Bioorganic & Medicinal Chemistry Letters 21 (2011) 5692–5696

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Bicyclic heteroaryl inhibitors of stearoyl-CoA desaturase: From systemic to liver-targeting inhibitors

Yeeman K. Ramtohul [a,*], David Powell [a], Jean-Philippe Leclerc [a], Serge Leger [a], Renata Oballa [a], Cameron Black [a], Elise Isabel [a], Chun Sing Li [a], Sheldon Crane [a], Joel Robichaud [a], Jocelyne Guay [b], Sébastien Guiral [b], Lei Zhang [b], Zheng Huang [b]

[a] Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, 16711 TransCanada Hwy, Kirkland, Quebec, Canada H9H 3L1
[b] Biochemistry and Molecular Biology, Merck Frosst Centre for Therapeutic Research, 16711 TransCanada Hwy, Kirkland, Quebec, Canada H9H 3L1

ARTICLE INFO

Article history:
Received 17 June 2011
Revised 5 August 2011
Accepted 5 August 2011
Available online 12 August 2011

Keywords:
Stearoyl-CoA
SCD1 inhibitors
Liver-selective inhibitors
Mouse liver PD
Desaturation index

ABSTRACT

Optimization of a lead thiazole amide **MF-152** led to the identification of potent bicyclic heteroaryl SCD1 inhibitors with good mouse pharmacokinetic profiles. In a view to target the liver for efficacy and to avoid SCD1 inhibition in the skin and eyes where adverse effects were previously observed in rodents, representative systemically-distributed SCD1 inhibitors were converted into liver-targeting SCD1 inhibitors.

The stearoyl-CoA desaturase (SCD) is a key enzyme involved in the regulation of metabolism[1] and has been implicated in a number of metabolic disorders including type II diabetes, obesity and other metabolic syndrome diseases.[2] These claims are supported by the observation that SCD-null mice display a beneficial metabolic profile, characterized by resistance to high fat diet-induced obesity, improved insulin sensitivity and reduced body adiposity.[3,4] In addition, similar beneficial effects were observed in high fat diet-induced obese (DIO) mice treated with SCD1 anti-sense oligonucleotide (ASO).[5] Moreover, in humans, an elevated SCD activity is positively correlated with high triglyceride level in familial hypertriglyceridemia subjects,[6] increased body mass index (BMI) and high plasma insulin levels.[7] Thus, inhibition of SCD1 enzyme represents a promising target for the treatment of these metabolic disorders.

SCD1 is a microsomal enzyme involved in the initial desaturation of long-chain fatty acyl-coenzyme A esters (LCFA-CoA), primarily stearoyl-CoA and palmitoyl-CoA, at the Δ9 (C_9–C_{10}) position to produce monounsaturated oleoyl-CoA and palmitoleoyl-CoA, respectively.[8] These monounsaturated LCFA-CoAs, are major building blocks for de novo lipid synthesis and therefore are crucial for the lipogenic pathway.[9] Four SCD isoforms (SCD1-4) are present in rodents and two in humans (SCD1 and SCD5). SCD1 with about 85% homology across all murine SCDs, is the major isoform present in lipogenic tissues (including liver and adipose tissues).

In humans, there are two additional fatty acyl-CoA specific desaturases, Δ5D and Δ6D, involved in the biosynthesis of long-chain polyunsaturated fatty acids which are crucial for cell signaling.[10] Therefore, it is important to identify selective SCD1 inhibitors against these desaturases. A number of reports on small molecule SCD1 inhibitors have recently been published.[11–16] In our previous communications, we reported a lead thiazole amide inhibitor **MF-152**[11a] (Fig. 1) and demonstrated that the metaboli-

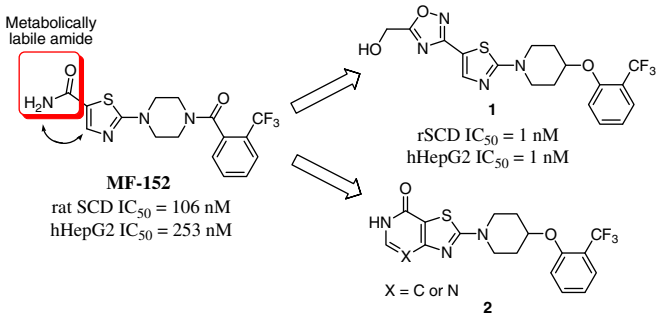


Figure 1. Replacement of the primary amide moiety with an oxadiazole ring and its modification into a bicyclic ring system.

