4-Bicyclic heteroaryl-piperidine derivatives as potent, orally bioavailable stearoyl-CoA desaturase-1 (SCD1) inhibitors: Part 2. Pyridazine-based analogs

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Graphical Abstract

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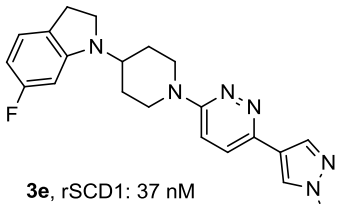
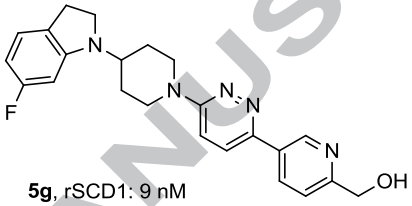


3e, rSCD1: 37 nM
A431: 15 nM



5g, rSCD1: 9 nM
A431: 0.5 nM

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4-Bicyclic heteroaryl-piperidine derivatives as potent, orally bioavailable stearoyl-CoA desaturase-1 (SCD1) inhibitors: Part 2. Pyridazine-based analogs

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ABSTRACT

Design, synthesis, and biological evaluation of pyridazine-based, 4-bicyclic heteroaryl-piperidine derivatives as potent Stearoyl-CoA desaturase-1 (SCD1) inhibitors are described. In a chronic study of selected analog (**3e**) in Zucker fa/fa (ZF) rat, dose-dependent decrease of body weight gain and plasma fatty acid desaturation index (DI) in both C16 and C18 are also demonstrated. The results indicate that the plasma fatty acid DI may serve as an indicator for direct target engagement and biomarker for SCD1 inhibition.

Stearoyl-CoA desaturase 1 (SCD1) is a major lipogenic enzyme that converts saturated fatty acid (FA)-CoAs to mono-unsaturated FA-CoAs.[1] These mono-unsaturated FA-CoAs are major components for the synthesis of lipids including phospholipids, triglycerides, cholesterol esters and wax esters.[2] SCD1 enzyme is abundantly expressed in liver and adipose tissue and is regulated by several hormonal factors, such as insulin, cholesterol, and poly-unsaturated fatty acids.[3] Studies with SCD1 knockout ($SCD1^{-/-}$) mice and antisense oligonucleotides against SCD1 suggested a beneficial role of SCD1 inhibition in reducing lipid synthesis, body weight and improving insulin sensitivity.[4] Additionally, the $SCD1^{-/-}$ mice also have lower levels of hepatic cholesterol esters and triglycerides.[5] Therefore, potential inhibition of SCD1 activity may serve as a considerable treatment for obesity, type-II diabetes, and other related metabolic syndromes.

Among the structurally diverse SCD1 inhibitors disclosed recently,[6,7] linear 4-phenoxy-piperidine derivatives, such as **1a** (MF-438)[6e] and **1b**[6f] (Figure 1), are quite interesting due to their remarkable potency and in vivo efficacy. We recently reported a series of 4-bicyclic heteroaryl-piperidine urea analogs as potent SCD1 inhibitors as exemplified by compound **2**, which demonstrated a trend of dose-dependent decrease in body weight gain in diet-induced obese (DIO) mice.[8] Based on these encouraging results, we were interested in further modifications of compound **2** with particular focus on replacing the urea functionality with an aryl-substituted pyridazine ring. Herein we report the structure-activity relationships (SAR) and *in vivo* efficacy studies of 4-bicyclic heteroaryl piperidine-based pyridazine analogs (**3**–**5**) as potent and orally efficacious SCD1 inhibitors.

