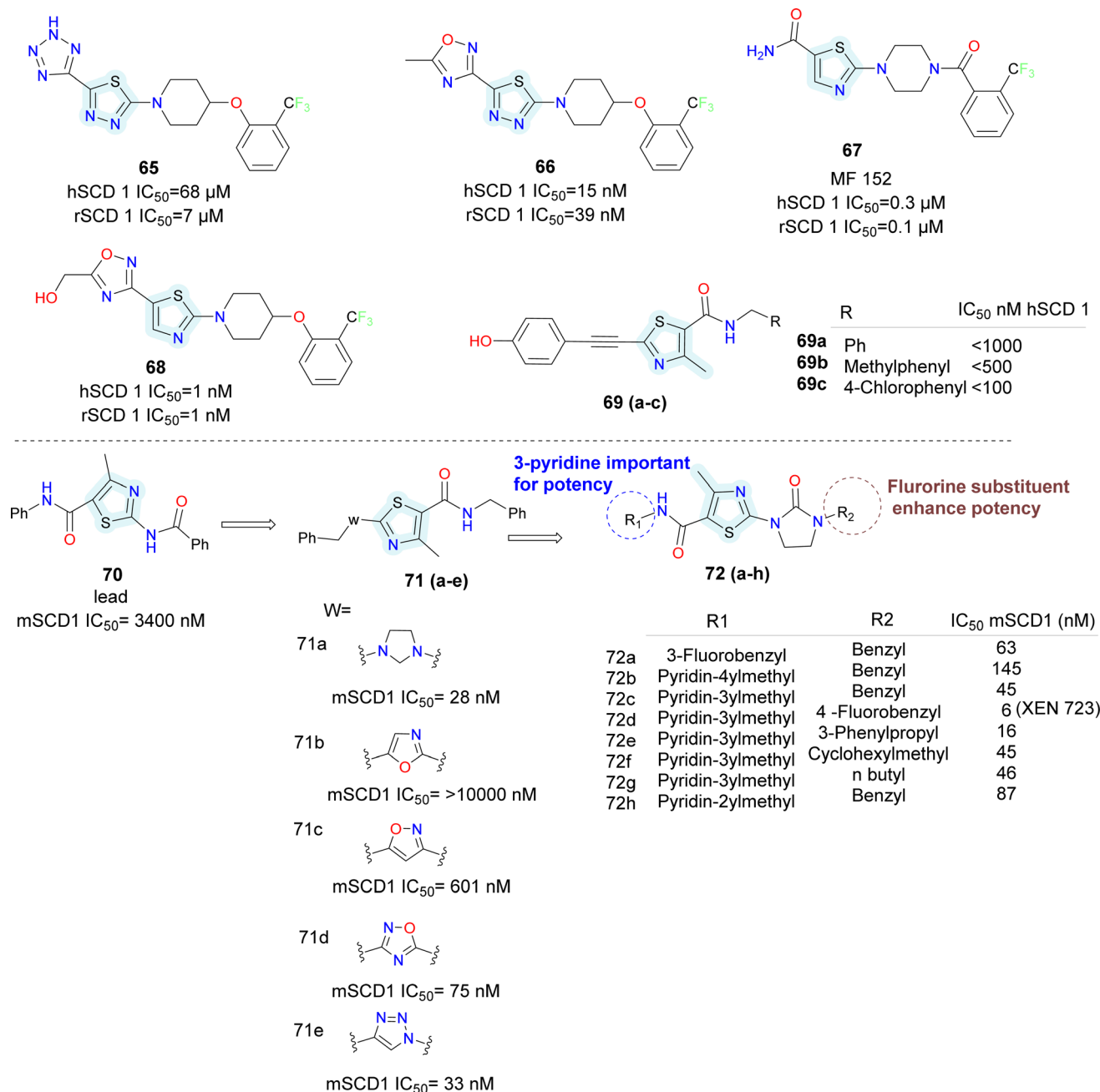


Fig. 10 Monocyclic SCD1 inhibitors: thiazole derivatives as SCD1 inhibitors.

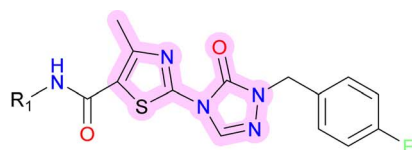
pyridin-3-yl-methyl R1 group for maintaining potency, as modifications to this moiety led to significant loss of activity. Despite challenges in modifying the left-hand side pyridin-3-yl-methyl R1, compound **74a** emerged as a potent, orally active SCD1 inhibitor with promising *in vivo* efficacy with a favorable safety profile, suggesting its potential as a therapeutic agent for metabolic disorders.

Further Sun *et al.* discovered novel thiazolylpyridinone-based SCD1 inhibitors by replacing the amide bond with a pyridinone moiety, exemplified by compound **75g** (Fig. 11), which showed potent SCD1 inhibition *in vitro* and *in vivo*.⁷⁸ This compound demonstrated a significant increase in potency

compared to the original hit, with improved liver distribution and a wide safety margin. Furthermore, compound **75g** demonstrated a dose-dependent reduction of plasma desaturation index, indicating potential efficacy *in vivo*. Additionally, flexible linkers between the pyridinone moiety and the terminal phenyl ring may enhance the potency and cellular activity, warranting further investigation.

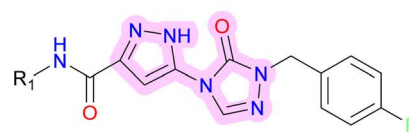
Medicis Pharmaceuticals reported a simple phenoxy pyrrolidine potent SCD1 inhibitor compound **76** (Fig. 11),⁷⁹ with aromatic rings substituted at either end and pyrrolidine as central ring.⁸⁰





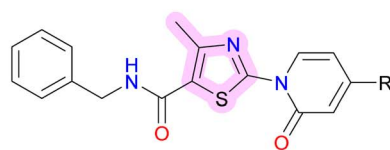
73 (a-e)

| | R1 | IC ₅₀ mSCD1 (nM) |
|-----|----------------------|-----------------------------|
| 73a | Pyridin-3-ylmethyl | 20 |
| 73b | Pyridin-2-ylmethyl | 22 |
| 73c | Piperidin-3-ylmethyl | >10000 |
| 73d | Thiazol-2-ylmethyl | 12 |
| 73e | Oxazol-2ylmethyl | 22 |



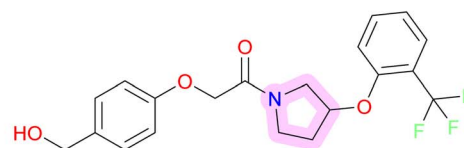
74 (a-e)

| | R1 | IC ₅₀ mSCD1 (nM) |
|-----|--------------------|-----------------------------|
| 74a | Pyridin-3-ylmethyl | 7 |
| 74b | Pyridin-2-ylmethyl | 23 |
| 74c | Pyridin-4-ylmethyl | 2673 |
| 74d | Oxazol-4ylmethyl | 165 |
| 74e | methyl | 385 |



75 (a-i)

| | R | IC ₅₀ mSCD1 nM |
|-----|-----------------|---------------------------|
| 75a | Phenyl | 141 |
| 75b | Benzyloxy | 25 |
| 75c | Phenethyl | 20 |
| 75d | Methoxyl | 90 |
| 75e | Trifluoromethyl | 24 |
| 75f | H | 63 |
| 75g | Hydroxyl | 14 |
| 75h | Benzylamino | 155 |
| 75i | NH ₂ | 387 |



76

hSCD1 IC₅₀ = 6.8 nM

Fig. 11 Monocyclic SCD1 inhibitors: five membered heterocycles reported for SCD1 inhibition.

3.1.1 Bicyclic ring systems. Using compound **1** reported by Xenon, the Sanofi-Aventis research team in Germany examined related compounds.⁸¹ The development of 1-benzoyl-4-pyridinyl piperazines were resulted from further modifications (compounds **77a–b**) (Fig. 12). With the aid of Abbott Lab's knowledge^{82,83} and ligand-based superposition with QXP-Tfit,⁸⁴ the pharmacophore was further understood.

Hexahydro-pyrrolo-pyrroles were substituted for the piperidine moiety using this data.^{85,86} SAR studies revealed that substituting aromatic pyridazine for pyridine and using an ether linkage rather than an amide resulted in promising compounds (**78a–c**). They called this compound **78c** as molecule SAR707. Despite demonstrating effectiveness *in vitro* and *in vivo* in terms of lowering body weight, improving lipid parameters and lowering serum desaturation index, SAR707 displayed adverse drug reaction (ADR) in the skin when used for an extended period *in vivo*.

To combat concerns about SAR707's adverse effects, Matter *et al.* at Sanofi Aventis also carried out ligand-based virtual screening and searched for additional chemotypes. They found that the benzimidazole-carboxamide scaffold was a good place to start and more 2D similarity searches produced compounds **79a–c**.⁸⁷

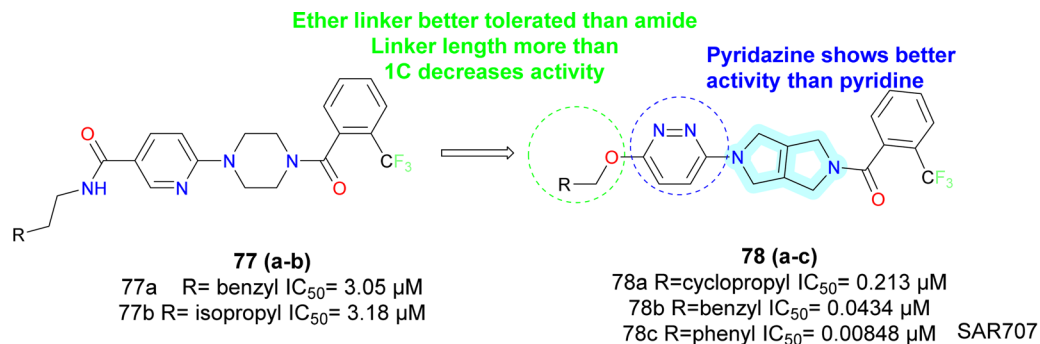
It was discovered that adding keto linker in place of carboxamide did not increase activity (compounds **79d–e**).

After more investigation on SAR, it was found that efficacy was reduced on the left side when benzyl substituents were used in place of thiophene group (compounds **79b–e**). Further research revealed that presence of a chloro-substituent on thiophene preserved activity, whereas substituting thiazole on thiophene lowered the activity (compounds **79f–g**). Conversely, substituting benzophenone derivatives on biphenyl ether (compound **79g**) resulted in finding of **SAR224** (compound **79h**) (Fig. 12). Serum fatty acid desaturation index significantly decreased in **SAR224** *in vivo*, and its optimal bioavailability and half-life were also demonstrated.

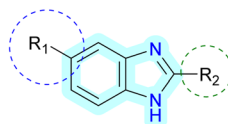
Powell and colleagues at Merck used the competitive rat SCD1 Scintillation Proximity binding Assay (SPA)⁸⁸ to identify structurally varied inhibitors *via* HTS, which resulted in the identification of 2-arylbenzimidazole inhibitors with moderate potency.⁸⁹

Initially taking compound **80a** as starting hit, the *t*-butyl group was replaced with either H or CN (compounds **80b–c**) (Fig. 13), which led to a decrease in efficacy. Conversely, analogues of sulfonamide showed comparable activity. The most active replacement among all was methylsulfone



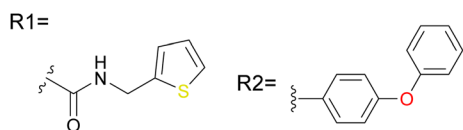


Amide linker essential for activity,
carbonyl linker not tolerated
Replacing phenyl with thiazole improves potency

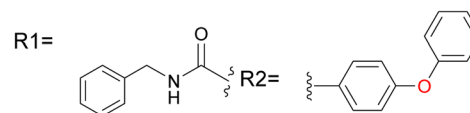


carbonyl linker enhances potency
compared to ether linker
CF₃ improves activity

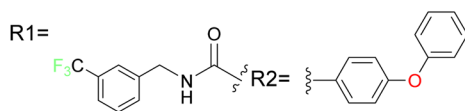
79 (a-h)



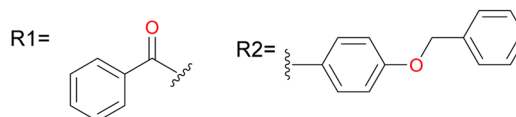
79a
SCD1 IC_{50} = 3.76 μ M



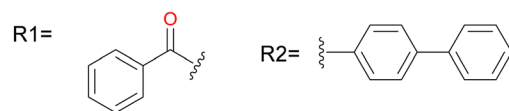
79b
SCD1 IC_{50} = 7.81 μ M



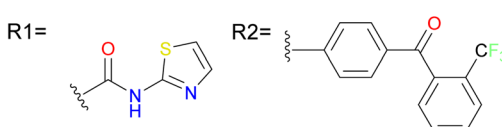
79c
SCD1 IC_{50} = 11.80 μ M



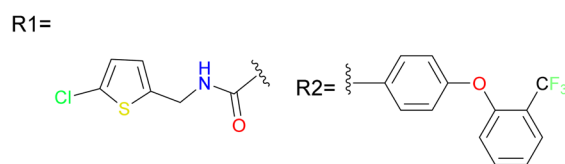
79d
SCD1 IC_{50} = 15.80 μ M



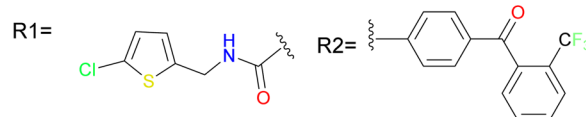
79e
SCD1 IC_{50} = >100 μ M



79f
SCD1 IC_{50} = 4.52 μ M



79g
SCD1 IC_{50} = 0.142 μ M



79h
SCD1 IC_{50} = 0.136 μ M
(SAR224)

IC_{50} = rat liver microsomes

Fig. 12 Bicyclic SCD1 inhibitors: development of SAR 707 and SAR 224.