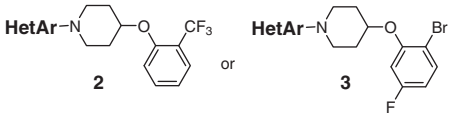
* Corresponding author.
E-mail address: ramtohul@hotmail.com (Y.K. Ramtohul).

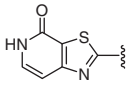
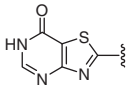
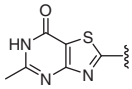
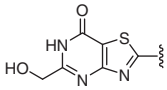
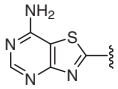
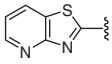
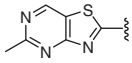
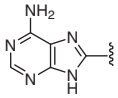
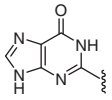
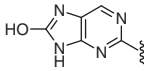
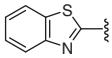
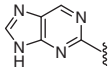
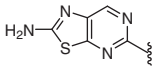
0960-894X/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2011.08.037

cally labile primary amide moiety which is hydrolyzed to the corresponding acid in vivo can be replaced with a more stable oxadiazole ring **1** leading to improved pharmacokinetic profiles.[11b] Herein, we wish to report further SAR on the thiazole series to identify other metabolically stable and structurally novel pharmacophores.

Another approach we considered to address the amide hydrolysis metabolism was to cyclize the primary amide functionality onto the thiazole ring to generate the bicyclic ring system **2** (Fig. 1) and at the same time explore other related 6-5 and 5-6 bicyclic ring systems as shown in Table 1. The synthesis of representative examples is shown in Scheme 1.[17] Reaction of *N*-cyano-dithioiminocarbonate **4** with the CF_3-aryl piperidine ether **5** afforded adduct **6** which upon treatment with 2-mercaptoacetamide **7** in the presence of triethylamine and ammonia furnished the aminothiazole amide **8**. Reaction of **8** with trimethylorthoformate in the presence of catalytic amount of *p*-TSA produced the desired bicyclic thiazolo pyrimidinone **2b**. Compounds **3b** and **3c** can be accessed via a nucleophilic displacement of the corresponding halo-bicyclic analogs **9** and **11**,[18] with the bromo-aryl piperidine ether **10**, respectively.

Table 1
SAR on the bicyclic ring[17]



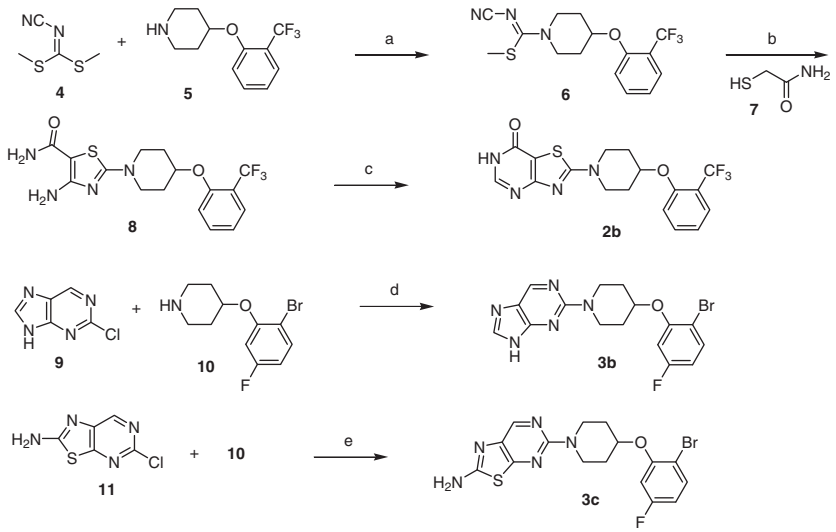
Compound	HetAr	Rat SCD IC_{50}[a] (nM)	hHepG2 IC_{50}[a] (nM)
2a		85	268
2b		7	29
2c		8	59
2d		2	16
2e		56	n.d.
2f		83	755
2g		54	182
2h		39	162
2i		97	378
2j		38	319
3a		477	10,639
2k		10	257
3b		3	47
3c		1	17
2l		10	48
3d		1	<39

