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Expert Opinion

Stearoyl-CoA desaturase inhibitors: update on patented compounds

Gang Liu
Ambit Biosciences, 4215 Sorrento Valley Blvd, San Diego, CA 92121, USA

Background: Stearoyl-CoA desaturase 1 (SCD1) has been implicated as a novel therapeutic target for the treatment of a variety of disease states, including hepatic steatosis, metabolic diseases, skin and eye disorders, and certain cancers. *Objective/method*: This review focuses on the novel composition of matter patents in the area of small molecule SCD1 inhibitors, along with their pharmacological effects in relevant disease models. The prospect of targeting SCD1 inhibition as a novel therapeutic approach is discussed. *Conclusion*: The rapid development of SCD1 inhibitors is evidenced by the increasing number of patent applications published and the number of promising preclinical compounds that have emerged in the past 5 years. Between January 2005 and February 2009, there were ~ 70 SCD1 inhibitor patent applications published.

Keywords: acne, antisense oligonucleotide, blepharitis, cancer, desaturation index, dry eye syndrome, dyslipidemia, epidermal lipid barrier, hepatic steatosis, insulin resistance, lipid metabolism, meibomian gland, meibum, mono-unsaturated fatty acid, obesity, rosacea, saturated fatty acid, sebaceous gland, seborrheic skin, stearoyl-CoA desaturase

Expert Opin. Ther. Patents (2009) 19(9):1169-1191

1. Introduction

Stearoyl-CoA desaturase (SCD) is a lipogenic enzyme that catalyzes the critical committed step in the biosynthesis of monounsaturated fatty acids (MUFA). The function of SCD is to introduce a *cis*-double bond between carbons 9 and 10 of long-chain saturated fatty acyl-CoAs either derived from the diet or synthesized *de novo* [1]. The major desaturation substrates are palmitoyl(16:0)-CoA and stearoyl(18:0)-CoA, which are converted to palmitoleoyl(16:1)-CoA and oleoyl (18:1)-CoA, respectively [2]. MUFAs derived from the activity of SCD are the most abundant MUFAs in various lipids, including triglycerides (TG), cholesterol esters, wax esters and phospholipids. SCD activity requires the presence of NADH and two other proteins, the electron acceptor cytochrome b5 and the flavoprotein cytochrome b5 reductase to function properly [1,3]. Recently, the functions of MUFA have expanded beyond the realm of lipid building blocks. It is demonstrated that adipose tissue uses lipokines such as C16:1-palmitoleate, but not C18:1-oleate, to communicate with distant organs and regulate systemic metabolic homeostasis [4].

A number of SCD genes have been identified (SCD1 – 4 in mouse, two SCD genes in rat, and SCD1 and SCD5 in humans). The SCD-gene products are integral endoplasmic reticulum membrane proteins with four *trans*-membrane domains. The SCD enzymes have a 30-aa N-terminal sequence responsible for their rapid degradation and short half-life of 3 – 4 h. In adult mice, the SCD1 is prominently expressed in lipogenic tissues (liver and adipose) and sebaceous glands, SCD2 in most tissues except liver [5], SCD3 in skin, preputial and harderian gland [6], and SCD4 in the heart [7]. The two human SCD genes show 85% homology to the murine SCD1 gene [4,8,9]. SCD genes are tightly regulated

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by signals such as insulin, leptin, carbohydrates, fatty acids, nutritional status and temperature.

Using genetic manipulation, SCD1 has been shown to play a crucial role in lipid synthesis and regulation of energy metabolism, at least in rodents. SCD1 deficiency in mice, either naturally in asebia (*ab*^{J}/*ab*^{J}) mice [10] or by targeted disruption [11], has been shown to reduce adiposity and increase energy expenditure. Despite the fact that SCD$^{-/-}$ mice consume more food, they clearly show a leaner phenotype when backcrossed to B6 *ob/ob* mice or placed on a high fat diet [12]. The increased energy expenditure is owing to increased fatty acid oxidation through activation of AMPK in liver [13]. SCD1-deficient mice also have decreased levels of tissue TG, cholesterol esters and wax esters, and lower TG content in plasma very-low-density lipoprotein and low-density lipoprotein (LDL) fractions [14-15]. Interestingly, it was shown recently that SCD deficiency in BTBR *ob/ob* mice accelerated the progression to severe diabetes, despite the improved insulin sensitivity [16].

Inhibition of SCD1 activity through antisense oligonucleotide (ASO) knockdown of gene expression in diet induced obese (DIO) mice also resulted in reduced adiposity, improved hepatic steatosis and increased energy expenditure [17-18]. ASO treatment led to the re-programming of the lipogenic genes and FAO genes. In Sprague-Dawley rats fed a high fat diet, SCD activity knockdown with ASOs improved hepatic insulin sensitivity, as indicated by increased glucose infusion rate and decreased hepatic glucose output during a hyperinsulinemic clamp study [17].

SCD1 plays a major role in the *de novo* synthesis of TGs, cholesterol esters and wax esters required for normal skin and eyelid function. Like the asebia mice, the SCD1$^{-/-}$ mice exhibited cutaneous abnormalities with atrophic sebaceous gland and narrow eye fissure with atrophic meibomian glands. The SCD1$^{-/-}$ mice were deficient in eyelid TGs, cholesterol esters and wax esters, and had significant elevation of free cholesterol in the skin and eyelid [19]. Interestingly, the dietary supplement with oleate could not reverse the skin and eyelid phenotypes in SCD1 deleted animals, suggesting compartmentalization in the production and utilization of the MUFA by the body.

In 2007, Binczek *et al.* published a detailed study linking the obesity resistance of the SCD1$^{-/-}$ mouse with disruption of the epidermal lipid barrier and adaptive thermoregulation [20]. It was demonstrated that SCD1 deficiency disrupts the epidermal lipid barrier and leads to uncontrolled transepidermal water loss, breakdown of adaptive thermoregulation and cold resistance, as well as a metabolic wasting syndrome. The loss of ω-hydroxylated very long-chain fatty acids and ceramides substituted with ω-hydroxylated very long-chain fatty acids covalently linked to corneocyte surface proteins leads to the disruption of the epidermal lipid barrier in SCD$^{-/-}$ mutants. SCD1 deficiency abolishes expression of the key transcription factor Lef1, which is essential for interfollicular epidermis, sebaceous glands and hair follicle development.

From therapeutic point of view, chronic blepharitis and dry eye syndrome, which constitute one of the most common and frustrating eye disease conditions in humans, are owing to lipid abnormalities in meibum. The alteration of SCD activity in the eyelid can be implicated in human eye diseases. The same rationale can be extended to treating certain skin disorders, characterized by excessive/imbalanced secretion of lipid from sebaceous gland, including acne, rosacea and seborrheic skin.

MUFAs are also involved in the regulation of cell proliferation, programmed cell death and lipid-mediated cytotoxicity. A positive correlation between high levels of tissue MUFA and several types of cancer has been reported. Recently, a couple of studies suggested a more robust causal relationship between the function of SCD1 and cancer development. In an RNAi-based screening, SCD1 specific siRNA significantly reduced the survival of multiple human tumor cell lines [21]. In a second study, the stable knockdown of SCD1 gene expression in A549 human lung adenocarcinoma cells decreased the ratio MUFA:SFA in total lipids, inhibited the incorporation of glucose into cell lipids, decreased cell proliferation and anchorage-independent growth, and elevated the rate of apoptosis. The reduction of SCD1 expression in lung cancer cells significantly delayed the formation of tumors and reduced the growth rate of tumor xenografts in mice [22].

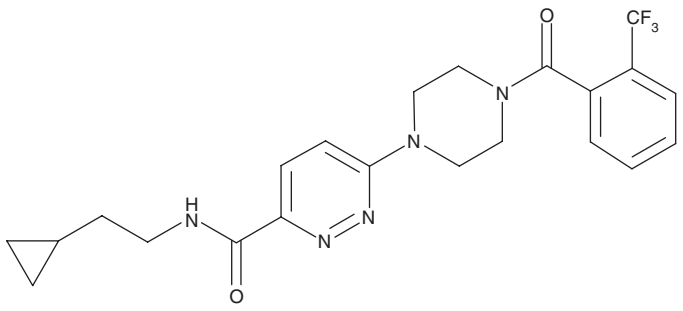
2. Small molecule inhibitors of SCD1

Although SCD1 has been known since the 1970s, the development of SCD1 inhibitors is a recent phenomenon, following the better understanding of SCD1 biological function in rodents and humans. Before then, there have been scattered reports on natural product-based SCD1 inhibitors, including 9-thiastearic acid [23], cyclopropenoid fatty acids [24] and certain conjugated linoleic acid isomers [25]. Unfortunately, these SCD inhibitors are not useful therapeutically due to lack of sufficient potency and specificity.

Because SCD is an integral membrane protein, no crystal structure of the enzyme is available for guiding structure-based drug design. The discovery of novel leads for inhibiting SCD1 relied on the traditional high-throughput screening and subsequent scaffold hopping. No SCD1 and SCD2 selectivity information regarding any of the SCD inhibitors described herein have been disclosed, and we can only assume that these are Δ-9 desaturase inhibitors that hit both SCD1 and SCD2 equally well.

2.1 Xenon Pharmaceuticals

The first reported SCD1 inhibitor was disclosed by Xenon Pharmaceuticals in 2005 [26,27,28]. The basic molecular scaffold is a central pyridazine (**1**)/pyridine (**2**) substituted by functionalized piperazine benzamide on the one end, and a carboxamide on the other end, as shown in **Figure 1**. Compound **2** was highlighted in one of the patent applications



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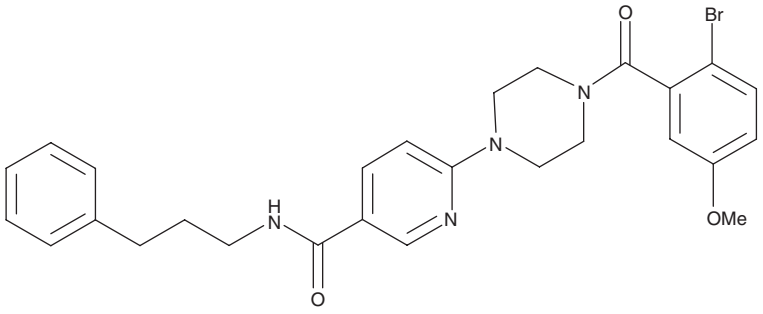


2

mSCD1 IC_{50} = 100 nM
(US2005/0119251)

Figure 1. First potent and specific SCD1 inhibitors reported.

as a sub-micromolar mouse SCD1 inhibitor. As this series of compounds evolved, all the three key elements (pyridazine/pyridine core, piperazine benzamide and carboxamide) have been modified to generate novel analogues. However, because no biological data have been reported for most of these compounds, it is difficult to accurately access the SAR progression represented by these compounds.

The pyridazine/pyridine core has been replaced with other monocyclic and bicyclic rings, including pyrimidine (both regioisomers) and pyrazine [26], pyridinone [29], phenyl ring [30], imidazolopyridazine and benzimidazole [31], as shown in **Figure 2**.

It seems that the six-membered heteroaryl ring can be replaced with the five-membered rings, such as [1,2,4]thiadiazole (**3**), pyrazole (**4**) and thiazole (**5**), as pyridazine surrogates [32] (**Figure 3**).

Interestingly, the pyridazine ring could even be changed to an acyclic amidine structure (**6**), as claimed in this application [33]. Non-aromatic thiazolidinedione piperidine derivatives, such as **7**, were also claimed as SCD1 inhibitors by Xenon [34]. Other uncommon heterocycles, including fused tetrahydro-1,6-naphthyridine (**8**) and tetrahydrofuro[2,3-c]pyridine (**9**), have been incorporated in the scaffold as SCD1 inhibitors (**Figure 4**)[35].

The piperazine benzamide portion of **1** was also extensively modified, as summarized in **Figure 5**. For example, piperazine benzamide was modified to a piperidine benzamide [36], and to an aniline piperidine (nitrogen on the other side) and a bicyclic 3-azabicyclo[3.1.0]hexan-6-amine [37]. A double bond linker between piperidine and phenyl ring can also be utilized to afford SCD1 inhibitors [38]. Piperazine could also be modified to cyclohexane [39] or tetrahydropyrimidine [40] to yield different sets of SCD1 inhibitors.

