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Systematic evaluation of amide bioisosteres leading to the discovery of novel and potent thiazolylimidazolidinone inhibitors of SCD1 for the treatment of metabolic diseases

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ABSTRACT

Several five- and six-membered heterocycles were introduced to replace the C2-position amide bond of the original 2-aminothiazole-based hit compound **5**. Specifically, replacement of the amide bond with an imidazolidinone moiety yielded a novel and potent thiazolylimidazolidinone series of SCD1 inhibitors. **XEN723** (compound **22**) was identified after optimization of the thiazolylimidazolidinone series. This compound demonstrated a 560-fold improvement in in vitro potency and reduced plasma desaturation indices in a dose dependent manner, with an EC_{50} of 4.5 mg/kg.

Stearoyl-CoA desaturase-1 (SCD1, also known as delta-9 desaturase, D9D) is a microsomal enzyme that catalyzes the de novo synthesis of monounsaturated fatty acids (MUFA) from saturated fatty acids by introducing a *cis*-double bond between carbons 9 and 10. The products, mainly oleate and palmitoleate, are substrates for synthesis of triglycerides, wax esters, cholesterol esters and phospholipids.[1] To date, four SCD isoforms (SCD1-4) have been characterized in rodents,[2–5] and two SCD isoforms (SCD1 and SCD5) in humans, with SCD1 identified as the predominant isoform expressed in the liver.[6,7] SCD1 knockout mice display a beneficial metabolic phenotype characterized by increased energy expenditure, reduced adiposity, improved insulin sensitivity and resistance to high fat diet-induced obesity.[8–10] These beneficial phenotypes are also observed in high fat diet-induced obese (DIO) mice treated with SCD1 antisense oligonucleotides.[11,12] In humans, elevated SCD1 activity is positively correlated with high triglyceride levels in familial hypertriglyceridemia subjects,[13] increased body mass index (BMI) and high plasma insulin levels.[14] Cross species studies provide solid evidence to support the view that SCD1 is a critical player in the regulation of skeletal muscle fat metabolism.[15] Even though the detailed mechanism by which SCD1 deficiency affects body weight, adiposity and glucose regulation is not completely understood, it is widely accepted that SCD1 plays an important role in lipid metabolism;[16] and further that inhibition of SCD1 represents a novel approach for the treatment of metabolic disorders.

Since we disclosed a series of small molecule SCD1 inhibitors, such as compound **1**, in 2005[17,18] (Fig. 1), many small-molecule SCD1 inhibitors have been reported.[19–25] Several reported SCD1 inhibitors have strikingly similar structural features to the scaffolds identified in our first high throughput screen (HTS). To identify additional novel, potent and structurally distinct SCD1 inhibitors, we conducted a second high throughput screen which identified a class of 2-aminothiazole-based SCD1 inhibitors with moderate activity against mouse SCD1 (**5**, Fig. 2). Initial modification of **5** led to the discovery of compound **6** with a more than 6-fold increase in activity against mouse SCD1; however, compound **6** had poor activity against human SCD1 as measured by a HepG2 cell assay (Fig. 2). The poor cell activity may be attributed to poor permeability and/or poor stability in the HepG2 cells due to the amide moieties at the 2- and 4-position of the thiadizole hit compounds. Therefore, we investigated the replacement of the 2-position amide moiety with other, more metabolically stable functionalities,. In this paper, we report the bioisostere replacements of the amide moiety at the C2-position in compound **6** with different heterocycles.

The application of heterocycles as amide bioisosteres is a well-known practice in medicinal chemistry.[26,27] These surrogates

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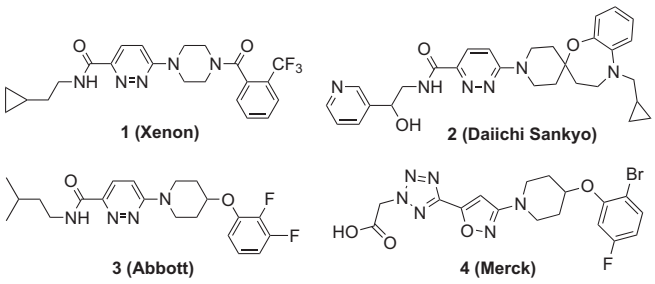


Figure 1. Selected reported SCD1 inhibitors.