(compound **80d**). While keeping methylsulfone, several aryl substituents were investigated to substitute the biphenyl group, but none of them showed superior activity. Moreover, these

substances reportedly exhibited selectivity for the hSCD1 enzyme in contrast to the hSCD5 isoform.



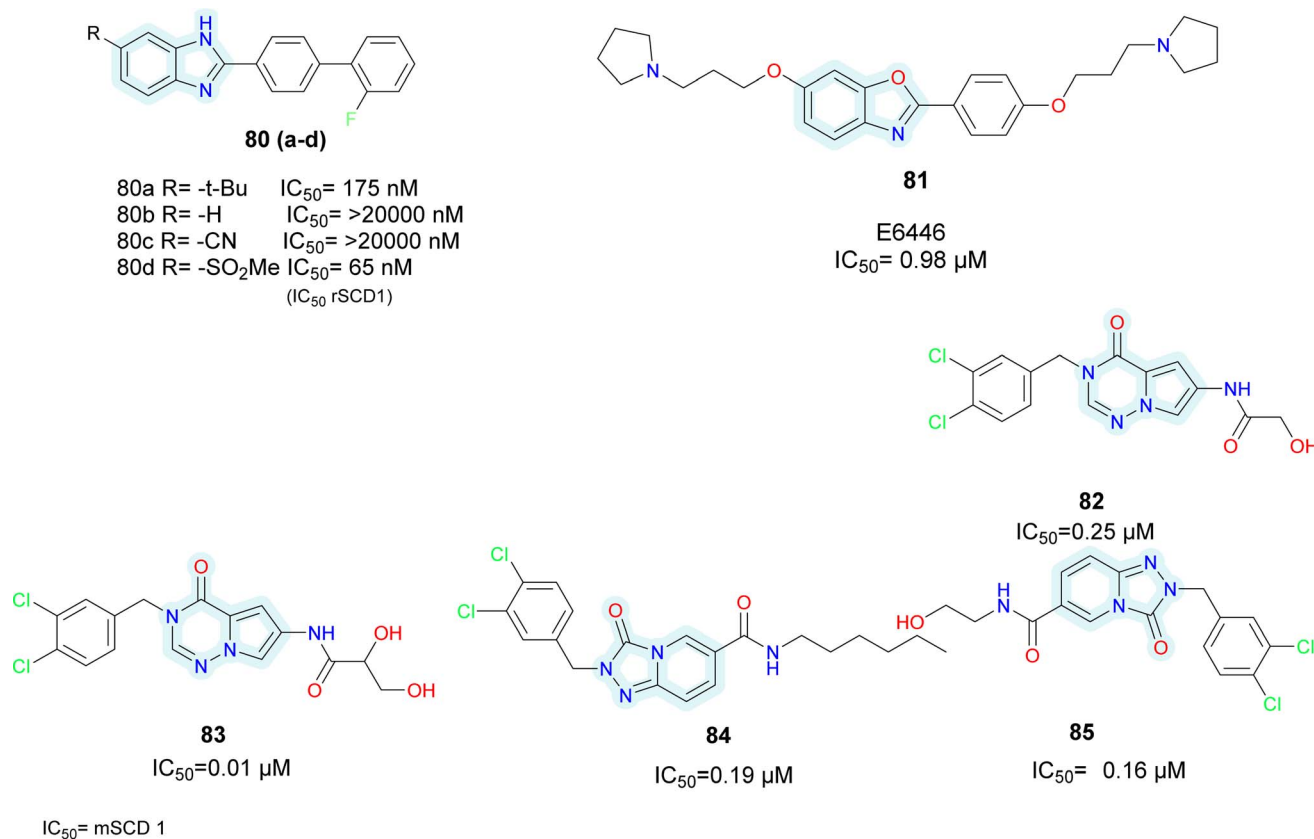


Fig. 13 Bicyclic SCD1 inhibitors: various bicyclic heterocycles as potential SCD1 inhibitors.

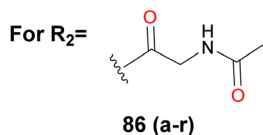
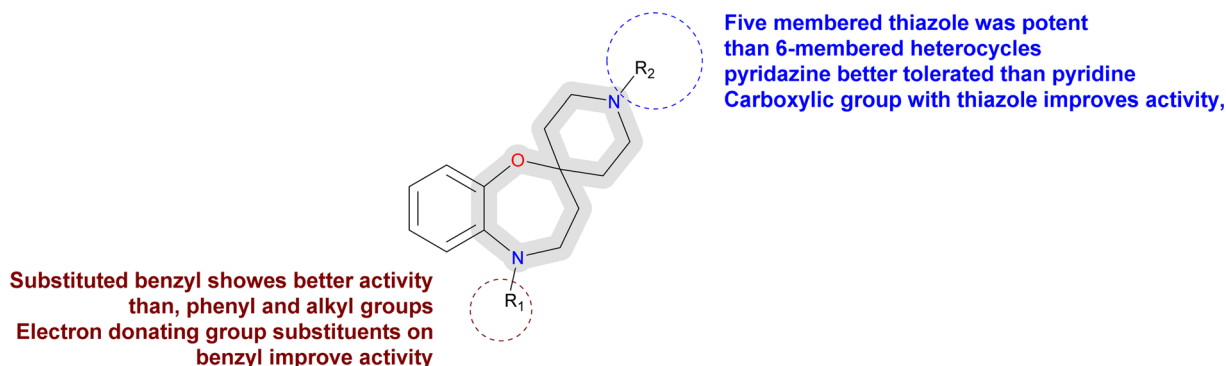
Wang *et al.* identified benzo-*[d]*-oxazole scaffold based **E6446** (compound **81**) (Fig. 13) using High Throughput Virtual Screening (HTVS).⁹⁰ **E6646** significantly inhibited adipogenic differentiation and hepatic lipogenesis *via* SCD1-ATF3 signaling. The SPR results showed that **E6446** exhibited strong interaction ability with SCD1 (KD:4.61 μM). Additionally, **E6646** significantly decreased hepatic steatosis, hepatic lipid droplet accumulation and insulin resistance in high-fat diet (HFD)-fed mice. It also showed excellent potency IC₅₀ = 0.98 μM compared to reference **A939572** which showed IC₅₀ = 2.8 μM. Other bicyclic ring based SCD1 inhibitors such as isoquinoline, pyrrolotriazine and triazolopyridinone have been reported in various patents (compounds **82–85**) (Fig. 13).^{91–93}

3.1.2 Spirocyclic SCD1 inhibitors. Deng *et al.* identified 4,5-dihydro-3*H*-spiro-[benzo[*b*][1,4]-oxazepine-2,4'-piperidine] derivatives as hit using high throughput screening (HTS) studies as potential SCD1 inhibitors with a favorable scaffold for further modifications (Fig. 14).⁹⁴ Modifications of R1 at the 5-position of the benzyl group revealed that a benzyl group (compound **86e**) and its extended form (compound **86f**) exhibited improved potency. Substituting hydrogen at the 2-position with chloride (compound **86h**) or ethyl (compound **86j**) further enhanced the potency. Chlorine substituent (compound **86l**) increased the potency at the benzyl group's 3-position, whereas trifluoromethoxy (compound **86n**) doubled it. Significant effects were seen from hydrophobicity at the 4-position, where a *t*-butyl group (compound **86r**) increased the potency

more than a methyl group (compound **86o**). At R2, tolerance for replacement at the α carbon was not shown. Various amide substituents were investigated. The examination of structures of other known compound, it was found that heterocycles—pyridazine (compound **87a**) in particular—had been used to link an amide to the core and demonstrated enhancement in activity. Other heterocycles were also investigated because it was known that pyridazine amide may be vulnerable to significant metabolism. Different substituents of amide were studied. After looking at the structures of other known inhibitors, it was discovered that pyridazine (compound **87a**) in particular, had been used to connect an amide to the core showed improved activity. Because, it was known that pyridazine amide may be susceptible to substantial metabolism, other heterocycles were also studied. Several carboxylic acids were synthesized because derivatives of carboxylic acids may be able to distribute preferentially into the liver tissues. Compared to pyridazine carboxylic acid derivative (compound **87c**), which showed modest efficacy, thiazole carboxylic acid derivative (compound **87d**) showed high potency and showed promising pharmacokinetic characteristics. An oral dose of 30 mg kg⁻¹ of SCD1 inhibitor (compound **87d**) for four hours resulted in a moderate decrease in the plasma desaturation index, suggesting that the drug may have some therapeutic benefit.

Various patents for spirocyclic SCD1 inhibitors have been reported (Fig. 15). Xenon reported a series of spiro (chromane-piperidine) analogues (compounds **88a–f**).⁹⁵ Fluorine





| R ₁ | mSCD1 IC ₅₀ (μ M) | |
|----------------|--|-------|
| 86a | iso-pentyl | 6.4 |
| 86b | iso-butyl | >10 |
| 86c | propyl | >10 |
| 86d | phenyl | >10 |
| 86e | benzyl | 1.2 |
| 86f | PhCH ₂ CH ₂ | 1.6 |
| 86g | 2-FPhCH ₂ | >10 |
| 86h | 2-Cl PhCH ₂ | 1.2 |
| 86i | 2-MePhCH ₂ | 1.2 |
| 86j | 2-EtPhCH ₂ | 0.43 |
| 86k | 3-FPhCH ₂ | >10 |
| 86l | 3-ClPhCH ₂ | 0.83 |
| 86m | 3-MeOPhCH ₂ | 1.8 |
| 86n | 3-F ₃ COPhCH ₂ | 0.68 |
| 86o | 4-MePhCH ₂ | 1.1 |
| 86p | 4-EtPhCH ₂ | 0.057 |
| 86q | 4-iPrPhCH ₂ CH ₂ | 0.042 |
| 86r | 4-tBuPhCH ₂ | 0.017 |

For R₁= 3-CF₃PhCH₂

| R ₂ | mSCD1 IC ₅₀ (μ M) |
|----------------|-----------------------------------|
| 87a | 0.004 |
| 87b | 0.012 |
| 87c | 4.7 |
| 87d | 0.008 |

Fig. 14 Spirocyclic SCD1 inhibitors: spiro benzo-oxapine based SCD1 inhibitors.

substitution in the chromane ring (compound **88c**) improved potency whereas oxo-chromane (compounds **88a–b**) showed reduced potency. Smaller substitution such as methyl on the amide group (compounds **88c–d**) showed better activity compared to bulky substitutions such as pyridine and pyrazole (compounds **88e–f**). Schering Corp. also reported a series of oxazepine based spiro compounds (compounds **89a–e**).⁹⁶ *N*-Piperidine substituted with heterocycle (compound **89d**) showed better activity than alkyl substitution. Substitutions like CF₃ (compound **89d**) on the aromatic ring improved the activity rather than alkyl substituents.

3.2 Liver targeted SCD1 inhibitors

Merck researchers in 2011,⁹⁷ with approach aiming to enhance drug exposure in the liver by utilizing liver-specific organic anion carrying polypeptides to facilitate active transport into hepatocytes (OATPs).⁹⁸ Their approach consists of the following: (i) using an *in vitro* rat microsomal enzyme assay to determine whether a compound is a SCD inhibitor; (ii) testing active SCD inhibitors in two cell assays, one containing functional active

OATPs (rat hepatocyte) and one lacking (HepG2 cell line); and (iii) conducting mouse tissue distribution studies on those compounds that are at least 4 to 5-fold more potent in the OATP vs. non-OATP cell assays.