It is interesting to note that a linker, such as oxygen, amino (**10**) and carbonyl groups, can be inserted between the pyridazine and the piperidine ring, as claimed in this application [41]. The linker between the piperazine and the aryl group may not be necessary as shown in this application claiming the directly-connected heteroarylpiperazine derivatives as SCD1 inhibitors, exemplified by **11** in **Figure 6** [42]. The pyridazine has been cyclized with the piperazine ring to give a novel series of tricyclic SCD1 inhibitors, as shown in **12** [43].

The carboxamide portion of the SCD1 inhibitor was also replaced with many of the known bioisosteres, such as imidazoline, oxadiazole (three different regioisomers), imidazopyridine and a cyclic urea, as shown in **Figure 7** [44].

According to this application, the carboxamide could also be moved from a 1,4 to a 1,3 arrangement (**13**) on the pyridine

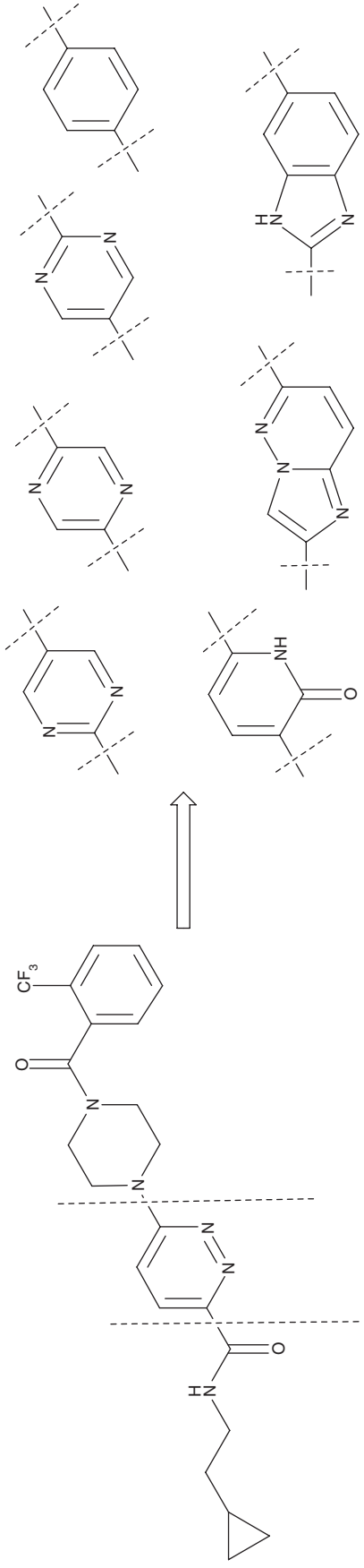


Figure 2. Pyridazine/pyridine core modification of SCD1 inhibitors.

template, as shown in **Figure 8** [45]. To further expand the structural diversity, the carboxamide has been cyclized to the neighboring pyridazine ring to give a tricyclic fused oxazepinone derivative **14** [46], or cyclized to the phenyl ring to generate a phthalimide type of compound **15** [47]. In an extreme case, a series of macrocycles has been claimed by cyclizing both ends of the compound, such as **16**, to generate an interesting scaffold [48].

In September 2004, Xenon and Novartis forged a partnership to co-develop SCD1 inhibitors. There have not been any updates regarding the status of the collaboration. We can only guess that the thiazole carboxamides, represented by **5**, have attracted most of the attention in the collaboration, based on the number of patent applications that have appeared since then.

A new series of thiazole carboxamides was reported, as exemplified by **17** in **Figure 9** [49]. Further modification of one of the carboxamides yielded interesting 2-oxopyridin-1(2H)-yl thiazole carboxamide derivatives [50]. Two examples **18** and **19** are shown in **Figure 9** with IC_{50} values of 50 and 30 nM against mouse SCD1, respectively.

A number of other motifs have been introduced as carboxamide replacements and yielded potent mouse SCD1 inhibitors. The two examples of 2-(pyrazin-2-yl)-thiazole (**20**) and 2-(1H-pyrazol-3-yl)-thiazole (**21**) derivatives (**Figure 10**) have IC_{50} values of 42 and 49 nM, respectively [51]. A series of thiazolyl pyrrolidinone and piperidinone-based SCD1 inhibitors has been disclosed in another application [52]. Two representative examples (**22** and **23**) are shown in **Figure 10** with no biological data disclosed. Similar to **21**, another application expanded on the triazolyl thiazole-based SCD1 inhibitors [53]. Two representative compounds (**24** and **25**) have been reported to have IC_{50} values of 120 and 10 nM, respectively. More recently, dihydroimidazolinone and imidazolidinone as carboxamide replacements have been claimed, as exemplified by compounds **26** and **27** (**Figure 10**) [54].

2.2 Merck Frosst Canada

Another major player in the field of SCD1 inhibitors is Merck Frosst Canada. A series of azacyclohexane derivatives have been claimed to be SCD1 inhibitors in a number of patent applications over the past 3 years. Because there are no biological data disclosed so far, it is hard to assess the status of the project. The first application contained thiazolyl oxadiazole compounds (**26** and **27**) shown in **Figure 11**, very similar to compound **5** from the Novartis/Xenon collaboration [55]. The second application included pyridazine derivatives with different carboxamide bioisosteres (**28** and **29**) [56].

The third application contains compounds with fused bicyclic heteroaryls (**Figure 12**), including thiazolopyrimidinone (**30**), thiazolopyrimidine (**31**), purine (**32**) or 1H-imidazo[4,5-c] pyridin-4-amine (**33**), replacing the pyridazine core [57-58]. In this particular patent application, further bicyclic examples (**34** and **35**) were claimed [59].

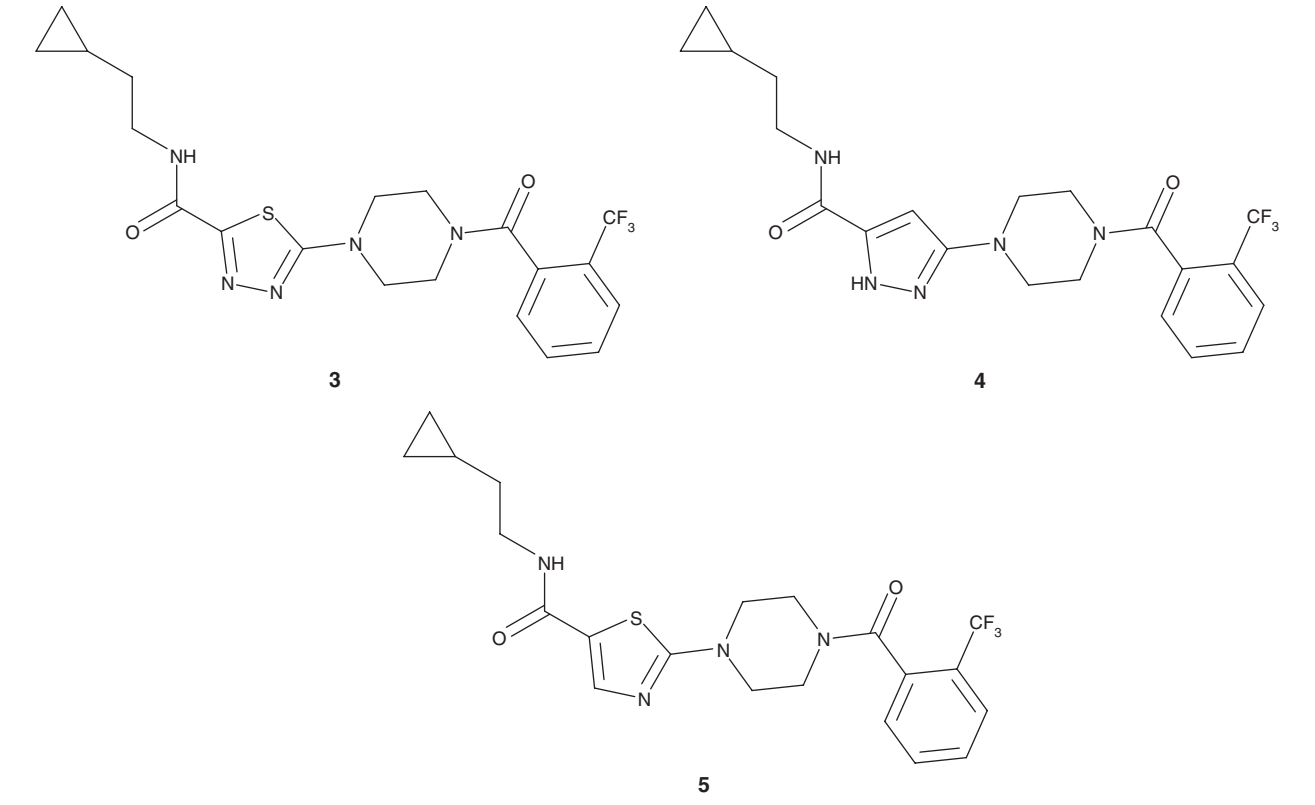


Figure 3. Five-membered ring replacements for pyridazine/pyridine core.

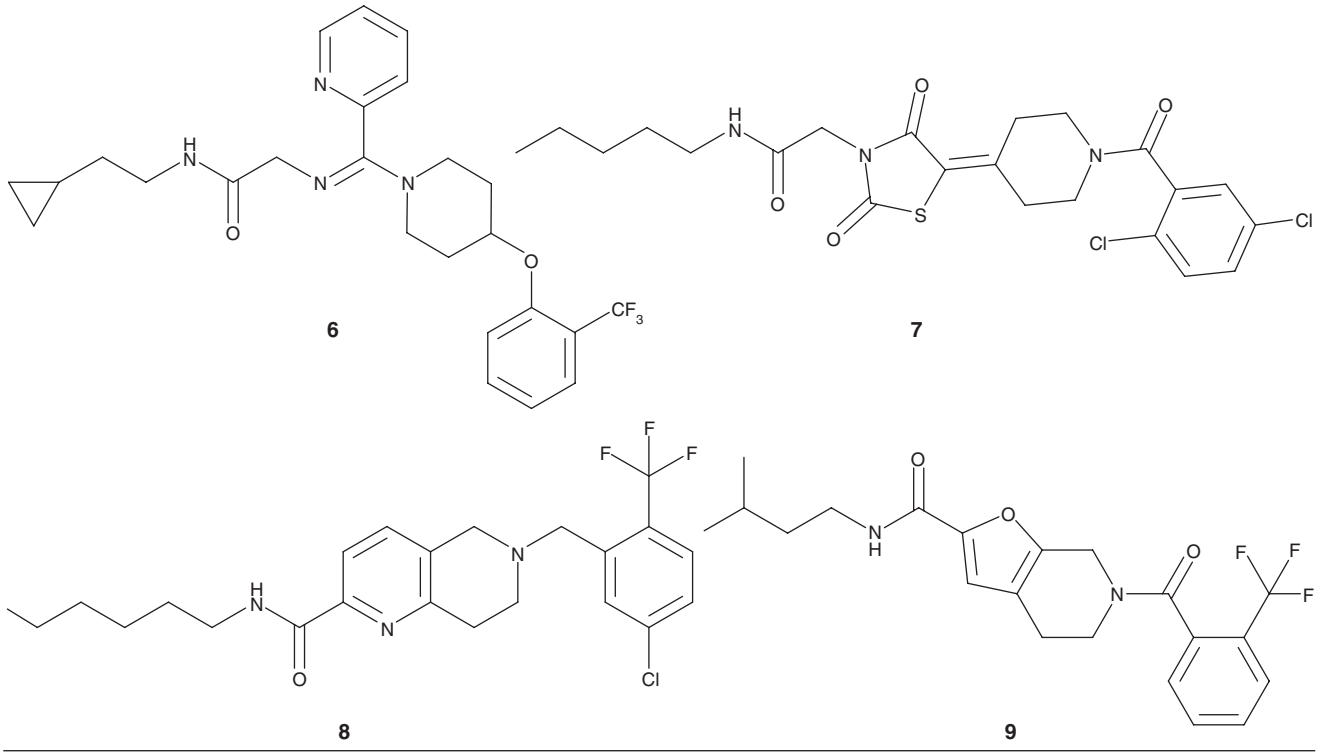


Figure 4. Other pyridazine/pyridine core replacements as SCD1 inhibitors.