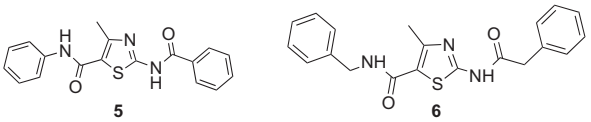


Figure 2. 2-Aminohiazole-based SCD1 inhibitors discovered at Xenon.

often introduce structural rigidity, which may lead to improved selectivity, metabolic stability and enhanced pharmacokinetic properties. We first examined the effect of several 5- or 6-membered heterocycles on potency (Table 1). The syntheses of these compounds are illustrated in Schemes 1–6.

As described in Scheme 1, imidazolidinone analogues **7** and **8** were prepared in a straightforward manner from ethyl 2-amino-4-methylthiazole-5-carboxylate (**7a**). Treatment of **7a** with 2-chloroethyl isocyanate, followed by in situ cyclization in the presence of potassium carbonate provided compound **7b**. Alkylation of **7b** with benzyl bromide afforded compound **7c**. Subsequent hydrolysis to generate the acid **7d**, followed by amide formation yielded compound **7**. Alternatively, treatment of compound **7a** with CDI, followed by reaction with (*R*)-(+)-2-amino-3-phenyl-1-propanol generated intermediate **8a**. Cyclization via the mesylate intermediate provided compound **8b**. Ester hydrolysis, followed by amide formation, then afforded compound **8**.

Synthesis of the oxazole isostere **9** (Scheme 2) began by treating 4-methylthiazole-5-carboxylic acid (**9a**) with benzylamine under standard EDCI–HOBt conditions. The resulting amide **9b** was treated with lithium bis(trimethylsilyl)-amide, followed by quenching with DMF to afford aldehyde **9c**. Subsequent treatment of **9c** with *p*-tosylmethyl isocyanide in the presence of potassium carbonate generated the oxazole intermediate **9d**. The oxazole intermediate **9d** was first converted to its corresponding 2-iodide by treating with *n*-butyllithium, followed by quenching with I_2 and in one pot, the iodide was then coupled with benzylzinc bromide under Negishi cross-coupling conditions to yield compound **9**.

As outlined in Scheme 3, isoxazole **10** and 1,2,3-triazole **12** were synthesized from intermediate **10b**, which was in turn prepared from 2-bromo-4-methylthiazole-5-carboxylic acid (**10a**) and benzylamine under standard amide formation conditions. Intermediate **10b** was further converted to compound **10c** under Sonogashira coupling conditions followed by a CuI-mediated cyclization of **10c** with benzyl azide to afford 1,2,3-triazole **12**. Similarly, treatment of **10c** with nitrile oxide **10d**[28] under CuI catalysis yielded isoxazole **10**.

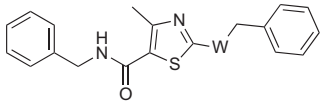
Compounds **11**, **13** and **14** were prepared from intermediate **11b** (Scheme 4), which was synthesized from 2-amino-4-methylthiazole-5-carboxylic acid (**11a**) and benzylamine as described above. Treatment of **11b** with isoamyl nitrite and copper cyanide generated nitrile **11c**. Addition of hydroxylamine to **11c** to generate the corresponding *N*-hydroxyamidine followed by cyclization with the mixed anhydride of phenylacetic acid afforded oxadiazole **11**. The nitrile intermediate **11c** was also converted to the corresponding 1,2,4-triazole **14** by treatment with phenylacetic hydrazide under microwave irradiation conditions. The regioisomeric 1,2,3-triazole **13** was obtained by treatment of **11b** with tosyl azide under phase transfer conditions, followed by a CuI-mediated cyclization with phenylacetylene.