Acidic moieties were positioned on the left or right side of the molecule, using compound **90 MF-438** (ref. 99) as a reference. It became clear that the molecule could only support acidic moieties on its left side (compound **91b**) (Fig. 16). Several acidic moieties were added, and the use of tetrazole caused a loss of efficacy and rendered the compound inert in the HepG2 test. Compound **91b** displayed a low level of activity. This proved that an acidic moiety's appendage might actively travel into a hepatocyte while reducing passive cell penetration. SAR experiments were conducted on the right-hand side phenoxy part to boost potency on the rat SCD enzyme assay. As previously reported by them, 2,5-dihalogen substitution resulted in a significant 8-fold improvement in potency.¹⁰⁰

The tetrazole heterocycle could have its potency increased even further by adding an acetic acid side chain (compound **92**). In this instance, a carboxylic acid essentially took the place of



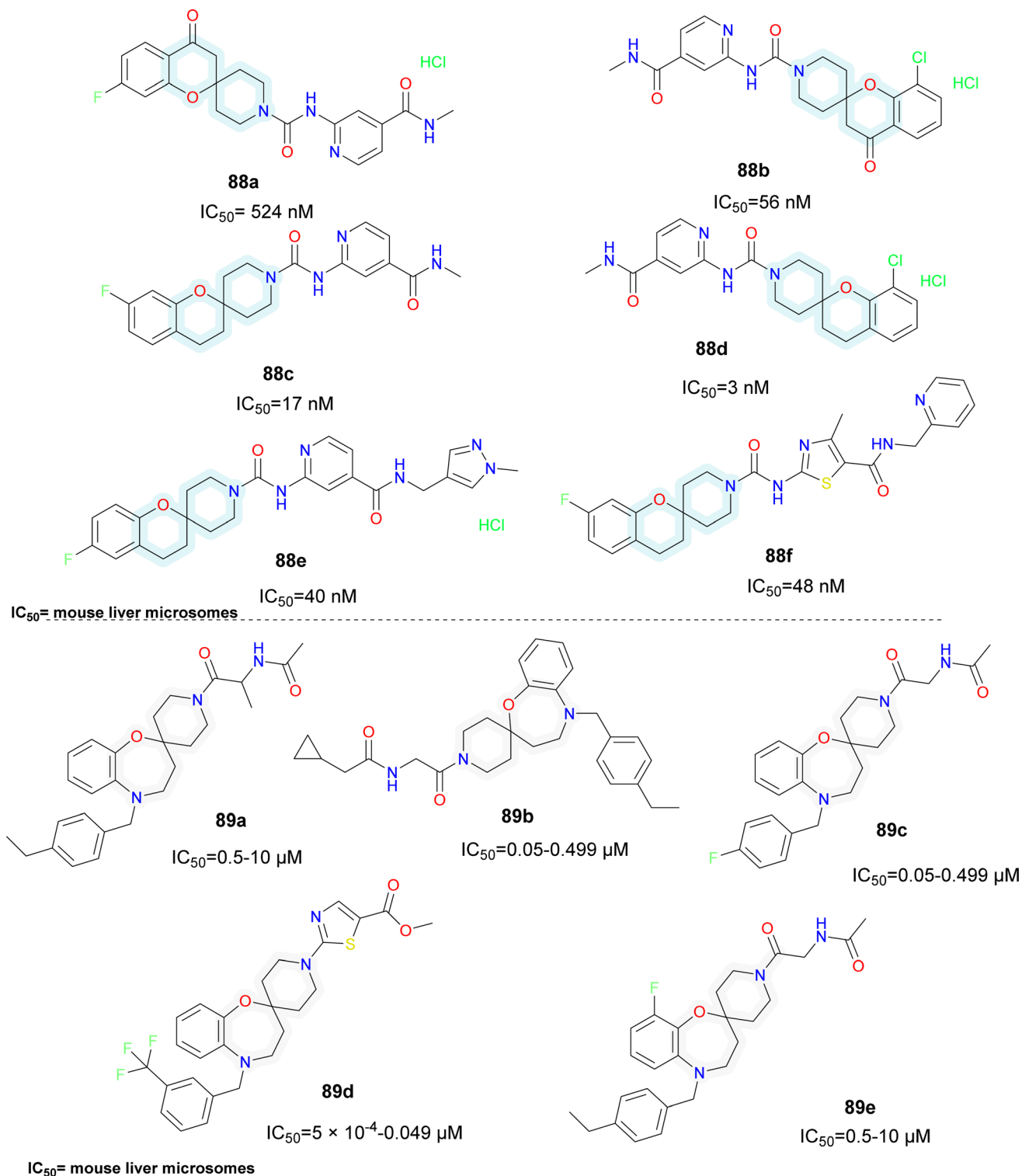


Fig. 15 Spirocyclic SCD1 inhibitors: oxazepane-piperidine based spirocyclic systemic SCD1 inhibitors.

the acidic tetrazole molecule. Compound **92** was more potent in the hepatocyte assay and >100-fold shifted in potency in the HepG2 cellular assay compared to molecule without $-\text{COOH}$. Finally, the potency in the rat enzyme and hepatocyte tests was further increased 2-fold while keeping a >300-fold shift in the HepG2 assay by substituting an isoxazole (compound **93**) (MK-

8245) nucleus instead of the middle thiaziazole ring with excellent potency.¹⁰¹

Compound **93** was able to exhibit maximum suppression of liver SCD while sparing the skin and eye tissues linked to adverse effects due to liver-targeting. At the end, this led to a safer profile for the liver-targeted SCD inhibitor (compound



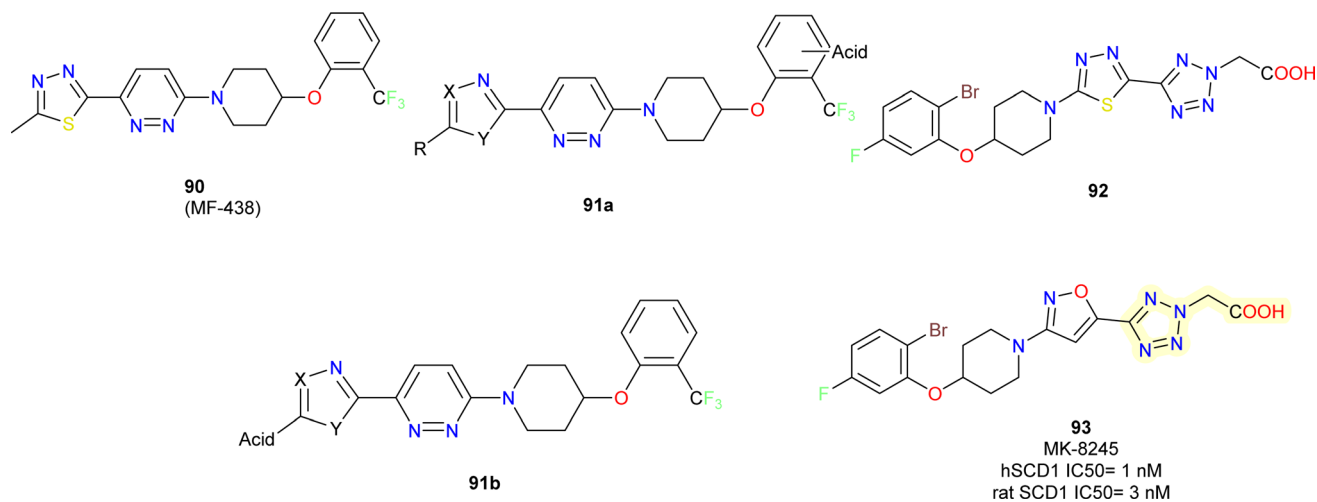


Fig. 16 Development of MK-8245 based SCD1 inhibitors.

93) in comparison to the systemically dispersed inhibitor that has been previously described.

Lachance *et al.*¹⁰² looked for structurally diverse liver-targeted SCD1 inhibitors, using **MK-8245** as a reference point. While leaving the remainder of **MK-8245** unaltered, they chose to replace out the piperidine linker for a bicyclic linker, such as, bis-pyrrolidine moiety. The isoxazole ring was found to be the ideal heterocycle in the bis-pyrrolidine analogues (compounds **94a, b**) (Fig. 17), whereas the thiazole ring is quite like the reference. Since, the thiazole is a good substitute for the isoxazole ring and the bis-pyrrolidine linker was the first alternative studied, they conducted more SAR exploration by evaluating a wide variety of heterocyclic linkers (compounds **94d, e**).

Following subsequent *in vivo* testing, the tissue distribution profile of compounds **94c** and **94d** found to be liver-selective. When compared to **MK-8245**, the mouse liver/plasma ratios were marginally lowered up to two folds, and the liver/Harderian glands ratios were improved. Given the link between suppressing SCD in the Harderian glands and AEs in the eyes, the liver organ's good tissue selectivity was desirable.

The moderately rigid heterocycles in these series substitute the piperidine core found in **MK-8245** and other widely used SCD-inhibitors by joining the thiazole or isoxazole ring with the phenyl ring *via* a C–N bond. The thiazole heterocycle and 2-chloro-5-trifluoromethoxyphenyl in compound **94c** were identified by SAR around the bis-pyrrolidine core as an excellent combination for both *in vitro* potency and *in vivo* efficacy.

In another report¹⁰³ the core of **MK-8245** was replaced using thiazole and an alkyl chain which was connected to the heterocycle using an oxygen atom (compound **95**) (Fig. 17). In the metabolic studies conducted, it was observed that fluorine substitution on the phenyl ring led to oxidative defluorination metabolism which was observed in hepatocyte incubations, among different replacements, they found out –OCF₃ was more metabolically stable resulting in a compound with good potency.

The researchers obtained compound **96** (Fig. 17), as HTS hit,¹⁰⁴ they focused on physicochemical properties such as total polar surface area (tPSA) and partition coefficient (*c* Log *P*) to minimize the off-target effects. Further modification by replacing ether linkage with an amine linkage and pyridine with a thiazole group gave a prominent lead (compound **97**) with improved potency but no selectivity towards the target. To obtain different compound exposure between liver and eyelids, further lead optimization was done. On the left had phenyl ring with hydrophobic groups such as CF₃ (compound **98b**), *n*-propyl (compound **98c**) were well tolerated, whereas polar substituents like COOH (compound **98d**) were not. It was also found that thiophene (compound **99c**) was an equipotent replacement for central phenyl ring. Alcohols with methylene linker were placed at 4th position of the thiazole ring linkers, up to 2 carbon length were tolerated and showed single digit nM potency but further longer chain length decreased the potency. The correlation plots indicated that compounds in the ranges of $3.9 \leq c \text{ Log } P \leq 5.0$ and $90 \leq \text{tPSA} \leq 98$ were highly selective for the liver targeting. Further optimization led to compound **100** which showed IC₅₀ = 5.4 nM (mouse liver microsomes), was orally available and liver selective.

The phenoxy piperidine isoxazole derivatives of **MK-8245** emerged as potent SCD1 inhibitors (compounds **101a–g**) (Fig. 18), exhibiting robust enzymatic potency against rat SCD, and demonstrating promising *in vivo* efficacy in mouse liver pharmacodynamic models without adverse effects. The liver-targeted distribution profile of **MK-8245** is attributed to substrate recognition by organic anionic transporter proteins (OATPs) in hepatocytes, primarily facilitated by the tetrazole acetic acid moiety. With a focus on maintaining this liver-targeting functionality while exploring structurally diverse SCD inhibitors, the piperidine core of **MK-8245** was replaced with acyclic linkers, leading to the identification of a novel series of SCD1 inhibitors.¹⁰⁵ Through SAR and metabolism studies, the optimal combination of a thiazole heterocycle and 2-bromo-5-trifluoromethoxyphenol in compound **101g** was



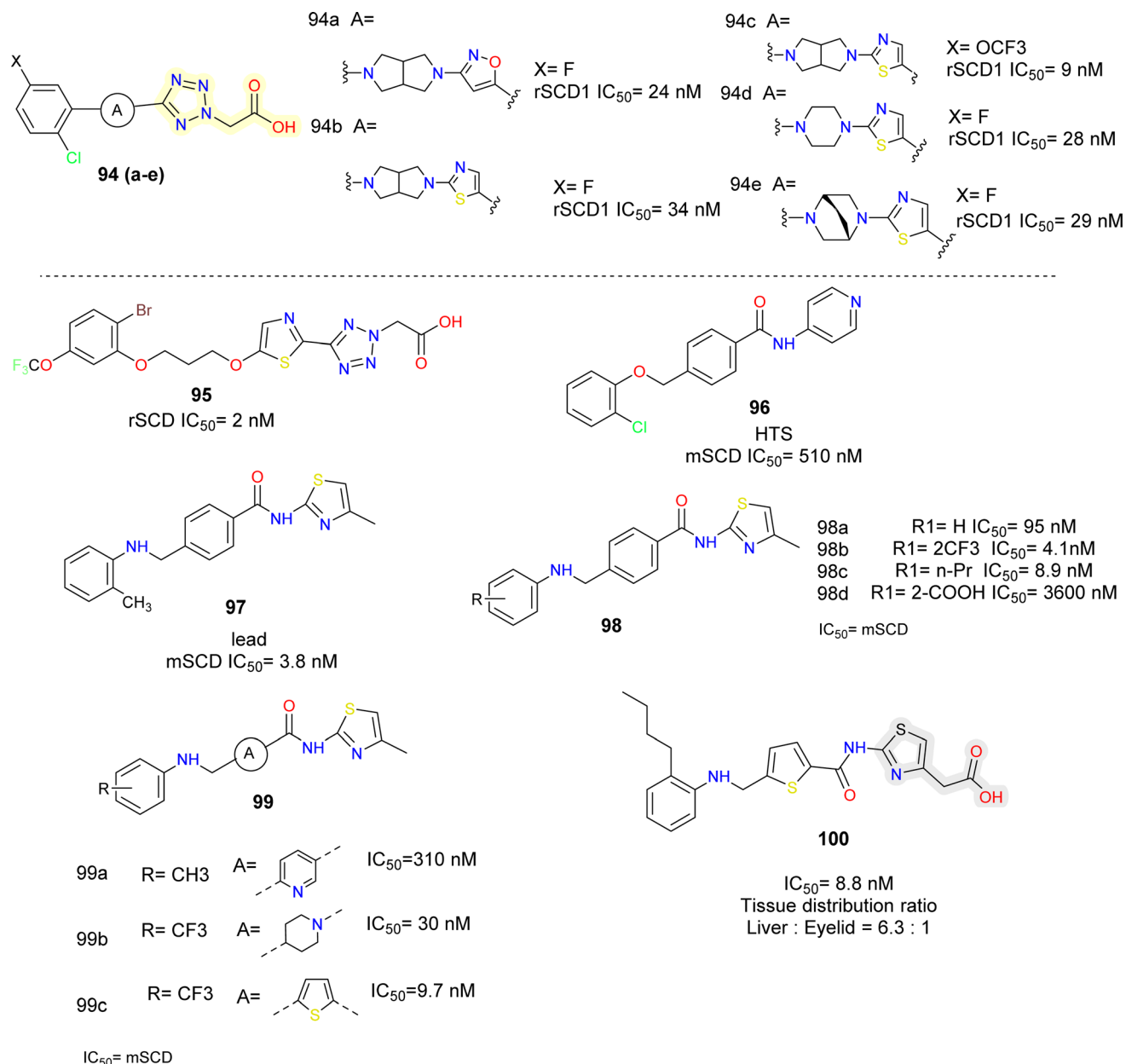


Fig. 17 Tetrazole and thiazole acetic acid based SCD1 inhibitors.

delineated for potent *in vitro* activity and *in vivo* efficacy. However, further efforts were required to enhance liver-selectivity and mitigate potential adverse effects associated with exposure to the Harderian gland.