[a] IC_{50}s are an average of at least two independent titrations.

The inhibitory activity of the compounds were assessed against the SCD1 enzyme in an SCD1-induced rat liver microsomal assay[19] and their cellular potency were evaluated in a human HepG2-based whole cell assay (hHepG2).[20] Both the CF_3 **5** and bromo-aryl piperidines **10** were used for the SAR and in general the bromo analogs are more potent than the corresponding CF_3 analogs (Table 1, cf. **2k**, **3b**, and **2l**, **3d**). As displayed in Table 1, the bicyclic thiazolo pyridinone **2a** and thiazolo pyrimidinone **2b** are good scaffolds for the SCD1 enzyme with **2b** being ~10-fold more potent in both the enzymatic and whole cell assays. Substitution at the 5-position with a methyl is tolerated (**2c**). As shown previously with compound **1**,[11b] addition of a hydroxyl moiety on the methyl group of **2c** led to a 4-fold improvement in potency (**2d**). The carbonyl group in **2b** can be substituted for an amino group (**2e**) with a modest loss in enzymatic potency relative to **2b** and **2c**, indicating that both hydrogen bond donor and acceptor are tolerated at that position. Removal of the amide functionality in **2f** and carbonyl in **2g** led to a modest loss in activity. However, replacement of the pyrimidinone ring with a phenyl ring in **3a** led to significant loss in potency both in the enzymatic and whole cell assays. The thiazole ring in **2e** can be substituted for an imidazole ring **2h** with no major effect on potency. Reversal of the linkage strategy connecting the piperidine via the 5-ring to 6-ring resulted in compounds **2i–l** and **3b–d**. In contrast to the previous SAR, the presence of a carbonyl was deleterious to potency (cf. **2i** and **2k**). Attachment of the bromo-aryl piperidine ring at the 4-position of the pyrimidine ring in **3d** is slightly more favored over the 2-position giving a 3-fold improvement in potency compared to **3b**. In addition, the compounds in Table 1 displayed selectivity for SCD1 and do not inhibit the Δ5D and Δ6D desaturases (data not shown).

Pharmacokinetic (PK) profiles for selected potent compounds were determined in C57BL6 mice following oral dosing at 10 mg/kg in 0.5% methocel as the vehicle. In general, the bicyclic compounds in Table 1 display improved drug exposure compared to **MF-152**, for instance, compound **2c** gave a whole blood exposure (AUC_{0-24h} = 30 μM h) compared to **MF-152** (AUC_{0-24h} = 11 μM h). We next examined the tissue distribution of compounds **2c** and **2j**, 6 h post oral dosing at 10 mg/kg in C57BL6 mice. As illustrated in Figure 2, the compounds **2c** (21.8 μM) and **2j** (24.7 μM) display high liver levels. Since these compounds are readily cell penetrant (qualitatively based on the low hHepG2 data, vide infra) they are also systemically distributed and high drug levels were observed in the peripheral tissues such as the white adipose, skin and the Harderian glands.