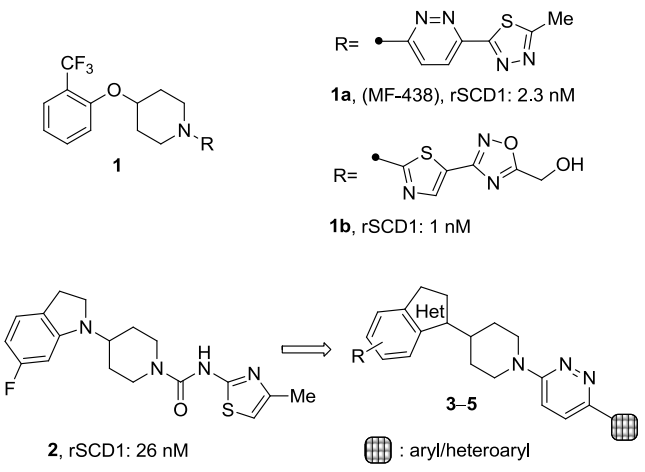

Figure 1. Representative 4-phenoxypiperidine-based and 4-bicyclic heteroaryl piperidine-based SCD1 inhibitors.

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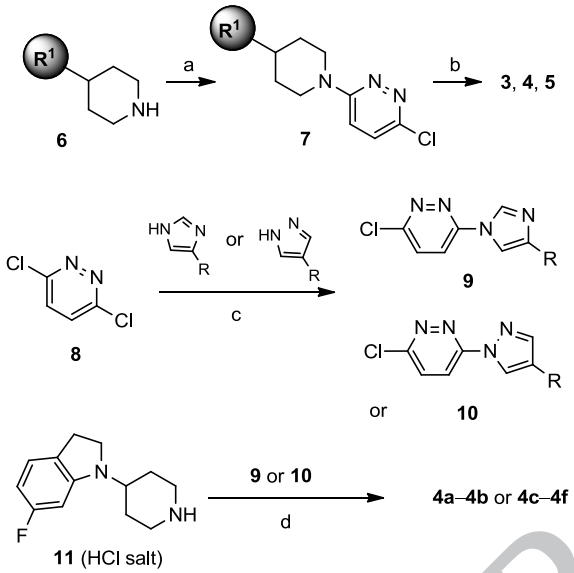
The general synthetic sequences for analogs **3**–**5** are outlined in Scheme 1. The synthesis began with the mono-displacement of 2,6-dichloropyridazine with 4-bicyclic heteroaryl piperidine **6** to afford intermediate **7**.[9] Subsequently, various aryl or heteroaryl rings were introduced through facile Suzuki coupling or Stille coupling with corresponding boronic acids, boronic esters, or organo-tin reagents. An alternative method to afford imidazole and 1-pyrazole analogs (**4a**–**4f**) utilized a displacement of intermediates **9**–**10,** which were prepared from the corresponding imidazole or pyrazole components and 2,6-dichloropyridazine (**8**), - with 4-(6-fluoroindolin-1-yl)piperidine (**11**) under microwave irradiation.



Scheme 1. R^1 represents bicyclic heteroaryl, such as indole, indoline, indazole, benzoisoxazole etc. *Reagents and conditions*: (a) 3,6-dichloropyridazine, Et_3N, DMSO, 80-100 °C, 60-83%; (b) organo-boronic acids or boronic esters (Suzuki coupling), $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O, 95-100 °C, 40-95%, or organo-Tin reagents (Stille coupling), $Pd(PPh_3)_4$, 1,4-dioxane, 120-140 °C, microwave, 38-76%; (c) Cs_2CO_3, MeCN, reflux; (d) **9** or **10**, $(i\text{-}Pr)_2NEt$, DMSO, 160-180 °C, microwave, 39-86%.

The compounds **3a-m** with *N*-methylpyrazole-4-yl substitution were synthesized and tested against rat SCD1 enzyme (rSCD1) and human epithelial carcinoma A431 cells.[7] The results in Table 1 focused on varying the substitution on the bicyclic heteroaryl ring revealed the potency was dramatically influenced by substituent type and the position substituted. Unsubstituted indoline (**3a**) or indole (**3b**) gave only moderate affinity. Consistent with previous findings,[7] halogen substitution on the 6-position of indole/indoline rings, such as F (**3e**, **3k**) or Cl (**3g**), significantly improved the potency to low nanomolar range in both rSCD1 and the A431 assay. Halogen substitution at the 5- and 4-position was less favorable, causing around 5- and 18-fold drop in potency (**3e** vs. **3d** and **3c**). A similar trend was observed in Cl-substitution (**3g** vs. **3f**). Small electron donating groups such as methyl and methoxy (**3h**, **3i**) as well as electron withdrawing groups such as $–CF_3$ (**3j**) also resulted in a 5-9 fold loss in potency. Modifying the bicyclic heteroaryl component with 5-fluorobenzoisoxazole (**3l**) and 6-fluoroindazole (**3m**), also provided comparable inhibitory activities as to the substituted indoline.

