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Discovery of thiazolylpyridinone SCD1 inhibitors with preferential liver distribution and reduced mechanism-based adverse effects

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ABSTRACT

We discovered a series of novel and potent thiazolylpyridinone-based SCD1 inhibitors based on a 2-aminothiazole HTS hit by replacing the amide bond with a pyridinone moiety. Compound **19** demonstrated good potency against SCD1 in vitro and in vivo. The mouse liver microsomal SCD1 in vitro potency for **19** was improved by more than 240-fold compared to the original HTS hit. Furthermore, **19** demonstrated a dose-dependent reduction of plasma desaturation index with an ED_{50} of 6.3 mg/kg. Compound **19** demonstrated high liver to plasma and liver to eyelid exposures, indicating preferential liver distribution. The preliminary toxicology study with compound **19** did not demonstrate adverse effects related to SCD1 inhibition, suggesting a wide safety margin with respect to other known SCD1 inhibitors with wider distribution profiles.

Obesity and type 2 diabetes are emerging as two major global health problems of the 21st Century. Evidence published over the past decade has shown that abnormal lipid metabolism is closely related to occurrences of metabolic syndrome, obesity, type 2 diabetes and dyslipidemia.[1,2] One potential target for the treatment of these diseases, which has recently received great attention in the scientific community, is stearoyl-CoA desaturase-1 (SCD1, commonly known as delta-9 desaturase, D9D). SCD1 catalyzes the de novo synthesis of monounsaturated fatty acids (MUFA) from saturated fatty acids by introduction of a *cis*-double bond between carbons 9 and 10. The products, mainly oleate and palmitoleate, are key substrates for the synthesis of triglycerides, wax esters, cholesterol esters and phospholipids.[3] SCD1, with about 85% homology across all murine SCDs, is the major isoform present in lipogenic tissues (including liver and adipose tissues) and functions as a key regulator of lipid and carbohydrate metabolism. SCD1-deficient mice have been shown to be lean and hypermetabolic.[4] In the leptin-deficient model for obesity, mice with an inactive *SCD1* gene were significantly less obese than the *ob*/*ob* controls and had markedly increased energy expenditure; in addition, these mice had histologically normal livers with significantly reduced triglyceride storage and VLDL production.[4] The main consequences of SCD1 deficiency are hypothesized to be activation of lipid oxidation and reduction of triglyceride synthesis and storage.[5–7] These beneficial phenotypes are also observed in high fat diet-induced obese (DIO) mice treated with antisense oligonucleotides directed towards SCD1.[8,9] In humans, elevated SCD1 activity positively correlates with high triglyceride levels in familial hypertriglyceridemia subjects,[10] increased body mass index (BMI) and high plasma insulin levels.[11] Therefore, compounds that inhibit SCD1 may hold significant therapeutic potential for the treatment of obesity, type 2 diabetes and other metabolic disorders.

Since we disclosed a series of small molecule SCD1 inhibitors in 2005, such as compound **1**[12,13] (Fig. 1), a number of subsequent inhibitors have been reported.[14–20] Many of these have strikingly similar structural features. In order to discover additional novel and structurally distinct SCD1 inhibitors, we conducted a second high throughput screen which lead to the discovery of a class of 2-aminothiazole-based SCD1 inhibitors with moderate mouse SCD1 activity (e.g., compound **5**, Fig. 2). Due to the labile nature of the amide bond motif of compound **5**, we initially sought replacements for the 2-position amide. Modification of **5** by the replacement of the C-2 amide bond with a pyridin-2(1*H*)-one moiety led to the discovery of compound **6** with greater than 24-fold increase in activity against mouse SCD1. Compound **6** had poor activity against human SCD1 as measured by a HepG2 cell assay; nonetheless, the pyridinone modification provided a good structural template for further optimization efforts. Herein, we report

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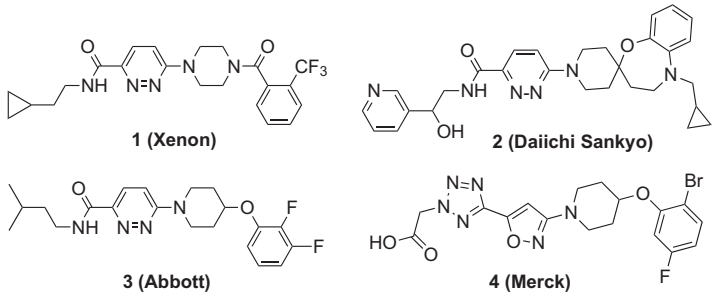


Figure 1. Selected reported SCD1 inhibitors.