As reported previously, systemically distributed SCD1 inhibitors **MF-152**[11a] and **1**[11b] developed partial eye closure and progressive alopecia after ~7 days of drug treatment. We believe that the dry eyes are a result of a decreased levels of oleate-derived lipids (triglycerides, cholesterol esters, and wax esters) secreted in tears by the Harderian glands, which are essential for eye lubrication. Similarly, a reduction of these lipids levels in the adipose tissues, skin and/or sebaceous glands may have led to the dry skin and hair loss. In addition, it was previously demonstrated that SCD1 liver-targeting inhibitors that distribute preferentially in the liver (target organ for efficacy) over the peripheral off-target tissues showed beneficial anti-diabetic and anti-dyslipidemic efficacies with no



Scheme 1. Reagents and conditions: (a) EtOH, Δ, quant.; (b) NEt_3, ammonia, MeOH, rt, 61–80%; (c) trimethylorthoformate, *p*-TSA, Δ, 80%; (d) NEt_3, 2-methoxyethanol/H_2O or EtOH, Δ, 46%; (e) NEt_3, DMF, Δ, 64–70%.

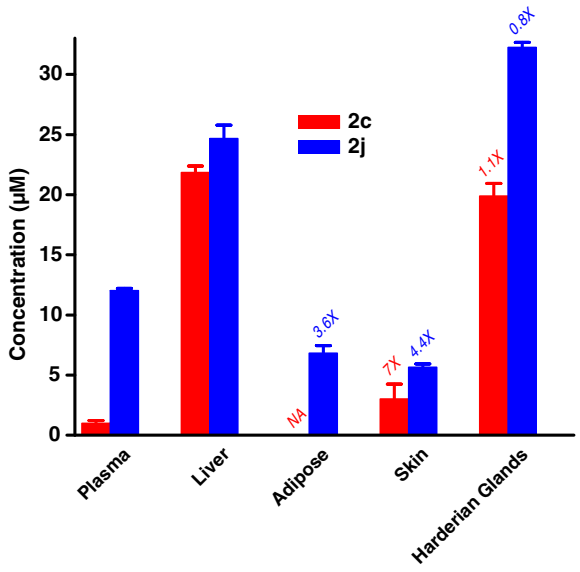


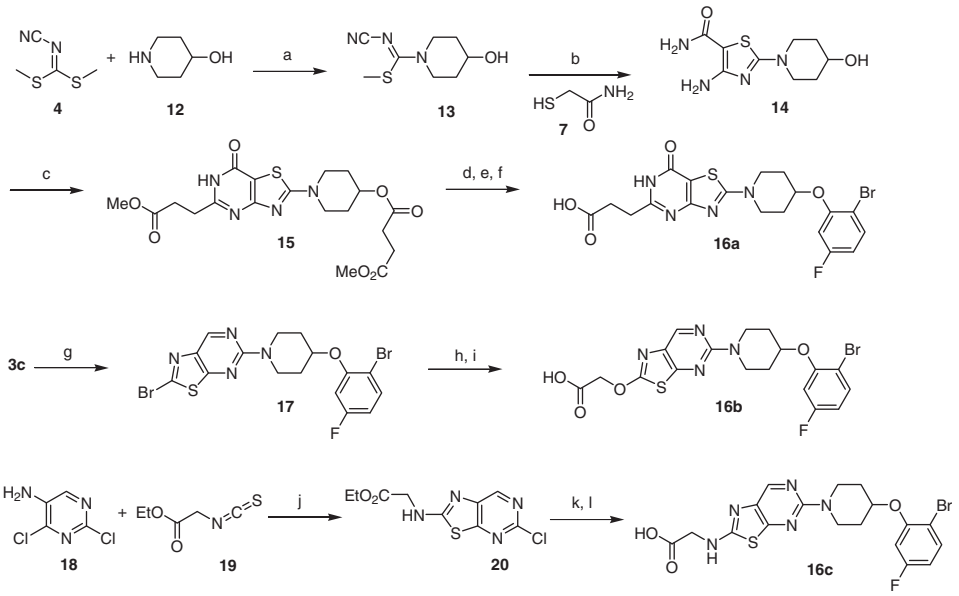
Figure 2. Tissue distribution of compounds **2c** and **2j**, 6 h post oral dosing at 10 mg/kg (0.5% methocel vehicle) in C57BL6 mice fed on a normal chow diet. The fold of liver/tissue selectivity is shown. Adipose tissue level for **2c** was not determined (NA–not available).