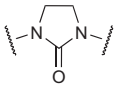
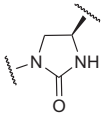
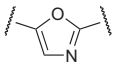
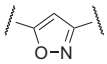
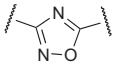
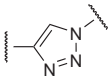
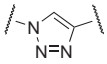
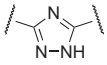
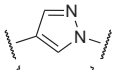
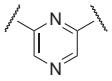
The pyrazole analogue **15** was prepared starting from a palladium-mediated cross coupling reaction of intermediate **10b** with 1*H*-pyrazol-4-boronic acid, followed by reaction with benzyl bromide in the presence of K_2CO_3 (Scheme 5).

The pyrazine compound **16** was obtained following the synthetic procedure outlined in Scheme 6. 2,6-Dichloropyrazine **16a** was converted to the corresponding diiodo compound **16b** by reaction with NaI in the presence of *p*-toluenesulfonic acid and 15-crown-5. Bromo intermediate **10b** was converted to its corresponding zinc intermediate by treatment with Rieke zinc under microwave irridation. Negishi cross-coupling between the resulting zinc intermediate and the diiodo intermediate **16b** afforded compound **16c**. The final pyrazine compound **16** was obtained via Suzuki cross-coupling methodology.

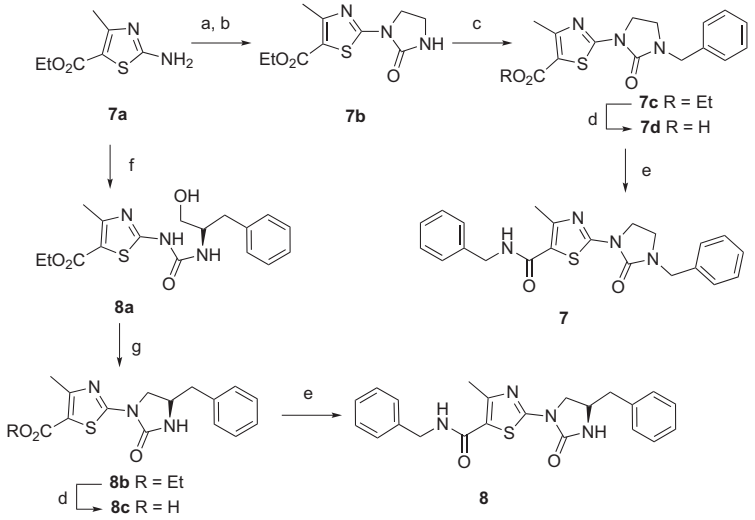
The inhibitory activity of these compounds against SCD1 was assessed by two assay systems: a mouse liver microsomal assay[29] and a human HepG2 cell-based assay.[30] Compounds with good po-

Table 1
SAR of heterocyclic amide bond bioisosteres

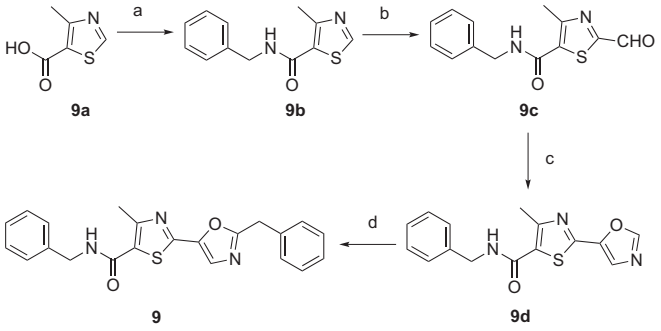


Compound	W	Mouse SCD1 IC_{50}[a] (nM)	HepG2 SCD1 IC_{50}[a] (nM)
7		28	53
8		154	2175
9		>10,000	nd
10		601	nd
11		75	1925
12		33	9983
13		55	675
14		27	236
15		1007	nd
16		200	618

[a] IC_{50}s are an average of at least two independent determinations; nd: not determined.