Developed from a benzo-fused spirocyclic oxazepine scaffold, inhibitors for SCD1 were crafted, demonstrating efficacy in lowering desaturation index in mice (Fig. 19).¹⁰⁶ During optimization, preferences emerged for the oxazepine core and benzylic positions, while flexibility in piperidine substitutions allowed for potency and pharmacokinetic adjustments. Investigating SAR at the 5-position highlighted the potency variances with different substituents, particularly noting the influence of electron donating or withdrawing groups (compounds **102a-e**). Shifting focus to the 1'-position, incorporation of R1 led to the

synthesis of compounds featuring diverse R2 groups, revealing changes in potency. Exploration of heterocycles, especially pyridazine and thiazole, as linker motifs unveiled promising potency and tissue distribution in compound **103d**, indicating potential for treating metabolic disorders. Further assessment, *in vivo* showed a moderate decrease in plasma desaturation index, prompting consideration for enhancing selective liver distribution to minimize side effects and enhance therapeutic efficacy. The SAR analysis focused on optimizing a benzo-fused spirocyclic oxazepine scaffold for SCD1 inhibition, revealing preferences for the oxazepine core and benzylic positions with substituents on the piperidine portion offering flexibility in potency and PK properties. Modifications at the 5-position showed that a benzyl group (compounds **102d-e**) has improved



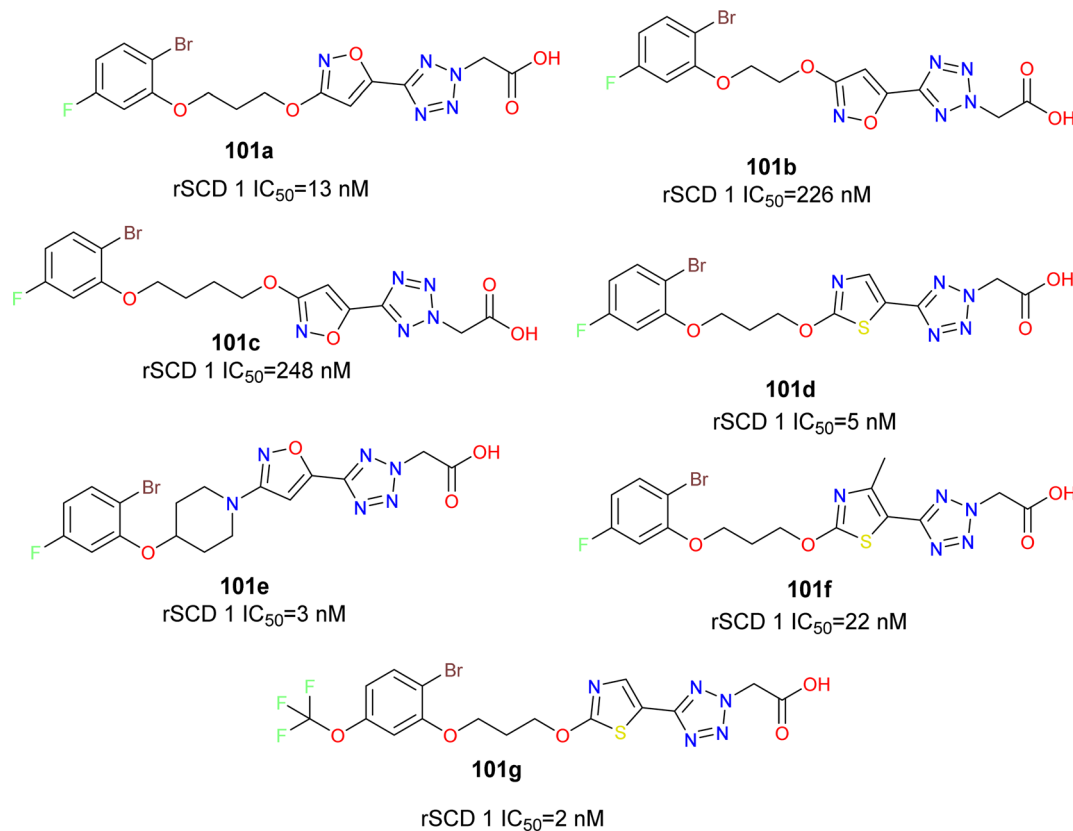


Fig. 18 Acyclic linker based liver targeted SCD1 inhibitors.

the potency, while substitutions on the benzyl group had varying effects, with electron-withdrawing groups enhanced the potency. Introduction of heterocycles, particularly pyridazine (compounds **103a–d**), further enhanced the potency, with thiazole derivatives (compounds **103c–d**) exhibiting favourable SCD1 inhibition. Compound **103d** emerged as a highly potent SCD1 inhibitor with excellent pharmacokinetic profiles and liver tissue distribution, suggesting promise for further development in metabolic disorder treatment. Merck reported a series of chromane-piperidine spiro compounds with various heterocyclic linkers, having tetrazole acetic acid as side chain, thiazole linker showed improved potency than pyridazine linkers. These compounds were reported to be liver selective (compounds **104a–f**).^{107,108}

4. Natural products as SCD1 inhibitors

Among the numerous small molecules reported, various natural products have been reported for SCD1 inhibition and/or by indirect de-regulation of lipid metabolizing molecules (Fig. 20).

Zhu *et al.*¹⁰⁹ showed that berberine (**105**) an isoquinoline alkaloid extracted from a Chinese herb, reduced hepatic lipid accumulation along with reduced expression of hepatic SCD1 and other related genes. They also reported that knockdown of SCD1 expression mimicked the effect of berberine decreasing hepatic steatosis. In HepG2 cells and the liver of mice fed with

a high-fat diet, berberine enhanced the phosphorylation of AMP-activated protein kinase (AMPK) and sterol regulatory element-binding protein-1c (SREBP-1c). The berberine-induced reduction of SCD1 was caused by activation of the AMPK-SREBP-1c pathway and the sterol regulatory element (SRE) motif in the SCD1 promoter (−920/−550).

Sterculic acid (SA) (**50**), a natural cyclopropene fatty acid found in plant *Sterculia foetida* is a natural inhibitor of SCD1.¹¹⁰ Its extremely strained and reactive propene ring as well as the double bond between C9 and C10 in its chemical structure have been suggested as contributing factors to this inhibitory effect. Research conducted on 3T3-L1 adipocyte cells has demonstrated that this inhibition takes place through the down regulation of enzyme activity, independent of SCD mRNA or protein levels.¹¹¹ Moreover, SA in *Toxoplasma gondii* does not change SCD's levels of transcription or translation. Therefore, this inhibition may result from SA's conversion to steruloyl-CoA, which appears to be the enzyme's active form or from the irreversible binding of the enzyme's sulfhydryl groups to cyclopropene groups as a substitute option. However, following a four days injection of sterulic oil (SO), Dallaire *et al.* observed a 31% rise in SCD1 mRNA levels in mammary cow tissue. According to the authors, this is the result of a drop in SCD product levels, which causes an increase in SCD1 transcription to compensate for the deficit.^{112,113} In a mouse model of NAFLD, (5*R*)-5-hydroxytriptolide (LLDT-8) (**106**), a triptolide analogue, demonstrated hepatoprotective benefits by reducing liver lipid



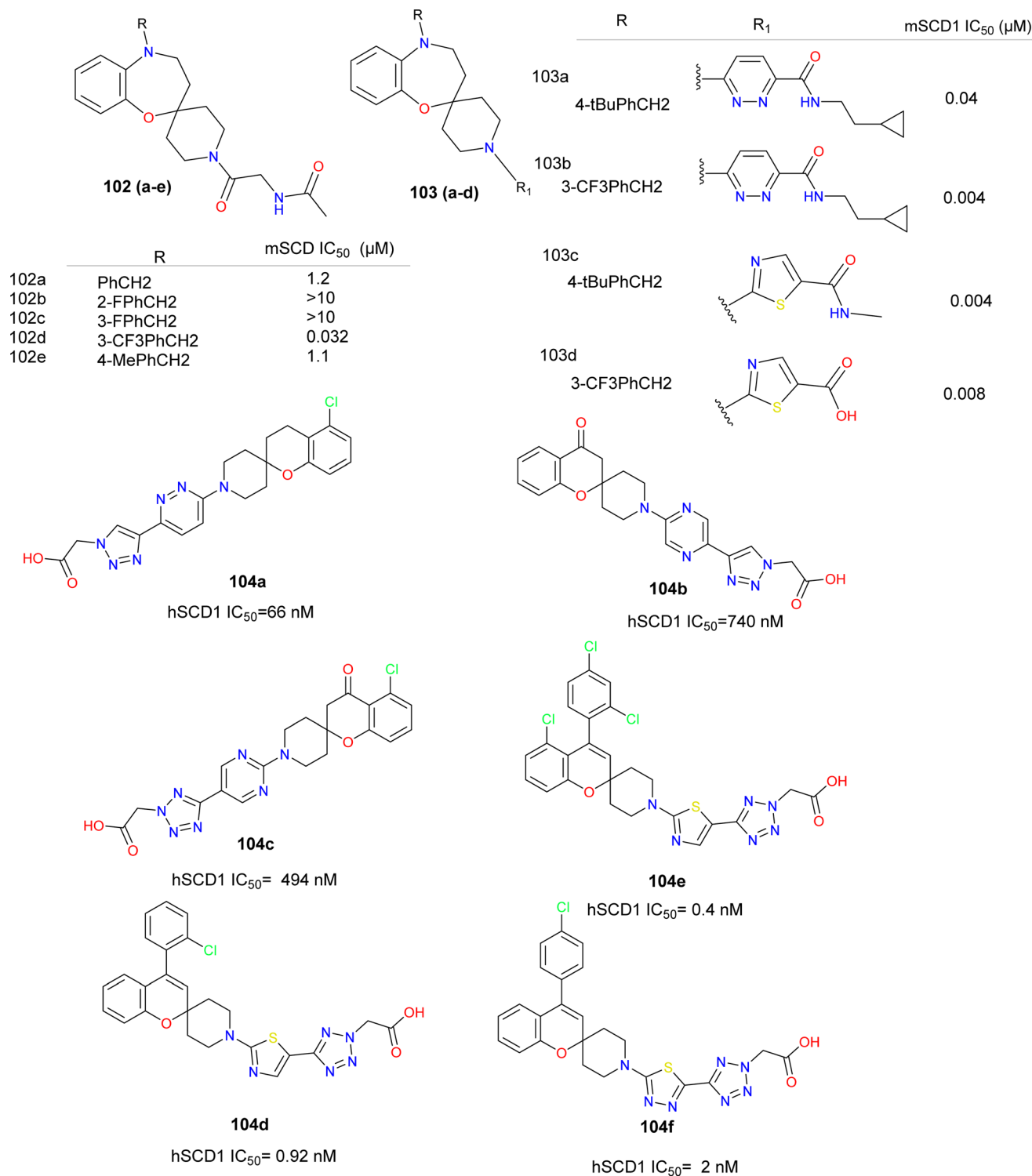


Fig. 19 Spirocyclic liver targeted SCD1 inhibitors.

accumulation.¹¹⁴ It reduced lipid synthesis by downregulating the expression of SCD1, which in turn caused the ratios of C16:1/C16:0 and C18:1/C18:0 to decrease. It also up-regulated the genes involved in fatty acid oxidation and promoted lipolysis. It lessened AST, ALT serum markers, hepatic ballooning, and macro vesicular steatosis.