adverse effects.[11f] With this in mind, we sought to convert the systemic SCD1 inhibitors as defined by core structures **2c** and **3c** into liver-targeting inhibitors. The strategy we employed is to attach a carboxylic acid moiety onto compounds **2c** and **3c**, which is known to be recognized and actively transported by the organic anion transporting polypeptides (OATPs). The OATPs are transporters that are highly expressed in the liver but not in the off-target tissues where adverse events were observed. Therefore, by making use of the OATPs transporters, a preferential distribution of the SCD1 inhibitors to the liver is favored over the undesired peripheral tissues.[21]

The synthesis of compounds **16a–c** is described in Scheme 2.[22] The aminothiazole amide **14** was obtained via a similar reaction pathway as described in Scheme 1, starting from *N*-cyano-dithioiminocarbonate **4** and 4-piperidinol (**12**). Reaction of thiazole amide **14** with 4-chloro-oxobutanoate in dimethyl succinate afforded the cyclized bicyclic ester **15**. Selective hydrolysis of the piperidinol ester followed by a Mitsunobu reaction with 2-bromo-5-fluorophenol and a subsequent hydrolysis of the methyl ester afforded the desired compound **16a**. Conversion of the amino group of **3c** to the corresponding bromide **17** was achieved by treatment with *tert*-butyl nitrite and copper(II) bromide. Displacement of bromide **17** with ethyl glycolate in the presence of sodium hydride followed by hydrolysis of the ethyl ester afforded the desired glycolate analog **16b**. Reaction of pyrimidine **18**[23] with ethyl isothiocyanatoacetate **19** produced the thiazolo pyrimidine analog **20** which upon reaction with piperidine ether **10** followed by ester hydrolysis furnished the desired amino acetic acid analog **16c**.

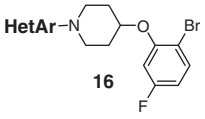
As shown in Table 2, in contrast to compound **16a**, the carboxylic acid analogs **16b** and **16c** maintain good enzymatic potency against the rat SCD1 enzyme. In addition to the human HepG2 whole cell assay which lacks the OATP transporters, the compounds were also tested in a rat hepatocyte whole cell assay (rat Hep.) where the OATP transporters are present. These three assays can be used in parallel to qualitatively determine if a compound is actively transported in the hepatocyte cells via the OATP transporters. For instance, compound **16a** demonstrates poor hHepG2 activity (IC_{50} = 24,345 nM, 91-fold shift vs enzymatic assay) indicating that this compound has a low passive diffusion rate across the cell membrane and therefore cannot effectively penetrate the cells to inhibit the SCD1 enzyme. This was further confirmed by determining its diffusion rate across LLC-PK1 monolayer cells which gave an apparent permeability, P_{app} of 2×10^{-6} cm/s, showing its poor cell permeability. Interestingly, the same compound is more potent in the rat hepatocyte assay (IC_{50} = 168 nM, 145-fold shift vs hHepG2 assay) indicating that it is actively transported by OATPs into the hepatocyte cells. Conversely, compounds **16b** and **16c** are less shifted in the hHepG2 (7- to 42-fold shift vs enzymatic assay) indicating that their rate of passive diffusion inside the whole cell is likely higher compared to **16a** and the observation that they are not more potent in the rat hepatocyte (⩽1-fold shift vs hHepG2 assay) indicate that these compounds are not efficiently transported into hepatocyte cells.