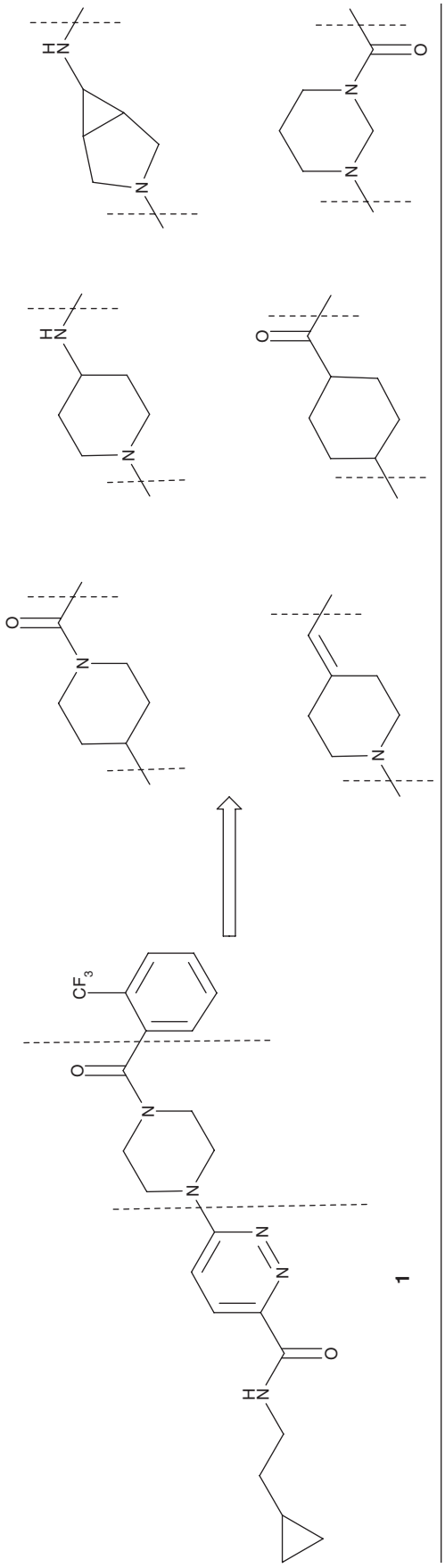


Figure 5. Piperazine modification of the SCD1 inhibitors.

Consistent with the claims by Xenon, the pyridazine ring was shown to be unnecessary. It can be replaced with a plain phenyl ring as shown with compounds **36** and **37** (**Figure 13**) [60].

The six-membered piperidine could also be replaced with a four membered azetidine (**Figure 14**, **38–39**) as demonstrated in this particular application [61], or a 5-membered pyrrolidine ring (**40**) in another application [62].

Presumably in an effort to increase aqueous solubility, a set of carboxylic acid containing compounds (**41** and **42**) were claimed as SCD1 inhibitors (**Figure 15**) [63]. A combination of many features of the previous series was reflected in the latest patent application from Merck Frosst, as represented by compounds **43** and **44** [64]. Another patent application also described tetrazole acetic acid as SCD inhibitors with the aliphatic portion of the molecule further extended out, as shown in examples **45** and **46** [65].

2.3 Abbott

A number of scaffold-hopping approaches were taken by Abbott Scientists to generate pharmacological tools for validating SCD1 as target for obesity and dyslipidemia. Based on SCD1 inhibitor **1**, a structure–activity relationship (SAR) campaign directed at addressing the metabolic stability and potency issues led to the discovery of highly potent, selective, orally bioavailable SCD1 inhibitors with robust cellular activity in HepG2 cells, as represented by compound **47** (**Figure 16**) [66]. Compound **47** is not only a potent SCD1 inhibitor against mouse and human SCD1s with IC_{50} values of 4.5 and 26 nM, respectively, but also potently inhibits the long-chain fatty acid-CoA desaturation in HepG2 cell with an IC_{50} value of 6.8 nM as measured by [^{13}C]-C16:1/[^{13}C]-C16:0. Compound **47** also exhibits favorable rat PK profiles suitable for *in vivo* studies (CL = 0.28 (l h)/kg, Vss = 0.71 l/kg, AUC = 10.66 (μg h)/ml and F = 59%).

Further SAR effort through scaffold hopping from the pyridazine template resulted in two different series of potent SCD1 inhibitors. The first glycine amide pyridine compound **48** inhibited potently human SCD1 with an IC_{50} value of 90 nM, while a pyrazine compound **49** demonstrated an IC_{50} value of 37 nM against human SCD1 (**Figure 17**) [67]. The second piperidine urea series was discovered at the same time. Lead compound **50** exhibited excellent *in vitro* profiles (IC_{50} < 4 nM versus mSCD1, 37 nM versus hSCD1) and PK properties (CL = 0.4 (l h)/kg, Vss = 0.4 l/kg, oral AUC = 13.3 (μg h)/ml, oral F = 102%) [68].

A desaturation index (DI), defined as the ratio of 16:0:16:1n7 or 18:0:18:1n9, has been used as an *in vivo* biomarker for SCD1 activity. SCD1 inhibitor **50** was evaluated in *ob/ob* mice for DI changes [68]. A dose-dependent liver TG DI lowering effect was observed with the treatment of SCD1 inhibitor **50** dosed at 0.3, 3, 10 mpk b.i.d. for four-and-a-half days, with the high dose demonstrating normalization of liver TAG DI. Similar degrees of DI decreases were observed with other liver lipid classes, including phospholipids, cholesterol ester and diacylglycerol. These

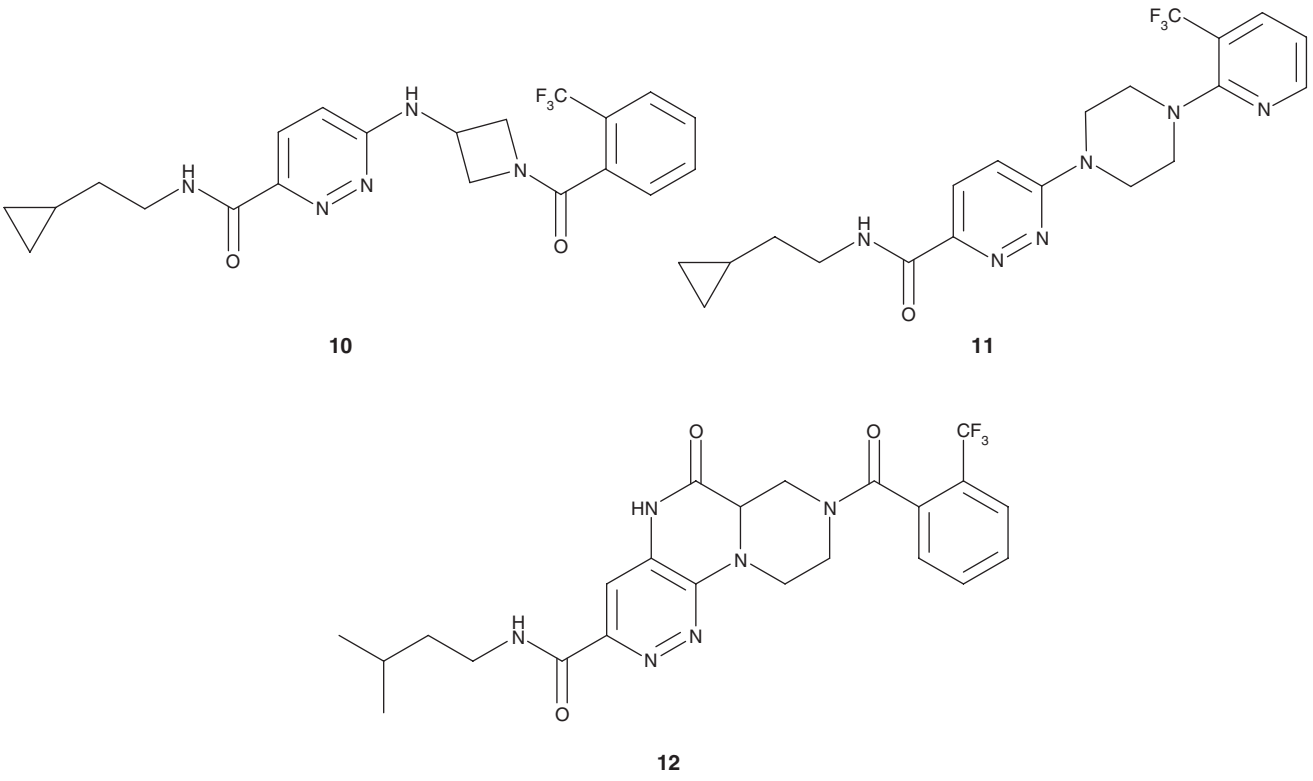


Figure 6. Other piperazine replacements for SCD1 inhibitor design.

observations demonstrated a clear correlation between *in vitro* inhibitory activity and *in vivo* DI reduction.

At the Chicago ACS National Meeting in March 2007, the profiles of compound **50** in an efficacy study in DIO mice were reported [69]. When compound **50** (10 mpk, b.i.d., p.o.) was tested in DIO mice following a 3-week treatment, ~ 10% body weight loss over the vehicle group and reduced food intake were observed. The insulin sensitivity was restored to the level of lean animals, as measured by an insulin sensitivity test on day 17. Unfortunately, after about a 2-week treatment the DIO mice developed alopecia on the neck and around the eye, as well as eye ptosis (squinting). Skin histology confirmed the atrophy of the sebaceous glands and thickening of the epidermal layer in the drug treated group. Apparently, SCD1 inhibition by compound **50** has disrupted the epidermal and follicular homeostasis. The TAG DIs in the same skin samples were significantly lowered, and the total TAG level was reduced to the lean level. More importantly, the total cholesterol ester in the skin was reduced beyond lean level, while the free cholesterol was increased. All these observations recapitulated the SCD1 gene depletion phenotypes, suggesting the interconnection between metabolic phenotypes and adverse skin/hair/ocular effects on inhibiting SCD1 activity.

Interestingly, no patent application from Abbott Laboratories has been published. It could be an indication of the abandonment of the approach of targeting SCD1 for metabolic diseases owing to the observed skin and eye side effects at efficacious doses.

2.4 CV Therapeutics

Recently, a number of patent applications and presentation featuring different scaffolds as SCD1 inhibitors have been reported by CV Therapeutics. Pteridinone derivatives described as SCD1 inhibitors served as the initial lead [70], and systematic modification of the core template led to improvement in both potency and *in vitro* ADME profiles [71-72]. One of the most potent pteridinone analogues (**51**) is shown in **Scheme 1** with IC_{50} values of 250 and 280 nM against rat and human SCD1, respectively. Further modification of the scaffold of the series led to 3-oxopyrido[3,2-b]pyrazine **52**, which exhibited rat SCD1 inhibitory IC_{50} of 7.8 nM. In comparison, the 2-oxopyrido[3,4-b]pyrazine analogue **53** was somewhat less potent. Deletion of both nitrogens of **51** led to a series of potent 2-oxoquinoxaline-based SCD1 inhibitors against both rat and human SCD1. For example, compound **54** was found to have subnanomolar IC_{50}s, to be selective against Δ5 and Δ6 desaturases, and to have greater than 50% stability in HLM and RLM (30 min incubation) [73].