Scheme 1. Reagents and conditions: (a) 2-chloroethyl isocyanate, THF, reflux; (b) K_2CO_3, THF, reflux; (c) K_2CO_3, benzyl bromide, acetone, reflux; (d) LiOH, THF, H_2O, reflux; (e) EDCI, HOBt, iPr$_2$NEt, DMF, benzylamine; (f) CDI, THF; (*R*)-(+)-2-amino-3-phenyl-1-propanol; (g) MsCl, iPr$_2$NEt, THF; K_2CO_3, reflux.

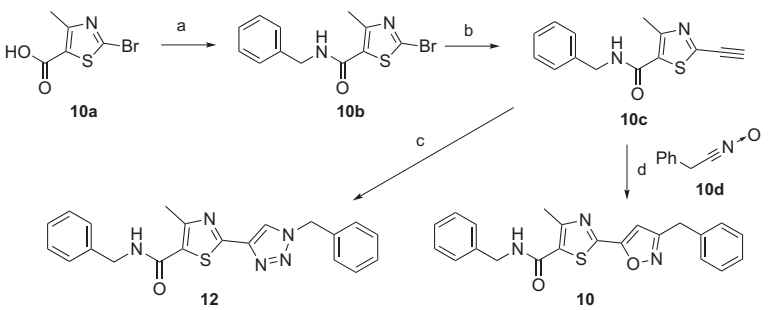


Scheme 2. Reagents and conditions: (a) EDCI, HOBt, iPr$_2$NEt, benzylamine, DMF; (b) LiHMDS, THF, −78 °C; then DMF, −78 °C to RT; (c) *p*-tosylmethyl isocyanide, K_2CO_3, MeOH; (d) *n*-BuLi, THF, −78 °C; then I_2, −78 °C to RT; BnZnBr, Pd(PPh$_3$)$_4$, 50 °C.

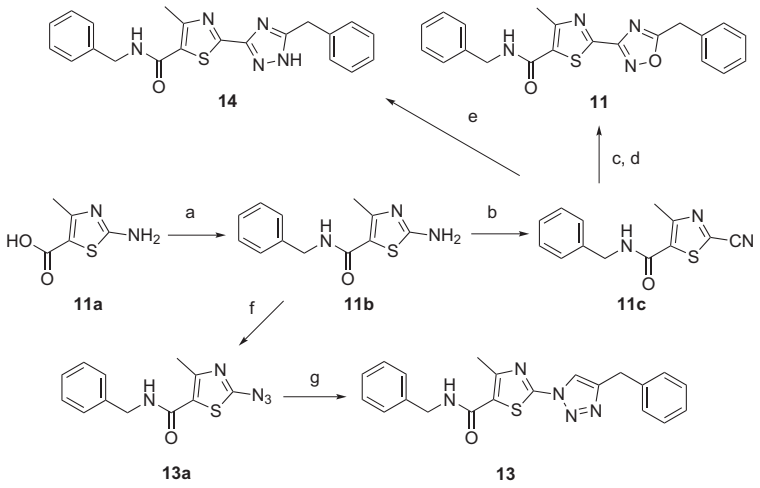
tency on SCD1 were also screened against delta-5 desaturase (D5D) and delta-6 desaturase (D6D) to determine the selectivity against these desaturases. In humans, these two desaturases are involved in the synthesis of highly unsaturated fatty acids which play crucial roles in maintaining membrane fluidity; therefore, achieving selectivity against D5D and D6D is essential to avoid undesirable toxicities.[31] None of the compounds evaluated (cell-based IC_{50} <100 nM on SCD1) demonstrate any D5D and D6D activity at 10 μM.

As shown in Table 1, SCD1 potency was highly dependent on the nature of the heterocyclic bioisosteric replacements. Imidazolidinone analogue **7** was the most potent compound in both the mouse SCD1 assay and in the HepG2 SCD1 assay; however, its metabolic stability was poor (10% remaining after a 30 min incubation with 0.5 mg/mL rat liver microsomes). Shifting the benzyl group from the nitrogen to the neighboring carbon, as in compound **8**, resulted in decreased activity in both assays. Although oxadiazole **11** and triazoles **12**, **13** and **14** exhibited comparable inhibitory activity against the mouse SCD1 enzyme, their cellular potencies were significantly decreased. This decreased potency in HepG2 cells may be attributed to differences in mouse versus human isoform selectivity or poor permeability. Oxazole **9**, isoxazole **10**, pyrazole **15** and pyrazine **16** were the least potent against SCD1 in mouse liver microsomal assay among all of the amide replacements reported herein. These results suggest that in our case, a desirable and effective heterocyclic amide bond bioisostere requires a hydrogen bond acceptor functionality to mimic the carbonyl group present in the original amide moiety.

