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2-Aryl benzimidazoles: Human SCD1-specific stearoyl coenzyme-A desaturase inhibitors

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ABSTRACT

A series of potent, benzimidazole-based SCD inhibitors which demonstrate selectivity for the *h*SCD1 enzyme over the *h*SCD5 isoform are described. The compounds possess suitable cellular activity and pharmacokinetic properties which render them capable of inhibiting liver SCD activity in a mouse pharmacodynamic assay. These 2-aryl benzimidazoles may serve as valuable tools for studying selective *h*SCD1-inhibition.

Stearoyl coenzyme-A desaturase (SCD) is an iron containing microsomal enzyme, which catalyzes the formation of a *cis*-double bond at the Δ9 position of saturated fatty acyl-coenzyme-A esters.[1] The monounsaturated lipid products [mainly palmitoleoyl-CoA (C16:1) and oleoyl-CoA (C18:1)] are major components of triglycerides, cholesterol esters, and membrane phospholipids. Lipids play a vital role in the pathology of metabolic disease[2] and consequently SCD dysregulation has been implicated in the development of dyslipidemia,[3] diabetes,[4] cancer,[5] and other metabolic disorders.[6,7] Supporting this hypothesis, rodents deficient in SCD1, either as a result of gene deletion,[8] antisense oligonucleotide (ASO) treatment,[9] or pharmacological inhibition,[10] are resistant to diet-induced weight gain, have an improved lipid profile and increased insulin sensitivity. Not surprisingly, substantial efforts have focused on the development of small-molecule SCD inhibitors for therapeutic application against these metabolic disorders.[11,12]

Human SCD1 (*h*SCD1) is the prevalent isoform of the enzyme found in humans, however a second SCD gene, *h*SCD5 (sometimes referred to as *h*SCD2), has also been described.[13] This evolutionarily distinct human SCD5 enzyme possesses 61% sequence identity to *h*SCD1 and is highly expressed in the brain and pancreas, whereas *h*SCD1 is expressed predominantly in liver and adipose tissues.[13] While little is known about the exact function of *h*SCD5, it has been suggested to serve a developmental and/or protective role.[13a,14] Indeed, a mutation in the *h*SCD5-encoding gene (ACOD4) has been associated with the congenital deformity, cleft-lip syndrome.[15] Additionally, SCD-inhibition has been linked to pancreatic β-cell death.[6a,16] Unfortunately there is no SCD5 equivalent gene present in rodents,[17] but SCD5 is expressed in primates, dogs, and other higher species.[14] To the best of our knowledge, no SCD inhibitors have been described which are selective for either the *h*SCD1 or *h*SCD5 isozymes.

In light of these findings, we initiated a campaign to identify SCD inhibitors which are selective for the *h*SCD1 isoform over the *h*SCD5 enzyme. Structurally diverse inhibitors identified from a previous high-throughput screening campaign using a competitive rat SCD1 (*r*SCD1)[18] scintillation proximity binding assay (SPA) were further screened against recombinant *h*SCD1 and *h*SCD5 enzymes expressed in Sf9 cells.[19] These efforts led to the identification of a series of modestly potent 2-aryl benzimidazole inhibitors, which demonstrate complete selectivity for the *h*SCD1 enzyme over the *h*SCD5 isoform.

These benzimidazoles are attractive lead compounds whose modular structure enables rapid analog synthesis (Scheme 1). Chemistry efforts were initiated with the goal of further improving the *h*SCD1 potency and exploring the structure–activity relationship in this series.

Benzimidazole **1**, containing a 6-*tert*-butyl group is representative of the potency observed in the initial hit series (Table 1). Initially, we elected to explore modifications at the 6-position of the benzimidazole scaffold and found the substituent here to be critical for SCD1 activity. Replacing the *tert*-butyl group with a proton **2** or nitrile **3** resulted in complete loss of activity. In contrast, the sulfonamides **4** and **5** displayed similar rat SCD1 activity as **1**. While the sulfide **6** and sulfoxide **7** analogs were reasonably potent and selective SCD1 inhibitors, methylsulfone **8** exhibited superior activity compared to all other 6-substituted derivatives explored.