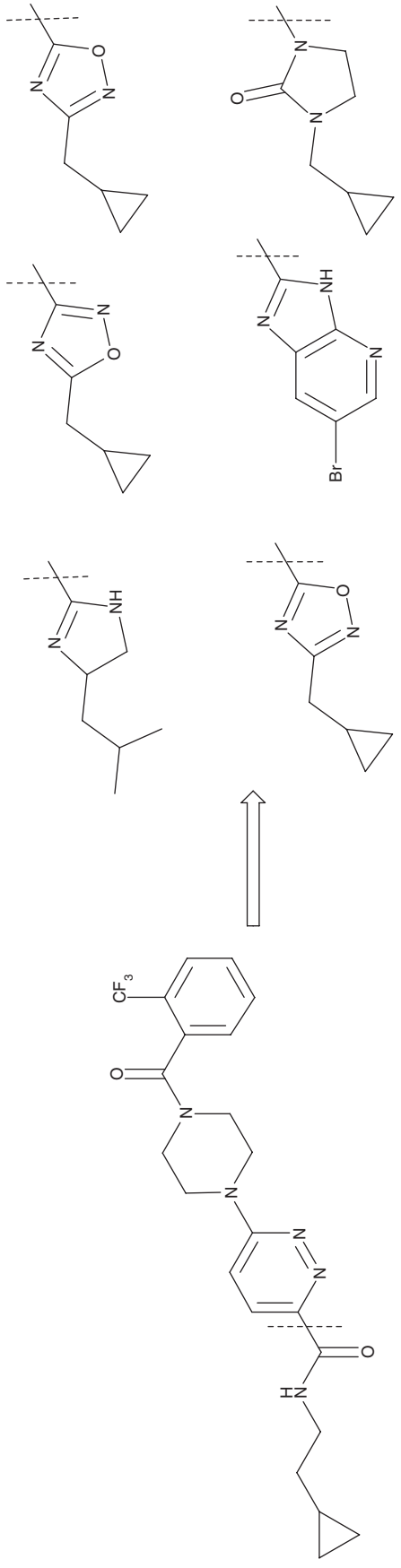


Figure 7. Carboxamide replacements for SCD1 inhibitor design.

2.5 GSK

GSK published a number of patent applications regarding SCD1 inhibitors. The first series involved pyrazolyl 4-amides as SCD1 inhibitors [74]. One example **55** was claimed to have pIC_{50} (-log IC_{50}) value < 5.5 against rat SCD1 (**Figure 18**). The second and third applications claimed pyrazolyl 3-amides as SCD1 inhibitors [75-76,77]. One compound **56** shown in **Figure 18** was claimed to inhibit rat SCD1 with pIC_{50} greater than 5.5. More recently, pyrazole has been modified to thiadiazole to give another series of SCD inhibitors [78]. One compound **57** shown in **Figure 18** was claimed to inhibit rat SCD1 with pIC_{50} greater than 5.5. More recently, a patent application claimed specifically compound **58** with similar *in vitro* and cellular potency (pIC_{50} between 7.00 and 7.25) [79]. The significance of such compound is unknown, although it could be highly interesting given that it is the sole example in the application.

2.6 Takeda

Takeda is also involved in SCD1 inhibitor discovery based on recent publication of two patent applications. The first patent application covered aromatic amine derivatives as SCD1 inhibitors [80]. One example (**59**) at 10 µM inhibited 100% of the microsomal SCD1 activity (**Figure 19**). In the second application [81], starting from the pyridazine template, structural novelty was introduced through a spiropiperidine system, as represented by compound **60** (**Figure 19**). The SCD inhibiting activity of compounds was demonstrated in an assay. DI (C18:1/C18:0) reduction in DIO mice was also demonstrated in a 4-week treatment with one example.

2.7 Daiichi Sankyo

Interestingly, Daiichi Sankyo also published a series of spiropiperidine derivatives as SCD1 inhibitors [82]. Many examples, including compound **61** shown in **Figure 20**, were claimed to have IC_{50} values below 0.2 µM against human SCD1 transfected in HEK293 cells. A more recent patent application from Daiichi Sankyo expanded on the existing genus, as shown below with example **62** [83]. Daiichi Sankyo also has an earlier patent application describing azole amides as SCD1 inhibitors [84]. For example, compound **63** was claimed to inhibit human SCD1 with an IC_{50} value < 1 µM.

2.8 Japan Tobacco

Japan Tobacco has claimed 2,5-disubstituted thiophene/furan derivatives as SCD1 inhibitors as shown in **Figure 21**. One representative compound **64** showed an IC_{50} value below 0.1 µM [85]. The thiophene of **64** can be modified to six-membered aryl rings as claimed in two follow-up applications [86,87]. For example, the benzamide analogue **65** was shown to have an IC_{50} value below 0.1 µM against rat SCD1 (**Figure 21**). The thiophene has been modified to piperidine to give a series of urea derivatives, which are similar to the analogues published by Abbott. Compound **66**, for example, was claimed to have an IC_{50} value below 0.1 µM against rat SCD1 [88].

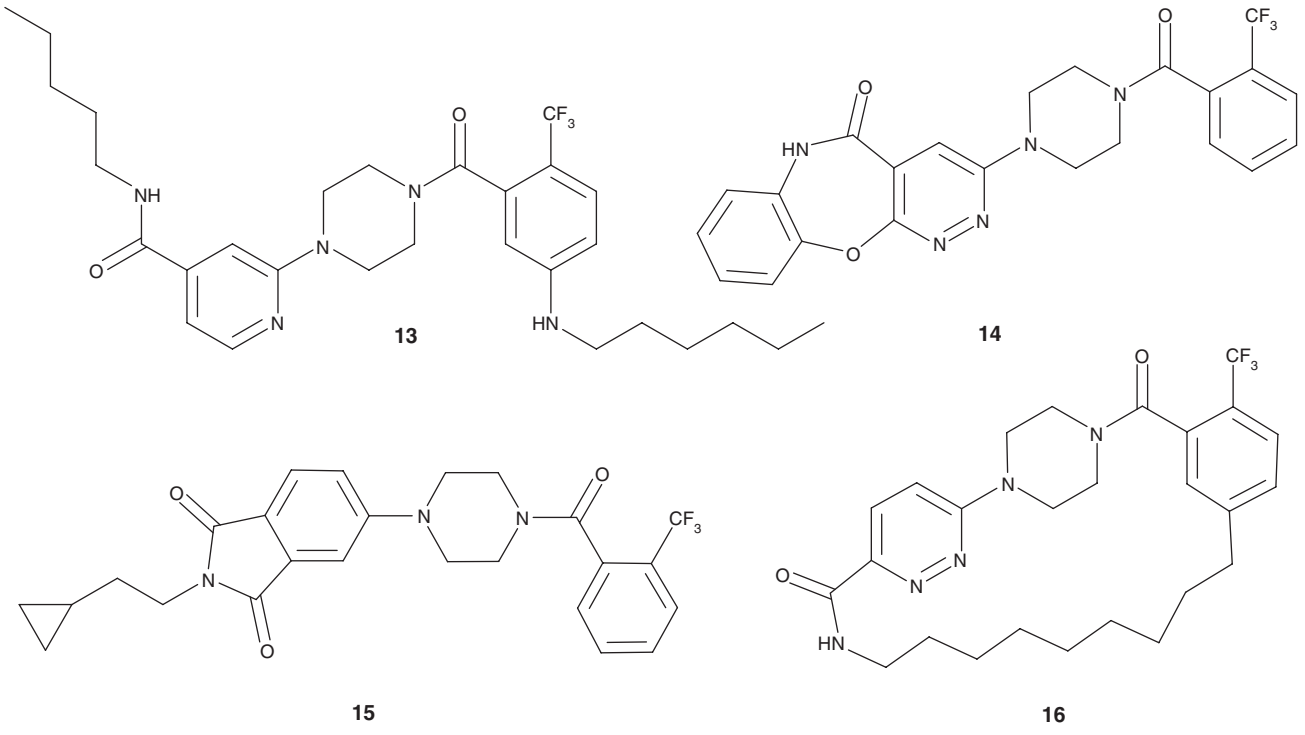


Figure 8. More carboxamide replacements for SCD1 inhibitor design.

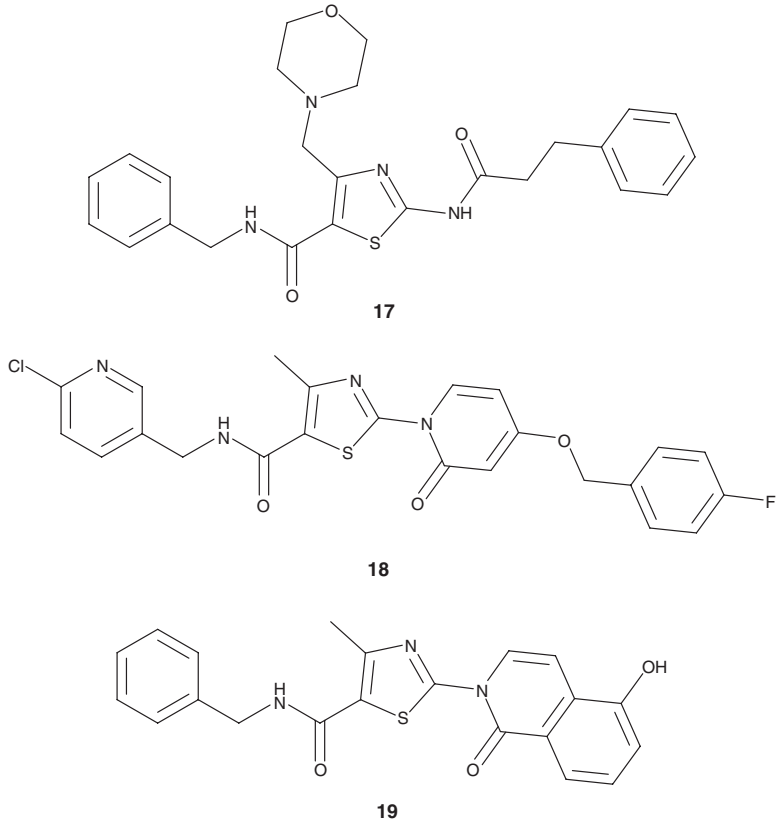


Figure 9. Thiazole carboxamide-based SCD1 inhibitors.

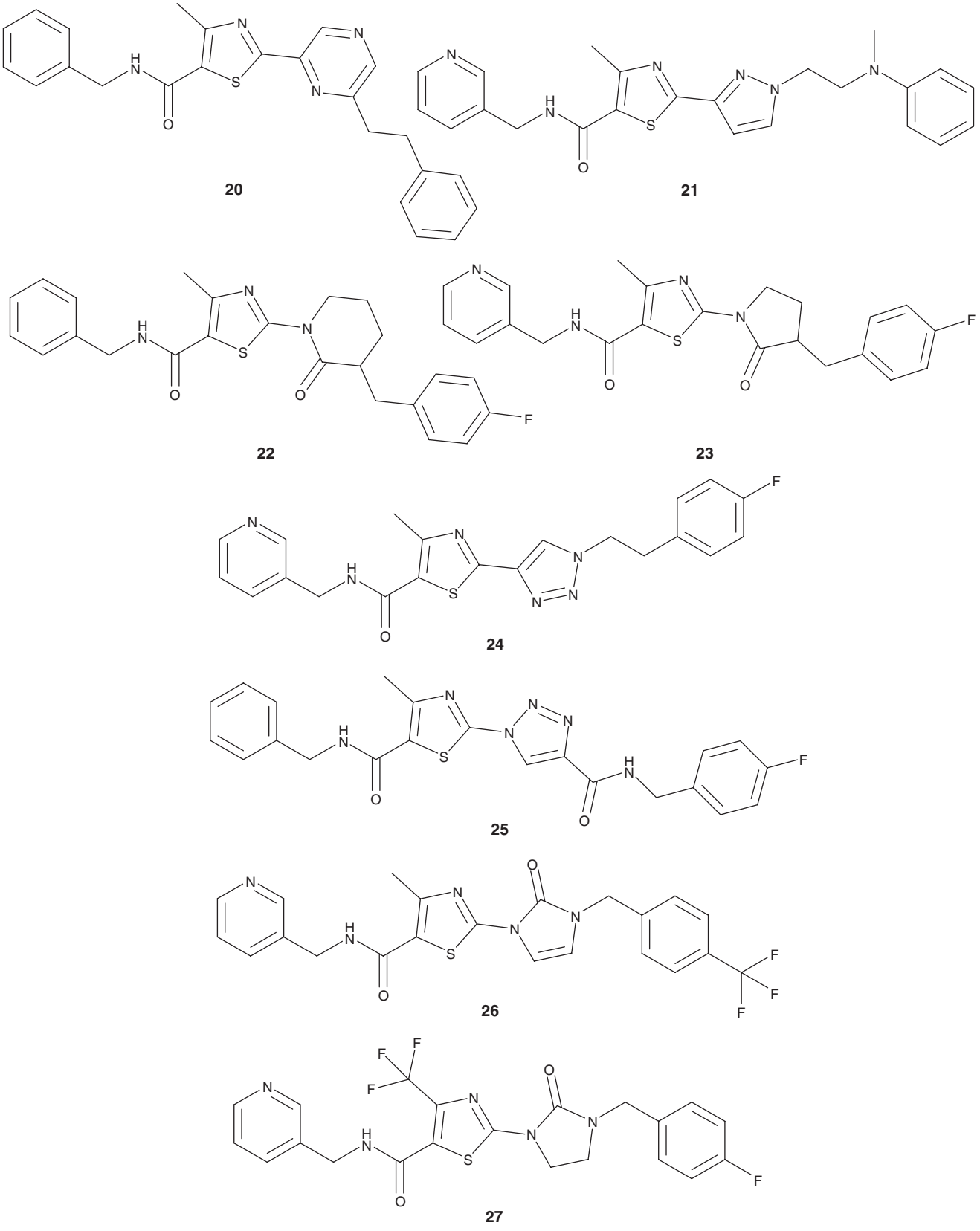


Figure 10. More thiazole carboxamide-based SCD1 inhibitors.