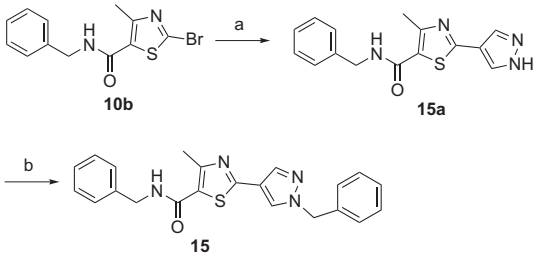
Given the good in vitro potencies observed in both SCD assays with the imidazolidinone bioisostere, we focused our efforts on this particular replacement moiety and further optimization was conducted with the thiazolylimidazolidinone as the central core structure. As outlined in Scheme 1 for compound **7**, a similar synthetic procedure was utilized to synthesize R^1 and R^2 analogues of the parent compound **7**. The activity of these analogues against SCD1 was assessed using the same methods as outlined above and the results are summarized in Table 2. In general, analogues



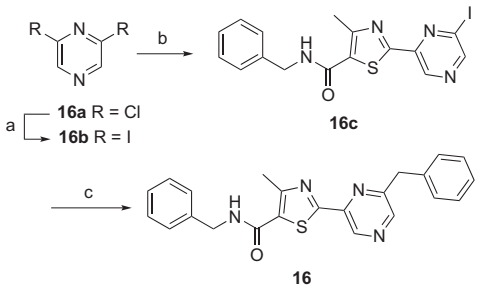
Scheme 3. Reagents and conditions: (a) benzylamine, EDCI, HOBt, iPr$_2$NEt, DMF; (b) trimethylsilyacetylene, Pd(PPh$_3$)$_2$Cl$_2$, CuI, iPr$_2$NEt, toluene, 60 °C; LiOH, MeOH, H_2O; (c) BnN_3, CuI, iPr$_2$NEt, THF; (d) **10d**, CuI, *t*BuOH, H_2O.



Scheme 4. Reagents and conditions: (a) benzylamine, EDCI, HOBt, iPr$_2$NEt, DMF; (b) isoamyl nitrite, CuCN, CH_3CN, reflux; (c) $NH_2OH.HCl$, Et_3N, ethanol, reflux; (d) $PhCH_2CO_2H$, CDI, DMF, then N-hydroxyamidine; (e) phenylacetic hydrazide, K_2CO_3, n-BuOH, 150 °C (microwave); (f) TsN_3, $BnMe_3N$ hydrochloride, NaOH, CH_2Cl_2, H_2O; (g) phenylacetylene, iPr$_2$NEt, CuI, THF.



Scheme 5. Reagents and conditions: (a) 1H-pyrazol-4-boronic acid, K_2CO_3, $Pd(PPh_3)_4$, toluene, 100 °C; (b) K_2CO_3, DMSO.



Scheme 6. Reagents and conditions: (a) NaI, p-toluenesulfonic acid, 15-crown-5, sulfolane, 150 °C, 2 h; (b) **10b**, Rieke zinc, THF, 100 °C, 15 min (microwave) under nitrogen atmosphere; then **16b**, $Pd(PPh_3)_4$, THF/DMF, 160 °C for 16 h under nitrogen atmosphere; (c) **16c**, Na_2CO_3, benzyl boronic acid pinacol ester, $PdCl_2$(dppf), DME, 100 °C, 4 h.