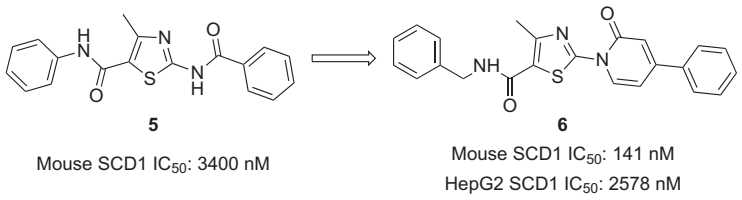


Figure 2. Thiazole-based SCD1 inhibitors discovered at Xenon.

the discovery of a series of novel, potent thiazolylpyridinone SCD1 inhibitors which demonstrate in vivo activity and high liver to plasma ratios. These results suggest the 4-hydroxy pyridinone functionality may be a suitable handle for liver-targeting or preferential liver distribution, and thus may lead to SCD1 inhibitors with improved safety and tolerability.

Compound **6** (Fig. 2) demonstrated improved SCD1 activity relative to the original hit compound **5**; however, this activity remained modest and likely insufficient to elicit in vivo effects. Based on our earlier work and knowledge from other scaffolds, we hypothesized that compound **6** was too conformationally constrained and that more flexibility might be required for binding to the SCD active site. Therefore, we introduced flexible linkers between the pyridin-2(1*H*)-one moiety and the terminal phenyl ring. Indeed, compounds **7** and **8** (Table 1) were roughly 7-fold more potent than compound **6** in the mouse liver microsomal SCD1 assay and, importantly, these modifications resulted in 50- to 100-fold increased potency in the HepG2 cell-based SCD1 assay. However, both compounds showed poor metabolic stability in rat liver microsomes and poor cell permeability as assessed in Caco-2 cells (Table 1). Therefore, our initial chemistry effort was focused on improving metabolic stability and cell permeability.

As outlined in Scheme 1, synthesis of pyridin-2(1*H*)-one analogues was achieved via a copper-catalyzed coupling reaction[21] between pyridin-2(1*H*)-ones and *N*-benzyl-2-bromo-4-methylthiazole-5-carboxamide, which were prepared from commercially available 2-bromo-4-methylthiazole-5-carboxylic acid and benzylamine under standard amide formation conditions. The resulting analogues were tested in SCD1 assays directly, or further elaborated to generate final target compounds.

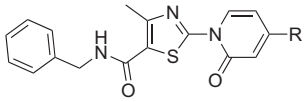
The inhibitory activity of these compounds against SCD1 was typically assessed by two assays: a mouse liver microsomal assay[22] and a human HepG2 cell-based assay.[23] Compounds with good potency on SCD1 were also screened against delta-5 (D5D) and delta-6 desaturase (D6D) to determine their selectivity 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, we felt that achieving selectivity against D5D and D6D is essential to avoid undesirable toxicities.[24] Active compounds described herein (HepG2 IC_{50} <100 nM) did not demonstrate D5D and D6D activity at 10 μM.

The activity data of these pyridin-2(*1H*)-one analogues is summarized in Table 1. Methoxyl (compound **9**) and cyclopropylethoxyl (compound **10**) analogues maintained good potency in both assays, and metabolic stability in rat liver microsomes was greatly improved compared to compounds **7** and **8**. Compound **9** also demonstrated significantly improved cell permeability. Analogues generated by replacement of the benzyloxyl group with a trifluoromethyl group, a small alkyl or a cycloalkyl group (compounds **13**, **14** and **15**) retained potency in the mouse liver microsomal SCD1 assay, but activity was reduced in the HepG2 cell-based assay. A similar trend was also observed when the benzyloxyl group was removed to generate the unsubstituted analogue **16**. The pyridine moieties (compounds **17** and **18**) were not well tolerated, resulting in decreased mouse liver microsomal activity. Removal of the benzyl group generated the 4-hydroxyl analogue **19**[25] which had good activity, displayed superior metabolic stability (~100% remaining after a 30 min incubation with 0.5 mg/mL rat liver microsomes), and had good permeability. Replacement of the oxygen atom with a nitrogen atom resulted in a decrease in activity. We found that modifications at the 4-position of the pyridinone could provide improved metabolic stability and cell permeability while maintaining the SCD1 potency.