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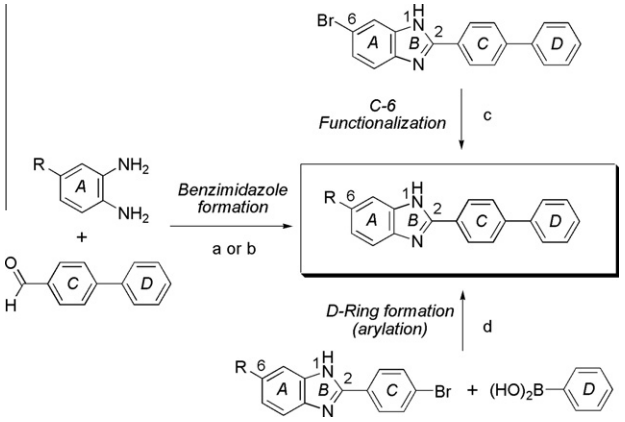
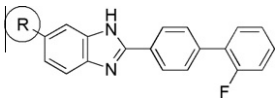


Scheme 1. Reagents and conditions: (a) 10 mol % *p*-TsOH, DMF, air, 80 °C, 2 h; (b) 2.5 equiv TMSCl, DMF, 90 °C, 4 h; (c) sulfinic acid sodium salt (2.0 equiv), 1 equiv CuOTf, 2 equiv *trans* 1,2-diaminocyclohexane, DMSO, 130 °C, 2–6 h; (d) 2.5 mol % $[PdBr(t\text{-}Bu_3P)]_2$, 2 equiv K_3PO_4, dioxane/H_2O (10:1), 100 °C, microwave, 20 min.

Table 1
SCD activity and selectivity of 6-substituted benzimidazole analogs



Compound	R	Enzyme IC_{50} (nM)		
		*r*SCD1	*h*SCD1	*h*SCD5
1	*t*-Bu	175	731	>20,000
2	H	>20,000	—	—
3	NC	>20,000	>20,000	>20,000
4	Me_2N–SO$_2$	528	—	—
5	H_2N–SO$_2$	343	74	>20,000
6	Me–S	697	—	—
7	Me–SO	472	96	>20,000
8	Me–SO$_2$	**65**	**27**	**>20,000**
9	Et–SO$_2$	1248	1308	>20,000
10	cyclopropyl–SO$_2$	401	—	—

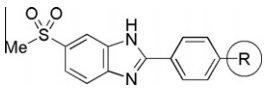
IC_{50}s are an average of at least two titrations.

Other sulfones (**9**–**10**), including the ethyl and cyclopropyl derivatives are inferior in terms of SCD potency, as compared to **8**.

Having established the 6-methyl sulfone substituent as beneficial for *h*SCD1 potency and selectivity over the *h*SCD5 isoform, investigations turned to modifications on the *D*-ring (Table 2). A variety of *ortho*-, *meta*- and *para*-substituents were explored at the terminal *D*-ring (compounds **11**–**24**). Surprisingly, the unsubstituted biaryl derivative **11** exhibited similar potency to fluoro analog **8**. Removal of the *D*-ring phenyl or replacement with a bromide (**26**) resulted in inactivity in the SCD1 enzyme assay. Heterocyclic *D*-rings were, for the most part, tolerated in terms of SCD1 potency (compounds **26**–**32**) however no real improvement was observed as compared to biphenyl analog **8**.

Finally, variations in the central rings *B* and *C* were explored and their effect on SCD1 potency and selectivity were examined (Table 3). Incorporation of nitrogen atoms onto the aromatic rings

Table 2
SCD activity and selectivity of *D*-ring benzimidazole derivatives



Compound	R	Enzyme IC_{50} (nM)		
		*r*SCD1	*h*SCD1	*h*SCD5
11		20	24	>10,000
12	X = Me	>20,000	—	—
13	X = Cl	>20,000	—	—
14	X = OH	304	2326	>20,000
15	X = F	25	—	—
16	X = Me	319	—	—
17	X = Cl	148	15	>10,000
18	X = OH	396	342	>20,000
19	X = F	21	30	>20,000
20	X = Me	3863	—	—
21	X = Cl	4489	255	>20,000
22	X = OH	336	—	—
8	X = F	65	27	>20,000
23		278	—	—
24		95	—	—
25	Br	>20,000	—	—
26		2473	4246	>20,000
27		425	—	—
28		1713	1760	>20,000
29		395	1705	>20,000
30		104	—	—
31	X = H	97	231	>20,000
32	X = Me	472	—	—