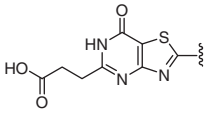
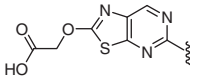
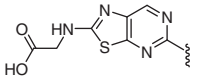
Tissue distribution of compounds **16a–c** was obtained 6 h post oral dosing at 10 mg/kg in C57BL6 mice. As shown in Figure 3, incorporation of a carboxylic acid moiety on these bicyclic cores led to a considerable reduction (~25–60×) in the liver drug exposures as compared to the systemically distributed inhibitors (Fig. 2). Interestingly, all three compounds showed a preferential distribution in the liver over the peripheral adipose, skin tissues



Scheme 2. Reagents and conditions: (a) EtOH, Δ, quant.; (b) NEt_3, ammonia, MeOH, rt, 62–80% ;(c) 4-chloro-oxobutanoate, dimethyl succinate, Δ, 30–51%; (d) NaOMe (1.1 equiv), MeOH, rt; (e) DEAD, PPh_3, 2-bromo-5-fluorophenol, THF, rt; (f) LiOH, THF/MeOH, 7-11% over three steps; (g) $CuBr_2$, *t*-BuONO, CH_3CN, Δ, 54–61%; (h) ethyl glycolate, NaH, DMF rt; (i) NaOH, THF/MeOH, 47% over two steps; (j) neat, Δ, used crude; (k) **10**, NEt_3, 2-methoxyethanol, Δ; (l) NaOH, THF/MeOH, 22% over two steps.

Table 2
Incorporation of carboxylic acid in the bicyclic analogs



Compound	HetAr	Rat SCD IC_{50}[a] (nM)	hHepG2 IC_{50}[a] (nM)	Rat Hep. IC_{50}[a] (nM)	Fold Shift Rat Hep. versus hHepG2
16a		266	24,345	168	145
16b		7	53	348	<1
16c		4	168	158	1

[a] IC_{50}s are an average of at least two independent titrations.

and Harderian glands, although only **16a** was predicted to have a liver-targeting property based on the high rat Hep. versus hHepG2 shift. However, compounds **16b** and **16c** which presumably have a higher passive diffusion rate (qualitatively based on the ⩽1-fold shift of rat hepatocyte assay vs hHepG2) did indeed accumulate more drugs in the Harderian glands compared to **16a** where the Harderian gland concentrations were undetectable. Compounds **16a** and **16c** having acceptable liver to Harderian gland selectivity were chosen for further in vivo profiling.

The in vivo potencies of **16a** and **16c** were assessed in a mouse liver PD assay. The compounds were dosed orally in mice fed on a high carbohydrate diet and after 3 h the SCD1 activity was determined by measuring the conversion of intravenously administered [1-^{14}C]-stearic acid tracer to the SCD-derived [1-^{14}C]-oleic acid in liver lipids. Due to the lower liver level of **16a** compared to **16c**, **16a** was administered at a higher dose of 60 mg/kg versus 30 mg/kg for **16c**. As illustrated in Figure 4, **16c** gave a robust 72% reduction of liver SCD1 activity desaturation index (ratio of ^{14}C-oleic acid/^{14}C-stearic acid), however to our surprise compound **16a** did not show any SCD1 inhibition. Although the liver level of **16a** (3.3 μM) was well above its rat hepatocyte whole cell potency (IC_{50} = 168 nM), the lack of in vivo efficacy with **16a** remains unclear at this time.[24] However, based on our experience with other liver-targeting SCD1 inhibitors, we observed that compounds with rat hepatocyte whole cell IC_{50} >200 nM and hHepG2 IC_{50} >15 μM are generally not active in the mouse liver PD assay. The high hHepG2 potency (IC_{50} ~24 μM) of compound **16a** might have been a contributing factor to the lack of efficacy. It seems that a fine balance between the rat hepatocyte and