Given the good in vitro potency in both SCD1 assays, good metabolic stability and reasonable cell permeability demonstrated by compound **19**, we then shifted our optimization effort to the C5 position amide functionality. Analogues were synthesized as outlined in Scheme 2. Similar to the chemistry described in Scheme 1, a copper-catalyzed coupling reaction between ethyl 2-bromo-4-methylthiazole-5-carboxylate and 4-(benzyloxy)-pyridin-2(1*H*)-one generated compound **23a**. Hydrolysis in the presence of lithium hydroxide yielded the corresponding acid **23b**. Subsequent amide formation under standard conditions afforded compounds **23c**–**31c**. The final 4-hydroxy compounds **23**–**31** were obtained after removal of the benzyl group via hydrogenation.

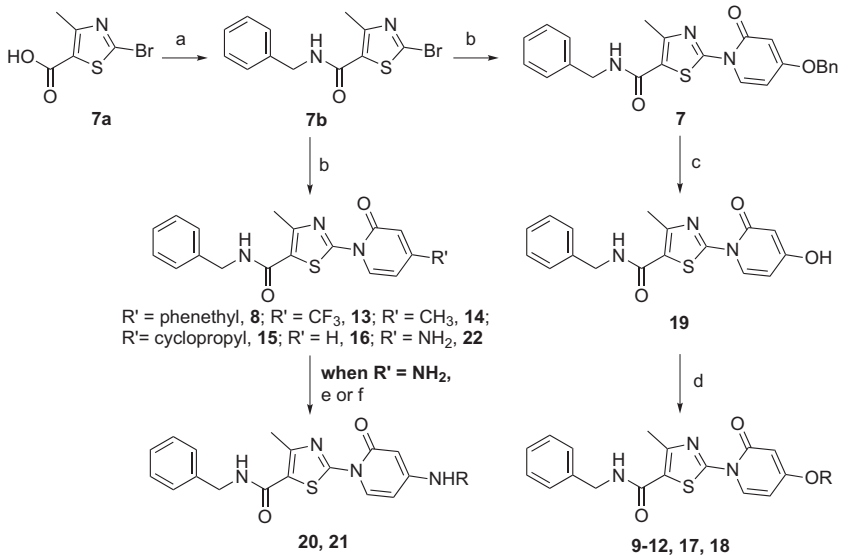
The SCD1 activity of these 4-hydroxy analogues was assessed using the same methods as outlined above and the results are summarized in Table 2. Fluorine substitution on the phenyl ring was well tolerated and maintained potency in both assays (**23**–**26**). Introduction of heteroaryl functionality was not tolerated as demonstrated by compounds **27**–**30**. Cycloalkylalkyl substitution maintained good potency in the mouse liver microsomal SCD1

Table 1
SAR summary of selected SCD1 inhibitors



Compound	R	Mouse SCD1 IC_{50}[a] (nM)	HepG2 SCD1 IC_{50}[a] (nM)	Rat liver microsome stability[b]	Permeability[c] ($\times 10^{-6}$ cm/s)
6	Phenyl	141	2578	17	1/0.2
7	Benzyloxyl	25	26	25	0.02/0.01
8	Phenethyl	20	50	22	0.6/0.2
9	Methoxyl	90	61	64	15/15
10	Cyclopropylethoxyl	40	12	71	0.05/0.04
11	(Tetrahydrofuran-2-yl)methoxyl	29	329	nd[d]	nd
12	Thiazol-4-ylmethoxyl	24	55	37	11/10
13	Trifluoromethyl	24	1510	nd	nd
14	Methyl	31	191	nd	nd
15	Cyclopropyl	40	458	62	28/22
16	H	63	2536	nd	nd
17	Pyridine-2-ylmethoxyl	1235	nd	nd	nd
18	Pyridine-3-ylmethoxyl	3430	nd	nd	nd
19	Hydroxyl	14	34	100	7/16
20	Benzylamino	155	nd	nd	nd
21	Benzamido	>10,000	nd	nd	nd
22	NH_2	387	nd	nd	nd

[a] IC_{50}s are an average of at least two independent determinations.
[b] Expressed as % remaining after a 30 min incubation with 0.5 mg/mL rat liver microsomes at 5 μM.
[c] Permeability was determined using Caco-2 cells. Data are expressed as P_{app}(a to b)/P_{app}(b to a).
[d] nd: not determined.