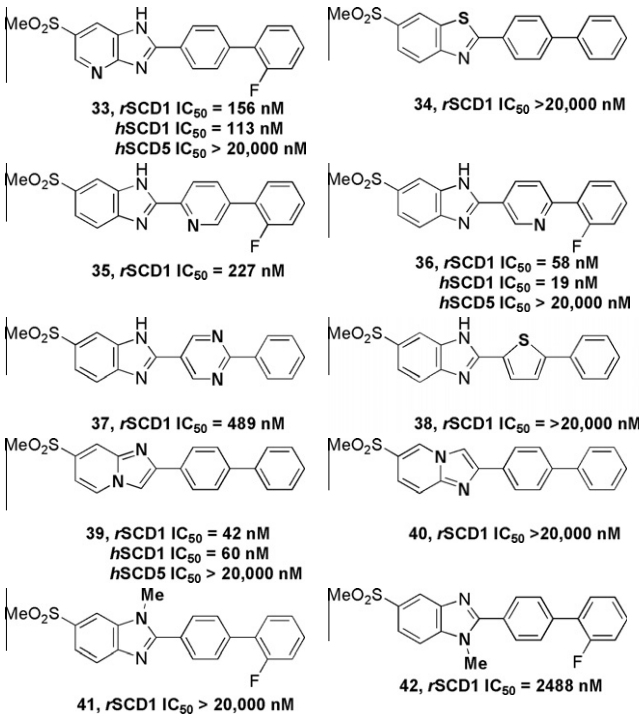
IC_{50}s are an average of at least two titrations.

resulted in only a modest loss of SCD1 potency (**33** and **35**–**37**). In contrast, substitution of the benzimidazole with a benzothiazole (**34**) or alkylation at either of the benzimidazole nitrogens (**41**–**42**) resulted in almost complete loss of SCD1 activity. Interestingly, the isomeric imidazo[1,2-*a*]pyridine **39** was identified as a highly potent SCD1 inhibitor, suggesting that a hydrogen bond donor is not essential for SCD activity.

Having identified a variety of potent benzimidazole-based SCD1 inhibitors, we proceeded to further profile representative analog **8** and characterize the in vitro and in vivo properties of this class of inhibitors. Benzimidazole **8** is not an inhibitor of rat or human Δ5-desaturase in an enzyme-based assay (Table 4). This result demonstrates that the inhibitory activity of **8** is unlikely a result of perturbation of the essential desaturation co-factors, including cytochrome b5 or cytochrome b5 reductase.[20] In two varying whole cell assays,[21] compound **8** demonstrated micromolar inhibition of SCD activity. In addition, **8** displays adequate pharmacokinetic properties in both mice and dogs (Table 5) with reasonable exposures and bioavailability to enable in vivo study of SCD1 inhibition.

Gratifyingly, hSCD1-selective inhibitor **8** demonstrated inhibition of liver SCD activity in a mouse liver pharmacodynamic assay (Fig. 1).[22] Benzimidazole **8** was administered orally at doses of 30

Table 3
SCD activity and selectivity of benzimidazole derivatives



IC_{50}s are an average of at least two titrations.

Table 4
In vitro properties of 2-aryl benzimidazole **8**

Assay		IC_{50} (nM)
Enzymatic	Rat SCD1	65
	Human SCD1	27
	Human SCD5	>20,000
Cellular	Rat D5D[a]	>50,000
	Human HepG2	1325
	Rat Hepatocyte[b]	5169

IC_{50}s are an average of at least two titrations.
[a] Δ5-desaturase enzyme.
[b] Freshly isolated rat hepatocytes were utilized.

and 100 mg/kg to mice on a high carbohydrate diet, followed by IV injection of a ^{14}C labeled stearic acid tracer. Inhibition of SCD activity in the liver was determined by comparing the conversion of ^{14}C-stearic acid to ^{14}C-oleic acid of treated animals versus the vehicle control group. This study demonstrates that benzimidazole **8** is capable of inhibiting SCD activity in vivo in a dose-dependant manner.