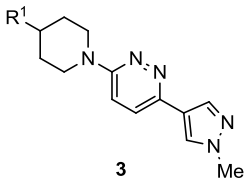
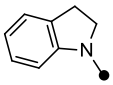
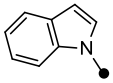
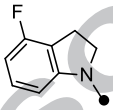
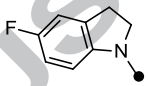
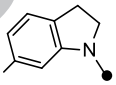
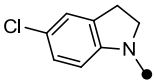
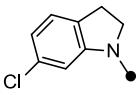
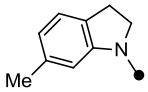
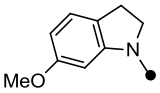
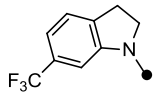
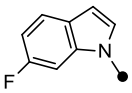
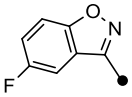
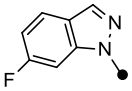


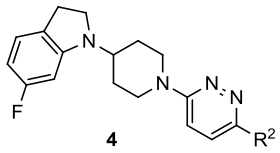
Table 1. SAR of bicyclic heteroaryl substitutions R^1.

Compds	R^1	rSCD1 IC_{50} (nM)[a]	A431 (nM)[b]
3a		394	–
3b		422	–
3c		678	–
3d		165	99
3e		37	15
3f		181	218
3g		35	28
3h		286	241
3i		317	407
3j		173	42
3k		23	25
3l		125	–
3m		38	51

[a]Single experiment or means of at least two runs.
[b]Using ^{13}C-palmitic acid and LC-MS method, see supplementary material.

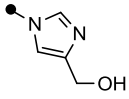
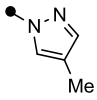
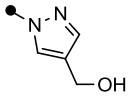
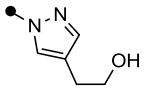
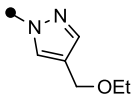
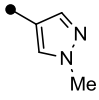
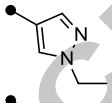
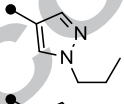
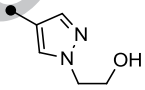
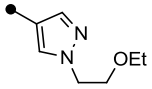
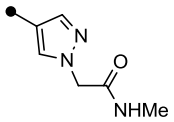
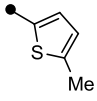
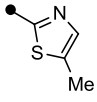
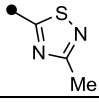
By using the 6-fluoroindoline as a left-hand side piece, our attention next focused on exploration of SAR by modifying the pyrazole ring with various substituted 5-membered heteroarenes (Table 2). An imidazole was first found to be a suitable replacement for the pyrazole that produced analogs **4a**–**4b** with excellent inhibitory activities. Unfortunately, these compounds also showed significant hERG channel affinity (IC_{50} < 10 μM) (blockade activity) precluding them from further investigation. Attaching a 3-substituted pyrazole through its N-1 nitrogen atom (**4c**–**4f**) also provided compounds with good potency against both rSCD1 and A431 assays. Modifying the methyl group of **3e** to straight chain alkyl (**4g**–**4h**), hydroxyalkyl (**4i**), and elongated

side chains (**4j**–**4k**) resulted in no significant change in potency. However, the linear side chains (such as **4f**, **4h**, and **4j**) did show a decrease in human and/or rat microsomal stabilities (< 50% remained at 10 minutes). With other 5-membered heteroarenes examined, thiophene (**4l**) showed a decrease of potency in rSCD1 enzymatic assay, while thiazole (**4m**–**4n**) and thioisodiazole (**4o**) demonstrated comparable affinity to those bearing pyrazole or imidazole rings.