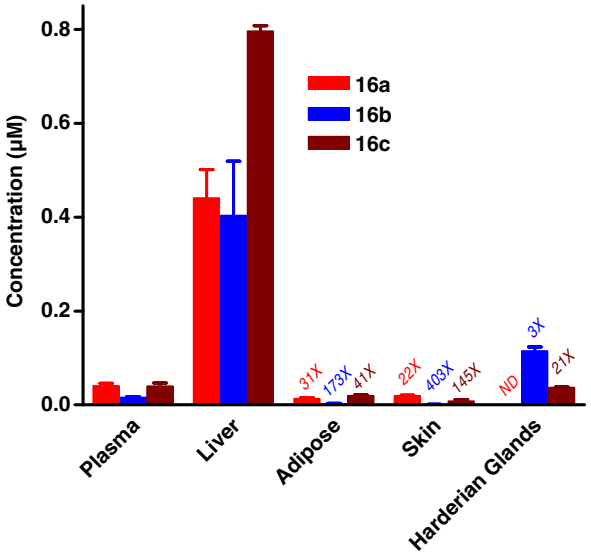


Figure 3. Tissue distribution of compounds **16a**, **16b**, and **16c**, 6 h post oral dosing at 10 mg/kg (0.5% methocel vehicle) in C57BL6 mice fed on normal chow diet. The fold of liver/tissue selectivity is shown. ND–not detected.

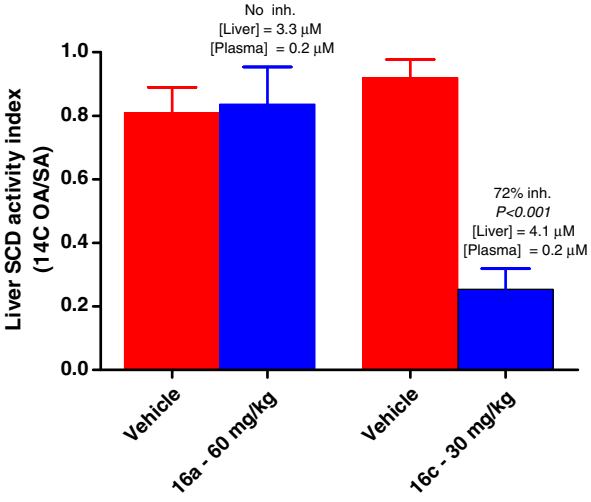


Figure 4. In vivo SCD1 inhibition of **16a** and **16c** dosed orally (0.5% methocel vehicle) in C57BL6 mice fed on a high carbohydrate diet. ^{14}C-stearic acid in 60% aqueous PEG 200 was administered intravenously at 1 h later and livers were harvested at 2 h post tracer-dosing. The SCD1 activity index [ratio of ^{14}C-oleic acid (OA)/^{14}C-stearic acid (SA) in hydrolyzed liver lipids] were measured (n = 5/group).

the hHepG2 whole cell potencies are required for in vivo efficacy in the mouse liver PD assay.

In summary, we have identified a number of potent systemic bicyclic heteroaryl SCD1 inhibitors from modification of an initial lead inhibitor, **MF-152**.[11a] Representative systemically-distributed SCD1 inhibitors were converted into liver-targeting SCD1 inhibitors by incorporation of carboxylic acid functionalities which have previously been shown to be recognized by the liver OATP transporters.[11f] The liver-targeting inhibitor **16c** demonstrated a robust 72% reduction of liver SCD1 activity index in C57BL6 mice. Further studies are underway to identify more potent bicyclic heteroaryl liver-targeting SCD1 inhibitors with good in vivo efficacy.