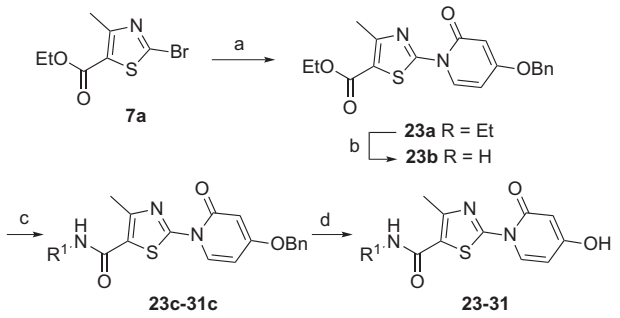
Scheme 1. Reagents and conditions: (a) EDCI, HOBt, $^{i}Pr_2NEt$, benzylamine, DMF; (b) 4-(benzyloxy)pyridin-2(1*H*)-one, CuI, 8-hydroxyquinoline, K_2CO_3, DMF, 80 °C; (c) H_2, Pd/C, MeOH; (d) RX, NaH or Cs_2CO_3, rt to 80 °C, DMF; (e) PhCHO, TFA, Et_3SiH, $CHCl_3$; (f) benzoyl chloride, pyridine.

assay, but the potency in the HepG2 cell assay decreased dramatically (compounds **31** and **32**). Compounds **19**, **23** and **25**, the most active analogs identified, maintained good metabolic stability, however are potential efflux transporter substrates as indicated by their Caco-2 P_{app}(b to a) to P_{app}(a to b) ratios (Table 2). This property could be due to the acidic nature of the hydroxyl group of 4-hydroxypyridinone (pK_a 5).

Based on the in vitro potencies and overall properties, we evaluated the in vivo effect of compounds **19**, **23** and **25** on the plasma C16:1/C16:0 triglycerides (TG) desaturation indices (DI)[26] in an acute Lewis rat pharmacodynamics (PD) model.[27] C16 DI has been well-documented as biomarkers for SCD1 target engagement.[9,28] The results of the C16:1/C16:0 plasma DI are illustrated in Figure 3. After a single oral administration, compounds **19** and **25** demonstrated statistically significant reductions of the plasma C16:1/C16:0 TG DI, by 40% and 26%, respectively, at a 4 h time point. Compound **23** had only a marginal effect on plasma DI reduction despite having a similar in vitro profile as the other two compounds tested.

Compound **19**, which had the most robust effect in the DI screening model, was then evaluated in a dose-responsive manner (2 mg/kg to 10 mg/kg with plasma sampling at the 4 h time point). The results indicated a dose-related reduction of plasma TG DI with the ED_{50} estimated to be 6.2 mg/kg (Fig. 4).

We further investigated the PK/PD relationship of compound **19**. In this study[27], Lewis rats were dosed orally at 10 mg/kg and plasma samples were collected at different time points for exposure and plasma DI measurements (Fig. 5). The maximum effect



Scheme 2. Reagents and conditions: (a) 4-(benzyloxy)pyridin-2(1*H*)-one, CuI, 8-hydroxyquinoline, K_2CO_3, DMF, 80 °C; (b) LiOH, THF, H_2O, reflux; (c) EDCI, HOBt, $^iPr_2NEt$, R^1NH_2, DMF; (d) H_2, Pd/C, MeOH.

in reduction of C16:1/C16:0 TG DI of about 65% was achieved at 2 h post oral administration. The effect was maintained at 8 h post dose (42% reduction) and at 24 h, the C16:1/C16:0 TG DI had recovered to about 70% of the level of the contemporaneous vehicle group. Plasma concentrations at the 2 to 8 h time points where profound DI reduction was observed, were surprisingly low: 0.46 μM at 2 h; 0.37 μM at 4 h; 0.21 μM at 6 h; 0.15 μM at 8 h. This observation prompted us to investigate the PK/PD relationship. We hypothesized that tissue distribution, specifically high liver concentration of compound **19**, could be a contributor to the apparent disconnection. Since plasma DI serves as a surrogate readout for liver SCD1 activity, high liver concentrations of compound **19** would explain the robust effect observed on plasma DI.

We evaluated the tissue distribution of compound **19** after 5 days of treatment (*qd*, *PO*, 10 mg/kg dose, Lewis rats), assuming that this duration would be sufficient to achieve steady state. The concentration of compound **19** in plasma, eyelid and liver was analyzed 2 h after the last dose (Fig. 6). At this time point, compound **19** had an exposure of 11,100 nM in liver, 309 nM in plasma, and 271 nM in eyelid, resulting a liver to plasma ratio of 36, and a liver to eyelid ratio of 41. These data support the hypothesis that compound **19** preferentially distributes to the liver. Also, at 2 h, the liver concentration of compound **19** was greater than 300-fold over the cell-based IC_{50}, which explains the robust effect on DI. Liver-selective SCD1 inhibitors could provide significant advantages in terms of safety, specifically reducing risks for known adverse effects, such as dry skin and dry eyes, related to the SCD1

