Bioorganic & Medicinal Chemistry Letters 20 (2010) 1593–1597

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

SAR and optimization of thiazole analogs as potent stearoyl-CoA desaturase inhibitors

Yeeman K. Ramtohul [a,*], Cameron Black [a], Chi-Chung Chan [c], Sheldon Crane [a], Jocelyne Guay [b], Sébastien Guiral [b], Zheng Huang [b], Renata Oballa [a], Li-Jing Xu [c], Lei Zhang [b], Chun Sing Li [a]

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

ARTICLE INFO

Article history:
Received 1 December 2009
Revised 12 January 2010
Accepted 13 January 2010
Available online 21 January 2010

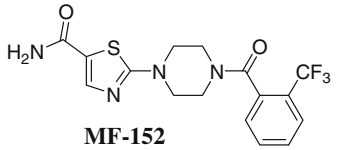
Keywords:
SCD inhibitors
Desaturation index
Body weight gain prevention
Insulin and glucose sensitivity

ABSTRACT

Elevated stearoyl-CoA desaturase (SCD) activity has been linked to a number of metabolic disorders including obesity and type II diabetes. Compound **3j**, a potent SCD inhibitor (human HepG2 IC_{50} = 1 nM) was identified from the optimization of a lead thiazole compound **MF-152** with over 100-fold improvement in potency. In a 4-week chronic oral dosing at 0.2 mg/kg, **3j** gave a robust 24% prevention of body weight gain in mice fed on a high fat diet accompanied with an improved metabolic profile on insulin and glucose levels.

Stearoyl-CoA desaturase (SCD) is a microsomal enzyme that catalyses 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.[1] These monounsaturated LCFA-CoAs, are major building blocks for de novo lipid synthesis and therefore play an important role in the lipogenic pathway.[2] Four SCD isoforms (SCD1–4) have been characterized in rodents and two in human (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) and is a key regulator of lipid and carbohydrate metabolism. In rodents, SCD-null mice display a beneficial metabolic phenotype characterised by resistance to high fat diet-induced obesity, improved insulin sensitivity and reduced body adiposity.[3,4] These beneficial phenotypes are also observed in high fat diet-induced obese (DIO) mice treated with anti-sense oligonucleotide (ASO)[5] or small molecule inhibitors.[6a,7–9] In human, an elevated SCD activity is positively correlated with high triglyceride in familial hypertriglyceridemia subjects,[11] increased body mass index (BMI) and high plasma insulin levels.[12] Therefore, the SCD1 enzyme represents an attractive target for the treatment of obesity, type-II diabetes, and related metabolic disorders.

In human, there are two additional fatty acyl-CoA specific desaturases, Δ5D and Δ6D which are involved in the biosynthesis of long-chain polyunsaturated fatty acids and are crucial in cell signaling.[13] Therefore, it is important to identify inhibitors which are selective for SCD1 over these desaturases. Recently, a number of reports have been published on small molecule inhibitors of SCD1.[6–10,14] In our previous communication,[9a] we reported a lead thiazole amide inhibitor **MF-152** (Fig. 1) which was suitable for in vivo SCD inhibition studies in rodents. However this compound was moderately potent (rat SCD IC_{50} = 0.1 μM and human HepG2 IC_{50} = 0.3 μM), the primary amide moiety was metabolically labile and to circumvent its short half-life a diet formulation had to be used for in vivo studies. Herein we wish to report further SAR in the five-membered ring thiazole series to improve potency and to identify a suitable compound for in vivo studies using oral dosing.[15]



MF-152

rSCD IC_{50} : 106 nM
hHepG2 IC_{50} : 253 nM

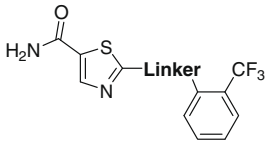
Figure 1. SCD1 lead inhibitor for in vivo studies.

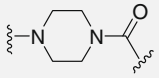
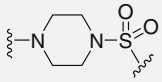
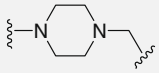
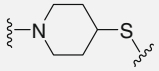
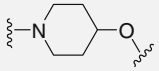
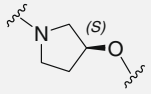
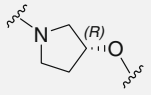
* Corresponding author.
E-mail address: yeeman_ramtohul@merck.com (Y.K. Ramtohul).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.01.083

In the absence of an SCD1 enzyme X-ray crystal structure, we chose to proceed with a systematic SAR study to guide our optimization efforts. We first set out to investigate the effect of the piperazine ring modification on the SCD1 inhibition. The representative general procedure for the synthesis of the compounds in Table 1 is depicted in Scheme 1.[16] Reaction of the 2-bromo-thiazole **4** with an appropriately substituted cyclic amine **5** affords a thiazole-ester adduct which can be converted to the corresponding primary amide by reaction with ammonia in a sealed tube.