Pédrono *et al.*¹¹⁵ reported that sciadonic acid, a distinguished fatty acid found in gymnosperm seeds such as pine nuts which has been reported for lowering hepatic and plasma triacylglycerols acts by inhibiting SCD1.^{116–118} When hepatic cells were treated with sciadonic acid (compound **107**), they modify the hepatic acid profile. Monounsaturated fatty acids (18:1n-9, 18:1n-7, 16:1n-7) were all decreased along with



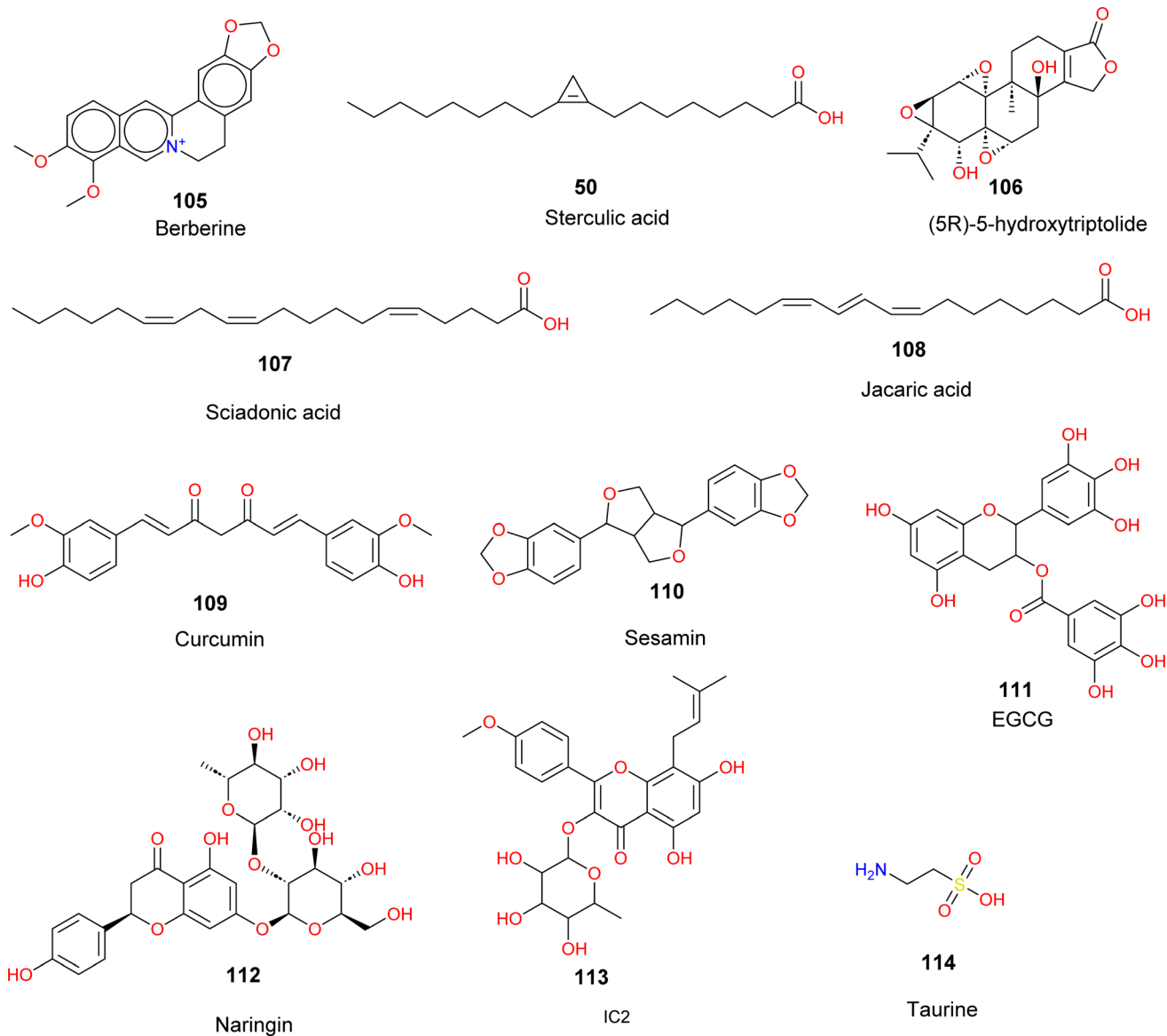


Fig. 20 Natural products based SCD1 inhibitors.

decrease in triacylglycerol amounts. Similarly, another seed oil Jacaric acid (compound **108**) reportedly decreased the desaturation index, an indicator of SCD1 activity also in further experiments it decreased the expression of SCD1 mRNA.¹¹⁹ Curcumin (compound **109**) a dietary polyphenol has been reported to suppress SCD1 regulation in various reports. Curcumin, increases fatty acid-oxidation, and reduces lipid synthesis.¹²⁰ Li *et al.* reported that curcumin inhibited SREBP-1c and SCD1, which were enhanced in liver injury and hepatic metabolic disorder.¹²¹ Bai *et al.*¹²² reported sesamin (compound **110**) a lignan from *Sesamum indicum*, showed anti-hepatic steatosis effects in MUFAs incubated mouse hepatocytes, HepG2 cells and high cholesterol diet induced NASH mice. It was found that sesamin reduced cluster of differentiation 36 (CD36) mediated fatty acid uptake and inhibited lipogenic genes like SCD1.¹²³ Li *et al.* reported Epigallocatechin-3-gallate (EGCG) (compound **111**) which is found in green tea,

inhibited the expression of SCD1, in HFD mouse groups. Treatment with EGCG improved lipid characteristic and obesity symptoms.¹²⁴

Naringin (compound **112**), a natural flavone has been reported for inhibiting SCD1 expression along with reducing weight and lipid accumulation.¹²⁵ Icarin obtained from the herb *Epimedium brevicornu* reduced lipid accumulation, increased fatty acid oxidation, showing ameliorative effect on hepatic steatosis induced by high fat diet and letrozole. Yang *et al.* showed that icaritin derivative IC2 (compound **113**) illustrated SCD1 inhibitory property in breast cancer cells.¹²⁶ Miyata *et al.* reported that taurine (compound **114**) a bile acid salt decreased hepatic damage related bio-markers, hepatic triglycerides, non-esterified fatty acids. Expression of SCD1 was significantly decreased in genetic model of hepatic steatosis.¹²⁷



Table 1 Key developments in SCD1 inhibitors during the last 10 years (2013–2023)

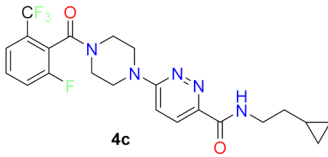
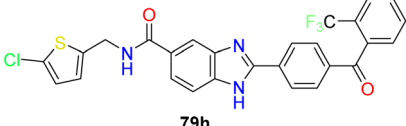
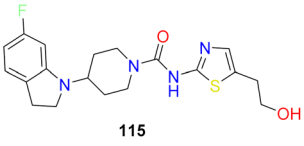
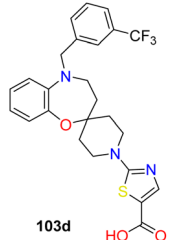
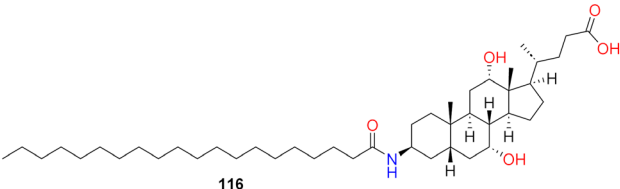
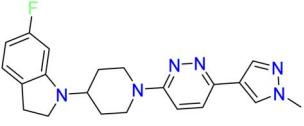
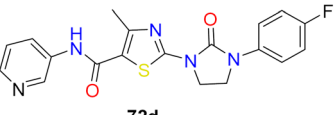
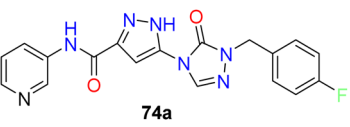
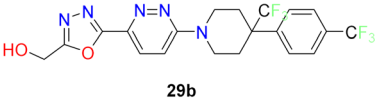
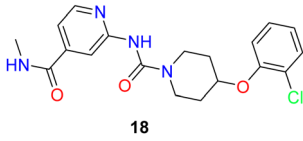
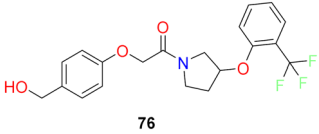
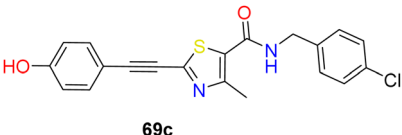
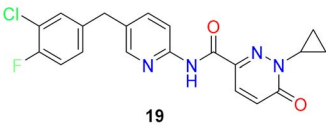
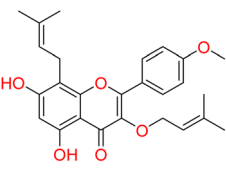
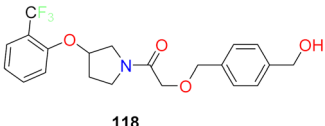
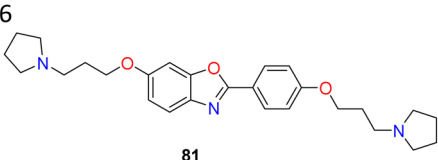
| S. no. | Structure | Remarks | Reference |
|--------|---|---|-----------|
| 1 | <p>XEN103</p>  <p>4c</p> | <p>Pyridazine showed 3-fold improved potency than pyridine. CF₃ group increases the potency</p> <p>XEN 103 showed IC₅₀ = 14 nM, with good potency and oral bioavailability</p> | 38 |
| 2 | <p>SAR 224</p>  <p>79h</p> | <p>Benzimidazole derivative SAR224 showed decrease in potency compared to the former compound SAR 707 but showed lesser side effects</p> | 87 |
| 3 |  <p>115</p> | <p>Urea based-piperidine SCD inhibitor showed good potency of IC₅₀ = 8 nM</p> | 128 |
| 4 |  <p>103d</p> | <p>Benzo-oxazepine based spirocyclic compounds showed excellent activity, pharmacokinetic properties and liver tissue distribution</p> | 106 |
| 5 | <p>Aramchol</p>  <p>116</p> | <p>Bile acid–arachidonic acid conjugate, has reached phase 3A of clinical trial, with no side effects reported till date for the treatment of NASH.</p> | 14 and 15 |
| 6 |  <p>36</p> | <p>Indoline based bicyclic heteroaryl compounds showed optimum activity but poor microsomal stability, affinity towards CYP450 inhibition</p> | 60 |
| 7 | <p>XEN 723</p>  <p>72d</p> | <p>Imidazolidinone based compound showed 560-fold improved activity than the hit molecule, and better pharmacodynamic properties</p> | 76 |
| 8 |  <p>74a</p> | <p>Maintained potency, but lesser side effects than XEN 723</p> | 77 |
| 9 | <p>T-3764518</p>  <p>29b</p> | <p>1,3,4-Oxadiazole improved pharmacokinetic properties demonstrated high binding affinity, GI activity and metabolic stability</p> | 58 and 59 |



Table 1 (Contd.)

| S. no. | Structure | Remarks | Reference |
|--------|--|--|-----------|
| 10 | <p>SSI-4</p>  <p>18</p> | Integrated <i>in silico</i> techniques that considered docking score, QSAR, pharmacophore and shape analysis yielded SSI-4 with good potency | 56 |
| 11 |  <p>76</p> | Phenoxy pyrrolidine based SCD1 inhibitor showed excellent potency IC_{50} hSCD1 = 6.8 nM | 79 |
| 12 |  <p>69c</p> | Electron withdrawing group substituted benzyl group on the right-hand side improve the potency | 75 |
| 13 |  <p>19</p> | Pyridine-pyridazinone carboxamide based SCD1 inhibitors showed optimum potency range (IC_{50} = 40–0.01 μ g) | 57 |
| 14 |  <p>117</p> | Icaritin derivative based SCD1 inhibitor | 129 |
| 15 |  <p>118</p> | Pyrrolidine based SCD1 inhibitor showed excellent potency in human liver microsomes IC_{50} = 0.9 nM | 130 |
| 16 | <p>E6446</p>  <p>81</p> | Benzo-oxazole based E6446 with flexible side chains showed IC_{50} = 0.98 μ M | 90 |

5. Summary: key SAR insights of SCD1 inhibitors

The development of potential novel SCD1 inhibitor has seen substantial progress, driven by the need to manage metabolic disorders effectively. Table 1 captures some of the significant developments in SCD1 inhibitors during the last decade. Initial efforts focused on identifying potent systemic inhibitors, but the associated adverse effects such as skin and eye reactions, necessitated a shift towards liver-targeted therapies. The liver-specific distribution of inhibitors like **MK-8245**, facilitated by organic anionic transporter proteins, underscores the importance of targeting to reduce off-target effects and enhance the therapeutic efficacy.