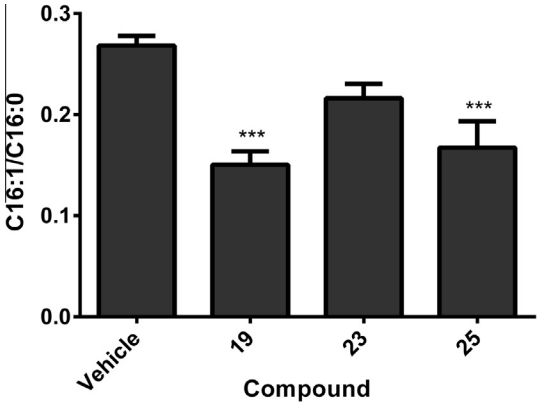


Figure 3. Effect of compounds **19**, **23** and **25** on plasma C16:1/C16:0 TG desaturation index 4 h after a 5 mg/kg oral dose in Lewis rats. Each bar represents the mean of at least 4 animals and the error bars represent standard errors of the mean. ***: One-way ANOVA analysis between vehicle group and compound treated groups with p <0.001.

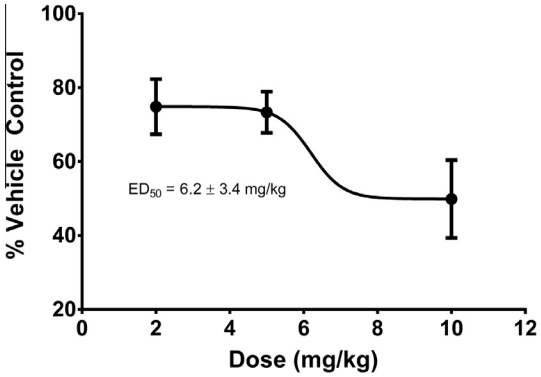
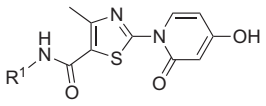


Figure 4. Dose response of compound **19** on plasma C16:1/C16:0 TG desaturation index 4 h after oral dosing in Lewis rats. Each data point represents the mean of at least 4 animals. The error bars represent the standard errors of the mean.

inhibition in meibomian and sebaceous glands.[28,29] Recently, other liver-selective SCD1 inhibitors have also been reported.[20,30–36]

To provide an initial safety assessment with respect to the adverse effects associated with SCD1 deficiency, compound **19** was

Table 2
SAR summary of selected SCD1 inhibitors



Compound	R^1	Mouse SCD1 IC_{50}[a] (nM)	HepG2 SCD1 IC_{50}[a] (nM)	Rat liver microsome stability[b]	Permeability[c] ($\times 10^{-6}$ cm/s)
19	Benzyl	14	34	100	7/16
23	4-Fluorobenzyl	15	30	85	9/23
24	3-Fluorobenzyl	20	137	nd[d]	nd
25	3,4-Difluorobenzyl	18	48	89	9/33
26	4-Fluorophenethyl	43	121	nd	nd
27	Pyridin-3-ylmethyl	231	nd	nd	nd
28	Pyridin-4-ylmethyl	103	>1000	nd	nd
29	(5-Methylpyrazin-2-yl)methyl	342	nd	nd	nd
30	Oxazol-2-ylmethyl	430	nd	nd	nd
31	Cyclopropylmethyl	49	1692	nd	nd
32	Cyclopropylethyl	69	783	nd	nd

[a] IC_{50}s are an average of at least two independent determinations.
[b] Expressed as% remaining after a 30 min incubation with 0.5 mg/mL rat liver microsomes at 5 μM.
[c] The data were determined using Caco-2 cells. Data are expressed as P_{app}(a to b)/P_{app}(b to a).
[d] nd: not determined.

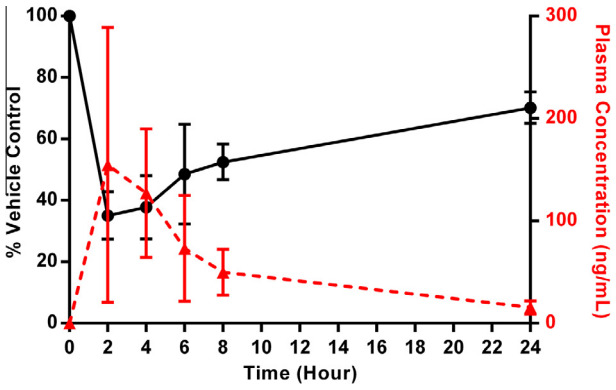


Figure 5. PK/PD relationship of compound **19** on plasma C16:1/C16:0 TG desaturation index after a 10 mg/kg oral dose in Lewis rats. Each data point represents the mean of at least 4 animals and the error bars represent standard errors of the mean.