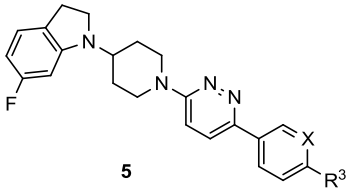
4

Table 2. SAR of 5-membered heteroaryl substituent R^2.

Compds	R^2	rSCD1 IC_{50} (nM)[a]	A431 (nM)[b]
4a		16	9
4b		11	3
4c		21	23
4d		17	6
4e		20	11
4f		8	9
3e		37	15
4g		17	30
4h		22	72
4i		22	21
4j		12	41
4k		15	12
4l		121	6
4m		31	12
4n		7	2
4o		11	–

[a]Single experiment or means of at least two runs.
[b]Using ^{13}C-palmitic acid and LC-MS method, see supplementary material.

Replacement of the pyrazole ring with para-substituted 6-membered rings, such as phenyl or pyridine, was also examined (Table 3). A direct comparison between **5a**–**c** and **5f**–**h** revealed that the pyridine analogs exhibited better inhibitory activity than phenyl analogs. In general, various substituents such as electron-donating groups (Me, OMe, NMe_2) or electron-withdrawing groups (CF_3, CONHMe) were well tolerated with exceptions of F (**5d**) and carboxylic acid (**5e**). Consistent with the results observed above for compounds **4b** and **4d**–**i**, the hydroxymethyl substitution on both phenyl and pyridine rings provided compounds with excellent *in vitro* potency in both the rSCD1 and A431 assays (**5b**, **5g**). Despite the important inhibitory activities, most of these potent inhibitors either suffered with low microsomal stabilities or displayed significant affinity towards CYP450 inhibition and/or hERG channel binding (data not shown) precluding them from further development.



5

Table 3. SAR of substituent R^3.

Compds	X	R^3	rSCD1 IC_{50} (nM)[a]	A431 (nM)[b]
5a	C	Me	79	11
5b	C	CH_2OH	22	8
5c	C	CF_3	90	54
5d	C	F	777	–
5e	C	CO_2H	349	390
5f	N	Me	13	2
5g	N	CH_2OH	9	0.5
5h	N	CF_3	16	14
5i	N	OMe	12	4
5j	N	NMe_2	17	30
5k	N	CONHMe	35	6

[a]Single experiment or means of at least two runs.
[b]Using ^{13}C-palmitic acid and LC-MS method, see supplementary material.

To further select suitable compounds for chronic studies in Zucker fa/fa rat (ZF), compounds with good *in vitro* potency and desirable early ADME properties were selected and quickly evaluated the effect on body weight (BW) change in DIO mice. These compounds, such as **3m**, **3e**, **4d**, **4i**, and **5g**, were tested in DIO mice at 30 mg/kg once-daily (qd) administration for 10 days. The results complied in Table 4 demonstrated a significant reduction of body weight (BW) gain when compared to vehicle-treated group.

Table 4. Body weight change in 10-day DIO mice study[a].

Compds	Body weight change (g)
vehicle	2.8 ± 0.3
3m	– 3.3 ± 0.5*
3e	– 2.1 ± 0.3*
4d	1.2 ± 0.3 *
4i	0.5 ± 0.1*
5g	– 2.2 ± 0.5*

[a]30 mg/kg (n= 8); *p< 0.05 vs. vehicle-treated group.