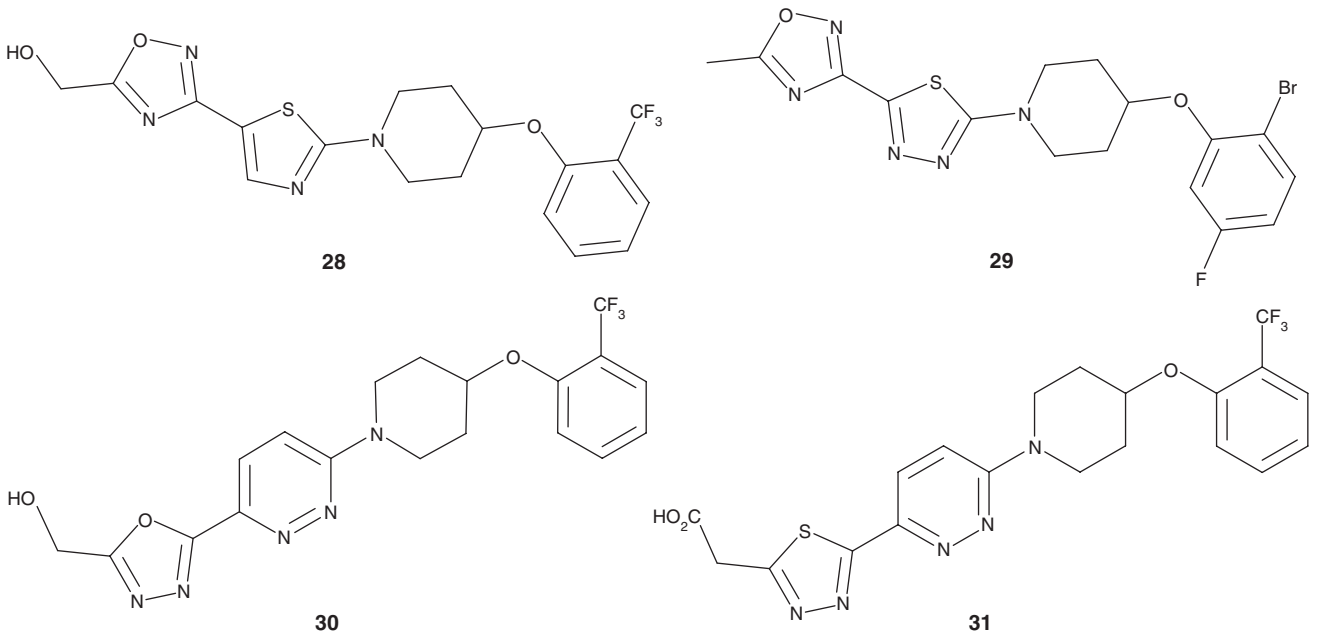


Figure 11. Thiazole carboxamide-based SCD1 inhibitors claimed by Merck Frosst.

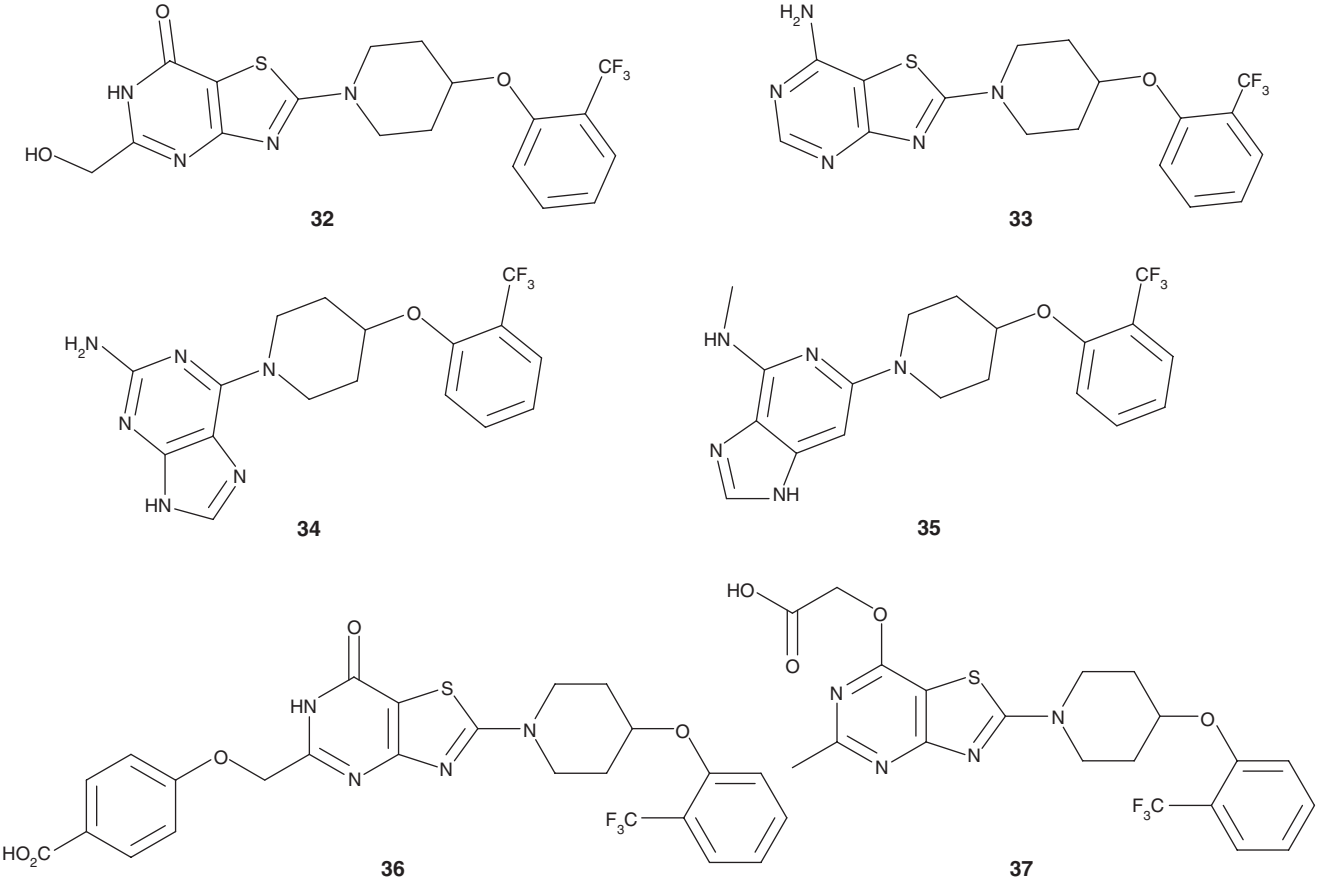
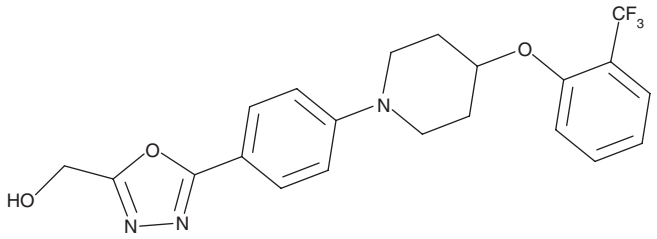


Figure 12. Bicyclic heteroaryl-based SCD1 inhibitors claimed by Merck Frosst.



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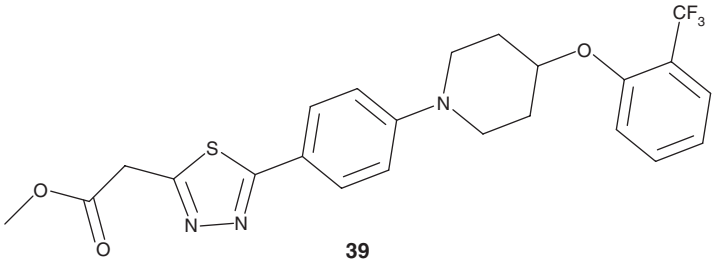

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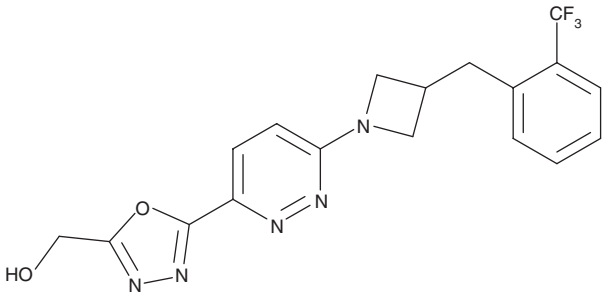
Figure 13. Phenyl-based SCD1 inhibitors claimed by Merck Frosst.



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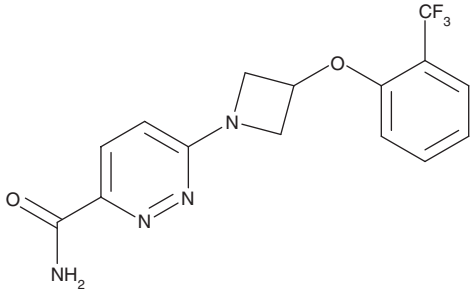

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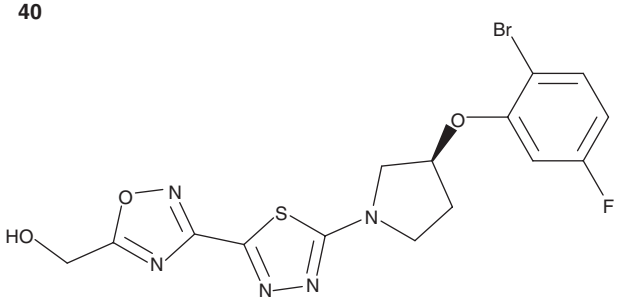

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Figure 14. Piperidine-replacement for SCD1 inhibitors claimed by Merck Frosst.

