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

David A. Powell *, Yeeman Ramtohul, Marie-Eve Lebrun, Renata Oballa, Sathesh Bhat, Jean-Pierre Falgueyret, Sebastien Guiral, Zheng Huang, Kathryn Skorey, Paul Tawa, Lei Zhang

Merck Frosst Centre for Therapeutic Research, 16711 Trans Canada Highway, Kirkland, Québec, Canada H9H 3L1

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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.

* Corresponding author. Tel.: +1 514 428 3098; fax: +1 514 428 4900.
E-mail address: david_powell2@merck.com (D.A. Powell).

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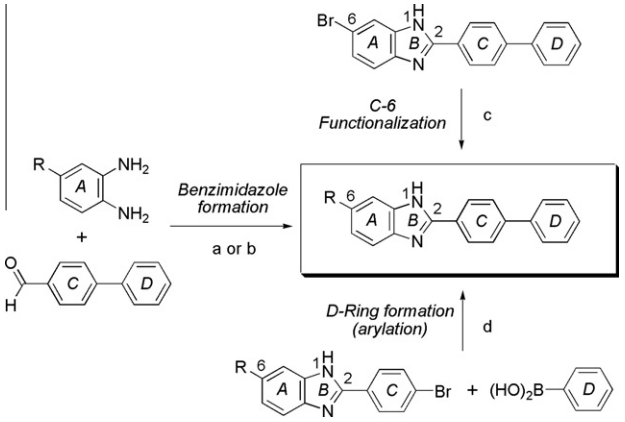
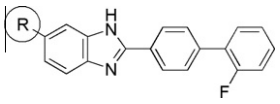


Scheme 1. Reagents and conditions: (a) 10 mol % *p*-TsOH, DMF, air, 80 °C, 2 h; (b) 2.5 equiv TMSCl, DMF, 90 °C, 4 h; (c) sulfinic acid sodium salt (2.0 equiv), 1 equiv CuOTf, 2 equiv *trans* 1,2-diaminocyclohexane, DMSO, 130 °C, 2–6 h; (d) 2.5 mol % $[PdBr(t\text{-}Bu_3P)]_2$, 2 equiv K_3PO_4, dioxane/H_2O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

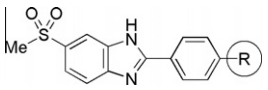
IC_{50}s are an average of at least two titrations.

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	–	–

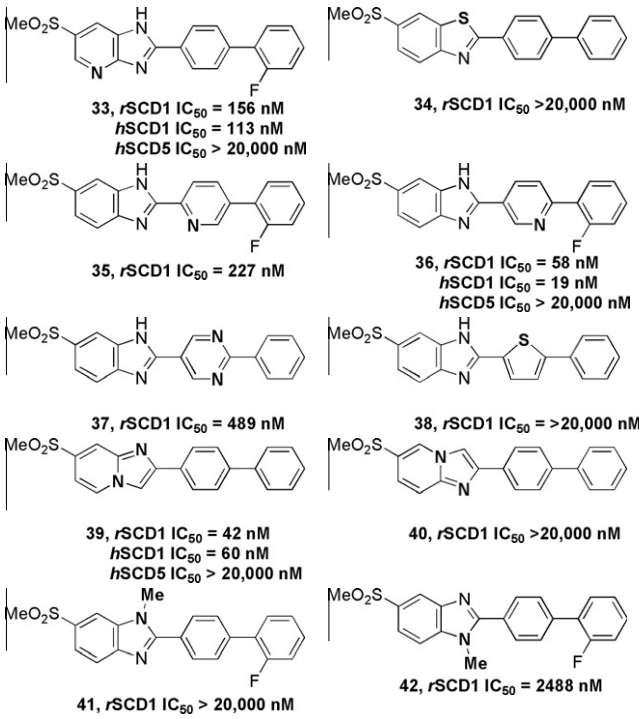
IC_{50}s are an average of at least two titrations.

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 Hepatocycte[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).

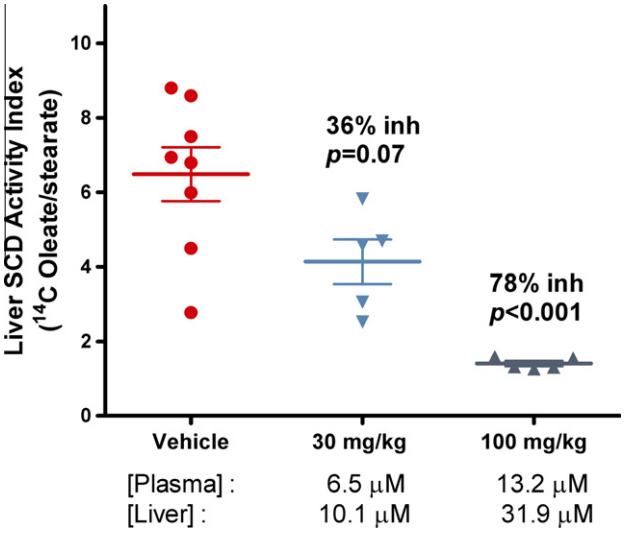


Figure 1. Male C57Bl6 mice were fed a high sucrose/fat-free diet for 2 days to induce liver SCD activity. Compound **8** was administered orally in 0.5% Methocel at 7:00 am on day 3. The [1-^{14}C]-stearic acid tracer (40 μCi/kg) was dosed via the jugular vein at 8:00 am and livers were harvested 2 h 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.

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