Subsequently, compound **3e** was chosen for further studies. The pharmacokinetic (PK) profiles of **3e** in Sprague Dawley (SD) rats and Zucker fa/fa (ZF) rats were determined. These PK results revealed that **3e** has moderate volume of distribution (0.52 L/kg) and low clearance level (3.3 mL/min/kg; iv: 2 mg/kg). A desirable plasma exposure for SD rats (po: 10 mg/kg; n= 4; C_{max}: 4.4 μg/mL; AUC_{24h}: 38.8 h*μg/mL) and ZF rats (po: 10 mg/k; n= 4; C_{max}: 1.6 μg/mL; AUC_{24h}: 10.8 h*μg/mL) were also obtained along with a 105% and 11% oral bioavailability, respectively. To further measure chronic *in vivo* efficacy, a 26-day study in ZF rats with compound **3e** was carried out at 1, 3, and 10 mg/kg. The results compiled in Table 5 and Figure 2 indicated that significant reduction of BW gain was obtained at day 15 for 1 and 3 mg/kg groups compared to vehicle-treated group, though no significant separation was observed between 1 mg/kg and 3 mg/kg groups. For 10 mg/kg treatment group, BW gain was significantly decreased as early as day 8. Effects on reduction of BW gain after 26 days treatment was 51%, 22% and 17% for 10 mg/kg, 3 mg/kg and 1 mg/kg groups, respectively. No significant change in food intake was found for 1 and 3 mg/kg groups throughout the study, while about a 10% decrease of food consumption was observed in 10 mg/kg group after day 22. In addition, no elevation of liver enzymes (ALT and AST) was observed at the end of the study. More importantly, dose-dependent decrease of plasma fatty acid desaturation index (DI) was observed for both C16:1/C16:0 and C18:1/C18:0 (Figure 3). This line of evidence strongly suggested that the plasma fatty acid DI may serve as an indicator for direct target engagement and biomarker for SCD1 inhibition.

Table 5. Effect of **3e** on body weight gain (g) in 26 days Zucker fa/fa rat (n= 8) study.

treatment	day 8	day 15	day 22	day 26
vehicle	61 ± 7	103 ± 4	142 ± 4	161 ± 8
3e (1 mg/kg)	42 ± 5	80 ± 4*	116 ± 5*	133 ± 5*
3e (3 mg/kg)	44 ± 4	80 ± 5*	112 ± 6*	125 ± 4*
3e (10 mg/kg)	29 ± 4*	57 ± 4*	72 ± 6*	78 ± 6*

*p< 0.05 vs. vehicle-treated group.

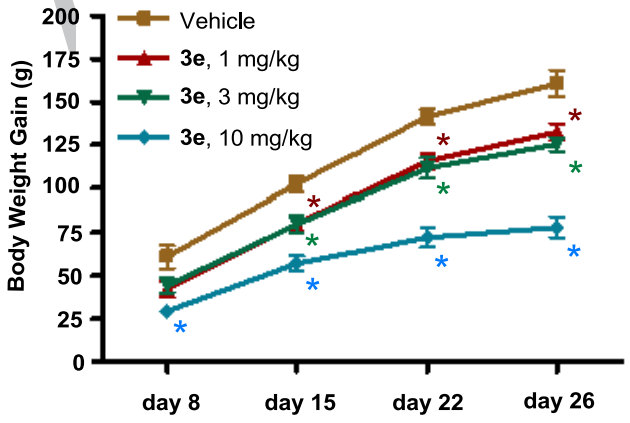


Figure 2. Effect of **3e** on reduction of body weight gain in 26 days Zucker fa/fa rat (n= 8) study (*p< 0.05 vs. vehicle-treated group).