Given the surprising *h*SCD1-selectivity observed with benzimidazole **8**, a separate competition binding experiment was conducted with **8** and a previously described, non-selective SCD

Table 5
Pharmacokinetics of 2-aryl benzimidazole **8**

Species	*F* (%)	$t_{1/2}$ (h)	AUC_p (μM h)	CL_p (mL/min/kg)	V_{dss} (L/kg)
C57BL6-mice[a]	39	$\alpha = 0.7$ $\beta = 35.5$	8.0	20	2.9
Beagle dog[b]	70	1.1	2.4	26	2.0

Average values, $n = 2$.
[a] Dose: 10 mg/kg po (0.5% Methocel); 2 mg/kg iv (60% PEG-200).
[b] Dose: 2 mg/kg po (0.5% Methocel); 0.5 mg/kg iv (60% PEG-200).

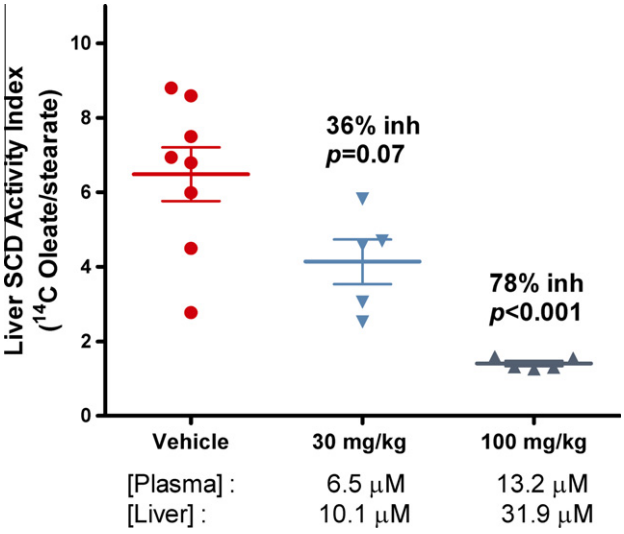


Figure 1. Male C57Bl6 mice were fed a high sucrose/fat-free diet for 2 days to induce liver SCD activity. Compound **8** was administered orally in 0.5% Methocel at 7:00 am on day 3. The [1-^{14}C]-stearic acid tracer (40 μCi/kg) was dosed via the jugular vein at 8:00 am and livers were harvested 2 h later. Liver SCD activity was measured by the ratio of [^{14}C]-oleic acid/[^{14}C]-stearic acid after complete lipid hydrolysis (mean ± SEM, $n = 5–8$/group). The corresponding liver and plasma concentrations of **8** in mice upon termination (3 h post dosing) are included.

inhibitor MK-8245.[23] 2-Aryl benzimidazole **8** was found to be competitive with MK-8245 for binding to *h*SCD1. MK-8245 has been demonstrated to bind competitively with stearoyl-CoA, the natural substrate for SCD1.

In conclusion, we have described a series of benzimidazole-based SCD inhibitors which demonstrate specificity for the *h*SCD1 enzyme over the *h*SCD5 isoform. Furthermore, we demonstrate that these compounds inhibit SCD-activity in vitro in liver-derived cells and in vivo in a mouse liver PD assay. Given the paucity of known selective *h*SCD1-inhibitors, these compounds may serve as valuable tools to enable further understanding of the specific role of *h*SCD1 as compared to *h*SCD5.