References and notes

1. Dobrzyn, A.; Ntambi, J. M. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 35.
2. Dobrzyn, A.; Ntambi, J. M. *Obesity Rev.* **2005**, *6*, 169.
3. (a) Miyazaki, M.; Kim, Y.-C.; Gray-Keller, M. P.; Attie, A. D. *J. Biol. Chem.* **2000**, *275*, 30132; (b) Miyazaki, M.; Man, W. C.; Ntambi, J. M. *J. Nutr.* **2001**, *131*, 2260.
4. 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.
5. (a) 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; (b) Gutierrez-Juarez, R.; Pocai, A.; Mulas, C.; Ono, H.; Bhanot, S.; Monia, B. P.; Rossetti, L. *J. Clin. Invest.* **2006**, *116*, 1686.
6. 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.
7. 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.
8. Enoch, H. G.; Catala, A.; Strittmatter, P. *J. Biol. Chem.* **1976**, *251*, 5095.
9. Ntambi, J. M. *Prog. Lipid Res.* **1995**, *34*, 139.
10. Nakamura, M. T.; Nara, T. Y. *Annu. Rev. Nutr.* **2004**, *24*, 345.
11. (a) 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; (b) 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; (c) Leger, S.; Black, C.; Deschenes, D.; Dolman, S.; 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; (d) 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. *Bioorg. Med. Chem. Lett* **2010**, *20*, 6366; (e) 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. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 479; (f) Oballa, R. M.; Belair, L.; 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.; Ramtohul, Y.; Skorey, K.; Sturkenboom, W.; Styhler, A.; Waddleton, D.; Wang, H.; Wong, S.; Xu, L.; Zhang, L. *J. Med. Chem.* **2011**, *54*, 5082.
12. 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. and references therein.
13. (a) Winther, M. D. 2nd Annual Drug Development for Diabetes and Obesity, London, UK, **2008**, Jan 17–18; (b) Atkinson, K. A.; Beretta, E. E.; Brown, J. A.; Castrodad, M.; Chen, Y.; Cosgrove, J. M.; Du, P.; Litchfield, J.; Makowski, M.; Martin, K.; McLellan, T. J.; Neagu, C.; Perry, D. A.; Piotrowski, D. W.; Steppan, C. M.; Trilles, R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1621.
14. 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. and references therein.
15. Uto, Y.; Kiyotsuka, Y.; Ueno, Y.; Miyazawa, Y.; Kurata, H.; Ogata, T.; Deguchi, T.; Yamada, M.; Watanabe, N.; Konishi, M.; Kurikawa, N.; Takagi, T.; Wakimoto, S.; Kono, K.; Ohsumi, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 746. and references therein.
16. Five initial applications from Xenon (WO2005/011653 to WO 2005/011657) were published on February 10, 2005. Representative one: Abreo, M.; Chafeev, M.; Chakka, N.; Chowdhury, S.; Fu, J. -M.; Gschwend, H. W.; Holladay, M. W.; Hou, D.; Kamboj, R.; Kodumuru, V.; Li, W.; Liu, S.; Raina, V.; Sun, S.; Sviridov, S.; Winther, M. D.; Zhang, Z. WO2005/011655.
17. For detailed experimental procedures, see: (a) Crane, S. N.; Robichaud, J. S.; Leger, S.; Ramtohul, Y. K. WO2007/056846; (b) Ramtohul, Y. K. WO2008/017161.
18. Golec, J. M. C.; Scrowston, R. M. *J. Chem. Res. Miniprint.* **1988**, *1*, 326.
19. For Rat microsomal assay conditions, see Li, C. S.; Ramtohul, Y.; Huang, Z.; Lachance, N. WO2006/130986.
20. Zhang, L.; Ramtohul, Y.; Gagné, S.; Styhler, A.; Guay, J.; Huang, Z. *J. Biomol. Screen.* **2010**, *15*, 169.
21. For a review on OATPs, see: Niemi, M. *Pharmacogenomics* **2007**, *8*, 787.
22. For detailed experimental procedures, see (a) Leger, S.; Deschenes, D.; Fortin, R.; Isabel, E.; Powell, D. WO2008/141455; (b) Ramtohul, Y. K.; Li, C. S.; Leclerc, J.-P. WO2009/012573.
23. Takahshi, T.; Naito, T.; Inoue, S. *Chem. Pharm. Bull.* **1958**, *6*, 334.
24. Plasma protein binding (PPB) for inhibitor **16a** was not measured and PPB is not likely a major contributing factor to the lack of its in vivo efficacy since a related liver targeting SCD1 inhibitor, MK-8245, containing a carboxylic acid moiety has very high PPB (>99% in several species) and yet is very efficacious in the mouse liver PD assay, Ref. 11f In addition, the rat hepatocyte assay was performed in the presence 10% fetal bovine serum and compound **16a** displayed good whole cell activity.