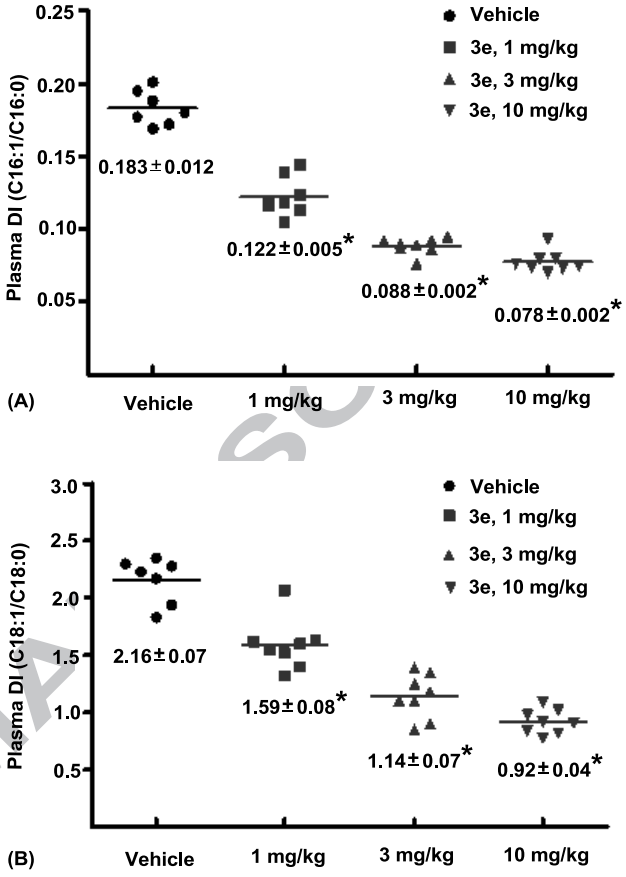


Figure 3. Effect of **3e** on dose dependent decrease of plasma DI after a 26-day study in ZF rats (n= 8) at 1, 3, and 10 mg/kg (*p< 0.05 vs. vehicle-treated group).

In conclusion, a new series of 4-bicyclic heteroaryl piperidine-based pyridazine analogs as potent SCD1 inhibitors is reported. Selected analog **3e** demonstrated *in vivo* efficacy by significantly decreasing body weight gain in ZF rats. The ability of compound **3e** to dose dependently decrease plasma fatty acid desaturation index (DI) in ZF rats strongly indicate that plasma fatty acid DI may potentially serve as a suitable target engagement biomarker for SCD1 inhibition. The detailed pharmacological findings of **3e** in ZF rats and DIO mice will be disclosed in near future.[10]

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Supplementary Material
Supplementary material associated with this article can be found, in the online version, at doi:

References and notes

1. (a) Dobrzyn, A.; Ntambi, J. M. *Obes. Rev.* **2005**, *6*, 169. (b) Ntambi, J. M.; Miyazaki, M. *Curr. Opin. Lipidol.* **2003**, *14*, 255.
2. Miyazaki, M.; Gomez, F. E.; Ntambi, J. M. *J. Lipid Res.* **2002**, *43*, 2146.
3. (a) Waters, K. M.; Ntambi, J. M. *J. Biol. Chem.* **1994**, *269*, 27773. (b) Ntambi, J. M. *J. Lipid Res.* **1999**, *40*, 1549.

4. (a) Ntambi, J. M.; Miyazaki, M.; Stoehr, J. P.; Lan, H.; Kendziorski, C. M.; Yandell, B. S.; Song, Y.; Cohen, P.; Friedman, J. M.; Attie, A. D. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11482. (b) Ntambi, J. M.; Miyazaki, M. *Prog. Lipid Res.* **2004**, *43*, 91.

5. Miyazaki, M.; Kim, Y. C.; Gray-Keller, M. P.; Attie, A. D.; Ntambi, J. M. *J. Biol. Chem.* **2000**, *275*, 30132.

6. Representative SCD1 inhibitors, see: (a) 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. (b) 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. (c) Xin, Z.; Zhao, H.; Serby, M. D.; Liu, B.;Liu, M.;Szczepankiewicz, B. G.; Nelson, L. T.; Smith, H. T.; Suhar, T. S.; Janis, R. S.; Cao, N.; Camp, H. S.; Collins, C. A.; Sham, H. L.; Surowy, T. K.; Liu, G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4298. (d) Li, C. S.; Belair, L.; Guay, J.; Murgasva, R.; Sturkenboom, W.; Ramtohul, Y. K.; Zhang, L.; Huang, Z. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5214. (e) Léger, S.; Black, W. C.; Deschenes, D.; Falgueyret, J.-P.; Gagnon, M.; Guiral, S.; Huang, Z.; Guay, J.; Leblanc. Y.; Li, C.-S.; Masse, F.; Oballa, R.; Zhang, L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 499. (f) Ramtohul, Y. K.; Black, C.; Chan, C.-C.; Crane, S.; Guay, J.; Gurial, S.; Huang, Z.; Oballa, R.; Xu, L.-J.; Zhang, L.; Li, C.-S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1593. (g) Isabel, E. Powell, D. A.; Black, W. C.; Chan, C.-C.; Crane, S.; Gordon, R.; Guay, J.; Guiral, S.; Huang, Z.; Robichaud, J.; Skorey, K.; Tawa, P.; Xu, L.; Zhang, L.; Oballa, R. *Biorg.Med. Chem. Lett.* **2011**, *21*, 479. For human SCD1-specific SCD inhibitors, see: (h) Powell, D. A.; Ramtohul, Y.; Lebrun, M.-E.; Oballa, R.; Bhat, S.; Falgueyret, J.-P.; Guiral, S.; Huang, Z.; Skorey, K.; Tawa, P.; Zhang, L. *Biorg.Med. Chem. Lett.* **2010**, *20*, 6366.