Initial compounds feature heterocyclic cores such as pyridine, pyrimidine, and pyrazine. Modifications have revealed that pyridazine and piperidine provide three-fold increase in potency compared to pyridine. Flexible linkers between core structures and terminal phenyl ring improves potency and cellular activity. In case of substituent effects, it has been observed that electron withdrawing groups on aromatic rings particularly CF_3 in several cases have generally enhanced the activity. Thiazole and pyridazine linkers have been extensively studied. Thiazole derivatives have shown favourable pharmacokinetic characteristics and high potency compared to other heterocycles. Other scaffolds such as imidazolidinone, thiazolopyridinone were common in certain potent compounds. In cases of six-membered systems like piperazinyl pyridazine



linker lengths have shown an influence on potency, for example cyclopropyl group with an ethyl chain showed higher potency. Chain length influenced the potency, with butyl being optimal. Amide linkage replaced with carbonyl, ether, amino or alkyl groups without significantly affecting the potency. Compounds with imidazole and pyrazole rings demonstrated significant SCD1 inhibitory activity. Substitutions at the 5-position of these rings, such as hydroxymethyl groups, enhanced the potency. Imidazole with a hydroxymethyl substitution improved the potency, indicating the importance of specific hydroxyl group positioning for activity. Bicyclic systems, such as those involving isoxazole and thiazole rings, have shown promising results. These linkers, when combined with a phenyl ring *via* a C–N bond, contributed to *in vitro* potency and *in vivo* efficacy. For example, the combination of thiazole and 2-chloro-5-trifluoromethoxyphenyl provided an excellent balance for systemic SCD1 inhibition. Substitutions at specific positions on bicyclic rings like 5-fluorobenzoisoxazole and indoline led to enhanced potency. Fluoro-substitution at the 6-position of these rings improved activity, suggesting a key role of fluorine in modulating SCD1 inhibitory effects. Spirocyclic compounds such as 4,5-dihydro-3*H*-spiro-[benzo-*b*][1,4]-oxazepine-2,4'-piperidine] exhibited favourable scaffolds for SCD1 inhibition. Substitutions at the benzyl group's 5-position, such as chlorine and trifluoromethoxy, significantly improved the potency, indicating the importance of specific hydrophobic and electron-withdrawing groups at these positions. When it comes to liver targeted distribution profile, it is attributed to moieties such as tetrazole acetic acid, which facilitate recognition by OATPs. Compounds with carboxylic acid groups demonstrated preferential liver distribution than other organs. Thiazole carboxylic acid derivatives exhibited higher potency and better pharmacokinetic profiles than pyridazine counterparts. Bicyclic linkers like bis-pyrrolidine showed improved liver selectivity.

Despite these advances, challenges remain in balancing potency, selectivity, and safety. The identification of novel scaffolds and the continuous refinement of SAR will be crucial in developing next-generation potential SCD1 inhibitor. Additionally, understanding the metabolic pathways and potential off-target effects are very much essential for optimizing these compounds for clinical use.

6. Conclusion and future prospects

The journey of development of potential SCD1 inhibitor has significantly progressed with the identification of potent systemic and liver-targeted inhibitors, and highlights the intricate balance between efficacy and safety. The structure-activity relationship studies reveal that specific heterocyclic rings, such as five-membered, bicyclic, and spirocyclic systems, play vital roles in determining the potency and selectivity of these inhibitors. Natural products have also contributed valuable scaffolds for SCD1 inhibition, demonstrating the broad potential for chemical diversity in drug design. Continued exploration of novel heterocyclic systems and their substitutions is essential to enhance the efficacy and safety profiles of identified SCD1 inhibitors. Future research can focus on

optimizing liver-targeted delivery mechanisms to minimize systemic side effects. Additionally, the integration of natural product scaffolds with synthetic modifications holds promise for developing more effective and safer SCD1 inhibitor. The future of SCD1 inhibitor development lies in the design of tissue-specific delivery strategies to mitigate systemic side effects. Nanoparticles and lipid nanoparticles targeting the liver, adipose tissue, and skeletal muscle hold promise for effectively delivering SCD1 inhibitors to their intended sites of action. A potential strategy to offset the side effects of systemic SCD1 inhibition can be to develop partial inhibitors of SCD1 enzyme, on the lines of Aramchol. It is envisaged that molecular hybridization by incorporating SCD1 inhibitory pharmacophore with anti-inflammatory pharmacophore may limit the unintended side effects of systemic SCD1 inhibition. Additionally, exploring the lipidomics of SCD1 and identifying new downstream lipid mediators will further elucidate its complex metabolic and signalling networks, offering new avenues for drug development. Understanding the dynamic conformations of SCD1 through computational studies will also enhance the design of novel inhibitors that can more effectively modulate its activity under various physiological and pathological conditions with maximum therapeutic effect and minimum side effects.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Conflicts of interest

There are no conflicts to declare.

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References

- 1 Q. Sun, X. Xing, H. Wang, K. Wan, R. Fan, C. Liu, Y. Wang, W. Wu, Y. Wang and R. Wang, *Biomed. Pharmacother.*, 2024, **170**, 115586.
- 2 N. Stefan, A. Peter, A. Cegan, H. Staiger, J. Machann, F. Schick, C. D. Claussen, A. Fritsche, H.-U. Häring and E. Schleicher, *Diabetologia*, 2008, **51**, 648–656.
- 3 Y. Zou, Y.-N. Wang, H. Ma, Z.-H. He, Y. Tang, L. Guo, Y. Liu, M. Ding, S.-W. Qian and Q.-Q. Tang, *J. Lipid Res.*, 2020, **61**, 1589–1604.
- 4 N. Zhang, Y. Wang, J. Zhang, B. Liu, X. Deng, S. Xin and K. Xu, *FASEB J.*, 2020, **34**, 15338–15363.
- 5 M. W. Hulver, J. R. Berggren, M. J. Carper, M. Miyazaki, J. M. Ntambi, E. P. Hoffman, J. P. Thyfault, R. Stevens,



- G. L. Dohm, J. A. Houmard and D. M. Muoio, *Cell Metab.*, 2005, **2**, 251–261.
- 6 P. Dobrzyn, M. Jazurek and A. Dobrzyn, *Biochim. Biophys. Acta, Bioenerg.*, 2010, **1797**, 1189–1194.
- 7 A. M. ALJohani, D. N. Syed and J. M. Ntambi, *Trends Endocrinol. Metab.*, 2017, **28**, 831–842.
- 8 U. N. Das, *Cell Chem. Biol.*, 2019, **26**, 309–311.
- 9 J. Wang, L. Yu, R. E. Schmidt, C. Su, X. Huang, K. Gould and G. Cao, *Biochem. Biophys. Res. Commun.*, 2005, **332**, 735–742.
- 10 Y. Bai, J. G. McCoy, E. J. Levin, P. Sobrado, K. R. Rajashankar, B. G. Fox and M. Zhou, *Nature*, 2015, **524**, 252–256.
- 11 B. Yang, F. Ding, F.-L. Wang, J. Yan, X.-W. Ye, W. Yu and D. Li, *Sci. Rep.*, 2016, **6**, 23446.
- 12 R. Safadi, F. M. Konikoff, M. Mahamid, S. Zelber-Sagi, M. Halpern, T. Gilat, R. Oren, R. Safadi, F. M. Konikoff, A. Hershkovitz, T. Gilat, M. Halpern, Z. Rosenthal-Galili, E. Zuckerman, S. Abu-Mouch, A. Fich, E. Sikuler, A. Issachar, N. Assy, Y. Baruch, Y. Lurie, M. Graif, N. Stern, M. Yaron, A. Blank, D. Ben Bashat, S. Zelber-Sagi, M. Mahamid, M. Mizrahi and R. Oren, *Clin. Gastroenterol. Hepatol.*, 2014, **12**, 2085–2091.
- 13 V. Ratziu, L. de Guevara, R. Safadi, F. Poordad, F. Fuster, J. Flores-Figueroa, M. Arrese, A. L. Fracanzani, D. Ben Bashat, K. Lackner, T. Gorfine, S. Kadosh, R. Oren, M. Halperin, L. Hayardeny, R. Loomba, S. Friedman, M. Abdelmalek, F. Angelico, M. Angelico, J. P. Arancibia, E. Bardou-Jacquet, F. Barrera, C. F. Barish, Y. Baruch, Z. Ben-Ari, T. Berg, M. Bourliere, J. Boursier, E. Broide, M. Carmiel, D. S. Denham, L. Di Cesare, D. L. Dumitrascu, A. Francis, S. Gawrieh, M. S. González-Huezo, P. Hillon, A. Iracheta, Z. Kayali, L. Kupcinkas, G. Lau, L. Serfaty, A. Le Cleach, C. Loguercio, M. Manns, B. I. Martinez Saldivar, E. A. Mena, L. A. Morales Garza, J. M. Neutel, L. Nikoleishvili, M. Noureddin, R. Pais, A. H. Paredes, M. Paredes, R. Peters Watkins, A. Picardi, M. Pirisi, G. P. Jofre, L. Preotescu, T. Saadi, D. Samuel, J. F. Sánchez Avila, I. Schiefke, O. Shibolet, M. S. Siddiqui, G. Torres-Mendoza, J. F. Trotter, E. Tsai, E. C. Verna, E. Zuckerman, D. Zur and A. J. Sanyal, *Nat. Med.*, 2021, **27**, 1825–1835.
- 14 R. Safadi, F. M. Konikoff, M. Mahamid, S. Zelber-Sagi, M. Halpern, T. Gilat, R. Oren, R. Safadi, F. M. Konikoff, A. Hershkovitz, T. Gilat, M. Halpern, Z. Rosenthal-Galili, E. Zuckerman, S. Abu-Mouch, A. Fich, E. Sikuler, A. Issachar, N. Assy, Y. Baruch, Y. Lurie, M. Graif, N. Stern, M. Yaron, A. Blank, D. Ben Bashat, S. Zelber-Sagi, M. Mahamid, M. Mizrahi and R. Oren, *Clin. Gastroenterol. Hepatol.*, 2014, **12**, 2085–2091.
- 15 D. Bhattacharya, B. Basta, J. M. Mato, A. Craig, D. Fernández-Ramos, F. Lopitz-Otsoa, D. Tsvirkun, L. Hayardeny, V. Chandar, R. E. Schwartz, A. Villanueva and S. L. Friedman, *JHEP Rep.*, 2021, **3**, 100237.
- 16 C. M. Paton and J. M. Ntambi, *Am. J. Physiol.: Endocrinol. Metab.*, 2009, **297**, E28–E37.
- 17 H. Sampath and J. M. Ntambi, *Ann. N. Y. Acad. Sci.*, 2011, **1243**, 47–53.
- 18 J. Shen, G. Wu, B. S. Pierce, A.-L. Tsai and M. Zhou, *J. Biol. Chem.*, 2023, **299**, 104897.
- 19 L. F. C. Castro, J. M. Wilson, O. Gonçalves, S. Galante-Oliveira, E. Rocha and I. Cunha, *BMC Evol. Biol.*, 2011, **11**, 132.
- 20 H. G. Enoch, A. Catalá and P. Strittmatter, *J. Biol. Chem.*, 1976, **251**, 5095–5103.
- 21 Y. Zheng, K. J. Eilertsen, L. Ge, L. Zhang, J. P. Sundberg, S. M. Prouty, K. S. Stenn and S. Parimoo, *Nat. Genet.*, 1999, **23**, 268–270.
- 22 M. Miyazaki, H. Sampath, X. Liu, M. T. Flowers, K. Chu, A. Dobrzyn and J. M. Ntambi, *Biochem. Biophys. Res. Commun.*, 2009, **380**, 818–822.
- 23 M. Minville-Walz, A.-S. Pierre, L. Pichon, S. Bellenger, C. Fèvre, J. Bellenger, C. Tessier, M. Narce and M. Rialland, *PLoS One*, 2010, **5**, e14363.
- 24 H. Sampath, M. T. Flowers, X. Liu, C. M. Paton, R. Sullivan, K. Chu, M. Zhao and J. M. Ntambi, *J. Biol. Chem.*, 2009, **284**, 19961–19973.
- 25 H. Sampath and J. M. Ntambi, *Curr. Opin. Clin. Nutr. Metab. Care*, 2006, **9**, 84–88.
- 26 J. M. Ntambi, *J. Lipid Res.*, 1999, **40**, 1549–1558.
- 27 J. M. Ntambi, *Prog. Lipid Res.*, 1995, **34**, 139–150.
- 28 K. H. Hellemans, J.-C. Hannaert, B. Denys, K. R. Steffensen, C. Raemdonck, G. A. Martens, P. P. Van Veldhoven, J.-Å. Gustafsson and D. Pipeleers, *PLoS One*, 2009, **4**, e7266.
- 29 H. Sampath and J. M. Ntambi, *Annu. Rev. Nutr.*, 2005, **25**, 317–340.
- 30 G. Bryzgalova, L. Lundholm, N. Portwood, J.-Å. Gustafsson, A. Khan, S. Efendic and K. Dahlman-Wright, *Am. J. Physiol.: Endocrinol. Metab.*, 2008, **295**, E904–E912.
- 31 S. B. Biddinger, M. Miyazaki, J. Boucher, J. M. Ntambi and C. R. Kahn, *Diabetes*, 2006, **55**, 2032–2041.
- 32 K. Liu, L. Lin, Q. Li, Y. Xue, F. Zheng, G. Wang, C. Zheng, L. Du, M. Hu, Y. Huang, C. Shao, X. Kong, G. Melino, Y. Shi and Y. Wang, *Proc. Natl. Acad. Sci. U. S. A.*, 2020, **117**, 2462–2472.
- 33 Z. Ye, Q. Zhuo, Q. Hu, X. Xu, M. Liu, Z. Zhang, W. Xu, W. Liu, G. Fan, Y. Qin, X. Yu and S. Ji, *Redox Biol.*, 2021, **38**, 101807.
- 34 E. Piccinin, M. Cariello and A. Moschetta, *Mol. Aspects Med.*, 2021, **78**, 100933.
- 35 A. Noto, S. Raffa, C. De Vitis, G. Roscilli, D. Malpicci, P. Coluccia, A. Di Napoli, A. Ricci, M. R. Giovagnoli, L. Aurisicchio, M. R. Torrisi, G. Ciliberto and R. Mancini, *Cell Death Dis.*, 2013, **4**, e947.
- 36 C. Wang, M. Shi, J. Ji, Q. Cai, Q. Zhao, J. Jiang, J. Liu, H. Zhang, Z. Zhu and J. Zhang, *Aging*, 2020, **12**, 15374–15391.
- 37 V. V. Balatskyi and P. Dobrzyn, *Int. J. Mol. Sci.*, 2023, **24**, 5531.
- 38 Z. Zhang, S. Sun, V. Kodumuru, D. Hou, S. Liu, N. Chakka, S. Sviridov, S. Chowdhury, D. G. McLaren, L. G. Ratkay, K. Khakh, X. Cheng, H. W. Gschwend, R. Kamboj, J. Fu and M. D. Winther, *J. Med. Chem.*, 2013, **56**, 568–583.
- 39 R. Kamboj, Z. Zhang, J. M. Fu, V. Kodumuru, S. Sviridov, K. Sadalapure, S. Liu, S. Sun, D. Hou, and N. Chakka,