Table 1
SAR on the piperazine ring



Compound	Linker	Rat SCD IC_{50}[a] (nM)	hHepG2 IC_{50}[a] (nM)
MF-152		106	254
1a		>3000	nd
1b		76	153
1c		4	24
1d		3	10
1e		12	84
1f		>20,000	nd

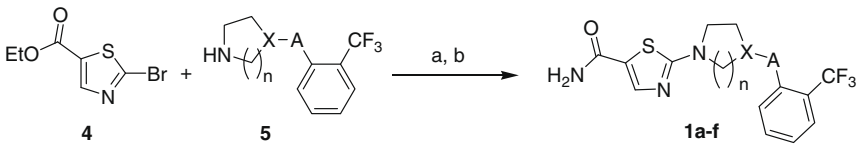
[a] IC_{50}s are an average of at least two independent titrations; nd—not determined.

The compounds were tested against the SCD1 enzyme in an SCD1-induced rat liver microsomal assay[16] and their cellular potencies were evaluated in a human HepG2-based whole cell assay.[17] As shown in Table 1, replacement of the benzamide functionality in **MF-152** with a with a more polar sulfonamide **1a** led to a significant loss in potency. However, the potency could be recovered with benzylamine **1b** and a further ~30-fold improvement in potency was achieved with the piperidine thioether **1c** as well as the piperidine ether **1d**.[18] The six-membered piperidine ring in **1d** can be substituted by a five-membered pyrolidine ring in **1e** possessing the *S*-configuration with a modest fourfold loss in potency, and in contrast the *R*-enantiomer **1f** was inactive. Overall, the piperidine ether moiety in **1d** was clearly an excellent replacement of the piperazine amide in **MF-152**.

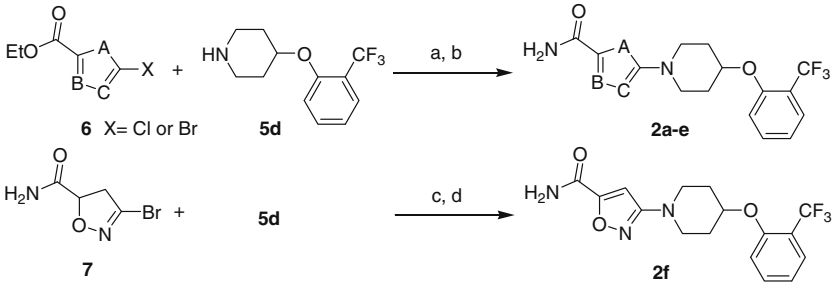
Having identified the piperidine ether **1d** as the optimal linker, we next examined the effect of five-membered heteroaromatic ring substitution on potency. The general synthetic route is summarized in Scheme 2.[16] Compounds **2a–e** can be prepared via displacement of a halo-heteroaromatic ring **6** with the phenoxypiperidine **5d** followed by conversion of the ester group to the corresponding primary amide with ammonia. However, for the isoxazole derivative **2f**, this strategy was unsuccessful and instead the bromo-dihydroisoxazole **7** was treated with the phenoxypiperidine **5d** followed by oxidation with iodine to furnish the isoxazole compound **2f**.[19]

The results showed that potency was highly dependent on subtle changes in this heterocycle (Table 2). For example, inversion of the thiazole ring from 1,3-thiazole-5-carboxamide **1d** to the regioisomer 1,3-thiazole-4-carboxamide **2a** led to a 225-fold loss in potency. The 1,3,4-thiadiazole **2b** was comparable in potency as the 1,3-thiazole **1d**. However, substitution of the 1,3,4-thiadiazole **2b** with a 1,3,4-oxadiazole **2c** led to a 27-fold loss in potency. Likewise, 1,2,4-oxadiazole **2d** and 1,2,4-triazole **2e** are less potent. Finally, the isoxazole ring **2f** showed similar potency to the thiadiazole. These modifications indicate that choosing the correct five-membered heteroaromatic ring is important to maximize the inhibitory activity. Given the equipotency of the thiazole **1d** and the thiadiazole **2b**, we chose to utilize the simpler thiazole ring for further SAR.

Our next approach was to replace the metabolically labile primary amide group in **MF-152** with more stable isosteres. As illustrated in Table 3.[16] conversion of the primary amide **1d** into a more stable primary sulfonamide led to a 13-fold loss in the enzyme



Scheme 1. Reagents: (a) DBU, THF, rt-Δ; (b) ammonia, MeOH, Δ, sealed tube.



Scheme 2. Reagents: (a) DBU, THF, rt-Δ; (b) ammonia, MeOH, Δ, sealed tube; (c) *N*,*N*-diisopropylethylamine, EtOH, Δ; (d) I_2, NaOAc, toluene, Δ.