7. For liver-targeted SCD1 inhibitors, see: (a) Oballa, R. M.; Belair, L.; Black, W. 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.; Sorensen, D.; Sturkenboom, W.; Styhler, A.; Waddleton, D. M.; Wang, H.; Wong, S.; Xu, L.; Zhang, L. *J. Med. Chem.* **2011**, *54*, 5082. (b) 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. *Biorg.Med. Chem. Lett.* **2009**, *19*, 4070. (c) 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. *Biorg.Med. Chem. Lett.* **2009**, *19*, 3050. (d) Leclerc, J. P.; Falgueyret, J.-P.; Girardin, M.; Guay, J.; Guiral, S.; Huang, Z.; Li, C. S.; Oballa, R.; Ramtohul, Y. K.; Skorey, K.; Tawa, P.; Wang, H.; Zhang, L. *Biorg.Med. Chem. Lett.* **2011**, *21*, 6505. (e) Powell, D. A.; Black, W. 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.-J.; Zhang, L.; Oballa, R. M. *Biorg.Med. Chem. Lett.* **2011**, *21*, 7281. (f) Ramtohul, Y. K.; Powell, D.; Leclerc, J.-P.; Leger, S.; Oballa, R.; Black, C.; Isabel, E.; Li, C. S.; Crane, S.; Robichaud, J.; Guay, J.; Guiral, S.; Zhang, L.; Huang, Z. *Biorg.Med. Chem. Lett.* **2011**, *21*, 5692. (g) Lachance, N.; Guiral, S.; Huang, Z.; Leclerc, J.-P.; Li, C. S.; Oballa, R. M.; Ramtohul, Y. K.; Wang, H.; Wu, J.; Zhang, L. *Biorg.Med. Chem. Lett.* **2012**, *22*, 623. (h) Lachance, N.; Gareau, Y.; Guiral, S.; Huang, Z.; Isabel, E.; Leclerc, J.-P.; Léger, S.; Martins, E.; Nadeau, C.; Oballa, R. M.; Ouellet, S. G.; Powell, D. A.; Ramtohul, Y. K.; Tranmer, G. K.; Trinh, T.; Wang, H.; Zhang, L. *Biorg.Med. Chem. Lett.* **2012**, *22*, 980. (h) Deng, Y.; Yang, Z.; Shipps Jr., G. W.; Lo, S.-M.; West, R.; Hwa, J.; Zheng, S.; Farley, C.; Lachowicz, J.; Heek, M. v.; Bass, A. S.; Sinha, D. P.; Mahon, C. R.; Cartwright, M. E. *Biorg.Med. Chem. Lett.* **2013**, *23*, 791.

8. Yang, S.-M.; Tang, Y.; Zhang, R.; Lu, H.; Kuo, G.-H.; Gaul, M. D.; Li, Y.; Ho, G.; Conway, J. G.; Liang, Y.; Lenhard, J. M.; Demarest, K. T.; Murray, W. V. *Bioorg. Med. Chem. Lett.* submitted.

9. Compound **6** are either commercially available or can be prepared according to literature procedures. Representative synthetic procedures for **3**–**5** are available in supplementary material.

10. The adverse events such as narrow eye fissure were observed in vivo in high dose-treated groups and are believed to be due to mechanism-based depletion of SCD-derived lubricating lipids, also see references 6d-6f.