- Heterocyclic derivatives and their use as therapeutic agents, WO2006/034440A2, 2006.
- 40 R. Kamboj, J. FU, V. Kodumuru, S. Liu, K. Sadalapure, N. Chakka, D. Hou and S. Sun, Bicyclic heterocyclic derivatives and their use as Stearoyl-CoA-desaturase (scd), WO2006034312A1, 2006.
- 41 R. Kamboj, Z. Zhang, S. Sviridov, V. Raina, D. Hou, V. Kodumuru and B. M. Seid, Heterocyclic derivatives and their use as stearyl-CoA desaturase, WO2006034441A1, 2006.
- 42 R. Kamboj, Z. Zaihui, J. Fu, B. M. Seid, S. Sviridov, S. Chowdhury, S. Liu and V. Kodumuru, Heterocyclic derivatives and their use as therapeutic agents, WO2006034279A1, 2006.
- 43 R. Kamboj, Z. Zhang, J. Fu, S. Sviridov, S. Sun, B. M. Seid, B. Raina, D. Hou, S. Chowdhury, S. Liu, V. Kodumuru and N. Chakka, Heterocyclic derivatives and their use as mediators of stearyl-CoA desaturase, WO2006034338A1, 2006.
- 44 R. Kamboj, Z. Zhang, J. Fu, S. Sviridov, S. Chowdhury and V. Kodumuru, Pyridazine derivatives for inhibiting human stearyl CoA-desaturase, WO2006034341A3, 2006.
- 45 G. Liu, J. K. Lynch, J. Freeman, B. Liu, Z. Xin, H. Zhao, M. D. Serby, P. R. Kym, T. S. Suhar, H. T. Smith, N. Cao, R. Yang, R. S. Janis, J. A. Krauser, S. P. Cepa, D. W. A. Beno, H. L. Sham, C. A. Collins, T. K. Surowy and H. S. Camp, *J. Med. Chem.*, 2007, **50**, 3086–3100.
- 46 H. Zhao, M. D. Serby, H. T. Smith, N. Cao, T. S. Suhar, T. K. Surowy, H. S. Camp, C. A. Collins, H. L. Sham and G. Liu, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3388–3391.
- 47 Z. Xin, H. Zhao, M. D. Serby, B. Liu, M. Liu, B. G. Szczepankiewicz, L. T. J. Nelson, H. T. Smith, T. S. Suhar, R. S. Janis, N. Cao, H. S. Camp, C. A. Collins, H. L. Sham, T. K. Surowy and G. Liu, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4298–4302.
- 48 Y. Uto, T. Ogata, Y. Kiyotsuka, Y. Ueno, Y. Miyazawa, H. Kurata, T. Deguchi, N. Watanabe, M. Konishi, R. Okuyama, N. Kurikawa, T. Takagi, S. Wakimoto and J. Ohsumi, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 341–345.
- 49 Y. Uto, Y. Kiyotsuka, Y. Ueno, Y. Miyazawa, H. Kurata, T. Ogata, T. Deguchi, M. Yamada, N. Watanabe, M. Konishi, N. Kurikawa, T. Takagi, S. Wakimoto, K. Kono and J. Ohsumi, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 746–754.
- 50 A. Thomas, V. S. Prasada Rao Lincam, S. K. Phatangare, J. N. Khairatkar, D. M. Shah, D. V. Ukirde, and D. A. More, Acetylene derivatives as stearyl Co-A desaturase inhibitors, WO2008062276A2, 2008.
- 51 S. S. Chaudhari, A. Thomas, G. B. Gudade, A. Kadam, N. P. Patil, N. Khairatkar-Joshi, D. M. Shah, Spirocyclic compounds as stearyl Co-A desaturase inhibitors, WO2009037542A2, 2009.
- 52 A. Bischoff, S. Subramanya, S. Kumar, S. Srinivasa, and A. Kumar, Novel piperazine derivatives as inhibitors of stearyl-Co-A desaturase, WO2008157844A1, 2008.
- 53 A. Bischoff, S. N. Raikar, S. R. Sammeta, G. Prabhu, H. Subramanya, and S. Kumar, Novel piperazine derivatives as inhibitors of stearyl-Co-A desaturase, WO2009117659A1, 2009.
- 54 A. Bischoff, S. Kumar, A. P. Bala Koteswara, B. Ainan, H. Ayyamperumal, A. R. Girish, S. Tatiparthi, G. Prabhu, and H. Subramanya, Novel piperidine derivatives as inhibitors of stearyl-Co-A desaturase, WO2009117676A2, 2009.
- 55 A. Bischoff, H. Subramanya, S. Kumar, S. R. Sammeta, and A. K. Vaka, Novel piperazine derivatives as inhibitors of stearyl-Co-A desaturase, *US Pat.*, US2010160323A1, 2010.
- 56 C. A. von Roemeling, T. R. Caulfield, L. Marlow, I. Bok, J. Wen, J. L. Miller, R. Hughes, L. Hazlehurst, A. B. Pinkerton, D. C. Radisky, H. W. Tun, Y. S. B. Kim, A. L. Lane and J. A. Copland, *Oncotarget*, 2018, **9**, 3–20.
- 57 K. O. Matthew, B. Pandya, D. Tardiff, P. Tivitmahaisoon and I. Wrona, Compounds and uses thereof, WO2020198026A1, 2020.
- 58 K. Imamura, N. Tomita, Y. Kawakita, Y. Ito, K. Ono, N. Nii, T. Miyazaki, K. Yonemori, M. Tawada, H. Sumi, Y. Satoh, Y. Yamamoto, I. Miyahisa, M. Sasaki, Y. Satomi, M. Hirayama, R. Nishigaki and H. Maezaki, *Bioorg. Med. Chem.*, 2017, **25**, 3768–3779.
- 59 S. Nishizawa, H. Sumi, Y. Satoh, Y. Yamamoto, S. Kitazawa, K. Honda, H. Araki, K. Kakoi, K. Imamura, M. Sasaki, I. Miyahisa, Y. Satomi, R. Nishigaki, M. Hirayama, K. Aoyama, H. Maezaki and T. Hara, *Eur. J. Pharmacol.*, 2017, **807**, 21–31.
- 60 S.-M. Yang, Y. Tang, T. Rano, H. Lu, G.-H. Kuo, M. D. Gaul, Y. Li, G. Ho, W. Lang, J. G. Conway, Y. Liang, J. M. Lenhard, K. T. Demarest and W. V. Murray, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1437–1441.
- 61 N. Kurikawa, T. Takagi, S. Wakimoto, Y. Uto, H. Terashima, K. Kono, T. Ogata and J. Ohsumi, *Biol. Pharm. Bull.*, 2013, **36**, 259–267.
- 62 H. W. Gschwend, V. Kodumuru, S. Liu, and R. Kamboj, Pyridazine Derivatives and Their Use as Inhibitors of Stearyl-CoA Desaturase-1 Activity in a Mammal, WO2005011653A2, 2005.
- 63 D. Powell and G. K. Tranmer, Azetidine derivatives as inhibitors of stearyl-coenzyme-A delta-9 desaturase, WO2010043052A1, 2010.
- 64 E. Dupont-Passelaigue, S. Mialhe, R. Jean-Pierre, J. Didier, and K. Valeille, Derivatives of 2H pyridazin-3-ones, their preparation and their use as SCD1 inhibitors, WO2011015629A1, 2011.
- 65 K. A. Atkinson, E. E. Beretta, J. A. Brown, M. Castrodad, Y. Chen, J. M. Cosgrove, P. Du, J. Litchfield, M. Makowski, K. Martin, T. J. McLellan, C. Neagu, D. A. Perry, D. W. Piotrowski, C. M. Stepan and R. Trilles, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1621–1625.
- 66 J. Fu, S. Sun, S. Serguei, Z. Zhang, D. Hou, R. Kamboj, V. Kodumuru, N. Pokrovskaja, and V. Raina, Aminothiazole derivatives as human stearyl-Co-A desaturase inhibitors, WO2007130075A1, 2007.
- 67 N. Davis and Z. Zhang, 2-(pyrazin-2-yl)-thiazole and 2-(1H-pyrazol-3-yl)-thiazole derivatives as well as related compounds as stearyl-coa desaturase (SCD) inhibitors