References and notes

1. (a) Ntambi, J. M.; Miyazaki, M. *Curr. Opin. Lipidol.* **2003**, *14*, 255; (b) Ntambi, J. M. *Prog. Lipid Res.* **1995**, *34*, 139; (c) Enoch, H. G.; Catala, A.; Strittmatter, P. *J. Biol. Chem.* **1976**, *251*, 5095.
2. (a) Chavez, J. A.; Summers, S. A. *Biochim. Biophys. Acta* **2010**, *18*, 252; (b) Kusunoki, J.; Kanatani, A.; Moller, D. E. *Endocrine* **2006**, *29*, 91.
3. (a) Mar-Heyming, R.; Miyazaki, M.; Weissglas-Volkov, D.; Kolaitis, N. A.; Sadaat, N.; Plaisier, C.; Pajukanta, P.; Cantor, R. M.; de Bruin, T. W.; Ntambi, J. M.; Lusis, A. J. *Arterioscler. Thromb. Vasc. Biol.* **2008**, *28*, 1193; (b) Attie, A. D.; Krauss, R. M.; Gray-Keller, M. P.; Brownlie, A.; Miyazaki, M.; Kastelein, J. J.; Lusis, A. J.; Stalenhoef, A. F. H.; Stoehr, J. P.; Hayden, M. R.; Ntambi, J. M. *J. Lipid Res.* **2002**, *43*, 1899.
4. (a) Stefan, N.; Peter, A.; Cegan, A.; Staiger, H.; Machann, J.; Schick, F.; Claussen, C. D.; Fritsche, A.; Häring, H. U.; Schleicher, E. *Diabetologia* **2008**, *51*, 648; (b) Rahman, S. M.; Dobrzyn, A.; Dobrzyn, P.; Lee, S.-H.; Miyazaki, M.; Ntambi, J. M. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *110*, 11110.
5. (a) Hess, D.; Chisholm, J. W.; Igal, R. A. *PLoS One* **2010**, *5*, e11394; (b) Scaglia, N.; Chisholm, J. W.; Igal, R. A. *PLoS One* **2009**, *4*, e6812; (c) Morgan-Lappe, S. E.; Tucker, L. A.; Huang, X.; Zhang, Q.; Sarthy, A. V.; Zakula, D.; Vernetti, L.; Schurdak, M.; Wang, J.; Fesik, S. W. *Cancer Res.* **2007**, *67*, 4390; (d) Li, J.; Ding, S.-F.; Habib, N. A.; Fermor, B. F.; Wood, C. B.; Gilmour, R. S. *Int. J. Cancer* **1994**, *57*, 348.
6. For leading references, see: (a) Brown, J. M.; Rudel, L. L. *Curr. Opin. Lipidol.* **2010**, *21*, 192; (b) Dobrzyn, A.; Ntambi, J. M. *Trends Cardiovasc. Med.* **2004**, *14*, 77.
7. Other postulated therapeutic applications of SCD inhibition: Dobrzyn, P.; Dobrzyn, A. *Drug Dev. Res.* **2006**, *67*, 643.
8. (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) Miyazaki, M.; Kim, Y.-C.; Gray-Keller, M. P.; Attie, A. D.; Ntambi, J. M. *J. Biol. Chem.* **2000**, *275*, 30132; (c) Cohen, 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; (d) Binczek, E.; Jenke, B.; Holz, B.; Günter, R. H.; Thevis, M.; Stoffel, W. *Biol. Chem.* **2007**, *388*, 405.
9. (a) Brown, J. M.; Chung, S.; Sawyer, J. K.; Degirolamo, C.; Alger, H. M.; Nguyen, T.; Zhu, X.; Duong, M.-N.; Wibley, A. L.; Shah, R.; Davis, M. A.; Kelley, K.; Wilson, M. D.; Kent, C.; Parks, J. S.; Rudel, L. L. *Circulation* **2008**, *118*, 1467; (b) Xu, H.; Wilcox, D.; Nguyen, P.; Voorbach, M.; Smith, H.; Brodjian, S.; Suhar, T.; Reilly, R. M.; Jacobsen, P. B.; Collins, C. A.; Landschulz, K.; Surowy, T. K. *Front. Biosci.* **2007**, *12*, 3781; (c) Gutiérrez-Juárez, R.; Pocai, A.; Mulas, C.; Ono, H.; Bhanot, S.; Monia, B. P.; Rossetti, L. *J. Clin. Invest.* **2006**, *116*, 1686; (d) 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.
10. (a) Ramtohul, Y. K.; Black, C.; Chan, C.-C.; Crane, S.; Guay, J.; Guiral, S.; Huang, Z.; Oballa, R.; Xu, L.-J.; Zhang, L.; Li, C. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1593; (b) Issandou, M.; Bouillot, A.; Brusq, J.-M.; Forest, M.-C.; Grillot, D.; Guillard, R.; Martin, S.; Michiels, C.; Sulpice, T.; Daugan, A. *Eur. J. Pharmacol.* **2009**, *618*, 28; (c) 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; (d) 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.