with an aryl or a heteroaryl group at R^1 displayed good potency in both assays. Compounds **19** and **22**[32] were the most potent in the mouse liver microsomal assay and by HepG2 cell-based assay. Moreover, **22** demonstrated better metabolic stability than compound **19**. While analogue of oxazole (**31**) displayed comparable potency, and most surprisingly the unsubstituted primary amide (**32**) was potent in both SCD assays. Extension of the chain length even by one carbon at R^1 led to decreased activity as illustrated by compound **30**, At R^2, a longer chain length such as the phenylpropyl group in compound **23** was well tolerated with regards to SCD1 inhibition but was much less metabolically stable in rat liver microsomes. Introduction of an alkyl or a cycloalkyl group at R^2 maintained potency by mouse liver microsomal SCD1 assay (compounds **24**, **26** and **27**). However, installation of a tetrahydropyran (compound **25**) was not tolerated and resulted in a significant decrease in potency.

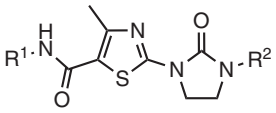
Based on the in vitro potencies in both SCD1 assays, we evaluated the in vivo effect of compounds **19**, **22**, and **23** on the plasma C16:1/C16:0 and C18:1/C18:0 triglycerides (TG) desaturation indices (DI)[33] in an acute Lewis rat model.[34] C16 and C18 DI have been well-documented as biomarkers for SCD1 target engagement.[12,36] The results of the C16:1/C16:0 plasma DI are illustrated in Figure 3. **22** was the most efficacious among the three compounds tested in this in vivo model as it reduced C16:1/C16:0 plasma DI by 59%. Compounds **19** and **23** did not have a significant effect on plasma DI reduction even though the in vitro potencies were similar to that of **22**. This discrepancy in PD effects may be attributed to poor metabolic stability of Compounds **19** and **23**.

Compound **22** was further evaluated in the acute DI model in a dose-responsive manner at doses ranging from 0.5 mg/kg to 10 mg/kg. The results are illustrated in Figure 4 and indicated a clear dose-related reduction of plasma TG DI with the ED_{50} estimated to be 4.5 mg/kg.

In order to provide an initial assessment of the therapeutic index of **22** with respect to the adverse effects associated with SCD1 deficiency,[35,36] a tolerability study was carried out. In this study, female Sprague–Dawley rats were dosed orally at 100 mg/kg once daily for ten days and the clinical signs, such as red eyes, hair loss and dry skin were assessed daily. Animals treated with **22** started to show mild eye symptoms on Day 3 and a dry skin phenotype on Day 4 of dosing. These clinical signs related to SCD1 inhibition in harderian and sebaceous glands slowly progressed to greater severity throughout the study, indicating that prolonged systemic exposure and SCD1 inhibition in tissues, such as in skin and eye glands, led to severe side effects. PK analysis at the end of this study indicated a relatively high exposure in plasma of the **22** (C_{max} = 6 μM and $AUC_{0-24\ h}$ = 78 μM h).

In conclusion, we discovered a number of heterocyclic amide bond replacements capable of retaining good activity and improved properties relative to the original 2-aminothiazole-based HTS hit. Furthermore, we discovered novel and potent thiazolylimidazolidinone SCD1 inhibitors, including **22** (**XEN723**), which demonstrates an improvement in SCD1 in vitro potency of more than 560-fold compared to the original HTS hit, and exhibits robust in vivo PD effects. Clinical observation studies with **XEN723** revealed adverse effects related to SCD1 inhibition. Therefore,