- for the treatment of metabolic, cardiovascular and other disorders, WO2008/024390A2, 2008.
- 68 N. Dales, Z. Zhang, J. Fonarev, J. Fu, R. Kamboj, V. Kodumuru, N. Pokrovskaia and S. Sun, 2-Substituted 5-membered heterocycles as SCD inhibitors, WO2008/074835A1, 2008.
- 69 N. Dales, Z. Zhang, R. Kamboj, J. Fu, S. Sun, N. Pokrovskaia, and S. Sviridov, Heterocyclic organic compounds, WO2008036715A1, 2008.
- 70 S. Chowdhury, N. Dales, J. Fonarev, J. Fu, D. Hou, Q. Jia, V. Kodumuru, N. Pokrovskaia, S. Sun and Z. Zhang, Heterocyclic inhibitors of stearyl-Co-A desaturase, WO2009103739A1, 2009.
- 71 N. Dales, J. Fonarev, J. Fu, R. Kamboj, V. Kodumuru, S. Liu, N. Pokrovskaia, V. Raina, S. Sun, Z. Zhang, Heterocyclic compounds suitable for the treatment of diseases related to elevated lipid level, WO2008127349A2, 2008.
- 72 C. S. Li, L. Belair, J. Guay, R. Murgasva, W. Sturkenboom, Y. K. Ramtohol, L. Zhang and Z. Huang, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5214–5217.
- 73 Y. K. Ramtohol, C. Black, C.-C. Chan, S. Crane, J. Guay, S. Guiral, Z. Huang, R. Oballa, L.-J. Xu, L. Zhang and C. S. Li, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1593–1597.
- 74 C. S. Li, L. Belair, J. Guay, R. Murgasva, W. Sturkenboom, Y. K. Ramtohol, L. Zhang and Z. Huang, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5214–5217.
- 75 A. Thomas, S. K. Phatangare, D. M. Shah, D. V. Ukirde, D. A. More, Acetylene derivatives as stearyl CoA desaturase inhibitors, CN101583600A, 2019.
- 76 S. Sun, Z. Zhang, V. Kodumuru, N. Pokrovskaia, J. Fonarev, Q. Jia, P.-Y. Leung, J. Tran, L. G. Ratkay, D. G. McLaren, C. Radomski, S. Chowdhury, J. Fu, B. Hubbard, M. D. Winther and N. A. Dales, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 520–525.
- 77 S. Sun, Z. Zhang, N. Pokrovskaia, S. Chowdhury, Q. Jia, E. Chang, K. Khakh, R. Kwan, D. G. McLaren, C. C. Radomski, L. G. Ratkay, J. Fu, N. A. Dales and M. D. Winther, *Bioorg. Med. Chem.*, 2015, **23**, 455–465.
- 78 S. Sun, Z. Zhang, V. Raina, N. Pokrovskaia, D. Hou, R. Namdari, K. Khakh, L. G. Ratkay, D. G. McLaren, M. Mork, J. Fu, S. Ferreira, B. Hubbard, M. D. Winther and N. Dales, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 526–531.
- 79 J. Li, and K. N. Lee, Phenoxy-Pyrrolidine Derivative and Its Use and Compositions, *US Pat.*, US8242286B2, 2018.
- 80 J. Li and K. N. Lee, Preparation of (S)-2-[4-(hydroxymethyl)phenoxy]-1-[3-[2-(trifluoromethyl)phenoxy]pyrrolidin-1-yl] ethanone as a stearyl-CoA desaturase (SCD1) inhibitor, WO2009019566, 2009.
- 81 M. D. Voss, G. Zoller, H. Matter, A. W. Herling, G. Biemer-Daub, A. Pfenninger, S. Haag-Diergarten, S. Keil, M. Kohlmann and H.-L. Schmidts, *Eur. J. Pharmacol.*, 2013, **707**, 140–146.
- 82 G. Liu, J. K. Lynch, J. Freeman, B. Liu, Z. Xin, H. Zhao, M. D. Serby, P. R. Kym, T. S. Suhar, H. T. Smith, N. Cao, R. Yang, R. S. Janis, J. A. Krauser, S. P. Cepa, D. W. A. Beno, H. L. Sham, C. A. Collins, T. K. Surowy and H. S. Camp, *J. Med. Chem.*, 2007, **50**, 3086–3100.
- 83 Z. Xin, H. Zhao, M. D. Serby, B. Liu, M. Liu, B. G. Szczepankiewicz, L. T. J. Nelson, H. T. Smith, T. S. Suhar, R. S. Janis, N. Cao, H. S. Camp, C. A. Collins, H. L. Sham, T. K. Surowy and G. Liu, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4298–4302.
- 84 C. McMartin and R. S. Bohacek, *J. Comput.-Aided Mol. Des.*, 1997, **11**, 333–344.
- 85 G. Zoller, M. Dietrich Voss, S. Keil, A. Herling and H. Matter, 2-heteroaryl-pyrrolo-[3, 4-c]-pyrrole derivatives and their use as SCD inhibitors, WO2008135141A1, 2008.
- 86 G. Zoller, M. D. Voss, H. Matter and A. Herling, 2-heteroaryl-pyrrolo-[3, 4-c]-pyrrole derivatives and the use thereof as SCD inhibitors, WO2010/028761A1, 2010.
- 87 H. Matter, G. Zoller, A. W. Herling, J.-A. Sanchez-Arias, C. Philippo, C. Namane, M. Kohlmann, A. Pfenninger and M. D. Voss, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1817–1822.
- 88 V. C. Joshi, A. C. Wilson and S. J. Wakil, *J. Lipid Res.*, 1977, **18**, 32–36.
- 89 D. A. Powell, Y. Ramtohol, M.-E. Lebrun, R. Oballa, S. Bhat, J.-P. Falguyret, S. Guiral, Z. Huang, K. Skorey, P. Tawa and L. Zhang, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6366–6369.
- 90 W. Wang, Y. Kong, X. Wang, Z. Wang, C. Tang, J. Li, Q. Yang, Y. Q. Chen and S. Zhu, *Cell Commun. Signaling*, 2023, **21**, 268.
- 91 D. A. Claude-marie, A. Dean, W. Fillmore, and C. Martin, N-thiazolyl-1, 2, 3, 4-tetrahydro-6-isoquinolinecarboxamide derivatives as inhibitors of stearyl coenzyme-A desaturase, WO2009150196A1, 2009.
- 92 K. Dmitry, J. Zablocki, and E. Parkhill, Pyrrolotriazinone derivatives for use as stearyl Co-A desaturase inhibitors, WO2009124259A1, 2009.
- 93 K. Dmitry and Z. Jeff, Triazolopyridinone derivatives for use as stearyl Co-A desaturase inhibitors, *US Pat.*, US20090253738A1, 2009.
- 94 Y. Deng, Z. Yang, G. W. Shipps, S.-M. Lo, R. West, J. Hwa, S. Zheng, C. Farley, J. Lachowicz, M. van Heek, A. S. Bass, D. P. Sinha, C. R. Mahon and M. E. Cartwright, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 791–796.
- 95 N. Dales, J. Fonarev, J. Fu, and Z. Zhang, Spiro derivatives for the modulation of stearyl-Co-A desaturase, *US Pat.*, US20120010135A1, 2013.
- 96 J. W. G. Shipps, Z. Yang, and R. West, Spirocyclic oxazepine compounds as stearyl-Co-A delta-9 desaturase inhibitors, WO2011/011506A1, 2011.
- 97 R. M. Oballa, L. Belair, W. C. Black, K. Bleasby, C. C. Chan, C. Desroches, X. Du, R. Gordon, J. Guay, S. Guiral, M. J. Hafey, E. Hamelin, Z. Huang, B. Kennedy, N. Lachance, F. Landry, C. S. Li, J. Mancini, D. Normandin, A. Pocaí, D. A. Powell, Y. K. Ramtohol, K. Skorey, D. Sørensen, W. Sturkenboom, A. Styhler, D. M. Waddleton, H. Wang, S. Wong, L. Xu and L. Zhang, *J. Med. Chem.*, 2011, **54**, 5082–5096.
- 98 M. Niemi, *Pharmacogenomics*, 2007, **8**, 787–802.
- 99 S. Léger, W. C. Black, D. Deschenes, S. Dolman, J.-P. Falguyret, M. Gagnon, S. Guiral, Z. Huang, J. Guay,



- Y. Leblanc, C.-S. Li, F. Massé, R. Oballa and L. Zhang, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 499–502.
- 100 G. Liu, J. K. Lynch, J. Freeman, B. Liu, Z. Xin, H. Zhao, M. D. Serby, P. R. Kym, T. S. Suhar, H. T. Smith, N. Cao, R. Yang, R. S. Janis, J. A. Krauser, S. P. Cepa, D. W. A. Beno, H. L. Sham, C. A. Collins, T. K. Surowy and H. S. Camp, *J. Med. Chem.*, 2007, **50**, 3086–3100.
- 101 D. Powell, M. Lebrun, S. Bhat and Y. K. Ramtohol, Novel substituted heteroaromatic compounds as inhibitors of stearoyl-coenzyme-A delta-9 desaturase, WO2009/129625, 2009.
- 102 N. Lachance, Y. Gareau, S. Guiral, Z. Huang, E. Isabel, J.-P. Leclerc, S. Léger, E. Martins, C. Nadeau, R. M. Oballa, S. G. Ouellet, D. A. Powell, Y. K. Ramtohol, G. K. Tranmer, T. Trinh, H. Wang and L. Zhang, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 980–984.
- 103 N. Lachance, S. Guiral, Z. Huang, J.-P. Leclerc, C. S. Li, R. M. Oballa, Y. K. Ramtohol, H. Wang, J. Wu and L. Zhang, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 623–627.
- 104 T. Iida, M. Ubukata, I. Mitani, Y. Nakagawa, K. Maeda, H. Imai, Y. Ogoshi, T. Hotta, S. Sakata, R. Sano, H. Morinaga, T. Negoro, S. Oshida, M. Tanaka and T. Inaba, *Eur. J. Med. Chem.*, 2018, **158**, 832–852.
- 105 N. Lachance, S. Guiral, Z. Huang, J.-P. Leclerc, C. S. Li, R. M. Oballa, Y. K. Ramtohol, H. Wang, J. Wu and L. Zhang, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 623–627.
- 106 Y. Deng, Z. Yang, G. W. Shipps, S.-M. Lo, R. West, J. Hwa, S. Zheng, C. Farley, J. Lachowicz, M. van Heek, A. S. Bass, D. P. Sinha, C. R. Mahon and M. E. Cartwright, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 791–796.
- 107 L. J. Philippe, C. S. Li, and O. M. Moradei, Novel spiro compounds useful as inhibitors of stearoyl-coenzyme-A delta-9 desaturase, WO2011011872A1, 2011.
- 108 F. Rejean, N. Lachance, C. S. Li, and G. Tranmer, Novel spiro compounds useful as inhibitors of stearoyl-coenzyme-A delta-9 desaturase, WO2011047481A1, 2011.
- 109 X. Zhu, H. Bian, L. Wang, X. Sun, X. Xu, H. Yan, M. Xia, X. Chang, Y. Lu, Y. Li, P. Xia, X. Li and X. Gao, *Free Radical Biol. Med.*, 2019, **141**, 192–204.
- 110 L. C. Ortinou, R. T. Pickering, K. J. Nickelson, K. L. Stromsdorfer, C. Y. Naik, R. A. Haynes, D. E. Bauman, R. S. Rector, K. L. Fritsche and J. W. Perfield, *ISRN Endocrinol.*, 2012, **2012**, 1–11.
- 111 F. Enrique Gomez, D. E. Bauman, J. M. Ntambi and B. G. Fox, *Biochem. Biophys. Res. Commun.*, 2003, **300**, 316–326.
- 112 C. A. Major, K. Ryan, A. J. Bennett, A. L. Lock, D. E. Bauman and A. M. Salter, *J. Lipid Res.*, 2008, **49**, 1456–1465.
- 113 M. P. Dallaire, H. Taga, L. Ma, B. A. Corl, R. Gervais, Y. Lebeuf, F. J. Richard and P. Y. Chouinard, *J. Dairy Sci.*, 2014, **97**, 6411–6425.
- 114 Y. Dong, H. Lu, Q. Li, X. Qi, Y. Li, Z. Zhang, J. Chen and J. Ren, *Life Sci.*, 2019, **232**, 116644.
- 115 F. Pédrone, N. Boulter-Monthéan, F. Boissel, J. Ossemond and F. Lohézic-Le Dévéhat, *Mol. Nutr. Food Res.*, 2017, **4**, 1700567.
- 116 Y. Endo, Y. Osada, F. Kimura and K. Fujimoto, *Nutrition*, 2006, **22**, 553–558.
- 117 Y. Endo, Y. Osada, F. Kimura, H. Shirakawa and K. Fujimoto, *Biosci., Biotechnol., Biochem.*, 2007, **71**, 231–233.
- 118 Y. Endo, K. Tsunokake and I. Ikeda, *Biosci., Biotechnol., Biochem.*, 2009, **73**, 577–581.
- 119 N. Shinohara, J. Ito, T. Tsuduki, T. Honma, R. Kijima, S. Sugawara, T. Arai, M. Yamasaki, A. Ikezaki, M. Yokoyama, K. Nishiyama, K. Nakagawa, T. Miyazawa and I. Ikeda, *J. Oleo Sci.*, 2012, **61**, 433–441.
- 120 R. Taebi, M. R. Mirzaiey, M. Mahmoodi, A. Khoshdel, M. A. Fahmidehkar, M. Mohammad-Sadeghipour and M. R. Hajizadeh, *Gene Rep.*, 2020, **18**, 100581.
- 121 N. Lu, X. Li, J. Yu, Y. Li, C. Wang, L. Zhang, T. Wang and X. Zhong, *Lipids*, 2018, **53**, 53–63.
- 122 Y. Bai, T. Zhang, Z. Hu, Y. Zhang, D. Wang, M. Zhou, Y. Zhang, F. Zhang and X. Kong, *Biochem. Pharmacol.*, 2024, **224**, 116240.
- 123 Y. Hai, L. Zuo, M. Wang, R. Zhang, M. Wang, L. Ren, C. Yang and J. Wang, *Molecules*, 2023, **28**, 517.
- 124 F. Li, C. Gao, P. Yan, M. Zhang, Y. Wang, Y. Hu, X. Wu, X. Wang and J. Sheng, *Front. Pharmacol.*, 2018, **9**, 1366.
- 125 H. Mu, Q. Zhou, R. Yang, J. Zeng, X. Li, R. Zhang, W. Tang, H. Li, S. Wang, T. Shen, X. Huang, L. Dou and J. Dong, *Front. Microbiol.*, 2020, **11**, 585066.
- 126 C. Yang, Y.-Y. Jin, J. Mei, D. Hu, X. Jiao, H.-L. Che, C.-L. Tang, Y. Zhang and G.-S. Wu, *Cancer Cell Int.*, 2022, **22**, 202.
- 127 M. Miyata, A. Funaki, C. Fukuhara, Y. Sumiya and Y. Sugiura, *J. Toxicol. Sci.*, 2020, **45**, 87–94.
- 128 S.-M. Yang, Y. Tang, R. Zhang, H. Lu, G.-H. Kuo, M. D. Gaul, Y. Li, G. Ho, J. G. Conway, Y. Liang, J. M. Lenhard, K. T. Demarest and W. V. Murray, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 6773–6776.
- 129 W. Guosheng, Y. Chen, J. Yiyuan, T. Chunlei, C. Yongquan and C. Guozhen, Medicine for inhibiting stearoyl-CoA desaturase1, CN113057955A, 2021.
- 130 D. A. Bullough, J. D. Roth and J. G. Foulkes, Methods of treating non-alcoholic steatohepatitis with a SCD-1 inhibitor, WO2022178261A1, 2022.