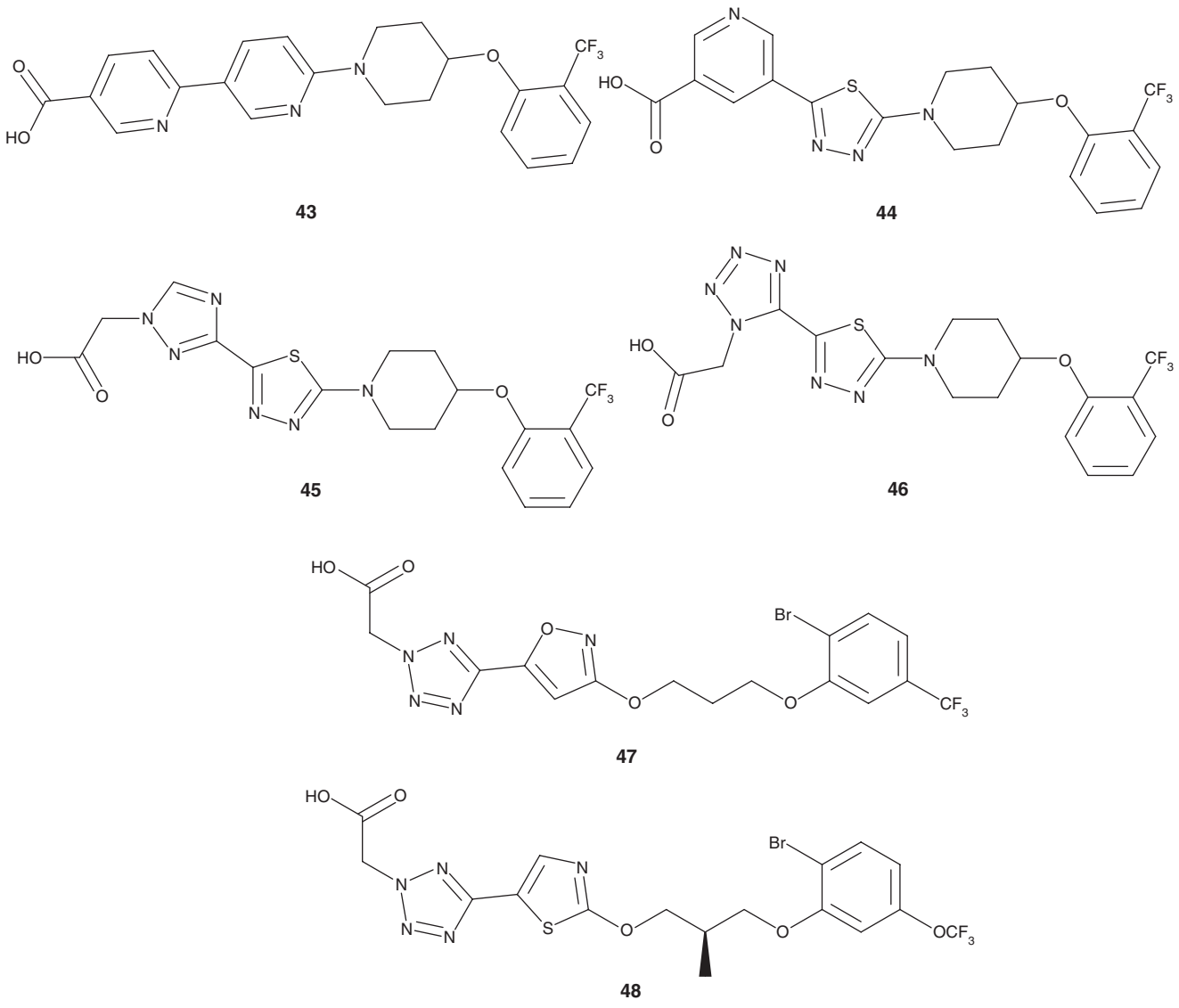


Figure 15. Carboxylic acid-containing SCD1 inhibitors claimed by Merck Frosst.

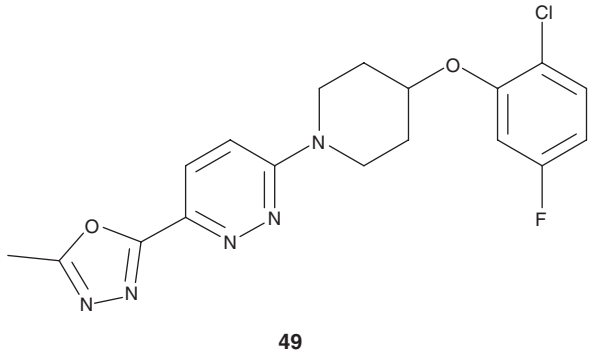


Figure 16. Pyridazine-based SCD1 inhibitor by Abbott.

2.9 Glenmark Pharmaceuticals

Glenmark Pharmaceuticals has claimed a series of pyridinyloxazolanones as SCD1 inhibitors [89]. For example, compound **67** as shown in **Figure 22** was claimed to inhibit human SCD1 99% at 10 μM. More recently, another series of acetylene containing pyridazines/pyridines was claimed to be SCD1 inhibitors [90]. For example, compound **68** as shown in **Figure 22**, was claimed to inhibit human SCD1 100% at 10 μM.

2.10 Biovitrum

Biovitrum claimed pyrazolo[1,5-a]pyrimidine derivatives as SCD1 inhibitors [91,92]. Compounds **69** and **70** have been found to inhibit rat SCD1 with IC_{50} values of 140 and 22 nM, respectively (**Figure 23**).

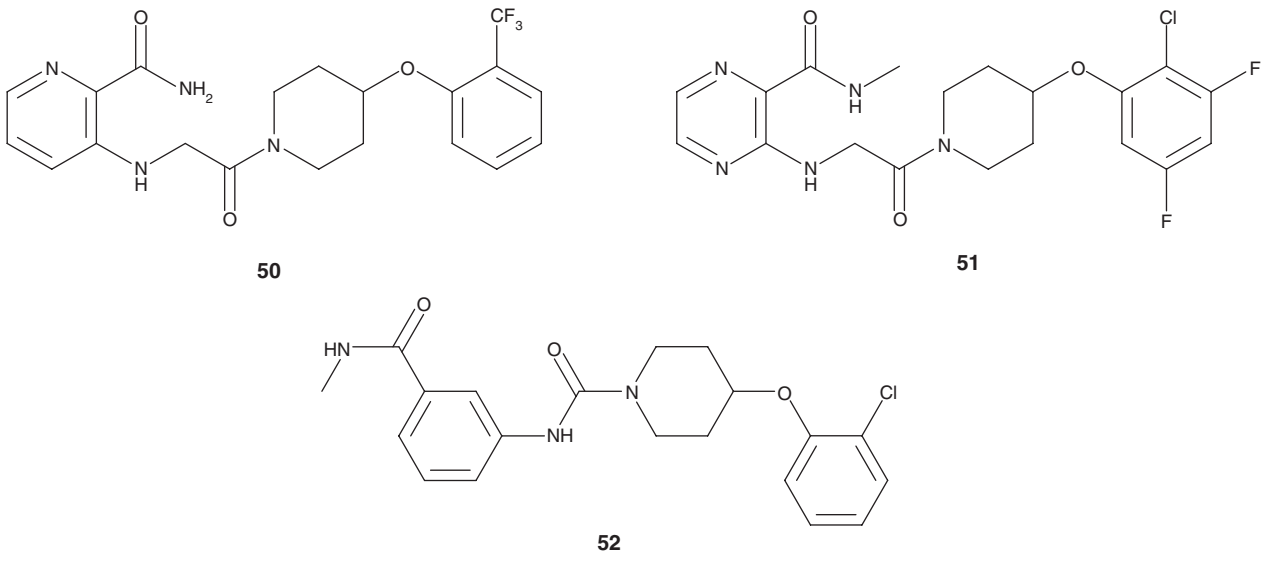


Figure 17. Rationally designed SCD1 inhibitors by Abbott.

2.11 Forest Laboratories

Forest Laboratories recently disclosed its own piperazine-based SCD1 inhibitors [93]. The prototypical compounds **71** and **72** are shown in **Figure 24**. No biological data were provided in the application, although the compounds are claimed to inhibit rat SCD1 with IC_{50} values < 10 mM.

2.12 Sanofi-Aventis

Sanofi-Aventis also joined the field of SCD1 inhibitors recently [94]. The series claimed in the patent application features a bicyclic pyrrolo[3,4-c]pyrrolo diamine core scaffold in place of the piperazine used by many other companies. Compound **73,74** shown below is claimed to inhibit rat SCD1 100% at 10 μM (**Figure 25**).

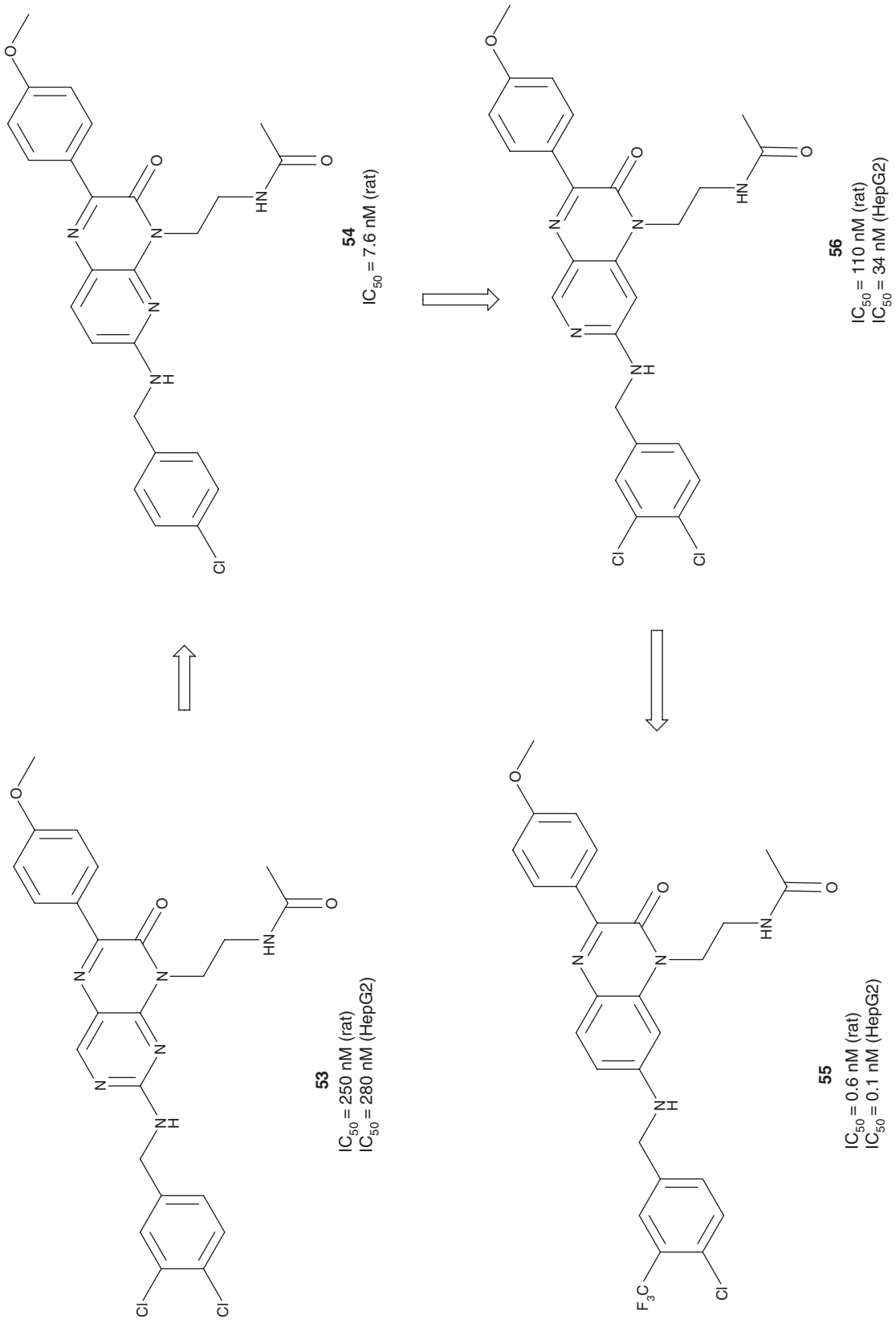
3. Conclusion

Over the past decade, major advances have been made in establishing SCD1 inhibitor as a novel approach in treating a variety of disease states, including obesity, dyslipidemia, skin disorders and cancers. During the past 5 years, many potent and selective SCD1 inhibitors have now been discovered and evaluated preclinically. These compounds, many of which are highlighted in this review, have provided novel tools and drug leads for further understanding of the role SCD1 plays in various pathological conditions. Unfortunately, the lack of *in vivo* biology data in patent disclosures and difficulty in guessing progress of compounds in clinical development have hindered the accurate assessment of the state of the field. Nevertheless, major advances in discovery and characterization of novel SCD1 inhibitors are providing new insights into the mechanisms of action, range of activities and keys to chemical optimization of these compounds as therapeutic agents. These advances will help provide the crucial information needed for developing the next generation SCD1 inhibitors that can fulfill the therapeutic potential for the treatment of a range of diseases, including metabolic diseases, skin and eye disorders, and cancers.