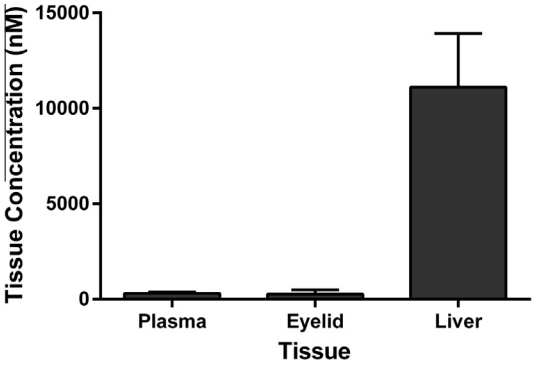


Figure 6. Tissue distribution of compound **19**. Each bar represents the mean of 6 animals and the error bars represent standard errors of the mean.

evaluated in a fourteen-day clinical observation study. In this study, female Sprague–Dawley rats were dosed orally at 100 mg/kg once daily for 13 days and the clinical signs, such as red eyes, hair loss and dry skin were assessed. No SCD1 inhibition related adverse effects, or any other side effects, were observed over the course of this study. The plasma exposure of compound **19** on Day 14 was 25 μM h ($AUC_{0-24\ h}$). Comparing this value to the exposure required in the Lewis rat model for maximum DI reduction (10 mg/kg, $AUC_{0-24\ h}$ = 1.9 μM h) a greater than 14-fold window exists between PD effects and adverse effects due to SCD1inhibition.

In conclusion, we discovered a series of novel and potent thiazolylpyridinone SCD1 inhibitors based on a 2-aminothiazole-based scaffold identified by HTS. Compound **19** demonstrated good potency against SCD1 in vitro and in vivo. The in vitro potency was improved >240-fold compared to the original HTS hit compound. Tissue distribution analyses revealed that compound **19** had significantly higher exposure in liver than in plasma and eyelid. In an initial safety assessment, compound **19** did not demonstrate adverse effects related to SCD1 inhibition. Thus, compound **19**, perhaps due to the 4-hydroxypyridinone functionality, provides a new structural motif which demonstrates preferential liver distribution. Furthermore, liver-selective SCD1 inhibitors are likely to provide improved therapeutic indices with respect to known mechanism-based adverse effects, and thereby may be more suitable molecules for clinical development in the area of metabolic diseases.