Table 2
SAR of thiazolylimidazolidinones



Compound	R^1	R^2	Mouse SCD1 IC_{50}[a] (nM)	HepG2 SCD1 IC_{50}[a] (nM)	Rat liver microsome stability[b]
17	3-Fluorobenzyl	Benzyl	63	219	16
18	4-Fluorobenzyl	Benzyl	91	194	40
19	5-Methylfuranylmethyl	Benzyl	5	14	27
20	Pyridin-4-ylmethyl	Benzyl	145	656	nd
21	Pyridin-3-ylmethyl	Benzyl	45	524	46
22 (XEN723)	Pyridin-3-ylmethyl	4-Fluorobenzyl	6	10	67
23	Pyridin-3-ylmethyl	3-Phenylpropyl	16	8	4
24	Pyridin-3-ylmethyl	Cyclohexylmethyl	45	135	43
25	Pyridin-3-ylmethyl	Tetrahydro-2*H*-pyran-2-yl	>1000	nd	nd
26	Pyridin-3-ylmethyl	Cyclopropylmethyl	47	63	55
27	Pyridin-3-ylmethyl	*n*-Butyl	46	748	67
28	Pyridin-2-ylmethyl	Benzyl	87	158	57
29	Pyridin-2-ylmethyl	4-Fluorobenzyl	13	40	54
30	Pyridin-2-ylethyl	4-Fluorobenzyl	3473	nd	nd
31	Oxazol-2-ylmethyl	4-Fluorobenzyl	11	95	88
32	H	4-Fluorobenzyl	15	55	82

[a] IC_{50}s are an average of at least two independent determinations; nd: not determined.
[b] Expressed as% of compound remaining after a 30 min incubation with 0.5 mg/mL rat liver microsomes.

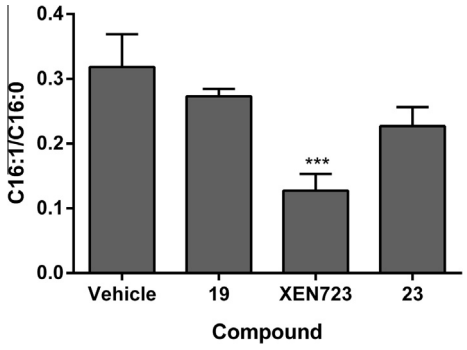


Figure 3. Effects of compounds **19**, **22** (**XEN723**), and **23** on plasma C16:1/C16:0 TG desaturation index 4 h after a 5 mg/kg oral dose in Lewis rats. Each bar represents the mean of at least 4 animals and the error bars represent standard errors of the mean. ***: One-way ANOVA analysis between vehicle group and XEN723 treated group with p <0.001.

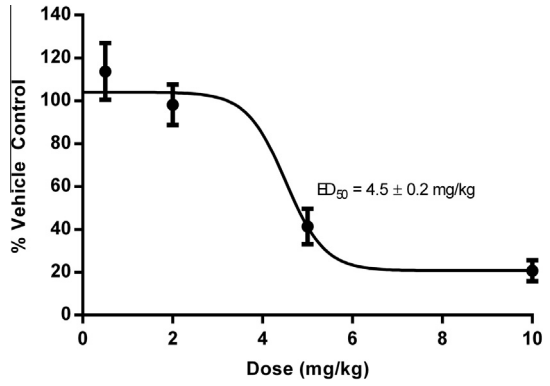


Figure 4. Dose response of **22** (**XEN723**) on plasma C16:1/C16:0 TG desaturation index 4 h after oral dosing in Lewis rats. Each data point represents the mean of at least 4 animals. The error bars represent standard errors of the mean.

development of SCD1 inhibitors with selective tissue distribution and/or reduced systemic exposure would be desirable to improve the therapeutic indices and thereby be more suitable for clinical development for metabolic diseases.

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32. *Characterization data for* ***22*** *(**XEN723**):* ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.50 (d, J = 3.9 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.29–7.21 (m, 3H), 7.04–6.97 (m, 2H), 6.23 (t, J = 5.7 Hz, 1H), 4.57 (d, J = 5.7 Hz, 2H), 4.42 (s, 2H), 4.04 (t, J = 8.1 Hz, 2H), 3.43 (t, J = 8.1 Hz, 2H), 2.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1, 162.6, 160.8, 157.3, 155.3, 153.6, 148.5, 136.0, 134.1, 131.3, 129.9, 123.7, 116.9, 115.9, 115.6, 47.2, 42.0, 41.6, 41.3, 17.2. MS (ES^+) m/z 475.0 (M+1). HPLC purity (a/a%): 99.9%.
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