4. Expert opinion

In contrast to mouse SCD1, information on the involvement of human SCD1 in obesity and lipid disorder is very preliminary. Positive correlations between SCD1 activity and plasma TGs in human hypertriglyceridemia [95] and dyslipidemia in familial combined hyperlipidemia [96] were established. Recently, a link between high muscle SCD1 activity and severe obesity in humans has been revealed [97]. Paradoxically, low hepatic SCD1 activity has been associated with fatty liver and insulin resistance in obese humans [98]. Additionally, starvation and exercise also increase SCD1 activity. Although the connection between SCD1 activity and lipid metabolism/energy expenditure seems solid, the true test will come when SCD1 inhibitors can be studied in well-designed human clinical trials.

Although SCD1 knockout mice have increased insulin sensitivity, food consumption and energy expenditure, as well as decreased body fat and resistance to diet induced obesity, complete absence of SCD-1 in mice also results in mechanism-based skin, hair and ocular abnormalities. Furthermore, based on the mechanism-based toxicity observed with compound **50**, which recapitulated the SCD1 KO phenotypes, it remains a challenge for a globally distributed small molecule inhibitor to achieve adequate therapeutic efficacy without affecting normal human skin and eye



Scheme 1. Development of pteridinone-based SCD1 inhibitors by CV Therapeutics.

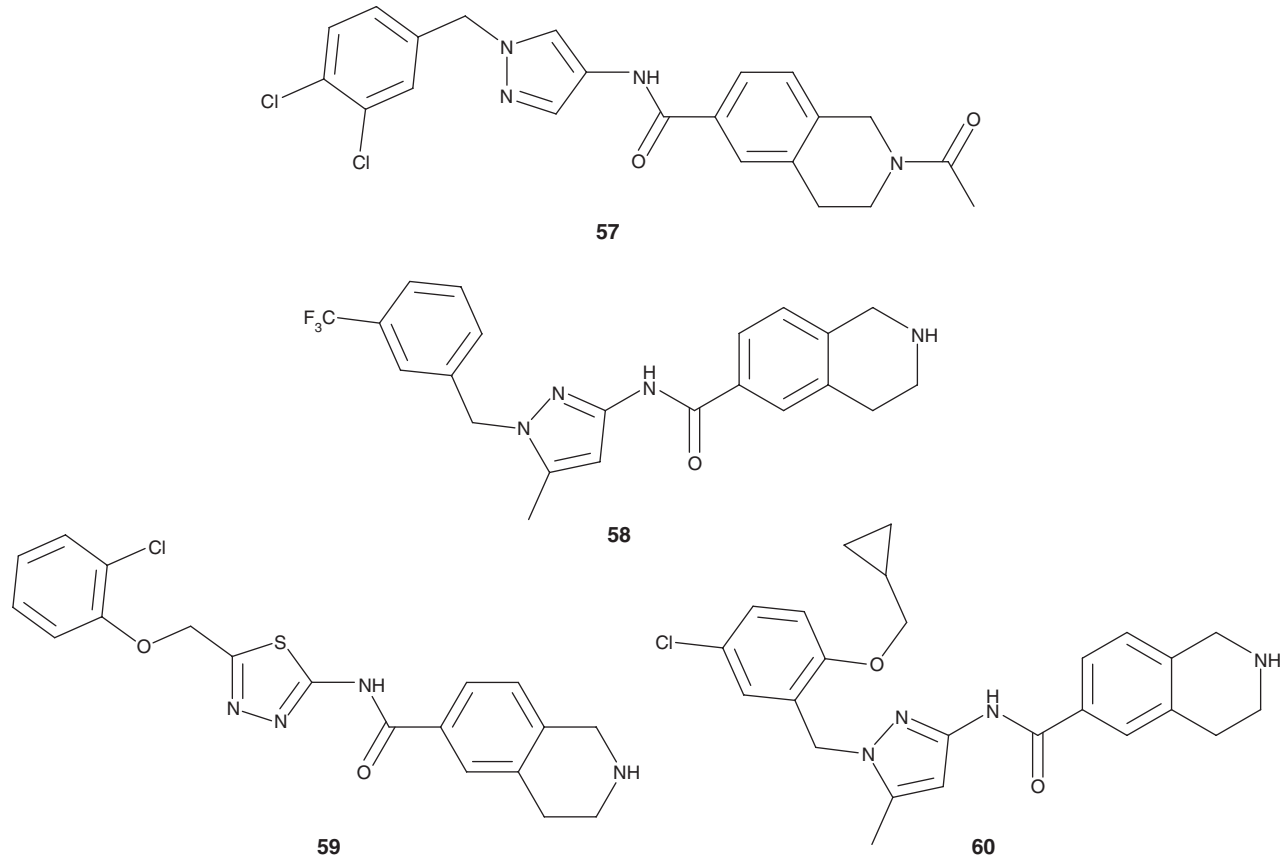


Figure 18. SCD1 inhibitors claimed by GSK.

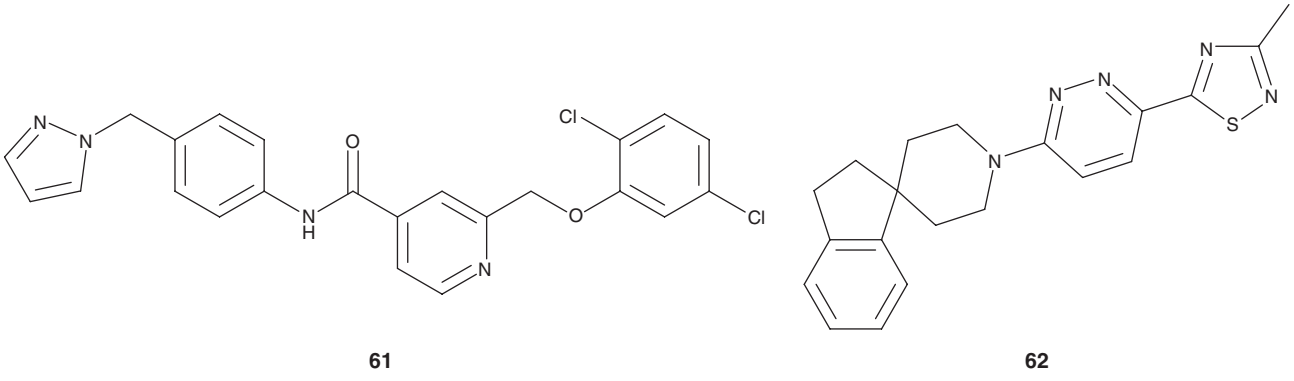


Figure 19. SCD1 inhibitors claimed by Takeda.

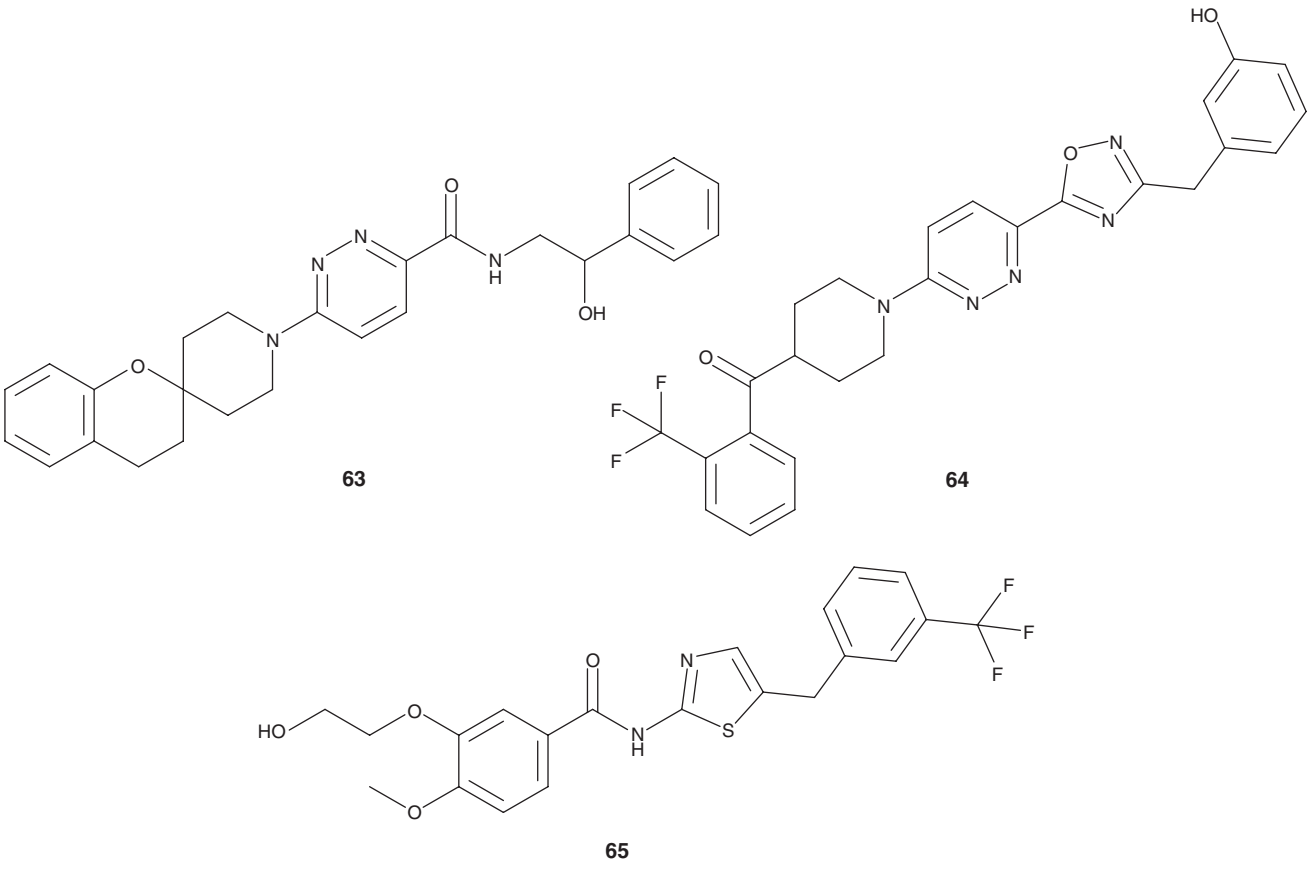


Figure 20. SCD1 inhibitors claimed by Daiichi Sankyo.