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References and notes

1. Kusunoki, J.; Kanatani, A.; Moller, D. E. *Endocrine* **2006**, *29*, 91.
2. Chavez, J. A.; Summers, S. A. *Biochim. Biophys. Acta* **2010**, *18*, 252.
3. Ntambi, J. M. *Prog. Lipid Res.* **1995**, *34*, 139.
4. Cohn, P.; Miyazaki, M.; Socci, N. D.; Hagge-Greenberg, A.; Liedtke, W.; Soukas, A. A.; Sharma, R.; Hudgins, L. C.; Ntambi, J. M.; Friedman, J. M. *Science* **2002**, *297*, 240.
5. Ntambi, J. M.; Miyazaki, M.; Stoehr, J. P.; Lan, H.; Kendziorski, C. M.; Yandell, B. S.; Song, Y.; Cohn, P.; Friedman, J. M.; Attie, A. D. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11482.
6. Dobrzyn, P.; Sampath, H.; Dobrzyn, A.; Miyazaki, M.; Ntambi, J. M. *Am. J. Physiol. Endocrinol. Metab.* **2008**, *294*, E357.
7. Jiang, G.; Li, Z.; Liu, F.; Ellsworth, K.; Dallas-Yang, Q.; Wu, M.; Ronan, J.; Esau, C.; Murphy, C.; Szalkowski, D.; Bergeron, R.; Doebber, T.; Zhang, B. B. *J. Clin. Invest.* **2005**, *115*, 1030.
8. Gutierrez-Juarez, R.; Pocai, A.; Mulas, C.; Ono, H.; Bhanot, S.; Monia, B. P.; Rossetti, L. *J. Clin. Invest.* **2006**, *116*, 1686.
9. Attie, A. D.; Krauss, R. M.; Gray-Keller, M. P.; Brownlie, A.; Miyazaki, M.; Kastelein, J. J.; Lusis, A. J.; Stalenhoef, A. F.; Stoehr, J. P.; Hayden, M. R.; Ntambi, J. M. *J. Lipid Res.* **2002**, *43*, 1899.
10. Hulver, M. W.; Berggren, J. R.; Carper, M. J.; Miyazaki, M.; Ntambi, J. M.; Hoffman, E. P.; Thyfault, J. P.; Stevens, R.; Dohm, G. L.; Houmard, J. A.; Muoio, D. M. *Cell Metab.* **2005**, *2*, 251.
11. Warensjö, E.; Ingelsson, E.; Lundmark, P.; Lannfelt, L.; Syvänen, L.-C.; Vessby, B.; Risérus, U. *Obesity* **2007**, *15*, 1732.
12. Abreo, M.; Chafeev, M.; Chakka, N.; Chowdhury, S.; Fu, J.; Gschwend, H.W.; Holladay, M.W.; Hou, D.; Kamboj, R.; Kodumuru, V.; Li, W.; Liu, S.; Raina, V.; Sun, S.; Sun, S.; Sviridov, S.; Tu, C.; Winther, M. D.; Zhang, Z. WO 2005/011655.
13. Zhang, Z.; Sun, S.; Kodumuru, V.; Hou, D.; Liu, S.; Chakka, N.; Sviridov, S.; Chowdhury, S.; McLaren, D. G.; Ratkay, L. G.; Khakh, K.; Cheng, X.; Gschwend, H. W.; Kamboj, R.; Fu, J.; Winther, W. D. *J. Med. Chem.* **2013**, *56*, 568.
14. Liu, G.; Lynch, J. K.; Freeman, J.; Liu, B.; Xin, Z.; Zhao, H.; Serby, M. D.; Kym, P. R.; Suhar, T. S.; Smith, H. T.; Cao, N.; Yang, R.; Janis, R. S.; Krauser, J. A.; Cepa, S. P.; Beno, D. W. A.; Sham, H. L.; Collins, C. A.; Surowy, T. K.; Camp, H. S. *J. Med. Chem.* **2007**, *50*, 3086. and references cited therein.
15. Zhao, H.; Serby, M. D.; Smith, H. T.; Cao, N.; Suhar, T. S.; Surowy, T. K.; Camp, H. S.; Collins, C. A.; Sham, H. L.; Liu, G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3388.
16. Koltun, D. O.; Parkhill, E. Q.; Vasilevich, N. I.; Glushkov, A. I.; Zilbershtein, T. M.; Ivanov, A. V.; Cole, A. G.; Henderson, I.; Zautke, N. A.; Brunn, S. A.; Mollova, N.; Leung, K.; Chisholm, J. W.; Zablocki, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2048.
17. Liu, G. *Curr. Top. Med. Chem.* **2010**, *10*, 419. and references cited therein.
18. Léger, S.; Black, W. C.; Deschenes, D.; Dolman, S.; Falgueyret, J.; Gagnon, M.; Guiral, S.; Huang, Z.; Guay, J.; Leblanc, Y.; Li, C.; Massé, F.; Oballa, R. M.; Zhang, L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 499.
19. Uto, Y.; Ueno, Y.; Kiyotsuka, Y.; Miyazawa, Y.; Kurata, H.; Ogata, T.; Takagi, T.; Wakimoto, S.; Ohsumi, J. *Eur. J. Med. Chem.* **2011**, *46*, 1892. and references cited therein.
20. Oballa, R. M.; Belair, L. W.; Black, C.; Bleasby, K.; Chan, C. C.; Desroches, C.; Du, X.; Gordon, R.; Guay, J.; Guiral, S.; Hafey, M. J.; Hamelin, E.; Huang, Z.; Kennedy, B.; Lachance, N.; Landry, F.; Li, C. S.; Mancini, J.; Normandin, D.; Pocai, A.; Powell, D. A.; Ramtohul, Y. K.; Skorey, K.; Sørensen, D.; Sturkenboom, W.; Styhler, A.; Waddleton, D. M.; Wang, H.; Wong, S.; Xu, L.; Zhang, L. *J. Med. Chem.* **2011**, *54*, 5082.
21. Filipski, K. J.; Kohrt, J. F.; Casimiro-Garcia, A.; Van Huis, C.; Dudley, D. A.; Cody, W. L.; Bigge, C. F.; Desiraju, S.; Sun, S.; Maiti, S. N.; Jaber, M. R.; Edmunds, J. J. *Tetrahedron Lett.* **2006**, *47*, 7677.
22. Talamo, B. R.; Bloch, K. *Anal. Biochem.* **1969**, *29*, 300.
23. The HepG2 assay was a variation of a cell-based assay for desaturases that uses radiolabeled fatty acids to measure substrate/product ratios. The SCD1 assay uses radiolabeled stearic acid as the substrate. Antueno, R. J.; Knickle, L. C.; Smith, H.; Elliot, M. L.; Allen, S. J.; Nwaka, S.; Winther, M. D. *FEBS Lett.* **2001**, *509*, 77.
24. Nakamura, M. T.; Nare, T. Y. *Annu. Rev. Nutr.* **2004**, *24*, 345.
25. *Characterization data for compound* ***19***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.51 (s br, 1H), 8.76 (t, *J* = 5.9 Hz, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 7.39–7.16 (m, 5H), 6.26 (dd, *J* = 8.0, 2.5 Hz, 1H), 5.81 (d, *J* = 2.5 Hz, 1H), 4.38 (d, *J* = 5.9 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 167.9, 162.0, 161.6, 154.1, 150.2, 139.9, 132.6, 128.7, 127.7, 127.2, 123.6, 104.4, 98.0, 43.1, 17.5; MS (ES^+) *m/z* 342.1 (M+1); HPLC purity (a/a%): 99.8%.
26. Desaturation indices were calculated from the fatty acid profile of circulating plasma triglycerides. Lipids were extracted from plasma using the procedure reported in Folch, J.; Lees, M.; Stanley, G. H. S. *J. Biol. Chem.* **1957**, *226*, 497.
27. In this study, the animals were maintained on a high carbohydrate diet for one week prior to dosing. The formulation was 1% carboxymethyl cellulose (low viscosity):0.2% Tween 20:98.8% water and doses were given orally at 3 mL/kg. The animals were dosed orally with SCD1 inhibitors at 5 mg/kg and plasma samples were collected 4 h after dosing. The plasma lipid profiles were determined after separation of different lipid species using thin layer chromatography and lipid analyses by gas chromatography. The contemporaneous plasma TG DI of a satellite vehicle control group was determined and the effect of compound **19** on plasma TG DI was assessed by