11. Reviews of small molecule SCD inhibitors: (a) Dobrzyn, P.; Dobrzyn, A. *Expert Opin. Ther. Patents* **2010**, *20*, 849; (b) Liu, G. *Curr. Top. Med. Chem.* **2010**, *10*, 419; (c) Liu, G. *Expert Opin. Ther. Patents* **2009**, *19*, 1169.
12. For some leading references, see: (a) Uto, Y.; Ueno, Y.; Kiyotsuka, Y.; Miyazawa, Y.; Kurata, H.; Ogata, T.; Yamada, M.; Deguchi, T.; Konishi, M.; Takagi, T.; Wakimoto, S.; Ohsumi, J. *Bioorg. Med. Chem. Lett.*, in press, *20*. doi:10.1016/j.ejmech.2010.07.044.; (b) Léger, S.; Black, C.; Deschenes, D.; Dolman, S.; Falgueyret, J.-P.; Gagnon, M.; Guiral, S.; Huang, Z.; Guay, J.; Leblanc, Y.; Li, C.-S.; Massé, F.; Oballa, R.; Zhang, L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 499; (c) Uto, Y.; Ogata, T.; Kiyotsuka, Y.; Miyazawa, Y.; Ueno, Y.; Kurata, H.; Deguchi, T.; Yamada, M.; Watanabe, N.; Takagi, T.; Wakimoto, S.; Okuyama, R.; Konishi, M.; Kurikawa, N.; Kono, K.; Osumi, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4159; (d) Uto, Y.; Ogata, T.; Harada, J.; Kiyotsuka, Y.; Ueno, Y.; Miyazawa, Y.; Kurata, H.; Deguchi, T.; Watanabe, N.; Takagi, T.; Wakimoto, S.; Okuyama, R.; Abe, M.; Kurikawa, N.; Kawamura, S.; Yamato, M.; Osumi, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4151; (e) 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; (f) 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; (g) Xin, Z.; Zhao, H.; Serby, M. D.; Liu, B.; Liu, M.; Szczepankiewicz, B. G.; Nelson, L. T. J.; 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; (h) 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; (i) 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.
13. (a) Wang, J.; Yu, L.; Schmidt, R. E.; Su, C.; Huang, X.; Gould, K.; Cao, G. *Biochem. Biophys. Res. Commun.* **2005**, *332*, 735; (b) Zhang, S.; Yang, Y.; Shi, Y. *Biochem. J.* **2005**, *388*, 135.
14. Lengi, A. J.; Corl, B. A. *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* **2008**, *150*, 440.
15. Beiraghi, S.; Zhou, M.; Talmadge, C. B.; Went-Sumegi, N.; David, J. R.; Huang, D.; Saal, H.; Seemayer, T. A.; Sumegi, J. *Gene* **2003**, *309*, 11.
16. (a) Hellemans, K. H.; Hanaert, J. C.; Denys, B.; Steffensen, K. R.; Raemdonck, C.; Martens, G. A.; Van Veldhoven, P. P.; Gustafsson, J.-A.; Pipeleers, D. *PLoS One* **2009**, *4*, e7266; (b) Busch, A. K.; Gurisik, E.; Cordery, D. V.; Sudlow, M.; Denyer, G. S.; Laybutt, D. R.; Hughes, W. E.; Biden, T. J. *Diabetes* **2005**, *54*, 2917.
17. Four isoforms of the SCD-enzyme have been characterized in mice (*m*SCD1–*m*SCD4) and two in rats (*r*SCD1 and *r*SCD2). These rodent isoforms, the result of gene duplication, are homologous to the human SCD1 gene (identity between rodent isoforms and *h*SCD1 is ~85%).
18. Joshi, V. C.; Wilson, A. C.; Wakil, S. J. *J. Lipid Res.* **1977**, *18*, 32.
19. Powell, D.; Lebrun, M.-E.; Bhat, S.; Ramtohul, Y. K. WO2009/129625.
20. Nakamura, M. T.; Nara, T. Y. *Annu. Rev. Nutr.* **2004**, *24*, 345.
21. (a) Zhang, L.; Ramtohul, Y.; Gagné, S.; Styler, A.; Wang, H.; Guay, J.; Huang, Z. *J. Biomol. Screen.* **2010**, *15*, 169; A similar rat hepatocycte assay as our own has recently been described, see: (b) Su, C.; Gullberg1, H.; Simko, H.; Luthman, M.; Edlund, P.-O.; Lundbäck, T. *J. Chromatogr., B* **2010**, *878*, 2427.
22. Li, C. S.; Ramtohul, Y. K.; Huang, Z.; Lachance, N. WO 2006/130986.
23. Oballa, R., manuscript in preparation.