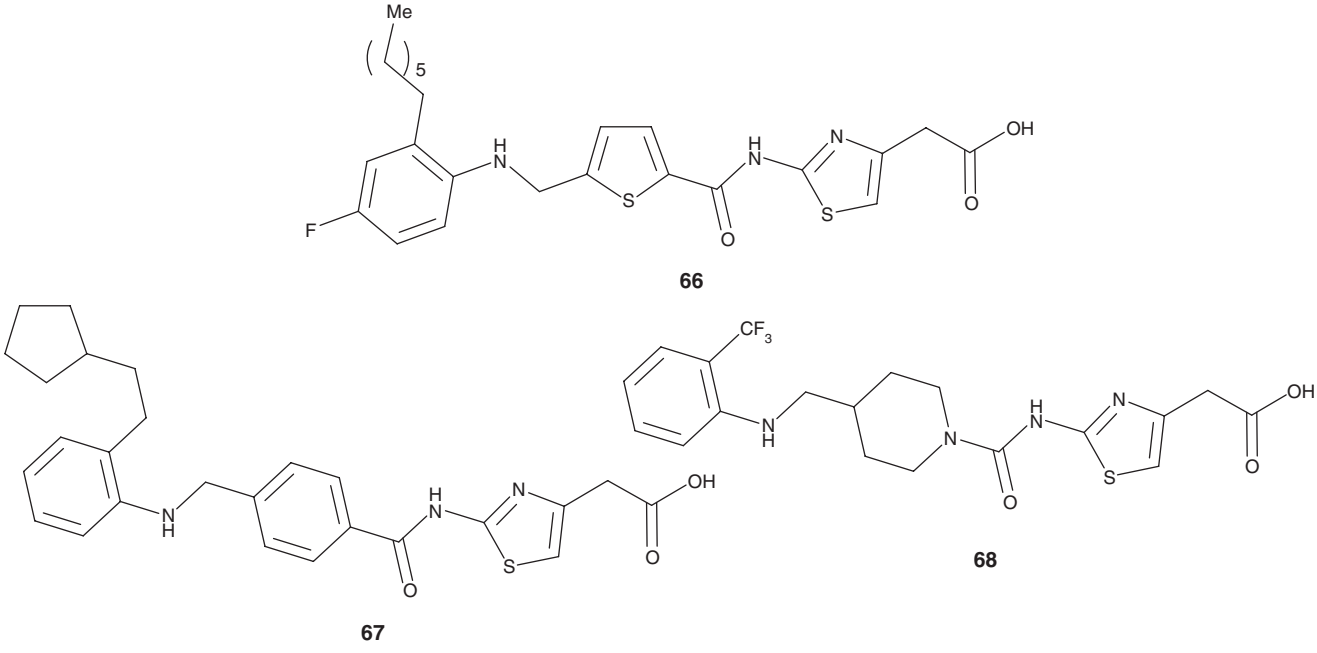
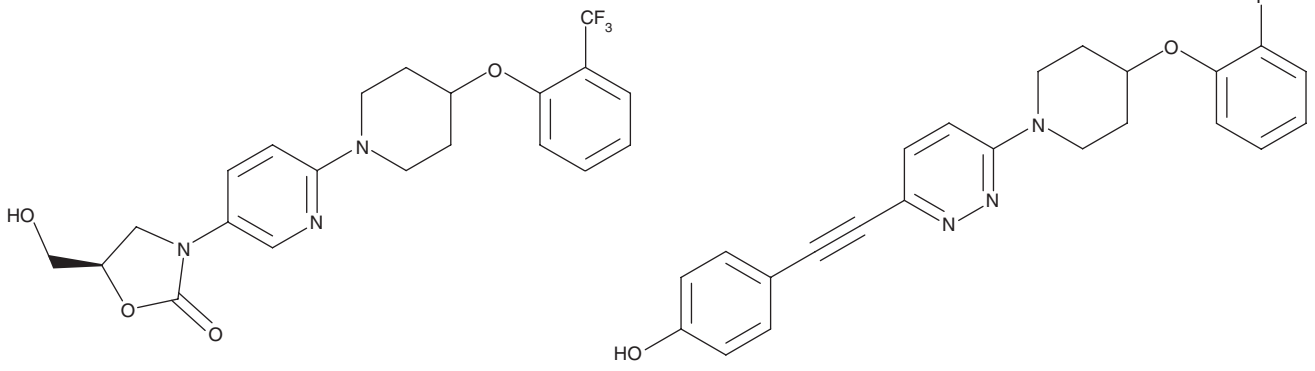


Figure 21. SCD1 inhibitors by Japan Tobacco.



69 70

Figure 22. SCD1 inhibitors reported by Glenmark.

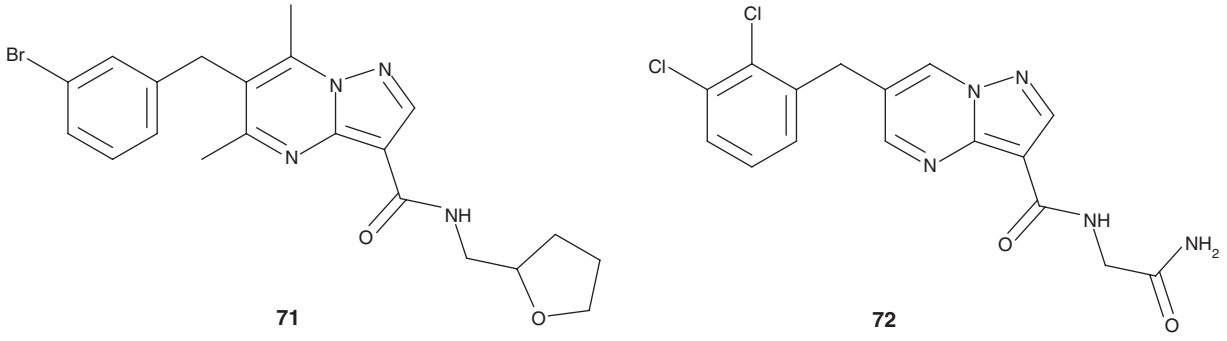


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Figure 23. Representative SCD1 inhibitors reported by Biovitrum.

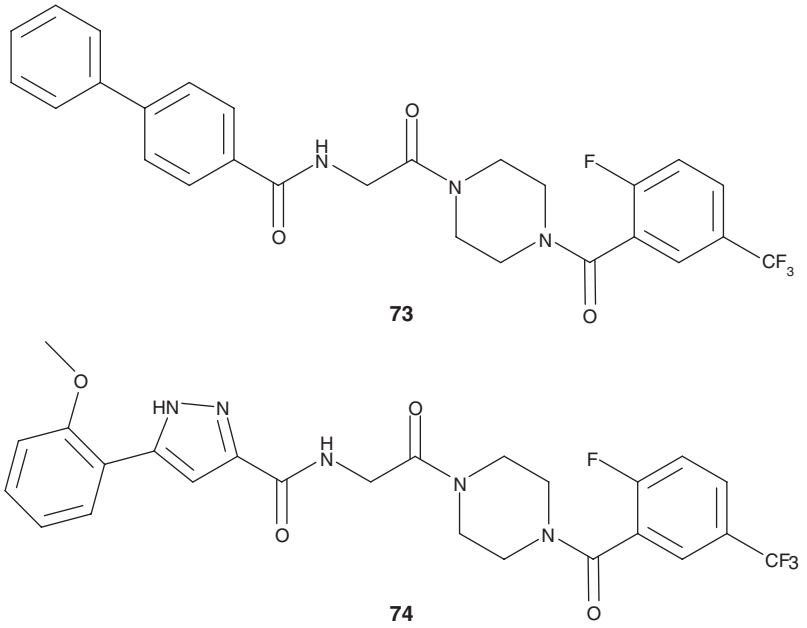

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Figure 24. Representative SCD1 inhibitors reported by Forest Laboratories.

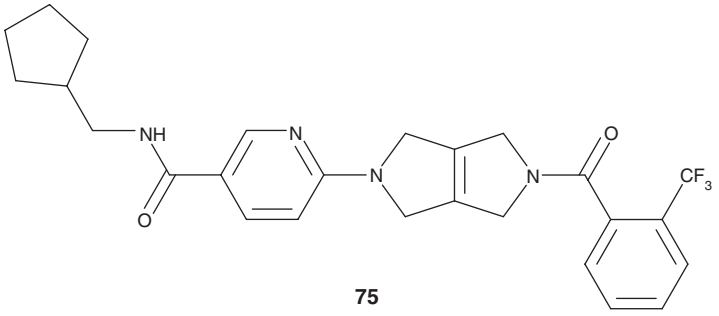

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Figure 25. SCD1 inhibitor claimed by Sanofi-Aventis.

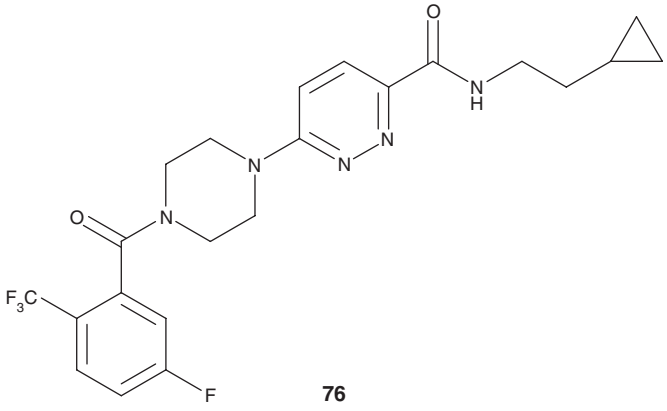

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Figure 26. SCD1 inhibitor LCF369 studied in skin disease model.

functions. Given the non-life threatening nature of metabolic diseases and the increasingly tight regulatory environment, it is paramount to establish sufficient therapeutic window for SCD1 inhibitors for treating metabolic syndromes before embarking on expensive human clinical trials. This issue seems to be one of the hurdles for moving small molecule SCD1 inhibitors into clinical development.

One potential way to circumvent the lack of sufficient therapeutic index of SCD1 inhibitors is the combination therapy so that SCD1 can be dosed at sub-optimal doses. In one of the patent applications, Xenon scientists have disclosed a combination study of a SCD1 inhibitor (presumably at sub-therapeutic dose) with rosiglitazone, a PPAR-γ agonist known to induce body weight gain in patients taking the drug, to reduce the adverse weight gain associated with the therapy of PPAR-γ agonists [99]. Male Zucker diabetic Fatty rats were dosed with an SCD1 inhibitor (structure unknown) at 5 mg/kg for 5 weeks. The vehicle treated group gained 100% body weight, the rosiglitazone group gained 198% body weight, while the SCD1 inhibitor and rosiglitazone combination induced 149% body weight gain and the SCD1 inhibitor alone group gained only 93%, less than the vehicle control group. The DI change of the circulating plasma TG was determined from this study. Rosiglitazone treatment increased DI (48% for 18:1/18:0, twofold increase for 16:1/16:0) and an SCD1 inhibitor alone reduced DI (6% 18:1/18:0, 32% reduction for 16:1/16:0), and the combination of rosiglitazone and SCD1 inhibitor reduced DI to below the SCD1 inhibitor alone group for 18:1/18:0 (27% reduction), and slightly above the level than the SCD1 inhibitors alone group for 16:1/16:0 (32% increase).

Recently, it was discovered that mice with a liver-specific knockout of SCD1 were protected from high-carbohydrate, but not high-fat, diet-induced adiposity and hepatic steatosis [100]. Furthermore, inhibition of SCD1 through ASOs or RNAi recapitulated only a subset of the phenotypes observed in the global SCD1 deficient mouse, indicating the involvement of several tissues in the regulation of metabolism by SCD1. Although the relatively narrower tissue distribution profile (liver, kidney, and adipose tissues) for ASO/RNAi may translate into less negative impact on skin and ocular systems, the metabolic efficacy of such agents may also be attenuated accordingly.

Very recently, ASOs inhibiting SCD1 were tested in a mouse model of hyperlipidemia and atherosclerosis (LDLr(-/-)Apob(100/100)). Unexpectedly, SCD1 inhibition strongly promoted aortic atherosclerosis, which could not be

reversed by dietary oleate [101]. Further analyses revealed that SCD1 inhibition promoted accumulation of saturated fatty acids in plasma and tissues and reduced plasma TG, yet had little impact on low-density lipoprotein cholesterol. This is consistent with another study demonstrating that upregulation of human SCD1 leads to a desaturation of saturated fatty acids and facilitates their esterification and storage, thereby, preventing downstream effects of lipotoxicity in primary human arterial endothelial cells [102]. These results further argue against SCD1 inhibition as a safe therapeutic approach for the metabolic syndrome.

On the other hand, topically applied SCD1 inhibitor may have limited therapeutic utility for skin and eye disorders. Xenon has also filed a patent application focusing on treating skin disorders with SCD1 inhibitors, including, but not limited to acne, rosacea and seborrheic skin [103]. The compound (LCF369, **Figure 26**) was shown to be efficacious in reducing the numbers of sebaceous glands by a factor of ~ 2.5 and the sizes by about 1.9-fold, respectively, when mice are treated twice daily with LCF369 for 7 days dosed at 1% concentration.

The last remaining frontier for SCD1 inhibitors is cancer treatment. Emerging biological data are establishing a link between lipid metabolism and tumor growth, and SCD1 has been implicated in such a process. With the availability of potent and selective SCD1 inhibitors, further studies of such molecules in relevant tumor models will inevitably shed more light on the viability of SCD1 inhibitors for the treatment of certain cancers. Such studies in the literature are the ones to look forward to in the near future.

Declaration of interest

The author is an employee of Ambit Biosciences.

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Affiliation

Gang Liu PhD
Ambit Biosciences,
4215 Sorrento Valley Blvd,
San Diego, CA 92121, USA
Tel: +1 858 334 2164; Fax: +1 858 334 2198;
E-mail: gliu@ambitbio.com