the direct comparison of the treated group with the contemporaneous vehicle control group.
28. Sundberg, J. P.; Boggess, D.; Sundberg, B. A.; Eilertsen, K.; Parimoo, S.; Filippi, M.; Stenn, K. *Am. J. Pathol.* **2000**, *156*, 2067.
29. Miyazaki, M.; Man, W. C.; Ntambi, J. M. *J. Nutr.* **2001**, *131*, 2260.
30. Ramtohul, Y. K.; Powell, D. A.; Leclerc, J.; Léger, S.; Oballa, R. M.; Black, C.; Isabel, E.; Li, C. S.; Crane, S.; Robichaud, J.; Guay, J.; Guiral, S.; Zhang, L.; Huang, Z. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5692.
31. Leclerc, J.; Falgueyret, J.; Girardin, M.; Guay, J.; Guiral, S.; Huang, Z.; Li, C. S.; Oballa, R. M.; Ramtohul, Y. K.; Skorey, K.; Tawa, P.; Wang, H.; Zhang, L. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6505.
32. Powell, D. A.; Black, C.; Bleasby, K.; Chan, C. C.; Deschenes, D.; Gagnon, M.; Gordon, R.; Guay, J.; Guiral, S.; Hafey, M. J.; Huang, Z.; Isabel, E.; Leblanc, Y.; Styhler, A.; Xu, L.; Zhang, L.; Oballa, R. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7281.
33. Lachance, N.; Guiral, S.; Huang, Z.; Leclerc, J.; Li, C. S.; Oballa, R. M.; Ramtohul, Y. K.; Wang, H.; Wu, J.; Zhang, L. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 623.
34. Lachance, N.; Gareau, Y.; Guiral, S.; Huang, Z.; Isabel, E.; Leclerc, J.; Léger, S.; Martins, E.; Nadeau, C.; Oballa, R. M.; Quellet, S.; Powell, D.; Ramtohul, Y. K.; Tranmer, G. K.; Trinh, T.; Wang, H.; Zhang, L. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 980.
35. Koltun, D. O.; Vasilevich, N. I.; Parkhill, E. Q.; Glushkov, A. I.; Zilbershtein, T. M.; Mayboroda, E. I.; Boze, M. A.; Cole, A. G.; Henderson, I.; Zautke, N. A.; Brunn, S. A.; Chu, N.; Hao, J.; Mollova, N.; Leung, K.; Chisholm, J. W.; Zablocki, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3050.
36. Koltun, D. O.; Zilbershtein, T. M.; Migulin, V. A.; Vasilevich, N. I.; Parkhill, E. Q.; Glushkov, A. I.; McGregor, M. J.; Brunn, S. A.; Chu, N.; Hao, J.; Mollova, N.; Leung, K.; Chisholm, J. W.; Zablocki, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4070.